



US012391686B2

(12) **United States Patent**
Ruppel et al.

(10) **Patent No.:** US 12,391,686 B2
(45) **Date of Patent:** Aug. 19, 2025

(54) **COMPOUNDS AND USES THEREOF**

- (71) Applicant: **Foghorn Therapeutics Inc.**,
Cambridge, MA (US)
- (72) Inventors: **Sabine K. Ruppel**, Cambridge, MA (US); **Zhaoxia Yang**, Belmont, MA (US); **Jason T. Lowe**, East Bridgewater, MA (US); **Johannes H. Voigt**, Cambridge, MA (US); **Matthew Netherton**, Cambridge, MA (US); **Francois Brucelle**, Belmont, MA (US)
- (73) Assignee: **FOGHORN THERAPEUTICS INC.**, Cambridge, MA (US)
- (*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1029 days.
- (21) Appl. No.: **17/425,132**
- (22) PCT Filed: **Jan. 29, 2020**
- (86) PCT No.: **PCT/US2020/015740**
 § 371 (c)(1),
 (2) Date: **Jul. 22, 2021**
- (87) PCT Pub. No.: **WO2020/160192**
 PCT Pub. Date: **Aug. 6, 2020**

(65) **Prior Publication Data**

US 2023/0077730 A1 Mar. 16, 2023

Related U.S. Application Data

- (60) Provisional application No. 62/798,434, filed on Jan. 29, 2019, provisional application No. 62/881,163, filed on Jul. 31, 2019, provisional application No. 62/881,018, filed on Jul. 31, 2019.
- (51) **Int. Cl.**
C07D 471/04 (2006.01)
A61K 31/4745 (2006.01)
A61P 35/00 (2006.01)
C07D 401/04 (2006.01)
C07D 401/14 (2006.01)
C07D 519/00 (2006.01)
- (52) **U.S. Cl.**
 CPC *C07D 471/04* (2013.01); *A61P 35/00* (2018.01); *C07D 401/14* (2013.01); *C07D 519/00* (2013.01)
- (58) **Field of Classification Search**
 CPC .. C07D 471/04; C07D 401/04; C07D 401/14;
 A61P 35/00; A61K 31/4745
 See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

- 5,858,358 A 1/1999 June et al.
 5,883,223 A 3/1999 Gray
 6,352,694 B1 3/2002 June et al.

6,534,055	B1	3/2003	June et al.
6,692,964	B1	2/2004	June et al.
6,797,514	B2	9/2004	Berenson et al.
6,867,041	B2	3/2005	Berenson et al.
6,887,466	B2	5/2005	June et al.
6,905,680	B2	6/2005	June et al.
6,905,681	B1	6/2005	June et al.
6,905,874	B2	6/2005	Berenson et al.
7,056,883	B2	6/2006	Ito et al.
7,067,318	B2	6/2006	June et al.
7,144,575	B2	12/2006	June et al.
7,172,869	B2	2/2007	June et al.
7,175,843	B2	2/2007	June et al.
7,205,103	B2	4/2007	Emerson
7,232,566	B2	6/2007	June et al.
7,572,631	B2	8/2009	Berenson et al.
8,476,434	B2	7/2013	Greuns-Meyer et al.
9,271,978	B2	3/2016	Liu et al.
9,353,051	B2	5/2016	Byrd et al.
9,410,943	B2	8/2016	Kadoch et al.
9,708,338	B2	7/2017	Yukimasa et al.
9,718,821	B2	8/2017	Woods et al.
9,908,885	B2	3/2018	Bennett et al.
9,919,998	B2	3/2018	Ebright et al.
10,023,592	B2	7/2018	Boloor
10,047,068	B2	8/2018	Tojo et al.
10,105,420	B2	10/2018	Kadoch et al.
10,138,827	B2	11/2018	Dudar
10,183,009	B2	1/2019	Albrecht et al.
10,321,345	B2	6/2019	Kazmi et al.
10,336,722	B2	7/2019	Bair et al.
10,464,925	B2	11/2019	Bradner et al.
10,584,101	B2	3/2020	Crew et al.
10,646,575	B2	5/2020	Phillips et al.
10,660,968	B2	5/2020	Phillips et al.

(Continued)

FOREIGN PATENT DOCUMENTS

- CN 107056772 A 8/2017
 CN 108690020 A 10/2018

(Continued)

OTHER PUBLICATIONS

- Pearce et al., Failure modes in anticancer drug discovery and development, Cancer Drug Design and Discovery Edited by Stephen Neidle, Chapter 18, pp. 424-435 (2008).*
- Johnson et al., Relationships between drug activity in NCI preclinical in vitro and in vivo models and early clinical trials, British Journal of Cancer (2001) 64(10): 1424-1431.*
- Simone, Oncology: Introduction, Cecil Textbook of Medicine, 20th Edition, vol. 1, pp. 1004-1010, 1996.*
- Gura, Systems for identifying New Drugs Are Often Faulty, Cancer Models, Science, vol. 278, No. 5340, pp. 1041-1042, Nov. 1997.*
- Acute Leukemia, Merck Manual (Online Edition) 6 pages, pp. 1-6 (2013).*
- U.S. Appl. No. 17/245,379, Sandoval et al.

(Continued)

Primary Examiner — Bruck Kifle*(74) Attorney, Agent, or Firm* — Clark & Elbing LLP(57) **ABSTRACT**

The present invention relates to methods and compositions for the treatment of BAF-related disorders such as cancers and viral infections.

22 Claims, 14 Drawing Sheets**Specification includes a Sequence Listing.**

US 12,391,686 B2

Page 2

(56)

References Cited

U.S. PATENT DOCUMENTS

10,725,057 B2	7/2020	Tojo et al.	WO	WO-2013/126656 A1	8/2013
10,799,508 B2	10/2020	Beeharry et al.	WO	WO-2016/133935 A1	8/2016
10,849,982 B2	12/2020	Phillips et al.	WO	WO-2017/197051 A1	11/2017
10,889,593 B2	1/2021	Chan et al.	WO	WO-2017/197056 A1	11/2017
10,905,768 B1	2/2021	Phillips et al.	WO	WO-2017/223452 A1	12/2017
10,976,320 B2	4/2021	Dykhuizen et al.	WO	WO-2018/102725 A1	6/2018
11,185,592 B2	11/2021	Phillips et al.	WO	WO-2018/177297 A1	10/2018
11,285,218 B2	3/2022	Buckley et al.	WO	WO-2019/099868 A2	5/2019
11,319,318 B2	5/2022	Martin et al.	WO	WO-2019/152437 A1	8/2019
11,376,264 B2	7/2022	Evans et al.	WO	WO-2019/152440 A1	8/2019
11,402,372 B2	8/2022	Matyskiela et al.	WO	WO-2019/195201 A1	10/2019
11,414,416 B1	8/2022	Ruppel et al.	WO	WO-2019/207538 A1	10/2019
11,459,335 B2	10/2022	Phillips et al.	WO	WO-2020/051235 A1	3/2020
11,560,381 B1	1/2023	Ruppel et al.	WO	WO-2020/078933 A1	4/2020
11,584,748 B2	2/2023	Nasveschuk et al.	WO	WO-2020/132561 A1	6/2020
11,623,929 B2	4/2023	Nasveschuk et al.	WO	WO-2020/160192 A1	8/2020
11,767,330 B2	9/2023	Gu et al.	WO	WO-2020/160193 A2	8/2020
11,773,085 B2	10/2023	Zhou et al.	WO	WO-2020/160198 A1	8/2020
11,787,800 B2	10/2023	Ruppel et al.	WO	WO-2020/239103 A1	12/2020
11,851,445 B2	12/2023	Ruppel et al.	WO	WO-2020/264177 A1	12/2020
12,048,747 B2	7/2024	Phillips et al.	WO	WO-2021/055295 A1	3/2021
2005/0079512 A1	4/2005	Emerson et al.	WO	WO-2021/1155225 A1	8/2021
2006/0121005 A1	6/2006	Berenson et al.	WO	WO-2021/178920 A1	9/2021
2011/0053897 A1	3/2011	Che et al.	WO	WO-2023/283263 A1	1/2023
2011/0061116 A1	3/2011	Haldar et al.	WO	WO-2023/039208 A1	3/2023
2011/0201602 A1	8/2011	Geuns-Meyer et al.	WO	WO-2023/200800 A1	10/2023
2016/0058872 A1	3/2016	Crew et al.	WO	WO-2024/006292 A2	1/2024
2016/0200721 A1	7/2016	Yukimasa et al.	WO	WO-2024/013766 A1	1/2024
2016/0347708 A1	12/2016	Ebright et al.	WO	WO-2024/013812 A1	1/2024
2017/0014491 A1	1/2017	Kadoch et al.	WO	WO-2024/014021 A1	1/2024
2017/0050968 A1	2/2017	Bennett et al.	WO	WO-2024/037578 A1	2/2024
2017/0158709 A1	6/2017	Boloor	WO	WO-2024/163609 A1	8/2024
2017/0190686 A1	7/2017	Tojo et al.	WO	WO-2024/163641 A2	8/2024
2017/0340605 A1	11/2017	Albrecht et al.	WO	WO-2024/163751 A1	8/2024
2018/0044335 A1	2/2018	Martin et al.	WO	WO-2025/015149 A2	1/2025
2018/0085465 A1	3/2018	Bradner et al.	WO	WO-2025/015152 A1	1/2025
2018/0187614 A1	7/2018	Dudar			
2018/0213422 A1	7/2018	Kazmi et al.			
2018/0215766 A1	8/2018	Bair et al.			
2018/0215866 A1	8/2018	Zhao et al.			
2018/0328913 A1	11/2018	Kadoch et al.			
2019/0076539 A1	3/2019	Phillips et al.			
2019/0219562 A1	7/2019	Matyskiela et al.			
2019/0247509 A1	8/2019	Buckley et al.			
2019/0322683 A1	10/2019	Chan et al.			
2020/0140456 A1	5/2020	Phillips et al.			
2020/0206344 A1	7/2020	Kadoch et al.			
2021/0009568 A1	1/2021	Zhou et al.			
2021/0198256 A1	7/2021	Nasveschuk et al.			
2021/0230190 A1	7/2021	Ruppel et al.			
2021/0290676 A1	9/2021	Chaudhary			
2021/0388040 A1	12/2021	Kadoch et al.			
2022/0048906 A1	2/2022	Ruppel et al.			
2022/0098190 A1	3/2022	Ruppel et al.			
2022/0265618 A1	8/2022	Malatesta et al.			
2022/0289711 A1	9/2022	Ruppel et al.			
2022/0315578 A1	10/2022	Chen et al.			
2023/0065463 A1	3/2023	Ruppel et al.			
2023/0066136 A1	3/2023	Ruppel et al.			
2023/0072053 A1	3/2023	Ruppel et al.			
2023/0142883 A1	5/2023	Ruppel et al.			
2023/0331722 A1	10/2023	Ruppel et al.			
2023/0416246 A1	12/2023	Ruppel et al.			
2024/0002382 A1	1/2024	Ruppel et al.			
2024/0067642 A1	2/2024	Ruppel et al.			
2024/0150328 A1	5/2024	Zhou et al.			
2024/0150348 A1	5/2024	Ruppel et al.			
2024/0166668 A1	5/2024	Ruppel et al.			
2024/0190894 A1	6/2024	Gu et al.			
2024/0325370 A1	10/2024	Chen et al.			

FOREIGN PATENT DOCUMENTS

JP	H0733773 A	2/1995
WO	WO-2011/014515 A1	2/2011

OTHER PUBLICATIONS

- Baheti et al., "Excipients used in lyophilization of small molecules," *J. Excipients and Food Chem.* 1(1):41-54 (2010).
- Börolid et al., "BRD9 is a druggable component of interferon-stimulated gene expression and antiviral activity," *EMBO Rep.* 22(10):e52823 (Aug. 16, 2021) (18 pages).
- Brien et al., "Targeted degradation of BRD9 reverses oncogenic gene expression in synovial sarcoma," *eLife.* 7:e41305 (Nov. 15, 2018) (26 pages).
- Choi et al., "Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria," *J Clin Oncol.* 25(13):1753-9 (May 1, 2007).
- Crawford et al., "Inhibition of bromodomain-containing protein 9 for the prevention of epigenetically-defined drug resistance," *Bioorg Med Chem Lett.* 27(15):3534-41(2017).
- Extended European Search Report for European Patent Application No. 20749033.5, dated Sep. 29, 2022 (5 pages).
- Extended European Search Report for European Patent Application No. 20749034.3, issued Jan. 16, 2023 (9 pages).
- International Search Report and Written Opinion for International Application No. PCT/US2023/018195, mailed Aug. 31, 2023 (13 pages).
- Hay et al., "Design and synthesis of potent and selective inhibitors of BRD7 and BRD9 bromodomains," *Med. Chem. Commun.* 6:1381-86 (2015).
- Hohmann et al., "Sensitivity and engineered resistance of myeloid leukemia cells to BRD9 inhibition," *Nat Chem Biol.* 12(9): 672-679 (Sep. 2016) (12 pages).
- Hu et al., "Genomic characterization of genes encoding histone acetylation modulator proteins identifies therapeutic targets for cancer treatment," *Nat Commun.* 10(1):733 (Feb. 2019) (17 pages).
- International Preliminary Report on Patentability for International Application No. PCT/US2020/015740, issued Jul. 27, 2021 (6 pages).

(56)

References Cited**OTHER PUBLICATIONS**

- International Preliminary Report on Patentability for International Application No. PCT/US2020/044508, mailed Feb. 10, 2022 (6 pages).
- International Preliminary Report on Patentability for International Patent Application No. PCT/US2020/015741, issued Jul. 27, 2021 (6 pages).
- International Preliminary Report on Patentability for International Patent Application No. PCT/US2020/044043, issued Jan. 31, 2023 (7 pages).
- International Search Report and Written Opinion for International Application No. PCT/US20/15740, mailed Jun. 26, 2020 (11 pages).
- International Search Report and Written Opinion for International Application No. PCT/US20/44043, mailed Nov. 9, 2020 (15 pages).
- International Search Report and Written Opinion for International Application No. PCT/US20/44508, mailed Jan. 12, 2021 (9 pages).
- International Search Report and Written Opinion for International Application No. PCT/US20/015741, mailed Jul. 20, 2020 (16 pages).
- International Search Report and Written Opinion for International Application No. PCT/US21/15630, mailed Apr. 8, 2021 (8 pages).
- International Search Report and Written Opinion for International Application No. PCT/US22/36252, mailed Nov. 15, 2022 (15 pages).
- International Search Report and Written Opinion for International Application No. PCT/US22/38641, mailed Nov. 17, 2022 (10 pages).
- International Search Report and Written Opinion for International Application No. PCT/US22/38668 mailed Jan. 20, 2023 (11 pages).
- International Search Report and Written Opinion for International Patent Application No. PCT/US2022/028511, mailed Aug. 1, 2022 (14 pages).
- International Search Report and Written Opinion for International Patent Application No. PCT/US21/15813, mailed Apr. 6, 2021 (24 pages).
- Kadoc et al., "Mammalian SWI/SNF chromatin remodeling complexes and cancer: Mechanistic insights gained from human genomics," *Sci Adv.* 1(5):e1500447 (2015) (17 pages).
- Kadoc et al., "Proteomic and bioinformatic analysis of mammalian SWI/SNF complexes identifies extensive roles in human malignancy," *Nat Genet.* 45(6):592-601 (2013) (11 pages).
- Kadoc et al., "Reversible Disruption of mSWI/SNF (BAF) Complexes by the SS18-SSX Oncogenic Fusion in Synovial Sarcoma," *Cell.* 153(1):71-85 (2013).
- Kotla et al., "Mechanism of action of lenalidomide in hematological malignancies," *J Hematol Oncol.* 2:36 (Aug. 12, 2009) (10 pages).
- Martin et al., "Structure-Based Design of an In Vivo Active Selective BRD9 Inhibitor," *J Med Chem.* 59(10):4462-75 (2016).
- McBride et al., "Disruption of mammalian SWI/SNF and polycomb complexes in human sarcomas: mechanisms and therapeutic opportunities," *J Pathol.* 244(5): 638-649 (Apr. 2018).
- Michel et al., "Abstract PR15: BRD9 defines a novel mammalian SWI/SNF(BAF) complex configuration which supports proliferation in AML," *Clin Cancer Res.* 23(24_Suppl) Abstract PR15 (2017) (4 pages).
- Muscal et al., "Plasma and cerebrospinal fluid pharmacokinetics of thalidomide and lenalidomide in nonhuman primates," Available in PMC Jun. 18, 2013. Published in final edited form as: *Cancer Chemother Pharmacol.* 69(4):943-7 (Apr. 2012) (10 pages).
- Pan et al., "A major chromatin regulator determines resistance of tumor cells to T cell-mediated killing," *Science.* 359(6377):770-75 (2018) (11 pages).
- Partial Supplementary European Search Report for European Application No. 20749034.3, dated Oct. 11, 2022 (12 pages).
- Picaud et al., "9H-purine scaffold reveals induced-fit pocket plasticity of the BRD9 bromodomain," *J Med Chem.* 58(6):2718-36 (2015).
- PubChem CID 12097004 "7-Phenyl-5H-furo[3,2-c] pyridin-4-one," created Feb. 7, 2007, retrieved Apr. 28, 2020 (9 pages).
- PubChem CID 68310947, "7-Methyl-4-phenyl-2H-isoquinolin-1-one," created Nov. 30, 2012, retrieved Apr. 28, 2020 (8 pages).
- Remillard et al., "Degradation of the BAF Complex Factor BRD9 by Heterobifunctional Ligands," *Angew Chem Int Ed Engl.* 56(21):5738-43 (2017) (7 pages).
- Remillard et al., "Degradation of the BAF Complex Factor BRD9 by Heterobifunctional Ligands," available in PMC May 24, 2018, published in final edited form as: *Angew Chem Int Ed Engl.* 56(21):5738-5743 (2017) (14 pages).
- Teuscher et al., "A Versatile Method to Determine the Cellular Bioavailability of Small-Molecule Inhibitors," *J Med Chem.* 60(1): 157-169 (2017).
- Theodoulou et al., "Discovery of I-BRD9, a Selective Cell Active Chemical Probe for Bromodomain Containing Protein 9 Inhibition," *J Med Chem.* 59(4):1425-39 (2015).
- Vangamudi et al., "The SMARCA2/4 ATPase Domain Surpasses the Bromodomain as a Drug Target in SWI/SNF-Mutant Cancers: Insights from cDNA Rescue and PFI-3 Inhibitor Studies," *Cancer Res.* 75(18):3865-78 (2015).
- Wang et al., "NMR Fragment Screening Hit Induces Plasticity of BRD7/9 Bromodomains," *Chembiochem.* 17(15):1456-63 (2016).
- Zhu et al., "Targeting BRD9 for Cancer Treatment: A New Strategy," *Oncotargets Ther.* 13:13191-13200 (Dec. 24, 2020).
- Zoppi et al., "Iterative Design and Optimization of Initially Inactive Proteolysis Targeting Chimeras (PROTACs) Identify VZ185 as a Potent, Fast, and Selective von Hippel-Lindau (VHL) Based Dual Degrader Probe of BRD9 and BRD7," *J Med Chem.* 62(2):699-726 (Jan. 2019).
- U.S. Appl. No. 18/292,426, Chen et al.
- U.S. Appl. No. 18/292,508, Huang, Liyue.
- Amako et al., "Development and Advances of PROTACs: Induced Protein Degradation by Hijacking Ubiquitin Ligase," *Journal of Synthetic Organic Chemistry, Japan* 76(4):358-9 (2018). English abstract included.
- Ballatore et al., "Aminothienopyridazine inhibitors of tau aggregation: evaluation of structure-activity relationship leads to selection of candidates with desirable in vivo properties," *Bioorg Med Chem.* 20(14):4451-61 (Jul. 15, 2012).
- Croce, "Oncogenes and cancer," *N Engl J Med.* 358(5):502-11 (Jan. 31, 2008).
- Cui et al., "The chromatin-remodeling BAF complex mediates cellular antiviral activities by promoter priming," *Mol Cell Biol.* 24(10):4476-86 (May 2004).
- Extended European Search Report for European Application No. 21748348.6, dated Jan. 4, 2024 (6 pages).
- International Preliminary Report on Patentability for International Application No. PCT/US2022/036252, mailed Dec. 14, 2023 (11 pages).
- International Search Report and Written Opinion for International Application No. PCT/US23/26363, mailed Jan. 4, 2024 (15 pages).
- International Search Report and Written Opinion for International Application No. PCT/US24/13766, mailed May 3, 2024 (10 pages).
- International Search Report and Written Opinion for International Application No. PCT/US24/13812, mailed Jul. 16, 2024 (17 pages).
- International Search Report and Written Opinion for International Application No. PCT/US24/14021, mailed Jun. 21, 2024 (15 pages).
- Khaminets et al., "Ubiquitin-Dependent And Independent Signals In Selective Autophagy," *Trends Cell Biol.* 26(1):6-16 (Jan. 2016).
- Kramer et al., "BRD9 Inhibition, Alone or in Combination with Cytostatic Compounds as a Therapeutic Approach in Rhabdoid Tumors," *Int J Mol Sci.* 18(7):1537 (Jul. 16, 2017) (12 pages).
- PCT/US2024/037567. Filed Jul. 11, 2024.
- PCT/US2024/037578. Filed Jul. 11, 2024.
- Search Report and Written Opinion for Singaporean Patent Application No. 11202251301D, dated Jan. 10, 2024 (10 Pages).
- Supporting Information for Remillard et al., "Degradation of the BAF Complex Factor BRD9 by Heterobifunctional Ligands," *Angew Chem Int Ed Engl.* 56(21):5738-43 (2017) (43 pages).
- Al-Hamdan et al., "Synthesis, structural characterization and antibacterial evaluation of some new 2-pyrazoline derivatives". *World Journal of Pharmacy and Pharmaceutical Sciences.* 7(11):200-211 (2018).

(56)

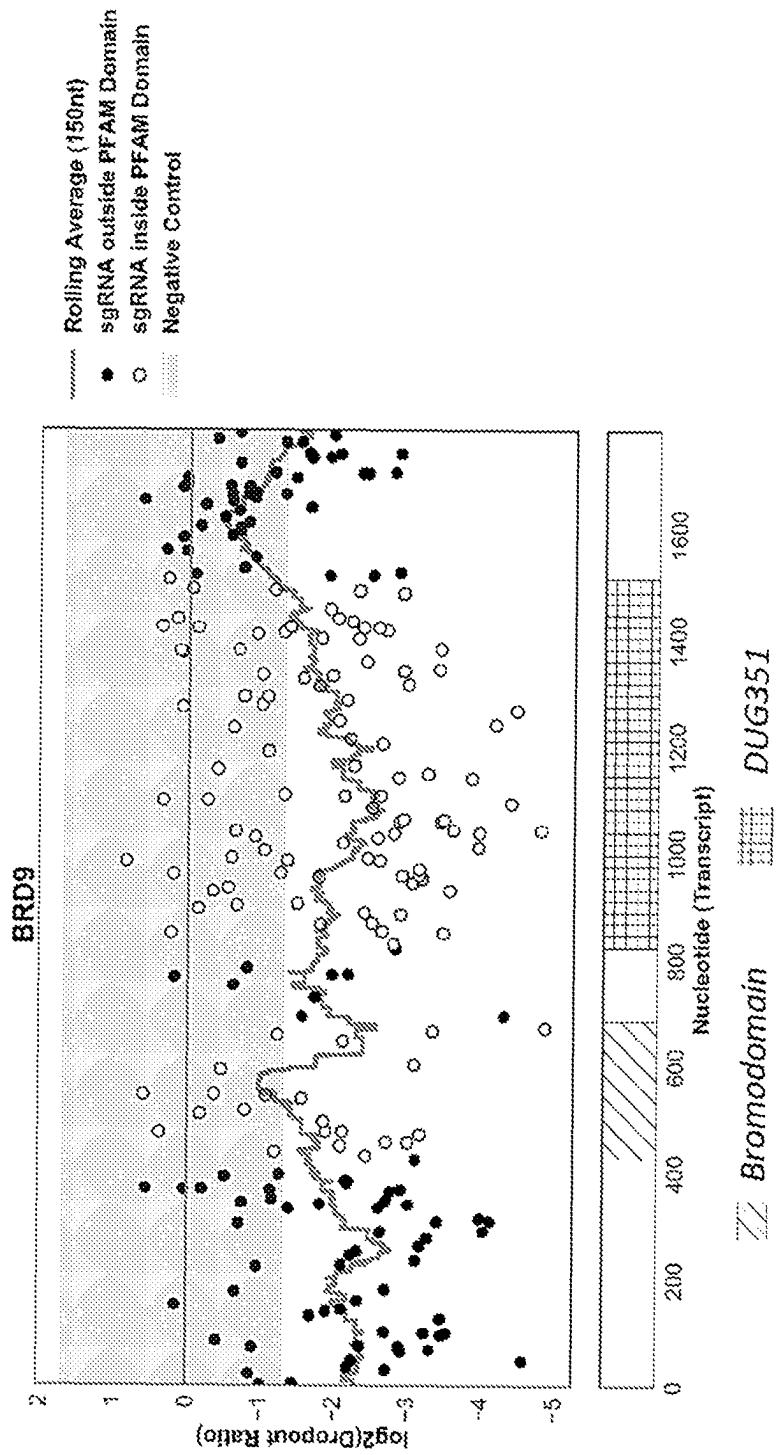
References Cited

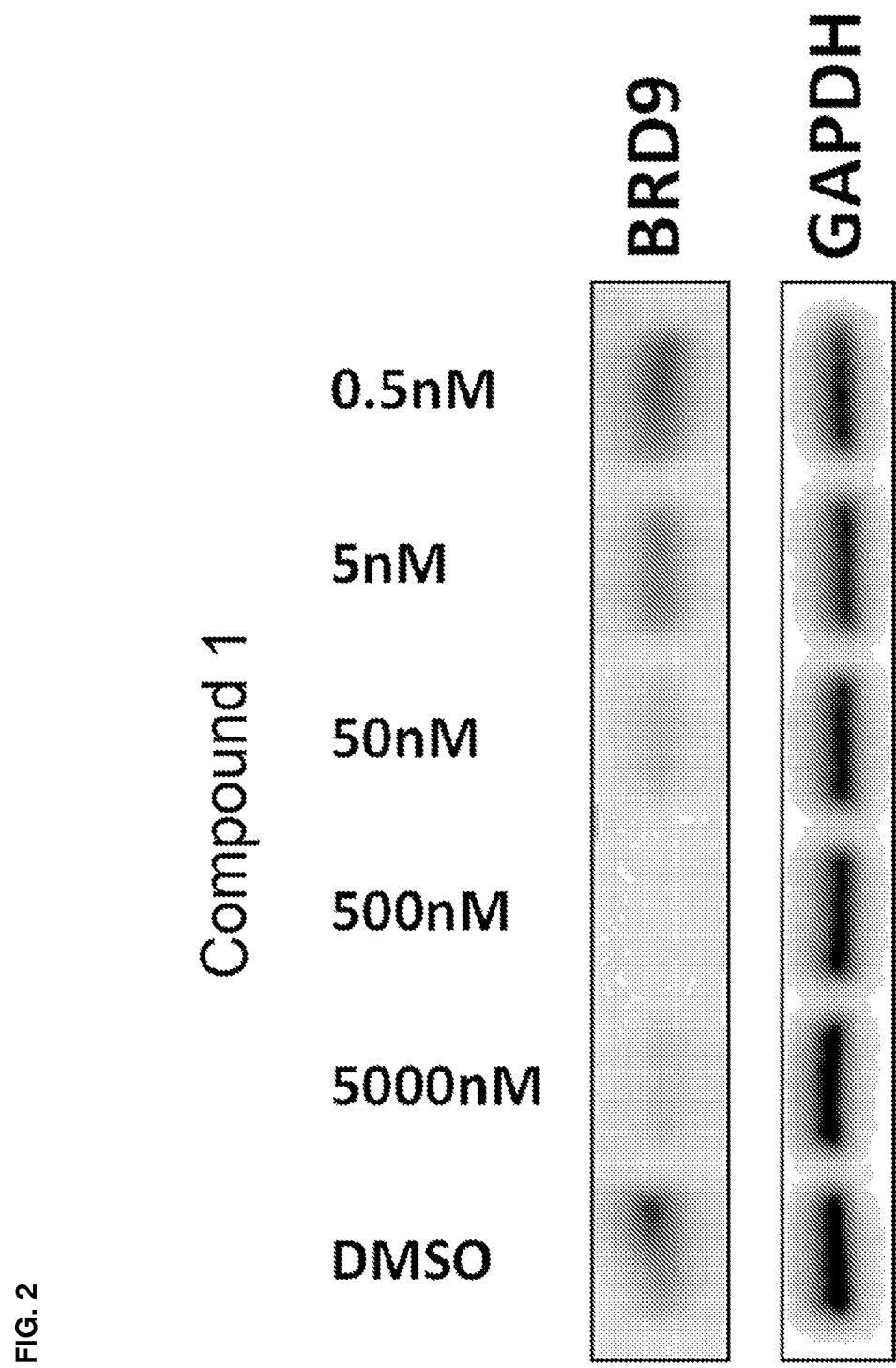
OTHER PUBLICATIONS

International Search Report and Written Opinion for International Patent Application No. PCT/US2024/037567, mailed Dec. 2, 2024 (16 pages).

Lopez-Girona et al. "Cereblon is a direct protein target for immunomodulatory and antiproliferative activities of lenalidomide and pomalidomide," Leukemia. 26(11):2326-2335 (2012).

* cited by examiner

FIG. 1



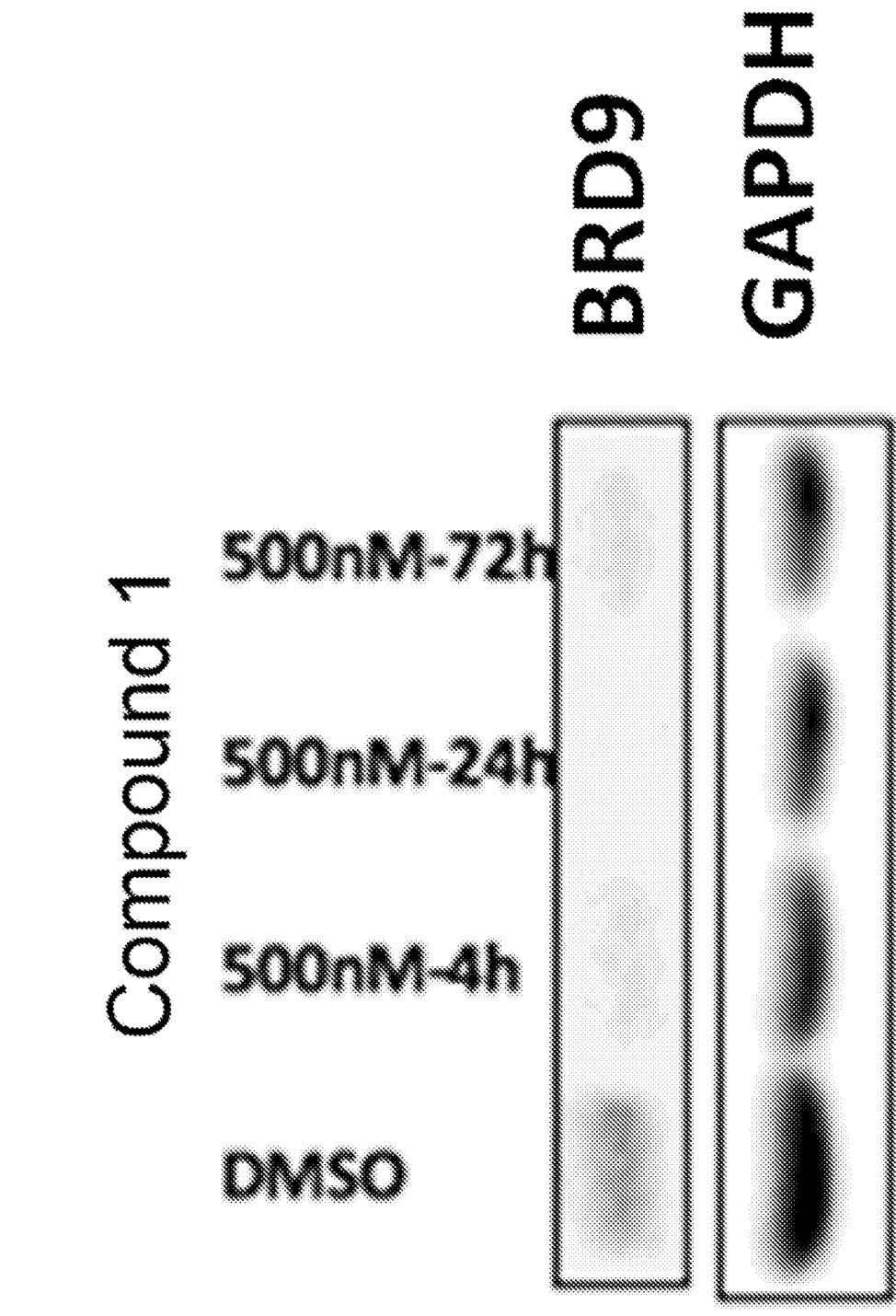


FIG. 3

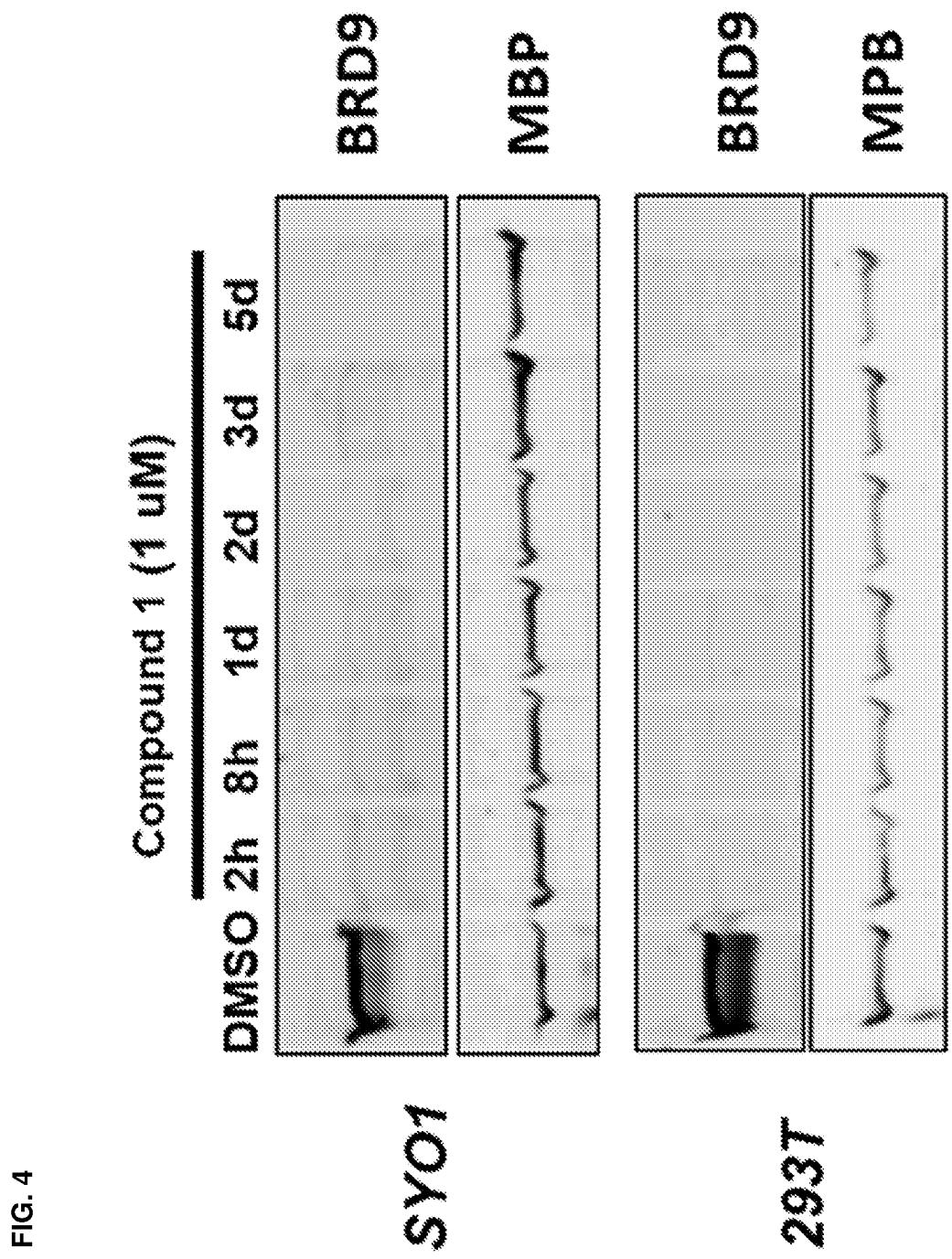
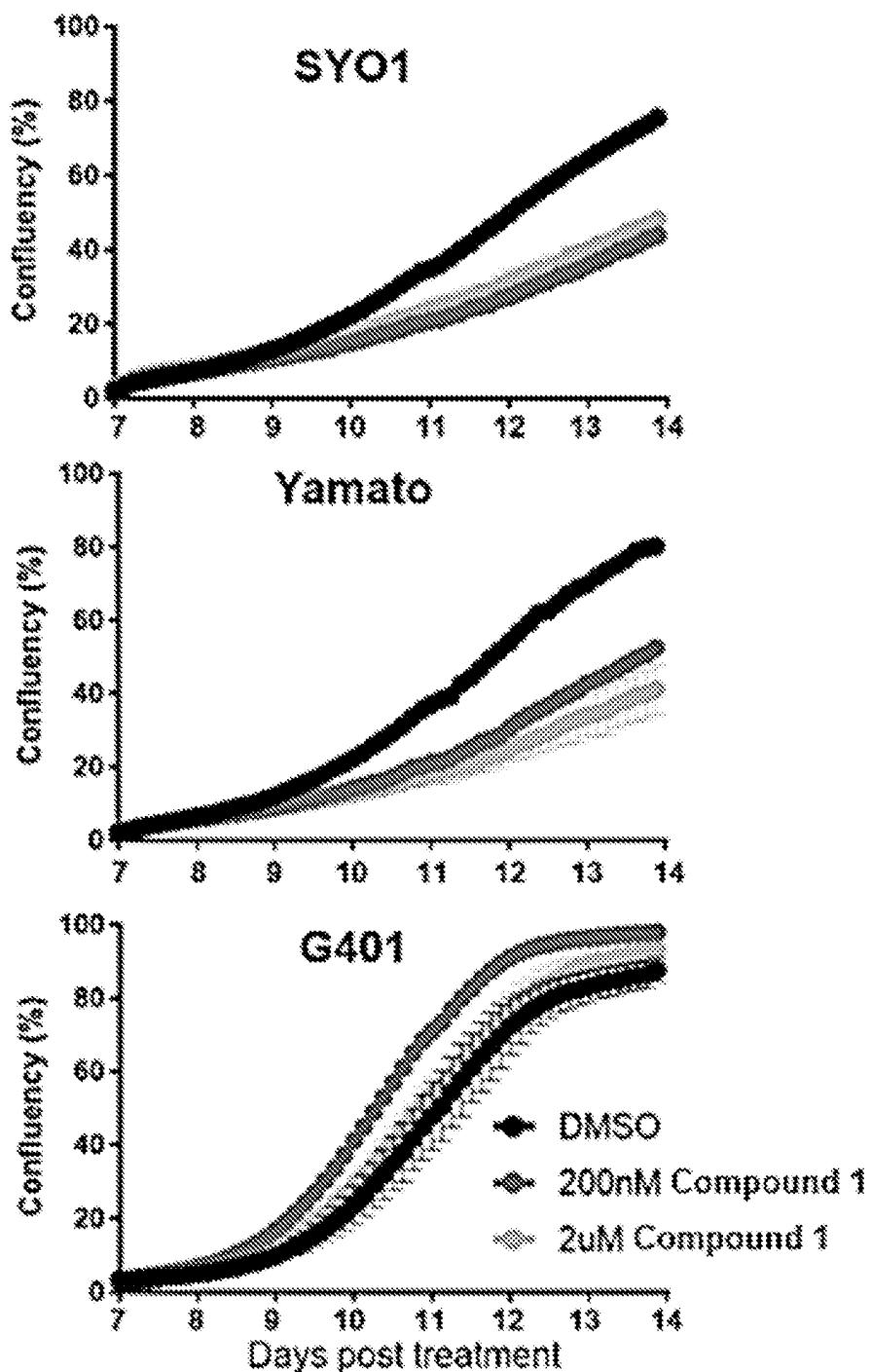
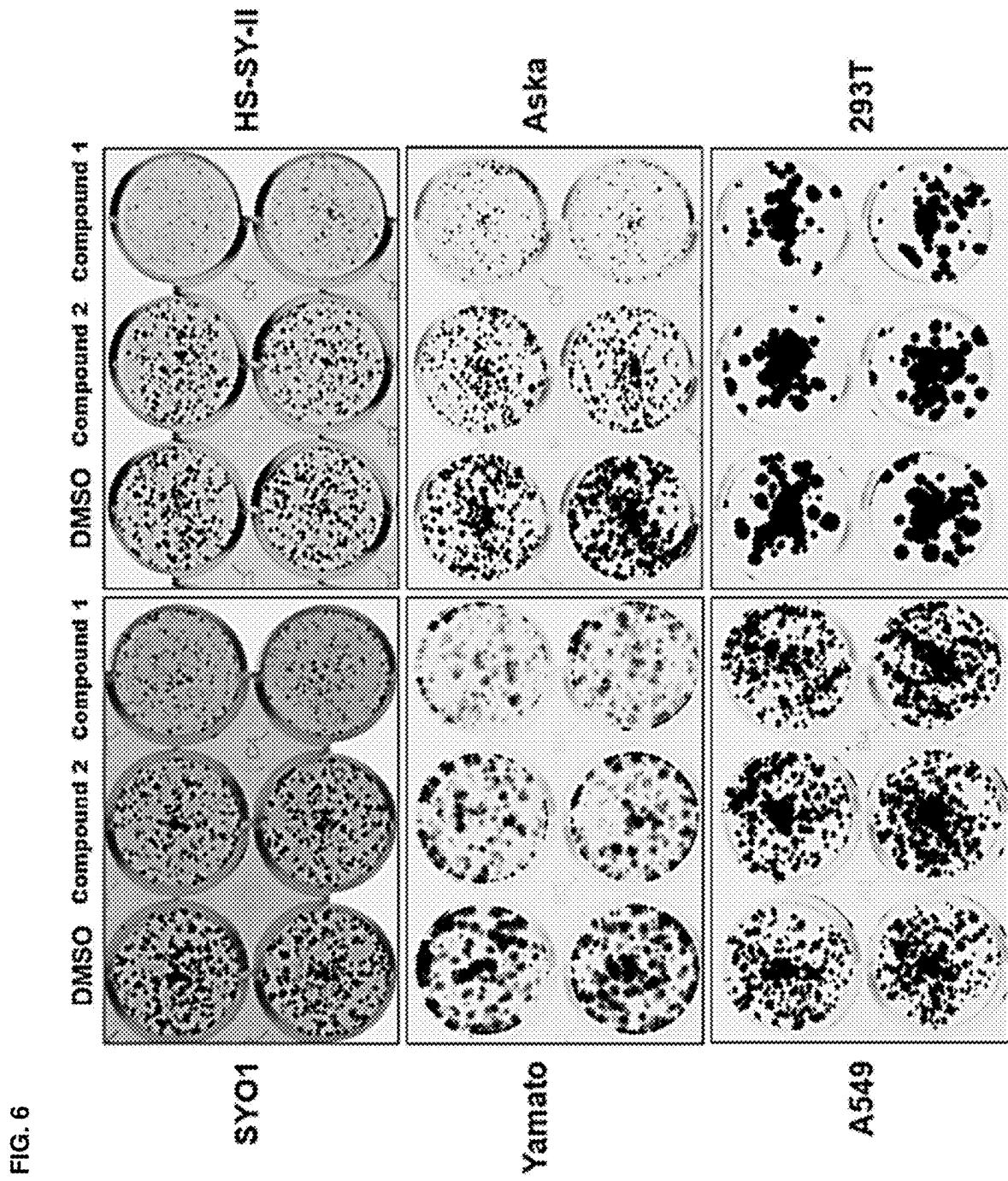


FIG. 5





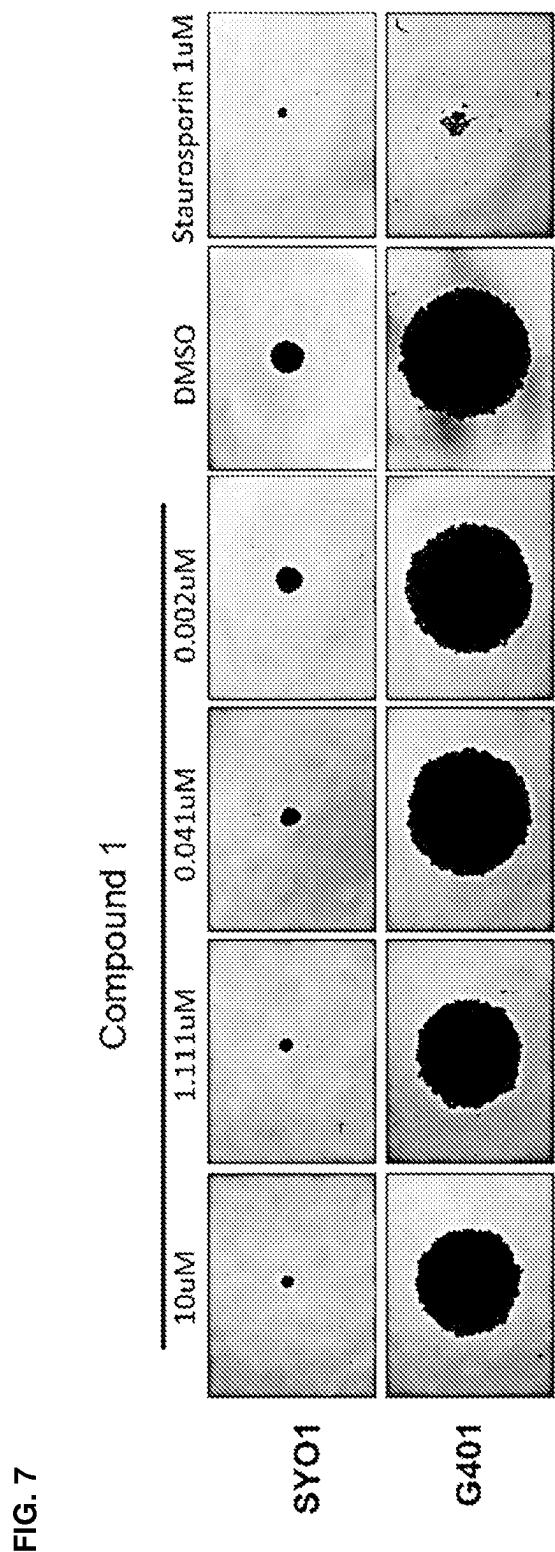
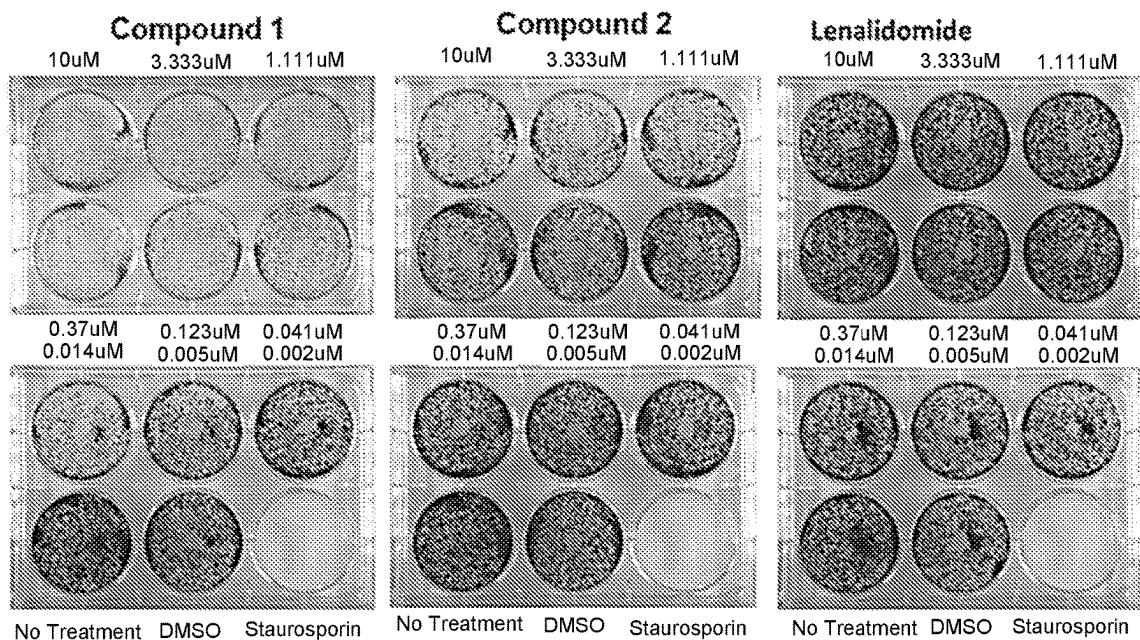


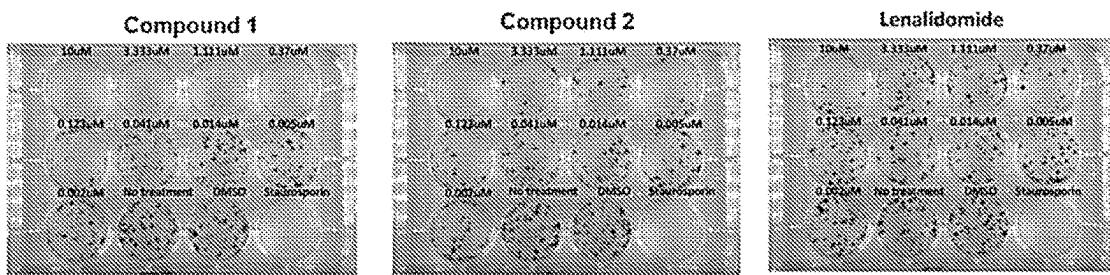
FIG. 7

FIG. 8

SYO1



HS-SY-II



ASKA

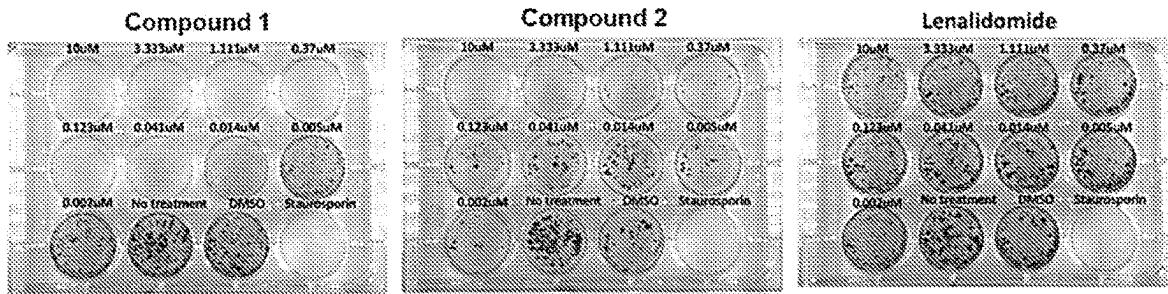
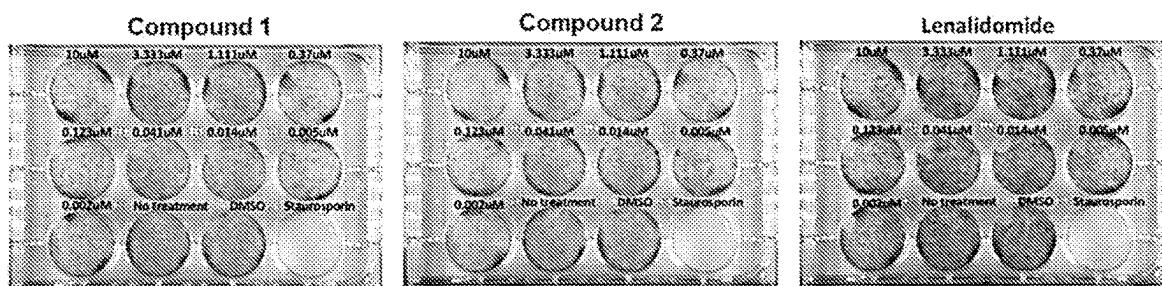
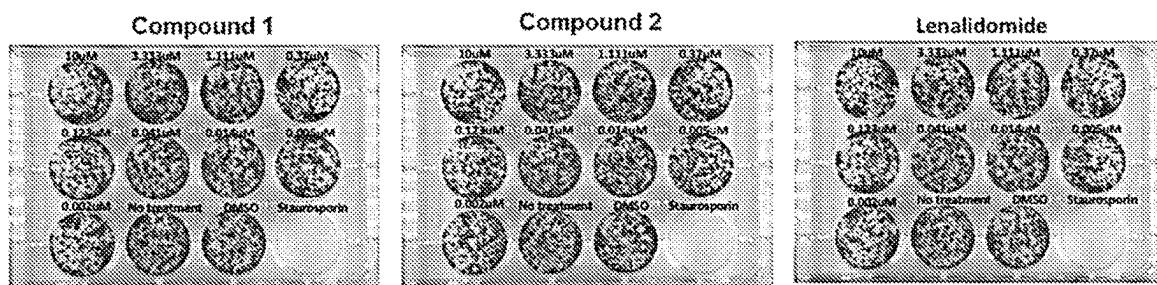


FIG. 9

RD



HCT116



Calu6

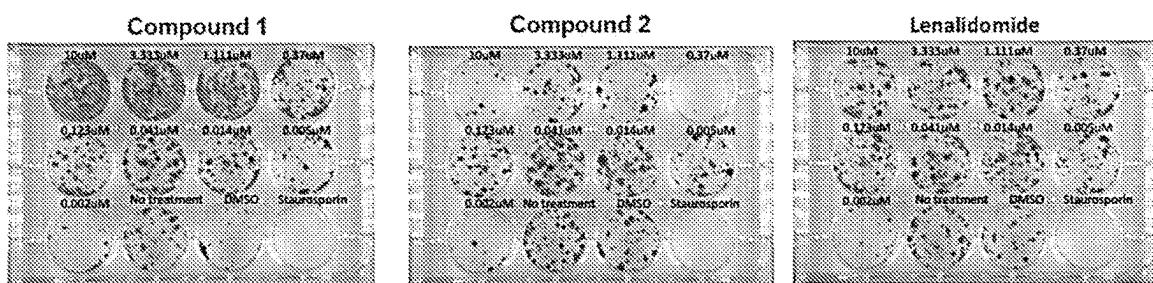


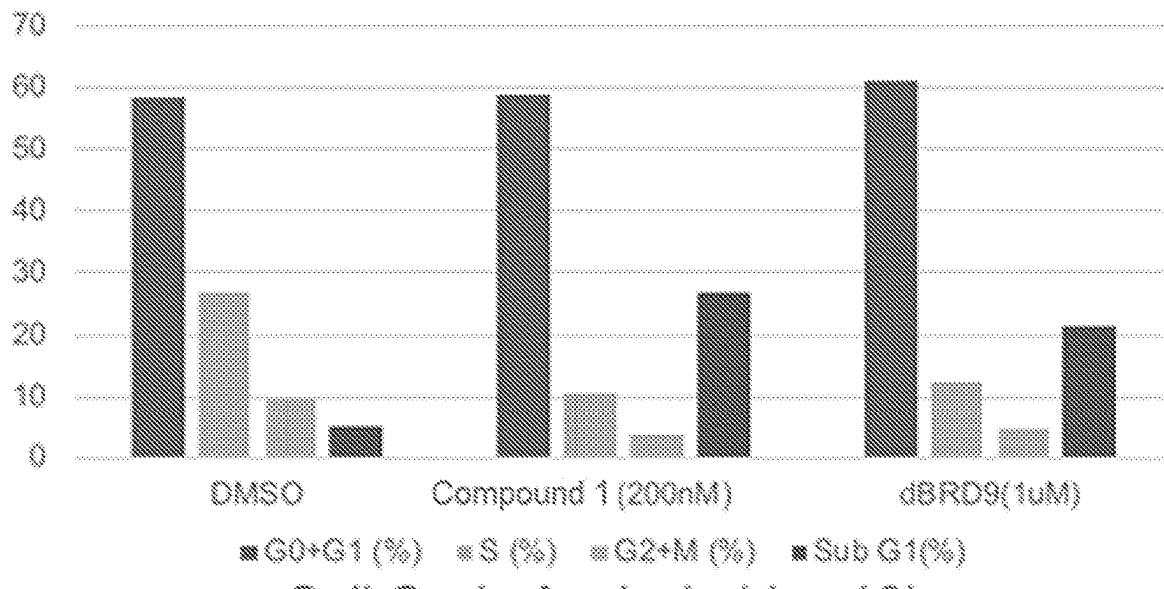
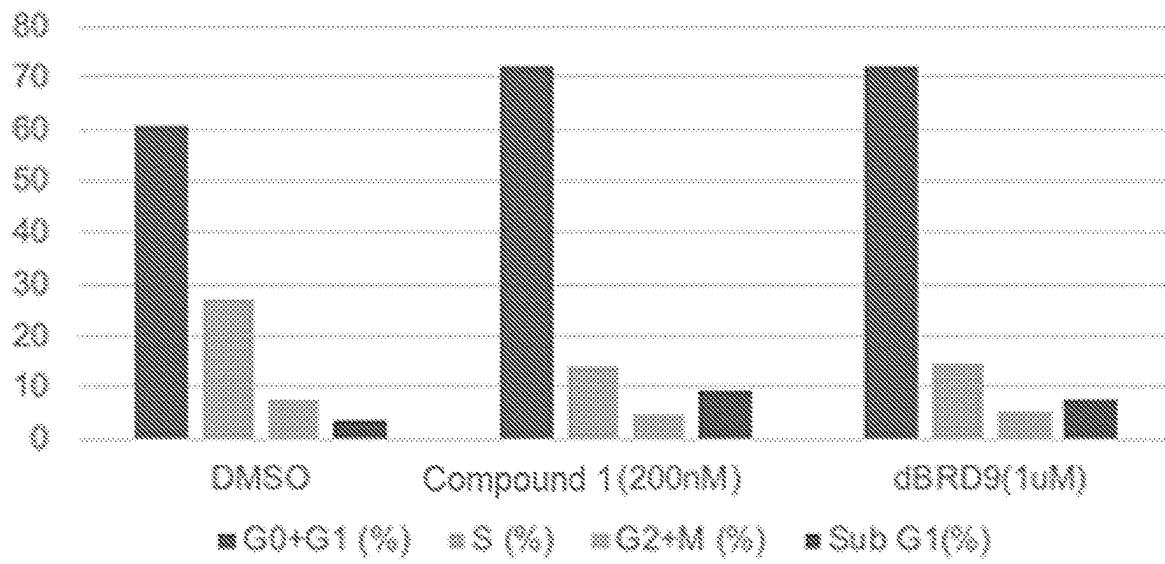
FIG. 10**Cell Cycle Analysis (day 8)****Cell Cycle Analysis (day 13)**

FIG. 11

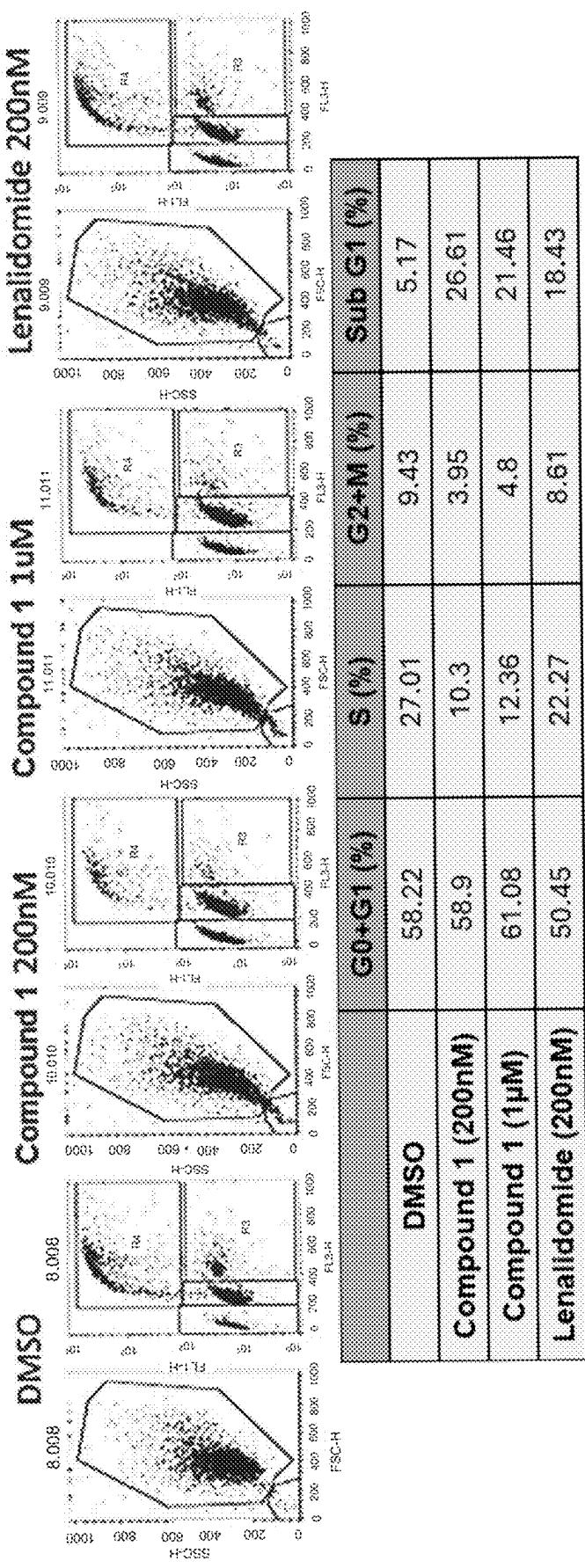


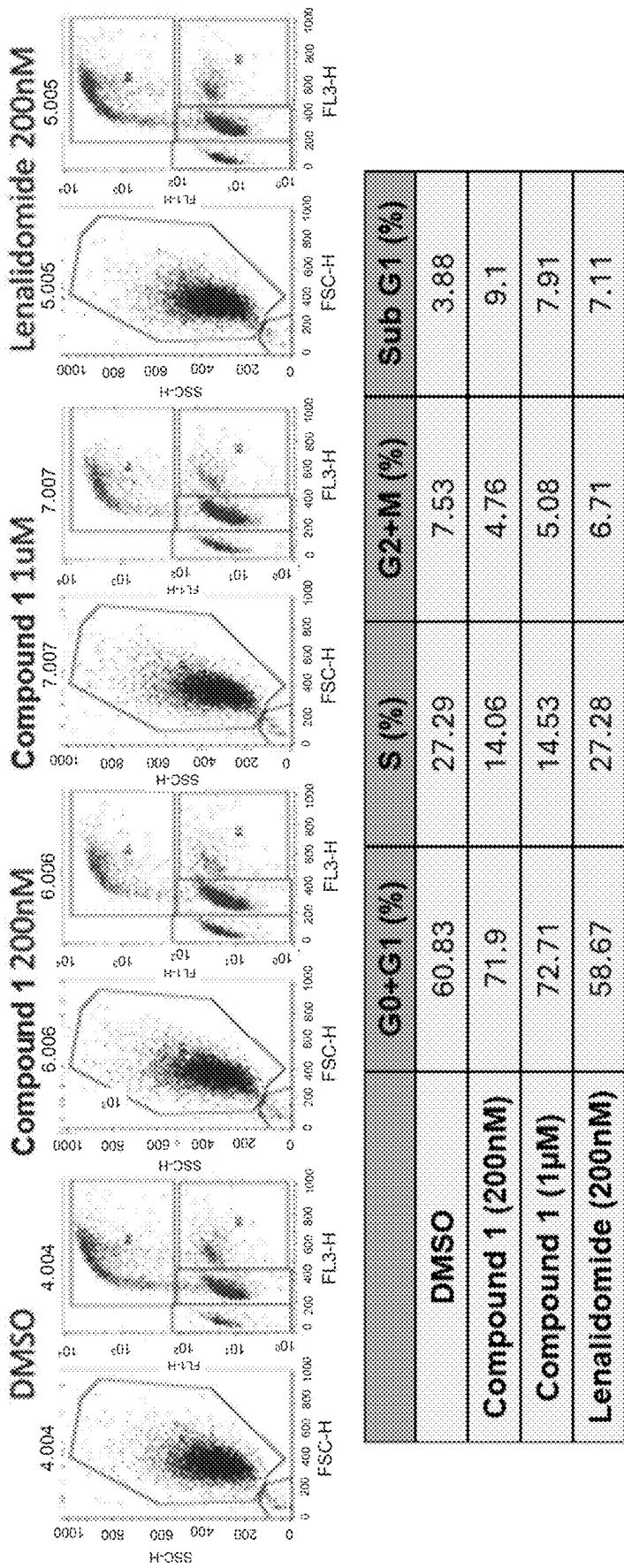
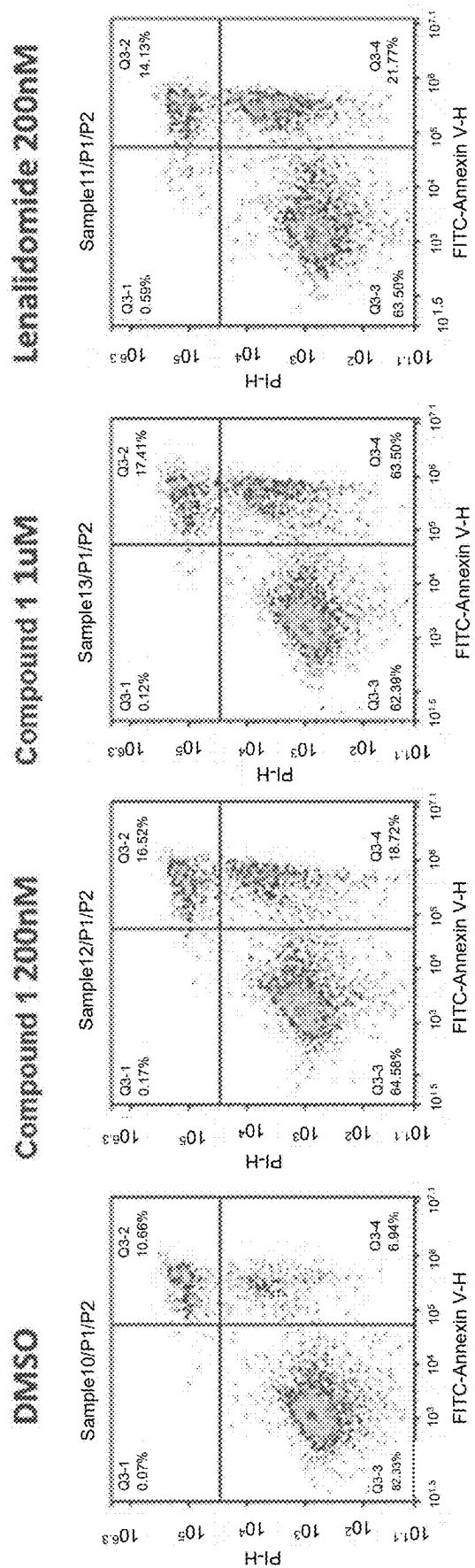
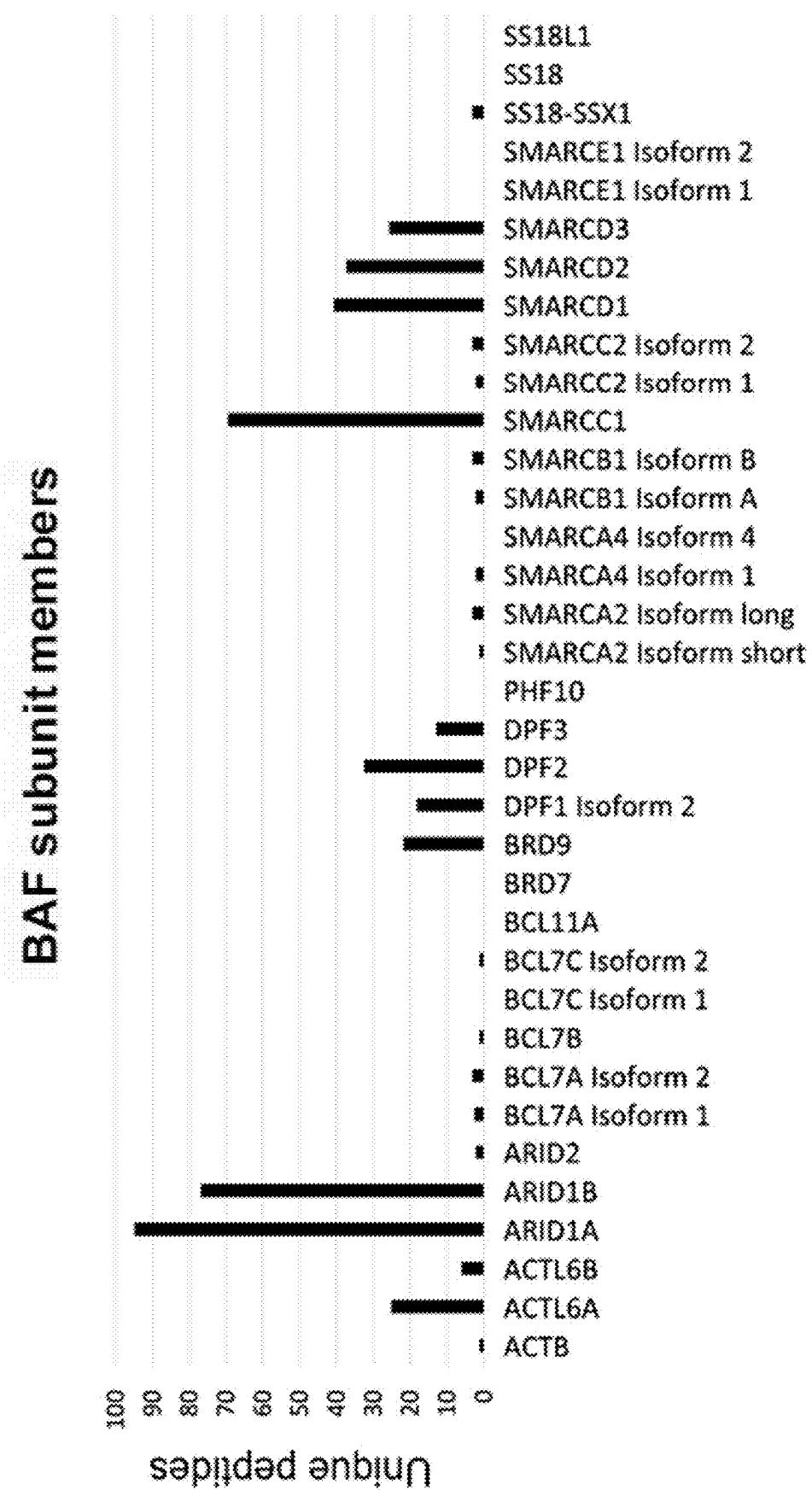
FIG. 12

FIG. 13

	DMSO	Compound 1 (1 μM)	Compound 1 (200nM)
Early Apoptosis Cell	6.94	18.72	20.08
Late Apoptosis Cell	10.66	16.52	17.41

FIG. 14



1
COMPOUNDS AND USES THEREOF

BACKGROUND

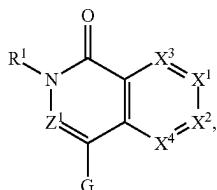
Disorders can be affected by the BAF complex. BRD9 is a component of the BAF complex. The present invention relates to useful compositions and methods for the treatment of BAF complex-related disorders, such as cancer and infection.

SUMMARY

Bromodomain-containing protein 9 (BRD9) is a protein encoded by the BRD9 gene on chromosome 5. BRD9 is a component of the BAF (BRG¹- or BRM-associated factors) complex, a SWI/SNF ATPase chromatin remodeling complex, and belongs to family IV of the bromodomain-containing proteins. BRD9 is present in several SWI/SNF ATPase chromatin remodeling complexes and is upregulated in multiple cancer cell lines. Accordingly, agents that reduce the levels and/or activity of BRD9 may provide new methods for the treatment of disease and disorders, such as cancer and infection. The inventors have found that depleting BRD9 in cells results in the depletion of the SS18-SSX fusion protein in those cells. The SS18-SSX fusion protein has been detected in more than 95% of synovial sarcoma tumors and is often the only cytogenetic abnormality in synovial sarcoma. Additionally, evidence suggests that the BAF complex is involved in cellular antiviral activities. Thus, agents that degrade BRD9 (e.g., compounds) are useful in the treatment of disorders (e.g., cancers or infections) related to BAF, BRD9, and/or SS18-SSX.

The present disclosure features compounds and methods useful for treating BAF-related disorders (e.g., cancer or infection).

In an aspect, the disclosure features a compound having the structure Formula I:



where

R¹ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ carbocyclyl;

Z¹ is CR² or N;

R² is H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, or optionally substituted C₂-C₉ heteroaryl;

X¹ is N or CH, and X² is C—R⁷; or X¹ is C—R⁷, and X² is N or CH;

R⁷ is optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₁-C₆ alkoxy, optionally substituted amino, optionally substituted sulfone, optionally substituted sulfonamide, optionally substituted carbocyclyl having 3 to 6 atoms, or optionally substituted heterocyclyl having 3 to 6 atoms;

X³ is N or CH;

X⁴ is N or CH;

2

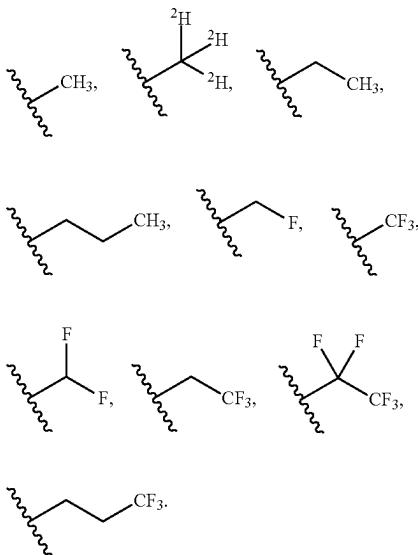
G is optionally substituted C₃-C₁₀ carbocyclyl, C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, or optionally substituted C₂-C₉ heteroaryl, or a pharmaceutically acceptable salt thereof.

In some embodiments, R¹ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ carbocyclyl. In some embodiments, R¹ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, or optionally substituted C₃-C₁₀ carbocyclyl. In some embodiments, R¹ is H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₃-C₁₀ carbocyclyl.

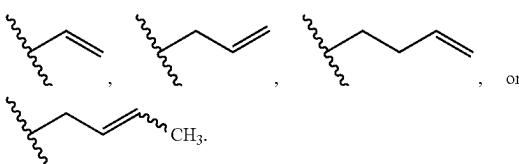
In some embodiments, R¹ is H. In some embodiments, R¹ is optionally substituted C₁-C₆ alkyl. In some embodiments, R¹ is optionally substituted C₂-C₆ alkenyl. In some embodiments, R¹ is optionally substituted C₃-C₁₀ carbocyclyl.

In some embodiments, optionally substituted C₁-C₆ alkyl is C₁-C₆ perfluoroalkyl.

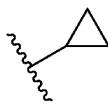
In some embodiments, R¹ is

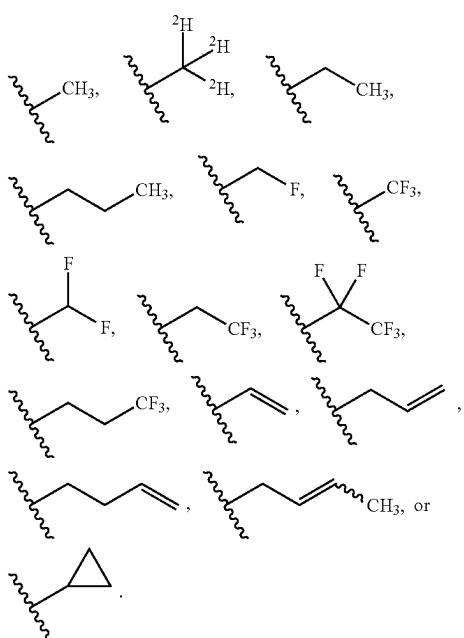
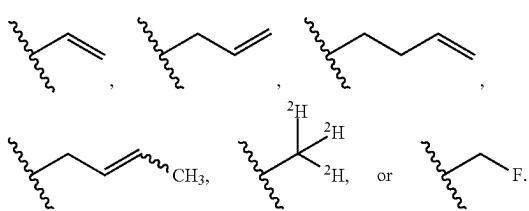
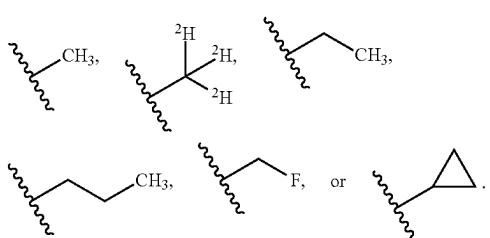
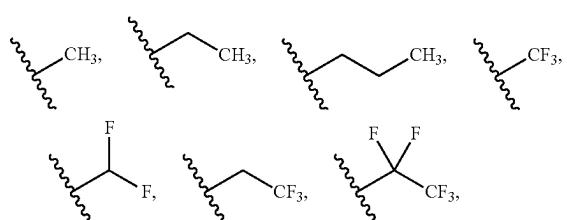


In some embodiments, R¹ is

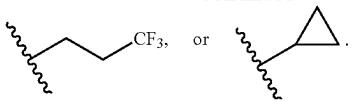
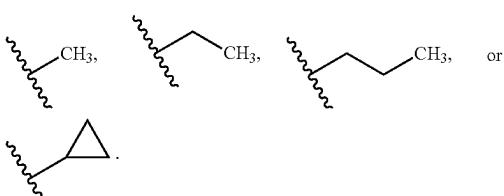


In some embodiments, R¹ is



3In some embodiments, R¹ is H,In some embodiments, R¹ isIn some embodiments, R¹ is H,In some embodiments, R¹ is H,**4**

-continued

In some embodiments, R¹ is H,In some embodiments, R¹ is H orIn some embodiments, R¹ is H. In some embodiments, R¹ isIn some embodiments, Z¹ is CR². In some embodiments, Z¹ is N.In some embodiments, R² is H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₁₀ carbocycliclyl, or optionally substituted C₆-C₁₀ aryl.In some embodiments, R² is H, halogen, or optionally substituted C₁-C₆ alkyl.In some embodiments, R² is H, F, orIn some embodiments, R² is H. In some embodiments, R² is F. In some embodiments, R² isIn some embodiments, R⁷ is optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₁-C₆ alkoxy, optionally substituted carbocycliclyl having 3 to 6 atoms, or optionally substituted heterocycliclyl having 3 to 6 atoms. In some embodiments, R⁷ is optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted carbocycliclyl having 3 to 6 atoms, or optionally substituted heterocycliclyl having 3 to 6 atoms. In some embodiments, R⁷ is optionally substituted

C_1-C_6 alkoxy or optionally substituted amino. In some embodiments, R^7 is optionally substituted sulfone or optionally substituted sulfonamide.

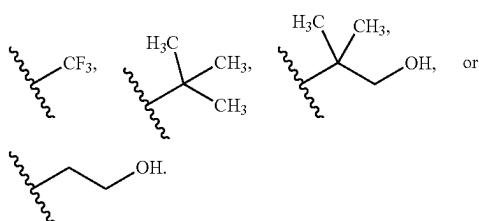
In some embodiments, R^7 is optionally substituted C_1-C_6 alkyl or optionally substituted carbocyclyl having 3 to 6 atoms. In some embodiments, R^7 is optionally substituted C_1-C_6 heteroalkyl or optionally substituted heterocyclyl having 3 to 6 atoms. In some embodiments, R^7 is optionally substituted C_1-C_6 alkyl or optionally substituted C_1-C_6 heteroalkyl.

In some embodiments, R^7 is optionally substituted C_1-C_6 alkyl. In some embodiments, R^7 is optionally substituted C_1-C_6 heteroalkyl. In some embodiments, R^7 is optionally substituted C_1-C_6 alkoxy.

In some embodiments, R^7 is optionally substituted amino. In some embodiments, R^7 is optionally substituted carbocyclyl having 3 to 6 atoms. In some embodiments, R^7 is optionally substituted heterocyclyl having 3 to 6 atoms. In some embodiments, R^7 is optionally substituted sulfone. In some embodiments, R^7 is optionally substituted sulfonamide.

In some embodiments, R^7 is optionally substituted C_1-C_3 alkyl. In some embodiments, R^7 is optionally substituted C_1-C_3 heteroalkyl.

In some embodiments, R^7 is



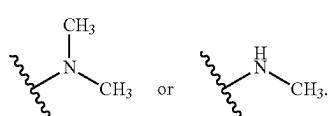
In some embodiments, R^7 is $-NR^3R^4$ or $-OR^4$, where R^3 is H or optionally substituted C_1-C_6 alkyl, and R^4 is optionally substituted C_1-C_6 alkyl.

In some embodiments, R^7 is $-NR^3R^4$. In some embodiments, R^7 is $-OR^4$.

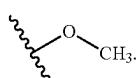
In some embodiments, R^3 is H. In some embodiments, R^3 is optionally substituted C_1-C_6 alkyl.

In some embodiments, R^3 is H and R^4 is methyl. In some embodiments, R^3 is methyl and R^4 is methyl.

In some embodiments, R^7 is



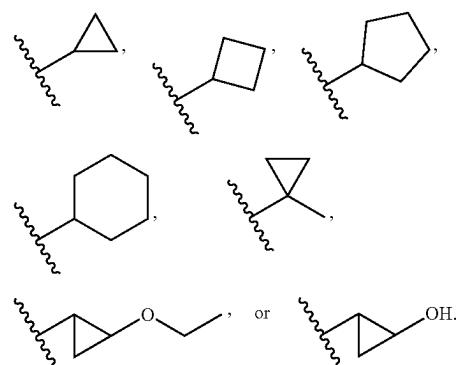
In some embodiments, R^7 is



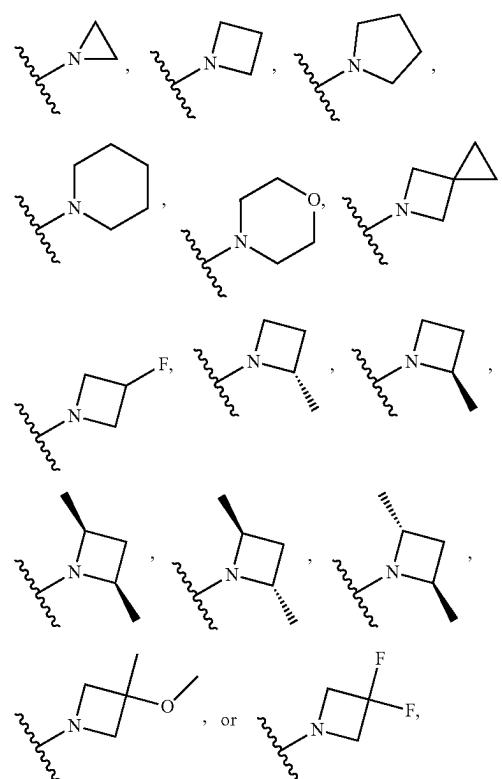
In some embodiments, R^7 is optionally substituted carbocyclyl having 3 to 6 atoms or optionally substituted heterocyclyl having 3 to 6 atoms. In some embodiments, R^7 is optionally substituted carbocyclyl having 3 to 6 atoms. In some embodiments, R^7 is optionally substituted heterocyclyl having 3 to 6 atoms.

In some embodiments, R^7 is carbocyclyl having 3 to 6 atoms or heterocyclyl having 3 to 6 atoms. In some embodiments, R^7 is carbocyclyl having 3 to 6 atoms. In some embodiments, R^7 is heterocyclyl having 3 to 6 atoms.

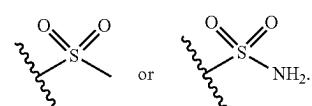
In some embodiments, R^7 is



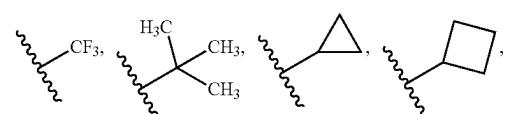
In some embodiments, R^7 is



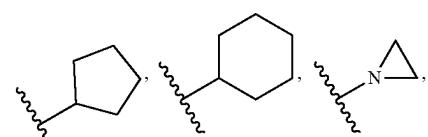
In some embodiments, R^7 is



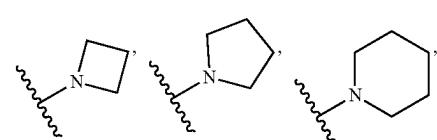
7

In some embodiments, R⁷ is

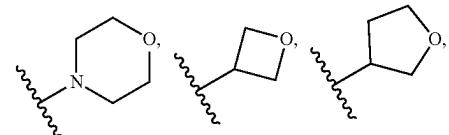
5



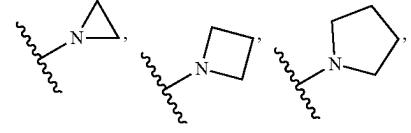
10



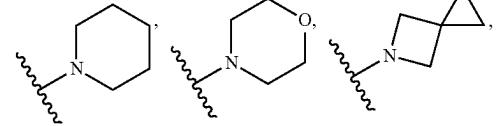
15



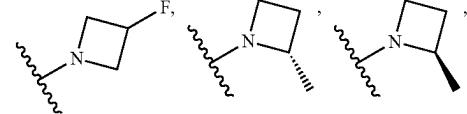
20



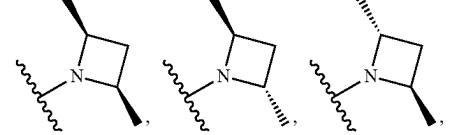
25



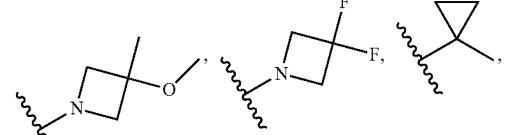
30



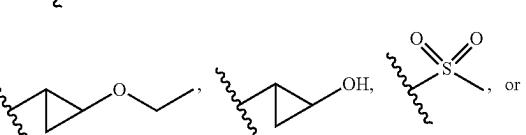
35



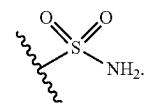
40



45

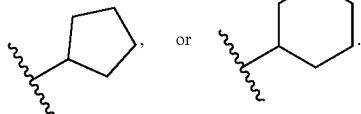
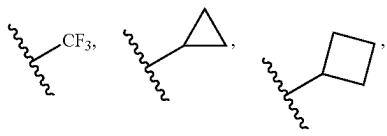


50

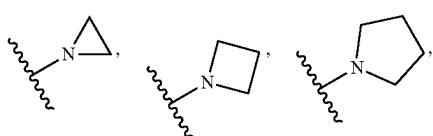


55

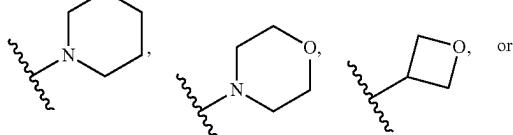
8

In some embodiments, R⁷ is

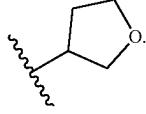
15

In some embodiments, R⁷ is

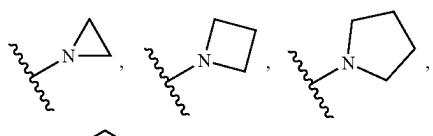
20



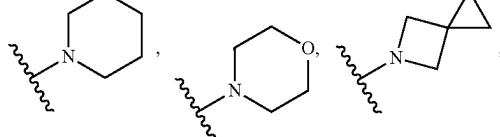
25



30

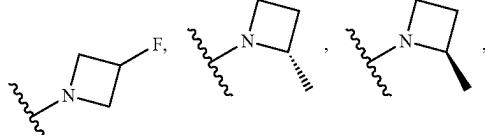
In some embodiments, R⁷ is

35



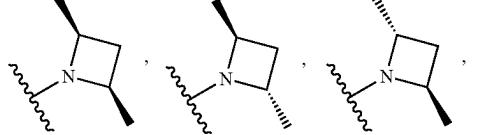
40

45



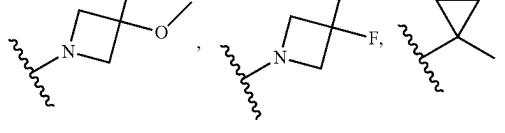
50

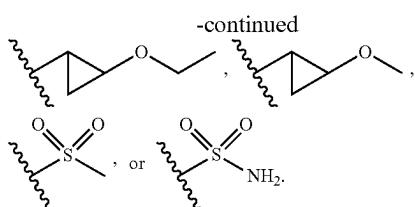
55



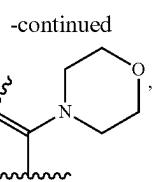
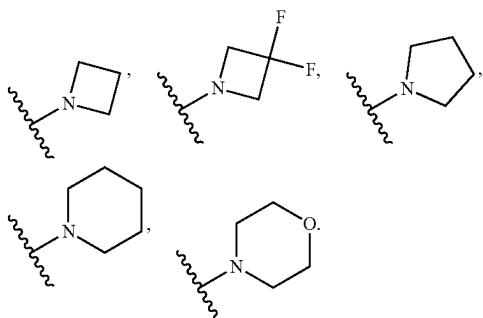
60

65



9

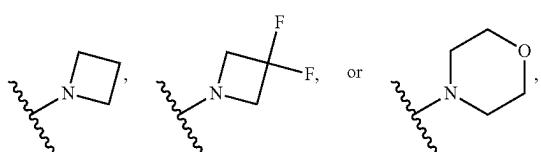
5

10In some embodiments, R⁷ is10 and X² is N or CH. In some embodiments, X¹ is N or CH, and X² is C—NR³R⁴,

15

20

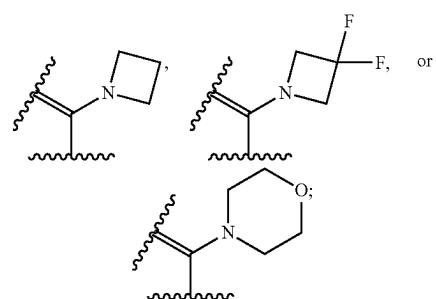
25

In some embodiments, R⁷ isor X¹ is C—NR³R⁴,

30

35

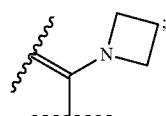
40

In some embodiments, X¹ is N and X² is C—R⁷. In some embodiments, X¹ is CH and X² is C—R⁷. In some embodiments, X¹ is C—R⁷ and X² is N. In some embodiments, X¹ is C—R⁷ and X² is CH.In some embodiments, X¹ is N or CH, and X² is C—NR³R⁴, C—OR⁴,

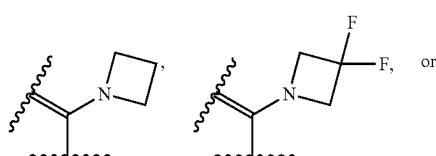
45

50

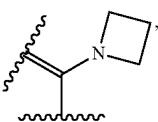
55

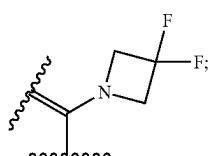
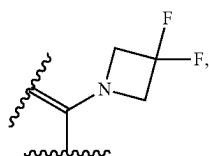
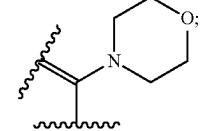
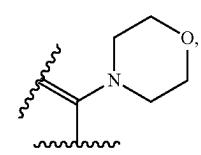
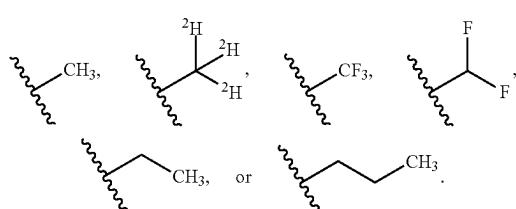
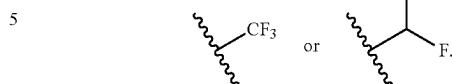
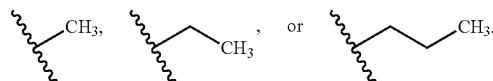
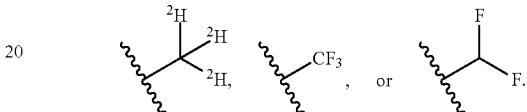
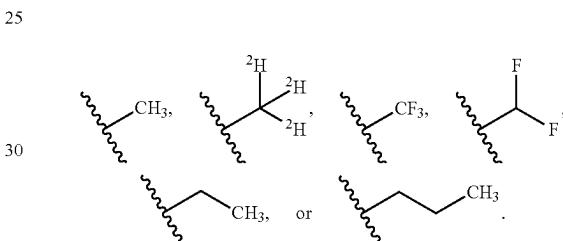
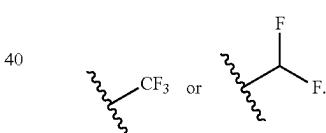
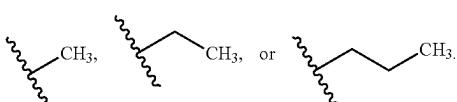
or X¹ is C—NR³R⁴, C—OR⁴,and X² is N or CH. In some embodiments, X¹ is N or CH, and X² is C—NR³R⁴ or

60

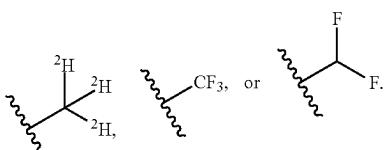


65

and X² is N or CH. In some embodiments, X¹ is N or CH, and X² is C—NR³R⁴ or

11or X^1 is $C-NR^3R^4$ orand X^2 is N or CH. In some embodiments, X^1 is N or CH, and X^2 is $C-NR^3R^4$ oror X^1 is $C-NR^3R^4$ orand X^2 is N or CH.In some embodiments, R^7 is $-NR^3R^4$, $-OR^4$, or optionally substituted heterocyclyl having 3 to 6 atoms.In some embodiments, X^1 is N and X^2 is $C-NR^3R^4$. In some embodiments, X^1 is $C-NR^3R^4$ and X^2 is N. In some embodiments, X^1 is N and X^2 is $C-OR^4$. In some embodiments, X^1 is $C-OR^4$ and X^2 is N.In some embodiments, R^3 is H. In some embodiments, R^3 is optionally substituted C_1-C_6 alkyl.In some embodiments, R^3 is**12**
In some embodiments, R^3 isIn some embodiments, R^3 isIn some embodiments, R^3 is methyl, ethyl,In some embodiments, R^4 isIn some embodiments, R^4 isIn some embodiments, R^4 isIn some embodiments, R^4 is methyl, ethyl,

55

In some embodiments, X^3 is N. In some embodiments, X^3 is CH.In some embodiments, X^4 is N. In some embodiments, X^4 is CH.

13

In some embodiments, X^3 is N and X^4 is N.

In some embodiments, X^3 is N and X^4 is CH.

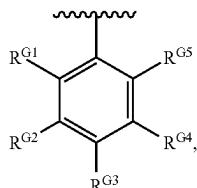
In some embodiments, X^3 is CH and X^4 is N.

In some embodiments, X^3 is CH and X^4 is CH.

In some embodiments, G is optionally substituted C_3 - C_{10} carbocyclyl or optionally substituted C_2 - C_9 heterocyclyl. In some embodiments, G is optionally substituted C_6 - C_{10} aryl or optionally substituted C_2 - C_9 heteroaryl.

In some embodiments, G is optionally substituted C_3 - C_{10} carbocyclyl. In some embodiments, G is optionally substituted C_6 - C_{10} aryl. In some embodiments, G is optionally substituted C_2 - C_9 heterocyclyl. In some embodiments, G is optionally substituted C_2 - C_9 heteroaryl.

In some embodiments, G is



where

each of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is, independently, H, halogen, optionally substituted C_1 - C_8 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, optionally substituted $—O—C_3-C_6$ carbocyclyl, optionally substituted $—C_1-C_3$ alkyl- C_3-C_6 carbocyclyl, optionally substituted $—C_1-C_3$ alkyl- C_2-C_5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R^{G1} and R^{G2} , R^{G2} and R^{G3} , R^{G3} and R^{G4} , and/or R^{G4} and R^{G5} , together with the carbon atoms to which each is attached, combine to form optionally substituted C_6 - C_{10} aryl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heteroaryl, or optionally substituted C_2 - C_9 heterocyclyl.

In some embodiments, each of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is, independently, H, halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, optionally substituted $—O—C_3-C_6$ carbocyclyl, optionally substituted $—C_1-C_3$ alkyl- C_3-C_6 carbocyclyl, optionally substituted $—C_1-C_3$ alkyl- C_2-C_5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R^{G1} and R^{G2} , R^{G2} and R^{G3} , R^{G3} and R^{G4} , and/or R^{G4} and R^{G5} , together with the carbon atoms to which each is attached, combine to form optionally substituted C_6 - C_{10} aryl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heteroaryl, or optionally substituted C_2 - C_9 heterocyclyl.

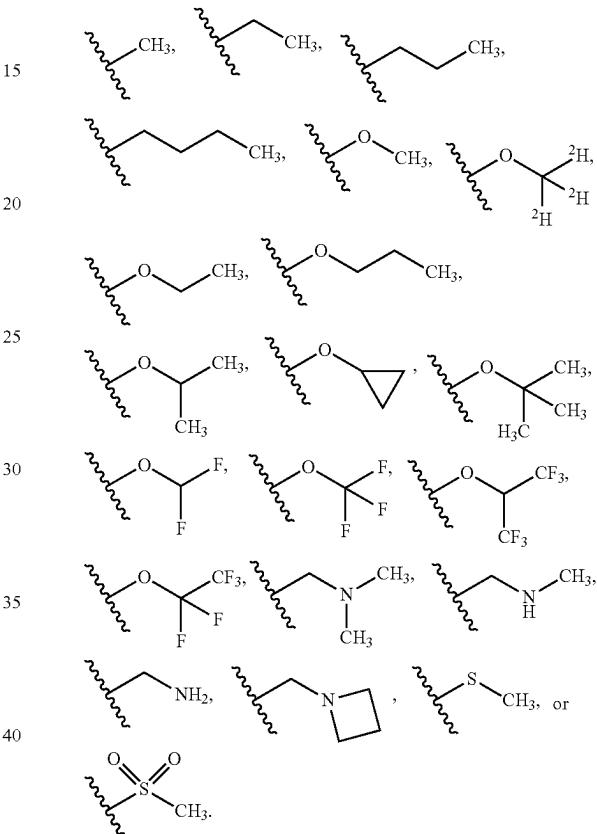
In some embodiments, each of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is, independently, H, halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted $—O—C_3-C_6$ carbocyclyl, or optionally substituted $—C_1-C_3$ alkyl- C_2-C_5 heterocyclyl; or R^{G1} and R^{G2} , R^{G2} and R^{G3} , R^{G3} and R^{G4} , and/or R^{G4} and R^{G5} , together with the carbon atoms to which each is attached,

14

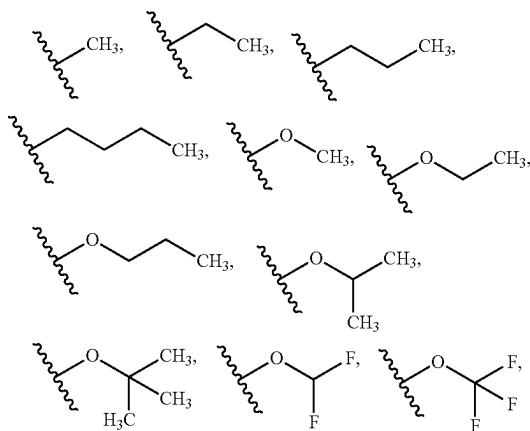
combine to form optionally substituted C_2 - C_9 heteroaryl or optionally substituted C_2 - C_9 heterocyclyl.

In some embodiments, each of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is, independently, H, halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted $—O—C_3-C_6$ carbocyclyl, or optionally substituted $—C_1-C_3$ alkyl- C_2-C_5 heterocyclyl.

In some embodiments, each of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is, independently, H, F, Cl,

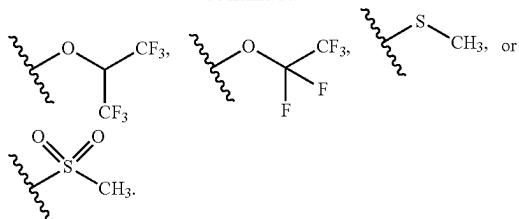


In some embodiments, each of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is, independently, H, F,

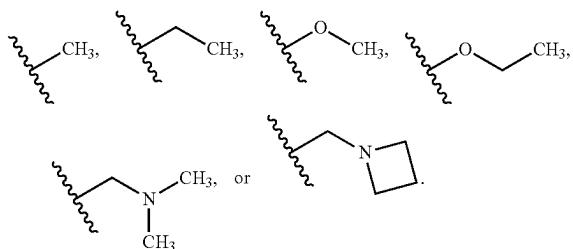


15

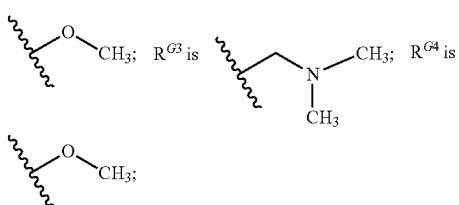
-continued



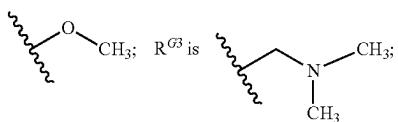
In some embodiments, each of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is, independently, H, F, Cl,



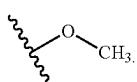
In some embodiments, R^{G1} is H; R^{G2} is



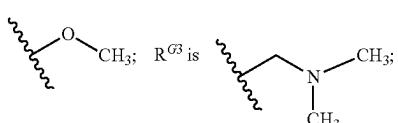
and R^{G5} is H. In some embodiments, R^{G1} is H; R^{G2} is



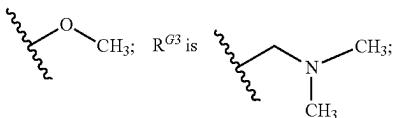
R^{G4} is H; and R^{G5} is



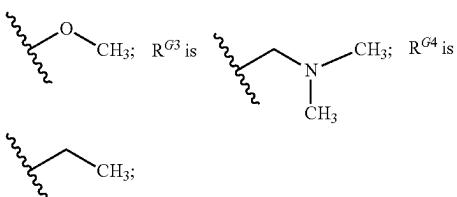
In some embodiments, R^{G1} is H; R^{G2} is



R^{G4} is Cl or F; and R^{G5} is H. In some embodiments, R^{G1} is H; R^{G2} is

16

R^{G4} is H; and R^{G5} is H. In some embodiments, R^{G1} is H; R^{G2} is

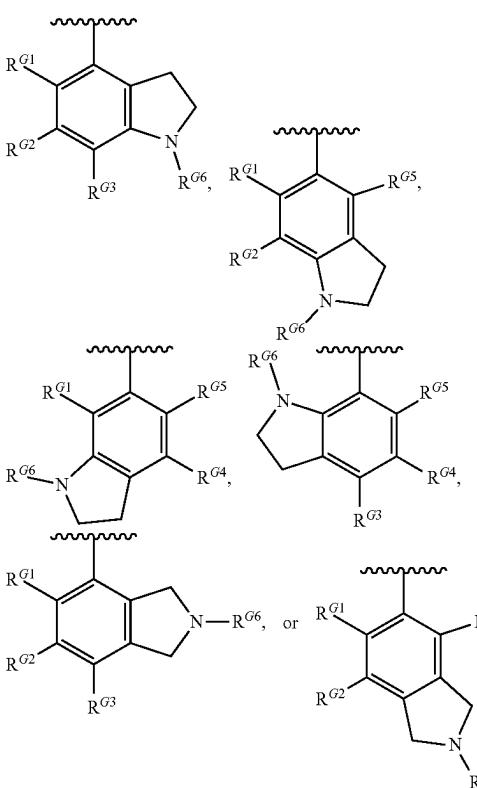


and R^{G5} is H.

In some embodiments, R^{G1} and R^{G2} , R^{G2} and R^{G3} , R^{G3} and R^{G4} , and/or R^{G4} and R^{G5} , together with the carbon atoms to which each is attached, combine to form optionally substituted C_2 - C_9 heteroaryl or optionally substituted C_2 - C_9 heterocyclyl.

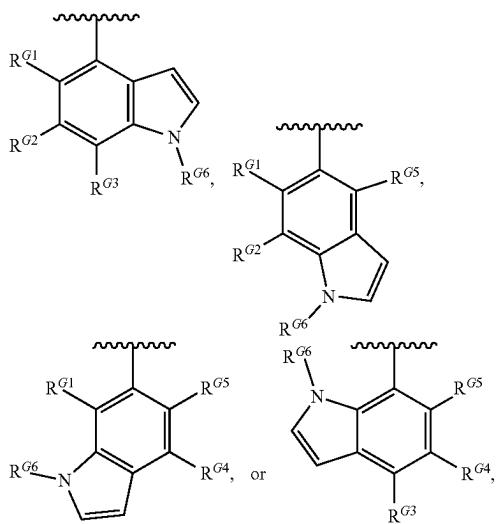
In some embodiments, R^{G1} and R^{G2} , R^{G2} and R^{G3} , R^{G3} and R^{G4} , and/or R^{G4} and R^{G5} , together with the carbon atoms to which each is attached, combine to form optionally substituted C_2 - C_9 heterocyclyl. In some embodiments, R^{G1} and R^{G2} , R^{G2} and R^{G3} , R^{G3} and R^{G4} , and/or R^{G4} and R^{G5} , together with the carbon atoms to which each is attached, combine to form optionally substituted C_2 - C_9 heteroaryl.

In some embodiments, G is



17

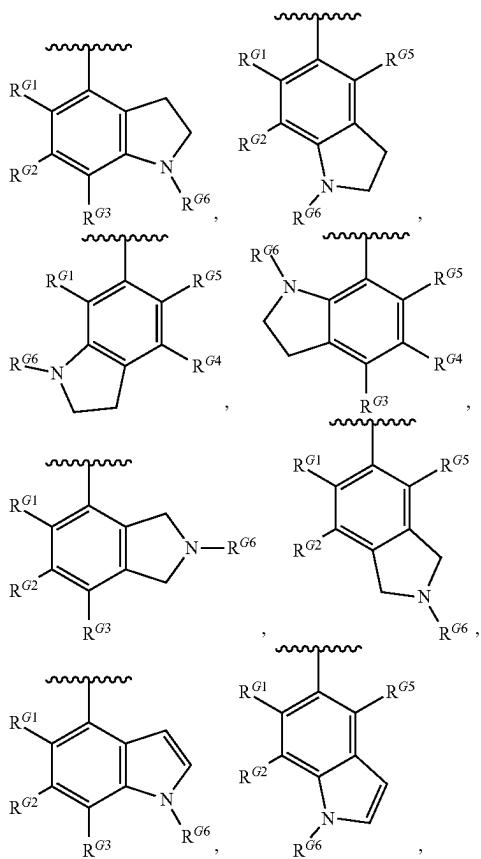
where R^{G6} is H or optionally substituted C_1 - C_6 alkyl. In some embodiments, G is



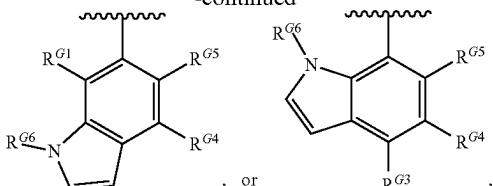
where R^{G6} is H or optionally substituted C_1 - C_6 alkyl.

In some embodiments, R^{G1} and R^{G2} , R^{G2} and R^{G3} , R^{G3} and R^{G4} , and/or R^{G4} and R^{G5} , together with the carbon atoms to which each is attached, combine to form optionally substituted C_2 - C_9 heterocyclol or optionally substituted C_2 - C_9 heteroaryl.

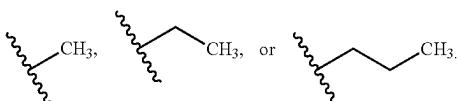
In some embodiments, G is

**18**

-continued



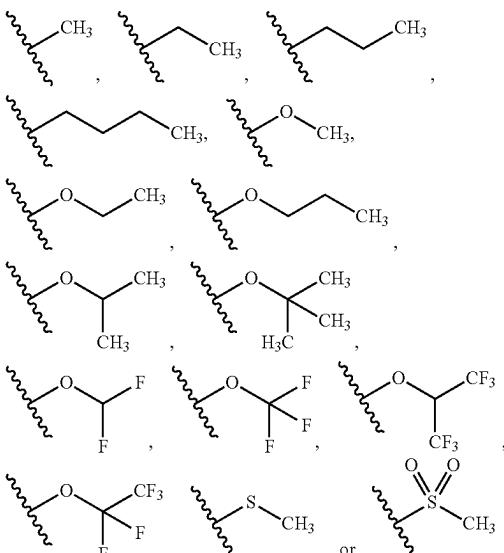
10 where R^{G6} is H or optionally substituted C_1 - C_6 alkyl.
In some embodiments, R^{G6} is H,



20 In some embodiments, R^{G6} is H or

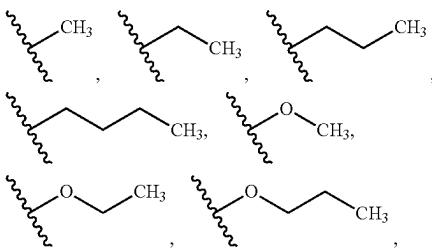


25 In some embodiments, R^{G6} is H.
In some embodiments, R^{G1} is H, F,



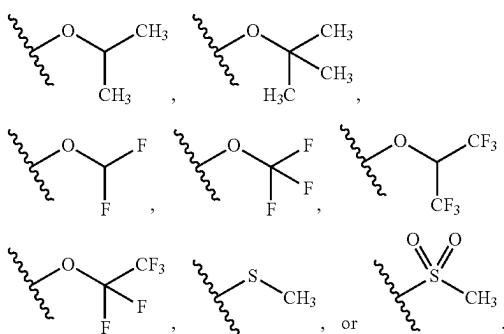
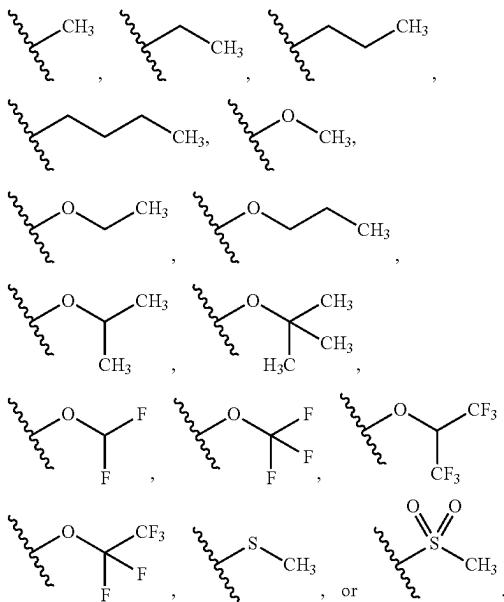
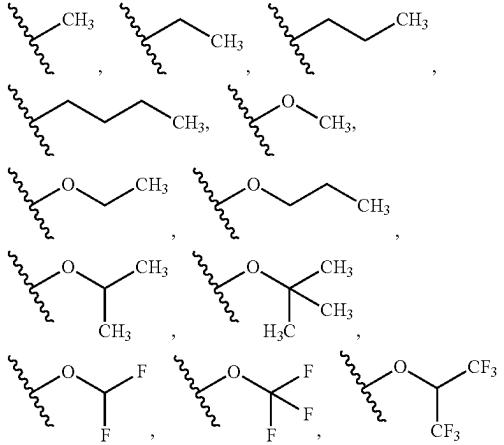
35
40
45
50
55
60
65

In some embodiments, R^{G1} is H.
In some embodiments, R^{G2} is H, F,

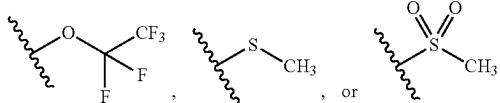
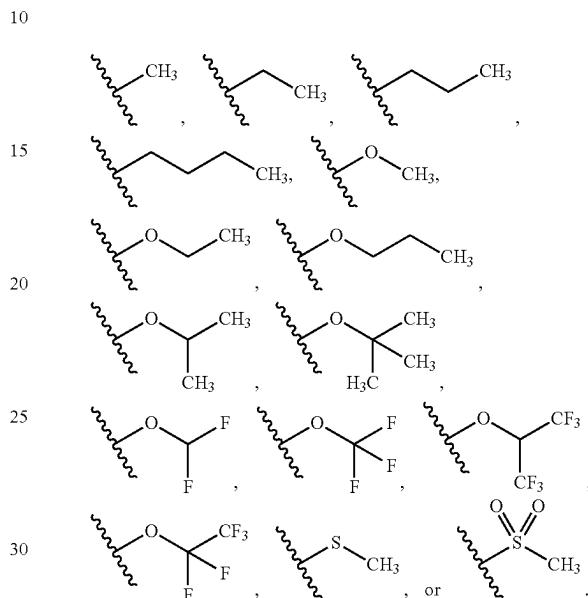


19

-continued

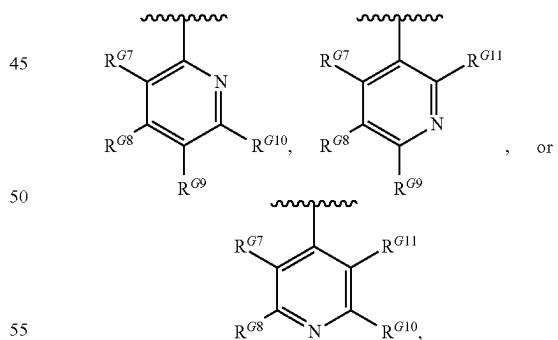
In some embodiments, R^{G2} is H.In some embodiments, R^{G3} is H, FIn some embodiments, R^{G3} is H.In some embodiments, R^{G4} is H, F**20**

-continued

In some embodiments, R^{G4} is H.In some embodiments, R^{G5} is H, F,In some embodiments, R^{G5} is H.

35 In some embodiments, one or more of R^{G1}, R^{G2}, R^{G3}, R^{G4}, and R^{G5} is H. In some embodiments, two or more of R^{G1}, R^{G2}, R^{G3}, R^{G4}, and R^{G5} is H. In some embodiments, three or more of R^{G1}, R^{G2}, R^{G3}, R^{G4}, and R^{G5} is H. In some embodiments, each of R^{G1}, R^{G2}, R^{G3}, R^{G4}, and R^{G5} is H.

40 In some embodiments, G is



where

each of R^{G7}, R^{G8}, R^{G9}, R^{G10}, and R^{G11} is, independently, H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted —O—C₃-C₆ carbocyclyl, optionally substituted —C₁-C₃ alkyl-C₃-C₆ carbocyclyl, optionally substituted

21

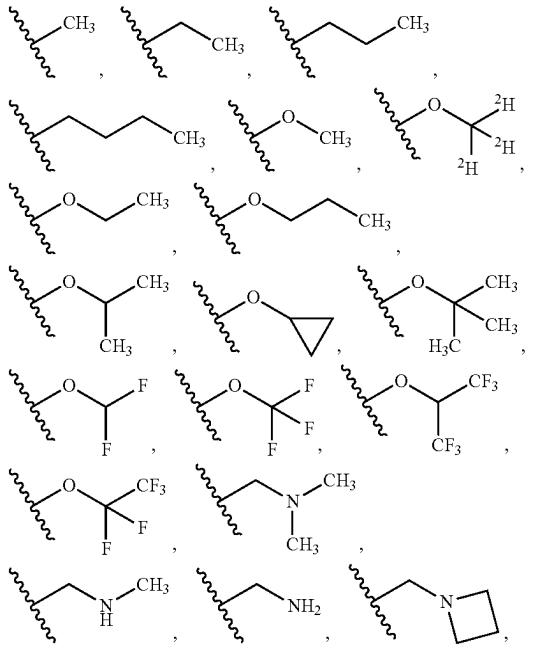
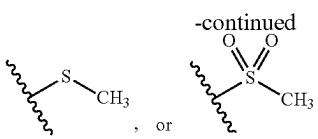
$-C_1-C_3$ alkyl- C_2-C_5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R^{G7} and R^{G8} , R^{G8} and R^{G9} , R^{G9} and R^{G10} , and/or R^{G10} and R^{G11} , together with the carbon atoms to which each is attached, combine to form optionally substituted C_6-C_{10} aryl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heteroaryl, or C_2-C_9 heterocyclyl.

In some embodiments, each of R^{G7} , R^{G8} , R^{G9} , R^{G10} , and R^{G11} is, independently, H, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; or R^{G7} and R^{G8} , R^{G8} and R^{G9} , R^{G9} and R^{G10} , and/or R^{G10} and R^{G11} , together with the carbon atoms to which each is attached, combine to form optionally substituted C_6-C_{10} aryl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heteroaryl, or C_2-C_9 heterocyclyl.

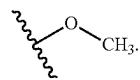
In some embodiments, each of R^{G7} , R^{G8} , R^{G9} , R^{G10} , and R^{G11} is, independently, H, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted $-O-C_3-C_6$ carbocyclyl, or optionally substituted $-C_1-C_3$ alkyl- C_2-C_5 heterocyclyl; or R^{G7} and R^{G8} , R^{G8} and R^{G9} , R^{G9} and R^{G10} , and/or R^{G10} and R^{G11} , together with the carbon atoms to which each is attached, combine to form optionally substituted C_6-C_{10} aryl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heteroaryl, or C_2-C_9 heterocyclyl.

In some embodiments, each of R^{G7} , R^{G8} , R^{G9} , R^{G10} , and R^{G11} is, independently, H, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted $-O-C_3-C_6$ carbocyclyl, or optionally substituted $-C_1-C_3$ alkyl- C_2-C_5 heterocyclyl.

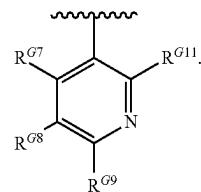
In some embodiments, each of R^{G7} , R^{G8} , R^{G9} , R^{G10} , and R^{G11} is, independently, H, F, Cl,

**22**

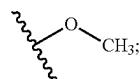
In some embodiments, R^{G8} is



In some embodiments, G is

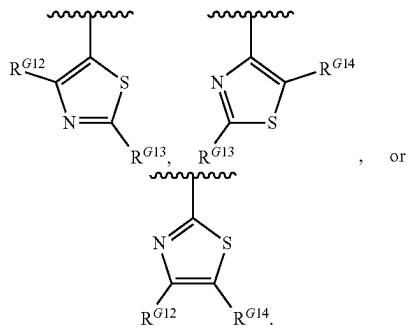


In some embodiments, R^{G7} is H; R^{G8} is



R^{G9} is H; and R^{G11} is H.

In some embodiments, G is



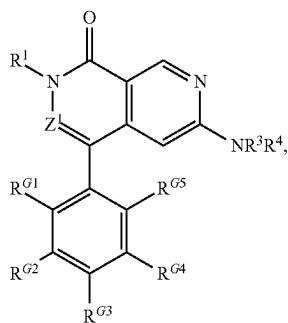
where

each of R^{G12} , R^{G13} , and R^{G14} is, independently, H, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted $-O-C_3-C_6$ carbocyclyl, optionally substituted $-C_1-C_3$ alkyl- C_2-C_6 carbocyclyl, optionally substituted $-C_1-C_3$ alkyl- C_2-C_5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R^{G12} and R^{G14} , together with the carbon atoms to which each is attached, combine to form optionally substituted C_6-C_{10} aryl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heteroaryl, or optionally substituted C_2-C_9 heterocyclyl.

23

In some embodiments, each of R^{G12}, R^{G13}, and R^{G14} is, independently, H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; or R^{G12} and R^{G14}, together with the carbon atoms to which each is attached, combine to form optionally substituted C₆-C₁₀ aryl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heteroaryl, or optionally substituted C₂-C₉ heterocyclyl.

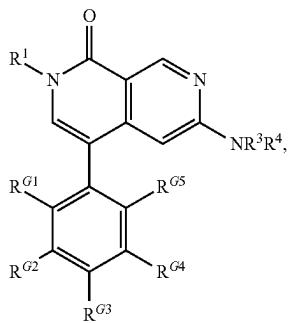
In some embodiments, the compound of Formula I has the structure of Formula Ia:



Formula Ia

or a pharmaceutically acceptable salt thereof.

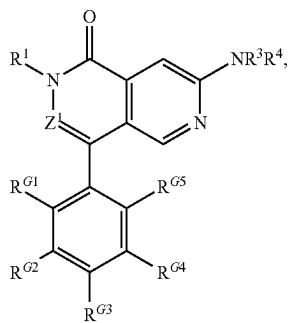
In some embodiments, the compound of Formula I has the structure of Formula Ib:



Formula Ib

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula I has the structure of Formula Ic:

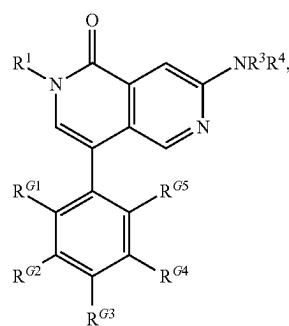


Formula Ic

or a pharmaceutically acceptable salt thereof.

24

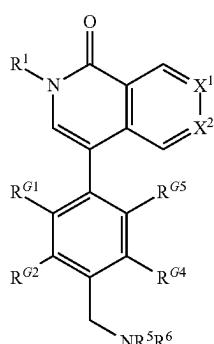
In some embodiments, the compound of Formula I has the structure of Formula Id:



Formula Id

or a pharmaceutically acceptable salt thereof.

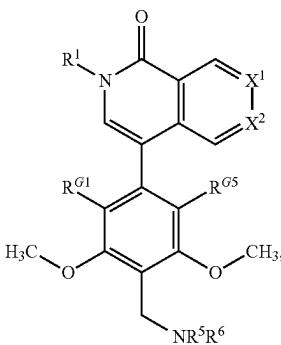
In some embodiments, the compound of Formula I has the structure of Formula Ie:



Formula Ie

where each of R⁵ and R⁶ is, independently, H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, or optionally substituted C₂-C₉ heterocyclyl; or R⁵ and R⁶, together with the nitrogen to which each is attached, combine to form an optionally substituted C₂-C₉ heterocyclyl, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula I has the structure of Formula If:



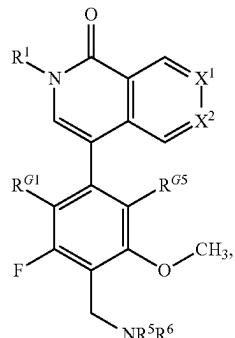
Formula If

where each of R⁵ and R⁶ is, independently, H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, or optionally substituted C₂-C₉ heterocyclyl; or R⁵ and R⁶,

25

together with the nitrogen to which each is attached, combine to form an optionally substituted C₂-C₉ heterocyclyl, or a pharmaceutically acceptable salt thereof.

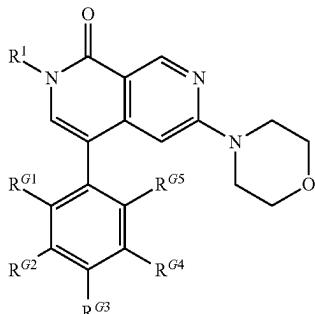
In some embodiments, the compound of Formula I has the structure of Formula Ig:



Formula Ig

5

In some embodiments, the compound of Formula I has the structure of Formula Ij:



Formula Ij

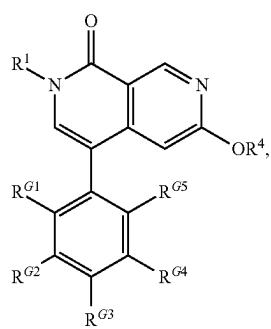
10

15

20

where each of R⁵ and R⁶ is, independently, H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, or optionally substituted C₂-C₉ heterocyclyl; or R⁵ and R⁶, together with the nitrogen to which each is attached, combine to form an optionally substituted C₂-C₉ heterocyclyl, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula I has the structure of Formula Ih:



Formula Ih

25

30

35

40

45

50

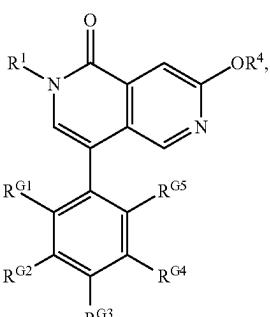
55

60

65

or a pharmaceutically acceptable salt thereof.

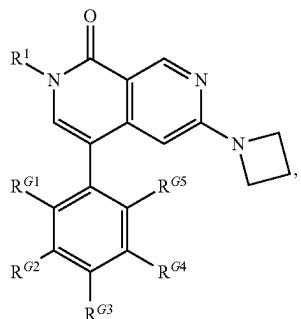
In some embodiments, the compound of Formula I has the structure of Formula Ik:



Formula Ik

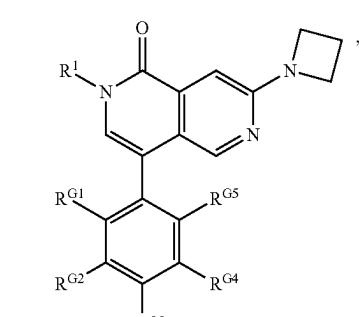
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula I has the structure of Formula II:



Formula II

50



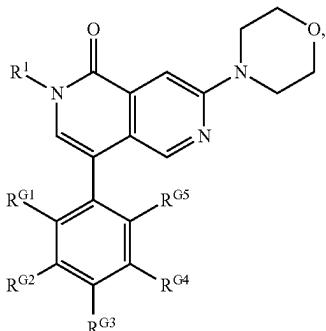
Formula Im

or a pharmaceutically acceptable salt thereof.

or a pharmaceutically acceptable salt thereof.

27

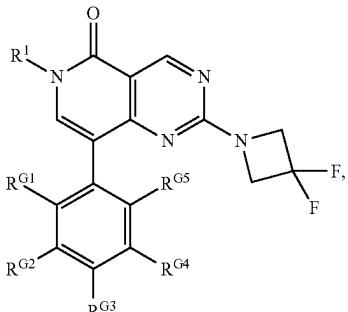
In some embodiments, the compound of Formula I has the structure of Formula In:



Formula In

28

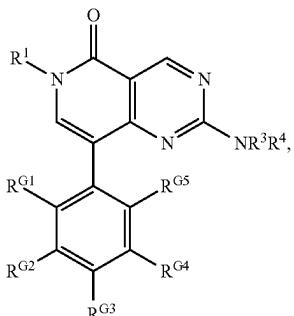
In some embodiments, the compound of Formula I has the structure of Formula Iq:



Formula Iq

or a pharmaceutically acceptable salt thereof.

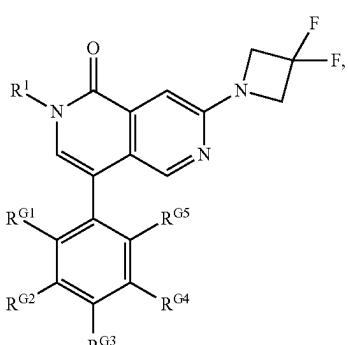
In some embodiments, the compound of Formula I has the structure of Formula Io:



Formula Io

or a pharmaceutically acceptable salt thereof.

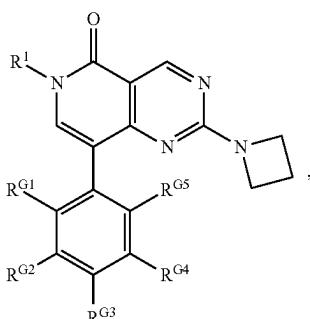
In some embodiments, the compound of Formula I has the structure of Formula Ir:



Formula Ir

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula I has the structure of Formula Ip:



Formula Ip

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound has the structure of any one of compounds B1-B6 in Table 1, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound has the structure of any one of compounds B1-B3 and B6 in Table 1, or a pharmaceutically acceptable salt thereof.

In an aspect, the disclosure features a compound having the structure of any one of compounds B1-B6 in Table 1, or a pharmaceutically acceptable salt thereof.

In an aspect, the disclosure features a compound having the structure of any one of compounds B1-B3 and B6 in Table 1, or a pharmaceutically acceptable salt thereof.

In an aspect, the disclosure features a compound having the structure of any one of compounds B4 and B5 in Table 1, or a pharmaceutically acceptable salt thereof.

or a pharmaceutically acceptable salt thereof.

29

TABLE 1

Compounds B1-B6 of the Disclosure

Compound No.	Structure
B1	
B2	
B3	
B4	

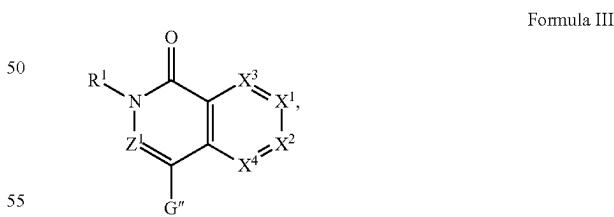
30

TABLE 1-continued

Compounds B1-B6 of the Disclosure

In an aspect, the disclosure features a compound having the structure of Formula II:

40 A-L-B Formula II,
where
L is a linker;
B is a degradation moiety; and
45 A has the structure of Formula III:



where

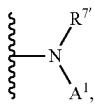
R¹ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ carbocyclyl;

Z^1 is CR² or N;

R² is H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, or optionally substituted C₂-C₉ heteroaryl;

31

X^1 is N or CH, and X^2 is C—R^{7"}; or X^1 is C—R^{7"}, and X^2 is N or CH;
R^{7"} is



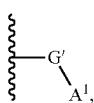
optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₁-C₆ alkoxy, optionally substituted amino, optionally substituted sulfone, optionally substituted sulfonamide, optionally substituted carbocyclyl having 3 to 6 atoms, or optionally substituted heterocyclyl having 3 to 6 atoms;

R^{7"} is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ carbocyclyl;

X³ is N or CH;

X⁴ is N or CH;

G" is

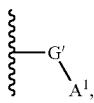


optionally substituted C₃-C₁₀ carbocyclyl, C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, or optionally substituted C₂-C₉ heteroaryl;

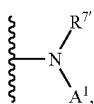
G' is optionally substituted C₃-C₁₀ carbocyclylene, C₂-C₉ heterocyclylene, optionally substituted C₆-C₁₀ arylene, or optionally substituted C₂-C₉ heteroarylene; and

A¹ is a bond between A and the linker,

where G" is



or R^{7"} is



or a pharmaceutically acceptable salt thereof.

In some embodiments, R¹ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ carbocyclyl. In some embodiments, R¹ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, or optionally substituted C₃-C₁₀ carbocyclyl. In some embodiments, R¹ is H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₃-C₁₀ carbocyclyl.

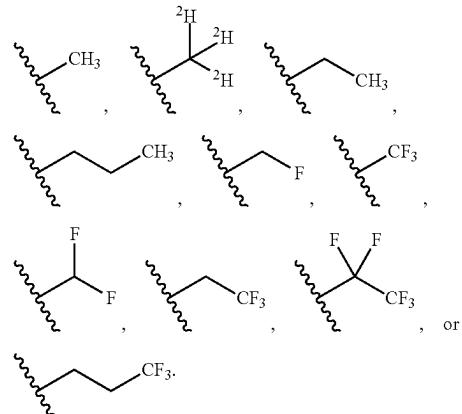
In some embodiments, R¹ is H. In some embodiments, R¹ is optionally substituted C₁-C₆ alkyl. In some embodiments, R¹ is optionally substituted C₂-C₆ alkenyl. In some embodiments, R¹ is optionally substituted C₃-C₁₀ carbocyclyl.

32

In some embodiments, optionally substituted C₁-C₆ alkyl is C₁-C₆ perfluoroalkyl.

In some embodiments, R¹ is

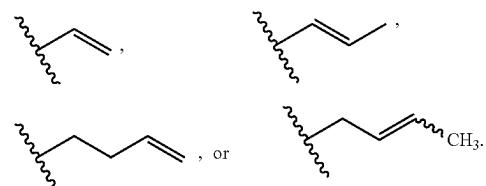
5



20

In some embodiments, R¹ is

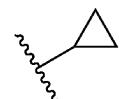
25



30

In some embodiments, R¹ is

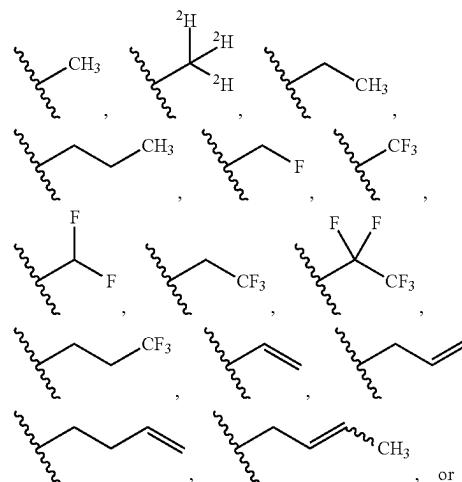
40



45

In some embodiments, R¹ is H,

50



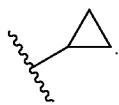
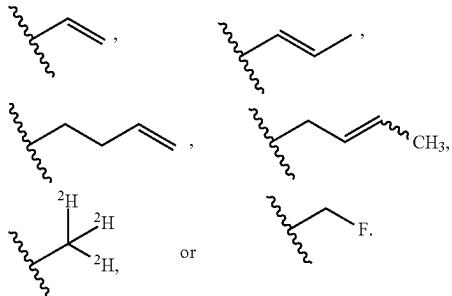
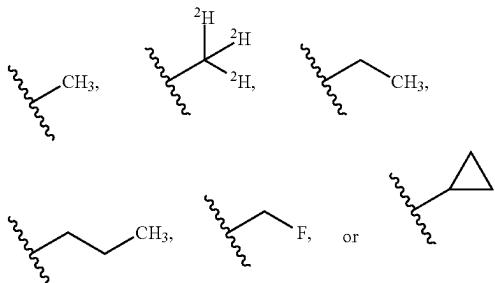
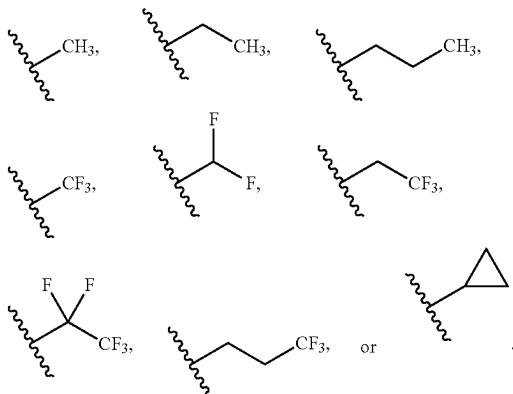
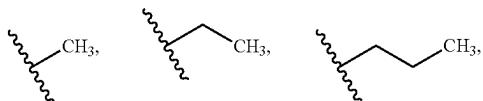
55

60

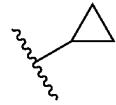
65

33

-continued

In some embodiments, R¹ isIn some embodiments, R¹ is H,In some embodiments, R¹ is H,In some embodiments, R¹ is H,**34**

-continued

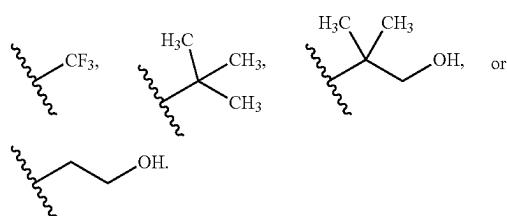
In some embodiments, R¹ is H or15 In some embodiments, R¹ is H. In some embodiments, R¹ is20 In some embodiments, Z¹ is CR². In some embodiments, Z¹ is N.25 In some embodiments, R² is H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₁₀ carbocyclyl, or optionally substituted C₆-C₁₀ aryl.30 In some embodiments, R² is H, halogen, or optionally substituted C₁-C₆ alkyl.In some embodiments, R² is H, F, or35 In some embodiments, R² is H. In some embodiments, R² is F. In some embodiments, R² is40 In some embodiments, R^{7"} is optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₁-C₆ alkoxy, optionally substituted carbocyclyl having 3 to 6 atoms, or optionally substituted heterocyclyl having 3 to 6 atoms. In some embodiments, R^{7"} is optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted carbocyclyl having 3 to 6 atoms, or optionally substituted heterocyclyl having 3 to 6 atoms. In some embodiments, R^{7"} is optionally substituted C₁-C₆ alkoxy or optionally substituted amino. In some embodiments, R^{7"} is optionally substituted sulfone or optionally substituted sulfonamide.45 In some embodiments, R^{7"} is optionally substituted C₁-C₆ alkyl or optionally substituted carbocyclyl having 3 to 6 atoms. In some embodiments, R^{7"} is optionally substituted C₁-C₆ heteroalkyl or optionally substituted heterocyclyl having 3 to 6 atoms. In some embodiments, R^{7"} is optionally substituted C₁-C₆ alkyl or optionally substituted C₁-C₆ heteroalkyl.50 In some embodiments, R^{7"} is optionally substituted C₁-C₆ alkyl. In some embodiments, R^{7"} is optionally substituted

35

C_1-C_6 heteroalkyl. In some embodiments, $R^{7''}$ is optionally substituted C_1-C_6 alkoxy. In some embodiments, $R^{7''}$ is optionally substituted amino. In some embodiments, $R^{7''}$ is optionally substituted carbocyclyl having 3 to 6 atoms. In some embodiments, $R^{7''}$ is optionally substituted heterocyclyl having 3 to 6 atoms. In some embodiments, $R^{7''}$ is optionally substituted sulfone. In some embodiments, $R^{7''}$ is optionally substituted sulfonamide.

In some embodiments, $R^{7''}$ is optionally substituted C_1-C_3 alkyl. In some embodiments, $R^{7''}$ is optionally substituted C_1-C_3 heteroalkyl.

In some embodiments, $R^{7''}$ is



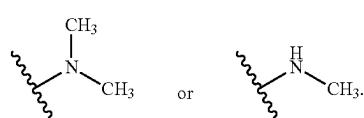
In some embodiments, $R^{7''}$ is $-NR^3R^4$ or $-OR^4$, where R^3 is H or optionally substituted C_1-C_6 alkyl, and R^4 is optionally substituted C_1-C_6 alkyl.

In some embodiments, $R^{7''}$ is $-NR^3R^4$. In some embodiments, $R^{7''}$ is $-OR^4$.

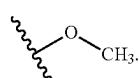
In some embodiments, R^3 is H. In some embodiments, R^3 is optionally substituted C_1-C_6 alkyl.

In some embodiments, R^3 is H and R^4 is methyl. In some embodiments, R^3 is methyl and R^4 is methyl.

In some embodiments, $R^{7''}$ is



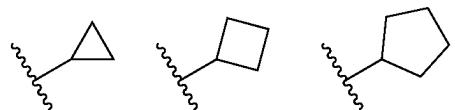
In some embodiments, $R^{7''}$ is



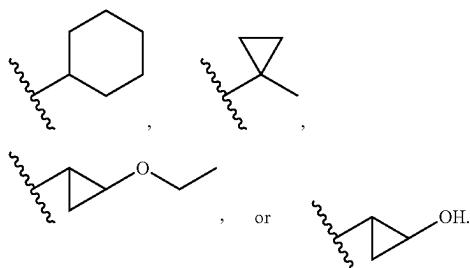
In some embodiments, $R^{7''}$ is optionally substituted carbocyclyl having 3 to 6 atoms or optionally substituted heterocyclyl having 3 to 6 atoms. In some embodiments, $R^{7''}$ is optionally substituted carbocyclyl having 3 to 6 atoms. In some embodiments, $R^{7''}$ is optionally substituted heterocyclyl having 3 to 6 atoms.

In some embodiments, $R^{7''}$ is carbocyclyl having 3 to 6 atoms or heterocyclyl having 3 to 6 atoms. In some embodiments, $R^{7''}$ is carbocyclyl having 3 to 6 atoms. In some embodiments, $R^{7''}$ is heterocyclyl having 3 to 6 atoms.

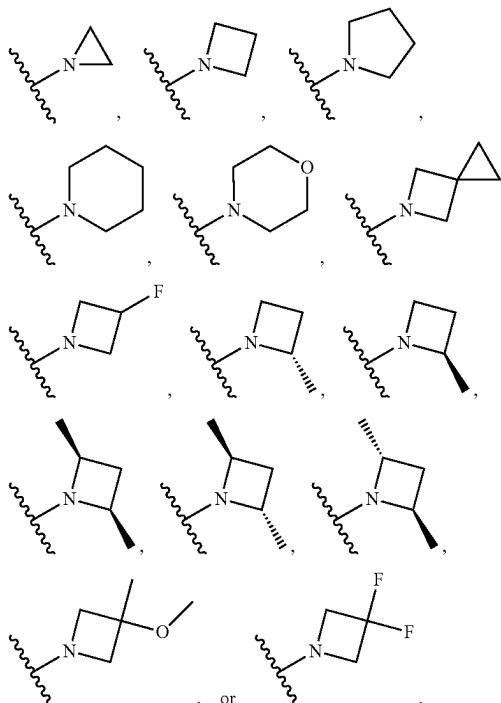
In some embodiments, $R^{7''}$ is



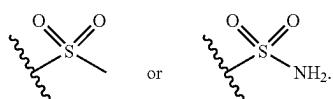
36
-continued



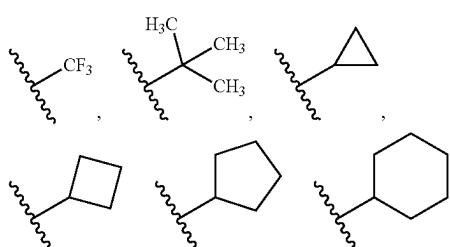
In some embodiments, $R^{7''}$ is



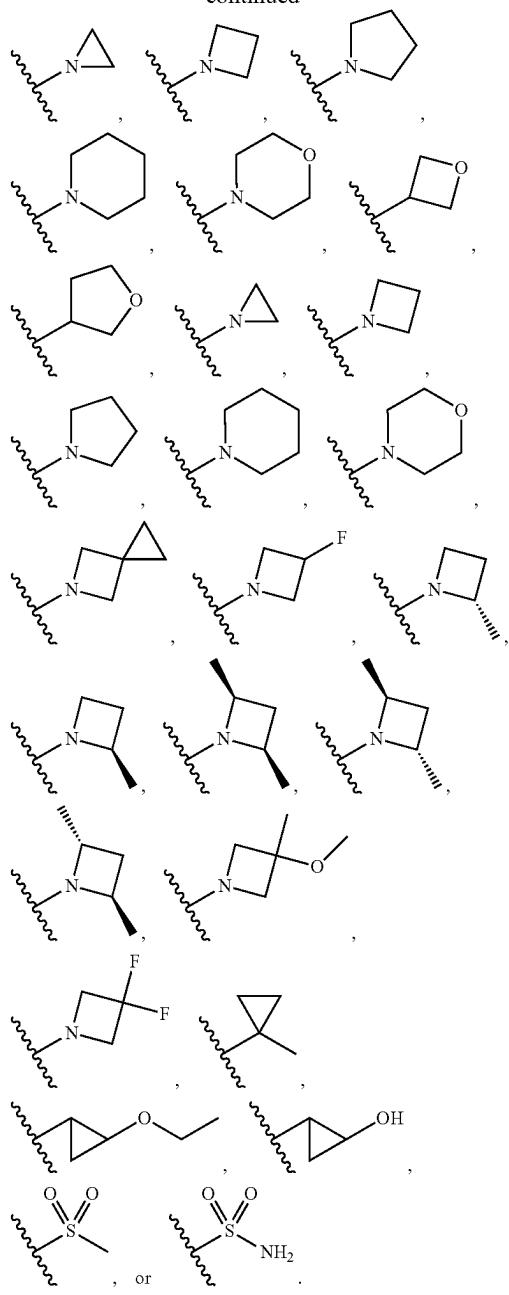
In some embodiments, $R^{7''}$ is



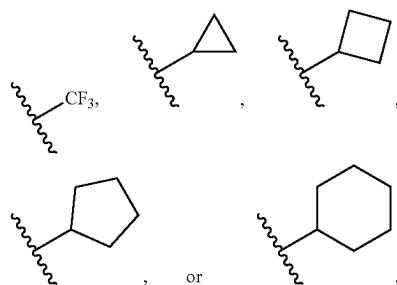
In some embodiments, $R^{7''}$ is



37
-continued

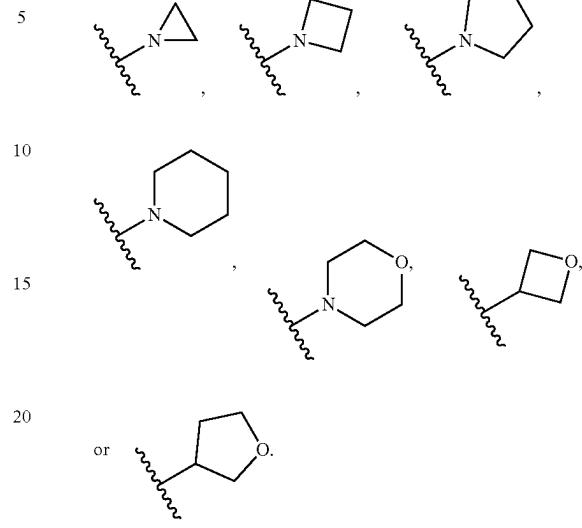


In some embodiments, R^{7''} is

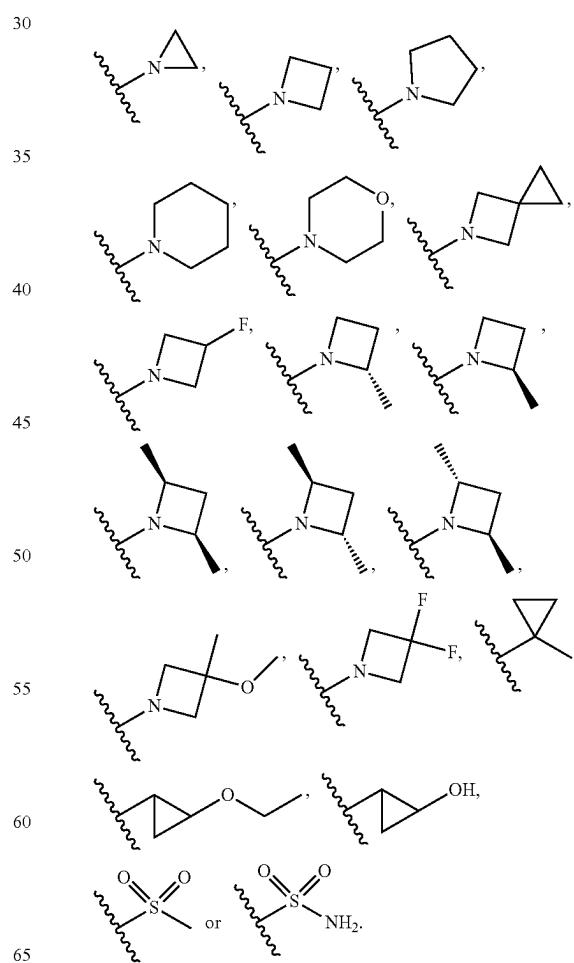


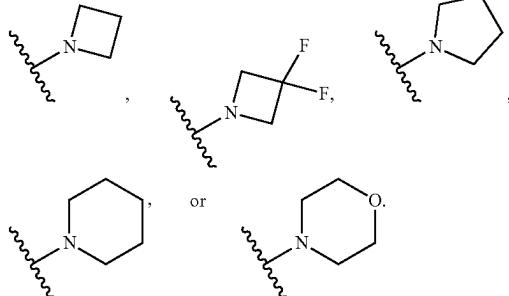
38

In some embodiments, R^{7''} is

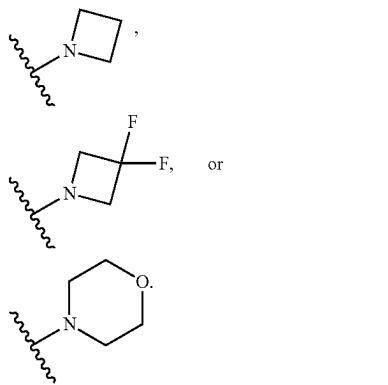


In some embodiments, R^{7''} is



39In some embodiments, R^{7"} is

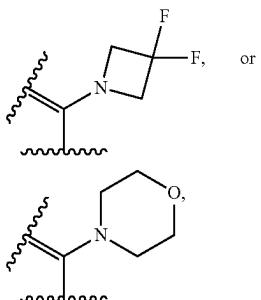
5

In some embodiments, R^{7"} is

10

15 and X² is N or CH. In some embodiments, X¹ is N or CH, and X² is C—NR³R⁴,**40**

-continued

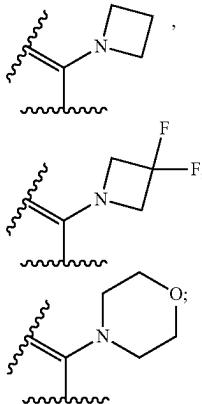


5

10

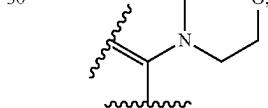
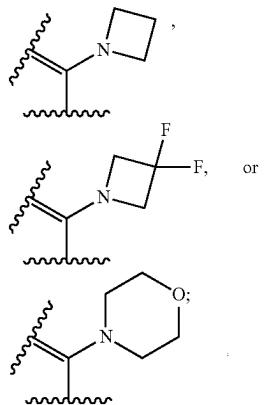
15 and X² is N or CH. In some embodiments, X¹ is N or CH, and X² is C—NR³R⁴,

20



25

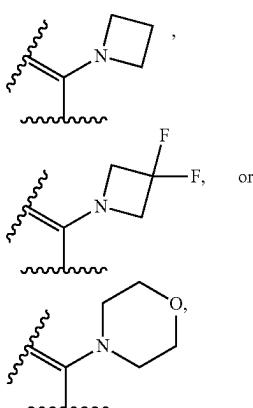
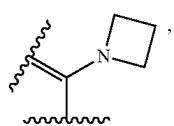
30

In some embodiments, X¹ is N and X² is C—R^{7"}. In some 35
embodiments, X¹ is CH and X² is C—R^{7"}. In some embodiments, X¹
is C—R^{7"} and X² is N. In some embodiments, X¹
is C—R^{7"} and X² is CH.In some embodiments, X¹ is N or CH, and X² is 40
C—NR³R⁴, C—OR⁴,

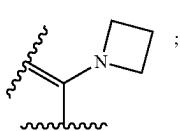
45

50

55

or X¹ is C—NR³R⁴, C—OR⁴,

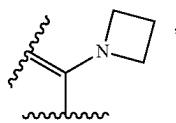
60



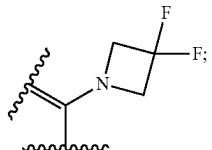
65

or X¹ is C—NR³R⁴ or

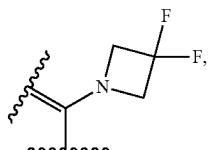
41



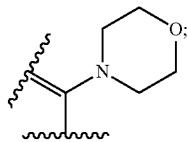
and X^2 is N or CH. In some embodiments, X^1 is N or CH, and X^2 is C—NR³R⁴ or



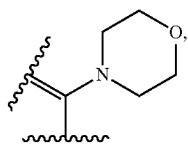
or X^1 is C—NR³R⁴ or



and X^2 is N or CH. In some embodiments, X^1 is N or CH, and X^2 is C—NR³R⁴ or



or X^1 is C—NR³R⁴ or



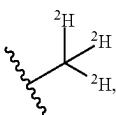
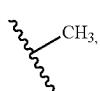
and X^2 is N or CH.

In some embodiments, R^{7"} is —NR³R⁴, —OR⁴, or optionally substituted heterocyclyl having 3 to 6 atoms.

In some embodiments, X¹ is N and X² is C—NR³R⁴. In some embodiments, X¹ is C—NR³R⁴ and X² is N.

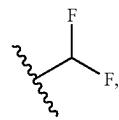
In some embodiments, R³ is H. In some embodiments, R³ is optionally substituted C₁-C₆ alkyl.

In some embodiments, R³ is



42

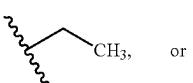
-continued



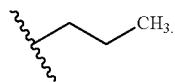
5



10

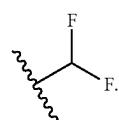
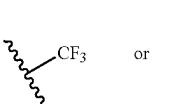


or



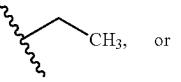
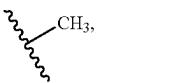
15

In some embodiments, R³ is



20

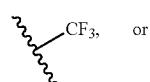
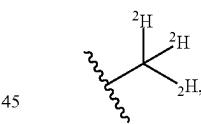
In some embodiments, R³ is



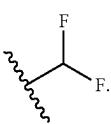
25

In some embodiments, R³ is methyl, ethyl,

30



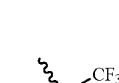
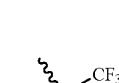
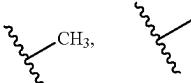
35



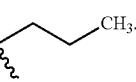
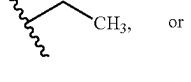
40

In some embodiments, R⁴ is

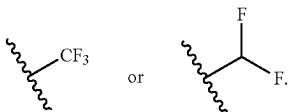
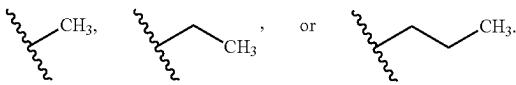
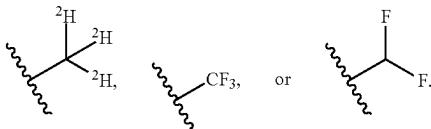
60



65



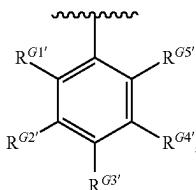
43

In some embodiments, R⁴ isIn some embodiments, R⁴ isIn some embodiments, R⁴ is methyl, ethyl,In some embodiments, X³ is N. In some embodiments, X³ is CH.In some embodiments, X⁴ is N. In some embodiments, X⁴ is CH.In some embodiments, X³ is N and X⁴ is N.In some embodiments, X³ is N and X⁴ is CH.In some embodiments, X³ is CH and X⁴ is N.In some embodiments, X³ is CH and X⁴ is CH.

In some embodiments, G" is

In some embodiments, G' is optionally substituted C₃-C₁₀ carbocyclene or optionally substituted C₂-C₉ heterocyclene. In some embodiments, G' is optionally substituted C₆-C₁₀ arylene or optionally substituted C₂-C₉ heteroarylene.In some embodiments, G' is optionally substituted C₃-C₁₀ carbocyclene. In some embodiments, G' is optionally substituted C₆-C₁₀ arylene. In some embodiments, G' is optionally substituted C₂-C₉ heterocyclene. In some embodiments, G' is optionally substituted C₂-C₉ heteroarylene.

In some embodiments, G' is

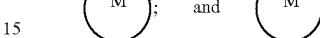


where

each of R^{G1'}, R^{G2'}, R^{G3'}, R^{G4'}, and R^{G5'} is, independently, H, A¹, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or

44

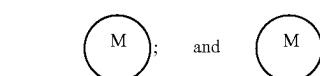
C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted —O—C₃-C₆ carbocyclyl, optionally substituted —C₁-C₃ alkyl-C₃-C₆ carbocyclyl, optionally substituted —C₁-C₃ alkyl-C₂-C₅ heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R^{G1'} and R^{G2'}, R^{G2'} and R^{G3'}, R^{G3'} and R^{G4'}, and/or R^{G4'} and R^{G5'}, together with the carbon atoms to which each is attached, combine to form



is optionally substituted C₆-C₁₀ aryl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heteroaryl, or optionally substituted C₂-C₉ heterocyclyl, any of which is optionally substituted with A¹, where one of R^{G1'}, R^{G2'}, R^{G3'}, R^{G4'}, and R^{G5'} is A¹, or

is substituted with A¹.

In some embodiments, each of R^{G1'}, R^{G2'}, R^{G3'}, R^{G4'}, and R^{G5'} is, independently, H, A¹, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted —O—C₃-C₆ carbocyclyl, optionally substituted —C₁-C₃ alkyl-C₃-C₆ carbocyclyl, optionally substituted —C₁-C₃ alkyl-C₂-C₅ heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R^{G1'} and R^{G2'}, R^{G2'} and R^{G3'}, R^{G3'} and R^{G4'}, and/or R^{G4'} and R^{G5'}, together with the carbon atoms to which each is attached, combine to form



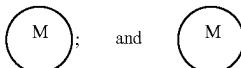
is optionally substituted C₆-C₁₀ aryl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heteroaryl, or optionally substituted C₂-C₉ heterocyclyl, any of which is optionally substituted with A¹, where one of R^{G1'}, R^{G2'}, R^{G3'}, R^{G4'}, and R^{G5'} is A¹, or

is substituted with A¹.

In some embodiments, each of R^{G1'}, R^{G2'}, R^{G3'}, R^{G4'}, and R^{G5'} is, independently, H, A¹, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted —O—C₃-C₆ carbocyclyl, or optionally substituted —C₁-C₃ alkyl-C₂-C₅ heterocyclyl; or R^{G1'}

45

and $R^{G2'}$, $R^{G2'}$ and $R^{G3'}$, $R^{G3'}$ and $R^{G4'}$, and/or $R^{G4'}$ and $R^{G5'}$, together with the carbon atoms to which each is attached, combine to form



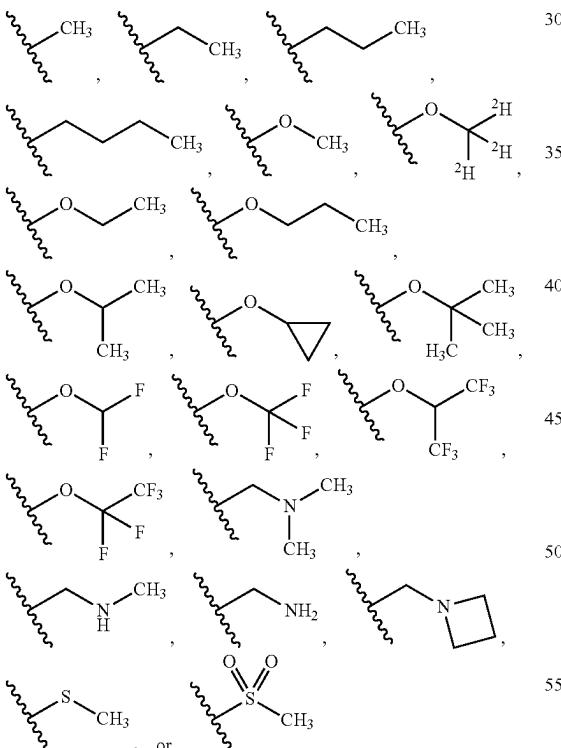
is optionally substituted C₂-C₉ heteroaryl or optionally substituted C₂-C₉ heterocycl¹, any of which is optionally substituted with A¹, where one of R^{G1}, R^{G2}, R^{G3}, R^{G4}, and R^{G5} is A¹, or



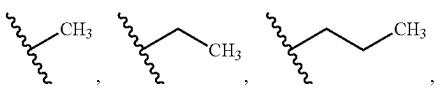
is substituted with A¹.

In some embodiments, each of R^{G1}, R^{G2}, R^{G3}, R^{G4}, and R^{G5} is, independently, H, A¹, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted —O—C₃-C₆ carbocyclyl, or optionally substituted —C₁-C₃ alkyl-C₂-C₅ heterocyclyl.

In some embodiments, each of R^{G1} , R^{G2} , $R^{G3'}$, $R^{G4'}$, and $R^{G5'}$ is, independently, H, A¹, F, Cl,

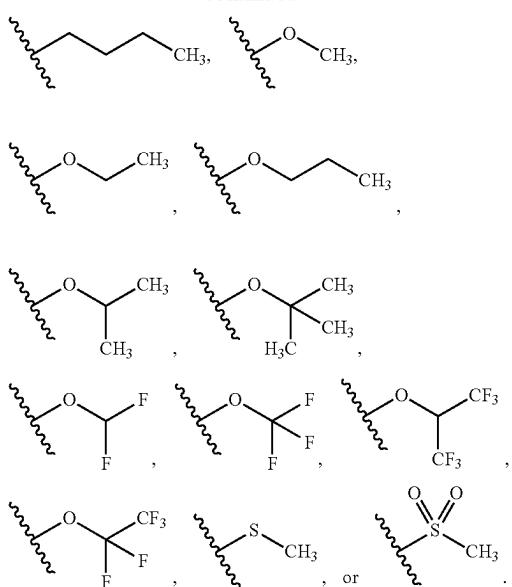


In some embodiments, each of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is H. In some embodiments, R^{G1} is H; R^{G2} is R^{G5} is, independently, H, A¹, F.

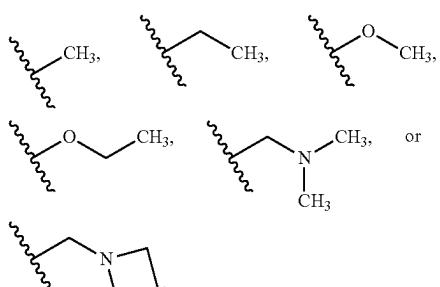


46

-continued

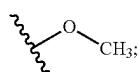


In some embodiments, each of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is, independently, H, A¹, F, Cl.

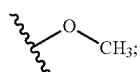
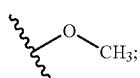


In some embodiments, R^{G3} is A^1 .

In some embodiments R^{G1} is H; R^{G2} is

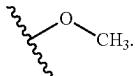


$R^{G3'}$ is A^1 . $R^{G4'}$ is

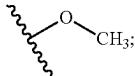


47

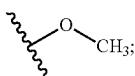
$R^{G3'}$ is A^1 ; $R^{G4'}$ is H; and $R^{G5'}$ is



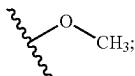
In some embodiments, $R^{G1'}$ is H; $R^{G2'}$ is



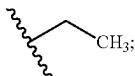
$R^{G3'}$ is A^1 ; $R^{G4'}$ is Cl or F; and $R^{G5'}$ is H. In some embodiments, $R^{G1'}$ is H; $R^{G2'}$ is



$R^{G3'}$ is A^1 ; $R^{G4'}$ is H; and $R^{G5'}$ is H. In some embodiments, $R^{G1'}$ is H; $R^{G2'}$ is

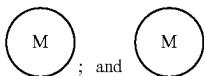


$R^{G3'}$ is A^1 ; $R^{G4'}$ is



and $R^{G5'}$ is H.

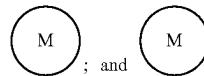
In some embodiments, $R^{G1'}$ and $R^{G2'}$, $R^{G2'}$ and $R^{G3'}$, $R^{G3'}$, $R^{G4'}$, and $R^{G4'}$, and/or $R^{G4'}$ and $R^{G5'}$, together with the carbon atoms to which each is attached, combine to form



is optionally substituted C_2 - C_9 heterocyclyl, which is optionally substituted with A^1 , where one of $R^{G1'}$, $R^{G2'}$, $R^{G3'}$, $R^{G4'}$, and $R^{G5'}$ is A^1 , or



is substituted with A^1 . In some embodiments, $R^{G1'}$ and $R^{G2'}$, $R^{G2'}$ and $R^{G3'}$, $R^{G3'}$ and $R^{G4'}$, and/or $R^{G4'}$ and $R^{G5'}$, together with the carbon atoms to which each is attached, combine to form

48**48**

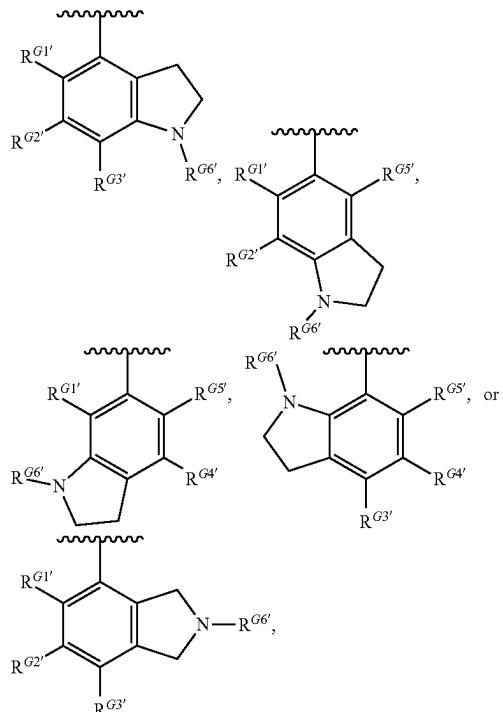
is optionally substituted C_2 - C_9 heteroaryl, which is optionally substituted with A^1 , where one of $R^{G1'}$, $R^{G2'}$, $R^{G3'}$, $R^{G4'}$, and $R^{G5'}$ is A^1 , or



is substituted with A^1 .

In some embodiments, G' is

20



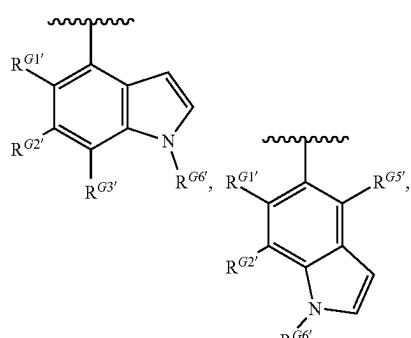
30

35

40

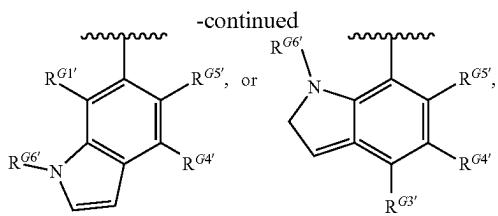
50

where $R^{G6'}$ is H, A^1 , or optionally substituted C_1 - C_6 alkyl. In some embodiments, G' is



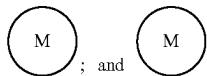
60

65

49

where $R^{G6'}$ is H, A^1 , or optionally substituted C_1 - C_6 alkyl.

In some embodiments, $R^{G1'}$ and $R^{G2'}$, $R^{G2'}$ and $R^{G3'}$, $R^{G3'}$ and $R^{G4'}$, and/or $R^{G4'}$ and $R^{G5'}$, together with the carbon atoms to which each is attached, combine to form

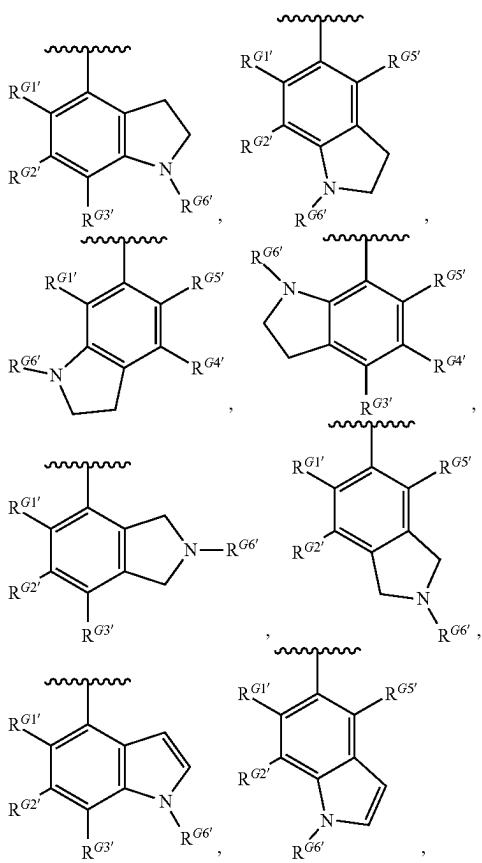
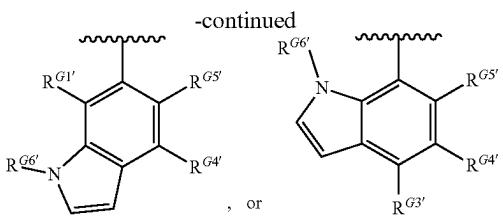


is optionally substituted C_2 - C_9 heterocyclyl or optionally substituted C_2 - C_9 heteroaryl, any of which is optionally substituted with A^1 , where one of $R^{G1'}$, $R^{G2'}$, $R^{G3'}$, $R^{G4'}$, and $R^{G5'}$ is A^1 , or



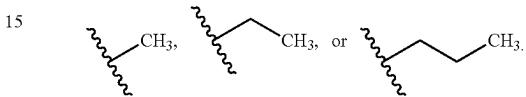
is substituted with A^1 .

In some embodiments, G' is

**50**

where $R^{G6'}$ is H, A^1 , or optionally substituted C_1 - C_6 alkyl.

In some embodiments, $R^{G6'}$ is H, A^1 ,



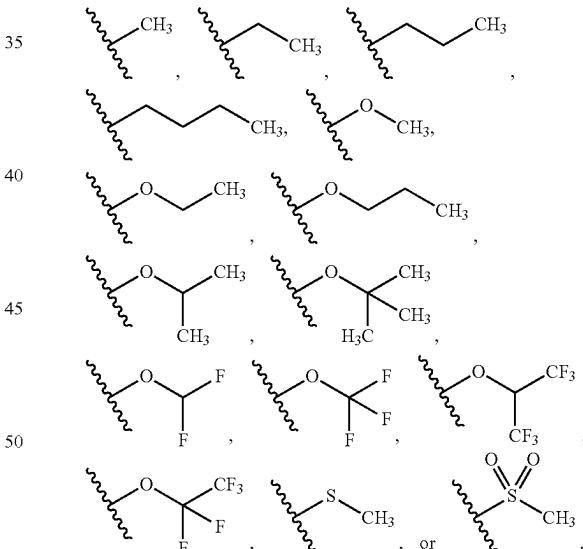
In some embodiments, $R^{G6'}$ is H, A^1 , or



In some embodiments, $R^{G6'}$ is H or A^1 .

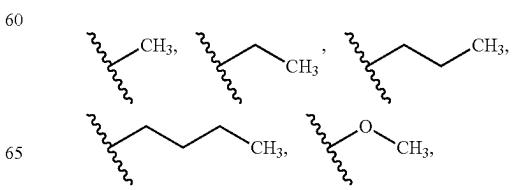
In some embodiments, $R^{G6'}$ is H. In some embodiments, $R^{G6'}$ is A^1 .

In some embodiments, $R^{G1'}$ is H, A^1 , F,



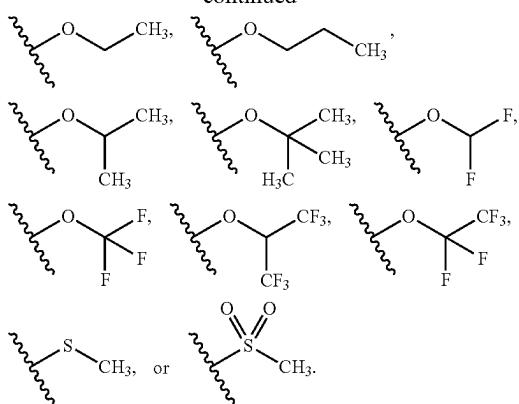
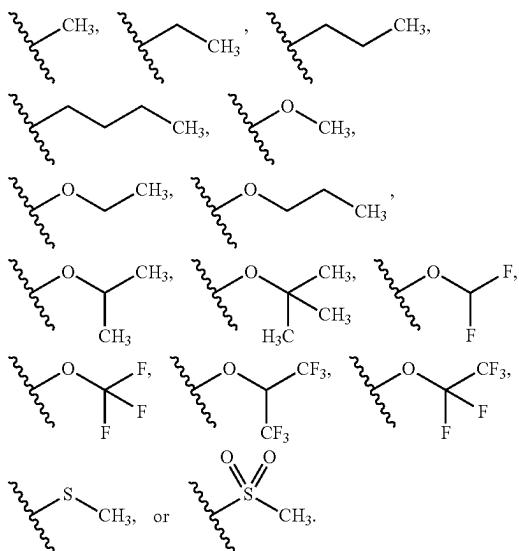
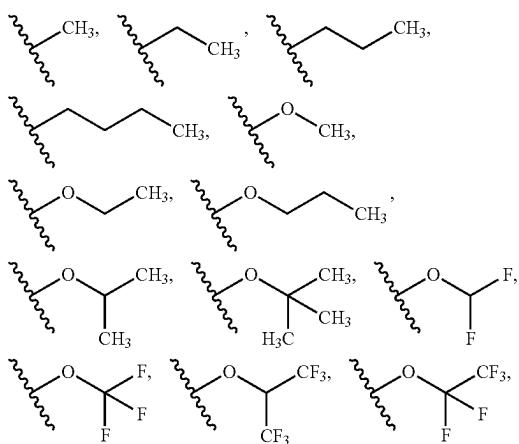
In some embodiments, $R^{G1'}$ is H.

In some embodiments, $R^{G2'}$ is H, A^1 , F,

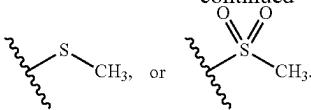
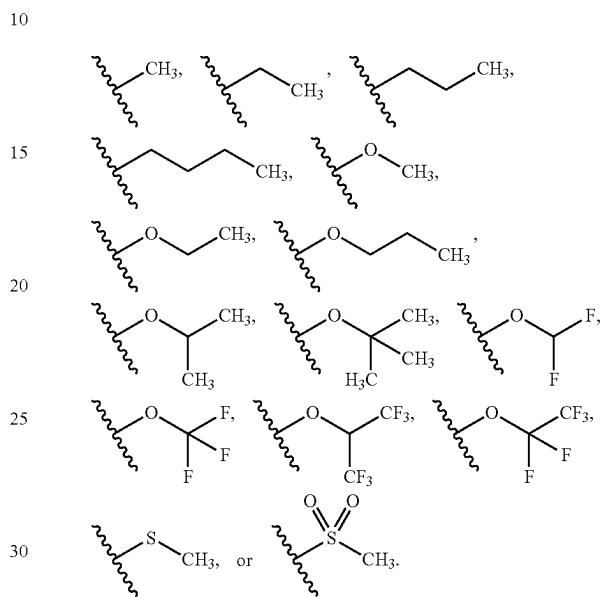


51

-continued

In some embodiments, $R^{G2'}$ is H.In some embodiments, $R^{G3'}$ is H, A¹, F,In some embodiments, $R^{G3'}$ is H.In some embodiments, $R^{G4'}$ is H, A¹, F,**52**

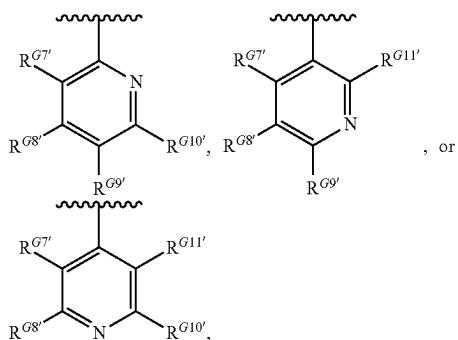
-continued

In some embodiments, $R^{G4'}$ is H.In some embodiments, $R^{G5'}$ is H, A¹, F,In some embodiments, $R^{G5'}$ is H.35 In some embodiments, one or more of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is H. In some embodiments, two or more of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is H. In some embodiments, three or more of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is H.In some embodiments, $R^{G1'}$ is A¹. In some embodiments, 40 $R^{G2'}$ is A¹. In some embodiments, $R^{G3'}$ is A¹. In some embodiments, $R^{G4'}$ is A¹. In some embodiments, $R^{G5'}$ is A¹. In some embodiments,

45

is substituted with A¹.

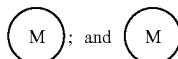
50 In some embodiments, G' is



where

53

each of R^{G7} , R^{G8} , R^{G9} , R^{G10} , and R^{G11} is, independently, H, A^1 , halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, optionally substituted $O-C_3-C_6$ carbocyclyl, optionally substituted $-C_1-C_3$ alkyl- C_3-C_6 carbocyclyl, optionally substituted $-C_1-C_3$ alkyl- C_2-C_5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R^{G7} and R^{G8} , R^{G8} and R^{G9} , R^{G9} and R^{G10} , and/or R^{G10} and R^{G11} , together with the carbon atoms to which each is attached, combine to form

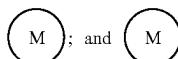


is optionally substituted C_6 - C_{10} aryl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heteroaryl, or C_2 - C_9 heterocyclyl, any of which is optionally substituted with A^1 , where one of R^{G7} , R^{G8} , R^{G9} , R^{G10} , and R^{G11} is A^1 ; or



is substituted with A^1 .

In some embodiments, each of R^{G7} , R^{G8} , R^{G9} , R^{G10} , and R^{G11} is, independently, H, A^1 , halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, optionally substituted $O-C_3-C_6$ carbocyclyl, optionally substituted $-C_1-C_3$ alkyl- C_3-C_6 carbocyclyl, optionally substituted $-C_1-C_3$ alkyl- C_2-C_5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R^{G7} and R^{G8} , R^{G8} and R^{G9} , R^{G9} and R^{G10} , and/or R^{G10} and R^{G11} , together with the carbon atoms to which each is attached, combine to form



is optionally substituted C_6 - C_{10} aryl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heteroaryl, or C_2 - C_9 heterocyclyl, any of which is optionally substituted with A^1 , where one of R^{G7} , R^{G8} , R^{G9} , R^{G10} , and R^{G11} is A^1 ; or

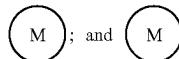


is substituted with A^1 .

In some embodiments, each of R^{G7} , R^{G8} , R^{G9} , R^{G10} , and R^{G11} is, independently, H, A^1 , halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted $O-C_3-C_6$ carbocyclyl, or option-

54

ally substituted $-C_1-C_3$ alkyl- C_2-C_5 heterocyclyl; or R^{G7} and R^{G8} , R^{G8} and R^{G9} , R^{G9} and R^{G10} , and/or R^{G10} and R^{G11} , together with the carbon atoms to which each is attached, combine to form



10

is optionally substituted C_6 - C_{10} aryl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heteroaryl, or C_2 - C_9 heterocyclyl, any of which is optionally substituted with A^1 , where one of R^{G7} , R^{G8} , R^{G9} , R^{G10} , and R^{G11} is A^1 ; or

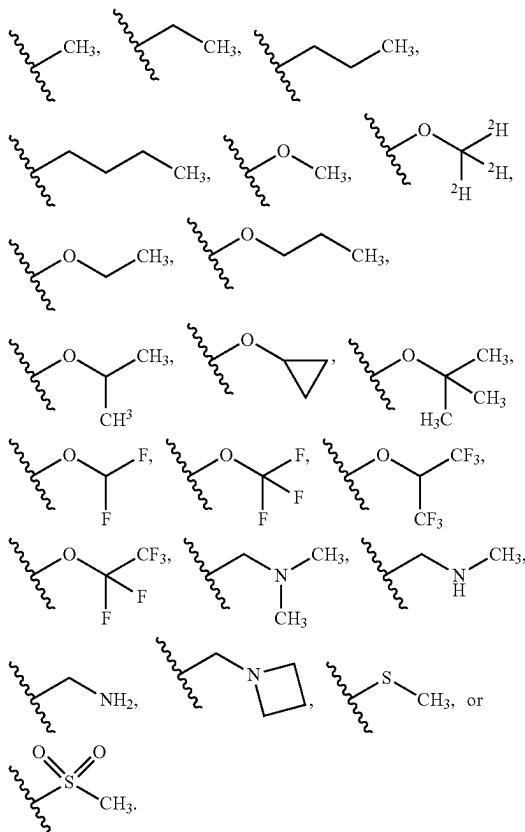


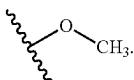
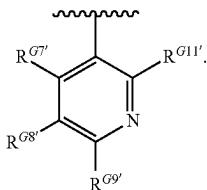
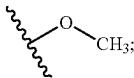
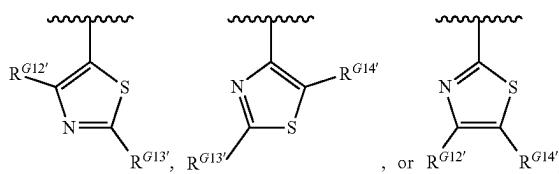
20

is substituted with A^1 .

25 In some embodiments, each of R^{G7} , R^{G8} , R^{G9} , R^{G10} , and R^{G11} is, independently, H, A^1 , halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted $O-C_3-C_6$ carbocyclyl, or optionally substituted $-C_1-C_3$ alkyl- C_2-C_5 heterocyclyl.

30 In some embodiments, each of R^{G7} , R^{G8} , R^{G9} , R^{G10} , and R^{G11} is, independently, H, A^1 , F, Cl,



55In some embodiments, $R^{G8'}$ isIn some embodiments, G' isIn some embodiments, $R^{G7'}$ is H; $R^{G8'}$ is $R^{G9'}$ is A^1 ; and $R^{G11'}$ is H.In some embodiments, G' is

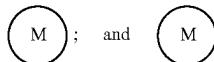
where

each of $R^{G12'}$, $R^{G13'}$, and $R^{G14'}$ is, independently, H, A^1 , halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, optionally substituted $O-C_3-C_6$ carbocyclyl, optionally substituted $-C_1-C_3$ alkyl- C_3-C_6 carbocyclyl, optionally substituted $-C_1-C_3$ alkyl- C_2-C_5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or $R^{G12'}$ and $R^{G14'}$, together with the carbon atoms to which each is attached, combine to form

56

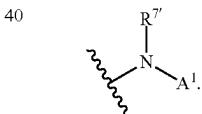
In some embodiments, each of $R^{G12'}$, $R^{G13'}$, and $R^{G14'}$ is, independently, H, A^1 , halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, optionally substituted $O-C_3-C_6$ carbocyclyl, optionally substituted $-C_1-C_3$ alkyl- C_3-C_6 carbocyclyl, optionally substituted $-C_1-C_3$ alkyl- C_2-C_5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or $R^{G12'}$ and $R^{G14'}$, together with the carbon atoms to which each is attached, combine to form

15



is optionally substituted C_6 - C_{10} aryl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heteroaryl, or optionally substituted C_2 - C_9 heterocyclyl, any of which is optionally substituted with A^1 , where one of $R^{G12'}$, $R^{G13'}$, and $R^{G14'}$ is A^1 ; or

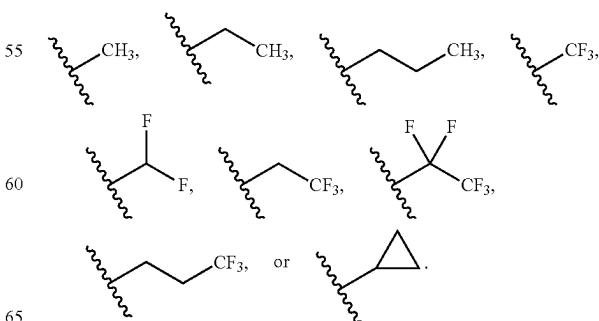
20

is substituted with A^1 .In some embodiments, R^7 is

40

In some embodiments, R^7 is H, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_3 - C_{10} carbocyclyl. In some embodiments, R^7 is H or optionally substituted C_1 - C_6 alkyl.

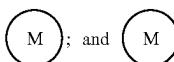
45

In some embodiments, R^7 is H,

55

60

65



is optionally substituted C_6 - C_{10} aryl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heteroaryl, or optionally substituted C_2 - C_9 heterocyclyl, any of which is optionally substituted with A^1 , where one of $R^{G12'}$, $R^{G13'}$, and $R^{G14'}$ is A^1 ; or

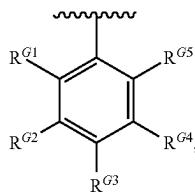
is substituted with A^1 .

57

In some embodiments, R^{7'} is H orIn some embodiments, R^{7'} is H. In some embodiments, R^{7'} is

In some embodiments, G^u is optionally substituted C₃-C₁₀ carbocyclyl or optionally substituted C₂-C₉ heterocyclyl. In some embodiments, G^u is optionally substituted C₆-C₁₀ aryl or optionally substituted C₂-C₉ heteroaryl.

In some embodiments, G^u is optionally substituted C₃-C₁₀ carbocyclyl. In some embodiments, G is optionally substituted C₆-C₁₀ aryl. In some embodiments, G is optionally substituted C₂-C₉ heterocyclyl. In some embodiments, G^u is optionally substituted C₂-C₉ heteroaryl.

In some embodiments, G^u is

where

each of R^{G1}, R^{G2}, R^{G3}, R^{G4}, and R^{G5} is, independently, H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted —O—C₃-C₆ carbocyclyl, optionally substituted —C₁-C₃ alkyl-C₃-C₆ carbocyclyl, optionally substituted —C₁-C₃ alkyl-C₂-C₅ heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R^{G1} and R^{G2}, R^{G2} and R^{G3}, R^{G3} and R^{G4}, and/or R^{G4} and R^{G5}, together with the carbon atoms to which each is attached, combine to form optionally substituted C₆-C₁₀ aryl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heteroaryl, or optionally substituted C₂-C₉ heterocyclyl.

In some embodiments, each of R^{G1}, R^{G2}, R^{G3}, R^{G4}, and R^{G5} is, independently, H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted —O—C₃-C₆ carbocyclyl, optionally substituted —C₁-C₃ alkyl-C₃-C₆ carbocyclyl, optionally substituted —C₁-C₃ alkyl-C₂-C₅ heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R^{G1} and R^{G2}, R^{G2} and R^{G3}, R^{G3} and R^{G4}, and/or R^{G4} and R^{G5}, together with the carbon atoms to which each is attached, combine to form optionally substituted C₆-C₁₀ aryl, option-

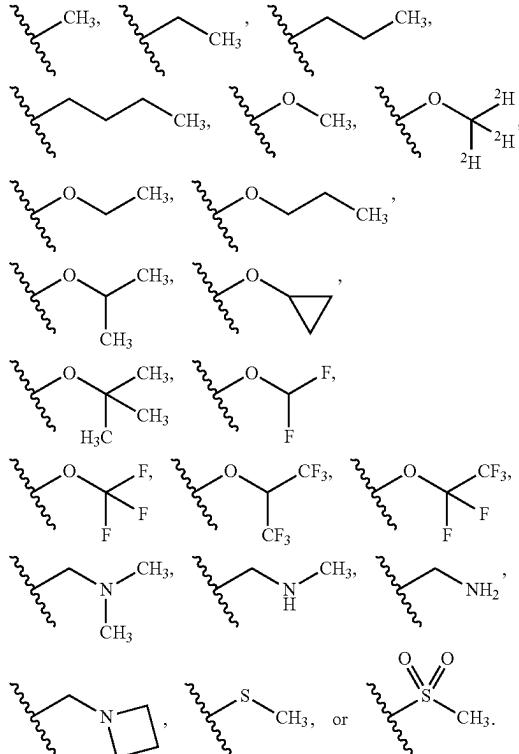
58

ally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heteroaryl, or optionally substituted C₂-C₉ heterocyclyl.

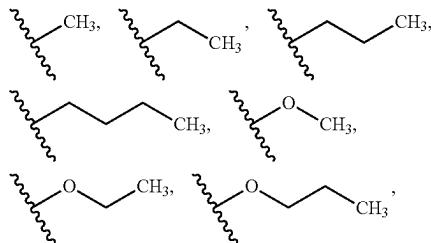
5 In some embodiments, each of R^{G1}, R^{G2}, R^{G3}, R^{G4}, and R^{G5} is, independently, H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted —O—C₃-C₆ carbocyclyl, or optionally substituted —C₁-C₃ alkyl-C₂-C₅ heterocyclyl; or R^{G1} and R^{G2}, R^{G2} and R^{G3}, R^{G3} and R^{G4}, and/or R^{G4} and R^{G5}, together with the carbon atoms to which each is attached, combine to form optionally substituted C₂-C₉ heteroaryl or optionally substituted C₂-C₉ heterocyclyl.

15 In some embodiments, each of R^{G1}, R^{G2}, R^{G3}, R^{G4}, and R^{G5} is, independently, H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted —O—C₃-C₆ carbocyclyl, or optionally substituted —C₁-C₃ alkyl-C₂-C₅ heterocyclyl.

20 In some embodiments, each of R^{G1}, R^{G2}, R^{G3}, R^{G4}, and R^{G5} is, independently, H, F, Cl,

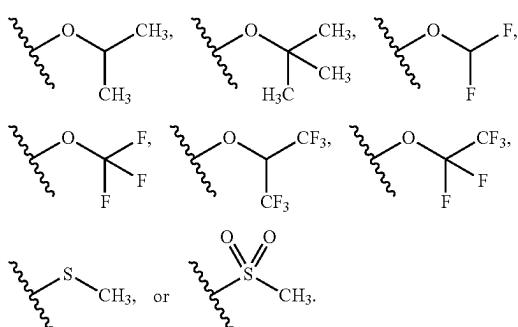


30 In some embodiments, each of R^{G1}, R^{G2}, R^{G3}, R^{G4}, and R^{G5} is, independently, H, F,



US 12,391,686 B2

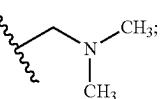
59
-continued



In some embodiments, each of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is, independently, H, F, Cl,

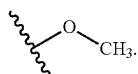
60

R^{G3} is



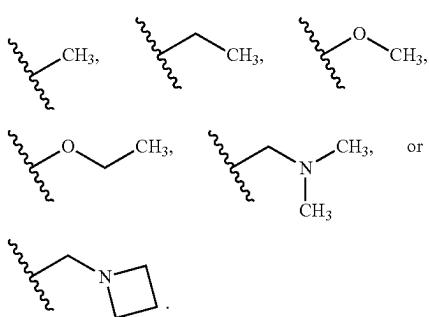
5

10 R^{G4} is H; and R^{G5} is

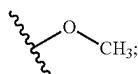


15

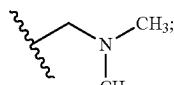
In some embodiments, R^{G1} is H; R^{G2} is



20



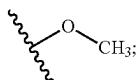
25 R^{G3} is



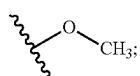
30

In some embodiments, R^{G1} is H; R^{G2} is

35 R^{G4} is Cl or F; and R^{G5} is H. In some embodiments, R^{G1} is
H; R^{G2} is

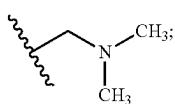


40

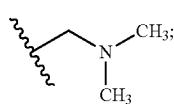


R^{G3} is

R^{G3} is



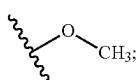
45



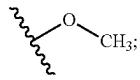
50

R^{G4} is

R^{G4} is H; and R^{G5} is H. In some embodiments, R^{G1} is H; R^{G2}

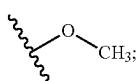


55

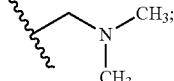


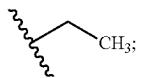
and R^{G5} is H. In some embodiments, R^{G1} is H; R^{G2} is

60 is R^{G3} is



65

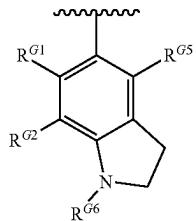
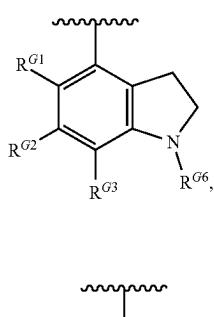


61 R^{G4} isand R^{G5} is H.

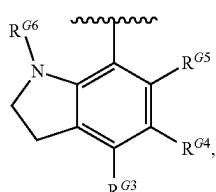
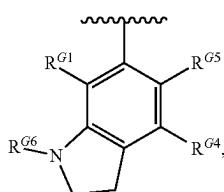
In some embodiments, R^{G1} and R^{G2} , R^{G2} and R^{G3} , R^{G3} and R^{G4} , and/or R^{G4} and R^{G5} , together with the carbon atoms to which each is attached, combine to form optionally substituted C_2 - C_9 heteroaryl or optionally substituted C_2 - C_9 heterocyclyl. 10

In some embodiments, R^{G1} and R^{G2} , R^{G2} and R^{G3} , R^{G3} and R^{G4} , and/or R^{G4} and R^{G5} , together with the carbon atoms to which each is attached, combine to form optionally substituted C_2 - C_9 heterocyclyl. In some embodiments, R^{G1} and R^{G2} , R^{G2} and R^{G3} , R^{G3} and R^{G4} , and/or R^{G4} and R^{G5} , together with the carbon atoms to which each is attached, combine to form optionally substituted C_2 - C_9 heteroaryl. 15

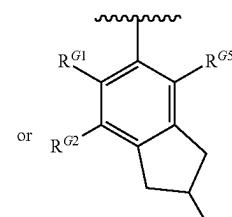
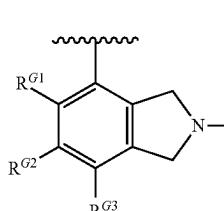
In some embodiments, R^{G1} and R^{G2} , R^{G2} and R^{G3} , R^{G3} and R^{G4} , and/or R^{G4} and R^{G5} , together with the carbon atoms to which each is attached, combine to form optionally substituted C_2 - C_9 heteroaryl. In some embodiments, R^{G1} and R^{G2} , R^{G2} and R^{G3} , R^{G3} and R^{G4} , and/or R^{G4} and R^{G5} , together with the carbon atoms to which each is attached, combine to form optionally substituted C_2 - C_9 heteroaryl. 20

In some embodiments, G'' is

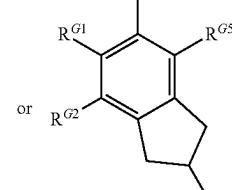
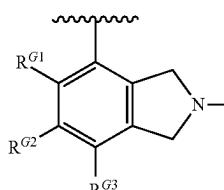
35



40



45



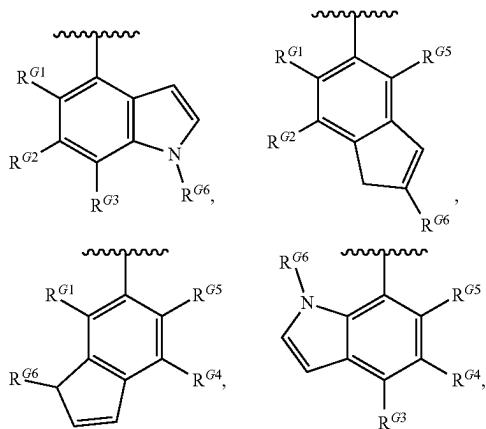
50

or

,

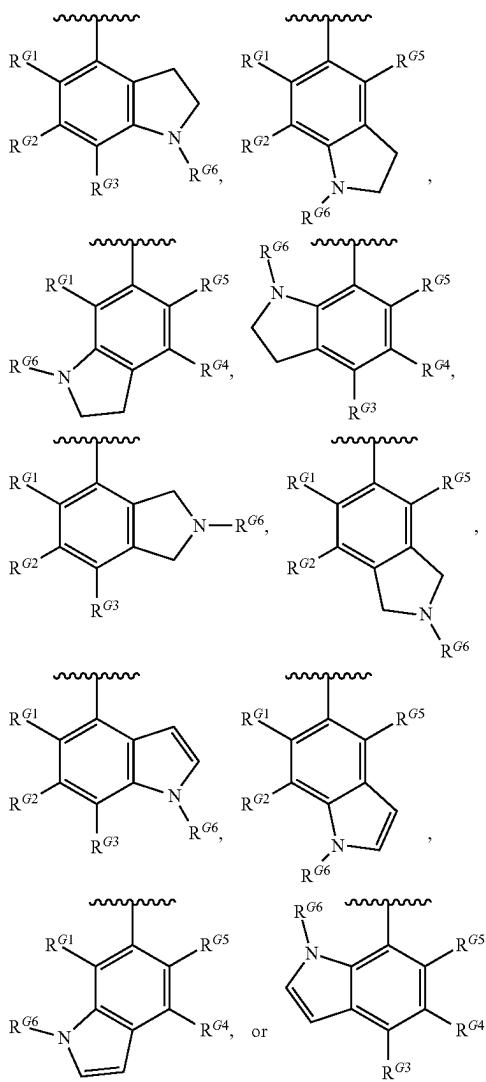
55

where R^{G6} is H or optionally substituted C_1 - C_6 alkyl. In some embodiments, G'' is

62

5

15

where R^{G6} is H or optionally substituted C_1 - C_6 alkyl.In some embodiments, G'' is

25

30

35

40

45

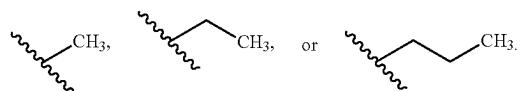
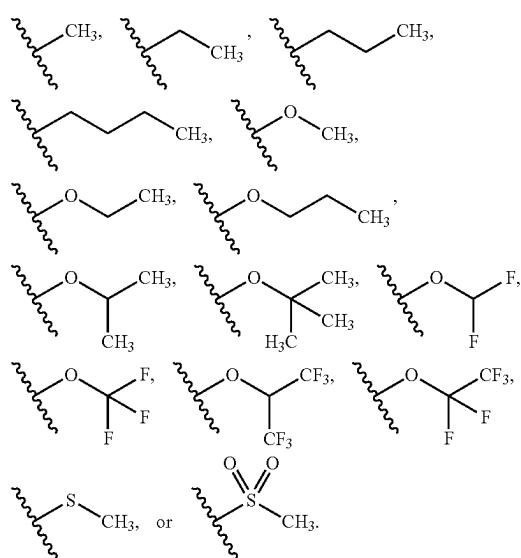
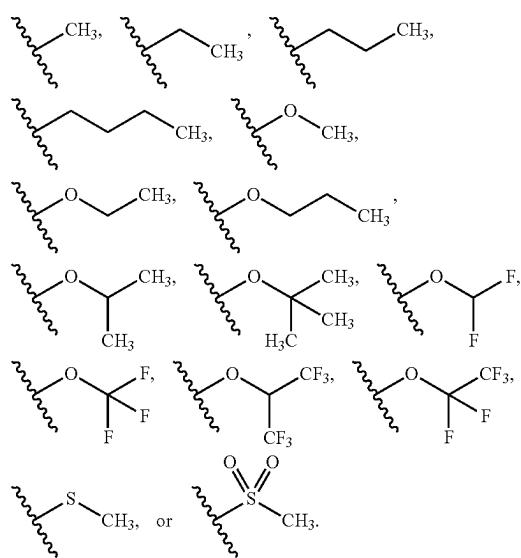
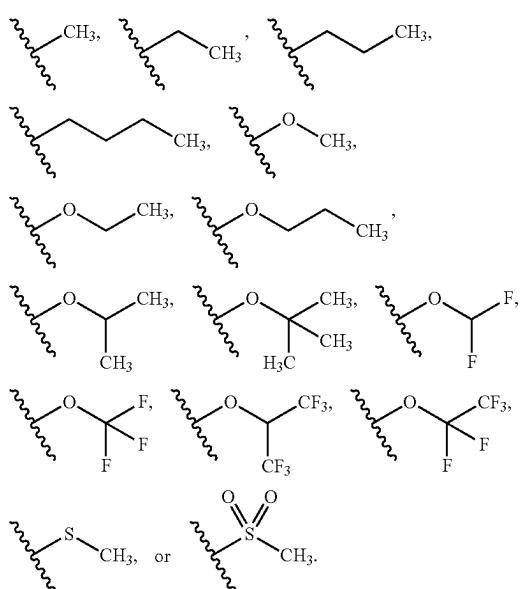
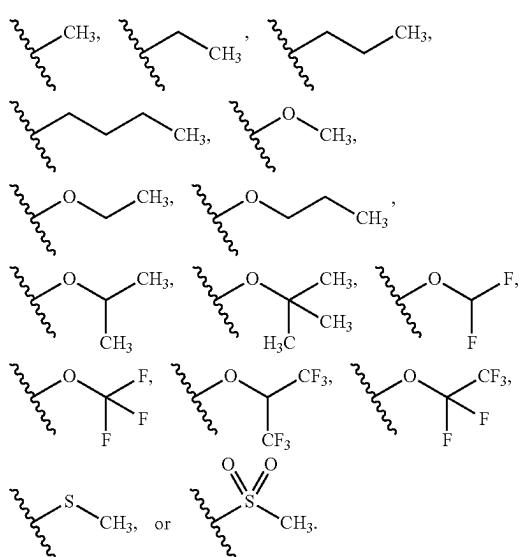
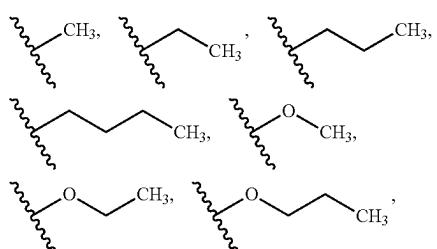
50

55

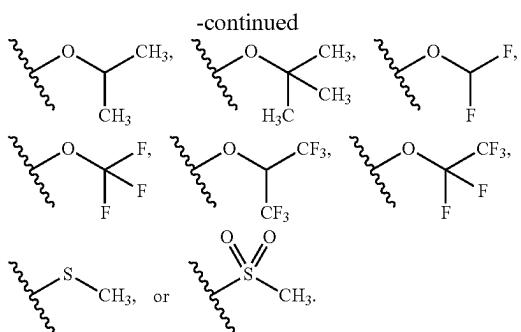
60

65

where R^{G6} is H or optionally substituted C_1 - C_6 alkyl.

63In some embodiments, R^{G6} is H,In some embodiments, R^{G6} is H orIn some embodiments, R^{G6} is H.In some embodiments, R^{G1} is H, F,In some embodiments, R^{G1} is H.In some embodiments, R^{G2} is H, F,In some embodiments, R^{G2} is H.**64**In some embodiments, R^{G3} is H, F,In some embodiments, R^{G3} is H.In some embodiments, R^{G4} is H, F,In some embodiments, R^{G4} is H.In some embodiments, R^{G5} is H, F,

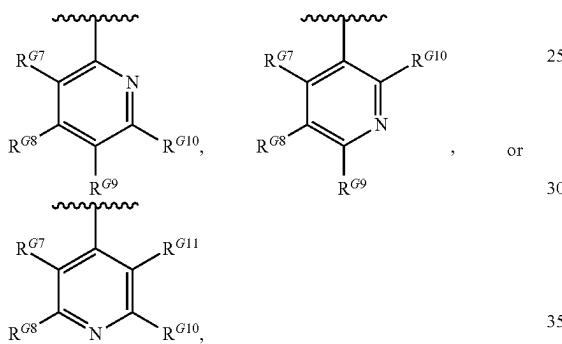
65



In some embodiments, R^{G5} is H.

In some embodiments, R^{G1} is H. In some embodiments, one or more of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is H. In some embodiments, two or more of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is H. In some embodiments, three or more of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is H. In some embodiments, each of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is H.

In some embodiments, G'' is



where

each of R^{G7} , R^{G8} , R^{G9} , R^{G10} , and R^{G11} is, independently, H, halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, optionally substituted $-O-C_3-C_6$ carbocyclyl, optionally substituted $-C_1-C_3$ alkyl- C_3-C_6 carbocyclyl, optionally substituted $-C_1-C_3$ alkyl- C_2-C_5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R^{G7} and R^{G8} , R^{G8} and R^{G9} , R^{G9} and R^{G10} , and/or R^{G10} and R^{G11} , together with the carbon atoms to which each is attached, combine to form optionally substituted C_6 - C_{10} aryl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heteroaryl, or C_2 - C_9 heterocyclyl.

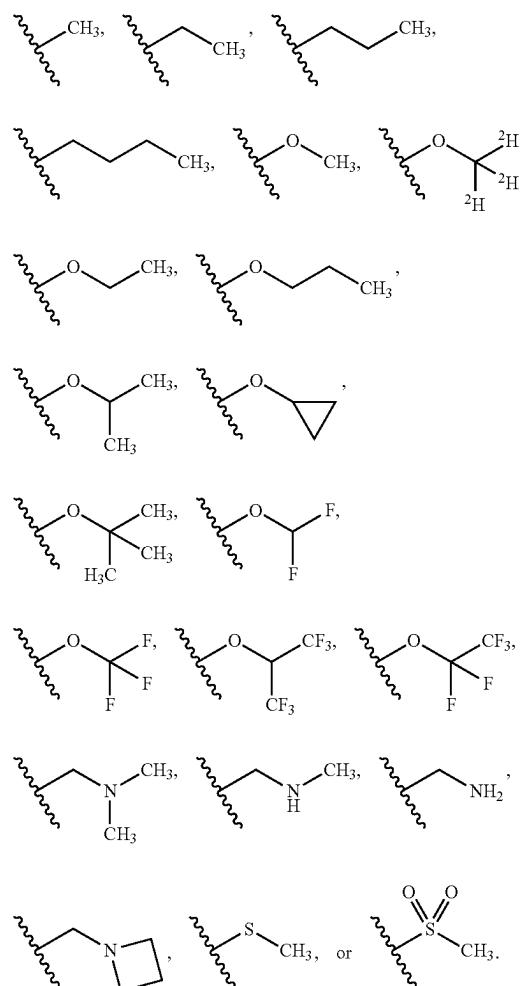
In some embodiments, each of R^{G7} , R^{G8} , R^{G9} , R^{G10} , and R^{G11} is, independently, H, halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; or R^{G7} and R^{G8} , R^{G8} and R^{G9} , R^{G9} and R^{G10} , and/or R^{G10} and R^{G11} , together with the carbon atoms to which each is attached, combine to form optionally substituted C_6 - C_{10} aryl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heteroaryl, or C_2 - C_9 heterocyclyl.

66

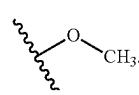
In some embodiments, each of R^{G7} , R^{G8} , R^{G9} , R^{G10} , and R^{G11} is, independently, H, halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted $—O—C_3-C_6$ carbocyclyl, or optionally substituted $—C_1-C_3$ alkyl- C_2-C_5 heterocyclyl; or R^{G7} and R^{G8} , R^{G8} and R^{G9} , R^{G9} and R^{G10} , and/or R^{G10} and R^{G11} , together with the carbon atoms to which each is attached, combine to form optionally substituted C_6 - C_{10} aryl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_6 heteroaryl, or C_2 - C_6 heterocyclyl.

In some embodiments, each of R^{G7} , R^{G8} , R^{G9} , R^{G10} , and R^{G11} is, independently, H, halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted $—O—C_3$ - C_6 carbocyclyl, or optionally substituted $—C_1$ - C_3 alkyl- C_2 - C_6 heterocyclyl.

In some embodiments, each of R^{G7} , R^{G8} , R^{G9} , R^{G10} , and R^{G11} is, independently, H, F, Cl.

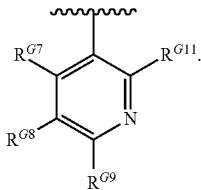


In some embodiments, R^{G8} is

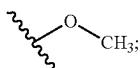


67

In some embodiments, G" is

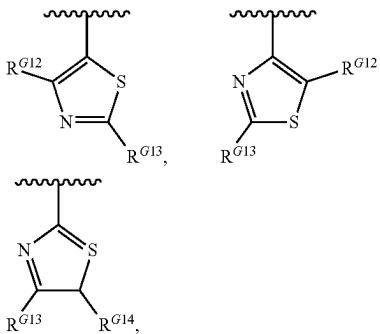


In some embodiments, R^{G7} is H; R^{G8} is



R^{G9} is H; and R^{G11} is H.

In some embodiments, G" is



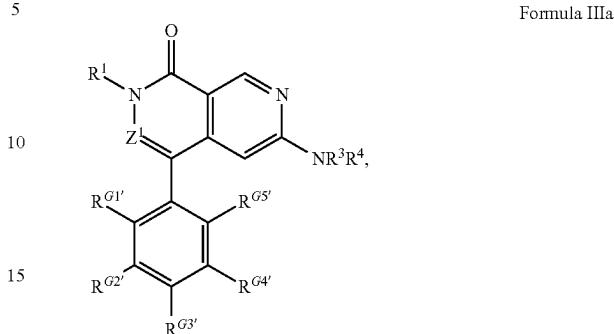
where

each of R^{G12}, R^{G13}, and R^{G14} is, independently, H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted —O—C₃-C₆ carbocyclyl, optionally substituted —C₁-C₃ alkyl-C₃-C₆ carbocyclyl, optionally substituted —C₁-C₃ alkyl-C₂-C₅ heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R^{G12} and R^{G14}, together with the carbon atoms to which each is attached, combine to form optionally substituted C₆-C₁₀ aryl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heteroaryl, or optionally substituted C₂-C₉ heterocyclyl.

In some embodiments, each of R^{G12}, R^{G13}, and R^{G14} is, independently, H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; or R^{G12} and R^{G14}, together with the carbon atoms to which each is attached, combine to form optionally substituted C₆-C₁₀ aryl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heteroaryl, or optionally substituted C₂-C₉ heterocyclyl.

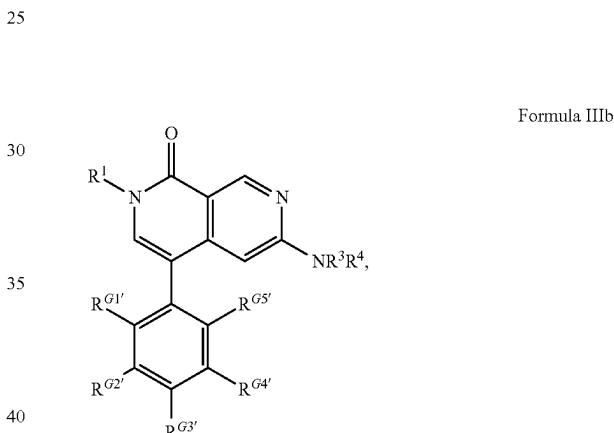
68

In some embodiments, A has the structure of Formula IIIa:



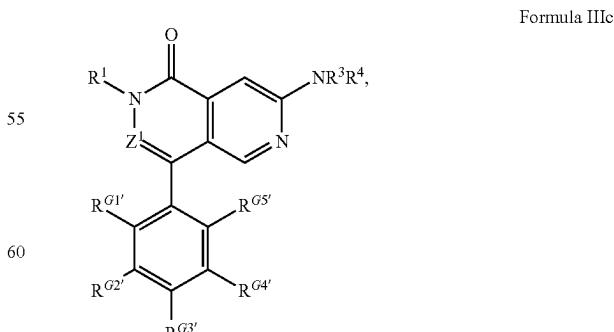
20 or a pharmaceutically acceptable salt thereof.

In some embodiments, A has the structure of Formula IIIb:



45 or a pharmaceutically acceptable salt thereof.

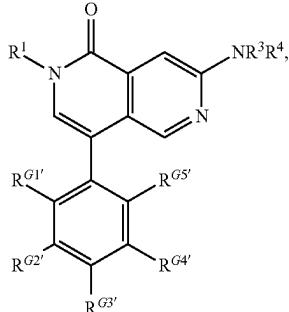
In some embodiments, A has the structure of Formula IIIc:



65 or a pharmaceutically acceptable salt thereof.

69

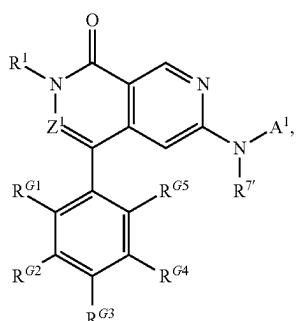
In some embodiments, A has the structure of Formula IIId:



Formula IIId

70

In some embodiments, A has the structure of Formula IIIg:



Formula IIIg

5

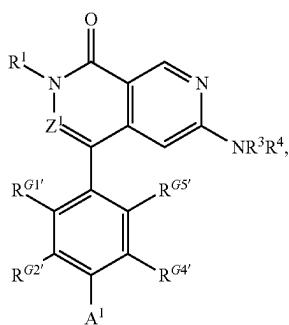
10

15

20

or a pharmaceutically acceptable salt thereof.

In some embodiments, A has the structure of Formula IIIe:



Formula IIIe

30

35

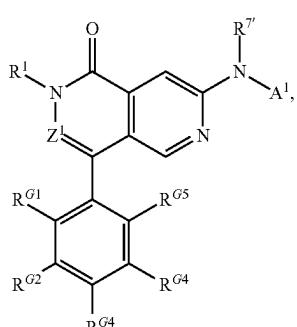
40

45

or a pharmaceutically acceptable salt thereof.

In some embodiments, A has the structure of Formula IIIe:

Formula IIIh



Formula IIIf

50

55

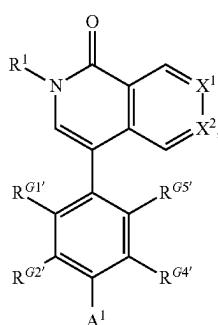
60

65

or a pharmaceutically acceptable salt thereof.

In some embodiments, A has the structure of Formula IIIf:

Formula IIIi

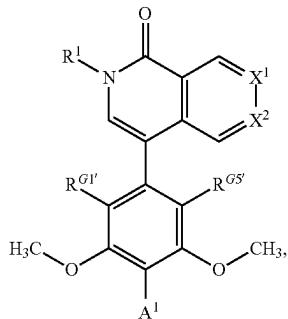


or a pharmaceutically acceptable salt thereof.

or a pharmaceutically acceptable salt thereof.

71

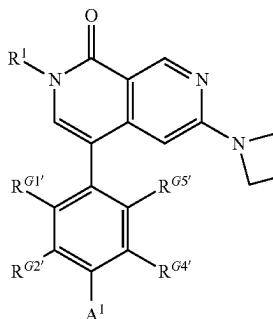
In some embodiments, A has the structure of Formula IIIj:



Formula IIIj 5

72

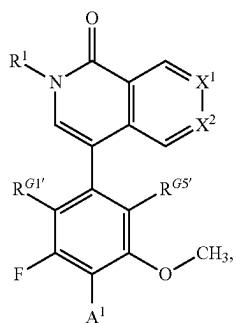
In some embodiments, A has the structure of Formula IIIIn:



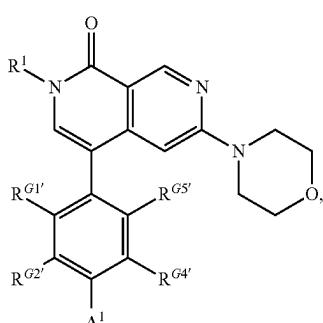
Formula IIIIn

10
1520
or a pharmaceutically acceptable salt thereof.
25

In some embodiments, A has the structure of Formula IIIk:



Formula IIIk

30
35
40or a pharmaceutically acceptable salt thereof.
In some embodiments, A has the structure of Formula IIIo:

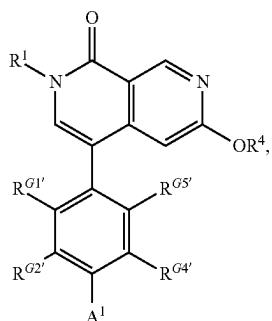
Formula IIIo

45
or a pharmaceutically acceptable salt thereof.

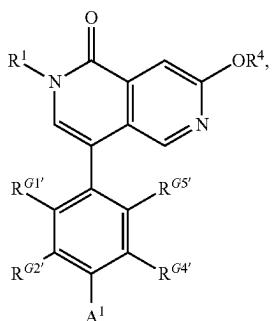
In some embodiments, A has the structure of Formula IIIm:

or a pharmaceutically acceptable salt thereof.

In some embodiments, A has the structure of Formula IIIp:



Formula IIIm

50
55
60

Formula IIIp

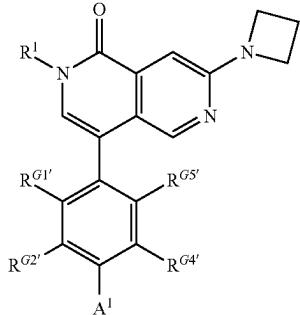
65

or a pharmaceutically acceptable salt thereof.

or a pharmaceutically acceptable salt thereof.

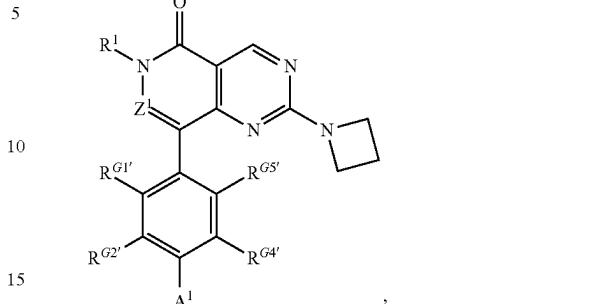
73

In some embodiments, A has the structure of Formula IIIq:



,

Formula IIIq



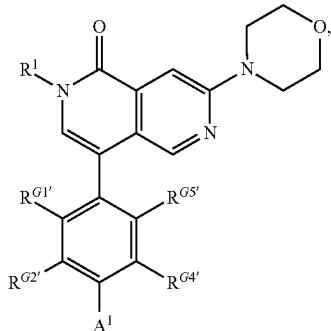
Formula IIIt

or a pharmaceutically acceptable salt thereof.

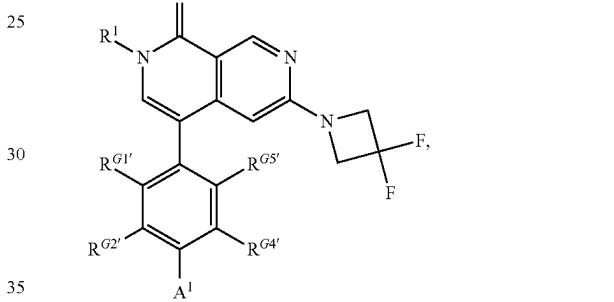
In some embodiments, A has the structure of Formula IIIu:

or a pharmaceutically acceptable salt thereof.

In some embodiments, A has the structure of Formula IIIr:



Formula IIIr



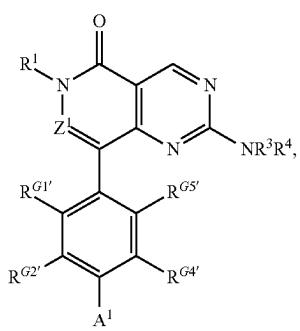
Formula IIIu

or a pharmaceutically acceptable salt thereof.

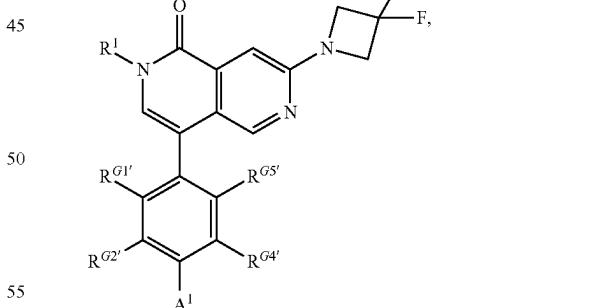
In some embodiments, A has the structure of Formula IIIv:

or a pharmaceutically acceptable salt thereof.

In some embodiments, A has the structure of Formula IIIs:



Formula IIIs



Formula IIIv

or a pharmaceutically acceptable salt thereof.

In some embodiments, the degradation moiety is a ubiquitin ligase binding moiety.

In some embodiments, the ubiquitin ligase binding moiety comprises Cereblon ligands, IAP (Inhibitors of Apoptosis) ligands, mouse double minute 2 homolog (MDM2), or von Hippel-Lindau (VHL) ligands, or derivatives or analogs thereof.

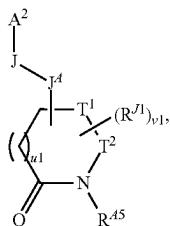
In some embodiments, the degradation moiety is a ubiquitin ligase binding moiety.

or a pharmaceutically acceptable salt thereof.

75

In some embodiments, the ubiquitin ligase binding moiety comprises Cereblon ligands, IAP (Inhibitors of Apoptosis) ligands, mouse double minute 2 homolog (MDM2), or von Hippel-Lindau (VHL) ligands, or derivatives or analogs thereof.

In some embodiments, the degradation moiety includes the structure of Formula Y:



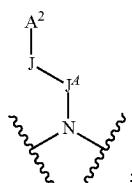
where

A^2 is a bond between the degradation moiety and the linker;

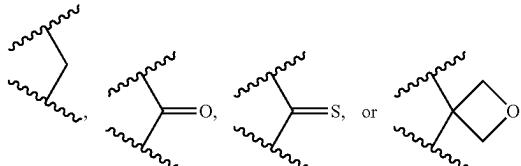
$v1$ is 0, 1, 2, 3, 4, or 5;

$u1$ is 1, 2, or 3;

T^1 is a bond or



T^2 is



R^{54} is H, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_1 - C_6 heteroalkyl;

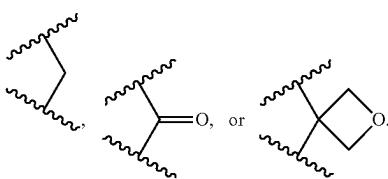
each R^{J1} is, independently, halogen, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_1 - C_6 heteroalkyl;

J^4 is absent, O, optionally substituted amino, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_1 - C_6 heteroalkyl; and

J is absent, optionally substituted C_3 - C_{10} carbocyclylene, optionally substituted C_6 - C_{10} arylene, optionally substituted C_2 - C_9 heterocyclylene, or optionally substituted C_2 - C_9 heteroarylene, or a pharmaceutically acceptable salt thereof.

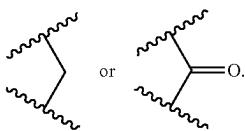
76

In some embodiments, T^2 is

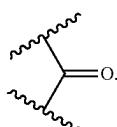


Formula Y

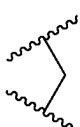
In some embodiments, T^2 is



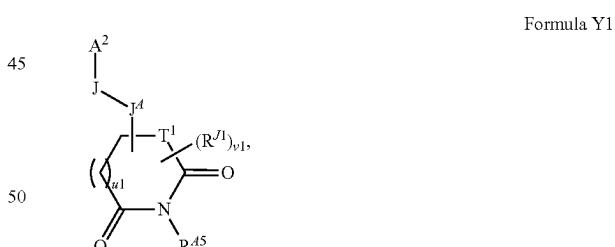
In some embodiments, T^2 is



In some embodiments, T^2 is

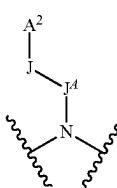


In some embodiments, the structure of Formula Y has the structure of Formula Y1:

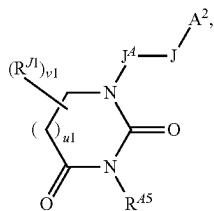


or a pharmaceutically acceptable salt thereof.

In some embodiments, T^1 is a bond. In some embodiments, T^1 is

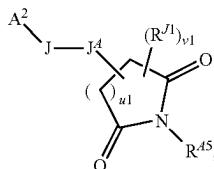


In some embodiments, the structure of Formula Y has the structure of Formula Y2:



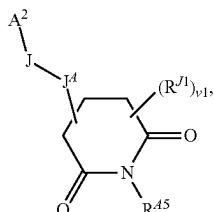
or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of Formula Y has the structure of Formula Z:



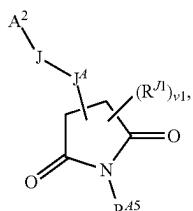
or a pharmaceutically acceptable salt thereof.

In some embodiments, u1 is 1. In some embodiments, u1 is 2. In some embodiments u1 is 3.



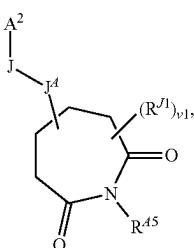
or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of Formula Z has the structure of Formula AB:



or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of Formula Z has the structure of Formula AC:

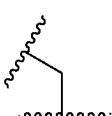


¹⁵ or a pharmaceutically acceptable salt thereof.

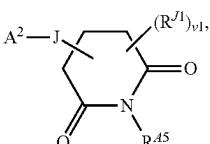
In some embodiments, J^4 is absent. In some embodiments, J^4 is optionally substituted C_1 - C_6 alkyl. In some embodiments, J^4 is optionally substituted C_1 - C_6 heteroalkyl.

In some embodiments, J^4 is O or optionally substituted amino.

In some embodiments, J^A is



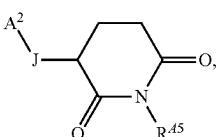
30 In some embodiments, the structure of Formula AA0 has the structure of Formula AA0:



or a pharmaceutically acceptable salt thereof.

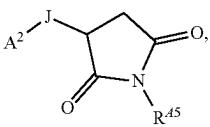
In some embodiments, v1 is 0, 1, 2, or 3. In some embodiments, v1 is 0. In some embodiments, v1 is 1. In some embodiments, v1 is 2. In some embodiments, v1 is 3.

45 In some embodiments, the structure of Formula AA has the structure of Formula AA1:



or a pharmaceutically acceptable salt thereof.

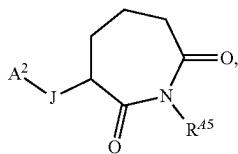
In some embodiments, the structure of Formula AB has the structure of Formula AB1:



or a pharmaceutically acceptable salt thereof.

79

In some embodiments, the structure of Formula AC has the structure of Formula AC1:

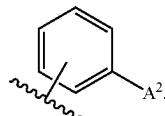


or a pharmaceutically acceptable salt thereof.

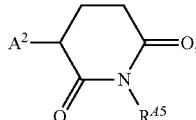
In some embodiments, J is absent. In some embodiments, J is optionally substituted C₃-C₁₀ carbocyclene or optionally substituted C₆-C₁₀ arylene. In some embodiments, J is optionally substituted C₂-C₉ heterocyclene or optionally substituted C₂-C₉ heteroarylene.

In some embodiments, J is optionally substituted heterocyclene. In some embodiments, J is optionally substituted C₆-C₁₀ arylene.

In some embodiments, J is

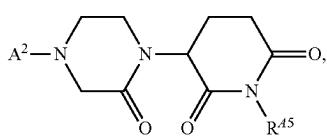


In some embodiments, the structure of Formula AA has the structure of Formula AA2:



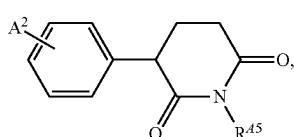
or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of Formula AA has the structure of Formula AA3:



or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of Formula AA has the structure of Formula AA4:

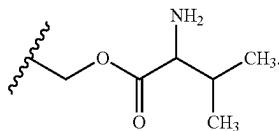


or a pharmaceutically acceptable salt thereof.

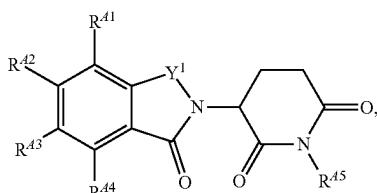
80

In some embodiments, R⁴⁵ is H or optionally substituted C₁-C₆ alkyl. In some embodiments, R⁴⁵ is optionally substituted C₁-C₆ heteroalkyl.

In some embodiments, R⁴⁵ is H or methyl. In some embodiments, R⁴⁵ is H. In some embodiments, R⁴⁵ is methyl. In some embodiments, R⁴⁵ is

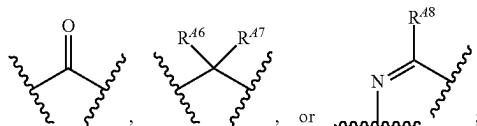


In some embodiments, the structure of Formula AA has the structure of Formula A:



Formula A

where
Y¹ is

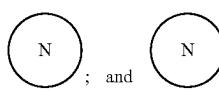


R⁴⁵ is H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl;

R⁴⁶ is H or optionally substituted C₁-C₆ alkyl; and R⁴⁷ is H or optionally substituted C₁-C₆ alkyl; or R⁴⁶ and R⁴⁷, together with the carbon atom to which each is bound, combine to form optionally substituted C₃-C₆ carbocycl or optionally substituted C₂-C₅ heterocycl; or R⁴⁶ and R⁴⁷, together with the carbon atom to which each is bound, combine to form optionally substituted C₃-C₆ carbocycl or optionally substituted C₂-C₅ heterocycl;

R⁴⁸ is H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl;

each of R⁴¹, R⁴², R⁴³, and R⁴⁴ is, independently, H, A², halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocycl, optionally substituted C₂-C₉ heterocycl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted —O—C₃-C₆ carbocycl, hydroxyl, thiol, or optionally substituted amino; or R⁴¹ and R⁴², R⁴² and R⁴³, and/or R⁴³ and R⁴⁴, together with the carbon atoms to which each is attached, combine to form



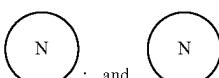
81

is optionally substituted C₆-C₁₀ aryl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heteroaryl, or C₂-C₉ heterocyclyl, any of which is optionally substituted with A², where one of R⁴¹, R⁴², R⁴³, and R⁴⁴ is A², or



is substituted with A², or a pharmaceutically acceptable salt thereof.

In some embodiments, each of R⁴¹, R⁴², R⁴³, and R⁴⁴ is, independently, H, A², halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; or R⁴¹ and R⁴², R⁴² and R⁴³, and/or R⁴³ and R⁴⁴, together with the carbon atoms to which each is attached, combine to form

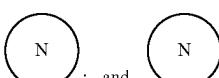


is optionally substituted C₆-C₁₀ aryl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heteroaryl, or C₂-C₉ heterocyclyl, any of which is optionally substituted with A², where one of R⁴¹, R⁴², R⁴³, and R⁴⁴ is A², or



is substituted with A², or a pharmaceutically acceptable salt thereof.

In some embodiments, each of R⁴¹, R⁴², R⁴³, and R⁴⁴ is, H, A², halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted —O—C₃-C₆ carbocyclyl, hydroxyl, optionally substituted amino; or R⁴¹ and R⁴², R⁴² and R⁴³, or R⁴³ and R⁴⁴, together with the carbon atoms to which each is attached, combine to form



is optionally substituted C₂-C₉ heterocyclyl, which is optionally substituted with A², where one of R⁴¹, R⁴², R⁴³, and R⁴⁴ is A², or

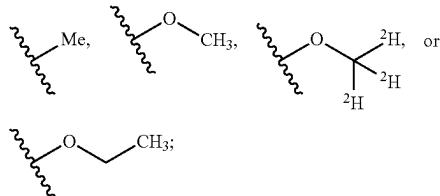


is substituted with A².

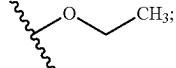
82

In some embodiments, each of R⁴¹, R⁴², R⁴³, and R⁴⁴ is, independently, H, A², F,

5

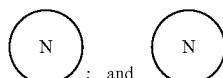


10



15

or R⁴¹ and R⁴², R⁴² and R⁴³, or R⁴³ and R⁴⁴, together with the carbon atoms to which each is attached, combine to form



20

is optionally substituted C₂-C₉ heterocyclyl, which is optionally substituted with A², where one of R⁴¹, R⁴², R⁴³, and R⁴⁴ is A², or



25

is substituted with A².

In some embodiments, R⁴¹ is A². In some embodiments, R⁴² is A². In some embodiments, R⁴³ is A². In some embodiments, R⁴⁴ is A². In some embodiments, R⁴⁵ is A².

In some embodiments, R⁴⁵ is H or optionally substituted C₁-C₆ alkyl.

In some embodiments, R⁴⁵ is H or



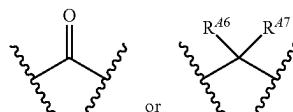
45

In some embodiments, R⁴⁵ is H. In some embodiments, R⁴⁵ is



55

In some embodiments, Y¹ is



60

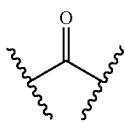
65

65

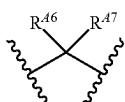
or

83

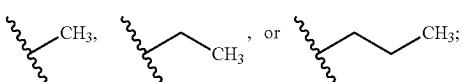
In some embodiments, Y¹ is



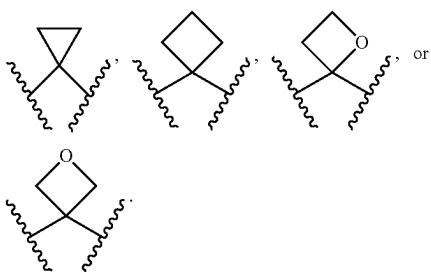
In some embodiments, Y¹ is



In some embodiments, each of R^{A6} and R^{A7} is, independently, H, F,

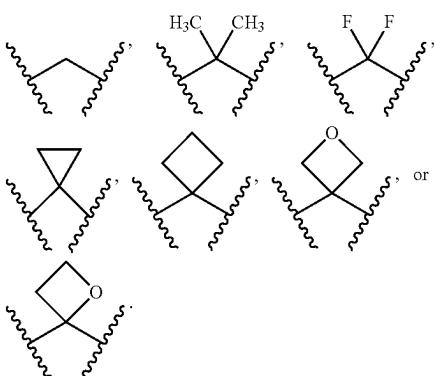


or R^{A6} and R^{A7}, together with the carbon atom to which each is bound, combine to form



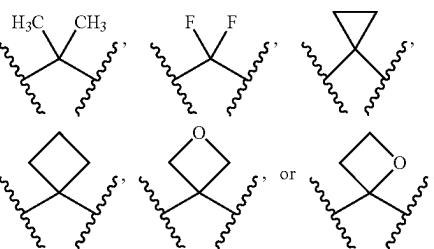
In some embodiments, R^{A6} is H and R^{A7} is H.

In some embodiments, Y¹ is



84

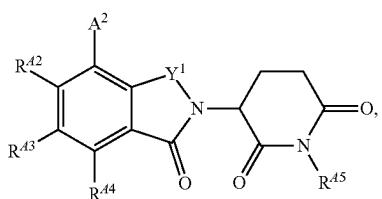
In some embodiments, Y¹ is



¹⁵ In some embodiments, Y¹ is

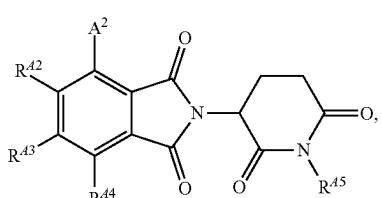


In some embodiments, the structure of Formula A has the structure of Formula A1:



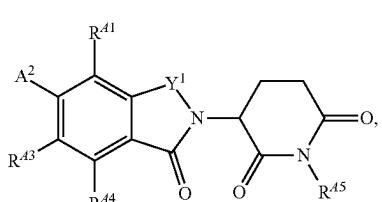
or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of Formula A has the structure of Formula A2:



or a pharmaceutically acceptable salt thereof.

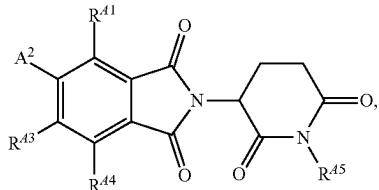
In some embodiments, the structure of Formula A has the structure of Formula A3:



or a pharmaceutically acceptable salt thereof.

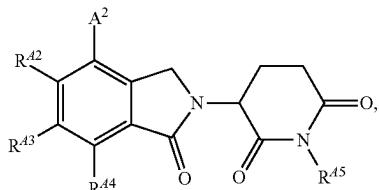
85

In some embodiments, the structure of Formula A has the structure of Formula A4:



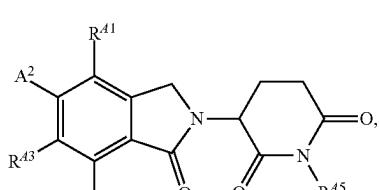
or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of Formula A has the structure of Formula A5:



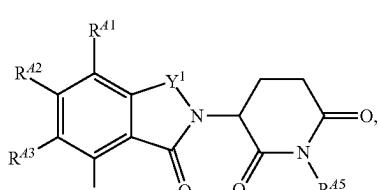
or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of Formula A has the structure of Formula A6:



or a pharmaceutically acceptable salt thereof.

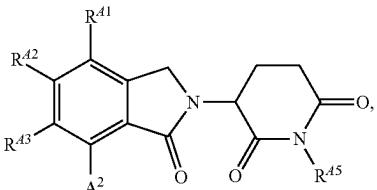
In some embodiments, the structure of Formula A has the structure of Formula A7:



or a pharmaceutically acceptable salt thereof.

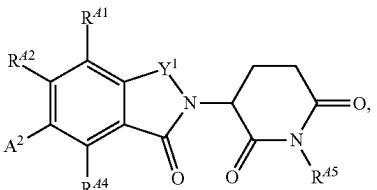
86

In some embodiments, the structure of Formula A has the structure of Formula A8:



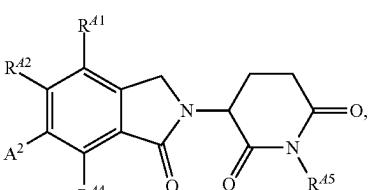
or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of Formula A has the structure of Formula A9:



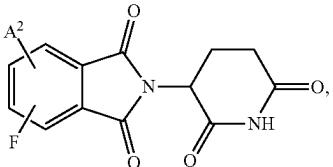
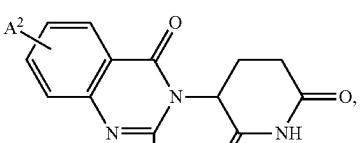
or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of Formula A has the structure of Formula A10:



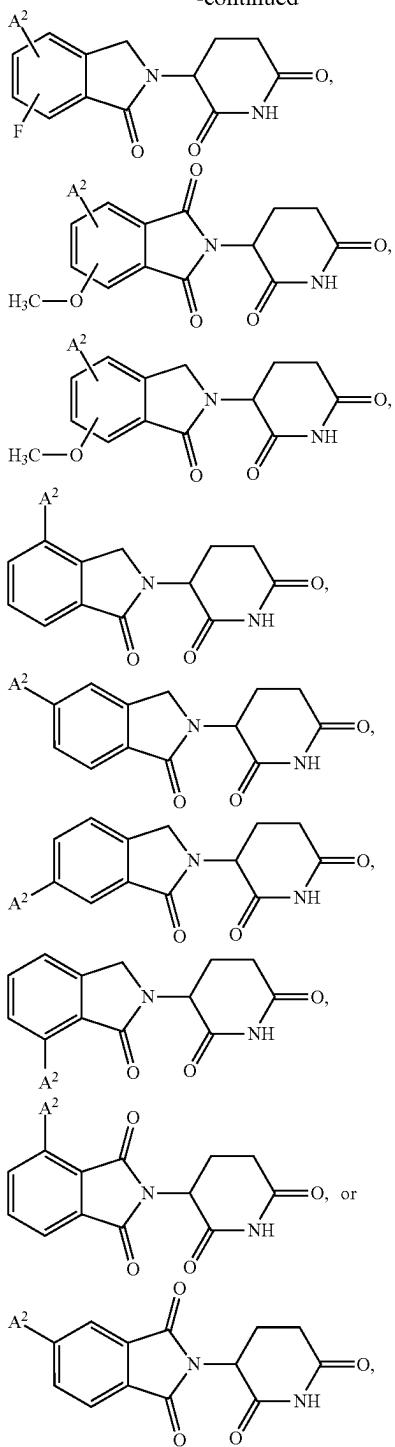
or a pharmaceutically acceptable salt thereof.

In some embodiments, wherein the structure of Formula A is

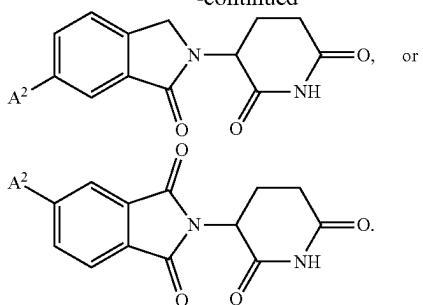


87

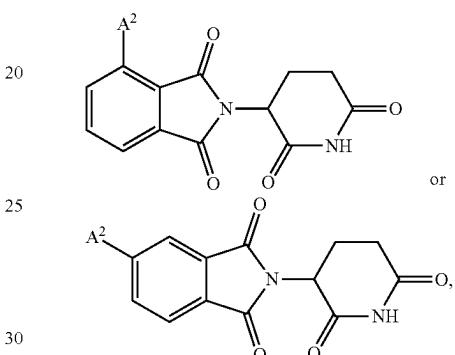
-continued

**88**

-continued

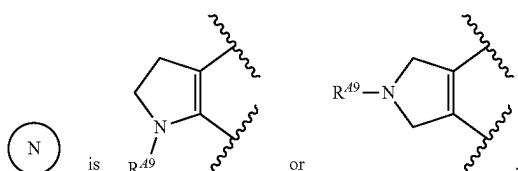


15 In some embodiments, the structure of Formula A is

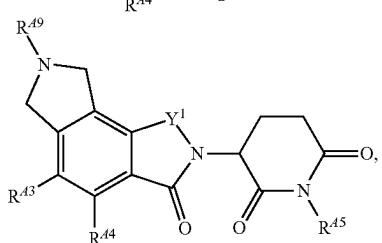
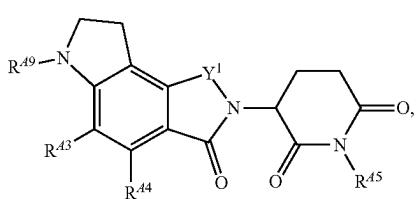


or derivative or analog thereof.

35 In some embodiments,

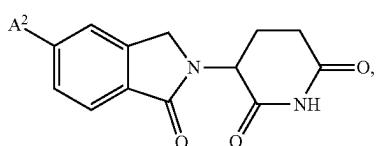
45 where R⁴⁹ is H, A², optionally substituted C₁-C₆ alkyl, or
optionally substituted C₁-C₆ heteroalkyl.

In some embodiments, the structure of Formula A is



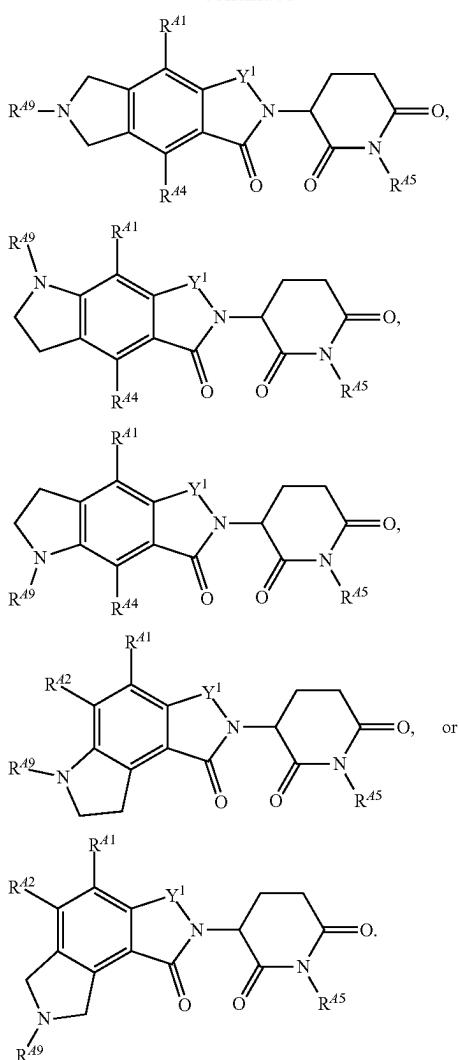
or derivative or analog thereof.

In some embodiments, the structure of Formula A is



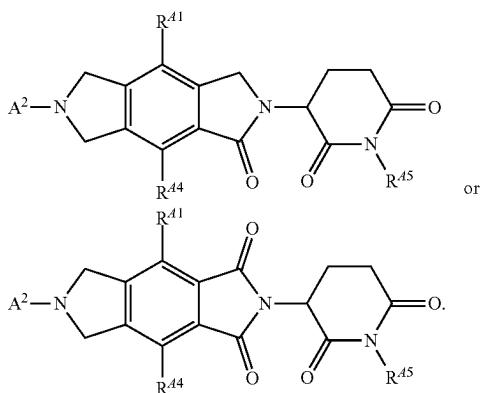
89

-continued

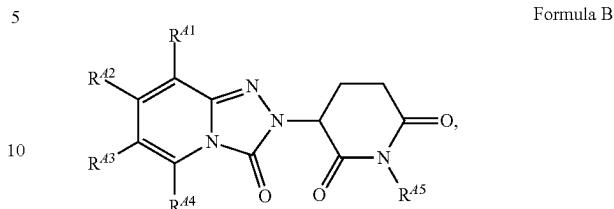


In some embodiments, R⁴⁹ is H, A², or optionally substituted C₁-C₆ alkyl. In some embodiments, R⁴⁹ is H, A², or methyl. In some embodiments, R⁴⁴ is H. In some embodiments, R⁴⁴ is methyl. In some embodiments, R⁴⁹ is A².

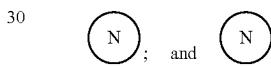
In some embodiments, the structure of Formula A is

**90**

In some embodiments, the structure of Formula AA has the structure of Formula B:



where
 15 R⁴⁵ is H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl;
 each of R⁴¹, R⁴², R⁴³, and R⁴⁴ is, independently, H, A²,
 halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀
 20 carbocycl, optionally substituted C₂-C₉ heterocycl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted —O—C₃-C₆ carbocycl, hydroxyl, thiol, or optionally substituted amino; or R⁴¹ and R⁴², R⁴² and R⁴³, and/or
 25 R⁴³ and R⁴⁴, together with the carbon atoms to which each is attached, combine to form



is optionally substituted C₆-C₁₀ aryl, optionally substituted C₃-C₁₀ carbocycl, optionally substituted C₂-C₉ heteroaryl, or C₂-C₉ heterocycl, any of which is optionally substituted with A², where one of R⁴¹, R⁴², R⁴³, and R⁴⁴ is A², or



is substituted with A², or a pharmaceutically acceptable salt thereof.

In some embodiments, each of R⁴¹, R⁴², R⁴³, and R⁴⁴ is, H, A², halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted —O—C₃-C₆ carbocycl, hydroxyl, optionally substituted amino; or R⁴¹ and R⁴², R⁴² and R⁴³, or R⁴³ and R⁴⁴, together with the carbon atoms to which each is attached, combine to form



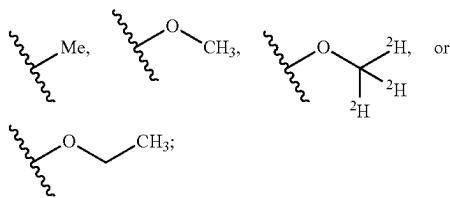
is optionally substituted C₂-C₉ heterocycl, which is optionally substituted with A², where one of R⁴¹, R⁴², R⁴³, and R⁴⁴ is A², or



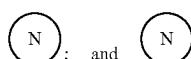
is substituted with A².

91

In some embodiments, each of R⁴¹, R⁴², R⁴³, and R⁴⁴ is, independently, H, A², F,



or R⁴¹ and R⁴², R⁴² and R⁴³, or R⁴³ and R⁴⁴, together with the carbon atoms to which each is attached, combine to form



is optionally substituted C₂-C₉ heterocyclyl, which is optionally substituted with A², where one of R⁴¹, R⁴², R⁴³, and R⁴⁴ is A², or



is substituted with A².

In some embodiments, R⁴¹ is A². In some embodiments, R⁴² is A². In some embodiments, R⁴³ is A². In some embodiments, R⁴⁴ is A². In some embodiments, R⁴⁵ is A².

In some embodiments, R⁴⁵ is H or optionally substituted C₁-C₆ alkyl.

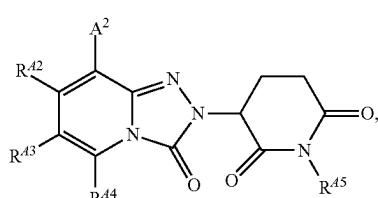
In some embodiments, R⁴⁵ is H or



In some embodiments, R⁴⁵ is H. In some embodiments, R⁴⁵ is



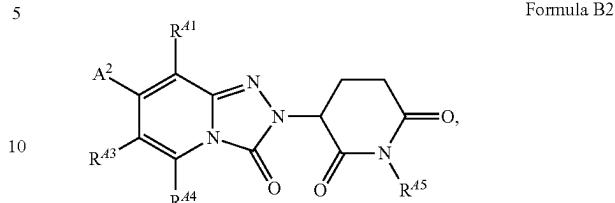
In some embodiments, the structure of Formula B has the structure of Formula B1:



or a pharmaceutically acceptable salt thereof.

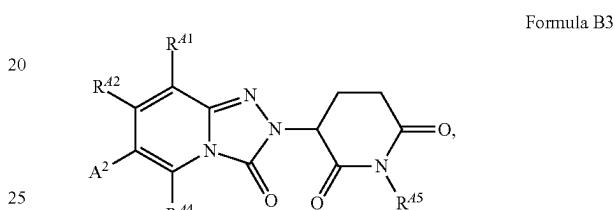
92

In some embodiments, the structure of Formula B has the structure of Formula B2:



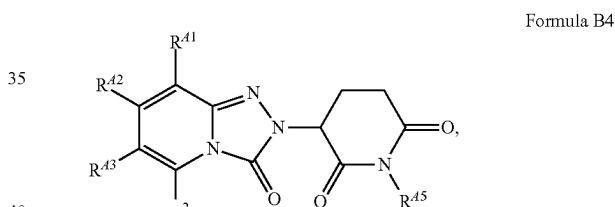
or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of Formula B has the structure of Formula B3:



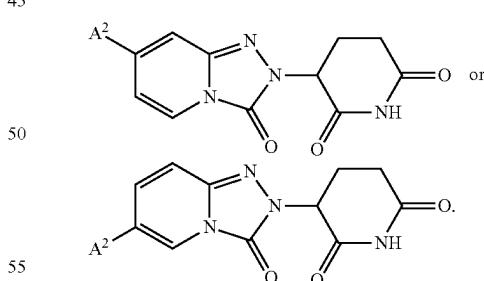
or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of Formula B has the structure of Formula B4:

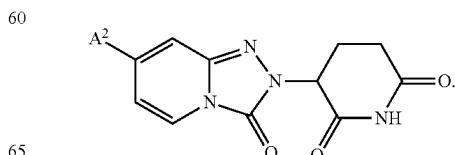


or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of Formula B is

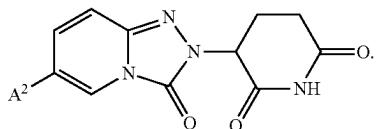


In some embodiments, the structure of Formula B is



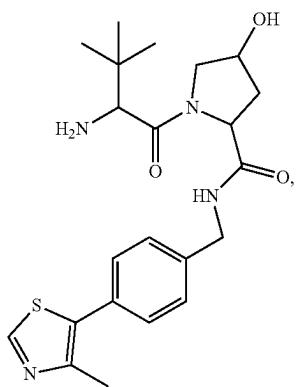
93

In some embodiments, the structure of Formula B is



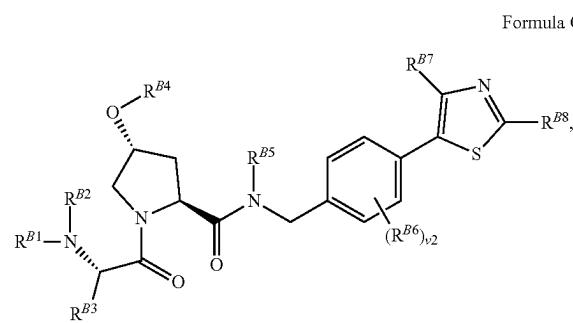
In some embodiments, the ubiquitin ligase binding moiety comprises a von Hippel-Lindau ligand.

In some embodiments, the von Hippel-Lindau ligand has the structure of



or derivative or analog thereof.

In some embodiments, the degradation moiety includes the structure of Formula C:



where

R^{B1} is H, A^2 , optionally substituted C_1 - C_6 alkyl, or optionally substituted C_1 - C_6 heteroalkyl;

R^{B2} is H, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_1 - C_6 heteroalkyl;

R^{B3} is A^2 , optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_1 - C_6 alkyl C_3 - C_{10} carbocyclyl, or optionally substituted C_1 - C_6 alkyl C_6 - C_{10} aryl;

R^{B4} is H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_1 - C_6 alkyl C_3 - C_{10} carbocyclyl, or optionally substituted C_1 - C_6 alkyl C_6 - C_{10} aryl;

94

R^{B5} is H, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_1 - C_6 heteroalkyl;

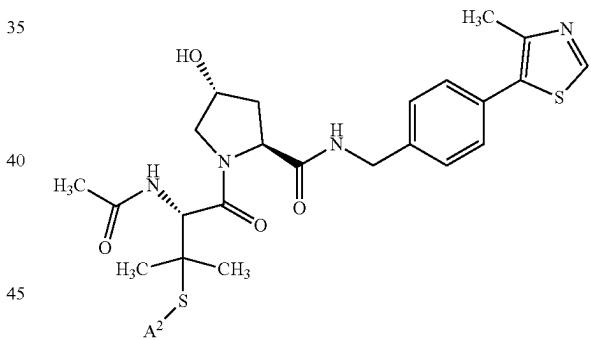
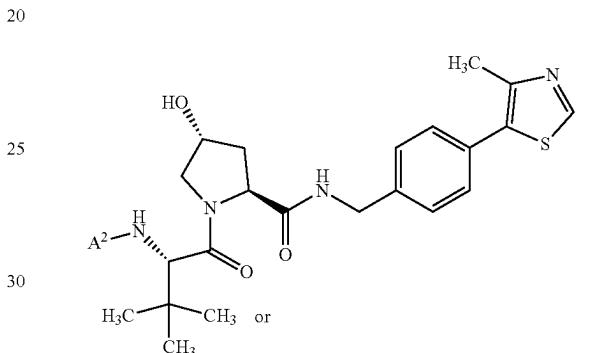
$v2$ is 0, 1, 2, 3, or 4;

each R^{B6} is, independently, halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocycl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino; and

each of R^{B7} and R^{B8} is, independently, H, halogen, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_6 - C_{10} aryl,

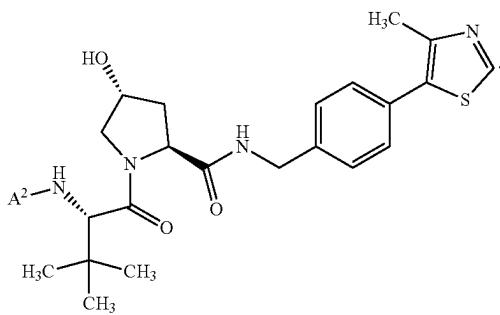
where one of R^{B1} and R^{B3} is A^2 , or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of Formula C is



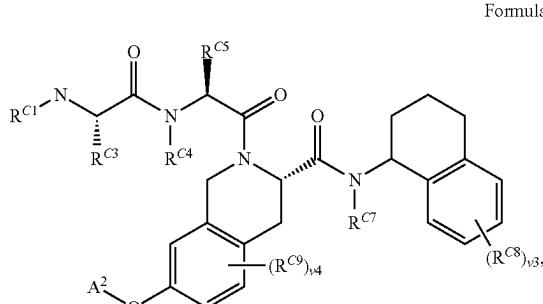
or derivative or analog thereof.

In some embodiments, the structure of Formula C is



95

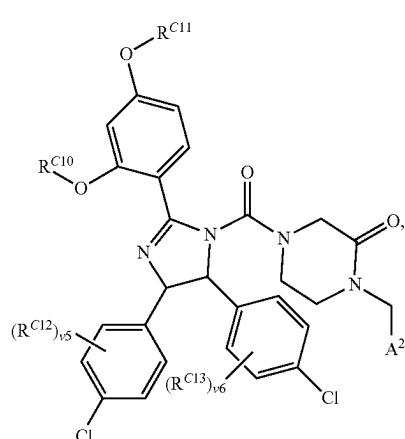
In some embodiments, the degrader moiety includes the structure of Formula D:



Formula D 5

96

In some embodiments, the degrader moiety includes the structure of Formula E:



Formula E

where
 A^2 is a bond between B and the linker;

each of R^{C1}, R^{C2}, and R^{C7} is, independently, H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl;

R^{C3} is optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₁-C₆ alkyl C₃-C₁₀ carbocyclyl, or optionally substituted C₁-C₆ alkyl C₆-C₁₀ aryl;

R^{C5} is optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₁-C₆ alkyl C₃-C₁₀ carbocyclyl, or optionally substituted C₁-C₆ alkyl C₆-C₁₀ aryl;

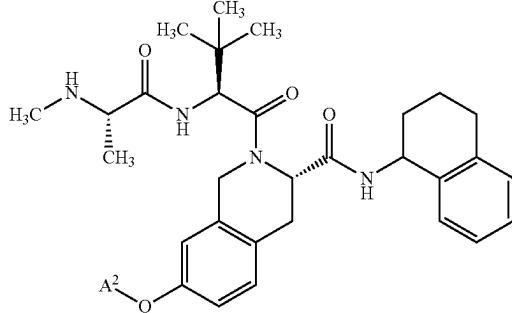
v3 is 0, 1, 2, 3, or 4;

each R^{C8} is, independently, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, hydroxy, thiol, or optionally substituted amino;

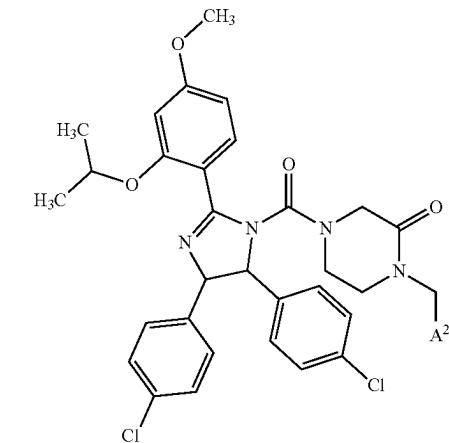
v4 is 0, 1, 2, 3, or 4; and

each R^{C9} is, independently, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, hydroxy, thiol, or optionally substituted amino, or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of Formula D is



50



55

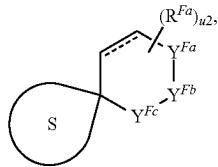
60

65

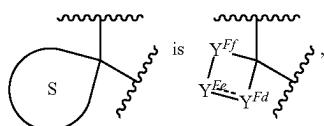
or derivative or analog thereof.

or derivative or analog thereof.

In some embodiments, the degradation moiety includes the structure of Formula FA:



where



or a bicyclic moiety which is substituted with A^2 and substituted with one or more groups independently selected from H, R^{FF1} , and oxo;

\equiv is a single bond or a double bond;

$u2$ is 0, 1, 2, or 3;

A^2 is a bond between the degrader and the linker;

Y^{Fa} is $CR^{Fd}R^{Fc}$, $C=O$, $C=S$, $C=CH_2$, SO_2 , $S(O)$, $P(O)Oalkyl$, $P(O)NHalkyl$, $P(O)N(alkyl)_2$, $P(O)alkyl$, $P(O)OH$, $P(O)NH_2$;

Y^{Fb} is NH , NR^{FF1} , CH_2 , CHR^{FF1} , $C(R^{FF1})_2$, O , or S ;

Y^{Fc} is $CR^{Fd}R^{Fe}$, $C=O$, $C=S$, $C=CH_2$, SO_2 , $S(O)$, $P(O)Oalkyl$, $P(O)NHalkyl$, $P(O)N(alkyl)_2$, $P(O)alkyl$, $P(O)OH$, $P(O)NH_2$;

each of R^{Fd} , R^{Fc} , R^{Fd} , and R^{Fe} is, independently, H, alkyl, aliphatic, heteroaliphatic, aryl, heteroaryl, carbocyclyl, hydroxyl, alkoxy, amino, $-NHalkyl$, or $-Nalkyl_2$;

or R^{Fd} and R^{Fc} , together with the carbon atom to which each is attached, combine to form a 3-, 4-, 5-, or 6-membered spirocarbocyclene, or a 4-, 5-, or 6-membered spiroheterocyclene comprising 1 or 2 heteroatoms selected from N and O;

or R^{Fd} and R^{Fe} , together with the carbon atom to which each is attached, combine to form a 3-, 4-, 5-, or 6-membered spirocarbocyclene, or a 4-, 5-, or 6-membered spiroheterocyclene comprising 1 or 2 heteroatoms selected from N and O; and

or R^{Fd} and R^{Fc} , together with the carbon atoms to which each is attached, combine to form a 1, 2, 3, or 4 carbon bridged ring;

each of Y^{Fd} and Y^{Fc} is, independently, CH_2 , CHR^{FF2} , $C(R^{FF2})_2$, $C(O)$, N , NH , NR^{FF3} , O , S , or $S(O)$;

Y^{Fe} is a bond or a divalent moiety attached to Y^{Fd} and Y^{Fc} that contains 1 to 5 contiguous carbon atoms that form a 3 to 8-membered ring,

wherein 1, 2, or 3 carbon atoms can be replaced with a nitrogen, oxygen, or sulfur atom;

wherein one of the ring atoms is substituted with A^2 and the others are substituted with one or more groups independently selected from H and R^{FF1} ; and

wherein the contiguous atoms of Y^{Fe} can be attached through a single or double bond;

each R^{FF1} is, independently, H, alkyl, alkenyl, alkynyl, aliphatic, heteroaliphatic, carbocyclyl, halogen, hydroxyl, amino, cyano, alkoxy, aryl, heteroaryl, heterocyclyl, alkylamino, alkylhydroxyl, or haloalkyl;

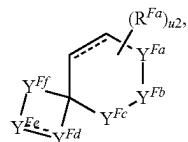
Formula FA

each R^{FF2} is, independently, alkyl, alkene, alkyne, halogen, hydroxyl, alkoxy, azide, amino, $-C(O)H$, $-C(O)OH$, $-C(O)(aliphatic, including alkyl)$, $-C(O)O(aliphatic, including alkyl)$, $-NH(aliphatic, including alkyl)$, $-N(aliphatic including alkyl)(aliphatic including alkyl)$, $-NHSO_2alkyl$, $-N(alkyl)SO_2alkyl$, $-NHSO_2aryl$, $-N(alkyl)SO_2aryl$, $-NHSO_2alkenyl$, $-N(alkyl)SO_2alkenyl$, $-N(alkyl)SO_2alkynyl$, $-N(alkyl)SO_2alkynyl$, aliphatic, heteroaliphatic, aryl, heteroaryl, heterocyclic, carbocyclic, cyano, nitro, nitroso, $-SH$, $-Salkyl$, or haloalkyl; and

R^{FF3} is alkyl, alkenyl, alkynyl, $-C(O)H$, $-C(O)OH$, $-C(O)alkyl$, or $-C(O)Oalkyl$,

wherein if Y^{Fd} or Y^{Fc} is substituted with A^2 , then Y^{Fe} is a bond, or a pharmaceutically acceptable salt thereof.

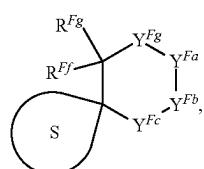
In some embodiments, the compound of Formula FA has the structure of Formula FA1:



Formula FA1

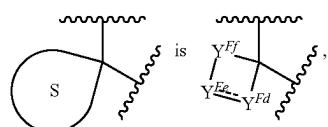
or a pharmaceutically acceptable salt thereof.

In some embodiments, the degradation moiety includes the structure of Formula FB:



Formula FB

where



or a bicyclic moiety which is substituted with A^2 and substituted with one or more groups independently selected from H, R^{FF1} , and oxo;

A^2 is a bond between the degrader and the linker;

Y^{Fa} is $CR^{Fd}R^{Fc}$, $C=O$, $C=S$, $C=CH_2$, SO_2 , $S(O)$, $P(O)Oalkyl$, $P(O)NHalkyl$, $P(O)N(alkyl)_2$, $P(O)alkyl$, $P(O)OH$, $P(O)NH_2$;

each of Y^{Fd} and Y^{Fc} is, independently, NH, NR^{FF1} , CH_2 , CHR^{FF1} , $C(R^{FF1})_2$, O , or S ;

Y^{Fc} is $CR^{Fd}R^{Fe}$, $C=O$, $C=S$, $C=CH_2$, SO_2 , $S(O)$, $P(O)Oalkyl$, $P(O)NHalkyl$, $P(O)N(alkyl)_2$, $P(O)alkyl$, $P(O)OH$, $P(O)NH_2$;

each of R^{Fd} , R^{Fc} , R^{Fd} , R^{Fe} , R^{Fg} , and R^{Fh} is, independently, H, alkyl, aliphatic, heteroaliphatic, aryl, heteroaryl, carbocyclyl, hydroxyl, alkoxy, amino, $-NHalkyl$, or $-Nalkyl_2$;

99

or R^{Fb} and R^{Fc} , together with the carbon atom to which each is attached, combine to form a 3-, 4-, 5-, or 6-membered spirocarbocyclene, or a 4-, 5-, or 6-membered spiroheterocyclene comprising 1 or 2 heteroatoms selected from N and O;

or R^{Fd} and R^{Fe} , together with the carbon atom to which each is attached, combine to form a 3-, 4-, 5-, or 6-membered spirocarbocyclene, or a 4-, 5-, or 6-membered spiroheterocyclene comprising 1 or 2 heteroatoms selected from N and O;

or R^{Ff} and R^{Fg} , together with the carbon atom to which each is attached, combine to form a 3-, 4-, 5-, or 6-membered spirocarbocyclene, or a 4-, 5-, or 6-membered spiroheterocyclene comprising 1 or 2 heteroatoms selected from N and O;

or R^{Fd} and R^{Fb} , together with the carbon atoms to which each is attached, combine to form a 1, 2, 3, or 4 carbon bridged ring;

or R^{Fd} and R^{Ff} , together with the carbon atoms to which each is attached, combine to form a 1, 2, 3, or 4 carbon bridged ring;

or R^{Fb} and R^{Fg} , together with the carbon atoms to which each is attached, combine to form a 1, 2, 3, or 4 carbon bridged ring;

each of Y^{Fd} and Y^{Ff} is, independently, CH_2 , CHR^{FF2} , $\text{C}(\text{R}^{FF2})_2$, $\text{C}(\text{O})$, N , NH , NR^{FF3} , O , S , or $\text{S}(\text{O})$;

Y^{Fe} is a bond or a divalent moiety attached to Y^{Fd} and Y^{Ff} that contains 1 to 5 contiguous carbon atoms that form a 3 to 8-membered ring,

wherein 1, 2, or 3 carbon atoms can be replaced with a nitrogen, oxygen, or sulfur atom;

wherein one of the ring atoms is substituted with A^2 and

the others are substituted with one or more groups independently selected from H and R^{FF1} ; and

wherein the contiguous atoms of Y^{Fe} can be attached through a single or double bond;

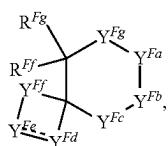
each R^{FF1} is, independently, H, alkyl, alkenyl, alkynyl, aliphatic, heteroaliphatic, carbocyclen, halogen, hydroxyl, amino, cyano, alkoxy, aryl, heteroaryl, heterocyclen, alkylamino, alkylhydroxyl, or haloalkyl;

each R^{FF2} is, independently, alkyl, alkene, alkyne, halogen, hydroxyl, alkoxy, azide, amino, $-\text{C}(\text{O})\text{H}$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})(\text{aliphatic, including alkyl})$, $-\text{C}(\text{O})\text{O}(\text{aliphatic, including alkyl})$, $-\text{NH}(\text{aliphatic, including alkyl})$, $-\text{N}(\text{aliphatic including alkyl})(\text{aliphatic including alkyl})$, $-\text{NHSO}_2\text{alkyl}$, $-\text{N}(\text{alkyl})\text{SO}_2\text{alkyl}$, $-\text{NHSO}_2\text{aryl}$, $-\text{N}(\text{alkyl})\text{SO}_2\text{aryl}$, $-\text{NHSO}_2\text{alkenyl}$, $-\text{N}(\text{alkyl})\text{SO}_2\text{alkenyl}$, $-\text{NHSO}_2\text{alkynyl}$, $-\text{N}(\text{alkyl})\text{SO}_2\text{alkynyl}$, aliphatic, heteroaliphatic, aryl, heteroaryl, heterocyclic, carbocyclic, cyano, nitro, nitroso, $-\text{SH}$, $-\text{Salkyl}$, or haloalkyl; and

R^{FF3} is alkyl, alkenyl, alkynyl, $-\text{C}(\text{O})\text{H}$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{alkyl}$, or $-\text{C}(\text{O})\text{Oalkyl}$,

wherein if Y^{Fd} or Y^{Ff} is substituted with A^2 , then Y^{Fe} is a bond, or a pharmaceutically acceptable salt thereof.

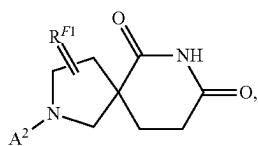
In some embodiments, the compound of Formula FB has the structure of Formula FB1:



Formula FB1 60

100

In some embodiments, the degradation moiety includes the structure of Formula F1:



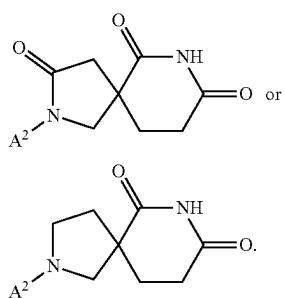
Formula F1

5

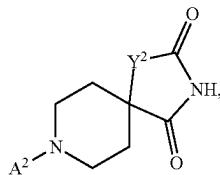
where A^2 is a bond between the degrader and the linker; and R^{F1} is absent or O, or a pharmaceutically acceptable salt thereof.

In some embodiments, R^{F1} is absent. In some embodiments, R^{F1} is O.

In some embodiments, the structure of Formula F1 is



In some embodiments, the degradation moiety includes the structure Formula F2:



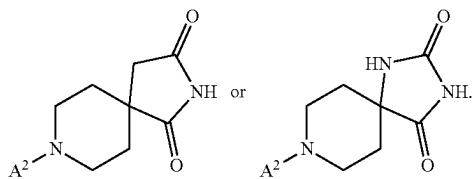
Formula F2

40

where A^2 is a bond between the degrader and the linker; and Y^2 is CH_2 or NH, or a pharmaceutically acceptable salt thereof.

In some embodiments, Y^2 is NH. In some embodiments, Y^2 is CH_2 .

In some embodiments, structure of Formula F2 is

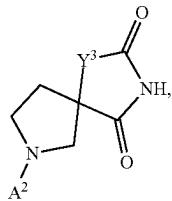


65

or a pharmaceutically acceptable salt thereof.

101

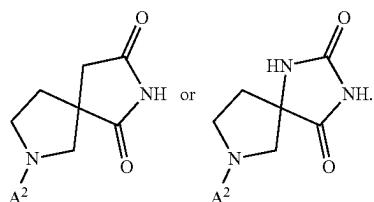
In some embodiments, the degradation moiety includes the structure Formula G:



where A^2 is a bond between the degrader and the linker; and Y^3 is CH_2 or NH , or a pharmaceutically acceptable salt thereof.

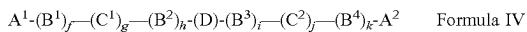
In some embodiments, Y^3 is NH . In some embodiments, Y^3 is CH_2 .

In some embodiments, structure of Formula G is



The degradation moiety may also include structures found in, e.g., WO2017/197036; WO2019/204354, WO2019/236483, WO2020/010177; and WO2020/010227, the structures of which are herein incorporated by reference.

In some embodiments, the linker has the structure of Formula IV:



where

A^1 is a bond between the linker and A;

A^2 is a bond between B and the linker;

each of B^1 , B^2 , B^3 , and B^4 is, independently, optionally substituted C_{1-2} alkylene, optionally substituted C_{1-3} heteroalkylene, O, S, S(O)_2 , or NR^N ;

each R^N is, independently, H, optionally substituted C_{1-4} alkyl, optionally substituted C_{2-4} alkenyl, optionally substituted C_{2-4} alkynyl, optionally substituted C_{2-6} heterocyclyl, optionally substituted C_{6-12} aryl, or optionally substituted C_{1-7} heteroalkyl;

each of C^1 and C^2 is, independently, carbonyl, thiocarbonyl, sulphonyl, or phosphoryl;

each of f, g, h, i, j, and k is, independently, 0 or 1; and

D is optionally substituted C_{1-10} alkylene, optionally substituted C_{2-10} alkenylene, optionally substituted C_{2-10} alkynylene, optionally substituted C_{2-6} heterocyclene, optionally substituted C_{6-12} arylene, optionally substituted C_{2-10} polyethylene glycol, or optionally substituted C_{1-10} heteroalkylene, or a chemical bond linking $\text{A}^1\text{-}(\text{B}^1)_f\text{-}(\text{C}^1)_g\text{-}(\text{B}^2)_h\text{-}$ to $\text{-}(\text{B}^3)_i\text{-}(\text{C}^2)_j\text{-}(\text{B}^4)_k\text{-}\text{A}^2$.

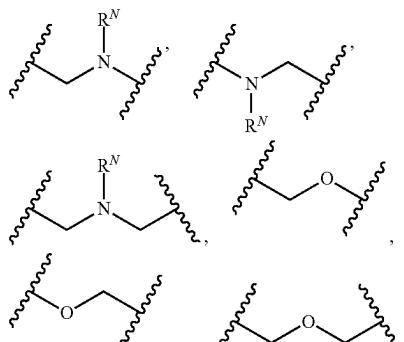
In some embodiments, each of B^1 , B^2 , B^3 , and B^4 is, independently, optionally substituted C_{1-4} alkylene, optionally substituted C_{1-4} heteroalkylene, or NR^N .

In some embodiments, each R^N is, independently, H or optionally substituted C_{1-4} alkylene.

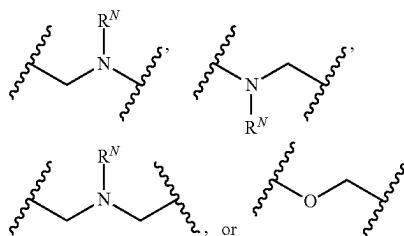
In some embodiments, each R^N is, independently, H or methyl.

102

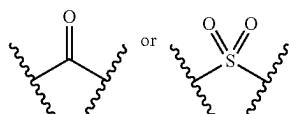
In some embodiments, each of B^1 and B^4 is, independently,



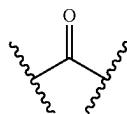
In some embodiments, B^1 is



In some embodiments, each of C^1 and C^2 is, independently,



In some embodiments, C^1 is

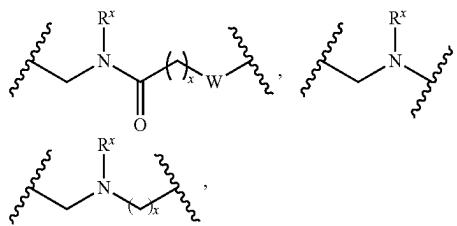


In some embodiments, B^2 is NR^N . In some embodiments, B^2 is optionally substituted C_{1-4} alkylene.

In some embodiments, f is 0. In some embodiments, f is

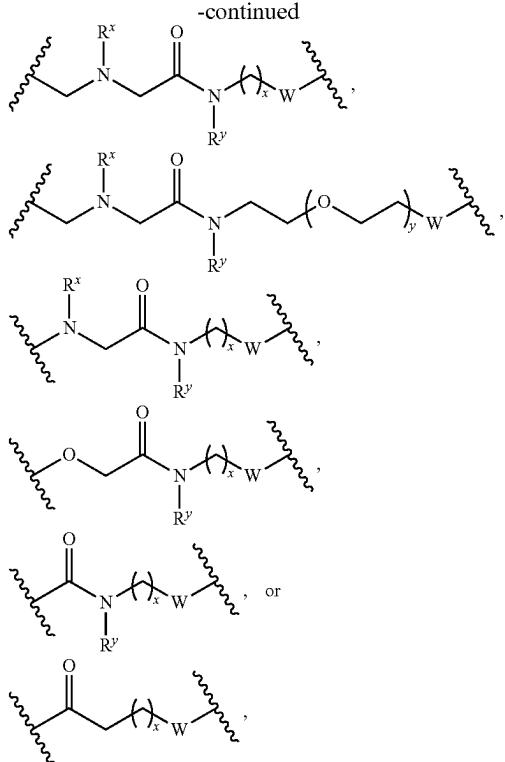
1. In some embodiments, g is 1. In some embodiments, h is 0. In some embodiments, h is 1. In some embodiments, i is 0. In some embodiments, j is 0. In some embodiments, k is 0.

In some embodiments, the linker has the structure of

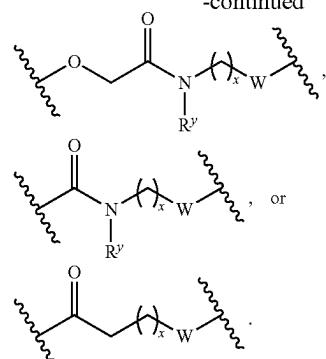


103

-continued

**104**

-continued



wherein

 x is 1, 2, 3, 4, 5, 6, 7, or 8; y is 1, 2, 3, or 4;

R^x is H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, or optionally substituted C_3 - C_6 carbocyclyl; ³⁵

R^y is H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, or optionally substituted C_3 - C_6 carbocyclyl; and ⁴⁰

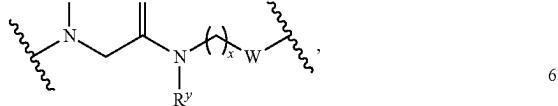
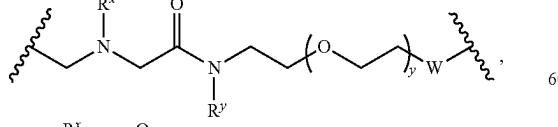
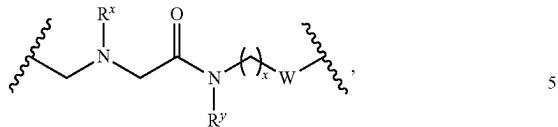
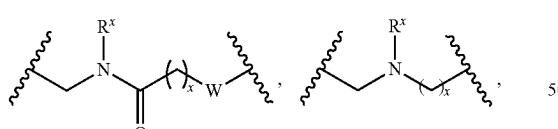
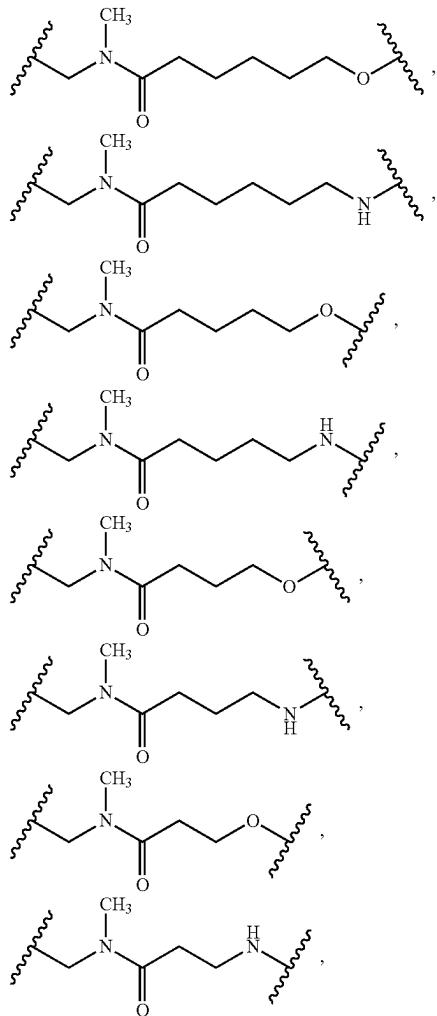
W is O or NR^w , wherein R^w is H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, or optionally substituted C_3 - C_6 carbocyclyl.

In some embodiments, the linker has the structure of

In some embodiments, R^x is H or me optionally substituted C_1 - C_6 alkyl. In some embodiments, R^y is H or optionally substituted C_1 - C_6 alkyl. In some embodiments, R^w is H or optionally substituted C_1 - C_6 alkyl. ²⁰

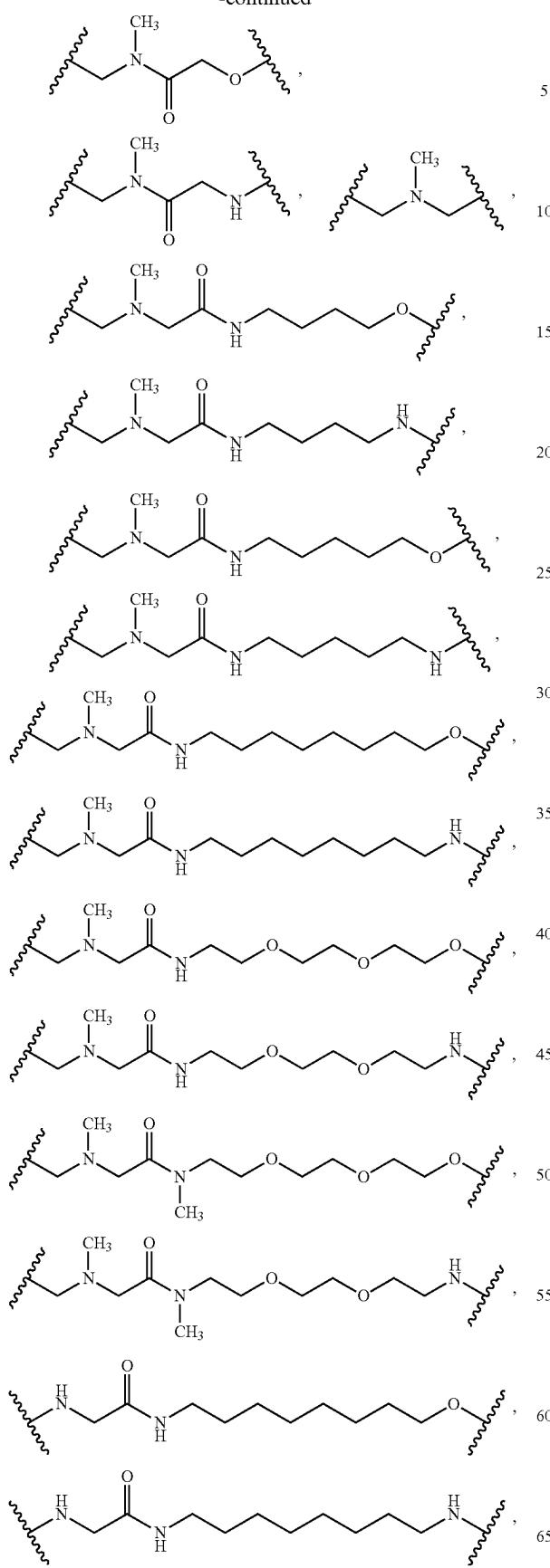
In some embodiments, R^x is H or methyl. In some embodiments, R^y is H or methyl. In some embodiments, R^w is H or methyl. ²⁵

In some embodiments, the linker has the structure of

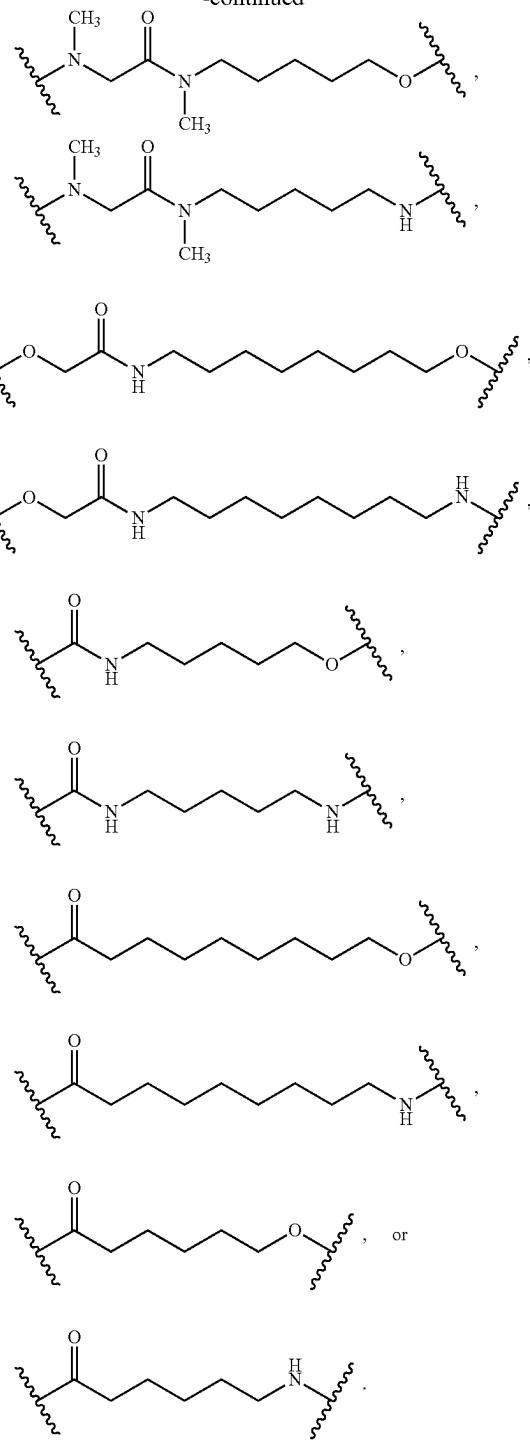


105

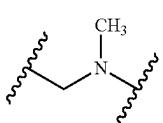
-continued

**106**

-continued

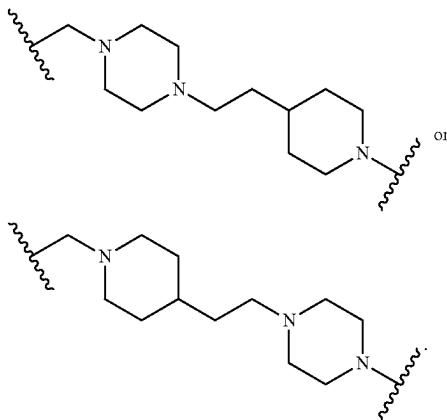


In some embodiments, the linker has the structure of

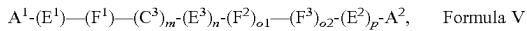


107

In some embodiments, the linker has the structure of



In some embodiments, the linker has the structure of Formula V:



where

A^1 is a bond between the linker and A;

A^2 is a bond between B and the linker;

each of m, n, o1, o2, and p is, independently, 0 or 1;

each of E^1 and E^2 is, independently, O, S, NR^N , optionally substituted C_{1-10} alkylene, optionally substituted C_{2-10} alkynylene, optionally substituted C_{2-10} alkynylene, optionally substituted C_{2-10} polyethylene glycol, or optionally substituted C_{1-10} heteroalkylene;

E^3 is optionally substituted C_1-C_6 alkylene, optionally substituted C_1-C_6 heteroalkylene, O, S, or NR^N ;

each R^N is, independently, H, optionally substituted C_{1-4} alkyl, optionally substituted C_{2-4} alkenyl, optionally substituted C_{2-4} alkynyl, optionally substituted C_{2-6} heterocycl, optionally substituted C_{6-12} aryl, or optionally substituted C_{1-7} heteroalkyl;

C^3 is carbonyl, thiocarbonyl, sulphonyl, or phosphoryl; and

each of F^1 , F^2 , and F^3 is, independently, optionally substituted C_3-C_{10} carbocyclylene, optionally substituted C_{2-10} heterocyclylene, optionally substituted C_6-C_{10} arylene, or optionally substituted C_2-C_9 heteroarylene.

In some embodiments, the linker has the structure of Formula Va:



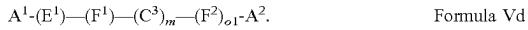
In some embodiments, the linker has the structure of Formula Vb:



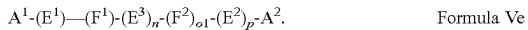
In some embodiments, the linker has the structure of Formula Vc:



In some embodiments, the linker has the structure of Formula Vd:

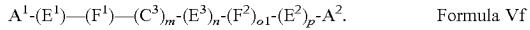


In some embodiments, the linker has the structure of Formula Ve:



108

In some embodiments, the linker has the structure of Formula Vf:



In some embodiments, the linker has the structure of Formula Vg:

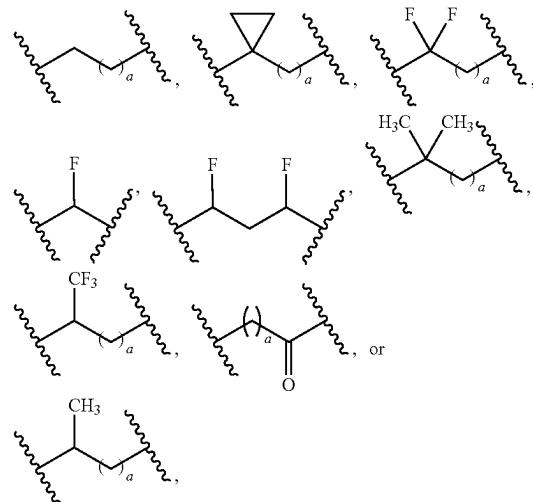


In some embodiments, each of E^1 and E^2 is, independently, NR^N , optionally substituted C_{1-10} alkylene, optionally substituted C_{2-10} polyethylene glycolene, or optionally substituted C_{1-10} heteroalkylene.

In some embodiments, E^3 is optionally substituted C_1-C_6 alkylene, O, S, or NR^N ; In some embodiments, E^3 is optionally substituted C_1-C_6 alkylene. In some embodiments, E^3 is optionally substituted C_1-C_3 alkylene. In some embodiments, E^3 is O, S, or NR^N .

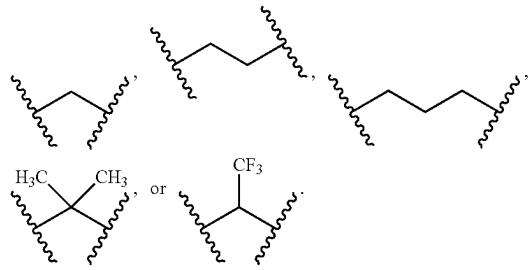
In some embodiments, E^3 is C_1-C_6 alkylene. In some embodiments, E^3 is C_1-C_3 alkylene. In some embodiments, E^3 is O.

In some embodiments, E^3 is



where a is 0, 1, 2, 3, 4, or 5.

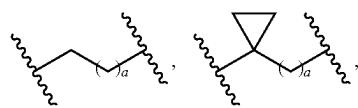
In some embodiments, E^3 is



In some embodiments, each R^N is, independently, H or optionally substituted C_{1-4} alkyl.

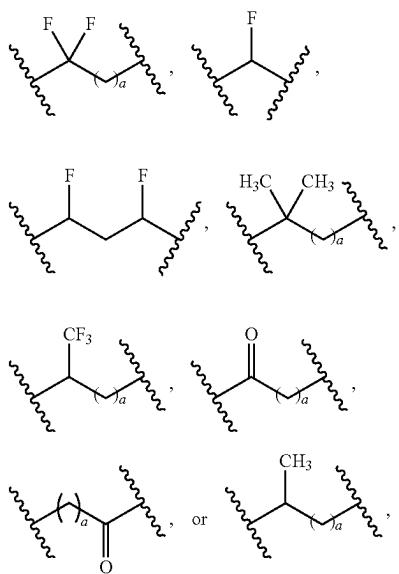
In some embodiments, each R^N is, independently, H or methyl.

In some embodiments, E^1 is



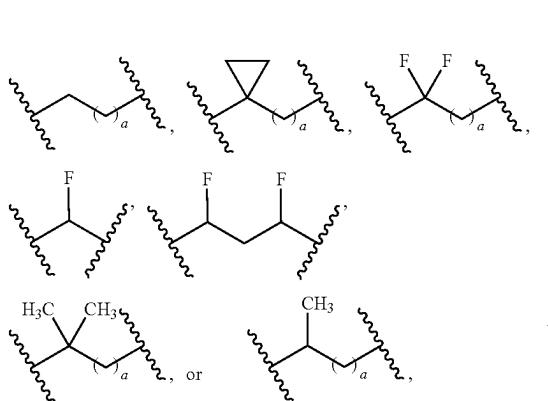
109

-continued



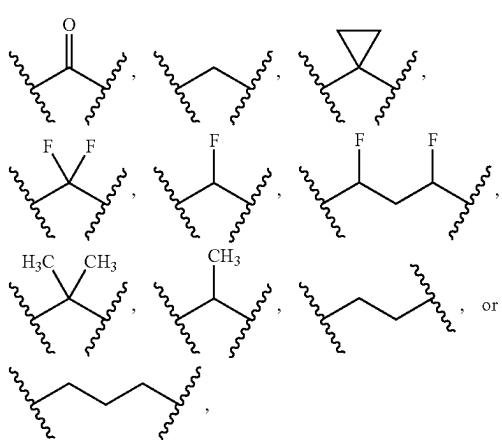
where a is 0, 1, 2, 3, 4, or 5.

In some embodiments, E¹ is



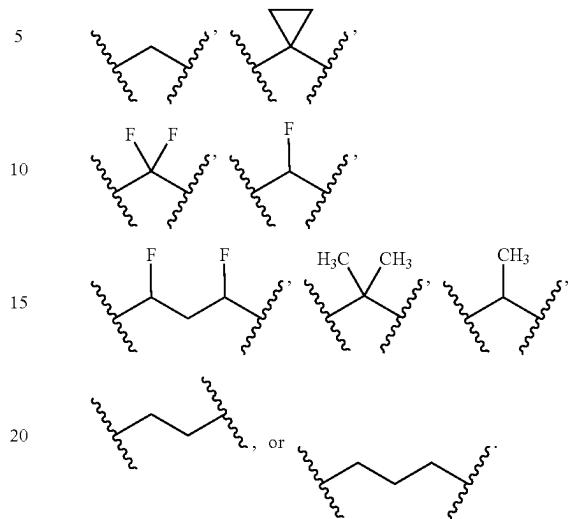
where a is 0, 1, 2, 3, 4, or 5.

In some embodiments, E¹ is

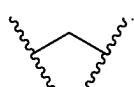


110

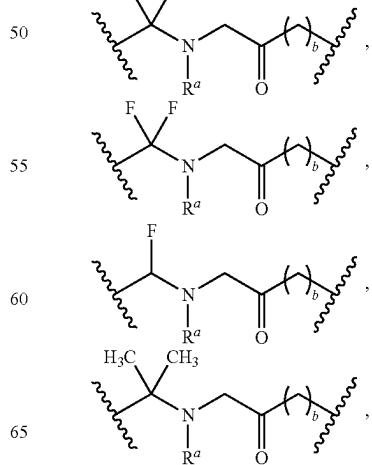
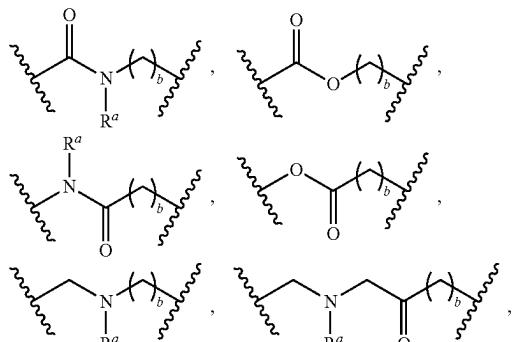
In some embodiments, E¹ is



25 In some embodiments, E¹ is

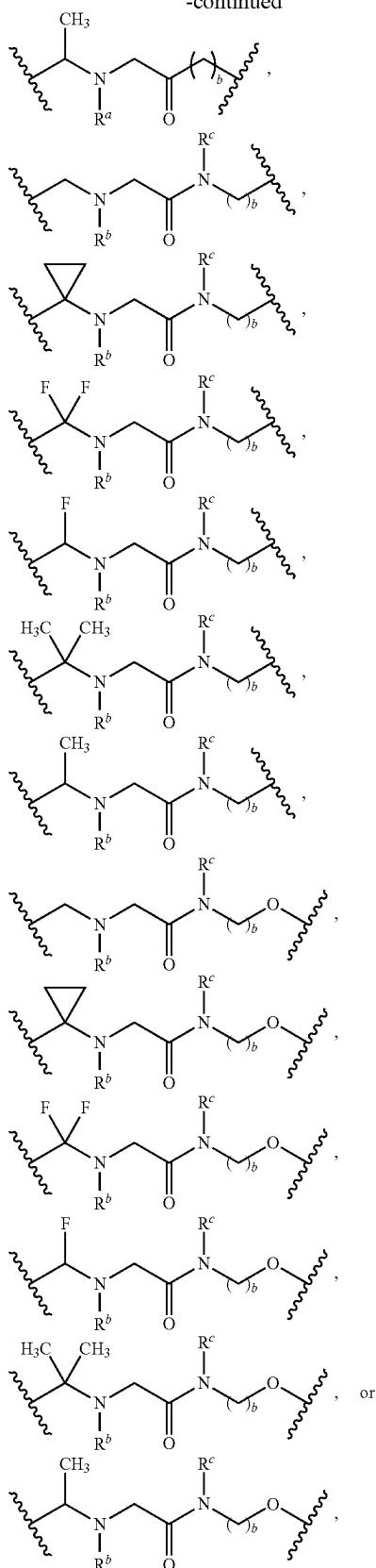


In some embodiments, E¹ is



111

-continued



where

where

b is 0, 1, 2, 3, 4, 5, or 6;

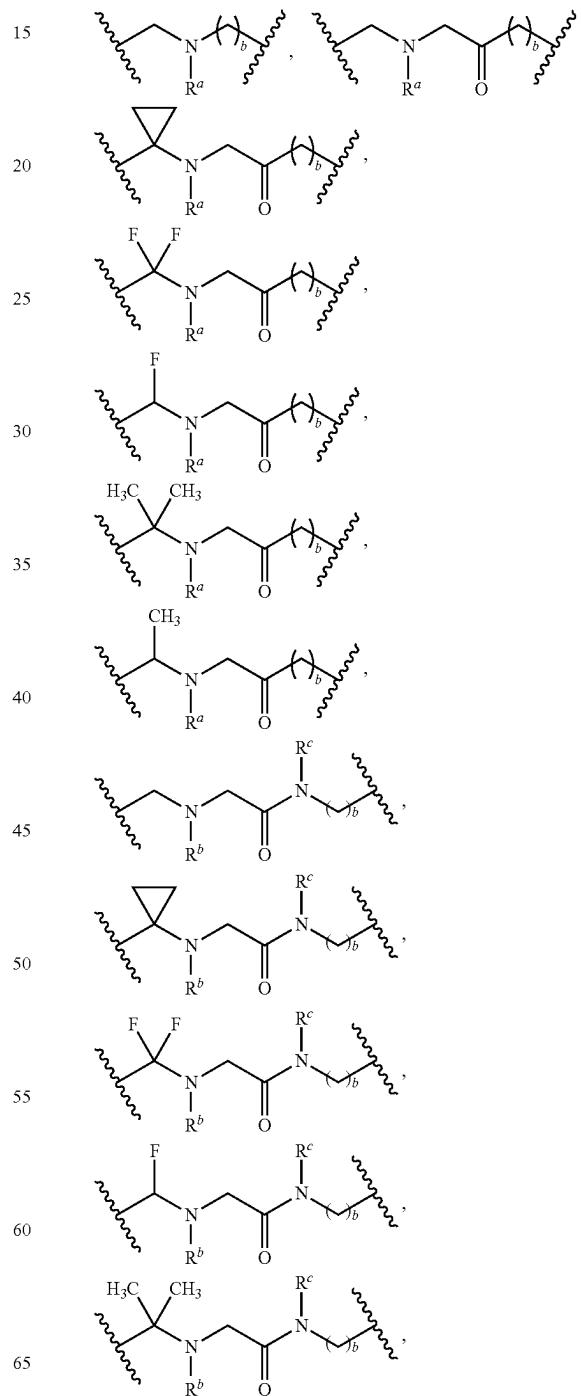
112

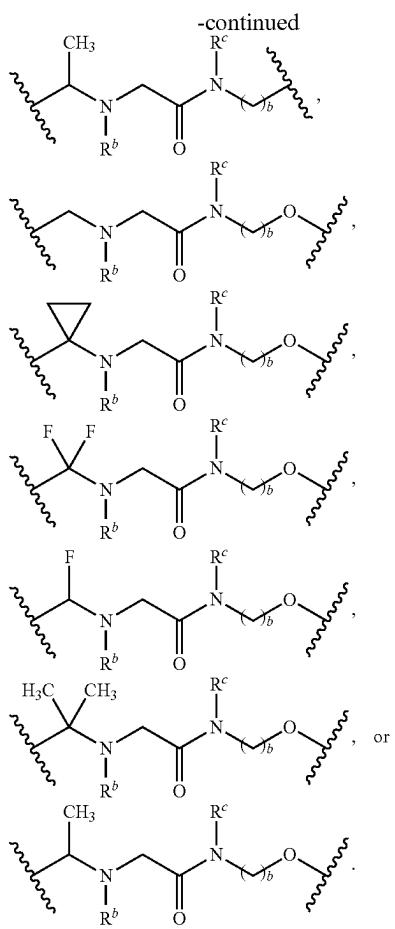
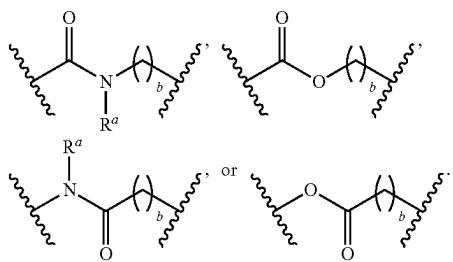
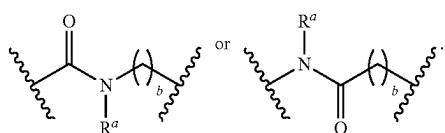
R^a is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₆ carbocyclyl;

⁵ R^b is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₆ carbocyclyl; and

R^c is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₆ carbocyclyl.

In some embodiments, E¹ is



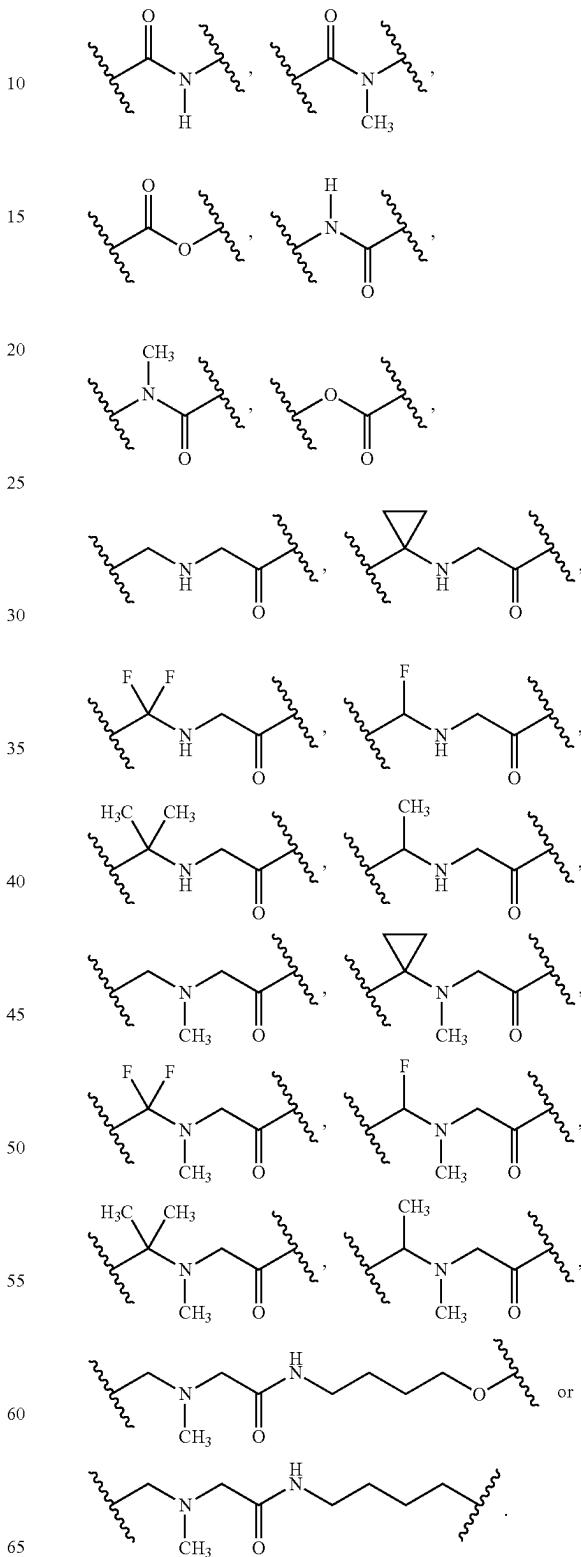
113In some embodiments, E¹ isIn some embodiments, E¹ is

In some embodiments, R^a is H or optionally substituted C₁-C₆ alkyl. In some embodiments, R^b is H or optionally substituted C₁-C₆ alkyl. In some embodiments, R^c is H or optionally substituted C₁-C₆ alkyl.

In some embodiments, R^a is H or methyl. In some 65 embodiments, R^b is H or methyl. In some embodiments, R^c is H or methyl.

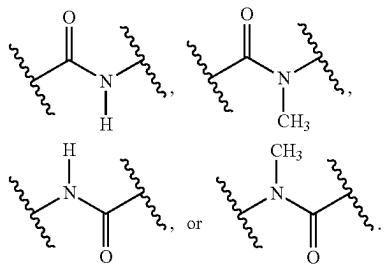
114

In some embodiments, b is 0, 1, 2, or 3. In some embodiments, b is 0. In some embodiments, b is 1. In some embodiments, b is 2. In some embodiments, b is 3.

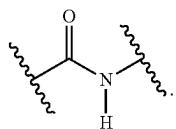
In some embodiments, E¹ is

115

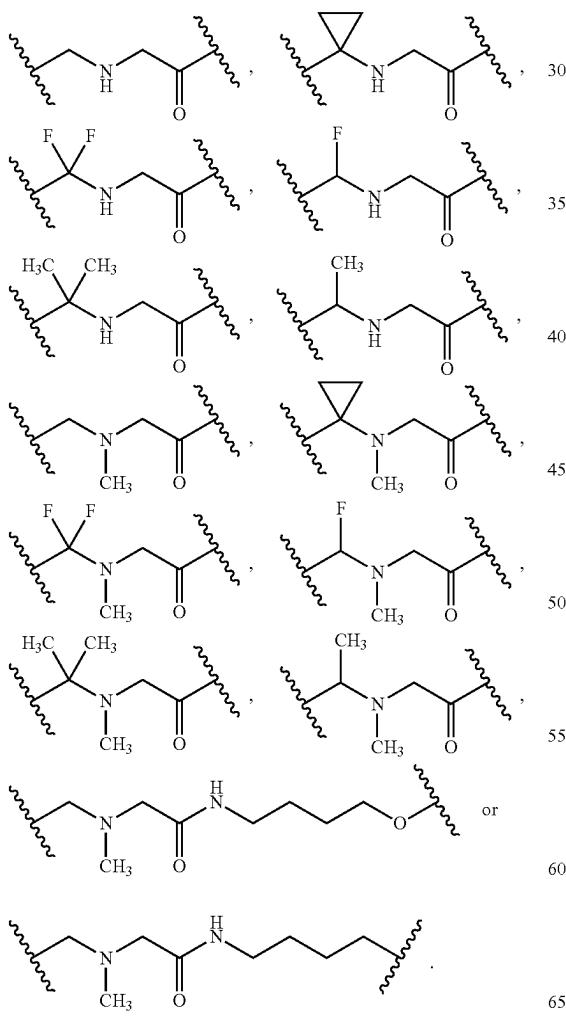
In some embodiments, E¹ is



In some embodiments, E¹ is

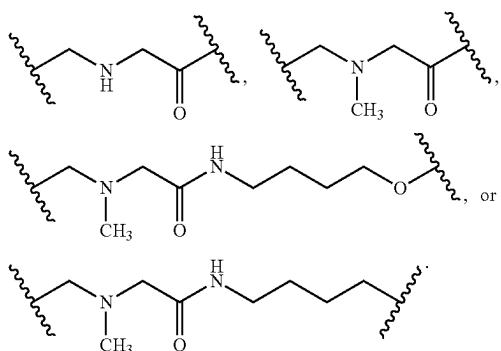


In some embodiments, E¹ is

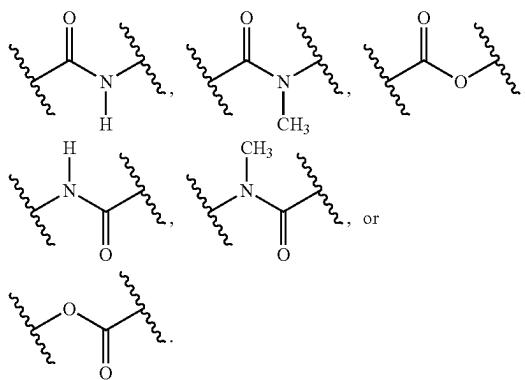


116

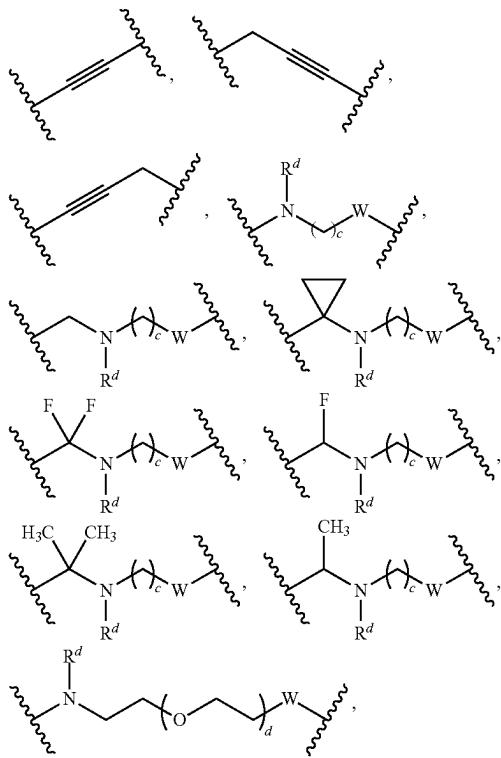
In some embodiments, E¹ is



In some embodiments, E¹ is

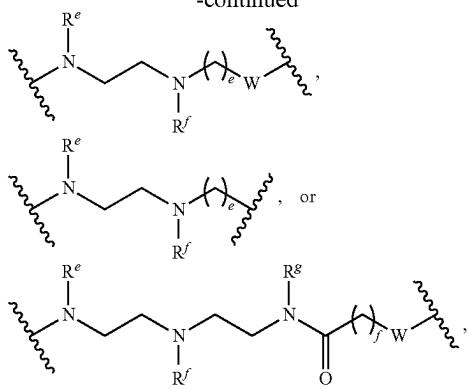


In some embodiments, E² is O, NR^w,



117

-continued



wherein

c is 0, 1, 2, 3, 4, 5, 6, 7, or 8;

d is 0, 1, 2, or 3;

e is 0, 1, 2, 3, 4, 5, or 6;

f is 0, 1, 2, 3, or 4;

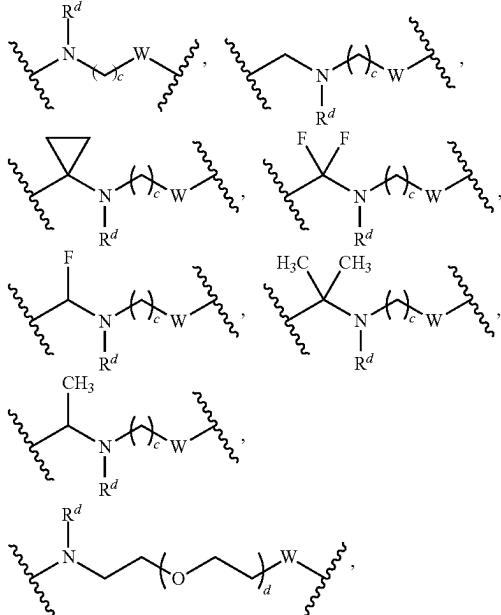
R^d is H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, or optionally substituted C_3 - C_6 carbocyclyl; 25

R^e is H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, or optionally substituted C_3 - C_6 carbocyclyl;

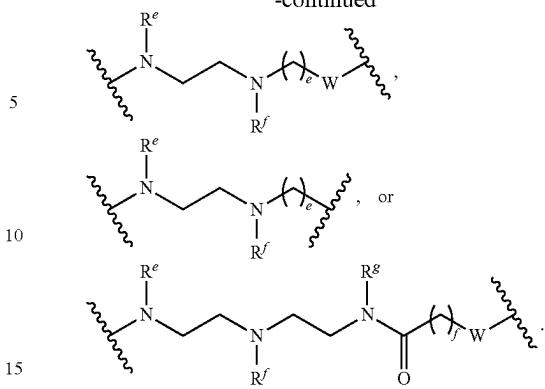
R^f is H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, or optionally substituted C_3 - C_6 carbocyclyl;

R^g is H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, or optionally substituted C_3 - C_6 carbocyclyl; and

W is O or NR^w , wherein R^w is H or optionally substituted C_1 - C_6 alkyl.

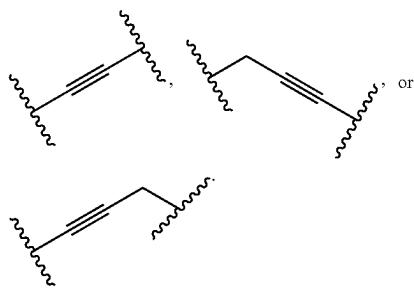
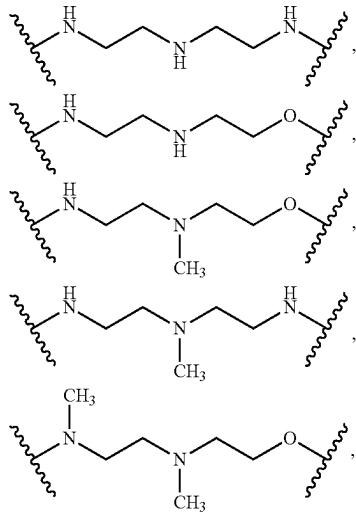
In some embodiments, E^2 is O, NR^w ,**118**

-continued



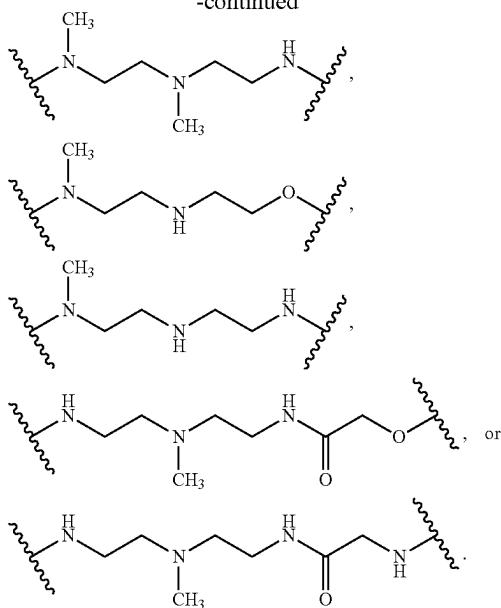
In some embodiments, R^d is H or optionally substituted C_1 - C_6 alkyl. In some embodiments, R^e is H or optionally substituted C_1 - C_6 alkyl. In some embodiments, R^f is H or optionally substituted C_1 - C_6 alkyl. In some embodiments, R^g is H or optionally substituted C_1 - C_6 alkyl. In some embodiments, R^w is H or optionally substituted C_1 - C_6 alkyl.

In some embodiments, R^d is H or methyl. In some embodiments, R^e is H or methyl. In some embodiments, R^f is H or methyl. In some embodiments, R^g is H or methyl. In some embodiments, R^w is H or methyl.

In some embodiments, E^2 isIn some embodiments, E^2 is O,

119

-continued



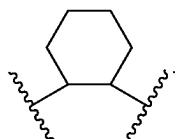
In some embodiments, each of F¹, F², or F³ is, independently, optionally substituted C₃-C₁₀ carbocyclene.

In some embodiments, the C₃-C₁₀ carbocyclene is monocyclic. In some embodiments, the C₃-C₁₀ carbocyclene is polycyclic.

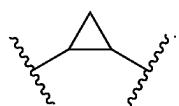
In some embodiments, the C₃-C₁₀ carbocyclene is bicyclic.

In some embodiments, the C₃-C₁₀ carbocyclene is bridged. In some embodiments, the C₃-C₁₀ carbocyclene is fused. In some embodiments, the C₃-C₁₀ carbocyclene is spirocyclic.

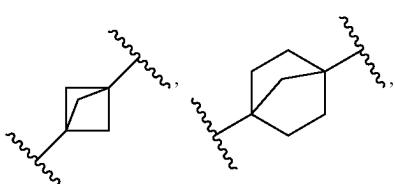
In some embodiments, the C₃-C₁₀ carbocyclene is



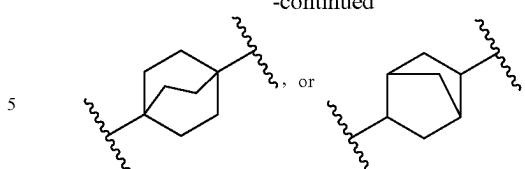
In some embodiments, F² is



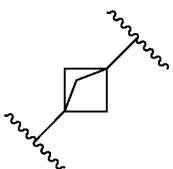
In some embodiments, the C₃-C₁₀ carbocyclene is

**120**

-continued



10 In some embodiments, F¹ is



15 20 In some embodiments, each of F¹, F², or F³ is, independently, optionally substituted C₂-C₉ heterocyclene.

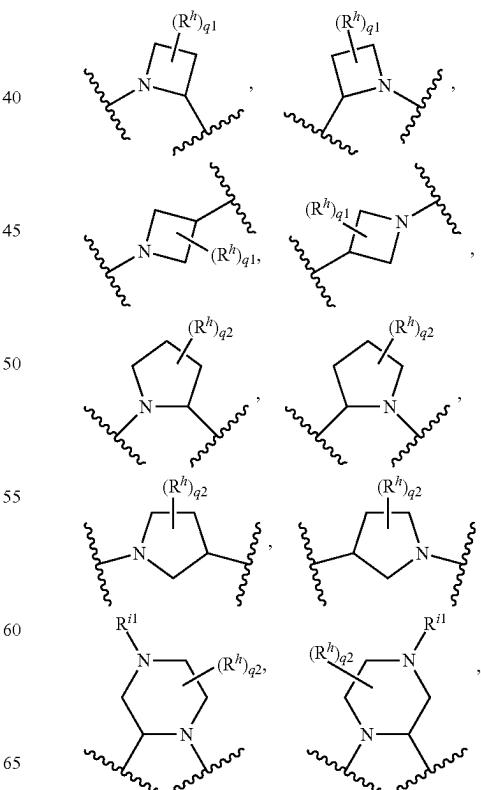
In some embodiments, the C₂-C₉ heterocyclene is monocyclic. In some embodiments, the C₂-C₉ heterocyclene is polycyclic.

25 In some embodiments, the C₂-C₉ heterocyclene is bicyclic.

In some embodiments, the C₂-C₉ heterocyclene is bridged. In some embodiments, the C₂-C₉ heterocyclene is fused. In some embodiments, the C₂-C₉ heterocyclene is spirocyclic.

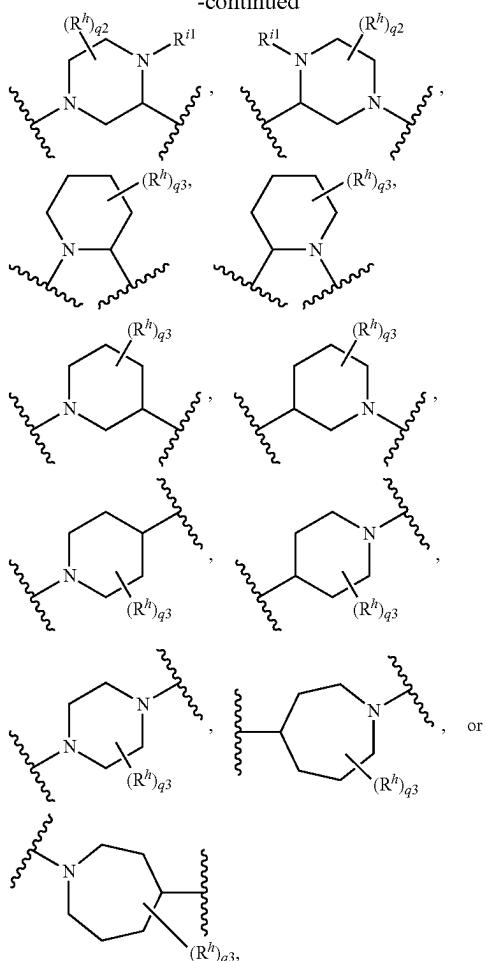
In some embodiments, the C₂-C₉ heterocyclene includes a quaternary amine.

In some embodiments, the C₂-C₉ heterocyclene is



121

-continued



where

q1 is 0, 1, 2, 3, or 4;

q2 is 0, 1, 2, 3, 4, 5, or 6;

q3 is 0, 1, 2, 3, 4, 5, 6, 7, or 8:

each R^h is, independently, 2H , halogen, optionally substituted C_1 - C_6 alkyl, OR^{12} , or $NR^{13}R^{14}$; or two R^h groups, together with the carbon atom to which each is attached, combine to form optionally substituted C_3 - C_{10} carbocyclyl or optionally substituted C_2 - C_9 heterocyclyl; or two R^h groups, together with the carbon atoms to which each is attached, combine to form optionally substituted C_3 - C_{10} carbocyclyl or optionally substituted C_2 - C_9 heterocyclyl;

R^{i1} is H or optionally substituted C₁-C₆ alkyl;

R^{12} is H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, or optionally substituted C_3 - C_6 carbocyclyl;

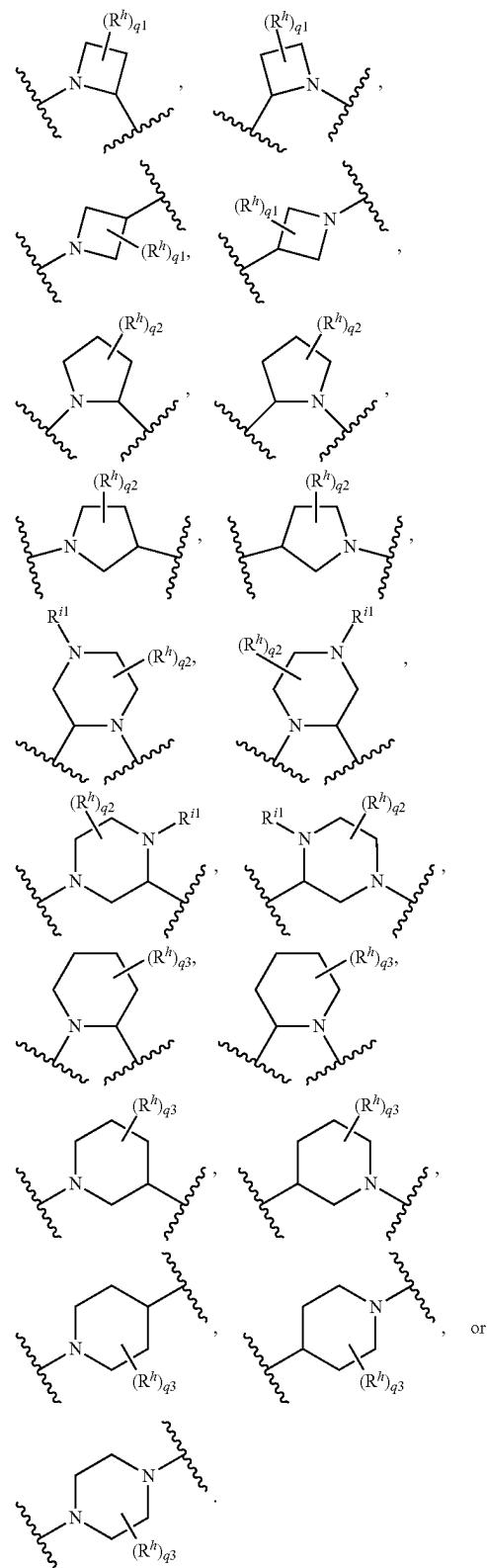
R^{i3} is H or optionally substituted C₁-C₆ alkyl; and

R^{i4} is H or optionally substituted C₁-C₆ alkyl.

In some embodiments, each R^h is, independently, halogen, optionally substituted C_1 - C_6 alkyl, ORⁱ², or NRⁱ³Rⁱ⁴. In some embodiments, Rⁱ¹ is H or optionally substituted C_1 - C_6 alkyl. In some embodiments, Rⁱ² is H or optionally substituted C_1 - C_6 alkyl. In some embodiments, Rⁱ³ is H or optionally substituted C_1 - C_6 alkyl. In some embodiments, Rⁱ⁴ is H or optionally substituted C_1 - C_6 alkyl.

122

In some embodiments, the C₂-C₉ heterocyclylene is

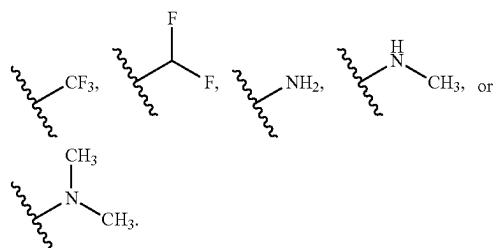


In some embodiments, each R^h is, independently, halogen, optionally substituted C_1 - C_6 alkyl, OR^{12} , or $NR^{13}R^{14}$. In some embodiments, each R^h is, independently, halogen, optionally substituted C_1 - C_6 alkyl, or $NR^{13}R^{14}$.

123

In some embodiments, each R^h is, independently, 2H , halogen, cyano, optionally substituted C_1 - C_6 alkyl, OR^{12} , or $NR^{13}R^{14}$. In some embodiments, two R^h groups, together with the carbon atom to which each is attached, combine to form optionally substituted C_3 - C_{10} carbocyclyl or optionally substituted C_2 - C_9 heterocyclyl. In some embodiments, two R^h groups, together with the carbon atoms to which each is attached, combine to form optionally substituted C_3 - C_{10} carbocyclyl or optionally substituted C_2 - C_9 heterocyclyl.

In some embodiments, each R^h is, independently, 2H , F, 10 methyl,



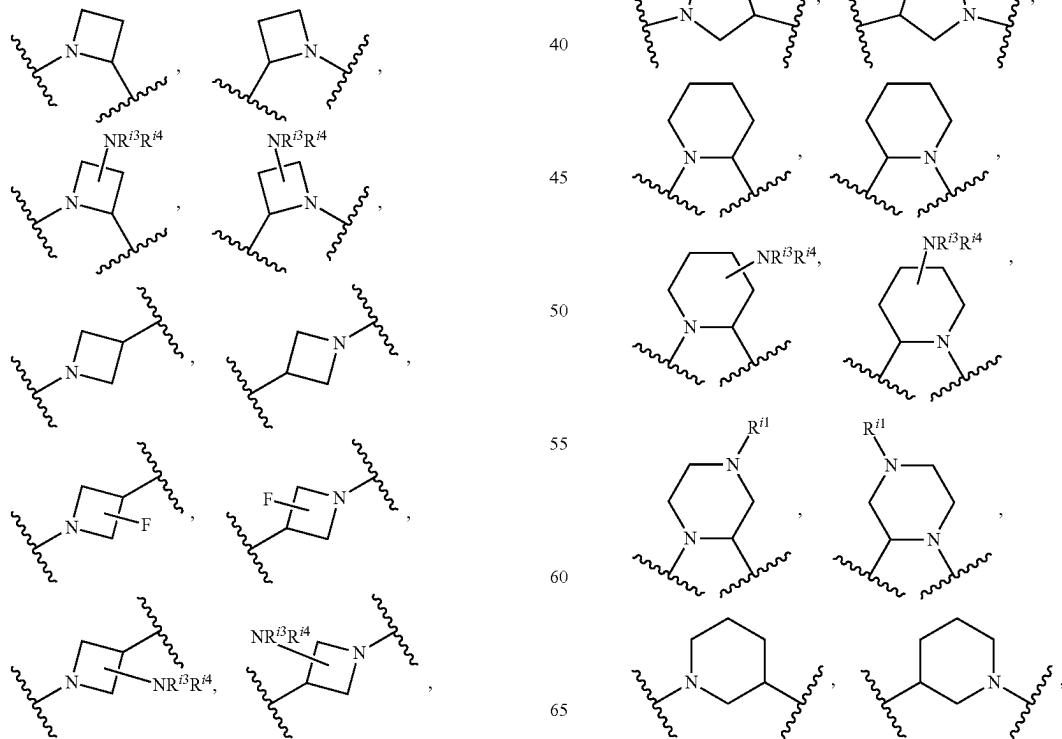
In some embodiments, each R^h is, independently, F, 25 methyl, or $NR^{13}R^{14}$.

In some embodiments, q_1 is 0, 1, or 2. In some embodiments, q_1 is 0. In some embodiments, q_1 is 1. In some embodiments, q_1 is 2.

In some embodiments, q_2 is 0, 1, or 2. In some embodiments, q_2 is 0. In some embodiments, q_2 is 1. In some embodiments, q_2 is 2.

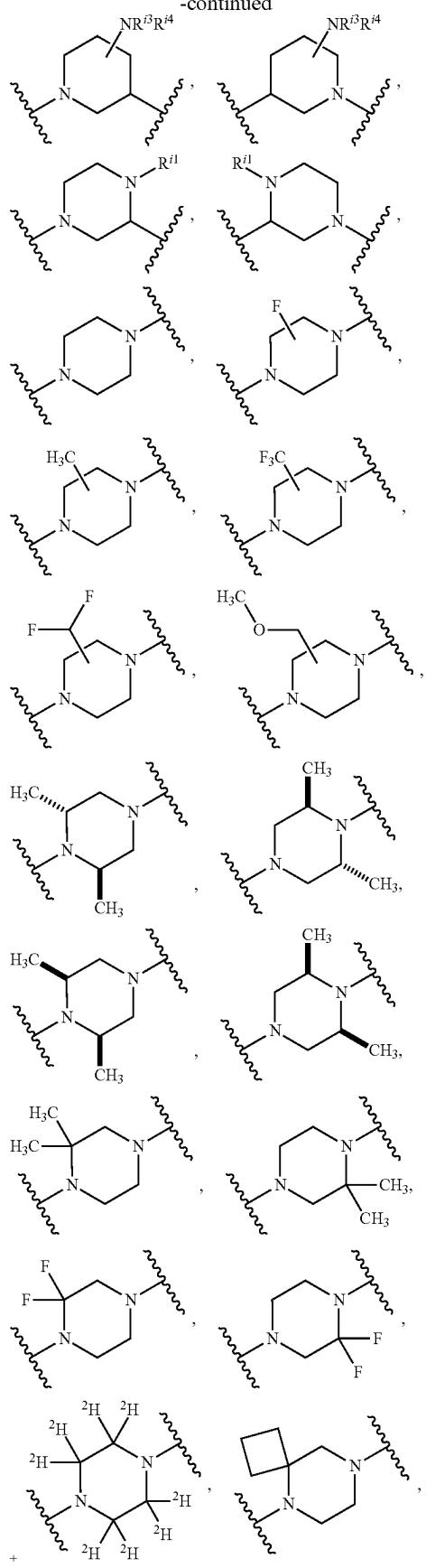
In some embodiments, q_3 is 0, 1, or 2. In some embodiments, q_3 is 0. In some embodiments, q_3 is 1. In some embodiments, q_3 is 2.

In some embodiments, the C_2 - C_9 heterocyclylene is

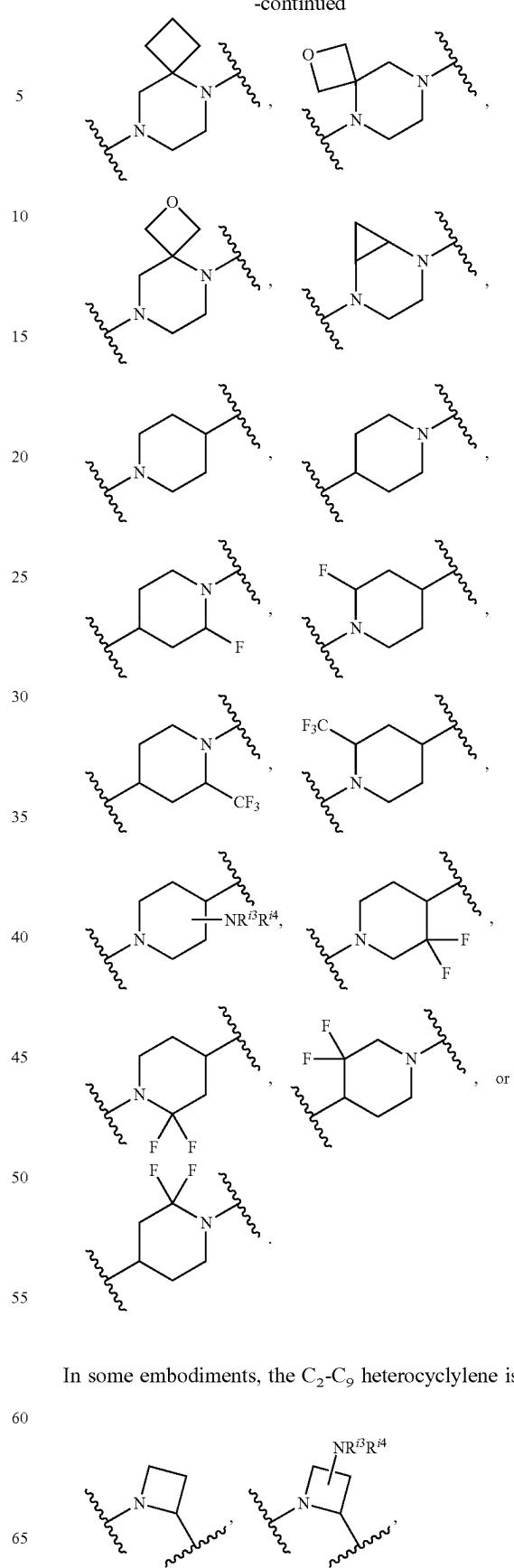


125

-continued

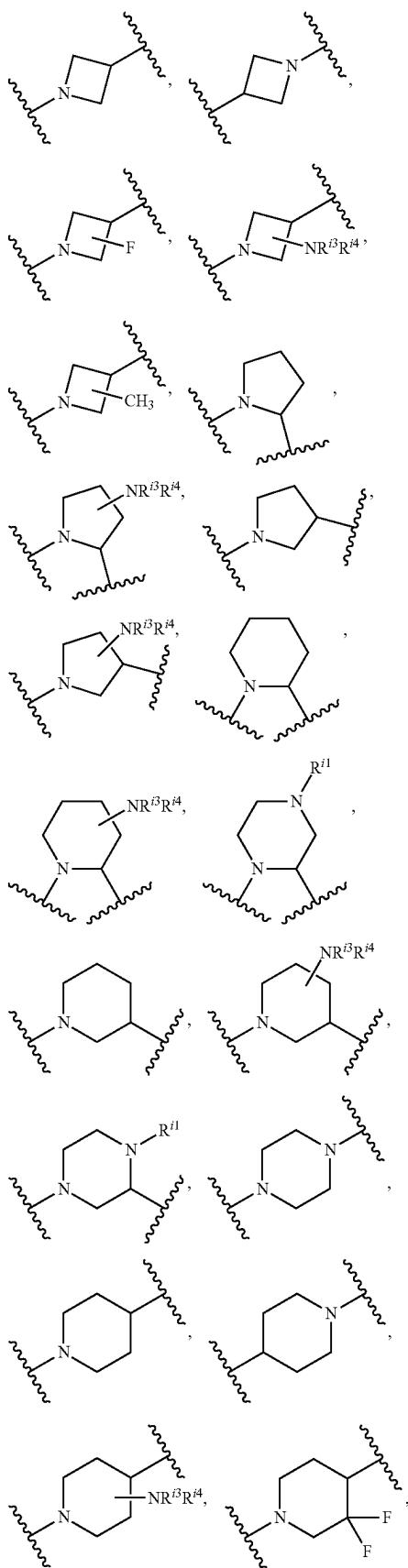
**126**

-continued



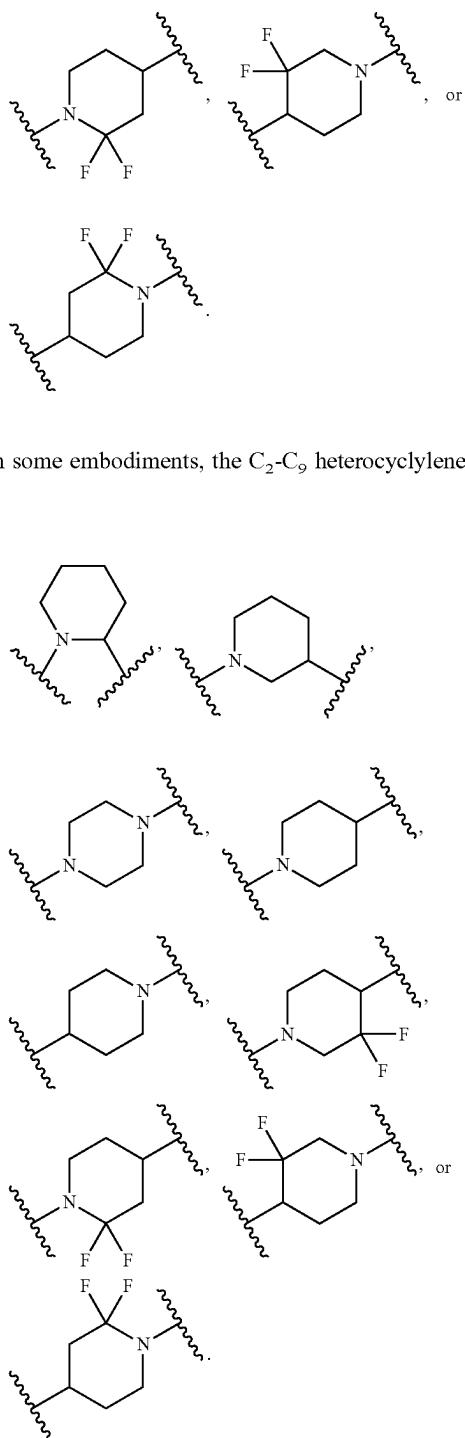
127

-continued

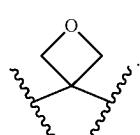


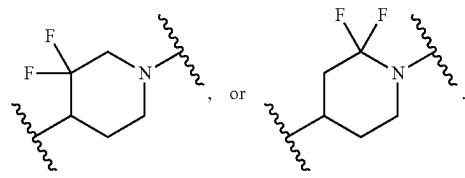
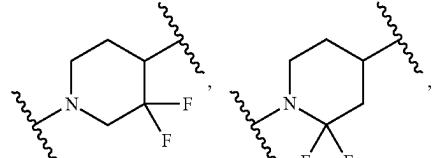
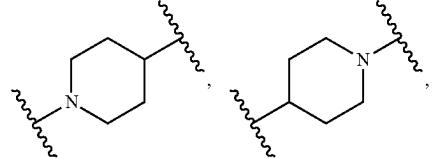
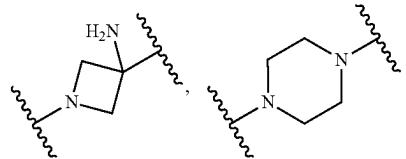
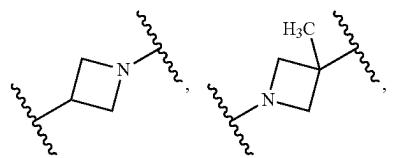
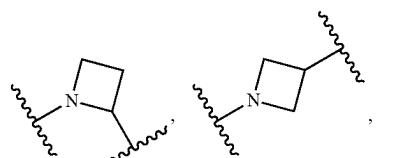
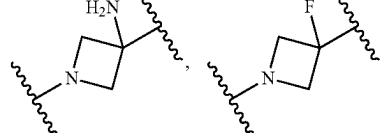
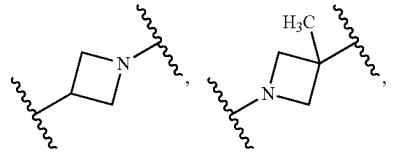
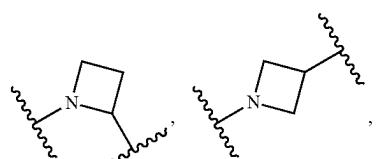
128

-continued

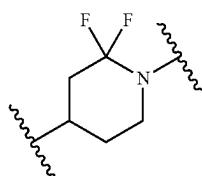
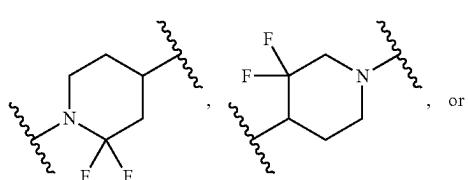
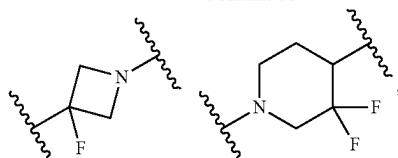
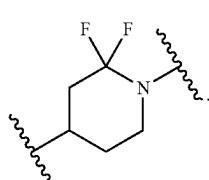
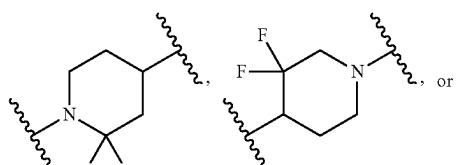
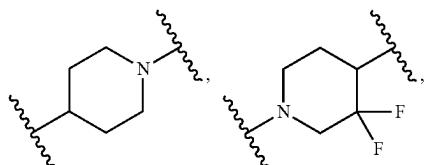
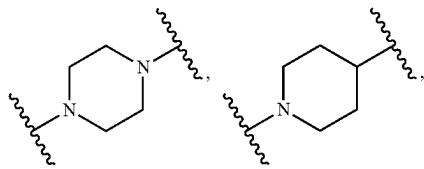
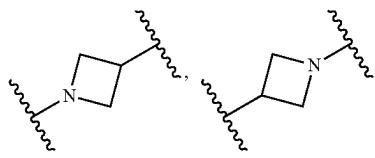


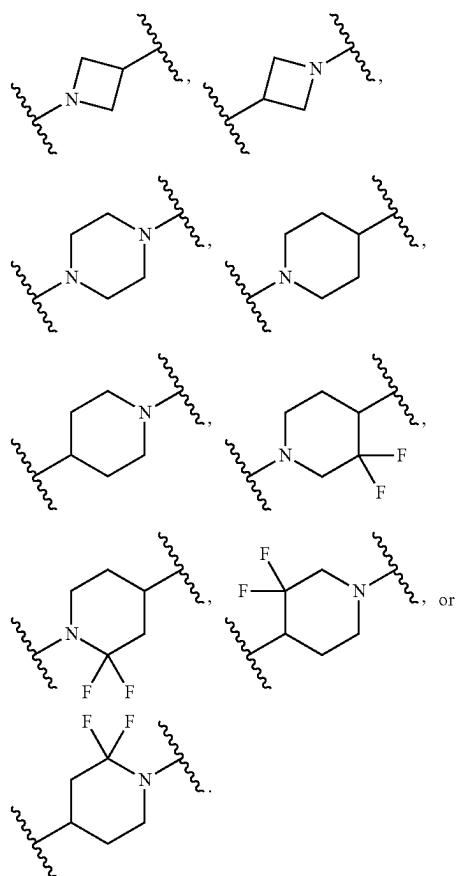
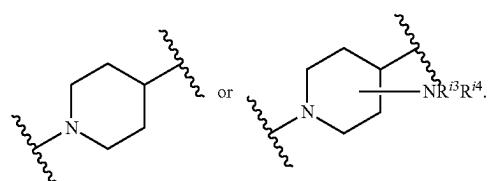
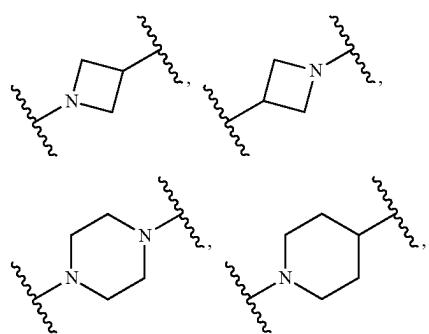
In some embodiments, the C₂-C₆ heterocyclylene is



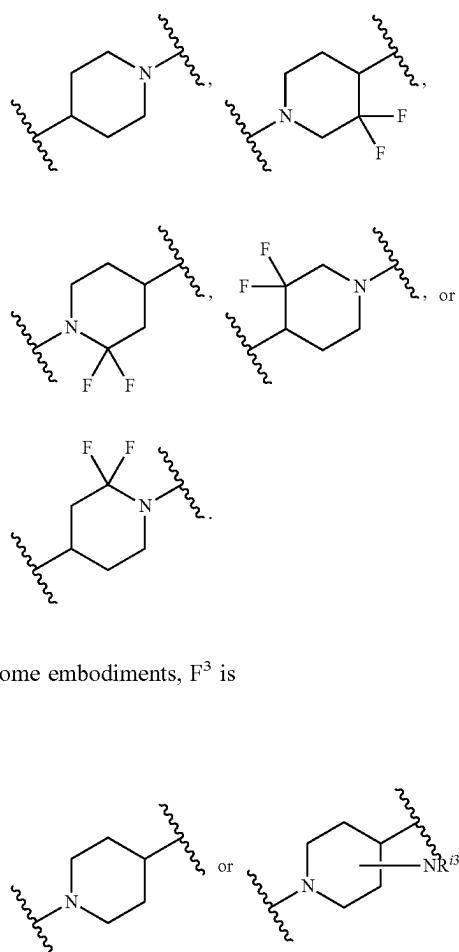
129In some embodiments, F¹ isIn some embodiments, F¹ is**130**

-continued

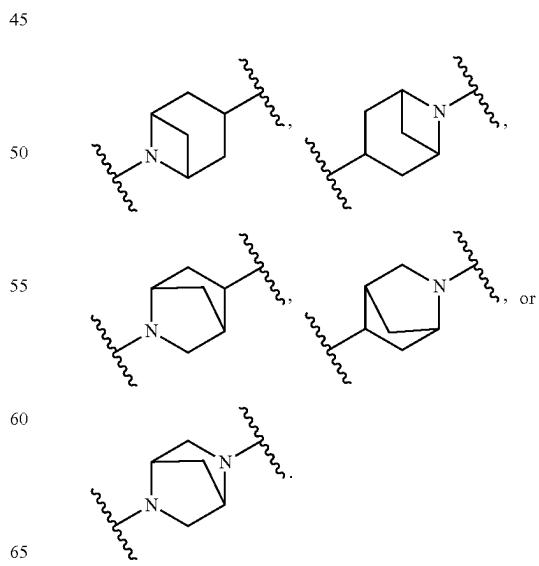
In some embodiments, F¹ is

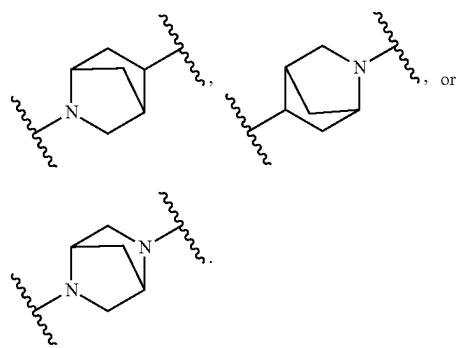
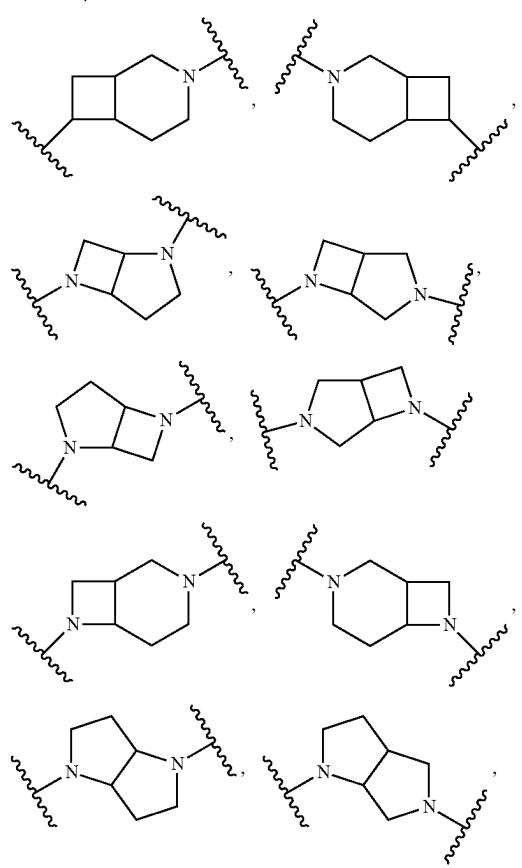
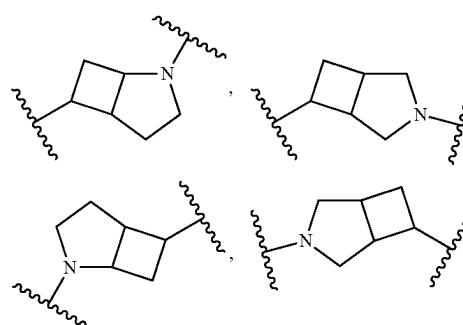
131In some embodiments, F^2 isIn some embodiments, F^2 isIn some embodiments, F^3 is**132**

-continued

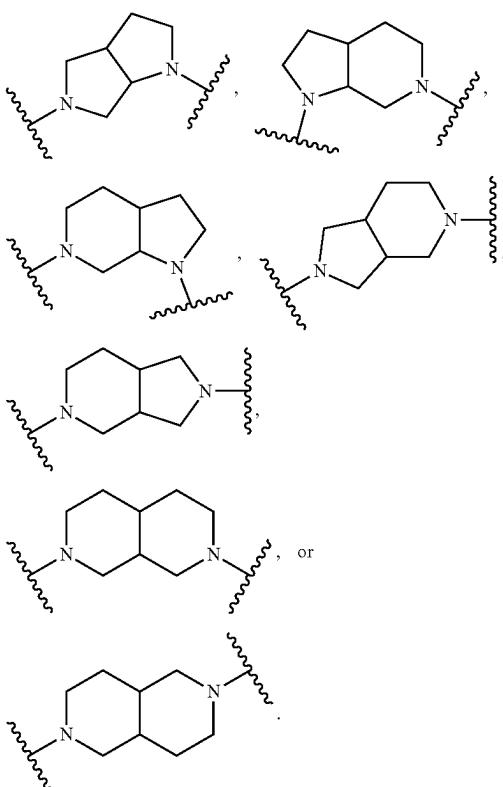
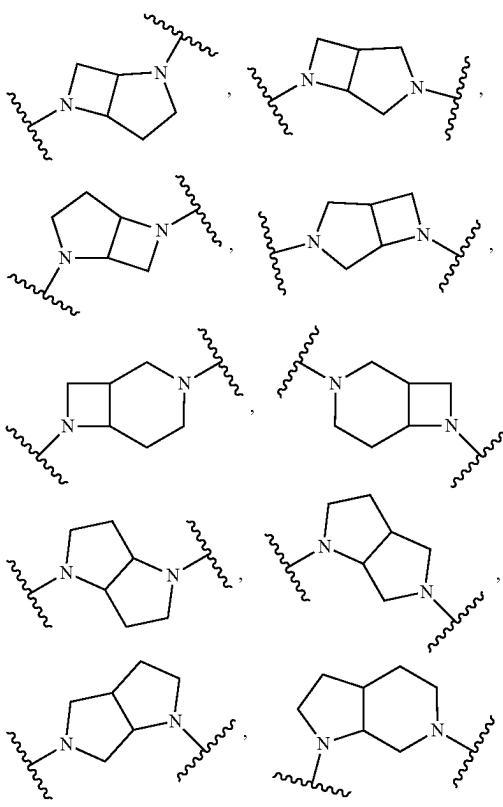


40 In some embodiments, R^{i1} is H or methyl. In some embodiments, R^{i2} is H or methyl. In some embodiments, R^{i3} is H or methyl. In some embodiments, R^{i4} is H or methyl.
In some embodiments, the C₂-C₉ heterocyclene is



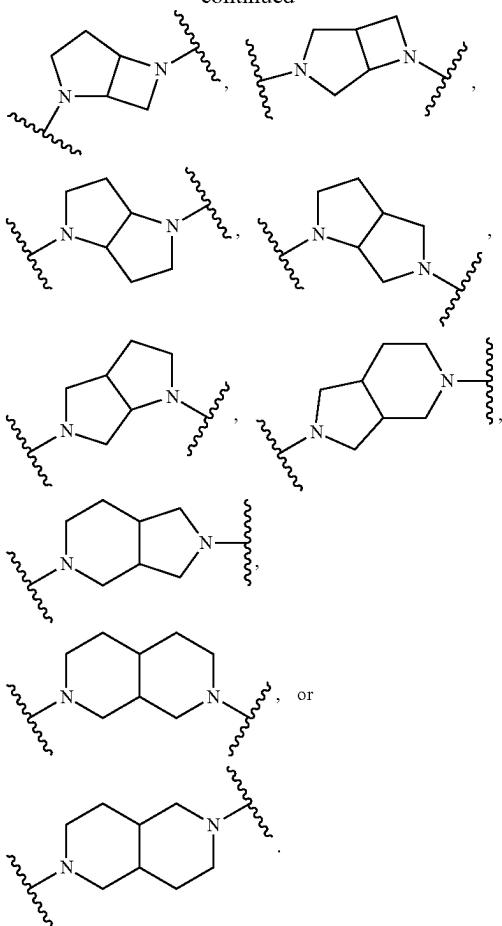
133In some embodiments, the C₂-C₉ heterocyclylene isIn some embodiments, the C₂-C₉ heterocyclylene is**134**

-continued

In some embodiments, the C₂-C₉ heterocyclylene is

137

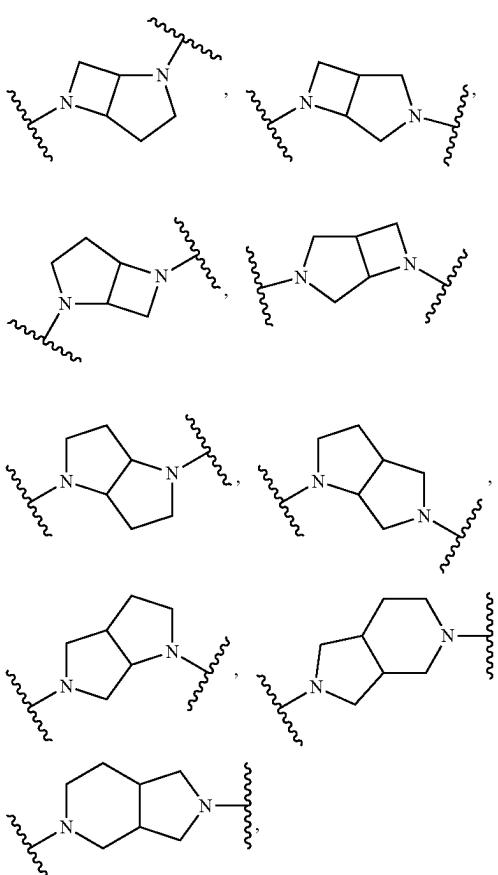
-continued



In some embodiments, F^1 is

138

In some embodiments, F^2 is



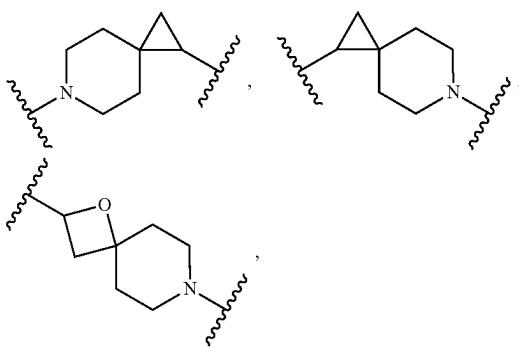
40

45

In some embodiments, the C₂-C₉ heterocyclyl is

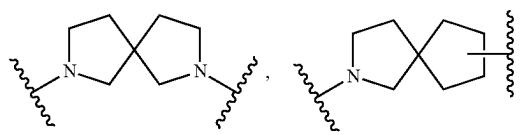
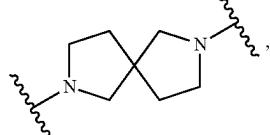
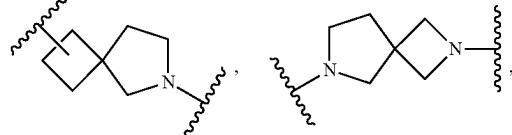
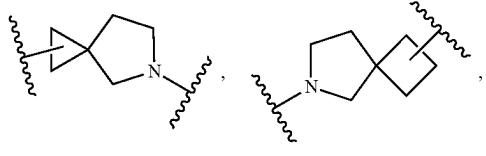
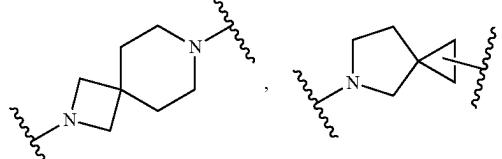
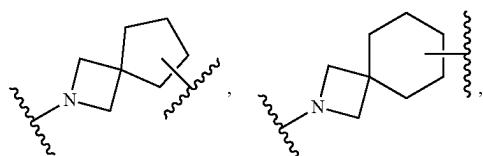
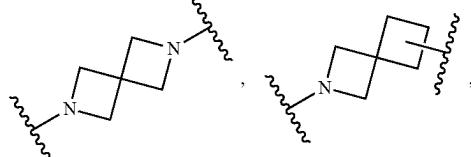
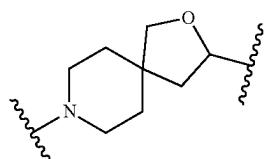
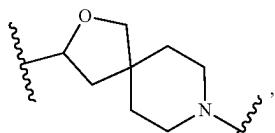
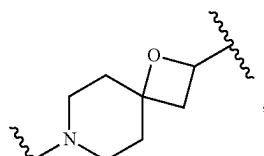
55

60



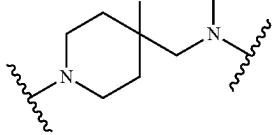
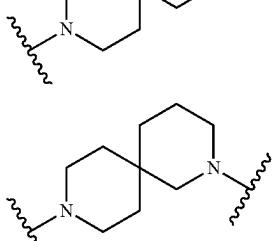
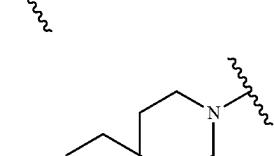
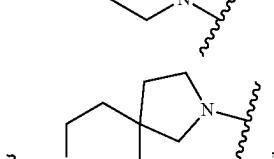
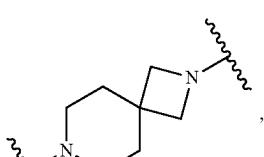
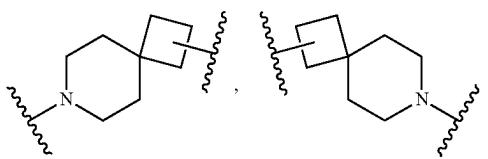
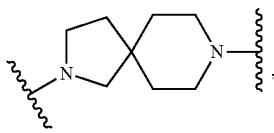
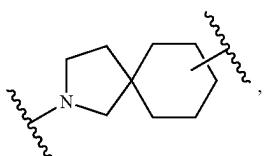
139

-continued



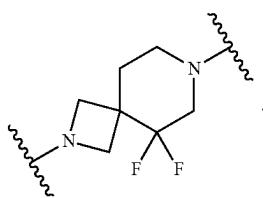
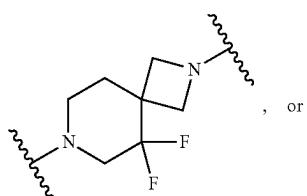
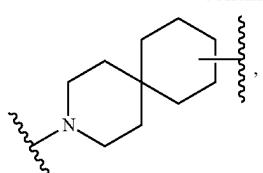
140

-continued

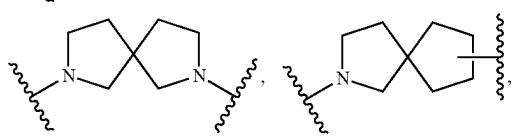
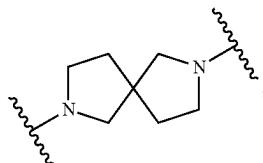
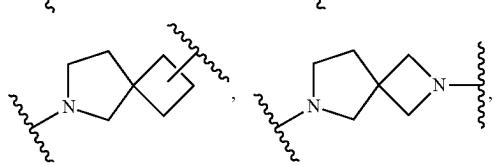
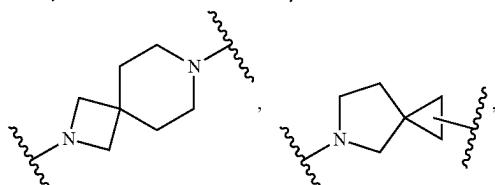
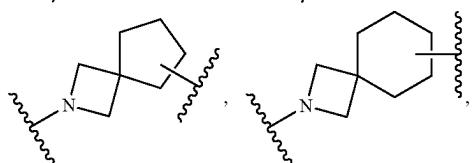
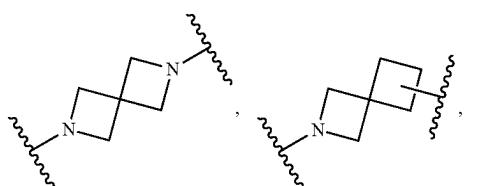


141

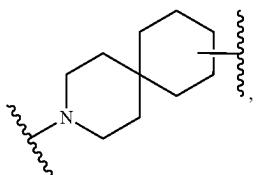
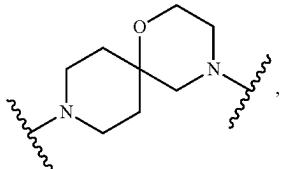
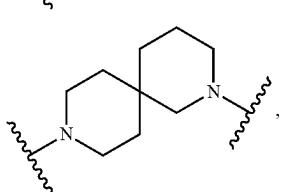
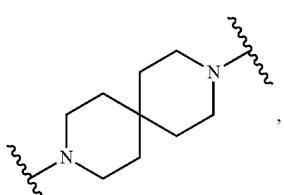
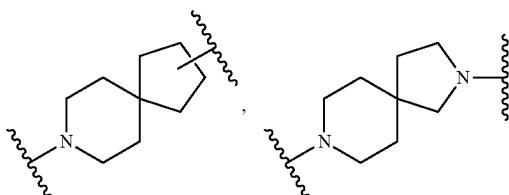
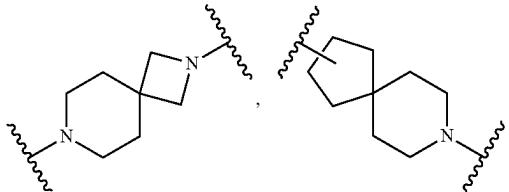
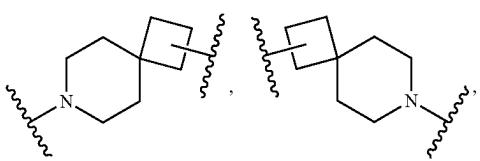
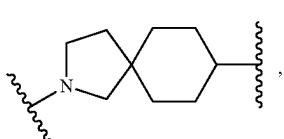
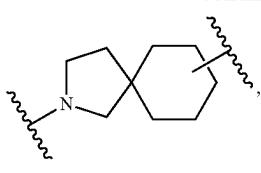
-continued



In some embodiments, the C₂-C₉ heterocyclyl is

**142**

-continued



5

10

15

20

25

30

35

40

45

50

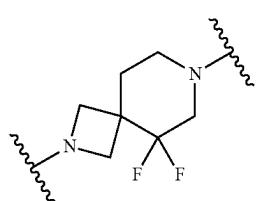
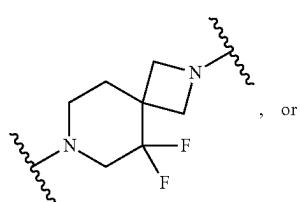
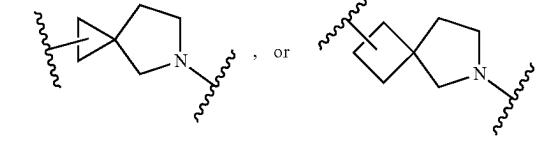
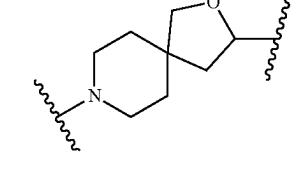
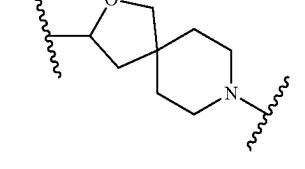
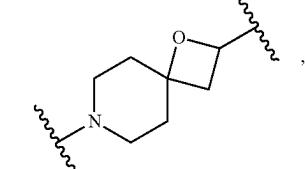
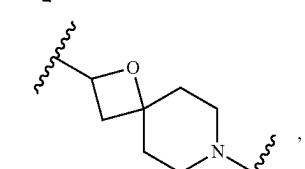
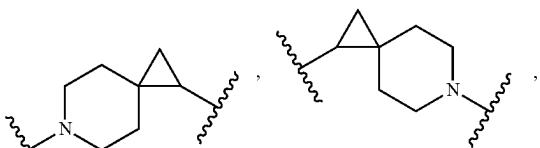
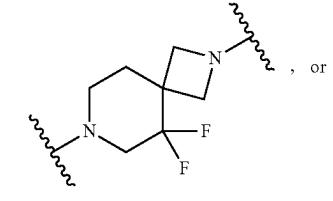
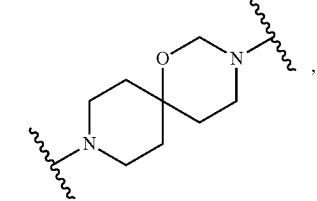
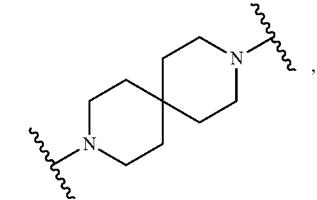
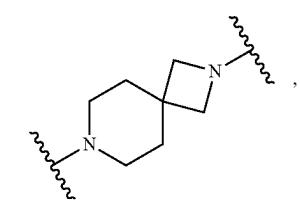
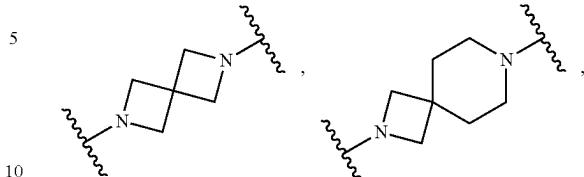
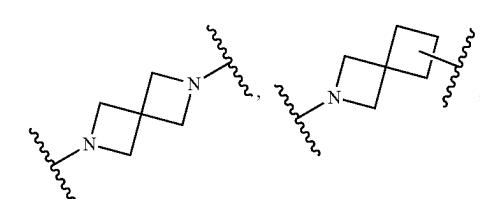
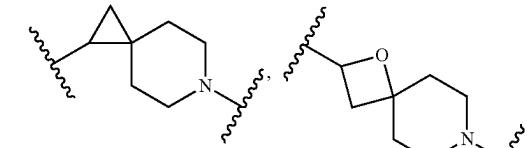
55

60

65

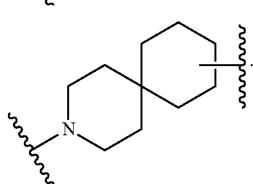
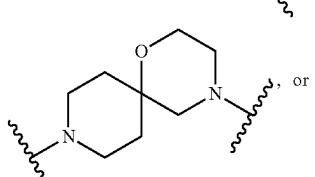
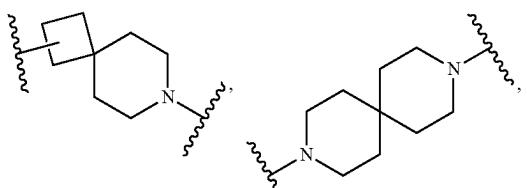
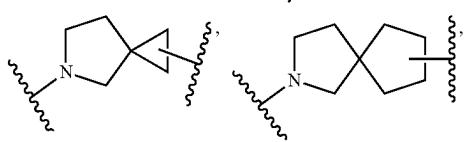
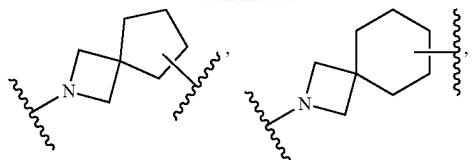
143

continued

In some embodiments, the C₂-C₉ heterocyclyl is**144**In some embodiments, the C₂-C₉ heterocyclyl isIn some embodiments, F¹ is

145

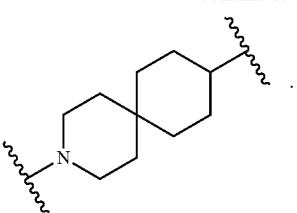
-continued



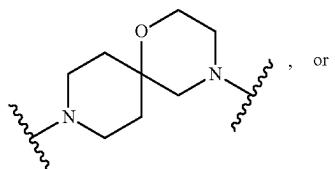
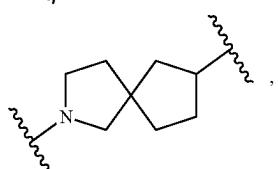
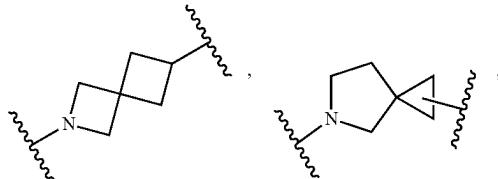
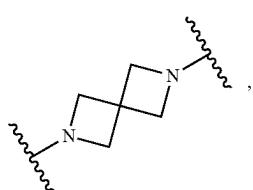
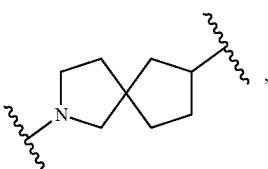
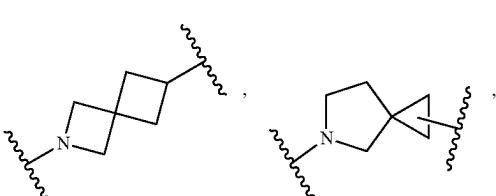
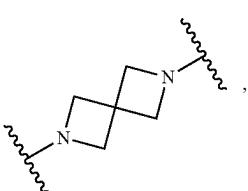
In some embodiments, F^1 is

146

-continued



In some embodiments, F^1 is

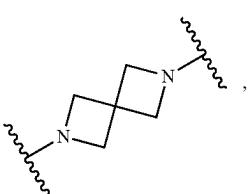


50

55

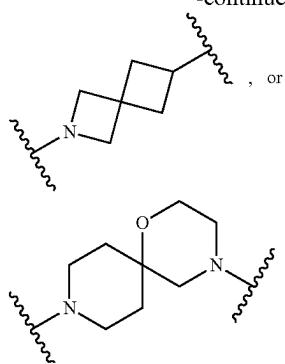
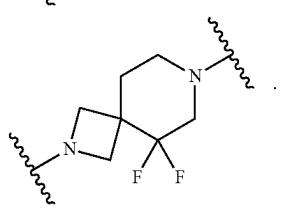
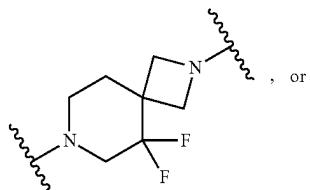
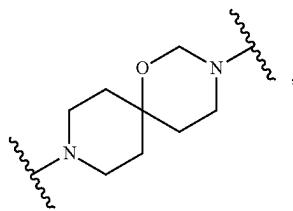
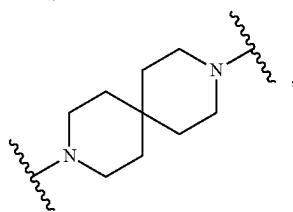
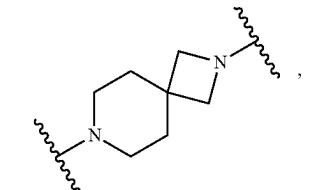
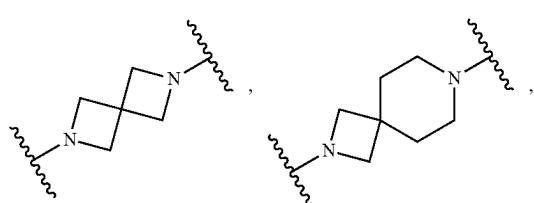
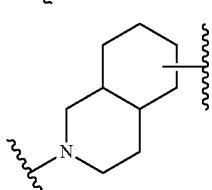
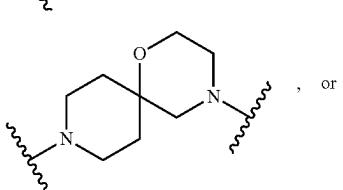
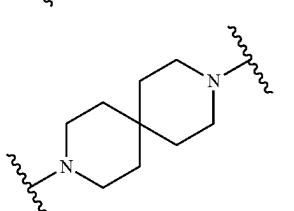
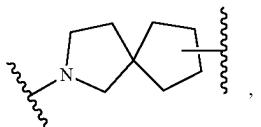
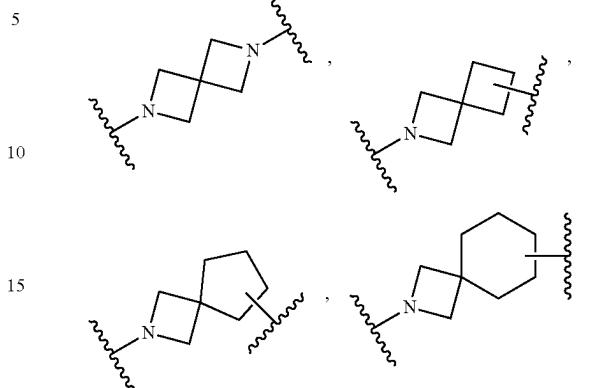
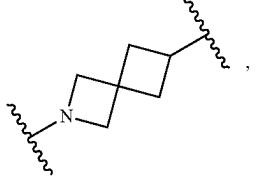
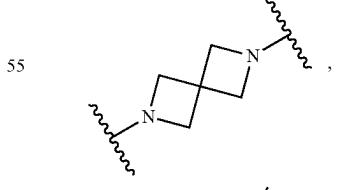
60

In some embodiments, F^1 is



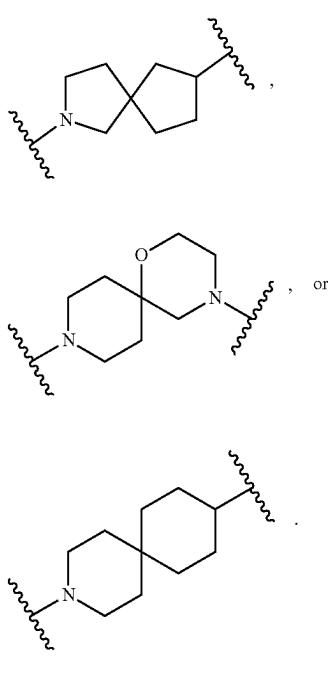
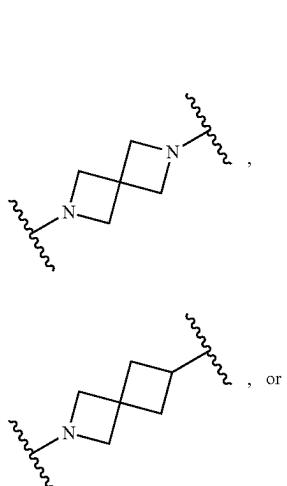
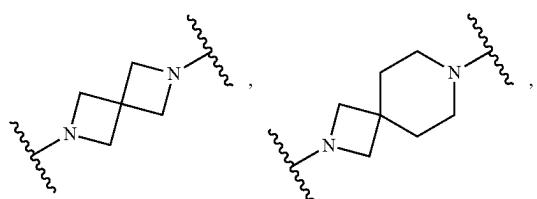
147

-continued

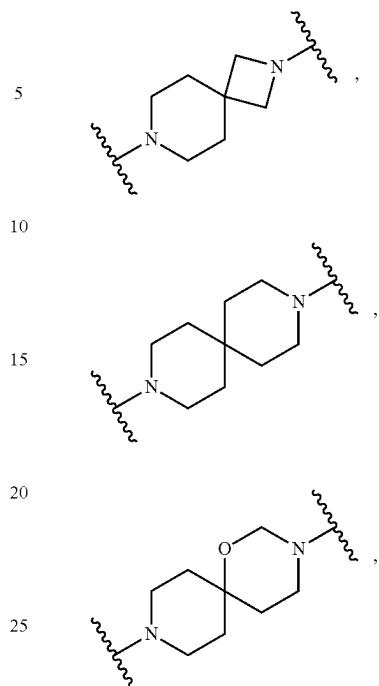
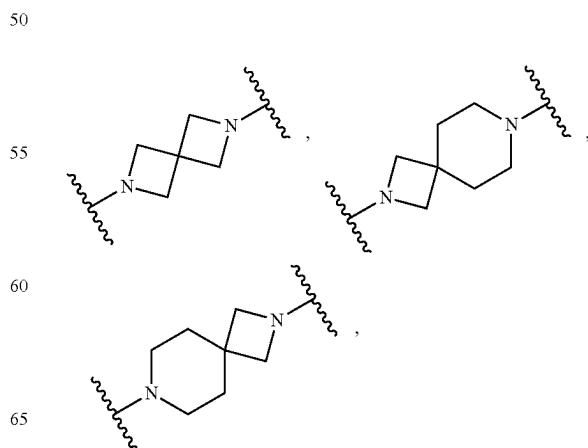
In some embodiments, F¹ is**148**In some embodiments, F² isIn some embodiments, F² is

149

-continued

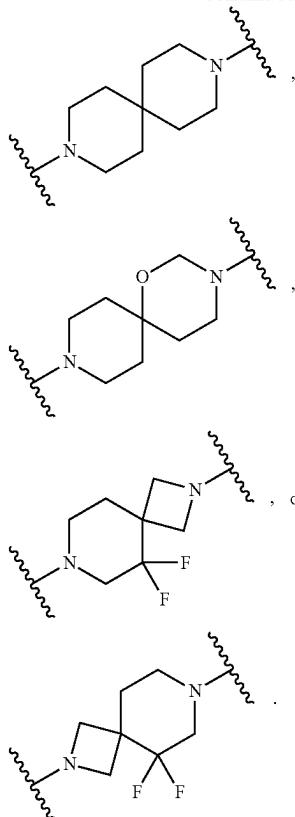
In some embodiments, F^2 isIn some embodiments, F^2 is**150**

-continued

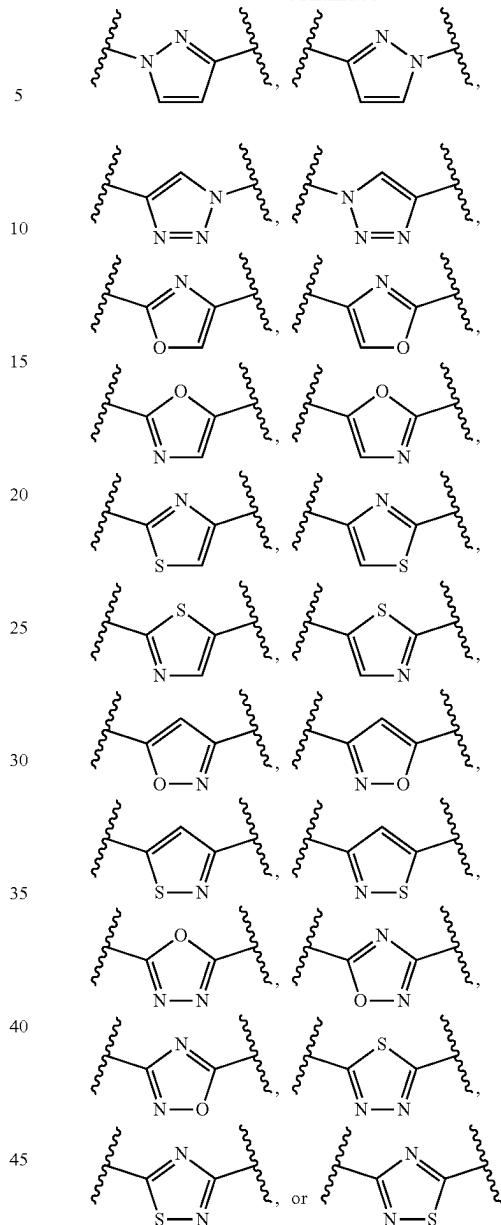
In some embodiments, F^3 is

151

-continued

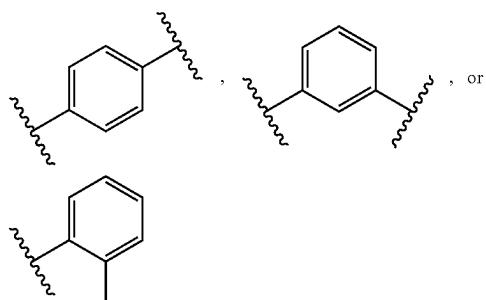
**152**

-continued



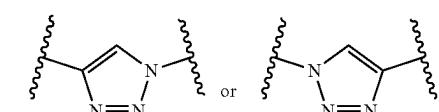
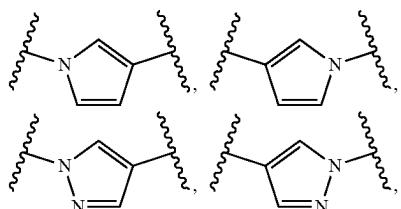
In some embodiments, each of F¹, F², or F³ is, independently, optionally substituted C₆-C₁₀ arylene.

In some embodiments, the C₆-C₁₀ arylene is

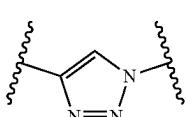


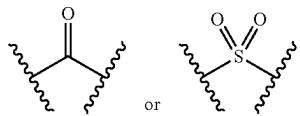
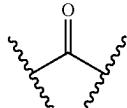
In some embodiments, each of F¹, F², or F³ is, independently, optionally substituted C₂-C₉ heteroarylene.

In some embodiments, the C₂-C₉ heteroarylene is



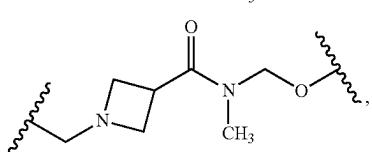
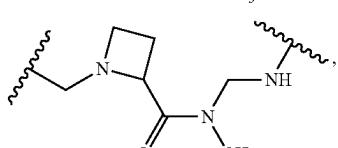
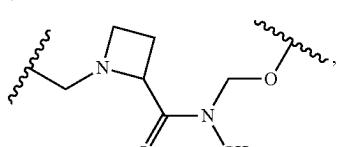
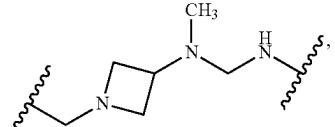
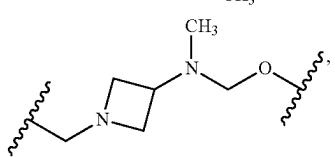
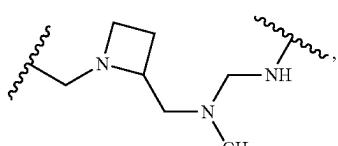
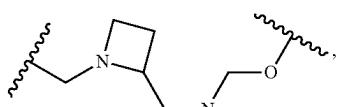
In some embodiments, F² is



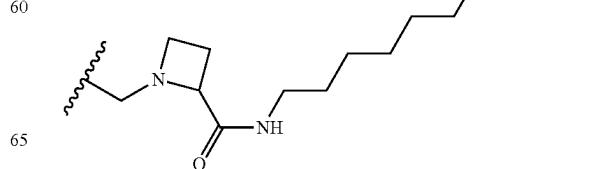
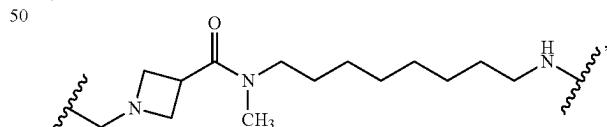
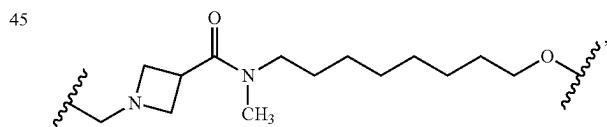
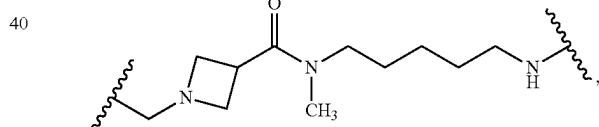
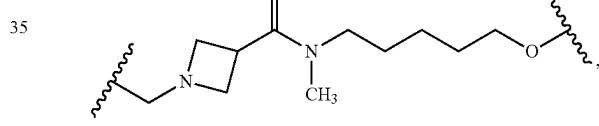
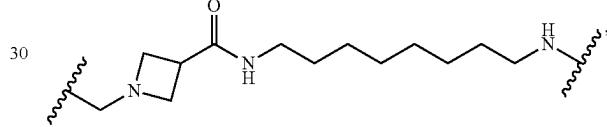
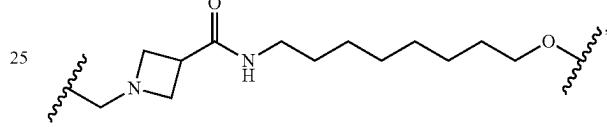
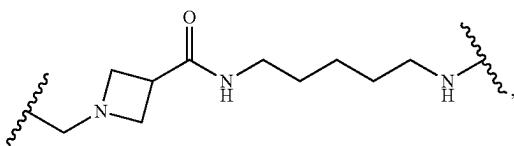
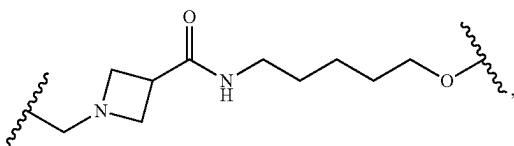
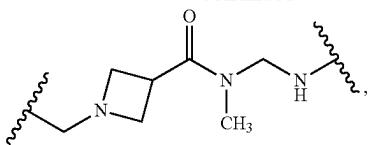
153In some embodiments, C³ isIn some embodiments, C³ is

In some embodiments, m is 1. In some embodiments, p is 1.

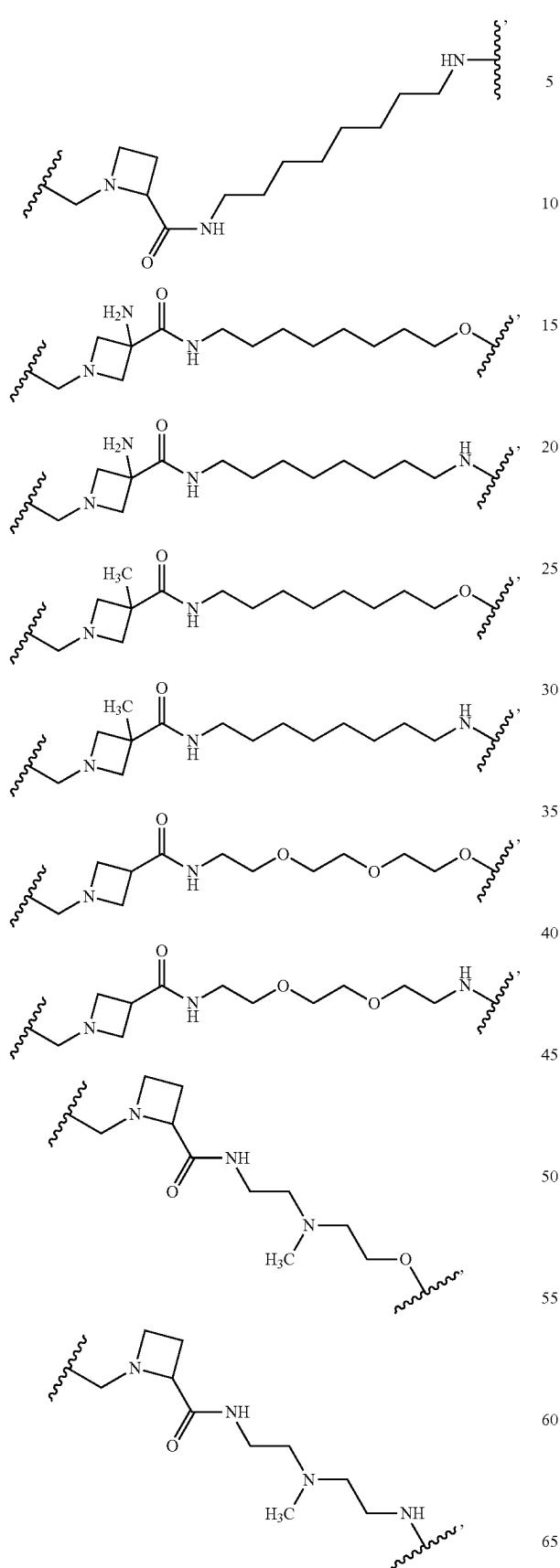
In some embodiments, the linker has the structure of

**154**

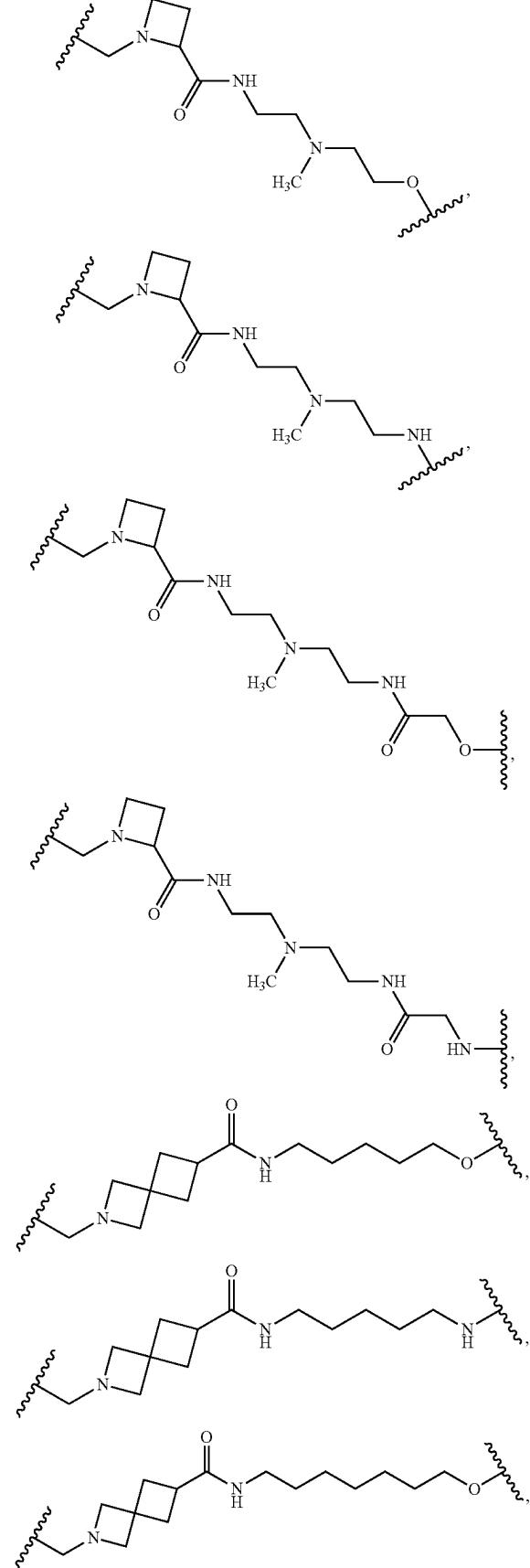
-continued



155
-continued

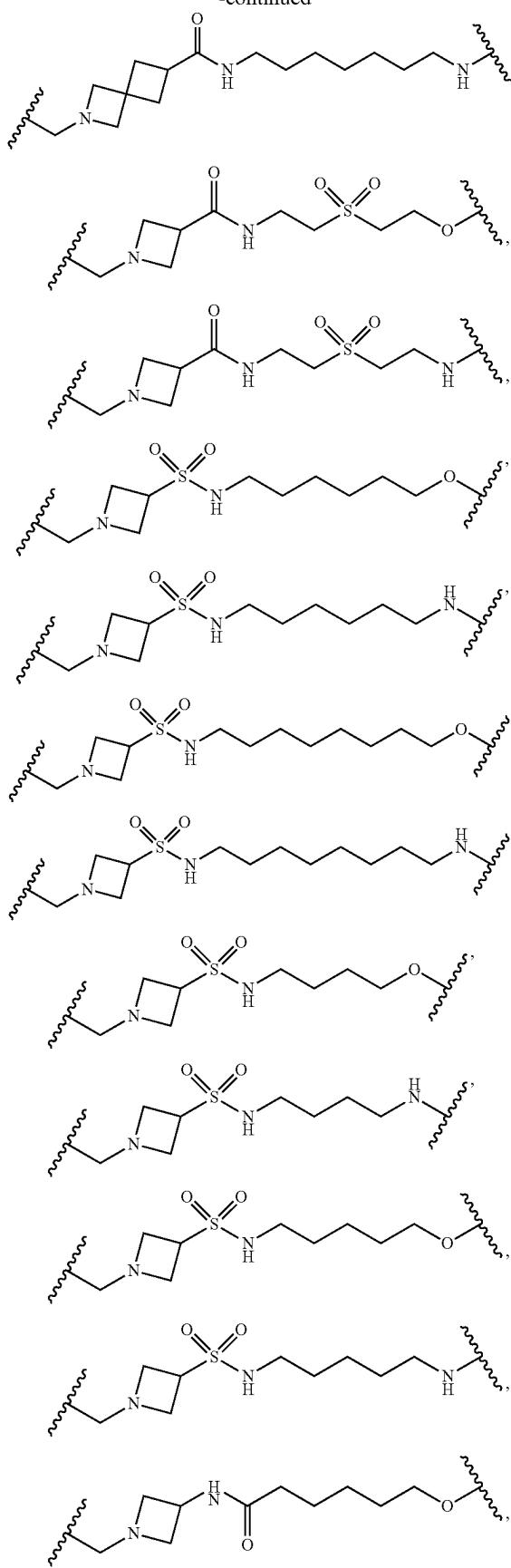


156
-continued

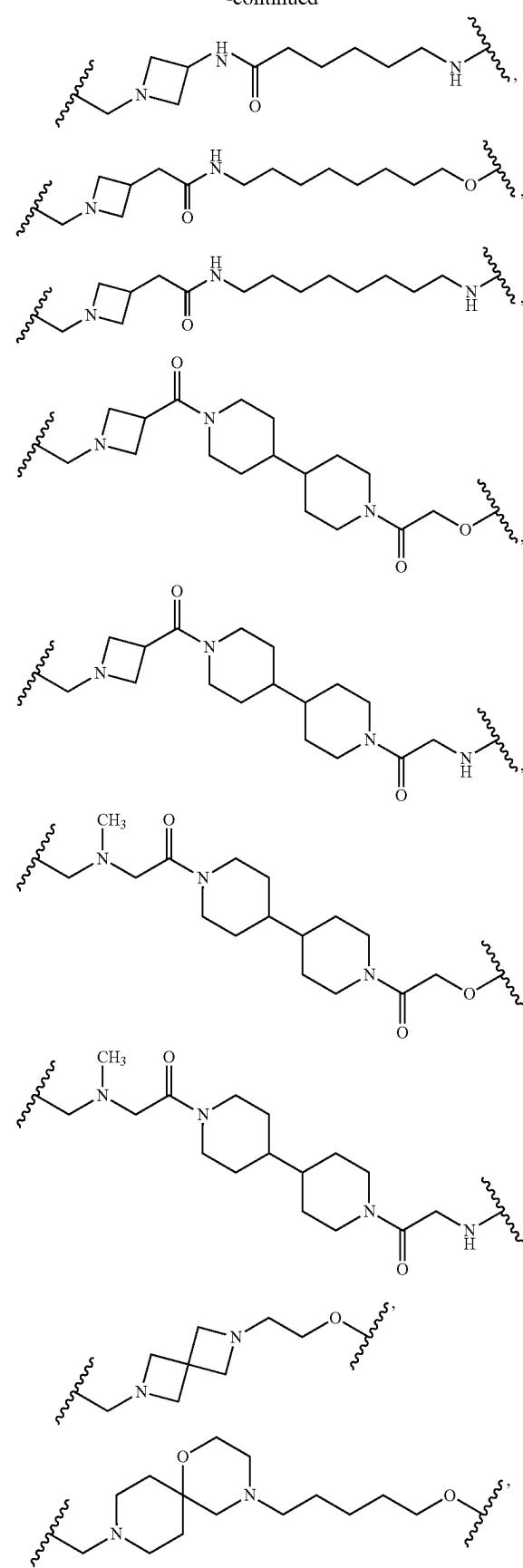


157

-continued

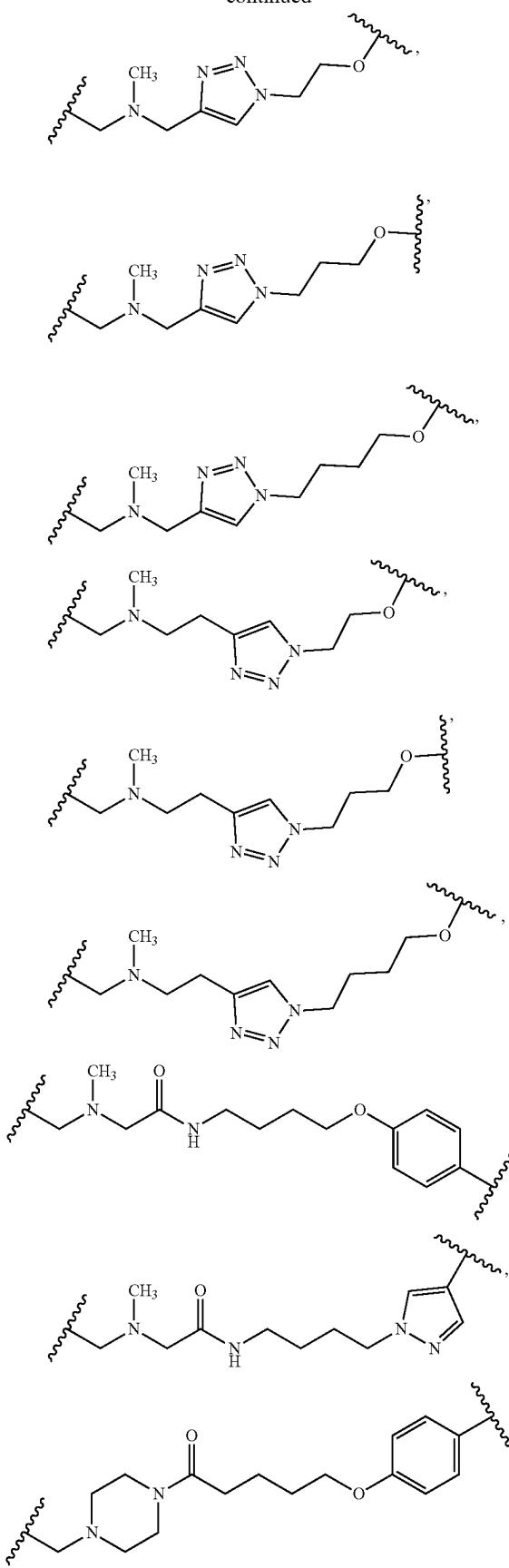
**158**

-continued

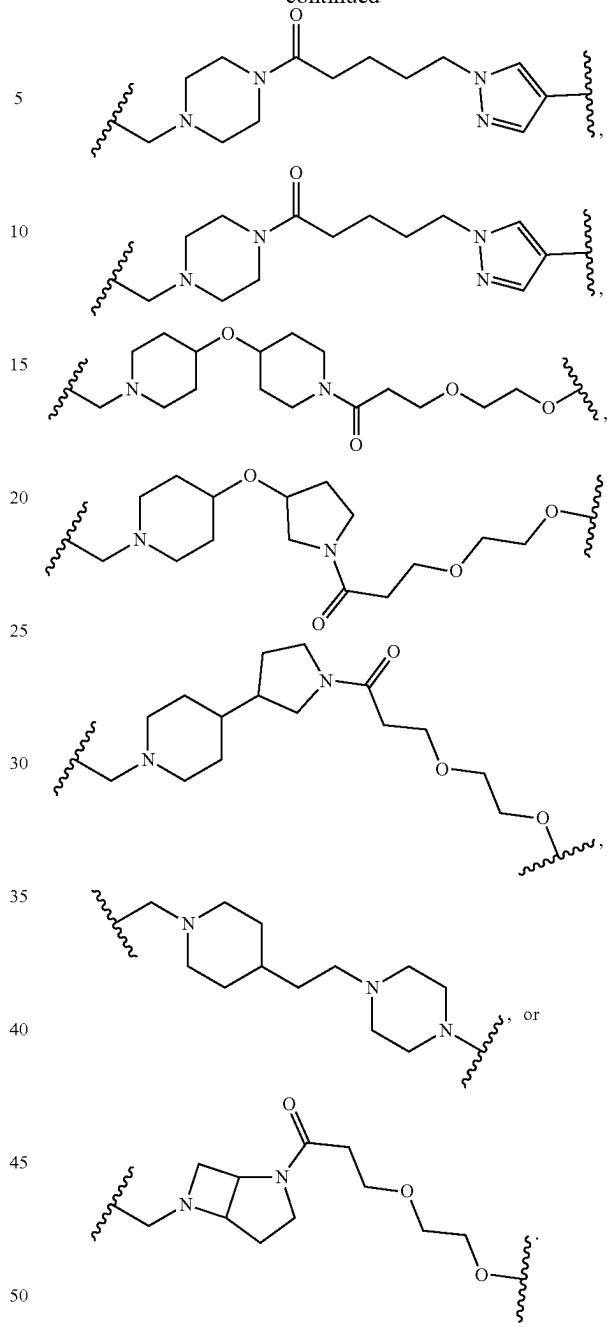


159

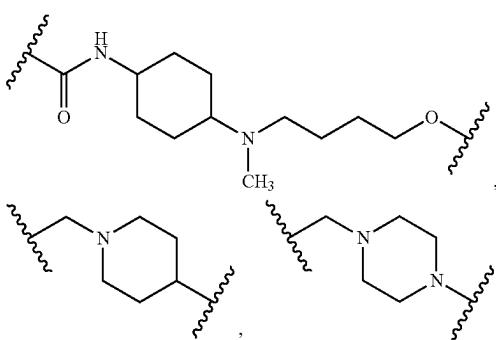
-continued

**160**

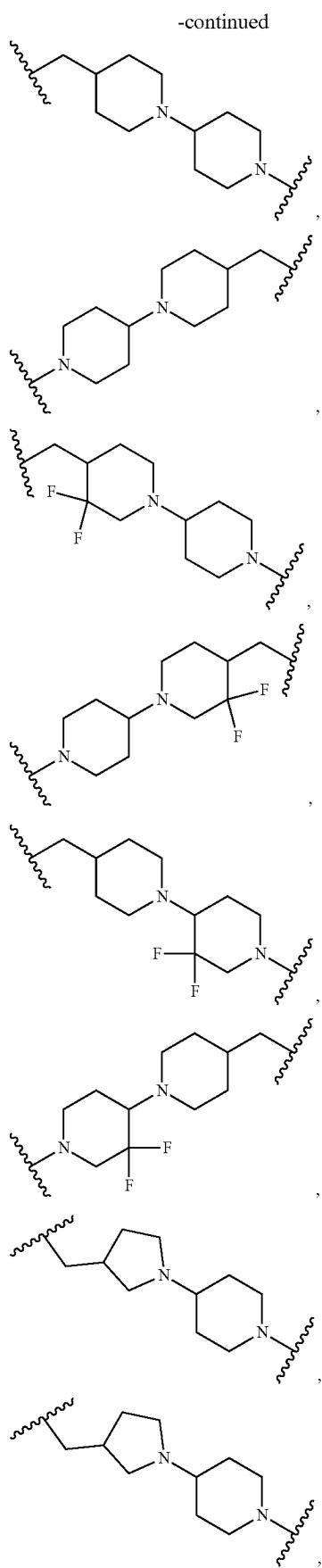
-continued



In some embodiments, the linker has the structure of

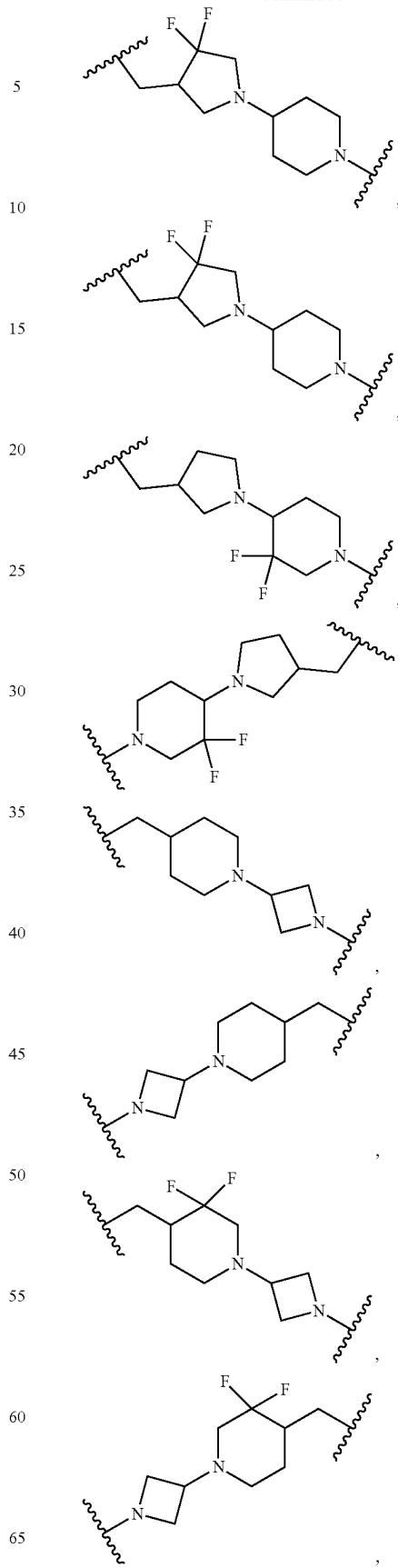


161



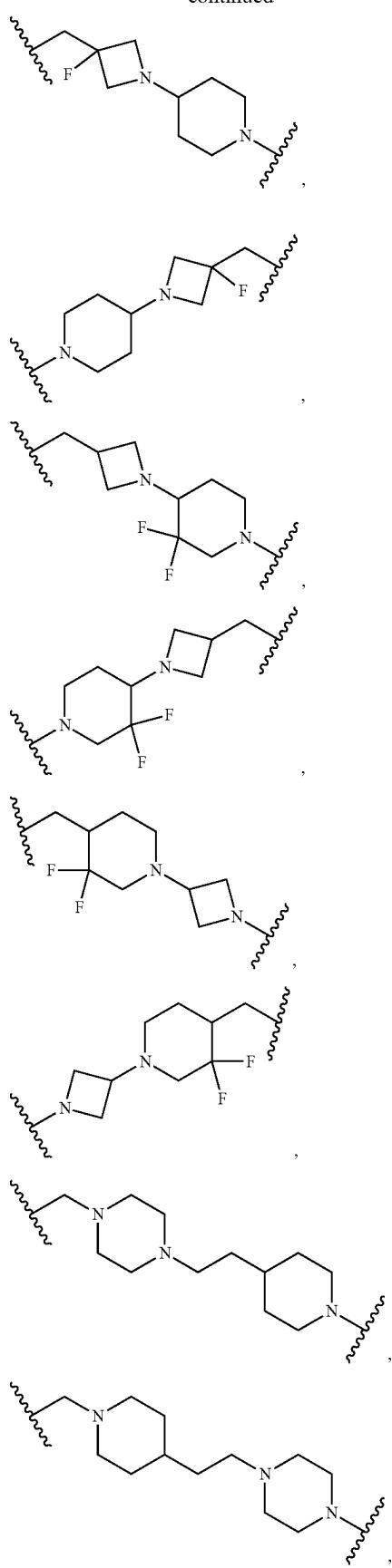
162

-continued



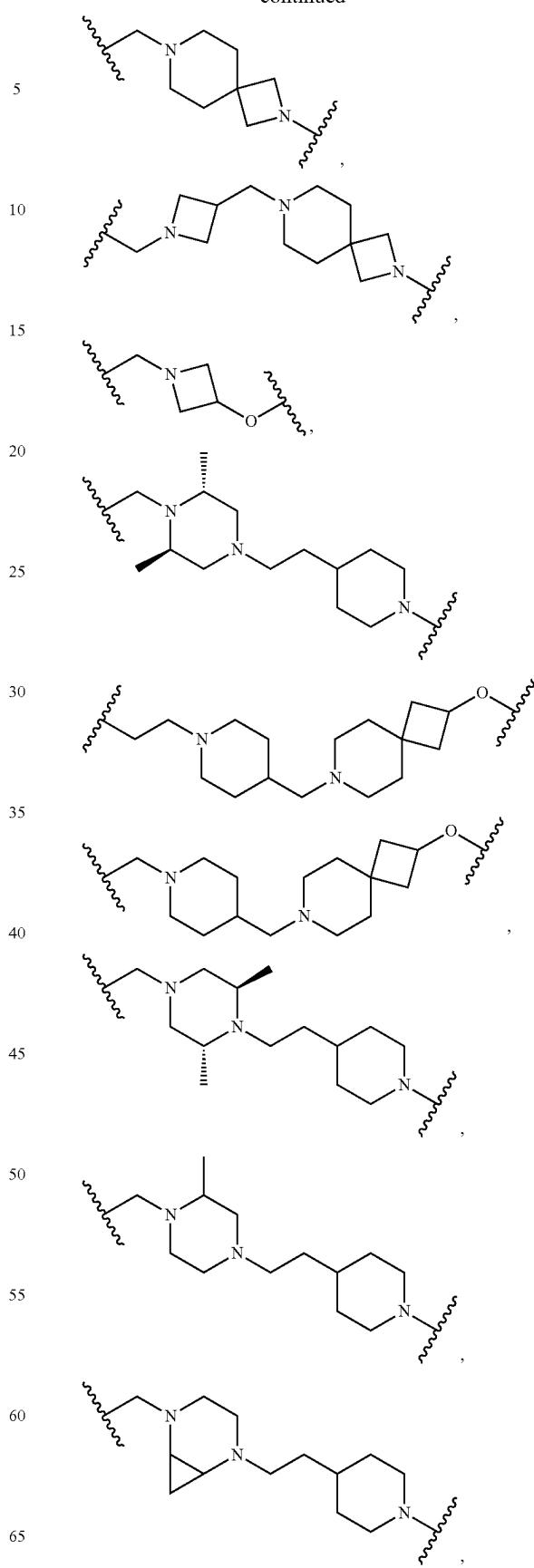
163

-continued



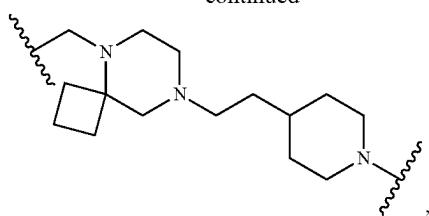
164

-continued



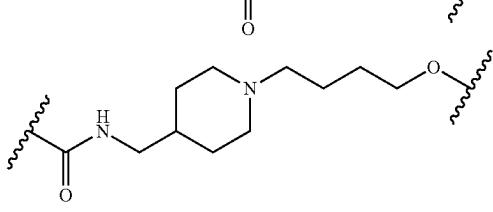
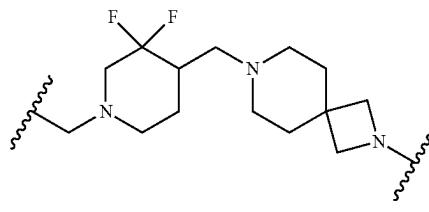
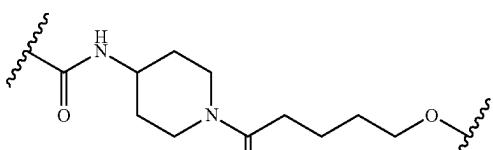
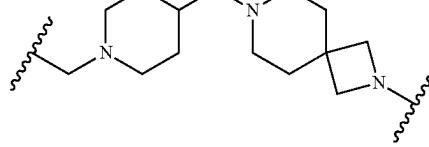
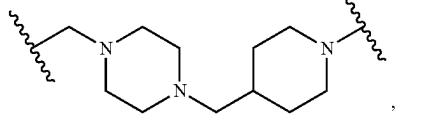
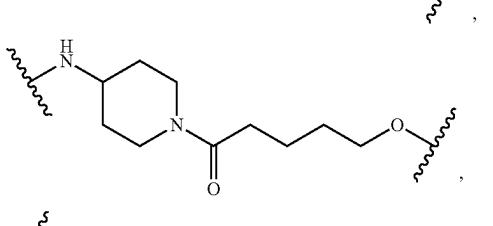
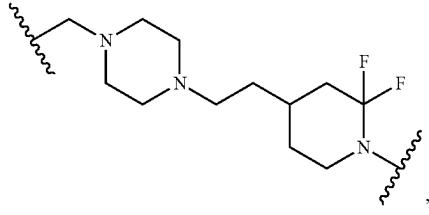
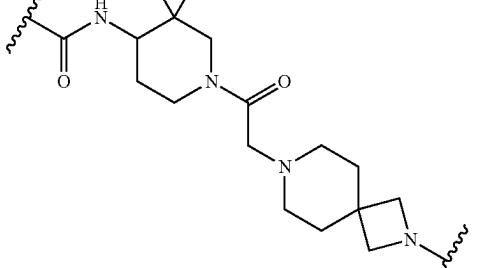
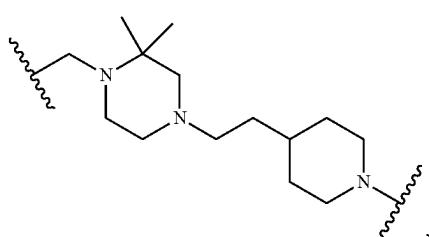
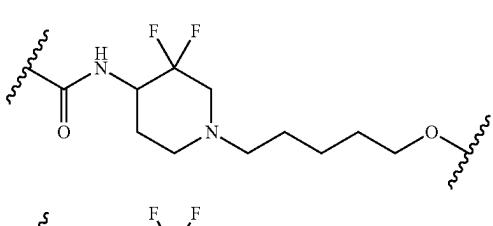
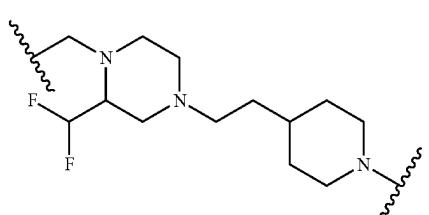
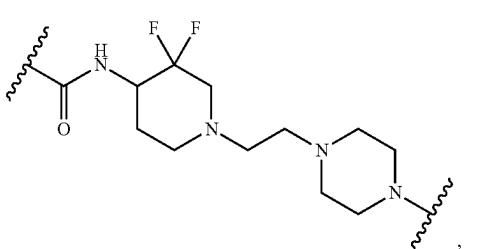
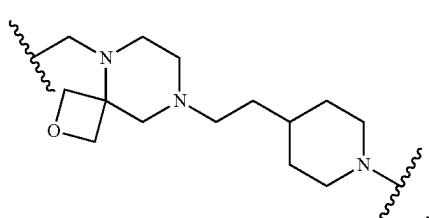
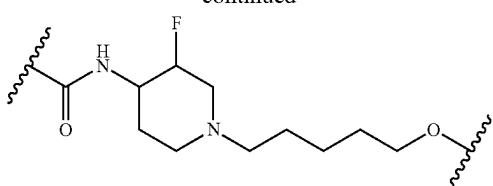
165

-continued



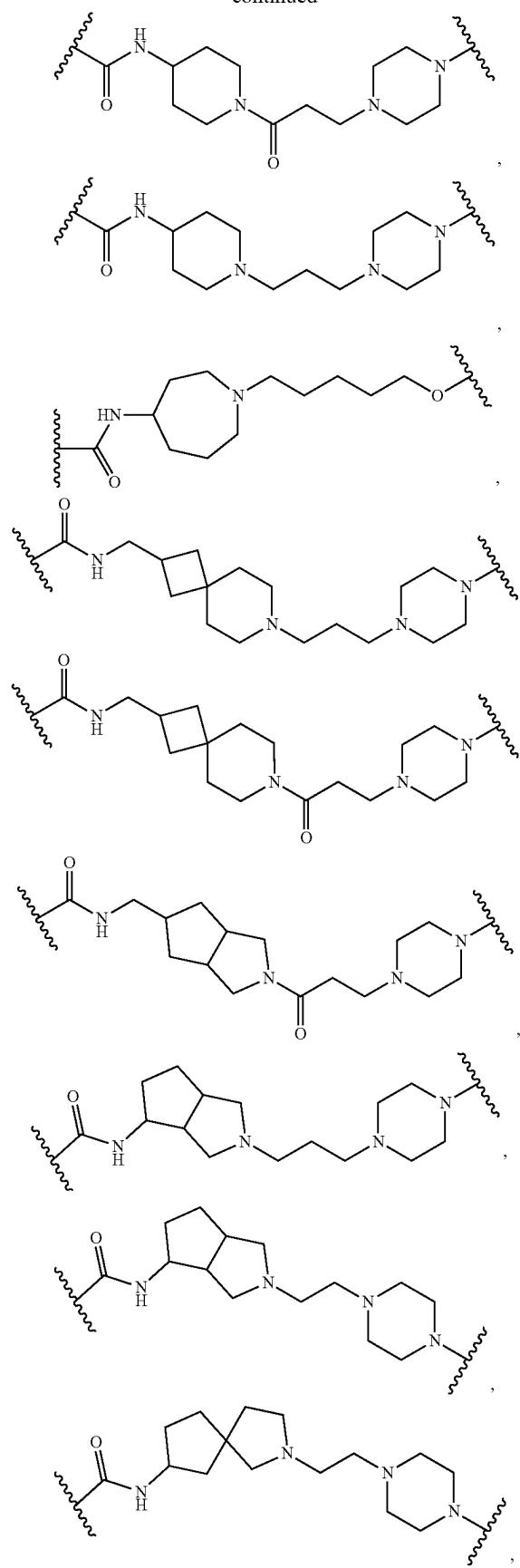
166

-continued

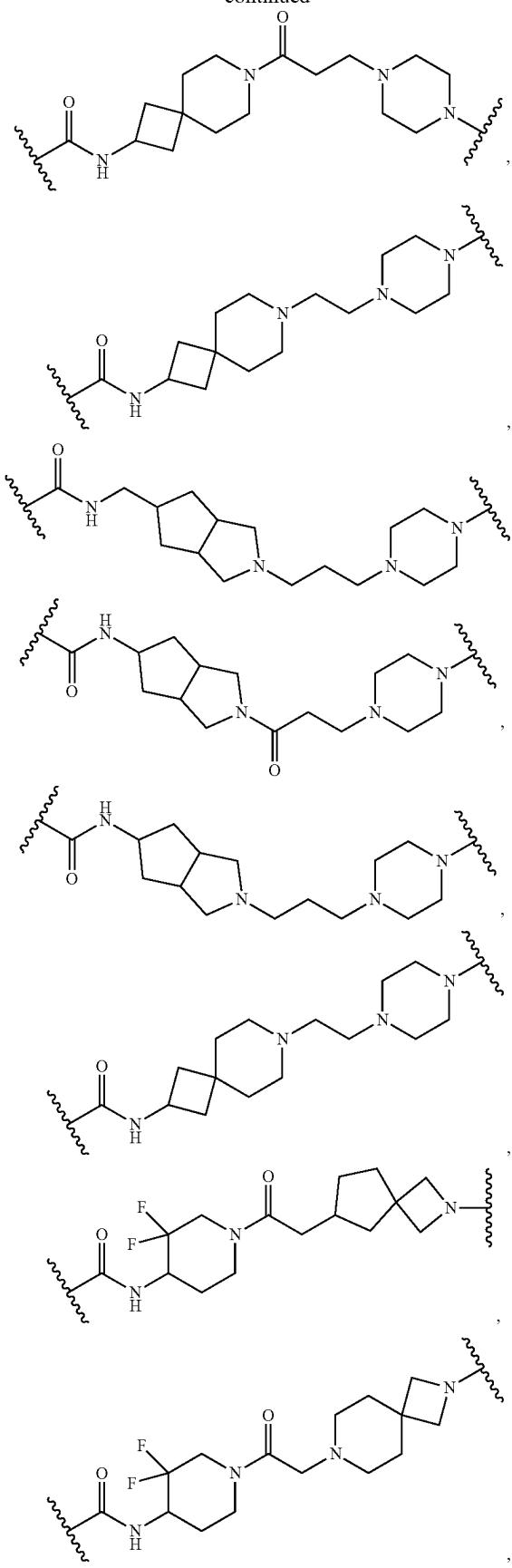


167

-continued

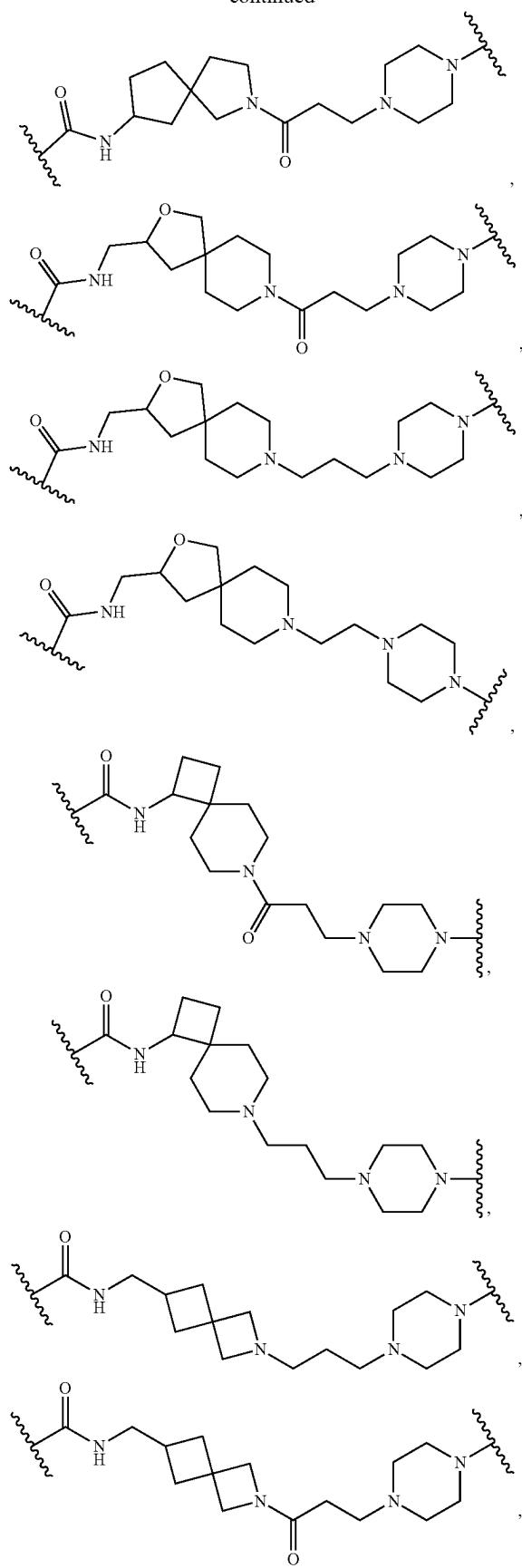
**168**

-continued

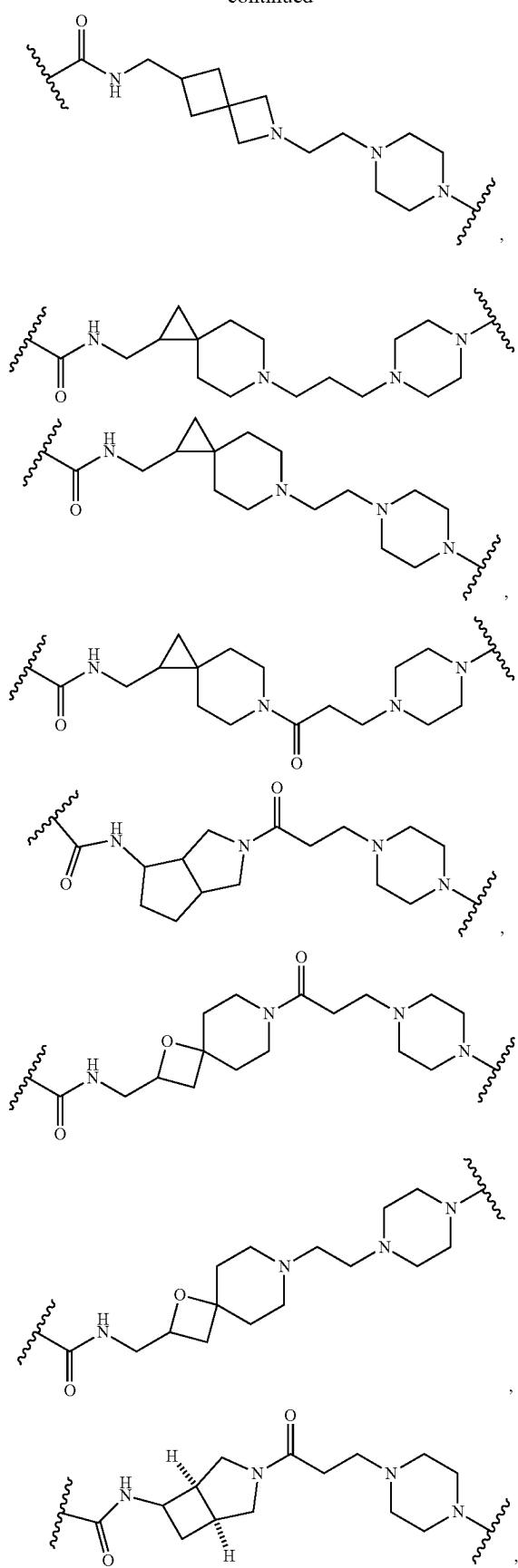


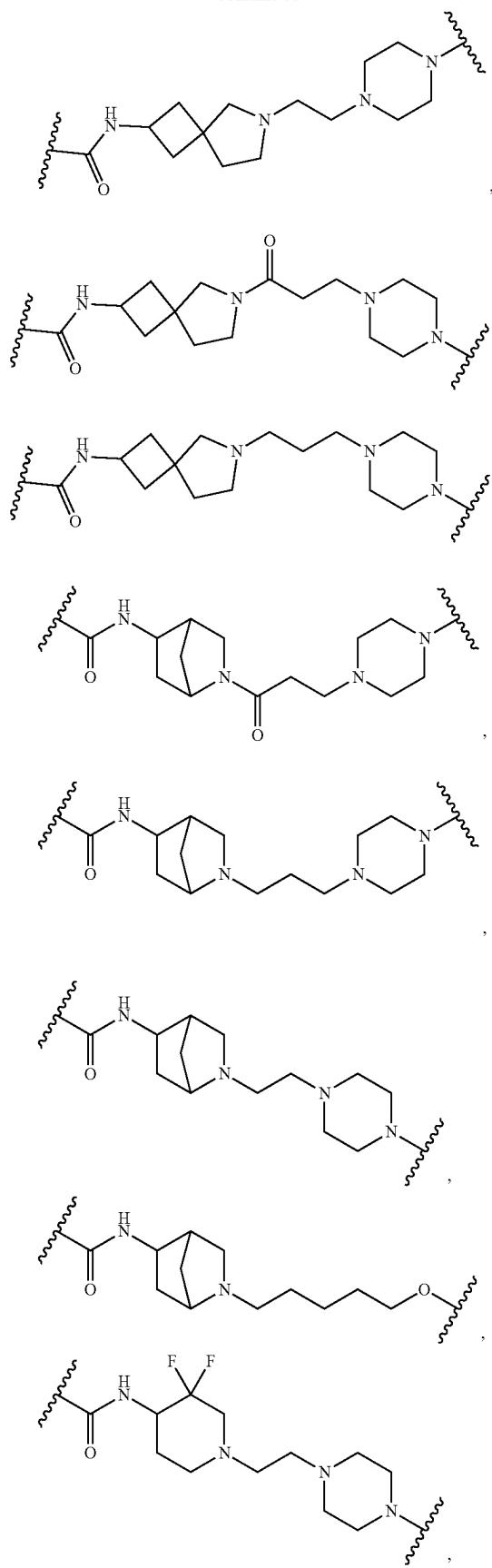
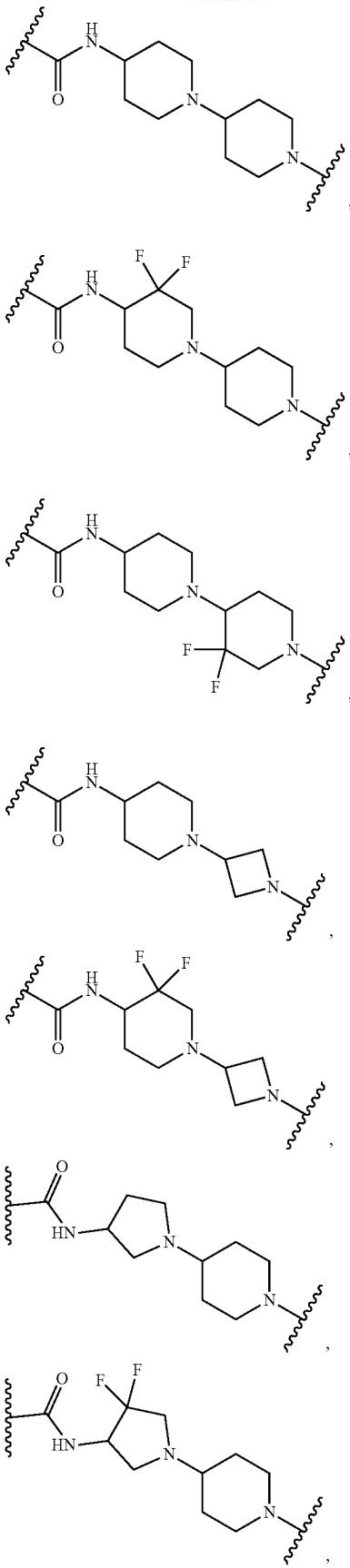
169

-continued

**170**

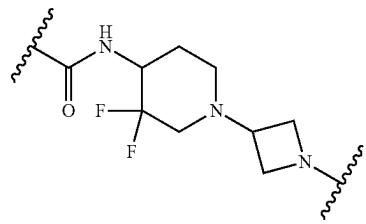
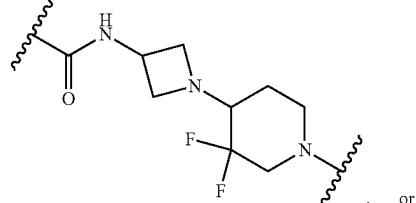
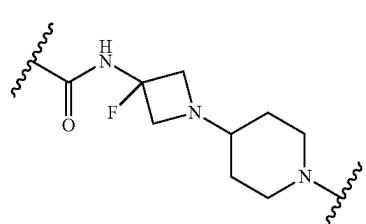
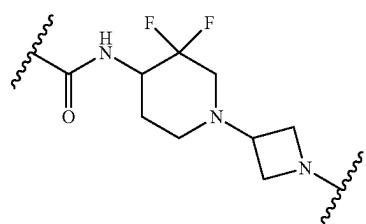
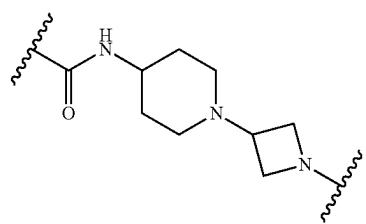
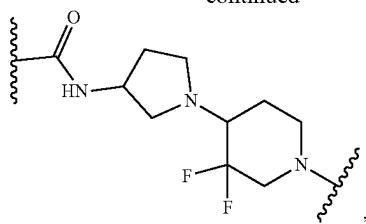
-continued



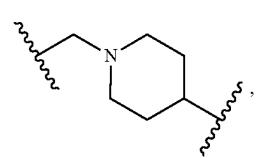
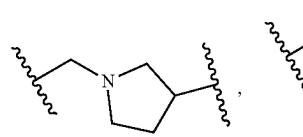
171
-continued**172**
-continued

173

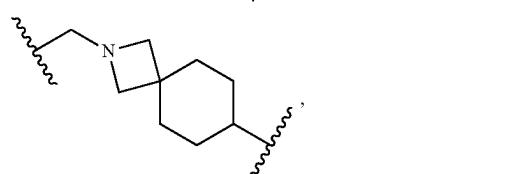
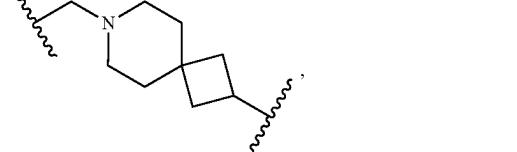
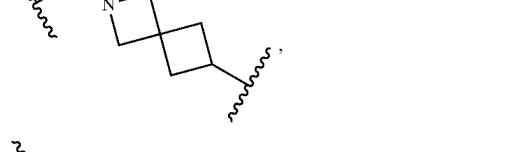
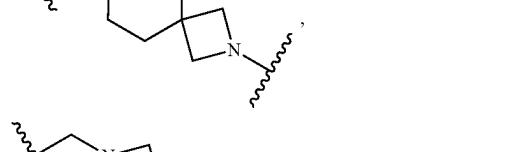
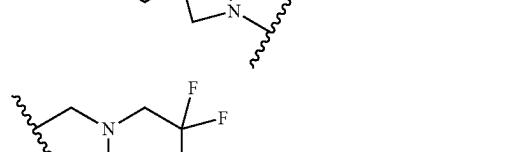
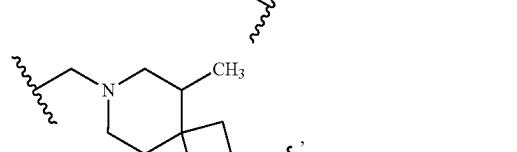
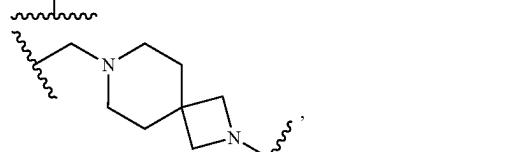
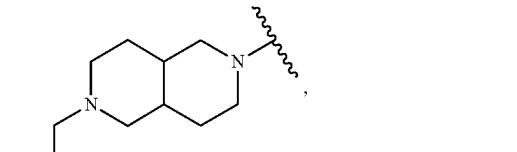
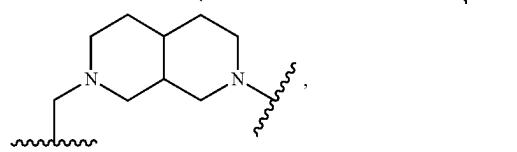
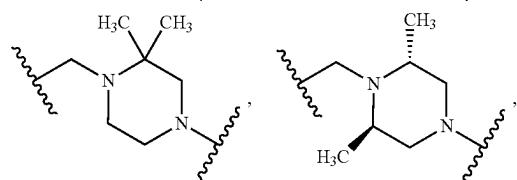
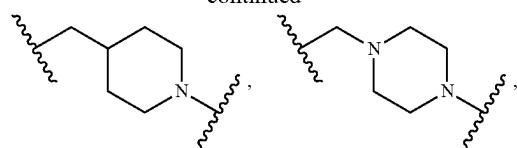
-continued



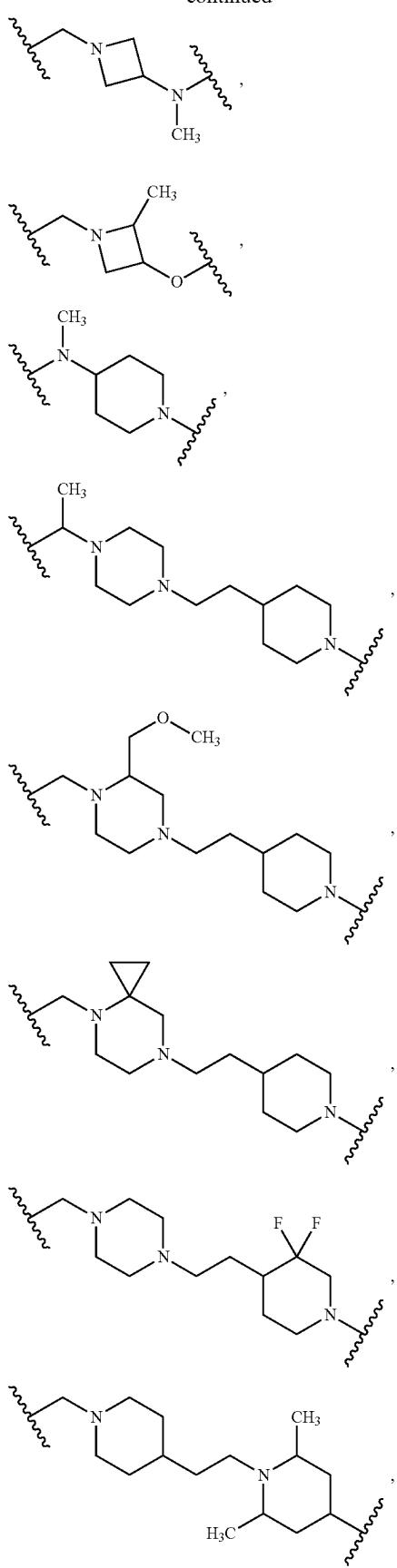
In some embodiments, the linker has the structure of:

**174**

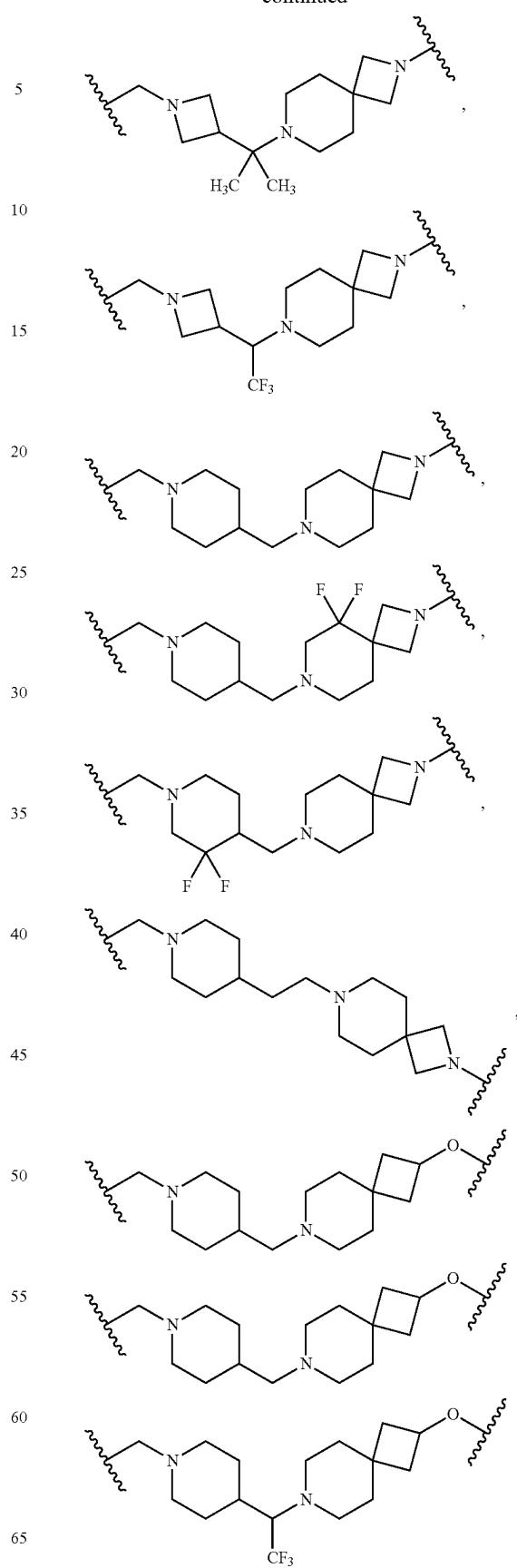
-continued



175

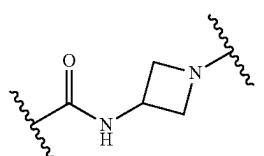
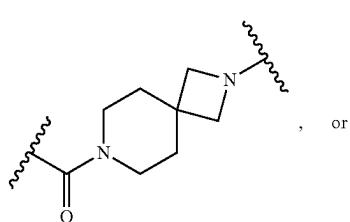
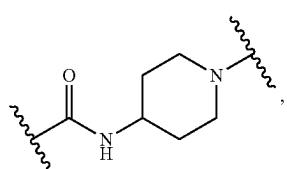
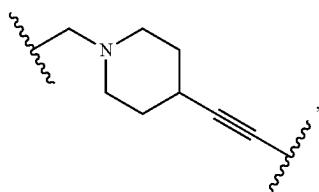
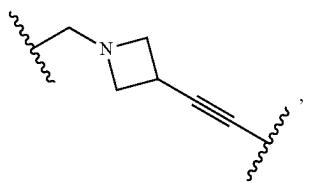


176



177

-continued



In some embodiments, the linker is absent.

In some embodiments, the linker is optionally substituted C₃-C₁₀ carbocyclylene, optionally substituted C₂-C₁₀ heterocyclylene, optionally substituted C₆-C₁₀ arylene, or optionally substituted C₂-C₉ heteroarylene.

In some embodiments, the linker is optionally substituted C₃-C₁₀ carbocyclylene or optionally substituted C₂-C₁₀ heterocyclylene. In some embodiments, the linker is optionally substituted C₆-C₁₀ arylene or optionally substituted C₂-C₉ heteroarylene.

In some embodiments, the linker is optionally substituted C₂-C₉ heterocyclylene.

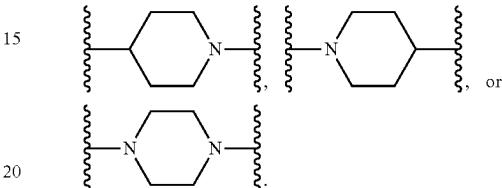
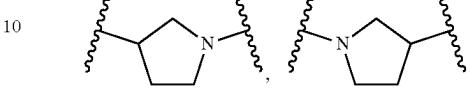
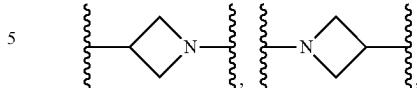
In some embodiments, the C₂-C₉ heterocyclylene is monocyclic. In some embodiments, the C₂-C₉ heterocyclylene is polycyclic.

In some embodiments, the C₂-C₉ heterocyclylene is bicyclic.

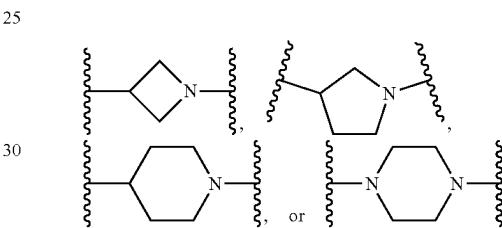
In some embodiments, the C₂-C₉ heterocyclylene is bridged. In some embodiments, the C₂-C₉ heterocyclylene is fused. In some embodiments, the C₂-C₉ heterocyclylene is spirocyclic.

178

In some embodiments, the linker has the structure of



In some embodiments, the linker has the structure of



35 In some embodiments, the compound has the structure of any one of compounds D1-D31 in Table 2A, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound has the structure of compounds D32-D184 in Table 2B, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound has the structure of any one of compounds D185-D316 in Table 2C, or a pharmaceutically acceptable salt thereof.

40 In some embodiments, the compound has the structure of any one of compounds D1, D7, D15-D21, D23, and D27-D30 in Table 2A, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound has the structure of any one of compounds D32-D42, D46, D48-D63, D65-D73, D75-D83, D85-D87, D89-D93, D95-D116, D118, D120-D164, D166-D168, D170, D171, D173, D174, D176-D178, D180, D182, and D184 in Table 2B, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound has the structure of any one of compounds D185-D190, D192-D204, D248, D254-D258, D260, D262-D269, D271-D280, D284, D286-D291, and D293-D316 in Table 2C, or a pharmaceutically acceptable salt thereof.

45 In an aspect, the disclosure features compounds D1-D31 in Table 2A, or a pharmaceutically acceptable salt thereof.

50 In an aspect, the disclosure features compounds D32-D184 in Table 2B, or a pharmaceutically acceptable salt thereof.

55 In an aspect, the disclosure features compounds D185-D316 in Table 2C, or a pharmaceutically acceptable salt thereof.

TABLE 2A

Compounds D1-D31 of the Disclosure

Com- ound No.	Structure
D1	
D2	
D3	

TABLE 2A-continued

Compound No.	Structure
D4	
D5	
D6	
D7	

TABLE 2A-continued

Compounds D1-D31 of the Disclosure

Com- ound No.	Structure
D8	
D9	
D10	

TABLE 2A-continued

Compounds D1-D31 of the Disclosure

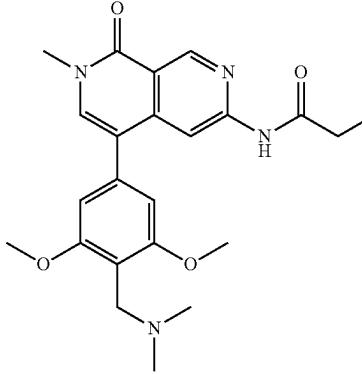
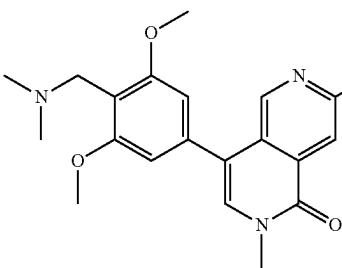
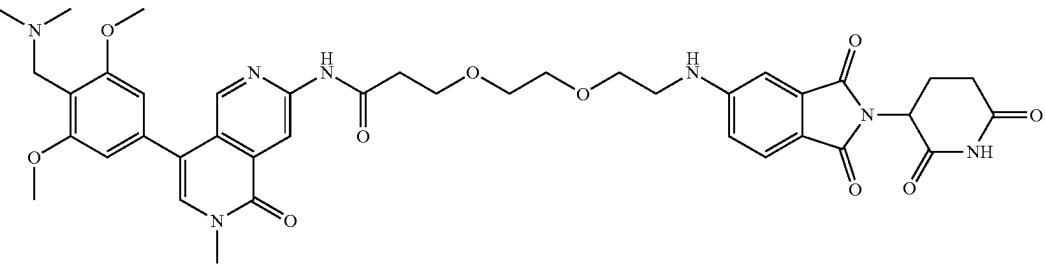
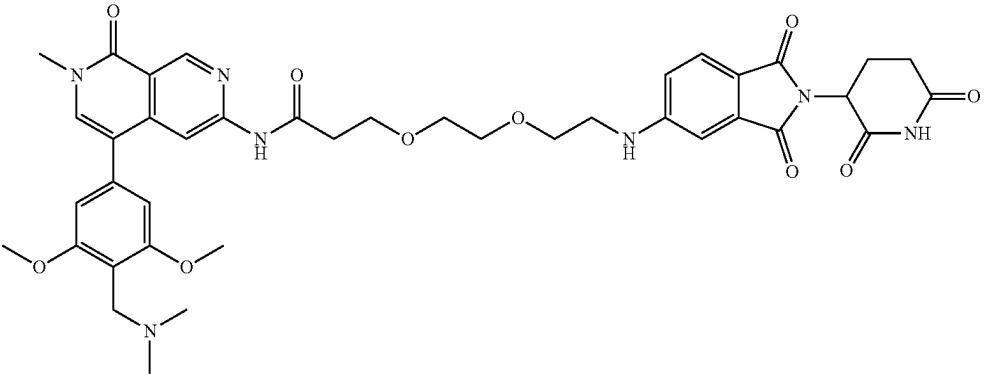
Compound No.	Structure
D11	
D12	
D13	
D14	

TABLE 2A-continued

Compounds D1-D31 of the Disclosure

Com- ound No.	Structure
D15	
D16	
D17	

TABLE 2A-continued

Compounds D1-D31 of the Disclosure

Com- ound No.	Structure
D18	
D19	
D20	
D21	

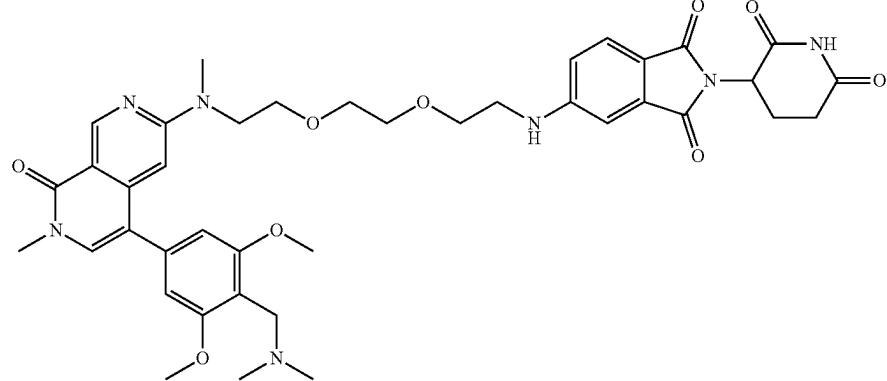
TABLE 2A-continued

Compounds D1-D31 of the Disclosure

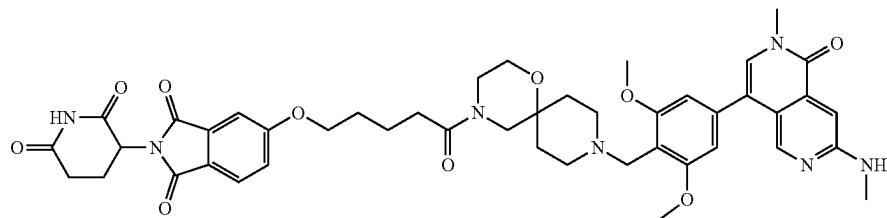
Com-
ound
No.

Structure

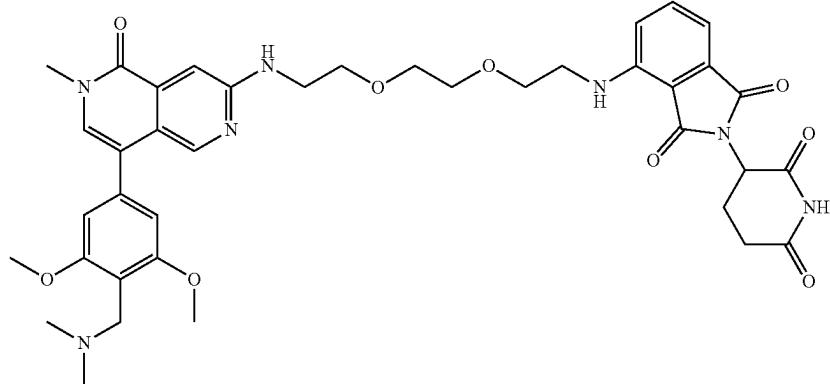
D22



D23



D24



D25

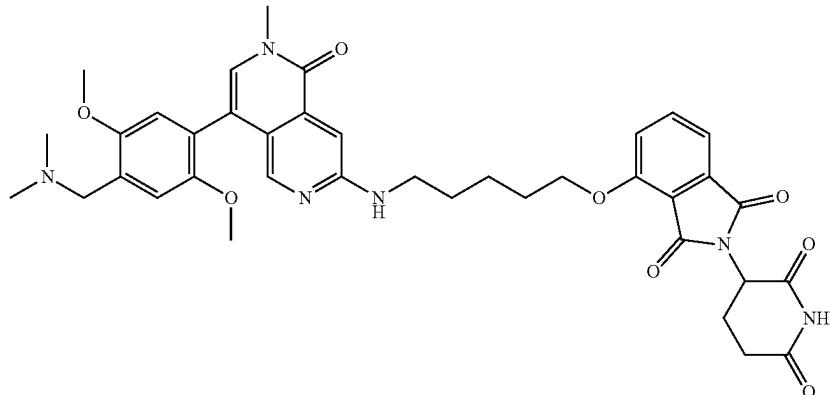


TABLE 2A-continued

Compounds D1-D31 of the Disclosure

Compound No.	Structure
D26	
D27	
D28	
D29	

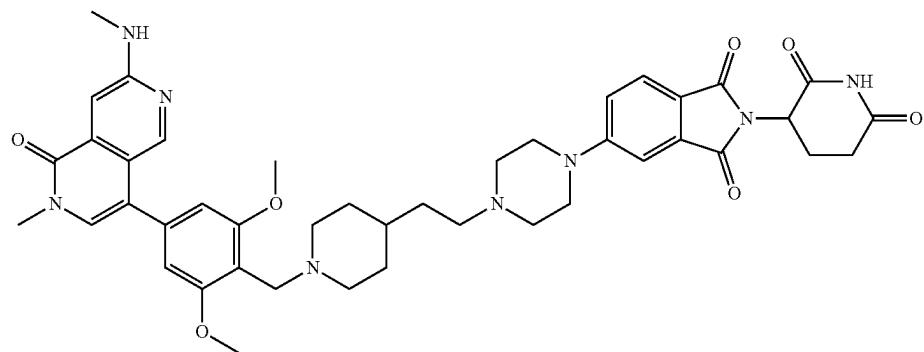
TABLE 2A-continued

Compounds D1-D31 of the Disclosure

Com-
ound
No.

Structure

D30



D31

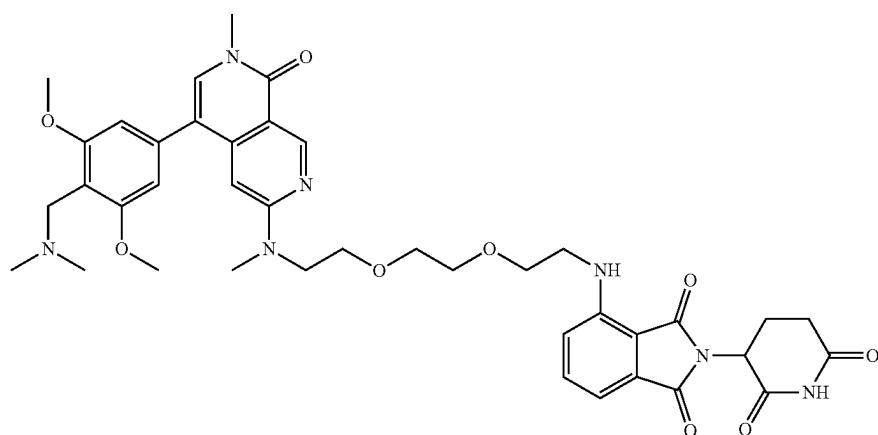


TABLE 2B

Compounds D32-D184 of the Disclosure

Com-
ound
No.

Structure

D32

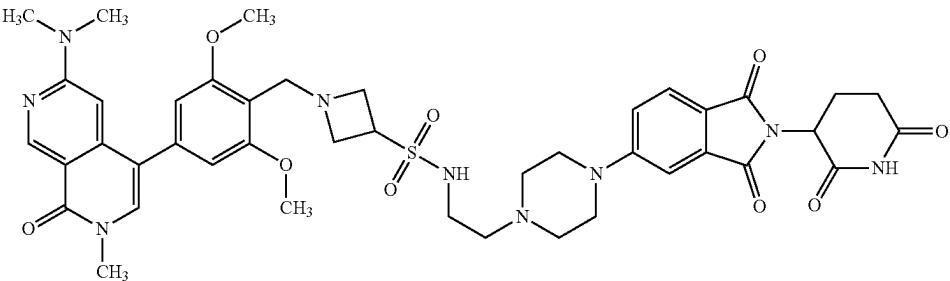


TABLE 2B-continued

Compounds D32-D184 of the Disclosure

Com- ound No.	Structure
D33	
D34	
D35	
D36	

TABLE 2B-continued

Compounds D32-D184 of the Disclosure

Com- ound No.	Structure
D37	
D38	
D39	
D40	

TABLE 2B-continued

Compounds D32-D184 of the Disclosure

Com- ound No.	Structure
D41	
D42	
D43	
D44	

TABLE 2B-continued

Compounds D32-D184 of the Disclosure

Com- ound No.	Structure
D45	
D46	
D47	
D48	

TABLE 2B-continued

Compounds D32-D184 of the Disclosure

Com- ound No.	Structure
D49	
D50	
D51	
D52	

TABLE 2B-continued

Compounds D32-D184 of the Disclosure

Com- ound No.	Structure
D53	
D54	
D55	
D56	

TABLE 2B-continued

Compounds D32-D184 of the Disclosure

Com- ound No.	Structure
D57	
D58	
D59	
D60	

TABLE 2B-continued

Compounds D32-D184 of the Disclosure

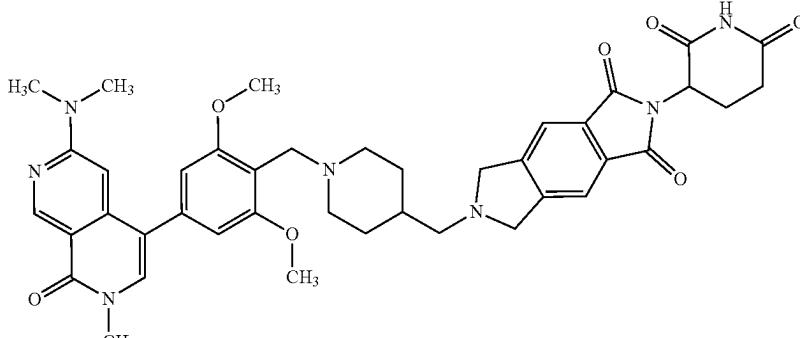
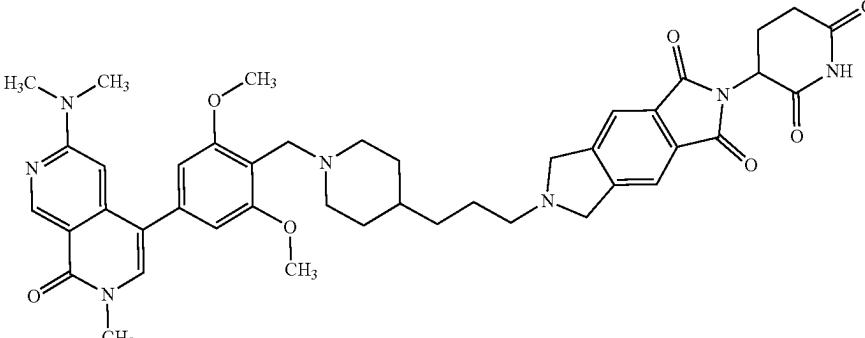
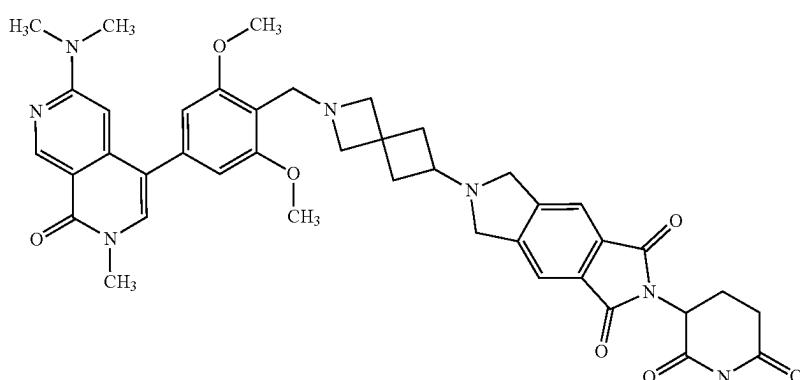
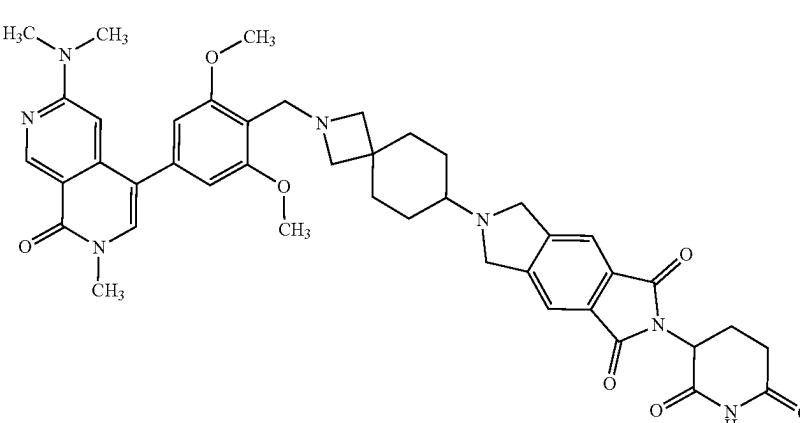
Compound No.	Structure
D61	
D62	
D63	
D64	

TABLE 2B-continued

Compounds D32-D184 of the Disclosure

Com- ound No.	Structure
D65	
D66	
D67	
D68	

TABLE 2B-continued

Compounds D32-D184 of the Disclosure

Com- ound No.	Structure
D69	
D70	
D71	
D72	

TABLE 2B-continued

Compounds D32-D184 of the Disclosure

Compound No.	Structure
D73	
D74	
D75	
D76	
D77	

TABLE 2B-continued

Compounds D32-D184 of the Disclosure

Com- ound No.	Structure
D78	
D79	
D80	
D81	

TABLE 2B-continued

Compounds D32-D184 of the Disclosure

Com- ound No.	Structure
D82	
D83	
D84	
D85	

TABLE 2B-continued

Compounds D32-D184 of the Disclosure

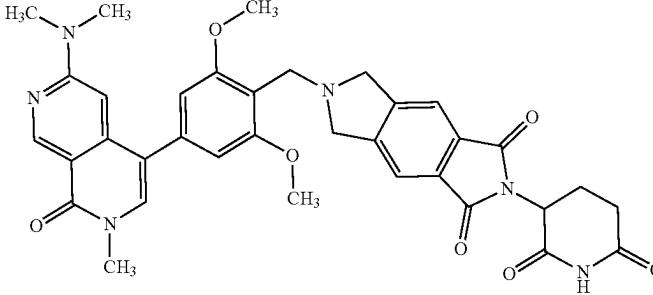
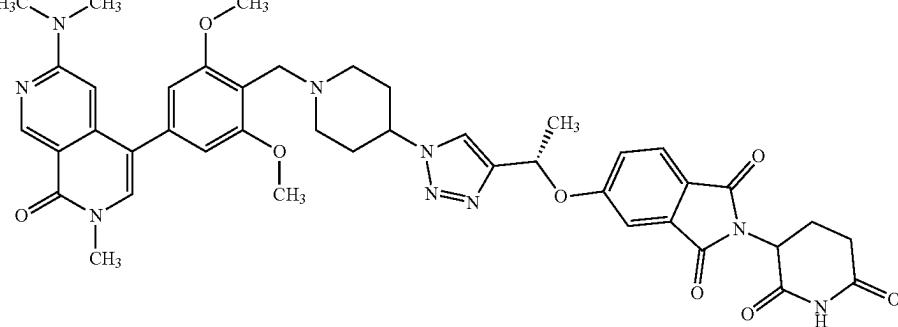
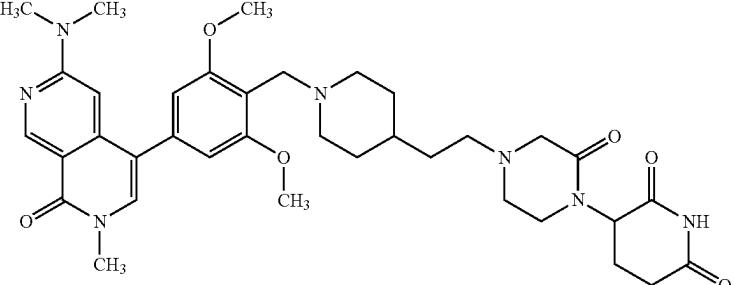
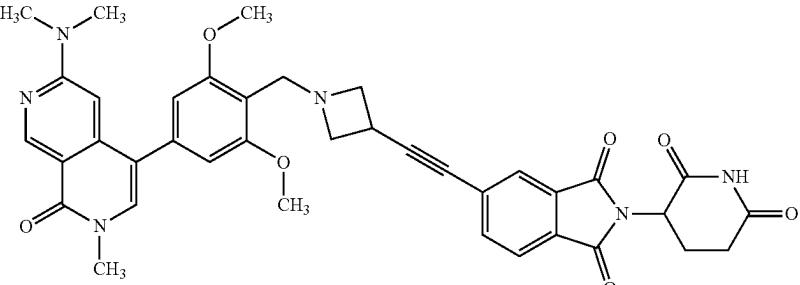
Com- ound No.	Structure
D86	
D87	
D88	
D89	

TABLE 2B-continued

Compounds D32-D184 of the Disclosure

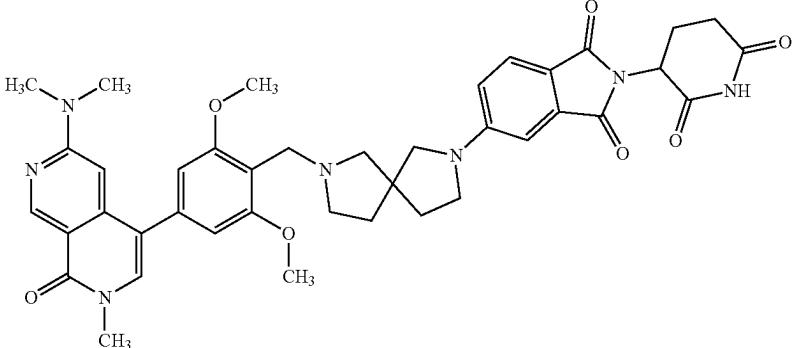
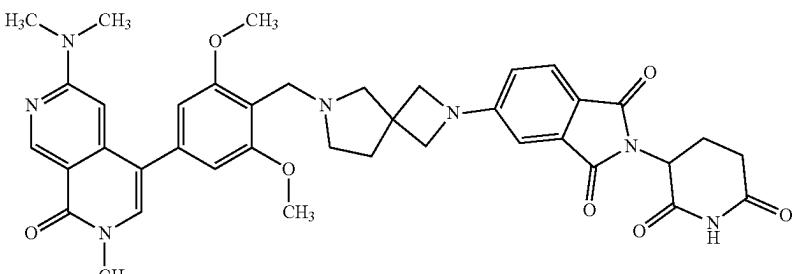
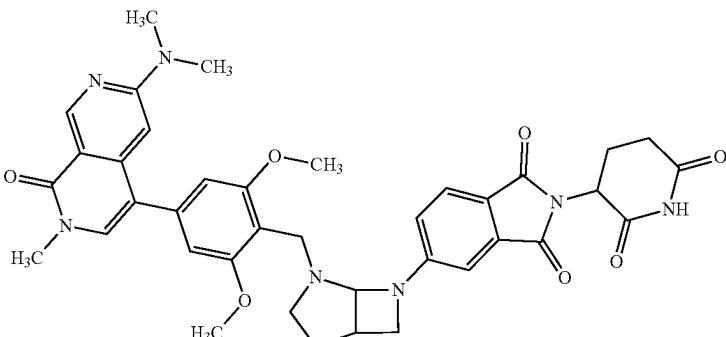
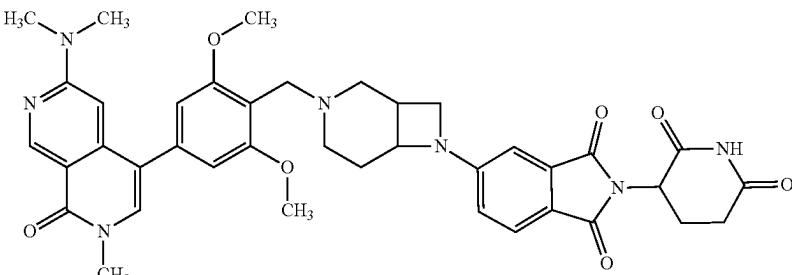
Com- ound No.	Structure
D90	
D91	
D92	
D93	

TABLE 2B-continued

Compounds D32-D184 of the Disclosure

Com- ound No.	Structure
D94	
D95	
D96	
D97	

TABLE 2B-continued

Compounds D32-D184 of the Disclosure

Compound No.	Structure
D98	
D99	
D100	
D101	
D102	

TABLE 2B-continued

Compounds D32-D184 of the Disclosure

Com- ound No.	Structure
D103	
D104	
D105	
D106	

TABLE 2B-continued

Compounds D32-D184 of the Disclosure

Com- ound No.	Structure
D107	
D108	
D109	
D110	

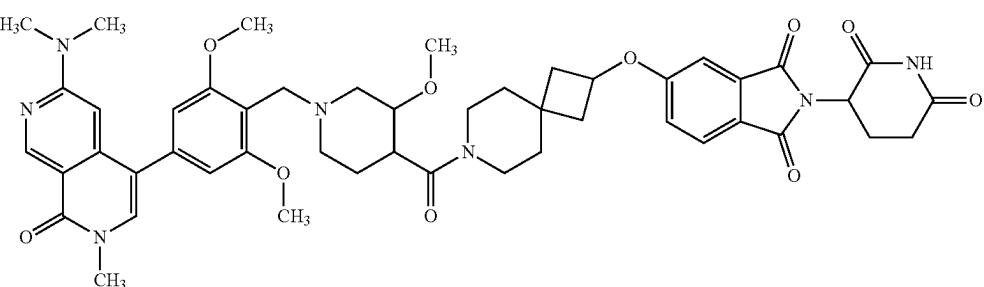
TABLE 2B-continued

Compounds D32-D184 of the Disclosure

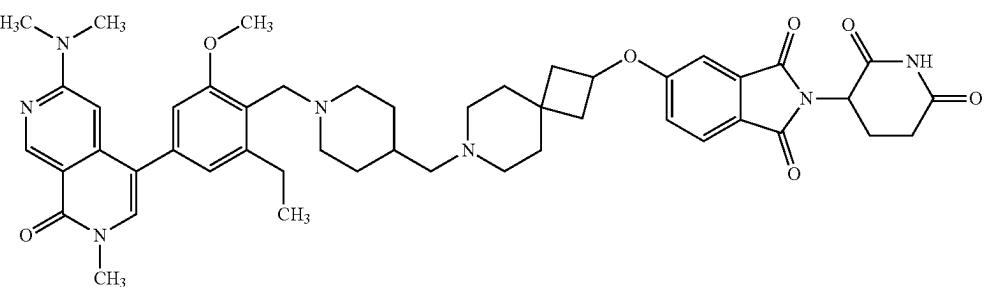
Com-
ound
No.

Structure

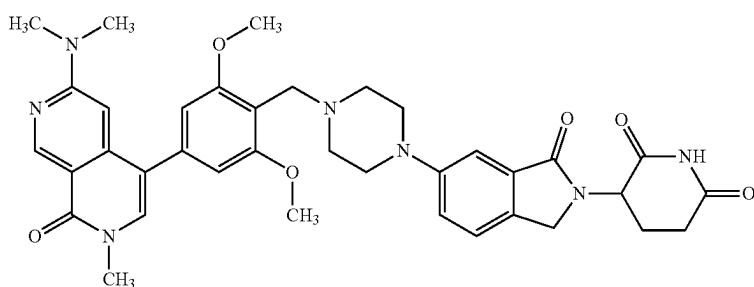
D111



D112



D113



D114

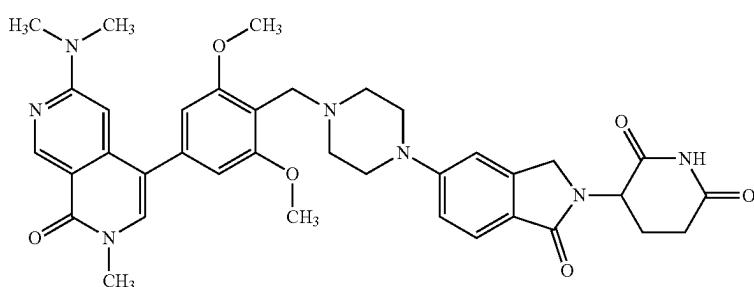


TABLE 2B-continued

Compounds D32-D184 of the Disclosure

Com- ound No.	Structure
D115	
D116	
D117	
D118	

TABLE 2B-continued

Compounds D32-D184 of the Disclosure

Com- ound No.	Structure
D119	
D120	
D121	
D122	

TABLE 2B-continued

Compounds D32-D184 of the Disclosure

Com- ound No.	Structure
D123	
D124	
D125	
D126	

TABLE 2B-continued

Compounds D32-D184 of the Disclosure

Com- ound No.	Structure
D127	
D128	
D129	
D130	

TABLE 2B-continued

Compounds D32-D184 of the Disclosure

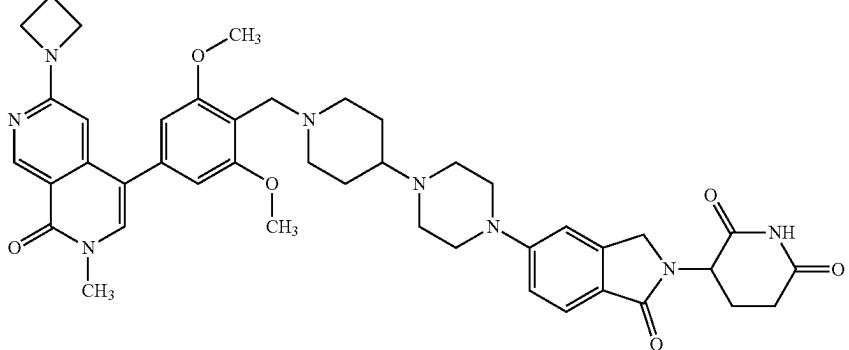
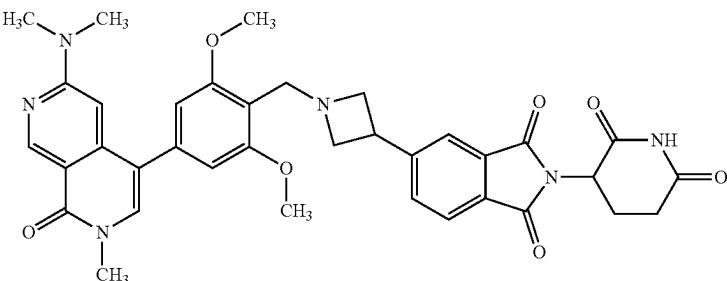
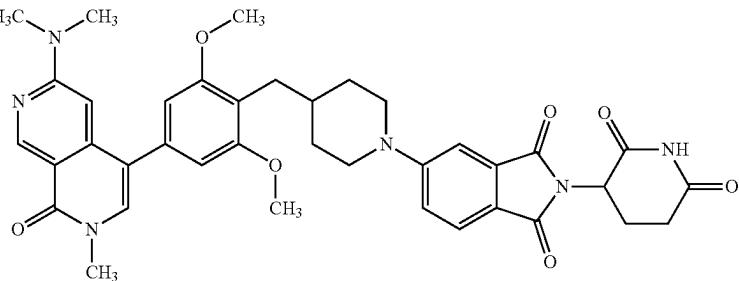
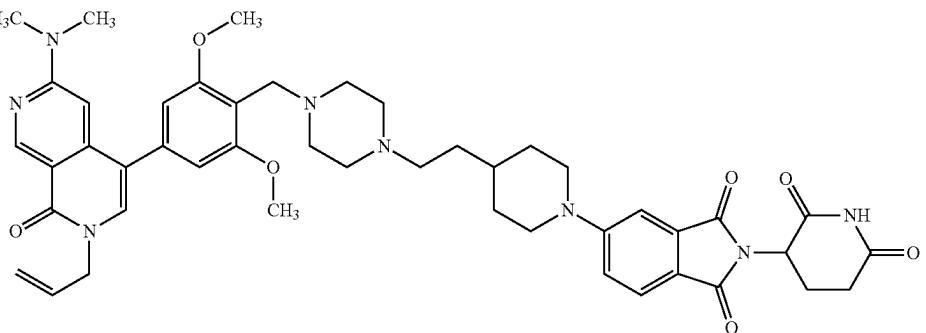
Com- ound No.	Structure
D131	
D132	
D133	
D134	

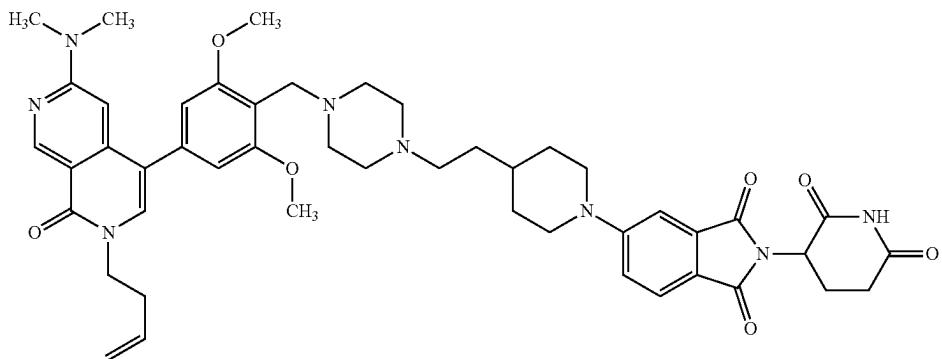
TABLE 2B-continued

Compounds D32-D184 of the Disclosure

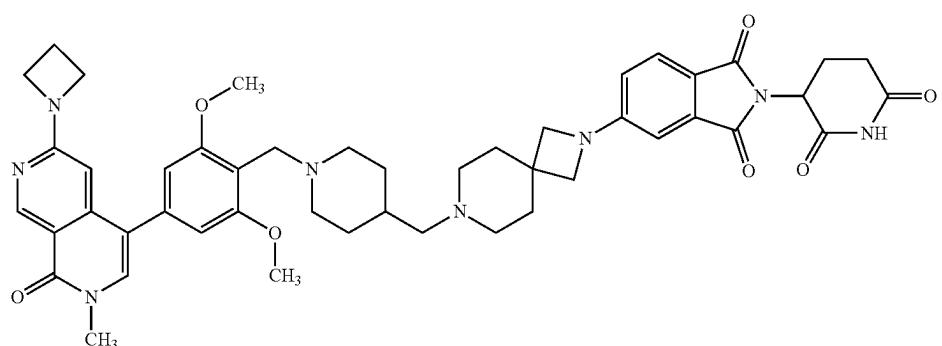
Com-
ound
No.

Structure

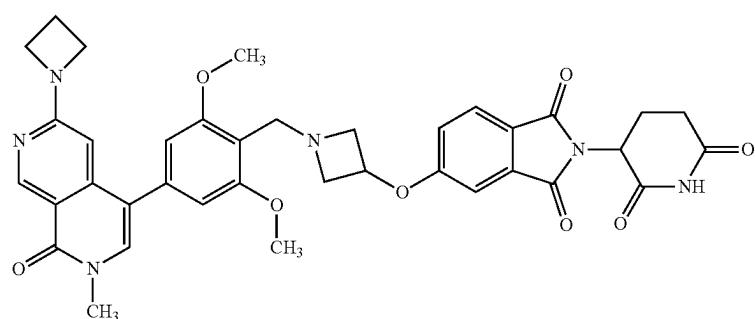
D135



D136



D137



D138

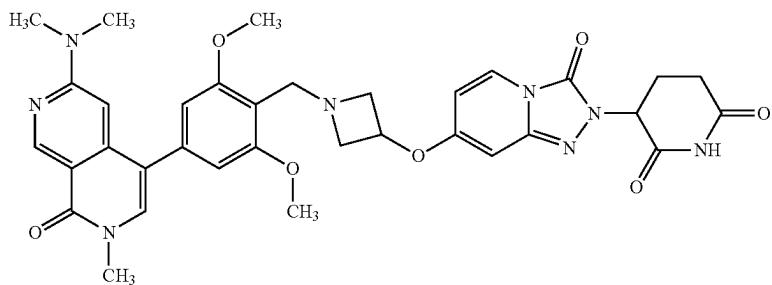


TABLE 2B-continued

Compounds D32-D184 of the Disclosure

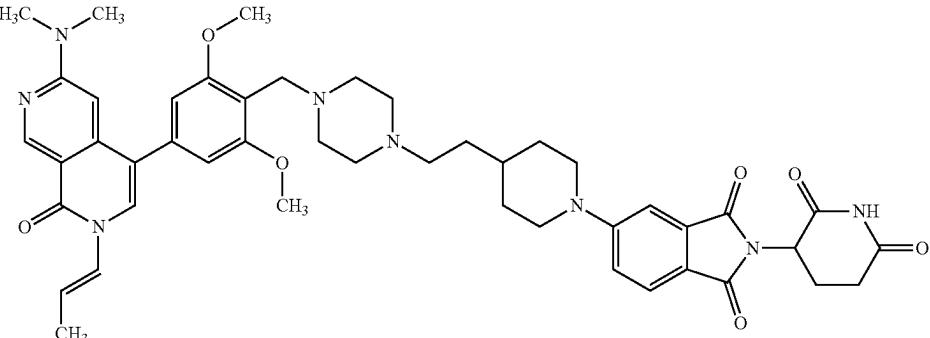
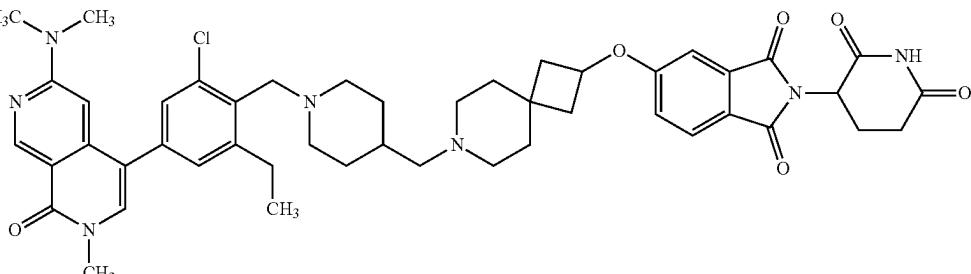
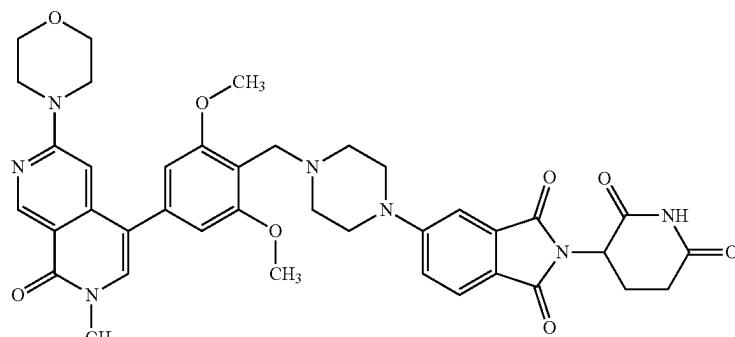
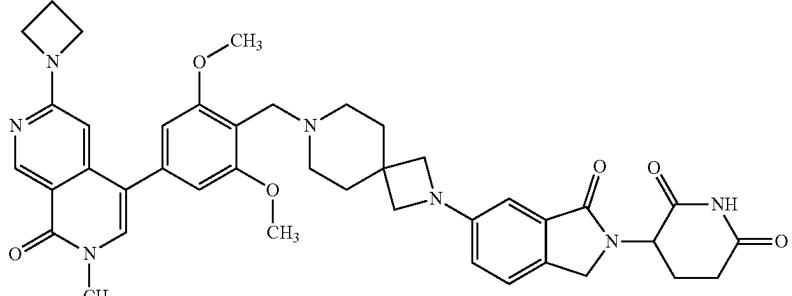
Com- ound No.	Structure
D139	
D140	
D141	
D142	

TABLE 2B-continued

Compounds D32-D184 of the Disclosure

Com- ound No.	Structure
D143	
D144	
D145	
D146	

TABLE 2B-continued

Compounds D32-D184 of the Disclosure

Com- ound No.	Structure
D147	
D148	
D149	
D150	

TABLE 2B-continued

Compounds D32-D184 of the Disclosure

Com- ound No.	Structure
D151	
D152	
D153	
D154	

TABLE 2B-continued

Compounds D32-D184 of the Disclosure

Com- ound No.	Structure
D155	
D156	
D157	
D158	

TABLE 2B-continued

Compounds D32-D184 of the Disclosure

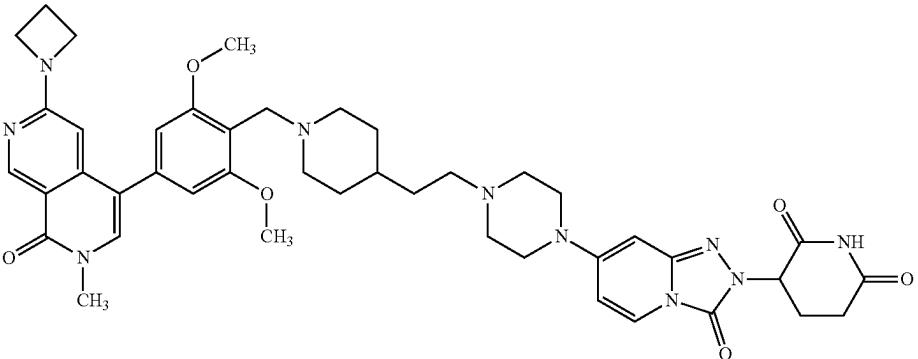
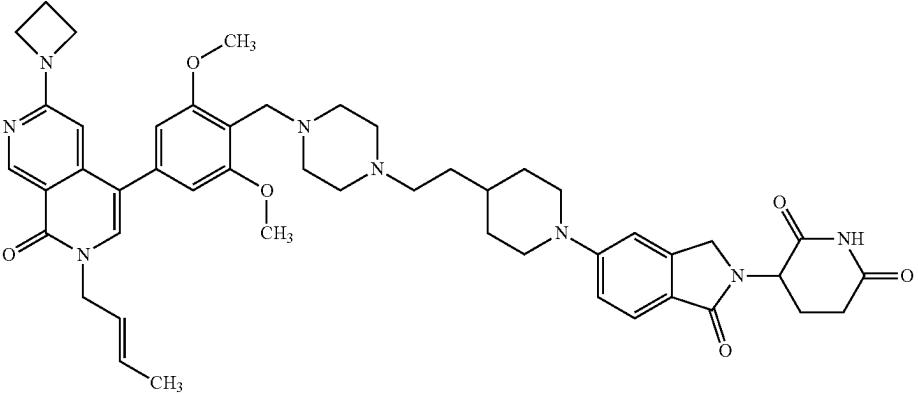
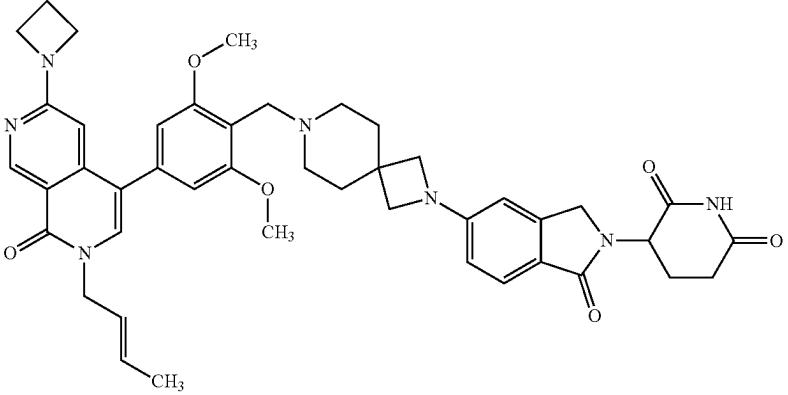
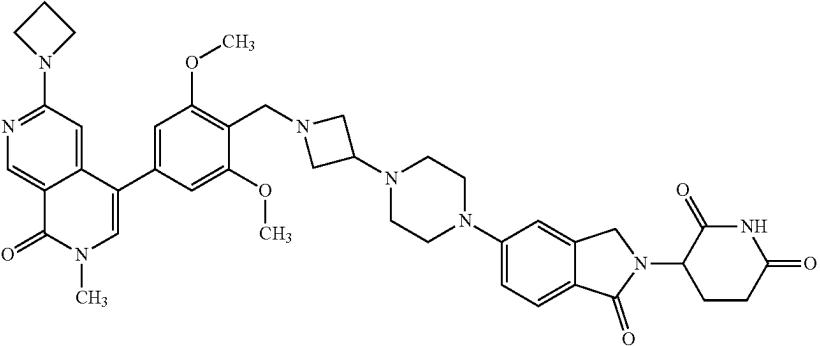
Compound No.	Structure
D159	
D160	
D161	
D162	

TABLE 2B-continued

Compounds D32-D184 of the Disclosure

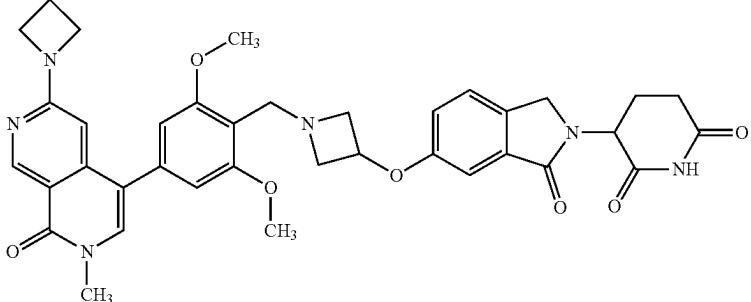
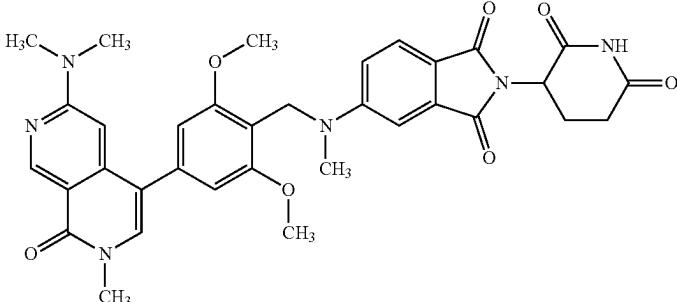
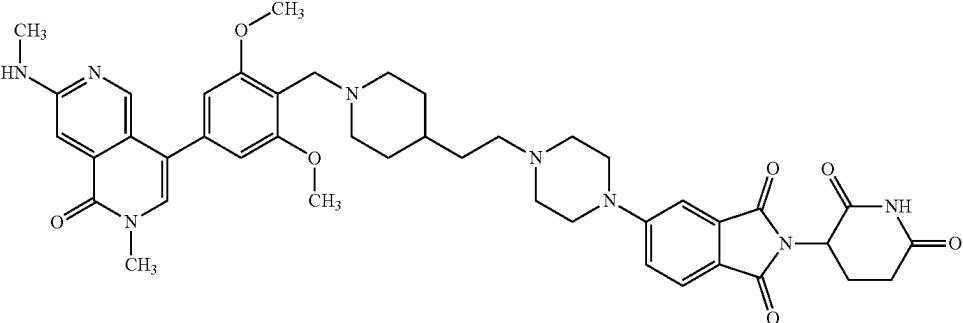
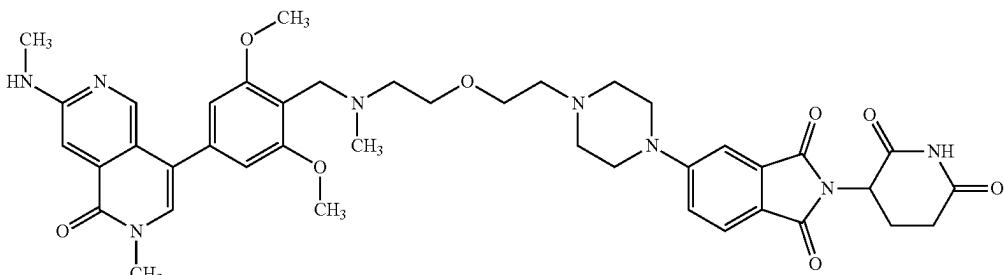
Com- ound No.	Structure
D163	
D164	
D165	
D166	

TABLE 2B-continued

Compounds D32-D184 of the Disclosure

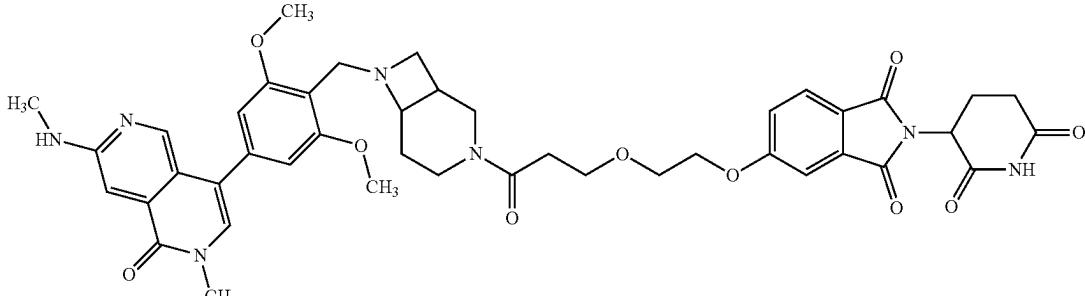
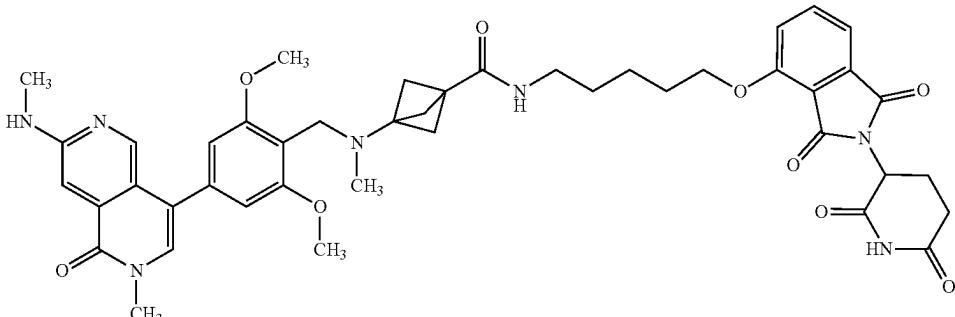
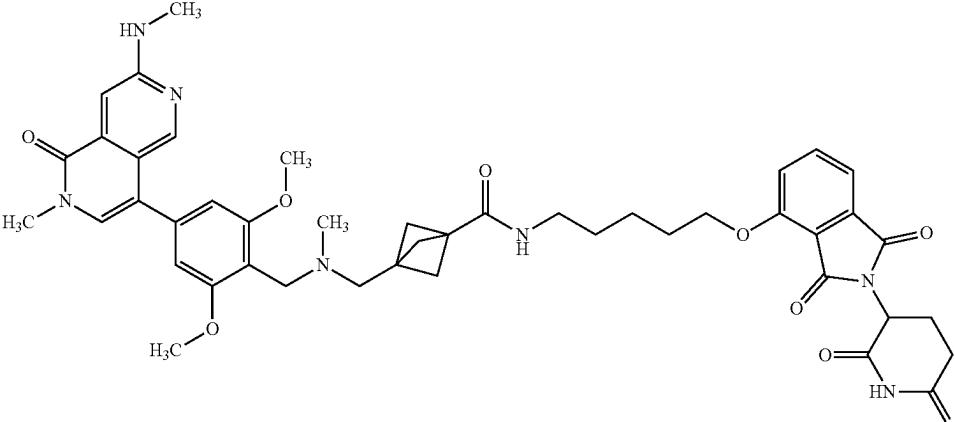
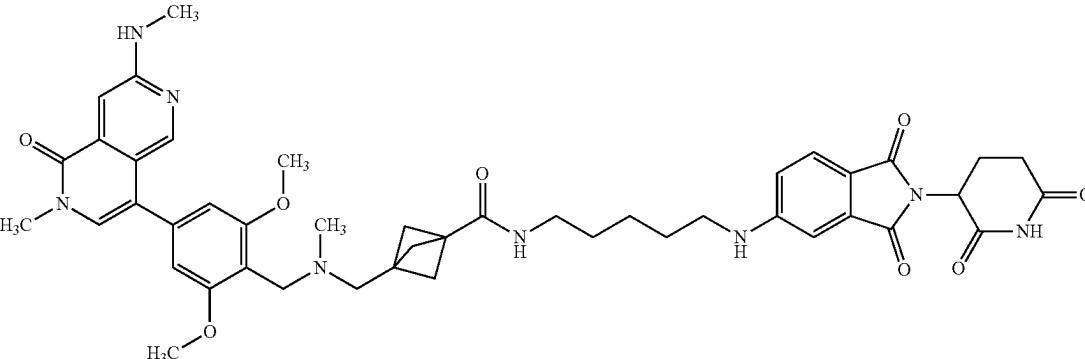
Compound No.	Structure
D167	
D168	
D169	
D170	

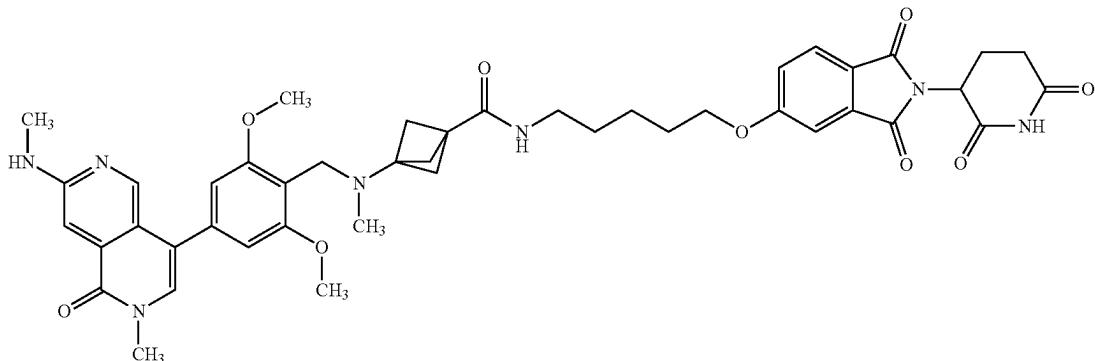
TABLE 2B-continued

Compounds D32-D184 of the Disclosure

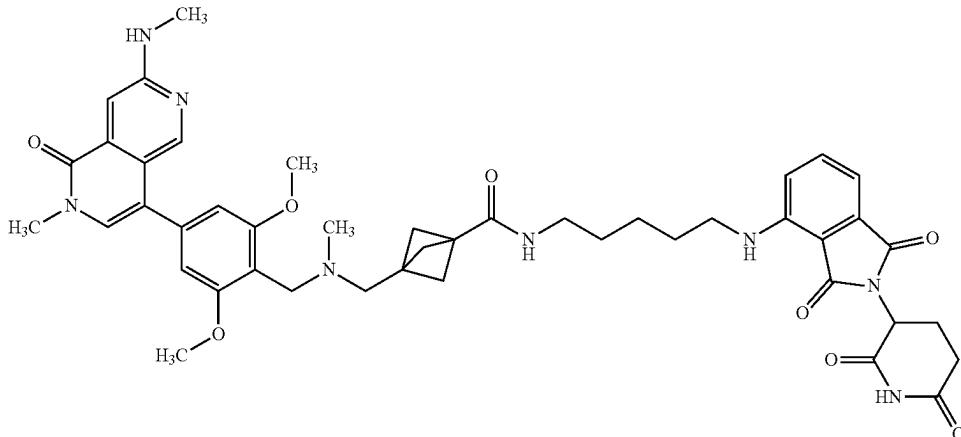
Compound No.

Structure

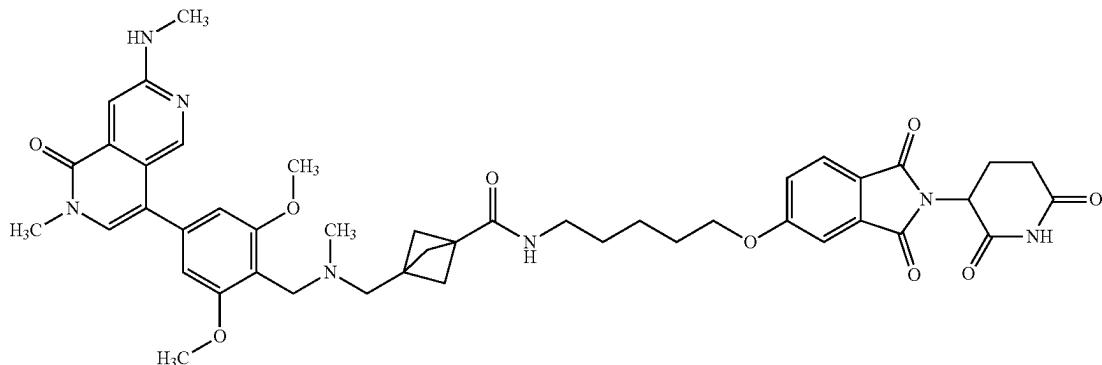
D171



D172



D173



D174

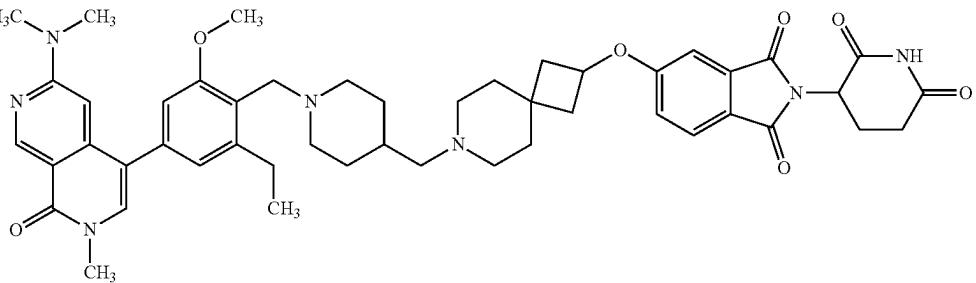


TABLE 2B-continued

Compounds D32-D184 of the Disclosure

Com- ound No.	Structure
D175	
D176	
D177	
D178	

TABLE 2B-continued

Compounds D32-D184 of the Disclosure

Com- ound No.	Structure
D179	
D180	
D181	
D182	

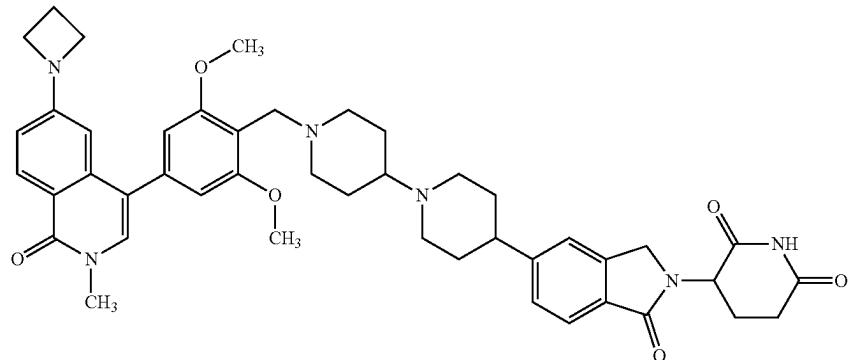
TABLE 2B-continued

Compounds D32-D184 of the Disclosure

Com-
ound
No.

Structure

D183



D184

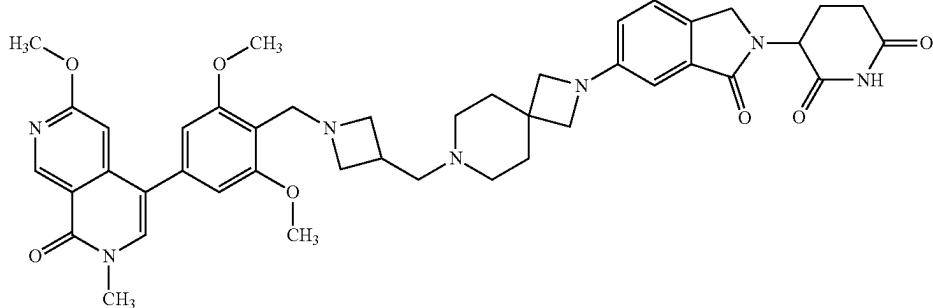


TABLE 2C

Compounds D185-D316 of the Disclosure

Compound No.

Structure

D185

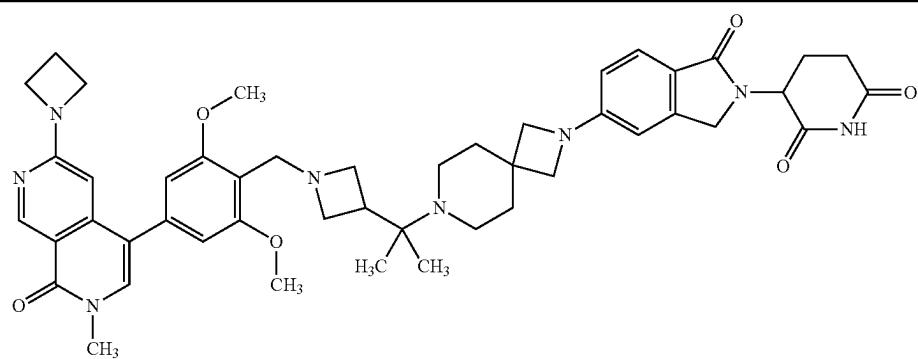


TABLE 2C-continued

Compounds D185-D316 of the Disclosure

Compound No.	Structure
D186	
D187	
D188	
D189	

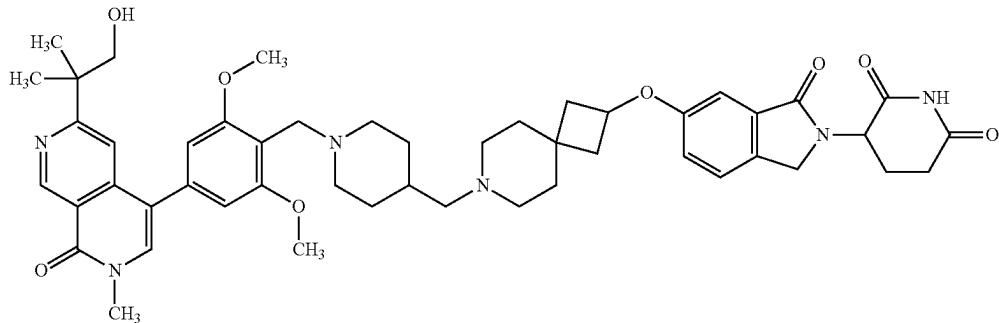
TABLE 2C-continued

Compounds D185-D316 of the Disclosure

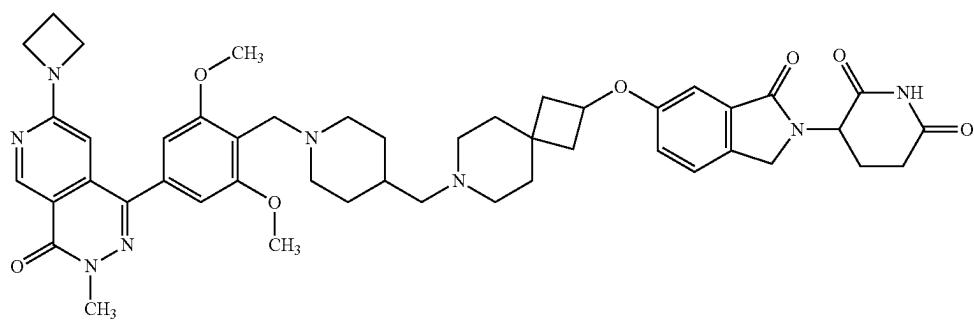
Compound No.

Structure

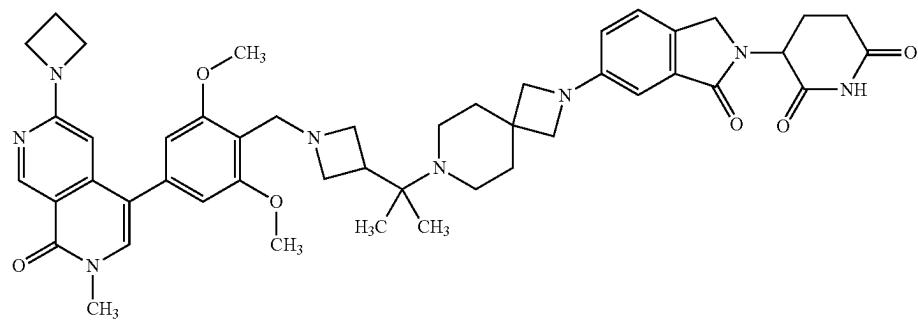
D190



D191



D192



D193

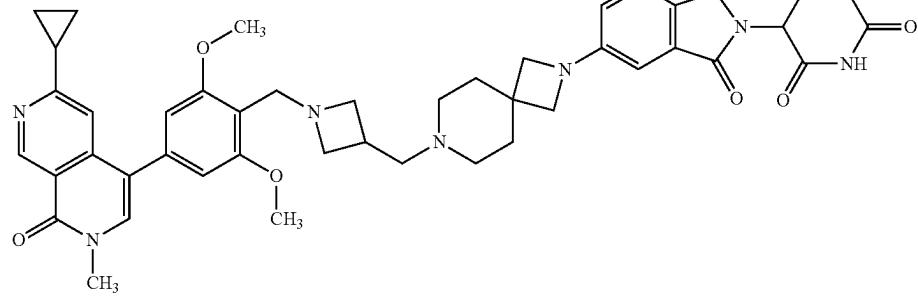


TABLE 2C-continued

Compounds D185-D316 of the Disclosure

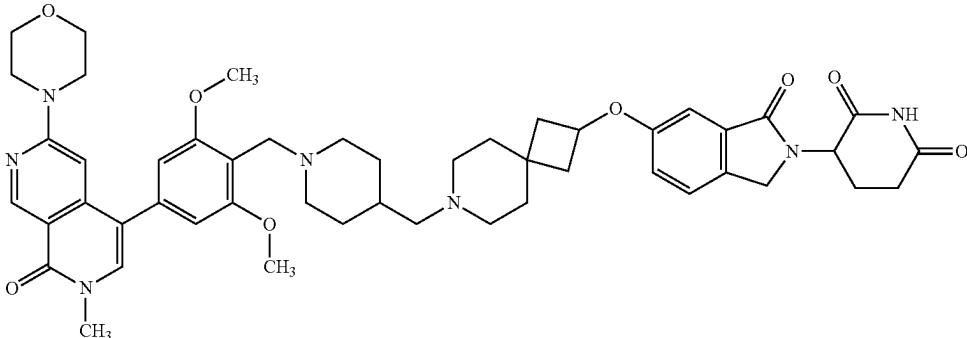
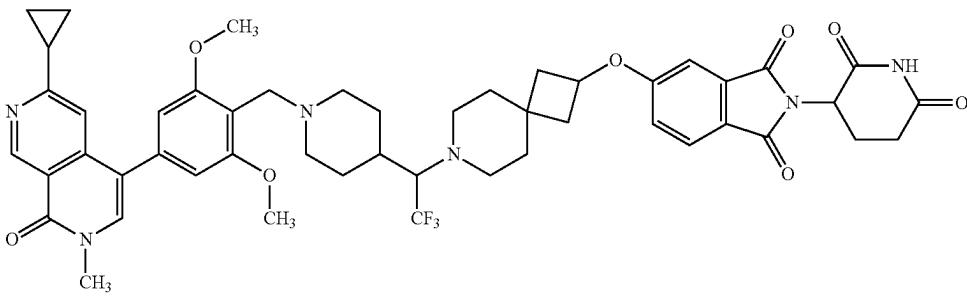
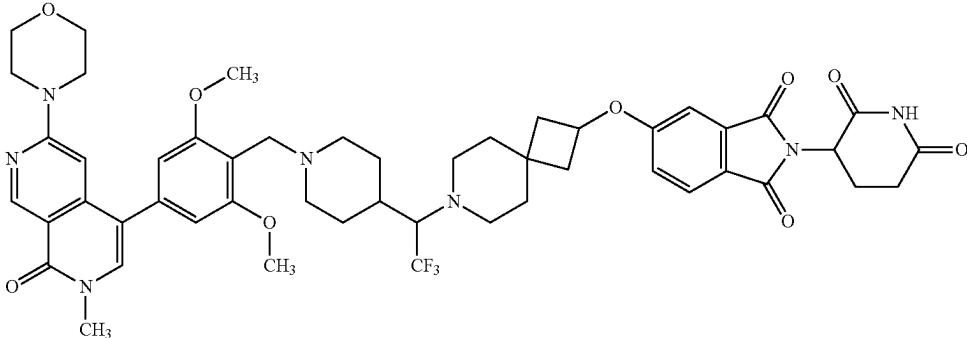
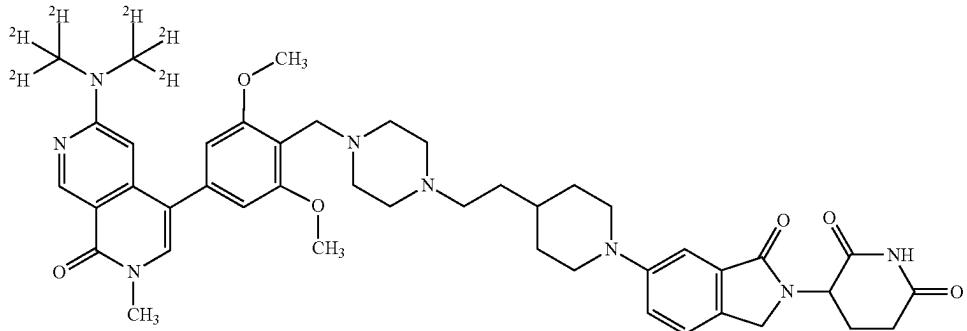
Compound No.	Structure
D194	
D195	
D196	
D197	

TABLE 2C-continued

Compounds D185-D316 of the Disclosure

Compound No.	Structure
D198	
D199	
D200	
D201	

TABLE 2C-continued

Compounds D185-D316 of the Disclosure

Compound No.	Structure
D202	
D203	
D204	
D205	

TABLE 2C-continued

Compounds D185-D316 of the Disclosure

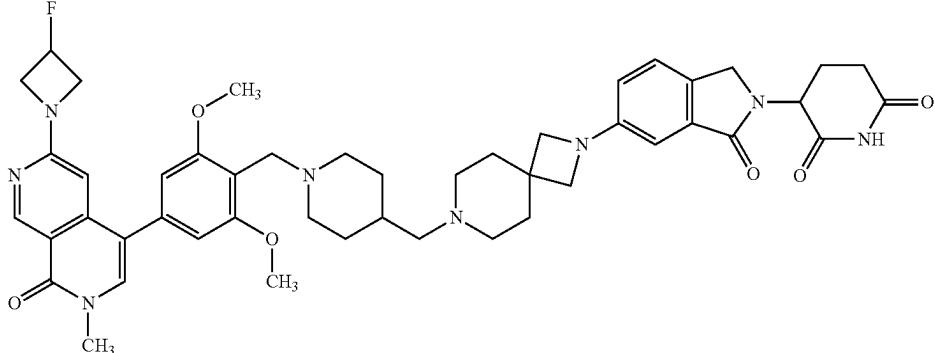
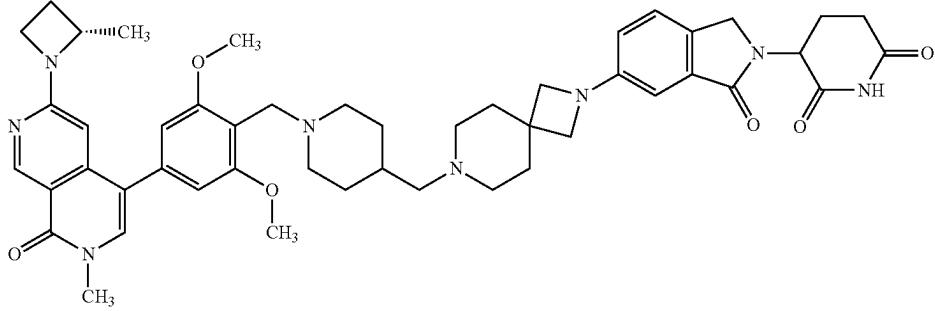
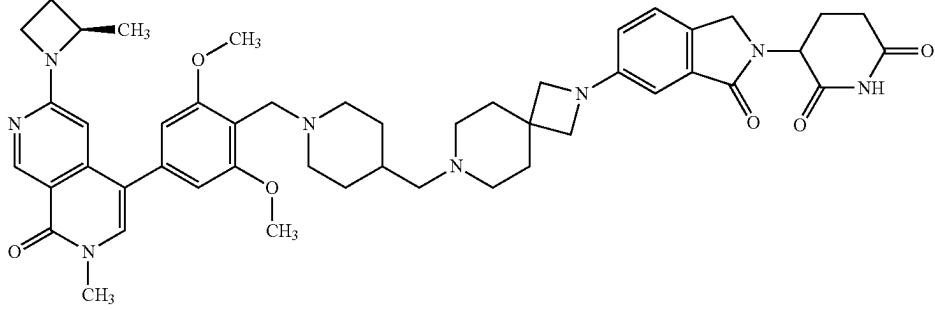
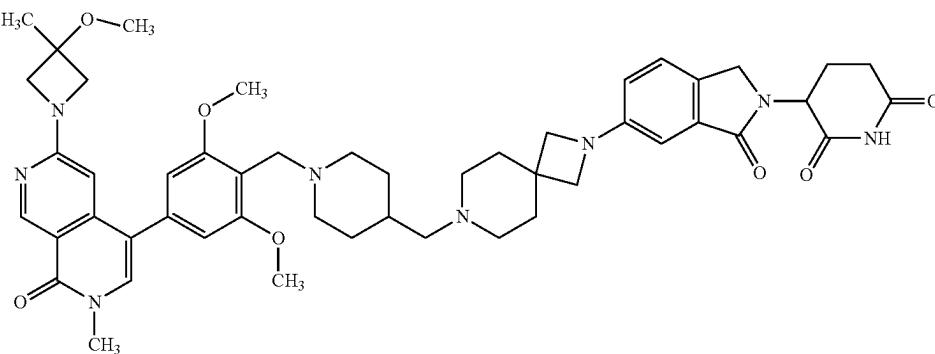
Compound No.	Structure
D206	
D207	
D208	
D209	

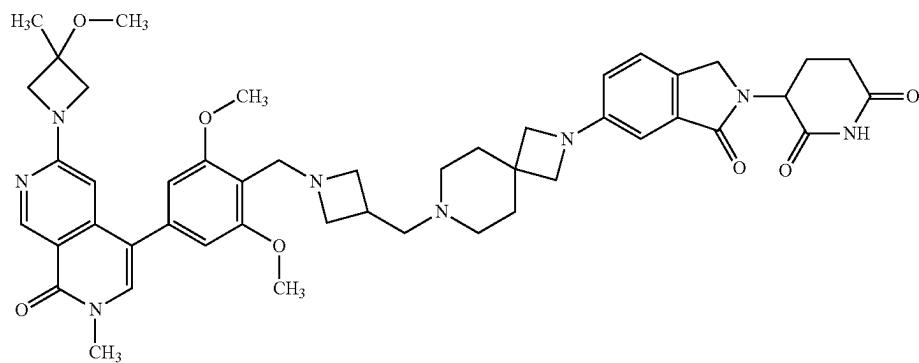
TABLE 2C-continued

Compounds D185-D316 of the Disclosure

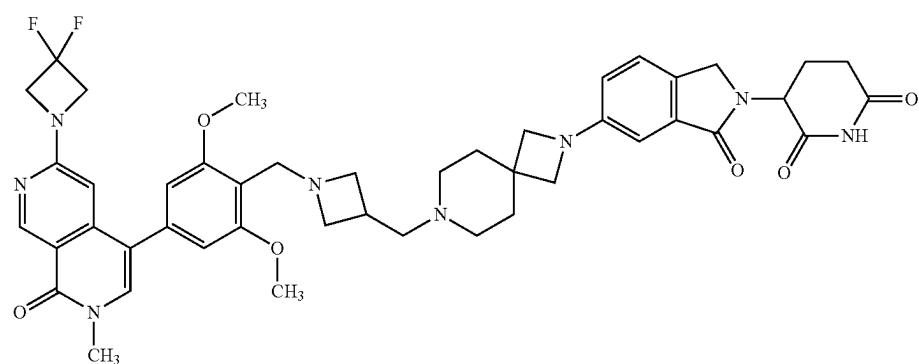
Compound No.

Structure

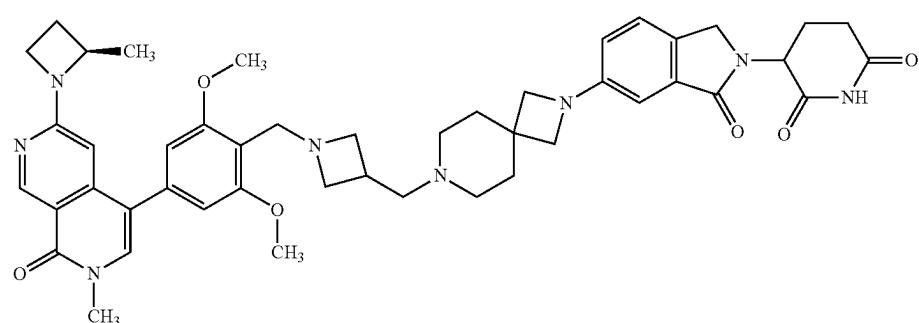
D210



D211



D212



D213

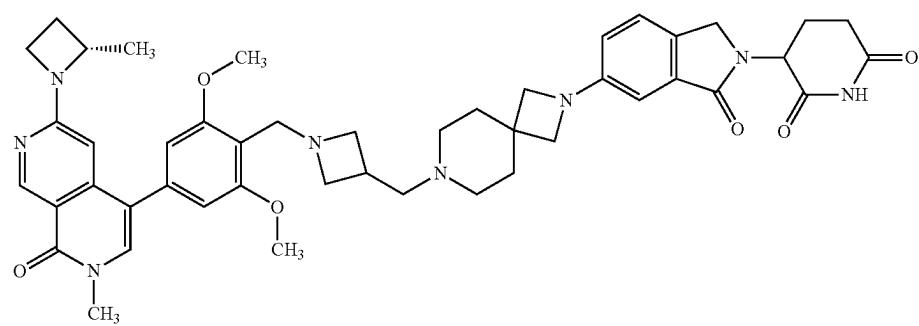


TABLE 2C-continued

Compounds D185-D316 of the Disclosure

Compound No.	Structure
D214	
D215	
D216	
D217	

TABLE 2C-continued

Compounds D185-D316 of the Disclosure

Compound No.	Structure
D218	
D219	
D220	
D221	

TABLE 2C-continued

Compounds D185-D316 of the Disclosure

Compound No.	Structure
D222	
D223	
D224	
D225	

TABLE 2C-continued

Compounds D185-D316 of the Disclosure

Compound No.	Structure
D226	
D227	
D228	
D229	
D230	

TABLE 2C-continued

Compounds D185-D316 of the Disclosure

Compound No.	Structure
D231	
D232	
D233	
D234	

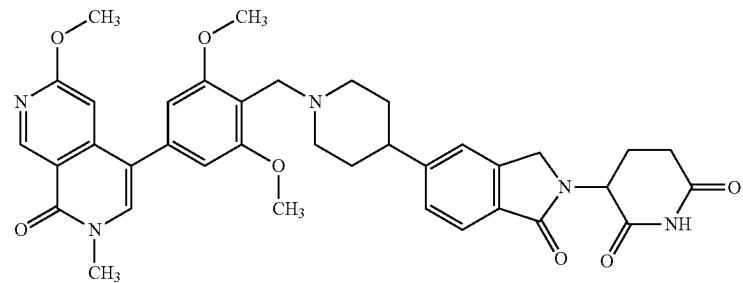
TABLE 2C-continued

Compounds D185-D316 of the Disclosure

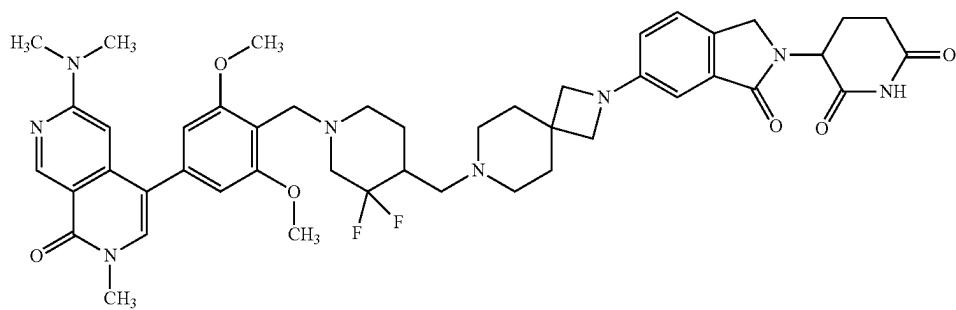
Compound No.

Structure

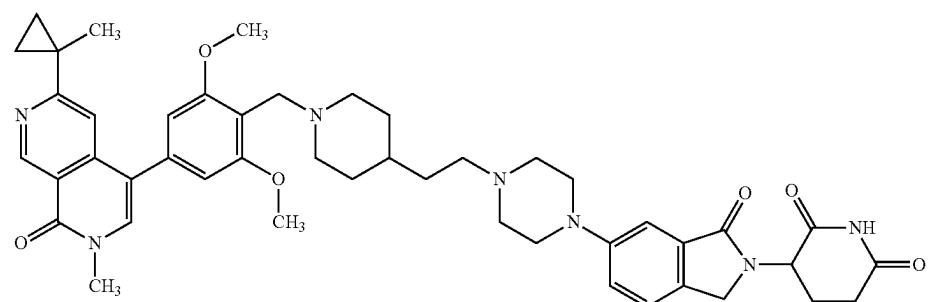
D235



D236



D237



D238

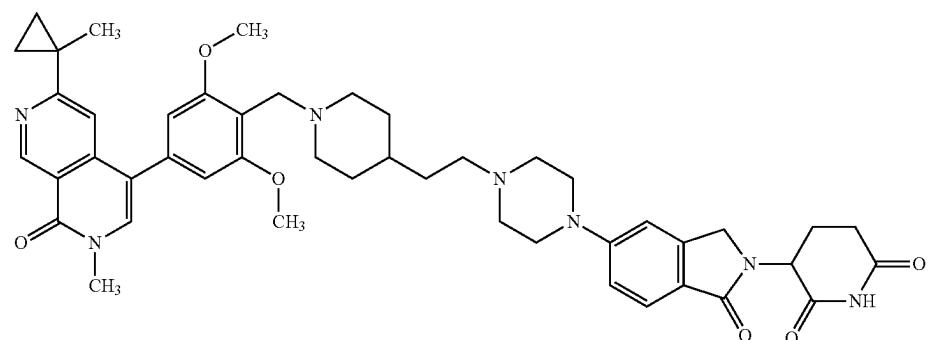


TABLE 2C-continued

Compounds D185-D316 of the Disclosure

Compound No.	Structure
D239	
D240	
D241	
D242	

TABLE 2C-continued

Compounds D185-D316 of the Disclosure

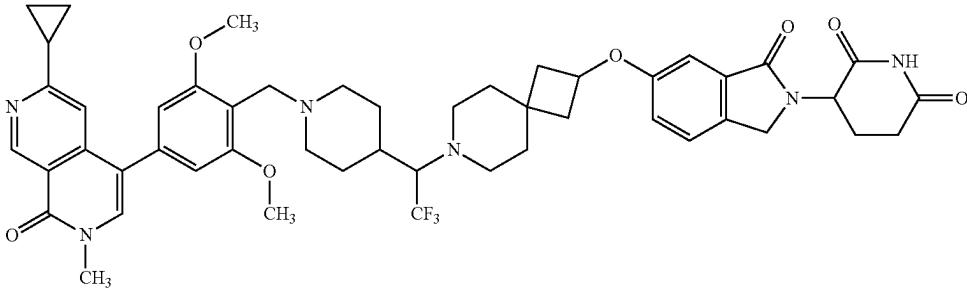
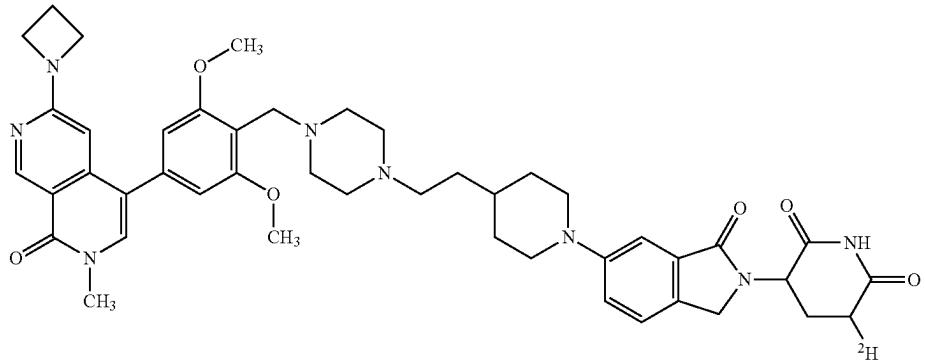
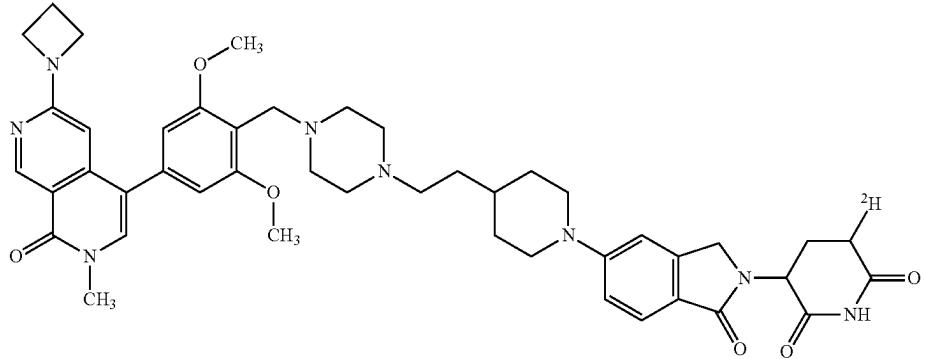
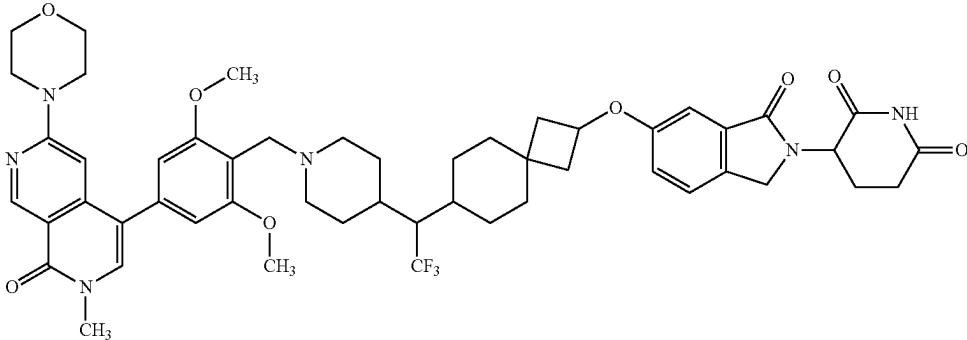
Compound No.	Structure
D243	
D244	
D245	
D246	

TABLE 2C-continued

Compounds D185-D316 of the Disclosure

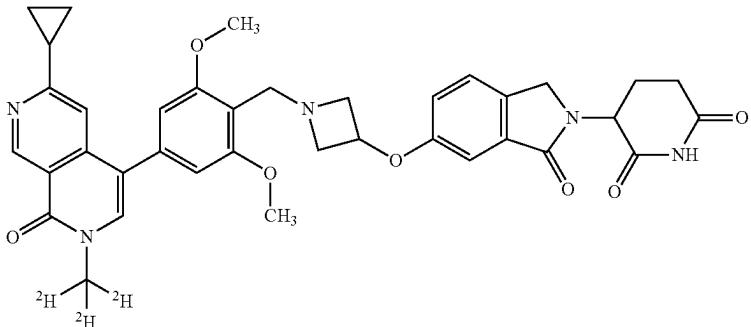
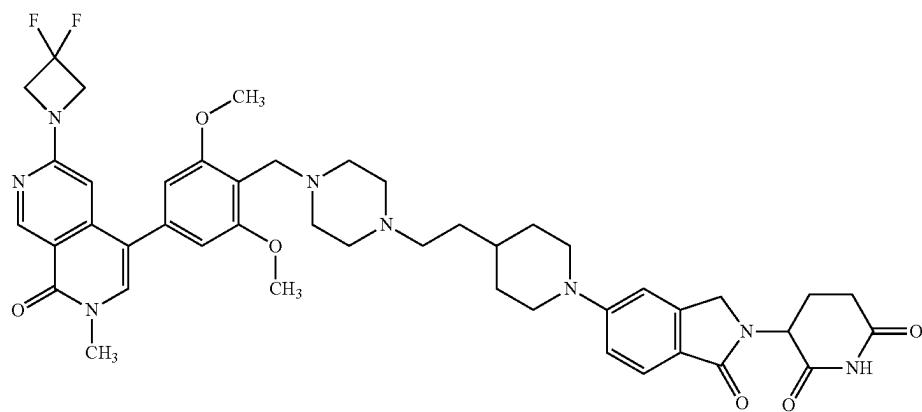
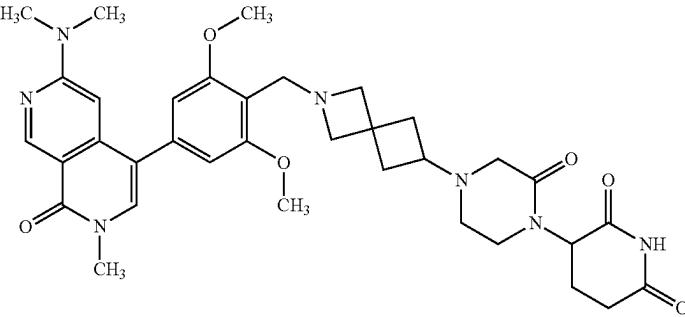
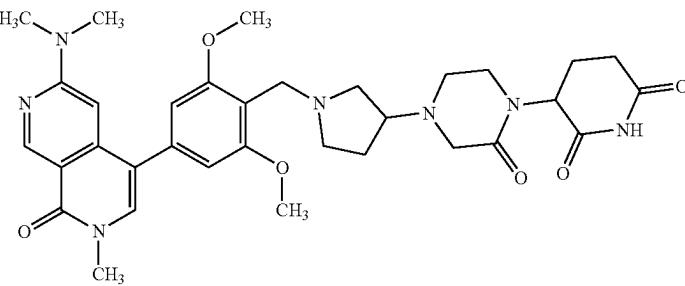
Compound No.	Structure
D247	
D248	
D249	
D250	

TABLE 2C-continued

Compounds D185-D316 of the Disclosure

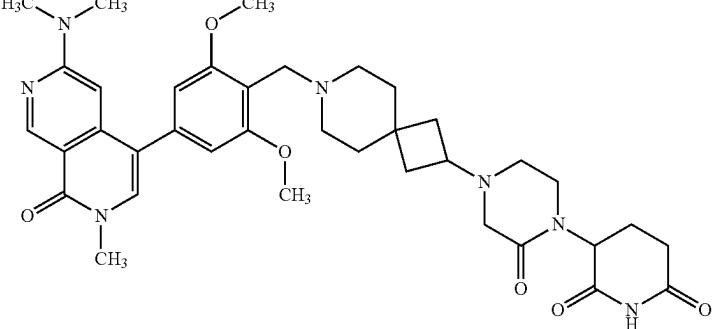
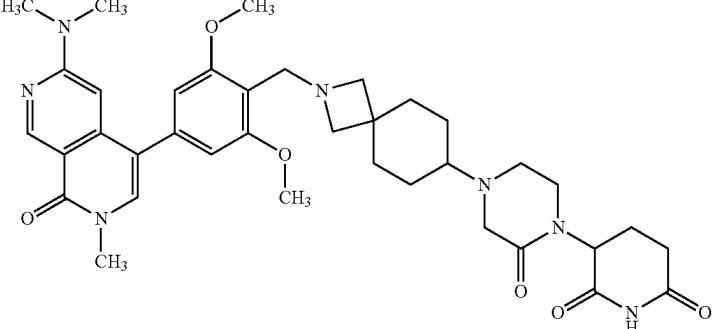
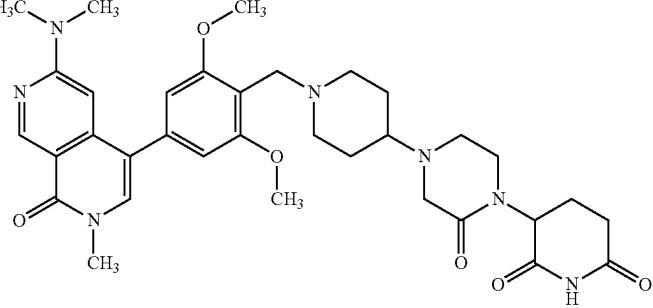
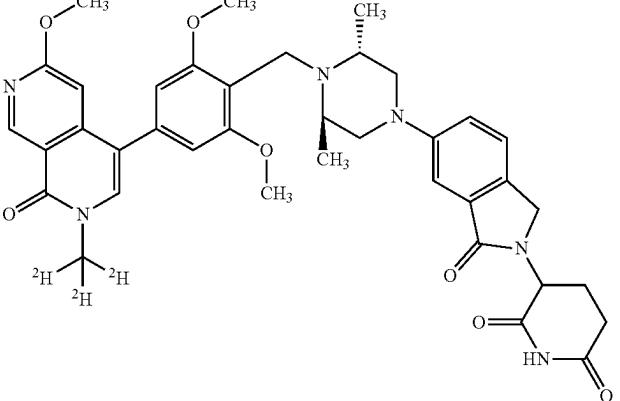
Compound No.	Structure
D251	
D252	
D253	
D254	

TABLE 2C-continued

Compounds D185-D316 of the Disclosure

Compound No.	Structure
D255	
D256	
D257	
D258	
D259	

TABLE 2C-continued

Compounds D185-D316 of the Disclosure

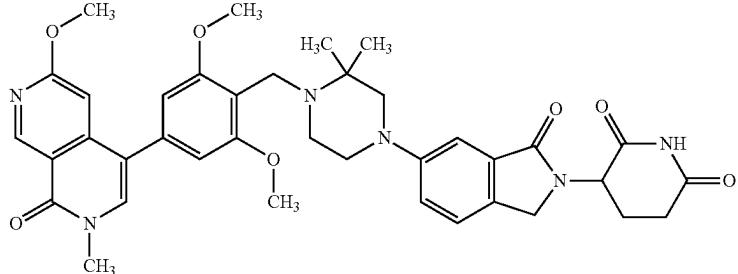
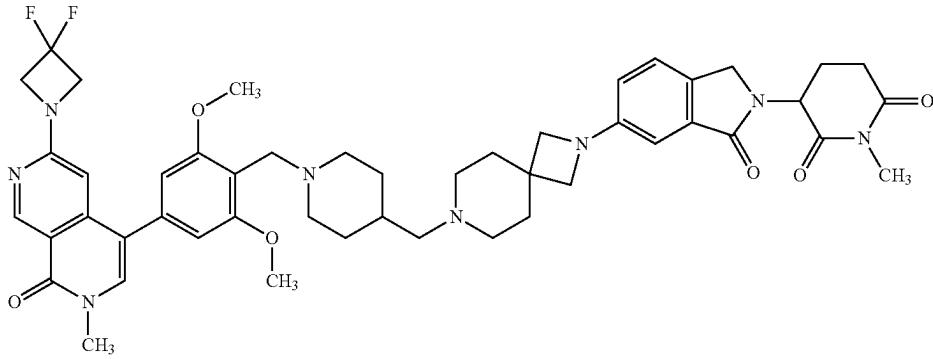
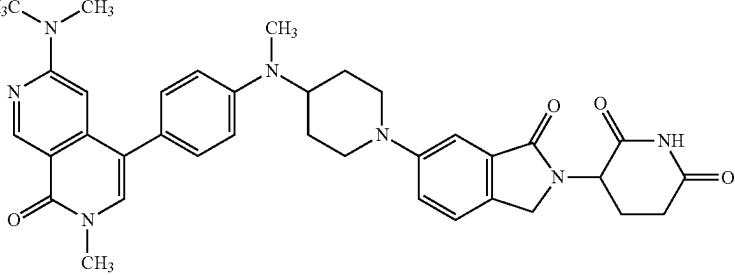
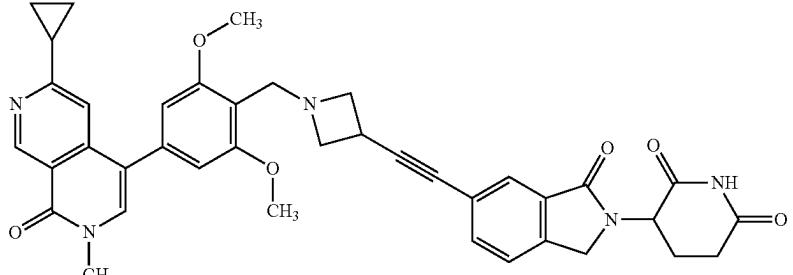
Compound No.	Structure
D260	
D261	
D262	
D263	

TABLE 2C-continued

Compounds D185-D316 of the Disclosure

Compound No.	Structure
D264	
D265	
D266	
D267	
D268	

TABLE 2C-continued

Compounds D185-D316 of the Disclosure

Compound No.	Structure
D269	
D270	
D271	
D272	
D273	

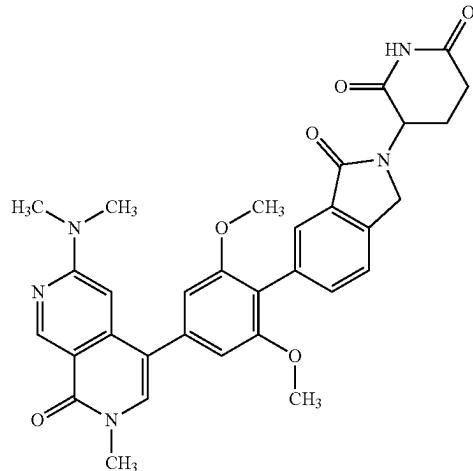
TABLE 2C-continued

Compounds D185-D316 of the Disclosure

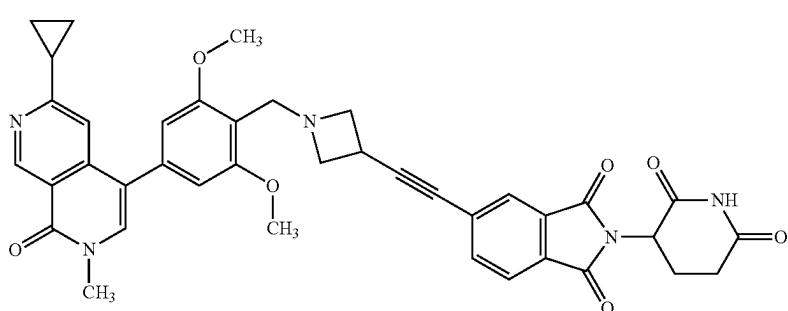
Compound No.

Structure

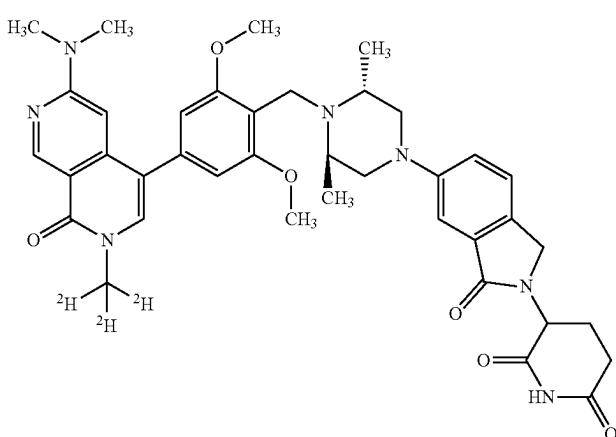
D274



D275



D276



D277

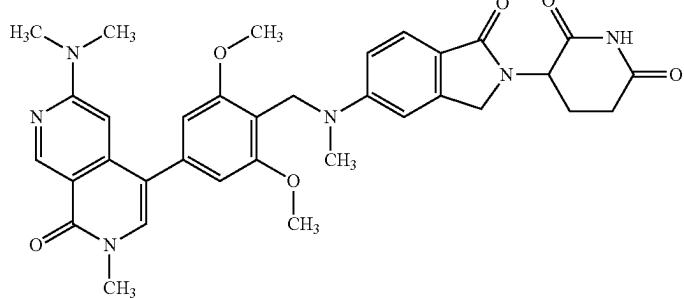


TABLE 2C-continued

Compounds D185-D316 of the Disclosure

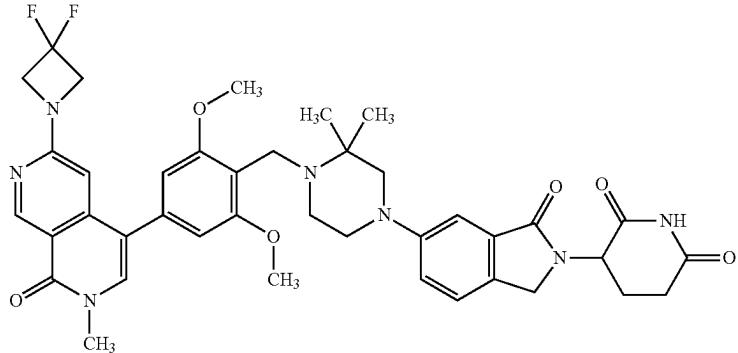
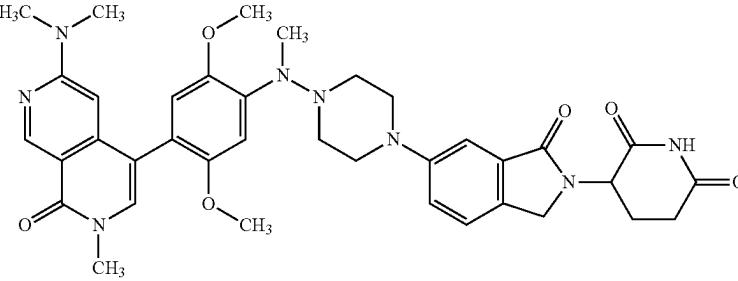
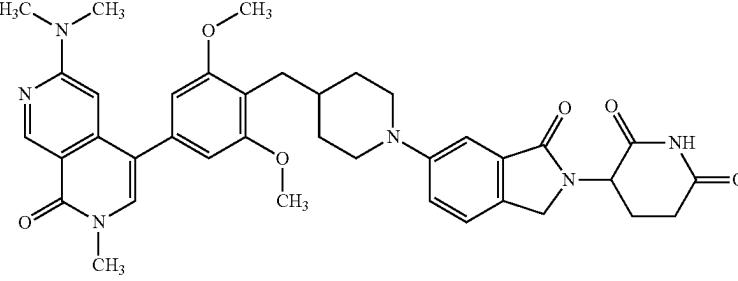
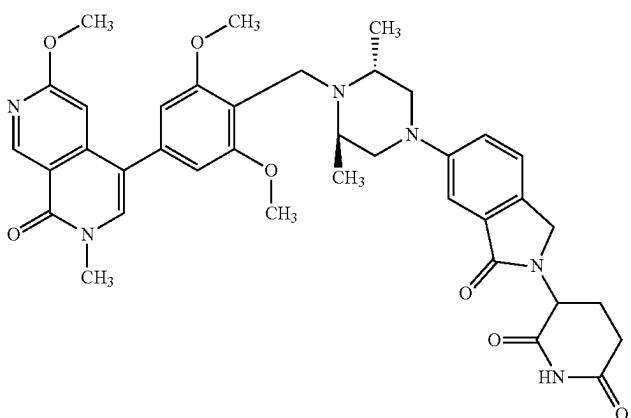
Compound No.	Structure
D278	
D279	
D280	
D281	

TABLE 2C-continued

Compounds D185-D316 of the Disclosure

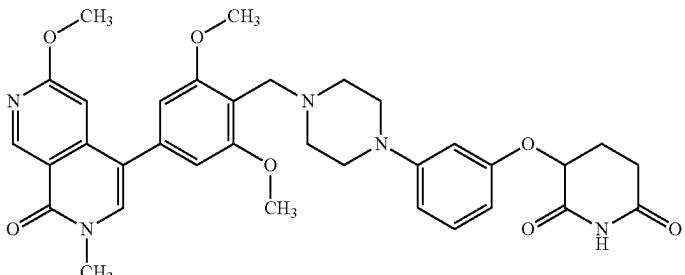
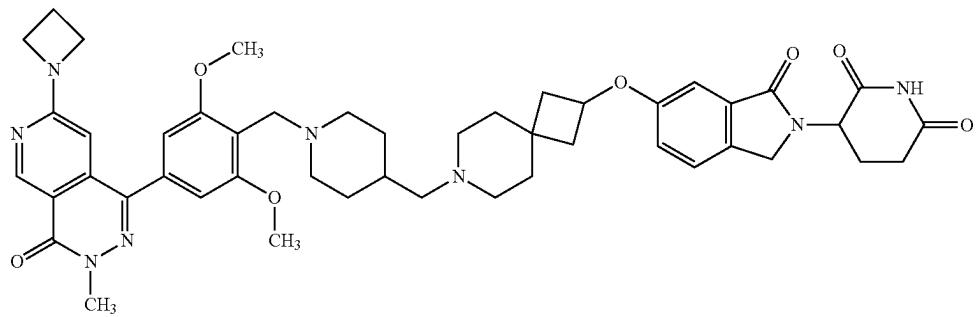
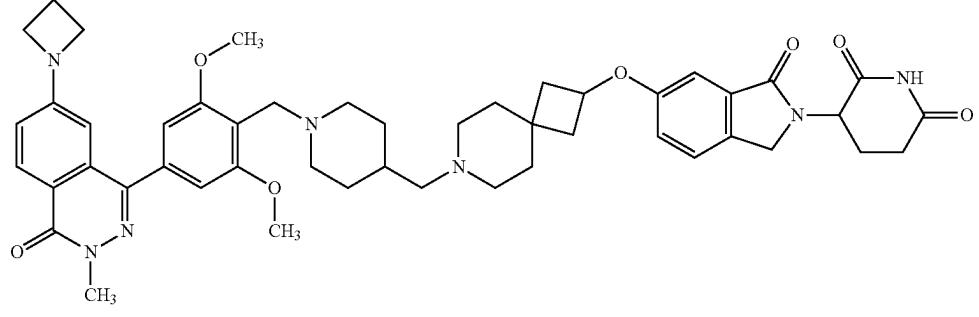
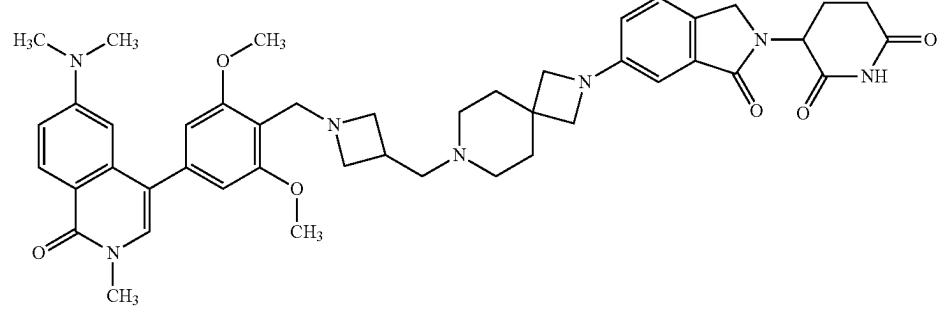
Compound No.	Structure
D282	
D283	
D284	
D285	

TABLE 2C-continued

Compounds D185-D316 of the Disclosure

Compound No.	Structure
D286	
D287	
D288	
D289	
D290	

TABLE 2C-continued

Compounds D185-D316 of the Disclosure

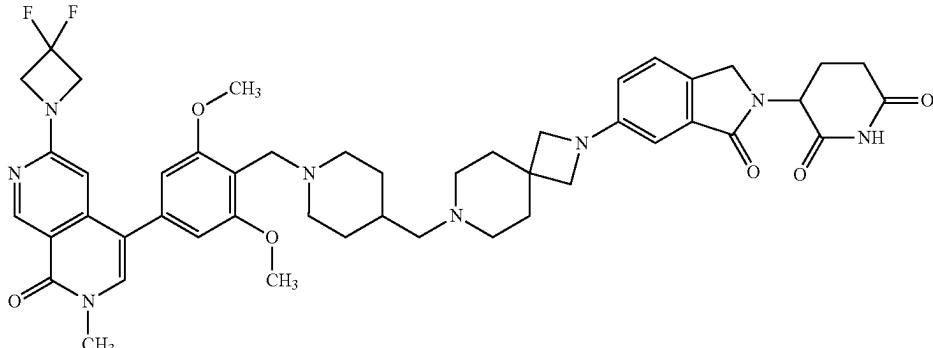
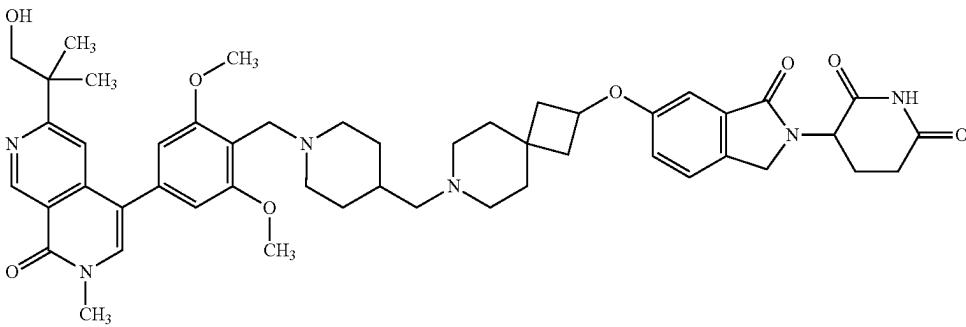
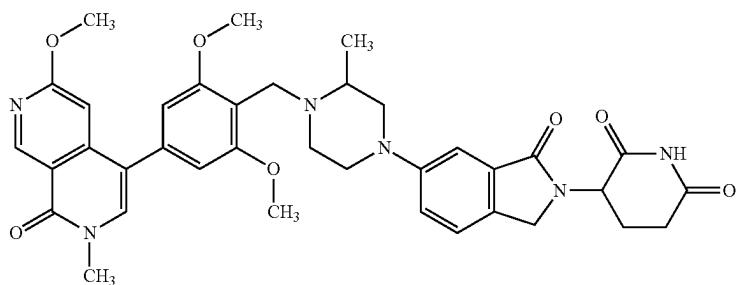
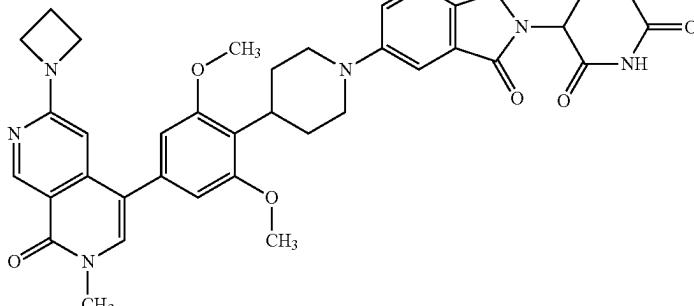
Compound No.	Structure
D291	
D292	
D293	
D294	

TABLE 2C-continued

Compounds D185-D316 of the Disclosure

Compound No.	Structure
D295	
D296	
D297	
D298	
D299	

TABLE 2C-continued

Compounds D185-D316 of the Disclosure

Compound No.	Structure
D300	
D301	
D302	
D303	

TABLE 2C-continued

Compounds D185-D316 of the Disclosure

Compound No.	Structure
D304	
D305	
D306	
D307	

TABLE 2C-continued

Compounds D185-D316 of the Disclosure

Compound No.	Structure
D308	
D309	
D310	
D311	

TABLE 2C-continued

Compounds D185-D316 of the Disclosure

Compound No.	Structure
D312	
D313	
D314	
D315	

TABLE 2C-continued

Compounds D185-D316 of the Disclosure

Compound No.	Structure
D316	

In another aspect, the disclosure features a pharmaceutical composition including any of the foregoing compounds, or pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable excipient.

In an aspect, the disclosure features a method of inhibiting the level and/or activity of BRD9 in a cell, the method involving contacting the cell with an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof.

In another aspect, the disclosure features a method of reducing the level and/or activity of BRD9 in a cell, the method involving contacting the cell with an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof.

In some embodiments, the cell is a cancer cell.

In some embodiments, the cancer is a malignant, rhabdoid tumor, a CD8+ T-cell lymphoma, endometrial carcinoma, ovarian carcinoma, bladder cancer, stomach cancer, pancreatic cancer, esophageal cancer, prostate cancer, renal cell carcinoma, melanoma, colorectal cancer, a sarcoma (e.g., a soft tissue sarcoma, synovial sarcoma, Ewing's sarcoma, osteosarcoma, rhabdomyosarcoma, adult fibrosarcoma, alveolar soft-part sarcoma, angiosarcoma, clear cell sarcoma, desmoplastic small round cell tumor, epithelioid sarcoma, fibromyxoid sarcoma, gastrointestinal stromal tumor, Kaposi's sarcoma, liposarcoma, leiomyosarcoma, malignant mesenchymoma, malignant peripheral nerve sheath tumors, myxofibrosarcoma, low-grade rhabdomyosarcoma), non-small cell lung cancer (e.g., squamous or adenocarcinoma), stomach cancer, or breast cancer. In some embodiments, the cancer is a malignant, rhabdoid tumor, a CD8+ T-cell lymphoma, endometrial carcinoma, ovarian carcinoma, bladder cancer, stomach cancer, pancreatic cancer, esophageal cancer, prostate cancer, renal cell carcinoma, melanoma, or colorectal cancer. In some embodiments, the cancer is a sarcoma (e.g., synovial sarcoma or Ewing's sarcoma), non-small cell lung cancer (e.g., squamous or adenocarcinoma), stomach cancer, or breast cancer. In some embodiments, the cancer is sarcoma (e.g., synovial sarcoma or Ewing's sarcoma). In some embodiments, the sarcoma is synovial sarcoma.

In an aspect, the disclosure features a method of treating a BAF complex-related disorder in a subject in need thereof, the method involving administering to the subject an effective amount of any of the foregoing compounds, or phar-

maceutically acceptable salts thereof, or a pharmaceutical composition thereof. In some embodiments, the BAF complex-related disorder is cancer. In some embodiments, the BAF complex-related disorder is infection.

In another aspect, the disclosure features a method of treating an SS18-SSX fusion protein-related disorder in a subject in need thereof, the method involving administering to the subject an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof. In some embodiments, the SS18-SSX fusion protein-related disorder is cancer. In some embodiments, the SS18-SSX fusion protein-related disorder is infection. In some embodiments of any of the foregoing methods, the SS18-SSX fusion protein is a SS18-SSX1 fusion protein, a SS18-SSX2 fusion protein, or a SS18-SSX4 fusion protein.

In yet another aspect, the disclosure features a method of treating a BRD9-related disorder in a subject in need thereof, the method involving administering to the subject an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof. In some embodiments, the BRD9-related disorder is cancer. In some embodiments, the BRD9-related disorder is infection.

In some embodiments, the cancer is squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, hepatocellular carcinomas, and renal cell carcinomas, cancer of the bladder, bowel, breast, cervix, colon, esophagus, head, kidney, liver, lung, neck, ovary, pancreas, prostate, and stomach; leukemias; benign and malignant lymphomas, particularly Burkitt's lymphoma and Non-Hodgkin's lymphoma; benign and malignant melanomas; myeloproliferative diseases; sarcomas, including Ewing's sarcoma, hemangiosarcoma, Kaposi's sarcoma, liposarcoma, myosarcomas, peripheral neuroepithelioma, synovial sarcoma, gliomas, astrocytomas, oligodendrogiomas, ependymomas, glioblastomas, neuroblastomas, ganglioneuromas, gangliogliomas, medulloblastomas, pineal cell tumors, meningiomas, meningeal sarcomas, neurofibromas, and Schwannomas; bowel cancer, breast cancer, prostate cancer, cervical cancer, uterine cancer, lung cancer, ovarian cancer, testicular cancer, thyroid cancer, astrocytoma, esophageal cancer, pancreatic cancer, stomach cancer, liver cancer, colon cancer, melanoma; carcinosarcoma, Hodgkin's disease, Wilms' tumor and teratocarcinomas. Additional cancers which may be treated using the disclosed compounds according to the

337

present invention include, for example, acute granulocytic leukemia, acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), adenocarcinoma, adenosarcoma, adrenal cancer, adrenocortical carcinoma, anal cancer, anaplastic astrocytoma, angiosarcoma, appendix cancer, astrocytoma, Basal cell carcinoma, B-Cell lymphoma, bile duct cancer, bladder cancer, bone cancer, bone marrow cancer, bowel cancer, brain cancer, brain stem glioma, breast cancer, triple (estrogen, progesterone and HER-2) negative breast cancer, double negative breast cancer (two of estrogen, progesterone and HER-2 are negative), single negative (one of estrogen, progesterone and HER-2 is negative), estrogen-receptor positive, HER2-negative breast cancer, estrogen receptor-negative breast cancer, estrogen receptor positive breast cancer, metastatic breast cancer, luminal A breast cancer, luminal B breast cancer, Her2-negative breast cancer, HER2-positive or negative breast cancer, progesterone receptor-negative breast cancer, progesterone receptor-positive breast cancer, recurrent breast cancer, carcinoid tumors, cervical cancer, cholangiocarcinoma, chondrosarcoma, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), colon cancer, colorectal cancer, craniopharyngioma, cutaneous lymphoma, cutaneous melanoma, diffuse astrocytoma, ductal carcinoma in situ (DCIS), endometrial cancer, ependymoma, epithelioid sarcoma, esophageal cancer, ewing sarcoma, extrahepatic bile duct cancer, eye cancer, fallopian tube cancer, fibrosarcoma, gallbladder cancer, gastric cancer, gastrointestinal cancer, gastrointestinal carcinoid cancer, gastrointestinal stromal tumors (GIST), germ cell tumor glioblastoma multiforme (GBM), glioma, hairy cell leukemia, head and neck cancer, hemangioendothelioma, Hodgkin lymphoma, hypopharyngeal cancer, infiltrating ductal carcinoma (IDC), infiltrating lobular carcinoma (ILC), inflammatory breast cancer (IBC), intestinal Cancer, intrahepatic bile duct cancer, invasive/infiltrating breast cancer, Islet cell cancer, jaw cancer, Kaposi sarcoma, kidney cancer, laryngeal cancer, leiomyosarcoma, leptomeningeal metastases, leukemia, lip cancer, liposarcoma, liver cancer, lobular carcinoma in situ, low-grade astrocytoma, lung cancer, lymph node cancer, lymphoma, male breast cancer, medullary carcinoma, medulloblastoma, melanoma, meningioma, Merkel cell carcinoma, mesenchymal chondrosarcoma, mesenchymous, mesothelioma metastatic breast cancer, metastatic melanoma metastatic squamous neck cancer, mixed gliomas, monodermal teratoma, mouth cancer mucinous carcinoma, mucosal melanoma, multiple myeloma, Mycosis Fungoïdes, myelodysplastic syndrome, nasal cavity cancer, nasopharyngeal cancer, neck cancer, neuroblastoma, neuroendocrine tumors (NETs), non-Hodgkin's lymphoma, non-small cell lung cancer (NSCLC), oat cell cancer, ocular cancer, ocular melanoma, oligodendrogloma, oral cancer, oral cavity cancer, oropharyngeal cancer, osteogenic sarcoma, osteosarcoma, ovarian cancer, ovarian epithelial cancer ovarian germ cell tumor, ovarian primary peritoneal carcinoma, ovarian sex cord stromal tumor, Paget's disease, pancreatic cancer, papillary carcinoma, paranasal sinus cancer, parathyroid cancer, pelvic cancer, penile cancer, peripheral nerve cancer, peritoneal cancer, pharyngeal cancer, pheochromocytoma, pilocytic astrocytoma, pineal region tumor, pineoblastoma, pituitary gland cancer, primary central nervous system (CNS) lymphoma, prostate cancer, rectal cancer, renal cell carcinoma, renal pelvis cancer, rhabdomyosarcoma, salivary gland cancer, soft tissue sarcoma, bone sarcoma, sarcoma, sinus cancer, skin cancer, small cell lung cancer (SCLC), small intestine cancer, spinal cancer, spinal column cancer, spinal cord cancer, squamous cell carcinoma, stomach can-

338

cer, synovial sarcoma, T-cell lymphoma, testicular cancer, throat cancer, thymoma/thymic carcinoma, thyroid cancer, tongue cancer, tonsil cancer, transitional cell cancer, tubal cancer, tubular carcinoma, undiagnosed cancer, ureteral cancer, urethral cancer, uterine adenocarcinoma, uterine cancer, uterine sarcoma, vaginal cancer, vulvar cancer, T-cell lineage acute lymphoblastic leukemia (T-ALL), T-cell lineage lymphoblastic lymphoma (T-LL), peripheral T-cell lymphoma, Adult T-cell leukemia, Pre-B ALL, Pre-B lymphomas, large B-cell lymphoma, Burkitts lymphoma, B-cell ALL, Philadelphia chromosome positive ALL, Philadelphia chromosome positive CML, juvenile myelomonocytic leukemia (JMML), acute promyelocytic leukemia (a subtype of AML), large granular lymphocytic leukemia, Adult T-cell chronic leukemia, diffuse large B cell lymphoma, follicular lymphoma; Mucosa-Associated Lymphatic Tissue lymphoma (MALT), small cell lymphocytic lymphoma, mediastinal large B cell lymphoma, nodal marginal zone B cell lymphoma (NMZL); splenic marginal zone lymphoma (SMZL); intravascular large B-cell lymphoma; primary effusion lymphoma; or lymphomatoid granulomatosis; B-cell prolymphocytic leukemia; splenic lymphoma/leukemia, unclassifiable, splenic diffuse red pulp small B-cell lymphoma; lymphoplasmacytic lymphoma; heavy chain diseases, for example, Alpha heavy chain disease, Gamma heavy chain disease, Mu heavy chain disease, plasma cell myeloma, solitary plasmacytoma of bone; extraosseous plasmacytoma; primary cutaneous follicle center lymphoma, T cell/histocyte rich large B-cell lymphoma, DLBCL associated with chronic inflammation; Epstein-Barr virus (EBV)-+ DLBCL of the elderly; primary mediastinal (thymic) large B-cell lymphoma, primary cutaneous DLBCL, leg type, ALK+ large B-cell lymphoma, plasmablastic lymphoma; large B-cell lymphoma arising in HHV8-associated multicentric, Castleman disease; B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma, or B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma.

In some embodiments, the cancer is a malignant, rhabdoid tumor, a CD8+ T-cell lymphoma, endometrial carcinoma, ovarian carcinoma, bladder cancer, stomach cancer, pancreatic cancer, esophageal cancer, prostate cancer, renal cell carcinoma, melanoma, colorectal cancer, a sarcoma (e.g., a soft tissue sarcoma, synovial sarcoma, Ewing's sarcoma, osteosarcoma, rhabdomyosarcoma, adult fibrosarcoma, alveolar soft-part sarcoma, angiosarcoma, clear cell sarcoma, desmoplastic small round cell tumor, epithelioid sarcoma, fibromyxoid sarcoma, gastrointestinal stromal tumor, Kaposi sarcoma, liposarcoma, leiomyosarcoma, malignant mesenchymoma, malignant peripheral nerve sheath tumors, myxofibrosarcoma, low-grade rhabdomyosarcoma), non-small cell lung cancer (e.g., squamous or adenocarcinoma), stomach cancer, or breast cancer. In some embodiments, the cancer is a malignant, rhabdoid tumor, a CD8+ T-cell lymphoma, endometrial carcinoma, ovarian carcinoma, bladder cancer, stomach cancer, pancreatic cancer, esophageal cancer, prostate cancer, renal cell carcinoma, melanoma, or colorectal cancer. In some embodiments, the cancer is a sarcoma (e.g., synovial sarcoma or Ewing's sarcoma), non-small cell lung cancer (e.g., squamous or adenocarcinoma), stomach cancer, or breast cancer. In some embodiments, the cancer is sarcoma (e.g., synovial sarcoma or Ewing's sarcoma). In some embodiments, the sarcoma is synovial sarcoma.

339

In some embodiments, the infection is viral infection (e.g., an infection with a virus of the Retroviridae family such as the lentiviruses (e.g. Human immunodeficiency virus (HIV) and deltaretroviruses (e.g., human T cell leukemia virus I (HTLV-I), human T cell leukemia virus II (HTLV-II)); Hepadnaviridae family (e.g. hepatitis B virus (HBV)); Flaviviridae family (e.g. hepatitis C virus (HCV)); Adenoviridae family (e.g. Human Adenovirus); Herpesviridae family (e.g. Human cytomegalovirus (HCMV), Epstein-Barr virus, herpes simplex virus 1 (HSV-1), herpes simplex virus 2 (HSV-2), human herpesvirus 6 (HHV-6), Herpesvitus K*, CMV, varicella-zoster virus); Papillomaviridae family (e.g. Human Papillomavirus (HPV, HPV E1)); Parvoviridae family (e.g. Parvovirus B19); Polyomaviridae family (e.g. JC virus and BK virus); Paramyxoviridae family (e.g. Measles virus); or Togaviridae family (e.g. Rubella virus)). In some embodiments, the disorder is Coffin Siris, Neurofibromatosis (e.g., NF-1, NF-2, or Schwannomatosis), or Multiple Meningioma. In an aspect, the disclosure features a method of treating a cancer in a subject in need thereof, the method including administering to the subject an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or any of the foregoing pharmaceutical compositions.

In some embodiments, the cancer is squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, hepatocellular carcinomas, and renal cell carcinomas, cancer of the bladder, bowel, breast, cervix, colon, esophagus, head, kidney, liver, lung, neck, ovary, pancreas, prostate, and stomach; leukemias; benign and malignant lymphomas, particularly Burkitt's lymphoma and Non-Hodgkin's lymphoma; benign and malignant melanomas; myeloproliferative diseases; sarcomas, including Ewing's sarcoma, hemangiosarcoma, Kaposi's sarcoma, liposarcoma, myosarcomas, peripheral neuroepithelioma, synovial sarcoma, gliomas, astrocytomas, oligodendrogiomas, ependymomas, glioblastomas, neuroblastomas, ganglioneuromas, gangliogliomas, medulloblastomas, pineal cell tumors, meningiomas, meningeal sarcomas, neurofibromas, and Schwannomas; bowel cancer, breast cancer, prostate cancer, cervical cancer, uterine cancer, lung cancer, ovarian cancer, testicular cancer, thyroid cancer, astrocytoma, esophageal cancer, pancreatic cancer, stomach cancer, liver cancer, colon cancer, melanoma; carcinosarcoma, Hodgkin's disease, Wilms' tumor and teratocarcinomas. Additional cancers which may be treated using the disclosed compounds according to the present invention include, for example, acute granulocytic leukemia, acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), adenocarcinoma, adenosarcoma, adrenal cancer, adrenocortical carcinoma, anal cancer, anaplastic astrocytoma, angiosarcoma, appendix cancer, astrocytoma, Basal cell carcinoma, B-Cell lymphoma, bile duct cancer, bladder cancer, bone cancer, bone marrow cancer, bowel cancer, brain cancer, brain stem glioma, breast cancer, triple (estrogen, progesterone and HER-2) negative breast cancer, double negative breast cancer (two of estrogen, progesterone and HER-2 are negative), single negative (one of estrogen, progesterone and HER-2 is negative), estrogen-receptor positive, HER2-negative breast cancer, estrogen receptor-negative breast cancer, estrogen receptor positive breast cancer, metastatic breast cancer, luminal A breast cancer, luminal B breast cancer, Her2-negative breast cancer, HER2-positive or negative breast cancer, progesterone receptor-negative breast cancer, progesterone receptor-positive breast cancer, recurrent breast cancer, carcinoid tumors, cervical cancer, cholangiocarcinoma, chondrosarcoma, chronic lymphocytic leukemia (CLL), chronic myel-

340

ogenous leukemia (CML), colon cancer, colorectal cancer, craniopharyngioma, cutaneous lymphoma, cutaneous melanoma, diffuse astrocytoma, ductal carcinoma in situ (DCIS), endometrial cancer, ependymoma, epithelioid sarcoma, esophageal cancer, ewing sarcoma, extrahepatic bile duct cancer, eye cancer, fallopian tube cancer, fibrosarcoma, gallbladder cancer, gastric cancer, gastrointestinal cancer, gastrointestinal carcinoid cancer, gastrointestinal stromal tumors (GIST), germ cell tumor glioblastoma multiforme (GBM), glioma, hairy cell leukemia, head and neck cancer, hemangiopericytoma, Hodgkin lymphoma, hypopharyngeal cancer, infiltrating ductal carcinoma (IDC), infiltrating lobular carcinoma (ILC), inflammatory breast cancer (IBC), intestinal Cancer, intrahepatic bile duct cancer, invasive/infiltrating breast cancer, Islet cell cancer, jaw cancer, Kaposi sarcoma, kidney cancer, laryngeal cancer, leiomyosarcoma, leptomeningeal metastases, leukemia, lip cancer, liposarcoma, liver cancer, lobular carcinoma in situ, low-grade astrocytoma, lung cancer, lymph node cancer, lymphoma, male breast cancer, medullary carcinoma, medulloblastoma, melanoma, meningioma, Merkel cell carcinoma, mesenchymal chondrosarcoma, mesenchymous, mesothelioma metastatic breast cancer, metastatic melanoma metastatic squamous neck cancer, mixed gliomas, monodermal teratoma, mouth cancer mucinous carcinoma, mucosal melanoma, multiple myeloma, Mycosis Fungoides, myelodysplastic syndrome, nasal cavity cancer, nasopharyngeal cancer, neck cancer, neuroblastoma, neuroendocrine tumors (NETs), non-Hodgkin's lymphoma, non-small cell lung cancer (NSCLC), oat cell cancer, ocular cancer, ocular melanoma, oligodendrogloma, oral cancer, oral cavity cancer, oropharyngeal cancer, osteogenic sarcoma, osteosarcoma, ovarian cancer, ovarian epithelial cancer ovarian germ cell tumor, ovarian primary peritoneal carcinoma, ovarian sex cord stromal tumor, Paget's disease, pancreatic cancer, papillary carcinoma, paranasal sinus cancer, parathyroid cancer, pelvic cancer, penile cancer, peripheral nerve cancer, peritoneal cancer, pharyngeal cancer, pheochromocytoma, pilocytic astrocytoma, pineal region tumor, pineoblastoma, pituitary gland cancer, primary central nervous system (CNS) lymphoma, prostate cancer, rectal cancer, renal cell carcinoma, renal pelvis cancer, rhabdomyosarcoma, salivary gland cancer, soft tissue sarcoma, bone sarcoma, sarcoma, sinus cancer, skin cancer, small cell lung cancer (SCLC), small intestine cancer, spinal cancer, spinal column cancer, spinal cord cancer, squamous cell carcinoma, stomach cancer, synovial sarcoma, T-cell lymphoma, testicular cancer, throat cancer, tonsil cancer, transitional cell cancer, tubal cancer, tubular carcinoma, undiagnosed cancer, ureteral cancer, urethral cancer, uterine adenocarcinoma, uterine cancer, uterine sarcoma, vaginal cancer, vulvar cancer, T-cell lineage acute lymphoblastic leukemia (T-ALL), T-cell lineage lymphoblastic lymphoma (T-LL), peripheral T-cell lymphoma, Adult T-cell leukemia, Pre-B ALL, Pre-B lymphomas, large B-cell lymphoma, Burkitts lymphoma, B-cell ALL, Philadelphia chromosome positive ALL, Philadelphia chromosome positive CML, juvenile myelomonocytic leukemia (JMML), acute promyelocytic leukemia (a subtype of AML), large granular lymphocytic leukemia, Adult T-cell chronic leukemia, diffuse large B cell lymphoma, follicular lymphoma; Mucosa-Associated Lymphatic Tissue lymphoma (MALT), small cell lymphocytic lymphoma, mediastinal large B cell lymphoma, nodal marginal zone B cell lymphoma (NMZL); splenic marginal zone lymphoma (SMZL); intravascular large B-cell lymphoma; primary effusion lymphoma; or lymphomatoid granulomatosis;

341

B-cell prolymphocytic leukemia; splenic lymphoma/leukemia, unclassifiable, splenic diffuse red pulp small B-cell lymphoma; lymphoplasmacytic lymphoma; heavy chain diseases, for example, Alpha heavy chain disease, Gamma heavy chain disease, Mu heavy chain disease, plasma cell myeloma, solitary plasmacytoma of bone; extraosseous plasmacytoma; primary cutaneous follicle center lymphoma, T cell/histocyte rich large B-cell lymphoma, DLBCL associated with chronic inflammation; Epstein-Barr virus (EBV)-+ DLBCL of the elderly; primary mediastinal (thymic) large B-cell lymphoma, primary cutaneous DLBCL, leg type, ALK+ large B-cell lymphoma, plasmablastic lymphoma; large B-cell lymphoma arising in HHV8-associated multicentric, Castleman disease; B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma, or B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma.

In some embodiments, the cancer is a malignant, rhabdoid tumor, a CD8+ T-cell lymphoma, endometrial carcinoma, ovarian carcinoma, bladder cancer, stomach cancer, pancreatic cancer, esophageal cancer, prostate cancer, renal cell carcinoma, melanoma, colorectal cancer, a sarcoma (e.g., a soft tissue sarcoma, synovial sarcoma, Ewing's sarcoma, osteosarcoma, rhabdomyosarcoma, adult fibrosarcoma, alveolar soft-part sarcoma, angiosarcoma, clear cell sarcoma, desmoplastic small round cell tumor, epithelioid sarcoma, fibromyxoid sarcoma, gastrointestinal stromal tumor, Kaposi sarcoma, liposarcoma, leiomyosarcoma, malignant mesenchymoma malignant peripheral nerve sheath tumors, myxofibrosarcoma, low-grade rhabdomyosarcoma), non-small cell lung cancer (e.g., squamous or adenocarcinoma), stomach cancer, or breast cancer. In some embodiments, the cancer is a malignant, rhabdoid tumor, a CD8+ T-cell lymphoma, endometrial carcinoma, ovarian carcinoma, bladder cancer, stomach cancer, pancreatic cancer, esophageal cancer, prostate cancer, renal cell carcinoma, melanoma, or colorectal cancer. In some embodiments, the cancer is a sarcoma (e.g., synovial sarcoma or Ewing's sarcoma), non-small cell lung cancer (e.g., squamous or adenocarcinoma), stomach cancer, or breast cancer. In some embodiments, the cancer is sarcoma (e.g., synovial sarcoma or Ewing's sarcoma). In some embodiments, the sarcoma is synovial sarcoma.

In another aspect, the disclosure features a method for treating a viral infection in a subject in need thereof. This method includes administering to the subject an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or any of the foregoing pharmaceutical compositions. In some embodiments, the viral infection is an infection with a virus of the Retroviridae family such as the lentiviruses (e.g. Human immunodeficiency virus (HIV) and deltaretroviruses (e.g., human T cell leukemia virus I (HTLV-I), human T cell leukemia virus II (HTLV-II)); Hepadnaviridae family (e.g. hepatitis B virus (HBV)), Flaviviridae family (e.g. hepatitis C virus (HCV)), Adenoviridae family (e.g. Human Adenovirus), Herpesviridae family (e.g. Human cytomegalovirus (HCMV), Epstein-Barr virus, herpes simplex virus 1 (HSV-1), herpes simplex virus 2 (HSV-2), human herpesvirus 6 (HHV-6), Herpesvirus K*, CMV, varicella-zoster virus), Papillomaviridae family (e.g. Human Papillomavirus (HPV, HPV E1)), Parvoviridae family (e.g. Parvovirus B19), Polyomaviridae family (e.g. JC virus and BK virus), Paramyxoviridae family (e.g. Measles virus), Togaviridae family (e.g. Rubella virus).

342

In another embodiment of any of the foregoing methods, the method further includes administering to the subject an additional anticancer therapy (e.g., chemotherapeutic or cytotoxic agent or radiotherapy).

In particular embodiments, the additional anticancer therapy is: a chemotherapeutic or cytotoxic agent (e.g., doxorubicin or ifosfamide), a differentiation-inducing agent (e.g., retinoic acid, vitamin D, cytokines), a hormonal agent, an immunological agent, or an anti-angiogenic agent. Chemotherapeutic and cytotoxic agents include, but are not limited to, alkylating agents, cytotoxic antibiotics, antimetabolites, vinca alkaloids, etoposides, and others (e.g., paclitaxel, taxol, docetaxel, taxotere, cis-platinum). A list of additional compounds having anticancer activity can be found in L. Brunton, B. Chabner and B. Knollman (eds). Goodman and Gilman's The Pharmacological Basis of Therapeutics, Twelfth Edition, 2011, McGraw Hill Companies, New York, NY

In particular embodiments, the compound of the invention and the additional anticancer therapy and any of the foregoing compounds or pharmaceutical compositions are administered within 28 days of each other (e.g., within 21, 14, 10, 7, 5, 4, 3, 2, or 1 days) or within 24 hours (e.g., 12, 6, 3, 2, or 1 hours; or concomitantly) each in an amount that together are effective to treat the subject.

Chemical Terms

The terminology employed herein is for the purpose of describing particular embodiments and is not intended to be limiting.

For any of the following chemical definitions, a number following an atomic symbol indicates that total number of atoms of that element that are present in a particular chemical moiety. As will be understood, other atoms, such as hydrogen atoms, or substituent groups, as described herein, may be present, as necessary, to satisfy the valences of the atoms. For example, an unsubstituted C₂ alkyl group has the formula —CH₂CH₃. When used with the groups defined herein, a reference to the number of carbon atoms includes the divalent carbon in acetal and ketal groups but does not include the carbonyl carbon in acyl, ester, carbonate, or carbamate groups. A reference to the number of oxygen, nitrogen, or sulfur atoms in a heteroaryl group only includes those atoms that form a part of a heterocyclic ring.

Herein a phrase of the form "optionally substituted X" (e.g., optionally substituted alkyl) is intended to be equivalent to "X, wherein X is optionally substituted" (e.g., "alkyl, wherein said alkyl is optionally substituted"). It is not intended to mean that the feature "X" (e.g., alkyl) per se is optional. As described herein, certain compounds of interest may contain one or more "optionally substituted" moieties. In general, the term "substituted", whether preceded by the term "optionally" or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent, e.g., any of the substituents or groups described herein. Unless otherwise indicated, an "optionally substituted" group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by the present disclosure are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable", as used herein, refers to compounds that are not substantially altered when subjected to conditions to

allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

The term "aliphatic," as used herein, refers to a saturated or unsaturated, straight, branched, or cyclic hydrocarbon. "Aliphatic" is intended herein to include, but is not limited to, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, and cycloalkynyl moieties, and thus incorporates each of these definitions. In one embodiment, "aliphatic" is used to indicate those aliphatic groups having 1-20 carbon atoms. The aliphatic chain can be, for example, mono-unsaturated, di-unsaturated, tri-unsaturated, or polyunsaturated, or alkynyl. Unsaturated aliphatic groups can be in a cis or trans configuration. In one embodiment, the aliphatic group contains from 1 to about 12 carbon atoms, more generally from 1 to about 6 carbon atoms or from 1 to about 4 carbon atoms. In one embodiment, the aliphatic group contains from 1 to about 8 carbon atoms. In certain embodiments, the aliphatic group is C₁-C₂, C₁-C₃, C₁-C₄, C₁-C₅, or C₁-C₆. The specified ranges as used herein indicate an aliphatic group having each member of the range described as an independent species. For example, the term C₁-C₆ aliphatic as used herein indicates a straight or branched alkyl, alkenyl, or alkynyl group having from 1, 2, 3, 4, 5, or 6 carbon atoms and is intended to mean that each of these is described as an independent species. For example, the term C₁-C₄ aliphatic as used herein indicates a straight or branched alkyl, alkenyl, or alkynyl group having from 1, 2, 3, or 4 carbon atoms and is intended to mean that each of these is described as an independent species. In one embodiment, the aliphatic group is substituted with one or more functional groups that results in the formation of a stable moiety.

The term "heteroaliphatic," as used herein, refers to an aliphatic moiety that contains at least one heteroatom in the chain, for example, an amine, carbonyl, carboxy, oxo, thio, phosphate, phosphonate, nitrogen, phosphorus, silicon, or boron atoms in place of a carbon atom. In one embodiment, the only heteroatom is nitrogen. In one embodiment, the only heteroatom is oxygen. In one embodiment, the only heteroatom is sulfur. "Heteroaliphatic" is intended herein to include, but is not limited to, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, and heterocycloalkynyl moieties. In one embodiment, "heteroaliphatic" is used to indicate a heteroaliphatic group (cyclic, acyclic, substituted, unsubstituted, branched or unbranched) having 1-20 carbon atoms. In one embodiment, the heteroaliphatic group is optionally substituted in a manner that results in the formation of a stable moiety. Nonlimiting examples of heteroaliphatic moieties are polyethylene glycol, polyalkylene glycol, amide, polyamide, polylactide, polyglycolide, thioether, ether, alkyl-heterocycle-alkyl, —O-alkyl-O-alkyl, and alkyl-O-haloalkyl.

The term "acyl," as used herein, represents a hydrogen or an alkyl group that is attached to a parent molecular group through a carbonyl group, as defined herein, and is exemplified by formyl (i.e., a carboxyaldehyde group), acetyl, trifluoroacetyl, propionyl, and butanoyl. Exemplary unsubstituted acyl groups include from 1 to 6, from 1 to 11, or from 1 to 21 carbons.

The term "alkyl," as used herein, refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of 1 to 20 carbon atoms (e.g., 1 to 16 carbon atoms, 1 to 10 carbon atoms, 1 to 6 carbon atoms, or 1 to 3 carbon atoms). An "alkylene" is a divalent alkyl group.

The term "alkenyl," as used herein, alone or in combination with other groups, refers to a straight chain or branched hydrocarbon residue having a carbon-carbon double bond

and having 2 to 20 carbon atoms (e.g., 2 to 16 carbon atoms, 2 to 10 carbon atoms, 2 to 6, or 2 carbon atoms). An "alkynylene" is a divalent alkynyl group.

The term "alkynyl," as used herein, alone or in combination with other groups, refers to a straight chain or branched hydrocarbon residue having a carbon-carbon triple bond and having 2 to 20 carbon atoms (e.g., 2 to 16 carbon atoms, 2 to 10 carbon atoms, 2 to 6, or 2 carbon atoms). An "alkynylene" is a divalent alkynyl group.

10 The term "amino," as used herein, represents —N(R^{N1})₂, wherein each R^{N1} is, independently, H, OH, NO₂, N(R^{N2})₂, SO₂OR^{N2}, SO₂R^{N2}, SOR^{N2}, an N-protecting group, alkyl, alkoxy, aryl, arylalkyl, cycloalkyl, acyl (e.g., acetyl, trifluoroacetyl, or others described herein), wherein each of these recited R^{N1} groups can be optionally substituted; or two R^{N1} combine to form an alkylene or heteroalkylene, and wherein each R^{N2} is, independently, H, alkyl, or aryl. The amino groups of the compounds described herein can be an unsubstituted amino (i.e., —NH₂) or a substituted amino (i.e., 20 —N(R^{N1})₂).

15 The term "aryl," as used herein, refers to an aromatic mono- or polycyclic radical of, e.g., 6 to 12, carbon atoms having at least one aromatic ring. Examples of such groups include, but are not limited to, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, 1,2-dihydronaphthyl, indanyl, and 1H-indenyl.

20 The term "arylalkyl," as used herein, represents an alkyl group substituted with an aryl group. Exemplary unsubstituted arylalkyl groups are from 7 to 30 carbons (e.g., from 7 to 16 or from 7 to 20 carbons, such as C₁-C₆ alkyl C₆-C₁₀ aryl, C₁-C₁₀ alkyl C₆-C₁₀ aryl, or C₁-C₂₀ alkyl C₆-C₁₀ aryl), such as, benzyl and phenethyl. In some embodiments, the alkyl and the aryl each can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective groups.

25 The term "azido," as used herein, represents a —N₃ group.

The term "bridged cyclyl," as used herein, refers to a bridged polycyclic group of 5 to 20 atoms, containing from 1 to 3 bridges. Bridged cyclyl includes bridged carbocyclyl (e.g., norbornyl) and bridged heterocyclyl (e.g., 1,4-diazabicyclo[2.2.2]octane).

30 The term "cyano," as used herein, represents a —CN group.

35 The term "carbocyclyl," as used herein, refers to a non-aromatic C₃-C₁₂, monocyclic or polycyclic (e.g., bicyclic or tricyclic) structure in which the rings are formed by carbon atoms. Carbocyclyl structures include cycloalkyl groups (e.g., cyclohexyl) and unsaturated carbocyclyl radicals (e.g., cyclohexenyl). Polycyclic carbocyclyl includes spirocyclic carbocyclyl, bridged carbocyclyl, and fused carbocyclyl. A "carbocyclene" is a divalent carbocyclyl group.

40 The term "cycloalkyl," as used herein, refers to a saturated, non-aromatic, monovalent mono- or polycarbocyclic radical of 3 to 10, preferably 3 to 6 carbon atoms. This term is further exemplified by radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, and adamantyl.

45 The terms "halo" or "halogen," as used herein, mean a fluorine (fluoro), chlorine (chloro), bromine (bromo), or iodine (iodo) radical.

50 The term "heteroalkyl," as used herein, refers to an alkyl group, as defined herein, in which one or more of the constituent carbon atoms have been replaced by nitrogen, oxygen, or sulfur. In some embodiments, the heteroalkyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkyl groups. Examples of

345

heteroalkyl groups are an “alkoxy” which, as used herein, refers to alkyl-O— (e.g., methoxy and ethoxy), and an “alkylamino” which, as used herein, refers to —N(alkyl) R^{N_a}, where R^{N_a} is H or alkyl (e.g., methylamino). A “heteroalkylene” is a divalent heteroalkyl group.

The term “heteroalkenyl,” as used herein, refers to an alkenyl group, as defined herein, in which one or more of the constituent carbon atoms have been replaced by nitrogen, oxygen, or sulfur. In some embodiments, the heteroalkenyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkenyl groups. Examples of heteroalkenyl groups are an “alkenoxy” which, as used herein, refers to alkenyl-O—. A “heteroalkenylene” is a divalent heteroalkenyl group.

The term “heteroalkynyl,” as used herein, refers to an alkynyl group, as defined herein, in which one or more of the constituent carbon atoms have been replaced by nitrogen, oxygen, or sulfur. In some embodiments, the heteroalkynyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkynyl groups. Examples of heteroalkynyl groups are an “alkynoxy” which, as used herein, refers to alkynyl-O—. A “heteroalkynylene” is a divalent heteroalkynyl group.

The term “heteroaryl,” as used herein, refers to an aromatic monocyclic or polycyclic structure of 5 to 12 atoms having at least one aromatic ring containing 1, 2, or 3 ring atoms selected from nitrogen, oxygen, and sulfur, with the remaining ring atoms being carbon. One or two ring carbon atoms of the heteroaryl group may be replaced with a carbonyl group. Examples of heteroaryl groups are pyridyl, pyrazoyl, benzoxazolyl, benzoimidazolyl, benzothiazolyl, imidazolyl, oxazolyl, and thiazolyl. A “heteroarylene” is a divalent heteroaryl group.

The term “heteroarylalkyl,” as used herein, represents an alkyl group substituted with a heteroaryl group. Exemplary unsubstituted heteroarylalkyl groups are from 7 to 30 carbons (e.g., from 7 to 16 or from 7 to 20 carbons, such as C₁-C₆ alkyl C₂-C₉ heteroaryl, C₁-C₁₀ alkyl C₂-C₉ heteroaryl, or C₁-C₂₀ alkyl C₂-C₉ heteroaryl). In some embodiments, the alkyl and the heteroaryl each can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective groups.

The term “heterocyclyl,” as used herein, refers a monocyclic or polycyclic radical (e.g., bicyclic or tricyclic) having 3 to 12 atoms having at least one non-aromatic ring containing 1, 2, 3, or 4 ring atoms selected from N, O, or S, and no aromatic ring containing any N, O, or S atoms. Polycyclic heterocyclyl includes spirocyclic heterocyclyl, bridged heterocyclyl, and fused heterocyclyl. Examples of heterocyclyl groups include, but are not limited to, morpholinyl, thiomorpholinyl, furyl, piperazinyl, piperidinyl, pyranyl, pyrrolidinyl, tetrahydropyranyl, tetrahydrofuranyl, and 1,3-dioxanyl. A “heterocyclylene” is a divalent heterocyclyl group.

The term “heterocyclylalkyl,” as used herein, represents an alkyl group substituted with a heterocyclyl group. Exemplary unsubstituted heterocyclylalkyl groups are from 7 to 30 carbons (e.g., from 7 to 16 or from 7 to 20 carbons, such as C₁-C₆ alkyl C₂-C₉ heterocyclyl, C₁-C₁₀ alkyl C₂-C₉ heterocyclyl, or C₁-C₂₀ alkyl C₂-C₉ heterocyclyl). In some embodiments, the alkyl and the heterocyclyl each can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective groups.

The term “hydroxalkyl,” as used herein, represents alkyl group substituted with an —OH group.

The term “hydroxyl,” as used herein, represents an —OH group.

346

The term “imine,” as used herein, represents =NR^{N_v} group, where R^{N_v} is, e.g., H or alkyl.

The term “N-protecting group,” as used herein, represents those groups intended to protect an amino group against undesirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in Greene, “Protective Groups in Organic Synthesis,” 3rd Edition (John Wiley & Sons, New York, 1999). N-protecting groups include, but are not limited to, acyl, aryl, or carbamyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxycetyl, α-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and chiral auxiliaries such as protected or unprotected D, L, or D, L-amino acids such as alanine, leucine, and phenylalanine; sulfonyl-containing groups such as benzenesulfonyl, and p-toluenesulfonyl; carbamate forming groups such as benzylloxycarbonyl, p-chlorobenzylloxycarbonyl, p-methoxybenzylloxycarbonyl, p-nitrobenzylloxycarbonyl, 2-nitrobenzylloxycarbonyl, p-bromobenzylloxycarbonyl, 3,4-dimethoxybenzylloxycarbonyl, 3,5-dimethoxybenzylloxycarbonyl, 2,4-20 dimethoxybenzylloxycarbonyl, 4-methoxybenzylloxycarbonyl, 2-nitro-4,5-dimethoxybenzylloxycarbonyl, 3,4,5-trimethoxybenzylloxycarbonyl, 1-(p-biphenyl)-1-methylethoxycarbonyl, α,α-dimethyl-3,5-dimethoxybenzylloxycarbonyl, benzhydryloxy carbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropylloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, phenoxy-carbonyl, 4-nitrophenoxy carbonyl, fluorenyl-9-methoxy-carbonyl, cyclopentyloxycarbonyl, adamantlyloxycarbonyl, cyclohexyloxycarbonyl, and phenylthiocarbonyl, arylalkyl groups such as benzyl, triphenylmethyl, and benzylloxymethyl, and silyl groups, such as trimethylsilyl. Preferred N-protecting groups are alloc, formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, alanyl, phenylsulfonyl, benzyl, t-butylcarbonyl (Boc), and benzylloxycarbonyl (Cbz).

The term “nitro,” as used herein, represents an —NO₂ group.

The term “oxo,” as used herein, represents an =O group.

The term “thiol,” as used herein, represents an —SH group.

The alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl (e.g., cycloalkyl), aryl, heteroaryl, and heterocyclyl groups may be substituted or unsubstituted. When substituted, there will generally be 1 to 4 substituents present, unless otherwise specified. Substituents include, for example: alkyl (e.g., unsubstituted and substituted, where the substituents include any group described herein, e.g., aryl, halo, hydroxy), aryl (e.g., substituted and unsubstituted phenyl), carbocyclyl (e.g., substituted and unsubstituted cycloalkyl), halogen (e.g., fluoro), hydroxyl, heteroalkyl (e.g., substituted and unsubstituted methoxy, ethoxy, or thioalkoxy), heteroaryl, heterocyclyl, amino (e.g., NH₂ or mono- or dialkyl amino), azido, cyano, nitro, oxo, sulfonyl, or thiol. Aryl, carbocyclyl (e.g., cycloalkyl), heteroaryl, and heterocyclyl groups may also be substituted with alkyl (unsubstituted and substituted such as arylalkyl (e.g., substituted and unsubstituted benzyl)).

Compounds described herein (e.g., compounds of the invention) can have one or more asymmetric carbon atoms and can exist in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, or mixtures of diastereoisomeric racemates. The optically active forms can be

obtained for example by resolution of the racemates, by asymmetric synthesis or asymmetric chromatography (chromatography with a chiral adsorbent or eluant). That is, certain of the disclosed compounds may exist in various stereoisomeric forms. Stereoisomers are compounds that differ only in their spatial arrangement. Enantiomers are pairs of stereoisomers whose mirror images are not superimposable, most commonly because they contain an asymmetrically substituted carbon atom that acts as a chiral center. "Enantiomer" means one of a pair of molecules that are mirror images of each other and are not superimposable. Diastereomers are stereoisomers that are not related as mirror images, most commonly because they contain two or more asymmetrically substituted carbon atoms and represent the configuration of substituents around one or more chiral carbon atoms. Enantiomers of a compound can be prepared, for example, by separating an enantiomer from a racemate using one or more well-known techniques and methods, such as, for example, chiral chromatography and separation methods based thereon. The appropriate technique and/or method for separating an enantiomer of a compound described herein from a racemic mixture can be readily determined by those of skill in the art. "Racemate" or "racemic mixture" means a compound containing two enantiomers, wherein such mixtures exhibit no optical activity; i.e., they do not rotate the plane of polarized light. "Geometric isomer" means isomers that differ in the orientation of substituent atoms in relationship to a carbon-carbon double bond, to a cycloalkyl ring, or to a bridged bicyclic system. Atoms (other than H) on each side of a carbon-carbon double bond may be in an E (substituents are on opposite sides of the carbon-carbon double bond) or Z (substituents are oriented on the same side) configuration. "R," "S," "S*," "R*," "E," "Z," "cis," and "trans," indicate configurations relative to the core molecule. Certain of the disclosed compounds may exist in atropisomeric forms. Atropisomers are stereoisomers resulting from hindered rotation about single bonds where the steric strain barrier to rotation is high enough to allow for the isolation of the conformers. The compounds described herein (e.g., the compounds of the invention) may be prepared as individual isomers by either isomer-specific synthesis or resolved from an isomeric mixture. Conventional resolution techniques include forming the salt of a free base of each isomer of an isomeric pair using an optically active acid (followed by fractional crystallization and regeneration of the free base), forming the salt of the acid form of each isomer of an isomeric pair using an optically active amine (followed by fractional crystallization and regeneration of the free acid), forming an ester or amide of each of the isomers of an isomeric pair using an optically pure acid, amine or alcohol (followed by chromatographic separation and removal of the chiral auxiliary), or resolving an isomeric mixture of either a starting material or a final product using various well known chromatographic methods. When the stereochemistry of a disclosed compound is named or depicted by structure, the named or depicted stereoisomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by weight relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by weight optically pure. When a single diastereomer is named or depicted by structure, the depicted or named diastereomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by weight pure. Percent optical purity is the ratio of the weight of the enantiomer or over the weight of the enantiomer plus the weight of its optical isomer. Diastereomeric purity by weight

is the ratio of the weight of one diastereomer or over the weight of all the diastereomers. When the stereochemistry of a disclosed compound is named or depicted by structure, the named or depicted stereoisomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by mole fraction pure relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by mole fraction pure. When a single diastereomer is named or depicted by structure, the depicted or named diastereomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by mole fraction pure. Percent purity by mole fraction is the ratio of the moles of the enantiomer or over the moles of the enantiomer plus the moles of its optical isomer. Similarly, percent purity by moles fraction is the ratio of the moles of the diastereomer or over the moles of the diastereomer plus the moles of its isomer. When a disclosed compound is named or depicted by structure without indicating the stereochemistry, and the compound has at least one chiral center, it is to be understood that the name or structure encompasses either enantiomer of the compound free from the corresponding optical isomer, a racemic mixture of the compound, or mixtures enriched in one enantiomer relative to its corresponding optical isomer. When a disclosed compound is named or depicted by structure without indicating the stereochemistry and has two or more chiral centers, it is to be understood that the name or structure encompasses a diastereomer free of other diastereomers, a number of diastereomers free from other diastereomeric pairs, mixtures of diastereomers, mixtures of diastereomeric pairs, mixtures of diastereomers in which one diastereomer is enriched relative to the other diastereomer(s), or mixtures of diastereomers in which one or more diastereomer is enriched relative to the other diastereomers. The invention embraces all of these forms.

Compounds of the present disclosure also include all of the isotopes of the atoms occurring in the intermediate or final compounds. "Isotopes" refers to atoms having the same atomic number but different mass numbers resulting from a different number of neutrons in the nuclei. For example, isotopes of hydrogen include tritium and deuterium.

Unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. Exemplary isotopes that can be incorporated into compounds of the present invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine, and iodine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{32}P , ^{33}P , ^{35}S , ^{18}F , ^{36}Cl , ^{123}I and ^{125}I . Isotopically-labeled compounds (e.g., those labeled with ^3H and ^{14}C) can be useful in compound or substrate tissue distribution assays. Tritiated (i.e., ^3H) and carbon-14 (i.e., ^{14}C) isotopes can be useful for their ease of preparation and detectability.

Further, substitution with heavier isotopes such as deuterium (i.e., ^2H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements). In some embodiments, one or more hydrogen atoms are replaced by ^2H or ^3H , or one or more carbon atoms are replaced by ^{13}C - or ^{14}C -enriched carbon. Positron emitting isotopes such as ^{15}O , ^{13}N , ^{11}C , and ^{18}F are useful for positron emission tomography (PET) studies to examine substrate receptor occupancy. Preparations of isotopically labelled compounds are known to those of skill in the art. For example, isotopically labeled compounds can generally be prepared by following procedures analogous to those disclosed for compounds of

349

the present invention described herein, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

As is known in the art, many chemical entities can adopt a variety of different solid forms such as, for example, amorphous forms or crystalline forms (e.g., polymorphs, hydrates, solvate). In some embodiments, compounds of the present invention may be utilized in any such form, including in any solid form. In some embodiments, compounds described or depicted herein may be provided or utilized in hydrate or solvate form.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Methods and materials are described herein for use in the present disclosure; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

Definitions

In this application, unless otherwise clear from context, (i) the term “a” may be understood to mean “at least one”; (ii) the term “or” may be understood to mean “and/or”; and (iii) the terms “including” and “including” may be understood to encompass itemized components or steps whether presented by themselves or together with one or more additional components or steps.

As used herein, the terms “about” and “approximately” refer to a value that is within 10% above or below the value being described. For example, the term “about 5 nM” indicates a range of from 4.5 to 5.5 nM.

As used herein, the term “administration” refers to the administration of a composition (e.g., a compound or a preparation that includes a compound as described herein) to a subject or system. Administration to an animal subject (e.g., to a human) may be by any appropriate route. For example, in some embodiments, administration may be bronchial (including by bronchial instillation), buccal, enteral, interdermal, intra-arterial, intradermal, intragastric, intramedullary, intramuscular, intranasal, intraperitoneal, intrathecal, intratumoral, intravenous, intraventricular, mucosal, nasal, oral, rectal, subcutaneous, sublingual, topical, tracheal (including by intratracheal instillation), transdermal, vaginal, and vitreal.

As used herein, the term “adult soft tissue sarcoma” refers to a sarcoma that develops in the soft tissues of the body, typically in adolescent and adult subjects (e.g., subjects who are at least 10 years old, 11 years old, 12 years old, 13 years old, 14 years old, 15 years old, 16 years old, 17 years old, 18 years old, or 19 years old). Non-limiting examples of adult soft tissue sarcoma include, but are not limited to, synovial sarcoma, fibrosarcoma, malignant fibrous histiocytoma, dermatofibrosarcoma, liposarcoma, leiomyosarcoma, hemangiosarcoma, Kaposi’s sarcoma, lymphangiosarcoma, malignant peripheral nerve sheath tumor/neurofibrosarcoma, extraskeletal chondrosarcoma, extraskeletal osteosarcoma, extraskeletal myxoid chondrosarcoma, and extraskeletal mesenchymal.

The term “antisense,” as used herein, refers to a nucleic acid comprising a polynucleotide that is sufficiently complementary to all or a portion of a gene, primary transcript, or

350

processed mRNA, so as to interfere with expression of the endogenous gene (e.g., BRD9). “Complementary” polynucleotides are those that are capable of base pairing according to the standard Watson-Crick complementarity rules. Specifically, purines will base pair with pyrimidines to form a combination of guanine paired with cytosine (G:C) and adenine paired with either thymine (A:T) in the case of DNA, or adenine paired with uracil (A:U) in the case of RNA. It is understood that two polynucleotides may hybridize to each other even if they are not completely complementary to each other, provided that each has at least one region that is substantially complementary to the other.

The term “antisense nucleic acid” includes single-stranded RNA as well as double-stranded DNA expression cassettes that can be transcribed to produce an antisense RNA. “Active” antisense nucleic acids are antisense RNA molecules that are capable of selectively hybridizing with a primary transcript or mRNA encoding a polypeptide having at least 80% sequence identity (e.g., 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.9% identity, or more) with the targeted polypeptide sequence (e.g., a BRD9 polypeptide sequence). The antisense nucleic acid can be complementary to an entire coding strand, or to only a portion thereof. In some embodiments, an antisense nucleic acid molecule is antisense to a “coding region” of the coding strand of a nucleotide sequence. The term “coding region” refers to the region of the nucleotide sequence comprising codons that are translated into amino acid residues. In some embodiments, the antisense nucleic acid molecule is antisense to a “noncoding region” of the coding strand of a nucleotide sequence. The term “noncoding region” refers to 5' and 3' sequences that flank the coding region that are not translated into amino acids (i.e., also referred to as 5' and 3' untranslated regions). The antisense nucleic acid molecule can be complementary to the entire coding region of mRNA, or can be antisense to only a portion of the coding or noncoding region of an mRNA. For example, the antisense oligonucleotide can be complementary to the region surrounding the translation start site. An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 nucleotides in length.

As used herein, the term “BAF complex” refers to the BR^{G1}- or HRBM-associated factors complex in a human cell.

As used herein, the term “BAF complex-related disorder” refers to a disorder that is caused or affected by the level and/or activity of a BAF complex.

As used herein, the terms “GBAF complex” and “GBAF” refer to a SWI/SNF ATPase chromatin remodeling complex in a human cell. GBAF complex subunits may include, but are not limited to, ACTB, ACTL6A, ACTL6B, BICRA, BICRAL, BRD9, SMARCA2, SMARCA4, SMARCC1, SMARCD1, SMARCD2, SMARCD3, and SS18. The term “cancer” refers to a condition caused by the proliferation of malignant neoplastic cells, such as tumors, neoplasms, carcinomas, sarcomas, leukemias, and lymphomas.

As used herein, the term “BRD9” refers to bromodomain-containing protein 9, a component of the BAF (BR^{G1}- or BRM-associated factors) complex, a SWI/SNF ATPase chromatin remodeling complex, and belongs to family IV of the bromodomain-containing proteins. BRD9 is encoded by the BRD9 gene, the nucleic acid sequence of which is set forth in SEQ ID NO: 1. The term “BRD9” also refers to natural variants of the wild-type BRD9 protein, such as proteins having at least 85% identity (e.g., 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%,

351

98%, 99%, 99.9% identity, or more) to the amino acid sequence of wild-type BRD9, which is set forth in SEQ ID NO: 2.

As used herein, the term “BRD9-related disorder” refers to a disorder that is caused or affected by the level and/or activity of BRD9. The term “cancer” refers to a condition caused by the proliferation of malignant neoplastic cells, such as tumors, neoplasms, carcinomas, sarcomas, leukemias, and lymphomas.

As used herein, a “combination therapy” or “administered in combination” means that two (or more) different agents or treatments are administered to a subject as part of a defined treatment regimen for a particular disease or condition. The treatment regimen defines the doses and periodicity of administration of each agent such that the effects of the separate agents on the subject overlap. In some embodiments, the delivery of the two or more agents is simultaneous or concurrent and the agents may be co-formulated. In some embodiments, the two or more agents are not co-formulated and are administered in a sequential manner as part of a prescribed regimen. In some embodiments, administration of two or more agents or treatments in combination is such that the reduction in a symptom, or other parameter related to the disorder is greater than what would be observed with one agent or treatment delivered alone or in the absence of the other. The effect of the two treatments can be partially additive, wholly additive, or greater than additive (e.g., synergistic). Sequential or substantially simultaneous administration of each therapeutic agent can be effected by any appropriate route including, but not limited to, oral routes, intravenous routes, intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents can be administered by the same route or by different routes. For example, a first therapeutic agent of the combination may be administered by intravenous injection while a second therapeutic agent of the combination may be administered orally.

A “compound of the present invention” and similar terms as used herein, whether explicitly noted or not, refers to compounds useful for treating BAF-related disorders (e.g., cancer or infection) described herein, including, e.g., compounds of Formula I or Formula II (e.g., compounds of Table 2A, Table 2B, and Table 2C), as well as salts (e.g., pharmaceutically acceptable salts), solvates, hydrates, stereoisomers (including atropisomers), and tautomers thereof. Those skilled in the art will appreciate that certain compounds described herein can exist in one or more different isomeric (e.g., stereoisomers, geometric isomers, atropisomers, and tautomers) or isotopic (e.g., in which one or more atoms has been substituted with a different isotope of the atom, such as hydrogen substituted for deuterium) forms. Unless otherwise indicated or clear from context, a depicted structure can be understood to represent any such isomeric or isotopic form, individually or in combination. Compounds described herein can be asymmetric (e.g., having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present disclosure that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically active starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present disclosure. Cis and trans geometric isomers of the compounds of the present

352

disclosure are described and may be isolated as a mixture of isomers or as separated isomeric forms. In some embodiments, one or more compounds depicted herein may exist in different tautomeric forms. As will be clear from context, unless explicitly excluded, references to such compounds encompass all such tautomeric forms. In some embodiments, tautomeric forms result from the swapping of a single bond with an adjacent double bond and the concomitant migration of a proton.

In certain embodiments, a tautomeric form may be a prototropic tautomer, which is an isomeric protonation states having the same empirical formula and total charge as a reference form. Examples of moieties with prototropic tautomeric forms are ketone-enol pairs, amide-imidic acid pairs, lactam-lactim pairs, amide-imidic acid pairs, enamine-imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, such as, 1H- and 3H-imidazole, 1H-, 2H- and 4H-1,2,4-triazole, 1H- and 2H-isoindole, and 1H- and 2H-pyrazole. In some embodiments, tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution. In certain embodiments, tautomeric forms result from acetal interconversion.

As used herein, the term “degrader” refers to a small molecule compound including a degradation moiety, wherein the compound interacts with a protein (e.g., BRD9) in a way which results in degradation of the protein, e.g., binding of the compound results in at least 5% reduction of the level of the protein, e.g., in a cell or subject.

As used herein, the term “degradation moiety” refers to a moiety whose binding results in degradation of a protein, e.g., BRD9. In one example, the moiety binds to a protease or a ubiquitin ligase that metabolizes the protein, e.g., BRD9.

By “determining the level of a protein” is meant the detection of a protein, or an mRNA encoding the protein, by methods known in the art either directly or indirectly. “Directly determining” means performing a process (e.g., performing an assay or test on a sample or “analyzing a sample” as that term is defined herein) to obtain the physical entity or value. “Indirectly determining” refers to receiving the physical entity or value from another party or source (e.g., a third-party laboratory that directly acquired the physical entity or value). Methods to measure protein level generally include, but are not limited to, western blotting, immunoblotting, enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), immunoprecipitation, immunofluorescence, surface plasmon resonance, chemiluminescence, fluorescent polarization, phosphorescence, immunohistochemical analysis, matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry, liquid chromatography (LC)-mass spectrometry, microcytometry, microscopy, fluorescence activated cell sorting (FACS), and flow cytometry, as well as assays based on a property of a protein including, but not limited to, enzymatic activity or interaction with other protein partners. Methods to measure mRNA levels are known in the art.

As used herein, the terms “effective amount,” “therapeutically effective amount,” and “a “sufficient amount” of an agent that reduces the level and/or activity of BRD9 (e.g., in a cell or a subject) described herein refer to a quantity sufficient to, when administered to the subject, including a human, effect beneficial or desired results, including clinical results, and, as such, an “effective amount” or synonym thereto depends on the context in which it is being applied. For example, in the context of treating cancer, it is an amount of the agent that reduces the level and/or activity of

353

BRD9 sufficient to achieve a treatment response as compared to the response obtained without administration of the agent that reduces the level and/or activity of BRD9. The amount of a given agent that reduces the level and/or activity of BRD9 described herein that will correspond to such an amount will vary depending upon various factors, such as the given agent, the pharmaceutical formulation, the route of administration, the type of disease or disorder, the identity of the subject (e.g., age, sex, and/or weight) or host being treated, and the like, but can nevertheless be routinely determined by one of skill in the art. Also, as used herein, a “therapeutically effective amount” of an agent that reduces the level and/or activity of BRD9 of the present disclosure is an amount which results in a beneficial or desired result in a subject as compared to a control. As defined herein, a therapeutically effective amount of an agent that reduces the level and/or activity of BRD9 of the present disclosure may be readily determined by one of ordinary skill by routine methods known in the art. Dosage regimen may be adjusted to provide the optimum therapeutic response.

As used herein, the term “inhibitor” refers to any agent which reduces the level and/or activity of a protein (e.g., BRD9). Non-limiting examples of inhibitors include small molecule inhibitors, degraders, antibodies, enzymes, or polynucleotides (e.g., siRNA).

The term “inhibitory RNA agent” refers to an RNA, or analog thereof, having sufficient sequence complementarity to a target RNA to direct RNA interference. Examples also include a DNA that can be used to make the RNA. RNA interference (RNAi) refers to a sequence-specific or selective process by which a target molecule (e.g., a target gene, protein, or RNA) is down-regulated. Generally, an interfering RNA (“iRNA”) is a double-stranded short-interfering RNA (siRNA), short hairpin RNA (shRNA), or single-stranded micro-RNA (miRNA) that results in catalytic degradation of specific mRNAs, and also can be used to lower or inhibit gene expression.

By “level” is meant a level of a protein, or mRNA encoding the protein, as compared to a reference. The reference can be any useful reference, as defined herein. By a “decreased level” or an “increased level” of a protein is meant a decrease or increase in protein level, as compared to a reference (e.g., a decrease or an increase by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 100%, about 150%, about 200%, about 300%, about 400%, about 500%, or more; a decrease or an increase of more than about 10%, about 15%, about 20%, about 50%, about 75%, about 100%, or about 200%, as compared to a reference; a decrease or an increase by less than about 0.01-fold, about 0.02-fold, about 0.1-fold, about 0.3-fold, about 0.5-fold, about 0.8-fold, or less; or an increase by more than about 1.2-fold, about 1.4-fold, about 1.5-fold, about 1.8-fold, about 2.0-fold, about 3.0-fold, about 3.5-fold, about 4.5-fold, about 5.0-fold, about 10-fold, about 15-fold, about 20-fold, about 30-fold, about 40-fold, about 50-fold, about 100-fold, about 1000-fold, or more). A level of a protein may be expressed in mass/vol (e.g., g/dL, mg/mL, μ g/mL, ng/mL) or percentage relative to total protein or mRNA in a sample.

The terms “miRNA” and “microRNA” refer to an RNA agent, preferably a single-stranded agent, of about 10-50 nucleotides in length, preferably between about 15-25 nucleotides in length, which is capable of directing or mediating RNA interference. Naturally-occurring miRNAs are generated from stem-loop precursor RNAs (i.e., pre-

354

miRNAs) by Dicer. The term “Dicer” as used herein, includes Dicer as well as any Dicer ortholog or homolog capable of processing dsRNA structures into siRNAs, miRNAs, siRNA-like or miRNA-like molecules. The term microRNA (“miRNA”) is used interchangeably with the term “small temporal RNA” (“stRNA”) based on the fact that naturally-occurring miRNAs have been found to be expressed in a temporal fashion (e.g., during development).

By “modulating the activity of a BAF complex,” is meant altering the level of an activity related to a BAF complex (e.g., GBAF), or a related downstream effect. The activity level of a BAF complex may be measured using any method known in the art, e.g., the methods described in Kadoch et al, Cell 153:71-85 (2013), the methods of which are herein incorporated by reference.

“Percent (%) sequence identity” with respect to a reference polynucleotide or polypeptide sequence is defined as the percentage of nucleic acids or amino acids in a candidate sequence that are identical to the nucleic acids or amino acids in the reference polynucleotide or polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. Alignment for purposes of determining percent nucleic acid or amino acid sequence identity can be achieved in various ways that are within the capabilities of one of skill in the art, for example, using publicly available computer software such as BLAST, BLAST-2, or Megalign software. Those skilled in the art can determine appropriate parameters for aligning sequences, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For example, percent sequence identity values may be generated using the sequence comparison computer program BLAST. As an illustration, the percent sequence identity of a given nucleic acid or amino acid sequence, A, to, with, or against a given nucleic acid or amino acid sequence, B, (which can alternatively be phrased as a given nucleic acid or amino acid sequence, A that has a certain percent sequence identity to, with, or against a given nucleic acid or amino acid sequence, B) is calculated as follows:

$$100 \text{ multiplied by} (\text{the fraction } X/Y)$$

where X is the number of nucleotides or amino acids scored as identical matches by a sequence alignment program (e.g., BLAST) in that program’s alignment of A and B, and where Y is the total number of nucleic acids in B. It will be appreciated that where the length of nucleic acid or amino acid sequence A is not equal to the length of nucleic acid or amino acid sequence B, the percent sequence identity of A to B will not equal the percent sequence identity of B to A.

A “pharmaceutically acceptable excipient,” as used herein, refers any ingredient other than the compounds described herein (for example, a vehicle capable of suspending or dissolving the active compound) and having the properties of being substantially nontoxic and non-inflammatory in a patient. Excipients may include, for example: antiadherents, antioxidants, binders, coatings, compression aids, disintegrants, dyes (colors), emollients, emulsifiers, fillers (diluents), film formers or coatings, flavors, fragrances, glidants (flow enhancers), lubricants, preservatives, sweeteners, and waters of hydration. Exemplary excipients include, but are not limited to: butylated hydroxytoluene (BHT), calcium carbonate, calcium phosphate (dibasic), calcium stearate, croscarmellose, crosslinked polyvinyl pyrrolidone, citric acid, crospovidone, cysteine, ethylcellulose, gelatin, hydroxypropyl cellulose, hydroxypropyl methylcel-

355

lulose, lactose, magnesium stearate, maltitol, mannitol, methionine, methylcellulose, methyl paraben, microcrystalline cellulose, polyethylene glycol, polyvinyl pyrrolidone, povidone, pregelatinized starch, propyl paraben, retinyl palmitate, shellac, silicon dioxide, sodium carboxymethyl cellulose, sodium citrate, sodium starch glycolate, sorbitol, starch (corn), stearic acid, sucrose, talc, titanium dioxide, vitamin A, vitamin E, vitamin C, and xylitol.

As used herein, the term “pharmaceutically acceptable salt” means any pharmaceutically acceptable salt of the compound of any of the compounds described herein. For example, pharmaceutically acceptable salts of any of the compounds described herein include those that are within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and animals without undue toxicity, irritation, allergic response and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, pharmaceutically acceptable salts are described in: Berge et al., *J. Pharmaceutical Sciences* 66:1-19, 1977 and in *Pharmaceutical Salts: Properties, Selection, and Use*, (Eds. P. H. Stahl and C. G. Wermuth), Wiley-VCH, 2008. The salts can be prepared *in situ* during the final isolation and purification of the compounds described herein or separately by reacting a free base group with a suitable organic acid.

The compounds described herein may have ionizable groups so as to be capable of preparation as pharmaceutically acceptable salts. These salts may be acid addition salts involving inorganic or organic acids or the salts may, in the case of acidic forms of the compounds described herein, be prepared from inorganic or organic bases. Frequently, the compounds are prepared or used as pharmaceutically acceptable salts prepared as addition products of pharmaceutically acceptable acids or bases. Suitable pharmaceutically acceptable acids and bases and methods for preparation of the appropriate salts are well-known in the art. Salts may be prepared from pharmaceutically acceptable non-toxic acids and bases including inorganic and organic acids and bases. Representative acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxyethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, and valerate salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, and magnesium, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, and ethylamine.

The term “pharmaceutical composition,” as used herein, represents a composition containing a compound described herein formulated with a pharmaceutically acceptable excipient, and manufactured or sold with the approval of a governmental regulatory agency as part of a therapeutic regimen for the treatment of disease in a mammal. Pharmaceutical compositions can be formulated, for example, for oral administration in unit dosage form (e.g., a tablet, capsule, caplet, gelcap, or syrup); for topical administration

356

(e.g., as a cream, gel, lotion, or ointment); for intravenous administration (e.g., as a sterile solution free of particulate emboli and in a solvent system suitable for intravenous use); or in any other pharmaceutically acceptable formulation.

By “reducing the activity of BRD9,” is meant decreasing the level of an activity related to an BRD9, or a related downstream effect. A non-limiting example of inhibition of an activity of BRD9 is decreasing the level of a BAF complex (e.g., GBAF) in a cell. The activity level of BRD9 may be measured using any method known in the art. In some embodiments, an agent which reduces the activity of BRD9 is a small molecule BRD9 inhibitor. In some embodiments, an agent which reduces the activity of BRD9 is a small molecule BRD9 degrader.

By “reducing the level of BRD9,” is meant decreasing the level of BRD9 in a cell or subject. The level of BRD9 may be measured using any method known in the art.

By a “reference” is meant any useful reference used to compare protein or mRNA levels. The reference can be any sample, standard, standard curve, or level that is used for comparison purposes. The reference can be a normal reference sample or a reference standard or level. A “reference sample” can be, for example, a control, e.g., a predetermined negative control value such as a “normal control” or a prior sample taken from the same subject; a sample from a normal healthy subject, such as a normal cell or normal tissue; a sample (e.g., a cell or tissue) from a subject not having a disease; a sample from a subject that is diagnosed with a disease, but not yet treated with a compound described herein; a sample from a subject that has been treated by a compound described herein; or a sample of a purified protein (e.g., any described herein) at a known normal concentration. By “reference standard or level” is meant a value or number derived from a reference sample. A “normal control value” is a pre-determined value indicative of non-disease state, e.g., a value expected in a healthy control subject. Typically, a normal control value is expressed as a range (“between X and Y”), a high threshold (“no higher than X”), or a low threshold (“no lower than X”). A subject having a measured value within the normal control value for a particular biomarker is typically referred to as “within normal limits” for that biomarker. A normal reference standard or level can be a value or number derived from a normal subject not having a disease or disorder (e.g., cancer); a subject that has been treated with a compound described herein. In preferred embodiments, the reference sample, standard, or level is matched to the sample subject sample by at least one of the following criteria: age, weight, sex, disease stage, and overall health. A standard curve of levels of a purified protein, e.g., any described herein, within the normal reference range can also be used as a reference.

The terms “short interfering RNA” and “siRNA” (also known as “small interfering RNAs”) refer to an RNA agent, preferably a double-stranded agent, of about 10-50 nucleotides in length, the strands optionally having overhanging ends comprising, for example 1, 2 or 3 overhanging nucleotides (or nucleotide analogs), which is capable of directing or mediating RNA interference. Naturally-occurring siRNAs are generated from longer dsRNA molecules (e.g., >25 nucleotides in length) by a cell’s RNAi machinery (e.g., Dicer or a homolog thereof).

The term “shRNA”, as used herein, refers to an RNA agent having a stem-loop structure, comprising a first and second region of complementary sequence, the degree of complementarity and orientation of the regions being sufficient such that base pairing occurs between the regions, the first and second regions being joined by a loop region, the

357

loop resulting from a lack of base pairing between nucleotides (or nucleotide analogs) within the loop region.

As used herein, the term “subject” refers to any organism to which a composition in accordance with the invention may be administered, e.g., for experimental, diagnostic, prophylactic, and/or therapeutic purposes. Typical subjects include any animal (e.g., mammals such as mice, rats, rabbits, non-human primates, and humans). A subject may seek or be in need of treatment, require treatment, be receiving treatment, be receiving treatment in the future, or be a human or animal who is under care by a trained professional for a particular disease or condition.

As used herein, the term “SS18-SSX fusion protein-related disorder” refers to a disorder that is caused or affected by the level and/or activity of SS18-SSX fusion protein.

As used herein, the terms “treat,” “treated,” or “treating” mean both therapeutic treatment and prophylactic or preventative measures wherein the object is to prevent or slow down (lessen) an undesired physiological condition, disorder, or disease, or obtain beneficial or desired clinical results. Beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of a condition, disorder, or disease; stabilized (i.e., not worsening) state of condition, disorder, or disease; delay in onset or slowing of condition, disorder, or disease progression; amelioration of the condition, disorder, or disease state or remission (whether partial or total), whether detectable or undetectable; an amelioration of at least one measurable physical parameter, not necessarily discernible by the patient; or enhancement or improvement of condition, disorder, or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment.

As used herein, the terms “variant” and “derivative” are used interchangeably and refer to naturally-occurring, synthetic, and semi-synthetic analogues of a compound, peptide, protein, or other substance described herein. A variant or derivative of a compound, peptide, protein, or other substance described herein may retain or improve upon the biological activity of the original material.

The details of one or more embodiments of the invention are set forth in the description below. Other features, objects, and advantages of the invention will be apparent from the description and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a series of graphs illustrating the effect of specific guide RNA (sgRNA) targeting of the BRD9 BAF complex subunit on synovial sarcoma cell growth. The Y-axis indicated the dropout ratio. The X-axis indicates the nucleotide position of the BRD9 gene. The grey box indicates the range of the negative control sgRNAs in the screen. The SYO1 cell line carries SS18-SSX2 fusion protein. The breakpoint joining the N-terminal region of SS18 to the C-terminal region of SSX2 are indicated by the black lines in their respective panel. The linear protein sequence is shown with BRD9 PFAM domains annotated from the PFAM database.

FIG. 2 is an image illustrating dose dependent depletion of BRD9 levels in a synovial sarcoma cell line (SYO1) in the presence of a BRD9 degrader.

358

FIG. 3 is an image illustrating sustained suppression of BRD9 levels in a synovial sarcoma cell line (SYO1) in the presence of a BRD9 degrader over 72 hours.

FIG. 4 is an image illustrating sustained suppression of BRD9 levels in two cell lines (293T and SYO1) in the presence of a BRD9 degrader over 5 days.

FIG. 5 is an image illustrating sustained suppression of BRD9 levels in synovial sarcoma cell lines (SYO1 and Yamato) in the presence of a BRD9 degrader over 7 days compared to the levels in cells treated with CRISPR reagents.

FIG. 6 is an image illustrating the effect on cell growth of six cell lines (SYO1, Yamato, A549, HS-SY-II, ASKA, and 293T) in the presence of a BRD9 degrader and a BRD9 inhibitor.

FIG. 7 is an image illustrating the effect on cell growth of two cell lines (SYO1 and G401) in the presence of a BRD9 degrader.

FIG. 8 is an image illustrating the effect on cell growth of three synovial sarcoma cell lines (SYO1, HS-SY-II, and ASKA) in the presence of a BRD9 degrader, BRD9 binder and E3 ligase binder.

FIG. 9 is an image illustrating the effect on cell growth of three non-synovial sarcoma cell lines (RD, HCT116, and Calu6) in the presence of a BRD9 degrader, BRD9 binder and E3 ligase binder.

FIG. 10 is a graph illustrating the percentage of SYO1 in various cell cycle phases following treatment with DMSO, Compound 1 at 200 nM, or Compound 1 at 1 μ M for 8 or 13 days.

FIG. 11 is a series of contour plots illustrating the percentage of SYO1 cells in various cell cycle phases following treatment with DMSO, Compound 1 at 200 nM, Compound 1 at 1 μ M, or lenalidomide at 200 nM for 8 days. Numerical values corresponding to each contour plot are found in the table below.

FIG. 12 is a series of contour plots illustrating the percentage of SYO1 cells in various cell cycle phases following treatment with DMSO, Compound 1 at 200 nM, Compound 1 at 1 μ M, or lenalidomide at 200 nM for 13 days. Numerical values corresponding to each contour plot are found in the table below.

FIG. 13 is a series of contour plots illustrating the percentage of early- and late-apoptotic SYO1 cells following treatment with DMSO, Compound 1 at 200 nM, Compound 1 at 1 μ M, or lenalidomide at 200 nM for 8 days. Numerical values corresponding to each contour plot are found in the table below.

FIG. 14 is a graph illustrating the proteins present in BAF complexes including the SS18-SSX fusion protein.

DETAILED DESCRIPTION

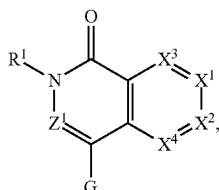
The present disclosure features compositions and methods useful for the treatment of BAF-related disorders (e.g., cancer and infection). The disclosure further features compositions and methods useful for inhibition of the level and/or activity of BRD9, e.g., for the treatment of disorders such as cancer (e.g., sarcoma) and infection (e.g., viral infection), e.g., in a subject in need thereof.

359

Compounds

Compounds described herein reduce the level of an activity related to BRD9, or a related downstream effect, or reduce the level of BRD9 in a cell or subject. Exemplary compounds described herein have the structure according to Formula I or Formula II.

Formula I is:



where

R¹ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ carbocyclyl;

Z¹ is CR² or N;

R² is H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, or optionally substituted C₂-C₉ heteroaryl;

X¹ is N or CH, and X² is C—R⁷; or X¹ is C—R⁷, and X² is N or CH;

R⁷ is optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₁-C₆ alkoxy, optionally substituted amino, optionally substituted sulfone, optionally substituted sulfonamide, optionally substituted carbocyclyl having 3 to 6 atoms, or optionally substituted heterocyclyl having 3 to 6 atoms;

X³ is N or CH;

X⁴ is N or CH;

G is optionally substituted C₃-C₁₀ carbocyclyl, C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, or optionally substituted C₂-C₉ heteroaryl, or a pharmaceutically acceptable salt thereof.

Formula II is:

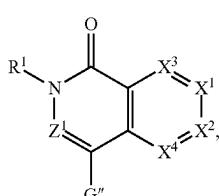
A-L-B

where

L is a linker;

B is a degradation moiety; and

A has the structure of Formula III:



where

R¹ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ carbocyclyl;

Z¹ is CR² or N;

Formula II,

45

50

55

60

65

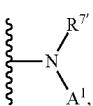
Formula III

360

R² is H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, or optionally substituted C₂-C₉ heteroaryl;

X¹ is N or CH, and X² is C—R⁷; or X¹ is C—R⁷, and X² is N or CH;

R⁷ is



15

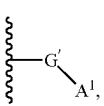
optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₁-C₆ alkoxy, optionally substituted amino, optionally substituted sulfone, optionally substituted sulfonamide, optionally substituted carbocyclyl having 3 to 6 atoms, or optionally substituted heterocyclyl having 3 to 6 atoms;

R⁷ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ carbocyclyl;

X³ is N or CH;

X⁴ is N or CH;

G'' is



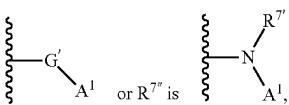
35

optionally substituted C₃-C₁₀ carbocyclyl, C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, or optionally substituted C₂-C₉ heteroaryl;

G' is optionally substituted C₃-C₁₀ carbocyclene, C₂-C₉ heterocyclene, optionally substituted C₆-C₁₀ arylene, or optionally substituted C₂-C₉ heteroarylene; and

A¹ is a bond between A and the linker,

where G'' is



or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound has the structure of any one of compounds B1-B6 in Table 1, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound has the structure of any one of compounds D1-D31 in Table 2A, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound has the structure of any one of compounds D32-D184 in Table 2B, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound has the structure of any one of compounds D185-D316 in Table 2C, or a pharmaceutically acceptable salt thereof.

Other embodiments, as well as exemplary methods for the synthesis of production of these compounds, are described herein.

361

Pharmaceutical Uses

The compounds described herein are useful in the methods of the invention and, while not bound by theory, are believed to exert their desirable effects through their ability to modulate the level, status, and/or activity of a BAF complex, e.g., by inhibiting the activity or level of the BRD9 protein in a cell within the BAF complex in a mammal.

An aspect of the present invention relates to methods of treating disorders related to BRD9 such as cancer in a subject in need thereof. In some embodiments, the compound is administered in an amount and for a time effective to result in one of (or more, e.g., two or more, three or more, four or more of): (a) reduced tumor size, (b) reduced rate of tumor growth, (c) increased tumor cell death (d) reduced tumor progression, (e) reduced number of metastases, (f) reduced rate of metastasis, (g) decreased tumor recurrence (h) increased survival of subject, and (i) increased progression free survival of a subject.

Treating cancer can result in a reduction in size or volume of a tumor. For example, after treatment, tumor size is reduced by 5% or greater (e.g., 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or greater) relative to its size prior to treatment. Size of a tumor may be measured by any reproducible means of measurement. For example, the size of a tumor may be measured as a diameter of the tumor.

Treating cancer may further result in a decrease in number of tumors. For example, after treatment, tumor number is reduced by 5% or greater (e.g., 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or greater) relative to number prior to treatment. Number of tumors may be measured by any reproducible means of measurement, e.g., the number of tumors may be measured by counting tumors visible to the naked eye or at a specified magnification (e.g., 2 \times , 3 \times , 4 \times , 5 \times , 10 \times , or 50 \times).

Treating cancer can result in a decrease in number of metastatic nodules in other tissues or organs distant from the primary tumor site. For example, after treatment, the number of metastatic nodules is reduced by 5% or greater (e.g., 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or greater) relative to number prior to treatment. The number of metastatic nodules may be measured by any reproducible means of measurement. For example, the number of metastatic nodules may be measured by counting metastatic nodules visible to the naked eye or at a specified magnification (e.g., 2 \times , 10 \times , or 50 \times).

Treating cancer can result in an increase in average survival time of a population of subjects treated according to the present invention in comparison to a population of untreated subjects. For example, the average survival time is increased by more than 30 days (more than 60 days, 90 days, or 120 days). An increase in average survival time of a population may be measured by any reproducible means. An increase in average survival time of a population may be measured, for example, by calculating for a population the average length of survival following initiation of treatment with the compound described herein. An increase in average survival time of a population may also be measured, for example, by calculating for a population the average length of survival following completion of a first round of treatment with a pharmaceutically acceptable salt of a compound described herein.

Treating cancer can also result in a decrease in the mortality rate of a population of treated subjects in comparison to an untreated population. For example, the mortality rate is decreased by more than 2% (e.g., more than 5%, 10%, or 25%). A decrease in the mortality rate of a population of treated subjects may be measured by any repro-

362

ducible means, for example, by calculating for a population the average number of disease-related deaths per unit time following initiation of treatment with a pharmaceutically acceptable salt of a compound described herein. A decrease in the mortality rate of a population may also be measured, for example, by calculating for a population the average number of disease-related deaths per unit time following completion of a first round of treatment with a pharmaceutically acceptable salt of a compound described herein.

10 Combination Therapies

A method of the invention can be used alone or in combination with an additional therapeutic agent, e.g., other agents that treat cancer or symptoms associated therewith, or in combination with other types of therapies to treat cancer. 15 In combination treatments, the dosages of one or more of the therapeutic compounds may be reduced from standard dosages when administered alone. For example, doses may be determined empirically from drug combinations and permutations or may be deduced by isobolographic analysis (e.g., Black et al., *Neurology* 65:S3-S6 (2005)). In this case, dosages of the compounds when combined should provide a therapeutic effect.

In some embodiments, the second therapeutic agent is a chemotherapeutic agent (e.g., a cytotoxic agent or other chemical compound useful in the treatment of cancer). 20 These include alkylating agents, antimetabolites, folic acid analogs, pyrimidine analogs, purine analogs and related inhibitors, vinca alkaloids, epipodophyllotoxins, antibiotics, L-Asparaginase, topoisomerase inhibitors, interferons, platinum coordination complexes, anthracenedione substituted urea, methyl hydrazine derivatives, adrenocortical suppressant, adrenocorticosteroids, progestins, estrogens, antiestrogen, androgens, antiandrogen, and gonadotropin-releasing hormone analog. Also included is 5-fluorouracil (5-FU), leucovorin (LV), irinotecan, oxaliplatin, capecitabine, paclitaxel, and doxetaxel. Non-limiting examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclophosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphoramide and trimethylololomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analogue topotecan); bryostatin; calystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chloranaphazine, chlophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, especially calicheamicin gammaII and calicheamicin omegaII (see, e.g., Agnew, *Chem. Int. Ed Engl.* 33:183-186 (1994)); dynemicin, including dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, caminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, ADRIAMYCIN® (doxorubicin,

363

including morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potifromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxypyridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as folinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demeclocine; diaziquone; elfomithine; elliptinium acetate; an epothilone; etoglibucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; niraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, OR); razoxane; rhizoxin; sizofuran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxoids, e.g., TAXOL® (paclitaxel; Bristol-Myers Squibb Oncology, Princeton, NJ), ABRAZAXANE®, cremophor-free, albumin-engineered nanoparticle formulation of paclitaxel (American Pharmaceutical Partners, Schaumberg, IL), and TAXOTERE® doxetaxel (Rhone-Poulenc Rorer, Antony, France); chlorambucil; GEMZAR® gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum coordination complexes such as cisplatin, oxaliplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; NAVELBINE® vinorelbine; novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeloda; ibandronate; irinotecan (e.g., CPT-11); topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above. Two or more chemotherapeutic agents can be used in a cocktail to be administered in combination with the first therapeutic agent described herein. Suitable dosing regimens of combination chemotherapies are known in the art and described in, for example, Saltz et al., *Proc. Am. Soc. Clin. Oncol.* 18:233a (1999), and Douillard et al., *Lancet* 355(9209):1041-1047 (2000).

In some embodiments, the second therapeutic agent is a therapeutic agent which is a biologic such as a cytokine (e.g., interferon or an interleukin (e.g., IL-2)) used in cancer treatment. In some embodiments the biologic is an anti-angiogenic agent, such as an anti-VEGF agent, e.g., bevacizumab (AVASTIN®). In some embodiments the biologic is an immunoglobulin-based biologic, e.g., a monoclonal antibody (e.g., a humanized antibody, a fully human antibody, an Fc fusion protein or a functional fragment thereof) that agonizes a target to stimulate an anti-cancer response, or antagonizes an antigen important for cancer. Such agents include RITUXAN® (rituximab); ZENAPAX® (daclizumab); SIMULECT® (basiliximab); SYNAGIS® (palivizumab); REMICADE® (infliximab); HERCEPTIN® (trastuzumab); MYLOTARG® (gemtuzumab ozogamicin); CAMPATH® (alemtuzumab); ZEVALIN® (ibritumomab tiuxetan); HUMIRA® (adalimumab); XOLAIR® (omalizumab); BEXXAR® (tositumomab-I-131); RAPTIVA® (efalizumab); ERBITUX® (cetuximab); AVASTIN® (bevacizumab); TYSABRI® (natalizumab); ACTEMRA® (tocilizumab); VECTIBIX® (panitumumab); LUCENTIS® (ranibizumab); SOLIRIS® (eculizumab); CIMZIA® (certolizumab pegol); SIMPONI® (golimumab); ILARIS® (canakinumab); STELARA® (ustekinumab); ARZERRA® (ofatumumab); PROLIA® (denosumab); NUMAX® (motavizumab); ABTHRAX® (raxibacumab); BENLYSTA® (belimumab); YERVOY® (ipilimumab); ADCETRIS® (brentuximab vedotin); PERJETA® (pertuzumab); KADCYLA® (ado-trastuzumab emtansine); and GAZYVA® (obinutuzumab). Also included are antibody-drug conjugates.

The second agent may be a therapeutic agent which is a non-drug treatment. For example, the second therapeutic agent is radiation therapy, cryotherapy, hyperthermia, and/or surgical excision of tumor tissue.

The second agent may be a checkpoint inhibitor. In one embodiment, the inhibitor of checkpoint is an inhibitory antibody (e.g., a monospecific antibody such as a monoclonal antibody). The antibody may be, e.g., humanized or fully human. In some embodiments, the inhibitor of checkpoint is a fusion protein, e.g., an Fc-receptor fusion protein. In some embodiments, the inhibitor of checkpoint is an agent, such as an antibody, that interacts with a checkpoint protein. In some embodiments, the inhibitor of checkpoint is an agent, such as an antibody, that interacts with the ligand of a checkpoint protein. In some embodiments, the inhibitor of checkpoint is an inhibitor (e.g., an inhibitory antibody or small molecule inhibitor) of CTLA-4 (e.g., an anti-CTLA4 antibody or fusion a protein such as ipilimumab/YERVOY® or tremelimumab). In some embodiments, the inhibitor of checkpoint is an inhibitor (e.g., an inhibitory antibody or small molecule inhibitor) of PD-1 (e.g., nivolumab/OPDIVO®; pembrolizumab/KEYTRUDA®; pidilizumab/CT-011). In some embodiments, the inhibitor of checkpoint is an inhibitor (e.g., an inhibitory antibody or small molecule inhibitor) of PDL1 (e.g., MPDL3280A/R^{G7446}, MEDI4736; MSB0010718C; BMS 936559). In some embodiments, the inhibitor of checkpoint is an inhibitor (e.g., an inhibitory antibody or Fc fusion or small molecule inhibitor) of PDL2 (e.g., a PDL2/Ig fusion protein such as AMP 224). In some embodiments, the inhibitor of checkpoint is an inhibitor (e.g., an inhibitory antibody or small molecule inhibitor) of B7-H3 (e.g., MGA271), B7-H4, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD160, CGEN-15049, CHK 1, CHK2, A2aR, B-7 family ligands, or a combination thereof.

In some embodiments, the anti-cancer therapy is a T cell adoptive transfer (ACT) therapy. In some embodiments, the T cell is an activated T cell. The T cell may be modified to express a chimeric antigen receptor (CAR). CAR modified T (CAR-T) cells can be generated by any method known in the art. For example, the CAR-T cells can be generated by introducing a suitable expression vector encoding the CAR to a T cell. Prior to expansion and genetic modification of the T cells, a source of T cells is obtained from a subject. T cells can be obtained from a number of sources, including peripheral blood mononuclear cells, bone marrow, lymph node tissue, cord blood, thymus tissue, tissue from a site of infection, ascites, pleural effusion, spleen tissue, and tumors. In certain embodiments of the present invention, any num-

364

365

ber of T cell lines available in the art, may be used. In some embodiments, the T cell is an autologous T cell. Whether prior to or after genetic modification of the T cells to express a desirable protein (e.g., a CAR), the T cells can be activated and expanded generally using methods as described, for example, in U.S. Pat. Nos. 6,352,694; 6,534,055; 6,905,680; 6,692,964; 5,858,358; 6,887,466; 6,905,681; 7,144,575; 7,067,318; 7,172,869; 7,232,566; 7,175,843; 5,883,223; 6,905,874; 6,797,514; 6,867,041; and U.S. Patent Application Publication No. 20060121005.

In any of the combination embodiments described herein, the first and second therapeutic agents are administered simultaneously or sequentially, in either order. The first therapeutic agent may be administered immediately, up to 1 hour, up to 2 hours, up to 3 hours, up to 4 hours, up to 5 hours, up to 6 hours, up to 7 hours, up to 8 hours, up to 9 hours, up to 10 hours, up to 11 hours, up to 12 hours, up to 13 hours, 14 hours, up to 16 hours, up to 17 hours, up 18 hours, up to 19 hours up to 20 hours, up to 21 hours, up to 22 hours, up to 23 hours up to 24 hours or up to 1-7, 1-14, 1-21 or 1-30 days before or after the second therapeutic agent.

Pharmaceutical Compositions

The pharmaceutical compositions described herein are preferably formulated into pharmaceutical compositions for administration to human subjects in a biologically compatible form suitable for administration *in vivo*.

The compounds described herein may be used in the form of the free base, in the form of salts, solvates, and as prodrugs. All forms are within the methods described herein. In accordance with the methods of the invention, the described compounds or salts, solvates, or prodrugs thereof may be administered to a patient in a variety of forms depending on the selected route of administration, as will be understood by those skilled in the art. The compounds described herein may be administered, for example, by oral, parenteral, buccal, sublingual, nasal, rectal, patch, pump, intratumoral, or transdermal administration and the pharmaceutical compositions formulated accordingly. Parenteral administration includes intravenous, intraperitoneal, subcutaneous, intramuscular, transepithelial, nasal, intrapulmonary, intrathecal, rectal, and topical modes of administration. Parenteral administration may be by continuous infusion over a selected period of time.

A compound described herein may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsules, or it may be compressed into tablets, or it may be incorporated directly with the food of the diet. For oral therapeutic administration, a compound described herein may be incorporated with an excipient and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, and wafers. A compound described herein may also be administered parenterally. Solutions of a compound described herein can be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, DMSO, and mixtures thereof with or without alcohol, and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms. Conventional procedures and ingredients for the selection and preparation of suitable formulations are described, for example, in Remington's Pharmaceutical Sciences (2012, 22nd ed.) and in The United States Pharmacopeia: The National Formulary (USP 41 NF36), published in 2018. The pharmaceutical forms suitable for injectable use include

366

sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that may be easily administered via syringe. Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels, and powders. Aerosol formulations typically include a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomizing device. Alternatively, the sealed container may be a unitary dispensing device, such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal after use. Where the dosage form includes an aerosol dispenser, it will contain a propellant, which can be a compressed gas, such as compressed air or an organic propellant, such as fluorochlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomizer. Compositions suitable for buccal or sublingual administration include tablets, lozenges, and pastilles, where the active ingredient is formulated with a carrier, such as sugar, acacia, tragacanth, gelatin, and glycerine. Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base, such as cocoa butter. A compound described herein may be administered intratumorally, for example, as an intratumoral injection. Intratumoral injection is injection directly into the tumor vasculature and is specifically contemplated for discrete, solid, accessible tumors. Local, regional, or systemic administration also may be appropriate. A compound described herein may advantageously be contacted by administering an injection or multiple injections to the tumor, spaced for example, at approximately, 1 cm intervals. In the case of surgical intervention, the present invention may be used preoperatively, such as to render an inoperable tumor subject to resection. Continuous administration also may be applied where appropriate, for example, by implanting a catheter into a tumor or into tumor vasculature.

The compounds described herein may be administered to an animal, e.g., a human, alone or in combination with pharmaceutically acceptable carriers, as noted herein, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration, and standard pharmaceutical practice.

Dosages

The dosage of the compounds described herein, and/or compositions including a compound described herein, can vary depending on many factors, such as the pharmacodynamic properties of the compound; the mode of administration; the age, health, and weight of the recipient; the nature and extent of the symptoms; the frequency of the treatment, and the type of concurrent treatment, if any; and the clearance rate of the compound in the animal to be treated. One of skill in the art can determine the appropriate dosage based on the above factors. The compounds described herein may be administered initially in a suitable dosage that may be adjusted as required, depending on the clinical response. In general, satisfactory results may be obtained when the compounds described herein are administered to a human at a daily dosage of, for example, between 0.05 mg and 3000 mg (measured as the solid form). Dose ranges include, for example, between 10-1000 mg (e.g., 50-800 mg). In some embodiments, 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, or 1000 mg of the compound is administered.

367

Alternatively, the dosage amount can be calculated using the body weight of the patient. For example, the dose of a compound, or pharmaceutical composition thereof, administered to a patient may range from 0.1-100 mg/kg (e.g., 0.1-50 mg/kg (e.g., 0.25-25 mg/kg)). In exemplary, non-limiting embodiments, the dose may range from 0.5-5.0 mg/kg (e.g., 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, or 5.0 mg/kg) or from 5.0-20 mg/kg (e.g., 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 mg/kg).

Kits

The invention also features kits including (a) a pharmaceutical composition including an agent that reduces the level and/or activity of BRD9 in a cell or subject described herein, and (b) a package insert with instructions to perform any of the methods described herein. In some embodiments, the kit includes (a) a pharmaceutical composition including an agent that reduces the level and/or activity of BRD9 in a cell or subject described herein, (b) an additional therapeutic agent (e.g., an anti-cancer agent), and (c) a package insert with instructions to perform any of the methods described herein.

EXAMPLES

**Example 1—High Density Tiling sgRNA Screen
Against Human BAF Complex Subunits in
Synovial Sarcoma Cell Line SYO1**

The following example shows that BRD9 sgRNA inhibits cell growth in synovial sarcoma cells.

Procedure: To perform high density sgRNA tiling screen, an sgRNA library against BAF complex subunits was custom synthesized at Cellecta (Mountain View, CA). Sequences of DNA encoding the BRD9-targeting sgRNAs used in this screen are listed in Table 3. Negative and positive control sgRNA were included in the library. Negative controls consisted of 200 sgRNAs that do not target human genome. The positive controls are sgRNAs targeting essential genes (CDC16, GTF2B, HSPA5, HSPA9, PAFAH1B1, PCNA, POLR2L, RPL9, and SF3A3). DNA sequences encoding all positive and negative control sgRNAs are listed in Table 4. Procedures for virus production, cell infection, and performing the sgRNA screen were previously described (Tscheriak et al, *Cell* 170:564-576 (2017); Munoz et al, *Cancer Discovery* 6:900-913 (2016)). For each sgRNA, 50 counts were added to the sequencing counts and for each time point the resulting counts were normalized to the total number of counts. The log 2 of the ratio between the counts (defined as dropout ratio) at day 24 and day 1 post-infection was calculated. For negative control sgRNAs, the 2.5 and 97.5 percentile of the log 2 dropout ratio of all non-targeting sgRNAs was calculated and considered as background (grey box in the graph). Protein domains were obtained from PFAM regions defined for the UNIPROT identifier: Q9H8M2.

Results: As shown in FIG. 1, targeted inhibition of the GBAF complex component BRD9 by sgRNA resulted in growth inhibition of the SYO1 synovial sarcoma cell line. sgRNAs against other components of the BAF complexes resulted in increased proliferation of cells, inhibition of cell growth, or had no effect on SYO1 cells. These data show that targeting various subunits of the GBAF complex represents a therapeutic strategy for the treatment of synovial sarcoma.

368

TABLE 3

BRD9 sgRNA Library	
SEQ ID NO	Nucleic Acid Sequence
203	CAAGAACACAAGAACACA
204	CTTGTGTTCTTGGCCATGG
205	CTTCTTGCTGCTTCTGCCCA
206	ACAAGAACACAAGGCCGAG
207	CTCGTAGGACGAGGCCACT
208	CGAGTGGCGCTCGTCTACG
209	GAGTGGCGCTCGTCTACGA
210	AGGCTTCTCAGGGCTTGT
211	AGATTATGCCGACAAGCCCC
212	ACCTTCAGGACTAGCTTAG
213	AGCTTTAGAGGCTTCTCCAG
214	CTAGCTTAGAGGCTTCTCC
215	TAGCTTTAGAGGCTTCTCCA
216	CTAAAGCTAGTCTGAAGGT
217	GCCTCTAAAGCTAGTCTGA
218	CTTCACTTCCCTCGACCTTC
219	AAGCTAGTCTGAAGGTCGG
220	AGTGAAGTGACTGAACCTCTC
221	GTGACTGAACCTCTCAGGATC
222	ATAGTAACTGGAGTCGTGGC
223	CATCATAGTAACTGGAGTCG
224	TGACCTGTATCATAGTAAC
225	ACTCCAGTTACTATGATGAC
226	CTTTGTGCCTCTCGCTCA
227	GGTCAGACCATGAGCGAGAG
228	GAAGAAGAAGAAGTCCGAGA
229	GTCCAGATGTTCTCCTTCT
230	GTCCGAGAAGGAGAACATC
231	GGAGAAGCATCTGGACGATG
232	TGAGGAAAGAAGGAAGCGAA
233	ATCTGGACGATGAGGAAAGA
234	AGAAGAACGGAAAGCGAGAG
235	GAAGAACGGAAAGCGAGAGA
236	CCGCCAGGAAGAGAACAGAAG
237	AGAGAGGGAGCACTGTGACA
238	AGGGAGCACTGTGACACGGA
239	GAGGGAGCACTGTGACACGG
240	GCACTGTGACACGGAGGGAG

US 12,391,686 B2

369

TABLE 3-continued

BRD9 sqRNA Library	
SEQ ID NO	Nucleic Acid Sequence
241	GAGGCTGACGACTTTGATCC
242	AGGCTGACGACTTTGATCCT
243	TCCACCTCACCTTCTTCCC
244	CGACTTTGATCCTGGAAAGA
245	CTTGATCCTGGAAAGAAGG
246	TGATCCTGGAAAGAAGGTGG
247	TCCTGGAAAGAAGGTGGAGG
248	CGGACTGGCGATCTGGGG
249	ACGCTCGGACTGGCGATCT
250	AGGTGGAGGCCGCCCCAGAT
251	CGCTCGGACTGGCGATCTG
252	GCTCGGACTGGCGATCTGG
253	CACGCTCGGACTGGCGATC
254	TGTGTCCGGACCGCTCGGAC
255	CTGGCTGTGTCCGGCACGCT
256	ATCGGCCAGTCCGAGCGTGC
257	CACCCCTGCTGGCTGTGTC
258	CGAGCGTGGCGGACACAGCC
259	TGTTCCAGGAGTTGCTGAAT
260	CACACCTATTCACTCC
261	GCTGGCGGAGGAAGTGTTC
262	TTTACCTCTGAAGCTGGCGG
263	CCCCGGTTAACCTCTGAAGC
264	ACTTCCTCCGCCAGCTTCAG
265	CAGGAAAAGCAAAAAATCCA
266	GCTTTCAGAAAAGATCCCCA
267	AGGAAAAGCAAAAAATCCAT
268	GGAAAAGCAAAAATCCATG
269	GGAGCAATTGCATCCGTGAC
270	GTCACGGATGCAATTGCTCC
271	TTTATTATCATTAATATCC
272	AATGATAATAAAACATCCA
273	ATAAAACATCCCAGGATT
274	TTCATGGTGCCAAAATCCAT
275	TTTCATGGTGCCAAAATCCA
276	TAATGAATAACAAGTCAGTTA
277	CAAGTCAGTACGGAAATTAA
278	ATAATGCAATGACATACAAT

370

TABLE 3-continued

BRD9 sqRNA Library	
SEQ ID NO	Nucleic Acid Sequence
5	AACTTGTAGTACACGGTATC
279	CTTCGCCAACCTGTAGTACA
280	AGATACCGTGTACTACAAGT
281	GCGAAGAAGATCCTCACGC
282	TCATCTTAAAGCCTGCGTGA
283	TTCTCAGCAGGAGCTCTTT
284	CAATGAAGATAACAGCTGTTG
285	ACTGGTACAACCTCAGGGAC
286	CTTGTACTGGTACAACATTCA
287	ACTTGTACTGGTACAACCTTC
288	TTGGCAGTTCTACTTGTAC
289	TACCTGATAACCTCTACT
290	AGCCGAGTAGAGAAGTTATC
291	AGCTGCATGTTGAGCCTGA
292	GCTGCATGTTGAGCCTGAA
293	AAGCTGCAGGCATTCCCTTC
294	GGTACTGTCCGTCAAGCTGC
295	TACCGCAGAGGAGCACGTGC
296	CTTGACGGACAGTACCGCAG
297	CGCCAGCACGTGCTCCCTCTG
298	AGAGGAGCACGTGCTGGC
299	GGAGCACGTGCTGGCGCTGG
300	AGACACGAGCTGACGAAGCT
301	GGAGCTGGACAGGATCAAC
302	GCAAGCAGCTGACGAAGCTC
303	CAGCTGACGAAGCTCGGGAC
304	AAGCTCGGGACAGGATCAAC
305	CCTTGCCGCTGGGAGGAAC
306	AGGATCAACCGGTTCCCTCCC
307	ATCAACCGGTTCCCTCCCAGG
308	GCACACTACCTGCCGCCTGGG
309	AGAGCACTACCTGCCGCCT
310	CCGGTTCCCTCCCAGGGCGCA
311	TCCTCTTCAGATAAGCCCAC
312	ATGGGCTATCTGAAGAGGAA
313	GGGCTATCTGAAGAGGAAAC
314	TGGGCTATCTGAAGAGGAAAC
315	TATCTGAAGAGGAAACGGGA
65	
316	

US 12,391,686 B2

371

TABLE 3-continued

BRD9 sqRNA Library	
SEQ ID NO	Nucleic Acid Sequence
317	ATCTGAAGAGGAACGGGGAC
318	TGTTGACCACGCTGTAGAGC
319	GCTCTACAGCGTGGTCAACA
320	CGGGAGCCTGCTCTACAGCG
321	CGTGGTCAACACGGCCGAGC
322	CCCACCATCAGCGTCCGGCT
323	ACGGCCGAGCCGGACGCTGA
324	GGGCACCCACCATCAGCGTC
325	GCCGAGCCGGACGCTGATGG
326	CCATGTCCGTGTTGAGAGG
327	CCGAGCCGGACGCTGATGGT
328	CGAGCTCAAGTCCACCGGGT
329	GCGAGCTCAAGTCCACCGGG
330	AGAGCGAGCTCAAGTCCACC
331	GAGAGCGAGCTCAAGTCCAC
332	GAAGCCTGGGAGTAGCTTAC
333	CTCTCCAGTAAGCTACTCCC
334	AGCCCAGCGTGGTGAAGCCT
335	AAGCCCAGCGTGGTGAAGCC
336	ACTCCCAGCGTGGTCAACCAC
337	CTCCCAGGCTTCACCACGCT
338	CTCGTCTTGAAGCCCAGCG
339	CACTGGAGAGAAAGGTGACT
340	GCACTGGAGAGAAAGGTGAC
341	AGTAGTGGCACTGGAGAGAA
342	CGAAAAGCGCAGTAGTGGCAC
343	CTGCATCGAAAGCGCAGTAG
344	ATGCAGAATAATTCAGTATT
345	AGTATTTGGCGACTTGAAGT
346	CGACTTGAAGTCGGACGAGA
347	GAGCTGCTCTACTCAGCCTA
348	CACGCCTGTCATCTCCGT
349	TCAGCCTACGGAGATGAGAC
350	CAGGCCTGCAGTGTGCGCTG
351	CCGCAGCCCCCTAGCCTGC
352	CATCCTTCACAAACTCCTGC
353	TAGCCTGCAGGAGTTGTGA
354	CAGGAGTTGTGAAGGATGC

372

TABLE 3-continued

BRD9 sqRNA Library	
SEQ ID NO	Nucleic Acid Sequence
5	AGGAGTTGTGAAGGATGCT
355	TGGGAGCTACAGCAAGAAAG
356	GAGCTACAGCAAGAAAGTGG
357	GAAAGTGGTGGACGACCTCC
358	CGCCTGTGATCTGGTCCAGG
359	CTCCGCCCTGTGATCTGGTCC
360	GACCTCCTGGACCAGATCAC
361	CTCCTGGACCAGATCACAGG
362	GCTGGAAGAGCGTCCTAGAG
363	TGCAGCCCACCTGCTTCAGC
364	GACGCTCTTCAGCTGAAGC
365	CTCTCCAGCTGAAGCAGGT
366	GCTCTCCAGCTGAAGCAGGG
367	CCTCCAGATGAAGCCAAGGT
368	GCTTCATCTGGAGGCTTCAT
369	GGCTTCATCTGGAGGCTTCAT
370	CTTACCTTGCTTCATCTGG
371	AAACTTACCTTGCTTCATC
372	GAAGCCTCCAGATGAAGCCA
373	TCCTAGGGTGTCCCCAACCT
374	CCTAGGGTGTCCCCAACCTG
375	GTGTCAGTGTCTCCACAGGTT
376	TGTGTCAGTGTCTCCACAGGTT
377	CCACAGGTTGGGACACCCCT
378	AGAGCTGCTGCTGTCTCCTA
379	CAGAGCTGCTGCTGTCTCCT
380	AGACAGCAGCAGCTGTGTT
381	ATCCACAGAAACGTCGGGAT
382	GAGATATCCACAGAAACGTC
383	GGAGATATCCACAGAAACGT
384	GTCCTATCCGACGTTCTG
385	TCTCCATGCTCAGCTCTG
386	CTCACCCAGAGAGCTGAGCA
387	ATCTCCATGCTCAGCTCTCT
388	TATCTCCATGCTCAGCTCTC
389	ATGTCCTGTTACACAGGGA
390	TTACACAGGAAGGTGAAGA
391	AGTTCAAATGGCTGTCGTCA
392	

373

TABLE 3-continued

BRD9 sgRNA Library	
SEQ ID NO	Nucleic Acid Sequence
393	TGACGACAGCCATTGAACT
394	AAGTCAATGGCTGTCGTC
395	TCGTCTCATCCAAGTTCAA
396	TGAGACGACGAAGCTCCTGC
397	GTGCTTCGTGCAGGTCTGC
398	GCAGGACCTGCACGAAGCAC
399	GCTCCGCCTGTGCTTCGTGC
400	GGACCTGCAACGAAGCACAGG
401	CACGAAGCACAGGCGGAGCG
402	AGGCGGAGCGCGGGCGCTCT
403	AGGGAGCTGAGGTTGGACCA
404	GTTGGACAGGGAGCTGAGGT
405	AGGCCTTGACAGGGAGCTG
406	CCCTCTCGAGGCCTGGAC
407	CCTCTCGGAGGCCTGGACA
408	CTGGTCCCTCTCGGAGGCCGT
409	CCCTGTCCAACGCCTCCGAG
410	CCTGTCCAACGCCTCCGAGA
411	GTGGTGCTGGTCCCTCTCGG
412	CAGGTGGTCTGGTCCCTCT
413	GCATCTCACCCAGGTGGTC

374

TABLE 3-continued

BRD9 sgRNA Library	
SEQ ID NO	Nucleic Acid Sequence
5	
414	CGAGAGGGACCAGCACCACC
415	GAGAGGGACCAGCACCACCT
10	GTGGGGGCATCTCACCCAGG
416	CCCCGACACTCAGGCAGAGAA
417	TCCCCGACACTCAGGCAGAGA
418	AGCCCTTCTCGCCTGAGTGTG
15	CTGGCTGCTCCCCGACACTC
419	CCCTTCTCGCCTGAGTGTG
420	GCCCTTCTCGCCTGAGTGTG
421	AGAGAAACTCATAGGGTCG
20	TAGGGTCTGGTGGACAGT
422	AAGAAACTCATAGGGTCG
423	GGAGACTGAAGAAACTCATAG
424	GAGACTGAAGAAACTCATAG
25	TGGAGACTGAAGAAACTCAT
425	GGAGACTGAAGAAACTCATAG
426	TCTTCAGTCTCCAGAGCCTG
427	TTGGCAGAGGCCGCAGGCTC
428	TAGGTCTTGGCAGAGGCCGC
30	CTAGAGTTAGGTCTTGGCAG
429	GGTGGTCTAGAGTTAGGTCT
430	
431	
35	
432	
433	

TABLE 4

Control sgRNA Library			
SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
434	1 sg_Non_Targeting_Human_0001 Non_Targeting_Human	Non_Targeting_Human	GTAGCGAACGTGTCCGGCGT
435	1 sg_Non_Targeting_Human_0002 Non_Targeting_Human	Non_Targeting_Human	GACCGGAACGATCTCGCGTA
436	1 sg_Non_Targeting_Human_0003 Non_Targeting_Human	Non_Targeting_Human	GGCAGTCGTTCGGTTGATAT
437	1 sg_Non_Targeting_Human_0004 Non_Targeting_Human	Non_Targeting_Human	GCTTGAGCACATACGCGAAT
438	1 sg_Non_Targeting_Human_0005 Non_Targeting_Human	Non_Targeting_Human	GTGGTAGAATAACGTATTAC
439	1 sg_Non_Targeting_Human_0006 Non_Targeting_Human	Non_Targeting_Human	GTCATACATGGATAAGGCTA

TABLE 4 -continued

Control sqRNA Library			
SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
440	1 sg_Non_Targeting_Human_0007 Non_Targeting_Human	Non_Targeting_Human	GATACACGAAGCATCACTAG
441	1 sg_Non_Targeting_Human_0008 Non_Targeting_Human	Non_Targeting_Human	GAACGTTGGCACTACTTCAC
442	1 sg_Non_Targeting_Human_0009 Non_Targeting_Human	Non_Targeting_Human	GATCCATGTAATGCGTTCGA
443	1 sg_Non_Targeting_Human_0010 Non_Targeting_Human	Non_Targeting_Human	GTCGTGAAGTGCATTGATC
444	1 sg_Non_Targeting_Human_0011 Non_Targeting_Human	Non_Targeting_Human	GTTCGACTCGCGTGACCGTA
445	1 sg_Non_Targeting_Human_0012 Non_Targeting_Human	Non_Targeting_Human	GAATCTACCGCAGCGGTTCG
446	1 sg_Non_Targeting_Human_0013 Non_Targeting_Human	Non_Targeting_Human	GAAGTGACGTCGATTGATA
447	1 sg_Non_Targeting_Human_0014 Non_Targeting_Human	Non_Targeting_Human	GCGGTGTATGACAACCGCCG
448	1 sg_Non_Targeting_Human_0015 Non_Targeting_Human	Non_Targeting_Human	GTACCGCGCCTGAAGTTCGC
449	1 sg_Non_Targeting_Human_0016 Non_Targeting_Human	Non_Targeting_Human	GCAGCTCGTGTGTCGTACTC
450	1 sg_Non_Targeting_Human_0017 Non_Targeting_Human	Non_Targeting_Human	GCGCCTTAAGAGTACTCATC
451	1 sg_Non_Targeting_Human_0018 Non_Targeting_Human	Non_Targeting_Human	GAGTGTGTCGTCGTTGCTCCTA
452	1 sg_Non_Targeting_Human_0019 Non_Targeting_Human	Non_Targeting_Human	GCAGCTCGACCTAACGGCGT
453	1 sg_Non_Targeting_Human_0020 Non_Targeting_Human	Non_Targeting_Human	GTATCCTGACCTACGCGCTG
454	1 sg_Non_Targeting_Human_0021 Non_Targeting_Human	Non_Targeting_Human	GTGTATCTCAGCACGGCTAAC
455	1 sg_Non_Targeting_Human_0022 Non_Targeting_Human	Non_Targeting_Human	GTCGTCATAACACGGCAACG
456	1 sg_Non_Targeting_Human_0023-51 Non_Targeting_Human	Non_Targeting_Human	GTCGTGCGCTTCCGGCGGTA
457	1 sg_Non_Targeting_Human_0024 Non_Targeting_Human	Non_Targeting_Human	GCGGTCCCTCAGTAAGCGCGT
458	1 sg_Non_Targeting_Human_0025 Non_Targeting_Human	Non_Targeting_Human	GCTCTGCTGCGGAAGGATTG

TABLE 4 -continued

Control sqRNA Library			
SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
459	1 sg_Non_Targeting_Human_0026 Non_Targeting_Human	Non_Targeting_Human	GCATGGAGGAGCGTCGAGA
460	1 sg_Non_Targeting_Human_0027 Non_Targeting_Human	Non_Targeting_Human	GTAGCGCGCTAGGAGTGGC
461	1 sg_Non_Targeting_Human_0028 Non_Targeting_Human	Non_Targeting_Human	GATCACCTGCATTCTGTACAC
462	1 sg_Non_Targeting_Human_0029 Non_Targeting_Human	Non_Targeting_Human	GCACACCTAGATATCGAATG
463	1 sg_Non_Targeting_Human_0030 Non_Targeting_Human	Non_Targeting_Human	GTTGATCAACGCGCTTCGCG
464	1 sg_Non_Targeting_Human_0031 Non_Targeting_Human	Non_Targeting_Human	GCGTCTCACTCACTCCATCG
465	1 sg_Non_Targeting_Human_0032 Non_Targeting_Human	Non_Targeting_Human	GCCGACCAACGTCAGCGGTA
466	1 sg_Non_Targeting_Human_0033 Non_Targeting_Human	Non_Targeting_Human	GGATAACGGTGCGTCAATCTA
467	1 sg_Non_Targeting_Human_0034 Non_Targeting_Human	Non_Targeting_Human	GAATCCAGTGGCGGCGACAA
468	1 sg_Non_Targeting_Human_0035 Non_Targeting_Human	Non_Targeting_Human	GCACTGTCAGTGCAACGATA
469	1 sg_Non_Targeting_Human_0036 Non_Targeting_Human	Non_Targeting_Human	GCGATCCTCAAGTATGCTCA
470	1 sg_Non_Targeting_Human_0037 Non_Targeting_Human	Non_Targeting_Human	GCTAATATCGACACGGCCGC
471	1 sg_Non_Targeting_Human_0038 Non_Targeting_Human	Non_Targeting_Human	GGAGATGCATCGAACGTCGAT
472	1 sg_Non_Targeting_Human_0039 Non_Targeting_Human	Non_Targeting_Human	GGATGCACTCCATCTCGTCT
473	1 sg_Non_Targeting_Human_0040 Non_Targeting_Human	Non_Targeting_Human	GTGCCGAGTAATAACGCGAG
474	1 sg_Non_Targeting_Human_0041 Non_Targeting_Human	Non_Targeting_Human	GAGATTCCGATGTAACGTAC
475	1 sg_Non_Targeting_Human_0042 Non_Targeting_Human	Non_Targeting_Human	GTCGTACGAGCAGGATTGC
476	1 sg_Non_Targeting_Human_0043 Non_Targeting_Human	Non_Targeting_Human	GCGTTAGTCACTTAGCTCGA

TABLE 4 -continued

Control sqRNA Library			
SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
477	1 sg_Non_Targeting_Human_0044 Non_Targeting_Human	Non_Targeting_Human	GTTCACACGGTGTGGATAG
478	1 sg_Non_Targeting_Human_0045 Non_Targeting_Human	Non_Targeting_Human	GGATAGGTGACCTTAGTACG
479	1 sg_Non_Targeting_Human_0046 Non_Targeting_Human	Non_Targeting_Human	GTATGAGTCAAGCTAATGCG
480	1 sg_Non_Targeting_Human_0047 Non_Targeting_Human	Non_Targeting_Human	GCAACTATTGGAATAACGTGA
481	1 sg_Non_Targeting_Human_0048 Non_Targeting_Human	Non_Targeting_Human	GTTACCTTCGCTCGTCTATA
482	1 sg_Non_Targeting_Human_0049 Non_Targeting_Human	Non_Targeting_Human	GTACCGAGCACCACAGGCCG
483	1 sg_Non_Targeting_Human_0050 Non_Targeting_Human	Non_Targeting_Human	GTCAGCCATCGGATAGAGAT
484	1 sg_Non_Targeting_Human_0051 Non_Targeting_Human	Non_Targeting_Human	GTACGGCACTCCTAGCCGCT
485	1 sg_Non_Targeting_Human_0052 Non_Targeting_Human	Non_Targeting_Human	GGTCCTGTCGTATGCTTGCA
486	1 sg_Non_Targeting_Human_0053 Non_Targeting_Human	Non_Targeting_Human	GCCGCAATATATGCGGTAAG
487	1 sg_Non_Targeting_Human_0054 Non_Targeting_Human	Non_Targeting_Human	GCGCACGTATAATCCTGCGT
488	1 sg_Non_Targeting_Human_0055 Non_Targeting_Human	Non_Targeting_Human	GTGCACAAACACGATCCACGA
489	1 sg_Non_Targeting_Human_0056 Non_Targeting_Human	Non_Targeting_Human	GCACAATGTTGACGTAAGTG
490	1 sg_Non_Targeting_Human_0057 Non_Targeting_Human	Non_Targeting_Human	GTAAGATGCTGCTCACCGTG
491	1 sg_Non_Targeting_Human_0058 Non_Targeting_Human	Non_Targeting_Human	GTCGGTGATCCAACGTATCG
492	1 sg_Non_Targeting_Human_0059 Non_Targeting_Human	Non_Targeting_Human	GAGCTAGTAGGACGCAAGAC
493	1 sg_Non_Targeting_Human_0060 Non_Targeting_Human	Non_Targeting_Human	GTACGTGGAAGCTTGTGGCC
494	1 sg_Non_Targeting_Human_0061 Non_Targeting_Human	Non_Targeting_Human	GAGAACTGCCAGTTCTCGAT
495	1 sg_Non_Targeting_Human_0062 Non_Targeting_Human	Non_Targeting_Human	GCCATTGGCGCGGGCACTTC

TABLE 4 -continued

Control sqRNA Library			
SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
496	1 sg_Non_Targeting_Human_0063 Non_Targeting_Human	Non_Targeting_Human	GCACACGGACCAATCCGCTTC
497	1 sg_Non_Targeting_Human_0064 Non_Targeting_Human	Non_Targeting_Human	GAGGTGATCGATTAAGTACA
498	1 sg_Non_Targeting_Human_0065 Non_Targeting_Human	Non_Targeting_Human	GTCACTCGCAGACGCCAAC
499	1 sg_Non_Targeting_Human_0066 Non_Targeting_Human	Non_Targeting_Human	GCGCTACGGAATCATACGTT
500	1 sg_Non_Targeting_Human_0067 Non_Targeting_Human	Non_Targeting_Human	GGTAGGACCTCACGGCGCG
501	1 sg_Non_Targeting_Human_0068 Non_Targeting_Human	Non_Targeting_Human	GAACTGCATTTGTTGTAGT
502	1 sg_Non_Targeting_Human_0069 Non_Targeting_Human	Non_Targeting_Human	GATCCTGATCCGGCGGCG
503	1 sg_Non_Targeting_Human_0070 Non_Targeting_Human	Non_Targeting_Human	GGTATGCGCGATCCTGAGTT
504	1 sg_Non_Targeting_Human_0071 Non_Targeting_Human	Non_Targeting_Human	GCGGAGCTAGAGAGCGGTCA
505	1 sg_Non_Targeting_Human_0072 Non_Targeting_Human	Non_Targeting_Human	GAATGGCAATTACGGCTGAT
506	1 sg_Non_Targeting_Human_0073 Non_Targeting_Human	Non_Targeting_Human	GTATGGTGAGTAGTCGCTTG
507	1 sg_Non_Targeting_Human_0074 Non_Targeting_Human	Non_Targeting_Human	GTGTAATTGCGTCTAGTCGG
508	1 sg_Non_Targeting_Human_0075 Non_Targeting_Human	Non_Targeting_Human	GGTCCTGGCGAGGAGCCTTG
509	1 sg_Non_Targeting_Human_0076 Non_Targeting_Human	Non_Targeting_Human	GAAGATAAGTCGCTGTCTCG
510	1 sg_Non_Targeting_Human_0077 Non_Targeting_Human	Non_Targeting_Human	GTCGGCGTTCTGTTGTGACT
511	1 sg_Non_Targeting_Human_0078 Non_Targeting_Human	Non_Targeting_Human	GAGGCAAGCCGTTAGGTGTA
512	1 sg_Non_Targeting_Human_0079 Non_Targeting_Human	Non_Targeting_Human	GCGGATCCAGATCTCATTCG
513	1 sg_Non_Targeting_Human_0080 Non_Targeting_Human	Non_Targeting_Human	GGAACATAGGAGCACGTAGT

TABLE 4 -continued

Control sqRNA Library			
SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
514	1 sg_Non_Targeting_Human_0081 Non_Targeting_Human	Non_Targeting_Human	GTCATCATTATGGCGTAAGG
515	1 sg_Non_Targeting_Human_0082 Non_Targeting_Human	Non_Targeting_Human	GCGACTAGGCCATGAGCGG
516	1 sg_Non_Targeting_Human_0083 Non_Targeting_Human	Non_Targeting_Human	GGCGAAGTTCGACATGACAC
517	1 sg_Non_Targeting_Human_0084 Non_Targeting_Human	Non_Targeting_Human	GCTGTCGTGTGGAGGCTATG
518	1 sg_Non_Targeting_Human_0085 Non_Targeting_Human	Non_Targeting_Human	GCGGAGAGCATTGACCTCAT
519	1 sg_Non_Targeting_Human_0086 Non_Targeting_Human	Non_Targeting_Human	GACTAAATGGACCAAGTCAGT
520	1 sg_Non_Targeting_Human_0087 Non_Targeting_Human	Non_Targeting_Human	GCGGATTAGAGGTAATGCGG
521	1 sg_Non_Targeting_Human_0088 Non_Targeting_Human	Non_Targeting_Human	GCCGACGGCAATCAGTACGC
522	1 sg_Non_Targeting_Human_0089 Non_Targeting_Human	Non_Targeting_Human	GTAACCTCTCGAGCGATAGA
523	1 sg_Non_Targeting_Human_0090 Non_Targeting_Human	Non_Targeting_Human	GACTTGTATGTGGCTTACGG
524	1 sg_Non_Targeting_Human_0091 Non_Targeting_Human	Non_Targeting_Human	GTCACTGTGGTCAACATGT
525	1 sg_Non_Targeting_Human_0092 Non_Targeting_Human	Non_Targeting_Human	GTACTCCAATCCGCGATGAC
526	1 sg_Non_Targeting_Human_0093 Non_Targeting_Human	Non_Targeting_Human	GCGTTGGCACGATGTTACGG
527	1 sg_Non_Targeting_Human_0094 Non_Targeting_Human	Non_Targeting_Human	GAACCAGCCGGCTAGTATGA
528	1 sg_Non_Targeting_Human_0095 Non_Targeting_Human	Non_Targeting_Human	GTATACTAGCTAACACACG
529	1 sg_Non_Targeting_Human_0096 Non_Targeting_Human	Non_Targeting_Human	GAATCGGAATAGTTGATTG
530	1 sg_Non_Targeting_Human_0097 Non_Targeting_Human	Non_Targeting_Human	GAGCACTTGCATGAGGCGGT
531	1 sg_Non_Targeting_Human_0098 Non_Targeting_Human	Non_Targeting_Human	GAACGGCGATGAAGCCAGCC
532	1 sg_Non_Targeting_Human_0099 Non_Targeting_Human	Non_Targeting_Human	GCAACCGAGATGAGAGGTTG

TABLE 4 -continued

Control sqRNA Library			
SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
533	1 sg_Non_Targeting_Human_0100 Non_Targeting_Human	Non_Targeting_Human	GCAAGATCAATATGCGTGAT
534	1 sg_Non_Targeting_Human_GA_0101 Non_Targeting_Human	Non_Targeting_Human	ACGGAGGCTAACGCGTCGCAA
535	1 sg_Non_Targeting_Human_GA_0102 Non_Targeting_Human	Non_Targeting_Human	CGCTTCCGCGGCCGTTCAA
536	1 sg_Non_Targeting_Human_GA_0103 Non_Targeting_Human	Non_Targeting_Human	ATCGTTCCGCTTAACGGCG
537	1 sg_Non_Targeting_Human_GA_0104 Non_Targeting_Human	Non_Targeting_Human	GTAGGC CGCCGCTCTCTAC
538	1 sg_Non_Targeting_Human_GA_0105 Non_Targeting_Human	Non_Targeting_Human	CCATATCGGGCGAGACATG
539	1 sg_Non_Targeting_Human_GA_0106 Non_Targeting_Human	Non_Targeting_Human	TACTAACGCCGCTCCTACAG
540	1 sg_Non_Targeting_Human_GA_0107 Non_Targeting_Human	Non_Targeting_Human	TGAGGATCATGTCGAGGCC
541	1 sg_Non_Targeting_Human_GA_0108 Non_Targeting_Human	Non_Targeting_Human	GGGCCCGCATAGGATATCGC
542	1 sg_Non_Targeting_Human_GA_0109 Non_Targeting_Human	Non_Targeting_Human	TAGACAACCGCGGAGAATGC
543	1 sg_Non_Targeting_Human_GA_0110 Non_Targeting_Human	Non_Targeting_Human	ACGGGGCGCTATCGCTGACT
544	1 sg_Non_Targeting_Human_GA_0111 Non_Targeting_Human	Non_Targeting_Human	CGCGGAATTTCGCGACGA
545	1 sg_Non_Targeting_Human_GA_0112 Non_Targeting_Human	Non_Targeting_Human	CTTACAATCGTCGGTCCAAT
546	1 sg_Non_Targeting_Human_GA_0113 Non_Targeting_Human	Non_Targeting_Human	GCGTGCGTCCC GGTTACCC
547	1 sg_Non_Targeting_Human_GA_0114 Non_Targeting_Human	Non_Targeting_Human	CGGAGTAACAAGCGGACGGA
548	1 sg_Non_Targeting_Human_GA_0115 Non_Targeting_Human	Non_Targeting_Human	CGAGTGTATACGCACCGTT
549	1 sg_Non_Targeting_Human_GA_0116 Non_Targeting_Human	Non_Targeting_Human	CGACTAACCGGAAACTTTTT
550	1 sg_Non_Targeting_Human_GA_0117 Non_Targeting_Human	Non_Targeting_Human	CAACGGTTCTCCGGCTAC

TABLE 4 -continued

Control sqRNA Library			
SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
551	1 sg_Non_Targeting_Human_GA_0118 Non_Targeting_Human	Non_Targeting_Human	CAGGAGTCGCCGATACCGT
552	1 sg_Non_Targeting_Human_GA_0119 Non_Targeting_Human	Non_Targeting_Human	TTCACAGTCGTCTCGCGACCA
553	1 sg_Non_Targeting_Human_GA_0120 Non_Targeting_Human	Non_Targeting_Human	GTGTCGGATTCCGCCGCTTA
554	1 sg_Non_Targeting_Human_GA_0121 Non_Targeting_Human	Non_Targeting_Human	CACGAACTCACACCGCGCGA
555	1 sg_Non_Targeting_Human_GA_0122 Non_Targeting_Human	Non_Targeting_Human	CGCTAGTAGCCTCCCTATA
556	1 sg_Non_Targeting_Human_GA_0123 Non_Targeting_i_Human	Non_Targeting_Human	TCGCCTGGTTATACGCT
557	1 sg_Non_Targeting_Human_GA_0124 Non_Targeting_Human	Non_Targeting_Human	CTATCTCGAGTGGTAATGCG
558	1 sg_Non_Targeting_Human_GA_0125 Non_Targeting_Human	Non_Targeting_Human	AATCGACTCGAACCTCGTGT
559	1 sg_Non_Targeting_Human_GA_0126 Non_Targeting_Human	Non_Targeting_Human	CCCGATGGACTATACCGAAC
560	1 sg_Non_Targeting_Human_GA_0127 Non_Targeting_Human	Non_Targeting_Human	ACGTTCGAGTACGACCAGCT
561	1 sg_Non_Targeting_Human_GA_0128 Non_Targeting_Human	Non_Targeting_Human	CGCGACGACTCAACCTAGTC
562	1 sg_Non_Targeting_Human_GA_0129 Non_Targeting_Human	Non_Targeting_Human	GGTCACCGATCGAGAGCTAG
563	1 sg_Non_Targeting_Human_GA_0130 Non_Targeting_Human	Non_Targeting_Human	CTCAACCGACCGTATGGTCA
564	1 sg_Non_Targeting_Human_GA_0131 Non_Targeting_Human	Non_Targeting_Human	CGTATTGACTCTCAACGCG
565	1 sg_Non_Targeting_Human_GA_0132 Non_Targeting_Human	Non_Targeting_Human	CTAGCCCCCAGATCGAGCC
566	1 sg_Non_Targeting_Human_GA_0133 Non_Targeting_Human	Non_Targeting_Human	GAATCGACCGACACTAATGT
567	1 sg_Non_Targeting_Human_GA_0134 Non_Targeting_Human	Non_Targeting_Human	ACTTCAGTTGGCGTAGTCA
568	1 sg_Non_Targeting_Human_GA_0135 Non_Targeting_Human	Non_Targeting_Human	GTGCGATGTCGCTTCAACGT
569	1 sg_Non_Targeting_Human_GA_0136 Non_Targeting_Human	Non_Targeting_Human	CGCCTAATTCCGGATCAAT

TABLE 4 -continued

Control sqRNA Library			
SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
570	1 sg_Non_Targeting_Human_GA_0137 Non_Targeting_Human	Non_Targeting_Human	CGTGGCCGGAACCGTCATAG
571	1 sg_Non_Targeting_Human_GA_0138 Non_Targeting_Human	Non_Targeting_Human	ACCCCTCCGAATCGTAACGGA
572	1 sg_Non_Targeting_Human_GA_0139 Non_Targeting_Human	Non_Targeting_Human	AAACGGTACGACAGCGTGTG
573	1 sg_Non_Targeting_Human_GA_0140 Non_Targeting_Human	Non_Targeting_Human	ACATAGTCGACGGCTCGATT
574	1 sg_Non_Targeting_Human_GA_0141 Non_Targeting_Human	Non_Targeting_Human	GATGGCGCTTCAGTCGTCGG
575	1 sg_Non_Targeting_Human_GA_0142 Non_Targeting_Human	Non_Targeting_Human	ATAATCCGAAACGCTCGAC
576	1 sg_Non_Targeting_Human_GA_0143 Non_Targeting_Human	Non_Targeting_Human	CGCCGGGCTGACAATTAACG
577	1 sg_Non_Targeting_Human_GA_0144 Non_Targeting_Human	Non_Targeting_Human	CGTCGCCATATGCCGGTGGC
578	1 sg_Non_Targeting_Human_GA_0145 Non_Targeting_Human	Non_Targeting_Human	CGGGCCTATAACACCATCGA
579	1 sg_Non_Targeting_Human_GA_0146 Non_Targeting_Human	Non_Targeting_Human	CGCCGTTCCGAGATACTTGA
580	1 sg_Non_Targeting_Human_GA_0147 Non_Targeting_Human	Non_Targeting_Human	CGGGACGTCGCAGAAAATGTA
581	1 sg_Non_Targeting_Human_GA_0148 Non_Targeting_Human	Non_Targeting_Human	TGGGCATACGGGACACACGC
582	1 sg_Non_Targeting_Human_GA_0149 Non_Targeting_Human	Non_Targeting_Human	AGCTCCATGCCGCGATAAT
583	1 sg_Non_Targeting_Human_GA_0150 Non_Targeting_Human	Non_Targeting_Human	ATCGTATCATCAGCTAGCGC
584	1 sg_Non_Targeting_Human_GA_0151 Non_Targeting_Human	Non_Targeting_Human	TCGATCGAGGTTGCATTGG
585	1 sg_Non_Targeting_Human_GA_0152 Non_Targeting_Human	Non_Targeting_Human	CTCGACAGTTCGTCCCGAGC
586	1 sg_Non_Targeting_Human_GA_0153 Non_Targeting_Human	Non_Targeting_Human	CGGTAGTATTAATCGCTGAC
587	1 sg_Non_Targeting_Human_GA_0154 Non_Targeting_Human	Non_Targeting_Human	TGAACGCGTGTTCCTTGCA

TABLE 4 -continued

Control sqRNA Library			
SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
588	1 sg_Non_Targeting_Human_GA_0155 Non_Targeting_Human	Non_Targeting_Human	CGACGCTAGGTAACGTAGAG
589	1 sg_Non_Targeting_Human_GA_0156 Non_Targeting_Human	Non_Targeting_Human	CATTGTTGAGCGGGCGCGCT
590	1 sg_Non_Targeting_Human_GA_0157 Non_Targeting_Human	Non_Targeting_Human	CCGCTATTGAAACCGCCCAC
591	1 sg_Non_Targeting_Human_GA_0158 Non_Targeting_Human	Non_Targeting_Human	AGACACGTCACCGGTAAAAA
592	1 sg_Non_Targeting_Human_GA_0159 Non_Targeting_Human	Non_Targeting_Human	TTTACGATCTAGCGGCGTAG
593	1 sg_Non_Targeting_Human_GA_0160 Non_Targeting_Human	Non_Targeting_Human	TTCGCACGATTGCACCTTGG
594	1 sg_Non_Targeting_Human_GA_0161 Non_Targeting_Human	Non_Targeting_Human	GGTTAGAGACTAGGCCGCGC
595	1 sg_Non_Targeting_Human_GA_0162 Non_Targeting_Human	Non_Targeting_Human	CCTCCGTGCTAACGCGGACG
596	1 sg_Non_Targeting_Human_GA_0163 Non_Targeting_Human	Non_Targeting_Human	TTATCGCGTAGTGCTGACGT
597	1 sg_Non_Targeting_Human_GA_0164 Non_Targeting_Human	Non_Targeting_Human	TACGCTTGCCTTTAGCGTCC
598	1 sg_Non_Targeting_Human_GA_0165 Non_Targeting_Human	Non_Targeting_Human	CGCGGCCACGCGTCATCGC
599	1 sg_Non_Targeting_Human_GA_0166 Non_Targeting_Human	Non_Targeting_Human	AGCTCGCCATGTCGGTTCTC
600	1 sg_Non_Targeting_Human_GA_0167 Non_Targeting_Human	Non_Targeting_Human	AACTAGCCGAGCAGCTTCG
601	1 sg_Non_Targeting_Human_GA_0168 Non_Targeting_Human	Non_Targeting_Human	CGCAAGGTGTCGGTAACCT
602	1 sg_Non_Targeting_Human_GA_0169 Non_Targeting_Human	Non_Targeting_Human	CTTCGACGCCATCGTGCTCA
603	1 sg_Non_Targeting_Human_GA_0170 Non_Targeting_Human	Non_Targeting_Human	TCCTGGATACCGCGTGGTTA
604	1 sg_Non_Targeting_Human_GA_0171 Non_Targeting_Human	Non_Targeting_Human	ATAGCCGCCGCTCATTACTT
605	1 sg_Non_Targeting_Human_GA_0172 Non_Targeting_Human	Non_Targeting_Human	GTCGTCCGGATTACAAAAT
606	1 sg_Non_Targeting_Human_GA_0173 Non_Targeting_Human	Non_Targeting_Human	TAATGCTGCACACGCCGAAT

TABLE 4 -continued

Control sqRNA Library			
SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
607	1 sg_Non_Targeting_Human_GA_0174 Non_Targeting_Human	Non_Targeting_Human	TATCGCTTCCGATTAGTCGG
608	1 sg_Non_Targeting_Human_GA_0175 Non_Targeting_Human	Non_Targeting_Human	GTACCATAACCGCGTACCCCTT
609	1 sg_Non_Targeting_Human_GA_0176 Non_Targeting_Human	Non_Targeting_Human	TAAGATCCCGGGTGGCAAC
610	1 sg_Non_Targeting_Human_GA_0177 Non_Targeting_Human	Non_Targeting_Human	GTAGACGTCGTGAGCTTCAC
611	1 sg_Non_Targeting_Human_GA_0178 Non_Targeting_Human	Non_Targeting_Human	TCGC GGACATAGGGCTCTAA
612	1 sg_Non_Targeting_Human_GA_0179 Non_Targeting_Human	Non_Targeting_Human	AGCGCAGATAGCGCGTATCA
613	1 sg_Non_Targeting_Human_GA_0180 Non_Targeting_Human	Non_Targeting_Human	GTTCGCTTCGTAACGAGGAA
614	1 sg_Non_Targeting_Human_GA_0181 Non_Targeting_Human	Non_Targeting_Human	GACCCCCGATAACTTTGAC
615	1 sg_Non_Targeting_Human_GA_0182 Non_Targeting_Human	Non_Targeting_Human	ACGTCCATACTGTCGGCTAC
616	1 sg_Non_Targeting_Human_GA_0183 Non_Targeting_Human	Non_Targeting_Human	GTACCATTGCCGGCTCCCTA
617	1 sg_Non_Targeting_Human_GA_0184 Non_Targeting_Human	Non_Targeting_Human	TGGTTCCGTAGGTCGGTATA
618	1 sg_Non_Targeting_Human_GA_0185 Non_Targeting_Human	Non_Targeting_Human	TCTGGCTTGACACGACCGTT
619	1 sg_Non_Targeting_Human_GA_0186 Non_Targeting_Human	Non_Targeting_Human	CGCTAGGTCCGGTAAGTGC
620	1 sg_Non_Targeting_Human_GA_0187 Non_Targeting_Human	Non_Targeting_Human	AGCACGTAATGTCCGTGGAT
621	1 sg_Non_Targeting_Human_GA_0188 Non_Targeting_Human	Non_Targeting_Human	AAGGCGCGCGAATGTGGCAG
622	1 sg_Non_Targeting_Human_GA_0189 Non_Targeting_Human	Non_Targeting_Human	ACTGCGGAGCGGCCAATATC
623	1 sg_Non_Targeting_Human_GA_0190 Non_Targeting_Human	Non_Targeting_Human	CGTCGAGTGCTCGAACTCCA
624	1 sg_Non_Targeting_Human_GA_0191 Non_Targeting_Human	Non_Targeting_Human	TCGCAGCGCGTGGGATCGG

TABLE 4 -continued

Control sgRNA Library			
SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
625	1 sg_Non_Targeting_Human_GA_0192 Non_Targeting_Human	Non_Targeting_Human	ATCTGTCCTAATCGGATCG
626	1 sg_Non_Targeting_Human_GA_0193 Non_Targeting_Human	Non_Targeting_Human	TGCAGCGTAATGCTTGAAAG
627	1 sg_Non_Targeting_Human_GA_0194 Non_Targeting_Human	Non_Targeting_Human	CGAACTTAATCCGTGGCAA
628	1 sg_Non_Targeting_Human_GA_0195 Non_Targeting_Human	Non_Targeting_Human	GCCGTGTTGCTGGATACGCC
629	1 sg_Non_Targeting_Human_GA_0196 Non_Targeting_Human	Non_Targeting_Human	TACCCCTCGGATACGGACTG
630	1 sg_Non_Targeting_Human_GA_0197 Non_Targeting_Human	Non_Targeting_Human	CCGTTGGACTATGGCGGGTC
631	1 sg_Non_Targeting_Human_GA_0198 Non_Targeting_Human	Non_Targeting_Human	GTACGGGGCGATCATCCACA
632	1 sg_Non_Targeting_Human_GA_0199 Non_Targeting_Human	Non_Targeting_Human	AAGAGTAGTAGACGCCCGGG
633	1 sg_Non_Targeting_Human_GA_0200 Non_Targeting_Human	Non_Targeting_Human	AAGAGCGAACATGATTCTGT
634	3 sg_hCDC16_CC_1 CDC16	CDC16	TCAACACCAGTGCCTGACGG
635	3 sg_hCDC16_CC_2 CDC16	CDC16	AAAGTAGCTTCACTCTCTCG
636	3 sg_hCDC16_CC_3 CDC16	CDC16	GAGCCAACCAATAGATGTCC
637	3 sg_hCDC16_CC_4 CDC16	CDC16	GCGCCGCCATGAACCTAGAG
638	3 sg_hGTF2B_CC_1 GTF2B	GTF2B	ACAAAGGTTGGAACAGAAC
639	3 sg_hGTF2B_CC_2 GTF2B	GTF2B	GGTGACCGGGTTATTGATGT
640	3 sg_hGTF2B_CC_3 GTF2B	GTF2B	TTAGTGGAGGACTACAGAGC
641	3 sg_hGTF2B_CC_4 GTF2B	GTF2B	ACATATAGCCCGTAAAGCTG
642	3 sg_hHSPA5_CC_1 HSPA5	HSPA5	CGTTGGCGATGATCTCACG
643	3 sg_hHSPA5_CC_2 HSPA5	HSPA5	TGGCCTTTCTACCTCGCGC
644	3 sg_hHSPA5_CC_3 HSPA5	HSPA5	AATGGAGATACTCATCTGGG
645	3 sg_hHSPA5_CC_4 HSPA5	HSPA5	GAAGCCCGTCCAGAAAGTGT
646	3 sg_hHSPA9_CC_1 HSPA9	HSPA9	CAATCTGAGGAACTCCACGA
647	3 sg_hHSPA9_CC_2 HSPA9	HSPA9	AGGCTGCGCGCCCACGAGA
648	3 sg_hHSPA9_CC_3 HSPA9	HSPA9	ACTTGACCAGGCCTTGCTA
649	3 sg_hHSPA9_CC_4 HSPA9	HSPA9	ACCTTCCATAACTGCCACGC

TABLE 4 -continued

Control sqRNA Library			
SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
650	3 sg_hPAFAH1B1_CC_1 PAFAH1B1	PAFAH1B1	CGAGGGCTACATACCCAAGG
651	3 sg_hPAFAH1B1_CC_2 PAFAH1B1	PAFAH1B1	ATGGTACGGCCAAATCAAGA
652	3 sg_hPAFAH1B1_CC_3 PAFAH1B1	PAFAH1B1	TCTTGTAATCCCATACCGT
653	3 sg_hPAFAH1B1_CC_4 PAFAH1B1	PAFAH1B1	ATTCACAGGACACAGAGAAT
654	3 sg_hPCNA_CC_1 PCNA	PCNA	CCAGGGCTCCATCCTCAAGA
655	3 sg_hPCNA_CC_2 PCNA	PCNA	TGAGCTGCACCAAAGAGACG
656	3 sg_hPCNA_CC_3 PCNA	PCNA	ATGTCTGCAGATGTACCCCT
657	3 sg_hPCNA_CC_4 PCNA	PCNA	CGAAGATAACGCGGATACCT
658	3 sg_hPOLR2L_CC_1 POLR2L	POLR2L	GCTGCAGGCCGAGTACACCG
659	3 sg_hPOLR2L_CC_2 POLR2L	POLR2L	ACAAGTGGGAGGCTTACCTG
660	3 sg_hPOLR2L_CC_3 POLR2L	POLR2L	GCAGCGTACAGGGATGATCA
661	3 sg_hPOLR2L_CC_4 POLR2L	POLR2L	GCAGTAGCGCTTCAGGCCA
662	3 sg_hRPL9_CC_1 RPL9	RPL9	CAAATGGTGGGTAACAGAA
663	3 sg_hRPL9_CC_2 RPL9	RPL9	GAAAGGAACTGGCTACCGTT
664	3 sg_hRPL9_CC_3 RPL9	RPL9	AGGGCTTCCGTTACAAGATG
665	3 sg_hRPL9_CC_4 RPL9	RPL9	GAACAAGCAACACCTAAAAG
666	3 sg_hSF3A3_CC_1 SF3A3	SF3A3	TGAGGAGAACGGACGGCTCA
667	3 sg_hSF3A3_CC_2 SF3A3	SF3A3	GGAAGAAATGCAGAGTATAAG
668	3 sg_hSF3A3_CC_3 SF3A3	SF3A3	GGAATTGAGGAACTCCTGA
669	3 sg_hSF3A3_CC_4 SF3A3	SF3A3	GCTCACCGGCCATCCAGGAA
670	3 sg_hSF3B3_CC_1 SF3B3	SF3B3	ACTGGCCAGGAACGATGCGA
671	3 sg_hSF3B3_CC_2 SF3B3	SF3B3	GCAGCTCCAAGATCTTCCCA
672	3 sg_hSF3B3_CC_3 SF3B3	SF3B3	GAATGAGTACACAGAACCGA
673	3 sg_hSF3B3_CC_4 SF3B3	SF3B3	GGAGCAGGACAAGGTGGGG

Example 2—BRD9 Degrader Depletes BRD9

Protein

55

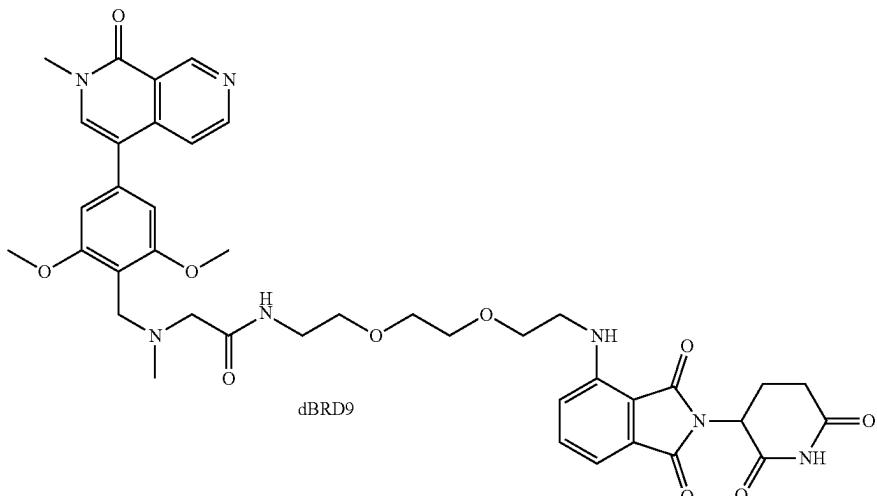
The following example demonstrates the depletion of the BRD9 protein in synovial sarcoma cells treated with a BRD9 degrader.

60

Procedure: Cells were treated with DMSO or the BRD9 degrader, Compound 1 (also known as dBRD9, see Remillard et al, *Angew. Chem. Int. Ed. Engl.* 56(21):5738-5743 (2017); see structure of Compound 1 below), for indicated doses and timepoints.

65

399



Whole cell extracts were fractionated by SDS-PAGE and transferred to a polyvinylidene difluoride membrane using a transfer apparatus according to the manufacturer's protocols (Bio-Rad). After incubation with 5% nonfat milk in TBST (10 mM Tris, pH 8.0, 150 mM NaCl, 0.5% Tween 20) for 60 minutes, the membrane was incubated with antibodies against BRD9 (1:1,000, Bethyl laboratory A³⁰³-781A), GAPDH (1:5,000, Cell Signaling Technology), and/or MBP (1:1,000, BioRad) overnight at 4° C. Membranes were washed three times for 10 min and incubated with anti-mouse or anti-rabbit antibodies conjugated with either horseradish peroxidase (HRP, FIGS. 2-3) or IRDye (FIG. 4, 1:20,000, LI-COR) for at least 1 h. Blots were washed with TBST three times and developed with either the ECL system according to the manufacturer's protocols (FIGS. 2-3) or scanned on an Odyssey CLx Imaging system (FIG. 4).

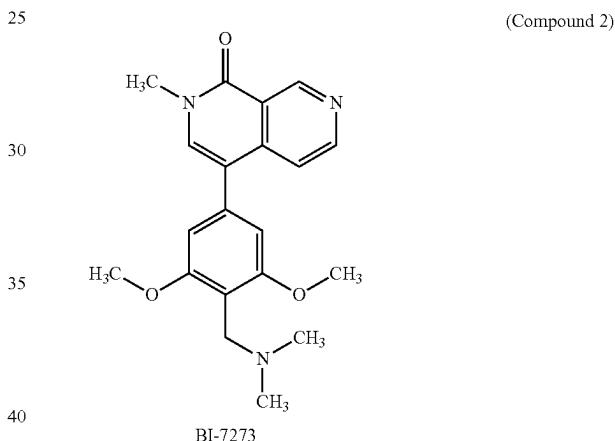
Results: Treatment of SYO1 synovial sarcoma cells with the BRD9 degrader Compound 1 results in dose dependent (FIG. 2) and time dependent (FIG. 3) depletion of BRD9 in the cells. Further, as shown in FIG. 4, the depletion of BRD9 by Compound 1 is replicated in a non-synovial sarcoma cell line (293T) and may be sustained for at least 5 days.

Example 3—Inhibition of Growth of Synovial Cell Lines by BRD9 Inhibitors and BRD9 Degraders

The following example demonstrates that BRD9 degraders and inhibitors selectively inhibit growth of synovial sarcoma cells.

Procedures: Cells were treated with DMSO or the BRD9 degrader, Compound 1, at indicated concentrations, and proliferation was monitored from day 7 to day 14 by measuring confluence over time using an IncuCyte live cell analysis system (FIG. 5). Growth medium and compounds were refreshed every 3-4 days.

Cells were seeded into 12-well plates and treated with DMSO, 1 μM BRD9 inhibitor, Compound 2 (also known as BI-7273, see Martin et al, *J Med Chem.* 59(10):4462-4475 (2016); see structure of Compound 2 below), or 1 μM BRD9 degrader, Compound 1.



The number of cells was optimized for each cell line. Growth medium and compounds were refreshed every 3-5 days. SYO1, Yamato, A549, 293T and HS-SY-II cells were fixed and stained at day 11. ASKA cells were fixed and stained at day 23. Staining was done by incubation with crystal violet solution (0.5 g Crystal Violet, 27 ml 37% Formaldehyde, 100 mL 10×PBS, 10 mL Methanol, 863 dH₂O to 1 L) for 30 min followed by 3× washes with water and drying the plates for at least 24 h at room temperature. Subsequently plates were scanned on an Odyssey CLx Imaging system (FIG. 6).

Cells were seeded into 96-well ultra low cluster plate (Costar, #7007) in 200 μL complete media and treated at day 2 with DMSO, Staurosporin, or BRD9 degrader, Compound 1, at indicated doses (FIG. 7). Media and compounds were changed every 5 d and cell colonies were imaged at day 14.

Results: As shown in FIGS. 5, 6, and 7, treatment of synovial sarcoma cell lines (SYO1, Yamato, HS-SY-II, and ASKA) with a BRD9 inhibitor, Compound 2, or a BRD9 degrader, Compound 1, results in inhibition of the growth of the cells, but does not result in inhibition of the growth of non-synovial control cancer cell lines (293T, A549, G401).

401

Example 4—Selective Inhibition of Growth of Synovial Cell Lines by BRD9 Degraders and BRD9 Binders

The following example demonstrates that BRD9 degraders and binders selectively inhibit growth of synovial sarcoma cells.

Procedure: Cells were seeded into 6-well or 12-well plates and were treated daily with a BRD9 degrader (Compound 1), a bromo-domain BRD9 binder (Compound 2), E3 ligase binder (lenalidomide), DMSO, or staurosporin (positive control for cell killing), at indicated concentrations. The number of cells was optimized for each cell line. Growth media was refreshed every 5 days. By day 14, medium was removed, cells were washed with PBS, and stained using 500 μ L of 0.005% (w/v) crystal violet solution in 25% (v/v) methanol for at least 1 hour at room temperature. Subsequently plates were scanned on an Odyssey CLx Imaging system.

Results: As shown in FIGS. 8 and 9, treatment of synovial sarcoma cell lines (SYO1, HS-SY-II, and ASKA) with Compound 1 or Compound 2 resulted in inhibition of the growth of the cells, but did not result in inhibition of the growth of non-synovial control cancer cell lines (RD, HCT116, and Calu6). Overall, Compound 1 showed most significant growth inhibition in all synovial cell lines.

Example 5—Inhibition of Cell Growth in Synovial Sarcoma Cells

The following example shows that BRD9 degraders inhibit cell growth and induce apoptosis in synovial sarcoma cells.

Procedure: SYO1 cells were treated for 8 or 13 days with DMSO, a BRD9 degrader (Compound 1) at 200 nM or 1 μ M, or an E3 ligase binder (lenalidomide) at 200 nM. Compounds were refreshed every 5 days. Cell cycle analysis was performed using the Click-iT™ Plus EdU Flow Cytometry Assay (Invitrogen). The apoptosis assay was performed using the Annexin V-FITC Apoptosis Detection Kit (Sigma A9210). Assays were performed according to the manufacturer's protocol.

Results: As shown in FIGS. 10-13, treatment with Compound 1 for 8 or 13 days resulted in reduced numbers of cells in the S-phase of the cell cycle as compared to DMSO and lenalidomide. Treatment with Compound 1 for 8 days also resulted in increased numbers of early- and late-apoptotic cells as compared to DMSO controls.

Example 6—Composition for SS18-SSX1-BAF

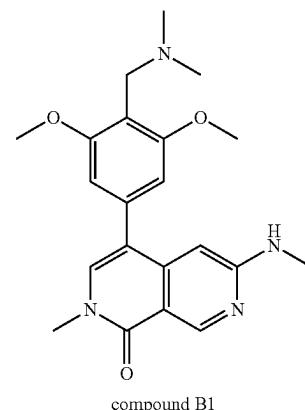
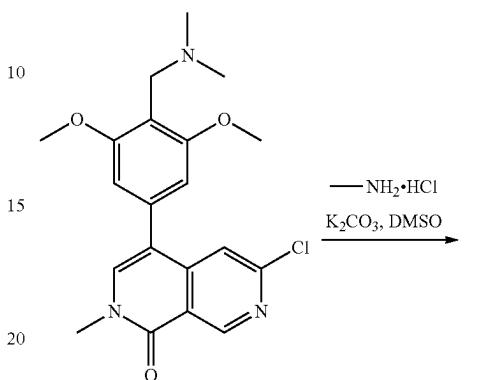
The following example shows the identification of BRD9 as a component of SS18-SSX containing BAF complexes.

Procedure: A stable 293T cell line expressing HA-SS18SSX1 was generated using lentiviral integration. SS18-SSX1 containing BAF complexes were subject to affinity purification and subsequent mass spectrometry analysis revealed SS18-SSX1 interacting proteins.

Results: As shown in FIG. 14, BAF complexes including the SS18-SSX fusion protein also included BRD9. More than 5 unique peptides were identified for ARID1A (95 peptides), ARID1B (77 peptides), SMARCC1 (69 peptides), SMARCD1 (41 peptides), SMARCD2 (37 peptides), DPF2 (32 peptides), SMARCD3 (26 peptides), ACTL6A (25 peptides), BRD9 (22 peptides), DPF1 Isoform 2 (18 peptides), DPF3 (13 peptides), and ACTL6B (6 peptides).

402

Example 7—Preparation of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-6-(methylamino)-1,2-dihydro-2,7-naphthyridin-1-one (Compound B1)

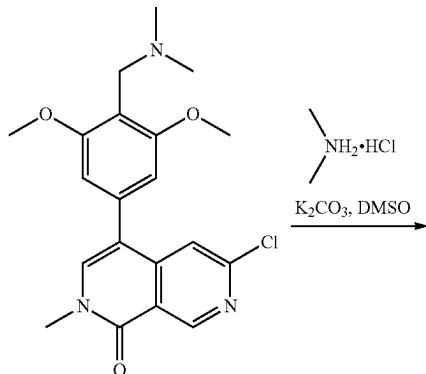


To a stirred mixture of 6-chloro-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (100 mg, 0.26 mmol, 1.0 equiv) and methanamine hydrochloride (174.08 mg, 2.58 mmol, 10.0 equiv) in DMSO (3 mL) was added K_2CO_3 (890.82 mg, 6.45 mmol, 25.0 equiv) at room temperature. The resulting mixture was stirred for 16 hours at 130° C., and then it was allowed to cool down to room temperature. The solid was filtered off, the crude solution was purified by Prep-HPLC (conditions: XBridge Shield RP18 OBD Column 30*150 mm, 5 μ m; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 40 mL/minute; Gradient: 18% B to 18% B in 2 minutes; 254/220 nm; Rt: 7.43 minutes) to afford 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-6-(methylamino)-1,2-dihydro-2,7-naphthyridin-1-one (27 mg, 26%). 1H NMR (400 MHz, Methanol-d4) δ 9.08 (s, 1H), 7.40 (s, 1H), 6.74 (s, 2H), 6.44 (s, 1H), 3.88 (s, 6H), 3.69 (s, 2H), 3.58 (s, 3H), 2.88 (s, 3H), 2.33 (s, 6H). LCMS (ESI) m/z: [M+H] $^+$ =383.20.

403

Example 8—Preparation of 6-(dimethylamino)-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (Compound B2)

5



10

15

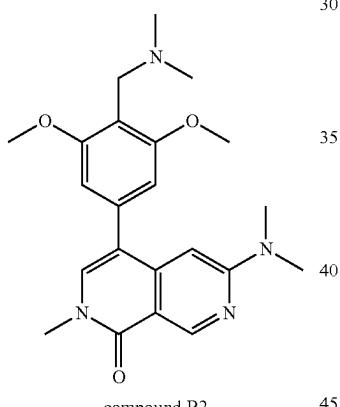
20

25

30

35

45

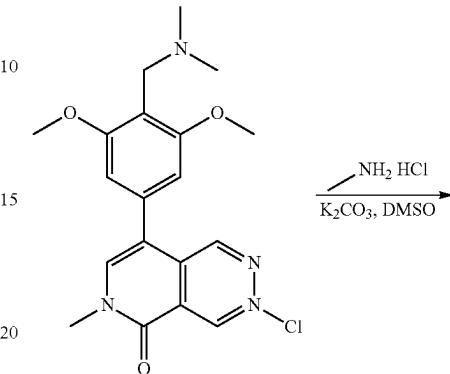


compound B2

404

Example 9—Preparation of 4-[4-[(Dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-7-(methylamino)-1,2-dihydro-2,6-naphthyridin-1-one (Compound B3)

5



10

15

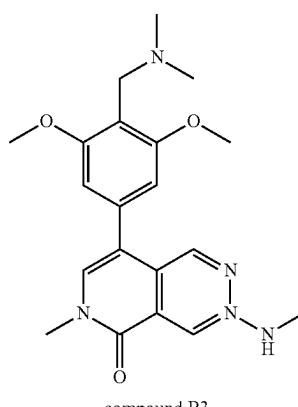
20

25

30

35

45



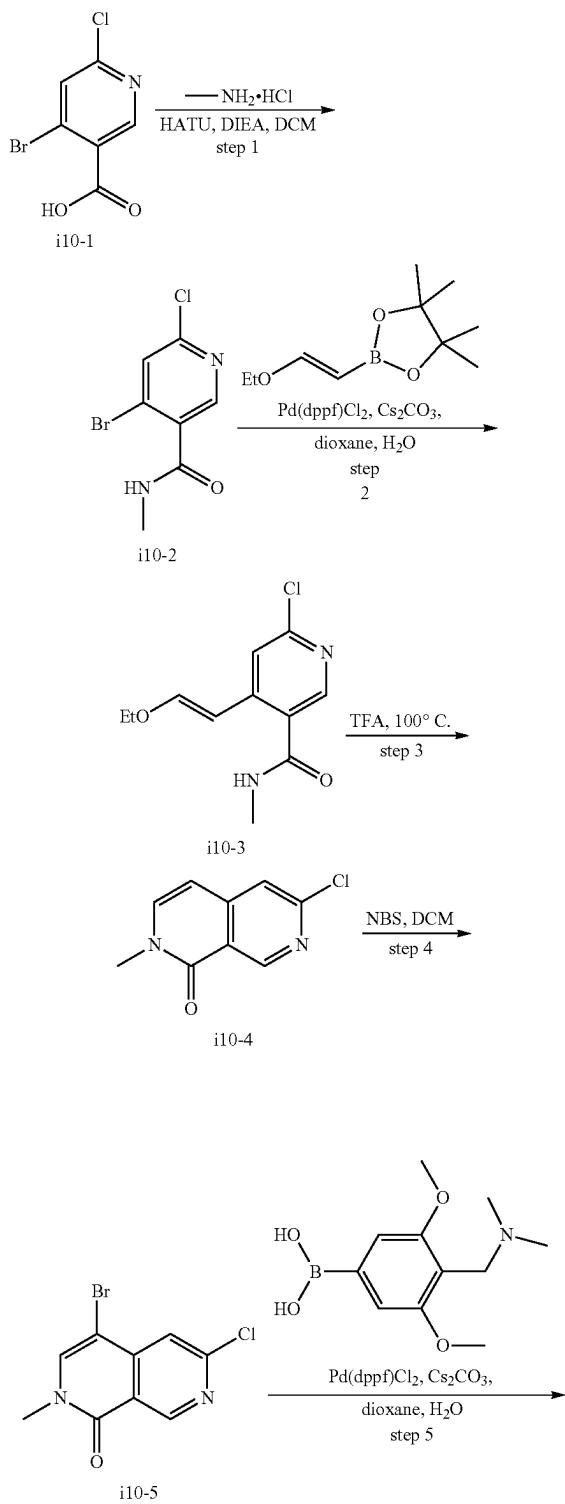
compound B3

To a stirred mixture of 6-chloro-4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (77.6 mg, 0.20 mmol, 1.0 equiv) and dimethylamine hydrochloride (163.14 mg, 2.0 mmol, 10.0 equiv) in DMF (6 mL) was added TEA (404.91 mg, 4.0 mmol, 20.0 equiv) at room temperature. The resulting mixture was stirred for 16 hours at 130° C. and then it was allowed to cool down to room temperature. The solid was filtered off, the filtrate was purified by Prep-HPLC with the following conditions (2#SHIMADZU (HPLC-01)): Column, X Bridge Shield RP18 OBD Column, 5 μm, 19*150 mm; mobile phase, Water (0.05% NH₃H₂O) and ACN (10% Phase B up to 70% in 8 minutes); To afford 23 mg (27%) of 6-(dimethylamino)-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one as a brown solid. ¹H NMR (400 MHz, Methanol-d4) δ 9.15 (s, 1H), 7.43 (s, 1H), 6.77 (s, 2H), 6.52 (s, 1H), 3.89 (s, 6H), 3.70 (s, 2H), 3.59 (s, 3H), 3.12 (s, 6H), 2.34 (s, 6H). LCMS (ESI) m/z: [M+H]⁺=397.40.

To a solution of 7-chloro-4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2-dihydro-2,6-naphthyridin-1-one (50 mg, 0.13 mmol, 1.0 equiv) and methanamine hydrochloride (87.0 mg, 1.29 mmol, 10.0 equiv) in solvent DMSO (2 mL) was added K₂CO₃ (445.4 mg, 3.22 mmol, 25.0 equiv). The resulting solution was stirred at 130° C. for overnight. After cooling, the solid was filtered off, the crude solution was purified by Prep-HPLC (conditions: XBridge Shield RP18 OBD Column, 5 μm, 19*150 mm; Mobile Phase A: Water (0.05% NH₃H₂O), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 30% B to 80% B in 8 minutes; 220 nm nm; Rt: 7.8 minutes) to afford 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-7-(methylamino)-1,2-dihydro-2,6-naphthyridin-1-one (15.5 mg, 31%) as a yellow solid. ¹H NMR (300 MHz, Methanol-d4) δ 8.53 (d, J=0.9 Hz, 1H), 7.24 (d, J=0.9 Hz, 1H), 7.09 (s, 1H), 6.76 (s, 2H), 3.88 (s, 6H), 3.67 (d, J=11.1 Hz, 5H), 2.97 (s, 3H), 2.31 (s, 6H). LCMS: (ES, m/z): [M+H]⁺=383.30.

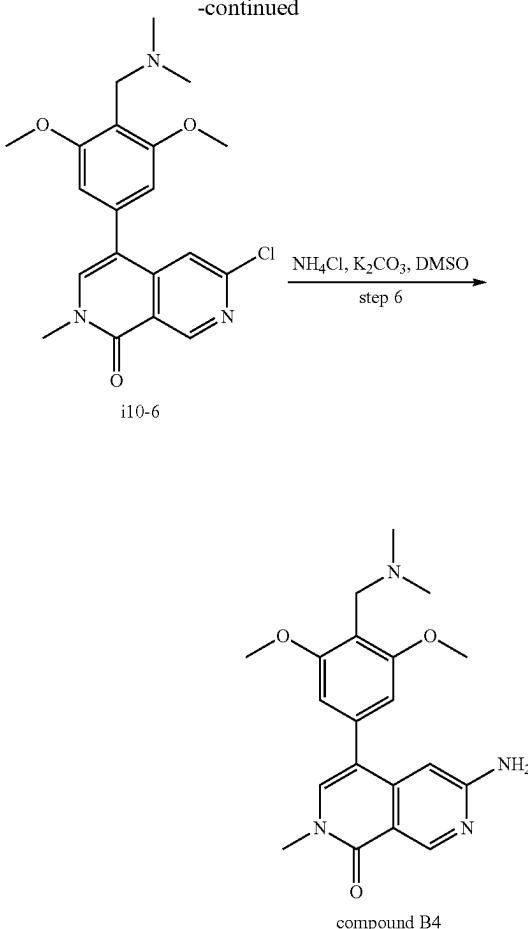
405

Example 10—Preparation of 6-amino-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (Compound B4) and 7-amino-4-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-2-methyl-2,6-naphthyridin-1(2H)-one (Compound B5)

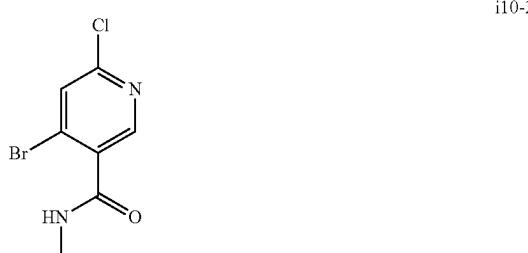


406

-continued



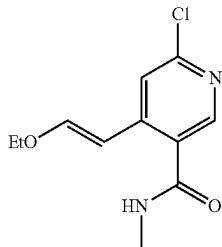
Step 1: Preparation of
4-bromo-6-chloro-N-methylpyridine-3-carboxamide
(i10-2)



To a solution of 4-bromo-6-chloropyridine-3-carboxylic acid (2.0 g, 8.46 mmol, 1.0 equiv), methanamine hydrochloride (0.63 g, 9.30 mmol, 1.1 equiv) and DIEA (3.28 g, 25.38 mmol, 3.0 equiv) in DCM (20 mL) was added HATU (4.82 g, 12.69 mmol, 1.5 equiv) at room temperature. The resulting mixture was stirred for another 1 hour. Then the reaction was washed with water (20 \times 2), and the organic layer was concentrated under vacuum to give a yellow syrup. The product was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H] $^{+}$ =249.

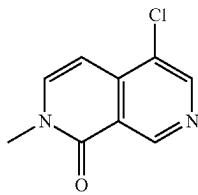
407

Step 2: Preparation of 6-chloro-4-[*(E*)-2-ethoxyethenyl]-N-methylpyridine-3-carboxamide (i10-3)



To a solution of 4-bromo-6-chloro-N-methylpyridine-3-carboxamide (1.0 g, 4.0 mmol, 1 equiv) and 2-[*(E*)-2-ethoxyethenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.95 g, 4.81 mmol, 1.2 equiv) in dioxane (10 mL) and H₂O (2 mL) was added Cs₂CO₃ (3.92 g, 12.03 mmol, 3.0 equiv) and Pd(dppf)Cl₂·CH₂Cl₂ (0.35 g, 0.48 mmol, 0.12 equiv). The mixture was stirred for 2 hours at 90° C. under nitrogen atmosphere, and the reaction mixture was dilute with water and extracted with ethyl acetate, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH₂Cl₂/MeOH (20:1) to afford 6-chloro-4-[*(E*)-2-ethoxyethenyl]-N-methylpyridine-3-carboxamide (680 mg, 57%) as an off-white solid. LCMS (ESI) m/z: [M+H]⁺=241.

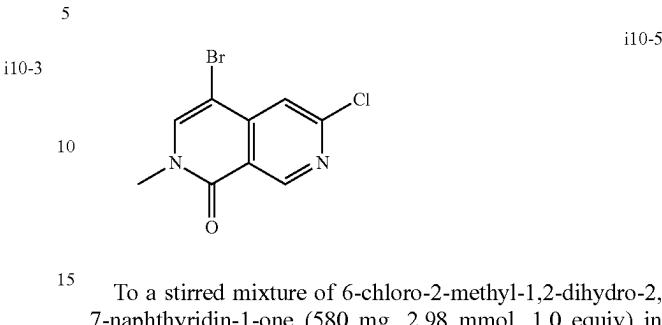
Step 3: 6-chloro-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (i10-4)



Into a 20 mL pressure tube was added 6-chloro-4-[*(E*)-2-ethoxyethenyl]-N-methylpyridine-3-carboxamide (680 mg, 2.83 mmol, 1.0 equiv) and TFA (5 mL, 67.32 mmol, 23.83 equiv) at room temperature, the reaction was stirred over night at 80° C. The resulting mixture was concentrated under vacuum to afford 6-chloro-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (580 mg, crude) as a dark yellow solid. The product was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H]⁺=195.

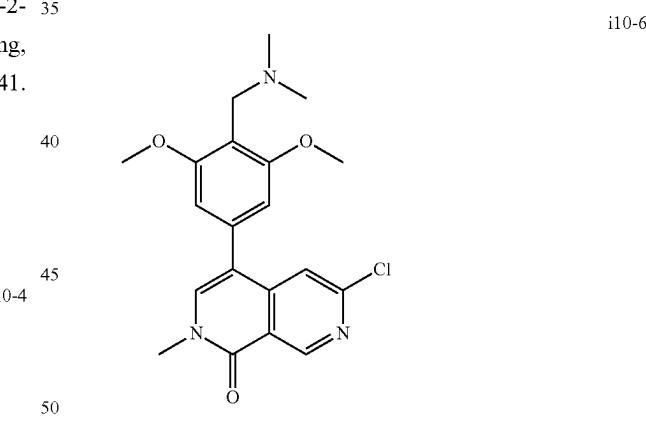
408

Step 4: Preparation of 4-bromo-6-chloro-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (i10-5)



To a stirred mixture of 6-chloro-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (580 mg, 2.98 mmol, 1.0 equiv) in DMF (10 mL) was added NBS (583.46 mg, 3.28 mmol, 1.1 equiv), and the resulting mixture was stirred for 2 hours at room temperature. The reaction mixture was diluted with DCM (50 mL) and washed with water (3×50 mL). The organic layer was dried over Na₂SO₄ and concentrated under vacuum. The crude product was purified by flash silica chromatography, eluted with 0 to 80% EtOAc in petroleum ether. Pure fractions were evaporated to dryness to afford 4-bromo-6-chloro-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (899 mg, 88%) as a yellow solid. LCMS (ESI) m/z: [M+H]⁺=273.

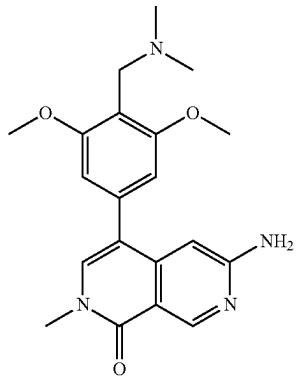
Step 5: Preparation of 6-chloro-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (i10-6)



To a solution of 4-bromo-6-chloro-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (843 mg, 3.08 mmol, 1.0 equiv) and [4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]boronic acid (736.88 mg, 3.08 mmol, 1.0 equiv) in dioxane (40 mL) and H₂O (4 mL) was added Cs₂CO₃ (3.01 g, 9.25 mmol, 3.0 equiv) and Pd(dppf)Cl₂·CH₂Cl₂ (302.04 mg, 0.37 mmol, 0.12 equiv). After stirring for 2 hours at 90° C. under a nitrogen atmosphere, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over Na₂SO₄ and then concentrated under reduced pressure. The crude product was purified by flash silica chromatography, eluted with 0 to 80% EtOAc in petroleum ether. Pure fractions were evaporated to dryness to afford 6-chloro-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (670 mg, 51%) as a yellow solid. LCMS (ESI) m/z: [M+H]⁺=388.

409

Step 6: Preparation of 6-amino-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (Compound B4)

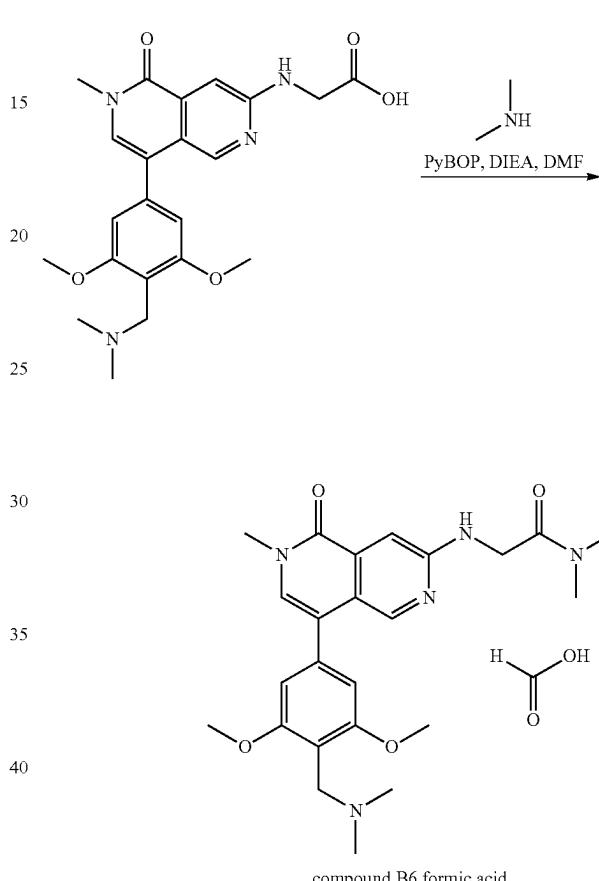


compound B4

410

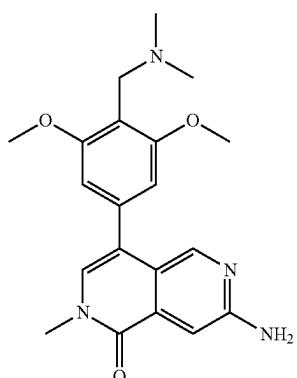
Methanol-d4 δ 8.39 (s, 1H), 7.65 (d, $J=2.2$ Hz, 1H), 7.23 (s, 1H), 6.89 (s, 2H), 4.42 (s, 2H), 3.98 (s, 6H), 3.64 (s, 3H), 2.92 (s, 6H). LCMS (ESI) m/z: [M+H]⁺=369.25.

Example 11—Preparation of 2-[(8-[(dimethylamino)methyl]-3,5-dimethoxyphenyl)-6-methyl-5-oxo-2,6-naphthyridin-3-yl]amino]-N,N-dimethylacetamide formic acid (Compound B6 Formic Acid)



To a stirred mixture of 6-chloro-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (232 mg, 0.60 mmol, 1.0 equiv) and NH₄Cl (479.94 mg, 8.97 mmol, 15.0 equiv) in DMSO (10 mL) was added K₂CO₃ (2.07 g, 14.95 mmol, 25.0 equiv). The resulting mixture was stirred overnight at 130° C. After completion of the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate, dried over Na₂SO₄, and then concentrated under reduced pressure. The crude product was purified by Prep-HPLC (conditions: X Select CSH Prep C18 OBD Column, 5 μ m, 19*150 mm; mobile phase, Water (0.1% FA) and ACN (hold 7% Phase B in 7 minutes); Detector, UV) to afford 3.4 mg (1.54%) of 6-amino-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one as an off-white solid. ¹H NMR (400 MHz, Methanol-d4) δ 9.04 (s, 1H), 7.44 (s, 1H), 6.84 (s, 2H), 6.54 (s, 1H), 4.34 (s, 2H), 3.97 (s, 6H), 3.59 (s, 3H), 2.85 (s, 6H). LCMS (ESI) m/z: [M+H]⁺=369.25.

Preparation of 7-amino-4-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-2-methyl-2,6-naphthyridin-1(2H)-one (Compound B5)



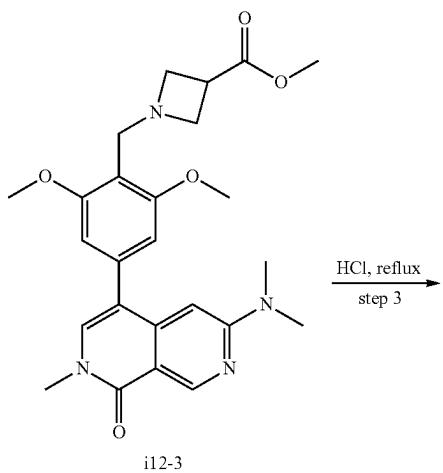
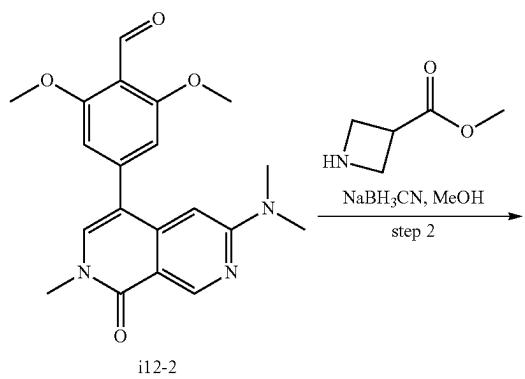
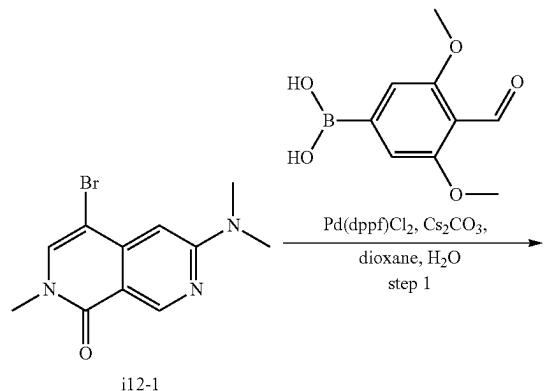
compound B5

To a stirred mixture of [(8-[(dimethylamino)methyl]-3,5-dimethoxyphenyl)-6-methyl-5-oxo-2,6-naphthyridin-3-yl]amino]acetic acid (60.0 mg, 0.141 mmol, 1.00 equiv) and dimethylamine hydrochloride (17.2 mg, 0.211 mmol, 1.50 equiv) in DMF (2.00 mL) was added DIEA (54.6 mg, 0.422 mmol, 3.00 equiv). The mixture was stirred at room temperature for 5 minutes, and then PyBOP (146.43 mg, 0.281 mmol, 2.00 equiv) was added. After stirring at room temperature for 2 hours, the reaction mixture was purified by Prep-HPLC (conditions: Sun Fire C18 OBD Prep Column, 100 Å, 5 μ m, 19 mm×250 mm; mobile phase, Water (0.1% FA) and ACN (10% Phase B up to 31% in 11 minutes)). This resulted in 2-[(8-[(dimethylamino)methyl]-3,5-dimethoxyphenyl)-6-methyl-5-oxo-2,6-naphthyridin-3-yl]amino]-N,N-dimethyl acetamide; formic acid (10.9 mg, 17.7%) as a dark yellow solid. ¹H NMR (300 MHz, Methanol-d4) δ 8.51 (br s, 0.5H, FA), 8.50 (s, 1H), 7.37 (s, 1H), 7.16 (s, 1H), 6.92 (s, 2H), 4.92 (s, 2H), 4.37 (s, 2H), 3.95 (s, 6H), 3.65 (s, 3H), 3.36 (s, 6H), 3.05 (d, $J=5.5$ Hz, 6H). LCMS (ESI) m/z: [M+H]⁺=454.20.

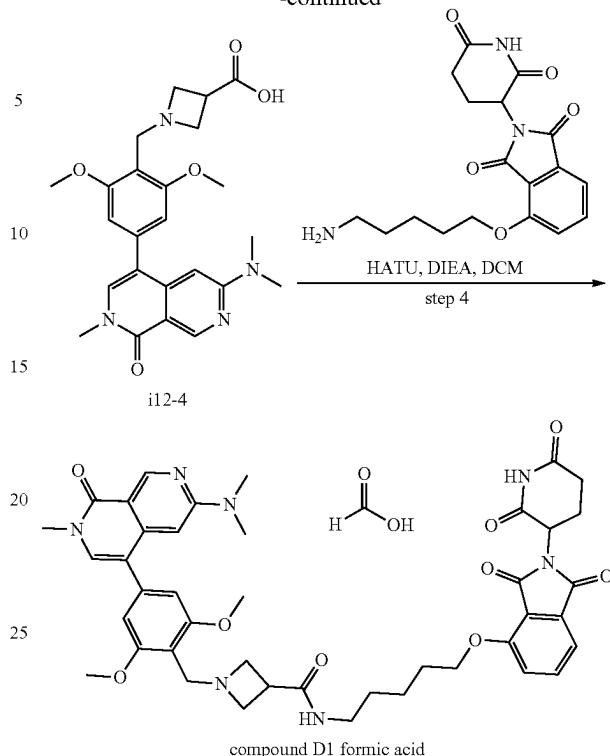
Compound B5 was prepared in a similar manner as described above for compound B4. ¹H NMR (300 MHz,

411

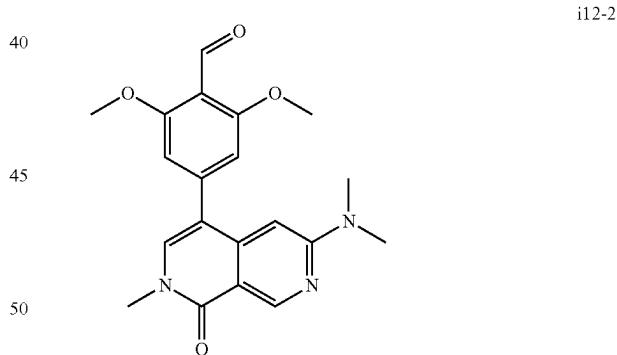
Example 12—Preparation of 1-[(4-[6-(Dimethylamino)-2-methyl-1-oxo-2,7-dihydro-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl)methyl]-N-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]oxy]pentyl)azetidine-3-carboxamide (Compound D1)

**412**

-continued



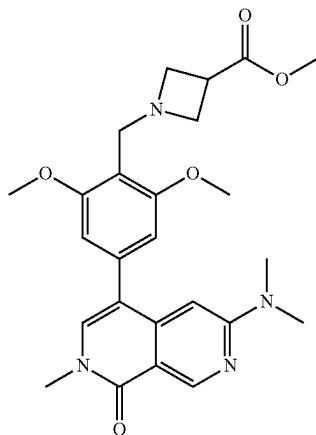
Step 1: Preparation of 4-[6-(Dimethylamino)-2-methyl-1-oxo-2,7-dihydro-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (i12-2)



To a solution of 4-bromo-6-(dimethylamino)-2-methyl-2,7-naphthyridin-1-one (400.00 mg, 1.42 mmol, 1.00 eq.) in dioxane (10.00 mL) and H_2O (1.00 mL) was added 2,6-dimethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) benzaldehyde (500 mg, 1.70 mmol, 1.2 eq.), $\text{Pd}(\text{dppf})\text{Cl}_2$ (100.0 mg, 0.14 mmol, 0.1 eq.), and Cs_2CO_3 (1.39 g, 4.14 mmol, 3 eq.). The resulting solution was stirred at 90°C. for 1 hour under a nitrogen atmosphere. The crude was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (10:1) to afford 4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (416.8 mg, 119.03%) as a light yellow solid. LCMS (ESI) m/z: $[\text{M}+\text{H}]^+=367.4$.

413

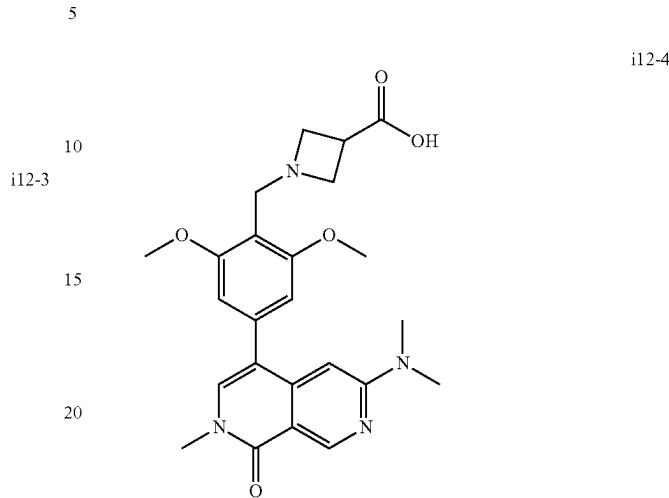
Step 2: Preparation of Methyl 1-([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)azetidine-3-carboxylate
(i12-3)



To a solution of 4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (331.00 mg, 0.901 mmol, 1.00 eq.) in MeOH (10.00 mL) was added methyl azetidine-3-carboxylate hydrochloride (163.88 mg, 1.081 mmol, 1.2 eq.) and NaBH₃CN (169.85 mg, 2.703 mmol, 3 eq.). The resulting solution was stirred at room temperature for 1 hour. The crude mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH₂Cl₂/MeOH (10:1) to afford methyl 1-([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)azetidine-3-carboxylate (279 mg, 66.38%) as a light yellow solid. LCMS (ESI) m/z: [M+H]⁺=466.5.

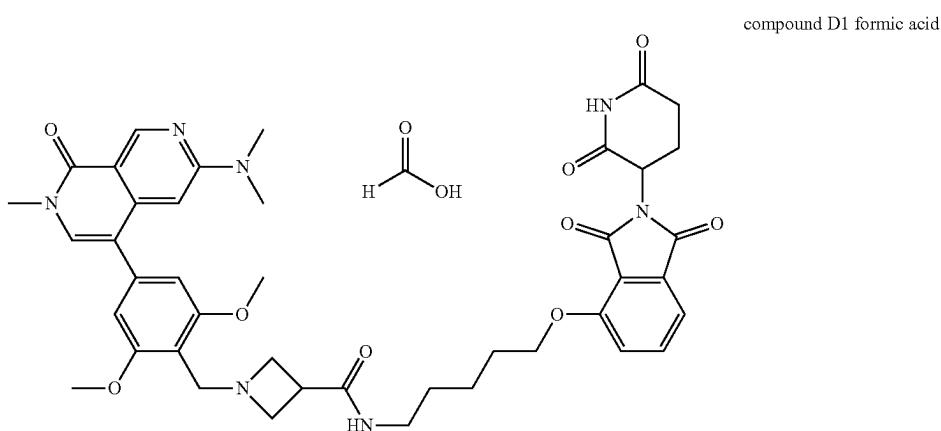
414

Step 3: Preparation of 1-([4-[6-(Dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)azetidine-3-carboxylic acid (i12-4)



25 To the solution of methyl 1-([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)azetidine-3-carboxylate (140.00 mg, 0.300 mmol, 1.00 eq.) in MeOH (3.00 mL) and H₂O (3.00 mL) was added LiOH (71.87 mg, 3.001 mmol, 10.00 eq.). The resulting solution was stirred at room temperature for 3 hours. The crude mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography (conditions: column, C18 silica gel; mobile phase, HCl in water, 10% to 70% gradient in 35 minutes; detector, UV 254 nm). This resulted in 1-([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)azetidine-3-carboxylic acid (120 mg, 88.37%) as a white solid.
30 LCMS (ESI) m/z: [M+H]⁺=452.5.

35 Step 4: Preparation of 1-([4-[6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)-N-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]oxy]pentyl)azetidine-3-carboxamide (Compound D1 Formic Acid)



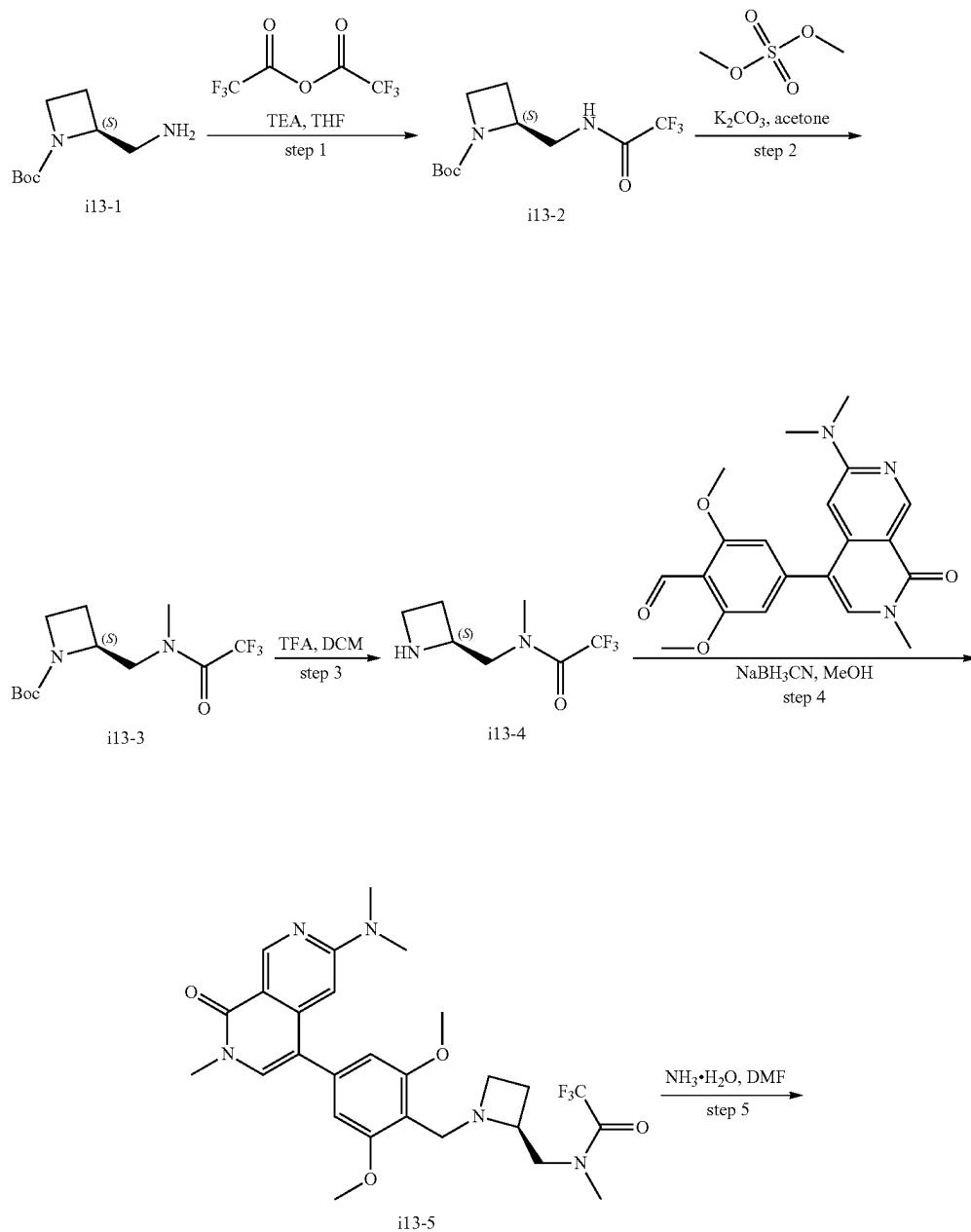
415

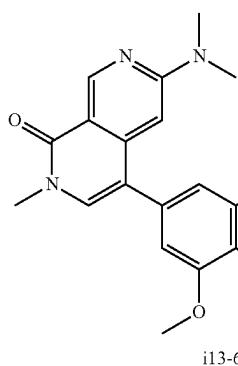
To a solution of 1-[(4-[6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl)methyl]azetidine-3-carboxylic acid (50.00 mg, 0.110 mmol, 1.00 eq.) and 4-[(5-aminopentyl)oxy]-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione (39.71 mg, 0.110 mmol, 1.00 eq.) in DMF (1.50 mL) was added DIEA (42.84 mg, 0.331 mmol, 3.00 eq.) and PyBOP (86.25 mg, 0.166 mmol, 1.50 eq.). The resulting solution was stirred at room temperature for 1 hour. The crude product (50 mg) was purified by Prep-HPLC (conditions: SunFire C18 OBD Prep Column, 100 Å, 5 µm, 19 mm×250 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 11% B to 27% B in 18 minutes; 254 nm; R_f: 16.87 minutes) to afford 1-[(4-[6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl)methyl]-N-(5-[[2-(2,6-

10 dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]oxy]pentyl)azetidine-3-carboxamide formate (13.5 mg) as a light yellow solid. ¹H NMR (300 MHz, Acetonitrile-d3) δ 9.12 (s, 1H), 8.17 (s, 0.3H, FA), 7.76 (dd, J=8.5, 7.3 Hz, 1H), 7.53-7.28 (m, 3H), 6.79 (s, 2H), 6.65 (s, 1H), 6.53 (s, 1H), 4.99 (dd, J=12.1, 5.4 Hz, 1H), 4.26 (s, 2H), 4.23-4.15 (m, 2H), 4.15-4.03 (m, 2H), 4.04-3.92 (m, 2H), 3.87 (s, 6H), 3.52 (s, 3H), 3.42 (t, J=8.1 Hz, 1H), 3.34-3.12 (m, 3H), 3.10 (s, 6H), 2.86-2.62 (m, 3H), 2.21-2.07 (m, 1H), 1.88-1.76 (m, 2H), 1.63-1.50 (m, 4H). LCMS (ESI) m/z: [M+H]⁺=452.45.

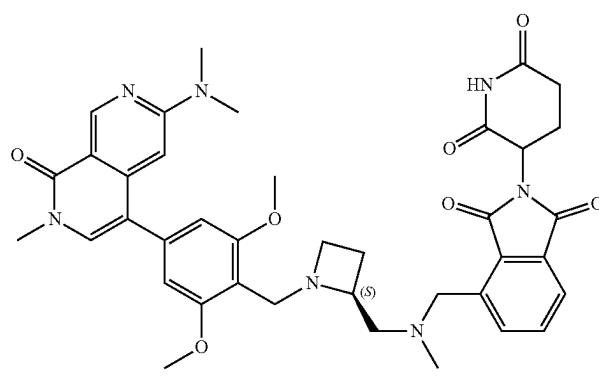
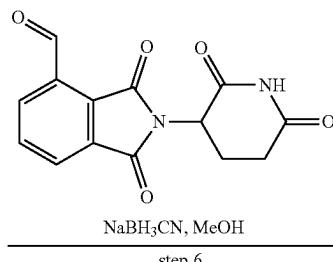
416

Example 13—Preparation of 4-((((S)-1-(4-(6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)azetidin-2-yl)methyl)(methyl)amino)methyl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione
(Compound D2)



417**418**

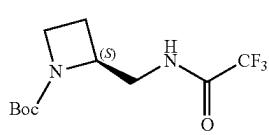
-continued



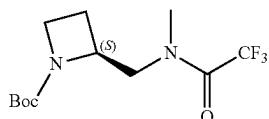
Step 1: Preparation of tert-butyl (S)-2((2,2,2-trifluoroacetamido)methyl)azetidine-1-carboxylate (i13-2)

Step 2: Preparation of tert-butyl (S)-2-((2,2,2-trifluoro-N-methylacetamido)methyl)azetidine-1-carboxylate (i13-3)

45



50

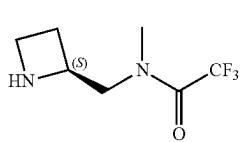


To a solution of tert-butyl (2S)-2-(aminomethyl)azetidine-1-carboxylate (900.00 mg, 4.832 mmol, 1.00 equiv) and trifluoroacetic anhydride (1.522 g, 7.248 mmol, 1.5 equiv) in THF (9.00 mL) was added TEA (977.92 mg, 9.664 mmol, 2 equiv). The resulting solution was stirred at 25° C. for 12 hours. The resulting solution was diluted with EtOAc. The resulting mixture was washed with water (3×50 mL), then dried over anhydrous sodium sulfate, filtered, and concentrated to give crude product that was applied onto a silica gel column with ethyl EA/PE (15:85) to afford tert-butyl (2S)-2-[(2,2,2-trifluoroacetamido)methyl]azetidine-1-carboxylate (1.27 g, 93.11%) as a yellow oil. LCMS (ESI) m/z: [M+H]⁺=283.

55 To a solution of tert-butyl (2S)-2-[(2,2,2-trifluoroacetamido)methyl]azetidine-1-carboxylate (1.27 g, 4.499 mmol, 1.00 equiv) and dimethyl sulfate (681.00 mg, 5.399 mmol, 1.2 equiv) in acetone (15.00 mL) was added K₂CO₃ (621.83 mg, 4.499 mmol, 1 equiv). The resulting solution was stirred at 25° C. for 12 hours. The resulting mixture was filtered, and the filtrate was evaporated to dryness to afford tert-butyl (2S)-2-[(2,2,2-trifluoro-N-methylacetamido)methyl]azetidine-1-carboxylate (1.64 g, crude) as a yellow oil that was used directly without further purification. LCMS (ESI) m/z: [M+H]⁺=297.

419

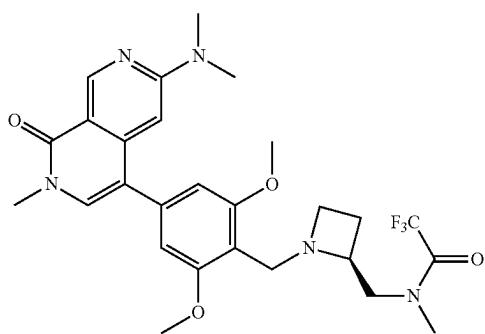
Step 3: Preparation of (S)—N-(azetidin-2-ylmethyl)-2,2,2-trifluoro-N-methylacetamide (i13-4)

5
i13-4

A solution of tert-butyl (2S)-2-[2,2,2-trifluoro-N-methylacetamido)methyl]azetidine-1-carboxylate (1.64 g, 5.535 mmol, 1.00 equiv) and TFA (3.50 mL, 47.121 mmol, 8.51 equiv) in DCM (16.00 mL) was stirred for 1 hour at 25° C. The mixture was concentrated to give N-[(2S)-azetidin-2-ylmethyl]-2,2,2-trifluoro-N-methylacetamide (2.08 g, 20 crude) as a brown oil that was used directly without further purification. LCMS (ESI) m/z: [M+H]+=197.

Step 4: Preparation of (S)—N-[(1-(4-(6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)azetidin-2-yl)methyl]-2,2,2-trifluoro-N-methylacetamide (i13-5)

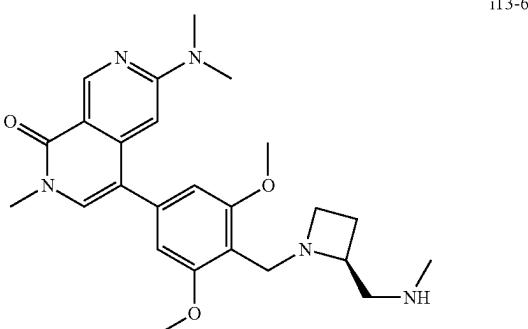
i13-5



To a solution of 4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (620.00 mg, 1.688 mmol, 1.00 equiv) and N-[(2S)-azetidin-2-ylmethyl]-2,2,2-trifluoro-N-methylacetamide (496.57 mg, 2.531 mmol, 1.50 equiv) in DMF (5.00 mL, 64.609 mmol, 38.29 equiv) was added NaBH(OAc)₃ (715.31 mg, 3.375 mmol, 2 equiv). The resulting solution was stirred at 25° C. for 1 hour. The mixture was concentrated to give crude product that was purified by chromatography on silica gel eluted with MeOH/DCM (4.2:95.8) to give N-[(2S)-1-[(4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl)methyl]azetidin-2-yl)methyl]-2,2,2-trifluoro-N-methylacetamide (436 mg, 47.18%) as a dark yellow solid. LCMS (ESI) m/z: [M+H]+=548.

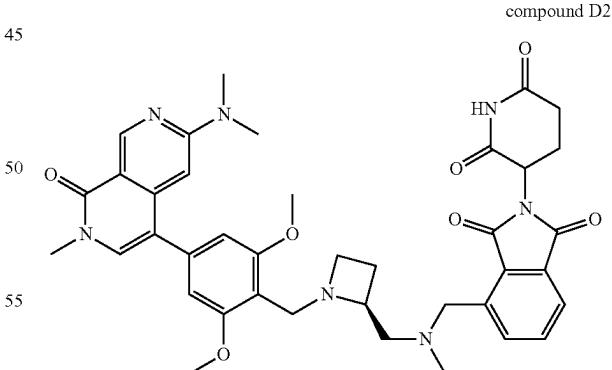
420

Step 5: Preparation of (S)-4-(3,5-dimethoxy-4-((2-((methylamino)methyl)azetidin-1-yl)methyl)phenyl)-6-(dimethylamino)-2-methyl-2,7-naphthyridin-1-(2H)-one (6)

10
i13-6

A solution of N-[(2S)-1-[(4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl)methyl]azetidin-2-yl]-2,2,2-trifluoro-N-methylacetamide (400.00 mg, 0.730 mmol, 1.00 equiv) and NH₃·H₂O (2.00 mL, 51.361 mmol, 70.31 equiv) in DMF (4.00 mL, 12.922 mmol, 196.55 equiv) was stirred at 25° C. for 12 hours. The resulting solution was concentrated to give crude product 4-(3,5-dimethoxy-4-[(2S)-2-[(methylamino)methyl]azetidin-1-yl)methyl]phenyl)-6-(dimethylamino)-2-methyl-2,7-naphthyridin-1-one (458 mg) as a brown solid that was used directly without further purification. LCMS (ESI) m/z: [M+H]+=452.

Step 6: Preparation of 4-(S)-1-(4-(6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)azetidin-2-yl)methyl(methylamino)methyl-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (Compound D2)



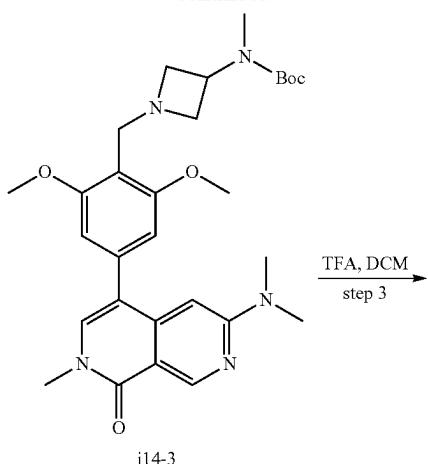
4-(3,5-dimethoxy-4-[(2R)-2-[(methylamino)methyl]azetidin-1-yl)methyl]phenyl)-6-(dimethylamino)-2-methyl-2,7-naphthyridin-1-one (100.00 mg, 0.221 mmol, 1.00 equiv) and 2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisooindole-4-carbaldehyde (63.39 mg, 0.221 mmol, 1.00 equiv) were dissolved in MeOH (2.00 mL). Then NaBH₃CN (69.58 mg, 1.107 mmol, 5 equiv) was added to the mixture, and the resulting solution was stirred at 25° C. for 1 hour. Without

421

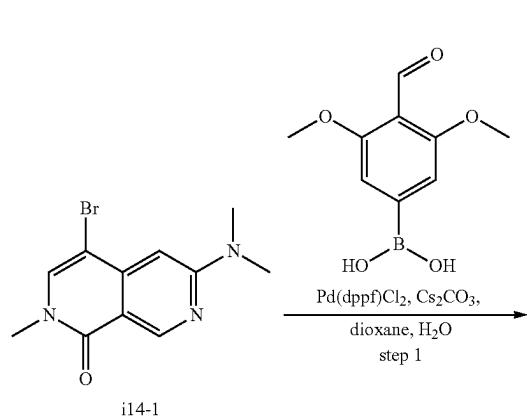
any additional work-up, the mixture was purified by prep-HPLC (conditions: SunFire C18 OBD Prep Column, 100 Å, 5 µm, 19 mm×250 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 9% B to 19% B in 15 minutes; 254 nm; Rt: 17.67 minutes) to give 4-((((S)-1-(4-(6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxy benzyl)azetidin-2-yl)methyl)(methylamino)methyl)-2-(2,6-dioxopiperidin-3-yl)isoindoli-ne-1,3-dione (20.4 mg, 12.76%) as a yellow solid. ¹H NMR (400 MHz, Methanol-d₄) δ 9.05 (s, 1H), 8.00-7.74 (m, 3H), 7.51 (d, J=6.9 Hz, 1H), 6.88 (d, J=5.4 Hz, 2H), 6.60 (d, J=4.5 Hz, 1H), 5.26-5.05 (m, 1H), 4.64 (dd, J=12.8, 10.2 Hz, 1H), 4.53 (dd, J=12.8, 5.7 Hz, 1H), 4.27-4.08 (m, 4H), 3.93 (d, J=10.8 Hz, 6H), 3.59 (d, J=2.1 Hz, 3H), 3.16 (s, 6H), 3.10 (s, 2H), 2.95-2.80 (m, 1H), 2.80-2.58 (m, 3H), 2.32 (dd, J=15.9, 2.4 Hz, 4H), 2.19-2.08 (m, 1H). LCMS (ESI) m/z: [M+H]⁺=722.20.

422

-continued



Example 14—Preparation of 4-([1-([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl)methyl]azetidin-3-yl)(methylamino)methyl)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (Compound D3 Formic Acid)



20

25

30

35

40

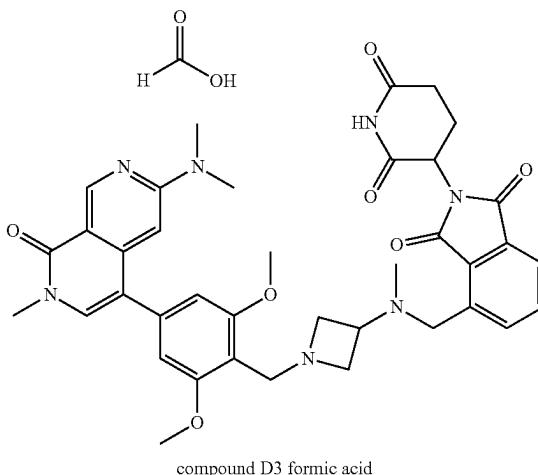
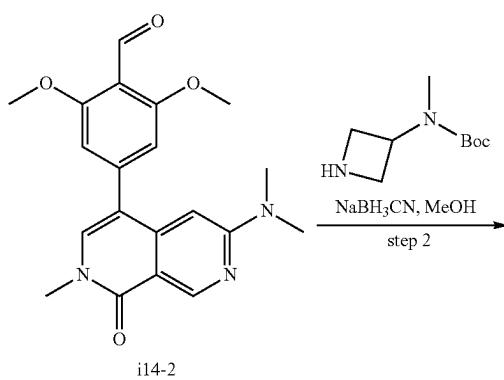
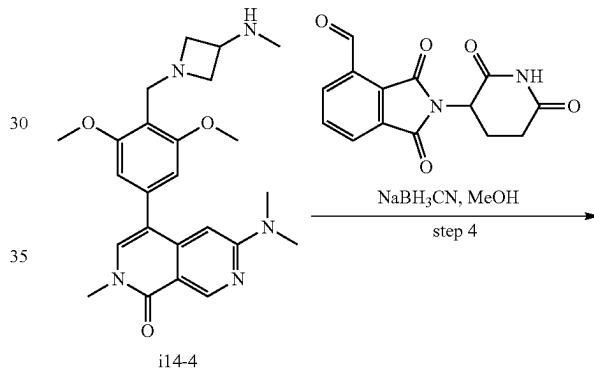
45

50

55

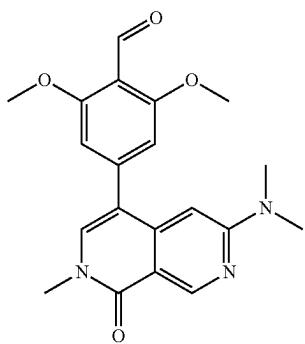
60

65



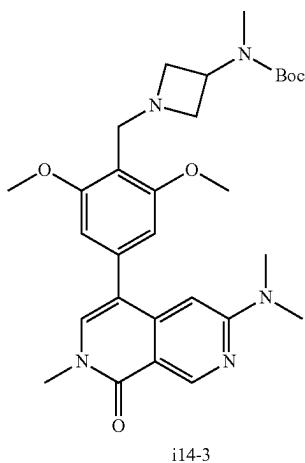
423

Step 1: Preparation of 4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (i14-2)



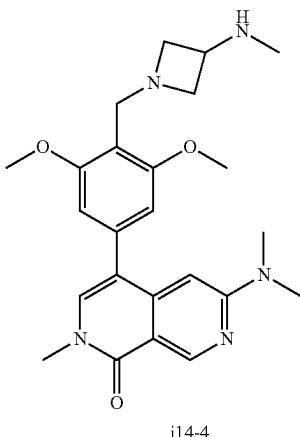
To a solution of 4-bromo-6-(dimethylamino)-2-methyl-2,7-naphthyridin-1-one (1.80 g, 6.380 mmol, 1.00 equiv) and 4-formyl-3,5-dimethoxyphenylboronic acid (1.34 g, 6.380 mmol, 1.00 equiv) in 1,4-dioxane and water was added CS₂CO₃ (4.16 g, 12.760 mmol, 2.00 equiv) and Pd(dppf)Cl₂ (0.47 g, 0.638 mmol, 0.10 equiv). After stirring for 2 hours at 80° C. under a nitrogen atmosphere, the resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:1) to afford 4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (1.5 g, 57.59%) as a grey solid. LCMS (ESI) m/z: [M+H]⁺= 368.

Step 2: Preparation of tert-butyl-N-[1-([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)azetidin-3-yl]-N-methylcarbamate (i14-3)

**424**

To a stirred mixture of 4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (100.00 mg, 0.272 mmol, 1.00 equiv) and tert-butyl N-(azetidin-3-yl)-N-methylcarbamate hydrochloride (90.93 mg, 0.408 mmol, 1.50 equiv) in MeOH was added NaBH₃CN (34.21 mg, 0.544 mmol, 2.00 equiv) in portions. The resulting mixture was stirred for 2 hours at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (20:1) to afford tert-butyl-N-[1-([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)azetidin-3-yl]-N-methylcarbamate (103 mg, 65.46%) as an off-white solid. LCMS (ESI) m/z: [M+H]⁺= 538.

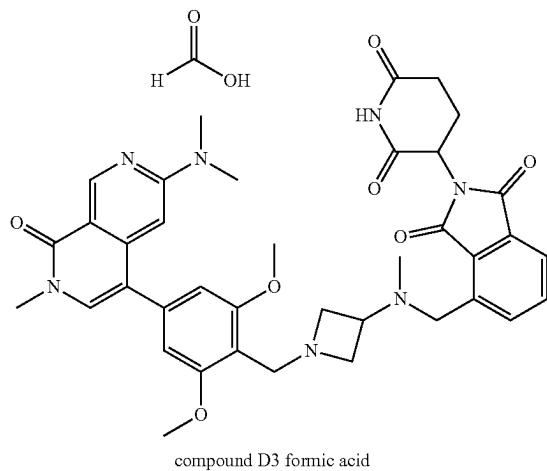
Step 3: 4-(3,5-dimethoxy-4-((3-(dimethylamino)azetidin-1-yl)methyl)phenyl)-6-(dimethylamino)-2-methyl-2,7-naphthyridin-1(2H)-one (i14-44)



To a stirred solution of tert-butyl-N-[1-([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)azetidin-3-yl]-N-methylcarbamate (100.00 mg, 0.186 mmol, 1.00 equiv) in DCM (1.00 mL) was added TFA (0.20 mL, 2.693 mmol, 14.48 equiv). The resulting mixture was stirred for 2 hours at room temperature and concentrated under reduced pressure. The residue was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H]⁺= 438.

425

Step 4: Preparation of 4-([1-([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl) azetidin-3-yl](methyl)amino)methyl)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (Compound D3 Formic Acid)

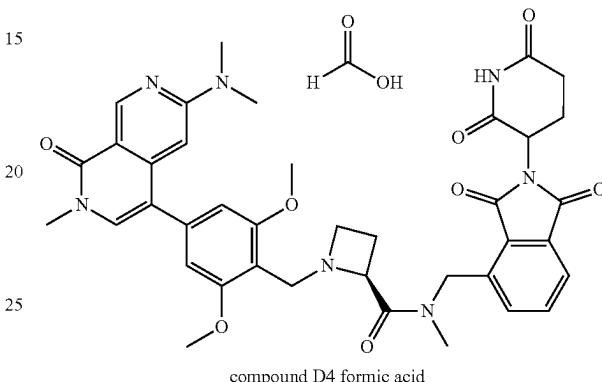


To a stirred mixture of 4-(3,5-dimethoxy-4-[3-(methylamino)azetidin-1-yl]methyl)phenyl)-6-(dimethylamino)-2-methyl-1,2,7-naphthyridin-1-one (50.00 mg, 0.114 mmol, 1.00 equiv) and 2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisooindole-4-carbaldehyde (65.42 mg, 0.229 mmol, 2.00 equiv) in MeOH was added NaBH₃CN (14.36 mg, 0.229 mmol, 2.00 equiv) in portions. The resulting mixture was stirred for 2 hours at room temperature. The mixture was purified by Prep-HPLC (conditions: XSelect CSH Prep C18 OBD Column, 5 μm, 19*150 mm; mobile phase, Water (0.1% FA) and ACN (16% PhaseB up to 26% in 8 minutes); Detector, UV). This resulted in 4-([1-([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)azetidin-3-yl](methyl)amino)methyl)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (2.8 mg, 3.17%) as a white solid. ¹H NMR (400 MHz, Methanol-d4) δ 9.16 (d, J=0.7 Hz, 1H), 8.56 (br s, 1H, FA), 7.90-7.79 (m, 3H), 7.43 (s, 1H), 6.85 (s, 2H), 6.47 (s, 1H), 5.14 (dd, J=12.3, 5.4 Hz, 1H), 4.37 (s, 2H), 4.06 (s, 3H), 3.98-3.85 (m, 9H), 3.59 (s,

426

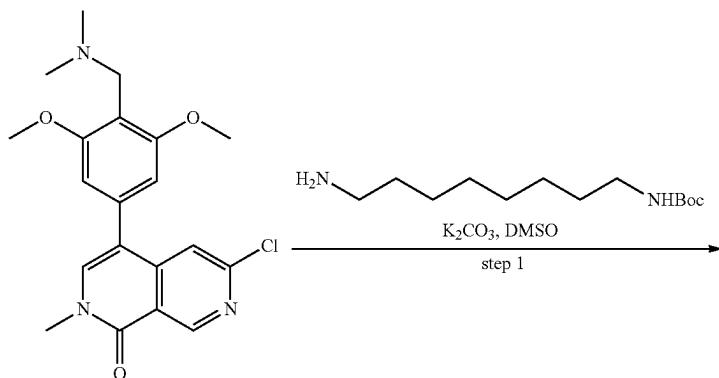
3H), 3.55-3.45 (m 1H), 3.11 (s, 6H), 2.89-2.80 (m, 1H), 2.77-2.66 (m, 2H), 2.16 (s, 3H), 2.14-2.07 (m, 1H). LCMS (ESI) m/z: [M+H]⁺=708.30.

5 Example 15—Preparation of (2S)-1-(4-(6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)-N-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisooindolin-4-yl)methyl)-N-methylazetidine-2-carboxamide formic acid (Compound D4 Formic Acid)



30 Compound D4 was prepared in a similar manner to Example 12. (2S)-1-(4-(6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)-N-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisooindolin-4-yl)methyl)-N-methylazetidine-2-carboxamide formic acid (9.1 mg, 17.56%) was obtained as a light yellow solid. ¹H NMR (400 MHz, Methanol-d4) δ 9.18-9.11 (m, 1H), 8.54 (s, 0.2H, FA), 7.93-7.52 (m, 2H), 7.46-7.27 (m, 2H), 6.85 (s, 2H), 6.54-6.30 (m, 1H), 5.34-4.94 (m, 4H), 4.48-4.31 (m, 2H), 4.03-3.79 (m, 8H), 3.91 (s, 3H), 3.14-2.93 (m, 9H), 2.90-2.67 (m, 4H), 2.60-2.38 (m, 1H), 2.23-2.09 (m, 1H). LCMS (ESI) m/z: [M+H]⁺=736.45.

45 Example 16—Preparation of 1[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]amino]butyl)azetidine-3-sulfonamide formic acid (Compound D5 Formic Acid)

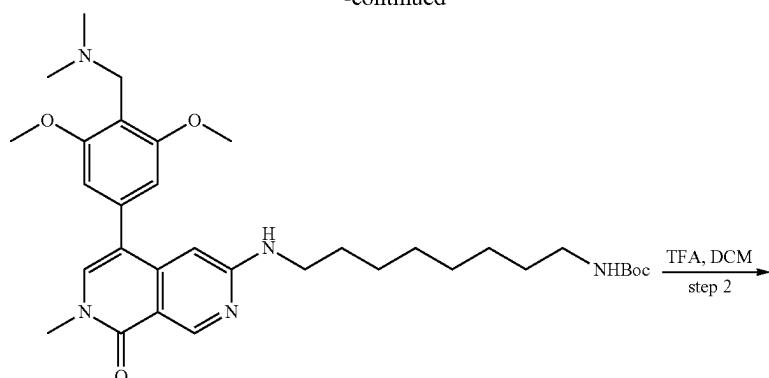


US 12,391,686 B2

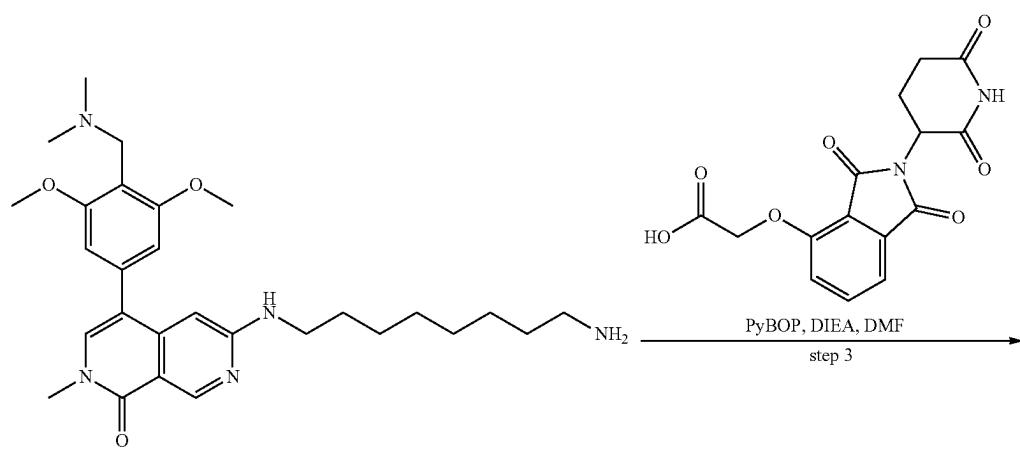
427

428

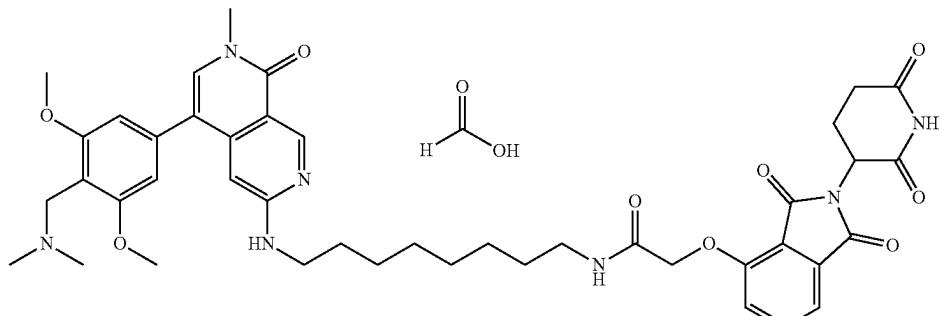
-continued



i16-1



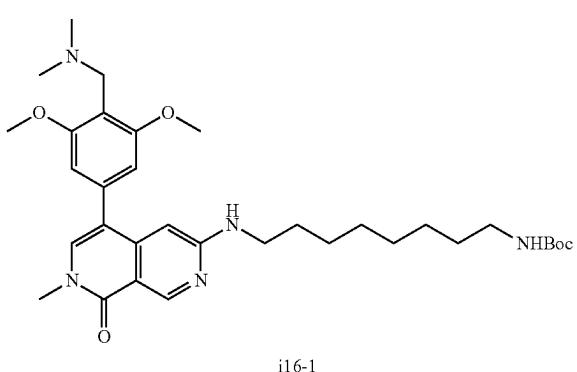
i16-2



compound D5 formic acid

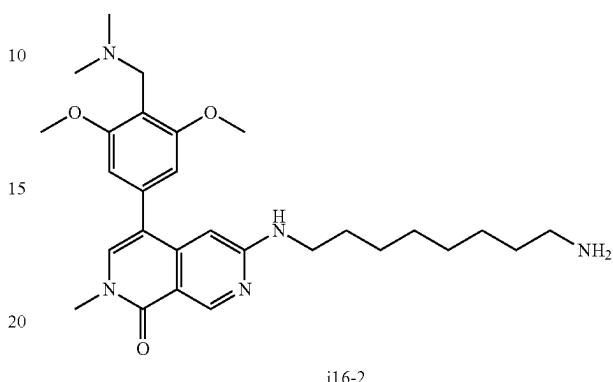
429

Step 1: Preparation of tert-butyl-N-[8-[(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naphthyridin-3-yl)amino]octyl]carbamate (i16-1)

**430**

Step 2: Preparation of 6-[(8-aminooctyl)amino]-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-2,7-naphthyridin-1-one (i16-2)

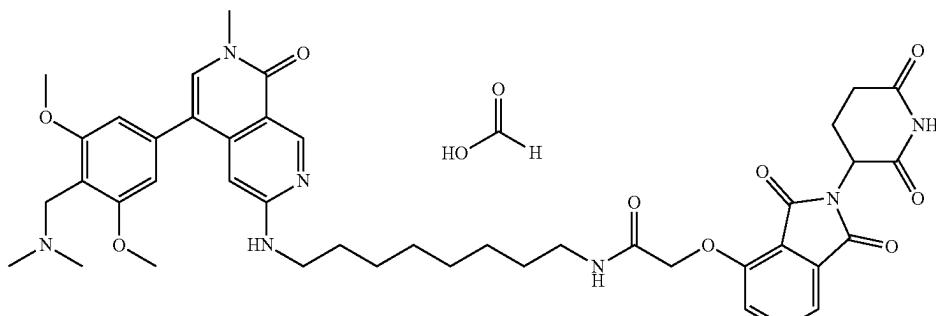
5



25 To a stirred mixture of tert-butyl-N-[8-[(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naphthyridin-3-yl)amino]octyl]carbamate (140 mg, 0.235 mmol, 1.00 equiv) in dichloromethane (2.0 mL) was added 30 trifluoroacetic acid (0.50 mL, 6.732 mmol, 28.65 equiv). The resulting mixture was stirred for 2 hours at room temperature. The resulting mixture was concentrated under reduced pressure, and the residue was purified by reverse 35 flash chromatography (conditions: column, C18 silica gel; mobile phase, acetonitrile in water (0.1% formic acid), 1% to 20% gradient in 20 minutes; detector, UV 254 nm) to give 40 6-[(8-aminooctyl)amino]-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-2,7-naphthyridin-1-one (100 mg, 80%) as a yellow syrup. LCMS (ESI) m/z: [M+H]⁺= 596.

Using a similar procedure as described in Example 7 and substituting with tert-butyl N-(8-aminooctyl)carbamate (945 mg, 3.867 mmol) afforded tert-butyl-N-[8-[(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naphthyridin-3-yl)amino]octyl]carbamate (140 mg, 82%) as a yellow syrup. LCMS (ESI) m/z: [M+H]⁺= 596.

45 Step 3: Preparation of N-[8-[(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naphthyridin-3-yl)amino]octyl]-2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]acetamide formic acid (Compound D5 Formic Acid)



compound D5 formic acid

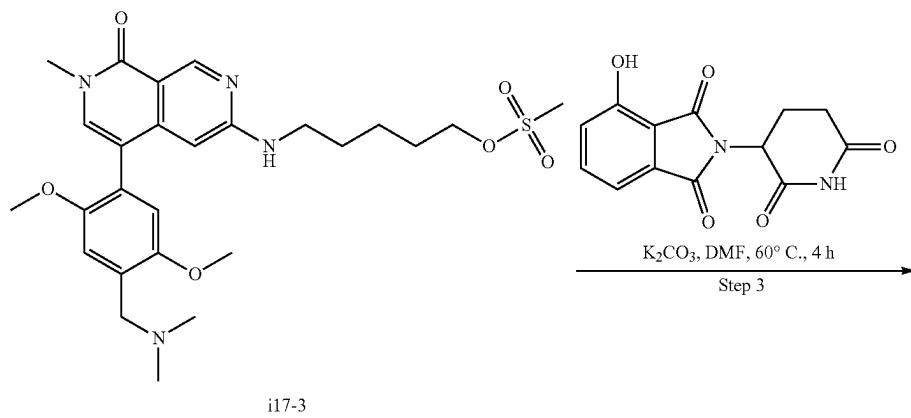
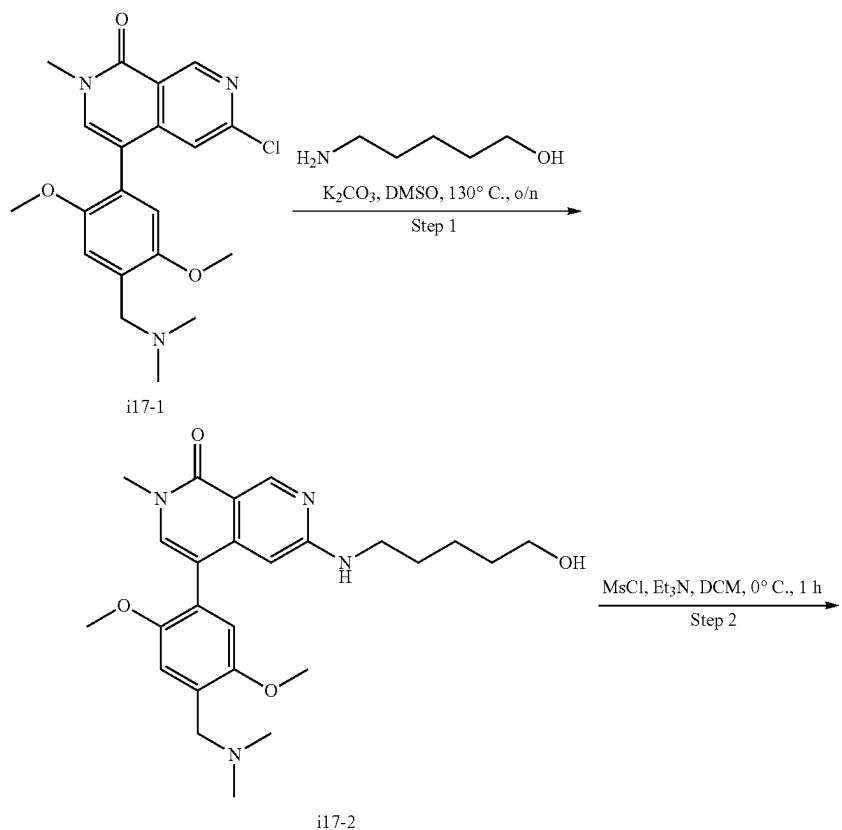
431

Using a similar procedure as described in Example 11 and substituting with of 6-[(8-aminoctyl)amino]-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-2,7-naphthyridin-1-one (50.0 mg, 0.101 mmol, 1.00 equiv) and [[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy] acetic acid (30.2 mg, 0.091 mmol, 0.90 equiv) afforded N-[8-[(5-4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naphthyridin-3-yl)amino]octyl]-2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy] acetamide formic acid (6.2 mg, 7%) as a white solid. ¹H NMR (400 MHz, Methanol-d₄) δ 9.05 (d, J=0.7 Hz, 1H), 8.57 (br s, 1H, FA), 7.81 (dd, J=8.4, 7.3 Hz, 1H), 7.53 (d,

432

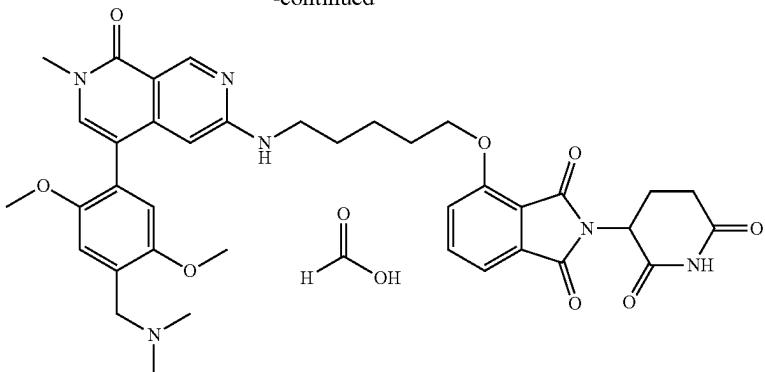
J=7.3 Hz, 1H), 7.46-7.38 (m, 2H), 6.83 (s, 2H), 6.40 (s, 1H), 5.13 (dd, J=12.6, 5.5 Hz, 1H), 4.76 (s, 2H), 4.60 (s, 3H), 4.23 (s, 2H), 3.95 (s, 6H), 3.57 (s, 3H), 3.34-3.23 (m, 2H), 2.93-2.81 (m, 2H), 2.80-2.67 (m, 6H), 2.19-2.10 (m, 1H), 1.62-1.54 (m, 4H), 1.37-1.33 (m, 8H). LCMS (ESI) m/z: [M+H]⁺=810.45.

Example 17—Preparation of 4-((5-((4-((dimethylamino)methyl)-2,5-dimethoxyphenyl)-7-methyl-8-oxo-7,8-dihydro-2,7-naphthyridin-3-yl)amino)pentyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione formic acid (Compound D6 Formic Acid)



433

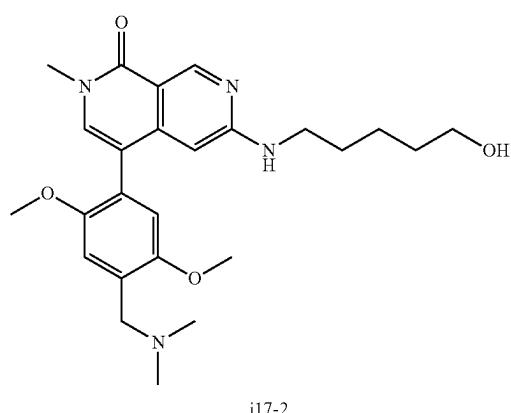
-continued



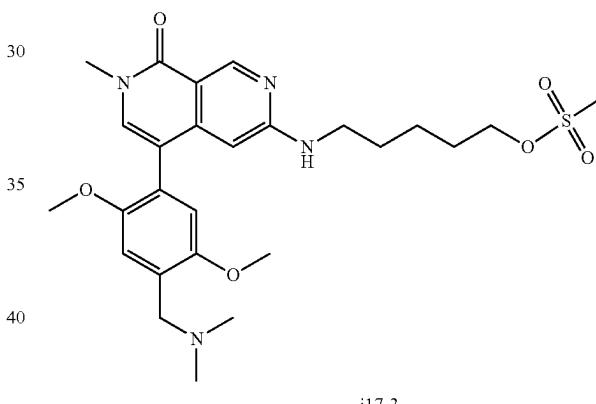
compound D6 formic acid

Step 1: Preparation of 4-((dimethylamino)methyl)-2,5-dimethoxyphenyl)-6-((5-hydroxypentyl)amino)-2-methyl-2,7-naphthyridin-1(2H)-one (i17-
2)

Step 2: Preparation of 5-((5-(4-((dimethylamino)methyl)-2,5-dimethoxyphenyl)-7-methyl-8-oxo-7,8-dihydro-2,7-naphthyridin-3-yl)amino)pentyl methanesulfonate (i17-3)



i17-2



i17-3

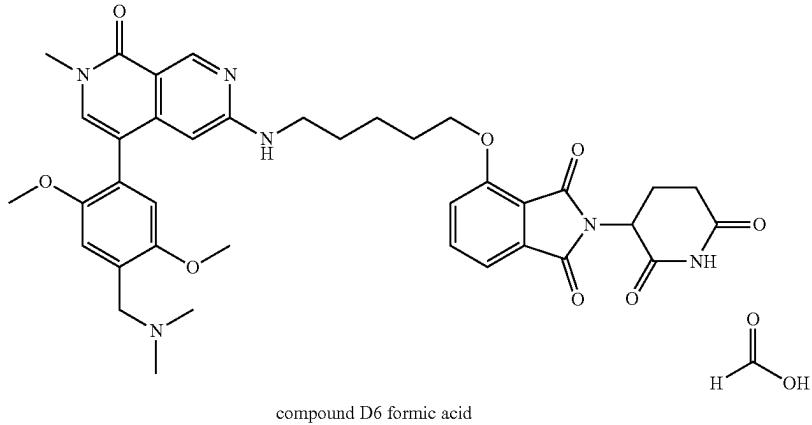
Using a similar procedure as described in Example 7 and substituting with 6-chloro-4-((dimethylamino)methyl)-2,5-dimethoxyphenyl)-2-methyl-2,7-naphthyridin-1(2H)-one (150.0 mg, 0.387 mmol, 1.00 equiv) and 5-aminopentanol (39.8 mg, 0.387 mmol, 1.00 equiv) afforded 4-((dimethylamino)methyl)-2,5-dimethoxyphenyl)-6-((5-hydroxypentyl)amino)-2-methyl-2,7-naphthyridin-1(2H)-one (90 mg, 51.4%) as a brown solid. LCMS (ESI) m/z: [M+H]⁺=455.

To a solution of 4-((dimethylamino)methyl)-2,5-dimethoxyphenyl)-6-((5-hydroxypentyl)amino)-2-methyl-2,7-naphthyridin-1(2H)-one (90 mg, 0.198 mmol, 1.00 equiv)
and triethylamine (100.2 mg, 0.990 mmol, 5.00 equiv) in dichloromethane (2.00 mL) was added methanesulfonyl chloride (45.4 mg, 0.396 mmol, 2.00 equiv) slowly at 0° C. The reaction mixture was stirred for 30 minutes at 0° C. and then warmed to room temperature slowly. The reaction was quenched with saturated sodium bicarbonate solution (50 mL) and extracted with dichloromethane (50 mL×3). The organic layers were combined and washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to afford 5-((5-(4-((dimethylamino)methyl)-2,5-dimethoxyphenyl)-7-methyl-8-oxo-7,8-dihydro-2,7-naphthyridin-3-yl)amino)pentyl methanesulfonate (80.0 mg, 68.3%) as a brown solid. LCMS (ESI) m/z: [M+H]⁺=533.

435

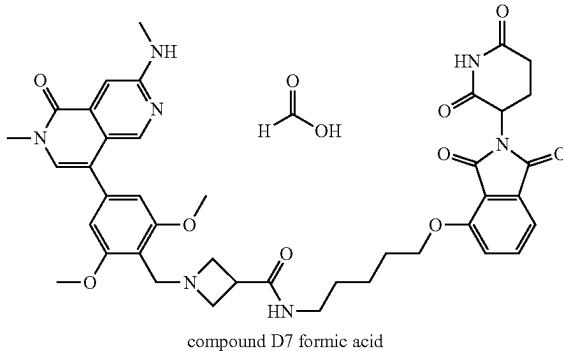
Step 3: Preparation of 4-((5-((4-((dimethylamino)methyl)-2,5-dimethoxyphenyl)-7-methyl-8-oxo-7,8-dihydro-2,7-naphthyridin-3-yl)amino)pentyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione formic acid (Compound D6 Formic Acid)

436



To a mixture of 5-((4-((dimethylamino)methyl)-2,5-dimethoxyphenyl)-7-methyl-8-oxo-7,8-dihydro-2,7-naphthyridin-3-yl)amino)pentyl methanesulfonate (80.0 mg, 0.150 mmol, 1.00 equiv) and 2-(2,6-dioxopiperidin-3-yl)-4-hydroxyisoindoline-1,3-dione (41.2 mg, 0.150 mmol, 1.00 equiv) in DMF (2.00 mL) was added K_2CO_3 (41.5 mg, 0.300 mmol, 2.00 equiv). The resulting mixture was stirred for 4 hours at 60° C. The resulting mixture was filtered, and the filtrate was purified by Prep-HPLC (column: SunFire C₁₈ OBD Prep Column, 100 Å, 5 µm, 19 mm×250 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 11% B to 26% B in 10 minutes; 254 nm; Rt: 8.78 minutes) to afford 4-((5-((4-((dimethylamino)methyl)-2,5-dimethoxyphenyl)-7-methyl-8-oxo-7,8-dihydro-2,7-naphthyridin-3-yl)amino)pentyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione; formate (15.3 mg, 11.6%) as a light yellow solid. LCMS (ESI) m/z: [M+H]⁺=711.65. ¹H NMR (400 MHz, Methanol-d4) δ 9.02 (s, 1H), 8.56 (br s, 0.6H, FA), 7.77 (dd, J=8.5, 7.3 Hz, 1H), 7.43 (dd, J=11.8, 7.8 Hz, 2H), 7.28 (s, 1H), 7.16 (s, 1H), 7.01 (s, 1H), 5.98 (s, 1H), 5.09 (dd, J=12.8, 5.4 Hz, 1H), 4.22 (t, J=6.2 Hz, 2H), 4.03 (s, 2H), 3.88 (s, 3H), 3.75 (s, 3H), 3.56 (s, 3H), 3.28 (t, J=6.6 Hz, 2H), 2.93-2.82 (m, 1H), 2.80-2.70 (m, 2H), 2.65 (s, 6H), 2.15-2.07 (m, 1H), 1.92-1.81 (m, 2H), 1.73-1.64 (m, 2H), 1.64-1.55 (m, 2H).

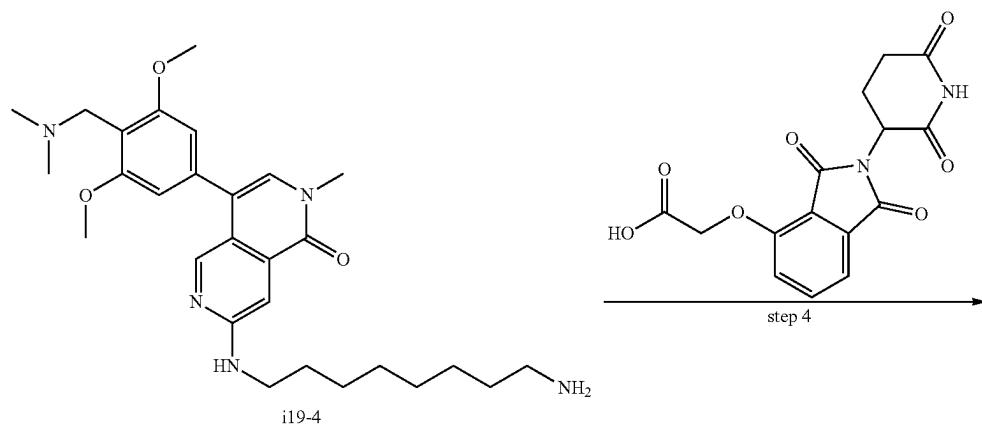
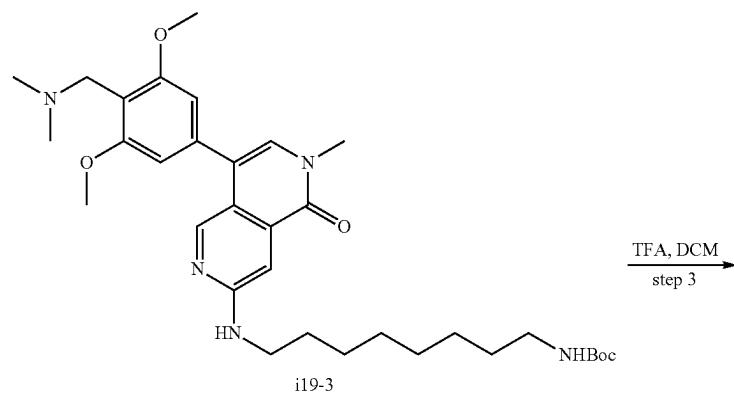
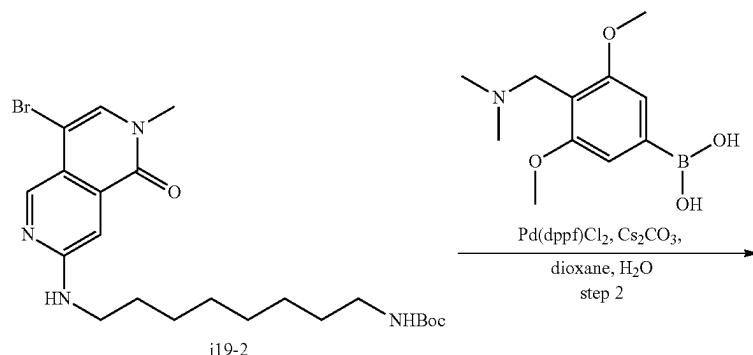
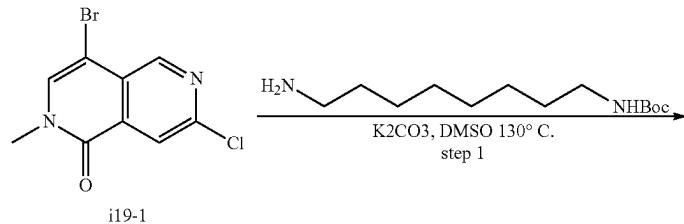
Example 18—Preparation of 1-([2,6-dimethoxy-4-[2-methyl-7-(methylamino)-1-oxo-2,6-naphthyridin-4-yl]phenyl]methyl)-N-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]pentyl)azetidine-3-carboxamide formic acid (Compound D7 Formic Acid)



Compound 7 was prepared in a similar manner to Example 10 and Example 12. 1-([2,6-dimethoxy-4-[2-methyl-7-(methylamino)-1-oxo-2,6-naphthyridin-4-yl]phenyl]methyl)-N-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]pentyl)azetidine-3-carboxamide formic acid (30 mg, 30.6%) was obtained as a yellow solid. ¹H NMR (300 MHz, Methanol-d4) δ 8.56 (br s, 0.7H, FA), 8.51 (d, J=0.9 Hz, 1H), 7.77 (dd, J=8.4, 7.4 Hz, 1H), 7.44 (dd, J=7.9, 2.5 Hz, 2H), 7.23 (d, J=0.9 Hz, 1H), 7.10 (s, 1H), 6.81 (s, 2H), 5.10 (dd, J=12.4, 5.5 Hz, 1H), 4.30-4.21 (m, 3H), 4.02 (d, J=8.1 Hz, 3H), 3.92 (s, 6H), 3.64 (s, 3H), 3.47 (t, J=8.2 Hz, 1H), 3.29-3.13 (m, 3H), 2.97 (s, 3H), 2.90-2.76 (m, 2H), 2.75-2.63 (m, 1H), 2.18-2.07 (m, 1H), 2.01-1.83 (m, 3H), 1.68-1.54 (m, 4H). LCMS (ESI) m/z: [M+H]⁺=780.60.

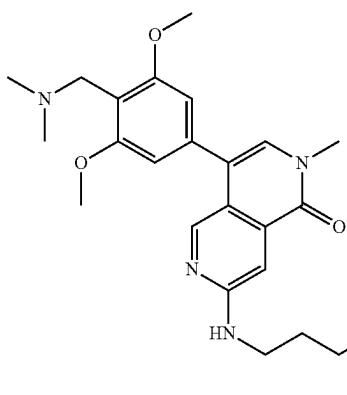
437

Example 19—Preparation of N-[8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl]amino]octyl]-2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]acetamide (Compound D8)

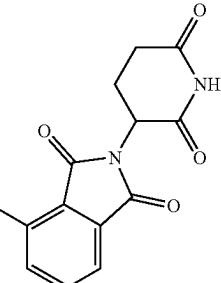
**438**

439

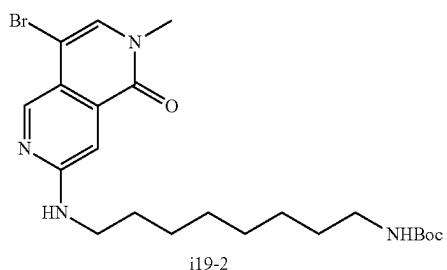
-continued



compound D8

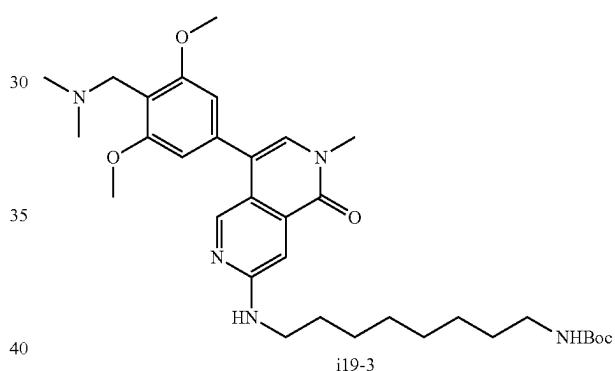
440

Step 1: Preparation of tert-butyl N-[8-[(8-bromo-6-methyl-5-oxo-2,6-naphthyridin-3-yl)amino]octyl] carbamate (i19-2)



To a mixture of 4-bromo-7-chloro-2-methyl-2,6-naphthyridin-1-one (100 mg, 0.366 mmol, 1.00 equiv) and tert-butyl N-(8-aminoctyl)carbamate (268.1 mg, 1.097 mmol, 3.00 equiv) in DMSO (3.00 mL) was added K_2CO_3 (505.3 mg, 3.656 mmol, 10.00 equiv). The resulting solution was stirred at 130° C. for 5 hours. The resulting solution was diluted with EtOAc (80 mL). The resulting mixture was washed with water (3×50 mL). The organic layer was concentrated under reduced pressure. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:1). Fractions containing the desired compound were evaporated to dryness to afford tert-butyl N-[8-[(8-bromo-6-methyl-5-oxo-2,6-naphthyridin-3-yl)amino]octyl]carbamate (50 mg, 28.4%) as a yellow solid. LCMS (ESI) m/z: [M+H]⁺=483.

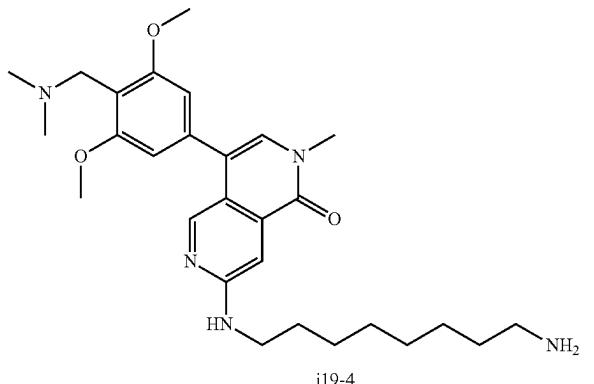
Step 2: Preparation of tert-butyl N-[8-[(8-[(dimethylamino)methyl]-3,5-dimethoxyphenyl)-6-methyl-5-oxo-2,6-naphthyridin-3-yl)amino]octyl] carbamate (i19-3)



To a solution of tert-butyl N-[8-[(8-bromo-6-methyl-5-oxo-2,6-naphthyridin-3-yl)amino]octyl]carbamate (50.0 mg, 0.104 mmol, 1.00 equiv) and 4-[(dimethylamino)methyl]-3,5-dimethoxyphenylboronic acid (37.2 mg, 0.156 mmol, 1.50 equiv) in H_2O (0.50 mL) and dioxane (1.50 mL) was added Cs_2CO_3 (67.7 mg, 0.208 mmol, 2.00 equiv) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (7.60 mg, 0.010 mmol, 0.10 equiv). The resulting solution was stirred at 90° C. for 1 hour under N_2 atmosphere. The resulting solution was diluted with EtOAc (50 mL). The resulting mixture was washed with water (3×30 mL). The resulting mixture was concentrated under reduced pressure. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (30:70). Fractions containing the desired compound were evaporated to dryness to afford tert-butyl N-[8-[(8-[(dimethylamino)methyl]-3,5-dimethoxyphenyl)-6-methyl-5-oxo-2,6-naphthyridin-3-yl)amino]octyl]carbamate (30 mg, 48.5%) as a yellow solid. LCMS (ESI) m/z: [M+H]⁺=596.

441

Step 3: Preparation of 7-[8-(8-aminoctyl)amino]-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-2,6-naphthyridin-1-one (i19-4)



442

5

10

15

20

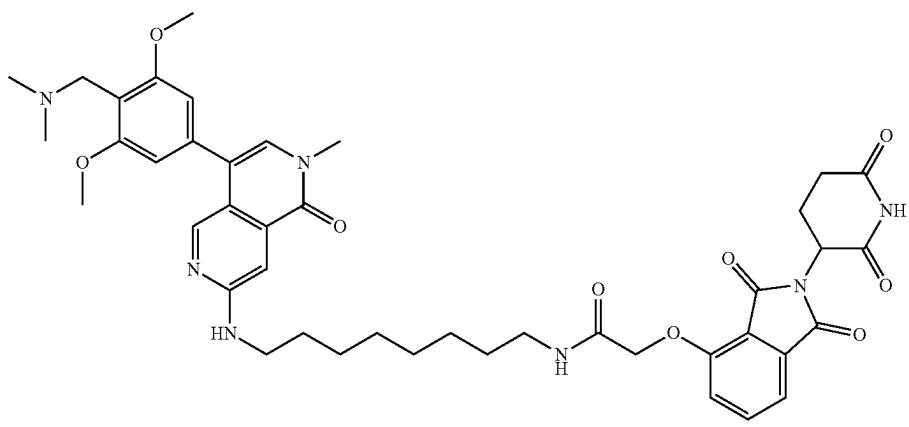
25

30

35

To a solution of tert-butyl N-[8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl]amino]octyl]carbamate (30 mg, 0.050 mmol, 1.00 equiv) in DCM (2.00 mL) was added TFA (2.00 mL), and the resulting solution was stirred at 25° C. for 1 hour. The resulting mixture was concentrated under reduced pressure to afford 7-[8-(8-aminoctyl)amino]-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-2,6-naphthyridin-1-one (35 mg, crude) as a yellow liquid that was used directly without further purification. LCMS (ESI) m/z: [M+H]⁺=496.

Step 4: Preparation of N-[8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl]amino]octyl]-2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]acetamide
(Compound D8)



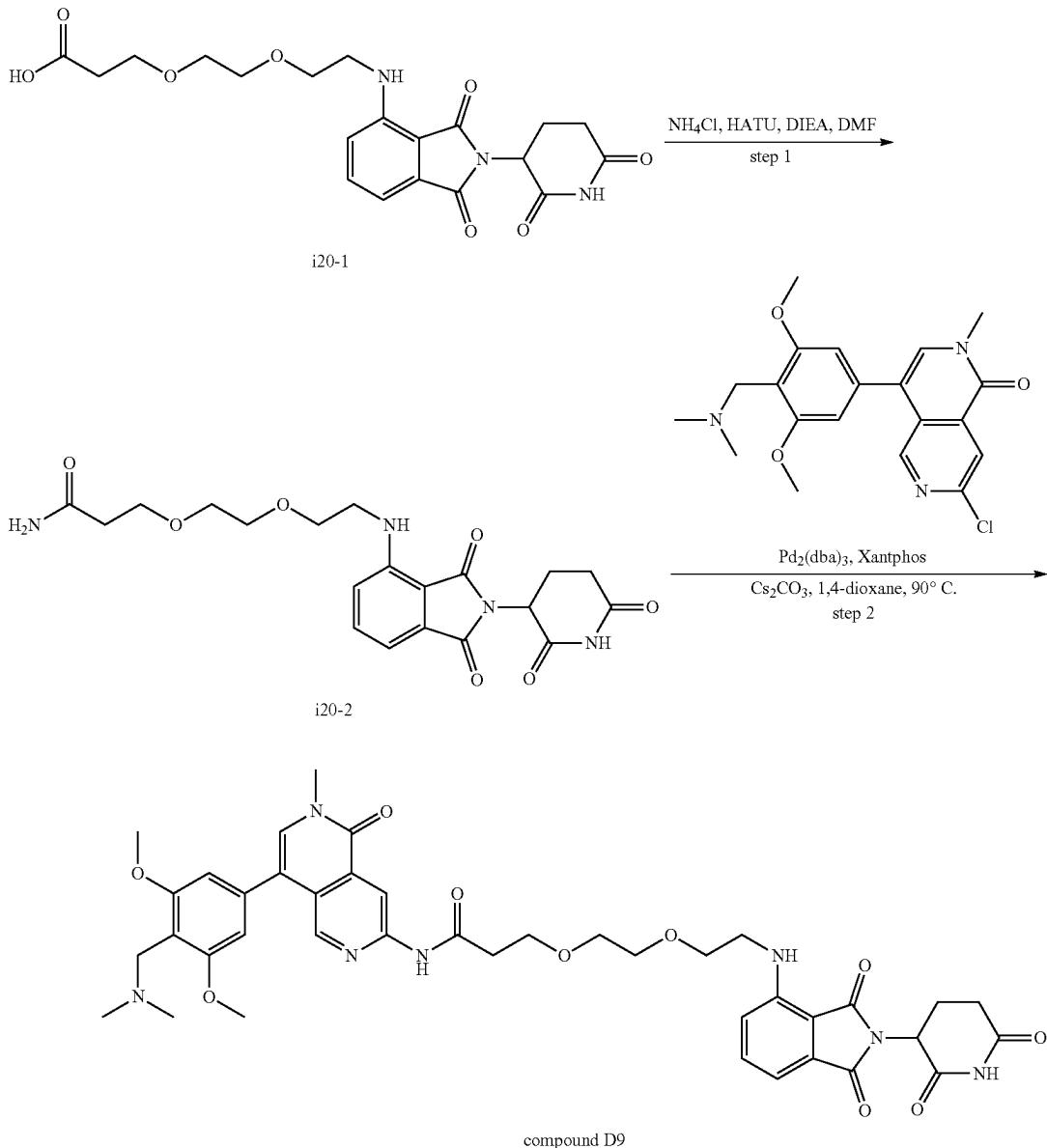
55

To a solution of [[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]acetic acid (24.1 mg, 0.073 mmol, 1.20 equiv) and HATU (46.0 mg, 0.121 mmol, 2.00 equiv) in DMF (2.00 mL) were added 7-[8-(8-aminoctyl)amino]-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-2,6-naphthyridin-1-one (30.0 mg, 0.061 mmol, 1.00 equiv) and DIEA (39.1 mg, 0.303 mmol, 5.00 equiv). The resulting solution was stirred at 25° C. for 2 hours. The crude product was purified by preparative HPLC (conditions: XSelect CSH Prep C18 OBD Column, 5 μm, 19*150 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 20% B to 55% B in 8 minutes; 254

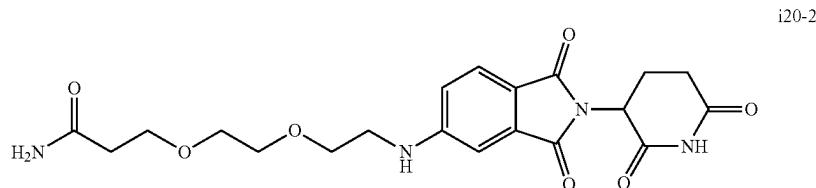
nm; Rt: 7.12 minutes) to afford N-[8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl]amino]octyl]-2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]acetamide (12 mg, 24.5%) as a yellow solid. ¹H NMR (300 MHz, Methanol-d4) δ 8.41 (s, 1H), 7.80 (dd, J=8.4, 7.4 Hz, 1H), 7.52 (d, J=7.3 Hz, 1H), 7.43 (d, J=9.1 Hz, 2H), 7.15 (s, 1H), 6.90 (s, 2H), 5.13 (dd, J=12.4, 5.4 Hz, 1H), 4.77 (s, 2H), 4.42 (s, 2H), 3.98 (s, 6H), 3.63 (s, 3H), 3.40-3.35 (m, 2H), 3.30-3.21 (m, 2H), 2.92 (s, 6H), 2.90-2.82 (m, 1H), 2.80-2.65 (m, 2H), 2.21-2.09 (m, 1H), 1.72-1.57 (m, 4H), 1.51-1.34 (m, 8H). LCMS (ESI) m/z: [M+H]⁺=810.60.

443

Example 20—Preparation of N-(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)-3-[2-(2-[(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]amino)ethoxy]ethoxy]propanamide (Compound D9)



Step 1: Preparation of 3-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)amino)ethoxy)ethoxy propanamide (i20-2) ⁵⁵



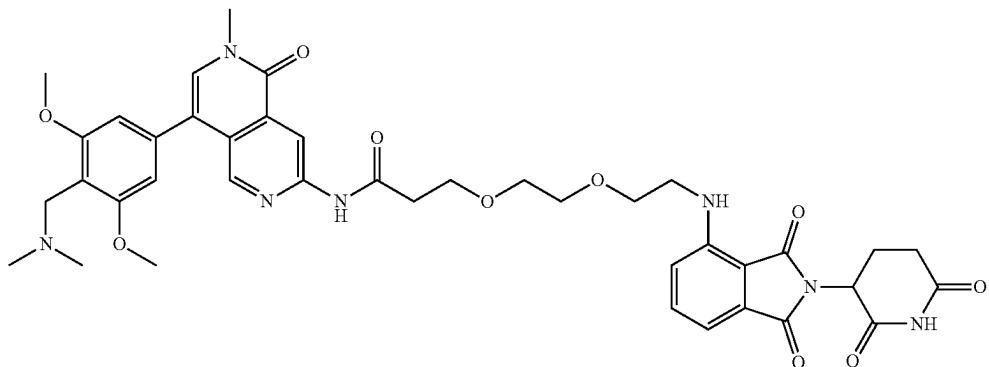
445

Using a similar procedure as described in Example 10, step 1 and substituting with 5-([2-[2-(3,3-dihydroxypropoxy)ethoxy]ethyl]amino)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (150 mg, 0.344 mmol, 1.00 equiv) and ammonium chloride (24 mg, 0.448 mmol, 1.30 equiv) 5 afforded 3-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)amino)ethoxy) propanamide (122 mg, 81.5%) as a yellow solid. LCMS (ESI) m/z: [M+H]⁺= 433.

Step 2: Preparation of N-(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)-3-[2-([2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]amino)ethoxy]propanamide (Compound D9)

10

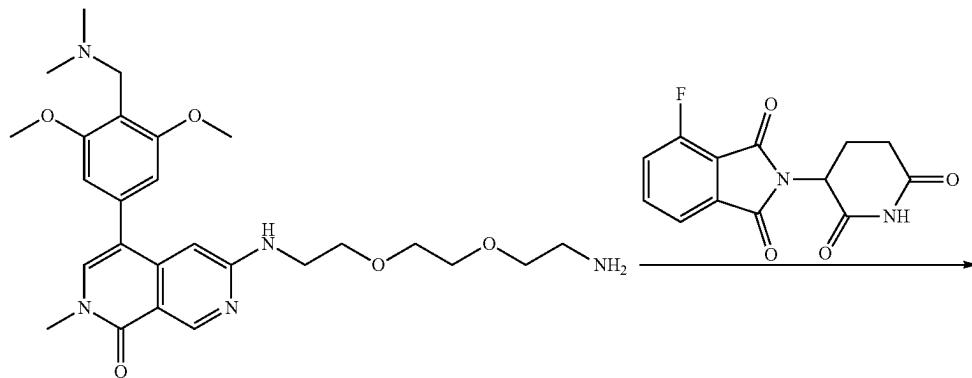
compound D9



To a solution of 7-chloro-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-2,6-naphthyridin-1-one (50 mg, 0.129 mmol, 1.00 equiv) and 3-[2-([2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]amino)ethoxy]ethoxypropanamide (55.8 mg, 0.129 mmol, 1 equiv) in dioxane (4 mL) was added tris(dibenzylideneacetone)dipalladium(O) (11.8 mg, 0.013 mmol, 0.10 equiv), cesium carbonate (84.0 mg, 0.258 mmol, 2.0 equiv) and Xantphos (14.9 mg, 0.026 mmol, 0.20 equiv), and the resulting solution was stirred at 90° C. for 3 hours. The mixture filtered through a short pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by 45 Prep-HPLC (conditions: SunFire C18 OBD Prep Column, 100 Å, 5 µm, 19 mm×250 mm; Mobile Phase A: water (0.1% formic acid), Mobile Phase B: acetonitrile; Flow rate: 25 mL/minute; Gradient: 9 B to 22 B in 18 minutes; 254 nm)

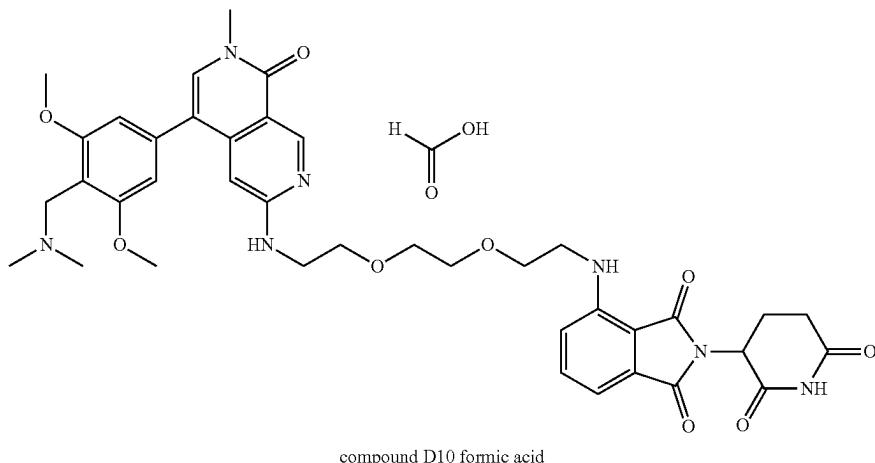
35 to give N-(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)-3-[2-([2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]amino)ethoxy]propanamide (6 mg, 5.6%) as a yellow solid. ¹H NMR (300 MHz, Methanol-d₄) δ 8.82 (s, 1H), 8.64 (s, 1H), 7.40-7.30 (m, 2H), 6.89 (s, 2H), 6.86-6.76 (m, 2H), 4.99 (dd, J=12.4, 5.4 Hz, 1H), 4.44 (s, 2H), 4.01 (s, 6H), 3.92 (t, J=5.7 Hz, 2H), 3.82-3.72 (m, 6H), 3.64 (s, 3H), 3.39 (t, J=5.0 Hz, 2H), 2.93 (s, 6H), 2.88-2.61 (m, 5H), 2.29-2.18 (m, 1H). LCMS (ESI) m/z: [M+H]⁺=784.50.

Example 21—Preparation of 4-[[2-(2-[2-[(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naphthyridin-3-yl)amino]ethoxy]ethyl]amino]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (Compound D10 Formic Acid)



447

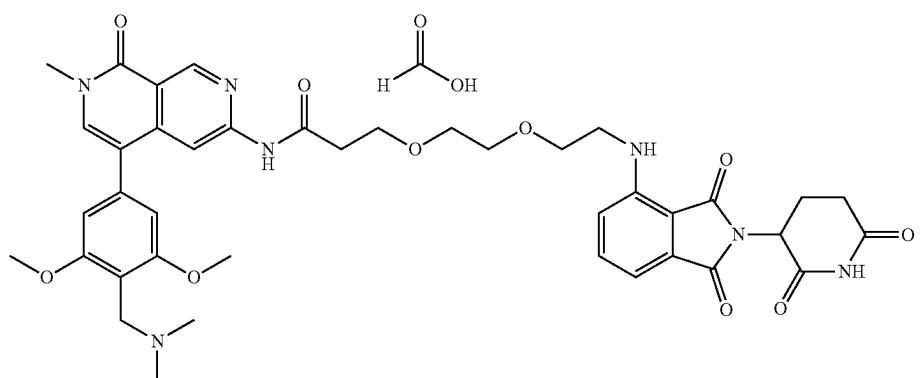
-continued



Intermediate i-21-1 was prepared in a similar manner to preparation of i19-4 in Example 19. To a stirred mixture of 6-[2-[2-(2-aminoethoxy)ethoxy]ethylamino]-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-2,7-naphthyridin-1-one (100 mg, 0.200 mmol, 1.00 equiv) and 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindole-1,3-dione (55.3 mg, 0.200 mmol, 1.00 equiv) in dimethylformamide (2 mL) was added diisopropylethylamine (129.3 mg, 1.001 mmol, 5.00 equiv). After stirring overnight at 90° C., the mixture was purified by Prep-HPLC (conditions: Atlantis HILIC OBD Column, 19*150 mm, 5 μm ; mobile phase: A, water (0.1% formic acid) and B, acetonitrile (12% to 21% B in 9 minutes) to afford 4-[[2-(2-[5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naphthyridin-3-yl)amino]ethoxy]ethoxy]ethylamino]-2-(2,6-di-

²⁵ oxopiperidin-3-yl)isoindole-1,3-dione formic acid (4 mg, 2.5%). ¹H NMR (300 MHz, Methanol-d4) δ 9.03 (s, 1H), 8.57 (br s, 0.83H, formic acid), 7.51 (t, $J=7.8$ Hz, 1H), 7.40 (s, 1H), 7.00 (d, $J=7.8$ Hz, 2H), 6.83 (s, 2H), 6.50 (s, 1H), 4.96-4.90 (m, 1H), 4.32 (s, 2H), 3.96 (s, 6H), 3.71-3.63 (m, 8H), 3.56 (s, 3H), 3.53-3.48 (m, 2H), 3.42 (t, $J=5.2$ Hz, 2H), 2.85 (s, 6H), 2.78-2.57 (m, 3H), 2.00 (d, $J=9.2$ Hz, 1H). LCMS (ESI) m/z: [M+H]⁺=756.45.

⁴⁰ Example 22—Preparation of N-(5-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-7-methyl-8-oxo-7,8-dihydro-2,7-naphthyridin-3-yl)-3-(2-(2-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)ethoxy)ethoxy)propanamide formic acid
(Compound D11 Formic Acid)



compound D11

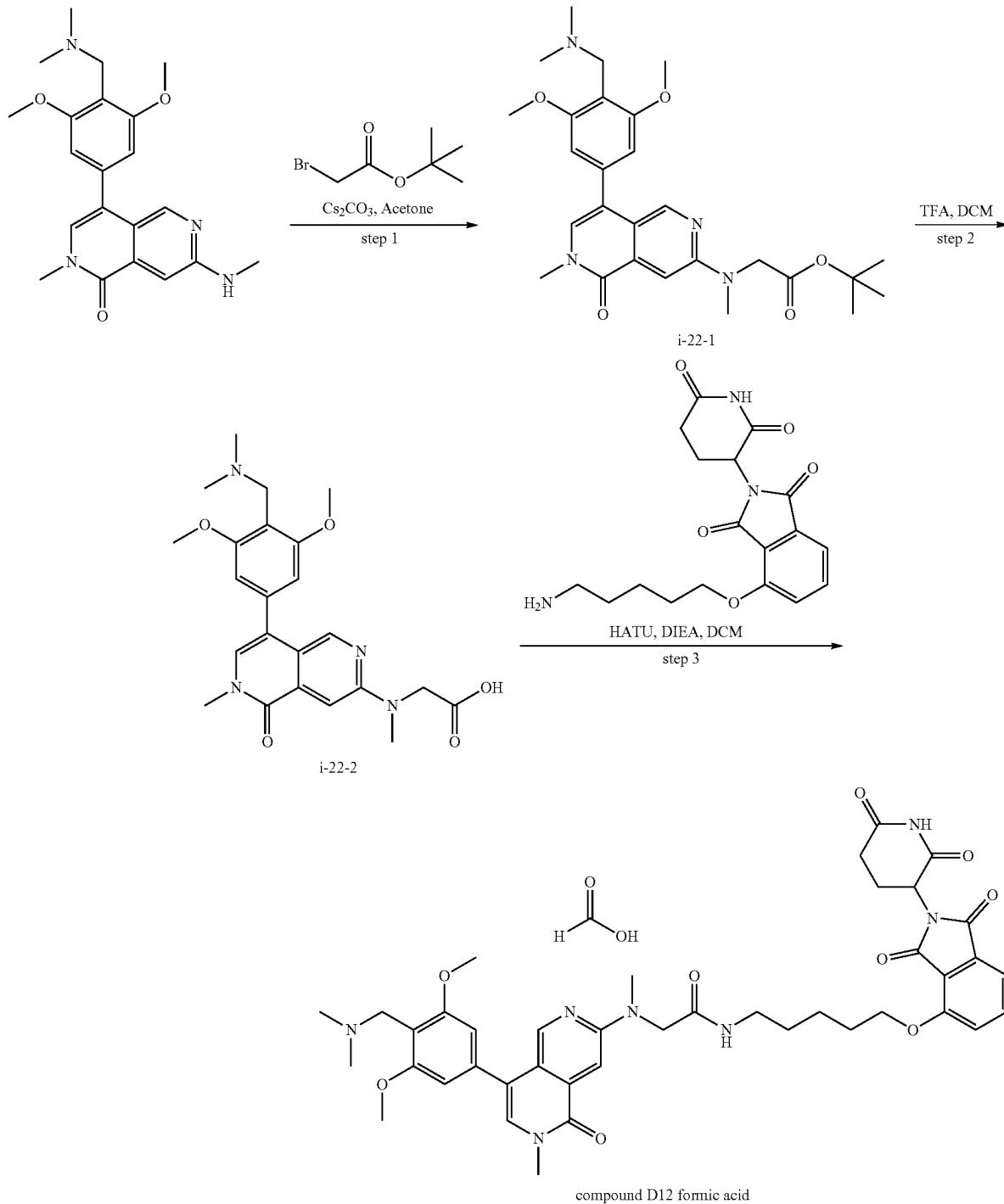
449

Compound D11 was prepared in a similar manner to Example 20. N-(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naphthyridin-3-yl)-3-[2-[[2-(2,6-dioxo piperidin-3-yl)-1,3-dioxoisoin dol-4-yl]amino]ethoxy]ethoxypropanamide formic acid (8.1 mg, 6.62%) was obtained as a yellow solid. ^1H NMR (300 MHz, Methanol-d4) δ 9.10 (s, 1H), 8.57 (br s, 1H, FA), 8.45 (s, 1H), 7.64 (s, 1H), 7.34 (dd, $J=8.6, 7.1$ Hz, 1H), 6.90-6.75 (m, 4H), 4.86-4.82 (m, 1H), 4.61 (s, 1H), 4.33 (s, 2H), 4.02 (s, 6H), 3.94-3.84 (m, 2H), 3.77-3.71 (m, 6H), 3.65 (s, 3H), 5

450

3.36 (s, 1H), 2.85 (s, 6H), 2.75-2.66 (m, 3H), 2.63-2.54 (m, 1H), 2.47-2.31 (m, 1H), 1.84-1.73 (m, 1H). LCMS (ESI) m/z: [M+H] $+=784.4$.

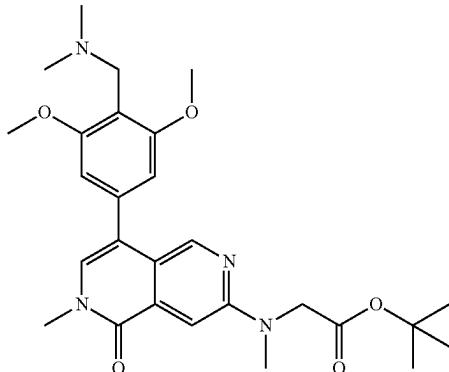
Example 23—Preparation of 2-[(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)(methyl)amino]-N-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisooindol-4-yl]oxy]pentyl)acetamide formic acid (Compound D12 Formic Acid)



451

Step 1: Preparation of tert-butyl 2-[(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)(methyl)amino]acetate (i22-1)

5

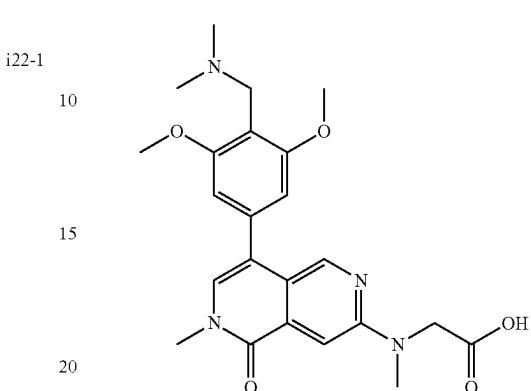


To a stirred solution of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-7-(methylamino)-2,6-naphthyridin-1-one (514 mg, 1.344 mmol, 1.00 equiv) and tert-butyl 2-bromoacetate (393.2 mg, 2.016 mmol, 1.50 equiv) in acetone was added cesium carbonate (875.8 mg, 2.688 mmol, 2.00 equiv) in portions at room temperature. The resulting mixture was stirred for 1 hour at room temperature. The resulting mixture was filtered, and the filter cake was washed with dichloromethane (3×10 mL). The filtrate was concentrated under reduced pressure. This resulted in tert-butyl 2-[(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)(methyl)amino]acetate (600 mg, 89.9%) as a light yellow solid. LCMS (ESI) m/z: [M+H]⁺=497.2

452

Step 2: Preparation of [(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)(methyl)amino]acetic acid (i22-2)

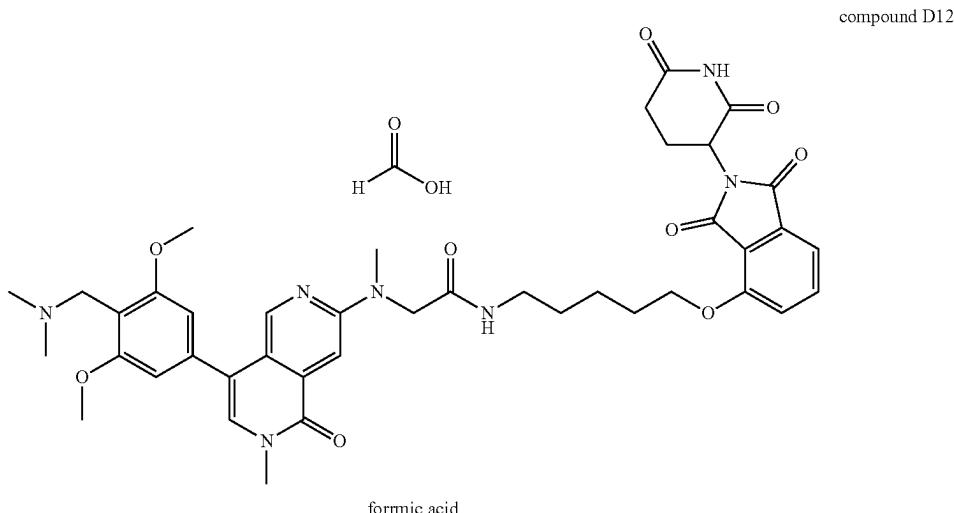
5



i22-2

To a stirred solution of tert-butyl 2-[(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)(methyl)amino]acetate (600 mg, 1.208 mmol, 1.00 equiv) in dichloromethane was added trifluoroacetic acid (4 mL) dropwise at room temperature. The resulting mixture was stirred for 2 hours at room temperature. The crude product was purified by Prep-HPLC (conditions: MeCN/water 30%) to afford [(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)(methyl)amino]acetic acid (450 mg, 84.6%) as a light yellow solid. LCMS (ESI) m/z: [M+H]⁺=441.

Step 3: Preparation of 2-[(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)(methyl)amino]-N-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]pentyl)acetamide formic acid (Compound D12 Formic Acid)



453

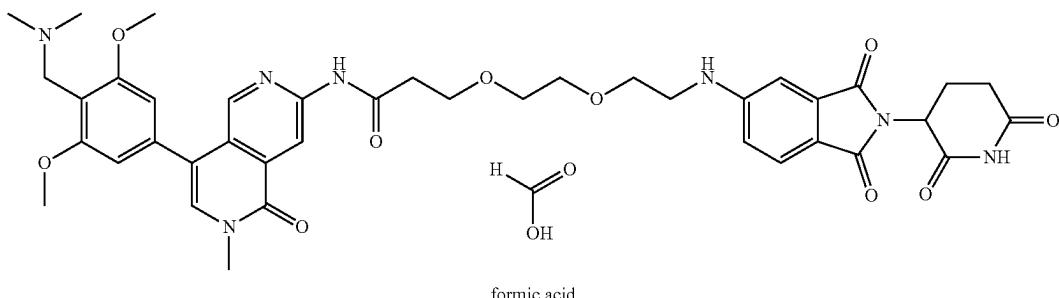
Using a similar procedure as described in Example 11 and substituting with [(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)-(methyl)amino]acetic acid (100 mg, 0.227 mmol, 1.00 equiv) and 4-[(5-aminopentyl)oxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (122.4 mg, 0.341 mmol, 1.50 equiv) afforded 2-[(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)-(methyl)amino]-N-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]pentyl)acetamide formic acid (80 mg, 42.6%) as a yellow solid.¹H NMR (300 MHz, Methanol-d4) δ 8.56 (s, 1H), 8.51 (brs, 0.8H, formic acid), 7.78 (dd, J=8.6, 7.2 Hz, 1H), 7.48-7.42 (m, 2H), 7.25 (s, 1H), 7.14 (s, 1H),

6.89 (s, 2H), 5.10 (dd, J=12.4, 5.4 Hz, 1H), 4.82 (s, 2H), 4.27 (t, J=5.9 Hz, 2H), 4.08 (s, 2H), 3.94 (s, 6H), 3.66 (s, 3H), 3.40-3.36 (m, 2H), 3.28 (s, 6H), 2.98 (s, 3H), 2.90-2.67 (m, 3H), 2.19-2.08 (m, 1H), 1.97-1.86 (m, 2H), 1.74-1.61 (m, 4H). LCMS (ESI) m/z: [M+H]⁺=782.50.

454

Example 24—Preparation of N-(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)-3-[2-[(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl)amino]ethoxy]propanamide formic acid (Compound D13 Formic Acid)

compound D13

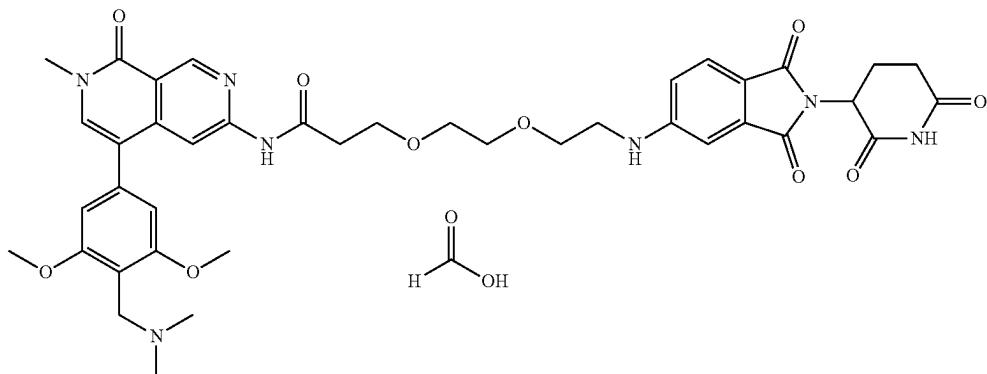


formic acid

Compound D13 was prepared in a similar manner to Example 20. N-(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)-3-[2-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl)amino]ethoxy]propanamide formic acid (7 mg, 6.9%) was obtained.¹H NMR (300 MHz, Methanol-d4) δ 8.86 (d, J=0.9 Hz, 1H), 8.70 (d, J=0.9 Hz, 1H), 8.56 (brs, 0.9H, FA), 7.40 (s, 1H), 7.28 (d, J=8.4 Hz, 1H), 6.82 (s, 2H), 6.63 (d, J=2.2 Hz, 1H), 6.54 (dd, J=8.4, 2.2 Hz, 1H), 5.05-4.97 (m, 1H), 4.33 (s, 2H), 3.98 (s, 6H), 3.93 (t, J=5.6 Hz, 2H), 3.75-3.70 (m, 6H), 3.58 (s, 3H), 3.18 (t, J=5.4 Hz, 2H), 2.85 (s, 6H), 2.79-2.57 (m, 5H), 2.08-1.97 (m, 1H). LCMS (ESI) m/z: [M+H]⁺=784.55.

Example 25—Preparation of N-(5-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-7-methyl-8-oxo-7,8-dihydro-2,7-naphthyridin-3-yl)-3-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)amino)ethoxy)ethoxy]propanamide formic acid (Compound D14 Formic Acid)

compound D14



formic acid

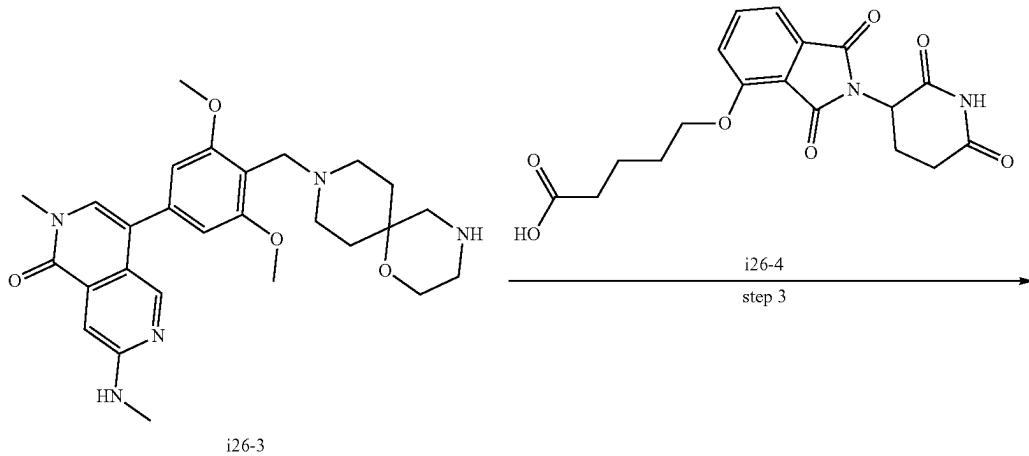
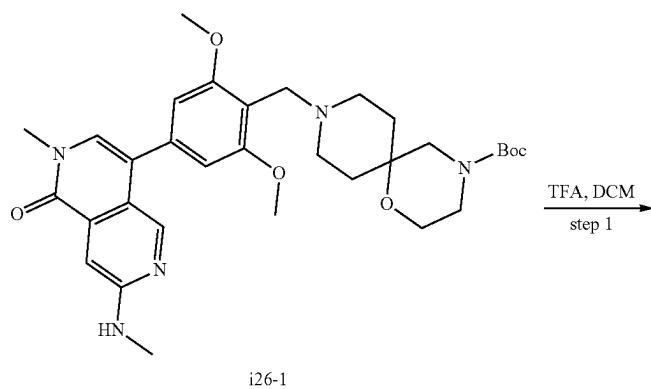
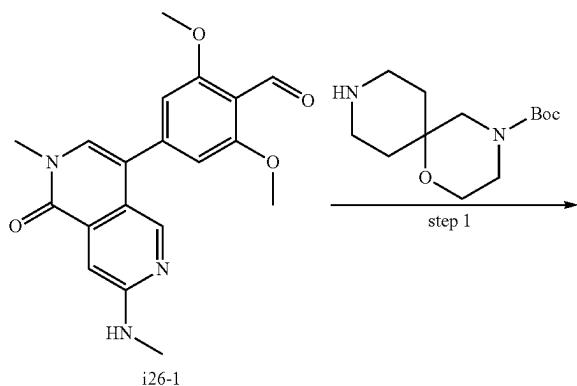
455

Compound D13 was prepared in a similar manner to Example 20. N-(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naphthyridin-3-yl)-3-[2-(2-[(2,6-dioxopiperidin-3-yl)-1,3-dioxoisooindol-5-yl]amino]ethoxy]ethoxypropanamide formic acid (6 mg, 6.62%) was obtained as a yellow solid. ¹H NMR (300 MHz, Methanol-d4) δ 9.19 (s, 1H), 8.55 (brs, 1.8H, FA), 8.51 (s, 1H), 7.65 (s, 1H), 7.33 (d, J=8.3 Hz, 1H), 6.83 (s, 2H), 6.67 (d, J=2.1 Hz, 1H), 6.56 (dd, J=8.4, 2.2 Hz, 1H), 5.05-4.98 (m, 1H), 4.36 (s, 2H), 4.00 (s, 6H), 3.87 (t, J=5.5 Hz, 2H), 5

456

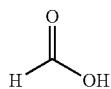
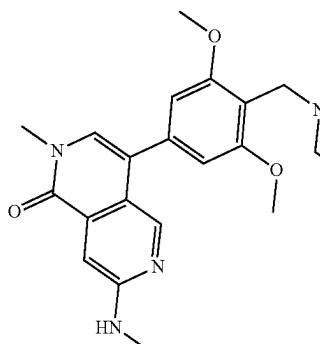
3.72-3.63 (m, 6H), 3.59 (s, 3H), 3.13 (t, J=5.4 Hz, 2H), 2.90 (s, 6H), 2.83-2.60 (m, 5H), 2.11-2.00 (m, 1H). LCMS (ESI) m/z: [M+H]⁺=784.5.

Example 26—Preparation of 4-([5-[9-([2,6-dimethoxy-4-[2-methyl-7-(methylamino)-1-oxo-2,6-naphthyridin-4-yl]phenyl)methyl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]-5-oxopentyl]oxy)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid
(Compound D15 Formic Acid)

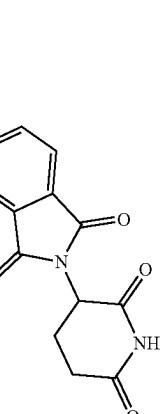


457

-continued



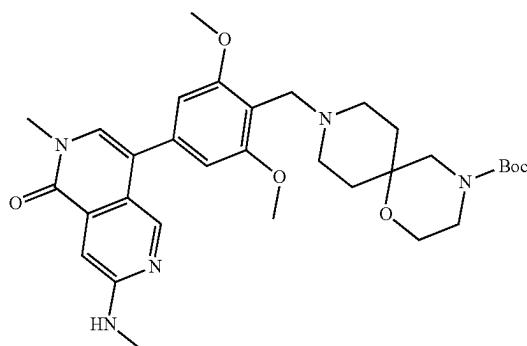
compound D15 formic acid

458

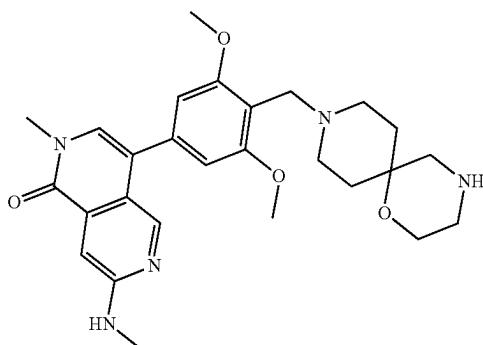
Step 1: Preparation of tert-butyl 9-([2,6-dimethoxy-
4-[2-methyl-7-(methylamino)-1-oxo-2,6-naphthyridin-4-yl]phenyl]-1-oxa-4,9-diazaspiro[5.5]
undecane-4-carboxylate (i26-2)

20
25

Step 2: Preparation of 4-(3,5-dimethoxy-4-[1-oxa-4,
9-diazaspiro[5.5]undecan-9-ylmethyl]phenyl)-2-
methyl-7-(methylamino)-2,6-naphthyridin-1-one
(i26-3)

30
i26-235
40
45

i26-3

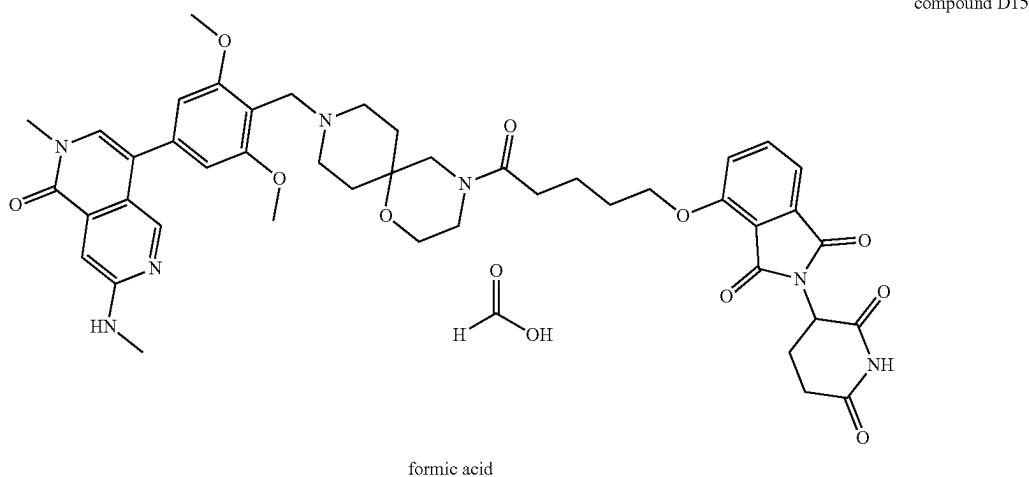


To a solution of 2,6-dimethoxy-4-[2-methyl-7-(methylamino)-1-oxo-2,6-naphthyridin-4-yl]benzaldehyde (100 mg, 0.283 mmol, 1.00 equiv) and tert-butyl 1-oxa-4,9-diazaspiro[5.5]undecane-4-carboxylate (87.1 mg, 0.340 mmol, 1.20 equiv) in MeOH (2.00 mL) was added NaBH₃CN (35.6 mg, 0.566 mmol, 2.00 equiv), and the resulting solution was stirred at 25° C. for 2 hours. The resulting mixture was concentrated. The residue was applied onto a silica gel column with DCM/MeOH (20:1). This resulted in tert-butyl 9-([2,6-dimethoxy-4-[2-methyl-7-(methylamino)-1-oxo-2,6-naphthyridin-4-yl]phenyl]-1-oxa-4,9-diazaspiro[5.5]undecane-4-carboxylate (110 mg, 65.5%) as a yellow solid. LCMS (ESI) m/z: [M+H]⁺=594.

To a solution of tert-butyl 9-([2,6-dimethoxy-4-[2-methyl-7-(methylamino)-1-oxo-2,6-naphthyridin-4-yl]phenyl]-1-oxa-4,9-diazaspiro[5.5]undecane-4-carboxylate (100.0 mg, 0.168 mmol, 1.00 equiv) in DCM (2.00 mL) was added TFA (2.00 mL), and the resulting solution was stirred at 25° C. for 2 h. The resulting mixture was concentrated under vacuum to give 4-(3,5-dimethoxy-4-[1-oxa-4,9-diazaspiro[5.5]undecan-9-ylmethyl]phenyl)-2-methyl-7-(methylamino)-2,6-naphthyridin-1-one (90 mg, crude) as a yellow solid that was used directly without further purification. LCMS (ESI) m/z: [M+H]⁺=494.

459

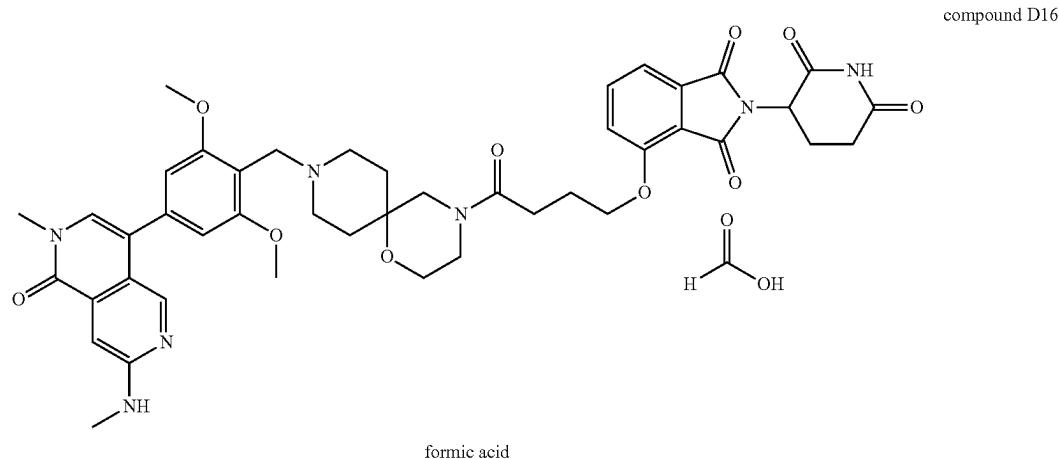
Step 3: Preparation of 4-((5-[9-([2,6-dimethoxy-4-[2-methyl-7-(methylamino)-1-oxo-2,6-naphthyridin-4-yl]phenyl)methyl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-5-oxopentyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (Compound D15 Formic Acid)



To a solution of 5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisooindol-4-yl]oxy]pentanoic acid (15.2 mg, 0.041 mmol, 1.00 equiv) and HATU (30.8 mg, 0.081 mmol, 2.00 equiv), in solvent DMF (2.00 mL) was added 4-(3,5-dimethoxy-4-[1-oxa-4,9-diazaspiro[5.5]undecan-9-ylmethyl]phenyl)-2-methyl-7-(methylamino)-2,6-naphthyridin-1-one (20.0 mg, 0.041 mmol, 1.00 equiv) and DIPEA (15.7 mg, 0.122 mmol, 3.00 equiv), and the resulting solution was stirred at 25° C. for 2 hours. The resulting mixture was concentrated. The crude product was purified by preparative HPLC (conditions: XSelect CSH Prep C18 OBD Column, 5 µm, 19*150 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 20% B to 55% B in 8 minutes; 254 nm; R_f: 7.12 minutes) to afford 4-((5-[9-([2,6-dimethoxy-4-[2-methyl-7-(methylamino)-1-oxo-2,6-naphthyridin-4-yl]phenyl)methyl]-1-oxa-4,9-diazaspiro

30 [5.5]undecan-4-yl)-5-oxopentyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (20 mg, 52.8%) as a yellow solid. ¹H NMR (300 MHz, Methanol-d4) δ 8.56 (br s, 0.5H, FA), 8.51 (s, 1H), 7.83-7.74 (m, 1H), 7.50-7.42 (m, 2H), 7.24 (d, J=3.8 Hz, 1H), 7.11 (s, 1H), 6.83 (d, J=9.2 Hz, 2H), 5.12 (dd, J=12.2, 5.3 Hz, 1H), 4.33-4.22 (m, 3H), 3.93 (d, J=8.5 Hz, 7H), 3.83-3.69 (m, 3H), 3.67-3.60 (m, 5H), 3.51 (s, 2H), 3.22-3.10 (m, 2H), 2.97 (s, 3H), 2.92-2.63 (m, 5H), 2.18-1.86 (m, 8H), 1.83-1.69 (m, 2H). LCMS (ESI) m/z: [M+H]⁺=850.60.

Example 27—Preparation of 4-(4-(2,6-dimethoxy-4-[2-methyl-7-(methylamino)-1-oxo-2,6-naphthyridin-4-yl]benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-4-oxobutoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione formic acid (Compound D16 Formic Acid)



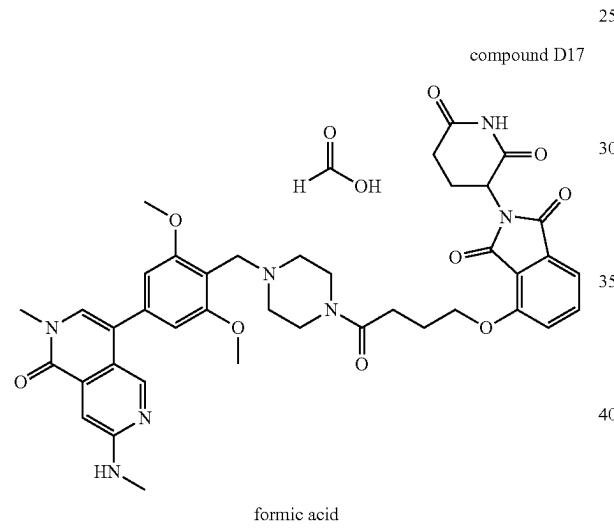
461

Compound D16 was prepared in a similar manner to Example 26. 4-[4-[9-([2,6-dimethoxy-4-[2-methyl-7-(methylamino)-1-oxo-2,6-naphthyridin-4-yl]phenyl)methyl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]-4-oxobutoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (16 mg, 20.0%) was obtained as a light brown solid. ¹H NMR (400 MHz, Methanol-d4) δ 8.57 (brs, 0.6H, FA), 8.54 (d, J=4.5 Hz, 1H), 7.80 (t, J=7.9 Hz, 1H), 7.48 (dd, J=7.2, 5.0 Hz, 2H), 7.25 (d, J=1.0 Hz, 1H), 7.13 (d, J=4.6 Hz, 1H), 6.83 (d, J=10.9 Hz, 2H), 5.13 (dd, J=12.5, 5.5 Hz, 1H), 4.31 (t, J=5.7 Hz, 2H), 4.26-4.16 (m, 2H), 3.92 (d, J=12.1 Hz, 6H), 3.75-3.69 (m, 3H), 3.65 (s, 3H), 3.60-3.48 (m, 3H), 3.24-3.02 (m, 4H), 2.97 (s, 3H), 2.81-2.65 (m, 5H), 2.24-2.12 (m, 3H), 2.10-1.84 (m, 3H), 1.79-1.65 (m, 1H). LCMS (ESI) m/z: [M+H]⁺ = 836.45.

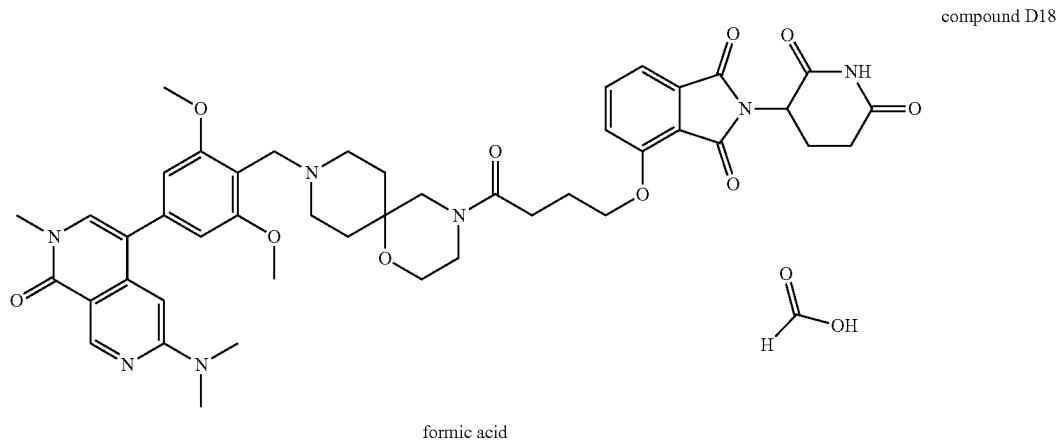
Example 28—Preparation of 4-(4-(4-(2,6-dimethoxy-4-(2-methyl-7-(methylamino)-1-oxo-1,2-dihydro-2,6-naphthyridin-4-yl)benzyl)piperazin-1-yl)-4-oxobutoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione formic acid (Compound D17 Formic Acid)

462

Compound D17 was prepared in a similar manner to Example 26. 4-[4-[4-[2,6-dimethoxy-4-[2-methyl-7-(methylamino)-1-oxo-2,6-naphthyridin-4-yl]phenyl)methyl]piperazin-1-yl]-4-oxobutoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (11.0 mg, 12.8%) was obtained as a yellow solid. ¹H NMR (400 MHz, DMSO-d6) δ 11.14 (s, 1H), 9.63 (s, 1H), 8.56 (brs, 0.9H, FA), 7.87-7.77 (m, 1H), 7.55 (d, J=8.5 Hz, 1H), 7.47 (d, J=7.2 Hz, 1H), 7.20 (s, 1H), 7.13 (s, 1H), 6.98 (d, J=4.8 Hz, 1H), 6.86 (s, 2H), 5.09 (dd, J=12.7, 5.4 Hz, 1H), 4.43 (d, J=12.5 Hz, 1H), 4.27 (dd, J=13.9, 7.8 Hz, 4H), 4.07 (d, J=13.6 Hz, 1H), 3.90 (s, 6H), 3.58-3.48 (m, 4H), 3.47-3.38 (m, 3H), 3.26-2.98 (m, 3H), 2.96-2.88 (m, 1H), 2.87-2.83 (m, 3H), 2.65-2.55 (m, 3H), 2.09-1.95 (m, 3H). LCMS (ESI) m/z: [M+H]⁺ = 766.50.



Example 29—Preparation of 4-(4-(9-(4-(6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-4-oxobutoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione formic acid (Compound D18 Formic Acid)



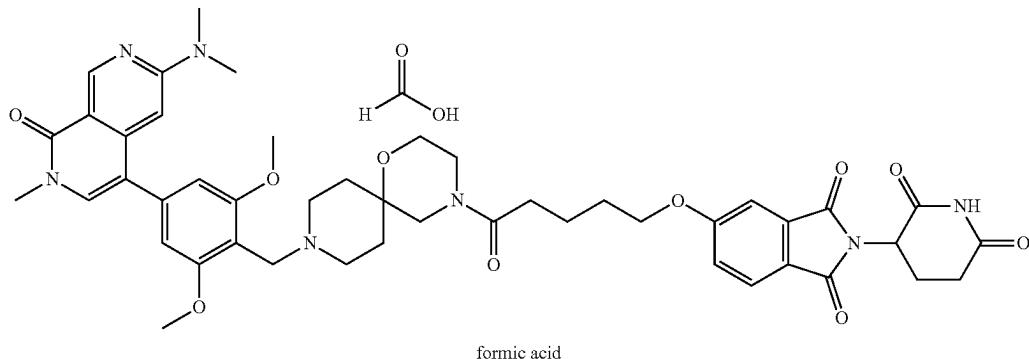
463

Compound D18 was prepared in a similar manner to Example 26. 4-[4-[9-([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl)methyl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]-4-oxobutoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (12.7 mg) was obtained as a white solid. LCMS (ESI) m/z: [M+H]⁺=850.55. ¹H NMR (400 MHz, Methanol-d4) δ 9.15 (s, 1H), 8.47 (brs, 1.2H, FA), 7.80 (t, J=7.9 Hz, 1H), 7.48 (d, J=9.9 Hz, 3H), 6.89 (d, J=7.2 Hz, 2H), 6.49 (d, J=3.7 Hz, 1H), 5.13 (dd, J=12.6, 5.5 Hz, 1H), 4.40 (s, 2H), 4.31 (s, 2H), 3.95 (d, J=12.5 Hz, 6H), 3.80-3.65 (m, 4H), 3.60 (d, J=3.1 Hz, 3H), 3.57-3.48 (m, 2H), 3.34 (s, 4H), 3.13 (s, 6H), 2.85-2.59 (m, 5H), 2.24-2.04 (m, 6H), 1.84-1.74 (m, 1H).

Example 30—Preparation of 5-((5-(9-(4-(6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-5-oxopentyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione formic acid (Compound D19 Formic Acid)

464

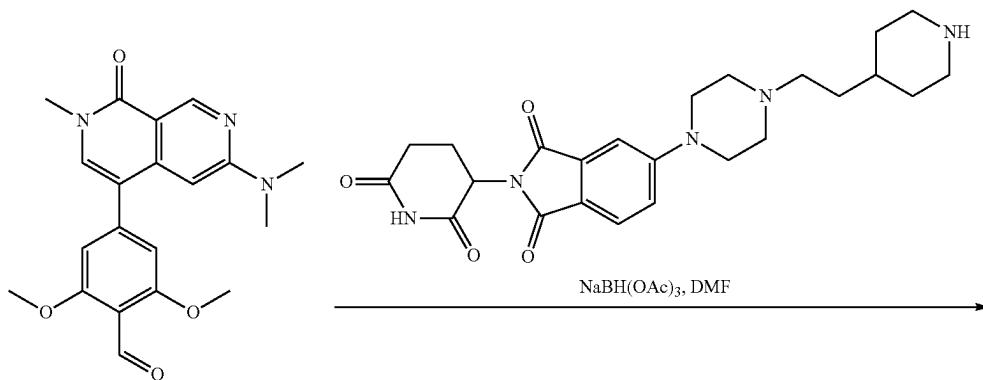
compound D19



Compound D19 was prepared in a similar manner to Example 26. 5-((5-[9-([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl)methyl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-5-oxopentyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (8.1 mg, 11.1%) was obtained as a white solid. LCMS (ESI) m/z: [M+H]⁺=864.55. ¹H NMR (400 MHz, Methanol-d4) δ 9.14 (d, J=1.8 Hz, 1H), 8.56 (brs, 0.5H, FA), 7.80 (t, J=9.0 Hz, 1H), 7.44 (d, J=2.6 Hz, 1H), 7.40 (dd, J=4.2, 2.2 Hz, 1H), 7.35-7.28 (m, 1H), 6.85 (d, J=6.7 Hz, 2H), 6.49 (s, 1H), 5.15-5.06 (m, 1H), 4.31-4.11 (m, 4H), 3.94 (d, J=4.9 Hz,

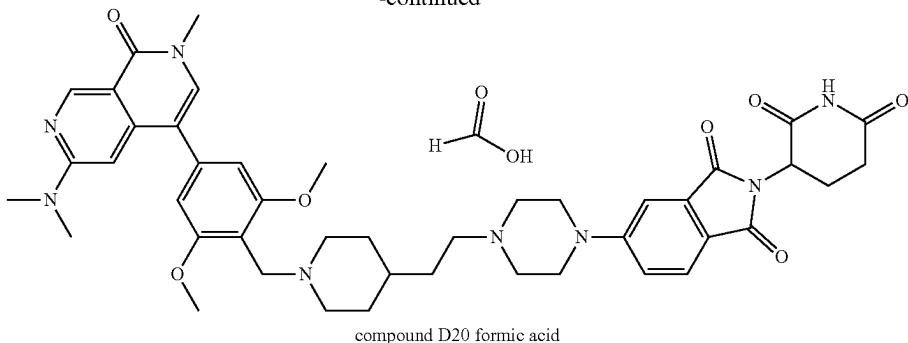
40 6H), 3.81-3.71 (m, 2H), 3.64-3.56 (m, 5H), 3.55-3.45 (m, 2H), 3.25-3.00 (m, 10H), 2.94-2.82 (m, 1H), 2.81-2.66 (m, 2H), 2.62-2.45 (m, 2H), 2.18-1.99 (m, 3H), 1.96-1.71 (m, 6H).

Example 31—Preparation of 5-(4-(2-(1-(4-(6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)piperidin-4-yl)ethyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione formic acid (Compound D20 Formic Acid)



465**466**

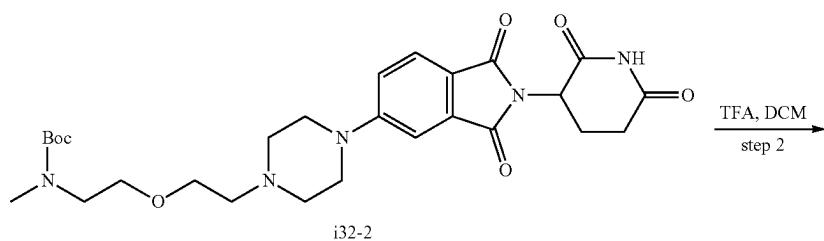
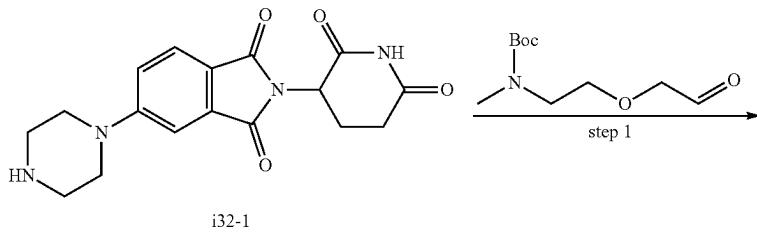
-continued



To a mixture of 4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (30.0 mg, 0.082 mmol, 1.00 equiv) in DMF (1.00 mL) was added 2-(2,6-dioxo piperidin-3-yl)-5-[4-[2-(piperidin-4-yl)ethyl]piperazin-1-yl]isoindole-1,3-dione (37.0 mg, 0.082 mmol, 1.00 equiv). The resulting mixture was stirred for 1 hour, and NaBH(OAc)₃ (34.6 mg, 0.163 mmol, 2.00 equiv) was added. The resulting mixture was stirred overnight at room temperature. Without any additional work-up, the mixture was purified by prep-HPLC (conditions: Phenomenex Gemini C6-Phenyl, 21.2*250 mm, 5 μ m; Mobile Phase A: Water (0.05% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 11% B to 17% B in 17 minutes; 254 nm; R_T: 14.2 minutes) to afford 5-(4-(2-(1-(4-(6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)piperidin-4-yl)ethyl)piperazin-1-

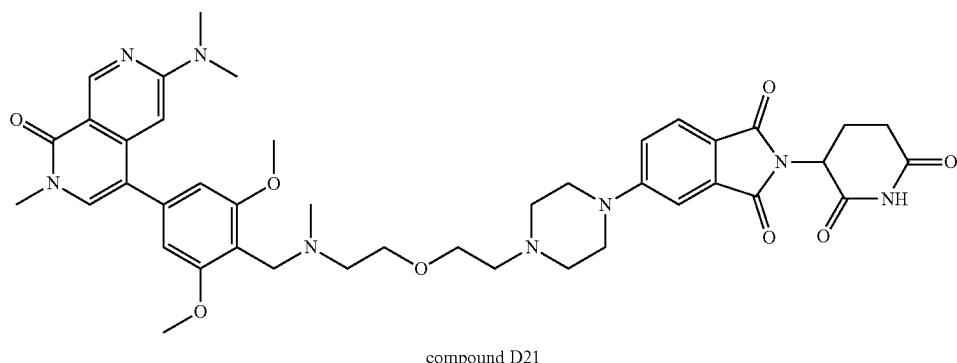
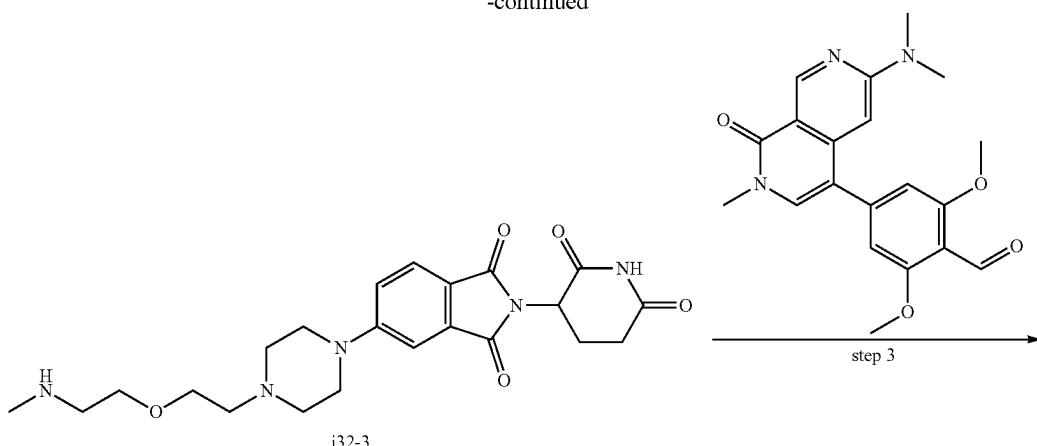
yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione; formic acid (9.0 mg, 13.8%) as a yellow solid. ¹H NMR (300 MHz, DMSO-d₆) δ 11.09 (s, 1H), 9.45 (brs, 0.6H, FA salt), 9.05 (s, 1H), 8.14 (s, 0.7H, FA), 7.75 (d, J=8.5 Hz, 1H), 7.61 (s, 1H), 7.46 (s, 1H), 7.34 (d, J=8.9 Hz, 1H), 6.90 (s, 2H), 6.52 (d, J=6.4 Hz, 1H), 5.09 (dd, J=12.7, 5.4 Hz, 1H), 4.21 (s, 3H), 3.91 (s, 7H), 3.50 (s, 4H), 3.47-3.37 (m, 4H), 3.20-3.05 (m, 9H), 3.04-2.86 (m, 4H), 2.74-2.54 (m, 3H), 2.09-1.98 (m, 1H), 1.97-1.75 (m, 3H), 1.70-1.48 (m, 4H). LCMS (ESI) m/z: [M+H]⁺=805.55.

Example 32—Preparation of 5-[4-(2-[(4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl]methyl)(methyl)amino]ethoxy]ethyl)piperazin-1-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (Compound D21)



467

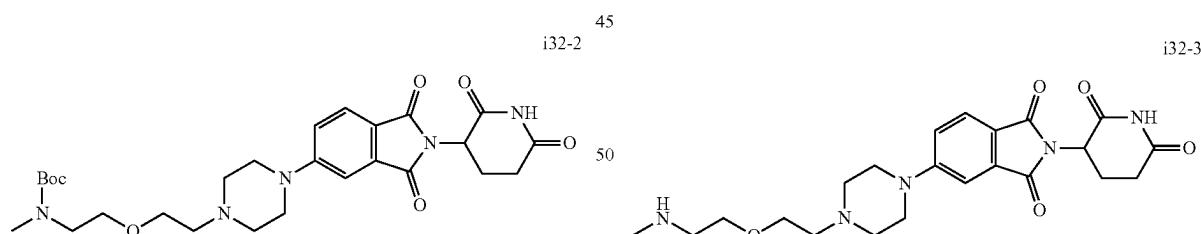
-continued

468

Step 1: Preparation of tert-butyl N-[2-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]piperazin-1-yl]ethoxy)ethyl]-N-methylcarbamate (i32-2)

40

Step 2: Preparation of 2-(2,6-dioxopiperidin-3-yl)-5-(4-[2-[2-(methylamino)ethoxy]ethyl]piperazin-1-yl)isoindole-1,3-dione (i32-3)

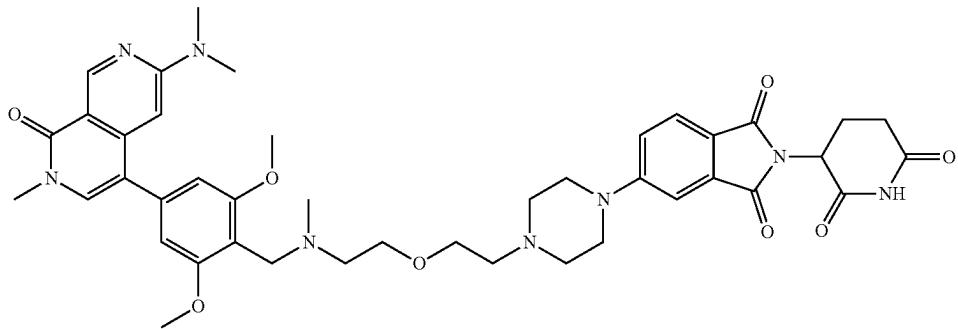


To a solution of 2-(2,6-dioxopiperidin-3-yl)-5-(piperazin-1-yl)isoindole-1,3-dione (50.00 mg, 0.146 mmol, 1.00 equiv) and tert-butyl N-methyl-N-[2-(2-oxoethoxy)ethyl] carbamate (47.60 mg, 0.219 mmol, 1.50 equiv), in DMF (2.00 mL) was added NaBH₃CN (18.36 mg, 0.292 mmol, 2.00 equiv), and the resulting solution was stirred at 25° C. for 3 hours. The resulting mixture was concentrated. The residue was applied onto a silica gel column with CH₂Cl₂/MeOH (20:1). This resulted in tert-butyl N-[2-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]piperazin-1-yl]ethoxy)ethyl]-N-methylcarbamate (45 mg, 56.68%) as a yellow solid. LCMS (ESI) m/z: [M+H]⁺= 544.50.

A solution of tert-butyl N-[2-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]piperazin-1-yl]ethoxy)ethyl]-N-methylcarbamate (45.00 mg, 0.083 mmol, 1.00 equiv) in TFA (1.00 mL) and CH₂Cl₂ (1.00 mL) was stirred at 25° C. for 1 hour. The resulting mixture was concentrated, and the crude material was used directly without further purification. 2-(2,6-dioxopiperidin-3-yl)-5-(4-[2-[2-(methylamino)ethoxy]ethyl]piperazin-1-yl)isoindole-1,3-dione was obtained as a yellow solid. LCMS (ESI) m/z: [M+H]⁺= 444.50.

469

Step 3: Preparation of 5-[4-(2-[(4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl)methyl](methyl)amino]ethoxy]ethyl)piperazin-1-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (Compound D21)

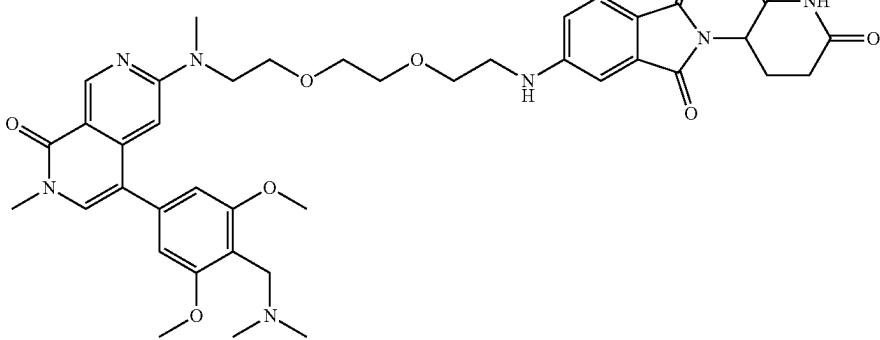


compound D21

470

To a solution of 2-(2,6-dioxopiperidin-3-yl)-5-(4-[2-[2-(methylamino)ethoxy]ethyl]piperazin-1-yl)isoindole-1,3-dione (50.00 mg, 0.113 mmol, 1.00 equiv) and 4-(6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzaldehyde (49.70 mg, 0.135 mmol, 1.20 equiv) in DMF (2.00 mL) was added NaBH₃CN (14.17 mg, 0.225 mmol, 2.00 equiv), and the resulting solution was stirred at 25° C. for 3 hours. The resulting mixture was concentrated. The crude product was purified by preparative HPLC (conditions: XSelect CSH Prep C18 OBD Column, 5 μm, 19*150 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 20% B to 55% B in 8 minutes; 254 nm; R_f: 7.12 minutes). This resulted in 5-[4-(2-[2-[(4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl)methyl](methyl)amino]ethoxy]ethyl)piperazin-1-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (10 mg, 18.60%) as a yellow solid. ¹H NMR (400 MHz, DMSO-d6) δ 11.07 (s, 1H), 9.04 (s, 1H), 8.14 (brs, 0.2H, FA), 7.67 (d, J=8.5 Hz, 1H), 7.58 (s, 1H), 7.32 (d, J=2.3 Hz, 1H), 7.23 (dd, J=8.7, 2.3 Hz, 1H), 6.85 (s, 2H), 6.46 (s, 1H), 5.07 (dd, J=12.9, 5.4 Hz, 1H), 4.39-4.01 (m, 2H), 3.88 (s, 7H), 3.76 (s, 3H), 3.62 (t, J=5.7 Hz, 3H), 3.48 (s, 5H), 3.37-3.26 (m, 4H), 3.06 (s, 6H), 2.94-2.84 (m, 1H), 2.63-2.56 (m, 8H), 2.07-1.98 (m, 1H). LCMS (ESI) m/z: [M+H]⁺=795.45.

Example 33—Preparation 5-[10-(5-[4-(dimethylamino)methyl]-3,5-dimethoxyphenyl)-7-methyl-8-oxo-2,7-naphthyridin-3-yl)-4,7-dioxa-1,10-diazaundecan-1-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (Compound D22 Formic Acid)



compound D22 formic acid

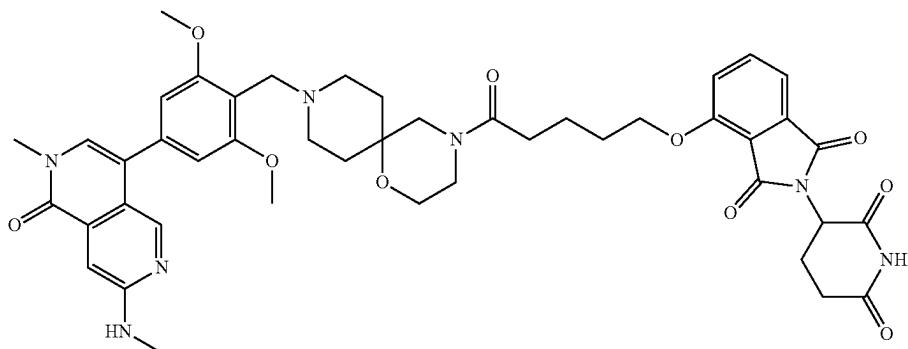
Compound D22 was prepared in a similar manner to Example 21. ¹H NMR (400 MHz, Methanol-d4) δ 9.06 (s, 1H), 8.55 (brs, 1.7H, FA), 7.45 (d, J=8.4 Hz, 1H), 7.40 (s, 1H), 6.89 (d, J=2.2 Hz, 1H), 6.83 (s, 2H), 6.74 (dd, J=8.4, 2.2 Hz, 1H), 6.51 (d, J=0.7 Hz, 1H), 5.03 (dd, J=12.7, 5.5 Hz, 1H), 4.56 (s, 2H), 3.95 (s, 6H), 3.72-3.62 (m, 8H), 3.58-3.52 (m, 5H), 3.29 (t, J=5.3 Hz, 2H), 3.13 (s, 9H), 2.95-2.81 (m, 1H), 2.79-2.61 (m, 2H), 2.13-2.04 (m, 1H). LCMS (ESI) m/z: [M+H]⁺=770.45.

471

Example 34—Preparation 5-[15-[9-([2,6-dimethoxy-
4-[2-methyl-7-(methylamino)-1-oxo-2,6-naphthyridin-4-yl]phenyl)methyl]-1-oxa-4,9-diazaspiro[5.5]
undecan-4-yl]-5-oxopentyl]oxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid
(Compound D23 Formic Acid)

472

compound D28

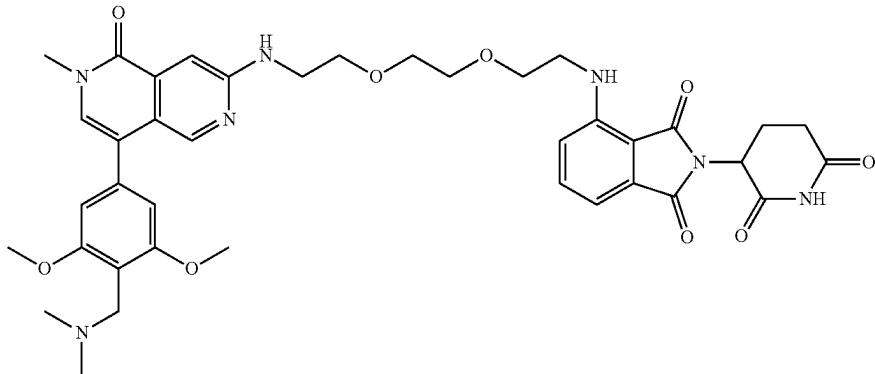


Compound D22 was prepared in a similar manner to Example 26. ¹H NMR (400 MHz, Methanol-d4) δ 8.58 (brs, 1H, formic acid), 8.51 (s, 1H), 7.80 (t, J=8.9 Hz, 1H), 7.43-7.39 (m, 1H), 7.35-7.29 (m, 1H), 7.24 (d, J=5.0 Hz, 1H), 7.10 (d, J=3.2 Hz, 1H), 6.83 (d, J=8.3 Hz, 2H), 5.10 (dt, J=11.0, 5.5 Hz, 1H), 4.22 (t, J=6.2 Hz, 3H), 4.10 (s, 1H), 3.93 (d, J=6.8 Hz, 6H), 3.81-3.75 (m, 1H), 3.75-3.70 (m, 1H), 3.65 (s, 3H), 3.63-3.49 (m, 4H), 3.22-3.03 (m, 4H), 2.97 (s, 3H), 2.90-2.71 (m, 3H), 2.52 (dt, J=30.3, 7.1 Hz, 2H), 2.18-2.08 (m, 1H), 2.07-1.97 (m, 2H), 1.96-1.69 (m, 6H). LCMS (ESI) m/z: [M+H]⁺=850.45.

35

Example 35—Preparation of 4-[2-[2-[2-[(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)amino]ethoxy]ethoxy]ethyl]amino]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (Compound D24)

compound D24



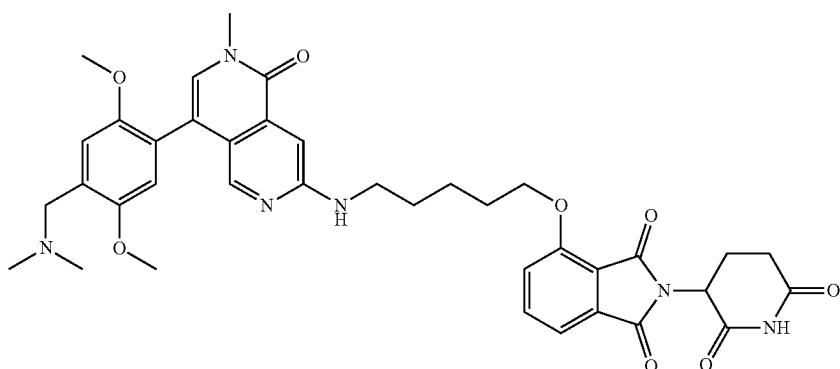
Compound D24 was prepared in a similar manner to Example 21. ¹H NMR (400 MHz, Methanol-d4) δ 8.44 (d, J=0.9 Hz, 1H), 7.52-7.42 (m, 1H), 7.23 (d, J=0.9 Hz, 1H), 7.07 (s, 1H), 6.97 (dd, J=18.7, 7.8 Hz, 2H), 6.83 (s, 2H), 5.02-4.96 (m, 1H), 4.28-4.11 (m, 2H), 3.96 (s, 6H), 3.80-3.75 (m, 4H), 3.74-3.70 (m, 4H), 3.61 (s, 3H), 3.55 (t, J=5.3 Hz, 2H), 3.47 (t, J=5.1 Hz, 2H), 2.81-2.63 (m, 9H), 2.12-2.04 (m, 1H). LCMS (ESI) m/z: [M+H]⁺=756.33.

60

65

473

Example 36—Preparation of 4-((5-((8-(4-((dimethylamino)methyl)-2,5-dimethoxyphenyl)-6-methyl-5-oxo-5,6-dihydro-2,6-naphthyridin-3-yl)amino)pentyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (Compound D25)



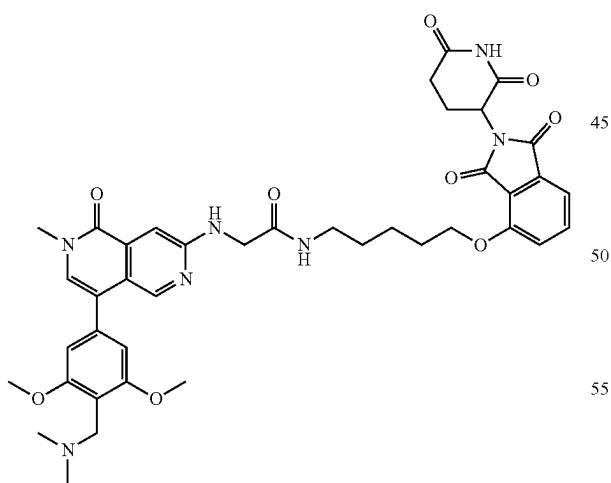
474

compound D25

Compound D25 was prepared in a similar manner to Example 17. ¹H NMR (300 MHz, Methanol-d4) δ 7.94 (s, 1H), 7.76 (dd, J=8.6, 7.2 Hz, 1H), 7.54 (s, 1H), 7.46-7.40 (m, 2H), 7.24 (s, 1H), 7.15 (s, 1H), 7.08 (s, 1H), 5.11 (d, J=10.8 Hz, 1H), 4.42 (s, 2H), 4.28 (t, J=5.8 Hz, 2H), 3.95 (s, 3H), 3.77 (s, 3H), 3.61 (s, 3H), 3.46 (t, J=6.5 Hz, 2H), 2.94 (s, 6H), 2.92-2.83 (m, 1H), 2.80-2.76 (m, 1H), 2.75-2.68 (m, 1H), 2.18-2.07 (m, 1H), 2.01-1.90 (m, 2H), 1.87-1.72 (m, 4H). LCMS (ESI) m/z: [M+H]⁺=711.85.

Example 37—Preparation 2-[(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)amino]-N-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]pentyl) acetamide (Compound D26)

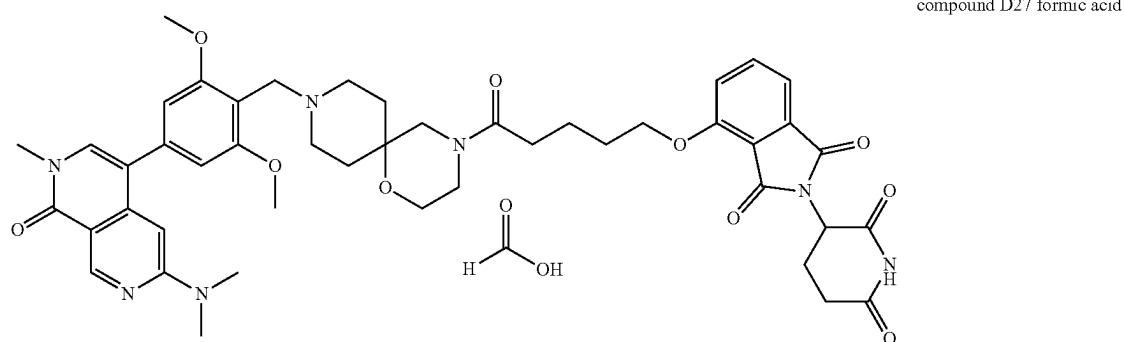
compound D26 40



Compound D26 was prepared in a similar manner to Example 22. ¹H NMR (300 MHz, Methanol-d4) δ 8.53 (br s, 1.3H, FA), 8.50 (s, 1H), 7.78 (dd, J=8.6, 7.2 Hz, 1H), 7.48-7.43 (m, 2H), 7.37 (s, 1H), 7.15 (s, 1H), 6.88 (s, 2H), 5.10 (dd, J=12.3, 5.4 Hz, 1H), 4.81 (s, 2H), 4.27 (t, J=5.9 Hz, 2H), 4.08 (s, 2H), 3.94 (s, 6H), 3.65 (s, 3H), 3.27 (s, 6H), 2.95-2.64 (m, 4H), 2.19-2.07 (m, 1H), 1.96-1.87 (m, 2H), 1.79-1.58 (m, 5H). LCMS (ESI) m/z: [M+H]⁺=768.40.

475

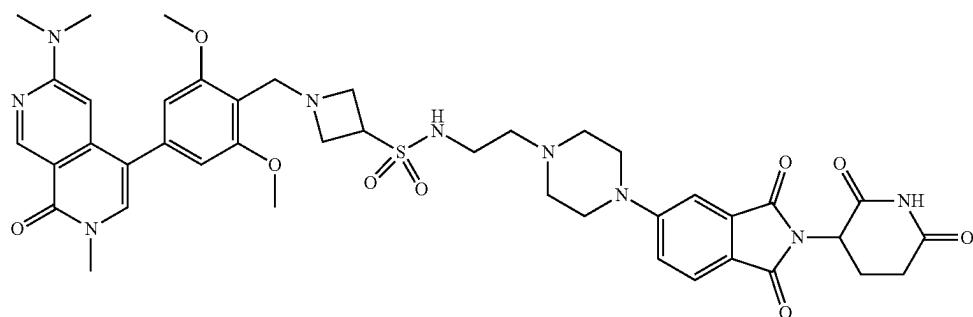
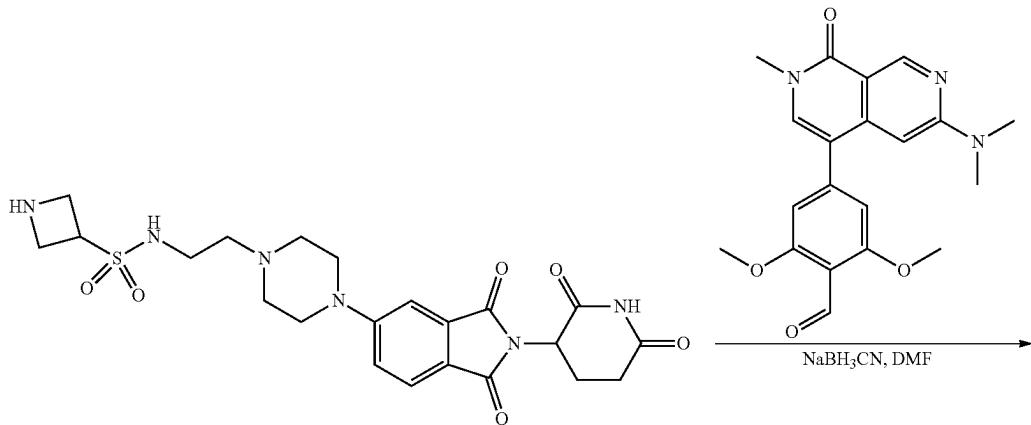
Example 38—Preparation 4-((5-(9-(4-(6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-5-oxopentyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione formic acid (Compound D27 Formic Acid)



Compound D27 was prepared in a similar manner to Example 23. ^1H NMR (300 MHz, Methanol-d4) δ 9.15 (s, 1H), 8.55 (brs, 1.0H, formic acid), 7.79 (t, $J=7.9$ Hz, 1H), 7.46 (d, $J=8.4$ Hz, 3H), 6.87 (d, $J=7.2$ Hz, 2H), 6.49 (s, 1H), 5.12 (dd, $J=12.1$, 5.4 Hz, 1H), 4.36-4.23 (m, 4H), 3.95 (d, $J=6.4$ Hz, 6H), 3.82-3.72 (m, 2H), 3.66-3.60 (m, 2H), 3.59 (s, 3H), 3.52 (s, 2H), 3.30-3.16 (m, 4H), 3.12 (s, 6H),

2.91-2.59 (m, 5H), 2.20-2.03 (m, 3H), 2.00-1.76 (m, 6H).
LCMS (ESI) m/z: [M+H] $=864.40$.

Example 39—Preparation of 1-([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)-N-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]piperazin-1-yl]ethyl)azeti dine-3-sulfonamide (Compound D28)



compound D28

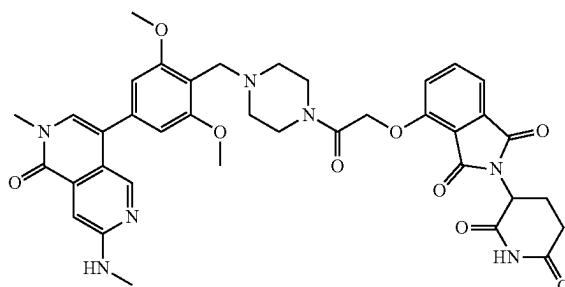
477

A solution of N-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethyl)azetidine-3-sulfonamide (60.00 mg, 0.119 mmol, 1.00 equiv) and 4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (52.43 mg, 0.143 mmol, 1.20 equiv) in DMF (1.50 mL) was stirred for 20 minute at room temperature. Then NaBH₃CN (14.95 mg, 0.238 mmol, 2.00 equiv) was added to the reaction mixture. The resulting mixture was stirred for 1 hour at room temperature. The crude product was purified by Prep-HPLC (conditions: Column, Phenomenex Gemini C6-Phenyl, 21.2*250 mm, 5 μ m; mobile phase, Water (0.05% FA) and ACN (5% PhaseB up to 23% in 20 minutes); Detector, UV). This resulted in 1-[4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)-N-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethyl)azetidine-3-sulfonamide (13.4 mg, 13.16%) as a green solid. ¹H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 9.02 (s, 1H), 8.26 (s, 0.3H, FA), 7.66 (d, J=8.5 Hz, 1H), 7.55 (s, 1H), 7.33 (d, J=2.3 Hz, 1H), 7.23 (dd, J=8.7, 2.3 Hz, 1H), 7.07 (t, J=5.9 Hz, 1H), 6.75 (s, 2H), 6.47 (s, 1H), 5.07 (dd, J=12.9, 5.4 Hz, 1H), 4.01 (q, J=7.2 Hz, 1H), 3.81 (s, 6H), 3.62 (s, 2H), 3.49-3.45 (m, 5H), 3.44-3.39 (m, 7H), 3.06 (s, 8H), 2.94-2.82 (m, 1H), 2.59 (d, J=16.8 Hz, 3H), 2.55 (s, 2H), 2.42 (t, J=6.7 Hz, 2H), 2.07-1.97 (m, 1H). LCMS (ESI) m/z: [M+H]⁺=856.34.

478

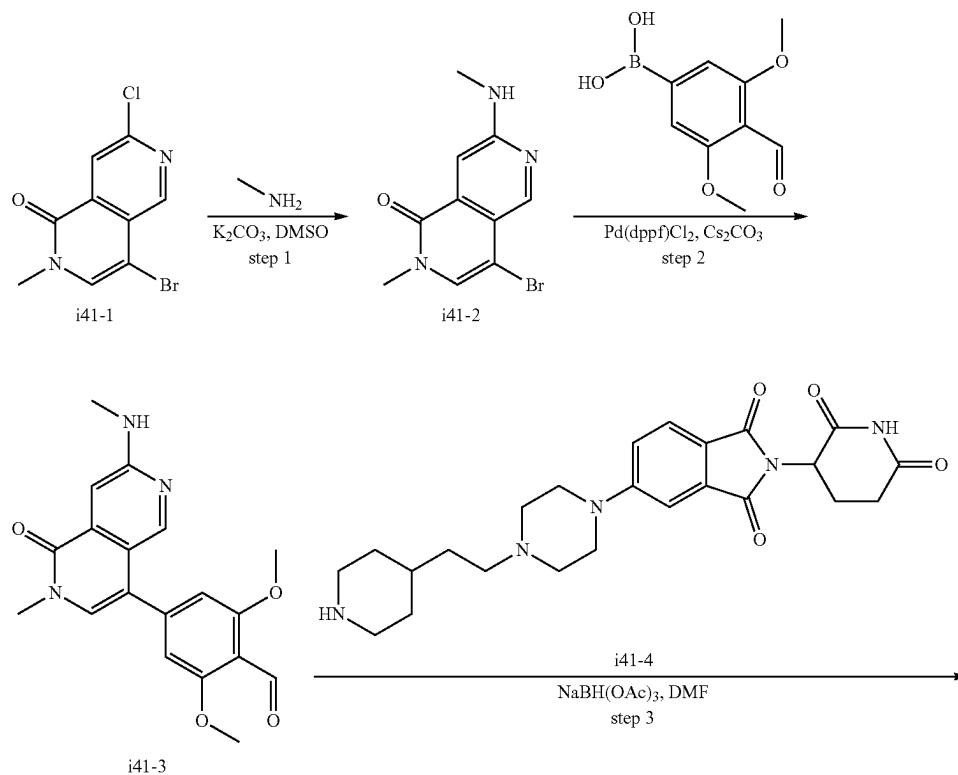
Example 40—Preparation 4-[2-[4-[2,6-dimethoxy-4-[2-methyl-7-(methylamino)-1-oxo-2,6-naphthyridin-4-yl]phenyl]methyl)piperazin-1-yl]-2-oxoethoxy-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (Compound D29)

compound D29



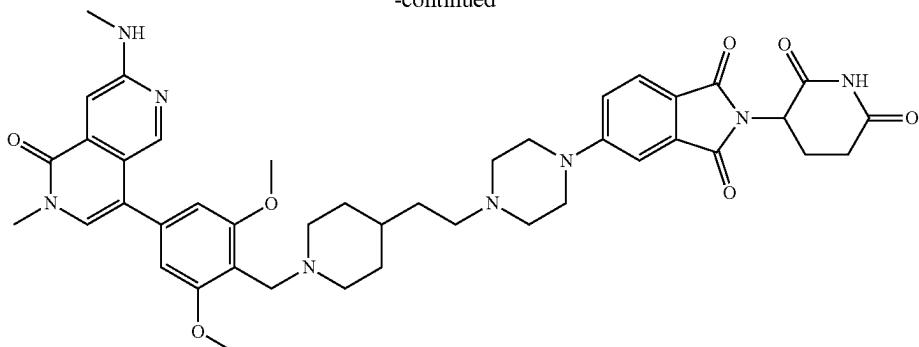
Compound D27 was prepared in a similar manner to Example 23. ¹H NMR (300 MHz, Methanol-d4) δ 8.55 (d, J=0.9 Hz, 1H), 7.79 (dd, J=8.5, 7.3 Hz, 1H), 7.52 (d, J=7.2 Hz, 1H), 7.40 (d, J=8.5 Hz, 1H), 7.24 (d, J=0.9 Hz, 1H), 7.10 (s, 1H), 6.81 (s, 2H), 5.16-5.07 (m, 3H), 4.06 (s, 2H), 3.91 (s, 6H), 3.83-3.69 (m, 4H), 3.65 (s, 3H), 3.00-2.85 (m, 7H), 2.83-2.68 (m, 3H), 2.21-2.07 (m, 1H). LCMS (ESI) m/z: [M+H]⁺=738.45.

Example 41—Preparation of 5-(4-[2-[1-([2,6-dimethoxy-4-[2-methyl-7-(methylamino)-1-oxo-2,6-naphthyridin-4-yl]phenyl)methyl)piperidin-4-yl]ethyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (Compound D30 Formic Acid)



479**480**

-continued



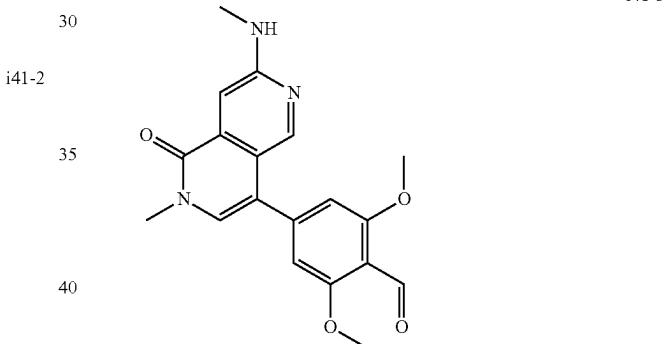
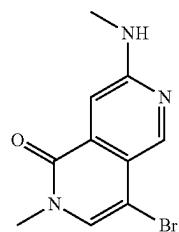
compound D30 formic acid

Step 1: Preparation of 4-bromo-2-methyl-7-(methylamino)-2,6-naphthyridin-1-one (i41-2)

20

Step 2: Preparation of 2, 6-dimethoxy-4-[2-methyl-7-(methylamino)-1-oxo-2, 6-naphthyridin-4-yl]benzaldehyde (i85-3)

25



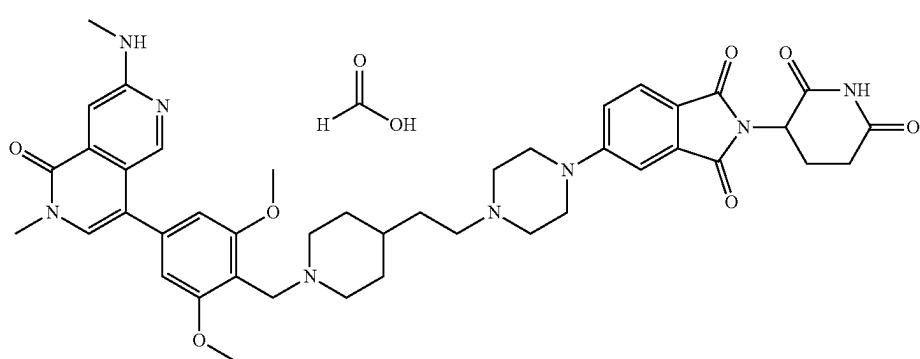
45

To a stirred solution of 4-bromo-7-chloro-2-methyl-2,6-naphthyridin-1-one (200.00 mg, 0.731 mmol, 1.00 equiv) and methanamine hydrochloride (493.73 mg, 7.312 mmol, 10.00 equiv) in DMSO (15.00 mL) was added K_2CO_3 (2021.21 mg, 14.625 mmol, 20.00 equiv). The resulting mixture was stirred for 16 hours at 130° C. under nitrogen atmosphere. The resulting mixture was diluted with water (50 mL). The aqueous layer was extracted with EtOAc (4×15 mL). The resulting mixture was washed with brine (15 mL). The resulting mixture was concentrated under reduced pressure to afford 4-bromo-2-methyl-7-(methylamino)-2,6-naphthyridin-1-one (100 mg, 51.01%) as a yellow solid.

To a stirred solution of 4-bromo-2-methyl-7-(methylamino)-2,6-naphthyridin-1-one (100.00 mg, 0.373 mmol, 1.00 equiv) and 4-formyl-3,5-dimethoxyphenylboronic acid (93.99 mg, 0.448 mmol, 1.20 equiv) in 1,4-dioxane/H₂O (4:1) (5.00 mL) was added cesium carbonate (243.80 mg, 0.746 mmol, 2.00 equiv) and Pd(dppf)Cl₂ (27.29 mg, 0.037 mmol, 0.10 equiv). The resulting mixture was stirred for 16 hours at 90° C. under nitrogen atmosphere. The resulting mixture was diluted with water (15 mL). The aqueous layer was extracted with EtOAc (3×20 mL). The organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM:MeOH (40:1 to 10:1) to afford 2,6-dimethoxy-4-[2-methyl-7-(methylamino)-1-oxo-2,6-naphthyridin-4-yl]benzaldehyde (30 mg, 22.76%) as a yellow solid.

481

Step 3: Preparation of 5-(4-[2-[1-([2,6-dimethoxy-4-[2-methyl-7-(methylamino)-1-oxo-2,6-naphthyridin-4-yl]phenyl)methyl]piperidin-4-yl]ethyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (Compound D30 Formic Acid)



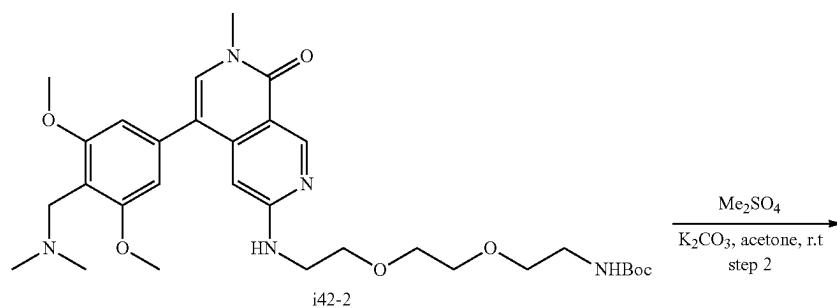
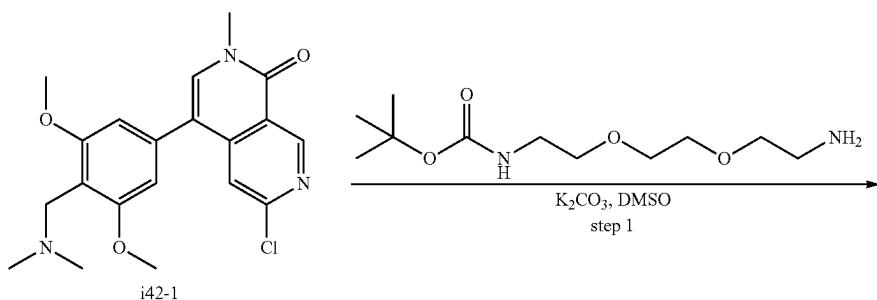
compound D30 formic acid

482

A solution of 2,6-dimethoxy-4-[2-methyl-7-(methylamino)-1-oxo-2,6-naphthyridin-4-yl]benzaldehyde (25.00 mg, 0.071 mmol, 1.00 equiv) and 2-(2,6-dioxopiperidin-3-yl)-5-[4-[2-(piperidin-4-yl)ethyl]piperazin-1-yl]isoindole-1,3-dione (32.09 mg, 0.071 mmol, 1.00 equiv) in DMF (1.00 mL) was stirred for 1 hour at 20° C. under nitrogen atmosphere. To the above mixture was added NaBH(OAc)₃ (29.99 mg, 0.141 mmol, 2 equiv). The resulting mixture was stirred for additional 1 hour at 20° C. The crude product was purified by Prep-HPLC (conditions: SunFire C18 OBD Prep Column, 100 Å, 5 µm, 19 mm×250 mm; Mobile Phase A: Water (0.05% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 9 B to 16 B in 13 minutes; 254 nm; R_f: 11.47 minutes) to afford 5-(4-[2-[1-([2,6-dimethoxy-4-[2-methyl-7-(methylamino)-1-oxo-2,6-naphthyridin-4-yl]phenyl)methyl]piperidin-4-yl]ethyl)piperazin-1-yl)-2-(2,6-

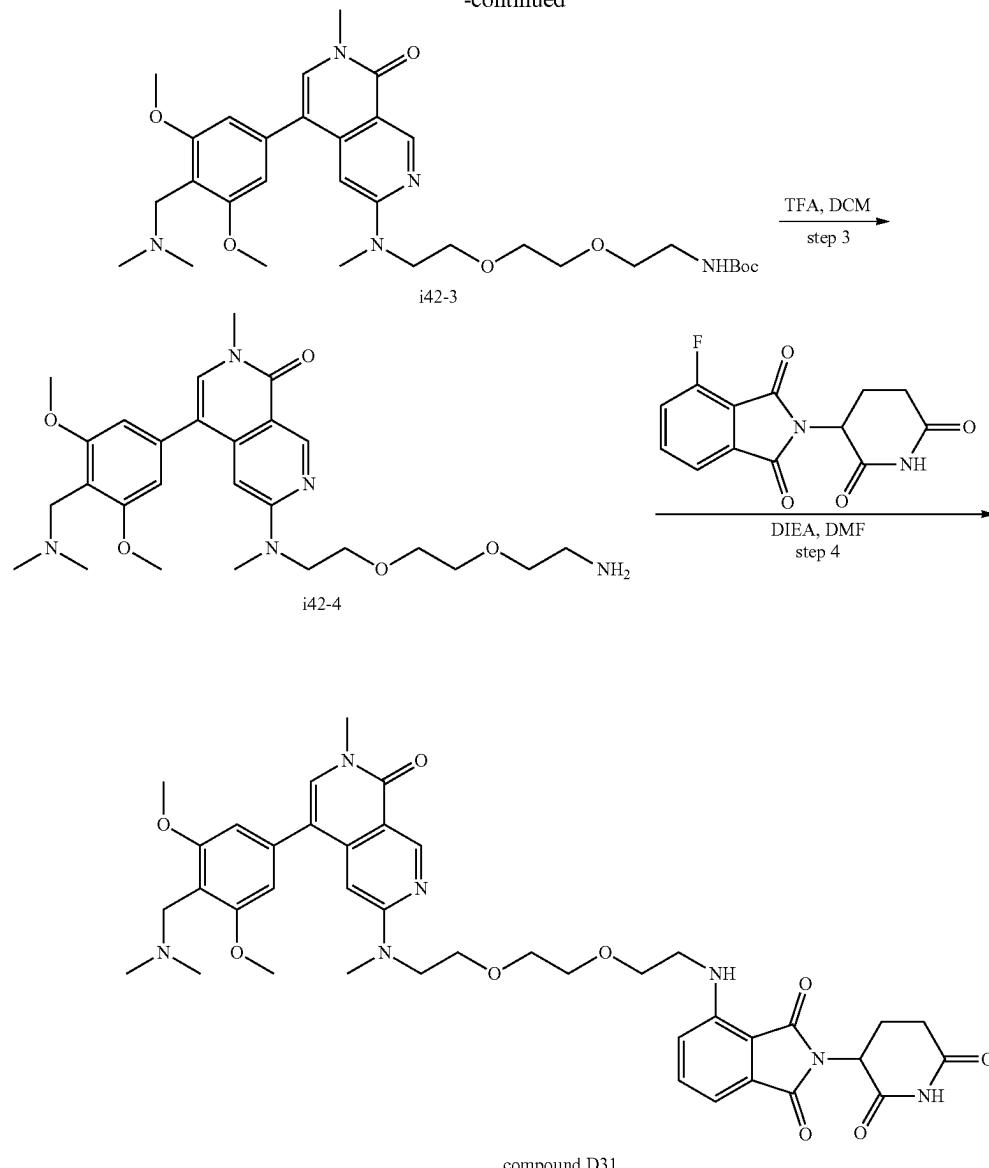
dioxopiperidin-3-yl)isoindole-1,3-dione (11.7 mg, 20.91%) as a yellow solid. ¹H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.54 (s, 1H), 8.15 (s, 0.9H, FA), 7.68 (d, J=8.4 Hz, 1H), 7.34 (d, J=2.4 Hz, 1H), 7.28-7.23 (m, 1H), 7.18 (s, 1H), 7.13 (s, 1H), 6.93 (d, J=5.1 Hz, 1H), 6.78 (s, 2H), 5.07 (dd, J=12.8, 5.4 Hz, 1H), 3.85 (s, 9H), 3.53 (s, 4H), 3.44-3.42 (m, 5H), 3.12-3.08 (m, 2H), 2.91-2.87 (m, 1H), 2.85 (d, J=4.9 Hz, 3H), 2.64-2.53 (m, 3H), 2.37-2.32 (m, 3H), 2.04-1.99 (m, 1H), 1.77-1.70 (m, 2H), 1.47-1.37 (m, 3H), 1.32-1.23 (m, 3H). LCMS (ESI) m/z: [M+H]⁺=791.50.

Example 42—Preparation of 4-[10-(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naphthyridin-3-yl)-4,7-dioxa-1,10-diazaundecan-1-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (Compound D31)



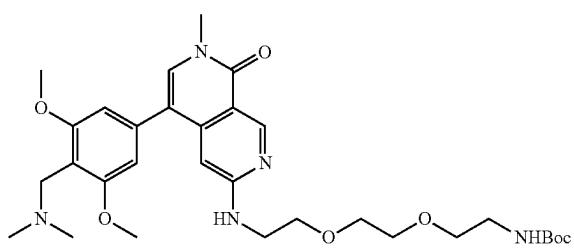
483**484**

-continued



Step 1: Preparation of tert-butyl N-[2-(2-[2-[(5-[dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naphthyridin-3-yl)amino]ethoxy]ethoxyethylcarbamate (i42-2)

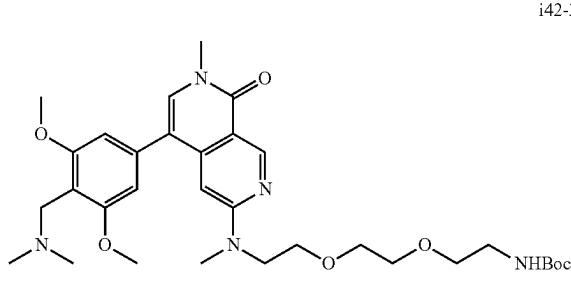
To a stirred solution of 6-chloro-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-2,7-naphthyridin-1-one (335.0 mg, 0.864 mmol, 1.00 equiv) and tert-butyl N-[2-(2-aminoethoxy)ethoxy]ethylcarbamate (643.4 mg, 2.591 mmol, 3.00 equiv) in DMSO (2 mL) was added K₂CO₃ (238.7 mg, 1.727 mmol, 2.00 equiv) at room temperature. The resulting mixture was stirred overnight at 130 degrees C. The mixture was allowed to cool down to room temperature. The resulting mixture was filtered, and the filter cake was washed with CH₂Cl₂ (2×3 mL). The filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography (conditions: column, C18 silica gel; Mobile Phase A: Water/0.05% TFA, Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 0% B to 40% B in 15 min; detector, 254 nm) to afford tert-butyl N-[2-(2-[2-[(5-[dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naphthyridin-3-yl)amino]ethoxy]ethoxyethylcarbamate (380 mg, 73.36%) as a yellow oil. LCMS (ESI) m/z: [M+H]⁺=600.



485

Step 2: Preparation of tert-butyl N-[2-(2-[2-[5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naphthyridin-3-yl](methyl)amino]ethoxy]ethoxyethyl]carbamate (i42-3)

5



To a stirred solution/mixture of tert-butyl N-[2-(2-[5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naphthyridin-3-yl)amino]ethoxy]ethoxyethyl]carbamate (190.0 mg, 0.317 mmol, 1.00 equiv) and K_2CO_3 (87.6 mg, 0.634 mmol, 2 equiv) in acetone (3 mL) was added dimethyl sulfate (44.0 mg, 0.348 mmol, 1.10 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with water at room temperature. The aqueous layer was extracted with CH_2Cl_2 /isopropanol (3×5 mL). The combined organic layers were washed with brine (1×10 mL) and dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure to afford tert-butyl N-[2-(2-[5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naphthyridin-3-yl)(methyl)amino]ethoxy]ethoxyethyl]carbamate (95.00 mg, 48.86%) as a yellow oil. The crude product was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H]⁺=614.

25

30

35

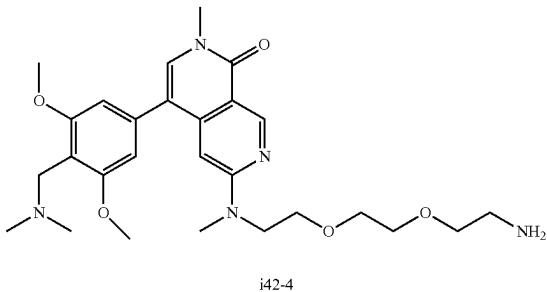
40

45

486

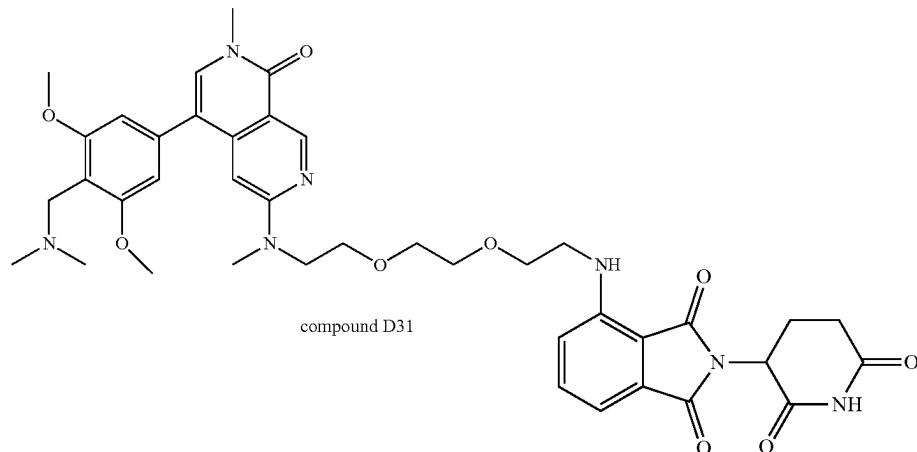
Step 3: Preparation of 3,3,3-trifluoropropionic acid; 6-([2-[2-(2-aminoethoxy)ethoxy]ethyl](methyl)amino)-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-2,7-naphthyridin-1-one (i42-4)

5



To a stirred solution of tert-butyl N-[2-(2-[5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naphthyridin-3-yl)amino]ethoxy]ethoxyethyl]carbamate (75.00 mg, 0.122 mmol, 1.00 equiv) in dichloromethane (3 mL) was added TFA (1 mL) dropwise at room temperature. The resulting mixture was concentrated under vacuum to afford 3,3,3-trifluoropropionic acid; 6-([2-[2-(2-aminoethoxy)ethoxy]ethyl](methyl)amino)-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-2,7-naphthyridin-1-one (103 mg, crude) as yellow oil. The crude product was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H]⁺=514.

Step 4: Preparation of 4-[10-(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naphthyridin-3-yl)-4,7-dioxa-1,10-diazaundecan-1-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (Compound D31)



487

To a stirred solution of 6-([2-[2-(2-aminoethoxy)ethoxy]ethyl](methyl)amino)-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-2,7-naphthyridin-1-one (68.00 mg, 0.132 mmol, 1.00 equiv) in DMF (1 mL) was added 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindole-1,3-dione (34.6 mg, 0.125 mmol, 0.95 equiv) and DIEA (85.6 mg, 0.662 mmol, 5.00 equiv) at room temperature. The resulting mixture was stirred for overnight at 80 degrees C. The crude product was purified by Prep-HPLC (conditions: Xselect CSH F-Phenyl OBD Column 19*150 mm 5 um; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 9 B to 19 B in 12 min; 254 nm; R_f: 12.63 minutes) to afford 4-[10-(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naph-

488

thyridin-3-yl)-4,7-dioxa-1,10-diazaundecan-1-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (3.2 mg, 3.14%) as a yellow solid. ¹H NMR (400 MHz, Methanol-d4) δ 8.96 (s, 1H), 7.54-7.46 (m, 2H), 6.99 (dd, J=15.8, 7.7 Hz, 2H), 6.84 (s, 2H), 6.74 (s, 1H), 4.96-4.94 (m, 1H), 4.57 (s, 2H), 3.97 (s, 6H), 3.77-3.69 (m, 8H), 3.59-3.53 (m, 5H), 3.41 (t, J=5.2 Hz, 2H), 3.17-3.11 (m, 9H), 2.83-2.53 (m, 3H), 2.04-1.95 (m, 1H). LCMS (ESI) m/z: [M+H]⁺=770.50.

¹⁰ Example 43—Preparation of Compounds D32-D184

In analogy to the procedures described in the examples above, compounds D32-D184 were prepared using the appropriate starting materials

Compound No.	LCMS ¹ H NMR
D32	856.34 ¹ H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 9.02 (s, 1H), 8.26 (s, 0.3H, FA), 7.66 (d, J = 8.5 Hz, 1H), 7.55 (s, 1H), 7.33 (d, J = 2.3 Hz, 1H), 7.23 (dd, J = 8.7, 2.3 Hz, 1H), 7.07 (t, J = 5.9 Hz, 1H), 6.75 (s, 2H), 6.47 (s, 1H), 5.07 (dd, J = 12.9, 5.4 Hz, 1H), 4.01 (q, J = 7.2 Hz, 1H), 3.81 (s, 6H), 3.62 (s, 2H), 3.49-3.45 (m, 5H), 3.44-3.39 (m, 7H), 3.06 (s, 8H), 2.94-2.82 (m, 1H), 2.59 (d, J = 16.8 Hz, 3H), 2.55 (s, 2H), 2.42 (t, J = 6.7 Hz, 2H), 2.07-1.97 (m, 1H).
D33	836.6 ¹ H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.03 (d, J = 1.6 Hz, 1H), 8.20 (s, 0.8H, FA), 7.82 (dd, J = 8.3, 2.3 Hz, 1H), 7.58 (s, 1H), 7.43 (d, J = 2.6 Hz, 1H), 7.35 (dd, J = 8.3, 2.3 Hz, 1H), 6.75 (s, 2H), 6.43 (s, 1H), 5.12 (dd, J = 12.9, 5.3 Hz, 1H), 4.38-4.17 (m, 3H), 3.98-3.88 (m, 1H), 3.79 (s, 6H), 3.77-3.65 (m, 6H), 3.65-3.60 (m, 3H), 3.26 (s, 2H), 3.05 (s, 6H), 2.99-2.79 (m, 4H), 2.63-2.52 (m, 4H), 2.29-2.12 (m, 1H), 2.10-1.99 (m, 1H), 1.54-1.29 (m, 2H).
D34	834.37 ¹ H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.04 (s, 1H), 7.82 (dd, J = 8.5, 7.3 Hz, 1H), 7.69 (s, 1H), 7.59-7.50 (m, 2H), 7.45 (d, J = 7.2 Hz, 1H), 6.73 (s, 2H), 6.46 (s, 1H), 5.08 (dd, J = 12.9, 5.4 Hz, 1H), 4.21 (t, J = 6.4 Hz, 2H), 3.80 (s, 6H), 3.48 (s, 5H), 3.07 (s, 9H), 2.94-2.81 (m, 1H), 2.62-2.54 (m, 2H), 2.04 (s, 4H), 1.91 (s, 5H), 1.82-1.72 (m, 2H), 1.53-1.39 (m, 4H).
D35	847.35 ¹ H-NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.04 (s, 1H), 8.17 (s, 1H, FA), 7.64 (t, J = 5.8 Hz, 1H), 7.61-7.55 (m, 2H), 7.10 (d, J = 8.6 Hz, 1H), 7.02 (d, J = 7.0 Hz, 1H), 6.76 (s, 2H), 6.52 (t, J = 5.9 Hz, 1H), 6.47 (s, 1H), 5.05 (dd, J = 12.8, 5.4 Hz, 1H), 3.82 (s, 6H), 3.60 (s, 2H), 3.48 (s, 3H), 3.31-3.25 (m, 2H), 3.06 (s, 6H), 3.05-3.00 (m, 2H), 2.93-2.85 (m, 1H), 2.62-2.52 (m, 4H), 2.16 (s, 3H), 2.06-1.99 (m, 1H), 1.85 (s, 6H), 1.63-1.54 (m, 2H), 1.49-1.40 (m, 2H), 1.36-1.26 (m, 2H).
D36	848.4 ¹ H-NMR (400 MHz, DMSO-d6) δ 11.13 (s, 1H), 9.04 (s, 1H), 8.17 (s, 1H, FA), 7.81 (dd, J = 8.5, 7.2 Hz, 1H), 7.66 (t, J = 5.8 Hz, 1H), 7.57 (s, 1H), 7.52 (d, J = 8.5 Hz, 1H), 7.44 (d, J = 7.2 Hz, 1H), 6.76 (s, 2H), 6.47 (s, 1H), 5.08 (dd, J = 12.9, 5.4 Hz, 1H), 4.20 (t, J = 6.3 Hz, 2H), 3.82 (s, 6H), 3.63 (s, 2H), 3.48 (s, 3H), 3.09-3.01 (m, 8H), 2.94-2.83 (m, 1H), 2.63-2.52 (m, 4H), 2.18 (s, 3H), 2.06-1.98 (m, 1H), 1.86 (s, 6H), 1.77 (t, J = 6.9 Hz, 2H), 1.53-1.38 (m, 4H).
D37	875.7 ¹ H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.03 (s, 1H), 8.30 (s, 1H, FA), 7.59-7.51 (m, 2H), 7.19-7.09 (m, 2H), 7.03 (d, J = 7.0 Hz, 1H), 6.74 (s, 2H), 6.60 (t, J = 5.8 Hz, 1H), 6.46 (s, 1H), 5.05 (dd, J = 12.9, 5.4 Hz, 1H), 3.97 (t, J = 7.5 Hz, 1H), 3.80 (s, 6H), 3.63-3.55 (m, 6H), 3.54-3.51 (m, 2H), 3.48-3.45 (m, 6H), 3.44-3.42 (m, 5H), 3.06 (s, 8H), 2.93-2.83 (m, 1H), 2.62-2.54 (m, 2H), 2.06-1.97 (m, 1H).
D38	848.35 ¹ H-NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.03 (s, 1H), 8.17 (s, 1H, FA), 7.83 (d, J = 8.3 Hz, 1H), 7.67 (t, J = 5.8 Hz, 1H), 7.57 (s, 1H), 7.42 (d, J = 2.3 Hz, 1H), 7.34 (dd, J = 8.3, 2.3 Hz, 1H), 6.76 (s, 2H), 6.47 (s, 1H), 5.12 (dd, J = 12.9, 5.4 Hz, 1H), 4.16 (t, J = 6.4 Hz, 2H), 3.82 (s, 6H), 3.62 (s, 2H), 3.48 (s, 3H), 3.09-3.02 (m, 8H), 2.94-2.84 (m, 1H), 2.64-2.53 (m, 4H), 2.18 (s, 3H), 2.10-2.01 (m, 1H), 1.87 (s, 6H), 1.80-1.72 (m, 2H), 1.52-1.35 (m, 4H).
D39	847.4 ¹ H-NMR (400 MHz, DMSO-d6) δ 11.06 (s, 1H), 9.04 (s, 1H), 8.19 (s, 1H, FA), 7.64 (t, J = 5.8 Hz, 1H), 7.56 (d, J = 9.5 Hz, 2H), 7.10 (t, J = 5.2 Hz, 1H), 6.94 (d, J = 2.0 Hz, 1H), 6.84 (dd, J = 8.5, 2.1 Hz, 1H), 6.75 (s, 2H), 6.47 (s, 1H), 5.03 (dd, J = 12.9, 5.4 Hz, 1H), 3.81 (s, 6H), 3.57 (s, 2H), 3.48 (s, 3H), 3.17-3.11 (m, 2H), 3.06 (s, 6H), 3.05-3.01 (m, 2H), 2.92-2.83 (m, 1H), 2.61-2.52 (m, 4H), 2.15 (s, 3H), 2.01-1.95 (m, 1H), 1.85 (s, 6H), 1.62-1.53 (m, 2H), 1.49-1.40 (m, 2H), 1.39-1.30 (m, 2H).

Compound No.	LCMS	¹ H NMR
D40	834.37	¹ H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.04 (s, 1H), 7.84 (d, J = 8.3 Hz, 1H), 7.70 (s, 1H), 7.56 (s, 1H), 7.43 (s, 1H), 7.36 (d, J = 8.5 Hz, 1H), 6.73 (s, 2H), 6.50 (d, J = 31.5 Hz, 1H), 5.12 (dd, J = 13.1, 5.3 Hz, 1H), 4.18 (t, J = 6.5 Hz, 2H), 3.80 (s, 6H), 3.48 (s, 5H), 3.07 (s, 8H), 2.95-2.84 (m, 1H), 2.70-2.59 (m, 2H), 2.31-2.18 (m, 1H), 2.04 (s, 4H), 1.91 (s, 5H), 1.82-1.70 (m, 2H), 1.54-1.32 (m, 4H).
D41	793.55	¹ H NMR (300 MHz, Methanol-d4) δ 9.15 (s, 1H), 8.43 (s, 2H, FA), 7.2 (d, J = 8.5 Hz, 1H), 7.47 (s, 1H), 7.40 (d, J = 2.2 Hz, 1H), 7.28 (dd, J = 8.6, 2.3 Hz, 1H), 7.12 (s, 1H), 7.07 (dd, J = 10.0, 1.4 Hz, 1H), 6.44 (d, J = 0.7 Hz, 1H), 5.10 (dd, J = 12.4, 5.4 Hz, 1H), 4.38 (s, 2H), 4.02 (s, 3H), 3.64-3.49 (m, 9H), 3.19-3.08 (m, 8H), 2.92-2.68 (m, 7H), 2.66-2.55 (m, 2H), 2.18-1.99 (m, 3H), 1.83-1.49 (m, 5H).
D42	846.5	¹ H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.04 (s, 1H), 8.18 (s, 1H, FA), 7.84 (d, J = 8.2 Hz, 1H), 7.59 (s, 1H), 7.35-7.26 (m, 2H), 6.80 (s, 2H), 6.47 (s, 1H), 5.12 (dd, J = 12.9, 5.3 Hz, 1H), 5.07-4.98 (m, 1H), 3.91 (s, 2H), 3.84 (d, J = 1.8 Hz, 6H), 3.68 (s, 2H), 3.49 (s, 4H), 3.45-3.40 (m, 3H), 3.07 (s, 7H), 2.95-2.84 (m, 1H), 2.76-2.58 (m, 5H), 2.58-2.53 (m, 3H), 2.09-1.99 (m, 1H), 1.92-1.82 (m, 2H), 1.67-1.44 (m, 4H).
D43	777.35	¹ H NMR (400 MHz, Methanol-d4) δ 9.15 (s, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 2.3 Hz, 1H), 7.46-7.36 (m, 2H), 6.85 (s, 2H), 6.49 (s, 1H), 5.12 (dd, J = 12.6, 5.4 Hz, 1H), 4.23 (s, 2H), 4.13-4.05 (m, 1H), 3.96 (s, 6H), 3.92-3.88 (m, 1H), 3.87-3.80 (m, 5H), 3.79-3.72 (m, 3H), 3.69-3.64 (m, 1H), 3.59 (s, 3H), 3.51-3.44 (m, 1H), 3.19-3.14 (m, 2H), 3.14-3.07 (m, 7H), 2.94-2.84 (m, 1H), 2.81-2.68 (m, 2H), 2.60-2.48 (m, 1H), 2.19-2.07 (m, 2H).
D44	791.4	¹ H NMR (300 MHz, Methanol-d4) δ 9.14 (s, 1H, FA), 8.52 (s, 2H), 7.80 (d, J = 8.3 Hz, 1H), 7.50 (s, 1H), 7.43-7.33 (m, 2H), 6.81 (s, 2H), 6.46 (s, 1H), 5.11 (dd, J = 12.4, 5.4 Hz, 1H), 4.09 (s, 3H), 3.92 (s, 7H), 3.91-3.69 (m, 9H), 3.58 (s, 3H), 3.10 (s, 7H), 2.91-2.74 (m, 5H), 2.60-2.42 (m, 1H), 2.21-1.98 (m, 4H), 1.41-1.30 (m, 1H).
D45	735.3	¹ H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.01 (s, 1H), 7.83 (d, J = 8.3 Hz, 1H), 7.45-7.41 (m, 2H), 7.35 (dd, J = 8.3, 2.3 Hz, 1H), 6.16-6.07 (m, 3H), 5.12 (dd, J = 12.9, 5.4 Hz, 1H), 4.18 (t, J = 6.5 Hz, 2H), 3.71 (s, 3H), 3.44 (s, 3H), 3.30-3.24 (m, 3H), 3.07 (s, 2H), 3.03 (s, 6H), 2.95-2.84 (m, 1H), 2.67-2.57 (m, 3H), 2.09-2.01 (m, 1H), 1.82-1.71 (m, 2H), 1.61-1.49 (m, 2H), 1.48-1.40 (m, 2H), 1.47 (s, 6H).
D46	816.5	¹ H NMR (400 MHz, Methanol-d4) δ 9.13 (s, 1H), 8.56 (s, 1H, fa), 7.82 (d, J = 8.3 Hz, 1H), 7.31-7.23 (m, 3H), 6.19 (d, J = 4.5 Hz, 3H), 5.13 (s, 1H), 4.98-4.96 (m, 1H), 4.62 (s, 4H), 3.78 (s, 3H), 3.56 (s, 3H), 3.37 (s, 1H), 3.15-3.13 (m, 1H), 3.10 (s, 6H), 2.94-2.83 (m, 4H), 2.80-2.67 (m, 4H), 2.64-2.56 (m, 2H), 2.18-2.10 (m, 1H), 2.08-2.03 (m, 3H), 1.98-1.85 (m, 4H), 1.83-1.67 (m, 4H), 1.57-1.44 (m, 2H).
D47	735.3	¹ H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.01 (s, 1H), 7.81 (dd, J = 8.5, 7.2 Hz, 1H), 7.52 (d, J = 8.5 Hz, 1H), 7.44 (t, J = 3.6 Hz, 2H), 6.15-6.07 (m, 3H), 5.08 (dd, J = 12.9, 5.4 Hz, 1H), 4.21 (t, J = 6.4 Hz, 2H), 3.71 (s, 3H), 3.44 (s, 3H), 3.32-3.22 (m, 3H), 3.09-3.05 (m, 2H), 3.03 (s, 6H), 2.93-2.83 (m, 1H), 2.68-2.55 (m, 3H), 2.07-1.98 (m, 1H), 1.77 (p, J = 6.5 Hz, 2H), 1.59-1.45 (m, 4H), 1.37 (s, 6H).
D48	776.04	¹ H NMR (300 MHz, Methanol-d4) δ 9.17 (s, 1H), 8.43 (s, 3H, FA), 8.37 (s, 1H), 7.75-7.66 (m, 2H), 7.50 (s, 1H), 7.41 (s, 1H), 7.28 (d, J = 8.3 Hz, 1H), 6.34 (s, 1H), 5.10 (dd, J = 12.3, 5.4 Hz, 1H), 4.50 (s, 2H), 4.01 (s, 3H), 3.71-3.52 (m, 10H), 3.19-3.09 (m, 8H), 2.96-2.82 (m, 1H), 2.79-2.71 (m, 5H), 2.61 (t, J = 7.6 Hz, 2H), 2.18-2.01 (m, 3H), 1.81-1.59 (m, 5H).
D49	789.4	
D50	803.5	¹ H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 9.04 (s, 1H), 8.21 (s, 2H, FA), 7.64 (d, J = 8.3 Hz, 1H), 7.58 (s, 1H), 6.80-6.75 (m, 3H), 6.64 (dd, J = 8.4, 2.1 Hz, 1H), 6.47 (s, 1H), 5.05 (dd, J = 12.9, 5.3 Hz, 1H), 3.83 (d, J = 1.3 Hz, 8H), 3.74 (s, 4H), 3.59 (s, 2H), 3.49 (s, 3H), 3.17 (s, 2H), 3.08 (s, 6H), 2.93-2.84 (m, 1H), 2.66-2.53 (m, 3H), 2.48-2.42 (m, 2H), 2.29 (s, 4H), 2.05-1.96 (m, 1H), 1.79-1.68 (m, 4H).
D51	789.65	
D52	777.5	¹ H NMR (300 MHz, DMSO-d6) δ 11.08 (s, 1H), 9.04 (s, 1H), 8.16 (s, 1H, FA), 7.68 (d, J = 8.6 Hz, 1H), 7.59 (s, 1H), 7.33 (d, J = 2.0 Hz, 1H), 7.25 (d, J = 8.9 Hz, 1H), 6.77 (s, 2H), 6.49 (s, 1H), 5.07

-continued

Compound No.	LCMS	^1H NMR
D53	777.3	(dd, $J = 12.6, 5.3$ Hz, 1H), 3.82 (s, 7H), 3.63-3.60 (m, 1H), 3.48 (s, 4H), 3.45-3.39 (m, 5H), 3.08 (s, 6H), 3.01-2.88 (m, 3H), 2.64-2.55 (m, 5H), 2.23-2.13 (m, 2H), 2.06-1.96 (m, 1H), 1.78-1.69 (m, 2H), 1.51-1.35 (m, 2H).
D54	846.8	^1H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 9.04 (s, 1H), 7.66 (d, $J = 8.6$ Hz, 1H), 7.58 (s, 1H), 7.32 (d, $J = 2.3$ Hz, 1H), 7.24 (dd, $J = 8.7, 2.3$ Hz, 1H), 6.75 (s, 2H), 6.49 (s, 1H), 5.07 (dd, $J = 12.9, 5.4$ Hz, 1H), 4.05 (d, $J = 12.8$ Hz, 2H), 3.81 (s, 6H), 3.56 (s, 2H), 3.48 (s, 3H), 3.28-3.20 (m, 2H), 3.07 (s, 6H), 3.01-2.83 (m, 3H), 2.64-2.53 (m, 3H), 2.48-2.41 (m, 6H), 2.06-1.96 (m, 1H), 1.83 (d, $J = 12.3$ Hz, 2H), 1.51-1.36 (m, 2H).
D55	860.75	^1H NMR (400 MHz, Methanol-d4) δ 9.16 (s, 1H), 8.56 (s, 1H, FA), 7.82 (d, $J = 8.3$ Hz, 1H), 7.43 (d, $J = 1.6$ Hz, 1H), 7.30 (d, $J = 2.0$ Hz, 1H), 7.25 (dd, $J = 8.3, 2.3$ Hz, 1H), 6.86 (s, 2H), 6.51 (s, 1H), 5.12 (dd, $J = 12.6, 5.5$ Hz, 1H), 5.01-4.93 (m, 1H), 4.18 (s, 2H), 3.94 (d, $J = 2.2$ Hz, 6H), 3.64-3.57 (m, 5H), 3.54 (s, 2H), 3.48-3.34 (m, 4H), 3.13 (s, 6H), 2.97-2.84 (m, 3H), 2.81-2.71 (m, 2H), 2.64-2.54 (m, 2H), 2.19-2.10 (m, 1H), 2.07-2.01 (m, 2H), 2.00-1.95 (m, 1H), 1.93-1.85 (m, 2H), 1.79-1.63 (m, 4H).
D56	817.4	^1H NMR (400 MHz, DMSO-d6) δ 11.09 (s, 1H), 9.04 (s, 1H), 8.21 (s, 1H, FA), 7.68 (d, $J = 8.5$ Hz, 1H), 7.58 (s, 1H), 7.34 (d, $J = 2.2$ Hz, 1H), 7.25 (dd, $J = 8.6, 2.3$ Hz, 1H), 6.76 (s, 2H), 6.48 (s, 1H), 5.07 (dd, $J = 12.9, 5.4$ Hz, 1H), 3.82 (s, 6H), 3.58 (s, 3H), 3.48 (s, 3H), 3.46-3.38 (m, 5H), 3.07 (s, 6H), 2.94-2.84 (m, 1H), 2.72-2.64 (m, 1H), 2.63-2.53 (m, 2H), 2.41-2.29 (m, 6H), 2.06-1.98 (m, 1H), 1.96-1.87 (m, 2H), 1.59-1.50 (m, 4H), 1.47 (s, 2H).
D57	791.4	^1H NMR (300 MHz, DMSO) δ 11.09 (s, 1H), 9.04 (s, 1H), 8.23 (s, 1H, FA), 7.68 (d, 1H), 7.58 (s, 1H), 7.33 (d, 1H), 7.25 (dd, 1H), 6.76 (s, 2H), 6.49 (s, 1H), 5.08 (dd, 1H), 3.81 (s, 6H), 3.56 (s, 2H), 3.48 (s, 3H), 3.45-3.40 (m, 4H), 3.07 (s, 6H), 2.87 (d, 3H), 2.64-2.53 (m, 2H), 2.45 (s, 4H), 2.20-1.98 (m, 5H), 1.66 (d, 2H), 1.52-1.45 (m, 1H), 1.21-1.99 (m, 2H).
D58	749.74	
D59	762.26	
D60	803.3	
D61	748.47	
D62	776.4	
D63	746.44	
D64	774.16	
D65	786.55	^1H NMR (400 MHz, DMSO-d6) δ 11.15 (s, 1H), 9.03 (s, 1H), 8.20 (s, 1H, FA), 7.97-7.79 (m, 3H), 7.58 (s, 1H), 6.76 (s, 2H), 6.46 (s, 1H), 5.17 (dd, $J = 12.8, 5.4$ Hz, 1H), 3.81 (s, 6H), 3.63 (d, $J = 15.9$ Hz, 4H), 3.48 (s, 3H), 3.06 (s, 6H), 2.95-2.85 (m, 1H), 2.68 (t, $J = 6.8$ Hz, 2H), 2.65-2.55 (m, 2H), 2.50-2.35 (m, 6H), 2.14-1.99 (m, 1H), 1.59-1.51 (m, 6H).
D66	803.45	^1H NMR (300 MHz, Methanol-d4) δ 9.15 (s, 1H), 7.68 (d, $J = 8.4$ Hz, 1H), 7.45 (s, 1H), 7.02 (d, $J = 2.2$ Hz, 1H), 6.92-6.83 (m, 3H), 6.48 (s, 1H), 5.08 (dd, $J = 12.4, 5.4$ Hz, 1H), 4.51 (s, 2H), 4.32-4.17 (m, 6H), 4.13-4.03 (m, 2H), 3.97 (s, 6H), 3.74-3.64 (m, 3H), 3.61-3.52 (m, 5H), 3.13 (s, 6H), 2.94-2.67 (m, 3H), 2.35 (t, $J = 6.9$ Hz, 2H), 2.17-2.06 (m, 1H).
D67	818.4	^1H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.04 (s, 1H), 8.18 (s, 1H, FA), 7.83 (d, $J = 8.1$ Hz, 1H), 7.59 (s, 1H), 7.36-7.20 (m, 2H), 6.83 (s, 2H), 6.47 (s, 1H), 5.12 (dd, $J = 12.9, 5.4$ Hz, 1H), 4.98 (s, 2H), 4.35 (s, p, $J = 7.0$ Hz, 1H), 4.03 (s, 2H), 3.89-3.76 (m, 8H), 3.53-3.36 (m, 6H), 3.08 (s, 6H), 2.96-2.83 (m, 1H), 2.80-2.70 (m, 1H), 2.64-2.53 (m, 3H), 2.48-2.33 (m, 4H), 2.28 (s, 2H), 2.09-2.00 (m, 1H), 1.87-1.75 (m, 2H), 1.67-1.50 (m, 4H).
D68	734.71	^1H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.45 (s, 1H), 8.72 (d, $J = 5.7$ Hz, 1H), 7.97 (s, 1H), 7.86 (s, 1H), 7.55 (d, $J = 5.7$ Hz, 1H), 6.84 (s, 2H), 5.14 (d, $J = 13.2$ Hz, 1H), 4.98 (s, 2H), 4.35 (s, 2H), 3.91-3.71 (m, 6H), 3.59 (s, 3H), 3.03-2.78 (m, 1H), 2.73 (s, 2H), 2.67-2.49 (m, 1H), 2.05 (s, 2H).
D69	749.52	
D70	694.5	
D71	752	^1H NMR (300 MHz, DMSO-d6) δ 11.10 (s, 1H), 9.04 (s, 1H), 8.18 (s, 0H, FA) 7.80 (dd, $J = 8.5, 7.2$ Hz, 1H), 7.58 (s, 1H), 7.54 (d, $J = 8.6$ Hz, 1H), 7.48-7.41 (m, 1H), 6.74 (s, 2H), 6.49 (s, 1H), 5.09

Compound No.	LCMS	^1H NMR
D72	772.4	(dd, $J = 12.9, 5.4$ Hz, 1H), 4.28 (dd, $J = 9.9, 5.2$ Hz, 1H), 4.12-4.02 (m, 1H), 3.80 (s, 6H), 3.53 (s, 2H), 3.48 (s, 3H), 3.07 (s, 6H), 3.03-2.76 (m, 3H), 2.64-2.54 (m, 6H), 2.40 (s, 3H), 2.08-1.98 (m, 1H), 1.11 (d, $J = 6.6$ Hz, 3H).
D73	800.5	^1H NMR (300 MHz, DMSO-d6) δ 9.04 (s, 1H), 7.99-7.90 (m, 3H), 7.57 (s, 1H), 6.85 (s, 2H), 6.44 (s, 1H), 5.16 (dd, $J = 12.9, 5.3$ Hz, 1H), 4.29 (d, $J = 19.7$ Hz, 6H), 3.88 (s, 6H), 3.48 (s, 6H), 3.06 (s, 6H), 2.92-2.80 (m, 1H), 2.77-2.55 (m, 3H), 2.14-2.00 (m, 1H), 1.22 (s, 6H).
D74	793.3	^1H NMR (400 MHz, DMSO-d6) δ 11.15 (s, 1H), 9.03 (s, 1H), 8.22 (s, 1H, FA), 7.97-7.88 (m, 1H), 7.88-7.79 (m, 2H), 7.56 (s, 1H), 6.75 (s, 2H), 6.45 (s, 1H), 5.16 (dd, $J = 12.8, 5.4$ Hz, 1H), 3.80 (s, 6H), 3.69 (s, 3H), 3.48 (s, 5H), 3.14-2.96 (m, 11H), 2.93-2.87 (m, 1H), 2.69-2.67 (m, 1H), 2.63-2.58 (m, 1H), 2.13-2.00 (m, 1H), 1.65 (s, 4H), 1.41 (s, 6H).
D75	861.43	^1H NMR (300 MHz, Methanol-d4) δ 9.15 (s, 1H), 7.68 (d, $J = 8.4$ Hz, 1H), 7.45 (s, 1H), 7.02 (d, $J = 2.2$ Hz, 1H), 6.92-6.83 (m, 3H), 6.48 (s, 1H), 5.08 (dd, $J = 12.4, 5.4$ Hz, 1H), 4.51 (s, 2H), 4.32-4.17 (m, 6H), 4.13-4.03 (m, 2H), 3.97 (s, 6H), 3.74-3.64 (m, 3H), 3.61-3.52 (m, 5H), 3.13 (s, 6H), 2.94-2.67 (m, 3H), 2.35 (t, $J = 6.9$ Hz, 2H), 2.17-2.06 (m, 1H).
D76	752	^1H NMR (400 MHz, DMSO-d6, D2O) δ 9.01 (s, 1H), 9.23 (s, 2H, TFA), 9.06 (s, 1H), 7.80 (d, $J = 8.2$ Hz, 1H), 7.60 (s, 1H), 7.36-7.25 (m, 2H), 6.92 (s, 2H), 6.51 (s, 1H), 5.17-4.98 (m, 2H), 4.22 (s, 2H), 3.91 (s, 6H), 3.54-3.19 (m, 9H), 3.09 (s, 8H), 2.95-2.84 (m, 2H), 2.71-2.54 (m, 3H), 2.46-2.39 (m, 1H), 2.25-2.12 (m, 1H), 2.06-1.65 (m, 11H), 1.20 (d, $J = 6.7$ Hz, 3H).
D77	752	^1H NMR (400 MHz, DMSO-d6, D2O) δ 9.00 (s, 1H), 7.85 (d, $J = 8.3$ Hz, 1H), 7.53 (d, $J = 3.3$ Hz, 1H), 7.48 (d, $J = 2.2$ Hz, 1H), 7.37 (dd, $J = 8.3, 2.2$ Hz, 1H), 6.83 (s, 2H), 6.47 (s, 1H), 5.08 (dd, $J = 12.9,$ 5.5 Hz, 1H), 5.04-4.95 (m, 1H), 4.23 (s, 2H), 3.85 (s, 6H), 3.50-3.42 (m, 4H), 3.37-3.09 (m, 5H), 3.04 (s, 8H), 2.96-2.78 (m, 5H), 2.65-2.57 (m, 1H), 2.08-1.99 (m, 1H), 1.27 (d, $J = 6.0$ Hz, 3H).
D78	766.3	^1H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.04 (s, 1H), 7.83 (d, $J = 8.2$ Hz, 1H), 7.59 (s, 1H), 7.51-7.37 (m, 2H), 6.77 (s, 2H), 6.49 (s, 1H), 5.13 (dd, $J = 12.9, 5.3$ Hz, 1H), 3.82 (s, 6H), 3.65 (s, 2H), 3.51 (s, 5H), 3.07 (s, 6H), 2.93-2.84 (m, 1H), 2.59 (d, $J = 11.6$ Hz, 10H), 2.06 (dd, $J = 10.9, 5.3$ Hz, 1H), 1.35 (s, 6H).
D79	872.4	^1H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.02 (s, 1H), 8.15 (s, 0H, FA), 7.84 (d, $J = 8.2$ Hz, 1H), 7.60 (s, 1H), 7.34-7.27 (m, 2H), 6.78 (s, 2H), 6.22 (s, 1H), 5.12 (dd, $J = 12.8, 5.4$ Hz, 1H), 5.03 (t, $J = 6.8$ Hz, 1H), 4.01 (t, $J = 7.4$ Hz, 4H), 3.84 (d, $J = 2.1$ Hz, 6H), 3.76 (s, 2H), 3.49 (s, 3H), 3.44 (s, 6H), 3.07-2.97 (m, 2H), 2.94-2.85 (m, 1H), 2.66-2.53 (m, 3H), 2.45-2.30 (m, 4H), 2.09-2.01 (m, 1H), 1.92-1.83 (m, 2H), 1.67-1.47 (m, 8H).
D80	858.45	^1H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.02 (s, 1H), 8.18 (s, 1H, FA), 7.83 (d, $J = 8.2$ Hz, 1H), 7.60 (s, 1H), 7.34-7.24 (m, 2H), 6.76 (s, 2H), 6.21 (s, 1H), 5.12 (dd, $J = 12.8, 5.4$ Hz, 1H), 4.98 (p, $J = 6.4$ Hz, 1H), 4.01 (t, $J = 7.4$ Hz, 4H), 3.83 (s, 6H), 3.70 (s, 2H), 3.48 (s, 3H), 3.02-2.80 (m, 4H), 2.67-2.59 (m, 1H), 2.47-2.39 (m, 3H), 2.37-2.22 (m, 7H), 2.14-2.01 (m, 3H), 1.87-1.75 (m, 2H), 1.71-1.48 (m, 7H), 1.22-1.03 (m, 2H).
D81	766.35	^1H NMR (300 MHz, DMSO-d6) δ 11.10 (s, 1H), 9.04 (s, 1H), 7.76 (t, $J = 7.8$ Hz, 1H), 7.65-7.56 (m, 2H), 7.52 (d, $J = 7.1$ Hz, 1H), 6.79 (s, 2H), 6.48 (s, 1H), 5.09 (dd, $J = 12.9, 5.3$ Hz, 1H), 3.83 (s, 6H), 3.73 (s, 2H), 3.48 (s, 3H), 3.43-3.35 (m, 2H), 3.07 (s, 6H), 2.95-2.81 (m, 1H), 2.75-2.54 (m, 10H), 2.10-1.97 (m, 1H), 1.40 (s, 6H).
D82	752.3	^1H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.04 (s, 1H), 8.18 (s, 1H, FA), 7.82 (d, $J = 8.3$ Hz, 1H), 7.58 (s, 1H), 7.47 (d, $J = 2.3$ Hz, 1H), 7.36 (dd, $J = 8.3, 2.3$ Hz, 1H), 6.75 (s, 2H), 6.48 (s, 1H), 5.12 (dd, $J = 12.9, 5.4$ Hz, 1H), 4.24 (dd, $J = 10.1, 5.6$ Hz, 1H), 4.04 (dd, $J = 9.9, 6.1$ Hz, 1H), 3.80 (s, 6H), 3.54 (s, 3H), 3.48 (s, 4H), 3.07 (s, 6H), 2.99-2.86 (m, 2H), 2.63-2.54 (m, 5H), 2.44 (s, 3H), 2.09-2.01 (m, 1H), 1.08 (d, $J = 6.6$ Hz, 3H).
D83	752.25	^1H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.04 (s, 1H), 8.32 (s, 2H, FA), 7.82 (d, $J = 8.3$ Hz, 1H), 7.58 (s, 1H), 7.47 (d, $J = 2.3$ Hz, 1H), 7.36 (dd, $J = 8.4, 2.3$ Hz, 1H), 6.74 (s, 2H), 6.48 (s, 1H),

Compound No.	LCMS	^1H NMR
D84	860.55	^1H NMR (300 MHz, DMSO-d6) δ 11.11 (s, 1H), 10.72 (s, 1H, HCl), 9.01 (s, 1H), 7.85 (dd, J = 10.0, 6.1 Hz, 1H), 3.80 (s, 6H), 3.53 (s, 3H), 3.48 (s, 4H), 3.07 (s, 6H), 2.96-2.86 (m, 2H), 2.63-2.54 (m, 5H), 2.42 (s, 3H), 2.09-2.00 (m, 1H), 1.07 (d, J = 6.7 Hz, 3H).
D85	461.55	^1H NMR (400 MHz, DMSO-d6) δ 9.04 (s, 1H), 8.15 (s, 1H, FA), 7.69 (d, J = 8.6 Hz, 1H), 7.58 (s, 1H), 7.35 (d, J = 2.2 Hz, 1H), 7.27 (dd, J = 8.6, 2.3 Hz, 1H), 6.78 (s, 2H), 6.49 (s, 1H), 5.71-5.60 (m, 2H), 5.27 (dd, J = 13.1, 5.4 Hz, 1H), 4.78 (p, J = 6.2 Hz, 1H), 3.83 (s, 6H), 3.66 (s, 2H), 3.48 (s, 3H), 3.43 (t, J = 5.3 Hz, 4H), 3.07 (s, 6H), 3.03-2.79 (m, 4H), 2.65-2.55 (m, 3H), 2.40-2.29 (m, 4H), 2.28-2.04 (m, 3H), 1.66 (d, J = 12.1 Hz, 2H), 1.44-1.27 (m, 3H), 1.26-1.15 (m, 8H).
D86	651.44	
D87	804.4	
D88	674.62	^1H NMR (400 MHz, DMSO-d6) δ 10.81 (s, 1H), 9.01 (s, 1H), 8.16 (s, 2H), 7.55 (s, 1H), 6.73 (s, 2H), 6.46 (s, 1H), 3.78 (s, 6H), 3.53 (s, 2H), 3.45 (s, 3H), 3.15 (s, 2H), 3.05 (s, 6H), 2.82 (d, J = 11.4 Hz, 2H), 2.40-2.24 (m, 3H), 2.05 (t, J = 11.5 Hz, 2H), 1.80 (dd, J = 9.7, 4.5 Hz, 1H), 1.58 (d, J = 12.3 Hz, 2H), 1.32 (q, J = 7.0 Hz, 2H), 1.09 (q, J = 11.6 Hz, 2H).
D89	689.53	
D90	734.26	
D91	720.54	
D92	706.65	
D93	720.4	
D94	618.61	^1H NMR (400 MHz, DMSO-d6) δ 10.82 (s, 1H), 9.01 (s, 1H), 8.17 (s, 1H), 7.56 (s, 1H), 6.73 (s, 2H), 6.44 (s, 1H), 4.94 (d, J = 45.9 Hz, 1H), 3.79 (s, 6H), 3.62 (s, 2H), 3.46 (s, 3H), 3.36-3.10 (m, 3H), 3.04 (s, 6H), 2.96 (q, J = 4.9, 3.2 Hz, 2H), 2.87 (dd, J = 14.8, 7.7 Hz, 3H), 2.84-2.62 (m, 1H), 2.34-2.17 (m, 1H), 1.86-1.71 (m, 1H).
D95	780.35	^1H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.04 (s, 1H), 7.85 (d, J = 8.3 Hz, 1H), 7.60-7.53 (m, 2H), 7.40 (dd, J = 8.3, 2.3 Hz, 1H), 6.74 (s, 2H), 6.48 (s, 1H), 5.13 (dd, J = 13.0, 5.4 Hz, 1H), 4.50 (s, 2H), 4.43 (q, J = 6.1 Hz, 4H), 3.79 (s, 6H), 3.55 (s, 2H), 3.47 (s, 3H), 3.07 (s, 6H), 3.04-2.81 (m, 2H), 2.65-2.54 (m, 4H), 2.49-2.39 (m, 5H), 2.10-2.00 (m, 1H).
D96	766.4	^1H NMR (400 MHz, DMSO-d6) δ 11.13 (s, 1H), 9.04 (s, 1H), 8.18 (s, 1H, FA), 7.83 (d, J = 8.2 Hz, 1H), 7.58 (s, 1H), 7.48 (d, J = 2.1 Hz, 1H), 7.41 (dd, J = 8.2, 2.2 Hz, 1H), 6.75 (s, 2H), 6.49 (s, 1H), 5.13 (dd, J = 12.9, 5.4 Hz, 1H), 3.81 (s, 6H), 3.56 (s, 2H), 3.51-3.45 (m, 5H), 3.06 (s, 6H), 2.94-2.84 (m, 1H), 2.59-2.53 (m, 6H), 2.49-2.43 (m, 4H), 2.08-2.01 (m, 1H), 1.35 (s, 6H).
D97	831.99	^1H NMR (400 MHz, Methanol-d4) δ 9.16 (s, 1H), 8.46 (s, 1H, FA), 7.64 (d, J = 8.3 Hz, 1H), 7.45 (s, 1H), 6.91 (s, 2H), 6.83 (d, J = 2.1 Hz, 1H), 6.66 (dd, J = 8.3, 2.1 Hz, 1H), 6.48 (s, 1H), 5.07 (dd, J = 12.3, 5.4 Hz, 1H), 4.45 (s, 2H), 4.06 (d, J = 9.2 Hz, 4H), 3.99 (s, 6H), 3.79 (s, 4H), 3.60 (s, 3H), 3.26-3.19 (m, 1H), 3.13 (s, 6H), 2.91-2.81 (m, 1H), 2.80-2.68 (m, 2H), 2.60 (s, 4H), 2.14-2.06 (m, 1H), 1.89 (s, 4H), 1.17 (s, 6H).
D98	681.35	^1H NMR (300 MHz, DMSO-d6) δ 11.13 (s, 1H), 9.04 (s, 1H), 8.17 (s, 1H, FA), 7.86-7.80 (m, 1H), 7.59 (s, 1H), 7.29-7.23 (m, 2H), 6.77 (s, 2H), 6.47 (s, 1H), 5.12 (dd, J = 12.9, 5.3 Hz, 1H), 4.95 (t, J = 5.5 Hz, 1H), 3.81 (s, 6H), 3.75-3.69 (m, 4H), 3.48 (s, 3H), 3.15-3.11 (m, 2H), 3.06 (s, 6H), 2.91-2.84 (m, 1H), 2.65-2.55 (m, 2H), 2.07-1.99 (m, 1H).
D99	914.5	^1H NMR (300 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.04 (s, 1H), 8.30 (s, 1H, FA), 7.82 (d, J = 8.0 Hz, 1H), 7.56 (s, 1H), 7.34-7.23 (m, 2H), 6.75 (s, 2H), 6.49 (s, 1H), 5.12 (dd, J = 12.8, 5.3 Hz, 1H), 5.04-4.91 (m, 1H), 3.80 (s, 6H), 3.52-3.48 (m, 6H), 3.07 (s, 6H), 2.99-2.67 (m, 8H), 2.44-2.40 (m, 2H), 2.08-1.94 (m, 3H), 1.89-1.75 (m, 3H), 1.64-1.45 (m, 6H), 1.35-1.12 (m, 3H).
D100	780.3	^1H NMR (400 MHz, DMSO-d6) δ 11.10 (s, 1H), 9.04 (s, 1H), 7.85 (dd, J = 8.5, 7.3 Hz, 1H), 7.62 (d, J = 8.6 Hz, 1H), 7.58 (s, 1H), 7.48 (d, J = 7.2 Hz, 1H), 6.74 (s, 2H), 6.48 (s, 1H), 5.09 (dd, J = 12.8, 5.4 Hz, 1H), 4.55 (s, 2H), 4.43 (s, 4H), 3.79 (s, 6H), 3.55 (s, 2H), 3.47 (s, 3H), 3.06 (s, 6H), 2.92-2.81 (m, 1H), 2.63-2.54 (m, 5H), 2.48-2.37 (m, 5H), 2.07-1.98 (m, 1H).

Compound No.	LCMS	^1H NMR
D101	850.55	^1H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.03 (s, 1H), 8.15 (s, 1H, FA), 7.83 (d, J = 8.2 Hz, 1H), 7.61 (s, 1H), 7.32-7.25 (m, 2H), 7.15 (d, J = 1.6 Hz, 1H), 7.11 (d, J = 1.6 Hz, 1H), 6.39 (s, 1H), 5.12 (dd, J = 12.8, 5.4 Hz, 1H), 4.99 (t, J = 6.8 Hz, 1H), 3.85 (s, 3H), 3.60 (s, 2H), 3.47 (s, 3H), 3.07 (s, 6H), 2.91-2.80 (m, 3H), 2.64-2.53 (m, 3H), 2.45-2.40 (m, 2H), 2.39-2.36 (m, 1H), 2.30-2.26 (m, 1H), 2.18-2.00 (m, 6H), 1.81 (dd, J = 12.3, 6.4 Hz, 2H), 1.68-1.55 (m, 6H), 1.53-1.46 (m, 1H), 1.10-0.98 (m, 2H).
D102	864.4	^1H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.04 (s, 1H), 7.84 (d, J = 8.2 Hz, 1H), 7.63 (s, 1H), 7.35-7.26 (m, 2H), 7.19 (d, J = 13.5 Hz, 2H), 6.40 (s, 1H), 5.12 (dd, J = 12.9, 5.4 Hz, 1H), 5.04 (t, J = 7.3 Hz, 1H), 3.99-3.59 (m, 5H), 3.47 (s, 5H), 3.42-3.35 (m, 4H), 3.11-3.03 (m, 7H), 3.02-2.82 (m, 3H), 2.71-2.53 (m, 3H), 2.44-2.34 (m, 1H), 2.10-2.00 (m, 1H), 1.93-1.83 (m, 2H), 1.70-1.45 (m, 8H).
D103	832.6	^1H NMR (300 MHz, Methanol-d4) δ 9.09 (s, 1H), 7.72 (d, J = 8.3 Hz, 1H), 7.49 (s, 1H), 7.05-6.98 (m, 2H), 6.90 (s, 2H), 6.60-6.55 (m, 1H), 5.13 (dd, J = 13.3, 5.1 Hz, 1H), 4.95-4.89 (m, 1H), 4.54-4.37 (m, 4H), 3.98 (s, 6H), 3.69-3.49 (m, 7H), 3.42-3.35 (m, 1H), 3.29-3.13 (m, 8H), 3.12-2.95 (m, 4H), 2.94-2.86 (m, 1H), 2.84-2.74 (m, 1H), 2.74-2.63 (m, 1H), 2.59-2.44 (m, 2H), 2.37-2.21 (m, 1H), 2.21-1.97 (m, 9H), 1.73-1.62 (m, 1H).
D104	693.3	^1H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.04 (s, 1H), 8.17 (s, 1H, FA), 7.88-7.73 (m, 3H), 7.60 (s, 1H), 6.78 (s, 2H), 6.50 (s, 1H), 5.14 (dd, J = 12.9, 5.3 Hz, 1H), 3.84 (s, 6H), 3.65 (s, 2H), 3.49 (s, 3H), 3.08 (s, 6H), 3.02 (d, J = 11.3 Hz, 2H), 2.97-2.70 (m, 3H), 2.63-2.55 (m, 1H), 2.30-2.20 (m, 2H), 2.10-2.00 (m, 1H), 1.83-1.63 (m, 4H).
D105	805.3	^1H NMR (300 MHz, DMSO-d6) δ 11.09 (s, 1H), 9.04 (s, 1H), 8.20 (s, 1H, FA), 7.65 (d, J = 8.5 Hz, 1H), 7.58 (s, 1H), 7.30 (d, J = 2.2 Hz, 1H), 7.22 (dd, J = 8.7, 2.3 Hz, 1H), 6.75 (s, 2H), 6.49 (s, 1H), 5.07 (dd, J = 12.7, 5.4 Hz, 1H), 4.03 (d, J = 12.9 Hz, 2H), 3.80 (s, 6H), 3.54 (s, 2H), 3.48 (s, 3H), 3.07 (s, 6H), 3.01-2.82 (m, 4H), 2.64-2.54 (m, 2H), 2.46-2.41 (m, 3H), 2.39-2.24 (m, 6H), 2.07-1.96 (m, 1H), 1.74 (d, J = 12.7 Hz, 2H), 1.64-1.51 (m, 1H), 1.41-1.30 (m, 2H), 1.24-1.08 (m, 2H).
D106	791.45	^1H NMR (300 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.97 (s, 1H), 8.16 (s, 1H, FA), 7.65 (d, J = 8.5 Hz, 1H), 7.51 (s, 1H), 7.30 (d, J = 2.2 Hz, 1H), 7.23 (dd, J = 8.7, 2.3 Hz, 1H), 7.15 (d, J = 4.9 Hz, 1H), 6.71 (s, 2H), 6.43 (s, 1H), 5.07 (dd, J = 12.7, 5.3 Hz, 1H), 4.04 (d, J = 12.7 Hz, 2H), 3.81 (s, 6H), 3.59 (s, 2H), 3.46 (s, 3H), 3.27-3.04 (m, 5H), 2.94 (t, J = 12.6 Hz, 3H), 2.80 (d, J = 4.6 Hz, 3H), 2.62-2.55 (m, 2H), 2.46-2.34 (m, 5H), 2.05-1.96 (m, 1H), 1.74 (d, J = 12.7 Hz, 2H), 1.65-1.51 (m, 1H), 1.44-1.32 (m, 2H), 1.25-1.11 (m, 2H).
D107	832.75	^1H NMR (300 MHz, MeOD) δ 9.04 (d, 1H), 7.59-7.45 (m, 2H), 7.24-7.12 (m, 2H), 6.91 (d, 2H), 6.72-6.60 (m, 1H), 5.15 (dd, 1H), 4.85-4.80 (m, 1H), 4.53-4.34 (m, 4H), 3.98 (d, 6H), 3.72-3.65 (m, 2H), 3.60-3.47 (m, 4H), 3.43-3.36 (m, 1H), 3.28-3.22 (m, 1H), 3.21-3.13 (m, 7H), 3.10 (d, 2H), 3.04-2.95 (m, 1H), 2.94-2.85 (m, 1H), 2.76-2.83 (m, 1H), 2.73-2.65 (m, 1H), 2.60-2.43 (m, 2H), 2.35-2.15 (m, 2H), 2.13-2.09 (m, 2H), 2.08-2.02 (m, 3H), 2.88-2.78 (m, 3H), 1.52-1.36 (m, 2H).
D108	874.35	1H NMR (300 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.05 (s, 1H), 8.15 (s, 0.4H, FA), 7.83 (d, J = 8.5 Hz, 1H), 7.59 (s, 1H), 7.32-7.23 (m, 2H), 6.85 (s, 2H), 6.50 (s, 1H), 5.12 (dd, J = 12.8, 5.4 Hz, 1H), 4.99 (t, J = 6.7 Hz, 1H), 3.96 (s, 2H), 3.87 (s, 6H), 3.49 (s, 3H), 3.27-3.19 (m, 6H), 3.08 (s, 6H), 2.95-2.81 (m, 1H), 2.66-2.53 (m, 2H), 2.45-2.37 (m, 4H), 2.10-1.98 (m, 1H), 1.87-1.67 (m, 5H), 1.59 (d, J = 17.9 Hz, 4H), 1.49-1.32 (m, 2H), 0.88 (s, 6H).
D109	764.25	^1H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.05 (s, 1H), 9.00 (br s, 0.9H, TFA salt), 7.88 (d, J = 8.3 Hz, 1H), 7.59 (s, 1H), 7.46 (d, J = 2.3 Hz, 1H), 7.36 (dd, J = 8.4, 2.3 Hz, 1H), 6.88 (s, 2H), 6.48 (s, 1H), 5.12 (dd, J = 12.9, 5.4 Hz, 1H), 4.25 (s, 4H), 3.88 (s, 6H), 3.49 (s, 6H), 3.35 (d, J = 11.0 Hz, 3H), 3.08 (s, 6H), 3.06-2.81 (m, 8H), 2.68-2.53 (m, 2H), 2.10-2.00 (m, 1H), 0.76 (d, J = 5.9 Hz, 3H).
D110	817.45	^1H NMR (400 MHz, Methanol-d4) δ 9.13 (s, 1H), 7.68 (d, J = 8.3 Hz, 1H), 7.46 (s, 1H), 6.94-6.85 (m, 3H), 6.71 (dd, J = 8.3, 2.2 Hz, 1H), 6.52 (s, 1H), 5.08 (dd, J = 12.4, 5.5 Hz, 1H), 4.53 (s, 2H), 4.40-4.12 (m, 4H), 3.99 (s, 6H), 3.95-3.78 (m, 5H), 3.58 (s, 3H), 3.46-3.33 (m, 3H), 3.15 (s, 8H), 2.91-2.66 (m, 3H), 2.29-2.08 (m, 5H), 1.40 (d, J = 6.7 Hz, 3H).
D111	890.4	^1H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.19 (s, 1H, TFA salt), 9.05 (d, J = 1.5 Hz, 1H), 7.84 (d, J = 8.2 Hz, 1H), 7.61 (d, J = 11.1 Hz, 1H), 7.35-7.24 (m, 2H), 6.91 (d, J = 4.1 Hz, 2H), 6.51 (d, J = 12.2 Hz, 1H), 5.18-4.99 (m, 2H), 4.25 (s, 1H), 3.91 (d, J = 1.3

US 12,391,686 B2

499

-continued

500

Compound No.	LCMS	¹ H NMR
D112	844.55	Hz, 6H), 3.81 (s, 1H), 3.57-3.33 (m, 9H), 3.30 (s, 3H), 3.23-3.01 (m, 8H), 2.99-2.81 (m, 2H), 2.66-2.53 (m, 2H), 2.53-2.39 (m, 2H), 2.40-2.30 (m, 1H), 2.11-2.00 (m, 1H), 1.89 (s, 2H), 1.67-1.45 (m, 5H).
D113	680.2	¹ H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.04 (s, 1H), 8.15 (s, 1H, FA), 7.83 (d, J = 8.2 Hz, 1H), 7.55 (s, 1H), 7.38-7.22 (m, 2H), 6.96 (d, J = 10.0 Hz, 2H), 6.45 (s, 1H), 5.12 (dd, J = 12.8, 5.4 Hz, 1H), 5.06-4.93 (m, 1H), 3.82 (s, 3H), 3.65 (s, 2H), 3.48 (s, 3H), 3.07 (s, 6H), 2.95-2.81 (m, 3H), 2.82-2.72 (m, 2H), 2.70-2.53 (m, 3H), 2.49-2.38 (m, 4H), 2.38-2.13 (m, 5H), 2.11-1.98 (m, 1H), 1.84 (dd, J = 11.9, 6.4 Hz, 2H), 1.77-1.41 (m, 7H), 1.22 (t, J = 7.5 Hz, 3H), 1.18-0.98 (m, 2H).
D114	680.3	¹ H NMR (300 MHz, DMSO-d6) δ 10.97 (s, 1H), 9.04 (s, 1H), 7.60 (s, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.26 (dd, J = 8.5, 2.3 Hz, 1H), 7.15 (d, J = 2.3 Hz, 1H), 6.79 (s, 2H), 6.50 (s, 1H), 5.09 (dd, J = 13.2, 5.0 Hz, 1H), 4.41-4.14 (m, 2H), 3.84 (s, 6H), 3.67 (s, 2H), 3.48 (s, 3H), 3.19 (s, 4H), 3.08 (s, 6H), 2.91 (ddd, J = 17.9, 13.6, 5.5 Hz, 1H), 2.65 (s, 4H), 2.48-2.24 (m, 2H), 2.06-1.92 (m, 1H).
D115	833.8	¹ H NMR (300 MHz, DMSO-d6) δ 10.94 (s, 1H), 9.04 (s, 1H), 7.60 (s, 1H), 7.52 (d, J = 8.7 Hz, 1H), 7.05 (d, J = 7.9 Hz, 2H), 6.79 (s, 2H), 6.50 (s, 1H), 5.05 (dd, J = 13.3, 5.1 Hz, 1H), 4.40-4.10 (m, 2H), 3.84 (s, 6H), 3.65 (s, 2H), 3.48 (s, 3H), 3.33-3.20 (m, 4H), 3.08 (s, 6H), 2.96-2.83 (m, 1H), 2.59 (d, J = 14.6 Hz, 4H), 2.45-2.25 (m, 2H), 1.95 (dd, J = 12.1, 6.5 Hz, 1H).
D116	815.35	¹ H NMR (400 MHz, DMSO-d6) δ 11.07 (s, 1H), 9.02 (s, 1H), 8.16 (s, 1H, FA), 7.65 (d, J = 8.5 Hz, 1H), 7.55 (s, 1H), 7.30 (d, J = 2.1 Hz, 1H), 7.23 (dd, J = 8.9, 2.1 Hz, 1H), 6.74 (s, 2H), 6.40 (s, 1H), 5.06 (dd, J = 12.7, 5.3 Hz, 1H), 4.03 (d, J = 13.0 Hz, 2H), 3.80 (s, 6H), 3.57 (s, 2H), 3.55-3.44 (m, 7H), 3.03-2.71 (m, 4H), 2.64-2.53 (m, 2H), 2.48-2.25 (m, 9H), 2.07-1.94 (m, 1H), 1.79-1.51 (m, 3H), 1.42-1.31 (m, 2H), 1.26-1.04 (m, 8H).
D117	688.91	¹ H NMR (400 MHz, DMSO-d6) δ 10.81 (s, 1H), 9.01 (s, 1H), 8.23 (s, 2H), 7.55 (s, 1H), 6.72 (s, 2H), 6.46 (s, 1H), 3.78 (s, 6H), 3.49 (s, 2H), 3.45 (s, 3H), 3.05 (s, 6H), 2.85-2.74 (m, 2H), 2.69-2.60 (m, 1H), 2.35-2.20 (m, 3H), 1.99 (t, J = 11.3 Hz, 2H), 1.85-1.74 (m, 1H), 1.56 (d, J = 12.0 Hz, 2H), 1.40 (s, 2H), 1.15 (s, 4H), 1.04 (d, J = 11.3 Hz, 2H).
D118	878.25	¹ H NMR (300 MHz, DMSO-d6) δ 9.04 (s, 1H), 7.87 (d, J = 9.3 Hz, 1H), 7.61 (d, J = 4.1 Hz, 1H), 7.51 (t, J = 6.9 Hz, 1H), 6.89 (s, 2H), 6.51 (d, J = 7.4 Hz, 1H), 5.18-5.06 (m, 2H), 4.21 (s, 2H), 3.90 (d, J = 1.7 Hz, 6H), 3.50 (s, 4H), 3.41-3.29 (m, 3H), 3.32-3.18 (m, 1H), 3.09 (s, 7H), 3.00-2.79 (m, 2H), 2.78-2.53 (m, 6H), 2.10-2.00 (m, 1H), 1.95-1.75 (m, 6H), 1.72-1.42 (m, 4H).
D119	854.45	¹ H NMR (400 MHz, Methanol-d4) δ 9.20-8.98 (m, 1H), 7.83 (d, J = 8.3 Hz, 1H), 7.78 (s, 2H), 7.50 (s, 1H), 7.31 (d, J = 2.2 Hz, 1H), 7.26 (dd, J = 8.3, 2.3 Hz, 1H), 6.37 (s, 1H), 5.12 (dd, J = 12.5, 5.4 Hz, 1H), 4.99 (t, J = 6.6 Hz, 1H), 4.75 (s, 2H), 3.88-3.75 (m, 2H), 3.68-3.51 (m, 5H), 3.44 (t, J = 12.4 Hz, 2H), 3.15 (s, 8H), 3.11-2.92 (m, 2H), 2.91-2.83 (m, 1H), 2.81-2.67 (m, 3H), 2.61-2.53 (m, 1H), 2.40-2.25 (m, 1H), 2.15 (d, J = 14.4 Hz, 6H), 2.02 (s, 3H), 1.78 (s, 2H).
D120	791.3	¹ H NMR (300 MHz, DMSO-d6) δ 10.96 (s, 1H), 9.04 (s, 1H), 8.16 (s, 1H, FA), 7.58 (s, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.31-7.11 (m, 2H), 6.76 (s, 2H), 6.49 (s, 1H), 5.09 (dd, J = 13.2, 5.1 Hz, 1H), 4.41-4.11 (m, 2H), 3.81 (s, 6H), 3.73 (d, J = 12.0 Hz, 2H), 3.57 (s, 2H), 3.48 (s, 3H), 3.07 (s, 6H), 2.98-2.81 (m, 1H), 2.80-2.59 (m, 3H), 2.58-2.57 (m, 1H), 2.46-2.43 (m, 3H), 2.43-2.22 (m, 7H), 2.06-1.92 (m, 1H), 1.83-1.67 (m, 2H), 1.46-1.34 (m, 3H), 1.33-1.17 (m, 2H).
D121	791.3	¹ H NMR (300 MHz, DMSO-d6) δ 10.93 (s, 1H), 9.04 (s, 1H), 8.14 (s, 1H, FA), 7.64-7.42 (m, 2H), 7.04 (d, J = 7.4 Hz, 2H), 6.78 (s, 2H), 6.49 (s, 1H), 5.04 (dd, J = 13.2, 5.1 Hz, 1H), 4.42-4.14 (m, 2H), 3.88 (s, 1H), 3.82 (s, 7H), 3.65 (s, 2H), 3.48 (s, 4H), 3.07 (s, 6H), 3.00-2.69 (m, 4H), 2.69-2.54 (m, 7H), 2.48-2.24 (m, 3H), 2.04-1.88 (m, 1H), 1.74 (d, J = 11.8 Hz, 2H), 1.47 (d, J = 26.5 Hz, 3H), 1.21 (q, J = 11.7, 10.6 Hz, 2H).
D122	801.5	¹ H NMR (400 MHz, Methanol-d4) δ 9.11 (s, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.37 (s, 1H), 7.11 (d, J = 8.5 Hz, 2H), 6.86 (s, 2H), 6.16 (s, 1H), 5.12 (dd, J = 13.3, 5.1 Hz, 1H), 4.49-4.35 (m, 4H), 4.08 (t, J =

US 12,391,686 B2

501

-continued

502

Compound No.	LCMS	¹ H NMR
D123	789.5	7.4 Hz, 4H), 3.98 (s, 6H), 3.60 (d, J = 12.3 Hz, 2H), 3.41 (t, J = 4.9 Hz, 4H), 3.31-3.27 (m, 1H), 3.19 (t, J = 12.4 Hz, 2H), 2.99-2.85 (m, 1H), 2.83-2.74 (m, 5H), 2.70-2.61 (m, 1H), 2.56-2.39 (m, 3H), 2.22-2.13 (m, 3H), 1.93 (s, 2H), 1.14 (q, J = 6.8 Hz, 2H), 0.96 (dd, J = 6.3, 4.1 Hz, 2H).
D124	819.65	¹ H NMR (400 MHz, DMSO-d6) δ 10.96 (s, 1H), 9.38 (bs, 1H, TFA salt), 9.04 (s, 1H), 7.65-7.57 (m, 2H), 7.21-7.12 (m, 2H), 6.90 (s, 2H), 6.22 (s, 1H), 5.07 (dd, J = 12.9, 5.0 Hz, 1H), 4.37 (d, J = 16.9 Hz, 1H), 4.30-4.20 (m, 2H), 4.01 (q, J = 7.3 Hz, 7H), 3.93 (s, 7H), 3.66-3.56 (m, 2H), 3.26-3.04 (m, 7H), 2.95-2.85 (m, 2H), 2.80-2.54 (m, 3H), 2.41-2.23 (m, 4H), 2.05-1.91 (m, 3H), 1.29 (t, J = 7.1 Hz, 3H).
D125	831.25	¹ H NMR (400 MHz, DMSO-d6): δ 11.08 (s, 1H), 9.04 (s, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.56 (s, 1H), 7.33 (s, J = 2.3 Hz, 1H), 7.25 (d, J = 8.7, 2.3 Hz, 1H), 6.89 (s, 2H), 6.48 (s, 1H), 5.07 (dd, J = 12.9, 5.4 Hz, 1H), 4.07 (d, J = 12.8 Hz, 2H), 3.88 (s, 6H), 3.62-3.26 (m, J = 7.0 Hz, 12H), 3.10 (s, 3H), 3.03-2.83 (m, 8H), 2.64-2.53 (m, 2H), 2.07-1.98 (m, 1H), 1.76 (d, J = 12.7 Hz, 2H), 1.58 (s, 3H), 1.29-1.15 (m, 2H), 1.09 (t, J = 7.0 Hz, 3H).
D126	746.2	¹ H NMR (400 MHz, Methanol-d4) δ 8.99-8.94 (m, 1H), 7.67 (d, J = 8.3 Hz, 1H), 7.59 (s, 1H), 6.88 (s, 2H), 6.87 (d, J = 2.0 Hz, 1H), 6.75-6.68 (m, 1H), 6.38 (d, J = 1.8 Hz, 1H), 5.12-5.02 (m, 1H), 4.44 (s, 2H), 4.23 (t, J = 7.6 Hz, 4H), 3.99 (s, 8H), 3.87 (s, 2H), 3.60 (s, 4H), 3.34 (s, 1H), 3.31-3.19 (m, 2H), 2.95-2.81 (m, 1H), 2.81-2.64 (m, 2H), 2.60-2.48 (m, 2H), 2.30 (d, J = 14.4 Hz, 2H), 2.21-2.07 (m, 3H).
D127	720.45	¹ H NMR (400 MHz, DMSO-d6) δ 10.90 (s, 1H), 9.01 (s, 1H), 8.17 (s, 1H), 7.51 (d, J = 37.4 Hz, 1H), 6.74 (s, 2H), 6.65-6.35 (m, 3H), 5.01 (dd, J = 13.3, 5.1 Hz, 1H), 4.37-3.99 (m, 2H), 3.80 (s, 5H), 3.59 (s, 3H), 3.54 (s, 2H), 3.46 (s, 2H), 3.15 (s, 1H), 3.05 (s, 5H), 2.58 (s, 1H), 2.45-2.39 (m, 5H), 2.39-2.27 (m, 1H), 1.93 (ddq, J = 10.4, 5.4, 3.2, 2.6 Hz, 1H), 1.71 (t, J = 5.4 Hz, 4H).
D128	720.52	¹ H NMR (400 MHz, DMSO-d6) δ 10.93 (s, 1H), 9.02 (s, 1H), 8.12 (s, 1H), 7.57 (s, 1H), 7.36 (d, J = 8.2 Hz, 1H), 6.80 (s, 2H), 6.67 (d, J = 7.5 Hz, 2H), 6.47 (s, 1H), 5.05 (dd, J = 13.3, 5.1 Hz, 1H), 4.37-4.07 (m, 2H), 3.84 (s, 7H), 3.60 (s, 4H), 3.47 (s, 3H), 3.06 (s, 6H), 2.97-2.84 (m, 1H), 2.81 (d, J = 25.0 Hz, 0H), 2.69-2.52 (m, 1H), 2.42-2.26 (m, 1H), 2.05-1.92 (m, 1H), 1.85 (s, 4H).
D129	864.3	¹ H NMR (400 MHz, Methanol-d4) δ 9.02 (s, 1H), 7.68 (d, J = 9.1 Hz, 1H), 7.58 (s, 1H), 7.45 (d, J = 6.7, 3.2 Hz, 1H), 6.91 (d, J = 4.3 Hz, 2H), 6.70 (d, J = 9.3 Hz, 1H), 5.17-5.03 (m, 2H), 4.41 (s, 2H), 3.98 (d, J = 4.1 Hz, 6H), 3.65 (d, J = 12.7 Hz, 2H), 3.60 (s, 3H), 3.54 (d, J = 15.9 Hz, 1H), 3.38 (s, 1H), 3.21 (s, 6H), 3.19-3.18 (m, 1H), 3.16-2.95 (m, 4H), 2.92-2.82 (m, 1H), 2.82-2.65 (m, 3H), 2.58 (s, 1H), 2.27 (s, 1H), 2.22-2.07 (m, 6H), 2.07-1.93 (m, 4H), 1.66 (q, J = 12.3 Hz, 2H).
D130	876.5	¹ H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.29 (s, 1H, TFA salt), 9.11 (s, 1H, TFA salt), 9.06 (s, 1H), 7.86 (dd, J = 8.2, 2.7 Hz, 1H), 7.63-7.55 (m, 1H), 7.37-7.24 (m, 2H), 6.96-6.87 (m, 2H), 6.56-6.46 (m, 1H), 5.12 (dd, J = 12.8, 5.4 Hz, 1H), 5.02 (t, J = 6.7 Hz, 1H), 4.38-4.21 (m, 2H), 3.91 (s, 6H), 3.50 (s, 3H), 3.43 (d, J = 2.2 Hz, 1H), 3.39 (s, 3H), 3.36-3.30 (m, 1H), 3.28-3.12 (m, 2H), 3.09 (s, 6H), 3.04-2.80 (m, 6H), 2.70-2.54 (m, 3H), 2.47-2.38 (m, 1H), 2.31-2.18 (m, 1H), 2.13-1.93 (m, 4H), 1.94-1.69 (m, 7H).
D131	775.2	¹ H NMR (400 MHz, Methanol-d4) δ 8.97 (d, J = 0.8 Hz, 1H), 7.73 (d, J = 9.2 Hz, 1H), 7.59 (s, 1H), 7.20 (d, J = 6.5 Hz, 2H), 6.88 (s, 2H), 6.39 (s, 1H), 5.14 (dd, J = 13.3, 5.1 Hz, 1H), 4.46 (d, J = 7.1 Hz, 4H), 4.23 (t, J = 7.6 Hz, 4H), 3.98 (s, 6H), 3.86-3.63 (m, 6H), 3.60 (s, 4H), 3.58-3.46 (m, 3H), 3.31-3.24 (m, 3H), 2.99-2.86 (m, 1H), 2.84-2.75 (m, 1H), 2.60-2.42 (m, 5H), 2.18 (d, J = 16.2 Hz, 3H).
D132	665.55	¹ H NMR (400 MHz, Methanol-d4) δ 8.97 (d, J = 0.8 Hz, 1H), 7.73 (d, J = 9.2 Hz, 1H), 7.59 (s, 1H), 7.20 (d, J = 6.5 Hz, 2H), 6.88 (s, 2H), 6.39 (s, 1H), 5.14 (dd, J = 13.3, 5.1 Hz, 1H), 4.46 (d, J = 7.1 Hz, 4H), 4.23 (t, J = 7.6 Hz, 4H), 3.98 (s, 6H), 3.86-3.63 (m, 6H), 3.60 (s, 4H), 3.58-3.46 (m, 3H), 3.31-3.24 (m, 3H), 2.99-2.86 (m, 1H), 2.84-2.75 (m, 1H), 2.60-2.42 (m, 5H), 2.18 (d, J = 16.2 Hz, 3H).

Compound No.	LCMS	^1H NMR
D133	693.35	^1H NMR (400 MHz, DMSO-d6) δ 11.09 (s, 1H), 9.04 (s, 1H), 7.64 (d, J = 9.0 Hz, 1H), 7.58 (d, J = 2.7 Hz, 1H), 7.14 (d, J = 7.2 Hz, 2H), 6.76 (s, 2H), 6.49 (s, 1H), 5.06 (dd, J = 12.9, 5.4 Hz, 1H), 3.97 (d, J = 13.3 Hz, 1H), 3.82 (s, 6H), 3.76 (d, J = 13.1 Hz, 1H), 3.48 (s, 3H), 3.06 (s, 7H), 2.95-2.82 (m, 2H), 2.71-2.54 (m, 4H), 2.01 (d, J = 12.7 Hz, 1H), 1.85 (s, 1H), 1.72 (d, J = 11.2 Hz, 2H), 1.35 (tt, J = 33.0, 18.0 Hz, 2H).
D134	831.6	^1H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 9.05 (s, 1H), 8.15 (s, 0.18H, FA), 7.66 (d, J = 8.5 Hz, 1H), 7.47 (s, 1H), 7.32 (s, 1H), 7.27-7.20 (m, 1H), 6.79 (s, 2H), 6.50 (s, 1H), 6.06-5.96 (m, 1H), 5.23-5.13 (m, 2H), 5.07 (dd, J = 13.0, 5.4 Hz, 1H), 4.57 (d, J = 5.5 Hz, 2H), 4.05 (d, J = 12.9 Hz, 2H), 3.83 (s, 6H), 3.62 (s, 1H), 3.39 (s, 3H), 3.08 (s, 6H), 3.03-2.75 (m, 7H), 2.59 (dd, J = 12.6, 2.9 Hz, 3H), 2.56 (d, J = 2.0 Hz, 3H), 2.08-1.98 (m, 1H), 1.75 (d, J = 12.8 Hz, 2H), 1.64-1.45 (m, 3H), 1.26-1.13 (m, 2H).
D135	845.5	^1H NMR (300 MHz, DMSO-d6) δ 11.08 (s, 1H), 9.04 (s, 1H), 8.15 (s, 0.48H, FA), 7.65 (d, J = 8.5 Hz, 1H), 7.55 (s, 1H), 7.34-7.20 (m, 2H), 6.77 (s, 2H), 6.51 (s, 1H), 5.95-5.76 (m, 1H), 5.14-4.99 (m, 3H), 4.09-3.96 (m, 4H), 3.82 (s, 6H), 3.64 (s, 2H), 3.07 (s, 6H), 2.99-2.86 (m, 3H), 2.65-2.52 (m, 8H), 2.49-2.40 (m, 6H), 2.08-1.94 (m, 1H), 1.74 (d, J = 12.7 Hz, 2H), 1.58 (s, 1H), 1.45-1.34 (m, 2H), 1.27-1.08 (m, 2H).
D136	843.5	^1H NMR (300 MHz, DMSO-d6) δ 11.08 (s, 1H), 9.42 (s, 2H, TFA salt), 9.03 (s, 1H), 7.73-7.58 (m, 2H), 6.91-6.62 (m, 4H), 6.22 (d, J = 5.7 Hz, 1H), 5.06 (dd, J = 12.9, 5.4 Hz, 1H), 4.40-4.19 (m, 2H), 4.03 (t, J = 7.4 Hz, 4H), 3.91 (s, 8H), 3.84 (d, J = 5.0 Hz, 2H), 3.22 (s, 3H), 3.12-2.81 (m, 7H), 2.62 (s, 1H), 2.59-2.53 (m, 4H), 2.34 (q, J = 7.5 Hz, 2H), 2.20-2.15 (m, 3H), 2.08-1.85 (m, 6H), 1.52-1.46 (m, 2H).
D137	693.1	^1H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.01 (s, 1H), 7.88-7.79 (m, 1H), 7.60 (s, 1H), 7.27 (d, 2H), 6.74 (s, 2H), 6.18 (s, 1H), 5.12-4.96 (m, 2H), 3.99 (t, 4H), 3.82 (s, 6H), 3.78-3.70 (m, 3H), 3.48 (s, 4H), 3.24-3.13 (m, 2H), 2.97-2.80 (m, 1H), 2.66-2.62 (m, 1H), 2.61-2.54 (m, 1H), 2.30-2.28 (m, 2H), 2.10-1.92 (m, 1H).
D138	669.15	^1H NMR (400 MHz, DMSO-d6) δ 11.09 (s, 1H), 9.04 (s, 1H), 8.16 (s, 1H, FA), 7.82 (dd, J = 7.5, 0.9 Hz, 1H), 7.59 (s, 1H), 6.76 (s, 2H), 6.46 (s, 1H), 6.38-6.30 (m, 2H), 5.29 (dd, J = 12.5, 5.2 Hz, 1H), 4.76 (t, J = 5.6 Hz, 1H), 3.81 (s, 6H), 3.76-3.63 (m, 4H), 3.48 (s, 3H), 3.10 (dd, J = 8.2, 4.8 Hz, 2H), 3.06 (s, 6H), 2.97-2.83 (m, 1H), 2.68-2.59 (m, 1H), 2.48-2.37 (m, 1H), 2.27-2.07 (m, 1H).
D139	831.8	^1H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 9.05 (s, 1H), 8.15 (s, 1H, FA), 7.67-7.62 (m, 2H), 7.33-7.21 (m, 3H), 6.79 (s, 2H), 6.47 (s, 1H), 6.06 (dd, J = 14.3, 6.8 Hz, 1H), 5.06 (dd, J = 12.9, 5.2 Hz, 1H), 4.03 (d, J = 12.8 Hz, 2H), 3.81 (s, 6H), 3.56 (s, 2H), 3.31 (s, 4H), 3.08 (s, 6H), 2.94-2.90 (m, 3H), 2.63-2.58 (m, 3H), 2.46-2.37 (m, 4H), 2.02 (s, 2H), 1.82 (dd, J = 6.7, 1.7 Hz, 3H), 1.74 (d, J = 12.8 Hz, 2H), 1.58 (s, 1H), 1.38-1.36 (m, 2H), 1.17-1.17 (m, 2H).
D140	848.45	^1H NMR (300 MHz, DMSO-d6) δ 11.13 (s, 1H), 9.03 (s, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.60 (s, 1H), 7.40-7.23 (m, 4H), 6.34 (s, 1H), 5.12 (dd, J = 12.9, 5.3 Hz, 1H), 5.04-4.94 (m, 1H), 3.65 (s, 2H), 3.47 (s, 3H), 3.06 (s, 6H), 2.89 (s, 1H), 2.86-2.76 (m, 4H), 2.63 (s, 5H), 2.13 (d, J = 11.0 Hz, 3H), 2.07 (s, 1H), 1.82 (dd, J = 11.9, 6.4 Hz, 4H), 1.68 (s, 2H), 1.63 (s, 7H), 1.24 (t, J = 7.4 Hz, 3H), 1.03 (d, J = 11.9 Hz, 2H).
D141	736.35	^1H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.52 (s, 1H, TFA), 9.09 (s, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.65 (s, 1H), 7.49 (d, J = 2.3 Hz, 1H), 7.35 (dd, J = 8.6, 2.3 Hz, 1H), 6.90 (s, 2H), 6.67 (s, 1H), 5.10 (dd, J = 13.0, 5.3 Hz, 1H), 4.42-4.31 (m, 2H), 4.20 (d, J = 12.6 Hz, 2H), 3.92 (s, 6H), 3.70 (t, J = 4.8 Hz, 5H), 3.63-3.55 (m, 8H), 3.32 (h, J = 11.6, 10.4 Hz, 4H), 2.90 (ddd, J = 17.4, 14.0, 5.4 Hz, 1H), 2.65-2.54 (m, 2H), 2.07-2.00 (m, 1H).
D142	732.5	^1H NMR (300 MHz, DMSO-d6) δ 10.97 (s, 1H), 9.02 (s, 1H), 8.24 (s, 1H, FA), 7.61 (s, 1H), 7.37 (d, J = 8.1 Hz, 1H), 6.78-6.63 (m, 4H), 6.21 (s, 1H), 5.09 (dd, J = 13.2, 5.1 Hz, 1H), 4.35-4.15 (m, 2H), 4.01 (t, J = 7.3 Hz, 4H), 3.82 (s, 6H), 3.58-3.48 (m, 8H), 2.97-2.85 (m, 1H), 2.67-2.55 (m, 2H), 2.42-2.26 (m, 7H), 1.98 (d, J = 12.6 Hz, 1H), 1.80-1.62 (m, 4H).
D143	789.55	^1H NMR (300 MHz, DMSO-d6) δ 10.96 (s, 1H), 9.85 (br s, 2H, TFA salt), 9.05 (s, 1H), 7.59 (s, 1H), 7.53 (d, J = 8.2 Hz, 1H), 6.90 (d, J = 3.5 Hz, 2H), 6.56-6.44 (m, 3H), 5.05 (dd, J = 13.2, 5.1 Hz, 1H), 4.42 (d, J = 5.4 Hz, 1H), 4.37 (s, 1H), 4.35 (s, 1H), 4.29 (s, 2H),

Compound No.	LCMS	^1H NMR
D144	711.3	4.25 (s, 1H), 4.05 (t, $J = 8.8$ Hz, 2H), 3.91 (s, 6H), 3.78 (s, 2H), 3.70 (s, 2H), 3.50 (s, 3H), 3.41 (d, $J = 17.2$ Hz, 4H), 3.17 (s, 1H), 3.09 (s, 6H), 3.00-2.84 (m, 3H), 2.59 (d, $J = 15.0$ Hz, 1H), 2.35 (dd, $J = 13.0, 4.5$ Hz, 1H), 2.13 (d, $J = 13.8$ Hz, 2H), 2.03-1.83 (m, 3H).
D145	805.25	^1H NMR (300 MHz, DMSO-d6) δ 11.09 (s, 1H), 9.07 (s, 1H), 8.19 (s, 0.6H, FA), 7.87-7.78 (m, 1H), 7.63 (s, 1H), 6.74 (s, 2H), 6.63 (s, 1H), 6.40-6.29 (m, 2H), 5.29 (dd, $J = 12.5, 5.2$ Hz, 1H), 4.76 (t, $J = 5.5$ Hz, 1H), 3.81 (s, 6H), 3.68-3.57 (m, 8H), 3.52-3.50 (m, 7H), 3.10 (t, $J = 6.4$ Hz, 2H), 2.99-2.81 (m, 1H), 2.66-2.50 (m, 1H), 2.49-2.38 (m, 1H), 2.16-2.08 (m, 1H).
D146	677.35	^1H NMR (400 MHz, DMSO-d6) δ 11.14 (s, 1H), 9.01 (s, 1H), 8.18 (s, 1H, FA), 7.90-7.82 (m, 2H), 7.81-7.74 (m, 1H), 7.62 (s, 1H), 6.75 (s, 2H), 6.19 (s, 1H), 5.15 (dd, $J = 12.8, 5.4$ Hz, 1H), 3.99 (t, $J = 7.4$ Hz, 4H), 3.83 (s, 6H), 3.79-3.60 (m, 6H), 3.48 (s, 3H), 3.26 (s, 1H), 2.98-2.80 (m, 1H), 2.66-2.52 (m, 2H), 2.33 (m, $J = 7.2$ Hz, 2H), 2.10-2.01 (m, 1H).
D147	831.4	^1H NMR (300 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.05 (s, 1H), 8.14 (s, 0.4H, FA), 7.47 (s, 1H), 7.39 (d, $J = 8.8$ Hz, 1H), 7.20 (s, 1H), 7.02 (s, 1H), 6.74-6.65 (m, 2H), 6.05 (s, 1H), 5.08 (dd, $J = 13.2, 5.0$ Hz, 1H), 4.40-4.14 (m, 4H), 4.16-4.06 (m, 2H), 3.82 (s, 3H), 3.70-3.51 (m, 8H), 3.63 (s, 3H), 3.51-3.48 (m, 8H), 3.43-3.34 (m, 4H), 3.11-2.70 (m, 1H), 2.76-2.57 (m, 4H), 2.41-2.27 (m, 2H), 2.03-1.93 (m, 1H), 1.98-1.85 (m, 4H).
D148	702.46	
D149	702.46	^1H NMR (400 MHz, DMSO-d6) δ 10.92 (s, 1H), 8.99 (s, 1H), 8.17 (s, 1H), 7.59-7.46 (m, 1H), 7.37 (dd, $J = 18.7, 7.8$ Hz, 2H), 7.17-6.87 (m, 2H), 6.67 (d, $J = 8.1$ Hz, 2H), 5.05 (dd, $J = 13.3, 5.2$ Hz, 1H), 4.39-4.05 (m, 2H), 4.07-3.89 (m, 5H), 3.82 (d, $J = 7.8$ Hz, 4H), 3.58 (s, 3H), 3.47 (d, $J = 16.6$ Hz, 5H), 2.97-2.79 (m, 1H), 2.67-2.51 (m, 2H), 2.45-2.26 (m, 9H), 2.08-1.88 (m, 2H), 1.77 (d, $J = 5.4$ Hz, 5H).
D150	773.42	
D151	845.25	^1H NMR (400 MHz, Methanol-d4) δ 9.10 (d, $J = 0.7$ Hz, 1H), 7.68 (d, $J = 8.5$ Hz, 1H), 7.40 (d, $J = 4.2$ Hz, 1H), 7.36 (d, $J = 2.4$ Hz, 1H), 7.23 (dd, $J = 8.6, 2.4$ Hz, 1H), 6.87 (d, $J = 1.3$ Hz, 2H), 6.57 (s, 1H), 5.87-5.76 (m, 1H), 5.73-5.51 (m, 1H), 5.08 (dd, $J = 12.5, 5.4$ Hz, 1H), 4.75-4.69 (m, 1H), 4.57 (d, $J = 6.2$ Hz, 2H), 4.35 (s, 2H), 4.07 (d, $J = 13.2$ Hz, 2H), 3.96 (s, 6H), 3.47-3.35 (m, 4H), 3.30-3.19 (m, 3H), 3.16 (s, 6H), 3.07-2.94 (m, 4H), 2.92-2.81 (m, 1H), 2.82-2.65 (m, 2H), 2.17-2.06 (m, 1H), 1.93-1.81 (m, 3H), 1.73 (dd, $J = 6.4, 1.4$ Hz, 3H), 1.71-1.60 (m, 2H), 1.44-1.31 (m, 2H).
D152	789.4	^1H NMR (300 MHz, Methanol-d4) δ 9.12 (s, 1H), 7.50-7.39 (m, 2H), 6.89 (d, $J = 2.7$ Hz, 3H), 6.81 (dd, $J = 8.2, 2.2$ Hz, 1H), 6.52 (s, 1H), 5.17-5.11 (m, 1H), 4.57-4.52 (m, 2H), 4.40 (d, $J = 6.5$ Hz, 4H), 4.18 (s, 2H), 3.97 (s, 6H), 3.78 (s, 4H), 3.67 (s, 1H), 3.60 (s, 4H), 3.57-3.50 (m, 4H), 3.15 (s, 8H), 2.98-2.80 (m, 2H), 2.60-2.44 (m, 1H), 2.32-2.01 (m, 5H).
D153	801.6	^1H NMR (300 MHz, DMSO-d6) δ 10.95 (s, 1H), 9.02 (s, 1H), 8.22 (s, 2H, FA), 7.60 (s, 1H), 7.48 (d, $J = 8.2$ Hz, 1H), 6.76 (s, 2H), 6.54-6.42 (m, 2H), 6.19 (s, 1H), 5.04 (dd, $J = 13.2, 5.1$ Hz, 1H), 4.30 (d, $J = 17.0$ Hz, 1H), 4.17 (d, $J = 17.0$ Hz, 1H), 4.01 (t, $J = 7.4$ Hz, 4H), 3.83 (s, 6H), 3.78 (s, 2H), 3.62 (s, 3H), 3.59-3.52 (m, 2H), 3.48 (s, 3H), 3.13 (s, 2H), 2.91 (ddd, $J = 17.8, 13.5, 5.4$ Hz, 1H), 2.64-2.57 (m, 2H), 2.56-2.49 (m, 3H), 2.44 (d, $J = 6.9$ Hz, 2H), 2.40-2.24 (m, 5H), 2.00-1.88 (m, 1H), 1.73 (t, $J = 5.4$ Hz, 4H).
D154	682.5	^1H NMR (300 MHz, Methanol-d4) δ 9.15 (s, 1H), 7.70 (d, $J = 8.1$ Hz, 1H), 7.43 (s, 1H), 6.81 (s, 2H), 6.72 (d, $J = 8.1$ Hz, 1H), 6.52 (s, 1H), 6.14 (s, 1H), 5.26 (d, $J = 10.2$ Hz, 1H), 3.92 (s, 8H), 3.59 (s, 3H), 3.42 (s, 4H), 3.12 (s, 6H), 3.0-2.80 (m, 6H), 2.70-2.52 (m, 1H), 2.40-2.20 (m, 1H).
D155	791.45	^1H NMR (300 MHz, Methanol-d4) δ 9.16 (d, $J = 0.7$ Hz, 1H), 8.53 (s, 1H), 7.68 (d, $J = 8.5$ Hz, 1H), 7.44 (s, 1H), 7.35 (d, $J = 2.3$ Hz, 1H), 7.23 (dd, $J = 8.7, 2.4$ Hz, 1H), 6.86 (s, 2H), 6.51 (s, 1H), 5.08 (dd, $J = 12.3, 5.4$ Hz, 1H), 4.21 (s, 2H), 4.06 (d, $J = 13.0$ Hz, 2H), 3.95 (s, 6H), 3.60 (s, 3H), 3.24-3.10 (m, 10H), 3.10-2.96 (m, 3H), 2.95-2.77 (m, 3H), 2.76-2.62 (m, 3H), 2.36 (d, $J = 6.6$ Hz, 2H), 2.17-2.06 (m, 1H), 1.98-1.86 (m, 3H), 1.39-1.22 (m, 2H).

Compound No.	LCMS	^1H NMR
D156	859.55	^1H NMR (300 MHz, DMSO-d6) δ 11.09 (s, 1H), 9.28 (s, 1H), 7.85 (s, 1H), 7.66 (d, J = 8.6 Hz, 1H), 7.32 (s, 1H), 7.24 (d, J = 11.1 Hz, 2H), 6.81 (s, 2H), 5.12-5.01 (m, 1H), 4.06 (d, J = 12.9 Hz, 2H), 3.83 (s, 6H), 3.71-3.43 (m, 5H), 3.17-2.70 (m, 9H), 2.66-2.52 (m, 4H), 2.52-2.13 (m, 5H), 2.06-2.00 (m, 1H), 1.75 (d, J = 12.3 Hz, 2H), 1.59-1.53 (m, 3H), 1.24-1.14 (m, 2H).
D157	682.1	^1H NMR (400 MHz, DMSO) δ 11.13 (s, 1H), 9.03 (s, 1H), 7.89-7.83 (m, 1H), 7.56 (s, 1H), 7.29 (d, J = 7.5 Hz, 2H), 6.81 (s, 2H), 6.47 (s, 1H), 5.28-5.18 (m, 1H), 5.13 (dd, J = 12.9, 5.4 Hz, 1H), 4.88 (tt, J = 7.1, 7.1, 3.9, 3.9 Hz, 1H), 3.85 (s, 6H), 3.47 (s, 3H), 3.07 (s, 6H), 2.90 (ddd, J = 18.9, 13.7, 5.3 Hz, 1H), 2.69 (ddd, J = 13.4, 6.3, 3.3 Hz, 2H), 2.64-2.51 (m, 2H), 2.40 (ddd, J = 12.3, 6.7, 4.2 Hz, 2H), 2.11-2.00 (m, 1H).
D158	805.4	^1H NMR (300 MHz, DMSO-d6) δ 11.07 (s, 1H), 10.20-9.86 (m, 1H), 9.30-9.10 (m, 1H), 9.02 (s, 1H), 7.84 (dd, J = 7.8, 4.2 Hz, 1H), 7.63 (d, J = 2.1 Hz, 1H), 6.87 (s, 2H), 6.80-6.68 (m, 1H), 6.35 (d, J = 5.7 Hz, 1H), 6.23 (d, J = 5.7 Hz, 1H), 5.27 (dd, J = 12.3, 5.1 Hz, 1H), 4.22 (d, J = 3.6 Hz, 2H), 4.10-3.96 (m, 6H), 3.90 (s, 6H), 3.65-3.52 (m, 2H), 3.50-3.34 (m, 5H), 3.30-3.10 (m, 6H), 3.08-2.80 (m, 2H), 2.75-2.60 (m, 1H), 2.50-2.42 (m, 2H), 2.42-2.28 (m, 2H), 2.20-2.08 (m, 1H), 1.96-1.70 (m, 3H), 1.70-1.40 (m, 4H).
D159	843.45	^1H NMR (300 MHz, DMSO-d6) δ 10.96 (s, 1H), 9.02 (s, 1H), 7.62-7.40 (m, 2H), 7.04 (d, J = 7.9 Hz, 2H), 6.75 (s, 2H), 6.20 (s, 1H), 5.86-5.53 (m, 2H), 5.05 (dd, J = 13.3, 5.1 Hz, 1H), 4.54 (dd, J = 34.6, 6.2 Hz, 2H), 4.38-4.14 (m, 2H), 4.01 (t, J = 7.4 Hz, 4H), 3.82 (s, 8H), 3.67 (s, 2H), 3.00-2.71 (m, 5H), 2.61 (s, 9H), 2.35 (d, J = 8.0 Hz, 3H), 1.95 (d, J = 11.4 Hz, 1H), 1.80-1.59 (m, 5H), 1.45 (s, 3H), 1.21 (d, J = 13.5 Hz, 2H).
D160	772.2	^1H NMR (300 MHz, DMSO-d6) δ 10.95 (s, 1H), 9.02 (s, 1H), 8.15 (s, 1H), 7.59-7.44 (m, 2H), 6.76 (s, 2H), 6.55-6.44 (m, 2H), 6.20 (s, 1H), 5.66 (qq, J = 10.0, 5.4, 5.0 Hz, 2H), 5.04 (dd, J = 13.2, 5.1 Hz, 1H), 4.55 (dd, J = 34.7, 6.0 Hz, 2H), 4.34-4.13 (m, 2H), 4.01 (t, J = 7.4 Hz, 4H), 3.84 (s, 6H), 3.68 (d, J = 16.8 Hz, 6H), 2.97-2.84 (m, 1H), 2.61 (s, 5H), 2.39-2.29 (m, 3H), 1.94 (dd, J = 11.2, 5.4 Hz, 1H), 1.78 (d, J = 8.0 Hz, 5H), 1.66 (d, J = 5.6 Hz, 2H).
D161	747.25	^1H NMR (400 MHz, DMSO-d6) δ 10.96 (s, 1H), 9.01 (s, 1H), 8.19 (s, 1H, FA salt), 7.60 (s, 1H), 7.52 (d, J = 9.1 Hz, 1H), 7.08-7.01 (m, 2H), 6.74 (s, 2H), 6.19 (s, 1H), 5.05 (dd, J = 13.3, 5.1 Hz, 1H), 4.33 (d, J = 16.9 Hz, 1H), 4.20 (d, J = 16.9 Hz, 1H), 4.00 (t, J = 7.4 Hz, 4H), 3.82 (s, 6H), 3.68 (s, 2H), 3.48 (s, 3H), 3.30-3.25 (m, 6H), 3.05 (t, J = 6.5 Hz, 2H), 2.97-2.80 (m, 2H), 2.63-2.54 (m, 1H), 2.44-2.26 (m, 7H), 2.00-1.92 (m, 1H).
D162	679.1	^1H NMR (400 MHz, Methanol-d4) δ 9.10 (s, 1H), 8.52 (s, FA, 1H), 7.56 (d, J = 8.3 Hz, 1H), 7.47 (s, 1H), 7.25-7.16 (m, 2H), 6.83 (s, 2H), 6.19 (s, 1H), 5.16 (dd, J = 13.4, 5.2 Hz, 1H), 5.11-5.03 (m, 1H), 4.63-4.43 (m, 2H), 4.38 (d, J = 23.9 Hz, 4H), 4.08 (d, J = 7.4 Hz, 4H), 4.05 (s, 1H), 3.93 (s, 6H), 3.59 (s, 3H), 2.93 (ddd, J = 17.6, 13.5, 5.4 Hz, 1H), 2.80 (ddd, J = 17.7, 4.7, 2.4 Hz, 1H), 2.60-2.37 (m, 3H), 2.19 (ddt, J = 12.8, 5.3, 2.4 Hz, 1H), 1.49 (s, 1H).
D163	639.2	^1H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 9.02 (s, 1H), 7.63 (d, J = 8.6 Hz, 1H), 7.58 (s, 1H), 7.31 (d, J = 2.4 Hz, 1H), 7.04 (dd, J = 8.7, 2.4 Hz, 1H), 6.80 (s, 2H), 6.44 (s, 1H), 5.05 (dd, J = 12.9, 5.4 Hz, 1H), 4.68 (s, 2H), 3.88 (s, 6H), 3.46 (s, 3H), 3.13 (s, 3H), 3.05 (s, 6H), 2.95-2.82 (m, 1H), 2.63-2.56 (m, 1H), 2.55 (s, 1H), 2.06-1.95 (m, 1H).
D164	791.5	^1H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.54 (s, 1H), 8.15 (s, 0.9H, FA), 7.68 (d, J = 8.4 Hz, 1H), 7.34 (d, J = 2.4 Hz, 1H), 7.28-7.23 (m, 1H), 7.18 (s, 1H), 7.13 (s, 1H), 6.93 (d, J = 5.1 Hz, 1H), 6.78 (s, 2H), 5.07 (dd, J = 12.8, 5.4 Hz, 1H), 3.85 (s, 9H), 3.53 (s, 4H), 3.44-3.42 (m, 5H), 3.12-3.08 (m, 2H), 2.91-2.87 (m, 1H), 2.85 (d, J = 4.9 Hz, 3H), 2.64-2.53 (m, 3H), 2.37-2.32 (m, 3H), 2.04-1.99 (m, 1H), 1.77-1.70 (m, 2H), 1.47-1.37 (m, 3H), 1.32-1.23 (m, 3H).
D165	781.45	^1H NMR (400 MHz, Methanol-d4) δ 8.49 (s, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.33-7.27 (m, 2H), 7.15 (s, 1H), 6.91 (s, 2H), 5.11 (dd, J = 12.5, 5.4 Hz, 1H), 4.54 (s, 2H), 3.99 (s, 10H), 3.78 (d, J = 25.5 Hz, 3H), 3.63 (s, 3H), 3.53 (s, 8H), 2.97 (d, J = 8.7 Hz, 6H), 2.93-2.66 (m, 4H), 2.20-2.11 (m, 1H).
D166	822.65	^1H NMR (400 MHz, Methanol-d4) δ 8.52 (s, 1H, FA), 8.50 (d, J = 8.1 Hz, 1H), 7.80-7.71 (m, 1H), 7.42 (dd, J = 5.6, 2.3 Hz, 1H), 7.34-7.28 (m, 1H), 7.23 (d, J = 0.9 Hz, 1H), 7.11-7.08 (m, 1H), 6.81 (d, J = 5.0 Hz, 2H), 5.09 (dd, J = 12.7, 5.5 Hz, 1H), 4.34-4.27 (m, 2H), 4.26-3.98 (m, 4H), 3.90 (s, 6H), 3.89-3.82 (m, 5H), 3.75-3.69 (m, 1H), 3.65 (s, 6H), 2.97 (s, 3H), 2.93-2.78 (m, 2H), 2.78-2.61 (m, 4H), 2.14-2.06 (m, 1H), 2.04-1.82 (m, 2H).

Compound No.	LCMS	^1H NMR
D167	820.35	^1H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 8.51 (s, 1H), 7.82 (dd, J = 8.5, 7.2 Hz, 1H), 7.70 (s, 1H), 7.53 (d, J = 8.5 Hz, 1H), 7.45 (d, J = 1.2 Hz, 1H), 7.17 (s, 1H), 7.11 (s, 1H), 6.93 (d, J = 5.2 Hz, 1H), 6.86-6.51 (m, 2H), 5.08 (dd, J = 12.9, 5.4 Hz, 1H), 4.21 (t, J = 6.3 Hz, 2H), 3.84 (s, 6H), 3.52 (s, 3H), 3.49 (s, 2H), 3.13-3.03 (m, 2H), 2.93-2.81 (m, 4H), 2.64-2.52 (m, 3H), 2.10-1.99 (m, 4H), 1.92 (s, 5H), 1.83-1.73 (m, 2H), 1.55-1.39 (m, 4H).
D168	834.5	^1H NMR (300 MHz, DMSO-d6) δ 11.14 (s, 1H), 8.52 (s, 1H), 8.19 (s, 1H, FA), 7.81 (dd, J = 8.5, 7.2 Hz, 1H), 7.65 (t, J = 5.8 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 7.2 Hz, 1H), 7.18 (s, 1H), 7.12 (s, 1H), 6.93 (d, J = 5.0 Hz, 1H), 6.72 (s, 2H), 5.08 (dd, J = 12.8, 5.4 Hz, 1H), 4.20 (t, J = 6.3 Hz, 2H), 3.80 (s, 6H), 3.57 (s, 2H), 3.53 (s, 3H), 3.28-3.13 (m, 2H), 3.09-3.01 (m, 2H), 2.95-2.81 (m, 4H), 2.64-2.53 (m, 2H), 2.13 (s, 3H), 2.08-1.97 (m, 1H), 1.86 (s, 6H), 1.77 (t, J = 6.7 Hz, 2H), 1.53-1.37 (m, 4H).
D169	833.25	^1H NMR (300 MHz, DMSO-d6) δ 11.07 (s, 1H), 8.85 (s, 1H), 8.55 (s, 1H), 7.82 (t, J = 5.8 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.20 (s, 1H), 7.16-7.07 (m, 2H), 6.95 (d, J = 2.1 Hz, 1H), 6.90-6.80 (m, 3H), 5.03 (dd, J = 12.8, 5.3 Hz, 1H), 4.37 (d, J = 12.5 Hz, 1H), 4.19 (dd, J = 12.7, 7.8 Hz, 1H), 3.91 (s, 6H), 3.54 (s, 3H), 3.39-3.26 (m, 2H), 3.15 (s, 2H), 3.10-3.02 (m, 2H), 3.02-2.76 (m, 5H), 2.67 (d, J = 4.7 Hz, 3H), 2.60 (s, 1H), 2.10 (s, 6H), 2.02-1.92 (m, 1H), 1.65-1.53 (m, 2H), 1.51-1.41 (m, 2H), 1.40-1.29 (m, 2H).
D170	820.4	^1H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.52 (d, J = 9.1 Hz, 1H), 8.07-7.67 (m, 2H), 7.43 (s, 1H), 7.36 (dd, J = 8.3, 2.2 Hz, 1H), 7.18 (d, J = 14.4 Hz, 1H), 7.12 (d, J = 7.3 Hz, 1H), 6.94 (s, 1H), 6.86 (d, J = 9.4 Hz, 1H), 6.70 (s, 1H), 5.12 (dd, J = 12.9, 5.4 Hz, 1H), 4.40-4.02 (m, 3H), 3.90 (d, J = 6.2 Hz, 3H), 3.79 (s, 3H), 3.53 (d, J = 3.9 Hz, 3H), 3.49 (s, 1H), 3.15-3.03 (m, 2H), 2.95-2.87 (m, 1H), 2.85 (d, J = 4.8 Hz, 3H), 2.67-2.53 (m, 4H), 2.31-2.25 (m, 2H), 2.11-2.00 (m, 3H), 1.92 (s, 3H), 1.82-1.73 (m, 2H), 1.54-1.36 (m, 4H).
D171	866.25	^1H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.52 (s, 1H), 8.36 (s, 1H, FA), 7.64 (t, J = 5.8 Hz, 1H), 7.58 (dd, J = 8.6, 7.0 Hz, 1H), 7.17 (s, 1H), 7.14-7.08 (m, 2H), 7.02 (d, J = 7.1 Hz, 1H), 6.96-6.90 (m, 1H), 6.72 (s, 2H), 6.53 (t, J = 6.0 Hz, 1H), 5.05 (dd, J = 12.9, 5.4 Hz, 1H), 3.80 (s, 6H), 3.54 (s, 2H), 3.53 (s, 3H), 3.28-3.26 (m, 2H), 3.06-3.00 (m, 2H), 2.90-2.82 (m, 4H), 2.62-2.54 (m, 3H), 2.46 (s, 1H), 2.11 (s, 3H), 2.07-1.99 (m, 1H), 1.85 (s, 6H), 1.63-1.53 (m, 2H), 1.49-1.40 (m, 2H), 1.36-1.27 (m, 2H).
D172	834.25	^1H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.83 (s, 1H, TFA), 8.55 (s, 1H), 7.88-7.80 (m, 2H), 7.43 (d, J = 2.2 Hz, 1H), 7.35 (dd, J = 8.3, 2.3 Hz, 1H), 7.20 (s, 1H), 7.14 (s, 1H), 6.97 (s, 1H), 6.87 (s, 2H), 5.12 (dd, J = 12.9, 5.3 Hz, 1H), 4.37 (d, J = 12.6 Hz, 1H), 4.24-4.12 (m, 3H), 3.91 (s, 6H), 3.54 (s, 5H), 3.13-3.03 (m, 2H), 2.93-2.79 (m, 4H), 2.71-2.60 (m, 4H), 2.58-2.56 (m, 1H), 2.13-1.99 (m, 7H), 1.76 (d, J = 6.8 Hz, 2H), 1.53-1.36 (m, 4H).
D173	834.25	^1H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.83 (s, 1H, TFA), 8.55 (s, 1H), 7.88-7.80 (m, 2H), 7.43 (d, J = 2.2 Hz, 1H), 7.35 (dd, J = 8.3, 2.3 Hz, 1H), 7.20 (s, 1H), 7.14 (s, 1H), 6.97 (s, 1H), 6.87 (s, 2H), 5.12 (dd, J = 12.9, 5.3 Hz, 1H), 4.37 (d, J = 12.6 Hz, 1H), 4.24-4.12 (m, 3H), 3.91 (s, 6H), 3.54 (s, 5H), 3.13-3.03 (m, 2H), 2.93-2.79 (m, 4H), 2.71-2.60 (m, 4H), 2.58-2.56 (m, 1H), 2.13-1.99 (m, 7H), 1.76 (d, J = 6.8 Hz, 2H), 1.53-1.36 (m, 4H).
D174	844.55	^1H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.04 (s, 1H), 8.15 (s, 1H, FA), 7.83 (d, J = 8.2 Hz, 1H), 7.55 (s, 1H), 7.38-7.22 (m, 2H), 6.96 (d, J = 10.0 Hz, 2H), 6.45 (s, 1H), 5.12 (dd, J = 12.8, 5.4 Hz, 1H), 5.06-4.93 (m, 1H), 3.82 (s, 3H), 3.65 (s, 2H), 3.48 (s, 3H), 3.07 (s, 6H), 2.95-2.81 (m, 3H), 2.82-2.72 (m, 2H), 2.70-2.53 (m, 3H), 2.49-2.38 (m, 4H), 2.38-2.13 (m, 5H), 2.11-1.98 (m, 1H), 1.84 (dd, J = 11.9, 6.4 Hz, 2H), 1.77-1.41 (m, 7H), 1.22 (t, J = 7.5 Hz, 3H), 1.18-0.98 (m, 2H).
D175	812.2	^1H NMR (400 MHz, Methanol-d4) δ 9.28 (d, J = 1.8 Hz, 1H), 8.57 (s, 1H, FA), 7.96-7.46 (m, 2H), 7.39 (d, J = 8.0 Hz, 1H), 6.97 (d, J = 1.9 Hz, 1H), 6.85 (d, J = 2.0 Hz, 3H), 6.81-6.73 (m, 1H), 5.12 (dd, J = 13.0, 5.3 Hz, 1H), 4.67-4.61 (m, 1H), 4.46-4.32 (m, 4H), 4.18-4.09 (m, 2H), 3.97 (d, J = 2.0 Hz, 6H), 3.87-3.78 (m, 2H), 3.67 (d, J = 2.0 Hz, 6H), 3.43-3.39 (m, 1H), 3.12-3.04 (m, 1H), 2.99-2.85 (m, 1H), 2.85-2.75 (m, 1H), 2.68 (d, J = 7.0 Hz, 2H), 2.57-2.38 (m, 4H), 2.23-2.13 (m, 1H), 1.93-1.84 (m, 4H).
D176	774.3	^1H NMR (300 MHz, DMSO-d6) δ 10.96 (s, 1H), 8.18 (s, 1H), 8.07 (d, J = 8.8 Hz, 1H), 7.52 (d, J = 8.6 Hz, 1H), 7.20 (d, J = 7.7 Hz, 1H), 7.05 (d, J = 8.2 Hz, 2H), 6.65 (d, J = 8.9 Hz, 1H), 6.53 (s, 2H), 5.86 (d, J = 7.6 Hz, 1H), 5.05 (dd, J = 13.2, 5.1 Hz, 1H), 4.38-4.14

Compound No.	LCMS	¹ H NMR
D177	746.2	(m, 2H), 3.75 (s, 6H), 3.65-3.51 (m, 6H), 3.41 (s, 5H), 3.01-2.84 (m, 3H), 2.61 (s, 4H), 2.42-1.87 (m, 9H), 1.80-1.67 (m, 2H), 1.56-1.37 (m, 2H).
D178	888.2	¹ H NMR (400 MHz, DMSO-d6) δ 10.99 (s, 1H), 9.02 (s, 1H), 8.26 (s, 2H, FA), 7.67-7.58 (m, 2H), 7.49 (s, 1H), 7.40 (d, J = 8.0 Hz, 1H), 6.74 (s, 2H), 6.20 (s, 1H), 5.11 (dd, J = 13.3, 5.1 Hz, 1H), 4.42 (d, J = 17.2 Hz, 1H), 4.28 (d, J = 17.3 Hz, 1H), 4.01 (t, J = 7.4 Hz, 4H), 3.82 (s, 6H), 3.64 (s, 2H), 3.49 (s, 3H), 3.35-3.34 (m, 2H), 2.97-2.92 (m, 2H), 2.90-2.86 (m, 1H), 2.82-2.73 (m, 3H), 2.66-2.56 (m, 2H), 2.41 (d, J = 4.6 Hz, 1H), 2.37-2.30 (m, 2H), 2.03-1.96 (m, 1H), 1.83 (t, J = 11.0 Hz, 2H), 1.78-1.71 (m, 2H), 1.70-1.60 (m, 2H).
D179	746.25	¹ H NMR (400 MHz, Methanol-d4) δ 9.14 (s, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.55-7.51 (m, 1H), 7.30 (d, J = 2.3 Hz, 1H), 7.28-7.23 (m, 1H), 6.88 (d, J = 4.7 Hz, 2H), 6.72 (s, 1H), 5.17-5.07 (m, 1H), 5.02-4.95 (m, 1H), 4.40 (s, 2H), 3.97 (d, J = 4.4 Hz, 6H), 3.88-3.77 (m, 5H), 3.66 (d, J = 12.8 Hz, 2H), 3.61 (s, 3H), 3.58 (d, J = 4.8 Hz, 4H), 3.44-3.37 (m, 1H), 3.18 (dd, J = 13.2, 10.3 Hz, 2H), 3.13-2.97 (m, 4H), 2.92-2.83 (m, 1H), 2.81-2.78 (m, 1H), 2.76-2.67 (m, 2H), 2.61-2.51 (m, 1H), 2.33-2.22 (m, 1H), 2.22-2.08 (m, 6H), 2.09-2.04 (m, 3H), 1.74-1.59 (m, 2H).
D180	780.3	¹ H NMR (400 MHz, DMSO-d6) δ 11.10 (s, 1H), 9.02 (s, 1H), 8.24 (s, 2H, FA), 7.62 (s, 1H), 7.58-7.48 (m, 3H), 6.74 (s, 2H), 6.20 (s, 1H), 5.11 (dd, J = 13.2, 5.0 Hz, 1H), 4.42 (d, J = 17.1 Hz, 1H), 4.28 (d, J = 17.1 Hz, 1H), 4.01 (t, J = 7.4 Hz, 4H), 3.82 (s, 6H), 3.67 (s, 2H), 3.48 (s, 3H), 3.40-3.37 (m, 2H), 3.04-2.97 (m, 2H), 2.94-2.87 (m, 1H), 2.82-2.74 (m, 3H), 2.65-2.56 (m, 2H), 2.44-2.38 (m, 1H), 2.38-2.30 (m, 2H), 2.05-1.97 (m, 1H), 1.89-1.73 (m, 4H), 1.73-1.60 (m, 2H).
D181	773.55	¹ H NMR (300 MHz, DMSO-d6) δ 10.96 (s, 1H), 8.21 (s, 1H, FA), 8.07 (d, J = 8.9 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.20 (d, J = 7.7 Hz, 1H), 7.04 (d, J = 7.7 Hz, 2H), 6.65 (d, J = 9.0 Hz, 1H), 6.52 (s, 2H), 5.85 (d, J = 7.6 Hz, 1H), 5.05 (dd, J = 13.2, 5.1 Hz, 1H), 4.25 (dd, J = 22.4 Hz, 2H), 3.90 (d, J = 12.2 Hz, 2H), 3.74 (s, 6H), 3.58 (d, J = 6.4 Hz, 6H), 3.55 (s, 3H), 2.95-2.85 (m, 3H), 2.82-2.66 (m, 2H), 2.61 (d, J = 3.6 Hz, 1H), 2.42-2.28 (m, 1H), 2.10-2.03 (m, 4H), 1.99-1.88 (m, 1H), 1.74 (d, J = 9.0 Hz, 2H), 1.64 (d, J = 12.1 Hz, 2H), 1.31-1.10 (m, 5H), 1.05 (d, J = 9.6 Hz, 1H).
D182	845.25	¹ H NMR (300 MHz, DMSO-d6) δ 10.99 (s, 1H), 9.25 (br s, 1H, TFA salt), 9.14 (s, 1H), 8.11 (s, 1H), 7.64 (dd, J = 8.4, 2.3 Hz, 1H), 7.20 (d, J = 4.5 Hz, 2H), 7.06 (d, J = 2.3 Hz, 1H), 6.98 (dd, J = 8.4, 2.2 Hz, 1H), 5.08 (dd, J = 13.3, 5.1 Hz, 1H), 4.87 (p, J = 6.7 Hz, 1H), 4.48-4.18 (m, 6H), 4.17-4.12 (m, 3H), 3.91 (s, 6H), 3.42 (s, 3H), 3.19 (s, 2H), 3.08-2.80 (m, 7H), 2.68-2.55 (m, 2H), 2.43-2.30 (m, 4H), 2.11-1.76 (m, 11H), 1.59-1.37 (m, 2H).
D183	773.2	¹ H NMR (400 MHz, DMSO-d6) δ 10.99 (s, 1H), 8.21 (s, 1H, FA), 8.07 (d, J = 8.9 Hz, 1H), 7.64 (d, J = 7.9 Hz, 1H), 7.49 (s, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.21 (d, J = 7.7 Hz, 1H), 6.65 (d, J = 9.0 Hz, 1H), 6.53 (s, 2H), 5.86 (d, J = 7.7 Hz, 1H), 5.11 (dd, J = 13.3, 5.1 Hz, 1H), 4.42 (d, J = 17.3 Hz, 1H), 4.28 (d, J = 17.3 Hz, 1H), 3.75 (s, 6H), 3.62-3.54 (m, 6H), 3.41 (s, 3H), 3.01-2.87 (m, 5H), 2.68-2.56 (m, 2H), 2.44-2.24 (m, 4H), 2.15-2.00 (m, 5H), 1.80-1.64 (m, 6H), 1.48 (q, J = 11.8 Hz, 2H).
D184	776.3	¹ H NMR (300 MHz, Methanol-d4) δ 9.25 (s, 1H), 7.57 (s, 1H), 7.41 (d, J = 8.2 Hz, 1H), 6.96-6.72 (m, 5H), 5.14 (dd, J = 13.2, 5.1 Hz, 1H), 4.55 (s, 2H), 4.49-4.30 (m, 4H), 4.27-4.07 (m, 2H), 3.99 (d, J = 9.8 Hz, 9H), 3.78 (s, 4H), 3.64 (s, 3H), 3.59-3.48 (m, 5H), 3.27-3.01 (m, 2H), 3.00-2.69 (m, 2H), 2.50 (dd, J = 13.1, 4.8 Hz, 1H), 2.35-2.00 (m, 5H).

Example 44—Preparation of Compounds
D185-D316

In analogy to the procedures described in the examples above, compounds D185-D316 were prepared using the appropriate starting materials

Compound No.	LCMS	^1H NMR
D185	829.45	^1H NMR (400 MHz, Methanol-d4) δ 9.02 (s, 1H), 7.62 (d, J = 8.2 Hz, 1H), 7.55 (s, 1H), 6.88 (s, 2H), 6.63-6.50 (m, 2H), 6.31 (s, 1H), 5.10 (dd, J = 13.3, 5.1 Hz, 1H), 4.56-4.30 (m, 6H), 4.19 (t, J = 7.5 Hz, 6H), 3.99 (s, 6H), 3.87 (s, 2H), 3.77 (s, 2H), 3.59 (s, 3H), 3.57-3.46 (m, 3H), 3.09-2.85 (m, 3H), 2.83-2.74 (m, 1H), 2.58-2.40 (m, 3H), 2.34-2.07 (m, 5H), 1.53 (s, 6H).
D186	814.35	^1H NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1H), 9.57 (s, 1H), 8.09 (s, 1H), 7.88 (s, 1H), 7.37 (d, J = 8.0 Hz, 1H), 6.81 (s, 2H), 6.68 (d, J = 7.9 Hz, 2H), 5.08 (dd, J = 13.3, 5.1 Hz, 1H), 4.36-4.14 (m, 2H), 3.81 (s, 6H), 3.67 (d, J = 15.0 Hz, 6H), 3.57 (s, 5H), 2.99 (t, J = 6.9 Hz, 2H), 2.96-2.84 (m, 1H), 2.70-2.56 (m, 2H), 2.46-2.38 (m, 2H), 2.37-2.17 (m, 5H), 2.06-1.90 (m, 1H), 1.78-1.65 (m, 4H).
D187	844.40	^1H NMR (400 MHz, MeOD) δ 9.11 (s, 1H), 8.49 (s, 3H), 7.52-7.45 (m, 2H), 7.21 (d, J = 2.4 Hz, 1H), 7.16 (dd, J = 8.3, 2.4 Hz, 1H), 6.87 (s, 2H), 6.21 (s, 1H), 5.17 (d, J = 5.2 Hz, 1H), 4.84-4.78 (m, 1H), 4.66-4.60 (m, 1H), 4.50-4.38 (m, 2H), 4.36-4.33 (m, 2H), 4.09 (t, J = 7.4, 7.4 Hz, 4H), 3.97 (s, 6H), 3.60 (s, 3H), 3.55-3.48 (m, 1H), 3.17-3.08 (m, 1H), 2.96-2.87 (m, 1H), 2.84-2.76 (m, 1H), 2.71-2.59 (m, 3H), 2.56-2.44 (m, 4H), 2.44-2.36 (m, 2H), 2.23-2.16 (m, 1H), 2.07-1.91 (m, 5H), 1.85-1.77 (m, 4H), 1.57-1.52 (m, 2H), 1.37-1.28 (m, 3H).
D188	868.30	^1H NMR (400 MHz, Methanol-d4) δ 9.62 (s, 1H), 8.46 (s, 1H), 8.16 (s, 1H, FA), 7.91 (s, 1H), 7.49 (d, J = 8.3 Hz, 1H), 7.21-7.16 (m, 2H), 6.90 (s, 2H), 5.15 (dd, J = 13.3, 5.1 Hz, 1H), 4.85-4.82 (m, 1H), 4.51-4.36 (m, 4H), 3.98 (s, 6H), 3.74 (s, 3H), 3.57 (d, J = 12.1 Hz, 2H), 3.18 (d, J = 12.3 Hz, 2H), 3.08-2.86 (m, 5H), 2.84-2.76 (m, 3H), 2.64-2.46 (m, 3H), 2.20 (m, 2H), 2.12-2.06 (m, 1H), 2.1-1.98 (m, 3H), 1.97-1.84 (m, 4H), 1.64 (s, 2H).
D189	809.20	^1H NMR (300 MHz, Methanol-d4) δ 9.15 (d, J = 0.7 Hz, 1H), 7.64 (d, J = 9.2 Hz, 1H), 7.46 (s, 1H), 7.28 (d, J = 1.3 Hz, 1H), 7.22 (d, J = 1.3 Hz, 1H), 7.10 (d, J = 7.8 Hz, 2H), 6.42 (s, 1H), 5.18-5.06 (m, 1H), 4.50-4.31 (m, 2H), 3.99 (s, 1H), 3.97-3.92 (m, 4H), 3.69-3.63 (m, 2H), 3.62-3.52 (m, 4H), 3.35 (s, 2H), 3.41-3.34 (m, 2H), 3.18-3.07 (m, 7H), 3.02-2.84 (m, 4H), 2.87-2.73 (m, 1H), 2.58-2.39 (m, 1H), 2.24-2.09 (m, 1H), 1.93-1.83 (m, 2H), 1.81-1.70 (m, 2H), 1.69-1.63 (m, 1H), 1.55-1.36 (m, 2H), 1.36-1.23 (m, 1H).
D190	861.30	^1H NMR (400 MHz, DMSO-d6) δ 11.00 (s, 1H), 9.41 (s, 1H), 7.88 (s, 1H), 7.65 (s, 1H), 7.49 (d, J = 8.3 Hz, 1H), 7.13 (dd, J = 8.3, 2.4 Hz, 1H), 7.07 (d, J = 2.4 Hz, 1H), 6.81 (s, 2H), 5.11 (dd, J = 13.3, 5.1 Hz, 1H), 4.88-4.79 (m, 1H), 4.69 (s, 1H), 4.41-4.18 (m, 2H), 3.85 (s, 6H), 3.79-3.74 (m, 2H), 3.60 (s, 3H), 3.55 (s, 2H), 3.03-2.85 (m, 3H), 2.64-2.55 (m, 1H), 2.39 (d, J = 13.1 Hz, 9H), 2.14 (d, J = 7.0 Hz, 2H), 2.04-1.96 (m, 1H), 1.83-1.55 (m, 9H), 1.26 (s, 6H), 1.18 (s, 2H).
D191	845.30	^1H NMR (300 MHz, Methanol-d4) δ 9.04 (s, 1H), 7.68 (s, 1H), 7.50 (d, J = 8.3 Hz, 1H), 7.24-7.13 (m, 2H), 6.81 (s, 2H), 5.18 (d, J = 5.1 Hz, 1H), 4.67 (s, 2H), 4.44 (d, J = 5.3 Hz, 4H), 3.95 (s, 6H), 3.68 (s, 5H), 3.58 (s, 4H), 3.43 (s, 1H), 3.22 (m, J = 12.3 Hz, 2H), 3.10 (d, J = 6.6 Hz, 3H), 3.03 (s, 1H), 2.98-2.85 (m, 2H), 2.83 (s, 1H), 2.52 (m, J = 12.9, 4.9 Hz, 2H), 2.32 (s, 3H), 2.21 (s, 1H), 2.10 (d, J = 14.3 Hz, 8H), 1.74 (t, J = 12.9 Hz, 2H).
D192	829.40	^1H NMR (400 MHz, Methanol-d4) δ 9.05 (s, 1H), 7.52 (s, 1H), 7.42 (d, J = 8.2 Hz, 1H), 6.91-6.86 (m, 3H), 6.83-6.77 (m, 1H), 6.27 (s, 1H), 5.14 (dd, J = 13.3, 5.1 Hz, 1H), 4.56-4.31 (m, 6H), 4.26-4.11 (m, 6H), 4.00 (s, 6H), 3.82 (s, 2H), 3.72 (s, 2H), 3.63-3.46 (m, 6H), 3.11-2.75 (m, 4H), 2.58-2.43 (m, 3H), 2.36-2.07 (m, 5H), 1.53 (s, 6H).
D193	786.55	^1H NMR (400 MHz, DMSO-d6) δ 9.30 (d, J = 0.7 Hz, 1H), 7.78 (s, 1H), 7.41 (d, J = 8.8 Hz, 1H), 7.38 (s, 1H), 6.87 (d, J = 4.4 Hz, 2H), 6.70 (dd, J = 4.6, 2.3 Hz, 2H), 5.06 (dd, J = 13.3, 5.1 Hz, 1H), 4.42 (d, J = 21.9 Hz, 2H), 4.36-4.15 (m, 4H), 4.11-4.00 (m, 2H), 3.91 (s, 6H), 3.69 (d, J = 33.2 Hz, 4H), 3.57 (s, 3H), 3.38 (s, 3H), 3.25-3.12 (m, 1H), 3.02-2.81 (m, 3H), 2.71-2.56 (m, 2H), 2.38 (dd, J = 13.3, 4.7 Hz, 1H), 2.24-2.05 (m, 3H), 1.95 (s, 3H), 1.01 (d, J = 6.4 Hz, 4H).
D194	874.30	^1H NMR (400 MHz, DMSO-d6) δ 10.99 (s, 1H), 9.07 (s, 1H), 8.25 (s, 2H, FA), 7.62 (s, 1H), 7.49 (d, J = 8.3 Hz, 1H), 7.15-7.04 (m, 2H), 6.69 (d, J = 32.4 Hz, 3H), 5.11 (dd, J = 13.3, 5.1 Hz, 1H), 4.89-4.78 (m, 1H), 4.45-4.19 (m, 2H), 3.80 (s, 5H), 3.69 (t, J = 4.9 Hz,

Compound No.	LCMS	^1H NMR
D195	911.35	^1H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.29 (s, 1H), 8.17 (s, FA, 1H), 7.82 (d, J = 8.2 Hz, 1H), 7.78 (s, 1H), 7.44 (s, 1H), 7.32-7.24 (m, 2H), 6.74 (s, 2H), 5.12 (dd, J = 12.8, 5.4 Hz, 1H), 5.02-4.94 (m, 1H), 3.82 (s, 6H), 3.61-3.54 (m, 5H), 3.05-2.85 (m, 4H), 2.83-2.69 (m, 2H), 2.64-2.57 (m, 1H), 2.48-2.39 (m, 4H), 2.32-2.21 (m, 1H), 2.09-2.04 (m, 3H), 1.96-1.85 (m, 1H), 1.85-1.74 (m, 2H), 1.55-1.50 (m, 6H), 1.36-1.12 (m, 3H), 1.07-0.92 (m, 4H).
D196	956.35	H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.08 (s, 1H), 8.17 (s, FA, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.61 (s, 1H), 7.32-7.24 (m, 2H), 6.73 (s, 2H), 6.65 (s, 1H), 5.12 (dd, J = 12.8, 5.4 Hz, 1H), 5.02-4.94 (m, 1H), 3.81 (s, 6H), 3.69 (t, J = 4.7 Hz, 4H), 3.57 (s, 2H), 3.51-3.47 (m, 7H), 2.99 (s, 1H), 2.96-2.78 (m, 5H), 2.74-2.69 (m, 1H), 2.64-2.55 (m, 2H), 2.46-2.39 (m, 3H), 2.10-2.02 (m, 3H), 1.91-1.76 (m, 3H), 1.65-1.46 (m, 6H), 1.35-1.12 (m, 2H).
D197	797.65	^1H NMR (300 MHz, DMSO) δ 10.98 (s, 1H), 9.03 (d, J = 0.7 Hz, 1H), 8.20 (s, FA, 1H), 7.59 (s, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.25 (dd, J = 8.5, 2.3 Hz, 1H), 7.14 (d, J = 2.3 Hz, 1H), 6.75 (s, 2H), 6.48 (d, J = 0.8 Hz, 1H), 5.10 (dd, J = 13.3, 5.0 Hz, 1H), 4.33 (d, J = 16.7 Hz, 1H), 4.19 (d, J = 16.7 Hz, 1H), 3.81 (s, 6H), 3.73 (d, J = 12.2 Hz, 3H), 3.55 (s, 3H), 3.00-2.83 (m, 2H), 2.75-2.61 (m, 3H), 2.57-2.51 (m, 2H), 2.49-2.24 (m, 9H), 2.03-1.94 (m, 1H), 1.74 (d, J = 12.4 Hz, 2H), 1.41-1.32 (m, 3H), 1.30-1.16 (m, 2H).
D198	781.55	^1H NMR (300 MHz, Methanol-d4) δ 9.25 (d, J = 0.7 Hz, 1H), 8.54 (s, 1H), 7.55 (s, 1H), 7.44 (d, J = 8.3 Hz, 1H), 7.37-7.28 (m, 2H), 6.80 (s, 3H), 5.15 (dd, J = 13.2, 5.1 Hz, 1H), 4.50-4.32 (m, 2H), 4.10 (s, 2H), 3.92 (s, 6H), 3.77 (d, J = 12.3 Hz, 2H), 3.64 (s, 3H), 3.01 (d, J = 23.7 Hz, 4H), 2.90 (dd, J = 13.1, 5.2 Hz, 3H), 2.85-2.75 (m, 4H), 2.72 (d, J = 9.3 Hz, 3H), 2.51 (qd, J = 13.2, 4.9 Hz, 1H), 2.24-2.13 (m, 1H), 1.88 (d, J = 12.3 Hz, 2H), 1.67-1.30 (m, 5H).
D199	818.30	^1H NMR (300 MHz, DMSO-d6) δ 9.17 (s, 1H), 7.71 (s, 1H), 7.41 (d, J = 8.8 Hz, 1H), 6.85 (d, J = 1.7 Hz, 2H), 6.78 (d, J = 6.8 Hz, 1H), 6.70 (h, J = 2.3 Hz, 2H), 5.05 (dd, J = 13.2, 5.1 Hz, 1H), 4.39-4.10 (m, 4H), 3.94 (s, 3H), 3.88 (d, J = 2.2 Hz, 6H), 3.78-3.60 (m, 4H), 3.60-3.56 (m, 3H), 3.49-3.38 (m, 4H), 3.13 (d, J = 36.5 Hz, 3H), 2.93 (dd, J = 35.7, 13.8 Hz, 4H), 2.67-2.55 (m, 1H), 2.43-2.26 (m, 1H), 2.12 (d, J = 13.1 Hz, 2H), 1.97 (d, J = 11.7 Hz, 2H), 1.86 (d, J = 13.0 Hz, 3H), 1.78-1.67 (m, 1H), 1.52 (d, J = 37.9 Hz, 4H).
D200	819.40	^1H NMR (300 MHz, DMSO-d6) δ 10.97 (s, 1H), 9.06 (s, 1H), 8.16 (t, J = 1.6 Hz, 1H, FA), 7.64 (s, 1H), 7.38 (d, J = 8.5 Hz, 1H), 6.78 (s, 2H), 6.70-6.61 (m, 2H), 6.30 (s, 1H), 5.52 (d, J = 57.4 Hz, 1H), 5.08 (dd, J = 13.3, 5.0 Hz, 1H), 4.35 (ddd, J = 21.3, 10.6, 5.8 Hz, 3H), 4.24-4.00 (m, 4H), 3.96-3.80 (m, 9H), 3.77-3.62 (m, 3H), 3.58 (s, 4H), 3.50 (s, 3H), 3.01-2.81 (m, 2H), 2.78-2.53 (m, 3H), 2.45-2.36 (m, 1H), 2.38-2.25 (m, 3H), 2.07-1.90 (m, 1H), 1.80-1.67 (m, 4H).
D201	827.00	^1H NMR (400 MHz, DMSO-d6) δ 9.04-8.93 (m, 1H), 7.58 (s, 1H), 7.41 (d, 1H), 6.83 (s, 2H), 6.72 (d, J = 2.4 Hz, 2H), 6.23 (s, 1H), 5.02 (d, J = 13.1 Hz, 1H), 4.33 (t, J = 17.3 Hz, 3H), 4.19 (d, J = 16.7 Hz, 2H), 4.09 (s, 3H), 4.05-3.95 (m, 2H), 3.89-3.85 (m, 6H), 3.71 (s, 3H), 3.64 (s, 3H), 3.48 (s, 3H), 3.39 (d, J = 23.0 Hz, 4H), 3.25-3.08 (m, 1H), 3.04-2.77 (m, 3H), 2.70-2.56 (m, 1H), 2.43-2.29 (m, 1H), 2.11 (d, J = 13.9 Hz, 2H), 2.05-1.80 (m, 3H), 0.67 (s, 4H).
D202	637.35	^1H NMR (300 MHz, DMSO-d6) δ 10.95 (s, 1H), 9.01 (s, 1H), 7.60 (s, 1H), 7.48 (d, J = 8.5 Hz, 1H), 6.95 (d, J = 8.2 Hz, 2H), 6.77 (s, 2H), 6.17 (s, 1H), 5.04 (dd, J = 13.2, 5.1 Hz, 1H), 4.58 (s, 2H), 4.31 (d, J = 16.6 Hz, 1H), 4.17 (d, J = 16.7 Hz, 1H), 4.00 (t, J = 7.4 Hz, 4H), 3.85 (s, 6H), 3.46 (s, 3H), 2.98 (s, 3H), 2.94-2.82 (m, 1H), 2.64-2.58 (m, 1H), 2.41-2.28 (m, 3H), 2.00-1.90 (m, 1H).
D203	832.40	^1H NMR (400 MHz, Methanol-d4) δ 9.36 (s, 1H), 7.65 (s, 1H), 7.47-7.39 (m, 2H), 7.37-7.27 (m, 2H), 6.78 (s, 2H), 5.14 (dd, J = 13.3, 5.2 Hz, 1H), 4.63 (s, 2H), 4.48-4.33 (m, 2H), 3.98-3.87 (m, 8H), 3.76 (d, J = 12.4 Hz, 2H), 3.71-3.64 (m, 4H), 3.62 (q, J = 7.0 Hz, 2H), 3.00-2.68 (m, 10H), 2.61-2.54 (m, 2H), 2.53-2.43 (m, 1H), 2.29 (ddd, J = 9.8, 6.1, 2.2 Hz, 1H), 2.18 (dt, J = 12.8, 5.3, 2.4 Hz, 1H), 1.87 (d, J = 12.4 Hz, 2H), 1.61-1.50 (m, 3H), 1.47-1.33 (m, 4H), 1.18 (t, J = 7.1 Hz, 3H).
D204	846.45	^1H NMR (400 MHz, Methanol-d4) δ 9.35 (s, 1H), 8.54 (s, 1H, Formic acid), 7.68-7.60 (m, 2H), 7.38 (d, J = 0.9 Hz, 1H), 7.33 (d, J = 2.3 Hz, 1H), 7.20 (dd, J = 8.7, 2.4 Hz, 1H), 6.76 (s, 2H), 5.06 (dd, J = 12.5, 5.5 Hz, 2H), 4.61 (s, 4H), 4.03 (d, J = 13.2 Hz, 2H), 3.89 (s, 6H), 3.71-3.64 (m, 4H), 3.60 (q, J = 7.0 Hz, 2H), 2.98 (t, J = 12.6

-continued

Compound No.	LCMS	^1H NMR
D205	855.00	^1H NMR (400 MHz, DMSO-d6) δ 9.02 (s, 1H), 7.56 (d, J = 2.5 Hz, 1H), 7.44-7.37 (m, 1H), 6.84 (s, 2H), 6.75-6.68 (m, 2H), 6.24 (d, J = 8.2 Hz, 1H), 5.05-4.96 (m, 1H), 4.37-4.16 (m, 4H), 4.07 (s, 4H), 3.87 (s, 6H), 3.67 (d, J = 28.6 Hz, 4H), 3.48 (s, 4H), 3.44 (d, 2H), 3.21-3.12 (m, 1H), 3.07-2.80 (m, 6H), 2.70-2.62 (m, 1H), 2.61-2.54 (m, 1H), 2.40-2.31 (m, 1H), 2.10 (d, J = 12.3 Hz, 3H), 2.03-1.87 (m, 5H), 1.55-1.37 (m, 2H), 0.67 (s, 4H).
D206	847.60	^1H NMR (300 MHz, DMSO-d6) δ 10.99 (s, 1H), 9.45-9.14 (m, 1H, TFA), 9.07 (s, 1H), 7.65 (d, J = 2.7 Hz, 1H), 7.42 (d, J = 8.5 Hz, 1H), 6.90 (s, 2H), 6.80-6.63 (m, 2H), 6.34 (d, J = 6.0 Hz, 1H), 5.53 (d, J = 56.8 Hz, 1H), 5.08 (dd, J = 13.2, 5.1 Hz, 1H), 4.54-4.02 (m, 9H), 3.92 (s, 6H), 3.70 (d, J = 21.7 Hz, 6H), 3.52 (s, 3H), 3.31-3.13 (m, 3H), 3.09-2.83 (m, 7H), 2.22-1.68 (m, 8H), 1.62-1.38 (m, 2H).
D207	843.55	^1H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.60-9.10 (m, 2H, TFA), 9.03 (s, 1H), 7.62 (d, J = 3.8 Hz, 1H), 7.42 (d, J = 8.9, 2.9 Hz, 1H), 6.89 (s, 2H), 6.70 (dq, J = 7.0, 2.4 Hz, 2H), 6.23 (d, J = 6.0 Hz, 1H), 5.07 (dd, J = 13.3, 5.1 Hz, 1H), 4.44-4.29 (m, 3H), 4.26-4.16 (m, 3H), 3.98-3.92 (m, 1H), 3.90 (s, 6H), 3.83-3.81 (m, 2H), 3.74 (s, 2H), 3.65 (s, 2H), 3.50 (s, 3H), 3.49-3.42 (m, 2H), 3.21 (s, 1H), 3.08-2.85 (m, 6H), 2.68-2.60 (m, 1H), 2.48-2.35 (m, 2H), 2.18-1.88 (m, 9H), 1.59-1.46 (m, 2H), 1.43 (d, J = 6.2 Hz, 3H).
D208	843.80	^1H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.22-9.12 (m, 1H, TFA salt), 9.03 (s, 1H), 7.62 (d, J = 4.1 Hz, 1H), 7.46-7.38 (m, 1H), 6.90 (s, 2H), 6.74-6.67 (m, 2H), 6.23 (d, J = 6.3 Hz, 1H), 5.07 (dd, J = 13.3, 5.2 Hz, 1H), 4.44-4.16 (m, 5H), 4.00-3.87 (m, 7H), 3.86-3.78 (m, 1H), 3.78-3.62 (m, 5H), 3.52-3.49 (m, 5H), 3.21 (s, 1H), 3.09-2.84 (m, 7H), 2.70-2.56 (m, 2H), 2.47-2.29 (m, 2H), 2.19-2.06 (m, 3H), 2.03-1.88 (m, 6H), 1.54-1.46 (m, 1H), 1.43 (d, J = 6.1 Hz, 3H).
D209	873.45	^1H NMR (300 MHz, Methanol-d4) δ 9.05 (s, 1H), 7.57 (s, 1H), 7.42 (d, J = 8.2 Hz, 1H), 6.88 (s, 3H), 6.81 (d, J = 8.1 Hz, 1H), 6.39 (d, J = 6.6 Hz, 1H), 5.15 (dd, J = 13.2, 5.1 Hz, 1H), 4.40 (d, J = 6.0 Hz, 4H), 4.09 (d, J = 9.0 Hz, 2H), 3.98 (s, 7H), 3.95 (s, 1H), 3.83 (s, 2H), 3.75 (s, 2H), 3.65 (s, 4H), 3.60 (s, 3H), 3.40 (s, 1H), 3.30 (s, 3H), 3.23 (d, J = 12.8 Hz, 2H), 3.14 (d, J = 7.1 Hz, 4H), 2.90 (dd, J = 12.9, 4.9 Hz, 1H), 2.79 (d, J = 17.5 Hz, 1H), 2.51 (dd, J = 13.1, 4.9 Hz, 1H), 2.28 (d, J = 13.4 Hz, 2H), 2.12 (d, J = 15.8 Hz, 5H), 1.71 (t, J = 13.0 Hz, 2H), 1.56 (s, 3H).
D210	845.35	^1H NMR (300 MHz, DMSO-d6) δ 9.01 (s, 1H), 8.32 (s, 1H), 7.58 (s, 1H), 7.38 (d, J = 8.2 Hz, 1H), 6.78 (s, 2H), 6.69 (d, J = 7.6 Hz, 2H), 6.23 (s, 1H), 5.02 (dd, J = 13.2, 5.1 Hz, 1H), 4.32 (d, J = 16.9 Hz, 1H), 4.20 (s, 1H), 4.13 (d, J = 9.2 Hz, 2H), 3.91 (d, J = 8.8 Hz, 4H), 3.85 (s, 6H), 3.82 (s, 3H), 3.56 (s, 6H), 3.47 (s, 3H), 3.17 (s, 3H), 2.84 (d, J = 13.2 Hz, 2H), 2.63 (s, 3H), 2.34 (s, 4H), 2.00 (s, 1H), 1.73 (s, 4H), 1.44 (s, 3H).
D211	837.25	^1H NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1H), 9.09 (s, 1H), 8.25 (s, 1H, FA), 7.67 (s, 1H), 7.37 (d, J = 8.1 Hz, 1H), 6.75 (s, 2H), 6.67 (s, 2H), 6.44 (s, 1H), 5.08 (dd, J = 13.2, 5.1 Hz, 1H), 4.48 (t, J = 12.3 Hz, 4H), 4.35-4.14 (m, 2H), 3.93 (d, J = 23.1 Hz, 1H), 3.83 (s, 6H), 3.69 (s, 2H), 3.57 (s, 3H), 3.51 (s, 3H), 3.46 (t, J = 7.4 Hz, 2H), 3.02 (s, 2H), 2.97-2.84 (m, 1H), 2.64-2.54 (m, 1H), 2.46-2.33 (m, 3H), 2.28 (s, 5H), 1.98 (d, J = 12.3 Hz, 1H), 1.73 (d, J = 5.3 Hz, 4H).
D212	815.40	^1H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 10.04-9.79 (m, 2H, TFA salt), 9.03 (s, 1H), 7.61 (s, 1H), 7.41 (d, J = 8.9 Hz, 1H), 6.87 (d, J = 4.5 Hz, 2H), 6.74-6.67 (m, 2H), 6.20 (s, 1H), 5.07 (dd, J = 13.2, 5.1 Hz, 1H), 4.46-4.29 (m, 4H), 4.27-4.16 (m, 3H), 4.08-3.99 (m, 2H), 3.97-3.90 (m, 1H), 3.90 (s, 6H), 3.86-3.77 (m, 2H), 3.73 (s, 2H), 3.68-3.63 (m, 2H), 3.50 (s, 3H), 3.46-3.43 (m, 1H), 3.39-3.32 (m, 2H), 3.23-3.14 (m, 1H), 3.03-2.84 (m, 3H), 2.68-2.55 (m, 1H), 2.46-2.30 (m, 2H), 2.12 (d, J = 13.9 Hz, 2H), 2.04-1.87 (m, 4H), 1.43 (d, J = 6.2 Hz, 3H).
D213	815.40	^1H NMR (400 MHz, DMSO-d6) δ 10.99 (s, 1H), 10.12-9.61 (m, TFA, 2H), 9.03 (s, 1H), 7.61 (s, 1H), 7.41 (d, J = 8.9 Hz, 1H), 6.87 (s, 2H), 6.70 (d, 2H), 6.20 (s, 1H), 5.07 (dd, J = 13.2, 5.1 Hz, 1H), 4.45-4.35 (m, 3H), 4.33-4.16 (m, 4H), 4.08-4.02 (m, 2H), 3.97-3.93 (m, 1H), 3.90 (s, 6H), 3.83-3.81 (m, 2H), 3.74 (s, 2H), 3.65 (s, 2H), 3.50 (s, 3H), 3.47 (s, 1H), 3.41-3.34 (m, 2H), 3.19 (s, 1H), 3.05-2.95 (m, 3H), 2.64-2.57 (m, 1H), 2.48-2.37 (m, 2H), 2.19-1.85 (m, 6H), 1.43 (d, J = 6.1 Hz, 3H).
D214	845.50	^1H NMR (300 MHz, Methanol-d4) δ 9.52 (d, J = 0.8 Hz, 1H), 8.35 (s, 1H, FA), 7.73 (s, 1H), 7.63 (d, J = 0.9 Hz, 1H), 7.49 (d, J = 8.3 Hz,

Compound No.	LCMS	^1H NMR
D215	861.35	1H), 7.21 (d, J = 2.3 Hz, 1H), 7.16 (dd, J = 8.2, 2.4 Hz, 1H), 6.91 (s, 2H), 5.16 (dd, J = 13.2, 5.2 Hz, 1H), 4.88-4.76 (m, 2H), 4.48-4.35 (m, 4H), 3.98 (s, 6H), 3.71 (s, 3H), 3.63-3.49 (m, 2H), 3.16-3.12 (m, 2H), 2.90-2.74 (m, 5H), 2.70-2.60 (m, 2H), 2.60-2.44 (m, 3H), 2.29-2.11 (m, 1H), 2.11-1.92 (m, 5H), 1.91-1.80 (m, 4H), 1.71-1.45 (m, 2H), 1.39 (s, 9H).
D216	816.45	^1H NMR (400 MHz, DMSO-d6) δ 11.09 (s, 1H), 9.02 (s, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.60 (s, 1H), 7.33 (d, J = 2.3 Hz, 1H), 7.25 (dd, J = 8.6, 2.2 Hz, 1H), 6.82 (s, 2H), 6.21 (s, 1H), 5.07 (dd, J = 12.9, 5.4 Hz, 1H), 4.12-3.97 (m, 6H), 3.87 (s, 6H), 3.79 (s, 2H), 3.49-3.41 (m, 10H), 3.02-2.77 (m, 4H), 3.02-2.77 (m, 5H), 2.71-2.50 (m, 3H), 2.34 (t, J = 11.3 Hz, 2H), 2.05-1.97 (m, 1H), 1.76 (d, J = 12.6 Hz, 2H), 1.62-1.57 (m, 3H), 1.26-1.16 (m, 2H).
D217	667.30	^1H NMR (300 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.16 (s, 1H), 7.75 (s, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.26 (d, J = 8.8 Hz, 1H), 7.17-7.11 (m, 1H), 6.78 (s, 1H), 6.74 (s, 2H), 5.10 (dd, J = 13.2, 5.2 Hz, 1H), 4.34 (d, J = 16.7 Hz, 1H), 4.20 (d, J = 16.9 Hz, 1H), 3.94 (s, 3H), 3.83 (s, 6H), 3.68-3.61 (m, 2H), 3.54 (s, 3H), 3.19-3.12 (m, 4H), 2.74 (d, J = 1.9 Hz, 1H), 2.65-2.58 (m, 5H), 2.38 (d, J = 8.0 Hz, 1H), 2.30-2.25 (m, 1H).
D218	829.45	^1H NMR (400 MHz, DMSO-d6) δ 10.95 (s, 1H), 9.25 (br s, TFA, 1H), 9.03 (s, 1H), 7.62 (s, 1H), 7.53 (d, J = 8.3, 2.9 Hz, 1H), 6.89 (s, 2H), 6.55-6.45 (m, 2H), 6.22 (d, J = 7.8 Hz, 1H), 5.05 (dd, J = 13.3, 5.1 Hz, 1H), 4.34-4.15 (m, 4H), 4.02 (t, J = 7.4 Hz, 4H), 3.91 (s, 6H), 3.79 (d, J = 8.2 Hz, 2H), 3.72 (d, J = 6.9 Hz, 2H), 3.50 (s, 5H), 3.22 (s, 1H), 3.01-2.85 (m, 6H), 2.64-2.53 (m, 2H), 2.41-2.33 (m, 3H), 2.14 (d, 3H) 2.03-1.87 (m, 6H), 1.56-1.42 (m, 2H).
D219	731.20	^1H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 9.28 (s, 1H), 8.23 (s, 1H, FA), 7.80 (s, 1H), 7.64 (d, J = 8.3 Hz, 1H), 7.44 (s, 1H), 6.81-6.72 (m, 3H), 6.65 (dd, J = 8.3, 2.1 Hz, 1H), 5.06 (dd, J = 12.9, 5.4 Hz, 1H), 3.83 (s, 6H), 3.74 (s, 4H), 3.56 (d, J = 5.4 Hz, 5H), 2.95-2.82 (m, 1H), 2.55 (s, 3H), 2.44 (s, 3H), 2.27 (tt, J = 7.8, 3.9 Hz, 1H), 2.06-1.97 (m, 1H), 1.74 (t, J = 5.4 Hz, 4H), 1.06-0.94 (m, 4H).
D220	717.25	^1H NMR (400 MHz, DMSO-d6) δ 10.95 (s, 1H), 9.28 (s, 1H), 8.21 (s, 1H, FA), 7.80 (s, 1H), 7.53-7.42 (m, 2H), 6.75 (s, 2H), 6.54-6.44 (m, 2H), 5.04 (dd, J = 13.2, 5.1 Hz, 1H), 4.36-4.13 (m, 2H), 3.83 (s, 6H), 3.63 (s, 4H), 3.56 (s, 5H), 2.90 (ddd, J = 17.0, 13.6, 5.4 Hz, 1H), 2.55 (s, 3H), 2.45 (s, 2H), 2.40-2.30 (m, 1H), 2.27 (td, J = 7.8, 3.9 Hz, 1H), 2.05-1.85 (m, 1H), 1.74 (t, J = 5.4 Hz, 4H), 1.06-0.94 (m, 4H).
D221	819.40	^1H NMR (300 MHz, MeOD) δ 8.92 (s, 1H), 7.41 (d, J = 8.2 Hz, 1H), 7.34 (s, 1H), 6.88 (d, J = 2.1 Hz, 1H), 6.79 (dd, J = 6.8, 2.1 Hz, 3H), 5.14 (dd, J = 13.2, 5.1 Hz, 1H), 4.60-4.48 (m, 2H), 4.45-4.32 (m, 4H), 4.31-4.09 (m, 6H), 3.95 (s, 6H), 3.82-3.74 (m, 4H), 3.64-3.46 (m, 8H), 3.27-3.03 (m, 2H), 3.00-2.73 (m, 2H), 2.61-2.35 (m, 3H), 2.30-2.04 (m, 5H).
D222	845.45	^1H NMR (400 MHz, Methanol-d4) δ 9.04 (s, 1H), 7.68 (d, J = 8.6 Hz, 1H), 7.53 (s, 1H), 7.36 (d, J = 2.4 Hz, 1H), 7.23 (dd, J = 8.7, 2.4 Hz, 1H), 6.88 (s, 2H), 6.28 (s, 1H), 5.09 (dd, J = 12.5, 5.4 Hz, 1H), 4.56 (d, J = 13.5 Hz, 1H), 4.44 (d, J = 13.8 Hz, 1H), 4.16 (t, J = 7.5 Hz, 4H), 4.07 (d, J = 13.2 Hz, 2H), 3.99 (s, 6H), 3.85-3.76 (m, 1H), 3.59 (s, 3H), 3.01 (t, J = 12.3 Hz, 3H), 2.92-2.82 (m, 2H), 2.80-2.73 (m, 2H), 2.73-2.66 (m, 2H), 2.50 (p, J = 7.5 Hz, 2H), 2.17-2.09 (m, 1H), 1.89 (d, J = 12.9 Hz, 2H), 1.78-1.69 (m, 1H), 1.57 (d, J = 7.1 Hz, 8H), 1.45-1.27 (m, 4H), 0.91 (d, J = 7.0 Hz, 1H).
D223	794.45	^1H NMR (300 MHz, DMSO-d6) δ 10.96 (s, 1H), 9.05 (s, 1H), 7.58 (s, 1H), 7.52 (d, J = 9.1 Hz, 1H), 7.06 (m, 2H), 6.90 (s, 2H), 6.52 (s, 1H), 5.05 (dd, J = 13.2, 5.1 Hz, 1H), 4.32 (d, J = 17.0 Hz, 2H), 4.19 (d, J = 16.8 Hz, 2H), 3.89 (s, 2H), 3.85-3.76 (m, 8H), 3.56-3.43 (m, 2H), 3.23-3.04 (m, 12H), 2.99-2.89 (m, 1H), 2.88-2.76 (m, 2H), 2.66-2.54 (m, 1H), 2.44-2.32 (m, 1H), 2.01-1.91 (m, 1H), 1.81-1.71 (m, 2H), 1.65-1.49 (m, 3H), 1.34-1.17 (m, 2H).
D224	778.40	^1H NMR (400 MHz, DMSO-d6) δ 10.95 (s, 1H), 9.16 (s, 1H), 7.73 (s, 1H), 7.49 (d, J = 8.5 Hz, 1H), 7.03 (d, J = 7.9 Hz, 2H), 6.74 (d, J = 20.0 Hz, 3H), 5.04 (dd, J = 13.3, 5.1 Hz, 1H), 4.31 (d, J = 16.8 Hz, 1H), 4.19 (d, J = 16.8 Hz, 1H), 3.93 (s, 3H), 3.85 (d, J = 12.7 Hz,

Compound No.	LCMS	^1H NMR
D225	778.45	^1H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.16 (s, 1H), 7.73 (s, 1H), 7.41 (d, J = 5.1 Hz, 5H), 2.90 (ddd, J = 17.8, 13.5, 5.5 Hz, 1H), 2.79 (t, J = 12.2 Hz, 2H), 2.69-2.55 (m, 1H), 2.47-2.36 (m, 5H), 2.36-2.23 (m, 6H), 2.01-1.91 (m, 1H), 1.73 (d, J = 12.6 Hz, 2H), 1.50 (s, 1H), 1.43-1.30 (m, 2H), 1.23-1.12 (m, 2H).
D226	717.25	^1H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.29 (s, 1H), 8.15 (s, 1H, FA), 7.81 (s, 1H), 7.44 (s, 1H), 7.38 (d, J = 8.1 Hz, 1H), 6.78 (s, 2H), 6.70 (d, J = 7.9 Hz, 2H), 5.08 (dd, J = 13.3, 5.1 Hz, 1H), 4.38-4.15 (m, 2H), 3.93 (s, 3H), 3.79 (s, 6H), 3.73 (d, J = 12.3 Hz, 3H), 3.57-3.52 (m, 5H), 2.97-2.84 (m, 1H), 2.75-2.64 (m, 2H), 2.64-2.55 (m, 1H), 2.48-2.38 (m, 4H), 2.38-2.20 (m, 6H), 2.03-1.94 (m, 1H), 1.74 (d, J = 12.4 Hz, 2H), 1.52-1.42 (m, 1H), 1.41-1.32 (m, 2H), 1.31-1.17 (m, 2H).
D227	865.55	^1H NMR (300 MHz, Methanol-d4) δ 9.11 (d, J = 0.8 Hz, 1H), 8.56 (s, 0.47H, FA), 7.50-7.39 (m, 2H), 6.90-6.77 (m, 4H), 6.22 (s, 1H), 5.15 (dd, J = 13.3, 5.1 Hz, 1H), 4.48-4.39 (m, 2H), 4.33 (d, J = 5.4 Hz, 2H), 4.09 (t, J = 7.5 Hz, 4H), 4.03-3.99 (m, 2H), 3.97 (s, 6H), 3.73 (d, J = 7.6 Hz, 2H), 3.60 (s, 3H), 3.56-3.47 (m, 2H), 3.00-2.91 (m, 1H), 2.90-2.82 (m, 1H), 2.81-2.74 (m, 1H), 2.74-2.63 (m, 2H), 2.60-2.40 (m, 6H), 2.39-2.31 (m, 2H), 2.22-2.12 (m, 3H), 2.03 (d, J = 14.3 Hz, 2H), 1.97-1.87 (m, 1H), 1.55-1.41 (m, 2H).
D228	847.45	^1H NMR (300 MHz, Methanol-d4) δ 9.49 (s, 1H), 7.97 (s, 1H), 7.86 (s, 1H), 7.50 (d, J = 8.3 Hz, 1H), 7.24-7.13 (m, 2H), 6.90 (s, 2H), 5.15 (dd, J = 13.2, 5.2 Hz, 1H), 4.54-4.35 (m, 4H), 3.98 (s, 6H), 3.72 (s, 3H), 3.70-3.61 (m, 4H), 3.56-3.46 (m, 1H), 3.45-3.33 (m, 1H), 3.21-3.19 (m, 1H), 3.14-2.97 (m, 4H), 2.96-2.80 (m, 1H), 2.77-2.67 (m, 2H), 2.58-2.47 (m, 2H), 2.31-2.12 (m, 2H), 2.17-1.96 (m, 8H), 1.77-1.66 (m, 2H), 1.60 (s, 6H).
D229	692.15	^1H NMR (300 MHz, DMSO-d6) δ 11.13 (s, 1H), 9.30 (s, 1H), 7.85 (d, J = 9.0 Hz, 2H), 7.52 (s, 1H), 7.28 (d, J = 7.9 Hz, 2H), 6.82 (s, 2H), 5.24-5.05 (m, 1H), 5.00 (s, 1H), 4.00-3.67 (m, 10H), 3.58 (s, 3H), 3.32-3.27 (m, 2H), 3.02-2.78 (m, 1H), 2.67-2.54 (m, 2H), 2.14-1.97 (m, 1H), 1.40 (s, 3H), 1.33-1.20 (m, 2H), 0.96-0.80 (m, 2H).
D230	781.25	^1H NMR (400 MHz, Methanol-d4) δ 9.26 (d, J = 0.8 Hz, 1H), 7.65 (d, J = 9.3 Hz, 1H), 7.56 (s, 1H), 7.12 (d, J = 7.3 Hz, 2H), 6.88-6.79 (m, 3H), 5.12 (dd, J = 13.3, 5.1 Hz, 1H), 4.49-4.34 (m, 4H), 4.01 (s, 3H), 3.96 (s, 6H), 3.93 (s, 2H), 3.51-3.47 (m, 4H), 3.41-3.34 (m, 4H), 3.09 (t, J = 7.6 Hz, 2H), 2.98-2.85 (m, 3H), 2.84-2.74 (m, 1H), 2.55-2.40 (m, 1H), 2.21-2.12 (m, 1H), 1.88 (d, J = 12.8 Hz, 2H), 1.70-1.66 (m, 3H), 1.42 (q, J = 10.8 Hz, 2H).
D231	781.30	^1H NMR (400 MHz, DMSO-d6) δ 10.99 (s, 1H), 9.18 (s, 1H), 7.72 (s, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.28 (dd, J = 8.6, 2.3 Hz, 1H), 7.19 (s, 1H), 6.84 (s, 2H), 6.78 (s, 1H), 5.09 (dd, J = 13.3, 5.1 Hz, 1H), 4.43-4.14 (m, 2H), 3.95 (s, 3H), 3.87 (s, 6H), 3.77 (d, J = 12.0 Hz, 2H), 3.17-3.00 (m, 8H), 2.98-2.85 (m, 2H), 2.80-2.69 (m, 2H), 2.65-2.52 (m, 3H), 2.43-2.28 (m, 2H), 1.99 (d, J = 10.8 Hz, 1H), 1.78 (d, J = 12.5 Hz, 2H), 1.61-1.45 (m, 3H), 1.35-1.27 (m, 2H).
D232	865.45	^1H NMR (400 MHz, DMSO-d6 with a drop of D2O) δ 8.91 (s, 1H), 7.63-7.49 (m, 2H), 6.77 (d, J = 2.2 Hz, 2H), 6.62-6.53 (m, 2H), 6.21 (d, J = 6.8 Hz, 1H), 4.92 (dd, J = 13.2, 5.2 Hz, 1H), 4.38-4.22 (m, 2H), 3.99 (t, J = 7.5 Hz, 6H), 3.86-3.75 (m, 8H), 3.53-3.36 (m, 6H), 3.20-2.74 (m, 5H), 2.87-2.70 (m, 3H), 2.71-2.57 (m, 2H), 2.34 (t, 3H), 2.24 (s, 2H), 2.01 (s, 2H), 1.91-1.70 (m, 3H), 1.43 (d, J = 12.9 Hz, 2H).
D233	720.35	^1H NMR (300 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.29 (s, 1H), 8.14 (s, 1H, FA), 7.80 (s, 1H), 7.44 (s, 1H), 7.38 (d, J = 7.9 Hz, 1H), 6.75 (s, 2H), 6.69 (d, J = 8.1 Hz, 2H), 5.09 (dd, J = 13.2, 5.2 Hz, 1H), 4.41-4.06 (m, 2H), 3.84 (s, 6H), 3.59 (s, 6H), 2.95-2.84 (m, 1H), 2.64-2.61 (m, 2H), 2.42-2.34 (m, 4H), 2.05-1.92 (m, 2H), 1.76 (s, 4H), 1.01 (s, 4H).
D234	710.35	^1H NMR (300 MHz, Methanol-d4) δ 9.26 (s, 1H), 7.58 (s, 1H), 7.42 (d, J = 8.2 Hz, 1H), 6.89 (d, J = 4.7 Hz, 3H), 6.85-6.79 (m, 2H), 5.15 (dd, J = 13.2, 5.1 Hz, 1H), 4.49-4.32 (m, 4H), 4.00 (d, J = 7.0 Hz, 9H), 3.87 (s, 2H), 3.74 (s, 2H), 3.64-3.52 (m, 2H), 3.29-3.19 (m, 2H), 3.01-2.86 (m, 1H), 2.85-2.74 (m, 1H), 2.60-2.41 (m, 1H), 2.36-2.25 (m, 2H), 2.24-2.04 (m, 3H).
D235	666.30	^1H NMR (300 MHz, Methanol-d4) δ 9.25 (s, 1H), 8.56 (d, 1H, FA), 7.79 (d, J = 7.9 Hz, 1H), 7.58 (s, 1H), 7.54 (s, 1H), 7.48 (d, J = 8.1

Compound No.	LCMS	¹ H NMR
D236	853.35	¹ H NMR (300 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.04 (s, 1H), 8.24 (s, 0.3H, FA), 7.60 (s, 1H), 7.37 (d, J = 8.1 Hz, 1H), 6.78 (s, 2H), 6.72-6.64 (m, 2H), 6.49 (s, 1H), 5.08 (dd, J = 13.2, 5.1 Hz, 1H), 4.31 (d, J = 16.5 Hz, 1H), 4.18 (d, J = 16.6 Hz, 1H), 3.82 (s, 6H), 3.66 (s, 2H), 3.58 (s, 4H), 3.48 (s, 3H), 3.07 (s, 6H), 2.99-2.82 (m, 3H), 2.64-2.54 (m, 2H), 2.47-2.35 (m, 4H), 2.29-2.13 (m, 4H), 2.02-1.84 (m, 3H), 1.79-1.67 (m, 4H), 1.36-1.23 (m, 1H).
D237	802.30	¹ H NMR (300 MHz, MeOD) δ 9.41 (d, J = 0.8 Hz, 1H), 7.74 (s, 1H), 7.62-7.50 (m, 2H), 7.44-7.34 (m, 2H), 6.92 (d, J = 3.9 Hz, 2H), 5.16 (dd, J = 13.3, 5.1 Hz, 1H), 4.58-4.36 (m, 4H), 4.08-3.97 (m, 6H), 3.95-3.85 (m, 1H), 3.77-3.54 (m, 7H), 3.45-3.35 (m, 3H), 3.32-3.25 (m, 2H), 3.24-3.09 (m, 3H), 3.02-2.69 (m, 2H), 2.61-2.40 (m, 1H), 2.24-2.17 (m, 1H), 2.12-1.89 (m, 3H), 1.85-1.79 (m, 2H), 1.71-1.58 (m, 2H), 1.47 (s, 3H), 1.38-1.26 (m, 3H), 0.98-0.88 (m, 2H).
D238	802.25	¹ H NMR (300 MHz, Methanol-d4) δ 9.41 (d, J = 0.8 Hz, 1H), 7.80-7.68 (m, 2H), 7.64-7.56 (m, 1H), 7.24-7.15 (m, 2H), 6.93 (d, J = 4.2 Hz, 2H), 5.14 (dd, J = 13.3, 5.1 Hz, 1H), 4.55-4.36 (m, 4H), 4.30-4.02 (m, 1H), 4.00 (d, J = 4.3 Hz, 6H), 3.82 (s, 4H), 3.70-3.64 (m, 3H), 3.47-3.35 (m, 2H), 3.30-3.20 (m, 3H), 3.18-3.07 (m, 3H), 3.02-2.78 (m, 2H), 2.57-2.39 (m, 1H), 2.27-2.11 (m, 1H), 2.10-1.90 (m, 3H), 1.82 (s, 3H), 1.68-1.52 (m, 2H), 1.48 (s, 3H), 1.38-1.25 (m, 2H), 1.00-0.90 (m, 2H).
D239	657.35	¹ H NMR (300 MHz, Methanol-d4) δ 7.70 (s, 1H), 6.04 (d, J = 9.4 Hz, 2H), 5.76-5.64 (m, 2H), 5.31 (s, 2H), 5.25 (s, 1H), 3.75-3.57 (m, 2H), 3.25-3.19 (m, 2H), 3.15-3.05 (m, 2H), 3.00-2.89 (m, 2H), 2.89-2.75 (m, 2H), 2.50-2.34 (m, 9H), 1.45-1.20 (m, 2H), 1.08-0.89 (m, 1H), 0.73-0.59 (m, 1H).
D240	794.50	¹ H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.04 (s, 1H), 8.29 (s, 1H, FA), 7.58 (s, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.28-7.21 (m, 1H), 7.17-7.11 (m, 1H), 6.75 (s, 2H), 6.49 (s, 1H), 5.10 (dd, J = 13.3, 5.1 Hz, 1H), 4.36-4.16 (m, 2H), 3.80 (s, 6H), 3.78-3.69 (m, 3H), 3.56-3.49 (m, 3H), 3.07 (s, 6H), 2.96-2.86 (m, 1H), 2.74-2.69 (m, 1H), 2.66-2.54 (m, 3H), 2.47-2.34 (m, 5H), 2.32-2.23 (m, 3H), 2.02-1.95 (m, 1H), 1.78-1.70 (m, 2H), 1.48-1.33 (m, 3H), 1.31-1.21 (m, 2H).
D241	879.50	¹ H NMR (300 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.10 (s, 1H), 8.15 (s, 1H, FA), 7.69 (s, 1H), 7.38 (d, J = 8.4 Hz, 1H), 6.81 (s, 2H), 6.69 (d, J = 7.3 Hz, 2H), 6.48 (s, 1H), 5.08 (dd, J = 13.2, 5.1 Hz, 1H), 4.49 (t, J = 12.3 Hz, 4H), 4.32 (d, J = 16.7 Hz, 1H), 4.18 (d, J = 16.6 Hz, 1H), 3.86 (s, 9H), 3.60 (s, 4H), 3.52 (s, 4H), 3.11-3.05 (m, 4H), 2.95-2.84 (m, 2H), 2.65-2.56 (m, 2H), 2.47-2.34 (m, 2H), 2.03-1.93 (m, 1H), 1.83-1.77 (m, 4H), 1.72 (d, J = 12.0 Hz, 2H), 1.48-1.20 (m, 6H).
D242	657.30	¹ H NMR (300 MHz, DMSO-d6) δ 11.00 (s, 1H), 10.29 (s, 1H, TFA), 9.17 (s, 1H), 7.77-7.66 (m, 2H), 7.24-6.99 (m, 2H), 6.80 (d, J = 30.9 Hz, 3H), 5.33-5.02 (m, 2H), 4.81-4.55 (m, 2H), 4.55-4.13 (m, 6H), 4.00-3.82 (m, 9H), 3.02-2.85 (m, 1H), 2.63 (s, 1H), 2.44-2.31 (m, 1H), 2.08-1.93 (m, 1H).
D243	897.60	¹ H NMR (300 MHz, Methanol-d4) δ 9.38 (s, 1H), 8.57 (s, FA, 1H), 7.66 (s, 1H), 7.48 (d, J = 8.3 Hz, 1H), 7.38 (d, J = 0.9 Hz, 1H), 7.23-7.12 (m, 2H), 6.83 (s, 2H), 5.17 (dd, 1H), 4.83-4.76 (m, 1H), 4.67-4.60 (m, 1H), 4.50-4.36 (m, 2H), 4.23-4.07 (m, 2H), 3.95 (s, 6H), 3.68 (s, 3H), 3.07-2.75 (m, 7H), 2.66-2.40 (m, 6H), 2.29-2.12 (m, 3H), 2.03-1.83 (m, 4H), 1.77-1.49 (m, 6H), 1.14-1.03 (m, 4H).
D244	803.95	¹ H NMR (300 MHz, Methanol-d4) δ 8.99 (d, J = 0.7 Hz, 1H), 7.62-7.46 (m, 4H), 6.87 (s, 2H), 6.37 (s, 1H), 5.17 (dd, J = 13.3, 5.2 Hz, 1H), 4.57-4.39 (m, 4H), 4.21 (t, J = 7.6 Hz, 4H), 3.97 (s, 6H), 3.79 (d, J = 12.3 Hz, 2H), 3.60 (s, 3H), 3.55-3.49 (m, 4H), 3.42-3.36 (m, 4H), 3.14-3.00 (m, 4H), 2.96-2.75 (m, 1H), 2.60-2.46 (m, 3H), 2.24-2.14 (m, 1H), 2.04-1.93 (m, 2H), 1.76-1.70 (m, 3H), 1.61-1.51 (m, 2H).
D245	804.10	¹ H NMR (300 MHz, Methanol-d4) δ 9.10 (d, J = 0.7 Hz, 1H), 8.52 (s, 1H, FA), 7.67-7.58 (m, 1H), 7.45 (s, 1H), 7.08 (d, J = 8.2 Hz, 2H), 6.82 (s, 2H), 6.22 (s, 1H), 5.11 (dd, J = 13.3, 5.1 Hz, 1H), 4.49-4.31 (m, 2H), 4.14-4.03 (m, 6H), 4.01-3.85 (m, 8H), 3.59 (s, 3H), 3.07 (s, 4H), 2.95-2.61 (m, 9H), 2.53-2.37 (m, 3H), 2.15 (dd, J = 12.7, 4.9 Hz, 1H), 1.85 (d, J = 12.6 Hz, 2H), 1.61-1.55 (m, 3H), 1.37 (q, J = 12.5, 11.5 Hz, 2H).

Compound No.	LCMS	^1H NMR
D246	942.50	^1H NMR (400 MHz, Methanol-d4) δ 9.20 (s, 1H), 8.55 (s, FA, 1H), 7.48 (t, J = 4.1 Hz, 2H), 7.20 (d, J = 2.4 Hz, 1H), 7.15 (d, J = 7.8 Hz, 1H), 6.87 (s, 2H), 6.64 (s, 1H), 5.16 (dd, J = 13.4, 5.1 Hz, 1H), 4.83-4.72 (m, 1H), 4.51-4.32 (m, 4H), 3.97 (s, 6H), 3.78 (t, J = 4.9 Hz, 4H), 3.68-3.49 (m, 9H), 3.21-3.04 (m, 2H), 3.02-2.75 (m, 5H), 2.72-2.42 (m, 5H), 2.42-2.26 (m, 1H), 2.24-2.00 (m, 3H), 1.97-1.86 (m, 2H), 1.81-1.45 (m, 6H).
D247	667.35	^1H NMR (300 MHz, Methanol-d4) δ 9.39 (s, 1H), 7.72 (s, 1H), 7.63-7.57 (m, 1H), 7.38 (d, J = 4.4 Hz, 1H), 7.32-7.19 (m, 2H), 6.89 (s, 2H), 5.17 (dd, J = 13.4, 5.2 Hz, 2H), 4.83-4.74 (m, 1H), 4.67 (d, J = 15.1 Hz, 2H), 4.51-4.30 (m, 4H), 3.98 (d, J = 16.9 Hz, 6H), 3.79-3.54 (m, 1H), 3.01-2.77 (m, 2H), 2.60-2.45 (m, 1H), 2.25-2.13 (m, 2H), 1.11 (d, J = 8.9 Hz, 4H).
D248	839.40	^1H NMR (300 MHz, Methanol-d4) δ 9.19 (d, J = 0.8 Hz, 1H), 8.54 (s, 1H, FA), 7.67-7.58 (m, 1H), 7.52 (s, 1H), 7.11-7.04 (m, 2H), 6.81 (s, 2H), 6.43 (s, 1H), 5.11 (dd, J = 13.3, 5.1 Hz, 1H), 4.50-4.31 (m, 6H), 4.05 (s, 2H), 3.95 (s, 1H), 3.92 (s, 7H), 3.62 (s, 3H), 3.13-2.99 (m, 4H), 2.95-2.73 (m, 8H), 2.68 (s, 2H), 2.56-2.37 (m, 1H), 2.25-2.08 (m, 1H), 1.85 (d, J = 12.7 Hz, 2H), 1.61-1.55 (m, 3H), 1.45-1.28 (m, 2H).
D249	658.81	
D250	632.41	
D251	686.53	
D252	686.46	
D253	646.48	
D254	698.35	^1H NMR (400 MHz, Methanol-d4) δ 9.25 (s, 1H), 8.55 (s, 1H, FA), 7.58 (s, 1H), 7.52 (d, J = 8.2 Hz, 1H), 7.39 (s, 1H), 7.37 (s, 1H), 6.88 (s, 2H), 6.83 (s, 1H), 5.16 (dd, J = 13.4, 5.1 Hz, 1H), 4.60 (d, J = 13.5 Hz, 1H), 4.52-4.37 (m, 3H), 4.00 (d, J = 7.0 Hz, 9H), 3.89-3.85 (m, 2H), 3.64-3.59 (m, 2H), 3.48-3.33 (m, 2H), 2.95-2.86 (m, 1H), 2.81 (d, J = 17.2 Hz, 1H), 2.59-2.44 (m, 1H), 2.23-2.16 (m, 1H), 1.62 (d, J = 6.4 Hz, 6H).
D255	708.45	^1H NMR (300 MHz, Methanol-d4) δ 9.16 (s, 1H), 8.56 (s, 1H, FA), 7.51 (d, J = 9.0 Hz, 1H), 7.44 (s, 1H), 7.35 (d, J = 7.1 Hz, 2H), 6.88 (s, 2H), 6.52 (s, 1H), 5.16 (dd, J = 13.2, 5.1 Hz, 1H), 4.64 (s, 2H), 4.52-4.35 (m, 2H), 4.25 (br s, 2H), 3.97 (s, 6H), 3.68-3.54 (m, 4H), 3.45-3.37 (m, 2H), 3.14 (s, 7H), 3.03-2.73 (m, 2H), 2.59-2.43 (m, 1H), 2.27-2.14 (m, 1H), 1.63 (s, 6H).
D256	692.20	^1H NMR (300 MHz, Methanol-d4) δ 9.09 (d, J = 3.5 Hz, 1H), 8.56 (s, 1H), 7.67-7.37 (m, 2H), 7.21 (dd, J = 8.4, 2.3 Hz, 1H), 7.11 (s, 1H), 6.85 (s, 2H), 6.18 (s, 1H), 5.15 (dd, J = 13.3, 5.1 Hz, 1H), 4.55-4.26 (m, 7H), 4.15-4.00 (m, 6H), 3.94 (s, 6H), 3.58 (d, J = 1.3 Hz, 3H), 2.96 (s, 3H), 2.95-2.87 (m, 1H), 2.85-2.73 (m, 1H), 2.55-2.29 (m, 3H), 2.25-2.12 (m, 1H).
D257	637.15	^1H NMR (300 MHz, Methanol-d4) δ 9.14 (d, J = 0.7 Hz, 1H), 7.46-7.36 (m, 2H), 6.94 (d, J = 2.1 Hz, 1H), 6.86 (dd, J = 8.2, 2.2 Hz, 1H), 6.73 (s, 2H), 6.52 (d, J = 0.8 Hz, 1H), 5.15 (dd, J = 13.2, 5.2 Hz, 1H), 4.55-4.33 (m, 5H), 4.14-4.00 (m, 2H), 3.80 (s, 6H), 3.58 (s, 3H), 3.12 (s, 6H), 2.98-2.86 (m, 1H), 2.85-2.76 (m, 1H), 2.57-2.44 (m, 1H), 2.24-2.13 (m, 1H).
D258	818.42	^1H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.15 (s, 1H), 8.21 (s, 1H, FA salt), 7.72 (s, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.26 (dd, J = 8.5, 2.4 Hz, 1H), 7.15 (d, J = 2.3 Hz, 1H), 6.76 (s, 1H), 6.70 (s, 2H), 5.10 (dd, J = 13.3, 5.1 Hz, 1H), 4.33-4.20 (m, 2H), 3.94 (s, 3H), 3.79 (s, 6H), 3.75 (d, J = 12.1 Hz, 3H), 3.53 (s, 4H), 2.98-2.85 (m, 1H), 2.75-2.65 (m, 2H), 2.64-2.55 (m, 1H), 2.48-2.43 (m, 3H), 2.43-2.30 (m, 8H), 2.04-1.95 (m, 1H), 1.82-1.74 (m, 6H), 1.52-1.40 (m, 3H), 1.35-1.22 (m, 2H).
D259	815.45	^1H NMR (400 MHz, DMSO-d6) δ 9.01 (s, 1H), 8.26 (s, 1H, FA), 7.58 (s, 1H), 7.37 (d, J = 8.2 Hz, 1H), 6.77 (s, 2H), 6.72-6.65 (m, 2H), 6.17 (s, 1H), 5.12 (dd, J = 13.4, 5.1 Hz, 1H), 4.35-4.13 (m, 2H), 4.04-3.94 (m, 6H), 3.84 (s, 6H), 3.78-3.69 (m, 2H), 3.57 (s, 4H), 3.48 (s, 3H), 3.41-3.34 (m, 2H), 2.99 (s, 3H), 2.97-2.90 (m, 1H), 2.80-2.65 (m, 2H), 2.51-2.45 (m, 2H), 2.42-2.23 (m, 7H), 2.04-1.94 (m, 1H), 1.76-1.69 (m, 4H).
D260	695.35	^1H NMR (400 MHz, Methanol-d4) δ 9.26 (s, 1H), 8.56 (s, 0.49H, FA), 7.57 (s, 1H), 7.50 (d, J = 8.2 Hz, 1H), 7.35 (d, J = 8.3 Hz, 2H), 6.83 (d, J = 5.9 Hz, 3H), 5.16 (dd, J = 13.4, 5.2 Hz, 1H), 4.46-4.39 (m, 2H), 4.28-4.11 (m, 2H), 4.01 (s, 3H), 3.96 (s, 6H), 3.65 (s, 4H), 3.42-3.36 (m, 2H), 3.30-3.18 (m, 3H), 2.95-2.89 (m, 1H), 2.83-2.77 (m, 1H), 2.54-2.47 (m, 1H), 2.22-2.16 (m, 1H), 1.62 (s, 6H).
D261	879.35	^1H NMR (300 MHz, Methanol-d4) δ 9.20 (d, J = 0.7 Hz, 1H), 7.53 (s, 1H), 7.39 (d, J = 8.2 Hz, 1H), 6.85 (s, 3H), 6.78 (dd, J = 8.2, 2.3 Hz, 1H), 6.43 (s, 1H), 5.15 (dd, J = 13.4, 5.1 Hz, 1H), 4.53-4.28 (m, 6H), 4.26 (s, 2H), 3.96 (s, 7H), 3.67 (s, 4H), 3.62 (s, 3H), 3.43 (s,

Compound No.	LCMS	^1H NMR
D262	634.30	^1H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.02 (s, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.36 (s, 1H), 7.34-7.25 (m, 3H), 7.21 (d, J = 2.4 Hz, 1H), 7.00-6.92 (m, 2H), 6.39 (s, 1H), 5.11 (dd, J = 13.3, 5.1 Hz, 1H), 4.40-4.15 (m, 2H), 4.03-3.81 (m, 3H), 3.46 (s, 3H), 3.06 (s, 6H), 2.99-2.85 (m, 3H), 2.78 (s, 3H), 2.70-2.58 (m, 1H), 2.44-2.32 (m, 1H), 2.05-1.95 (m, 1H), 1.97-1.80 (m, 2H), 1.75 (d, J = 12.0 Hz, 2H).
D263	672.35	^1H NMR (400 MHz, DMSO-d6 with a drop of D2O) δ 9.28 (s, 1H), 8.22 (s, 1H, FA), 7.78 (s, 1H), 7.69-7.59 (m, 3H), 7.40 (s, 1H), 6.74 (s, 2H), 5.11 (dd, J = 13.3, 5.0 Hz, 1H), 4.51-4.32 (m, 2H), 3.83 (s, 6H), 3.63 (s, 2H), 3.56 (s, 6H), 3.20 (t, J = 6.5 Hz, 2H), 2.97-2.85 (m, 1H), 2.64-2.57 (m, 1H), 2.46-2.37 (m, 1H), 2.28-2.19 (m, 1H), 2.06-1.97 (m, 1H), 0.98 (t, J = 6.1 Hz, 4H).
D264	730.45	^1H NMR (300 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.03 (s, 1H), 8.70 (s, 1H, TFA salt), 7.59 (s, 1H), 7.42 (d, J = 8.8 Hz, 1H), 7.08 (s, 2H), 6.75-6.67 (m, 2H), 6.17 (s, 1H), 5.08 (dd, J = 13.2, 5.0 Hz, 1H), 4.34 (s, 2H), 4.31 (s, 1H), 4.20 (d, J = 16.7 Hz, 1H), 4.01 (t, J = 7.4 Hz, 4H), 3.93 (s, 3H), 3.79 (s, 2H), 3.65 (s, 2H), 3.50 (s, 3H), 3.45-3.34 (m, 2H), 3.33-3.15 (m, 2H), 2.88-2.75 (m, 3H), 2.66-2.54 (m, 1H), 2.44-2.30 (m, 3H), 2.20-2.09 (m, 2H), 2.08-1.94 (m, 3H), 1.22 (t, J = 7.4 Hz, 3H).
D265	665.30	^1H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.04 (s, 1H), 7.57 (s, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.36-7.29 (m, 1H), 7.20 (d, J = 2.3 Hz, 1H), 6.75 (s, 2H), 6.55-6.49 (m, 1H), 5.11 (dd, J = 13.3, 5.1 Hz, 1H), 4.39-4.19 (m, 2H), 3.89-3.83 (m, 2H), 3.81 (s, 6H), 3.48 (s, 3H), 3.45-3.37 (m, 2H), 3.08 (s, 6H), 2.99-2.86 (m, 1H), 2.82-2.70 (m, 2H), 2.65-2.56 (m, 1H), 2.47-2.35 (m, 2H), 2.06-1.96 (m, 1H), 1.61-1.53 (m, 2H).
D266	707.20	^1H NMR (300 MHz, Methanol-d4) δ 9.48 (s, 1H), 8.55 (s, 1H, FA), 7.85-7.69 (m, 2H), 7.34 (d, J = 8.6 Hz, 1H), 7.08-6.93 (m, 2H), 6.86 (s, 2H), 5.24-5.06 (m, 1H), 4.82 (s, 2H), 4.63 (d, J = 8.0 Hz, 2H), 4.46-4.26 (m, 2H), 3.92-3.83 (m, 6H), 3.76-3.69 (m, 4H), 3.65 (d, J = 20.3 Hz, 3H), 3.56-3.46 (m, 2H), 3.29-3.17 (m, 2H), 2.97-2.73 (m, 2H), 2.60-2.41 (m, 1H), 2.39-2.12 (m, 3H), 2.03-1.85 (m, 2H).
D267	675.35	^1H NMR (400 MHz, Methanol-d4) δ 9.13 (d, J = 0.7 Hz, 1H), 8.52 (0.3H, FA), 7.77 (d, J = 1.3 Hz, 1H), 7.65 (dd, J = 7.9, 1.5 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.45 (s, 1H), 6.89 (s, 2H), 6.44 (s, 1H), 5.22-5.11 (m, 1H), 4.48 (d, J = 3.2 Hz, 2H), 4.22 (s, 2H), 4.16-1.09 (m, 2H), 3.96 (s, 6H), 3.87 (s, 2H), 3.73-3.63 (ms, 1H), 3.60 (s, 3H), 3.08 (s, 6H), 3.01-2.88 (m, 1H), 2.86-2.77 (m, 1H), 2.58-2.44 (m, 1H), 2.28-2.19 (m, 1H).
D268	694.35	^1H NMR (400 MHz, Methanol-d4) δ 9.15 (d, J = 0.8 Hz, 1H), 8.48 (s, 0.2H, FA), 7.73 (d, J = 8.5 Hz, 1H), 7.42 (s, 1H), 7.19 (d, J = 2.3 Hz, 1H), 7.06 (dd, J = 8.5, 2.4 Hz, 1H), 6.90-6.83 (m, 2H), 6.48 (s, 1H), 5.10 (dd, J = 12.5, 5.4 Hz, 1H), 4.38-4.17 (m, 4H), 4.08-3.77 (m, 8H), 3.67-3.54 (m, 3H), 3.22-2.96 (m, 9H), 2.95-2.67 (m, 4H), 2.16-2.07 (m, 1H).
D269	700.35	^1H NMR (300 MHz, DMSO-d6) δ 11.01 (s, 1H), 9.28 (s, 1H), 7.80 (s, 1H), 7.71-7.53 (m, 3H), 7.42 (s, 1H), 6.78 (s, 2H), 5.11 (dd, J = 13.3, 5.1 Hz, 1H), 4.54-4.27 (m, 2H), 3.86 (s, 6H), 3.79-3.67 (m, 2H), 3.56 (s, 3H), 3.02-2.82 (m, 3H), 2.81-2.66 (m, 1H), 2.66-2.53 (m, 1H), 2.47-2.16 (m, 4H), 2.08-1.83 (m, 3H), 1.80-1.57 (m, 2H), 1.09-0.89 (m, 4H).
D270	615.25	^1H NMR (300 MHz, Methanol-d4) δ 9.05 (d, J = 1.4 Hz, 2H), 7.57 (d, J = 1.4 Hz, 1H), 7.47 (d, J = 1.0 Hz, 1H), 7.41 (d, J = 0.9 Hz, 1H), 6.92 (s, 2H), 6.68 (d, J = 2.3 Hz, 1H), 5.22 (dd, J = 12.0, 5.1 Hz, 1H), 4.50 (s, 2H), 3.99 (s, 6H), 3.69-3.50 (m, 7H), 3.50-3.38 (m, 2H), 3.20 (s, 6H), 3.13-2.99 (m, 2H), 2.90-2.79 (m, 2H), 2.73-2.55 (m, 1H), 2.42-2.29 (m, 1H).
D271	672.35	^1H NMR (400 MHz, Methanol-d4) δ 9.35 (s, 1H), 8.53 (s, 1H, FA), 7.76 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 2.0 Hz, 2H), 7.60-7.53 (m, 1H), 7.33 (d, J = 0.9 Hz, 1H), 6.81 (s, 2H), 5.19-5.10 (m, 1H), 4.53-4.38 (m, 2H), 4.20 (s, 2H), 4.10 (t, J = 8.4 Hz, 2H), 3.93 (s, 6H), 3.89-3.81 (m, 2H), 3.77-3.67 (m, 1H), 3.64 (s, 3H), 2.98-2.84 (m, 1H), 2.84-2.73 (m, 1H), 2.55-2.40 (m, 1H), 2.22-2.13 (m, 1H), 2.13-2.03 (m, 1H), (d, J = 6.5 Hz, 4H).
D272	714.30	^1H NMR (300 MHz, DMSO-d6) δ 11.15 (s, 1H), 9.28 (s, 1H), 7.94-7.78 (m, 4H), 7.41 (s, 1H), 6.81 (s, 2H), 5.16 (dd, J = 12.8, 5.4 Hz, 1H), 3.87 (s, 8H), 3.57 (s, 4H), 3.02 (s, 2H), 2.96-2.78 (m, 3H), 2.67-2.55 (m, 2H), 2.21 (dd, J = 9.0, 4.1 Hz, 1H), 2.11-1.95 (m, 3H), 1.79 (s, 2H), 1.05-0.94 (m, 4H).

Compound No.	LCMS	¹ H NMR
D273	717.20	¹ H NMR (300 MHz, Methanol-d4) δ 9.10 (dd, J = 9.6, 0.7 Hz, 1H), 7.93-7.80 (m, 3H), 7.49 (d, J = 2.4 Hz, 1H), 6.93 (d, J = 7.2 Hz, 2H), 6.57 (s, 1H), 5.14 (ddd, J = 17.9, 12.7, 5.5 Hz, 1H), 4.52 (s, 1H), 4.44 (s, 1H), 4.00 (d, J = 2.0 Hz, 6H), 3.60 (d, J = 2.2 Hz, 5H), 3.51-3.40 (m, 1H), 3.31-3.18 (m, 2H), 3.16 (s, 3H), 3.07 (s, 3H), 2.93-2.63 (m, 3H), 2.37 (d, J = 13.9 Hz, 1H), 2.25-1.93 (m, 4H).
D274	582.30	¹ H NMR (400 MHz, DMSO-d6) δ 11.01 (s, 1H), 9.05 (s, 1H), 7.68-7.57 (m, 3H), 7.57-7.50 (m, 1H), 6.89 (s, 2H), 6.59 (s, 1H), 5.14 (dd, J = 13.2, 5.1 Hz, 1H), 4.51 (d, J = 17.2 Hz, 1H), 4.36 (d, J = 17.2 Hz, 1H), 3.74 (s, 6H), 3.50 (s, 3H), 3.10 (s, 6H), 3.01-2.87 (m, 1H), 2.67-2.58 (m, 1H), 2.48-2.37 (m, 1H), 2.10-2.00 (m, 1H).
D275	686.20	¹ H NMR (300 MHz, DMSO-d6) δ 11.16 (s, 1H), 10.15 (d, 1H, TFA), 9.29 (d, J = 4.1 Hz, 1H), 7.96 (d, J = 7.3 Hz, 3H), 7.81 (s, 1H), 7.38 (d, J = 11.7 Hz, 1H), 6.88 (d, J = 3.5 Hz, 2H), 5.17 (dd, J = 12.8, 5.3 Hz, 1H), 4.48 (s, 4H), 4.22 (d, J = 41.8 Hz, 2H), 3.92 (s, 6H), 3.57 (d, J = 1.9 Hz, 3H), 2.88 (d, J = 11.7 Hz, 1H), 2.71-2.54 (m, 2H), 2.32-2.02 (m, 3H), 0.99 (d, J = 8.2 Hz, 4H).
D276	711.20	¹ H NMR (400 MHz, DMSO-d6) δ 10.96 (s, 1H), 9.03 (s, 1H), 7.59 (s, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.22 (dd, J = 8.5, 2.4 Hz, 1H), 7.13 (d, J = 2.3 Hz, 1H), 6.75 (s, 2H), 6.49 (s, 1H), 5.09 (dd, J = 13.3, 5.1 Hz, 1H), 4.37-4.15 (m, 2H), 3.91 (d, J = 12.1 Hz, 1H), 3.83 (s, 6H), 3.53 (d, J = 12.9 Hz, 1H), 3.15 (d, J = 10.9 Hz, 2H), 3.07 (s, 6H), 3.04-2.98 (m, 2H), 2.96-2.84 (m, 3H), 2.69-2.54 (m, 1H), 2.45-2.30 (m, 1H), 2.04-1.92 (m, 1H), 1.22 (d, J = 6.1 Hz, 6H).
D277	625.20	¹ H NMR (300 MHz, DMSO-d6) δ 10.93 (s, 1H), 9.03 (s, 1H), 7.59 (s, 1H), 7.47 (d, J = 8.5 Hz, 1H), 6.95 (d, J = 8.1 Hz, 2H), 6.79 (s, 2H), 6.45 (s, 1H), 5.03 (dd, J = 13.3, 5.2 Hz, 1H), 4.58 (s, 2H), 4.35-4.15 (m, 2H), 3.85 (s, 6H), 3.46 (s, 3H), 3.06 (s, 6H), 2.98 (s, 3H), 2.92-2.80 (m, 1H), 2.66-2.55 (m, 1H), 2.41-2.32 (m, 1H), 2.02-1.90 (m, 1H).
D278	756.35	¹ H NMR (300 MHz, DMSO-d6) δ 10.97 (s, 1H), 9.10 (s, 1H), 7.69 (s, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.31-7.18 (m, 1H), 7.14 (d, J = 2.3 Hz, 1H), 6.75 (s, 2H), 6.49 (s, 1H), 5.10 (dd, J = 13.3, 5.1 Hz, 1H), 4.49 (t, J = 12.3 Hz, 4H), 4.41-4.12 (m, 2H), 3.83 (s, 6H), 3.58 (s, 2H), 3.51 (s, 3H), 3.02 (d, J = 23.7 Hz, 5H), 2.63 (s, 3H), 2.46-2.24 (m, 1H), 2.10-1.91 (m, 1H), 1.25 (s, 6H).
D279	694.40	¹ H NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1H), 8.99 (s, 1H), 8.13 (s, 0.2H, FA), 7.45-7.38 (m, 2H), 7.28 (dd, J = 8.6, 2.5 Hz, 1H), 7.18 (d, J = 2.4 Hz, 1H), 6.83 (s, 1H), 6.72 (s, 1H), 5.97 (s, 1H), 5.20-5.03 (m, 1H), 4.41-4.15 (m, 2H), 3.85 (d, J = 11.8 Hz, 2H), 3.76 (s, 3H), 3.66 (s, 3H), 3.51 (s, 1H), 3.44 (s, 3H), 3.01 (s, 6H), 5.23-4.94 (m, 1H), 2.82-2.68 (m, 5H), 2.65-2.55 (m, 1H), 2.45-2.30 (m, 1H), 7.31-7.25 (m, 1H), 1.81 (s, 4H).
D280	679.30	¹ H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.02 (s, 1H), 7.58 (s, 1H), 7.55-7.51 (m, 1H), 7.47 (s, 2H), 6.76 (s, 2H), 6.51 (s, 1H), 5.10 (dd, J = 13.3, 5.1 Hz, 1H), 4.39 (d, J = 17.1 Hz, 1H), 4.26 (d, J = 17.1 Hz, 1H), 3.83 (s, 6H), 3.70 (d, J = 11.9 Hz, 2H), 3.48 (s, 3H), 3.08 (s, 6H), 3.03-2.83 (m, 3H), 2.65-2.56 (m, 3H), 2.47-2.32 (m, 1H), 2.06-1.94 (m, 1H), 1.82 (s, 1H), 1.72 (d, J = 12.8 Hz, 2H), 1.54-1.47 (m, 2H).
D281	695.50	¹ H NMR (400 MHz, Methanol-d4) δ 9.27 (s, 1H), 7.59 (s, 1H), 7.53 (d, J = 8.3 Hz, 1H), 7.39 (d, J = 9.7 Hz, 2H), 6.89 (s, 2H), 6.83 (s, 1H), 5.17 (dd, J = 13.3, 5.2 Hz, 1H), 4.63 (d, J = 20.8 Hz, 1H), 4.57-4.38 (m, 3H), 4.01 (d, J = 5.1 Hz, 10H), 3.96-3.85 (m, 3H), 3.65 (s, 3H), 3.60-3.44 (m, 1H), 2.99-2.87 (m, 1H), 2.86-2.75 (m, 1H), 2.59-2.45 (m, 1H), 2.25-2.13 (m, 1H), 1.74-1.51 (m, 7H).
D282	628.40	¹ H NMR (300 MHz, DMSO-d6) δ 10.90 (s, 1H), 9.16 (s, 1H), 8.14 (0.4 H, FA), 7.74 (s, 1H), 7.08 (t, J = 8.4 Hz, 1H), 6.79-6.72 (m, 3H), 6.56-6.49 (m, 2H), 6.46-6.40 (m, 1H), 5.18 (dd, J = 10.5, 5.2 Hz, 1H), 3.94 (s, 3H), 3.82 (s, 6H), 3.64 (s, 2H), 3.54 (s, 3H), 3.15-3.04 (m, 4H), 2.75-2.55 (m, 6H), 2.24-2.02 (m, 2H).
D283	845.3	¹ H NMR (300 MHz, Methanol-d4) δ 9.04 (s, 1H), 7.68 (s, 1H), 7.50 (d, J = 8.3 Hz, 1H), 7.24-7.13 (m, 2H), 6.81 (s, 2H), 5.18 (d, J = 5.1 Hz, 1H), 4.67 (s, 2H), 4.44 (d, J = 5.3 Hz, 4H), 3.95 (s, 6H), 3.68 (s, 5H), 3.58 (s, 4H), 3.43 (s, 1H), 3.22 (m, J = 12.3 Hz, 2H), 3.10 (d, J = 6.6 Hz, 3H), 3.03 (s, 1H), 2.98-2.85 (m, 2H), 2.83 (s, 1H), 2.52 (m, J = 12.9, 4.9 Hz, 2H), 2.32 (s, 3H), 2.21 (s, 1H), 2.10 (d, J = 14.3 Hz, 8H), 1.74 (t, J = 12.9 Hz, 2H).
D284	843.4	¹ H NMR (400 MHz, Methanol-d4) δ 8.22 (d, J = 9.0 Hz, 1H), 7.49 (d, J = 8.3 Hz, 1H), 7.28-7.07 (m, 3H), 6.84-6.67 (m, 3H), 6.11 (d, J = 7.6 Hz, 1H), 5.15 (dd, J = 13.2, 5.2 Hz, 1H), 4.85-4.77 (m, 1H), 4.55-4.34 (m, 4H), 3.92 (s, 6H), 3.70 (t, J = 7.3 Hz, 4H), 3.61-3.48 (m, 5H), 3.22-3.04 (m, 2H), 2.97-2.44 (m, 11H), 2.27-1.75 (m, 12H), 1.74-1.42 (m, 2H).

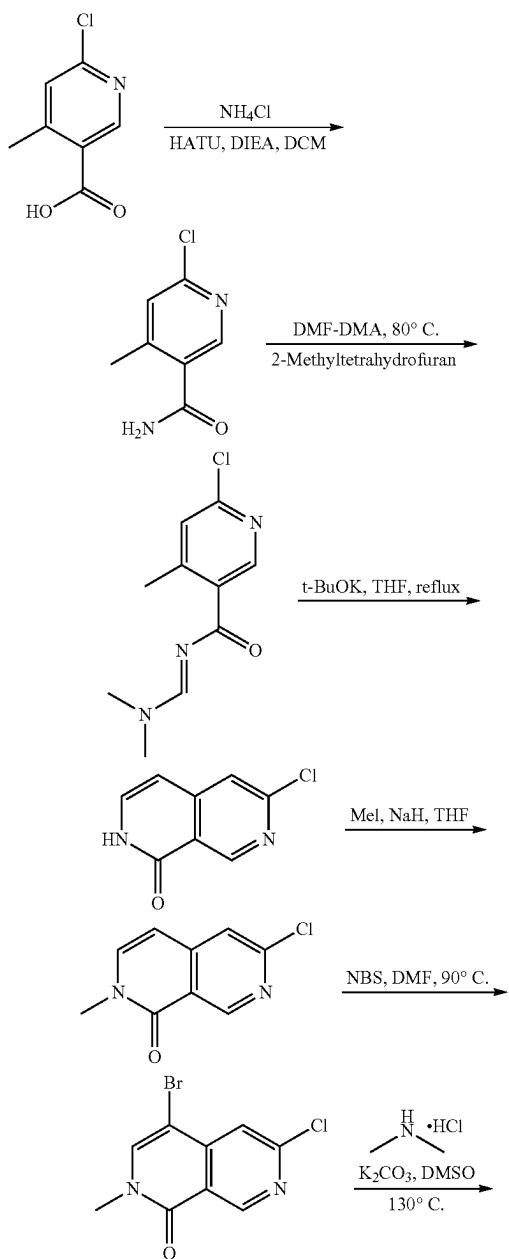
Compound No.	LCMS	¹ H NMR
D285	788.6	¹ H NMR (400 MHz, MeOD) δ 8.85-8.50 (m, FA, 1H), 8.31 (d, J = 9.0 Hz, 1H), 7.37 (dd, J = 18.8, 8.6 Hz, 2H), 7.18 (d, J = 7.8 Hz, 1H), 6.85 (d, J = 2.2 Hz, 1H), 6.77 (dd, J = 8.2, 2.2 Hz, 1H), 6.75 (s, 2H), 6.32 (d, J = 7.7 Hz, 1H), 5.14 (dd, J = 13.3, 5.1 Hz, 1H), 4.52 (s, 2H), 4.45-4.33 (m, 2H), 4.31-4.22 (m, 2H), 4.06-3.95 (m, 2H), 3.93 (s, 6H), 3.68 (s, 4H), 3.58 (s, 3H), 3.22-3.13 (m, 1H), 2.99-2.85 (m, 1H), 2.85-2.72 (m, 3H), 2.70 (s, 6H), 2.60-2.43 (m, 5H), 2.23-2.11 (m, 1H), 1.96-1.88 (m, 4H).
D286	845.4	¹ H NMR (300 MHz, DMSO-d6) δ 11.00 (s, 1H), 9.35 (s, 1H), 9.14 (s, 1H), 8.11 (s, 1H), 7.51 (d, J = 8.2 Hz, 1H), 7.20-7.11 (m, 4H), 5.13-5.07 (m, 1H), 4.90-4.85 (m, 1H), 4.38 (d, J = 17.0 Hz, 1H), 4.34-4.07 (m, 7H), 3.91 (s, 6H), 3.54 (s, 3H), 3.19 (s, 2H), 2.97-2.76 (m, 7H), 2.60 (d, J = 15.7 Hz, 2H), 2.40-2.27 (m, 5H), 2.02-1.83 (m, 11H), 1.50 (q, J = 12.2 Hz, 2H).
D287	806	¹ H NMR (300 MHz, DMSO-d6) δ 11.00 (s, 1H), 8.01 (dd, J = 9.5, 2.8 Hz, 1H), 7.74 (m, J = 9.1, 5.3 Hz, 1H), 7.68-7.57 (m, 2H), 7.50 (d, J = 8.3 Hz, 1H), 7.20-7.02 (m, 2H), 6.82 (s, 2H), 5.11 (m, J = 13.2, 5.1 Hz, 1H), 4.93-4.75 (m, 1H), 4.35 (m, 1H), 4.26 (m, 1H), 4.10 (m, 1H), 3.87 (s, 6H), 3.61 (s, 3H), 3.29 (s, 2H), 3.01-2.81 (m, 3H), 2.78-2.56 (m, 2H), 2.49-2.25 (m, 7H), 2.10-1.93 (m, 1H), 1.73 (m, J = 48.1 Hz, 10H), 1.43-1.22 (m, 3H).
D288	666.25	¹ H NMR (300 MHz, Methanol-d4) δ 9.25 (s, 1H), 8.56 (d, 1H), 7.79 (d, J = 7.9 Hz, 1H), 7.58 (s, 1H), 7.54 (s, 1H), 7.48 (d, J = 8.1 Hz, 1H), 6.94-6.78 (m, 3H), 5.17 (dd, J = 13.3, 5.1 Hz, 1H), 4.51 (d, J = 5.0 Hz, 2H), 4.37-4.24 (m, 2H), 4.01 (s, 3H), 3.97 (s, 6H), 3.65 (s, 3H), 3.57 (d, J = 12.0 Hz, 2H), 3.16-2.97 (m, 3H), 2.97-2.86 (m, 1H), 2.86-2.75 (m, 1H), 2.51 (qd, J = 13.1, 4.7 Hz, 1H), 2.27-2.15 (m, 1H), 2.15-2.03 (m, 4H).
D289	804.45	¹ H NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1H), 9.17 (s, 1H), 7.73 (s, 1H), 7.38 (d, J = 8.0 Hz, 1H), 6.79 (d, J = 5.4 Hz, 3H), 6.69 (d, J = 8.0 Hz, 2H), 5.08 (dd, J = 13.2, 5.2 Hz, 1H), 4.36-4.12 (m, 2H), 3.94 (s, 3H), 3.90 (s, 2H), 3.85 (s, 6H), 3.59 (s, 4H), 3.55 (s, 3H), 3.19-3.15 (m, 2H), 2.96-2.84 (m, 1H), 2.70-2.60 (m, 2H), 2.42-2.33 (m, 2H), 2.37 (s, 4H), 2.17 (s, 2H), 1.99 (d, J = 12.8 Hz, 1H), 1.82-1.67 (m, 7H), 1.42-1.07 (m, 2H).
D290	720.40	¹ H NMR (300 MHz, Methanol-d4) δ 9.10 (s, 1H), 8.51 (s, 0.2H, FA), 7.46 (d, J = 11.0 Hz, 2H), 7.31 (d, J = 9.3 Hz, 2H), 6.80 (s, 2H), 6.23 (s, 1H), 5.21-5.09 (m, 1H), 4.51-4.33 (m, 2H), 4.14-4.03 (m, 4H), 3.93 (s, 8H), 3.59 (s, 3H), 3.20-3.14 (m, 5H), 2.96-2.70 (m, 3H), 2.56-2.37 (m, 3H), 2.24-2.13 (m, 1H), 1.49 (s, 6H).
D291	865.50	¹ H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.46 (d, J = 40.5 Hz, 1H, TFA), 9.11 (s, 1H), 7.69 (s, 1H), 7.45-7.38 (m, 1H), 6.90 (s, 2H), 6.74-6.67 (m, 2H), 6.49 (s, 1H), 5.08 (dd, J = 13.2, 5.1 Hz, 1H), 4.50 (t, J = 12.3 Hz, 4H), 4.33 (d, J = 16.6 Hz, 1H), 4.26-4.16 (m, 3H), 3.91 (s, 6H), 3.71 (dd, J = 30.9, 7.8 Hz, 4H), 3.53 (s, 3H), 3.47 (d, J = 12.9 Hz, 3H), 3.22 (s, 1H), 3.01 (s, 6H), 2.60 (d, J = 17.1 Hz, 1H), 2.39 (dd, J = 13.1, 4.5 Hz, 1H), 2.37-2.30 (m, 1H), 2.12 (d, J = 12.9 Hz, 3H), 1.97 (t, J = 16.1 Hz, 5H), 1.83 (s, 6H), 1.59-1.48 (m, 2H).
D292	875.3	¹ H NMR (400 MHz, DMSO-d6) δ 10.99 (s, 1H), 9.41 (s, 1H), 8.18 (s, 2H, FA), 7.87 (s, 1H), 7.56 (s, 1H), 7.49 (d, J = 8.3 Hz, 1H), 7.13 (dd, J = 8.3, 2.4 Hz, 1H), 7.07 (d, J = 2.4 Hz, 1H), 6.77 (s, 2H), 5.11 (dd, J = 13.3, 5.1 Hz, 1H), 4.84 (t, J = 6.9 Hz, 1H), 4.42-4.19 (m, 2H), 3.83 (s, 7H), 3.67 (s, 2H), 3.60 (s, 3H), 3.51 (s, 3H), 3.11 (s, 3H), 2.97-2.88 (m, 3H), 2.60 (d, J = 17.2 Hz, 1H), 2.41-2.27 (m, 4H), 2.21 (d, J = 14.0 Hz, 3H), 2.10 (d, J = 7.0 Hz, 2H), 2.00 (d, J = 12.9 Hz, 1H), 1.78 (s, 2H), 1.60 (d, J = 27.7 Hz, 6H), 1.49 (s, 1H), 1.29 (s, 6H), 1.12 (t, J = 12.9 Hz, 2H).
D293	681.40	¹ H NMR (300 MHz, DMSO-d6) δ 10.97 (s, 1H), 9.16 (s, 1H), 7.74 (s, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.32-7.21 (m, 1H), 7.16 (d, J = 2.3 Hz, 1H), 6.78 (s, 1H), 6.74 (s, 2H), 5.10 (dd, J = 13.2, 5.0 Hz, 1H), 4.40-4.13 (m, 2H), 4.09-3.98 (m, 1H), 3.94 (s, 3H), 3.83 (s, 6H), 3.64-3.46 (m, 5H), 3.00-2.68 (m, 4H), 2.67-2.53 (m, 3H), 2.46-2.25 (m, 2H), 2.07-1.90 (m, 1H), 1.30 (d, J = 5.0 Hz, 3H).
D294	677.45	¹ H NMR (400 MHz, Methanol-d4) δ 8.91 (s, 1H), 7.95 (d, J = 2.2 Hz, 1H), 7.85 (dd, J = 8.3, 2.3 Hz, 1H), 7.76 (d, J = 8.3 Hz, 1H), 7.54 (s, 1H), 6.75 (s, 2H), 6.43 (s, 1H), 5.18 (dd, J = 13.3, 5.1 Hz, 1H), 4.63-4.47 (m, 2H), 4.24 (t, J = 7.6 Hz, 4H), 3.89 (s, 6H), 3.87-3.73 (m, 3H), 3.63 (t, J = 12.1 Hz, 2H), 3.57 (s, 3H), 2.99-2.74 (m, 4H), 2.60-2.44 (m, 3H), 2.21 (ddd, J = 9.7, 5.3, 2.7 Hz, 1H), 1.86 (d, J = 13.8 Hz, 2H).

533

-continued

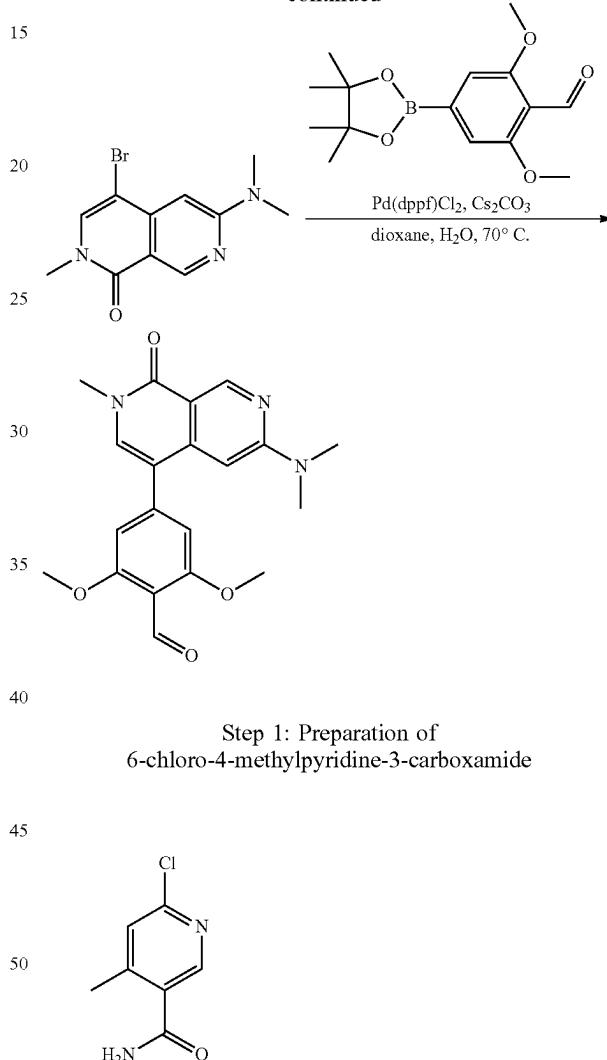
Compound No.	LCMS ^1H NMR
D295	652.40 ^1H NMR (400 MHz, Methanol-d4) δ 9.23 (s, 1H), 8.09 (d, J = 2.2 Hz, 1H), 7.97 (dd, J = 8.3, 2.3 Hz, 1H), 7.84 (d, J = 8.3 Hz, 1H), 7.51 (s, 1H), 6.80 (s, 1H), 6.74 (s, 2H), 5.19 (dd, J = 13.3, 5.1 Hz, 1H), 4.67-4.49 (m, 2H), 3.99 (s, 3H), 3.90 (s, 6H), 3.88-3.76 (m, 5H), 3.62 (s, 3H), 3.03-2.86 (m, 3H), 2.80 (ddd, J = 17.5, 4.8, 2.4 Hz, 1H), 2.53 (qd, J = 13.2, 4.7 Hz, 1H), 2.21 (ddd, J = 10.9, 5.4, 3.0 Hz, 1H), 1.95 (d, J = 13.5 Hz, 2H).

Example 45—Preparation of 4-(6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzaldehyde



534

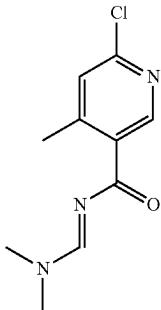
-continued



To a stirred mixture of 6-chloro-4-methylpyridine-3-carboxylic acid (20.0 g, 116.564 mmol, 1.00 equivalent) and NH_4Cl (62.35 g, 1.17 mol, 10.00 equivalent) in DCM (400 mL) was added DIEA (22.60 g, 174.846 mmol, 3.00 equivalent). After stirring for 5 min, HATU (66.48 g, 174.846 mmol, 1.50 equivalent) was added in portions. The resulting mixture was stirred for 3 hours at room temperature. The resulting mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography, eluted with PE/EtOAc from 1/1 to 3/2 to afford 6-chloro-4-methylpyridine-3-carboxamide (18.30 g, 61.3%) as a yellow solid. LCMS (ESI) m/z: $[\text{M}+\text{H}]^+ = 171$.

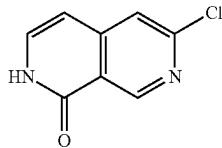
535

Step 2: Preparation of 6-chloro-N-[(1E)-(dimethylamino)methylidene]-4-methylpyridine-3-carboxamide



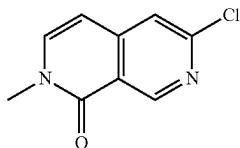
To a stirred mixture of 6-chloro-4-methylpyridine-3-carboxamide (18.30 g, 107.268 mmol, 1.00 equivalent) and in 2-methyltetrahydrofuran (100 mL) was added DMF-DMA (19.17 g, 160.903 mmol, 1.50 equivalent) at 80° C. under nitrogen atmosphere and stirred for additional 1 hour. Then the mixture was cooled and concentrated to afford 6-chloro-N-[(1E)-(dimethylamino)methylidene]-4-methylpyridine-3-carboxamide (26.3 g, 91.3%) as a yellow crude solid, that was used directly without further purification. LCMS (ESI) m/z: [M+H]⁺=226.

Step 3: Preparation of 6-chloro-2H-2,7-naphthyridin-1-one



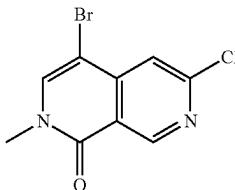
To a stirred mixture of 6-chloro-N-[(1E)-(dimethylamino)methylidene]-4-methylpyridine-3-carboxamide (26.30 g) in THF (170.00 mL) was added t-BuOK (174.00 mL, 1 mol/L in THF), the resulting solution was stirred at 60° C. under nitrogen atmosphere for 30 min. Then the mixture was cooled and concentrated under reduced pressure, the crude solid was washed with saturated NaHCO₃ solution (100 mL) and collected to give 6-chloro-2H-2,7-naphthyridin-1-one (14.1 g, 67.0%) as a pink solid, that was used directly without further purification. LCMS (ESI) m/z: [M+H]⁺=181.

Step 4: Preparation of 6-chloro-2-methyl-2,7-naphthyridin-1-one

**536**

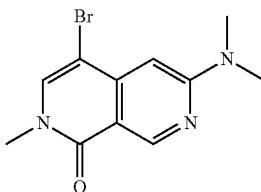
To a stirred mixture of 6-chloro-2H-2,7-naphthyridin-1-one (14.10 g, 78.077 mmol, 1.00 equivalent) in anhydrous THF (280.00 mL) was added NaH (9.37 g, 234.232 mmol, 3.00 equivalent, 60%) in portions at 0° C. After 10 min, to above mixture was added MeI (33.25 g, 234.232 mmol, 3.00 equivalent) at 0° C., the mixture was allowed to stir for 10 min at 0 degrees. Then the mixture was allowed to stir for 12 h at room temperature. The resulting mixture was concentrated under reduced pressure. The crude solid was slurried with water (100 mL), and the solid was filtered and collected to give the 6-chloro-2-methyl-2,7-naphthyridin-1-one (14.6 g, 94.1%) as a yellow solid, that was used directly without further purification. LCMS (ESI) m/z: [M+H]⁺=195.

Step 5: Preparation of 4-bromo-6-chloro-2-methyl-2,7-naphthyridin-1-one



To a stirred mixture of 6-chloro-2-methyl-2,7-naphthyridin-1-one (8.00 g, 41.106 mmol, 1.00 equivalent) in DMF (160.00 mL) was added NBS (8.78 g, 49.327 mmol, 1.20 equivalent), the resulting mixture was stirred for 2 h at 90° C. The reaction mixture was cooled and diluted with DCM (150 mL), and washed with water (3×100 mL), the organic layers were dried and concentrated. Then the residue was slurried with EtOAc (20 mL), the slurry was filtered, the filter cake was washed with EtOAc (20 mL) to give 4-bromo-6-chloro-2-methyl-2,7-naphthyridin-1-one (6.32 g, 55.7%) as a white solid, that was used directly without further purification. LCMS (ESI) m/z: [M+H]⁺=273.

Step 6: Preparation of 4-bromo-6-(dimethylamino)-2-methyl-2,7-naphthyridin-1-one

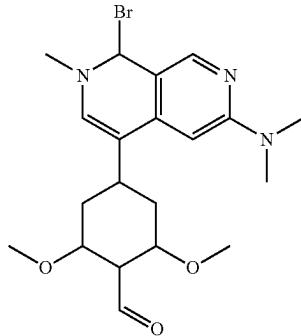


A stirred mixture of 4-bromo-6-chloro-2-methyl-2,7-naphthyridin-1-one (6.00 g, 21.937 mmol, 1.00 equivalent), dimethylamine hydrochloride (5.37 g, 65.811 mmol, 3.00 equivalent) and K₂CO₃ (15.16 g, 109.685 mmol, 5.00 equivalent) in DMSO (60.00 mL) was heated at 130° C. under nitrogen atmosphere. After 3 h, the resulting mixture was cooled and diluted with water (100 mL), and then extracted with EtOAc (3×100 mL). The combined organic layers were washed with saturated NaCl solution (3×50 mL), dried over anhydrous Na₂SO₄, concentrated under reduced pressure to afford 4-bromo-6-(dimethylamino)-2-methyl-2,

537

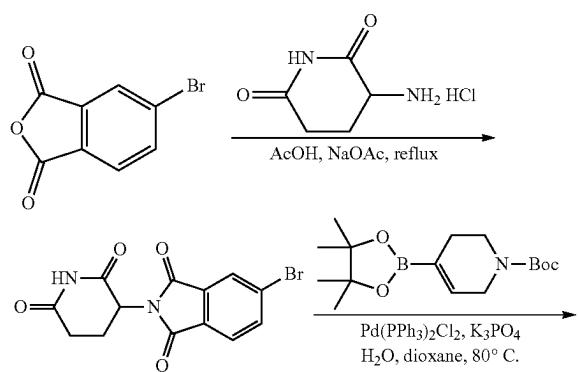
7-naphthyridin-1-one (5.91 g, 93.6%) as a yellow solid, that was used directly without further purification. LCMS (ESI) m/z: [M+H]⁺=282.

Step 7: Preparation of (4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde

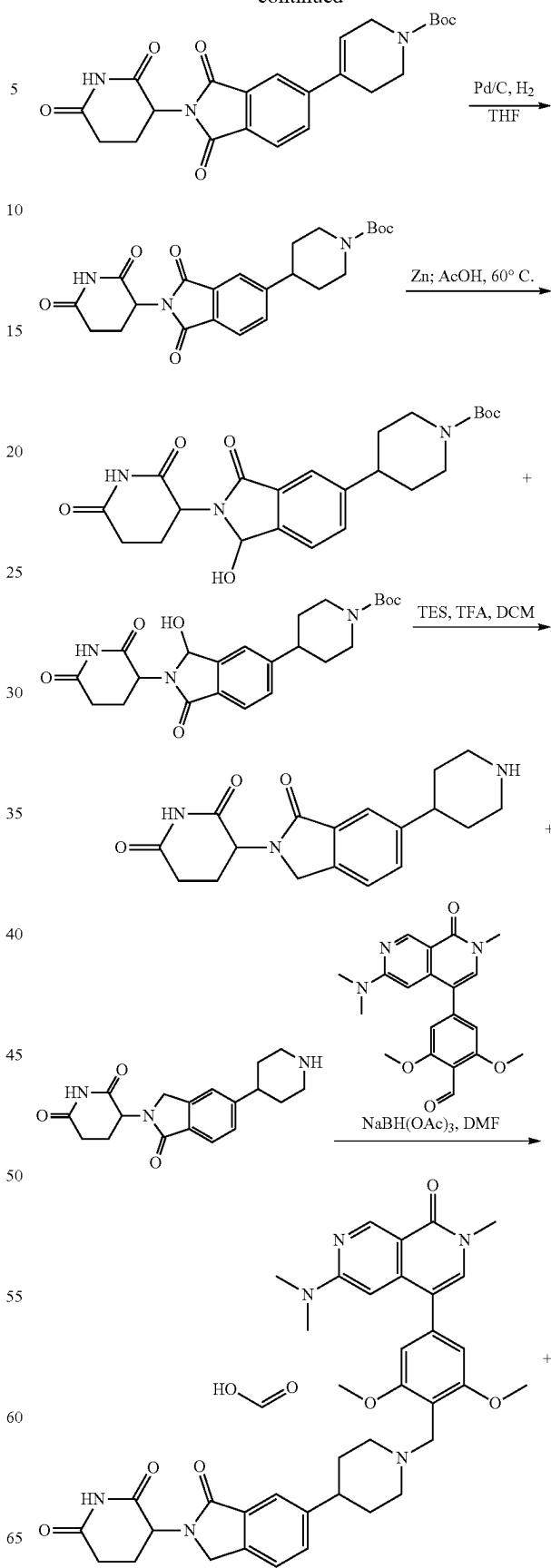


To a stirred mixture of 4-bromo-6-(dimethylamino)-2-methyl-2,7-naphthyridin-1-one (5.70 g, 20.203 mmol, 1.00 equivalent) and 2,6-dimethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (8.26 g, 28.284 mmol, 1.40 equivalent) in dioxane (100.00 mL) and H₂O (10.00 mL) was added Pd(dppf)Cl₂CH₂Cl₂ (1.65 g, 2.020 mmol, 0.10 equivalent) and 052003 (13.16 g, 40.405 mmol, 2.00 equivalent), then the mixture was allowed to stir for 4 h at 70° C. under nitrogen atmosphere. The resulting mixture was cooled and concentrated under reduced pressure, the residue was slurried with water (100 mL) and filtered, the filter cake was collected. And this solid was further slurried with MeOH (100 mL) and filtered, the solid was collected to afford product to afford 4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (6.10 g, 77.6%) as a brown solid. LCMS (ESI) m/z: [M+H]⁺ = 368.

Example 46—Preparation of 3-(6-(1-(4-(6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)piperidin-4-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione formic acid; and 3-(5-(1-(4-(6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)piperidin-4-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione formic acid

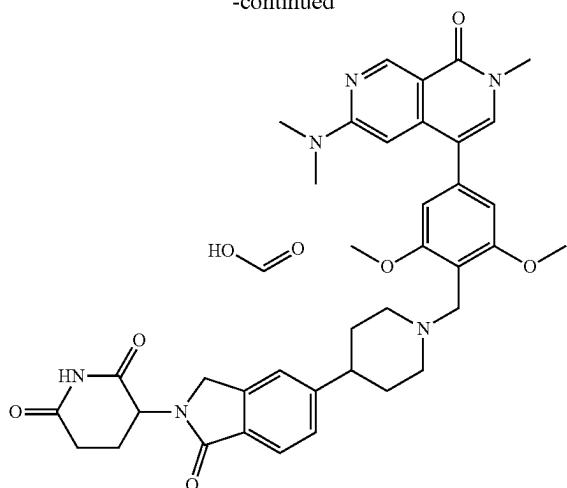
**538**

-continued

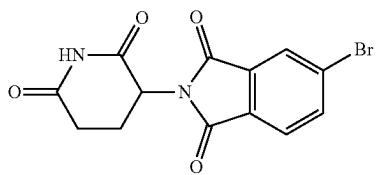


539

-continued

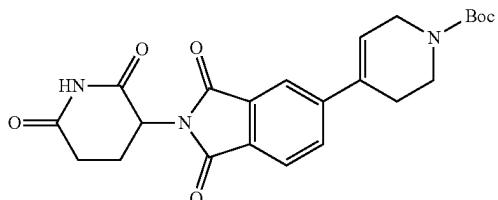


Step 1: Preparation of 5-bromo-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione



To a stirred solution of 5-bromo-2-benzofuran-1,3-dione (10.00 g, 44.050 mmol, 1.00 equivalent), NaOAc (7.23 mg, 88.134 mmol, 2.00 equivalent) and 3-aminopiperidine-2,6-dione (11.29 g, 88.113 mmol, 2.00 equivalent) in AcOH (80.00 mL) at room temperature. The resulting mixture was stirred for 16 h at 115° C. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with petroleum ether/EtOAc (10:1) to afford 5-bromo-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (13.6 g, 91.6%) as a dark brown solid. LCMS (ESI) m/z: [M+H]⁺=337.

Step 2: Preparation of tert-butyl 4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-3,6-dihydro-2H-pyridine-1-carboxylate

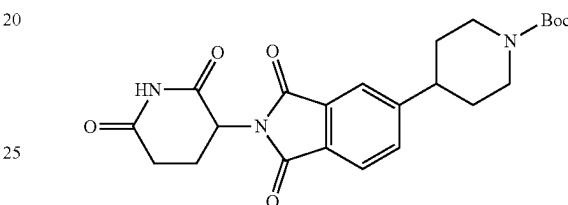


To a stirred solution of 5-bromo-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (3.00 g, 8.899 mmol, 1.00 equivalent), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (3.30 g, 10.672 mmol, 1.20 equivalent), K₃PO₄ (5.67 g, 26.712

540

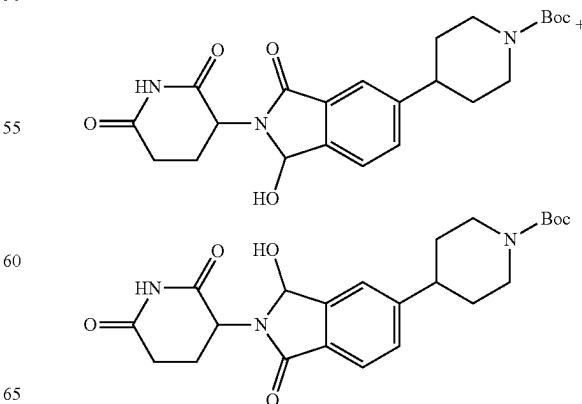
mmol, 3.00 equivalent) in dioxane (20.00 mL) and H₂O (4.00 mL) was added Pd(PPh₃)₂Cl₂ (0.62 g, 0.883 mmol, 0.10 equivalent) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 16 h at 80° C. under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (8/1) to afford tert-butyl 4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (0.8 g, 20.5%) as a colorless oil. LCMS (ESI) m/z: [M+H]⁺=440.

Step 3: Preparation of tert-butyl 4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperidine-1-carboxylate



To a stirred solution of tert-butyl 4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (0.80 g) in THF (20.00 mL) was added 10% Pd/C (500.0 mg) under nitrogen atmosphere in a 100 mL round-bottom flask. The mixture was hydrogenated at room temperature for 12 h under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. This resulted in tert-butyl 4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperidine-1-carboxylate (0.73 g, crude) as a white solid that was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H]⁺=442.

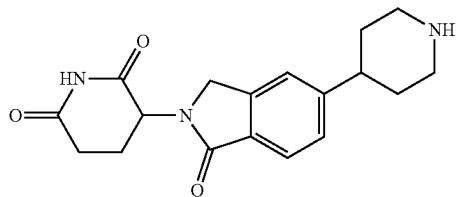
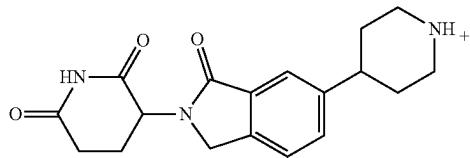
Step 4: Preparation of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-hydroxy-3-oxoisoindolin-5-yl)piperidine-1-carboxylate; tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-3-hydroxy-1-oxoisoindolin-5-yl)piperidine-1-carboxylate



541

To a stirred solution of tert-butyl 4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl]piperidine-1-carboxylate (0.73 g, 16.55 mmol, 1.00 equivalent) and Zn (1.08 g, 1.65 mmol, 10.00 equivalent) in AcOH (10.00 mL) at room temperature. The resulting mixture was stirred for 2 h at 60° C. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2:1) to afford tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-hydroxy-3-oxoisindolin-5-yl)piperidine-1-carboxylate; tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-3-hydroxy-1-oxoisindolin-5-yl)piperidine-1-carboxylate (0.546 g, 74.8%, mixture of two regio-isomers) as a colorless solid. LCMS (ESI) m/z: [M+H]⁺=444.

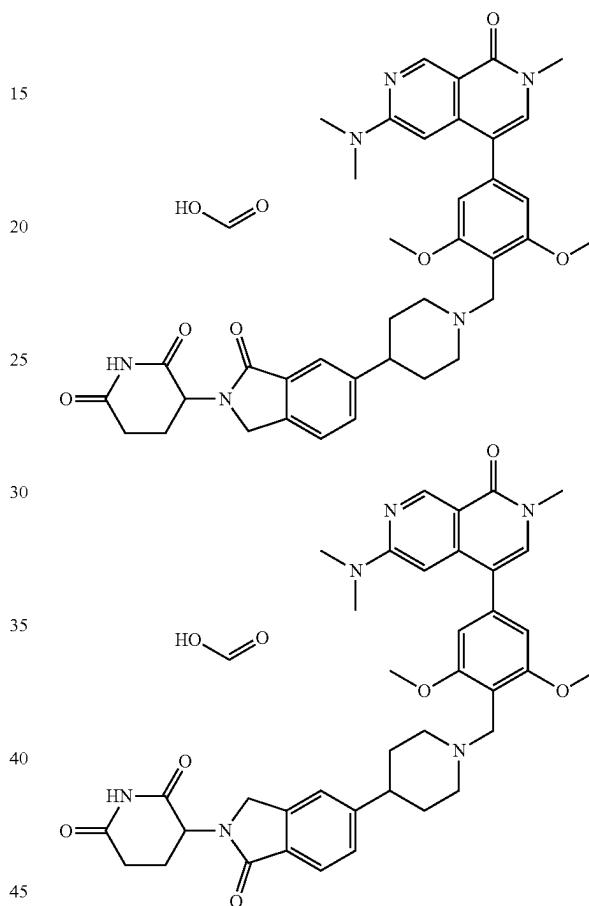
Step 5: Preparation of 3-(1-oxo-6-(piperidin-4-yl)isoindolin-2-yl)piperidine-2, 6-dione; 3-(1-oxo-5-(piperidin-4-yl)isoindolin-2-yl)piperidine-2, 6-dione



To a stirred solution of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-hydroxy-3-oxoisindolin-5-yl)piperidine-1-carboxylate; tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-3-hydroxy-1-oxoisindolin-5-yl)piperidine-1-carboxylate (mixture of two regio-isomers, 573.00 mg, 1.00 equivalent) and TFA (3.00 mL) in DCM (9.00 mL) was added TES (450.7 mg, 3.876 mmol, 3.00 equivalent) at room temperature. The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure. This was used directly without further purification, to afford 3-(1-oxo-6-(piperidin-4-yl)isoindolin-2-yl)piperidine-2, 6-dione; 3-(1-oxo-5-(piperidin-4-yl)isoindolin-2-yl)piperidine-2, 6-dione (200 mg 36.6% mixture of two regio-isomers) as an off-white oil. LCMS (ESI) m/z: [M+H]⁺=328.

542

Step 6: Preparation of 3-(6-(1-(4-(6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)piperidin-4-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione formic acid; and 3-(5-(1-(4-(6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)piperidin-4-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione formic acid



To a stirred solution of 3-[1-oxo-6-(piperidin-4-yl)-3H-isoindol-2-yl]piperidine-2, 6-dione (165.0 mg, 0.504 mmol, 1.00 equivalent), and 3-(1-oxo-6-(piperidin-4-yl)isoindolin-2-yl)piperidine-2, 6-dione; 3-(1-oxo-5-(piperidin-4-yl)isoindolin-2-yl)piperidine-2, 6-dione (mixture of two regio-isomers, 222.2 mg, 0.605 mmol, 1.20 equivalent) in DMF (4.00 mL) was added NaBH(OAc)₃ (427.3 mg, 2.016 mmol, 4.00 equivalent) at room temperature. The resulting mixture was stirred for 16 h at room temperature. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, CH₃CN in water (0.05% FA), 0% to 50% gradient in 30 min; detector, UV 254 nm. The crude product was purified by Prep-HPLC with the following conditions: Column, Sunfire Prep C18 OBD Column, 10 μm , 19*250 mm; mobile phase, water (0.05% FA) and CH₃CN (15% to 22% CH₃CN in 15 min); Detector, UV 254 nm. This resulted in 3-[6-[1-(4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl]methyl)piperidin-4-yl]-1-oxo-3H-isoindol-2-yl)piperidine-2, 6-dione; formic acid (52.5 mg, 26.3%) as

543

a white solid and 3-[5-[1-([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl)methyl]piperidin-4-yl]-1-oxo-3H-isooindol-2-yl]piperidine-2,6-dione; formic acid (68.4 mg, 34.2%) as a yellow solid.

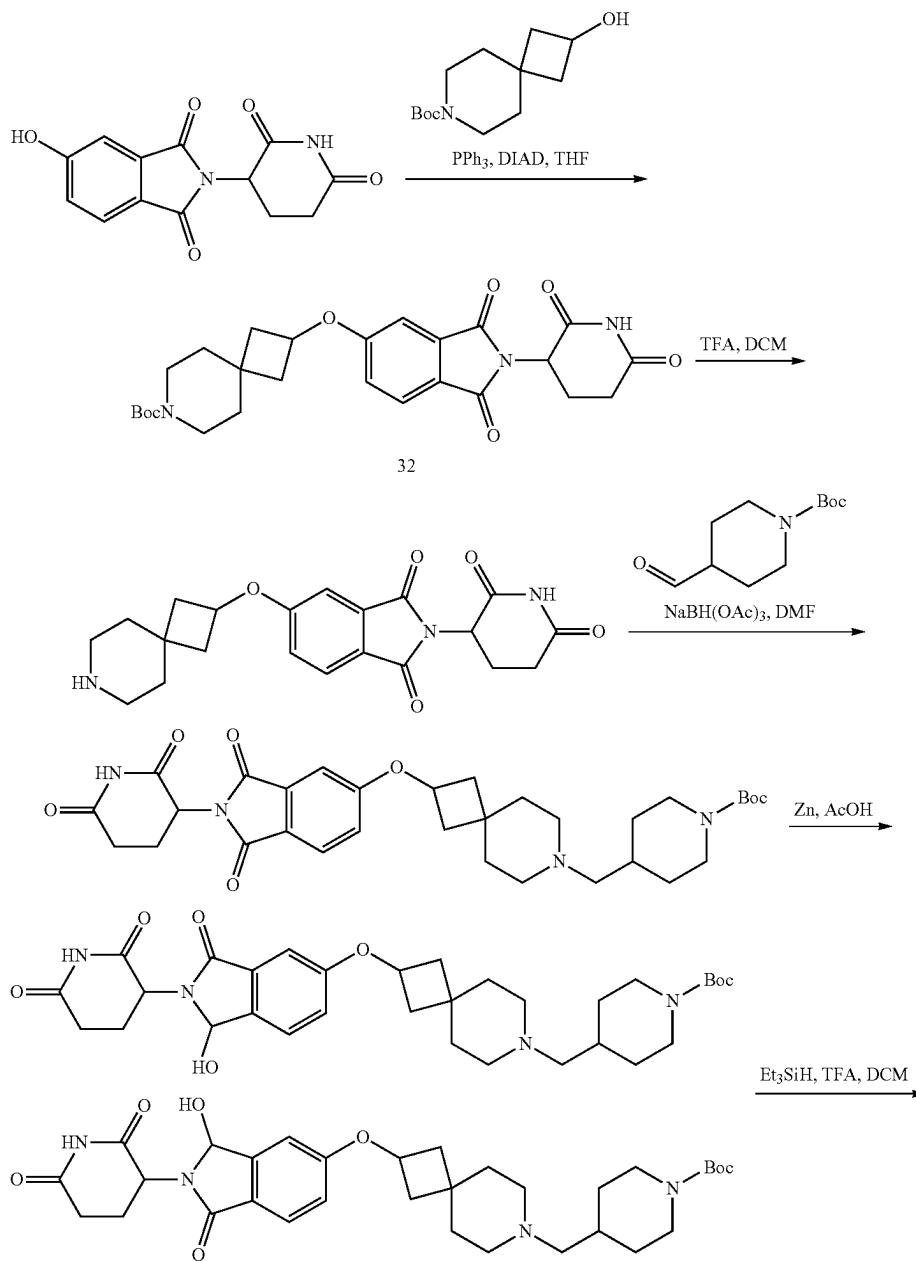
For 3-[6-[1-([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl)methyl]piperidin-4-yl]-1-oxo-3H-isooindol-2-yl]piperidine-2,6-dione; formic acid: ¹H NMR (400 MHz, DMSO-d₆) δ 10.97 (s, 1H), 9.04 (s, 1H), 8.20 (s, 1H, FA), 7.58 (d, J=14.5 Hz, 2H), 7.52 (s, 2H), 6.79 (s, 2H), 6.50 (s, 1H), 5.10 (dd, J=13.4, 5.1 Hz, 1H), 4.41 (d, J=17.1 Hz, 1H), 4.28 (d, J=17.0 Hz, 1H), 3.84 (s, 6H), 3.68 (s, 2H), 3.49 (s, 3H), 3.08-3.05 (m, 8H), 2.91-2.89 (m, 1H), 2.66-2.56 (m, 2H), 2.40-2.35 (m, 1H), 2.30 (t, J=11.3 Hz, 2H), 2.03-1.95 (m, 1H), 1.88-1.57 (m, 4H). LCMS (ESI) m/z: [M+H]⁺=679.32.

For 3-[5-[1-([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl)methyl]piperidin-

544

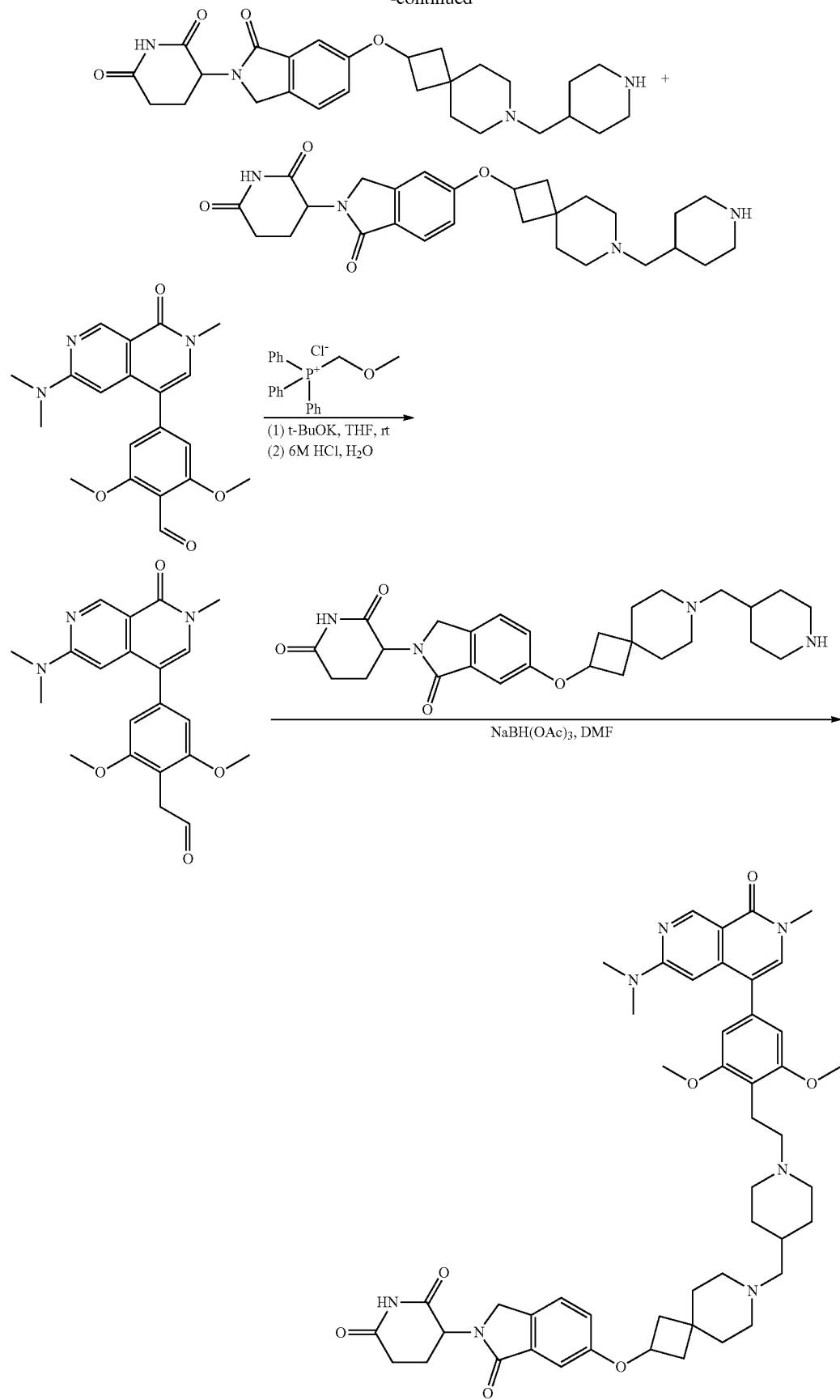
4-yl]-1-oxo-3H-isooindol-2-yl]piperidine-2,6-dione; formic acid: ¹H NMR (400 MHz, DMSO-d₆) δ 10.98 (s, 1H), 9.05 (s, 1H), 8.15 (s, 1H, FA), 7.69 (d, J=7.8 Hz, 1H), 7.60 (s, 1H), 7.48 (s, 1H), 7.40 (d, J=7.9 Hz, 1H), 6.87 (s, 2H), 6.51 (s, 1H), 5.11 (dd, J=13.3, 5.1 Hz, 1H), 4.44 (d, J=17.3 Hz, 1H), 4.31 (d, J=17.3 Hz, 1H), 4.05 (s, 2H), 3.90 (s, 6H), 3.49 (s, 3H), 3.31 (d, J=11.7 Hz, 2H), 3.09 (s, 6H), 2.99-2.71 (m, 4H), 2.65-2.56 (m, 1H), 2.47-2.33 (m, 1H), 2.04-1.96 (m, 1H), 1.92 (m, 4H). LCMS (ESI) m/z: [M+H]⁺=679.32.

Example 47—Preparation of 3-[6-[1-[(2-[4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]ethyl)piperidin-4-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]oxy]-1-oxo-3H-isooindol-2-yl]piperidine-2,6-dione bis(trifluoroacetic acid)



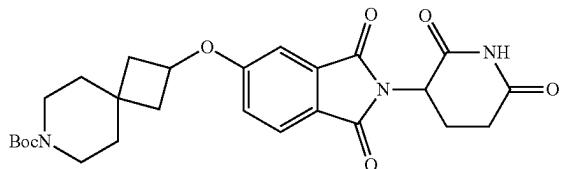
545**546**

-continued



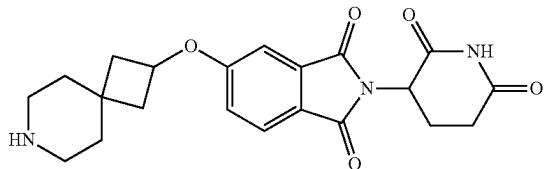
547

Step 1: Preparation of tert-butyl 2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]oxy]-7-azaspiro[3.5]nonane-7-carboxylate



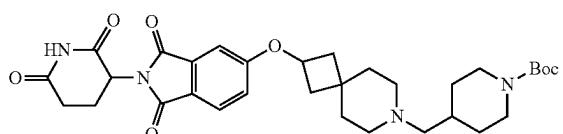
To a solution of 2-(2,6-dioxopiperidin-3-yl)-5-hydroxyisindole-1,3-dione (1.37 g, 4.996 mmol, 1.00 equivalent) and tert-butyl 2-hydroxy-7-azaspiro[3.5]nonane-7-carboxylate (1.81 g, 7.494 mmol, 1.5 equivalent) in THF (30.00 mL) was added PPh₃ (1.97 g, 7.494 mmol, 1.5 equivalent). To the above mixture was added DIAD (1.52 g, 7.494 mmol, 1.5 equivalent) dropwise over 10 min at 0° C. The resulting mixture was stirred for additional 5 h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, FA in water, 0% to 100% gradient in 45 min; detector, UV 254 nm. This resulted in tert-butyl 2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]oxy]-7-azaspiro[3.5]nonane-7-carboxylate (1.964 g, 79.0%) as a white solid. LCMS (ESI) m/z: [M+H]⁺=498.

Step 2: Preparation of 5-[7-azaspiro[3.5]nonan-2-yloxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione; formic acid



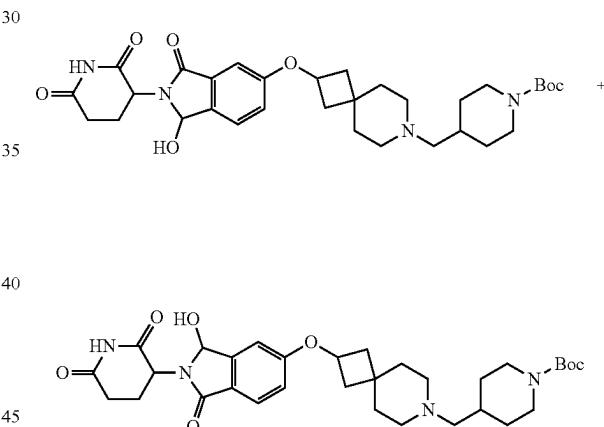
To a solution of tert-butyl 2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]oxy]-7-azaspiro[3.5]nonane-7-carboxylate (1.96 g, 3.939 mmol) in DCM (10.00 mL) was added TFA (10.00 mL). The resulting mixture was stirred for 5 h at room temperature. The reaction mixture was concentrated in vacuo to give crude 5-[7-azaspiro[3.5]nonan-2-yloxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione; formic acid, which was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H]⁺=398.

Step 3: Preparation of tert-butyl 4-[(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]oxy]-7-azaspiro[3.5]nonan-7-yl)methyl]piperidine-1-carboxylate

**548**

To a solution of 5-[7-azaspiro[3.5]nonan-2-yloxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (2.65 g, 6.668 mmol, 1.00 equivalent) and tert-butyl 4-formylpiperidine-1-carboxylate (1.42 g, 6.668 mmol, 1 equivalent) in DMF (30.00 mL) was added NaBH(OAc)₃ (4.24 g, 20.003 mmol, 3 equivalent) at room temperature. The resulting mixture was stirred for 3 h at room temperature. The reaction was quenched by the addition of water (100 mL) at room temperature. The resulting mixture was extracted with EtOAc (3×150 mL). The combined organic layers were washed with brine (3×150 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. This resulted in tert-butyl 4-[(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]oxy]-7-azaspiro[3.5]nonan-7-yl)methyl]piperidine-1-carboxylate (3.11 g, 78.4%) as a light yellow solid; LCMS (ESI) m/z: [M+H]⁺=595.

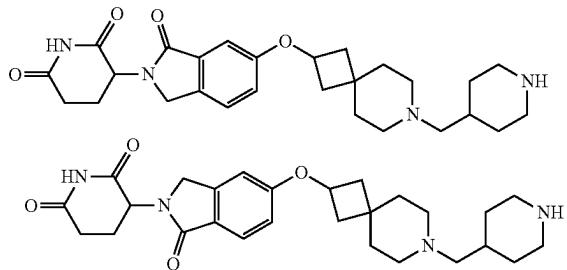
Step 4: Preparation of tert-butyl 4-[(2-[[2-(2,6-dioxopiperidin-3-yl)-1-hydroxy-3-oxo-1H-isindol-5-yl]oxy]-7-azaspiro[3.5]nonan-7-yl)methyl]piperidine-1-carboxylate and tert-butyl 4-[(2-[[2-(2,6-dioxopiperidin-3-yl)-3-hydroxy-1-oxo-3H-isindol-5-yl]oxy]-7-azaspiro[3.5]nonan-7-yl)methyl]piperidine-1-carboxylate



To a solution of tert-butyl 4-[(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]oxy]-7-azaspiro[3.5]nonan-7-yl)methyl]piperidine-1-carboxylate (3.00 g, 5.044 mmol, 1.00 equivalent) in AcOH (60.00 mL) were added Zn (3.30 g, 50.445 mmol, 10 equivalent) at room temperature. The resulting mixture was stirred for 3 h at 60° C. The resulting mixture was filtered, and the filter cake was washed with MeCN (3×100 mL). The filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, FA in water, 0% to 100% gradient in 35 min; detector, UV 254 nm. This resulted in the mixture of tert-butyl 4-[(2-[[2-(2,6-dioxopiperidin-3-yl)-1-hydroxy-3-oxo-1H-isindol-5-yl]oxy]-7-azaspiro[3.5]nonan-7-yl)methyl]piperidine-1-carboxylate and tert-butyl 4-[(2-[[2-(2,6-dioxopiperidin-3-yl)-3-hydroxy-1-oxo-3H-isindol-5-yl]oxy]-7-azaspiro[3.5]nonan-7-yl)methyl]piperidine-1-carboxylate (mixture, 1.6 g, 53.2%) a light yellow solid. LCMS (ESI) m/z: [M+H]⁺=597.

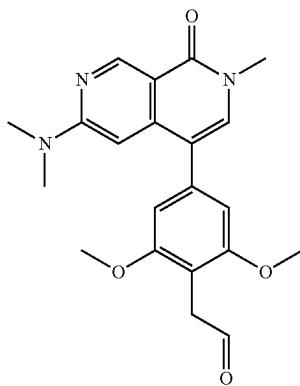
549

Step 5: Preparation of 3-(1-oxo-6-[[7-(piperidin-4-ylmethyl)-7-azaspiro[3.5]nonan-2-yl]oxy]-3H-isoindol-2-yl)piperidine-2,6-dione and 3-(1-oxo-5-[[7-(piperidin-4-ylmethyl)-7-azaspiro[3.5]nonan-2-yl]oxy]-3H-isoindol-2-yl)piperidine-2,6-dione



To a solution of the mixture of tert-butyl 4-[(2-[[2-(2,6-dioxopiperidin-3-yl)-1-hydroxy-3-oxo-1H-isoindol-5-yl]oxy]-7-azaspiro[3.5]nonan-7-yl)methyl]piperidine-1-carboxylate (2.40 g, 4.022 mmol, 1.00 equivalent) and tert-butyl 4-[(2-[[2-(2,6-dioxopiperidin-3-yl)-3-hydroxy-1-oxo-3H-isoindol-5-yl]oxy]-7-azaspiro[3.5]nonan-7-yl)methyl]piperidine-1-carboxylate (DCM (50.00 mL)) were added TFA (5.00 mL, 67.315 mmol, 16.74 equivalent) and Et₃SiH (4.68 g, 40.220 mmol, 10 equivalent) at room temperature. The resulting mixture was stirred for 12 h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, TFA in water, 0% to 10% gradient in 45 min; detector, UV 254 nm. This resulted in 3-(1-oxo-6-[[7-(piperidin-4-ylmethyl)-7-azaspiro[3.5]nonan-2-yl]oxy]-3H-isoindol-2-yl)piperidine-2,6-dione (600 mg, 31.0%) and 3-(1-oxo-5-[[7-(piperidin-4-ylmethyl)-7-azaspiro[3.5]nonan-2-yl]oxy]-3H-isoindol-2-yl)piperidine-2,6-dione (1.2 g, 62.1%) as a light yellow solid. LCMS (ESI) m/z: [M+H]⁺= 481.

Step 6: 2-[4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]acetaldehyde

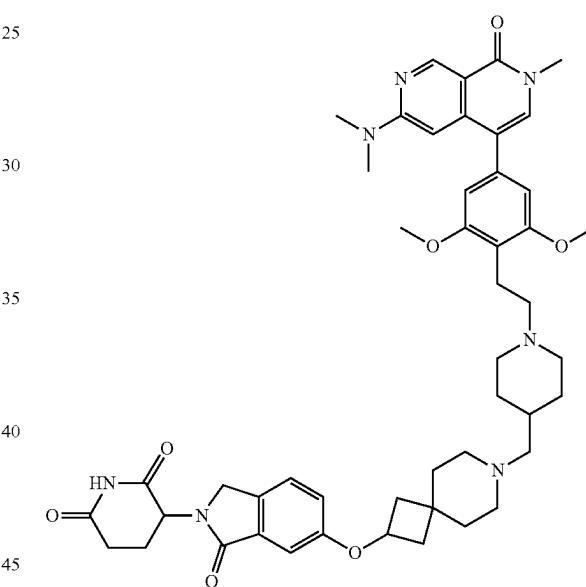


To a stirred mixture of 4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (150.0 mg, 0.408 mmol, 1.00 equivalent) and (methoxym-

550

ethyl)triphenylphosphonium chloride (559.8 mg, 1.633 mmol, 4 equivalent) in THF (5.0 mL) was added t-BuOK (183.2 mg, 1.633 mmol, 4 equivalent). The resulting mixture was stirred for 30 min at room temperature under nitrogen atmosphere. To the above mixture was added HCl (6M, 0.5 mL, 0.30 mmol) dropwise. The resulting mixture was stirred for additional 30 min at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by reverse phase column with the following conditions: column, C18 silica gel; mobile phase, ACN in water, 10% to 80% gradient in 15 min; detector, UV 254 nm. This resulted in 2-[4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]acetaldehyde (160 mg, 95.1%) as a white solid. LCMS (ESI) m/z: [M+H]⁺= 382.

Step 7: 3-[6-[[7-[[1-(2-[4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]ethyl]piperidin-4-yl]ethyl]-7-azaspiro[3.5]nonan-2-yl]oxy]-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione bis(trifluoroacetic acid)

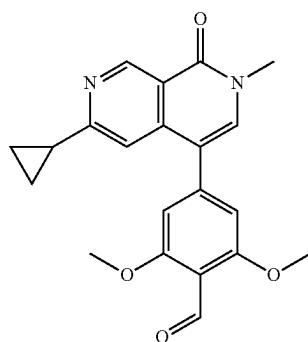
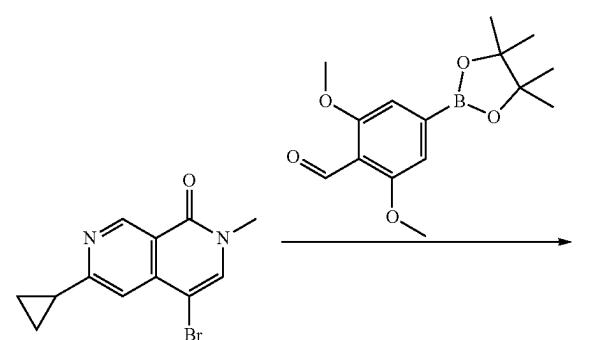
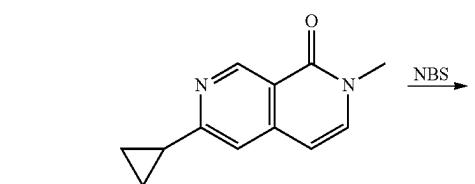
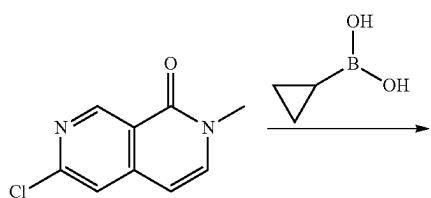


To a stirred solution of 2-[4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]acetaldehyde (150.0 mg, 0.393 mmol, 1.00 equivalent) and 3-(1-oxo-6-[[7-(piperidin-4-ylmethyl)-7-azaspiro[3.5]nonan-2-yl]oxy]-3H-isoindol-2-yl)piperidine-2,6-dione (189.0 mg, 0.393 mmol, 1 equivalent) in DMF (2.0 mL) was added NaBH(OAc)₃ (250.0 mg, 1.180 mmol, 3 equivalent). The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The crude reaction mixture was purified by Prep-HPLC with the following conditions (Column: XSelect CSH Prep C18 OBD Column, 19*250 mm, 5 μ m; Mobile Phase A: Water (0.05% TFA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 8 B to 25 B in 15 min; 254/220 nm; RT1: 12.28 min) to afford 3-[6-[[7-[[1-(2-[4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]ethyl]piperidin-4-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]oxy]-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione; bis(trifluoroacetic acid) (101.2 mg, 30.4%) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ 11.00 (s, 1H), 9.49 (d, J=109.5 Hz, 2H, TFA

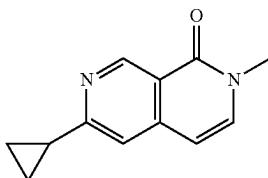
551

salt), 9.04 (s, 1H), 7.57-7.48 (m, 2H), 7.18-7.09 (m, 2H), 6.81 (d, J=2.8 Hz, 2H), 6.48 (s, 1H), 5.11 (dd, J=13.1, 5.2 Hz, 1H), 4.89 (p, J=6.8 Hz, 1H), 4.38 (d, J=17.0 Hz, 1H), 4.28-4.22 (m, 2H), 3.85 (s, 6H), 3.68 (d, J=11.3 Hz, 2H), 3.48 (s, 3H), 3.40 (d, J=11.9 Hz, 1H), 3.33-3.18 (m, 1H), 3.08 (s, 6H), 3.06-2.84 (m, 9H), 2.65-2.56 (m, 2H), 2.46-2.36 (m, 2H), 2.14-1.93 (m, 6H), 1.92-1.79 (m, 5H), 1.46 (q, J=12.2 Hz, 2H). LCMS (ESI) m/z: [M+H]⁺=846.25.

Example 48—Preparation 4-(6-cyclopropyl-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzaldehyde

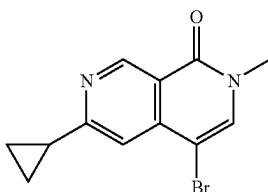
**552**

Step 1: Preparation of 6-cyclopropyl-2-methyl-2,7-naphthyridin-1-one



15 To a stirred solution of 6-chloro-2-methyl-2,7-naphthyridin-1-one (500.00 mg, 2.569 mmol, 1.00 equivalent) and cyclopropylboronic acid (441.37 mg, 5.138 mmol, 2 equivalent) in toluene (20.00 mL) and water (1.00 mL) was added 20 tricyclohexylphosphane (144.09 mg, 0.514 mmol, 0.20 equivalent), Pd(AcO)₂ (57.68 mg, 0.257 mmol, 0.10 equivalent) and K₃PO₄ (1636.01 mg, 7.707 mmol, 3.00 equivalent) 25 at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 110° C. The mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 30 CH₂Cl₂/MeOH (50:1) to afford 6-cyclopropyl-2-methyl-2,7-naphthyridin-1-one (340 mg, 59.48%) as a brown solid. LCMS (ESI) m/z: [M+H]⁺=201.

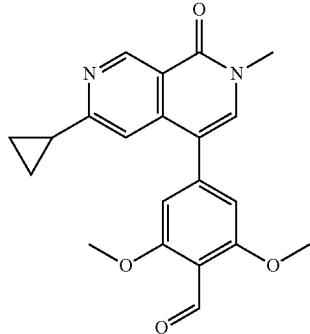
35 Step 2: Preparation of 4-bromo-6-cyclopropyl-2-methyl-2,7-naphthyridin-1-one



50 To a stirred solution of 6-cyclopropyl-2-methyl-2,7-naphthyridin-1-one (100.00 mg, 0.499 mmol, 1.00 equivalent) in DMF (4.00 mL) was added NBS (106.66 mg, 0.599 mmol, 1.20 equivalent) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 90° C. 55 The resulting mixture was diluted with water (12 mL), extracted with EtOAc (3×100 mL). The combined organic 60 layers were washed with brine (2×50 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford 4-bromo-6-cyclopropyl-2-methyl-2,7-naphthyridin-1-one (400 mg, 75.96%) as a brown solid. That was used directly without further purification. LCMS (ESI) m/z: [M+H]⁺=279.

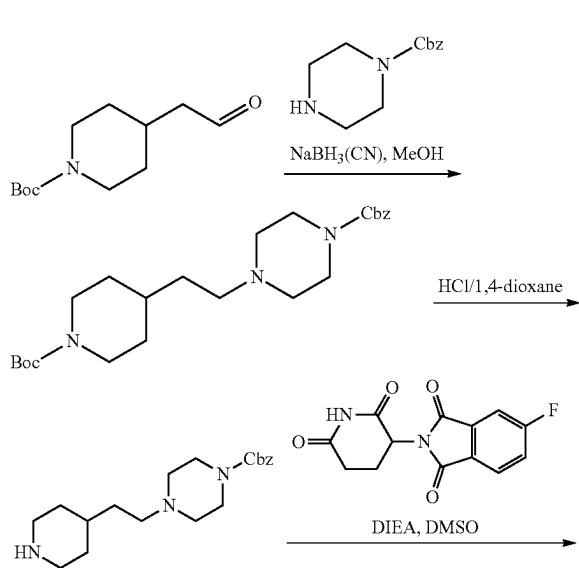
553

Step 3: Preparation of 4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzaldehyde

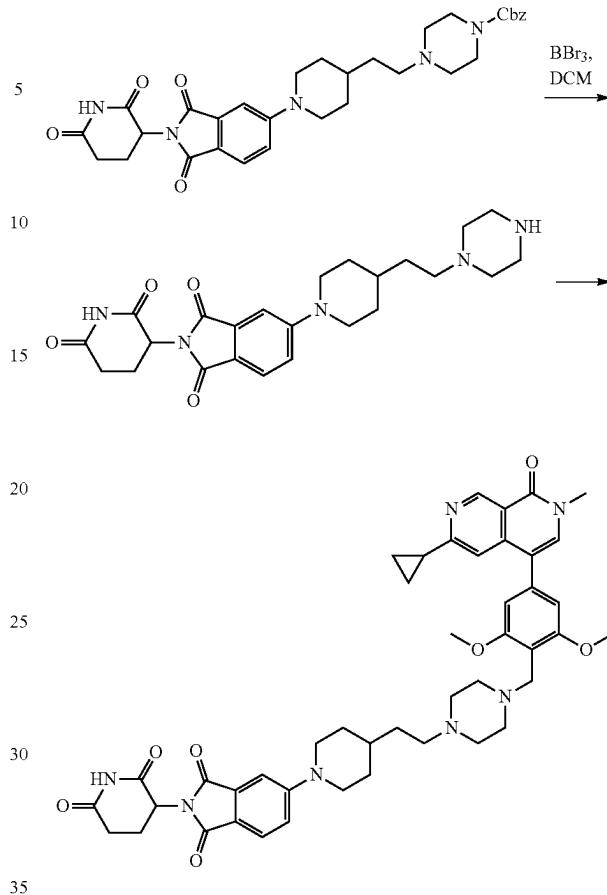


To a stirred solution of 4-bromo-6-cyclopropyl-2-methyl-2,7-naphthyridin-1-one (420.00 mg, 1.505 mmol, 1.00 equivalent) and 2,6-dimethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (527.48 mg, 1.806 mmol, 1.2 equivalent) in dioxane (10.00 mL) and water (2.00 mL) was added Pd(dppf)Cl₂ (110.09 mg, 0.150 mmol, 0.10 equivalent) and K₂CO₃ (415.90 mg, 3.009 mmol, 2.00 equivalent) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at 80° C. The mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH₂Cl₂/MeOH 50:1) to afford 4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzaldehyde (440 mg, 72.22%) as a yellow solid. LCMS (ESI) m/z: [M+H]⁺=365.

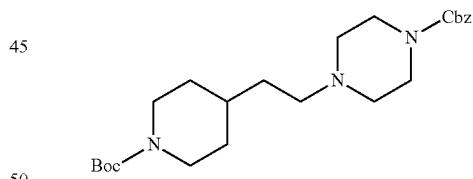
Example 49—Preparation of 5-[4-[2-(4-[4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl]methyl]piperazin-1-yl]ethyl]piperidin-1-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione

**554**

-continued



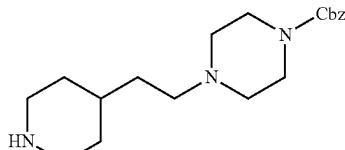
Step 1: Preparation of benzyl 4-(2-(1-(tert-butoxy-carbonyl)piperidin-4-yl)ethyl)piperazine-1-carboxylate



To a solution of tert-butyl 4-(2-oxoethyl)piperidine-1-carboxylate (4.02 g, 17.709 mmol, 1.00 equivalent) and benzyl piperazine-1-carboxylate (3.90 g, 17.727 mmol, 1.00 equivalent) in MeOH (40 mL) was added NaBH₃CN (2.26 g, 35.313 mmol, 2 equivalent), the resulting solution was stirred at 25° C. for 1 hours. The resulting mixture was diluted with water (50 mL), extracted with EA (30 mL×3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 45% THF in petroleum ether. Pure fractions were evaporated to dryness to afford benzyl 4-(2-(1-(tert-butoxycarbonyl)piperidin-4-yl)ethyl)piperazine-1-carboxylate (2.76 g, 35.71%) as a colorless oil. LCMS (ESI) m/z: [M+H]⁺=432.

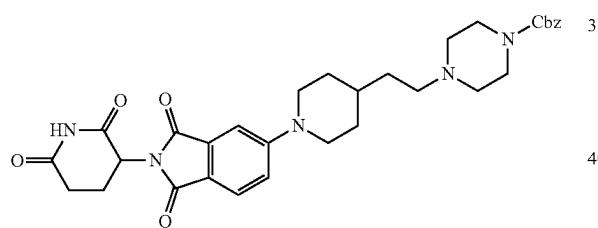
555

Step 2: Preparation of benzyl 4-(2-(piperidin-4-yl)ethyl)piperazine-1-carboxylate



To a solution of benzyl 4-(2-(1-(tert-butoxycarbonyl)piperidin-4-yl)ethyl)piperazine-1-carboxylate (2.76 g, 6.403 mmol, 1.00 equivalent) in DCM (8.00 mL) was added a solution of HCl in 1,4-dioxane (8.00 mL, 4 mol/L), the resulting mixture was stirred at 25° C. for 1 hour. The resulting mixture was filtered, the filter cake was washed with DCM (5 mL). The collected solid was dried under reduced pressure to afford 4-(2-(piperidin-4-yl)ethyl)piperazine-1-carboxylate (2.08 g, 98.11%) as a white solid. LCMS (ESI) m/z: [M+H]⁺=331.

Step 3: Preparation of benzyl 4-(2-(1-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)piperidin-4-yl)ethyl)piperazine-1-carboxylate

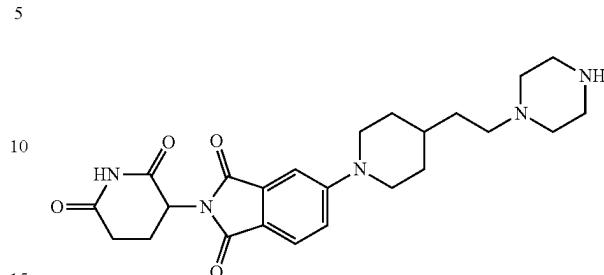


To a solution of 4-(2-(piperidin-4-yl)ethyl)piperazine-1-carboxylate (1.50 g, 4.532 mmol, 1.00 equivalent) and 2-(2,6-dioxopiperidin-3-yl)-5-fluoroisoindoline-1,3-dione (1.25 g, 4.532 mmol, 1 equivalent) in DMSO (15.00 mL) was added DIEA (3.51 g, 27.192 mmol, 6 equivalent), the resulting solution was stirred at 100° C. for 2 hour. The reaction mixture was diluted with EA (500 mL).

The resulting mixture was washed with water (300 mL×3) and saturated brine (300 mL×1). The organic layer was dried over Na₂SO₄, filtered and evaporated to afford crude product. The crude product was purified by silica gel column chromatography, elution gradient 0 to 100% EtOAc in petroleum ether. Pure fractions were evaporated to dryness to afford benzyl 4-(2-(1-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)piperidin-4-yl)ethyl)piperazine-1-carboxylate (1.44 g, 54.13%) as a yellow solid. LCMS (ESI) m/z: [M+H]⁺=588.

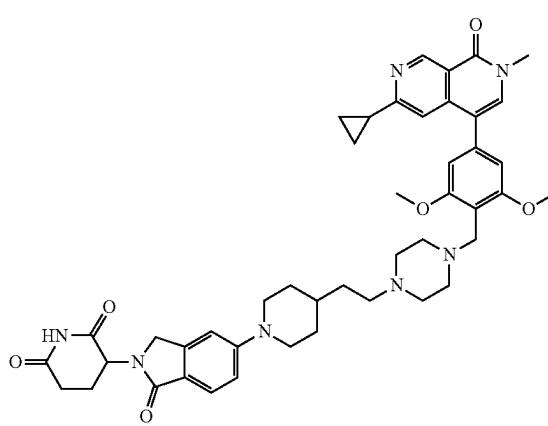
556

Step 4: Preparation of 2-(2,6-dioxopiperidin-3-yl)-5-(4-(2-(piperazin-1-yl)ethyl)piperidin-1-yl)isoindole-1,3-dione



To a solution 4-(2-(1-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)piperidin-4-yl)ethyl)piperazine-1-carboxylate (1.04 g, 1.772 mmol, 1.00 equivalent) in DCM (30.00 mL) was added a solution of BBr₃ in DCM (20 mL, 1M), the resulting mixture was stirred at 0° C. for 1 hour. The reaction mixture was poured into ice-water (100 mL), extracted with DCM (30 mL×3), the aqueous layer was concentrated under reduced pressure. The residue was purified by flash C18-flash chromatography, elution gradient 0 to 50% MeCN in water (containing 0.1% HCl). Pure fractions were evaporated to dryness to afford 2-(2,6-dioxopiperidin-3-yl)-5-(4-(2-(piperazin-1-yl)ethyl)piperidin-1-yl)isoindole-1,3-dione (794 mg, 98.75%) as a yellow solid. LCMS (ESI) m/z: [M+H]⁺=454.

Step 5: Preparation of 5-[4-[2-(4-[4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl]methyl]piperazin-1-yl]ethyl]piperidin-1-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione



To a stirred mixture of 4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzaldehyde (200.00 mg, 0.549 mmol, 1.00 equivalent) and 2-(2,6-dioxopiperidin-3-yl)-5-[4-[2-(piperazin-1-yl)ethyl]piperidin-1-yl]isoindole-1,3-dione (373.39 mg, 0.823 mmol, 1.50 equivalent) in DMF (3.00 mL) was added NaBH(OAc)₃ (68.98 mg, 1.098 mmol, 2.00 equivalent) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 40° C. The mixture solution was purified by Prep-HPLC with the following conditions (Column: Xselect CSH F-Phenyl OBD column, 19*250, 5 μm; Mobile Phase A: Water (0.1% FA),

US 12,391,686 B2

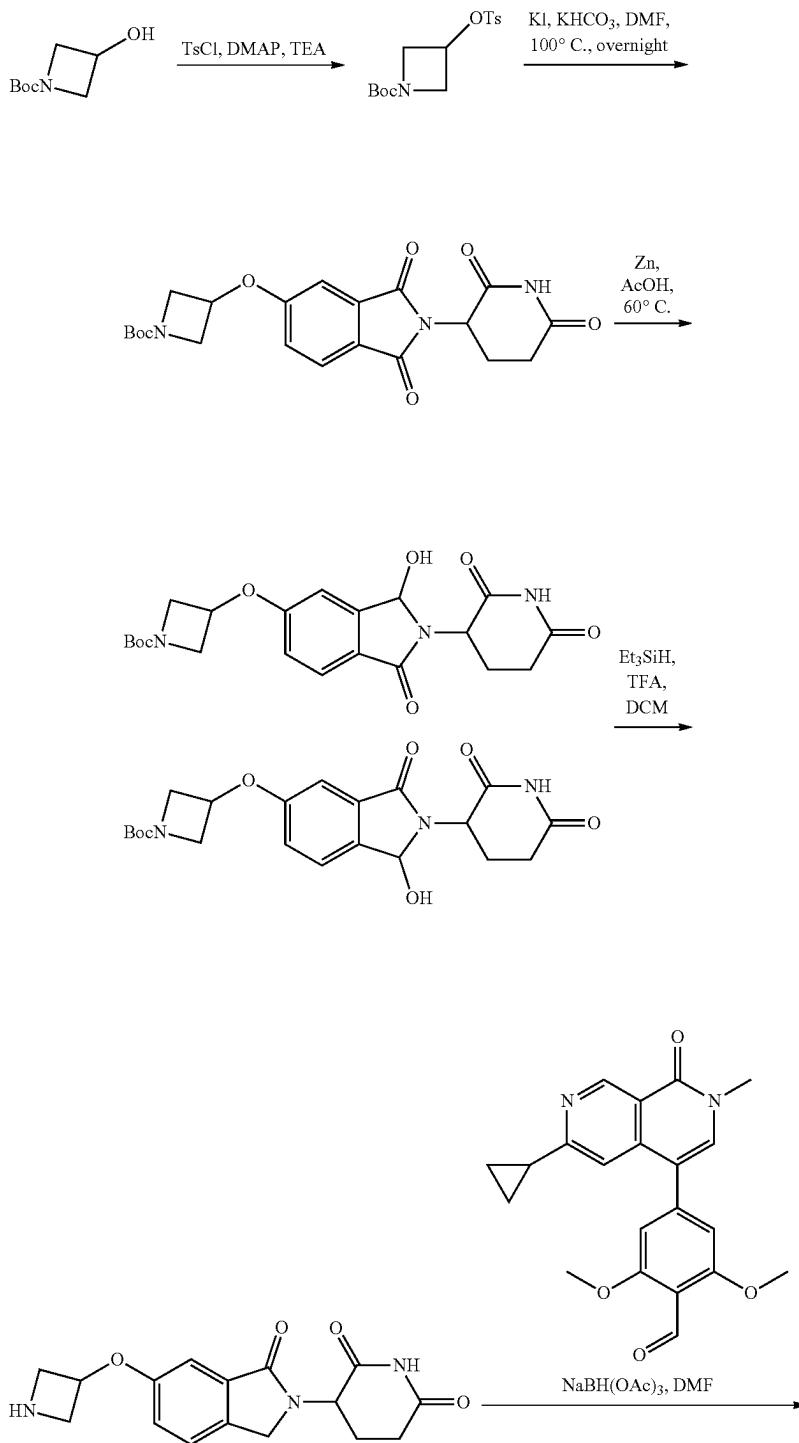
557

Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 6 B to 27 B in 16 min; 254/220 nm; RT1: 15.34 min) to afford 5-[4-[2-(4-[(4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl]methyl)piperazin-1-yl]ethyl]piperidin-1-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (165 mg, 28.16%) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ 11.09 (s, 1H), 9.30 (s, 1H), 7.80 (s, 1H), 7.67 (d, J=8.5 Hz, 1H), 7.44 (s, 1H), 7.34 (s, 1H), 7.26 (d, J=8.8 Hz, 1H), 6.88 (s, 2H), 5.07 (dd, J=12.9, 5.5 Hz, 1H), 4.35 (s, 2H), 4.08 (d, J=12.7 Hz, 2H), 3.90 (s, 7H), 3.58 (s,

558

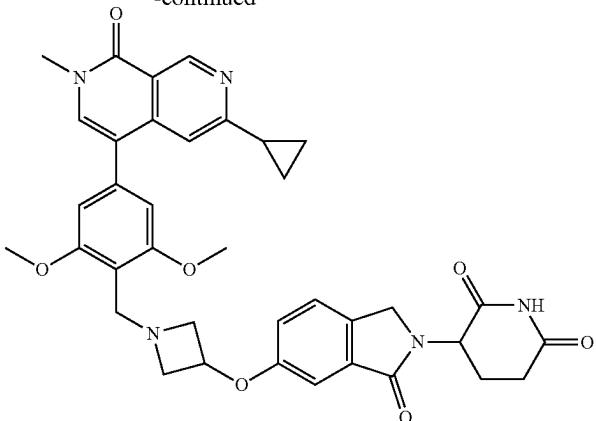
7H), 3.27-3.21 (m, 5H), 3.01-2.82 (m, 3H), 2.64-2.53 (m, 2H), 2.22 (t, J=6.5 Hz, 1H), 2.02 (d, J=12.0 Hz, 1H), 1.77 (d, J=12.6 Hz, 2H), 1.63 (s, 3H), 1.22 (d, J=11.6 Hz, 2H), 1.02 (d, J=8.0 Hz, 4H). LCMS (ESI) m/z: [M+H]⁺=802.15.

Example 50—Preparation of 3-[6-[(1-[[4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl]methyl]335zetidine-3-yl)oxy]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione

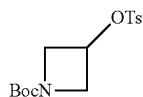


559

-continued

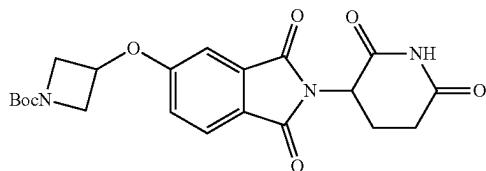


Step 1: Preparation of tert-butyl 3-[(4-methylbenzenesulfonyl)oxy]azetidine-1-carboxylate (25)



To a stirred solution of tert-butyl 3-hydroxyazetidine-1-carboxylate (2.50 g, 14.433 mmol, 1.00 equivalent) and TsCl (4.13 g, 21.650 mmol, 1.50 equivalent) in DCM were added DMAP (264.49 mg, 2.165 mmol, 0.15 equivalent) and TEA (4.38 g, 43.300 mmol, 3.00 equivalent) in portions at 0° C. under air atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with Petroleum ether/EtOAc (1:1) to afford tert-butyl 3-[(4-methylbenzenesulfonyl)oxy]azetidine-1-carboxylate (4.4 g, 93.11%) as a brown oil. LCMS (ESI) m/z: [M+H]⁺=328.

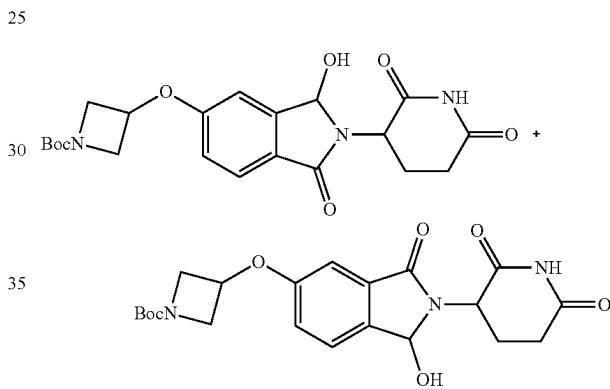
Step 2: Preparation of tert-butyl 3-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]oxy]azetidine-1-carboxylate



To a solution of tert-butyl 3-[(4-methylbenzenesulfonyl)oxy]azetidine-1-carboxylate (4.40 g, 13.439 mmol, 1.00 equivalent) and KI (0.22 g, 1.344 mmol, 0.10 equivalent) in DMF was added KHCO₃ (4.04 g, 40.318 mmol, 3.00 equivalent) in portions at 100° C. under air atmosphere. The resulting mixture was washed with 3×150 mL of EtOAc. The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 0% to 100% gradient in 40 min; detector, UV 254 nm. This resulted in tert-butyl 3-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]oxy]azetidine-1-carboxylate (1.73 g, 29.98%) as an off-white solid. LCMS (ESI) m/z: [M+H]⁺=430.

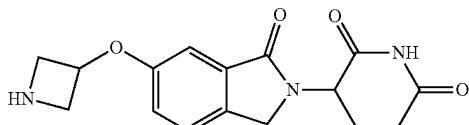
560

Step 3: Preparation of tert-butyl 3-[[2-(2,6-dioxopiperidin-3-yl)-1-hydroxy-3-oxo-1H-isindol-5-yl]oxy]azetidine-1-carboxylate, and tert-butyl 3-[[2-(2,6-dioxopiperidin-3-yl)-3-hydroxy-1-oxo-3H-isindol-5-yl]oxy]azetidine-1-carboxylate



A solution of tert-butyl 3-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]oxy]azetidine-1-carboxylate (1.73 g, 4.029 mmol, 1.00 equivalent) and Zn (2.64 g, 40.286 mmol, 10.00 equivalent) in AcOH was stirred for 2 h at 60° C. under air atmosphere. The resulting mixture was washed with 3×100 mL of ethyl acetate. The resulting mixture was concentrated under reduced pressure. The crude product was used in the next step directly without further purification to afford tert-butyl 3-[[2-(2,6-dioxopiperidin-3-yl)-1-hydroxy-3-oxo-1H-isindol-5-yl]oxy]azetidine-1-carboxylate and tert-butyl 3-[[2-(2,6-dioxopiperidin-3-yl)-3-hydroxy-1-oxo-3H-isindol-5-yl]oxy]azetidine-1-carboxylate (2.73 g, 78.53%) as an off-white solid. LCMS (ESI) m/z: [M+H]⁺=432.

Step 4: Preparation of 3-[6-(336azetidine-3-yloxy)-1-oxo-3H-isindol-2-yl]piperidine-2,6-dione

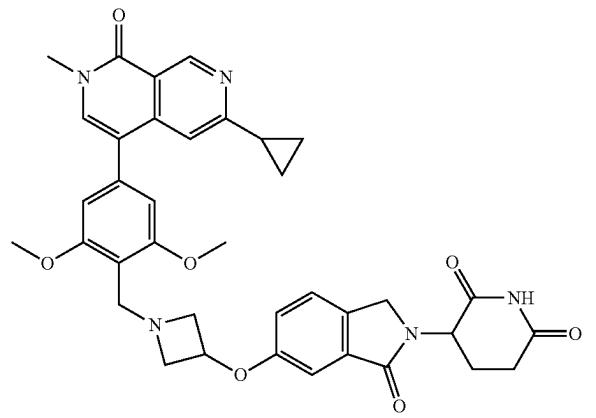


To a solution of tert-butyl 3-[[2-(2,6-dioxopiperidin-3-yl)-1-hydroxy-3-oxo-1H-isindol-5-yl]oxy]azetidine-1-carboxylate and tert-butyl 3-[[2-(2,6-dioxopiperidin-3-yl)-3-hydroxy-1-oxo-3H-isindol-5-yl]oxy]azetidine-1-carboxylate

561

ylate (2.73 g, 3.164 mmol, 1.00 equivalent) and TFA (1.50 mL, 20.195 mmol, 6.38 equivalent) in DCM was added Et₃SiH (3.68 g, 31.638 mmol, 10.00 equivalent) in portions at room temperature under air atmosphere. The resulting mixture was concentrated under reduced pressure. The crude product (mg) was purified by Prep-HPLC with the following conditions (Column: Xcellect CSH F-phenyl OBD Column, 19*250 mm, 5 μm; Mobile Phase A: Water (0.05% TFA), Mobile Phase B: can; Flow rate: 30 mL/min; Gradient: 5 B to 21 B in 10 min; 254/220 nm; RT1: 7.20/8.67 min) to afford 3-[6-(azetidin-3-yloxy)-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione (165 mg, 8.27%) as an off-white solid. LCMS (ESI) m/z: [M+H]⁺=316.

Step 5: Preparation of 3-[6-[(1-[[4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl]methyl]azetidin-3-yl)oxy]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione

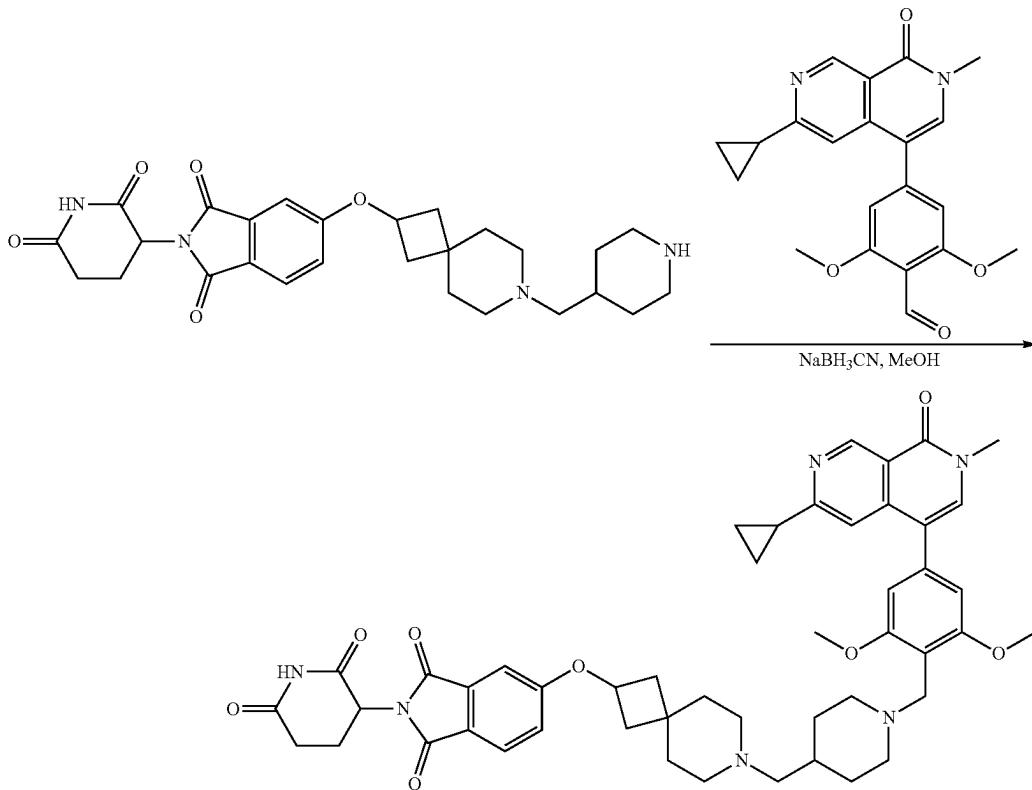


30

562

To a stirred solution of 3-[6-(azetidin-3-yloxy)-1-oxo-3H-isoindol-2-yl] piperidine-2,6-dione (75.00 mg, 0.238 mmol, 1.00 equivalent) and 4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzaldehyde (86.67 mg, 0.238 mmol, 1.00 equivalent) in DMF was added NaBH(OAc)₃ (100.82 mg, 0.476 mmol, 2.00 equivalent) dropwise at room temperature under air atmosphere for 2 hours. The crude product (mg) was purified by Prep-HPLC with the following conditions (Column: XSelect CSH Prep C18 OBD Column, 19*250 mm, 5 μm; Mobile Phase A: Water (0.05% TFA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 15 B to 23 B in 12 min; 254/220 nm; RT1: 10.38 min) to afford 3-[6-[(1-[[4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl] methyl]azetidin-3-yl)oxy]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione (18.9 mg, 11.69%) as an off-white solid. ¹H NMR (400 MHz, Methanol-d4) δ 9.39 (d, J=0.8 Hz, 1H), 7.80 (d, J=4.5 Hz, 1H), 7.60 (t, J=7.2 Hz, 1H), 7.42 (d, J=5.4 Hz, 1H), 7.32-7.24 (m, 1H), 7.22 (d, J=3.2 Hz, 1H), 6.89 (s, 2H), 5.35-5.19 (m, 1H), 5.16 (dd, J=13.3, 5.2 Hz, 1H), 4.84-4.69 (m, 2H), 4.65 (s, 2H), 4.48 (d, J=10.6 Hz, 2H), 4.42 (s, 2H), 3.98 (d, J=22.6 Hz, 6H), 3.69 (s, 3H), 2.93 (ddd, J=17.6, 13.5, 5.4 Hz, 1H), 2.80 (ddd, J=17.6, 4.7, 2.4 Hz, 1H), 2.52 (qd, J=13.2, 4.7 Hz, 1H), 2.21 (dddd, J=14.5, 10.7, 6.9, 3.9 Hz, 2H), 1.23-1.12 (m, 2H), 1.09 (d, J=4.4 Hz, 2H). LCMS (ESI) m/z: [M+H]⁺=664.

Example 51. Preparation of 5-((7-((1-(4-(6-cyclopropyl-2-methyl-1-oxo-2,7-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione



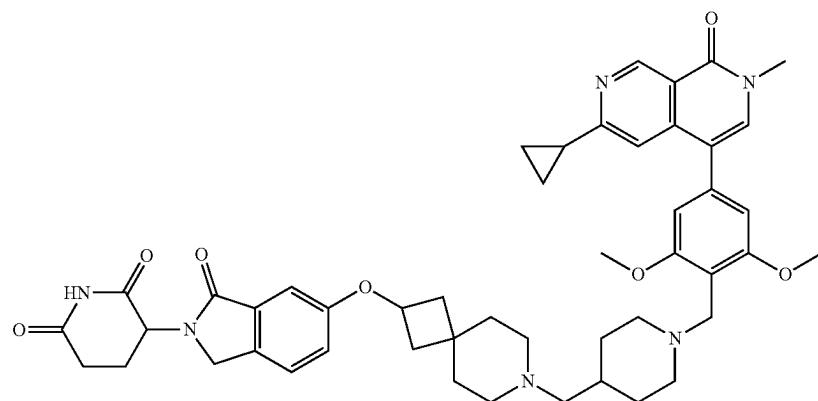
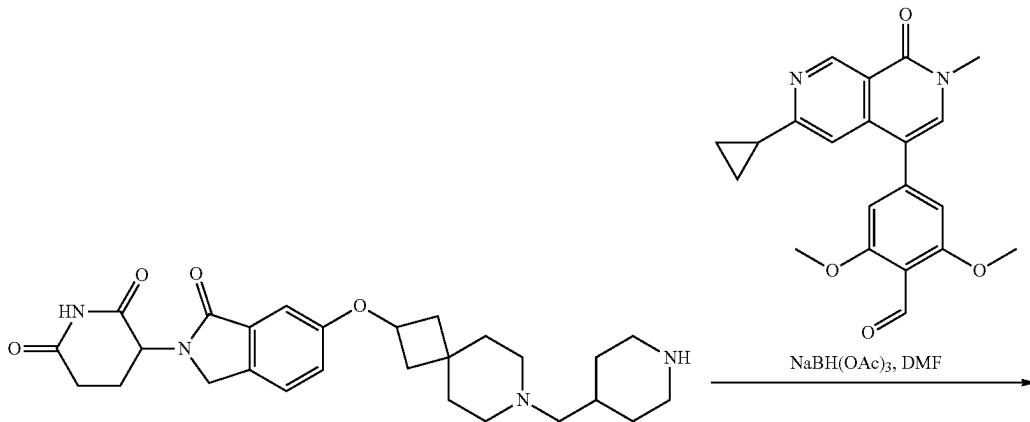
563

To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-5-[[7-(piperidin-4-ylmethyl)-7-azaspiro[3.5]nonan-2-yl]oxy]isoindole-1,3-dione (100.00 mg, 0.202 mmol, 1.00 equivalent) and 4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzaldehyde (73.68 mg, 0.202 mmol, 1 equivalent) in MeOH (3.00 mL) was added NaBH₃CN (25.41 mg, 0.404 mmol, 2 equivalent). The resulting mixture was stirred at 40° C. for 4 hours. Without any additional work-up, the mixture was purified by prep-HPLC (Column: Kinetex EVO C18 Column, 21.2*150.5 μm; Mobile Phase A: Water (10 mM NH₄HCO₃), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 25 B to 50 B in 12 min; 254/220 nm; RT1:11.92 min) to give 5-([7-[(1-[[4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl]methyl]piperidin-4-yl)methyl]-7-azaspiro[3.5]nonan-2-yl]oxy)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (35

564

mg, 20.53%) as a white solid. ¹H NMR (300 MHz, DMSO-d₆) δ 11.13 (s, 1H), 9.29 (s, 1H), 8.19 (s, 2H), 7.87-7.74 (m, 2H), 7.44 (s, 1H), 7.35-7.21 (m, 2H), 6.74 (s, 2H), 5.12 (dd, J=12.8, 5.4 Hz, 1H), 4.99 (t, J=6.9 Hz, 1H), 3.82 (s, 6H), 3.60 (s, 2H), 3.59-3.57 (m, 3H) 2.93-2.84 (m, 4H), 2.63 (s, 1H), 2.62-2.60 (s, 1H), 2.55 (s, 3H), 2.23 (d, J=6.9 Hz, 3H), 2.20-2.15 (s, 1H), 2.10 (dd, J=15.2, 4.6 Hz, 4H), 1.80 (dd, J=12.0, 6.3 Hz, 2H), 1.69-1.60 (m, 4H), 1.60-1.50 (m, 2H) 1.47 (s, 1H), 1.07 (d, J=11.5 Hz, 2H), 1.03-0.96 (m, 4H). LCMS (ESI) m/z: [M+H]⁺ = 843.55.

Example 52—Preparation of 3-[6-([7-[(1-[[4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl]methyl]piperidin-4-yl)methyl]-7-azaspiro[3.5]nonan-2-yl]oxy)-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione



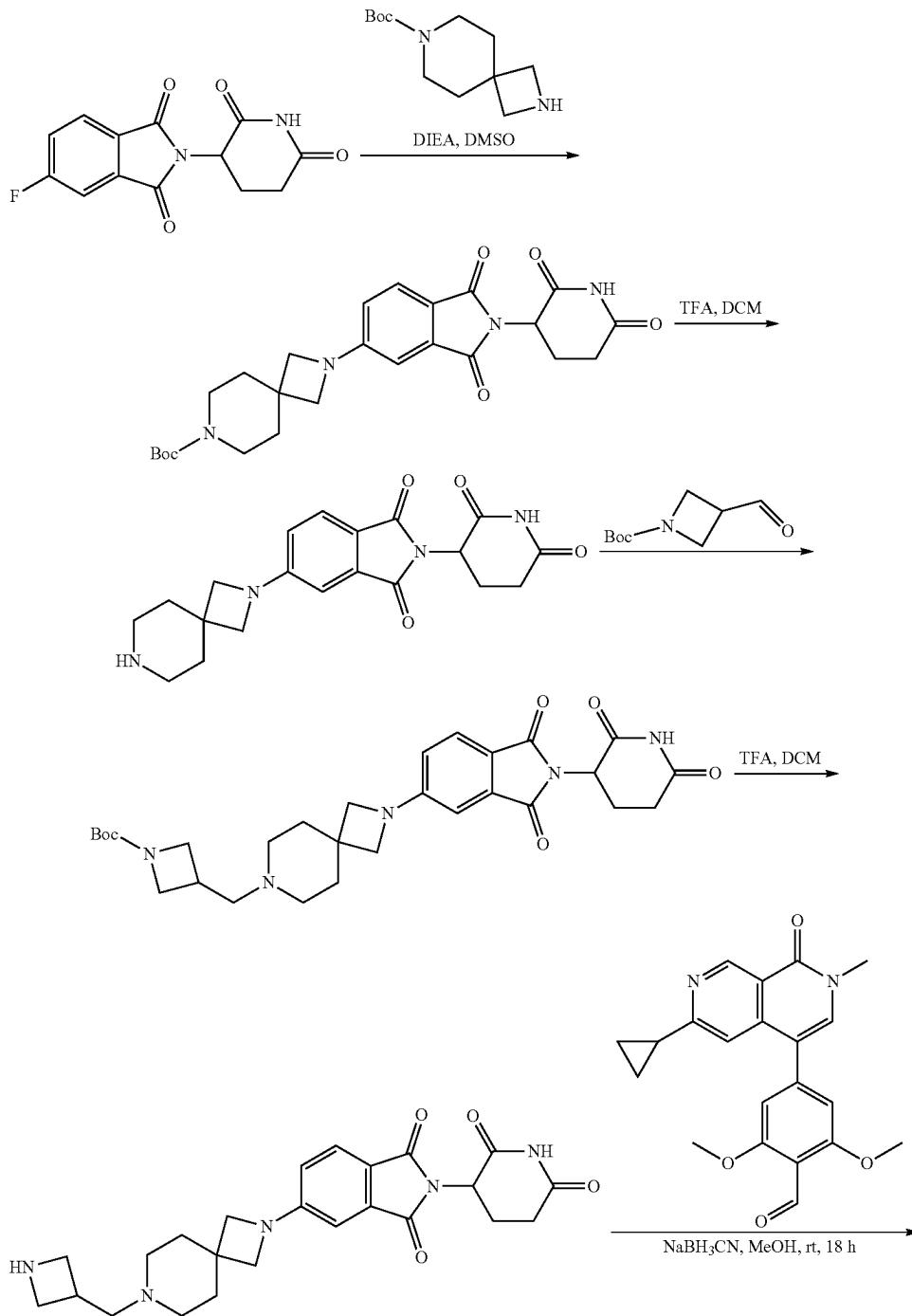
565

To a stirred solution of 4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzaldehyde¹⁰ and 3-(1-oxo-6-[[7-(piperidin-4-ylmethyl)-7-azaspiro[3.5]nonan-2-yl]oxy]-3H-isoindol-2-yl)piperidine-2,6-dione in DMF (10 mL) was added NaBH(OAc)₃ in portions at room temperature. The resulting mixture was stirred for 12 h at room temperature. The crude product was purified by Prep-HPLC to afford 3-[6-[(1-[[4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl]methyl]piperidin-4-yl)methyl]-7-azaspiro[3.5]nonan-2-yl]oxy]-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione (14.6 mg, 8.0%) as an off-white solid.¹¹ ¹H NMR (300 MHz, Methanol-d₄) δ 9.40 (s, 1H), 7.76 (s, 1H), 7.51 (d, J=8.4 Hz, 1H), 7.42 (d,

566

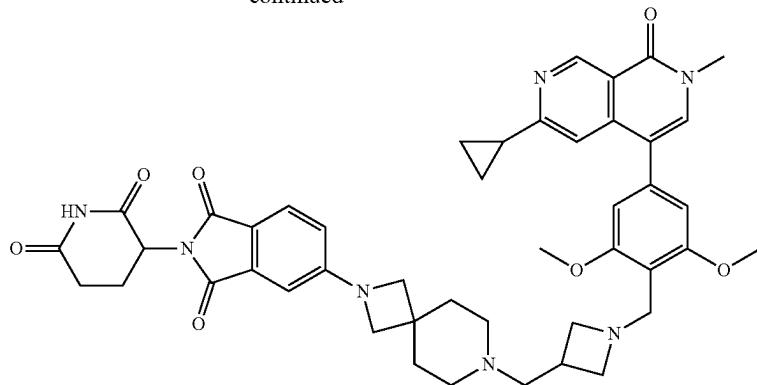
J=6.3 Hz, 1H), 7.25-7.14 (m, 2H), 6.89 (s, 2H), 5.16 (dd, J=13.3, 5.1 Hz, 1H), 4.92-4.83 (m, 1H), 4.58-4.35 (m, 4H), 3.99 (s, 6H), 3.69 (s, 3H), 3.67-3.44 (m, 4H), 3.28-2.63 (m, 9H), 2.61-2.46 (m, 2H), 2.36-1.86 (m, 11H), 1.68 (q, J=13.1 Hz, 2H), 1.23-1.08 (m, 4H). LCMS (ESI) m/z: [M+H]⁺= 830.01.

Example 53—Preparation of 5-[7-[(1-[[4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl]methyl]azetidin-3-yl)methyl]-2,7-diazaspiro[3.5]nonan-2-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione

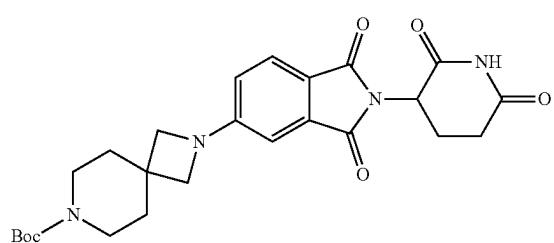


567

-continued

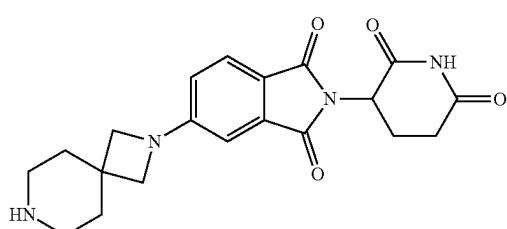


Step 1: Preparation of tert-butyl 2-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl]-2,7-diazaspiro[3.5]nonane-7-carboxylate



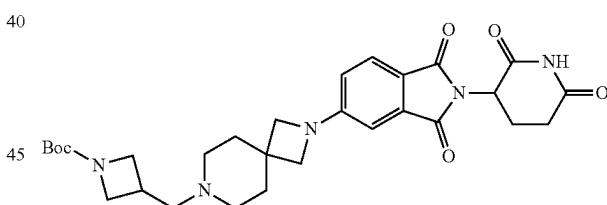
To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-5-fluoroisoindole-1,3-dione (5.00 g, 18.101 mmol, 1.00 equivalent) and tert-butyl 2,7-diazaspiro[3.5]nonane-7-carboxylate (4.10 g, 0.018 mmol, 1 equivalent) in DMSO (50 mL) was added DIEA (9.36 g, 72.422 mmol, 4.00 equivalent), the resulting solution was stirred at 100° C. for 4 hours under nitrogen atmosphere. The resulting mixture was diluted with EtOAc (500 mL), the resulting mixture was washed with 3×300 mL of water and 300 mL saturated brine. The organic layer was dried over Na₂SO₄, filtered and evaporated to afford tert-butyl 2-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl]-2,7-diazaspiro[3.5]nonane-7-carboxylate (9 g, crude) as a yellow solid. The crude product was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H]⁺=483

Step 2: Preparation of 5-[2,7-diazaspiro[3.5]nonan-2-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione



To a solution of tert-butyl 2-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl]-2,7-diazaspiro[3.5]nonane-7-carboxylate (9.00 g, 18.651 mmol, 1.00 equivalent) in DCM (90.00 mL) was added TFA (30.00 mL), the resulting solution was stirred at 25° C. for 1 hour. The resulting mixture were evaporated to dryness to afford 5-[2,7-diazaspiro[3.5]nonan-2-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (11.4 g, crude) as a yellow solid that was used directly without further purification. LCMS (ESI) m/z: [M+H]⁺=383.

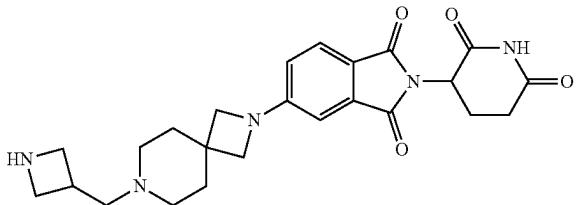
Step 3: Preparation of tert-butyl 3-[(2-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl]-2,7-diazaspiro[3.5]nonan-7-yl)methyl]azetidine-1-carboxylate



To a stirred solution of 5-[2,7-diazaspiro[3.5]nonan-2-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (3.00 g, 7.845 mmol, 1.00 equivalent) and tert-butyl 3-formylazetidine-1-carboxylate (1.45 g, 7.845 mmol, 1.00 equivalent) in DMF (30.00 mL) was added NaBH(OAc)₃ (3.33 g, 15.690 mmol, 2 equivalent), the resulting solution was stirred at 25° C. for 12 hours. The reaction mixture was diluted with EA (500 mL). The resulting mixture was washed with 3×300 mL of water and 300 mL saturated brine. The organic layer was dried over Na₂SO₄, filtered and evaporated to afford tert-butyl 3-[(2-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl]-2,7-diazaspiro[3.5]nonan-7-yl)methyl]azetidine-1-carboxylate (3.13 g, 72.33%) as a yellow solid that was used directly without further purification. LCMS (ESI) m/z: [M+H]⁺=552

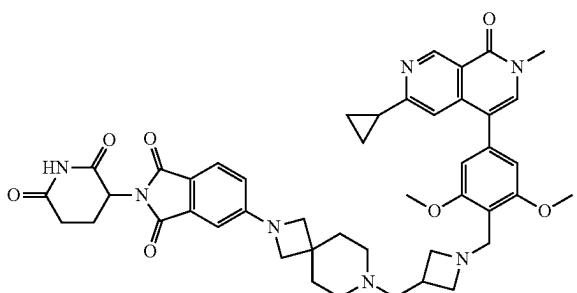
569

Step 4: Preparation of 5-[7-(azetidin-3-ylmethyl)-2,7-diazaspiro[3.5]nonan-2-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione



To a stirred solution of tert-butyl 3-([2-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]-2,7-diazaspiro[3.5]nonan-7-yl)methyl)azetidine-1-carboxylate (3.13 g, 5.674 mmol, 1.00 equivalent) in DCM (30.00 mL) was added TFA (10.00 mL), the resulting solution was stirred at 25° C. for 1 hour. The resulting mixture were evaporated to dryness to afford 5-[7-(azetidin-3-ylmethyl)-2,7-diazaspiro[3.5]nonan-2-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (4.1 g, crude) as a yellow solid that was used directly without further purification. LCMS (ESI) m/z: [M+H]⁺=452

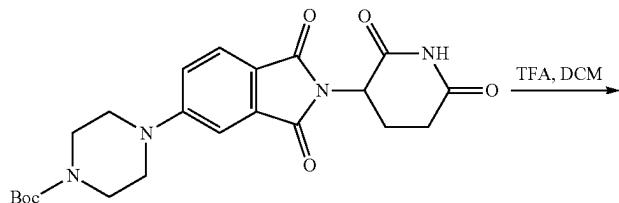
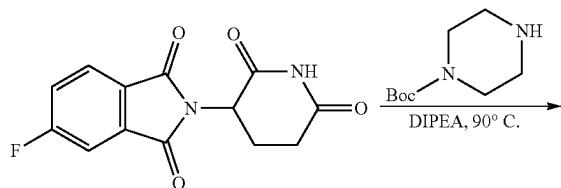
Step 5: Preparation of 5-[7-[(1-[[4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl]methyl]azetidin-3-yl)methyl]-2,7-diazaspiro[3.5]nonan-2-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione

**570**

To a stirred solution of 5-[7-(azetidin-3-ylmethyl)-2,7-diazaspiro[3.5]nonan-2-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (110.00 mg, 0.244 mmol, 1.00 equivalent)

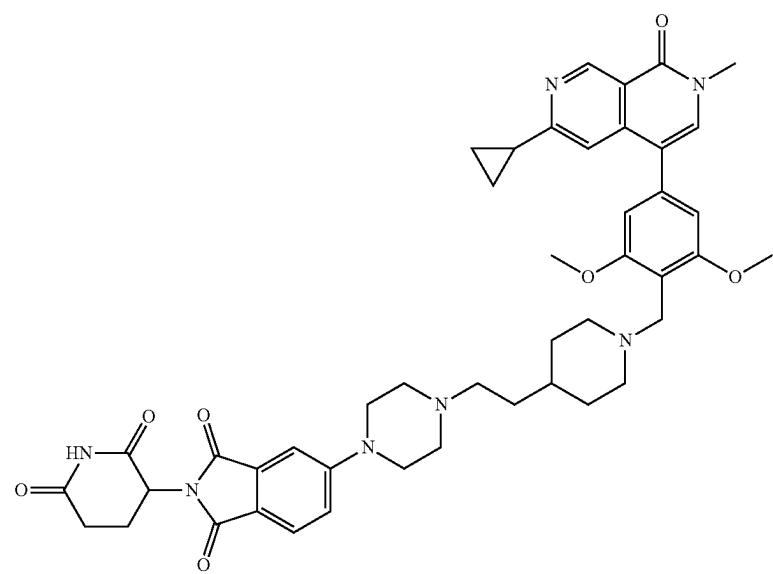
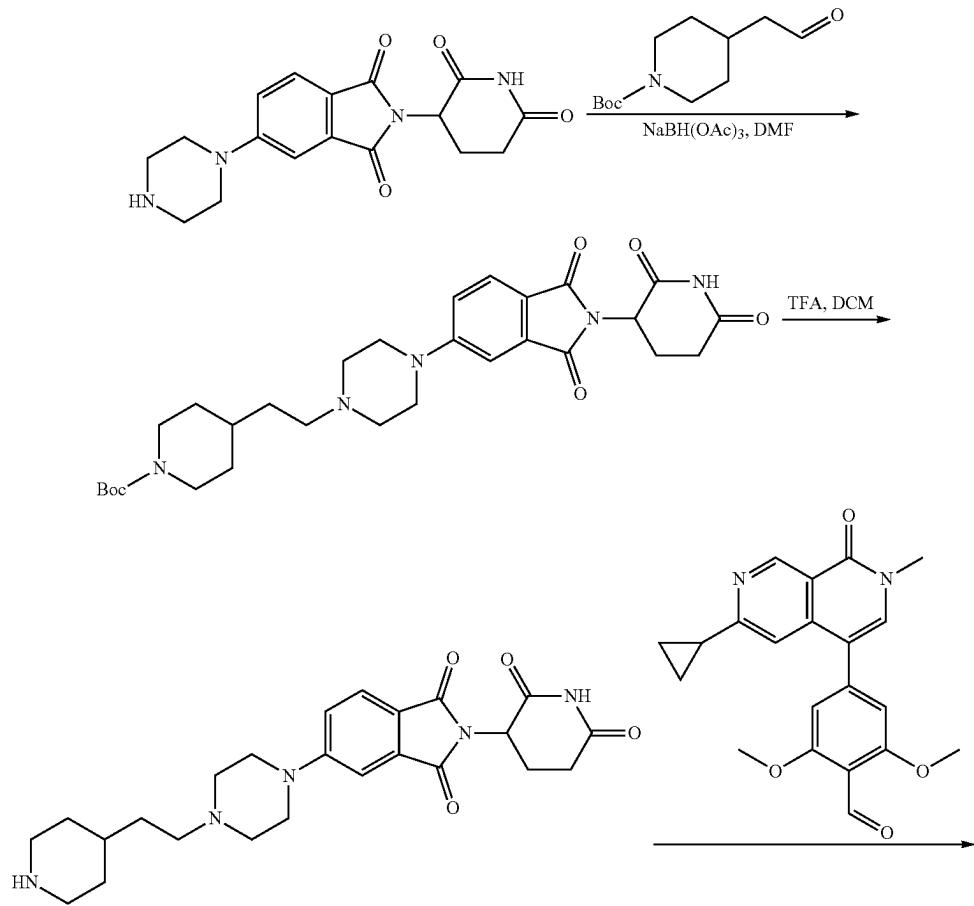
and 4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzaldehyde (88.77 mg, 0.244 mmol, 1.00 equivalent) in MeOH (2.00 mL, 24.699 mmol, 1115.22 equivalent) was added NaBH₃CN (30.62 mg, 0.487 mmol, 2.00 equivalent). The resulting mixture was stirred for overnight at room temperature. The mixture solution was purified by Prep-HPLC with the following conditions (Column: XSelect CSH Prep C18 OBD Column, 5 μm, 19*150 mm; Mobile Phase A: Water (0.05% TFA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 5 B to 27 B in 15 min; 254/220 nm; RT1:12.38 min) to afford 5-[7-[(1-[[4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl]methyl]azetidin-3-yl)methyl]-2,7-diazaspiro[3.5]nonan-2-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (63.9 mg, 31.71%) as a yellow solid. LCMS (ESI) m/z: [M+H]⁺=800. ¹H NMR (400 MHz, Methanol-d4) δ 9.39 (s, 1H), 7.79 (d, J=6.3 Hz, 1H), 7.68 (d, J=8.4, 1.2 Hz, 1H), 7.41 (d, J=2.9 Hz, 1H), 6.88 (s, 3H), 6.76-6.67 (m, 1H), 5.13-5.02 (m, 1H), 4.55 (d, 2H), 4.40 (t, J=9.3 Hz, 2H), 4.29-4.11 (m, 2H), 4.05-3.76 (m, 10H), 3.69 (s, 3H), 3.61-3.43 (m, 5H), 3.22-2.98 (m, 2H), 2.94-2.80 (m, 1H), 2.79-2.65 (m, 2H), 2.43-1.93 (m, 6H), 1.27-1.14 (m, 2H), 1.14-1.05 (m, 2H).

Example 54—Preparation of 5-[4-[2-(1-[[4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl]methyl]piperidin-4-yl)ethyl]piperazin-1-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione



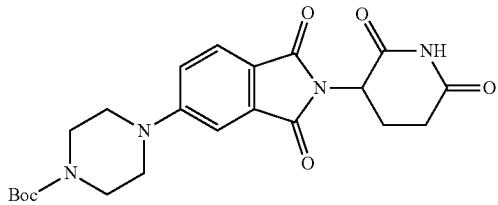
571**572**

-continued



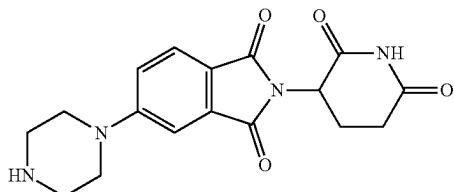
573

Step 1: tert-butyl 4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazine-1-carboxylate



To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-5-fluoroisoindole-1,3-dione (3.00 g, 10.861 mmol, 1.00 equivalent) and tert-butyl piperazine-1-carboxylate (2.02 g, 10.861 mmol, 1.00 equivalent) in NMP (30.00 mL) was added DIPEA (4.21 g, 32.574 mmol, 3.00 equivalent). The resulting mixture was stirred for 2 hours at 90° C. under nitrogen atmosphere. The resulting mixture was diluted with water (100 mL). The aqueous layer was extracted with EtOAc (3×30 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 5% to 90% gradient in 30 min; detector, UV 254 nm. This resulted in tert-butyl 4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazine-1-carboxylate (1.6 g, 33.29%) as a yellow solid. LCMS (ESI) m/z: [M+H]⁺=443.

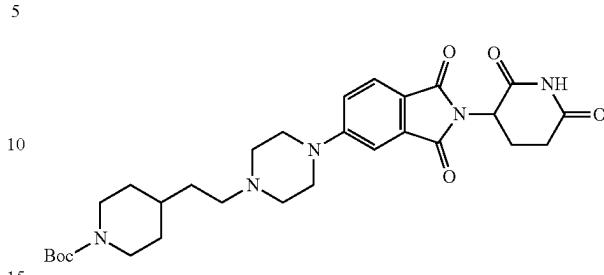
Step 2: 2-(2,6-dioxopiperidin-3-yl)-5-(piperazin-1-yl)isoindole-1,3-dione



To a stirred solution of tert-butyl 4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazine-1-carboxylate (2.10 g, 4.746 mmol, 1.00 equivalent) in DCM (32.00 mL) was added TFA (8.00 mL). The resulting mixture was stirred for 2 hours at room temperature. The resulting mixture was concentrated under vacuum to afford 2-(2,6-dioxopiperidin-3-yl)-5-(piperazin-1-yl)isoindole-1,3-dione (2.6 g, 160%) as a yellow solid. That was used directly without further purification. LCMS (ESI) m/z: [M+H]⁺=343.

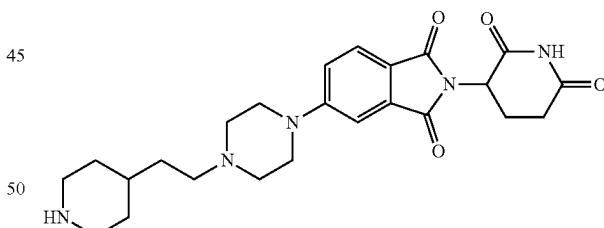
574

Step 3: tert-butyl 4-(2-[4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl)piperazin-1-yl]ethyl)piperidine-1-carboxylate



To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-5-(piperazin-1-yl)isoindole-1,3-dione (2.00 g, 5.842 mmol, 1.00 equivalent) in DMF (25.00 mL) were added tert-butyl 4-(2-oxoethyl)piperidine-1-carboxylate (1.33 g, 5.842 mmol, 1.00 equivalent) under nitrogen atmosphere. The resulting mixture was stirred for 16 hours at 15° C. under nitrogen atmosphere. To the above mixture was added NaBH(OAc)₃ (2.48 g, 11.684 mmol, 2.00 equivalent) at 15° C. The resulting mixture was stirred for additional 2 hours at 15° C. The resulting mixture was diluted with water (70 mL). The aqueous layer was extracted with EtOAc (4×30 mL). The organic layers were concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with DCM:MeOH (50:1 to 10:1) to afford tert-butyl 4-(2-[4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl)piperazin-1-yl]ethyl)piperidine-1-carboxylate (3 g, 92.75%) as a yellow oil. LCMS (ESI) m/z: [M+H]⁺=555.

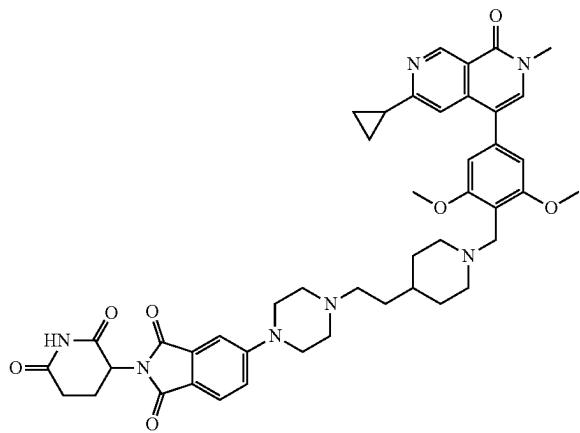
Step 4: 2-(2,6-dioxopiperidin-3-yl)-5-[4-(2-(piperidin-4-yl)ethyl)piperazin-1-yl]isoindole-1,3-dione



To a stirred solution of tert-butyl 4-(2-[4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl)piperazin-1-yl]ethyl)piperidine-1-carboxylate (3.00 g, 5.418 mmol, 1.00 equivalent) in DCM (20.00 mL) was added TFA (5.00 mL) at room temperature. The resulting mixture was stirred for overnight at room temperature. The resulting mixture was concentrated under vacuum to afford 2-(2,6-dioxopiperidin-3-yl)-5-[4-(2-(piperidin-4-yl)ethyl)piperazin-1-yl]isoindole-1,3-dione (3.5 g, 126.33%) as a yellow oil. That was used directly without further purification. LCMS (ESI) m/z: [M+H]⁺=454.

575

Step 5: 5-[4-[2-(1-[[4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl]methyl]piperidin-4-yl)ethyl]piperazin-1-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione

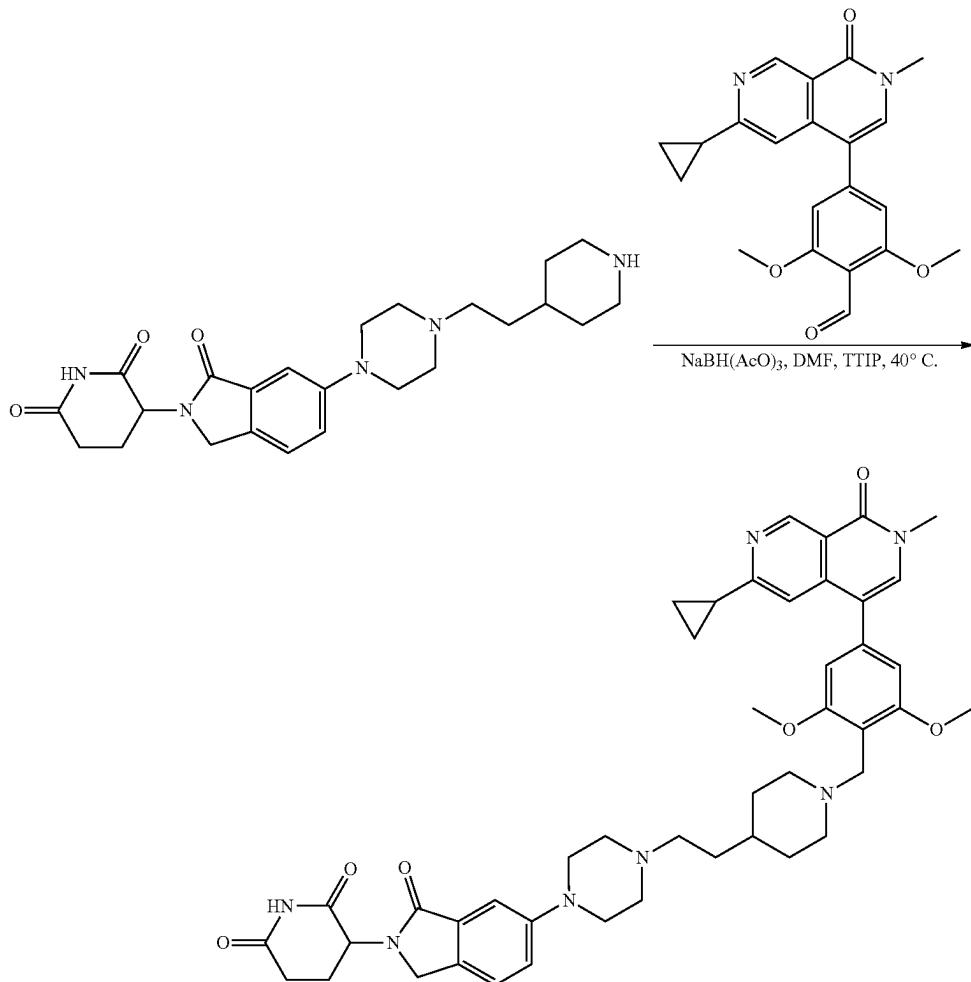


To a stirred solution of 4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzaldehyde (150.00 mg, 0.412 mmol, 1.00 equivalent) and 2-(2,6-dioxopiperidin-3-yl)-5-[4-[2-(piperidin-4-yl)ethyl]piperazin-1-yl]isoindole-1,3-dione²⁵

576

dole-1,3-dione (186.69 mg, 0.412 mmol, 1.00 equivalent) in DMF (3.00 mL) was added NaBH(OAc)₃ (261.73 mg, 1.235 mmol, 3.00 equivalent) dropwise at room temperature under air atmosphere. The resulting mixture was stirred for overnight at room temperature. The mixture solution was purified by Prep-HPLC with the following conditions (Column: Xselect CSH F-Phenyl OBD column, 19*250, 5 µm; Mobile Phase A: Water (0.05% TFA), Mobile Phase B: ACN; Row rate: 25 mL/min; Gradient: 12 B to 12 B in 2 min; 254/220 nm; RT1: 11.13 min) to afford 5-[4-[2-(1-[[4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl]methyl]piperidin-4-yl)ethyl]piperazin-1-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (62 mg, 18.78%) as a light yellow solid, LCMS (ESI) m/z: [M+H]⁺=802.30, ¹H NMR (400 MHz, DMSO-d₆) δ 9.30 (s, 1H), 7.83 (d, J=1.7 Hz, 1H), 7.77 (dd, J=8, 4, 4.8 Hz, 1H), 7.51-7.40 (m, 2H), 7.40-7.32 (m, 1H), 6.85 (s, 2H), 5.13-5.03 (m, 1H), 4.24 (s, 4H), 3.88 (s, 6H), 3.57 (s, 5H), 3.44 (d, J=11.9 Hz, 2H), 3.20 (q, J=10.4, 9.5 Hz, 6H), 3.02 (t, J=12.2 Hz, 2H), 2.94-2.80 (m, 1H), 2.65-2.56 (m, 1H), 2.54 (d, J=4.9 Hz, 1H), 2.30-2.19 (m, 1H), 2.08-1.99 (in, 1H), 1.91-1.70 (m, 3H), 1.67-1.41 (m, 4H), 1.11-0.98 (m, 4H).

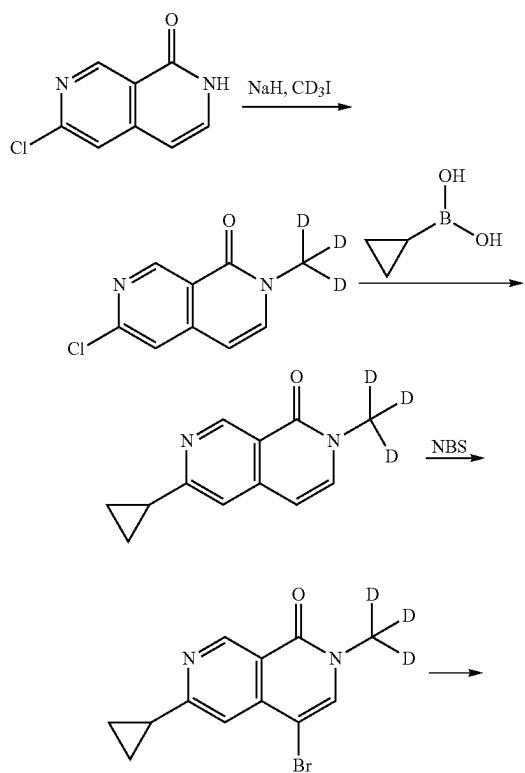
Example 55. Preparation of 3-(6-[4[2-(1-[[4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl]methyl]piperidin-4-yl)ethyl]piperazin-1-yl]-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione formic acid



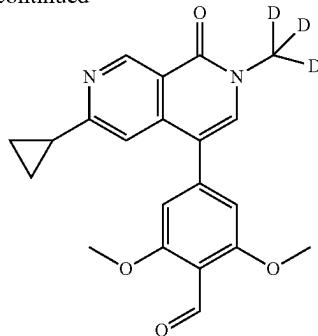
577

To a stirred solution of 3-(1-oxo-6-[4-[2-(piperidin-4-yl)ethyl]piperazin-1-yl]-3H-isoindol-2-yl)piperidine-2,6-dione (160.00 mg, 0.364 mmol, 1.00 equivalent) and 4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzaldehyde (132.64 mg, 0.364 mmol, 1.00 equivalent) in DMF (2.00 mL) was added NaBH(AcO)₃ (154.29 mg, 0.728 mmol, 2.00 equivalent) and titanium isopropoxide (10.35 mg, 0.036 mmol, 0.10 equivalent). The resulting mixture was stirred for 28 h at room temperature. The mixture solution was purified by Prep-HPLC with the following conditions: Column: Xselect CSH F-Phenyl OBD column, 19*250, 5 μ m; Mobile Phase A: Water (0.05% FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 8 B to 19 B in 10 min; 220/254 nm; RT1: 8.28 min. This resulted in 3-(6-[4-[2-(1-[[4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl]methyl]piperidin-4-yl)ethyl]piperazin-1-yl]-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione; formic acid (16.6 mg, 5.78%) as a white solid. LCMS (ESI) m/z: [M+H]⁺=788. ¹H NMR (400 MHz, DMSO-d₆) δ 10.98 (s, 1H), 9.28 (s, 1H), 8.18 (s, 4H, FA), 7.80 (s, 1H), 7.45-7.39 (m, 2H), 7.26 (dd, J=8.4, 2.4 Hz, 1H), 7.16 (d, J=2.4 Hz, 1H), 6.74 (s, 2H), 5.10 (dd, J=13.3, 5.1 Hz, 1H), 4.39-4.16 (m, 2H), 3.82 (s, 6H), 3.60 (s, 3H), 3.56 (s, 4H), 3.18 (s, 5H), 2.90 (d, J=11.6 Hz, 3H), 2.73-2.56 (m, 3H), 2.35-2.32 (m, 2H), 2.30-2.22 (m, 1H), 2.18-2.08 (m, 2H), 2.05-1.90 (m, 1H), 1.64 (d, J=12.3 Hz, 2H), 1.39 (d, J=7.7 Hz, 2H), 1.26-1.19 (m, 1H), 1.19-1.09 (m, 2H), 0.99 (dd, J=10.0, 3.7 Hz, 4H).

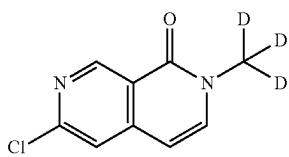
Example 56—Preparation of 4-(6-cyclopropyl-2-(methyl-d₃)-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzaldehyde

**578**

-continued

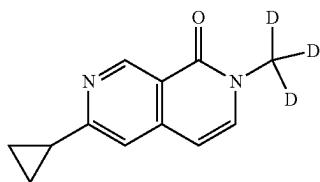


Step 1: Preparation of 6-chloro-2-(2H3)methyl-2,7-naphthyridin-1-one



A solution of 6-chloro-2H-2,7-naphthyridin-1-one (500.00 mg, 2.769 mmol, 1.00 equivalent) in THF (5.00 mL) was treated with NaH (132.89 mg, 5.537 mmol, 2.00 equivalent) for 5 min at 0° C. followed by the addition of CD₃I (802.69 mg, 5.537 mmol, 2.00 equivalent) in portions at 0° C. After stirring at 0° C. for 1 h, the reaction mixture was poured into ice-water (50 mL), the precipitated solids were collected by filtration and washed with water (3×50 mL), then the solid was dried under vacuum to afford 6-chloro-2-(2H3)methyl-2,7-naphthyridin-1-one (500 mg, 91.37%) as a light yellow solid that was used directly without further purification. LCMS (ESI) m/z: [M+H]⁺=198.

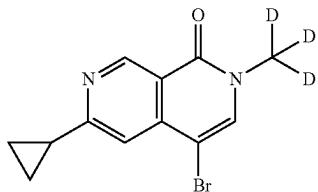
Step 2: Preparation of 6-cyclopropyl-2-(2H3)methyl-2,7-naphthyridin-1-one



A mixture of 6-chloro-2-(2H3)methyl-2,7-naphthyridin-1-one (400.00 mg, 2.024 mmol, 1.00 equivalent), cyclopropylboronic acid (260.78 mg, 3.036 mmol, 1.50 equivalent), K₃PO₄ (1288.81 mg, 6.072 mmol, 3.00 equivalent), PCy₃ (113.51 mg, 0.405 mmol, 0.20 equivalent) and Pd(AcO)₂ (45.44 mg, 0.202 mmol, 0.10 equivalent) in Toluene (20.00 mL) and H₂O (1.00 mL) was stirred for 2 h at 110° C. under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH₂Cl₂/MeOH (10:1) to afford 6-cyclopropyl-2-(2H3)methyl-2,7-naphthyridin-1-one (350 mg, 85.08%) as a white solid. LCMS (ESI) m/z: [M+H]⁺=204

579

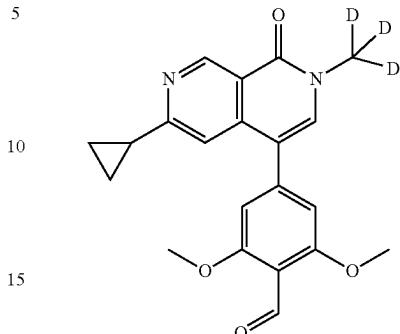
Step 3: Preparation of 4-bromo-6-cyclopropyl-2-(2H3)methyl-2,7-naphthyridin-1-one



A mixture of 6-cyclopropyl-2-(2H3)methyl-2,7-naphthyridin-1-one (300.00 mg, 1.476 mmol, 1.00 equivalent) and NBS (315.23 mg, 1.771 mmol, 1.20 equivalent) in ACN (3.00 mL) was stirred for 2 h at 90° C. The resulting mixture was diluted with 1×50 mL of water. The resulting mixture was extracted with EtOAc (3×50 mL). The combined organic layers were washed with water (3×50 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The resulting mixture was concentrated under reduced pressure. to afford 4-bromo-6-cyclopropyl-2-(2H3)methyl-2,7-naphthyridin-1-one (350 mg, 84.04%) as a yellow solid that was used directly without further purification. LCMS (ESI) m/z: [M+H]⁺=282.

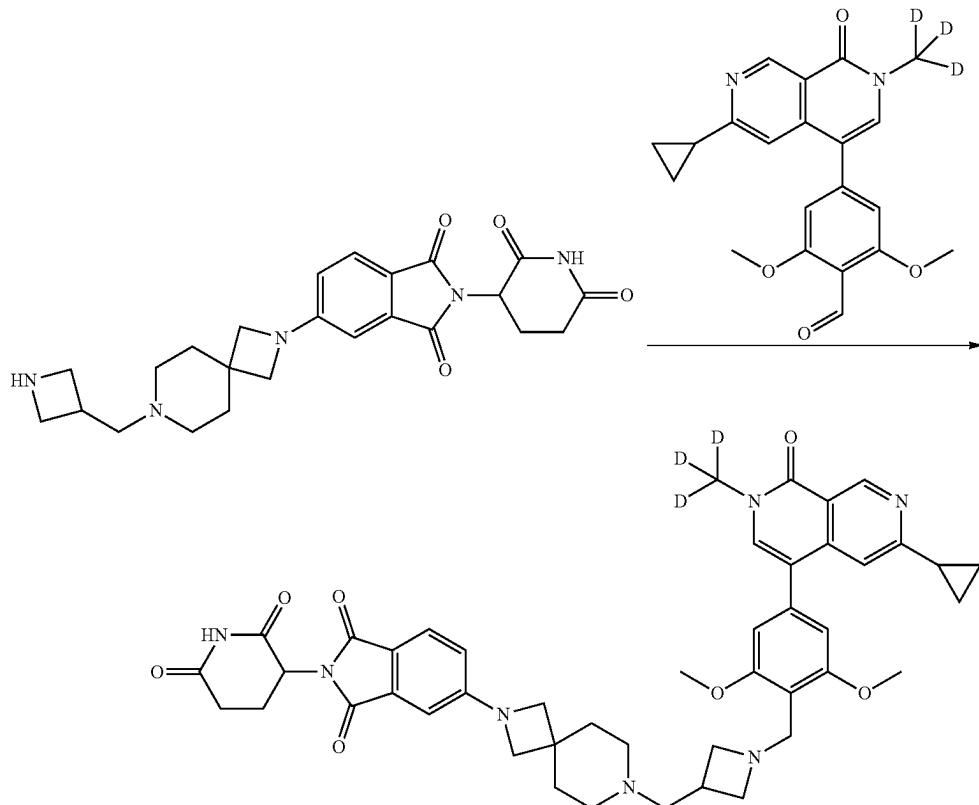
580

Step 4: Preparation of 4-[6-cyclopropyl-2-(2H3)methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde



A mixture of 4-bromo-6-cyclopropyl-2-(2H3)methyl-2,7-naphthyridin-1-one (350.00 mg, 1.240 mmol, 1.00 equivalent), 2,6-dimethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (434.86 mg, 1.489 mmol, 1.20 equivalent), Cs₂CO₃ (808.33 mg, 2.481 mmol, 2.00 equivalent) and Pd(dppf)Cl₂ (90.76 mg, 0.124 mmol, 0.10 equivalent) in dioxane (3.00 mL) and H₂O (1.00 mL) was stirred for 3 hours at 90° C. under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH₂Cl₂/MeOH (10:1) to afford 4-[6-cyclopropyl-2-(2H3)methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (200 mg, 43.88%) as an orange solid. LCMS (ESI) m/z: [M+H]⁺=368.

Example 57—Preparation of 5-(7-[[1-([4-[6-cyclopropyl-2-(2H3)methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)azetidin-3-yl]methyl]-2,7-diazaspiro[3.5]nonan-2-yl)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid



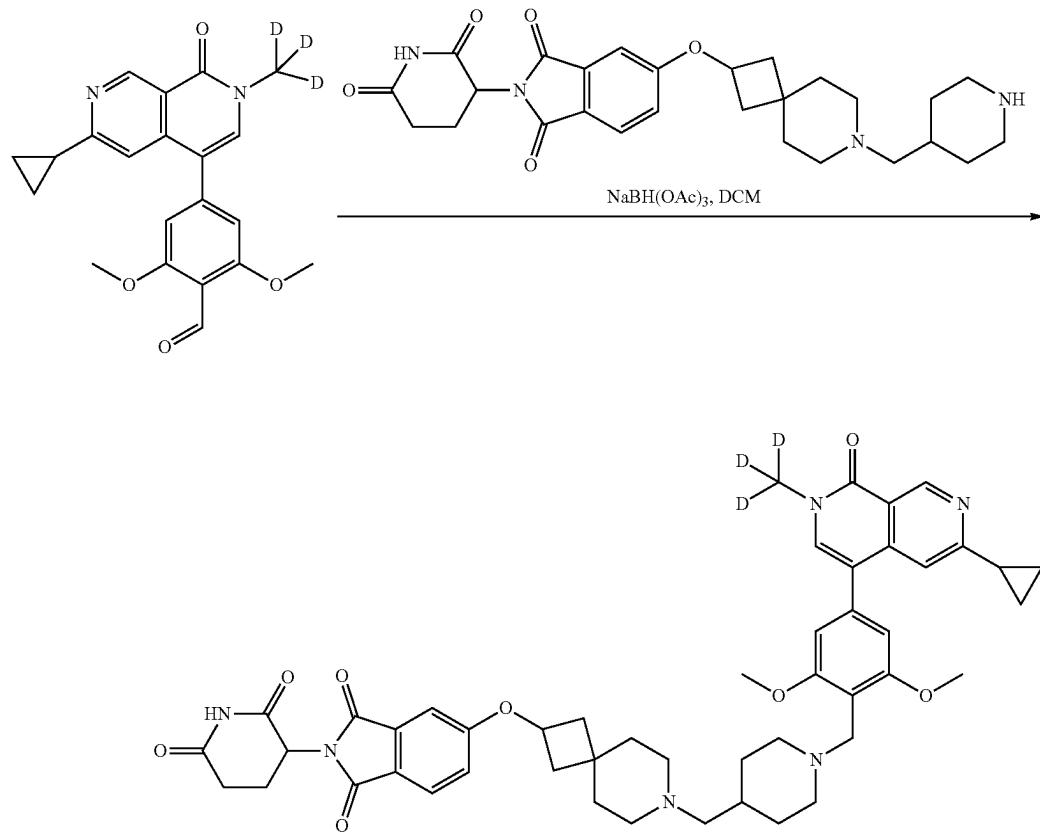
581

A mixture of 4-[6-cyclopropyl-2-(2H3)methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (120.00 mg, 0.327 mmol, 1.00 equivalent), 2-(2,6-dioxopiperidin-3-yl)-5-[[7-(piperidin-4-ylmethyl)-7-azaspiro[3.5]nonan-2-yl]oxy]isoindole-1,3-dione (161.54 mg, 0.327 mmol, 1.00 equivalent) and NaBH(AcO)₃ (138.44 mg, 0.653 mmol, 2.00 equivalent) in DMF (3.00 mL) was stirred for 2 hours at room temperature. Without any additional work-up, the mixture was purified by Prep-HPLC with the following conditions (Column: XSelect CSH Prep C18 OBD Column, 5 μ m, 19*150 mm; Mobile Phase A: Water (0.05% FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 10 B to 18 B in 15 min; 254/220 nm; RT1:12.37; RT2: Injection Volume: mL; Number Of Runs) to afford 5-[(1-([4-[6-cyclopropyl-2-(2H3)methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl)methyl)azetidin-3-yl)methyl]-2,7-diazaspiro[3.5]nonan-2-yl)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione; formic acid (12.2 mg) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ 11.08 (s, 1H), 9.29 (s, 1H), 8.20 (s, 1H, FA), 7.78 (s, 1H), 7.64 (d, J=8.2 Hz, 1H), 7.40 (s, 1H), 6.76 (d, J=4.0 Hz, 3H), 6.64 (dd, J=8.4, 2.1 Hz, 1H), 5.05 (dd, J=12.9, 5.4 Hz, 1H), 3.84 (s, 6H), 3.79 (s, 2H), 3.74 (s, 4H), 3.55 (s, 3H), 3.13 (s, 3H), 2.97-2.79 (m, 1H), 2.71-2.56 (m, 2H), 2.46 (d, J=7.0 Hz, 2H), 2.36-2.21 (m, 4H), 2.05-1.95 (m, 1H), 1.78-1.69 (m, 4H), 1.00 (dd, J=6.6, 4.3 Hz, 4H). LCMS (ESI) m/z: [M+H]⁺=803.

Example 58—Preparation of 5-[(7-[[1-([4-[6-cyclopropyl-2-(2H3)methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl)methyl)piperidin-4-yl)methyl]-7-azaspiro[3.5]nonan-2-yl)oxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione

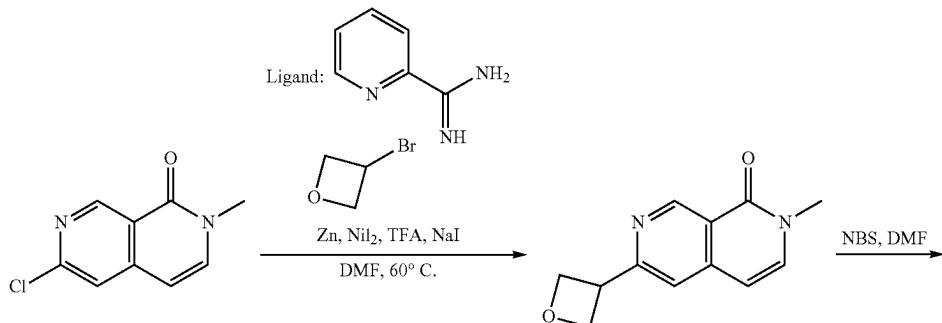
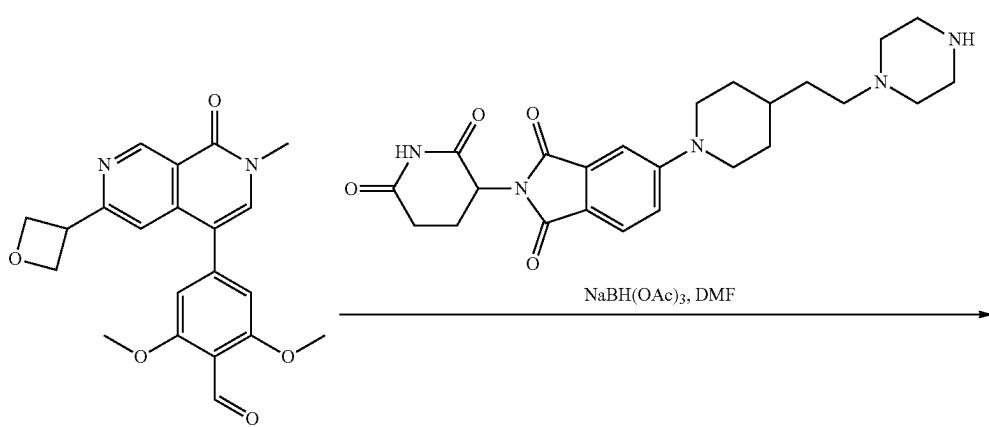
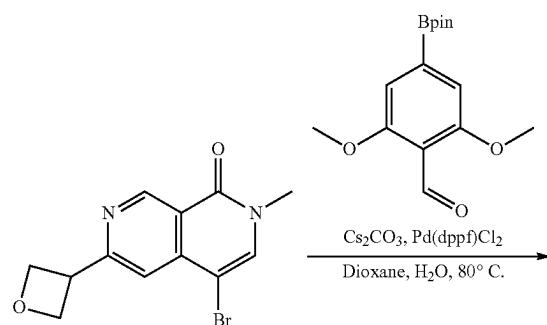
582

A mixture of 4-[6-cyclopropyl-2-(2H3)methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (60.00 mg, 0.163 mmol, 1.00 equivalent), 2-(2,6-dioxopiperidin-3-yl)-5-[[7-(piperidin-4-ylmethyl)-7-azaspiro[3.5]nonan-2-yl]oxy]isoindole-1,3-dione (80.77 mg, 0.163 mmol, 1.00 equivalent) and NaBH(AcO)₃ (69.22 mg, 0.327 mmol, 2.00 equivalent) in DCM (2.00 mL) was stirred for 2 hours at room temperature. The crude product was purified by Prep-HPLC with the following conditions (Column: XSelect CSH Prep C18 OBD Column, 19*250 mm, 5 μ m; Mobile Phase A: Water (0.05% TFA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 16 B to 21 B in 13 min; 254/220 nm; RT1:10.97 min) to afford 5-[(7-[[1-([4-[6-cyclopropyl-2-(2H3)methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl)methyl)piperidin-4-yl)methyl]-7-azaspiro[3.5]nonan-2-yl)oxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (11.1 mg) as a white solid. ¹H NMR (300 MHz, Methanol-d₄) δ 9.38 (s, 1H), 8.56 (s, 1H), 7.81 (d, J=8.2 Hz, 1H), 7.66 (s, 1H), 7.38 (d, J=0.9 Hz, 1H), 7.31-7.20 (m, 2H), 6.86 (s, 2H), 5.13 (dd, J=12.4, 5.4 Hz, 1H), 4.32 (s, 2H), 3.97 (s, 6H), 3.50 (d, J=12.2 Hz, 2H), 3.03 (s, 2H), 2.91-2.70 (m, 3H), 2.51 (d, J=8.6 Hz, 6H), 2.33 (d, J=6.7 Hz, 2H), 2.21-2.08 (m, 2H), 2.07-1.89 (m, 5H), 1.83-1.70 (m, 4H), 1.51 (s, 2H), 1.17-1.04 (m, 4H). LCMS (ESI) m/z: [M+H]⁺=846.



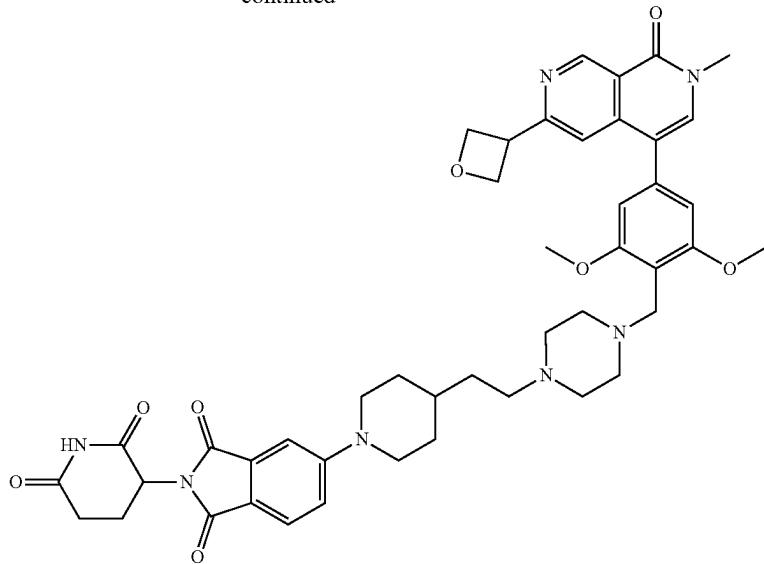
583

Example 59—Preparation of 5-(4-[2-[4-([2,6-dimethoxy-4-[2-methyl-6-(oxetan-3-yl)-1-oxo-2,7-naphthyridin-4-yl]phenyl)methyl]piperazin-1-yl)ethyl]piperidin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid

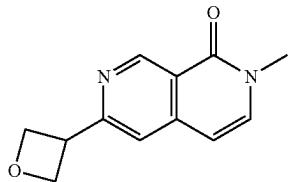
**584**

585**586**

-continued

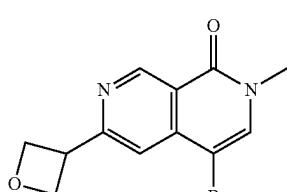


Step 1: Preparation of 2-methyl-6-(oxetan-3-yl)-2,7-naphthyridin-1-one



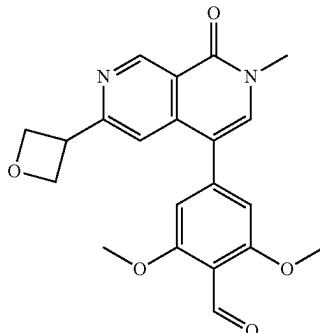
To a solution of 6-chloro-2-methyl-2,7-naphthyridin-1-one (300.0 mg, 1.541 mmol, 1.00 equivalent) and 3-bromo-⁴⁰ oxetane (422.3 mg, 3.083 mmol, 2.00 equivalent) in DMF (3.00 mL) was added Zn (302.5 mg, 4.624 mmol, 3.00 equivalent) and NaI (57.8 mg, 0.385 mmol, 0.25 equivalent). The resulting mixture was stirring at 60° C. for 12 hours under a nitrogen atmosphere. The resulting mixture was ⁴⁵ concentrated. The crude mixture was purified by reverse phase column directly with the following conditions (Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 45 mL/min; Gradient: 8% B to 80% B in 20 min; 254/220 nm) to afford 4-bromo-2-methyl-6-(oxetan-3-yl)-2,7-naphthyridin-1-one (⁵⁰ 150 mg, 45.0%) as a white solid. LCMS (ESI) m/z: [M+H]⁺=217.

Step 2: Preparation of 4-bromo-2-methyl-6-(oxetan-⁵⁵ 3-yl)-2,7-naphthyridin-1-one



²⁵ To a solution of 2-methyl-6-(oxetan-3-yl)-2,7-naphthyridin-1-one (100.0 mg, 0.462 mmol, 1.00 equivalent) in DMF (3.00 mL) was added NBS (90.5 mg, 0.509 mmol, 1.10 equivalent). The resulting mixture was stirring at 25° C. for 2 hours. The resulting mixture was concentrated. The crude mixture was purified by reverse phase column directly with the following conditions (Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 45 mL/min; Gradient: 8% B to 80% B in 20 min; 254/220 nm) to afford 4-bromo-2-methyl-6-(oxetan-3-yl)-2,7-naphthyridin-1-one (³⁰ 105 mg, 76.9%) as a white solid. LCMS (ESI) m/z: [M+H]⁺=295.

Step 3: Preparation of 2,6-dimethoxy-4-[2-methyl-6-(oxetan-3-yl)-1-oxo-2,7-naphthyridin-4-yl]benzaldehyde

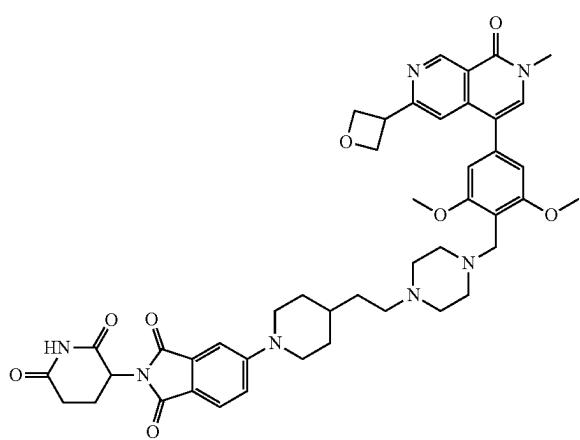


⁴⁰ To a solution of 4-bromo-2-methyl-6-(oxetan-3-yl)-2,7-naphthyridin-1-one (100.0 mg, 0.339 mmol, 1.00 equivalent) and 2,6-dimethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxa-borolan-2-yl)benzaldehyde (148.5 mg, 0.508 mmol, 1.50 equivalent) in dioxane (3.00 mL) and H₂O (1.00 mL) were added Cs₂CO₃ (331.2 mg, 1.016 mmol, 3.00 equivalent) and Pd(dppf)Cl₂ (24.8 mg, 0.034 mmol, 0.10 equivalent) under ⁴⁵ nitrogen atmosphere. The resulting mixture was stirring at 80 degree for 3 hours under nitrogen atmosphere. The resulting mixture was concentrated. The crude mixture was

587

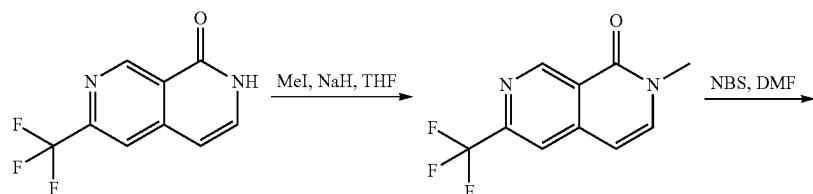
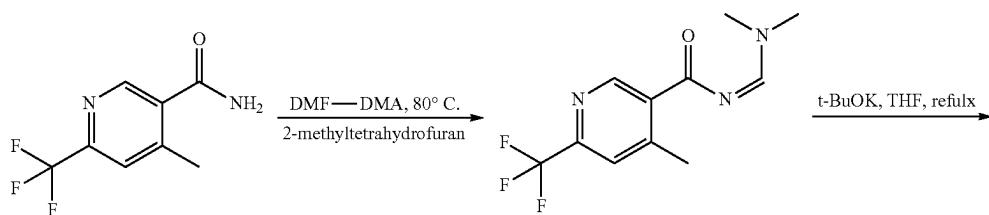
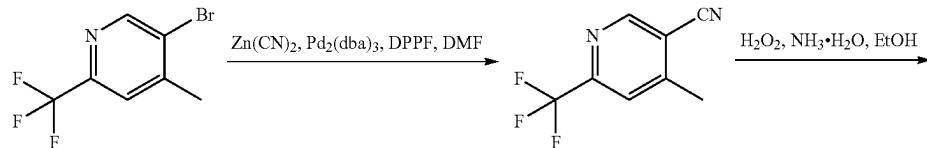
purified by reverse phase column directly with the following conditions (Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 45 mL/min; Gradient: 8% B to 80% B in 20 min; 254/220 nm) to afford. This resulted in (130 mg, crude) of 2,6-dimethoxy-4-[2-methyl-6-(oxetan-3-yl)-1-oxo-2,7-naphthyridin-4-yl]benzaldehyde (110 mg, 85.3%) as a yellow solid. LCMS (ESI) m/z: [M+H]⁺=381.

Step 4: Preparation of 5-(4-[2-[4-([2,6-dimethoxy-4-[2-methyl-6-(oxetan-3-yl)-1-oxo-2,7-naphthyridin-4-yl]phenyl)methyl]piperazin-1-yl]ethyl)piperidin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione; formic acid

**588**

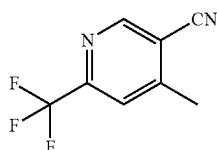
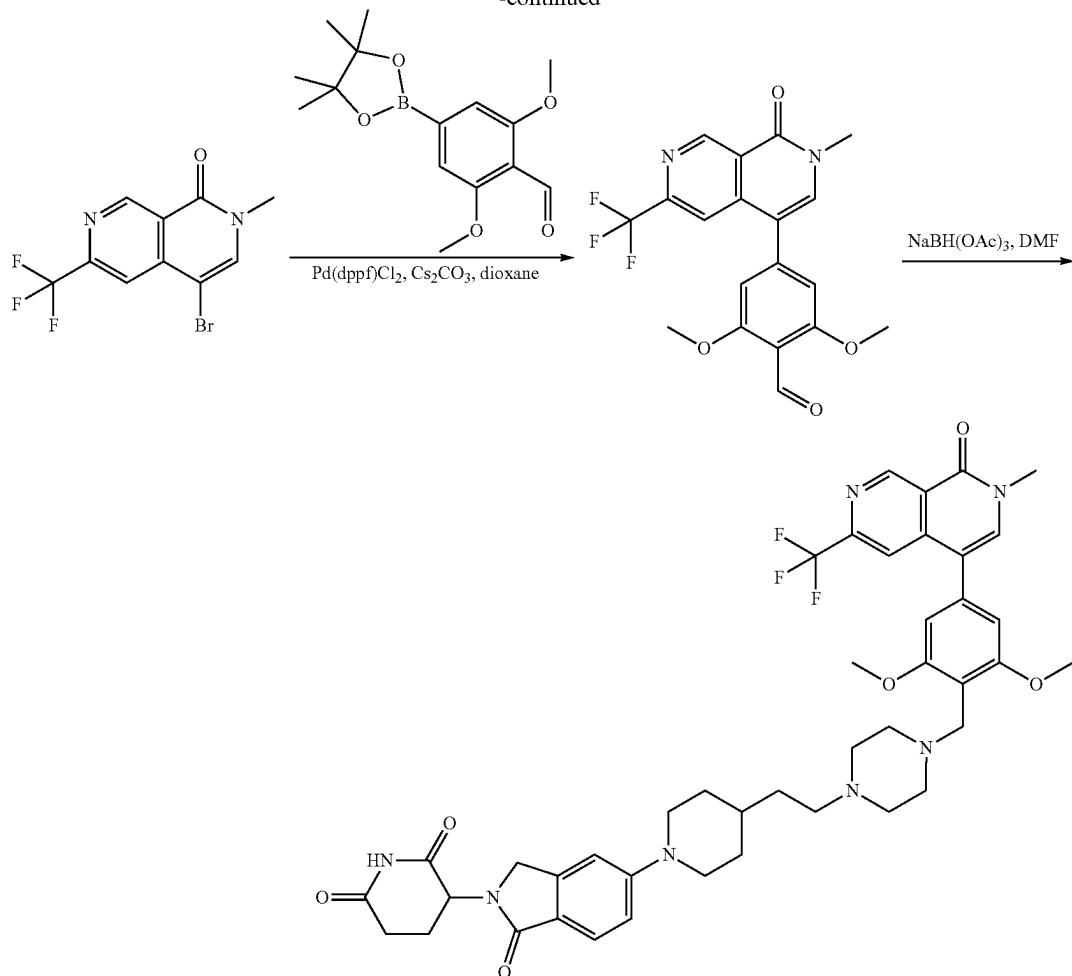
To a stirred mixture of 2,6-dimethoxy-4-[2-methyl-6-(oxetan-3-yl)-1-oxo-2,7-naphthyridin-4-yl]benzaldehyde (50.0 mg, 0.131 mmol, 1.00 equivalent) and 2-(2,6-dioxopiperidin-3-yl)-5-[4-[2-(piperazin-1-yl)ethyl]piperidin-1-yl]isoindole-1,3-dione (65.6 mg, 0.145 mmol, 1.10 equivalent) in DMF (2.00 mL) was added NaBH(OAc)₃ (55.72 mg, 0.263 mmol, 2.00 equivalent) at room temperature. The above mixture was stirred for 3 hours. Then the crude reaction mixture was directly purified by Prep-HPLC (Column: Xselect CSH F-phenyl OBD Column, 19*250 mm, 5 μ m; Mobile Phase A: Water (0.05% TFA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 15% B to 24% B in 14 min; 254/220 nm; Rt: 12.97 min). This resulted in 5-(4-[2-[4-([2,6-dimethoxy-4-[2-methyl-6-(oxetan-3-yl)-1-oxo-2,7-naphthyridin-4-yl]phenyl)methyl]piperazin-1-yl]ethyl)piperidin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione; formic acid (40 mg, 37.2%) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ 11.08 (s, 1H), 9.50 (s, 1H), 8.15 (s, 1H, FA), 7.87 (s, 1H), 7.65 (d, J=8.5 Hz, 1H), 7.46 (s, 1H), 7.30 (d, J=2.2 Hz, 1H), 7.23 (dd, J=8.8, 2.3 Hz, 1H), 6.74 (s, 2H), 5.07 (dd, J=13.0, 5.3 Hz, 1H), 4.89 (dd, J=8.4, 5.5 Hz, 2H), 4.79 (dd, J=6.7, 5.5 Hz, 2H), 4.59-4.47 (m, 1H), 4.04 (d, J=13.0 Hz, 2H), 3.81 (s, 6H), 3.58 (d, J=8.8 Hz, 6H), 3.00-2.82 (m, 3H), 2.73-2.57 (m, 4H), 2.55-2.41 (m, 4H), 2.40-2.23 (m, 3H), 2.05-1.97 (m, 1H), 1.78-1.71 (m, 2H), 1.66-1.51 (m, 1H), 1.42-1.34 (m, 2H), 1.24-1.11 (m, 2H). LCMS (ESI) m/z: [M+H]⁺=818.60.

Example 60—Preparation of 3-[5-(4-[2-[4-([2,6-dimethoxy-4-[2-methyl-1-oxo-6-(trifluoromethyl)-2,7-naphthyridin-4-yl]phenyl)methyl]piperazin-1-yl]ethyl)piperidin-1-yl]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione

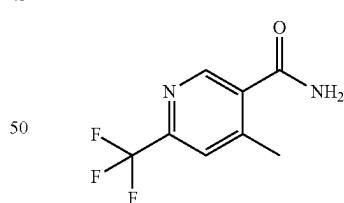


589**590**

-continued



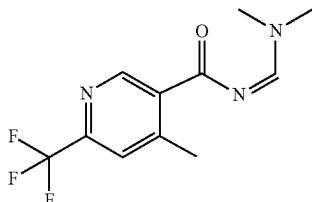
To a stirred solution of 5-bromo-4-methyl-2-(trifluoromethyl)pyridine (500.00 mg, 2.083 mmol, 1.00 equivalent) and $Zn(CN)_2$ (146.79 mg, 1.250 mmol, 0.6 equivalent) in DMF (5.00 mL) was added $Pd_2(db\alpha)_3$ (38.15 mg, 0.042 mmol, 0.02 equivalent) and DPPF (46.03 mg, 0.083 mmol, 0.04 equivalent), the resulting solution was stirred at 120° C. for 3 hours. Without any additional work-up, the mixture was purified by flash C18-flash chromatography, elution gradient 0 to 80% MeCN in water (containing 0.1% NH_4HCO_3). Pure fractions were evaporated to dryness to afford 4-methyl-6-(trifluoromethyl)pyridine-3-carbonitrile (220 mg, 56.74%) as a yellow oil. LCMS (ESI) m/z: [M+H]⁺=187.



To a stirred solution of 4-methyl-6-(trifluoromethyl)pyridine-3-carbonitrile (200.00 mg, 1.074 mmol, 1.00 equivalent) and $NH_3 \cdot H_2O$ (1.00 mL) in EtOH (1.00 mL) was added H_2O_2 (0.20 mL), the resulting solution was stirred at 25° C. for 4 hours. The reaction mixture was concentrated under reduced pressure to afford 4-methyl-6-(trifluoromethyl)pyridine-3-carboxamide (372 mg, crude) as a white solid that was used directly without further purification. LCMS (ESI) m/z: [M+H]⁺=205.

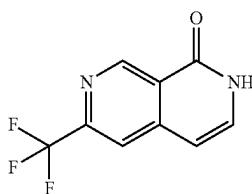
591

Step 3: Preparation of N-[(1Z)-(dimethylamino)methylidene]-4-methyl-6-(trifluoromethyl)pyridine-3-carboxamide



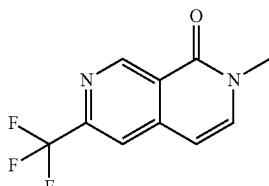
To a stirred solution of 4-methyl-6-(trifluoromethyl)pyridine-3-carboxamide (350.00 mg, 1.714 mmol, 1.00 equivalent) and DMF-DMA (306.44 mg) in 2-methyltetrahydrofuran (5.00 mL) was stirred at 80° C. for 2 hours. Then the mixture was concentrated under reduced pressure to afford N-[(1Z)-(dimethylamino)methylidene]-4-methyl-6-(trifluoromethyl)pyridine-3-carboxamide (360 mg crude) as a yellow solid that was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H]⁺=260.

Step 4: Preparation of 6-(trifluoromethyl)-2H-2,7-naphthyridin-1-one



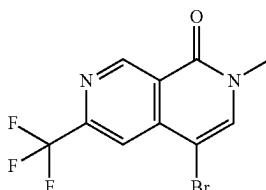
To a stirred solution of N-[(1Z)-(dimethylamino)methylidene]-4-methyl-6-(trifluoromethyl)pyridine-3-carboxamide (350.00 mg, 1.350 mmol, 1.00 equivalent) and t-BuOK (227.25 mg, 2.025 mmol, 1.50 equivalent) in THF (4.00 mL) was stirred at 60° C. for 2 hours. The resulting mixture was cooled and concentrated under reduced pressure, the residue was washed with saturated NaHCO₃ solution (100 mL). Then the solid was dried under vacuum to give 6-(trifluoromethyl)-2H-2,7-naphthyridin-1-one (295 mg, crude) as an off-white solid. The crude product was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H]⁺=215.

Step 5: Preparation of 2-methyl-6-(trifluoromethyl)-2,7-naphthyridin-1-one

**592**

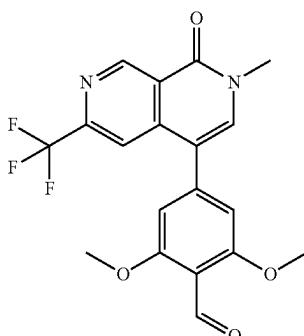
To a stirred mixture of 6-(trifluoromethyl)-2H-2,7-naphthyridin-1-one (275.00 mg, 1.284 mmol, 1.00 equivalent) in anhydrous DMF (3.00 mL) was added NaH (36.98 mg, 1.541 mmol, 1.20 equivalent, 60%) in portions at 0° C. After 10 minutes, to above mixture was added Mel (546.82 mg, 3.852 mmol, 3.00 equivalent) at 0° C. and the mixture was allowed to stir for 10 min at 0° C. Then the mixture was allowed to stir for 12 hr at room temperature under nitrogen atmosphere. The crude solid was slurried with water (100 mL), and the solid was filtered and collected to give the 2-methyl-6-(trifluoromethyl)-2,7-naphthyridin-1-one (242 mg, 82.59%) as a yellow solid, that was used directly without further purification. LCMS (ESI) m/z: [M+H]⁺=229.

Step 6: Preparation of 4-bromo-2-methyl-6-(trifluoromethyl)-2,7-naphthyridin-1-one



To a stirred mixture of 2-methyl-6-(trifluoromethyl)-2,7-naphthyridin-1-one (220.00 mg, 0.964 mmol, 1.00 equivalent) in anhydrous DMF (5.00 mL) was added NBS (188.77 mg, 1.061 mmol, 1.10 equivalent), the mixture was stirred at 90° C. for 2 hours. Without any additional work-up, the residue was purified by Prep-TLC (PE/EtOAc 1:1) to afford 4-bromo-2-methyl-6-(trifluoromethyl)-2,7-naphthyridin-1-one (192 mg, 64.85%) as a white solid. LCMS (ESI) m/z: [M+H]⁺=307.

Step 7: Preparation of 2,6-dimethoxy-4-[2-methyl-1-oxo-6-(trifluoromethyl)-2,7-naphthyridin-4-yl]benzaldehyde

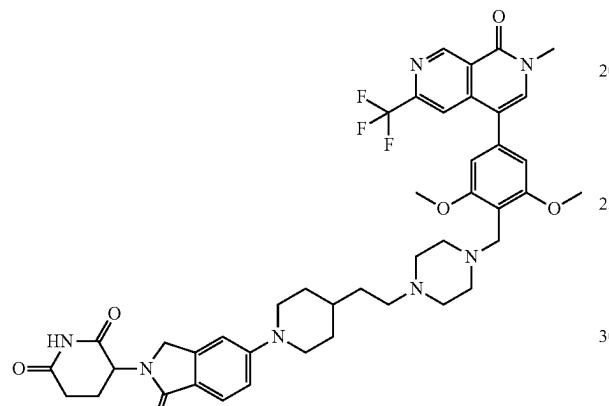


To a solution of 4-bromo-2-methyl-6-(trifluoromethyl)-2,7-naphthyridin-1-one (142.00 mg, 0.462 mmol, 1.00 equivalent) and 2,6-dimethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (189.13 mg, 0.647 mmol, 1.4 equivalent) in dioxane (3.00 mL) was added Pd(dppf)Cl₂ (33.84 mg, 0.046 mmol, 0.10 equivalent) and Cs₂CO₃ (301.34 mg, 0.925 mmol, 2 equivalent), the resulting solution was stirred at 70° C. for 3 hours. Without any additional

593

work-up, the residue was purified by silica gel column chromatography, eluted with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (10:1) to afford 2,6-dimethoxy-4-[2-methyl-1-oxo-6-(trifluoromethyl)-2,7-naphthyridin-4-yl]benzaldehyde (275 mg, crude) as a brown solid, that was used directly without further purification. LCMS (ESI) m/z: $[\text{M}+\text{H}]^+=393$.

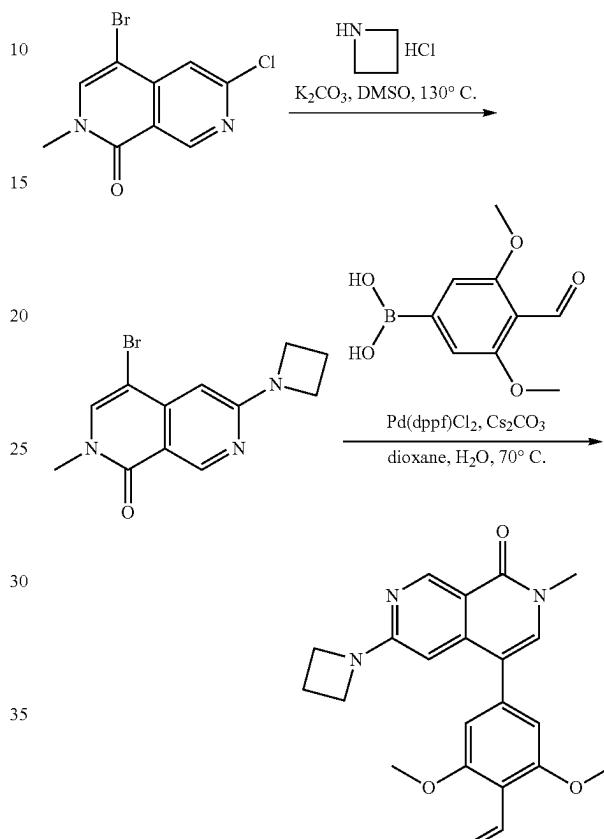
Step 8: Preparation of 3-[5-(4-[2-[4-([2,6-dimethoxy-4-[2-methyl-1-oxo-6-(trifluoromethyl)-2,7-naphthyridin-4-yl]phenyl)methyl)piperazin-1-yl]ethyl)piperidin-1-yl]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione



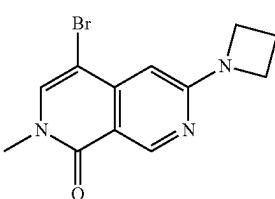
To a solution of 2,6-dimethoxy-4-[2-methyl-1-oxo-6-(trifluoromethyl)-2,7-naphthyridin-4-yl]benzaldehyde (78.00 mg, 0.199 mmol, 1.00 equivalent) and 3-(1-oxo-5-[4-[2-(piperazin-1-yl)ethyl]piperidin-1-yl]-3H-isoindol-2-yl)piperidine-2,6-dione (131.08 mg, 0.298 mmol, 1.50 equivalent) in DMF (2.00 mL) was added $\text{NaBH}(\text{OAc})_3$ (84.27 mg, 0.398 mmol, 2 equivalent), the resulting solution was stirred at 25° C. for 12 hours. Without any additional work-up, the mixture was purified by prep-HPLC (Column: SunFire Prep C18 OBD Column, 19×150 mm 5 μm 10 nm; Mobile Phase A: Water (0.05% TFA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 10 B to 32 B in 10 min; 254/220 nm; RT1: 8.95 min) to afford 3-[5-(4-[2-[4-([2,6-dimethoxy-4-[2-methyl-1-oxo-6-(trifluoromethyl)-2,7-naphthyridin-4-yl]phenyl)methyl)piperazin-1-yl]ethyl)piperidin-1-yl]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione (25 mg, 15.41%) as a light brown solid. ^1H NMR (400 MHz, DMSO-d₆) δ 10.96 (s, 1H), 9.59 (s, 1H), 8.08 (s, 1H), 7.93 (s, 1H), 7.52 (d, $J=8.5$ Hz, 1H), 7.06 (d, $J=8.2$ Hz, 2H), 6.94 (d, $J=18.1$ Hz, 2H), 5.05 (dd, $J=13.4$, 5.1 Hz, 1H), 4.38-4.15 (m, 3H), 3.87 (s, 8H), 3.67 (s, 3H), 3.63 (s, 3H), 3.11-3.25 (m, 4H), 2.87 (dt, $J=36.3$, 12.4 Hz, 6H), 2.59 (d, $J=18.0$ Hz, 2H), 2.36-2.29 (m, 1H), 2.00-1.91 (m, 1H), 1.75 (d, $J=12.5$ Hz, 2H), 1.57 (s, 3H), 1.25 (d, $J=11.0$ Hz, 2H). LCMS (ESI) m/z: $[\text{M}+\text{H}]^+=816.15$.

594

Example 61—Preparation of 3-[5-[7-([4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl)methyl)-2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione formic acid



Step 1: Preparation of 6-(azetidin-1-yl)-4-bromo-2-methyl-2,7-naphthyridin-1-one

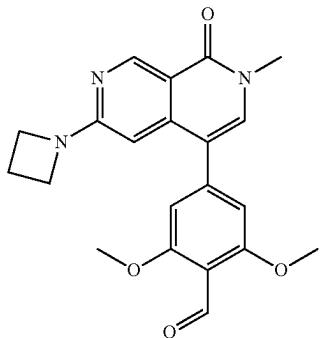


To a solution of 4-bromo-6-chloro-2-methyl-2,7-naphthyridin-1-one (5.00 g, 18.281 mmol, 1.00 equivalent) and azetidine hydrochloride (3.2 g, 54.843 mmol, 3 equivalent) in DMSO (50.00 mL) was added K_2CO_3 (12.6 g, 91.404 mmol, 5 equivalent). The resulting solution was stirred at 130° C. for 2 hours. The resulting mixture was cooled and diluted with water (100 mL), and then extracted with EtOAc (3×100 mL). The combined organic layers were washed with saturated NaCl solution (3×50 mL), dried over anhydrous Na_2SO_4 , concentrated under reduced pressure to afford 6-(azetidin-1-yl)-4-bromo-2-methyl-2,7-naphthyri-

595

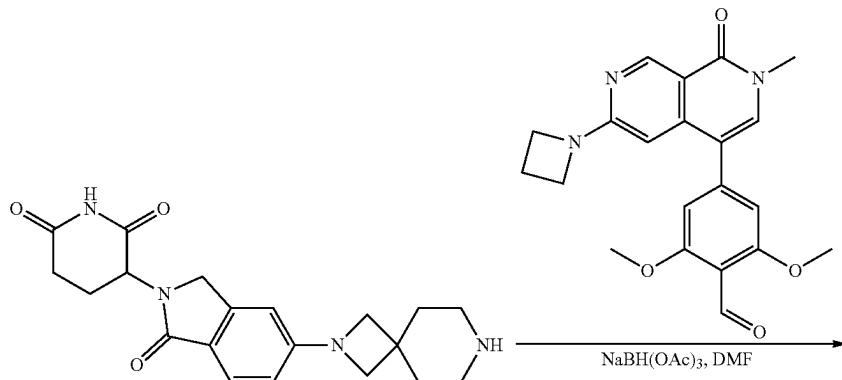
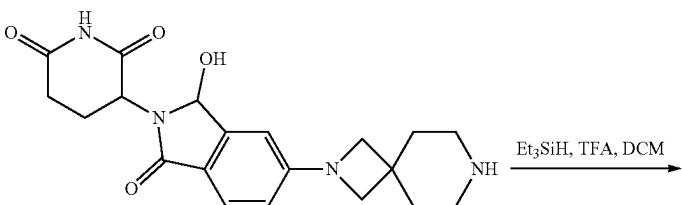
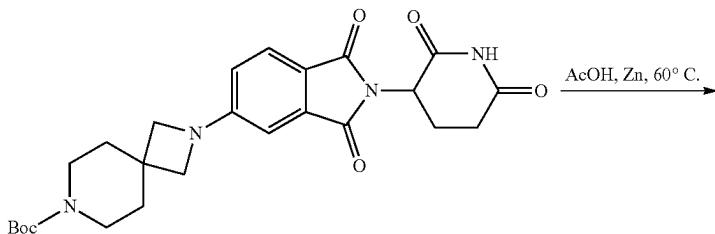
din-1-one (3.7 g, 68.8%) as a grey solid, that was used directly without further purification. LCMS (ESI) m/z: [M+H]⁺=294.

Step 2: Preparation of 4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde

**596**

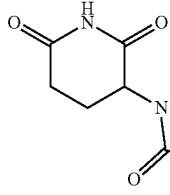
To a solution of 6-(azetidin-1-yl)-4-bromo-2-methyl-2,7-naphthyridin-1-one (1.42 g, 4.827 mmol, 1.00 equivalent) and 4-formyl-3,5-dimethoxyphenylboronic acid (1.52 g, 7.241 mmol, 1.5 equivalent) in dioxane (16.00 mL) and H₂O (4.00 mL) were added Pd(dppf)Cl₂ (353.2 mg, 0.483 mmol, 0.1 equivalent) and Cs₂CO₃ (3.15 g, 9.655 mmol, 2 equivalent), and the resulting solution was stirred at 70° C. for 2 hours. The resulting mixture was cooled and concentrated under reduced pressure. The residue was slurried with water (30 mL) and filtered, the filter cake was collected. And this solid was further slurried with MeOH (30 mL) and filtered. The solid was collected to afford product to afford 4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (1.42 g, 77.5%) as a grey and solid. LCMS (ESI) m/z: [M+H]⁺=380.

Example 62—Preparation of 3-[5-[7-(4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl)methyl]-2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione formic acid

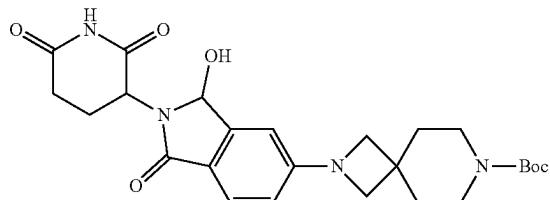


597

-continued

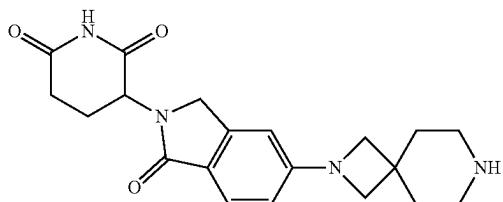


Step 1: Preparation of tert-butyl 2-[2-(2,6-dioxopiperidin-3-yl)-3-hydroxy-1-oxo-3H-isoindol-5-yl]-2,7-diazaspiro[3.5]nonane-7-carboxylate



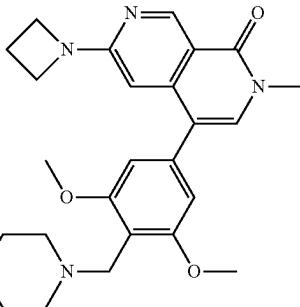
To a stirred solution of tert-butyl 2-[2-(2,6-dioxopiperidin-3-yl)-3-hydroxy-1-oxo-3H-isoindol-5-yl]-2,7-diazaspiro[3.5]nonane-7-carboxylate (500.0 mg, 1.036 mmol, 1.00 equivalent) in AcOH (4.00 mL) was added Zn (677.7 mg, 10.362 mmol, 10.00 equivalent). The resulting mixture was stirred at 60° C. for 2 h. The reaction mixture was filtered, and the filtrate was evaporated to afford crude product. The crude product was purified by reverse phase column, elution gradient 0 to 30% MeCN in water (containing 0.1% formic acid). Pure fractions were evaporated to dryness to afford tert-butyl 2-[2-(2,6-dioxopiperidin-3-yl)-3-hydroxy-1-oxo-3H-isoindol-5-yl]-2,7-diazaspiro[3.5]nonane-7-carboxylate (277.3 mg, 55.2%) as a yellow solid. LCMS (ESI) m/z: [M+H]⁺=485.

Step 2: Preparation of 3-(5-[2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione



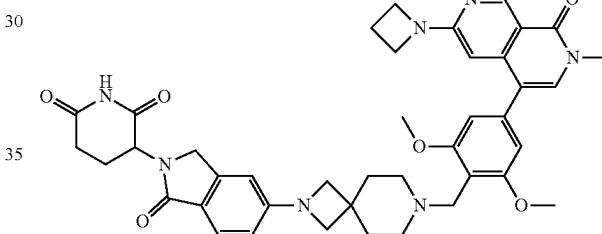
To a stirred solution of tert-butyl 2-[2-(2,6-dioxopiperidin-3-yl)-3-hydroxy-1-oxo-3H-isoindol-5-yl]-2,7-diazaspiro[3.5]nonane-7-carboxylate (250.0 mg, 0.516 mmol, 1.00 equivalent) in DCM (2.00 mL) were added TFA (0.50 mL) and Et₃SiH (0.20 mL). The resulting mixture was stirred at room temperature for 1 hour. The resulting mixture was concentrated under reduced pressure. This resulted in

598



15 3-(5-[2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione (267.5 mg, crude) as a yellow gum. The crude product was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H]⁺=369.

20 Step 3: Preparation of 3-[5-[7-([4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl)methyl]-2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione; formic acid



30 To a stirred solution of 3-(5-[2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione (400.0 mg, 1.086 mmol, 1.00 equivalent) and 4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (494.3 mg, 1.303 mmol, 1.20 equivalent) in DMF (3.00 mL) was added NaBH(OAc)₃ (920.4 mg, 4.343 mmol, 4.00 equivalent) at room temperature. The resulting mixture was stirred at room temperature for 2 hours. The crude reaction solution was directly purified by Prep-HPLC with

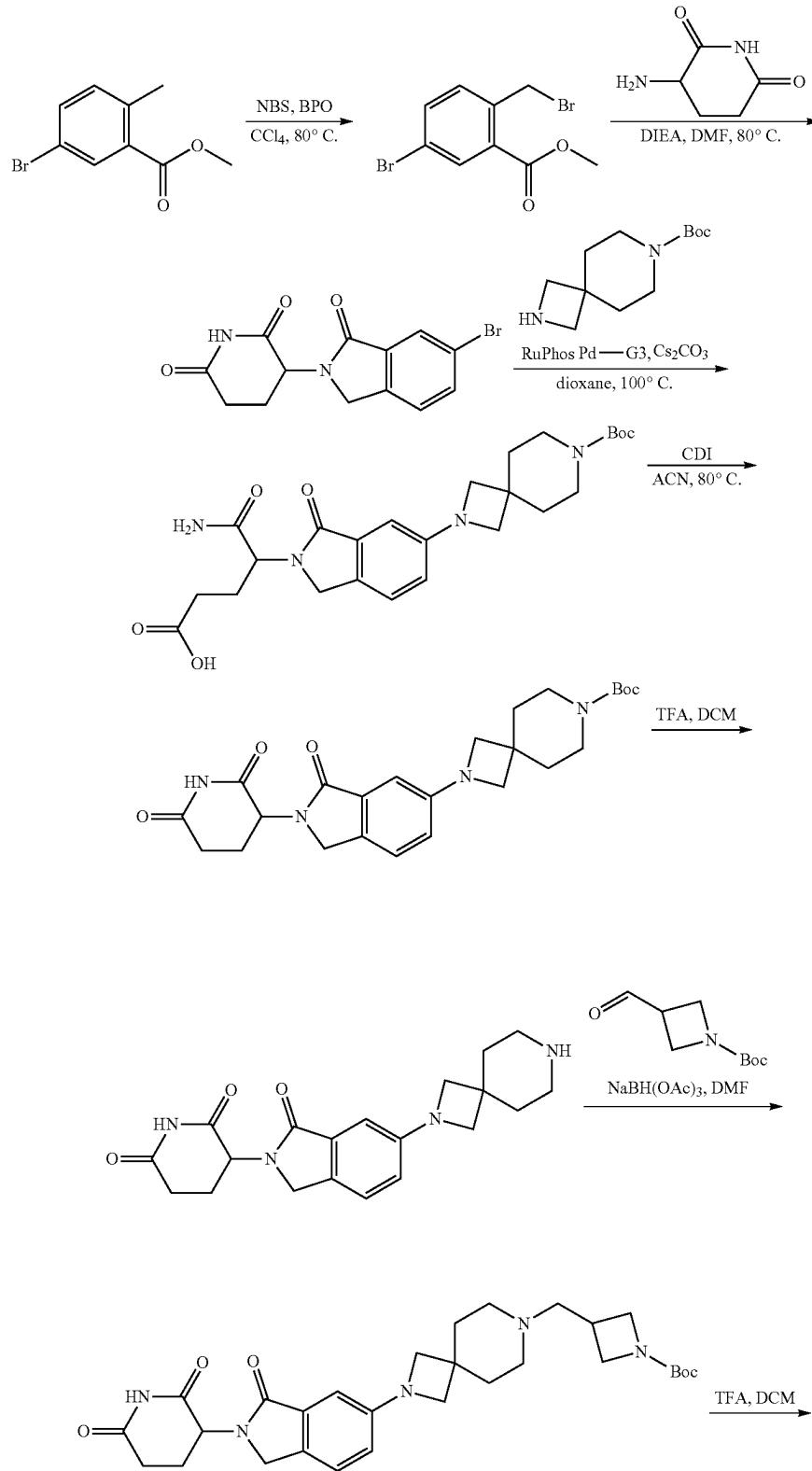
45 the following conditions (Column: XSelect CSH Prep C18 OBD Column, 5 μm, 19*150 mm; Mobile Phase A: Water (0.05% FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 14 B to 22 B in 15 min; 254/220 nm; RT1: 11.72 min) to afford 3-[6-[7-([4-[6-(azetidin-1-yl)-2-methyl-1-

50 oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl)methyl]-2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione; formic acid (99.2 mg, 12.5%) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 10.94 (s, 1H), 9.02

55 (s, 1H), 8.15 (s, 1H, FA), 7.61 (s, 1H), 7.48 (d, J=8.2 Hz, 1H), 6.75 (s, 2H), 6.53-6.44 (m, 2H), 6.21 (s, 1H), 5.04 (dd, J=13.3, 5.2 Hz, 1H), 4.30 (d, J=17.0 Hz, 1H), 4.17 (d, J=16.9 Hz, 1H), 4.01 (t, J=7.4 Hz, 4H), 3.83 (s, 6H), 3.61 (d, J=13.2 Hz, 6H), 3.48 (s, 3H), 2.96-2.84 (m, 1H), 2.63-2.54 (m, 3H), 2.51-2.45 (m, 2H), 2.35 (q, J=6.6 Hz, 3H), 1.95 (d, J=12.9 Hz, 1H), 1.75 (s, 4H). LCMS (ESI) m/z: [M+H]⁺=732.45.

599**600**

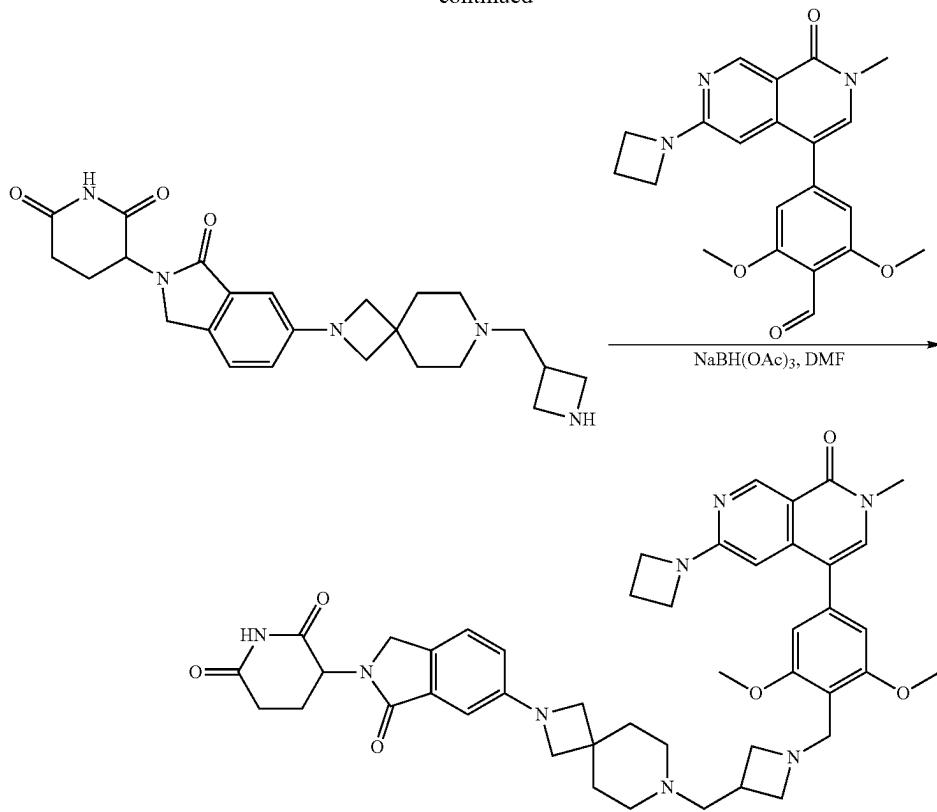
Example 63—Preparation of 3-[5-(7-[[1-([4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl)methyl]azetidin-3-yl)methyl]-2,7-diazaspiro[3.5]nonan-2-yl)-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione bis(formic acid)



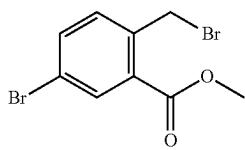
601

602

-continued

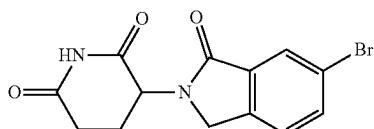


Step 1: Preparation of methyl 5-bromo-2-(bromomethyl)benzoate



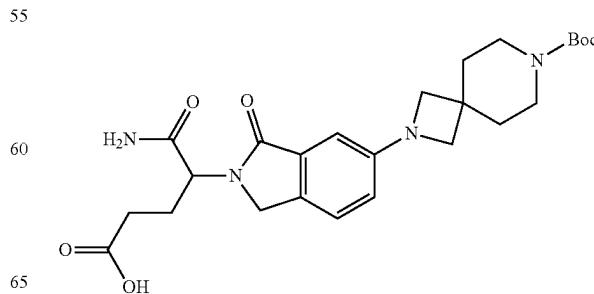
A solution of methyl 5-bromo-2-methylbenzoate (1.0 g, 4.365 mmol, 1.00 equivalent), BPO (223.7 mg, 0.873 mmol, 0.20 equivalent) and NBS (777.0 mg, 4.365 mmol, 1.00 equivalent) in solvent CCl_4 (10.00 mL) was stirred at 80 degree for 3 hours. The resulting mixture was concentrated. The residue was applied onto a silica gel column, eluted with petroleum ether/EtOAc (20:1) to afford methyl 5-bromo-2-(bromomethyl)benzoate (1.1 g, 81.8%) as a light-yellow liquid.

Step 2: Preparation of 3-(6-bromo-1-oxo-3H-isindol-2-yl)piperidine-2,6-dione



35 To a solution of methyl 5-bromo-2-(bromomethyl)benzoate (1.0 g, 3.247 mmol, 1.00 equivalent), 3-aminopiperidine-2,6-dione (499.26 mg, 3.896 mmol, 1.20 equivalent) in solvent DMF (10.00 mL) was added DIEA (1.26 g, 9.741 mmol, 3.00 equivalent) at room temperature, and the resulting solution was stirred at 80 degree for 12 hours. The resulting mixture was concentrated. The residue was dissolved in water (100 mL) and extracted with 30% i-PrOH/ CH_2Cl_2 (100 mL \times 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to afford of 45 3-(6-bromo-1-oxo-3H-isindol-2-yl)piperidine-2,6-dione (500 mg, 47.7%) as a grey solid. LCMS (ESI) m/z: [M+H] $^+$ = 323.

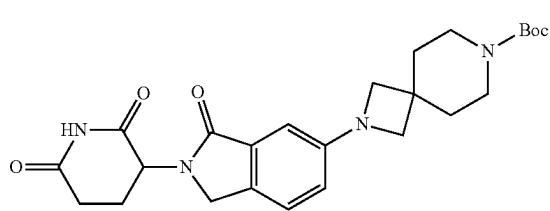
50 Step 3: Preparation of 4-[6-[7-(tert-butoxycarbonyl)-2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isindol-2-yl]-4-carbamoylbutanoic acid



603

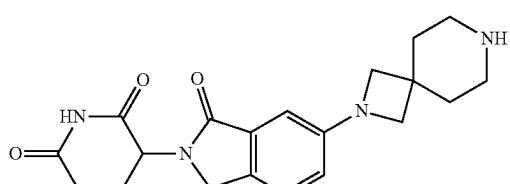
To a mixture of 3-(6-bromo-1-oxo-3H-isoindol-2-yl)pyridine-2,6-dione (500.0 mg, 1.547 mmol, 1.00 equivalent), tert-butyl 2,7-diazaspiro[3.5]nonane-7-carboxylate (350.2 mg, 1.547 mmol, 1.00 equivalent), Cs₂CO₃ (1.51 g, 4.642 mmol, 3.00 equivalent) and RuPhos Palladacycle Gen 3 (129.4 mg, 0.155 mmol, 0.10 equivalent) was added solvent dioxane (5.00 mL) under nitrogen atmosphere, and the resulting mixture was stirred at 100 degree for 6 hours under nitrogen atmosphere. The resulting mixture was concentrated. The crude product was purified by reverse phase column directly with the following conditions (Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 45 mL/min; Gradient: 8% B to 80% B in 20 min; 254/220 nm) to afford 4-[6-[7-(tert-butoxycarbonyl)-2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isoindol-2-yl]-4-carbamoylbutanoic acid (150 mg, 19.9%) as a yellow solid. LCMS (ESI) m/z: [M+H]⁺=487.

Step 4: Preparation of tert-butyl 2-[2-(2,6-dioxopiperidin-3-yl)-3-oxo-1H-isoindol-5-yl]-2,7-diazaspiro[3.5]nonane-7-carboxylate



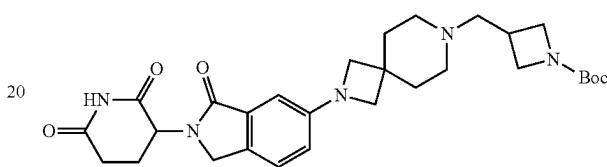
To a solution of 4-[6-[7-(tert-butoxycarbonyl)-2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isoindol-2-yl]-4-carbamoylbutanoic acid (200.0 mg, 0.411 mmol, 1.00 equivalent) in solvent CH₃CN (5.00 mL) was added CDI (133.3 mg, 0.822 mmol, 2.00 equivalent). The resulting solution was stirred at 80 degree for 6 hours. The resulting mixture was concentrated. The crude product was purified by reverse phase column directly with the following conditions (Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 45 mL/min; Gradient: 8% B to 80% B in 20 min; 254/220 nm) to afford tert-butyl 2-[2-(2,6-dioxopiperidin-3-yl)-3-oxo-1H-isoindol-5-yl]-2,7-diazaspiro[3.5]nonane-7-carboxylate (170 mg, 88.3%) as a yellow solid. LCMS (ESI) m/z: [M+H]⁺=469.

Step 5: Preparation of 3-(6-[2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione

**604**

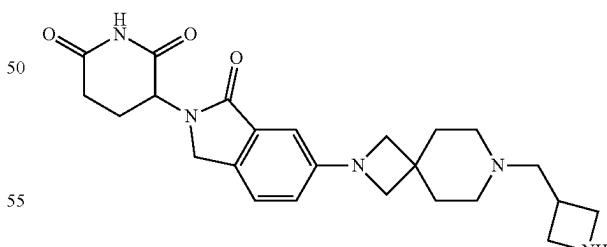
To a solution of tert-butyl 2-[2-(2,6-dioxopiperidin-3-yl)-3-oxo-1H-isoindol-5-yl]-2,7-diazaspiro[3.5]nonane-7-carboxylate (100.0 mg, 0.213 mmol, 1.00 equivalent) in DCM (3.00 mL) was added TFA (1.00 mL) at room temperature. The resulting mixture was stirred for 1 hour at room temperature. It was then concentrated in vacuo to give a crude product which was used directly in the next step. LCMS (ESI) m/z: [M+H]⁺=369.

Step 6: Preparation of tert-butyl 3-([2-[2-(2,6-dioxopiperidin-3-yl)-3-oxo-1H-isoindol-5-yl]-2,7-diazaspiro[3.5]nonan-7-yl]methyl)azetidine-1-carboxylate



To a solution of 3-(6-[2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione (100.0 mg, 0.271 mmol, 1.00 equivalent), tert-butyl 3-formylazetidine-1-carboxylate (50.3 mg, 0.271 mmol, 1.00 equivalent) in solvent DMF (3.00 mL) was added NaBH(OAc)₃ (172.6 mg, 0.814 mmol, 3.00 equivalent). The resulting solution was stirred at 25 degree for 3 hours. The mixture was concentrated. The crude product was purified by reverse phase column directly with the following conditions (Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 45 mL/min; Gradient: 8% B to 80% B in 20 min; 254/220 nm) to afford tert-butyl 3-([2-[2-(2,6-dioxopiperidin-3-yl)-3-oxo-1H-isoindol-5-yl]-2,7-diazaspiro[3.5]nonan-7-yl]methyl)azetidine-1-carboxylate (60 mg, 41.1%) as a yellow solid. LCMS (ESI) m/z: [M+H]⁺=538.

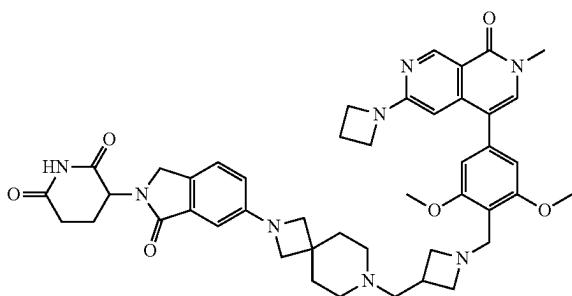
Step 7: Preparation of 3-[6-[7-(azetidin-3-ylmethyl)-2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione



To a solution of tert-butyl 3-([2-[2-(2,6-dioxopiperidin-3-yl)-3-oxo-1H-isoindol-5-yl]-2,7-diazaspiro[3.5]nonan-7-yl]methyl)azetidine-1-carboxylate (100.0 mg, 0.186 mmol, 1.00 equivalent) in DCM (3.00 mL) was added TFA (1.00 mL) at room temperature. The resulting mixture was stirred for 1 hour at room temperature. It was then concentrated in vacuo to give a crude product which was used directly in the next step. LCMS (ESI) m/z: [M+H]⁺=438.

605

Step 8: 3-[5-[[1-([4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)azetidin-3-yl)methyl]-2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione bis(formic acid)



To a stirred solution of 3-[5-[7-(azetidin-3-ylmethyl)-2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione (35.0 mg, 0.080 mmol, 1.00 equivalent) and 4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (30.4 mg, 0.080 mmol, 1.00 equivalent) in DMF (4.00 mL) was added NaBH(OAc)₃ (50.9 mg, 0.240 mmol, 3.00 equivalent) at room tempera-

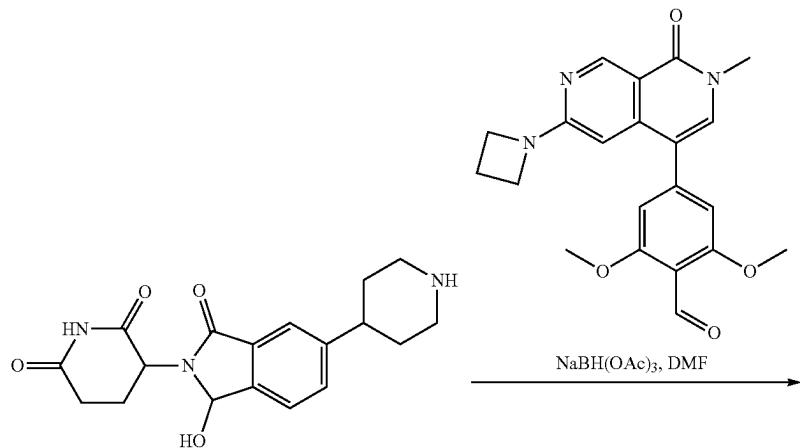
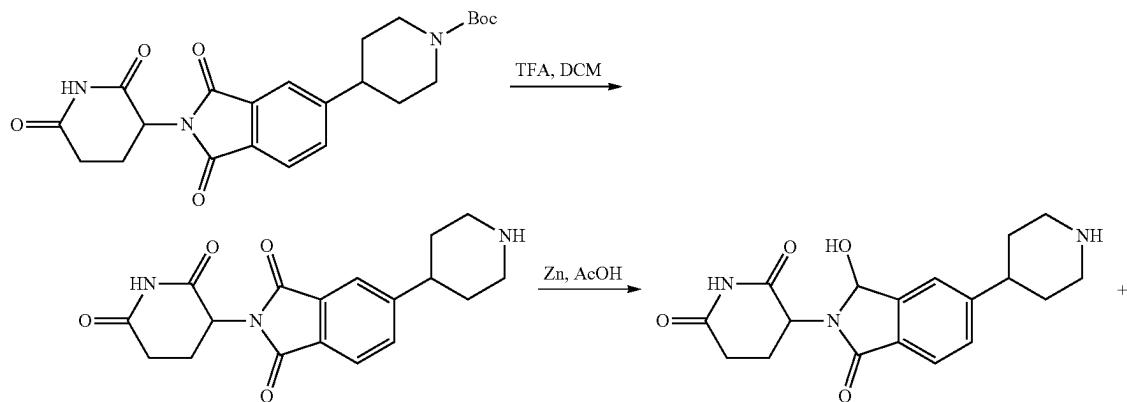
606

ture. The resulting mixture was stirred for overnight at room temperature. The mixture was filtered, and the filtrate was purified by Prep-HPLC (Column: XSelect CSH Prep C18 OBD Column, 19*250 mm, 5 μ m; Mobile Phase A: Water (0.05% FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 5 B to 17 B in 12 min; 254/220 nm; RT1: 8.9-9.53 min) to afford 3-[6-[[1-([4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)azetidin-3-yl)methyl]-2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione; bis(formic acid) (5.1 mg, 7.6%) as a light yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ 10.97 (s, 1H), 9.02 (s, 1H), 8.18 (s, 2H, FA), 7.61 (s, 1H), 7.38 (d, J =8.2 Hz, 1H), 6.79 (s, 2H), 6.68 (d, J =7.5 Hz, 2H), 6.18 (s, 1H), 5.08 (dd, J =13.2, 5.1 Hz, 1H), 4.31 (d, J =16.6 Hz, 1H), 4.18 (d, J =16.7 Hz, 1H), 4.11-3.97 (m, 6H), 3.86 (s, 6H), 3.82-3.69 (m, 4H), 3.58 (s, 3H), 3.49 (s, 3H), 2.96-2.85 (m, 2H), 2.78-2.71 (m, 1H), 2.64-2.60 (m, 1H), 2.59-2.55 (m, 1H), 2.43-2.26 (m, 7H), 2.06-1.95 (m, 2H), 1.78-1.67 (m, 4H). LCMS (ESI) m/z: [M+H]⁺=800.96.

20

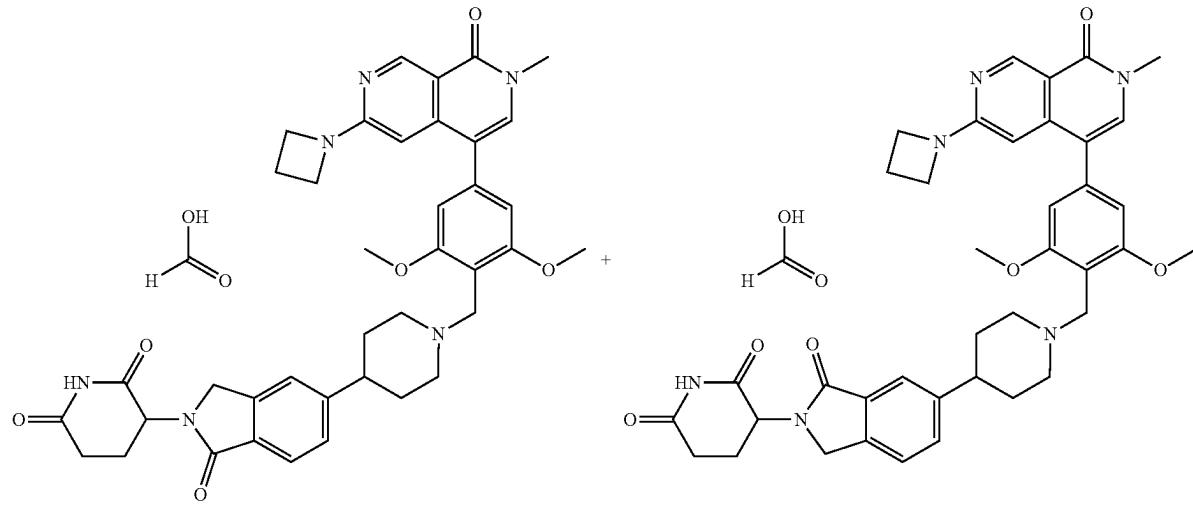
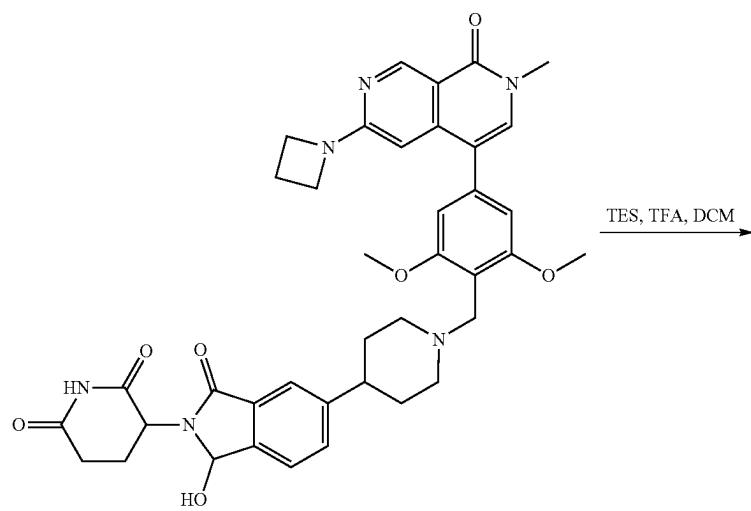
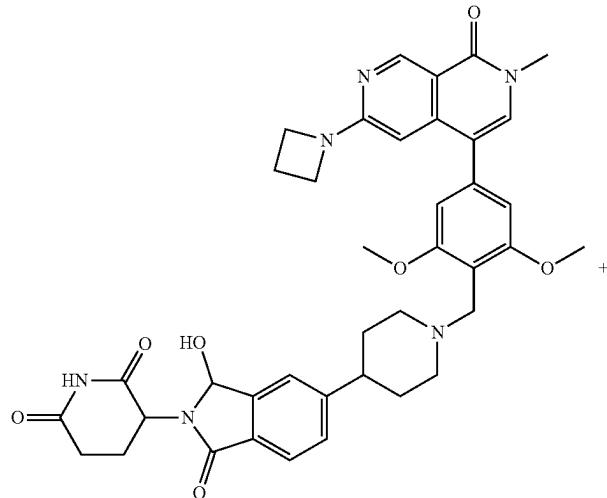
Example 64—Preparation of 3-[5-[[1-([4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)piperidin-4-yl]-oxo-3H-isoindol-2-yl)piperidine-2,6-dione formic acid; and 3-[6-[[1-([4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)piperidin-4-yl]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione formic acid

25



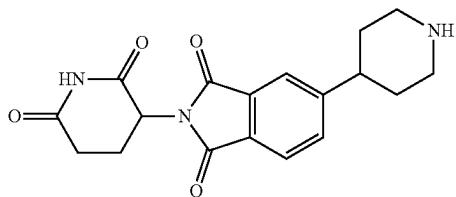
607**608**

-continued



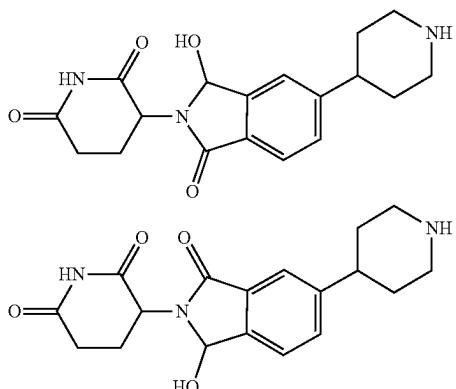
609

Step 1: Preparation of 2-(2, 6-dioxopiperidin-3-yl)-5-(piperidin-4-yl)isoindole-1,3-dione



To a stirred solution of tert-butyl 4-[2-(2, 6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperidine-1-carboxylate (1.00 g, 2.265 mmol, 1.00 equivalent) in DCM (8 mL) was added TFA (2.00 mL) at room temperature. The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure. This resulted in 2-(2,6-dioxopiperidin-3-yl)-5-(piperidin-4-yl)isoindole-1,3-dione (1.23 g, crude) as a white solid that was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H]⁺=342.

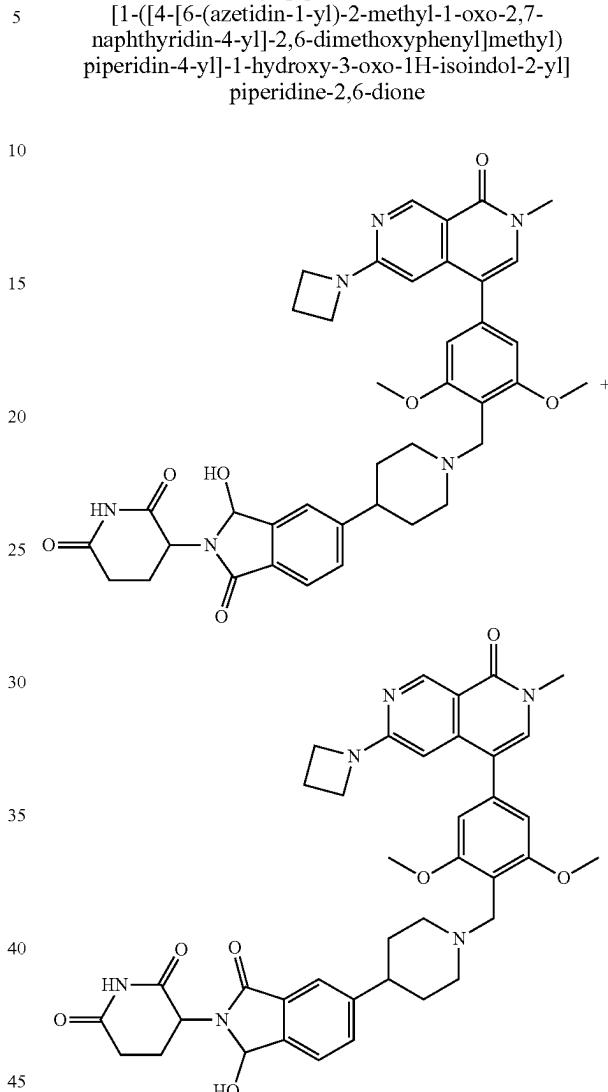
Step 2: Preparation of 3-[3-hydroxy-1-oxo-5-(piperidin-4-yl)-3H-isoindol-2-yl]piperidine-2,6-dione and 3-[1-hydroxy-3-oxo-5-(piperidin-4-yl)-1H-isoindol-2-yl]piperidine-2,6-dione



To a solution of 2-(2,6-dioxopiperidin-3-yl)-5-(piperidin-4-yl)isoindole-1,3-dione (300.0 mg, 0.879 mmol, 1.00 equivalent) in AcOH (5.00 mL) was added Zn (574.9 mg, 8.788 mmol, 10 equivalent), and the resulting solution was stirred at 25° C. for 2 hours. The mixture was diluted with EtOAc (30 mL) and washed with water (30 mL×3). The organic layers were combined and dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product. The crude product was purified by flash C18 chromatography (elution gradient 0 to 11% ACN in H₂O) to give 3-[3-hydroxy-1-oxo-5-(piperidin-4-yl)-3H-isoindol-2-yl]piperidine-2,6-dione and 3-[1-hydroxy-3-oxo-5-(piperidin-4-yl)-1H-isoindol-2-yl]piperidine-2,6-dione (280 mg, mixture of two regio-isomers, 92.8%) as a white solid. LCMS (ESI) m/z: [M+H]⁺=344.

610

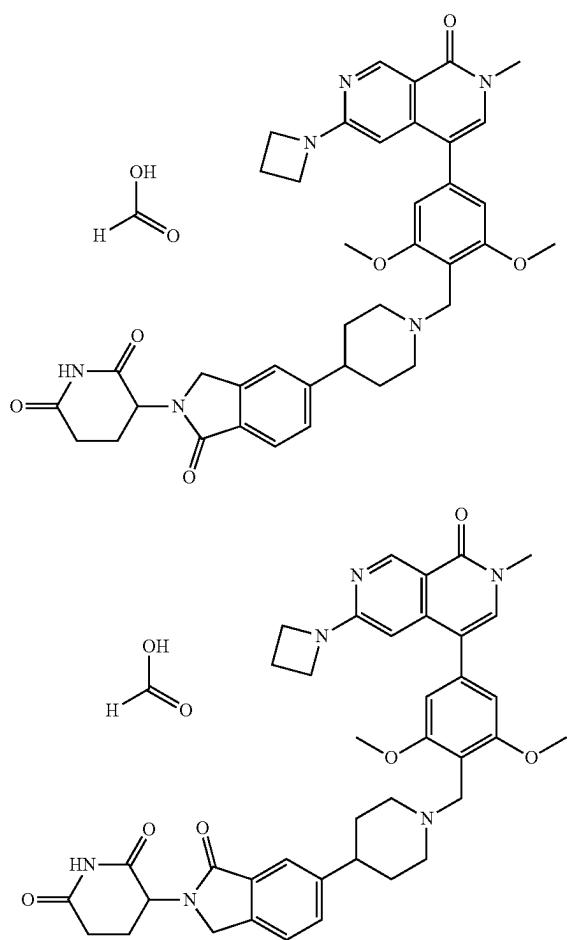
Step 3: Preparation of 3-[5-[1-(4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl)methyl]piperidin-4-yl]-3-hydroxy-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione and 3-[5-[1-(4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl)methyl]piperidin-4-yl]-1-hydroxy-3-oxo-1H-isoindol-2-yl)piperidine-2,6-dione



To a solution of 3-[3-hydroxy-1-oxo-5-(piperidin-4-yl)-3H-isoindol-2-yl]piperidine-2,6-dione and 3-[1-hydroxy-3-oxo-5-(piperidin-4-yl)-1H-isoindol-2-yl]piperidine-2,6-dione (mixture of two regio-isomers, 260.0 mg, 0.757 mmol, 1.00 equivalent), 4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (287.3 mg, 0.757 mmol, 1 equivalent) in DMF (3 mL) was added NaBH(OAc)₃ (321.0 mg, 1.514 mmol, 2 equivalent), and the resulting solution was stirred at 25° C. for 4 hours. The mixture was diluted with EtOAc (20 mL) and washed with water (20 mL×3). The organic layers were combined and dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product. The crude product was purified by Prep-TLC (CH₂Cl₂/MeOH 10:1) to give 3-[5-[1-(4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl)methyl]piperidin-4-yl]-3-hydroxy-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione and 3-[5-[1-(4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl)methyl]piperidin-4-yl]-1-hydroxy-3-oxo-1H-isoindol-2-yl)piperidine-2,6-dione (208 mg, mixture of two regio-isomers, 38.9%) as a white solid. LC-MS (ESI) m/z: [M+H]⁺=707.

611

Step 4: Preparation of 3-[5-[1-([4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxy phenyl)methyl] piperidin-4-yl]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione formic acid; and 3-[6-[1-([4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl)methyl] piperidin-4-yl]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione formic acid



To a solution of 3-[5-[1-([4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl)methyl]

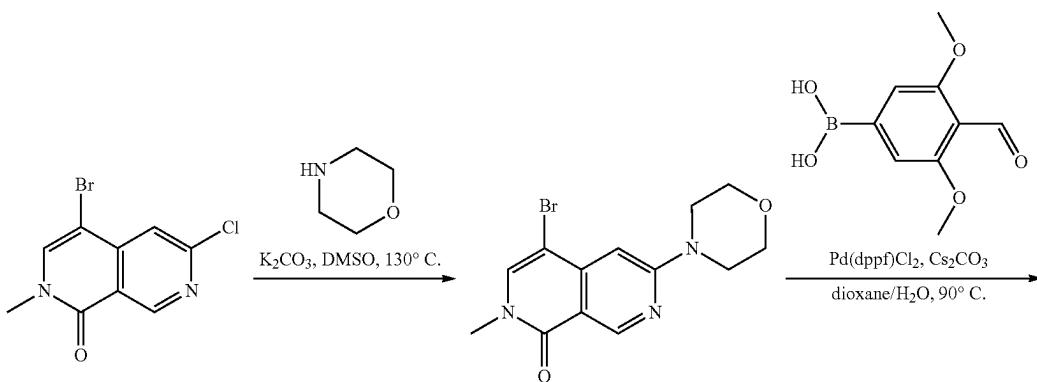
612

piperidin-4-yl]-3-hydroxy-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione and 3-[5-[1-([4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl)methyl] piperidin-4-yl]-1-hydroxy-3-oxo-1H-isoindol-2-yl]piperidine-2,6-dione (mixture of two regio-isomers, 200.0 mg, 0.141 mmol, 1.00 equivalent) in DCM (3.00 mL) was added TFA (2.00 mL, 26.926 mmol, 95.16 equivalent) and triethylsilane (1.00 mL, 6.192 mmol, 21.88 equivalent), and the resulting solution was stirred at 25°C. for 1 hour. The crude product was purified by Prep-HPLC (Column: XSelect CSH Prep C18 OBD Column, 5 μm, 19*150 mm; Mobile Phase A: Water (0.05% FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 3 B to 26 B in 14 minutes; 254 nm; RT1: 13.32 min) to afford 3-[5-[1-([4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl)methyl] piperidin-4-yl]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione (39.5 mg, 39.1%) and 3-[6-[1-([4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl)methyl] piperidin-4-yl]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione; formic acid (24.8 mg, 22.7%) both as a white solid.

For 3-[5-[1-([4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl)methyl] piperidin-4-yl]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione: ¹H NMR (400 MHz, DMSO-d₆) δ 10.99 (s, 1H), 9.02 (s, 1H), 8.16 (s, 1H, FA), 7.68-7.60 (m, 2H), 7.49 (s, 1H), 7.39 (dd, J=7.8, 1.4 Hz, 1H), 6.76 (s, 2H), 6.22 (s, 1H), 5.10 (dd, J=13.3, 5.1 Hz, 1H), 4.42 (d, J=17.3 Hz, 1H), 4.28 (d, J=17.3 Hz, 1H), 4.01 (t, J=7.4 Hz, 4H), 3.84 (s, 6H), 3.69 (s, 2H), 3.49 (s, 3H), 3.05 (d, J=11.2 Hz, 2H), 2.92 (ddd, J=17.3, 13.6, 5.4 Hz, 1H), 2.66-2.60 (m, 1H), 2.60-2.55 (m, 1H), 2.46-2.38 (m, 1H), 2.37-2.28 (m, 4H), 2.04-1.95 (m, 1H), 1.78-1.65 (m, 4H). LCMS (ESI) m/z: [M+H]⁺=691.35.

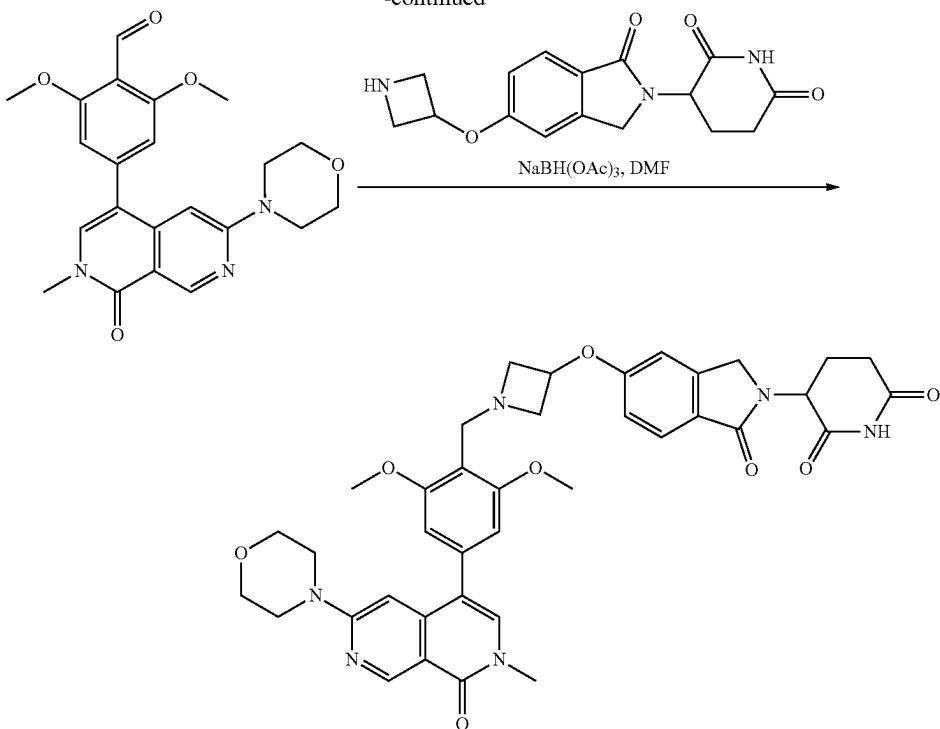
For 3-[6-[1-([4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl)methyl] piperidin-4-yl]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione; formic acid: ¹H NMR (400 MHz, DMSO-d₆) δ 10.99 (s, 1H), 9.02 (s, 1H), 8.18 (s, FA), 7.62 (s, 1H), 7.58-7.48 (m, 3H), 6.75 (s, 2H), 6.22 (s, 1H), 5.10 (dd, J=13.3, 5.1 Hz, 1H), 4.41 (d, J=17.1 Hz, 1H), 4.27 (d, J=17.1 Hz, 1H), 4.01 (t, J=7.4 Hz, 4H), 3.84 (s, 6H), 3.63 (s, 2H), 3.48 (s, 3H), 3.00 (d, J=11.0 Hz, 2H), 2.97-2.85 (m, 1H), 2.65-2.60 (m, 1H), 2.60-2.56 (m, 1H), 2.45-2.37 (m, 1H), 2.37-2.30 (m, 1H), 2.24 (t, J=11.3 Hz, 2H), 2.03-1.96 (m, 1H), 1.80-1.73 (m, 2H), 1.73-1.62 (m, 2H). LCMS (ESI) m/z: [M+H]⁺=691.55.

Example 65—Preparation of 3-(5-[1-([2,6-dimethoxy-4-[2-methyl-6-(morpholin-4-yl)-1-oxo-2,7-naphthyridin-4-yl]phenyl)methyl]azetidin-3-yl)oxy]-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione



613**614**

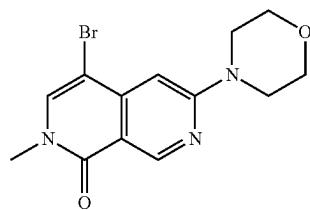
-continued



Step 1: Preparation of 4-bromo-2-methyl-6-(morpholin-4-yl)-2,7-naphthyridin-1-one

Step 2: Preparation of 2, 6-dimethoxy-4-[2-methyl-6-(morpholin-4-yl)-1-oxo-2, 7-naphthyridin-4-yl]benzaldehyde

35



To a stirred solution of 4-bromo-6-chloro-2-methyl-2,7-naphthyridin-1-one (547.00 mg, 2.000 mmol, 1.00 equivalent) and morpholine (522.71 mg, 6.000 mmol, 3.00 equivalent) in DMSO (6.00 mL) was added K₂CO₃ (1382.00 mg, 10.000 mmol, 5.00 equivalent). The resulting mixture was stirred for 1 h at 130° C. under nitrogen atmosphere. The reaction mixture was diluted with EA (100 mL).

The resulting mixture was washed with 3×100 mL of water and 1×100 mL saturated brine. The organic layer was dried over Na₂SO₄, filtered and evaporated to afford crude product. The residue was purified by silica gel column chromatography, elution gradient 0 to 10% MeOH in DCM. Pure fractions were evaporated to dryness to afford 4-bromo-2-methyl-6-(morpholin-4-yl)-2,7-naphthyridin-1-one (541 mg, 83.44%) as a light yellow solid. LCMS (ESI) m/z: [M+H]⁺=324.

35

40

45

50

55

60

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

65

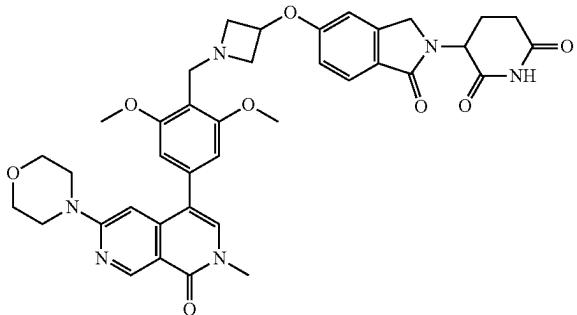
65

65

65

615

Step 3: Preparation of 3-[5-[[1-([2, 6-dimethoxy-4-[2-methyl-6-(morpholin-4-yl)-1-oxo-2, 7-naphthyridin-4-yl]phenyl)methyl]azetidin-3-yl]oxy]-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione

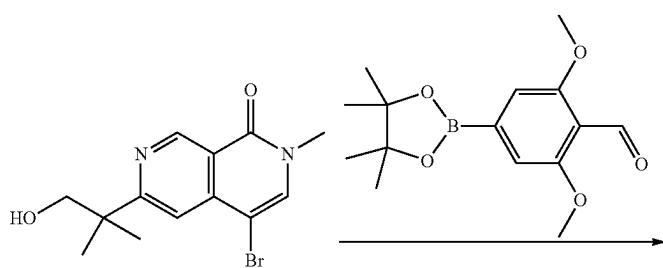
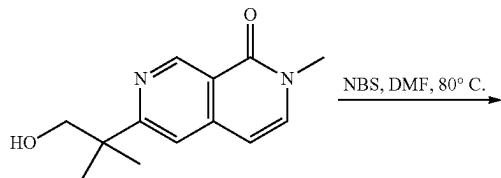
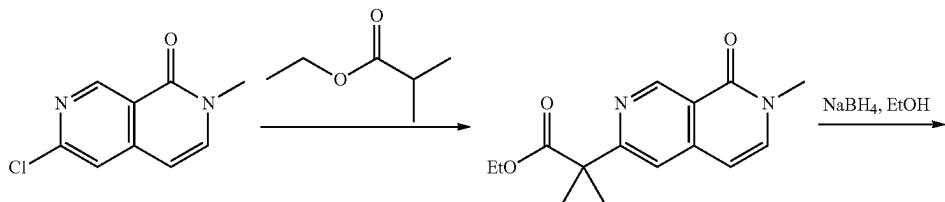


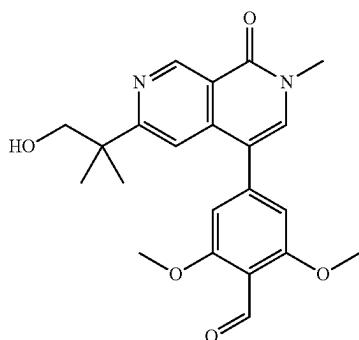
To a stirred solution of 3-[5-(azetidin-3-yloxy)-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione (100.00 mg, 0.317 mmol, 1.00 equivalent) and 2,6-dimethoxy-4-[2-methyl-6-(morpholin-4-yl)-1-oxo-2,7-naphthyridin-4-yl]benzaldehyde (129.85 mg, 0.317 mmol, 1.00 equivalent) in DMF was added NaBH(OAc)₃ (134.43 mg, 0.634 mmol, 2.00 equivalent) dropwise at room temperature under air atmosphere for

616

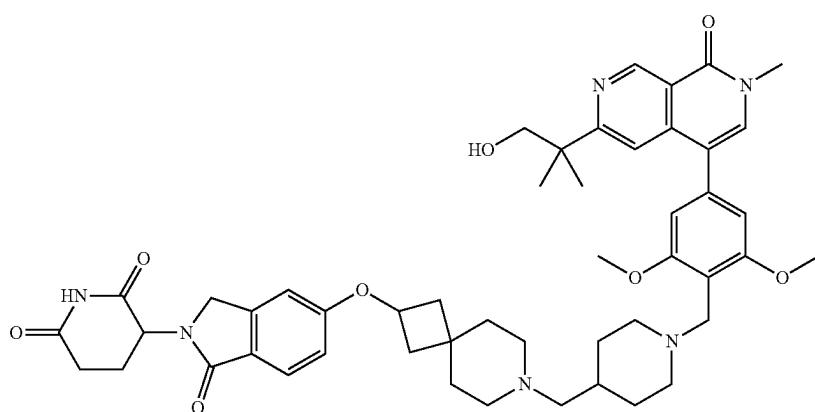
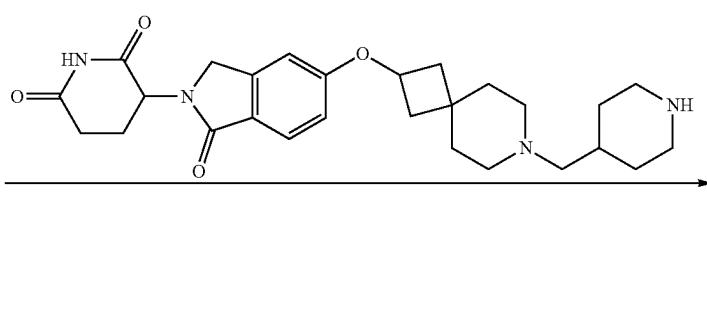
2 hours. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 0% to 100% gradient in 45 min; detector, UV 254 nm. The crude product was purified by Prep-HPLC with the following conditions (Column: Xselect CSH F-phenyl OBD Column, 19*250 mm, 5 μ m; Mobile Phase A: Water (0.05% FA); Mobile Phase B: ACN; Flow rate: 30 mL/min; Gradient: 13 B to 33 B in 14 min; 254/220 nm; RT1: 12.85 min) to afford 3-[5-[[1-([2,6-dimethoxy-4-[2-methyl-6-(morpholin-4-yl)-1-oxo-2,7-naphthyridin-4-yl]phenyl)methyl]azetidin-3-yl]oxy]-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione (100 mg, 44.15%) as a yellow solid. ¹H NMR (400 MHz, Methanol-d4) δ 9.18 (s, 1H), 7.80 (t, J=6.7 Hz, 1H), 7.49 (s, 1H), 7.09 (t, J=7.3 Hz, 2H), 6.88 (s, 2H), 6.63 (d, J=4.9 Hz, 1H), 5.40-5.20 (m, 1H), 5.15 (dd, J=13.3, 5.2 Hz, 1H), 4.77 (ddd, J=24.3, 12.5, 6.8 Hz, 2H), 4.65 (d, J=22.0 Hz, 2H), 4.48 (d, J=6.3 Hz, 2H), 4.44-4.28 (m, 2H), 3.96 (d, J=23.6 Hz, 6H), 3.78 (t, J=4.8 Hz, 4H), 3.61 (s, 3H), 3.56 (d, J=4.7 Hz, 4H), 2.93 (ddd, J=18.5, 13.5, 5.3 Hz, 1H), 2.80 (ddd, J=17.5, 4.6, 2.3 Hz, 1H), 2.49 (qd, J=13.2, 4.7 Hz, 1H), 2.23-2.14 (m, 1H). LCMS (ESI) m/z: [M+H]⁺=709.

Example 66—Preparation of 3-[5-[(7-[[1-([4-[6-(1-hydroxy-2-methylpropan-2-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl)methyl]piperidin-4-yl)methyl]-7-azaspiro[3.5]nonan-2-yl]oxy]-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione

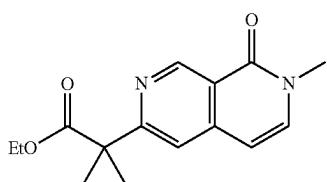


617

-continued

618

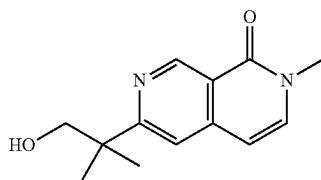
Step 1: Preparation of ethyl 2-methyl-2-(7-methyl-8-oxo-2,7-naphthyridin-3-yl)propanoate



The resulting mixture was extracted with CH_2Cl_2 (100 mL).
 45 The combined organic layers were washed with water (100 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The reaction mixture was purified by reverse phase flash with the following conditions (Mobile Phase A: Water (0.3% FA);
 50 Mobile Phase B: ACN; Flow rate: 80 mL/min; Gradient: 5% B to 50% B in 30 min) to afford ethyl 2-methyl-2-(7-methyl-8-oxo-2,7-naphthyridin-3-yl)propanoate (320 mg, 11.35%) as a yellow solid. LCMS (ESI) m/z: $[\text{M}+\text{H}]^+=275$.

55 Step 2: Preparation of 6-(1-hydroxy-2-methylpropen-2-yl)-2-methyl-2,7-naphthyridin-1-one

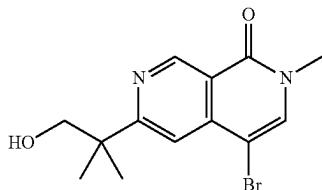
To a stirred mixture of LDA (825.63 mg, 7.707 mmol, 1.5 equivalent) in THF (20 mL) was added ethyl isobutyrate (895.28 mg, 7.707 mmol, 1.5 equivalent) dropwise at -78° C. under nitrogen atmosphere. The resulting mixture was stirred for 30 min at -78° C. under nitrogen atmosphere. To the above mixture was added 6-chloro-2-methyl-2,7-naphthyridin-1-one (1.00 g, 5.138 mmol, 1.00 equivalent) in THF (1 mL) dropwise over 2 min at -78° C. The resulting mixture
 60 was stirred for additional 2 hours at room temperature. The reaction was quenched with aqueous NH_4Cl (5 mL) at 0° C.
 65



619

To a stirred mixture of ethyl 2-methyl-2-(7-methyl-8-oxo-2,7-naphthyridin-3-yl)propanoate (240.00 mg, 0.875 mmol, 1.00 equivalent) in EtOH (20.00 mL) was added LiBH₄ (209.64 mg, 9.624 mmol, 11.00 equivalent) in portions at 0° C. under nitrogen atmosphere. The resulting mixture was stirred for 16 h at room temperature under nitrogen atmosphere. The reaction was quenched with Water at room temperature. The resulting mixture was extracted with CH₂Cl₂ (20 mL). The combined organic layers were washed with water (2×20 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH₂Cl₂/MeOH (20:1) to afford 6-(1-hydroxy-2-methylpropan-2-yl)-2-methyl-2,7-naphthyridin-1-one (120 mg, 53.14%) as a white solid. LCMS (ESI) m/z: [M+H]⁺=233.

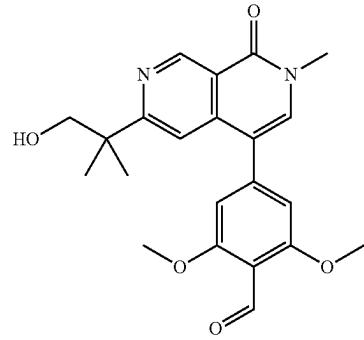
Step 3: Preparation of 4-bromo-6-(1-hydroxy-2-methylpropan-2-yl)-2-methyl-2,7-naphthyridin-1-one



To a stirred mixture of 6-(1-hydroxy-2-methylpropan-2-yl)-2-methyl-2,7-naphthyridin-1-one (90.00 mg, 0.387 mmol, 1.00 equivalent) in DMF (1.00 mL) was added NBS (82.75 mg, 0.465 mmol, 1.2 equivalent) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 hours at 80° C. under nitrogen atmosphere. The residue was purified by silica gel column chromatography, eluted with CH₂Cl₂/MeOH (17:1) to afford 4-bromo-6-(1-hydroxy-2-methylpropan-2-yl)-2-methyl-2,7-naphthyridin-1-one (80 mg, 66.35%) as a yellow oil. LCMS (ESI) m/z: [M+H]⁺=311.

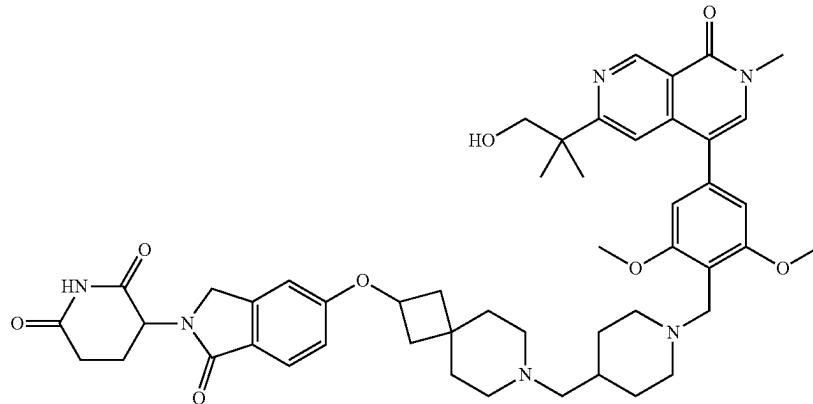
620

Step 4: Preparation of 4-[6-(1-hydroxy-2-methylpropan-2-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde



To a solution of 4-bromo-6-(1-hydroxy-2-methylpropan-2-yl)-2-methyl-2,7-naphthyridin-1-one (50.00 mg, 0.161 mmol, 1.00 equivalent) and 2,6-dimethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (70.41 mg, 0.241 mmol, 1.50 equivalent) in dioxane (2.00 mL) and water (0.40 mL) were added K₃PO₄ (102.32 mg, 0.482 mmol, 3.00 equivalent) and Pd(PPh₃)₂Cl₂ (11.28 mg, 0.016 mmol, 0.10 equivalent). After stirring for 16 hours at 80° C. under a nitrogen atmosphere, the resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH₂Cl₂/MeOH (17:1) to afford 4-[6-(1-hydroxy-2-methylpropan-2-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (38 mg, 53.69%) as a yellow oil. LCMS (ESI) m/z: [M+H]⁺=397.

Step 5: Preparation of 3-[5-[(7-[[1-([4-(1-hydroxy-2-methylpropan-2-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl)methyl]piperidin-4-yl)methyl]-7-azaspiro[3.5]nonan-2-yl]oxy]-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione



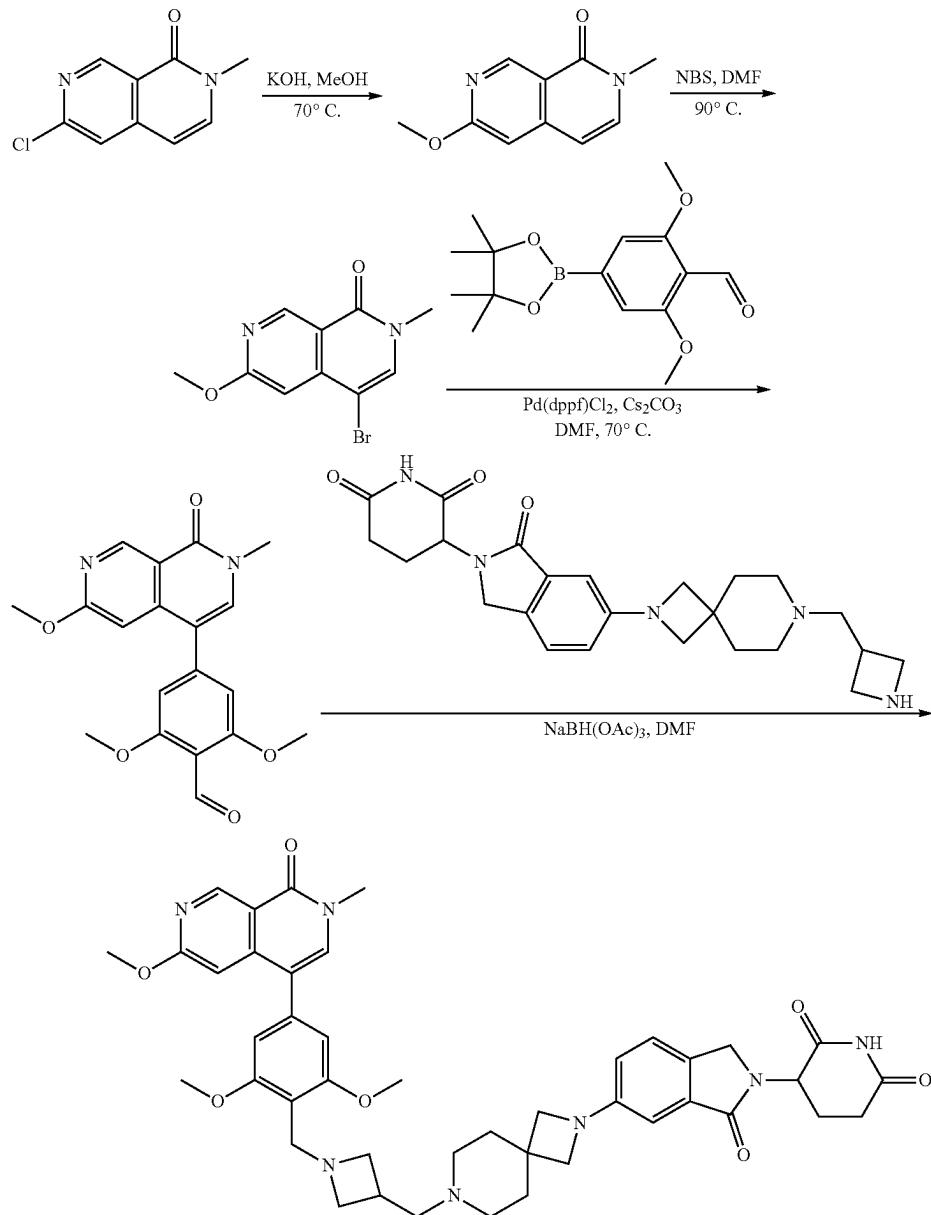
621

To a stirred mixture of 4-[6-(1-hydroxy-2-methylpropan-2-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (80.00 mg, 0.202 mmol, 1.00 equivalent) and 3-(1-oxo-5-[[7-(piperidin-4-ylmethyl)-7-azaspido[3.5]nonan-2-yl]oxy]-3H-isoindol-2-yl)piperidine-2,6-dione (96.98 mg, 0.202 mmol, 1.00 equivalent) in DMF (1.00 mL) was added NaBH(OAc)₃ (85.54 mg, 0.404 mmol, 2.00 equivalent) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 hours at room temperature under nitrogen atmosphere. The crude product was purified by Prep-HPLC with the following conditions (Column: Xselect CSH F-Phenyl OBD Column 19*150 mm 5 μ m; Mobile Phase A: Water (0.05% TFA); Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 12 B to 24 B in 12 min; 254/220 nm; RT1: 9.07 min) to afford 3-[5-[(1-[[4-[6-(1-hydroxy-2-methylpropan-2-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)piperi-

622

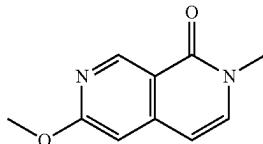
din-4-yl]methyl]-7-azaspido[3.5]nonan-2-yl]oxy]-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione (73.3 mg, 41.60%) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ 9.42 (d, J=0.7 Hz, 1H), 7.89 (d, J=2.9 Hz, 1H), 7.70-7.61 (m, 2H), 7.06 (d, J=2.2 Hz, 1H), 6.98 (dd, J=8.4, 2.3 Hz, 1H), 6.91 (s, 2H), 5.05 (dd, J=13.2, 5.1 Hz, 1H), 4.87 (q, J=6.5 Hz, 1H), 4.43-4.32 (m, 2H), 4.26 (d, J=13.6 Hz, 2H), 3.91 (s, 6H), 3.55 (s, 3H), 3.45 (d, J=12.0 Hz, 2H), 3.37 (s, 4H), 3.23-3.14 (m, 1H), 3.10-2.83 (m, 6H), 2.61 (d, J=16.6 Hz, 2H), 2.45-2.33 (m, 2H), 2.08 (d, J=11.8 Hz, 1H), 1.87 (d, J=28.7 Hz, 9H), 1.55-1.41 (m, 2H), 1.27 (s, 6H). LCMS (ESI) m/z: [M+H]⁺=861.

Example 67—Preparation of 3-(6-[[1][2,6-dimethoxy-4-(6-methoxy-2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]azetidin-3-yl)methyl]-2,7-diazaspido[3.5]nonan-2-yl]-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione



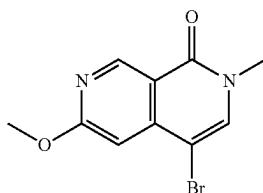
623

Step 1: Preparation of
6-methoxy-2-methyl-2,7-naphthyridin-1-one



A mixture of 6-chloro-2-methyl-2,7-naphthyridin-1-one (1.00 g, 5.138 mmol, 1.00 equiv) and KOH (0.43 g, 7.707 mmol, 1.50 equiv) in MeOH (10.00 mL) was stirred for 4 hours at 70° C. under nitrogen atmosphere. The resulting mixture was diluted with 100 mL of water. The resulting mixture was extracted with EtOAc (3×100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH₂Cl₂/MeOH (10:1) to afford 6-methoxy-2-methyl-2,7-naphthyridin-1-one (800 mg, 81.86%) as a white solid. LCMS (ESI) m/z: [M+H]⁺=191.

Step 2: Preparation of
4-bromo-6-methoxy-2-methyl-2,7-naphthyridin-1-one



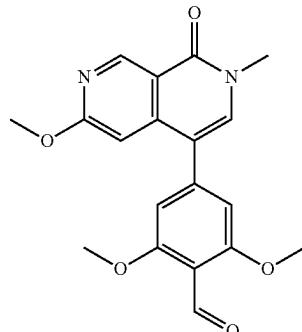
A mixture of 6-methoxy-2-methyl-2,7-naphthyridin-1-one (800.00 mg, 4.206 mmol, 1.00 equiv) and NBS (898.33 mg, 5.047 mmol, 1.20 equiv) in DMF (10.00 mL) was stirred for 2 hours at 90° C. under nitrogen atmosphere. The resulting mixture was diluted with 100 mL of water. The resulting mixture was extracted with EtOAc (3×100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄. After filtration, the

filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH₂Cl₂/MeOH (10:1) to afford 4-bromo-6-methoxy-2-methyl-2,7-naphthyridin-1-one (600 mg, 53.01%) as a white solid. LCMS (ESI) m/z: [M+H]⁺=269.

624

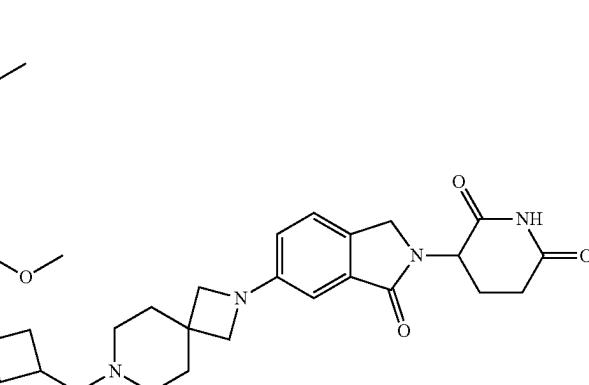
Step 3: Preparation of tert-butyl 4-[3-(2,6-dioxopiperidin-3-yl)-2-methyl-4-oxoquinazolin-6-yl]piperazine-1-carboxylate

10



A mixture of 4-bromo-6-methoxy-2-methyl-2,7-naphthyridin-1-one (600.00 mg, 2.230 mmol, 1.00 equiv), 4-boronyl-2,6-dimethoxybenzaldehyde (396.86 mg, 2.230 mmol, 1.00 equiv), Pd(dppf)Cl₂ (163.15 mg, 0.223 mmol, 0.10 equiv) and Cs₂CO₃ (1452.94 mg, 4.459 mmol, 2.00 equiv) in DMF (10.00 mL) was stirred for 4 hours at 70° C. under nitrogen atmosphere. The resulting mixture was diluted with 100 mL of water, the resulting mixture was extracted with EtOAc (2×100 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH₂Cl₂/MeOH (10:1) to afford 2,6-dimethoxy-4-(6-methoxy-2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (100 mg, 12.66%) as a yellow solid. LCMS (ESI) m/z: [M+H]⁺=355.

Step 4: Preparation of 3-(6-[7-[(1-[[2,6-dimethoxy-4-(6-methoxy-2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]azetidin-3-yl)methyl]-2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isindol-2-yl)piperidine-2,6-dione



625

A mixture of 2,6-dimethoxy-4-(6-methoxy-2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (80.00 mg, 0.226 mmol, 1.00 equiv), 3-[6-[7-(azetidin-3-ylmethyl)-2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isindol-2-yl]piperidine-2,6-dione (98.78 mg, 0.226 mmol, 1.00 equiv) and NaBH₄ (AcO)₃ (95.69 mg, 0.452 mmol, 2.00 equiv) in DMF (2.00 mL) was stirred for 3 hours at room temperature. Without any additional work-up, the mixture was purified by Prep-HPLC with the following conditions (Column: XSelect CSH Prep C18 OBD Column 5 um, 19*150 mm; Mobile Phase A: Water (0.05% FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 13 B to 20 B in 15 min; 254/220 nm; RT1:13.18-14 min) to afford 3-(6-[7-[(1[[2,6-dimethoxy-4-(6-methoxy-2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]azetidin-3-yl)methyl]-2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isindol-2-yl)piperidine-2,6-dione (11.8 mg, 6.74%) as a yellow solid. ¹H NMR (300 MHz, Methanol-d4) δ 9.25 (s, 1H), 7.57 (s, 1H), 7.41 (d, J=8.2 Hz, 1H), 6.96-6.72 (m, 5H), 5.14 (dd, J=13.2, 5.1 Hz, 1H), 4.55 (s, 2H), 4.49-4.30 (m, 4H), 4.27-4.07 (m, 2H), 3.99 (d, J=9.8 Hz, 9H), 3.78 (s, 4H), 3.64 (s, 3H), 3.59-3.48 (m, 5H), 3.27-3.01 (m, 2H), 3.00-2.69 (m, 2H), 2.50 (dd, J=13.1, 4.8 Hz, 1H), 2.35-2.00 (m, 5H). LCMS (ESI) m/z: [M+H]⁺= 776.

Example 68—BRD9 Bromodomain TR-FRET Competition Binding Assay

This example demonstrates the ability of the compounds of the disclosure to biochemically inhibit BRD9 bromodomain in a competition binding assay.

Procedure: His-Flag-BRD9 (P133-K239; Swiss Prot Q9H8M2; SEQ ID NO:1 mgsshhhhhenlyfq/gdykddddkgsvlelfqg/PAENESTPIQQLLEHFLRQLQRKDPHGFFAF PVTDAIAPGYSMII KHPMDFGTMKDKIVANEYKS VTEFKADFJKLMCDNAMTYNPDTVYYKLAKKIL-HAGFKMMMSK) was cloned, expressed, purified, and then treated with TEV protease. Cleaved His tag was removed by purification. The binding of a biotinylated small molecule ligand of BRD9 was assessed via the LANCE® TR-FRET platform (PerkinElmer), and the compounds were assayed for inhibitory activity against this interaction.

Results: A mixture of biotinylated-ligand and SureLight™ Allophycocyanin-Streptavidin (APC-SA, PerkinElmer AD0201) in 50 mM HEPES (pH 7.4), 50 mM NaCl, 1 mM TCEP (pH 7), 0.01% (v/v) Tween-20, 0.01% (w/v) bovine serum albumin was added to a white 384-well PerkinElmer Proxiplate Plus plate. DMSO or 3-fold serially diluted compounds were then added to the Proxiplate followed by addition of Flag-BRD9. After a 10-minute incubation at room temperature, Eu-W1024 anti-FLAG (PerkinElmer, AD0273) was added. The final reaction mixture that contained 3.75 nM biotinylated ligand, 3 nM Flag-BRD9, 7.5 nM SureLight™ Allophycocyanin-Streptavidin, and 0.2 nM Eu-W1024 anti-FLAG was incubated at room temperature for 90 minutes.

The plates were then read on a PerkinElmer Envision plate reader to determine the ratio of emission at 665 nm over 615 nm. Data was normalized to a DMSO control (100%) and a no protein control (0%) and then fit to a four parameter, non-linear curve fit to calculate an IC₅₀ (μ M) as shown in Table 5. As shown by the results in Table 5, a number of compounds of the present disclosure exhibit an IC₅₀ value of <1 μ M for BRD9 binding, indicating their affinity for targeting BRD9.

626

TABLE 5

Compound No.	Bromodomain TR-FRET Binding	
	Bromodomain	BRD9 IC ₅₀ (nM)
B1	++++	
B2	++++	
B3	+++	
B4	+++	
B5	+++	
B6	+++	
D1	++++	
D2	++++	
D3	++++	
D4	++++	
D5	+++	
D6	+++	
D7	++++	
D8	+++	
D9	++	
D10	+++	
D11	+++	
D12	++++	
D13	++	
D14	+++	
D15	++++	
D16	++++	
D17	+++	
D18	++++	
D19	++++	
D20	++++	
D21	++++	
D22	+++	
D23	++++	
D24	+++	
D25	+	
D26	+++	
D27	++++	
D28	++++	
D29	++++	
D30	++++	
D31	+++	

“+” indicates inhibitory effect of \geq 1000 nM;

“++” indicates inhibitory effect of \geq 100 nM;

“+++” indicates inhibitory effect of \geq 10 nM;

“++++” indicates inhibitory effect of < 10 nM;

“NT” indicates not tested

Example 69—SYO1 BRD9 NanoLuc Degradation Assay

This example demonstrates the ability of the compounds of the disclosure to degrade a Nanoluciferase-BRD9 fusion protein in a cell-based degradation assay.

Procedure: A stable SYO-1 cell line expressing 3xFLAG-NLuc-BRD9 was generated. On day 0 cells were seeded in 30 μ L media into each well of 384-well cell culture plates. The seeding density was 8000 cells/well. On day 1, cells were treated with 30 nL DMSO or 30 nL of 3-fold serially DMSO-diluted compounds (10 points in duplicates with 1 μ M as final top dose). Subsequently plates were incubated for 6 hours in a standard tissue culture incubator and equilibrated at room temperature for 15 minutes. Nanoluciferase activity was measured by adding 15 μ L of freshly prepared Nano-Glo Luciferase Assay Reagent (Promega N1130), shaking the plates for 10 minutes and reading the bioluminescence using an EnVision reader.

Results: The Inhibition % was calculated using the following formula: % Inhibition=100×(Lum_{HC}-Lum_{sample})/(Lum_{HC}-Lum_{LC}). DMSO treated cells are employed as High Control (HC) and 1 μ M of a known BRD9 degrader standard treated cells are employed as Low Control (LC). The data was fit to a four parameter, non-linear curve fit to

627

calculate IC₅₀ (μ M) values as shown in Table 6A, Table 6B, and Table 6C. As shown by the results in Table 6A, Table 6B, and Table 6C, a number of compounds of the present disclosure exhibit an IC₅₀ value of <1 μ M for the degradation of BRD9, indicating their use as compounds for reducing the levels and/or activity of BRD9 and their potential for treating BRD9-related disorders.

TABLE 6A

SYO1 BRD9-NanoLuc Degradation		10
Compound No.	SYO1 BRD9-NanoLuc degradation IC ₅₀ (nM)	
D1	++++	
D2	++	
D3	+++	
D4	++	
D5	++	
D6	+++	
D7	++++	
D8	+++	15
D9	+	
D10	+++	
D11	++	
D12	+++	
D13	+	
D14	++	
D15	++++	
D16	++++	
D17	++++	
D18	++++	
D19	++++	
D20	++++	20
D21	++++	
D22	++	
D23	++++	
D24	+++	
D25	++	
D26	+++	
D27	++++	
D28	++++	
D29	++++	
D30	++++	
D31	++	

"+" indicates inhibitory effect of \geq 1000 nM;

"++" indicates inhibitory effect of \geq 100 nM;

"+++” indicates inhibitory effect of \geq 10 nM;

"++++" indicates inhibitory effect of < 10 nM;

"NT" indicates not tested

TABLE 6B

SYO1 BRD9-NanoLuc Degradation		40
Compound No.	SYO1 BRD9-NanoLuc degradation IC ₅₀ (nM)	
D32	++++	
D33	++++	
D34	++++	
D35	++++	
D36	++++	
D37	++++	
D38	++++	
D39	++++	
D40	++++	
D41	++++	
D42	++++	45
D43	+	
D44	+++	
D45	++	
D46	+++	
D47	+++	
D48	++++	
D49	++++	50
D50	++++	

628

TABLE 6B-continued

SYO1 BRD9-NanoLuc Degradation		5
Compound No.	SYO1 BRD9-NanoLuc degradation IC ₅₀ (nM)	
D51	++++	
D52	++++	
D53	++++	
D54	++++	
D55	++++	
D56	++++	
D57	++++	
D58	++++	
D59	++++	
D60	++++	
D61	++++	
D62	++++	
D63	++++	
D64	++	
D65	++++	
D66	++++	
D67	++++	
D68	++++	
D69	++++	
D70	++++	
D71	++++	
D72	++++	
D73	++++	
D74	+++	
D75	++++	
D76	++++	
D77	++++	
D78	++++	
D79	++++	
D80	++++	30
D81	++++	
D82	++++	
D83	++++	
D84	+++	
D85	++++	
D86	++++	
D87	++++	
D88	+++	
D89	++++	
D90	++++	
D91	++++	
D92	++++	
D93	++++	40
D94	+++	
D95	++++	
D96	++++	
D97	++++	
D98	++++	
D99	++++	
D100	++++	
D101	++++	
D102	++++	
D103	++++	
D104	++++	
D105	++++	
D106	++++	
D107	++++	
D108	++++	
D109	++++	
D110	++++	
D111	++++	
D112	++++	
D113	++++	
D114	++++	
D115	++++	
D116	++++	
D117	+++	
D118	++++	60
D119	+++	
D120	++++	
D121	++++	
D122	++++	
D123	++++	
D124	++++	65
D125	++++	

US 12,391,686 B2

629

TABLE 6B-continued

SYO1 BRD9-NanoLuc Degradation	
Compound No.	SYO1 BRD9-NanoLuc degradation IC ₅₀ (nM)
D126	++++
D127	++++
D128	++++
D129	++++
D130	++++
D131	++++
D132	++++
D133	++++
D134	++++
D135	++++
D136	++++
D137	++++
D138	++++
D139	++++
D140	++++
D141	++++
D142	++++
D143	++++
D144	++++
D145	++++
D146	++++
D147	++++
D148	++++
D149	++++
D150	++++
D151	++++
D152	++++
D153	++++
D154	++++
D155	++++
D156	++++
D157	++++
D158	++++
D159	++++
D160	++++
D161	++++
D162	++++
D163	++++
D164	++++
D165	+++
D166	++++
D167	++++
D168	++++
D169	+++
D170	++++
D171	++++
D172	+++
D173	++++
D174	++++
D175	+
D176	++++
D177	++++
D178	++++
D179	+
D180	++++
D181	+
D182	++++
D183	+
D184	++++

“+” indicates inhibitory effect of ≥ 1000 nM;

“++” indicates inhibitory effect of ≥ 100 nM;

“+++” indicates inhibitory effect of ≥ 10 nM;

“++++” indicates inhibitory effect of < 10 nM;

“NT” indicates not tested

630

TABLE 6C

SYO1 BRD9-NanoLuc Degradation	
Compound No.	SYO1 BRD9-NanoLuc degradation IC ₅₀ (nM)
D185	++++
D186	++++
D187	++++
D188	++++
D189	++++
D190	++++
D191	++
D192	++++
D193	++++
D194	++++
D195	++++
D196	++++
D197	++++
D198	++++
D199	++++
D200	++++
D201	++++
D202	++++
D203	++++
D204	++++
D205	+++
D206	++++
D207	++++
D208	++++
D209	++++
D210	++++
D211	++++
D212	++++
D213	++++
D214	++++
D215	++++
D216	++++
D217	++++
D218	++++
D219	++++
D220	++++
D221	++++
D222	++++
D223	++++
D224	++++
D225	++++
D226	++++
D227	++++
D228	++++
D229	++++
D230	++++
D231	++++
D232	++++
D233	++++
D234	++++
D235	++++
D236	++++
D237	++++
D238	++++
D239	++++
D240	++++
D241	++++
D242	++++
D243	++++
D244	++++
D245	++++
D246	++++
D247	++++
D248	++++
D249	++
D250	++
D251	+
D252	+++
D253	+
D254	++++
D255	++++
D256	++++
D257	++++
D258	++++
D259	+

65

631

TABLE 6C-continued

Compound No.	SYO1 BRD9-NanoLuc degradation IC ₅₀ (nM)
D260	++++
D261	+
D262	++++
D263	++++
D264	++++
D265	++++
D266	++
D267	++++
D268	++++
D269	++++
D270	+++
D271	+++
D272	++++
D273	++++
D274	++++
D275	++++
D276	++++
D277	++++
D278	++++
D279	++++
D280	++++
D281	++++
D282	++
D283	++
D284	++++
D285	+
D286	++++
D287	++++
D288	++++
D289	++++
D290	++++
D291	++++
D292	++
D293	++++
D294	++++
D295	++++
D296	++++
D297	++++
D298	++++
D299	++++
D300	++++
D301	++++
D302	++++
D303	++++
D304	++++

5

10

15

20

TABLE 6C-continued

Compound No.	SYO1 BRD9-NanoLuc degradation IC ₅₀ (nM)
D305	++++
D306	++++
D307	++++
D308	++++
D309	++++
D310	++++
D311	++++
D312	++++
D313	++++
D314	++++
D315	++++
D316	++++

“+” indicates inhibitory effect of ≥ 1000 nM;

“++” indicates inhibitory effect of ≥ 100 nM;

“+++” indicates inhibitory effect of ≥ 10 nM;

“++++” indicates inhibitory effect of < 10 nM;

“NT” indicates not tested

Other Embodiments

25 All publications, patents, and patent applications mentioned in this specification are incorporated herein by reference in their entirety to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference in its entirety. Where a term in the present application is found to be defined differently in a document incorporated herein by reference, the definition provided herein is to serve as the definition for the term.

While the invention has been described in connection with specific embodiments thereof, it will be understood that 35 invention is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure that come within known or customary practice 40 within the art to which the invention pertains and may be applied to the essential features hereinbefore set forth, and follows in the scope of the claims.

Other embodiments are in the claims.

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 673

<210> SEQ ID NO 1

<211> LENGTH: 141

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 1

Met	Gly	Ser	Ser	His	His	His	His	Glu	Asn	Leu	Tyr	Phe	Gln
1		5		10				15					

Gly	Asp	Tyr	Lys	Asp	Asp	Asp	Asp	Lys	Gly	Ser	Leu	Glu	Val	Leu	Phe
20			25					30							

Gln	Gly	Pro	Ala	Glu	Asn	Glu	Ser	Thr	Pro	Ile	Gln	Gln	Leu	Leu	Glu
35			40					45							

His	Phe	Leu	Arg	Gln	Leu	Gln	Arg	Lys	Asp	Pro	His	Gly	Phe	Phe	Ala
50			55					60							

US 12,391,686 B2

633**634**

-continued

Phe	Pro	Val	Thr	Asp	Ala	Ile	Ala	Pro	Gly	Tyr	Ser	Met	Ile	Ile	Lys
65															80
					70					75					
His	Pro	Met	Asp	Phe	Gly	Thr	Met	Lys	Asp	Lys	Ile	Val	Ala	Asn	Glu
															95
						85			90						
Tyr	Lys	Ser	Val	Thr	Glu	Phe	Lys	Ala	Asp	Phe	Lys	Leu	Met	Cys	Asp
															110
								100							
Asn	Ala	Met	Thr	Tyr	Asn	Arg	Pro	Asp	Thr	Val	Tyr	Tyr	Lys	Leu	Ala
															125
							115			120					
Lys	Lys	Ile	Leu	His	Ala	Gly	Phe	Lys	Met	Met	Ser	Lys			
															140
130					135										

<210> SEQ ID NO 2

<400> SEQUENCE: 2

000

<210> SEQ ID NO 3

<400> SEQUENCE: 3

000

<210> SEQ ID NO 4

<400> SEQUENCE: 4

000

<210> SEQ ID NO 5

<400> SEQUENCE: 5

000

<210> SEQ ID NO 6

<400> SEQUENCE: 6

000

<210> SEQ ID NO 7

<400> SEQUENCE: 7

000

<210> SEQ ID NO 8

<400> SEQUENCE: 8

000

<210> SEQ ID NO 9

<400> SEQUENCE: 9

000

<210> SEQ ID NO 10

<400> SEQUENCE: 10

000

-continued

<210> SEQ ID NO 11

<400> SEQUENCE: 11

000

<210> SEQ ID NO 12

<400> SEQUENCE: 12

000

<210> SEQ ID NO 13

<400> SEQUENCE: 13

000

<210> SEQ ID NO 14

<400> SEQUENCE: 14

000

<210> SEQ ID NO 15

<400> SEQUENCE: 15

000

<210> SEQ ID NO 16

<400> SEQUENCE: 16

000

<210> SEQ ID NO 17

<400> SEQUENCE: 17

000

<210> SEQ ID NO 18

<400> SEQUENCE: 18

000

<210> SEQ ID NO 19

<400> SEQUENCE: 19

000

<210> SEQ ID NO 20

<400> SEQUENCE: 20

000

<210> SEQ ID NO 21

<400> SEQUENCE: 21

000

<210> SEQ ID NO 22

US 12,391,686 B2

637**638**-continued

<400> SEQUENCE: 22

000

<210> SEQ ID NO 23

<400> SEQUENCE: 23

000

<210> SEQ ID NO 24

<400> SEQUENCE: 24

000

<210> SEQ ID NO 25

<400> SEQUENCE: 25

000

<210> SEQ ID NO 26

<400> SEQUENCE: 26

000

<210> SEQ ID NO 27

<400> SEQUENCE: 27

000

<210> SEQ ID NO 28

<400> SEQUENCE: 28

000

<210> SEQ ID NO 29

<400> SEQUENCE: 29

000

<210> SEQ ID NO 30

<400> SEQUENCE: 30

000

<210> SEQ ID NO 31

<400> SEQUENCE: 31

000

<210> SEQ ID NO 32

<400> SEQUENCE: 32

000

<210> SEQ ID NO 33

<400> SEQUENCE: 33

US 12,391,686 B2

639

640

-continued

000

<210> SEQ ID NO 34

<400> SEQUENCE: 34

000

<210> SEQ ID NO 35

<400> SEQUENCE: 35

000

<210> SEQ ID NO 36

<400> SEQUENCE: 36

000

<210> SEQ ID NO 37

<400> SEQUENCE: 37

000

<210> SEQ ID NO 38

<400> SEQUENCE: 38

000

<210> SEQ ID NO 39

<400> SEQUENCE: 39

000

<210> SEQ ID NO 40

<400> SEQUENCE: 40

000

<210> SEQ ID NO 41

<400> SEQUENCE: 41

000

<210> SEQ ID NO 42

<400> SEQUENCE: 42

000

<210> SEQ ID NO 43

<400> SEQUENCE: 43

000

<210> SEQ ID NO 44

<400> SEQUENCE: 44

000

-continued

<210> SEQ ID NO 45

<400> SEQUENCE: 45

000

<210> SEQ ID NO 46

<400> SEQUENCE: 46

000

<210> SEQ ID NO 47

<400> SEQUENCE: 47

000

<210> SEQ ID NO 48

<400> SEQUENCE: 48

000

<210> SEQ ID NO 49

<400> SEQUENCE: 49

000

<210> SEQ ID NO 50

<400> SEQUENCE: 50

000

<210> SEQ ID NO 51

<400> SEQUENCE: 51

000

<210> SEQ ID NO 52

<400> SEQUENCE: 52

000

<210> SEQ ID NO 53

<400> SEQUENCE: 53

000

<210> SEQ ID NO 54

<400> SEQUENCE: 54

000

<210> SEQ ID NO 55

<400> SEQUENCE: 55

000

<210> SEQ ID NO 56

-continued

<400> SEQUENCE: 56

000

<210> SEQ ID NO 57

<400> SEQUENCE: 57

000

<210> SEQ ID NO 58

<400> SEQUENCE: 58

000

<210> SEQ ID NO 59

<400> SEQUENCE: 59

000

<210> SEQ ID NO 60

<400> SEQUENCE: 60

000

<210> SEQ ID NO 61

<400> SEQUENCE: 61

000

<210> SEQ ID NO 62

<400> SEQUENCE: 62

000

<210> SEQ ID NO 63

<400> SEQUENCE: 63

000

<210> SEQ ID NO 64

<400> SEQUENCE: 64

000

<210> SEQ ID NO 65

<400> SEQUENCE: 65

000

<210> SEQ ID NO 66

<400> SEQUENCE: 66

000

<210> SEQ ID NO 67

<400> SEQUENCE: 67

US 12,391,686 B2

645

-continued

000

<210> SEQ ID NO 68

<400> SEQUENCE: 68

000

<210> SEQ ID NO 69

<400> SEQUENCE: 69

000

<210> SEQ ID NO 70

<400> SEQUENCE: 70

000

<210> SEQ ID NO 71

<400> SEQUENCE: 71

000

<210> SEQ ID NO 72

<400> SEQUENCE: 72

000

<210> SEQ ID NO 73

<400> SEQUENCE: 73

000

<210> SEQ ID NO 74

<400> SEQUENCE: 74

000

<210> SEQ ID NO 75

<400> SEQUENCE: 75

000

<210> SEQ ID NO 76

<400> SEQUENCE: 76

000

<210> SEQ ID NO 77

<400> SEQUENCE: 77

000

<210> SEQ ID NO 78

<400> SEQUENCE: 78

000

646

-continued

<210> SEQ ID NO 79

<400> SEQUENCE: 79

000

<210> SEQ ID NO 80

<400> SEQUENCE: 80

000

<210> SEQ ID NO 81

<400> SEQUENCE: 81

000

<210> SEQ ID NO 82

<400> SEQUENCE: 82

000

<210> SEQ ID NO 83

<400> SEQUENCE: 83

000

<210> SEQ ID NO 84

<400> SEQUENCE: 84

000

<210> SEQ ID NO 85

<400> SEQUENCE: 85

000

<210> SEQ ID NO 86

<400> SEQUENCE: 86

000

<210> SEQ ID NO 87

<400> SEQUENCE: 87

000

<210> SEQ ID NO 88

<400> SEQUENCE: 88

000

<210> SEQ ID NO 89

<400> SEQUENCE: 89

000

US 12,391,686 B2

649

-continued

650

<210> SEQ ID NO 90

<400> SEQUENCE: 90

000

<210> SEQ ID NO 91

<400> SEQUENCE: 91

000

<210> SEQ ID NO 92

<400> SEQUENCE: 92

000

<210> SEQ ID NO 93

<400> SEQUENCE: 93

000

<210> SEQ ID NO 94

<400> SEQUENCE: 94

000

<210> SEQ ID NO 95

<400> SEQUENCE: 95

000

<210> SEQ ID NO 96

<400> SEQUENCE: 96

000

<210> SEQ ID NO 97

<400> SEQUENCE: 97

000

<210> SEQ ID NO 98

<400> SEQUENCE: 98

000

<210> SEQ ID NO 99

<400> SEQUENCE: 99

000

<210> SEQ ID NO 100

<400> SEQUENCE: 100

000

<210> SEQ ID NO 101

-continued

<400> SEQUENCE: 101

000

<210> SEQ ID NO 102

<400> SEQUENCE: 102

000

<210> SEQ ID NO 103

<400> SEQUENCE: 103

000

<210> SEQ ID NO 104

<400> SEQUENCE: 104

000

<210> SEQ ID NO 105

<400> SEQUENCE: 105

000

<210> SEQ ID NO 106

<400> SEQUENCE: 106

000

<210> SEQ ID NO 107

<400> SEQUENCE: 107

000

<210> SEQ ID NO 108

<400> SEQUENCE: 108

000

<210> SEQ ID NO 109

<400> SEQUENCE: 109

000

<210> SEQ ID NO 110

<400> SEQUENCE: 110

000

<210> SEQ ID NO 111

<400> SEQUENCE: 111

000

<210> SEQ ID NO 112

<400> SEQUENCE: 112

-continued

000

<210> SEQ ID NO 113

<400> SEQUENCE: 113

000

<210> SEQ ID NO 114

<400> SEQUENCE: 114

000

<210> SEQ ID NO 115

<400> SEQUENCE: 115

000

<210> SEQ ID NO 116

<400> SEQUENCE: 116

000

<210> SEQ ID NO 117

<400> SEQUENCE: 117

000

<210> SEQ ID NO 118

<400> SEQUENCE: 118

000

<210> SEQ ID NO 119

<400> SEQUENCE: 119

000

<210> SEQ ID NO 120

<400> SEQUENCE: 120

000

<210> SEQ ID NO 121

<400> SEQUENCE: 121

000

<210> SEQ ID NO 122

<400> SEQUENCE: 122

000

<210> SEQ ID NO 123

<400> SEQUENCE: 123

000

-continued

<210> SEQ ID NO 124

<400> SEQUENCE: 124

000

<210> SEQ ID NO 125

<400> SEQUENCE: 125

000

<210> SEQ ID NO 126

<400> SEQUENCE: 126

000

<210> SEQ ID NO 127

<400> SEQUENCE: 127

000

<210> SEQ ID NO 128

<400> SEQUENCE: 128

000

<210> SEQ ID NO 129

<400> SEQUENCE: 129

000

<210> SEQ ID NO 130

<400> SEQUENCE: 130

000

<210> SEQ ID NO 131

<400> SEQUENCE: 131

000

<210> SEQ ID NO 132

<400> SEQUENCE: 132

000

<210> SEQ ID NO 133

<400> SEQUENCE: 133

000

<210> SEQ ID NO 134

<400> SEQUENCE: 134

000

<210> SEQ ID NO 135

-continued

<400> SEQUENCE: 135

000

<210> SEQ ID NO 136

<400> SEQUENCE: 136

000

<210> SEQ ID NO 137

<400> SEQUENCE: 137

000

<210> SEQ ID NO 138

<400> SEQUENCE: 138

000

<210> SEQ ID NO 139

<400> SEQUENCE: 139

000

<210> SEQ ID NO 140

<400> SEQUENCE: 140

000

<210> SEQ ID NO 141

<400> SEQUENCE: 141

000

<210> SEQ ID NO 142

<400> SEQUENCE: 142

000

<210> SEQ ID NO 143

<400> SEQUENCE: 143

000

<210> SEQ ID NO 144

<400> SEQUENCE: 144

000

<210> SEQ ID NO 145

<400> SEQUENCE: 145

000

<210> SEQ ID NO 146

<400> SEQUENCE: 146

US 12,391,686 B2

659

-continued

660

000

<210> SEQ ID NO 147

<400> SEQUENCE: 147

000

<210> SEQ ID NO 148

<400> SEQUENCE: 148

000

<210> SEQ ID NO 149

<400> SEQUENCE: 149

000

<210> SEQ ID NO 150

<400> SEQUENCE: 150

000

<210> SEQ ID NO 151

<400> SEQUENCE: 151

000

<210> SEQ ID NO 152

<400> SEQUENCE: 152

000

<210> SEQ ID NO 153

<400> SEQUENCE: 153

000

<210> SEQ ID NO 154

<400> SEQUENCE: 154

000

<210> SEQ ID NO 155

<400> SEQUENCE: 155

000

<210> SEQ ID NO 156

<400> SEQUENCE: 156

000

<210> SEQ ID NO 157

<400> SEQUENCE: 157

000

-continued

<210> SEQ ID NO 158

<400> SEQUENCE: 158

000

<210> SEQ ID NO 159

<400> SEQUENCE: 159

000

<210> SEQ ID NO 160

<400> SEQUENCE: 160

000

<210> SEQ ID NO 161

<400> SEQUENCE: 161

000

<210> SEQ ID NO 162

<400> SEQUENCE: 162

000

<210> SEQ ID NO 163

<400> SEQUENCE: 163

000

<210> SEQ ID NO 164

<400> SEQUENCE: 164

000

<210> SEQ ID NO 165

<400> SEQUENCE: 165

000

<210> SEQ ID NO 166

<400> SEQUENCE: 166

000

<210> SEQ ID NO 167

<400> SEQUENCE: 167

000

<210> SEQ ID NO 168

<400> SEQUENCE: 168

000

-continued

<210> SEQ ID NO 169

<400> SEQUENCE: 169

000

<210> SEQ ID NO 170

<400> SEQUENCE: 170

000

<210> SEQ ID NO 171

<400> SEQUENCE: 171

000

<210> SEQ ID NO 172

<400> SEQUENCE: 172

000

<210> SEQ ID NO 173

<400> SEQUENCE: 173

000

<210> SEQ ID NO 174

<400> SEQUENCE: 174

000

<210> SEQ ID NO 175

<400> SEQUENCE: 175

000

<210> SEQ ID NO 176

<400> SEQUENCE: 176

000

<210> SEQ ID NO 177

<400> SEQUENCE: 177

000

<210> SEQ ID NO 178

<400> SEQUENCE: 178

000

<210> SEQ ID NO 179

<400> SEQUENCE: 179

000

<210> SEQ ID NO 180

US 12,391,686 B2

665

-continued

<400> SEQUENCE: 180

000

<210> SEQ ID NO 181

<400> SEQUENCE: 181

000

<210> SEQ ID NO 182

<400> SEQUENCE: 182

000

<210> SEQ ID NO 183

<400> SEQUENCE: 183

000

<210> SEQ ID NO 184

<400> SEQUENCE: 184

000

<210> SEQ ID NO 185

<400> SEQUENCE: 185

000

<210> SEQ ID NO 186

<400> SEQUENCE: 186

000

<210> SEQ ID NO 187

<400> SEQUENCE: 187

000

<210> SEQ ID NO 188

<400> SEQUENCE: 188

000

<210> SEQ ID NO 189

<400> SEQUENCE: 189

000

<210> SEQ ID NO 190

<400> SEQUENCE: 190

000

<210> SEQ ID NO 191

<400> SEQUENCE: 191

666

-continued

000

<210> SEQ ID NO 192

<400> SEQUENCE: 192

000

<210> SEQ ID NO 193

<400> SEQUENCE: 193

000

<210> SEQ ID NO 194

<400> SEQUENCE: 194

000

<210> SEQ ID NO 195

<400> SEQUENCE: 195

000

<210> SEQ ID NO 196

<400> SEQUENCE: 196

000

<210> SEQ ID NO 197

<400> SEQUENCE: 197

000

<210> SEQ ID NO 198

<400> SEQUENCE: 198

000

<210> SEQ ID NO 199

<400> SEQUENCE: 199

000

<210> SEQ ID NO 200

<400> SEQUENCE: 200

000

<210> SEQ ID NO 201

<400> SEQUENCE: 201

000

<210> SEQ ID NO 202

<400> SEQUENCE: 202

000

-continued

<210> SEQ ID NO 203
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 203

caagaagcac aagaagcaca

20

<210> SEQ ID NO 204
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 204

cttgtgttcc ttgccccatgg

20

<210> SEQ ID NO 205
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 205

cttccttggtc ttcttgccca

20

<210> SEQ ID NO 206
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 206

acaagaagca caaggccgag

20

<210> SEQ ID NO 207
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 207

ctcgtaggac gagcgccact

20

<210> SEQ ID NO 208
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 208

cgagtgccgc tcgtccctacg

20

<210> SEQ ID NO 209
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

-continued

<400> SEQUENCE: 209

gagtggcgct cgtcctacga

20

<210> SEQ ID NO 210
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 210

aggcttctcc agggggttgt

20

<210> SEQ ID NO 211
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 211

agattatgcc gacaagcccc

20

<210> SEQ ID NO 212
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 212

accttcagga ctagctttag

20

<210> SEQ ID NO 213
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 213

agcttttagag gtttctccag

20

<210> SEQ ID NO 214
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 214

ctagctttag aggcttctcc

20

<210> SEQ ID NO 215
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 215

tagctttaga ggcttctcca

20

<210> SEQ ID NO 216

-continued

<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 216

ctaaagcttag tcctgaagg

20

<210> SEQ ID NO 217
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 217

gcctctaaag ctagtcctga

20

<210> SEQ ID NO 218
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 218

cttcacttcc tccgaccc

20

<210> SEQ ID NO 219
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 219

aagcttagtcc tgaaggtcgg

20

<210> SEQ ID NO 220
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 220

agtgaagtga ctgaactctc

20

<210> SEQ ID NO 221
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 221

tgactgaac tctcaggatc

20

<210> SEQ ID NO 222
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 222

-continued

atagtaactg gagtcgtggc	20
-----------------------	----

<210> SEQ ID NO 223
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 223

catcatagta actggagtcg	20
-----------------------	----

<210> SEQ ID NO 224
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 224

tgacctgtca tcatacgtaac	20
------------------------	----

<210> SEQ ID NO 225
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 225

actccagttt ctagatgac	20
----------------------	----

<210> SEQ ID NO 226
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 226

cttttgtgcct ctctcgctca	20
------------------------	----

<210> SEQ ID NO 227
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 227

ggtcagacca tgagcgagag	20
-----------------------	----

<210> SEQ ID NO 228
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 228

gaagaagaag aagtccgaga	20
-----------------------	----

<210> SEQ ID NO 229
<211> LENGTH: 20
<212> TYPE: DNA

-continued

<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<223> OTHER INFORMATION: Synthetic Construct	
<400> SEQUENCE: 229	
gtccagatgc ttctccttct	20
<210> SEQ ID NO 230	
<211> LENGTH: 20	
<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<223> OTHER INFORMATION: Synthetic Construct	
<400> SEQUENCE: 230	
gtccgagaag gagaaggcatc	20
<210> SEQ ID NO 231	
<211> LENGTH: 20	
<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<223> OTHER INFORMATION: Synthetic Construct	
<400> SEQUENCE: 231	
ggagaaggcat ctggacgatg	20
<210> SEQ ID NO 232	
<211> LENGTH: 20	
<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<223> OTHER INFORMATION: Synthetic Construct	
<400> SEQUENCE: 232	
tgaggaaaga aggaagcgaa	20
<210> SEQ ID NO 233	
<211> LENGTH: 20	
<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<223> OTHER INFORMATION: Synthetic Construct	
<400> SEQUENCE: 233	
atctggacga tgaggaaaga	20
<210> SEQ ID NO 234	
<211> LENGTH: 20	
<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<223> OTHER INFORMATION: Synthetic Construct	
<400> SEQUENCE: 234	
agaagaagcg gaagcgagag	20
<210> SEQ ID NO 235	
<211> LENGTH: 20	
<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<223> OTHER INFORMATION: Synthetic Construct	
<400> SEQUENCE: 235	
gaagaagcgg aagcgagaga	20

<210> SEQ ID NO 236	
<211> LENGTH: 20	
<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<223> OTHER INFORMATION: Synthetic Construct	
 <400> SEQUENCE: 236	
ccgcccagga agagaagaag	20
 <210> SEQ ID NO 237	
<211> LENGTH: 20	
<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<223> OTHER INFORMATION: Synthetic Construct	
 <400> SEQUENCE: 237	
agagagggag cactgtgaca	20
 <210> SEQ ID NO 238	
<211> LENGTH: 20	
<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<223> OTHER INFORMATION: Synthetic Construct	
 <400> SEQUENCE: 238	
agggagcac gtgacacacg	20
 <210> SEQ ID NO 239	
<211> LENGTH: 20	
<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<223> OTHER INFORMATION: Synthetic Construct	
 <400> SEQUENCE: 239	
gaggagcac tgtgacacacgg	20
 <210> SEQ ID NO 240	
<211> LENGTH: 20	
<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<223> OTHER INFORMATION: Synthetic Construct	
 <400> SEQUENCE: 240	
gcactgtgac acggagggag	20
 <210> SEQ ID NO 241	
<211> LENGTH: 20	
<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<223> OTHER INFORMATION: Synthetic Construct	
 <400> SEQUENCE: 241	
gaggctgacg actttatcc	20
 <210> SEQ ID NO 242	
<211> LENGTH: 20	
<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	

-continued

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 242

aggctgacga ctttgatcct

20

<210> SEQ ID NO 243

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 243

tccacacctca ccttcttccc

20

<210> SEQ ID NO 244

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 244

cgactttgat cctggaaaga

20

<210> SEQ ID NO 245

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 245

cttgatcct ggaaagaagg

20

<210> SEQ ID NO 246

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 246

tgatcctggg aagaagggtgg

20

<210> SEQ ID NO 247

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 247

tcctggaaag aaggtggagg

20

<210> SEQ ID NO 248

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 248

cggactggcc gatctggggg

20

-continued

<210> SEQ ID NO 249
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 249

acgctcggac tggccgatct

20

<210> SEQ ID NO 250
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 250

aggtggagcc gccccagat

20

<210> SEQ ID NO 251
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 251

cgctcggact ggccgatctg

20

<210> SEQ ID NO 252
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 252

gctcggactg gccgatctgg

20

<210> SEQ ID NO 253
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 253

cacgctcggaa ctggccgatc

20

<210> SEQ ID NO 254
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 254

tgtgtccggc acgctcggac

20

<210> SEQ ID NO 255
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

-continued

<400> SEQUENCE: 255

ctggctgtgt ccggcacgct

20

<210> SEQ ID NO 256
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 256

atcggccagt ccgagcgtgc

20

<210> SEQ ID NO 257
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 257

cacccttgcc tggctgtgtc

20

<210> SEQ ID NO 258
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 258

cgagcgtgcc ggacacagcc

20

<210> SEQ ID NO 259
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 259

tttccagga gttgctgaat

20

<210> SEQ ID NO 260
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 260

cacaccttatt cagcaactcc

20

<210> SEQ ID NO 261
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 261

gctggcggag gaagtgttcc

20

<210> SEQ ID NO 262
<211> LENGTH: 20

-continued

<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct
<400> SEQUENCE: 262

tttacacctg aagctggcg

20

<210> SEQ ID NO 263
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct
<400> SEQUENCE: 263

ccccgggtta cctctgaagc

20

<210> SEQ ID NO 264
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct
<400> SEQUENCE: 264

acttcctccg ccagcttcag

20

<210> SEQ ID NO 265
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct
<400> SEQUENCE: 265

caggaaaagc aaaaaatcca

20

<210> SEQ ID NO 266
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct
<400> SEQUENCE: 266

gctttcagaa aagatccca

20

<210> SEQ ID NO 267
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct
<400> SEQUENCE: 267

aggaaaagca aaaaatccat

20

<210> SEQ ID NO 268
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct
<400> SEQUENCE: 268

US 12,391,686 B2

689**690**

-continued

ggaaaagcaa aaaatccatg	20
-----------------------	----

<210> SEQ ID NO 269
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 269

ggagcaattt catccgtgac	20
-----------------------	----

<210> SEQ ID NO 270
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 270

gtcacggatg caatttgtcc	20
-----------------------	----

<210> SEQ ID NO 271
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 271

tttatttatca ttgaatatcc	20
------------------------	----

<210> SEQ ID NO 272
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 272

aatgataata aaacatcccc	20
-----------------------	----

<210> SEQ ID NO 273
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 273

ataaaaacatc ccatggattt	20
------------------------	----

<210> SEQ ID NO 274
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 274

ttcatgggtgc caaaatccat	20
------------------------	----

<210> SEQ ID NO 275
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 275

tttcatggtg caaaaatcca

20

<210> SEQ ID NO 276
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 276

taatgaatac aagtcatgtt

20

<210> SEQ ID NO 277
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 277

caagtcagtt acggaattta

20

<210> SEQ ID NO 278
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 278

ataatgcaat gacataacaat

20

<210> SEQ ID NO 279
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 279

aactttagt acacggtatac

20

<210> SEQ ID NO 280
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 280

cttcgccaac ttgttagtaca

20

<210> SEQ ID NO 281
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 281

agataccgtg tactacaagt

20

-continued

<210> SEQ ID NO 282
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 282

gcgaagaaga tccttcacgc

20

<210> SEQ ID NO 283
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 283

tcatcttaaa gcctgcgtga

20

<210> SEQ ID NO 284
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 284

tttcagcag gcagctttt

20

<210> SEQ ID NO 285
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 285

caatgaagat acagctttt

20

<210> SEQ ID NO 286
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 286

actggtacaa cttcaggac

20

<210> SEQ ID NO 287
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 287

cttgtaactgg tacaacttca

20

<210> SEQ ID NO 288
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

-continued

<400> SEQUENCE: 288

acttgtactg gtacaacctc

20

<210> SEQ ID NO 289

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 289

ttggcagttt ctacttgtac

20

<210> SEQ ID NO 290

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 290

tacctgataa cttctctact

20

<210> SEQ ID NO 291

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 291

agcccgagtag agaaggttac

20

<210> SEQ ID NO 292

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 292

agctgcatgt ttgagcctga

20

<210> SEQ ID NO 293

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 293

gctgcatttt tgagcctgaa

20

<210> SEQ ID NO 294

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 294

aagctgcagg cattcccttc

20

<210> SEQ ID NO 295

-continued

<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 295

ggtaactgtcc gtcaagctgc

20

<210> SEQ ID NO 296
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 296

agggaatgcc tgcagcttga

20

<210> SEQ ID NO 297
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 297

cttgacggac agtaccgcag

20

<210> SEQ ID NO 298
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 298

cgccagcacg tgctccctcg

20

<210> SEQ ID NO 299
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 299

taccgcagag gagcacgtgc

20

<210> SEQ ID NO 300
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 300

agaggaggcac gtgctggcgc

20

<210> SEQ ID NO 301
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 301

-continued

ggagcacgtg ctggcgctgg	20
-----------------------	----

<210> SEQ ID NO 302
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 302

agcacgcaga tgacgaagct	20
-----------------------	----

<210> SEQ ID NO 303
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 303

gcacgcagct gacgaagctc	20
-----------------------	----

<210> SEQ ID NO 304
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 304

cagctgacga agctcgggac	20
-----------------------	----

<210> SEQ ID NO 305
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 305

aagctcggga caggatcaac	20
-----------------------	----

<210> SEQ ID NO 306
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 306

ccttgccgcc tgggaggaac	20
-----------------------	----

<210> SEQ ID NO 307
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 307

aggatcaacc gtttccccc	20
----------------------	----

<210> SEQ ID NO 308
<211> LENGTH: 20
<212> TYPE: DNA

701

-continued

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct
<400> SEQUENCE: 308

atcaaccgggt tcctcccagg 20

<210> SEQ ID NO 309
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 309
gcactaacctt gccgcctggg 20

<210> SEQ ID NO 310
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 310
agagcactac cttggccgcct 20

<210> SEQ ID NO 311
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 311
ccgggttcctc ccaggcgcca 20

<210> SEQ ID NO 312
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 312
tcctttcag atagccccatc 20

<210> SEQ ID NO 313
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 313
atgggctatac tgaagaggaa 20

<210> SEQ ID NO 314
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 314
gggctatctg aagaggaacg 20

-continued

<210> SEQ ID NO 315
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 315

tgggctatct gaagaggaac

20

<210> SEQ ID NO 316
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 316

tatctgaaga ggaacgggga

20

<210> SEQ ID NO 317
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 317

atctgaagag gaacggggac

20

<210> SEQ ID NO 318
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 318

tgttgaccac gctgttagagc

20

<210> SEQ ID NO 319
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 319

gctctacagc gtggtaaca

20

<210> SEQ ID NO 320
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 320

cgggagcctg ctctacagcg

20

<210> SEQ ID NO 321
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

-continued

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 321

cgtggtaaac acggccgagc

20

<210> SEQ ID NO 322

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 322

cccaccatca gcgtccggct

20

<210> SEQ ID NO 323

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 323

acggccgagc cggacgctga

20

<210> SEQ ID NO 324

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 324

gggcacccac catcagcgtc

20

<210> SEQ ID NO 325

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 325

gccgagccgg acgctgatgg

20

<210> SEQ ID NO 326

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 326

ccatgtccgt gttcagagg

20

<210> SEQ ID NO 327

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 327

ccgagccgga cgctgatggt

20

-continued

<210> SEQ ID NO 328
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 328

cgagctcaag tccaccgggt

20

<210> SEQ ID NO 329
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 329

gcgagctaa gtccaccggg

20

<210> SEQ ID NO 330
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 330

agagc gagct caagtccacc

20

<210> SEQ ID NO 331
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 331

gagagc gagc tcaagtccac

20

<210> SEQ ID NO 332
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 332

gaaggc tggg agtagttac

20

<210> SEQ ID NO 333
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 333

ctctccagta agctactccc

20

<210> SEQ ID NO 334
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

-continued

<400> SEQUENCE: 334

agccccagcggtggtaaggcct

20

<210> SEQ ID NO 335

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 335

aagcccagcggtggtaaggcc

20

<210> SEQ ID NO 336

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 336

actccccaggc ttccaccacgc

20

<210> SEQ ID NO 337

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 337

ctccccaggct tcaccacgct

20

<210> SEQ ID NO 338

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 338

ctcgtctttg aagccccaggc

20

<210> SEQ ID NO 339

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 339

cactggagag aaagggtgact

20

<210> SEQ ID NO 340

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 340

gcactggaga gaaagggtgac

20

<210> SEQ ID NO 341

<211> LENGTH: 20

-continued

<212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 341

agttagtggca ctggagagaa

20

<210> SEQ ID NO 342
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 342

cgaaggcgca gtagtggcac

20

<210> SEQ ID NO 343
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 343

ctgcatecgaa agcgcagtag

20

<210> SEQ ID NO 344
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 344

atgcagaata attcagtatt

20

<210> SEQ ID NO 345
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 345

agtatttggc gacttgaagt

20

<210> SEQ ID NO 346
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 346

cgacttgaag tcggacgaga

20

<210> SEQ ID NO 347
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 347

-continued

gagctgctct actcagcccta	20
------------------------	----

<210> SEQ ID NO 348
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 348

cacgcctgtc tcatctccgt	20
-----------------------	----

<210> SEQ ID NO 349
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 349

tcagcctacg gagatgagac	20
-----------------------	----

<210> SEQ ID NO 350
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 350

caggcgtgca gtgtgcgcgt	20
-----------------------	----

<210> SEQ ID NO 351
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 351

ccgcggcccc tcttagcctgc	20
------------------------	----

<210> SEQ ID NO 352
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 352

catccttcac aaactcctgc	20
-----------------------	----

<210> SEQ ID NO 353
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 353

tagcctgcag gagtttgtga	20
-----------------------	----

<210> SEQ ID NO 354
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 354

caggagtttg tgaaggatgc

20

<210> SEQ ID NO 355
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 355

aggagtttgt gaaggatgct

20

<210> SEQ ID NO 356
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 356

tgggagctac agcaagaaag

20

<210> SEQ ID NO 357
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 357

gagctacagc aagaaaagtgg

20

<210> SEQ ID NO 358
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 358

gaaaagtggtg gacgaccc

20

<210> SEQ ID NO 359
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 359

cgcctgtat ctggccagg

20

<210> SEQ ID NO 360
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 360

ctccgcctgt gatctggtcc

20

-continued

<210> SEQ ID NO 361
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 361

gacctcctgg accagatcac

20

<210> SEQ ID NO 362
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 362

ctcctggacc agatcacagg

20

<210> SEQ ID NO 363
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 363

gctggaagag cgtcctagag

20

<210> SEQ ID NO 364
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 364

tgcagccccac ctgcttcagc

20

<210> SEQ ID NO 365
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 365

gacgcttcttc cagctgaagc

20

<210> SEQ ID NO 366
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 366

ctcttccagc tgaagcagg

20

<210> SEQ ID NO 367
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

-continued

<400> SEQUENCE: 367

gctcttccag ctgaaggcagg

20

<210> SEQ ID NO 368
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 368

cctccagatg aagccaagg

20

<210> SEQ ID NO 369
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 369

gcttcatctg gaggctcat

20

<210> SEQ ID NO 370
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 370

ggcttcatct ggaggctca

20

<210> SEQ ID NO 371
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 371

cttaccttgg cttcatctgg

20

<210> SEQ ID NO 372
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 372

aaacttacct tggcttcata

20

<210> SEQ ID NO 373
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 373

gaagcctcca gatgaaggca

20

<210> SEQ ID NO 374

-continued

<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 374

tcttagggtg tccccaacct

20

<210> SEQ ID NO 375
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 375

ccttagggtgt ccccaacctg

20

<210> SEQ ID NO 376
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 376

gtgtctgtct ccacaggttg

20

<210> SEQ ID NO 377
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 377

tgtgtctgtc tccacaggtt

20

<210> SEQ ID NO 378
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 378

ccacaggttg gggacacct

20

<210> SEQ ID NO 379
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 379

agagctgctg ctgtctccta

20

<210> SEQ ID NO 380
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 380

-continued

cagagctgct gctgttcct	20
----------------------	----

<210> SEQ ID NO 381
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 381

agacacagc agcttgttgc	20
----------------------	----

<210> SEQ ID NO 382
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 382

atccacagaa acgtcggtat	20
-----------------------	----

<210> SEQ ID NO 383
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 383

gagatatcca cagaaacgtc	20
-----------------------	----

<210> SEQ ID NO 384
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 384

ggagatatcc acagaaacgt	20
-----------------------	----

<210> SEQ ID NO 385
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 385

gtccttatccc gacgttctg	20
-----------------------	----

<210> SEQ ID NO 386
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 386

tctccatgct cagctctctg	20
-----------------------	----

<210> SEQ ID NO 387
<211> LENGTH: 20
<212> TYPE: DNA

-continued

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct
<400> SEQUENCE: 387
ctcacccaga gagctgagca

20

<210> SEQ ID NO 388
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct
<400> SEQUENCE: 388
atctccatgc tcagctctct

20

<210> SEQ ID NO 389
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct
<400> SEQUENCE: 389
tatctccatg ctcagctctc

20

<210> SEQ ID NO 390
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct
<400> SEQUENCE: 390
atgtcctgtt tacacaggaa

20

<210> SEQ ID NO 391
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct
<400> SEQUENCE: 391
ttacacaggaa aaggtgaaga

20

<210> SEQ ID NO 392
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct
<400> SEQUENCE: 392
agttcaaatg gctgtcgta

20

<210> SEQ ID NO 393
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct
<400> SEQUENCE: 393
tgacgacagc catttgaact

20

-continued

<210> SEQ ID NO 394
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 394

aagttcaaat ggctgtcg

20

<210> SEQ ID NO 395
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 395

tcgtctcatc caagttcaa

20

<210> SEQ ID NO 396
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 396

tgagacgacg aagctcctgc

20

<210> SEQ ID NO 397
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 397

tgcttcgtg caggcctgc

20

<210> SEQ ID NO 398
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 398

gcaggacctg cacgaagcac

20

<210> SEQ ID NO 399
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 399

gctccgcctg tgcttcgtgc

20

<210> SEQ ID NO 400
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

-continued

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 400

ggacctgcac gaagcacagg

20

<210> SEQ ID NO 401

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 401

cacgaaggcac aggcggagcg

20

<210> SEQ ID NO 402

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 402

aggcggagcg cggcggtct

20

<210> SEQ ID NO 403

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 403

agggagctga ggttggacga

20

<210> SEQ ID NO 404

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 404

gttggacagg gagctgaggt

20

<210> SEQ ID NO 405

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 405

aggcggttga caggagactg

20

<210> SEQ ID NO 406

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 406

ccctctcgga ggcgttggac

20

-continued

<210> SEQ ID NO 407
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 407

cctctcgag gcgttggaca

20

<210> SEQ ID NO 408
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 408

ctgggtccctc tcggaggcgt

20

<210> SEQ ID NO 409
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 409

ccctgtccaa cgcctccgag

20

<210> SEQ ID NO 410
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 410

cctgtcaac gcctccgaga

20

<210> SEQ ID NO 411
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 411

gtggtgctgg tccctctcg

20

<210> SEQ ID NO 412
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 412

caggtggtgc tggtccctct

20

<210> SEQ ID NO 413
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

-continued

<400> SEQUENCE: 413

gcatctcacc caggtggtgc

20

<210> SEQ ID NO 414

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 414

cgagagggac cagcaccacc

20

<210> SEQ ID NO 415

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 415

gagagggacc agcaccaccc

20

<210> SEQ ID NO 416

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 416

gtggggcat ctcaccagg

20

<210> SEQ ID NO 417

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 417

ccccgacact caggcgagaa

20

<210> SEQ ID NO 418

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 418

tccccgacac tcaggcgaga

20

<210> SEQ ID NO 419

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 419

agcccttctc gcctgagtgt

20

<210> SEQ ID NO 420

<211> LENGTH: 20

-continued

<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 420

ctggctgctc cccgacactc

20

<210> SEQ ID NO 421
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 421

cccttctcg ctgagtgtcg

20

<210> SEQ ID NO 422
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 422

cccctttcg cctgagtgta

20

<210> SEQ ID NO 423
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 423

taggggtcgt gggtgacgta

20

<210> SEQ ID NO 424
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 424

aagaaaactca taggggtcgt

20

<210> SEQ ID NO 425
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 425

gaagaaaactc ataggggtcgt

20

<210> SEQ ID NO 426
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 426

-continued

gagactgaag aaactcatag

20

<210> SEQ ID NO 427
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 427

ggagactgaa gaaactcata

20

<210> SEQ ID NO 428
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 428

tggagactga agaaaactcat

20

<210> SEQ ID NO 429
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 429

ttttcagtct ccagagcctg

20

<210> SEQ ID NO 430
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 430

ttggcagagg ccgcaggcgt

20

<210> SEQ ID NO 431
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 431

taggtcttgg cagaggccgc

20

<210> SEQ ID NO 432
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 432

ctagagttag gtcttggcag

20

<210> SEQ ID NO 433
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 433

ggtgtgtctag agttaggtct

20

<210> SEQ ID NO 434
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 434

gttagcgaacg tgtccggcgat

20

<210> SEQ ID NO 435
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 435

gaccggaaacg atctcgcgta

20

<210> SEQ ID NO 436
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 436

ggcagtcgtt cggttgatata

20

<210> SEQ ID NO 437
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 437

gcttgagcac atacgcaaat

20

<210> SEQ ID NO 438
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 438

gtggtagaaat aacgttattac

20

<210> SEQ ID NO 439
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 439

gtcatacatg gataaggcta

20

-continued

<210> SEQ ID NO 440
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 440

gatacacgaa gcatcaactag

20

<210> SEQ ID NO 441
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 441

gaacgttggc actacttcac

20

<210> SEQ ID NO 442
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 442

gtccatgtatgcgttcga

20

<210> SEQ ID NO 443
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 443

gtcgtaagt gcattcgatc

20

<210> SEQ ID NO 444
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 444

gttcgactcg cgtgaccgta

20

<210> SEQ ID NO 445
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 445

gaatctaccg cagcggttcg

20

<210> SEQ ID NO 446
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

-continued

<400> SEQUENCE: 446

gaagtgacgt cgattcgata

20

<210> SEQ ID NO 447
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 447

gcggtgtatg acaaccgccc

20

<210> SEQ ID NO 448
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 448

gtaccgcgcc tgaagttcgc

20

<210> SEQ ID NO 449
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 449

gcagctcgta tgtcgtaactc

20

<210> SEQ ID NO 450
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 450

gcccctaag agtactcatc

20

<210> SEQ ID NO 451
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 451

gagtgtcgta gttgctccata

20

<210> SEQ ID NO 452
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 452

gcagctcgac ctcaagccgt

20

<210> SEQ ID NO 453

-continued

<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 453

gtatcctgac ctacgcgctg

20

<210> SEQ ID NO 454
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 454

gtgtatctca gcacgctaac

20

<210> SEQ ID NO 455
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 455

gtcgtcatac aacggcaacg

20

<210> SEQ ID NO 456
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 456

gtcgtgcgt tccggcggtt

20

<210> SEQ ID NO 457
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 457

gcggtcctca gtaagcgcgt

20

<210> SEQ ID NO 458
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 458

gctctgtgc ggaaggattc

20

<210> SEQ ID NO 459
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 459

-continued

gcatggagga gcgtcgacaga 20

<210> SEQ ID NO 460
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 460

gtagcgcgcg taggagtggc 20

<210> SEQ ID NO 461
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 461

gatcacctgc attcgtacac 20

<210> SEQ ID NO 462
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 462

gcacacacctatcgaatg 20

<210> SEQ ID NO 463
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 463

gttgatcaac gcgcttcgcg 20

<210> SEQ ID NO 464
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 464

gcgtctcaact cactccatcg 20

<210> SEQ ID NO 465
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 465

gccgaccaac gtcagcggtt 20

<210> SEQ ID NO 466
<211> LENGTH: 20
<212> TYPE: DNA

-continued

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct
<400> SEQUENCE: 466

ggatacggtg cgtcaatcta

20

<210> SEQ ID NO 467
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct
<400> SEQUENCE: 467

gaatccagtg gccccgacaa

20

<210> SEQ ID NO 468
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct
<400> SEQUENCE: 468

gcactgtcag tgcaacgata

20

<210> SEQ ID NO 469
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct
<400> SEQUENCE: 469

gcgatcctca agtatgctca

20

<210> SEQ ID NO 470
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct
<400> SEQUENCE: 470

gctaatatcg acacggccgc

20

<210> SEQ ID NO 471
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct
<400> SEQUENCE: 471

ggagatgcat cgaagtgcgt

20

<210> SEQ ID NO 472
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct
<400> SEQUENCE: 472

ggatgcactc catctcgct

20

<210> SEQ ID NO 473
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 473

gtgccgactataacgcgag

20

<210> SEQ ID NO 474
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 474

gagattccgatgttaacgtac

20

<210> SEQ ID NO 475
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 475

gtcgtacacgacgaggattgc

20

<210> SEQ ID NO 476
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 476

gcgttagtca cttagtcga

20

<210> SEQ ID NO 477
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 477

gttcacacgg tgtcgatag

20

<210> SEQ ID NO 478
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 478

ggatagggtaccccttagtacg

20

<210> SEQ ID NO 479
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

-continued

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 479

gtatgagtca agctaattgcg

20

<210> SEQ ID NO 480

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 480

gcaactatttgaataacgtga

20

<210> SEQ ID NO 481

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 481

gttacaccttcg ctcgtctata

20

<210> SEQ ID NO 482

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 482

gtaccggaca ccacaggccg

20

<210> SEQ ID NO 483

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 483

gtcagccatc ggatagagat

20

<210> SEQ ID NO 484

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 484

gtacggcaact ccttagccgct

20

<210> SEQ ID NO 485

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 485

ggtcctgtcg tatgcttgca

20

-continued

<210> SEQ ID NO 486
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 486

ggcgcaatat atgcggtaag

20

<210> SEQ ID NO 487
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 487

gcgcacgtat aatcctgcgt

20

<210> SEQ ID NO 488
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 488

gtgcacaaca ccatccacga

20

<210> SEQ ID NO 489
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 489

gcacaatgtt gacgtaagt

20

<210> SEQ ID NO 490
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 490

gtaagatgct gtcaccgtg

20

<210> SEQ ID NO 491
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 491

gtcgggtgatc caacgtatcg

20

<210> SEQ ID NO 492
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

-continued

<400> SEQUENCE: 492

gagcttagtag gagcgaagac

20

<210> SEQ ID NO 493
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 493

gtacgtggaa gtttgtggcc

20

<210> SEQ ID NO 494
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 494

gagaactgcc agttctcgat

20

<210> SEQ ID NO 495
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 495

gccattcggc gcggcacttc

20

<210> SEQ ID NO 496
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 496

gcacacgacc aatccgcttc

20

<210> SEQ ID NO 497
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 497

gaggtgatcg attaagtaca

20

<210> SEQ ID NO 498
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 498

gtcactcgca gacgcctaacc

20

<210> SEQ ID NO 499
<211> LENGTH: 20

-continued

<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 499

gcgctacgga atcatacgtt

20

<210> SEQ ID NO 500
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 500

ggtaggacct cacggcgcc

20

<210> SEQ ID NO 501
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 501

gaaactgcac tcgttgttagt

20

<210> SEQ ID NO 502
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 502

gatcctgatc cggcgccgcg

20

<210> SEQ ID NO 503
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 503

ggtatgcgcg atcctgagtt

20

<210> SEQ ID NO 504
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 504

gcggagctag agagcggtca

20

<210> SEQ ID NO 505
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 505

-continued

gaatggcaat tacggctgat 20

<210> SEQ ID NO 506
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 506

gtatggtgag tagtcgcttg 20

<210> SEQ ID NO 507
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 507

gtgttaattgc gtctagtcgg 20

<210> SEQ ID NO 508
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 508

ggtcctggcg aggagccttg 20

<210> SEQ ID NO 509
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 509

gaagataagt cgctgtctcg 20

<210> SEQ ID NO 510
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 510

gtcggcggttc tgttgtgact 20

<210> SEQ ID NO 511
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 511

gaggcaagcc gtttaggtgta 20

<210> SEQ ID NO 512
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 512

gcggatccag atctcattcg

20

<210> SEQ ID NO 513
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 513

ggaacatagg agcacgtagt

20

<210> SEQ ID NO 514
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 514

gtcatcatta tggcgtaagg

20

<210> SEQ ID NO 515
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 515

gcgactagcg ccatgagcgg

20

<210> SEQ ID NO 516
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 516

ggcgaagttc gacatgacac

20

<210> SEQ ID NO 517
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 517

gctgtcggtt ggaggctatg

20

<210> SEQ ID NO 518
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 518

gcggagagca ttgacctcat

20

-continued

<210> SEQ ID NO 519
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 519

gactaatggc ccaagtcagt

20

<210> SEQ ID NO 520
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 520

gcggattaga ggtatgcgg

20

<210> SEQ ID NO 521
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 521

gccgacggca atcagtagcgc

20

<210> SEQ ID NO 522
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 522

gtaacctctc gagcgataga

20

<210> SEQ ID NO 523
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 523

gacttgtatg tggcttacgg

20

<210> SEQ ID NO 524
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 524

gtcactgtgg tcgaacatgt

20

<210> SEQ ID NO 525
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

-continued

<400> SEQUENCE: 525

gtactccaat ccgcgatgac

20

<210> SEQ ID NO 526
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 526

gcgttggcac gatgttacgg

20

<210> SEQ ID NO 527
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 527

gaaccagccg gctagtatga

20

<210> SEQ ID NO 528
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 528

gtatactagc taaccacacg

20

<210> SEQ ID NO 529
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 529

gaatcgaaat agttgattcg

20

<210> SEQ ID NO 530
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 530

gagcacttgc atgaggcggt

20

<210> SEQ ID NO 531
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 531

gaacggcgt gaagccagcc

20

<210> SEQ ID NO 532

-continued

<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 532

gcaaccgaga tgagagggttc

20

<210> SEQ ID NO 533
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 533

gcaagatcaa tatgcgttat

20

<210> SEQ ID NO 534
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 534

acggaggctt agcgtcgcaa

20

<210> SEQ ID NO 535
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 535

cgttccgcg gcccgttcaa

20

<210> SEQ ID NO 536
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 536

atcggttccg cttAACGGCG

20

<210> SEQ ID NO 537
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 537

gtaggcgcgc cgctctctac

20

<210> SEQ ID NO 538
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 538

-continued

ccatatcggg gcgagacatg 20

<210> SEQ ID NO 539
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 539

tactaacgcc gtccttacag 20

<210> SEQ ID NO 540
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 540

tgaggatcat gtcgagcgcc 20

<210> SEQ ID NO 541
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 541

gggccccat aggatatcgc 20

<210> SEQ ID NO 542
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 542

tagacaaccg cggagaatgc 20

<210> SEQ ID NO 543
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 543

acggggcgct atcgctgact 20

<210> SEQ ID NO 544
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 544

cgcggaaatt ttaccgacga 20

<210> SEQ ID NO 545
<211> LENGTH: 20
<212> TYPE: DNA

-continued

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 545

cttacaatcg tcgggtccaaat 20

<210> SEQ ID NO 546
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 546

gcgtgcgtcc cgggttaccc 20

<210> SEQ ID NO 547
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 547

cggagtaaca agcggacgga 20

<210> SEQ ID NO 548
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 548

cgagtgttat acgcaccgtt 20

<210> SEQ ID NO 549
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 549

cgactaaccg gaaacttttt 20

<210> SEQ ID NO 550
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 550

caacgggttc tcccggtac 20

<210> SEQ ID NO 551
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 551

caggagtgcg cgtatacgct 20

-continued

<210> SEQ ID NO 552
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 552

ttcacgtcgt ctgcgacca

20

<210> SEQ ID NO 553
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 553

gtgtcggatt ccggcgctta

20

<210> SEQ ID NO 554
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 554

cacgaactca caccgcgcga

20

<210> SEQ ID NO 555
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 555

cgctagtagc ctcctctata

20

<210> SEQ ID NO 556
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 556

tcgcgcgttgg gttatacgct

20

<210> SEQ ID NO 557
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 557

ctatctcgag tggtaatgcg

20

<210> SEQ ID NO 558
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

-continued

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 558

aatcgactcg aacttcgtgt

20

<210> SEQ ID NO 559

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 559

cccgatggac tataccgaac

20

<210> SEQ ID NO 560

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 560

acgttcagtg acgaccagct

20

<210> SEQ ID NO 561

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 561

cgcgacgact caacctagtc

20

<210> SEQ ID NO 562

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 562

ggtcaccgat cgagagctag

20

<210> SEQ ID NO 563

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 563

ctcaaccgac cgtatggtca

20

<210> SEQ ID NO 564

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 564

cgtattcgac tctcaacgcg

20

779

-continued

<210> SEQ ID NO 565
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 565

ctagccgccc agatcgagcc

20

<210> SEQ ID NO 566
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 566

gaatcgcaccg acactaatgt

20

<210> SEQ ID NO 567
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 567

acttcagttc ggcgttagtca

20

<210> SEQ ID NO 568
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 568

gtgcgatgtc gttcaacgt

20

<210> SEQ ID NO 569
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 569

cgccctaattt ccggatcaat

20

<210> SEQ ID NO 570
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 570

cgtggccgga accgtcatag

20

<210> SEQ ID NO 571
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

780

-continued

<400> SEQUENCE: 571

accctccgaa tcgttaacgga

20

<210> SEQ ID NO 572
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 572

aacacggtagc acagcggtgt

20

<210> SEQ ID NO 573
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 573

acatacgatcg cggctcgatt

20

<210> SEQ ID NO 574
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 574

gatggcgctt cagtcgtcgg

20

<210> SEQ ID NO 575
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 575

ataatccgga aacgctcgac

20

<210> SEQ ID NO 576
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 576

cgccggggctg acaattaacg

20

<210> SEQ ID NO 577
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 577

cgtcgcccata tgcccggtggc

20

<210> SEQ ID NO 578
<211> LENGTH: 20

-continued

<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 578

cgggcctata acaccatcga

20

<210> SEQ ID NO 579
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 579

cgccgttccg agataacttga

20

<210> SEQ ID NO 580
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 580

cgggacgtcg cgaaaaatgta

20

<210> SEQ ID NO 581
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 581

tcggcatacg ggacacacgc

20

<210> SEQ ID NO 582
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 582

agctccatcg ccgcgataat

20

<210> SEQ ID NO 583
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 583

atcgatcat cagctagcgc

20

<210> SEQ ID NO 584
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 584

-continued

tcgatcgagg ttgcattcgg	20
-----------------------	----

<210> SEQ ID NO 585
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 585

ctcgacagtt cgtcccgagc	20
-----------------------	----

<210> SEQ ID NO 586
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 586

cggtagtatt aatcgctgac	20
-----------------------	----

<210> SEQ ID NO 587
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 587

tgaacgcgtg tttccttgca	20
-----------------------	----

<210> SEQ ID NO 588
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 588

cgacgctagg taacgtagag	20
-----------------------	----

<210> SEQ ID NO 589
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 589

cattgttgag cgggcgcgct	20
-----------------------	----

<210> SEQ ID NO 590
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 590

ccgctattga aaccgcccac	20
-----------------------	----

<210> SEQ ID NO 591
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 591

agacacgtca ccggtaaaaa

20

<210> SEQ ID NO 592
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 592

tttacgatct agcggcgtag

20

<210> SEQ ID NO 593
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 593

tccgcacat tgcacacctgg

20

<210> SEQ ID NO 594
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 594

ggtagagac taggcgcgcg

20

<210> SEQ ID NO 595
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 595

cctccgtgct aacgcggacg

20

<210> SEQ ID NO 596
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 596

ttatcgcgtta gtgctgacgt

20

<210> SEQ ID NO 597
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 597

tacgcttgcg tttagcggtcc

20

-continued

<210> SEQ ID NO 598
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 598

cgcgccac gcgtcatcgc

20

<210> SEQ ID NO 599
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 599

agctcgccat gtcggttctc

20

<210> SEQ ID NO 600
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 600

aactagcccg agcagcttcg

20

<210> SEQ ID NO 601
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 601

cgcagggtgt cggtaaccct

20

<210> SEQ ID NO 602
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 602

tttcgacgcc atcgtgctca

20

<210> SEQ ID NO 603
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 603

tcctggatac cgcgtggtta

20

<210> SEQ ID NO 604
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

-continued

<400> SEQUENCE: 604

atagccgccc ctcattactt

20

<210> SEQ ID NO 605
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 605

gtcgtccggg attacaaaat

20

<210> SEQ ID NO 606
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 606

taatgctgca cacgcccata

20

<210> SEQ ID NO 607
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 607

tatcgcttcc gattagtccg

20

<210> SEQ ID NO 608
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 608

gtaccataacc gcgtaccctt

20

<210> SEQ ID NO 609
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 609

taagatccgc gggtgccaac

20

<210> SEQ ID NO 610
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 610

gtagacgtcg tgagcttac

20

<210> SEQ ID NO 611

-continued

<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 611

tcgcggacat agggctctaa

20

<210> SEQ ID NO 612
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 612

agcgcagata ggcgtatca

20

<210> SEQ ID NO 613
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 613

gttcgcttcg taacgaggaa

20

<210> SEQ ID NO 614
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 614

gaccggcgat aactttgac

20

<210> SEQ ID NO 615
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 615

acgtccatac tgcggctac

20

<210> SEQ ID NO 616
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 616

gtaccattgc cggctcccta

20

<210> SEQ ID NO 617
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 617

-continued

tggttccgta ggtcggtata	20
-----------------------	----

<210> SEQ ID NO 618
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 618

tctggcttga cacgaccgtt	20
-----------------------	----

<210> SEQ ID NO 619
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 619

cgcgttaggtcc ggtaagtgcg	20
-------------------------	----

<210> SEQ ID NO 620
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 620

agcacgtaat gtccgtggat	20
-----------------------	----

<210> SEQ ID NO 621
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 621

aaggcgcgcg aatgtggcag	20
-----------------------	----

<210> SEQ ID NO 622
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 622

actgcggagc gcccaatatac	20
------------------------	----

<210> SEQ ID NO 623
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 623

cgtcgagtgc tcgaactcca	20
-----------------------	----

<210> SEQ ID NO 624
<211> LENGTH: 20
<212> TYPE: DNA

-continued

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct
<400> SEQUENCE: 624

tcgcageggc gtgggatcg

20

<210> SEQ ID NO 625
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct
<400> SEQUENCE: 625

atctgtccta attcggatcg

20

<210> SEQ ID NO 626
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct
<400> SEQUENCE: 626

tgcggcgtaa tgcttgaaag

20

<210> SEQ ID NO 627
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct
<400> SEQUENCE: 627

cgaacttaat cccgtggcaa

20

<210> SEQ ID NO 628
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct
<400> SEQUENCE: 628

gccgttgtgc tggatacgcc

20

<210> SEQ ID NO 629
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct
<400> SEQUENCE: 629

taccctccgg atacggactg

20

<210> SEQ ID NO 630
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct
<400> SEQUENCE: 630

ccgttggact atggcggtc

20

-continued

<210> SEQ ID NO 631
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 631

gtacggggcg atcatccaca

20

<210> SEQ ID NO 632
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 632

aagagtagta gacgccccgg

20

<210> SEQ ID NO 633
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 633

aagagcgaat cgatttcgtg

20

<210> SEQ ID NO 634
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 634

tcaacaccag tgcctgacgg

20

<210> SEQ ID NO 635
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 635

aaagttagctt cactctctcg

20

<210> SEQ ID NO 636
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 636

gagccaaacca atagatgtcc

20

<210> SEQ ID NO 637
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

-continued

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 637

gccccgcacat gAACCTAGAG

20

<210> SEQ ID NO 638

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 638

acaaagggtt gAACAGAACC

20

<210> SEQ ID NO 639

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 639

ggtgaccggg ttattgtgt

20

<210> SEQ ID NO 640

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 640

ttagtggagg actacagagc

20

<210> SEQ ID NO 641

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 641

acatatagcc cgttaaagctg

20

<210> SEQ ID NO 642

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 642

cgttggcgt gatctccacg

20

<210> SEQ ID NO 643

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 643

tggcctttc tacctcgcgc

20

-continued

<210> SEQ ID NO 644
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 644

aatggagata ctcatctggg

20

<210> SEQ ID NO 645
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 645

gaagcccgta cagaaaagtgt

20

<210> SEQ ID NO 646
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 646

caaatctgagg aactccacga

20

<210> SEQ ID NO 647
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 647

aggctgcggc gccccacgaga

20

<210> SEQ ID NO 648
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 648

actttgacca ggccttgcta

20

<210> SEQ ID NO 649
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 649

acottccata actgccacgc

20

<210> SEQ ID NO 650
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

-continued

<400> SEQUENCE: 650

cgaggcgtac atacccaagg

20

<210> SEQ ID NO 651
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 651

atggtaacgc caaatcaaga

20

<210> SEQ ID NO 652
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 652

tcttgtaatac ccatacgcgt

20

<210> SEQ ID NO 653
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 653

attcacagga cacagagaat

20

<210> SEQ ID NO 654
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 654

ccagggtctcc atcctaaga

20

<210> SEQ ID NO 655
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 655

tgagctgcac caaagagacg

20

<210> SEQ ID NO 656
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 656

atgtctgcag atgtaccct

20

<210> SEQ ID NO 657
<211> LENGTH: 20

-continued

<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 657

cgaagataac gcggataacct

20

<210> SEQ ID NO 658
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 658

gctgcaggcc gagtacacccg

20

<210> SEQ ID NO 659
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 659

acaagtggaa ggcttacactg

20

<210> SEQ ID NO 660
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 660

gcagcgtaca gggatgtaca

20

<210> SEQ ID NO 661
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 661

gcagtagcgc ttcaaggccca

20

<210> SEQ ID NO 662
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 662

caaatggtgg ggttaacagaa

20

<210> SEQ ID NO 663
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 663

-continued

gaaaggaact ggctaccgtt	20
-----------------------	----

<210> SEQ ID NO 664
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 664

agggcttccg ttacaagatg	20
-----------------------	----

<210> SEQ ID NO 665
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 665

gaacaagcaa cacctaaaag	20
-----------------------	----

<210> SEQ ID NO 666
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 666

tgaggagaag gaacggctca	20
-----------------------	----

<210> SEQ ID NO 667
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 667

ggaagaatgc agagtataag	20
-----------------------	----

<210> SEQ ID NO 668
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 668

ggaatttgag gaactcctga	20
-----------------------	----

<210> SEQ ID NO 669
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 669

gctcaccggc catccagggaa	20
------------------------	----

<210> SEQ ID NO 670
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 670

actggccagg aacgatgcga

20

<210> SEQ ID NO 671

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 671

gcagctccaa gatcttccca

20

<210> SEQ ID NO 672

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 672

gaatgagtagc acagaacgga

20

<210> SEQ ID NO 673

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 673

ggagcaggac aaggtcgggg

20

The invention claimed is:

1. A compound having the structure of Formula II:

40

B is a degradation moiety having the structure of
Formula A

A-L-B

Formula II,

wherein

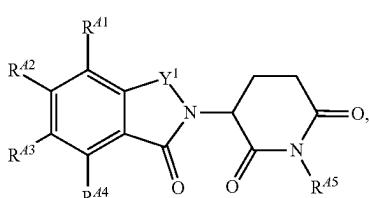
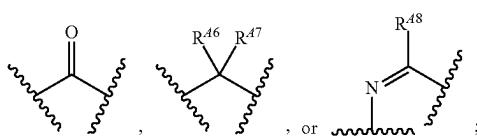
L is a linker having the structure of Formula IV

 $A^1-(B^1)_f-(C^1)_g-(B^2)_h-(D)-(B^3)_i-(C^2)_j-(B^4)_k-A^2$ Formula IV 45

wherein

 A^1 is a bond between the linker and A; A^2 is a bond between B and the linker;each of B^1 , B^2 , B^3 , and B^4 is, independently, optionally substituted C_{1-2} alkyl, optionally substituted C_{1-2} heteroalkyl, O, S, $S(O)_2$, or NR^N ;each R^N is, independently, H, optionally substituted C_{1-4} alkyl, optionally substituted C_{2-4} alkenyl, optionally substituted C_{2-4} alkynyl, optionally substituted C_{2-6} heterocyclyl, optionally substituted C_{6-12} aryl, or optionally substituted C_{1-7} heteroalkyl;each of C^1 and C^2 is, independently, carbonyl, thiocarbonyl, sulphonyl, or phosphoryl;

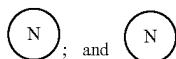
each of f, g, h, i, j, and k is, independently, 0 or 1; and

D is optionally substituted C_{1-10} alkyl, optionally substituted C_{2-10} alkenyl, optionally substituted C_{2-10} alkynyl, optionally substituted C_{2-6} heterocyclyl, optionally substituted C_{6-12} aryl, optionally substituted C_{2-10} polyethylene glycol, or optionally substituted C_{1-10} heteroalkyl, or a chemical bond linking $A^1-(B^1)_f-(C^1)_g-(B^2)_h$ -to-($B^3)_i-(C^2)_j-(B^4)_k-A^2$;wherein in
 Y^1 is R^45 is H, optionally substituted C_{1-6} alkyl, or optionally substituted C_{1-6} heteroalkyl; R^46 is H or optionally substituted C_{1-6} alkyl; and R^47 is H or optionally substituted C_{1-6} alkyl; or R^46 and R^47 , together with the carbon atom to which each is bound,

combine to form optionally substituted $C_3\text{-}C_6$ carbocyclyl or optionally substituted $C_2\text{-}C_5$ heterocyclyl; or R^{46} and R^{47} , together with the carbon atom to which each is bound, combine to form optionally substituted $C_3\text{-}C_6$ carbocyclyl or optionally substituted $C_2\text{-}C_5$ heterocyclyl;

R^{48} is H, optionally substituted $C_1\text{-}C_6$ alkyl, or optionally substituted $C_1\text{-}C_6$ heteroalkyl;

each of R^{41} , R^{42} , R^{43} , and R^{44} is, independently, H, A^2 , halogen, optionally substituted $C_1\text{-}C_6$ alkyl, optionally substituted $C_1\text{-}C_6$ heteroalkyl, optionally substituted $C_3\text{-}C_{10}$ carbocyclyl, optionally substituted $C_2\text{-}C_9$ heterocyclyl, optionally substituted $C_6\text{-}C_{10}$ aryl, optionally substituted $C_2\text{-}C_9$ heteroaryl, optionally substituted $C_2\text{-}C_6$ heteroalkenyl, optionally substituted-O— $C_3\text{-}C_6$ carbocyclyl, hydroxyl, mercapto, or optionally substituted amino; or R^{41} and R^{42} , R^{42} and R^{43} , and/or R^{43} and R^{44} , together with the carbon atoms to which each is attached, combine to form



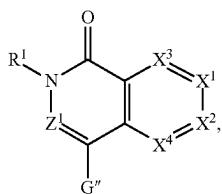
is optionally substituted $C_6\text{-}C_{10}$ aryl, optionally substituted $C_3\text{-}C_{10}$ carbocyclyl, optionally substituted $C_2\text{-}C_9$ heteroaryl, or $C_2\text{-}C_9$ heterocyclyl, any of which is optionally substituted with A^2 ,

wherein one of R^{41} , R^{42} , R^{43} , and R^{44} is A^2 , or



is substituted with A^2 ; and

A has the structure of Formula III:



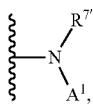
wherein R^1 is H, optionally substituted $C_1\text{-}C_6$ alkyl, optionally substituted $C_2\text{-}C_6$ alkenyl, optionally substituted $C_1\text{-}C_6$ heteroalkyl, or optionally substituted $C_3\text{-}C_{10}$ carbocyclyl;

Z^1 is CR^2 or N;

R^2 is H, halogen, optionally substituted $C_1\text{-}C_6$ alkyl, optionally substituted $C_1\text{-}C_6$ heteroalkyl, optionally substituted $C_3\text{-}C_{10}$ carbocyclyl, optionally substituted $C_2\text{-}C_9$ heterocyclyl, optionally substituted $C_6\text{-}C_{10}$ aryl, or optionally substituted $C_2\text{-}C_9$ heteroaryl;

X^1 is N or CH, and X^2 is $C\text{—}R^{7u}$; or X^1 is $C\text{—}R^{7u}$, and X^2 is N or CH;

R^{7u} is



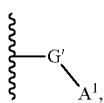
optionally substituted $C_1\text{-}C_6$ alkoxy, optionally substituted amino, optionally substituted sulfone, optionally substituted sulfonamide, optionally substituted carbocyclyl having 3 to 6 atoms, or optionally substituted heterocyclyl having 3 to 6 atoms;

R^7 is H, optionally substituted $C_1\text{-}C_6$ alkyl, optionally substituted $C_1\text{-}C_6$ heteroalkyl, or optionally substituted $C_3\text{-}C_{10}$ carbocyclyl;

X^3 is N or CH;

X^4 is N or CH;

G'' is



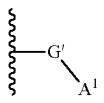
optionally substituted $C_3\text{-}C_{10}$ carbocyclyl, $C_2\text{-}C_9$ heterocyclyl, optionally substituted $C_6\text{-}C_{10}$ aryl, or optionally substituted $C_2\text{-}C_9$ heteroaryl;

G' is optionally substituted $C_3\text{-}C_{10}$ carbocyclene, $C_2\text{-}C_9$ heterocyclene, optionally substituted $C_6\text{-}C_{10}$ arylene, or optionally substituted $C_2\text{-}C_9$ heteroarylene; and

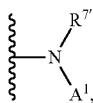
A^1 is a bond between A and the linker,

where G'' is

35



or R^{7u} is



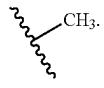
50 or a pharmaceutically acceptable salt thereof, wherein optionally substituted moieties when substituted comprise a substituent selected from alkyl, aryl, carbocyclyl, halogen, hydroxyl, heteroalkyl, heteroaryl, heterocyclyl, amino, azido, cyano, nitro, oxo, sulfonyl, or thiol.

2. The compound of claim 1, wherein R^1 is H, optionally substituted $C_1\text{-}C_6$ alkyl, optionally substituted $C_2\text{-}C_6$ alkenyl, or optionally substituted $C_3\text{-}C_{10}$ carbocyclyl.

3. The compound of claim 2, wherein R^1 is optionally substituted $C_1\text{-}C_6$ alkyl.

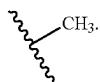
4. The compound of claim 1, wherein R^1 is

60



815

5. The compound of claim 1, wherein Z^1 is CR^2 .
 6. The compound of claim 1, wherein R^2 is H, F, or

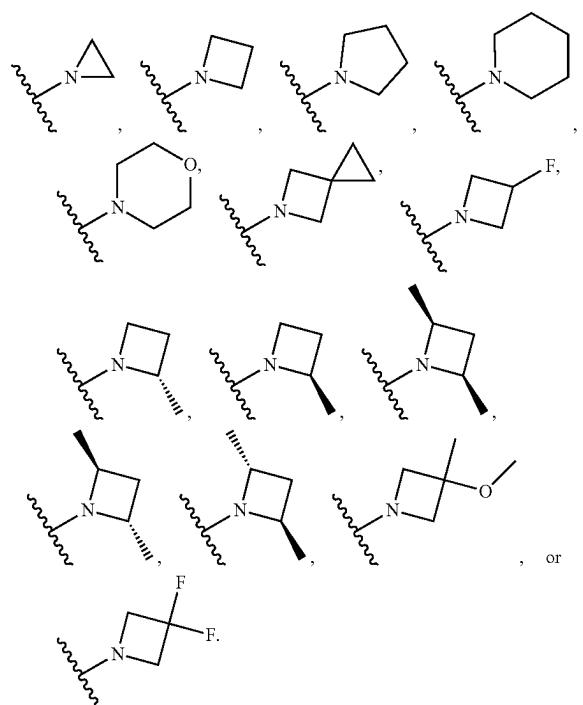


7. The compound of claim 1, wherein X^1 is N and X^2 is 10
 $C—R^{7''}$.

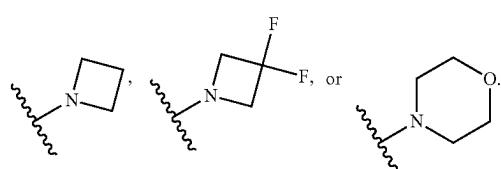
8. The compound of claim 1, wherein $R^{7''}$ is optionally substituted carbocycll having 3 to 6 atoms, or optionally substituted heterocycll having 3 to 6 atoms.

9. The compound of claim 8, wherein $R^{7''}$ is optionally 15 substituted heterocycll having 3 to 6 atoms.

10. The compound of claim 9, wherein $R^{7''}$ is



11. The compound of claim 9, wherein $R^{7''}$ is



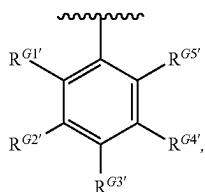
12. The compound of claim 1, wherein G'' is



5

816

13. The compound of claim 1, wherein G' is



wherein

each of $R^{G1'}$, $R^{G2'}$, $R^{G3'}$, $R^{G4'}$, and $R^{G5'}$ is, independently, H, A^1 , halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocycll, optionally substituted C_2-C_9 heterocycll, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted $O—C_3-C_6$ carbocycll, optionally substituted C_1-C_3 alkyl- C_3-C_6 carbocycll, optionally substituted C_1-C_3 alkyl- C_2-C_5 heterocycll, hydroxyl, mercapto, or optionally substituted amino; or $R^{G1'}$ and $R^{G2'}$, $R^{G2'}$ and $R^{G3'}$, $R^{G3'}$ and $R^{G4'}$, and/or $R^{G4'}$ and $R^{G5'}$, together with the carbon atoms to which each is attached, combine to form



and



45 is optionally substituted C_6-C_{10} aryl, optionally substituted C_3-C_{10} carbocycll, optionally substituted C_2-C_9 heteroaryl, or optionally substituted C_2-C_9 heterocycll, any of which is optionally substituted with A^1 ,

wherein one of $R^{G1'}$, $R^{G2'}$, $R^{G3'}$, $R^{G4'}$, and $R^{G5'}$ is A^1 , or

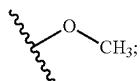
50



is substituted with A^1 .

14. The compound of claim 13, wherein $R^{G1'}$ is H; $R^{G2'}$ is

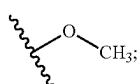
60



65

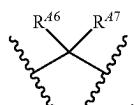
817

R^{G3} is A^1 ; R^{G4} is

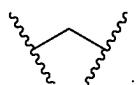


and $R^{G5'}$ is H.

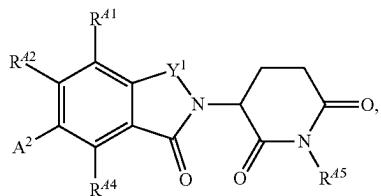
15. The compound of claim 1, wherein Y¹ is



16. The compound of claim 1, wherein Y¹ is

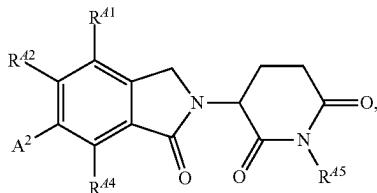


17. The compound of claim 1, wherein the structure of ³⁰ Formula A has the structure of Formula A⁹:



or a pharmaceutically acceptable salt thereof.

5

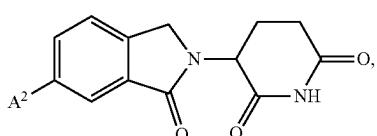
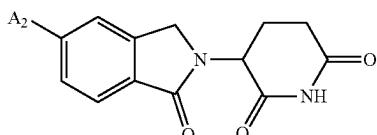


Formula A10

or a pharmaceutically acceptable salt thereof.

19. The compound of claim 1, wherein the structure of Formula A is

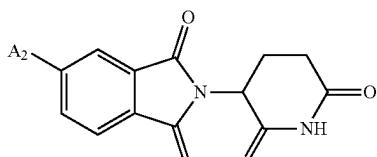
20



or

Formula A9 35

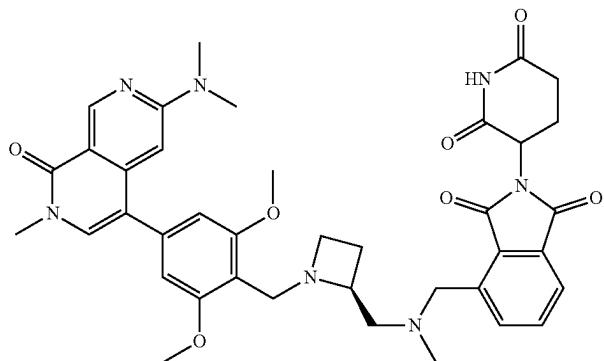
Formula 13



20. The compound of claim 1, wherein the compound has the structure;

Com- ound No.	Structure
---------------------	-----------

D2

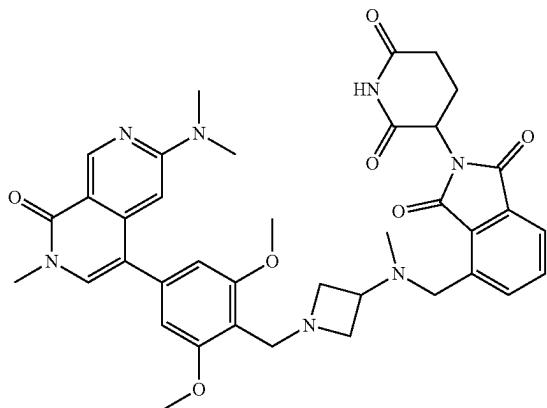


-continued

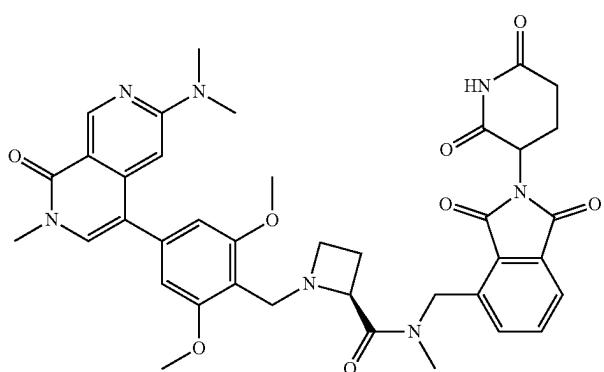
Com-
ound
No.

Structure

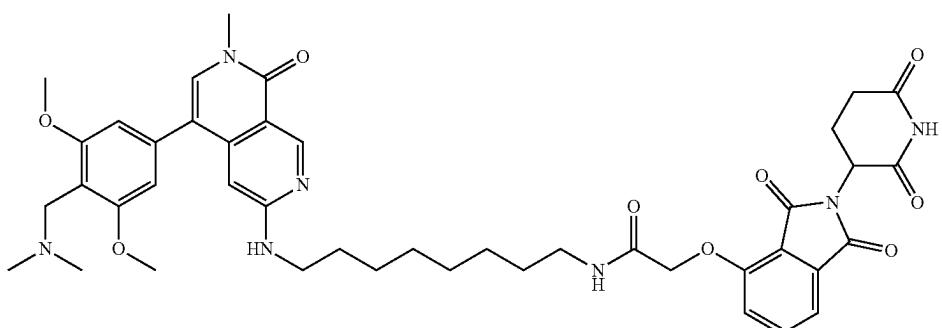
D3



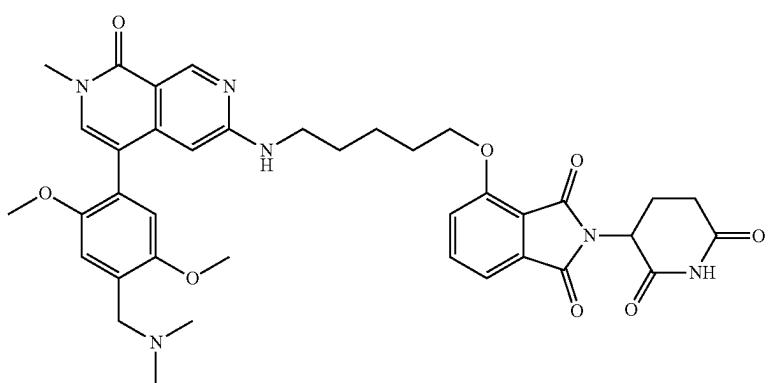
D4



D5



D6

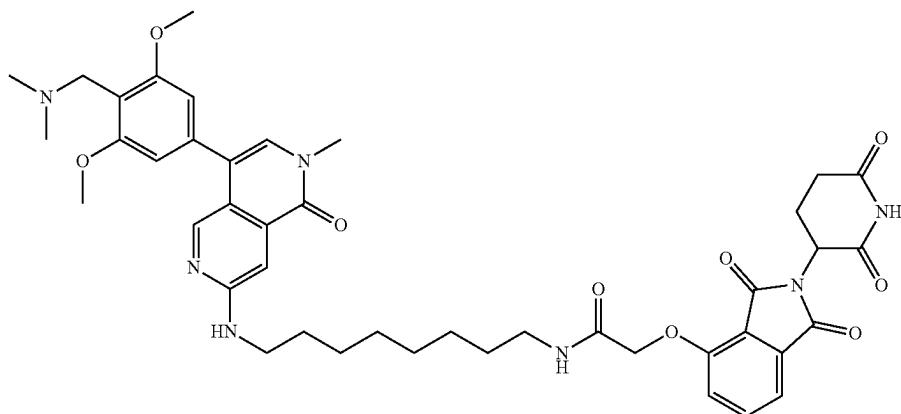


-continued

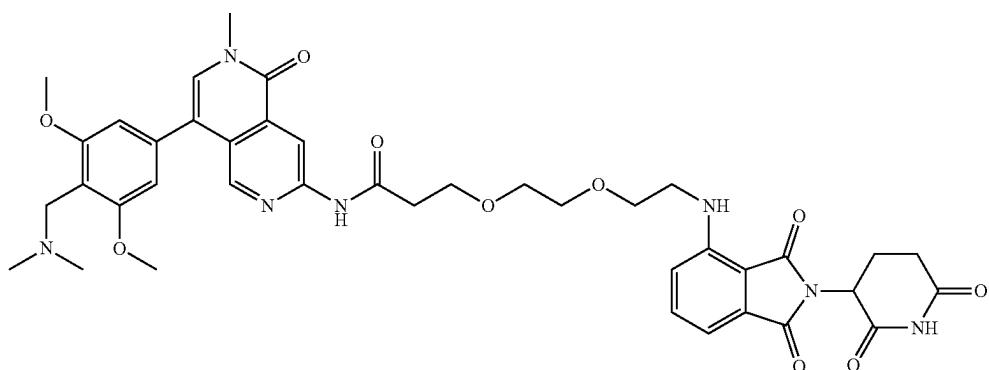
Com-
ound
No.

Structure

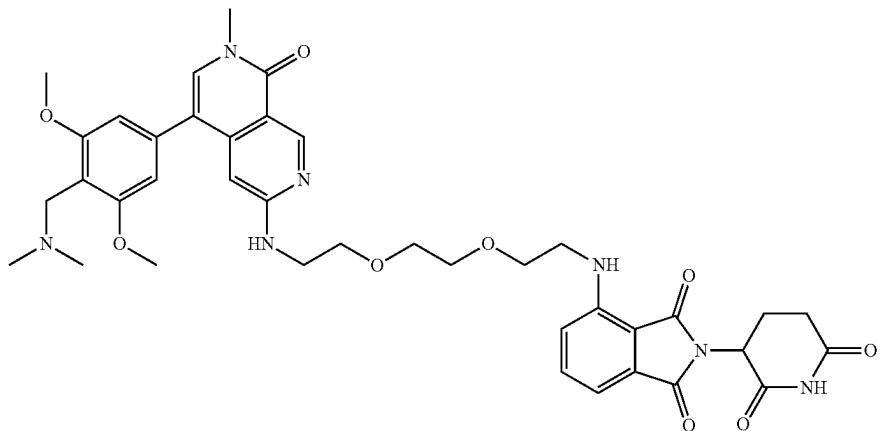
D8



D9



D10



-continued

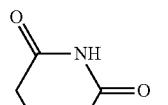
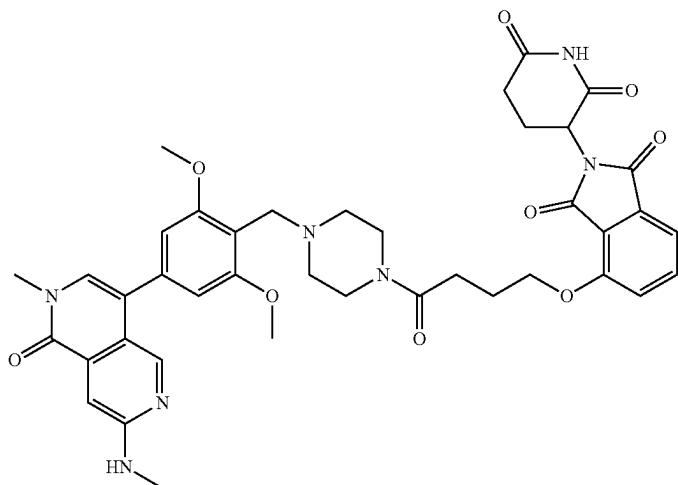
Compound No.	Structure
D11	
D12	
D13	
D14	

-continued

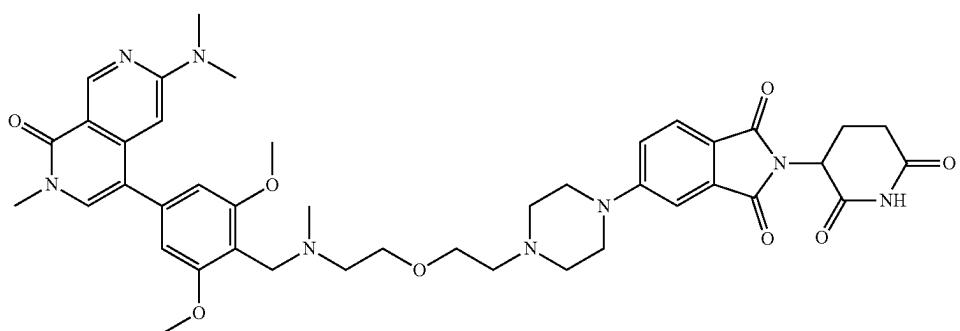
Com-
ound
No.

Structure

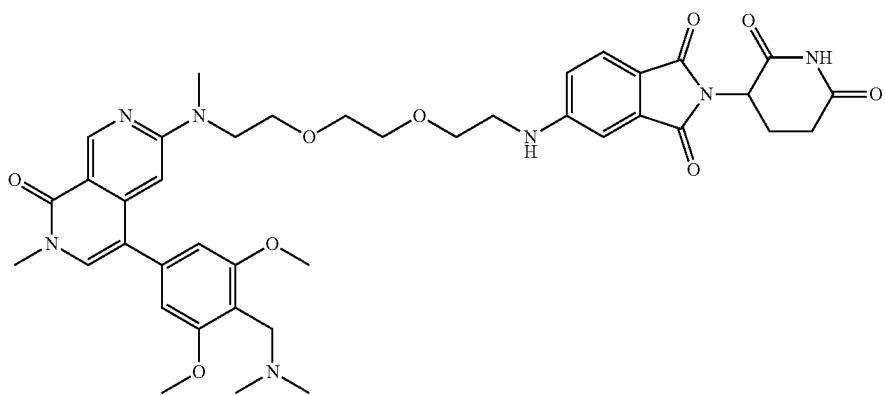
D17



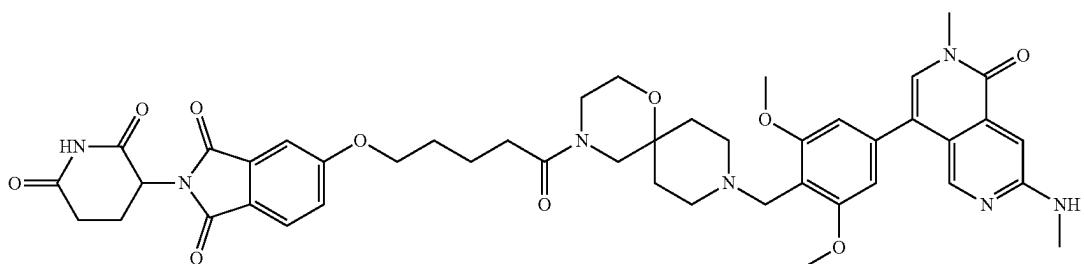
D21



D22



D23

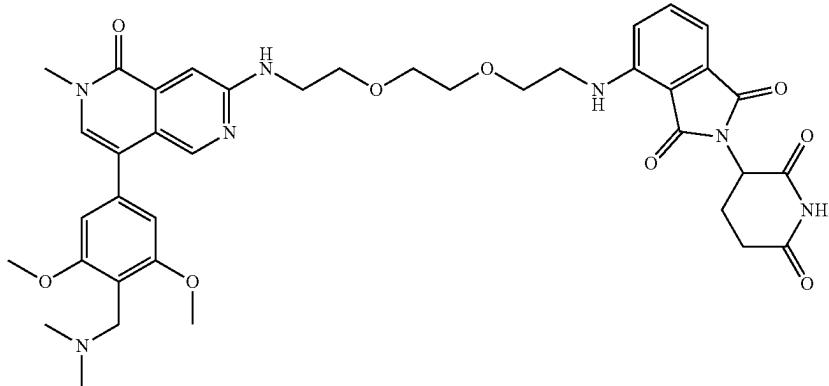


-continued

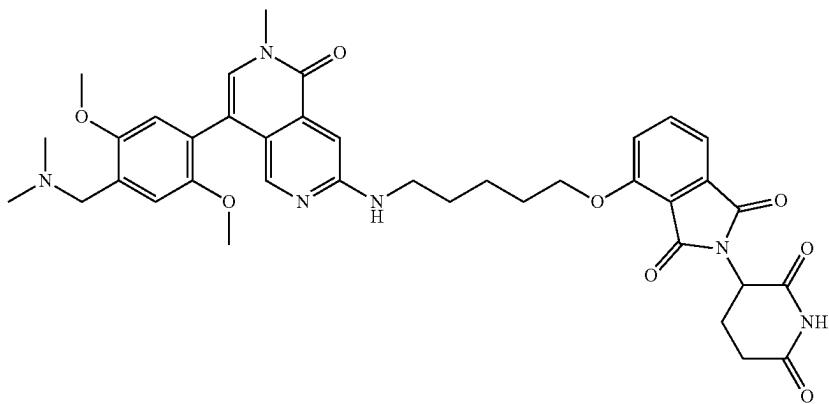
Compound
No.

Structure

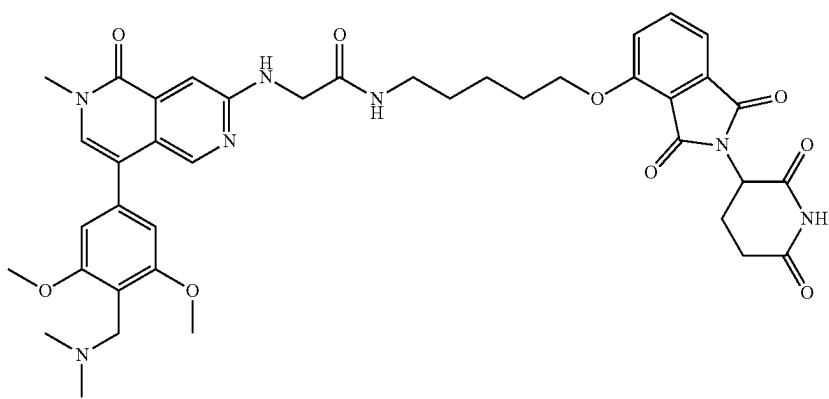
D24



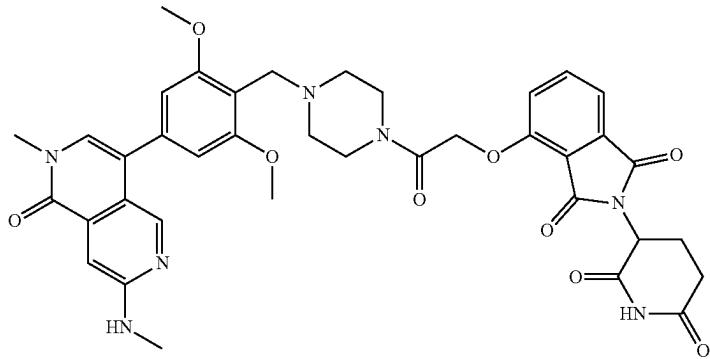
D25



D26



D29

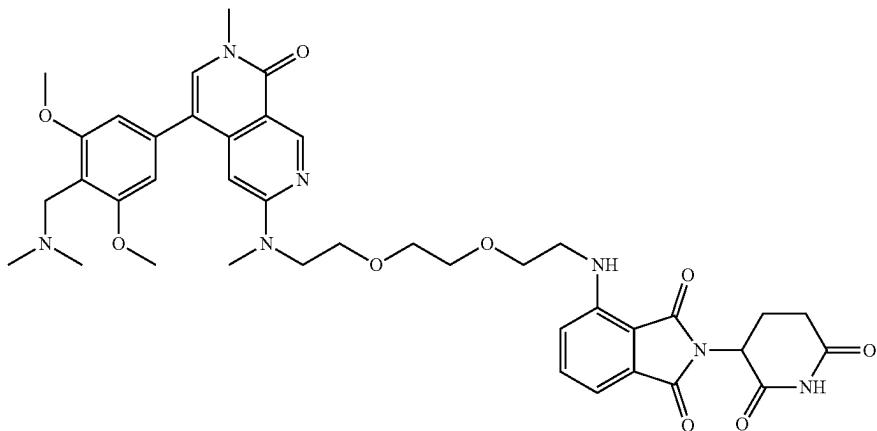


-continued

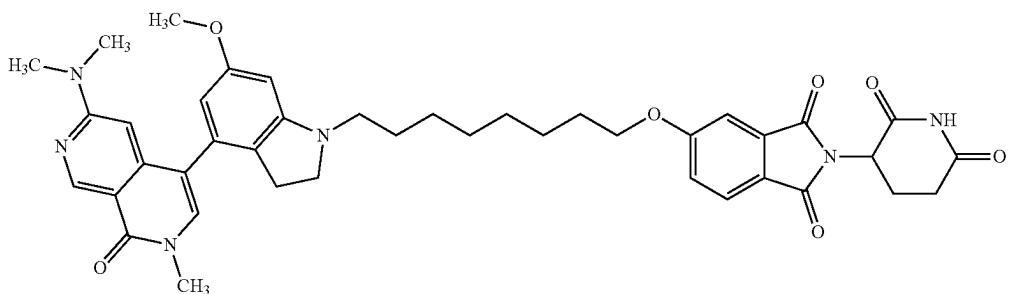
Com-
ound
No.

Structure

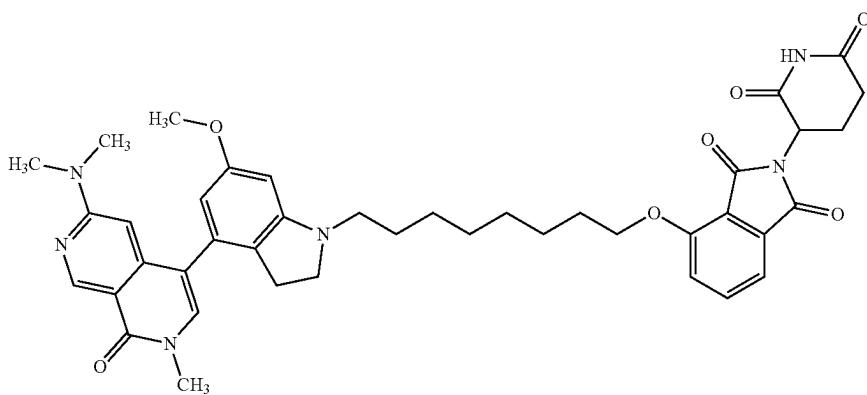
D31



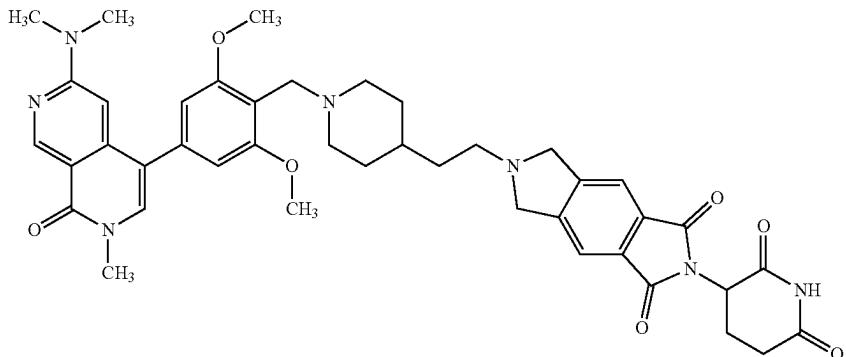
D45



D47



D59



831

832

-continued

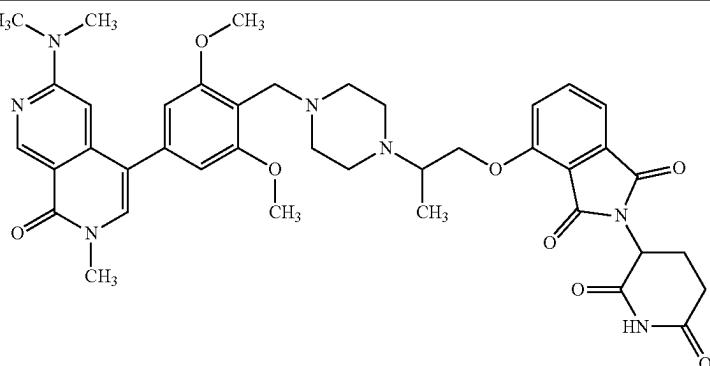
Compound No.	Structure
D61	
D62	
D63	
D70	

-continued

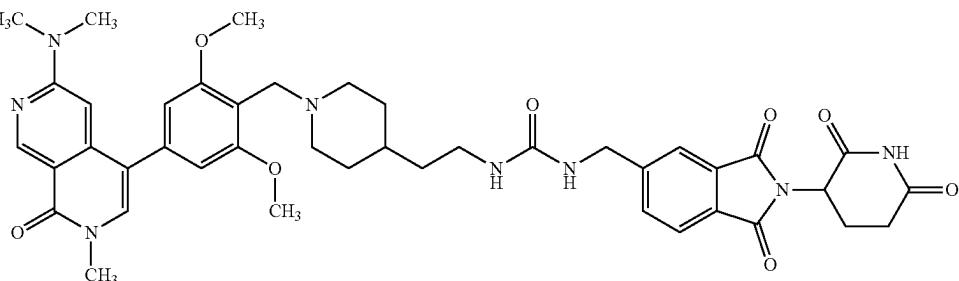
Compound
No.

Structure

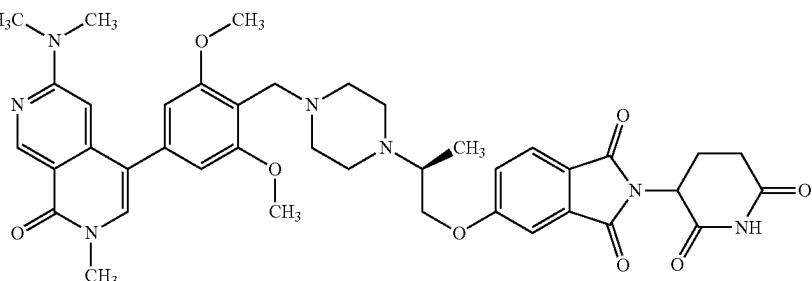
D71



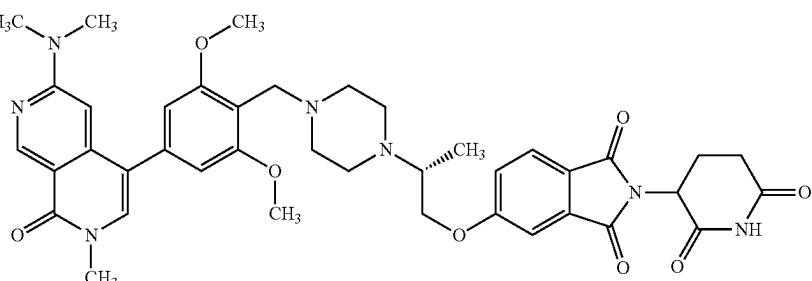
D74



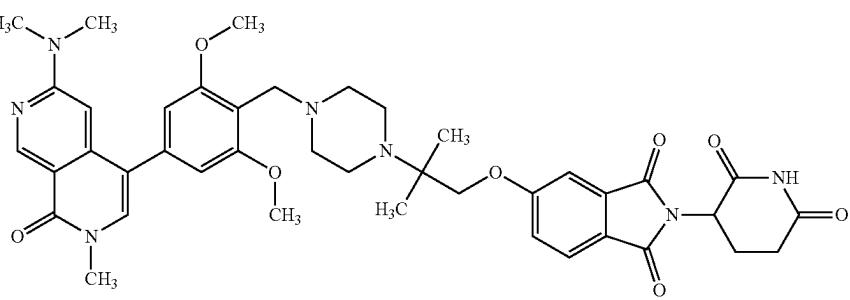
D76



D77



D78

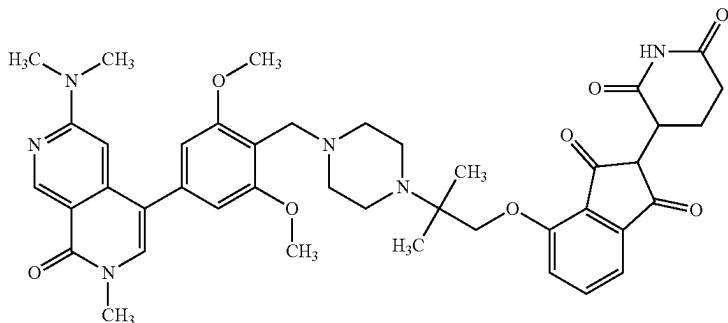


-continued

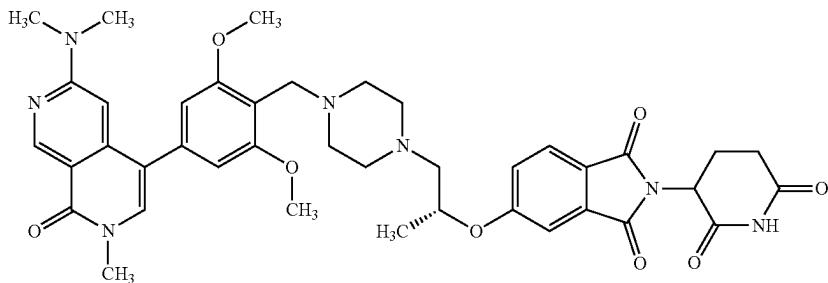
Compound
No.

Structure

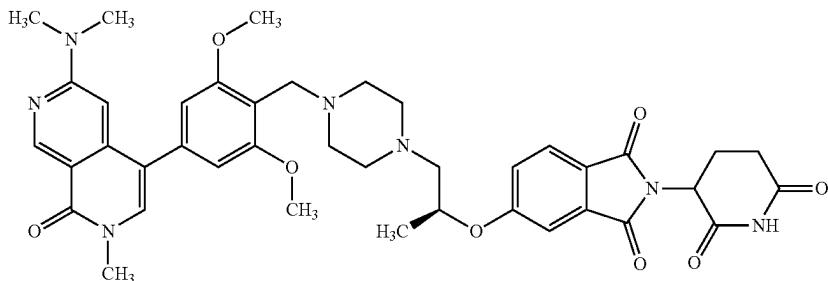
D81



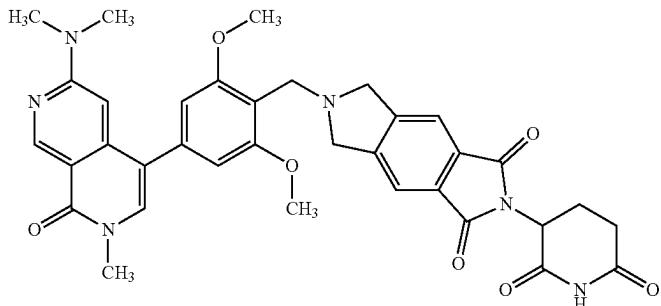
D82



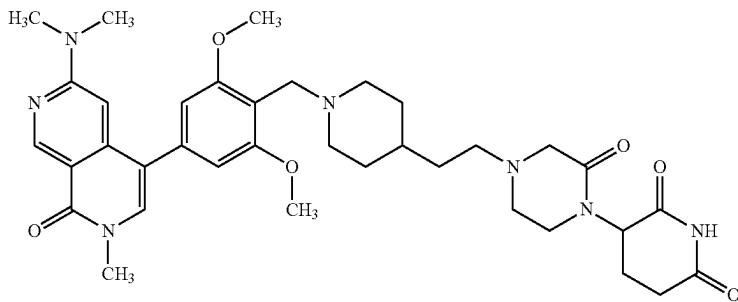
D83



D86



D88

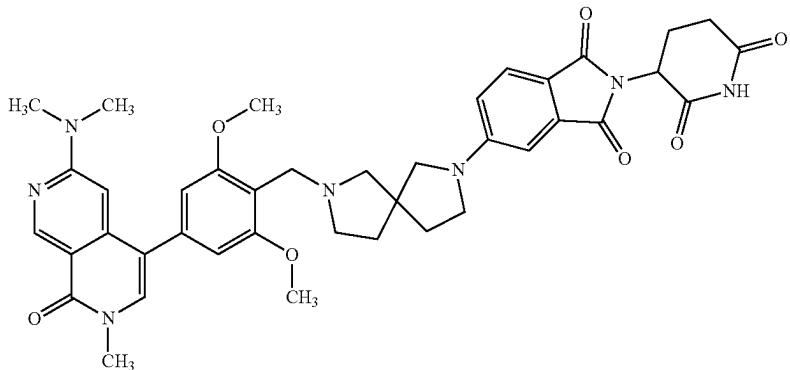


-continued

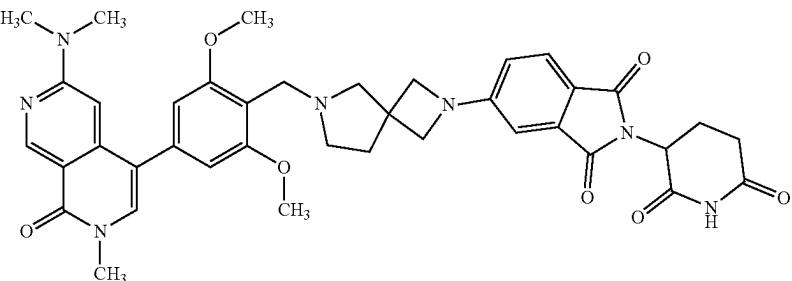
Com-
ound

No. Structure

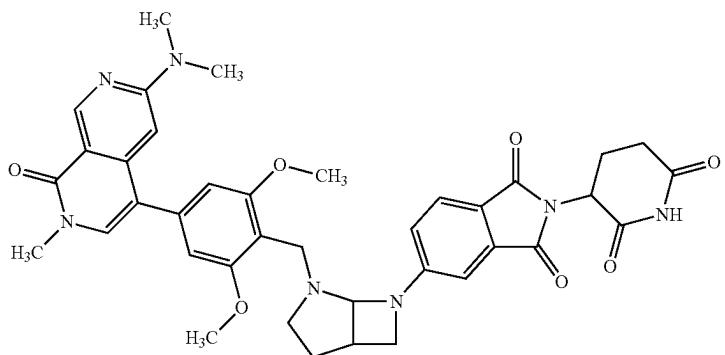
D90



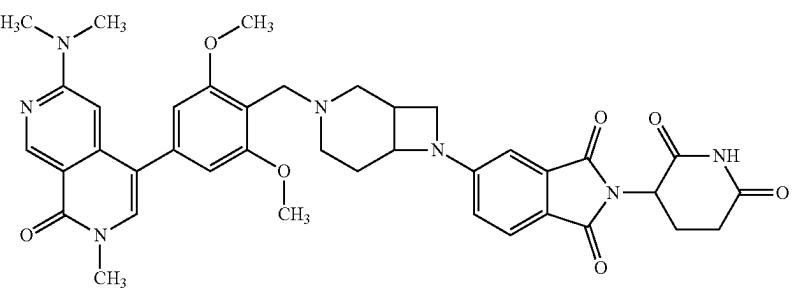
D91



D92



D93

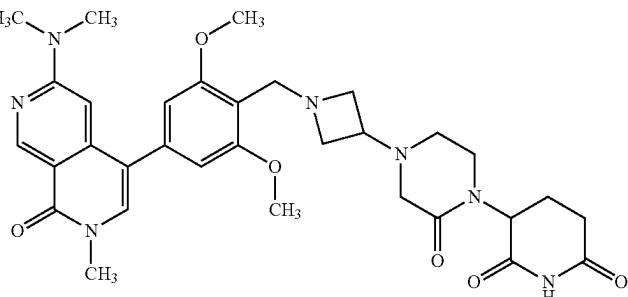


-continued

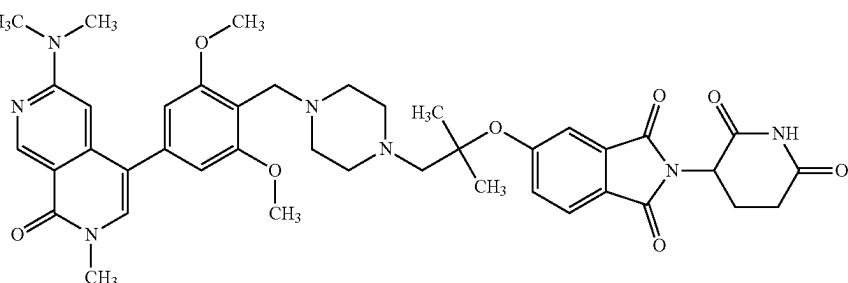
Com-
ound
No.

Structure

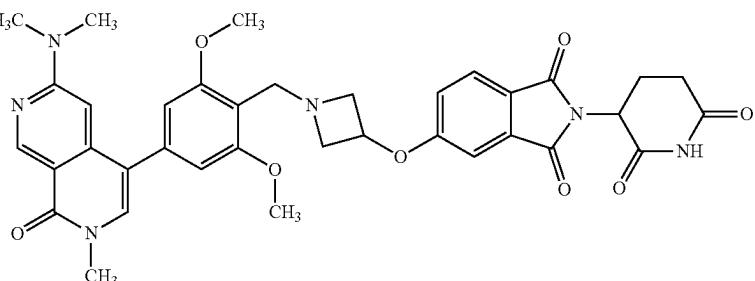
D94



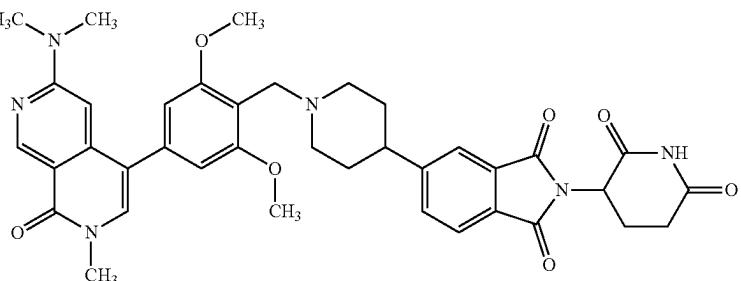
D96



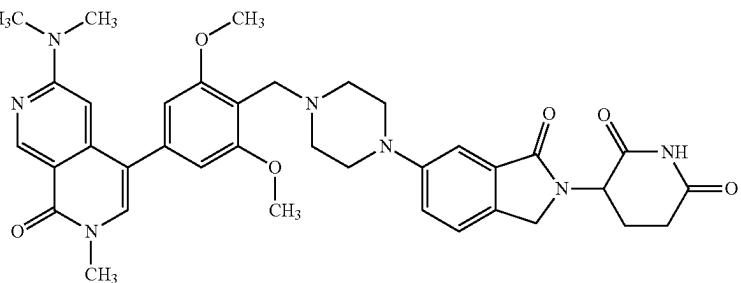
D98



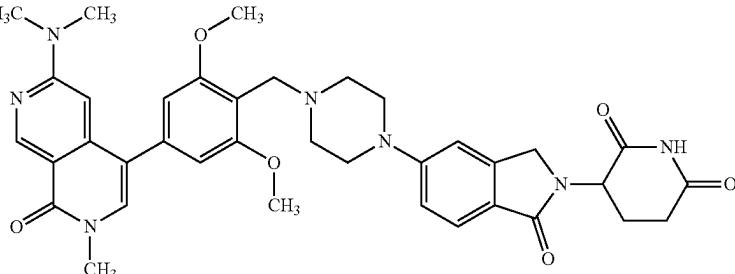
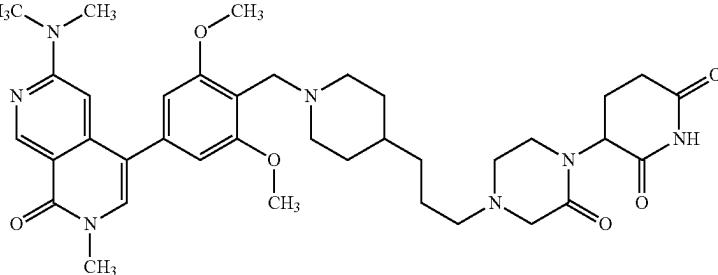
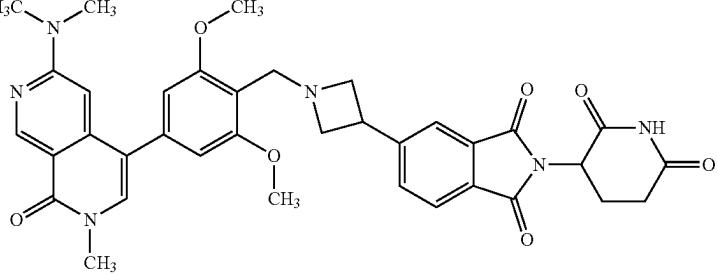
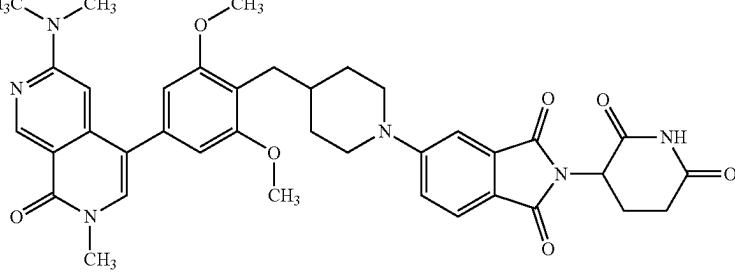
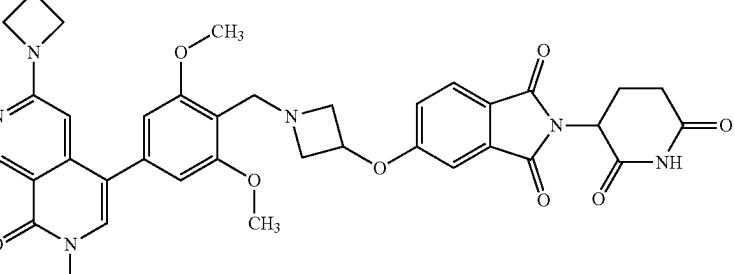
D104



D113



-continued

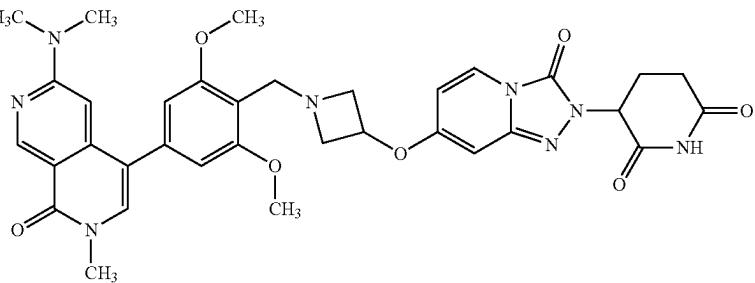
Compound No.	Structure
D114	
D117	
D132	
D133	
D137	

-continued

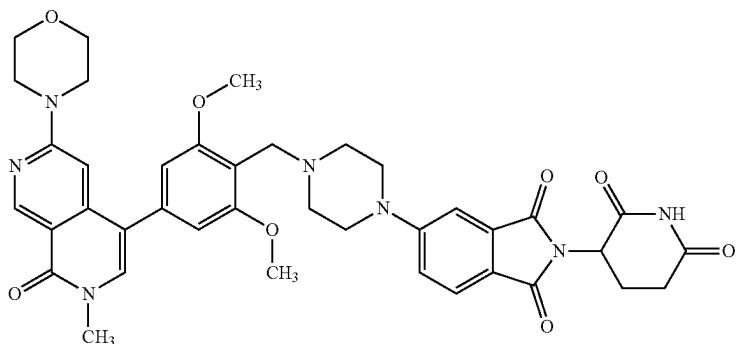
Com-
ound

No. Structure

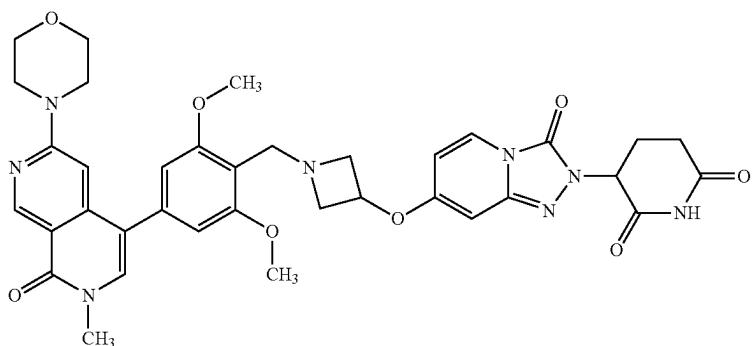
D138



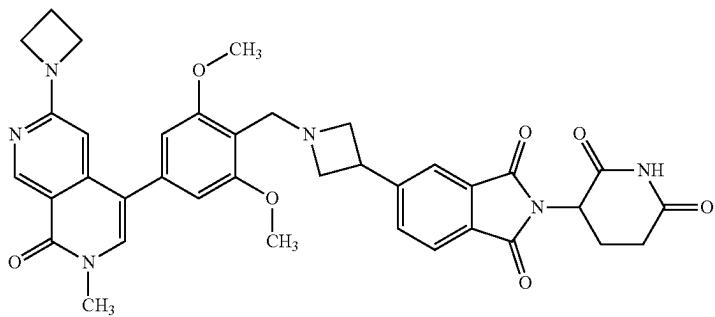
D141



D144



D146

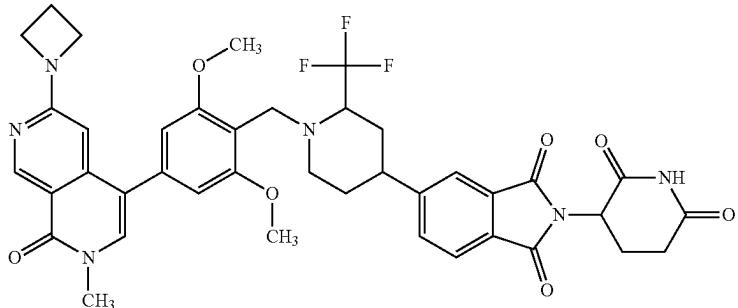


-continued

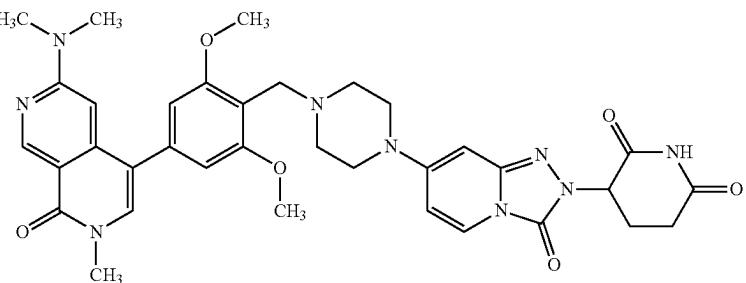
Compound
No.

Structure

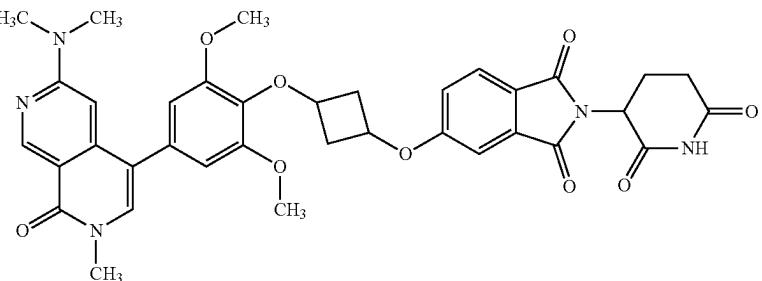
D150



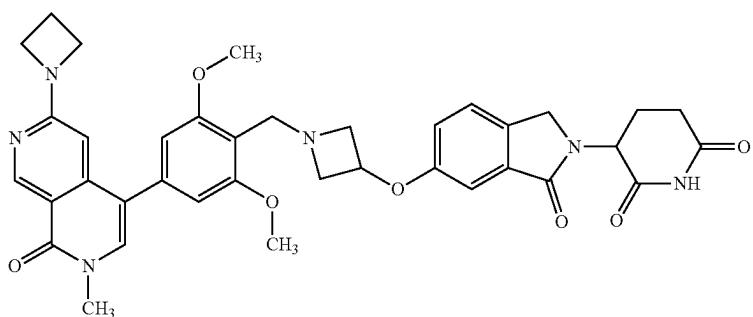
D154



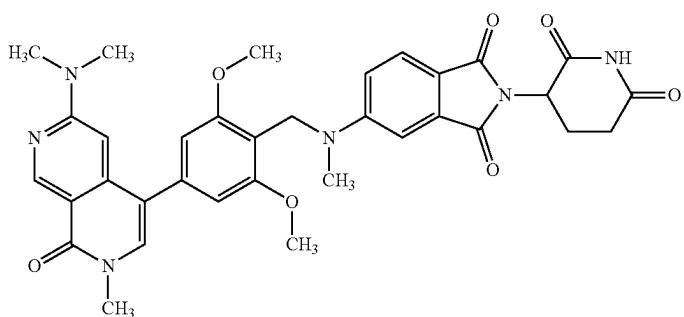
D158



D163



D164

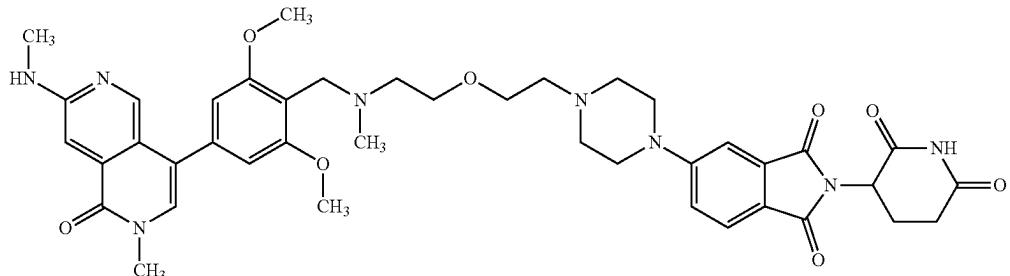


-continued

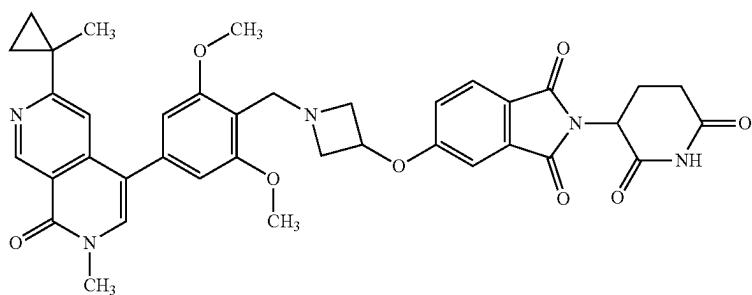
Compound
No.

Structure

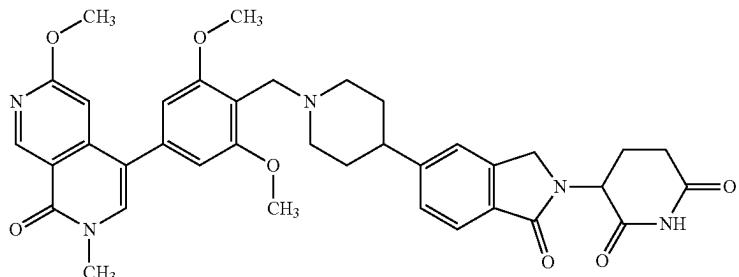
D166



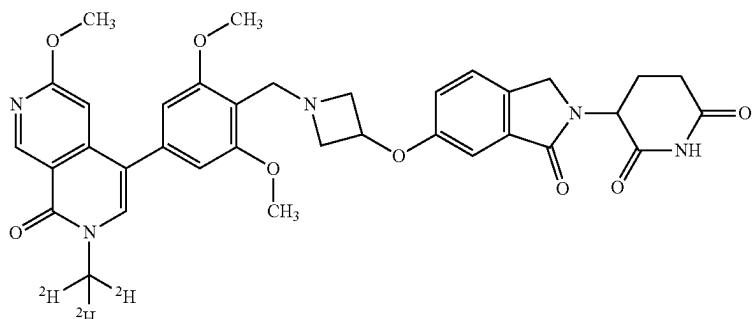
D229



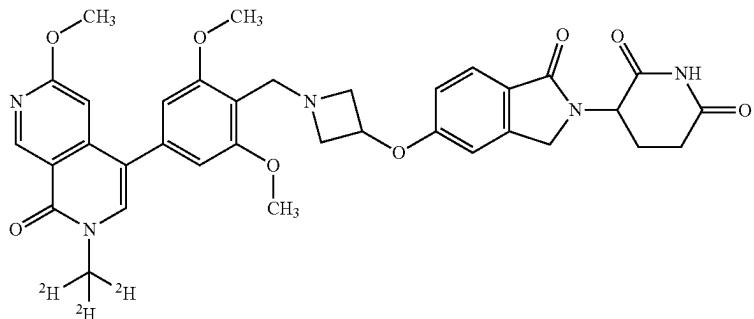
D235



D239



D242

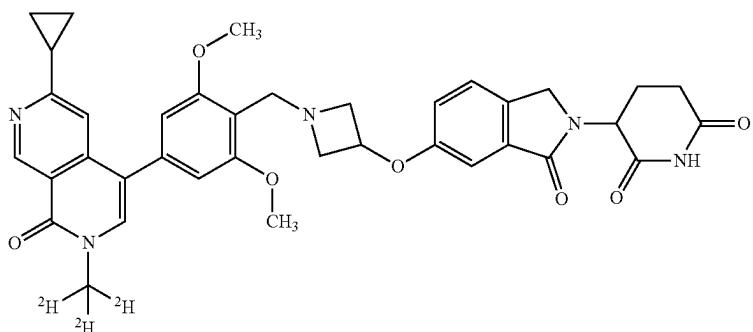


-continued

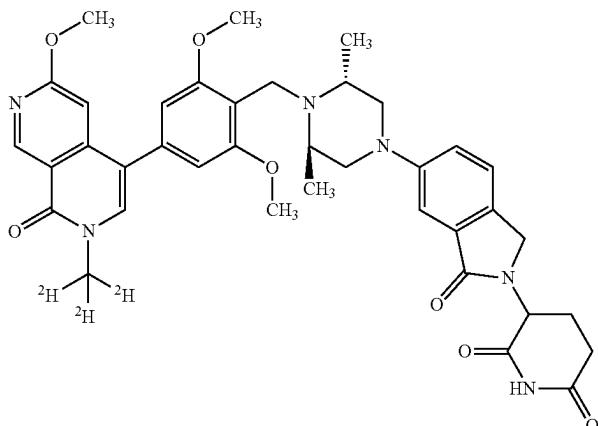
Com-
ound
No.

Structure

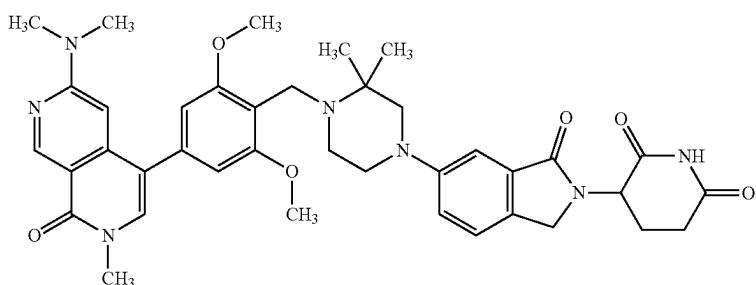
D247



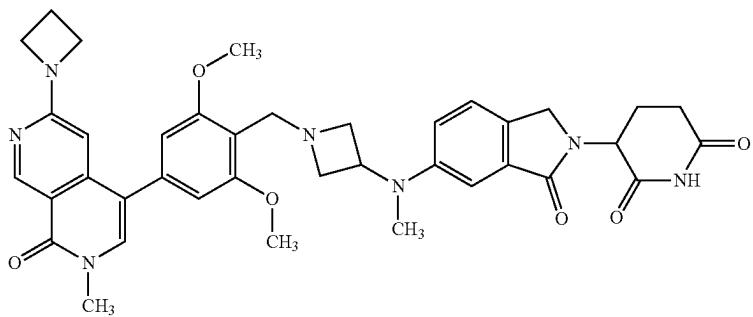
D254



D255



D256

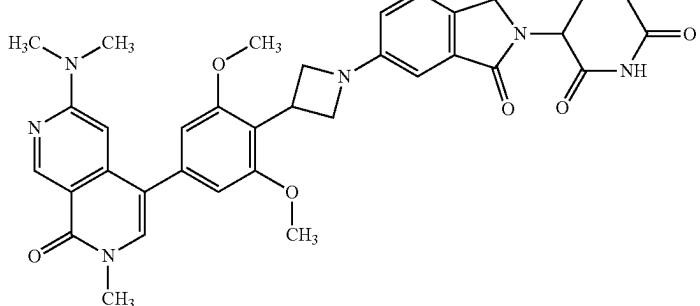


-continued

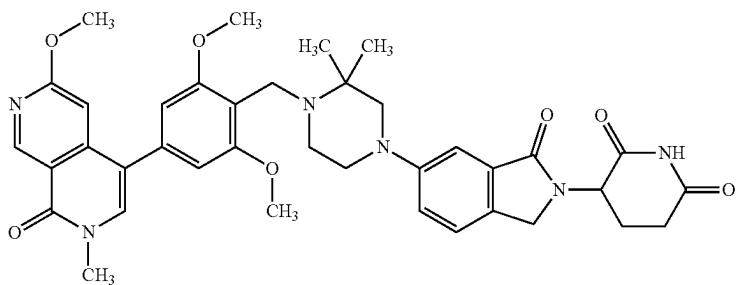
Compound
No.

Structure

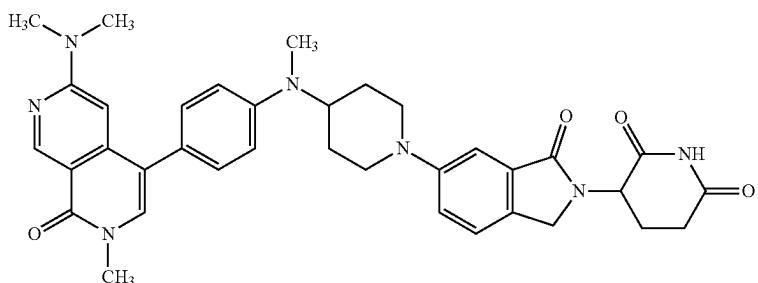
D257



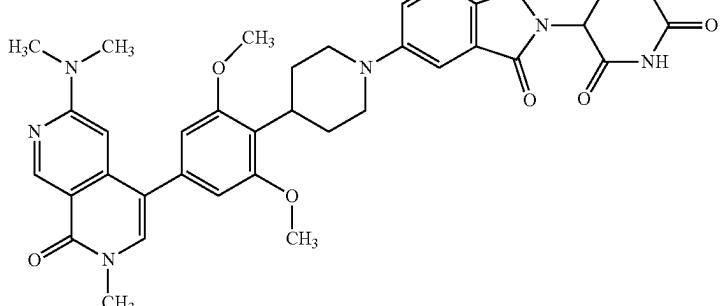
D260



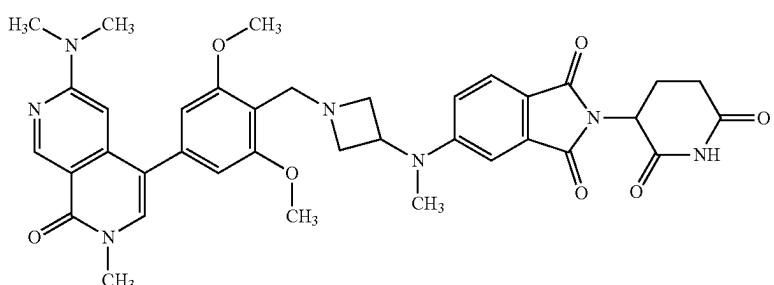
D262



D265



D268



-continued

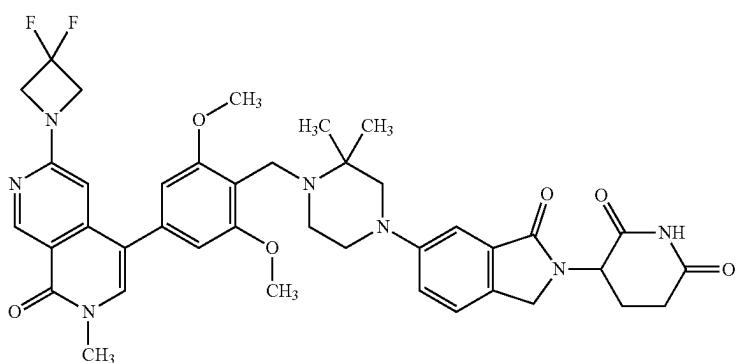
Compound No.	Structure
D270	
D274	
D276	
D277	

-continued

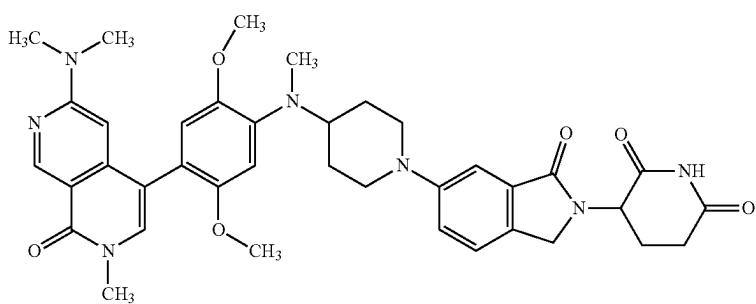
Com-
ound
No.

Structure

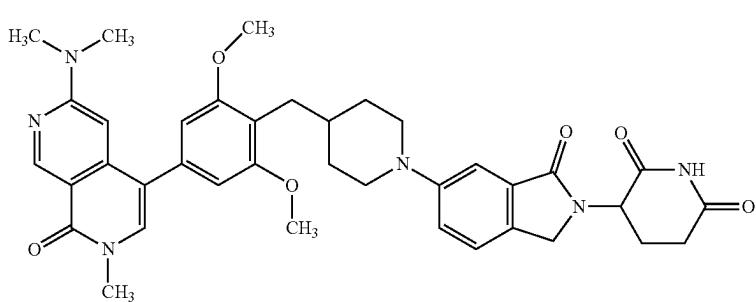
D278



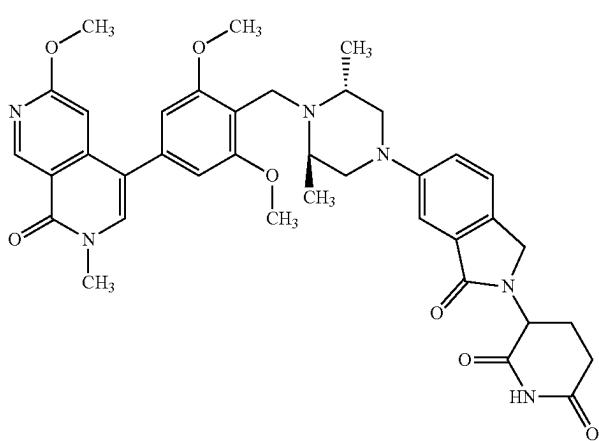
D279



D280



D281

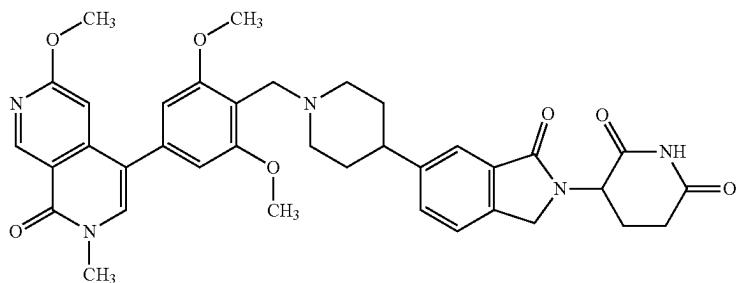


-continued

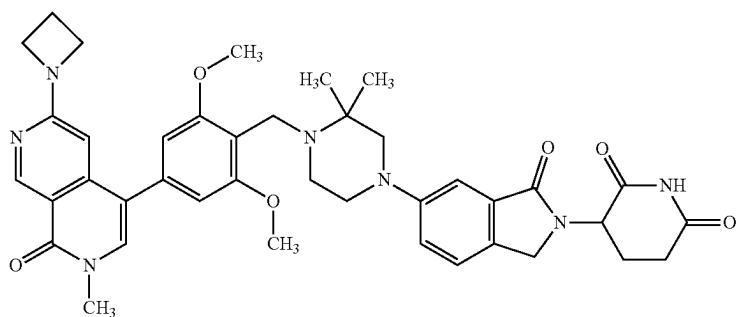
Com-
ound
No.

Structure

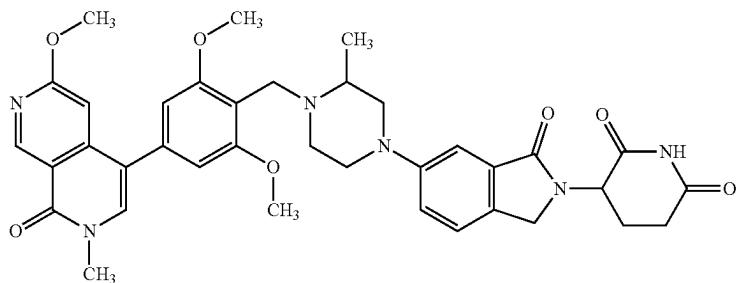
D288



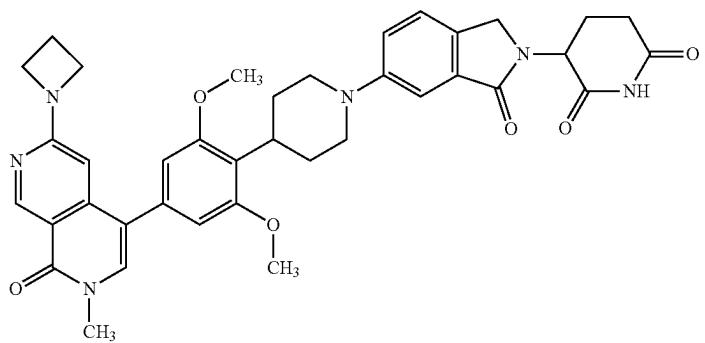
D290



D293



D294

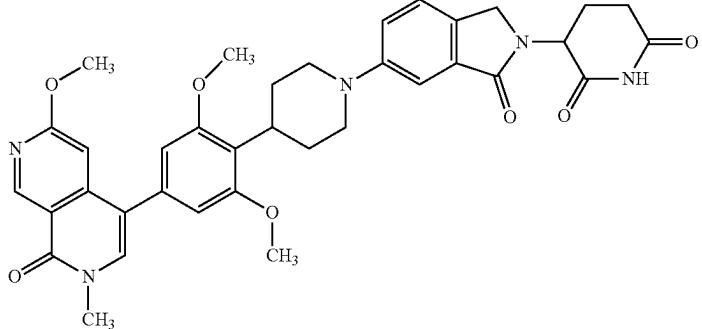


-continued

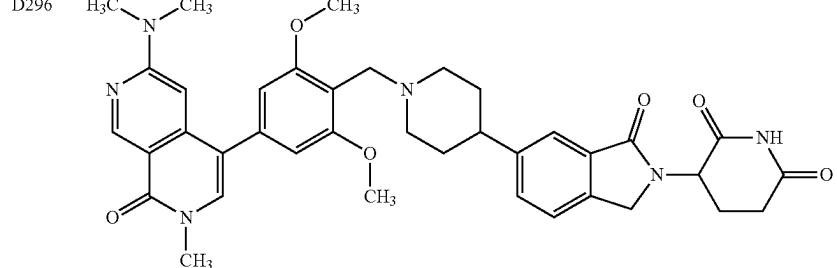
Compound
No.

Structure

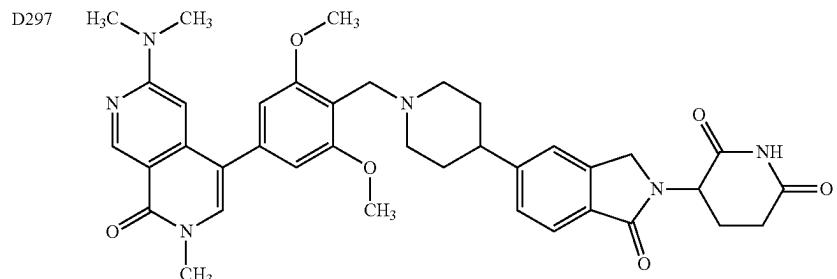
D295



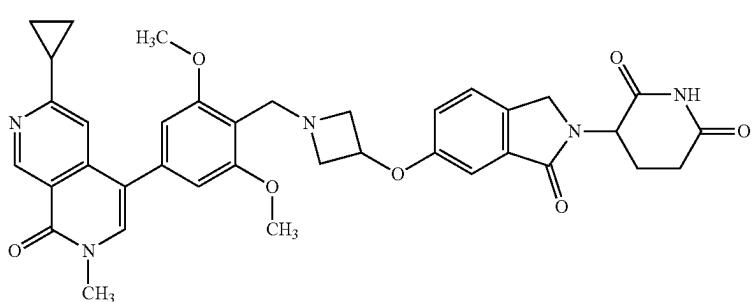
D296



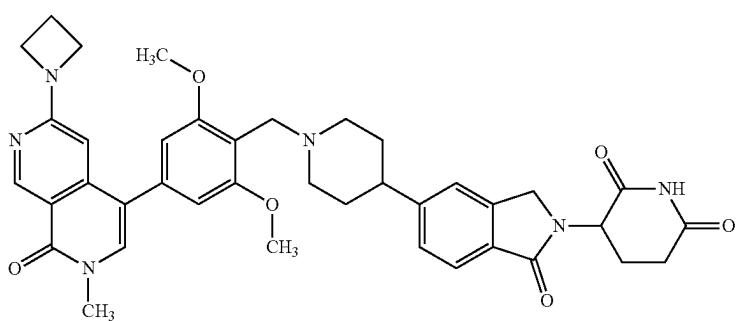
D297



D300



D312

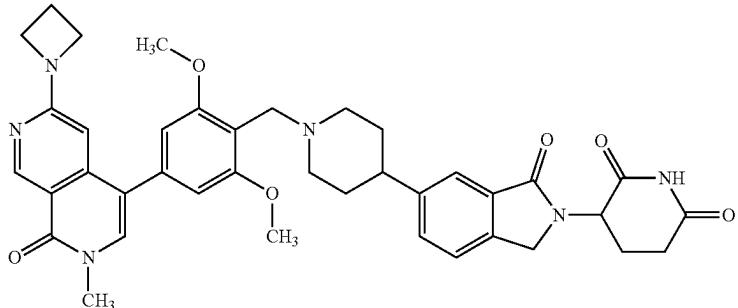


-continued

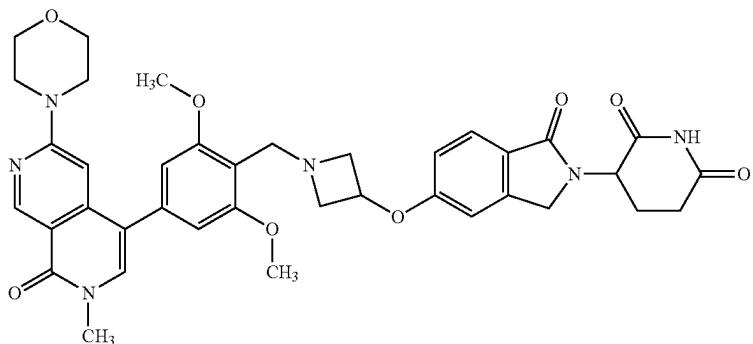
Compound
No.

Structure

D313



D314



or a pharmaceutically acceptable salt thereof.

21. A pharmaceutical composition comprising the compound of claim 1 and a pharmaceutically acceptable excipient.

22. A method of treating synovial sarcoma in a subject in need thereof, the method including administering to the subject an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof.

* * * * *