US Patent & Trademark Office
Patent Public Search | Text View

United States Patent	12384776
Kind Code	B2
Date of Patent	August 12, 2025
Inventor(s)	Ruppel; Sabine K. et al.

Compounds and uses thereof

Abstract

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

Inventors: **Ruppel; Sabine K. (Cambridge, MA), Yang; Zhaoxia (Belmont, MA), Lowe; Jason T. (East Bridgewater, MA), Voigt; Johannes H. (Cambridge, MA), Netherton; Matthew (Cambridge, MA), Brucelle; Francois (Belmont, MA), Vaswani; Rishi G. (Lexington, MA)**

Applicant: **Foghorn Therapeutics Inc.** (Cambridge, MA)

Family ID: **1000008748097**

Assignee: **FOGHORN THERAPEUTICS INC. (Cambridge, MA)**

Appl. No.: **17/425250**

Filed (or PCT Filed): **January 29, 2020**

PCT No.: **PCT/US2020/015744**

PCT Pub. No.: **WO2020/160196**

PCT Pub. Date: August 06, 2020

Prior Publication Data

Document Identifier	Publication Date
US 20220098190 A1	Mar. 31, 2022

Related U.S. Application Data

us-provisional-application US 62881114 20190731
us-provisional-application US 62798384 20190129

Publication Classification

Int. Cl.: **C07D471/04** (20060101); **C07D401/14** (20060101); **C07D471/10** (20060101); **C07D491/048** (20060101); **C07D519/00** (20060101)

U.S. Cl.:

CPC **C07D471/04** (20130101); **C07D401/14** (20130101); **C07D471/10** (20130101); **C07D491/048** (20130101); **C07D519/00** (20130101);

Field of Classification Search

CPC: C07D (471/04); C07D (401/14); C07D (471/10); C07D (491/048); C07D (519/00)

References Cited

U.S. PATENT DOCUMENTS

Patent No.	Issued Date	Patentee Name	U.S. Cl.	CPC
2788341	12/1956	Schwyzer et al.	N/A	N/A
3717642	12/1972	Von Strandtmann	N/A	N/A
4109496	12/1977	Allemann et al.	N/A	N/A
4650796	12/1986	George et al.	N/A	N/A
4868103	12/1988	Stavrianopoulos et al.	N/A	N/A
5223409	12/1992	Ladner et al.	N/A	N/A
5225422	12/1992	Nagata et al.	N/A	N/A
5283317	12/1993	Saifer et al.	N/A	N/A
5631169	12/1996	Lakowicz et al.	N/A	N/A
5677158	12/1996	Zhou et al.	N/A	N/A
5801030	12/1997	McVey et al.	N/A	N/A
5858358	12/1998	June et al.	N/A	N/A
5883223	12/1998	Gray	N/A	N/A
6180612	12/2000	Hockensmith et al.	N/A	N/A
6309634	12/2000	Bankiewicz et al.	N/A	N/A
6352694	12/2001	June et al.	N/A	N/A
6534055	12/2002	June et al.	N/A	N/A
6551786	12/2002	Manfredi	N/A	N/A
6683058	12/2003	Tuszynski	N/A	N/A
6692964	12/2003	June et al.	N/A	N/A
6716622	12/2003	Curiel et al.	N/A	N/A
6797514	12/2003	Berenson et al.	N/A	N/A
6867041	12/2004	Berenson et al.	N/A	N/A
6887466	12/2004	June et al.	N/A	N/A
6905680	12/2004	June et al.	N/A	N/A
6905681	12/2004	June et al.	N/A	N/A
6905874	12/2004	Berenson et al.	N/A	N/A
6995011	12/2005	Itoh et al.	N/A	N/A
7056883	12/2005	Ito et al.	N/A	N/A
7067318	12/2005	June et al.	N/A	N/A
7144575	12/2005	June et al.	N/A	N/A
7172869	12/2006	June et al.	N/A	N/A
7175843	12/2006	June et al.	N/A	N/A
7205103	12/2006	Emerson	N/A	N/A
7232566	12/2006	June et al.	N/A	N/A
8324367	12/2011	Kaemmerer et al.	N/A	N/A

8642660	12/2013	Goldfarb	N/A	N/A
8697359	12/2013	Zhang	N/A	N/A
8703761	12/2013	Forster et al.	N/A	N/A
8771945	12/2013	Zhang	N/A	N/A
8795965	12/2013	Zhang	N/A	N/A
8945861	12/2014	Bomgarden et al.	N/A	N/A
8946268	12/2014	Lau et al.	N/A	N/A
9072052	12/2014	Griffin et al.	N/A	N/A
9126985	12/2014	Kley et al.	N/A	N/A
9271978	12/2015	Liu et al.	N/A	N/A
9353051	12/2015	Byrd et al.	N/A	N/A
9410943	12/2015	Kadoch et al.	N/A	N/A
9546206	12/2016	Ring et al.	N/A	N/A
9636323	12/2016	Lin et al.	N/A	N/A
9708338	12/2016	Yukimasa et al.	N/A	N/A
9708348	12/2016	Castro et al.	N/A	N/A
9750816	12/2016	Bradner et al.	N/A	N/A
9821068	12/2016	Bradner et al.	N/A	N/A
9850543	12/2016	Jagani et al.	N/A	N/A
9919998	12/2017	Ebright et al.	N/A	N/A
9932340	12/2017	Dai et al.	N/A	N/A
10105420	12/2017	Kadoch et al.	N/A	N/A
10131637	12/2017	Abdel-Meguid et al.	N/A	N/A
10207998	12/2018	Derbyshire et al.	N/A	N/A
10239888	12/2018	Bradner et al.	N/A	N/A
10266850	12/2018	Doudna et al.	N/A	N/A
10308614	12/2018	Albrecht et al.	N/A	N/A
10464925	12/2018	Bradner et al.	N/A	N/A
10646575	12/2019	Phillips et al.	N/A	N/A
10660968	12/2019	Phillips et al.	N/A	N/A
10669253	12/2019	Bradner et al.	N/A	N/A
10849982	12/2019	Phillips et al.	N/A	N/A
10905768	12/2020	Phillips et al.	N/A	N/A
10976320	12/2020	Dykhuizen et al.	N/A	N/A
11059801	12/2020	Bradner et al.	N/A	N/A
11149254	12/2020	Szalay et al.	N/A	N/A
11185592	12/2020	Phillips et al.	N/A	N/A
11285218	12/2021	Buckley	N/A	A61P 35/00
11306105	12/2021	Bradner et al.	N/A	N/A
11414416	12/2021	Ruppel et al.	N/A	N/A
11485732	12/2021	Vaswani et al.	N/A	N/A
11485743	12/2021	Mainolfi et al.	N/A	N/A
11497752	12/2021	Anthony et al.	N/A	N/A
11524949	12/2021	Phillips et al.	N/A	N/A
11560381	12/2022	Ruppel et al.	N/A	N/A
11583586	12/2022	Bradner et al.	N/A	N/A
11639345	12/2022	Bloch et al.	N/A	N/A
11691972	12/2022	Nasveschuk et al.	N/A	N/A
11773085	12/2022	Zhou et al.	N/A	N/A
2002/0037281	12/2001	Davidson et al.	N/A	N/A
2003/0027335	12/2002	Ruley et al.	N/A	N/A
2004/0216178	12/2003	Jones et al.	N/A	N/A

2005/0079512	12/2004	Emerson et al.	N/A	N/A
2005/0130919	12/2004	Xu et al.	N/A	N/A
2006/0058255	12/2005	Chen et al.	N/A	N/A
2006/0121005	12/2005	Berenson et al.	N/A	N/A
2007/0105181	12/2006	Pope et al.	N/A	N/A
2008/0221157	12/2007	Chakravarty et al.	N/A	N/A
2010/0048565	12/2009	Frenkel et al.	N/A	N/A
2011/0061116	12/2010	Haldar et al.	N/A	N/A
2012/0035244	12/2011	Chinnaiyan et al.	N/A	N/A
2014/0287931	12/2013	Bernards et al.	N/A	N/A
2015/0057169	12/2014	Siu et al.	N/A	N/A
2016/0058872	12/2015	Crew et al.	N/A	N/A
2016/0130663	12/2015	Kohno et al.	N/A	N/A
2016/0176916	12/2015	Bradner et al.	N/A	N/A
2017/0014491	12/2016	Kadoch et al.	N/A	N/A
2017/0050968	12/2016	Bennett et al.	N/A	N/A
2017/0158709	12/2016	Boloor	N/A	N/A
2018/0044335	12/2017	Martin et al.	N/A	N/A
2018/0085465	12/2017	Bradner et al.	N/A	N/A
2018/0105500	12/2017	Derbyshire et al.	N/A	N/A
2018/0134684	12/2017	Bradner et al.	N/A	N/A
2018/0140722	12/2017	Willis et al.	N/A	N/A
2018/0187614	12/2017	Dudar	N/A	N/A
2018/0213422	12/2017	Kazmi et al.	N/A	N/A
2018/0215766	12/2017	Bair et al.	N/A	N/A
2018/0258491	12/2017	Jagani et al.	N/A	N/A
2018/0327419	12/2017	Bradner et al.	N/A	N/A
2018/0328913	12/2017	Kadoch et al.	N/A	N/A
2019/0071415	12/2018	Bradner et al.	N/A	N/A
2019/0076539	12/2018	Phillips et al.	N/A	N/A
2019/0247509	12/2018	Buckley et al.	N/A	N/A
2020/0069669	12/2019	Grassian et al.	N/A	N/A
2020/0140456	12/2019	Phillips et al.	N/A	N/A
2020/0206344	12/2019	Kadoch et al.	N/A	N/A
2021/0009568	12/2020	Zhou et al.	N/A	N/A
2021/0116454	12/2020	Anton et al.	N/A	N/A
2021/0171958	12/2020	Chan et al.	N/A	N/A
2021/0198256	12/2020	Nasveschuk et al.	N/A	N/A
2021/0230190	12/2020	Ruppel et al.	N/A	N/A
2021/0251988	12/2020	Zhou et al.	N/A	N/A
2021/0260171	12/2020	Zhou et al.	N/A	N/A
2022/0016083	12/2021	Centore et al.	N/A	N/A
2022/0079940	12/2021	Centore et al.	N/A	N/A
2022/0098194	12/2021	Nasveschuk et al.	N/A	N/A
2022/0119378	12/2021	Anthony et al.	N/A	N/A
2022/0289711	12/2021	Ruppel et al.	N/A	N/A
2023/0035235	12/2022	Kadoch et al.	N/A	N/A
2023/0060334	12/2022	Nasveschuk et al.	N/A	N/A
2023/0065463	12/2022	Ruppel et al.	N/A	N/A
2023/0066136	12/2022	Ruppel et al.	N/A	N/A
2023/0072053	12/2022	Ruppel et al.	N/A	N/A
2023/0077730	12/2022	Ruppel et al.	N/A	N/A

2023/0079819	12/2022	Vaswani et al.	N/A	N/A
2023/0121497	12/2022	Vaswani et al.	N/A	N/A
2023/0138480	12/2022	Anthony et al.	N/A	N/A
2023/0142883	12/2022	Ruppel et al.	N/A	N/A
2023/0331722	12/2022	Ruppel et al.	N/A	N/A
2023/0416246	12/2022	Ruppel et al.	N/A	N/A
2024/0002382	12/2023	Ruppel et al.	N/A	N/A
2024/0067642	12/2023	Ruppel et al.	N/A	N/A
2024/0101550	12/2023	Vaswani et al.	N/A	N/A
2024/0150328	12/2023	Zhou et al.	N/A	N/A
2024/0150348	12/2023	Ruppel et al.	N/A	N/A
2024/0158387	12/2023	Vaswani et al.	N/A	N/A
2024/0166668	12/2023	Ruppel et al.	N/A	N/A
2024/0189318	12/2023	Huang	N/A	N/A
2024/0190894	12/2023	Gu et al.	N/A	N/A

FOREIGN PATENT DOCUMENTS

Patent No.	**Application Date**	**Country**	**CPC**
104530013	12/2015	CN	N/A
108690020	12/2017	CN	N/A
202192101	12/2020	EA	N/A
WO-94/10300	12/1993	WO	N/A
WO-95/30761	12/1994	WO	N/A
WO-2000/024392	12/1999	WO	N/A
WO-00/59888	12/1999	WO	N/A
WO-00/59905	12/1999	WO	N/A
WO-2005/039643	12/2004	WO	N/A
WO-2005/112620	12/2004	WO	N/A
WO-2006/005941	12/2005	WO	N/A
WO-2006/051063	12/2005	WO	N/A
WO-2008/022396	12/2007	WO	N/A
WO-2009/086303	12/2008	WO	N/A
WO-2010/007046	12/2009	WO	N/A
WO-2011/115998	12/2010	WO	N/A
WO-2012/003281	12/2011	WO	N/A
WO-2012/085650	12/2011	WO	N/A
WO-2013/106643	12/2012	WO	N/A
WO-2013/116663	12/2012	WO	N/A
WO-2014/150395	12/2013	WO	N/A
WO-2015/103317	12/2014	WO	N/A
WO-2015/120320	12/2014	WO	N/A
WO-2015/121688	12/2014	WO	N/A
WO-2016/054491	12/2015	WO	N/A
WO-2016/105518	12/2015	WO	N/A
WO-2016/138114	12/2015	WO	N/A
WO-2016/139361	12/2015	WO	N/A
WO-2016/160718	12/2015	WO	N/A
WO-2016/207212	12/2015	WO	N/A
WO-2017/007612	12/2016	WO	N/A
WO-2017/024317	12/2016	WO	N/A
WO-2017/024318	12/2016	WO	N/A
WO-2017/087885	12/2016	WO	N/A
WO-2017/118734	12/2016	WO	N/A

WO-2017/158381	12/2016	WO	N/A
WO-2017/197036	12/2016	WO	N/A
WO-2017/197046	12/2016	WO	N/A
WO-2017/197051	12/2016	WO	N/A
WO-2017/197055	12/2016	WO	N/A
WO-2017/197056	12/2016	WO	N/A
WO-2017/223452	12/2016	WO	N/A
WO-2018/064589	12/2017	WO	N/A
WO-2018/148443	12/2017	WO	N/A
WO-2018/160636	12/2017	WO	N/A
WO-2018/177297	12/2017	WO	N/A
WO-2019/040098	12/2018	WO	N/A
WO-2019/099868	12/2018	WO	N/A
WO-2019/152437	12/2018	WO	N/A
WO-2019/152440	12/2018	WO	N/A
WO-2019/165229	12/2018	WO	N/A
WO-2019/226915	12/2018	WO	N/A
WO-2020/010227	12/2019	WO	N/A
WO-2020/035779	12/2019	WO	N/A
WO-2020/051235	12/2019	WO	N/A
WO-2020/081556	12/2019	WO	N/A
WO-2020/081588	12/2019	WO	N/A
WO-2020/106915	12/2019	WO	N/A
WO-2020/127685	12/2019	WO	N/A
WO-2020/132561	12/2019	WO	N/A
WO-2020/160100	12/2019	WO	N/A
WO-2020/160180	12/2019	WO	N/A
WO-2020/160192	12/2019	WO	N/A
WO-2020/160193	12/2019	WO	N/A
WO-2020/160196	12/2019	WO	N/A
WO-2020/160198	12/2019	WO	N/A
WO-2020/264177	12/2019	WO	N/A
WO-2021/022163	12/2020	WO	N/A
WO-2021/055295	12/2020	WO	N/A
WO-2021/081032	12/2020	WO	N/A
WO-2021/155100	12/2020	WO	N/A
WO-2021/155262	12/2020	WO	N/A
WO-2021/155264	12/2020	WO	N/A
WO-2021/155316	12/2020	WO	N/A
WO-2021/155320	12/2020	WO	N/A
WO-2021/155321	12/2020	WO	N/A
WO-2021/178920	12/2020	WO	N/A
WO-2021/183218	12/2020	WO	N/A
WO-2021/236080	12/2020	WO	N/A
WO-2022/198043	12/2021	WO	N/A
WO-2023/009834	12/2022	WO	N/A
WO-2023/039208	12/2022	WO	N/A
WO-2023/109892	12/2022	WO	N/A
WO-2023/196560	12/2022	WO	N/A
WO-2023/196565	12/2022	WO	N/A
WO-2023/196567	12/2022	WO	N/A

OTHER PUBLICATIONS

"FLI1 gene," MedlinePlus, published May 1, 2012, <https://medlineplus.gov/genetics/> (3 pages). cited by applicant
Adamo et al., "The oncogene ERG: a key factor in prostate cancer," Oncogene 35(4):403-14 (Jan. 28, 2016). cited by applicant
Advani et al., "A Phase 1 study of imatinib mesylate in combination with cytarabine and daunorubicin for c-kit positive relapsed acute myeloid leukemia," Leuk Res. 34(12):1622-6 (Dec. 2010). cited by applicant
Alazawi, "Foghorn Therapeutics," Blackseed Bio, last updated Mar. 4, 2022, retrieved Jul. 24, 2023, from <https://blackseedbio.com/reports/fhtx#pipeline> (26 pages). cited by applicant
Anders et al., "HTSeq—a Python framework to work with high-throughput sequencing data," Bioinformatics 31(2):166-9 (Jan. 15, 2015). cited by applicant
Asangani et al., "Therapeutic targeting of BET bromodomain proteins in castration-resistant prostate cancer," available in PMC Dec. 12, 2014. Published in final edited form as: Nature. 510(7504):278-82 (2014) (44 pages). cited by applicant
Attard et al., "Duplication of the fusion of TMPRSS2 to ERG sequences identifies fatal human prostate cancer," available in PMC Feb. 24, 2009. Published in final edited form as: Oncogene. 27(3):253-63 (2008) (19 pages). cited by applicant
Basuyaux et al., "The Ets transcription factors interact with each other and with the c-Fos/c-Jun complex via distinct protein domains in a DNA-dependent and -independent manner," J Biol Chem. 272(42):26188-95 (1997). cited by applicant
Bendall et al., "Prevention of amino acid conversion in SILAC experiments with embryonic stem cells," Mol Cell Proteomics. 7(9):1587-97 (2008). cited by applicant
Berger et al., "Androgen-induced differentiation and tumorigenicity of human prostate epithelial cells," Cancer Res. 64(24):8867-75 (2004). cited by applicant
Boulay et al., "Cancer-Specific Retargeting of BAF Complexes by a Prion-like Domain," Cell 171(1):163-78 (Sep. 21, 2017) (36 pages). cited by applicant
Börno et al., "Genome-wide DNA methylation events in TMPRSS2-ERG fusion-negative prostate cancers implicate an EZH2-dependent mechanism with miR-26a hypermethylation," Cancer Discov. 2(11):1024-35 (2012). cited by applicant
Camuzeaux et al., "Imaging Erg and Jun transcription factor interaction in living cells using fluorescence resonance energy transfer analyses," Biochem Biophys Res Commun. 332(4):1107-14 (2005). cited by applicant
Cancer Genome Atlas Research Network, "The Molecular Taxonomy of Primary Prostate Cancer," Cell. 163(4):1011-25 (2015) (16 pages). cited by applicant
Carell et al., "A novel procedure for the synthesis of libraries containing small organic molecules," Angew Chem Int Ed Engl. 33(20):2059-2061 (1994). cited by applicant
Carell et al., "A Solution-Phase Screening Procedure for the Isolation of Active Compounds from a Library of Molecules," Angewandte Chemie International Edition in English. 33(20): 2061-2064 (1994). cited by applicant
Centore et al., "Abstract 1224: Discovery of novel BAF inhibitors for the treatment of transcription factor-driven cancers," Poster Presentations—Proffered abstracts, Cancer Research 81(13_Supplement):1224 (Jul. 1, 2021) (2 pages). cited by applicant
Chandler et al., "ARID1a-DNA interactions are required for promoter occupancy by SWI/SNF," Mol Cell Biol. 33(2):265-80 (Jan. 2013). cited by applicant
Chen et al., "ETS factors reprogram the androgen receptor cistrome and prime prostate tumorigenesis in response to PTEN loss," available in PMC Feb. 1, 2014. Published in final edited form as: Nat Med. 19(8):1023-9 (2013) (21 pages). cited by applicant
Chng et al., "A transcriptional repressor co-regulatory network governing androgen response in prostate cancers," EMBO J. 31(12):2810-23 (2012). cited by applicant
Cho et al., "An unnatural biopolymer," Science. 261(5126):1303-1305 (1993). cited by applicant
Cull et al., "Screening for receptor ligands using large libraries of peptides linked to the C terminus of the lac repressor," Proc Natl Acad Sci. 89(5):1865-1869. (1992). cited by applicant

Cwirla et al., “Peptides on phage: A vast library of peptides for identifying ligands,” Proc Nati Acad Sci. 87:6378-6382 (1990). cited by applicant
Database Registry, RN 1004932-80-2, entered Feb. 21, 2008 (1 page). cited by applicant
Database Registry, RN 1175782-23-6, entered Aug. 26, 2009 (1 page). cited by applicant
Database Registry, RN 1315743-98-6, entered Aug. 11, 2011 (1 page). cited by applicant
Database Registry, RN 878254-76-3, entered Mar. 28, 2006 (1 page). cited by applicant
Delattre et al., “Gene fusion with an ETS DNA-binding domain caused by chromosome translocation in human tumours,” Nature. 359(6391):162-5 (1992). cited by applicant
Demichelis et al., “TMPRSS2:ERG gene fusion associated with lethal prostate cancer in a watchful waiting cohort,” Oncogene 26:4596-4599 (2007). cited by applicant
Devlin et al., “Random Peptide Libraries: a Source of Specific Protein Binding Molecules,” Science. 249(4967):404-406 (1990). cited by applicant
DeWitt et al., “‘Diversomers’: an approach to nonpeptide, nonoligomeric chemical diversity,” Proc Natl Acad Sci. 90(15):6909-6913 (1993). cited by applicant
Dobin et al., “STAR: ultrafast universal RNA-seq aligner,” Bioinformatics. 29(1):15-21 (2013). cited by applicant
Dominguez et al. “Beyond editing: Repurposing CRISPR-Cas9 for Precision Genome Regulation and Interrogation,” available in PMC Jun. 27, 2016, published in final edited form as: Nat Rev Mol Cell Biol. 17(1):5-15 (Jan. 2016) (24 pages). cited by applicant
Donaldson et al., “Solution structure of the ETS domain from murine Ets-1: a winged helix-turn-helix DNA binding motif,” EMBO J. 15(1):125-34 (1996). cited by applicant
Erb et al., “Recursive deconvolution of combinatorial chemical libraries,” Proc Natl Acad Sci. 91(24):11422-11426 (1994). cited by applicant
Extended European Search Report for European Application No. 19748410.8, dated Sep. 24, 2021 (10 pages). cited by applicant
Extended European Search Report for European Application No. 19887386.1, dated Dec. 5, 2022 (18 pages). cited by applicant
Extended European Search Report for European Application No. 20749261.2, dated Oct. 18, 2022 (8 pages). cited by applicant
Extended European Search Report for European Application No. 21748261.1, dated Jan. 29, 2024 (17 pages). cited by applicant
Fadul et al., “EWS/FLI utilizes NKX2-2 to repress mesenchymal features of Ewing sarcoma,” Genes Cancer 6(3-4):129-43 (Mar. 2015). cited by applicant
Fathi et al., “Differentiation syndrome with lower-intensity treatments for acute myeloid leukemia,” Am J Hematol. 96(6):735-46 (Jun. 1, 2021) (13 Pages). cited by applicant
Felici et al., “Selection of antibody ligands from a large library of oligopeptides expressed on a multivalent exposition vector,” J Mol Biol. 222(2):301-10 (1991). cited by applicant
Feng et al., “GFOLD: a generalized fold change for ranking differentially expressed genes from RNA-seq data,” Bioinformatics. 28(21):2782-8 (2012). cited by applicant
Fodor et al., “Multiplexed biochemical assays with biological chips,” Nature. 364:555-556 (1993). cited by applicant
Gaj et al. “ZFN, TALEN and CRISPR/Cas-based Methods for Genome Engineering,” available in PMC Jul. 1, 2014, published in final edited form as: Trends Biotechnol. 31(7):397-405 (Jul. 2013) (20 pages). cited by applicant
Gallop et al., “Applications of Combinatorial Technologies to Drug Discovery. 1. Background and Peptide Combinatorial Libraries,” J Med Chem 37(9):1233-51 (1994). cited by applicant
Gene Ontology Consortium, “Gene Ontology Consortium: going forward,” Nucleic Acids Res. 43(Database issue):D1049-56 (2015). cited by applicant
Godwin et al., “Gemtuzumab ozogamicin in acute myeloid leukemia,” Leukemia 31(9):1855-68 (Sep. 2017). cited by applicant
Grohar et al., “Ecteinascidin 743 interferes with the activity of EWS-FLI1 in Ewing sarcoma cells,” Neoplasia 13(2):145-53 (Feb. 2011). cited by applicant

Helgeson et al., “Characterization of TMPRSS2:ETV5 and SLC45A3:ETV5 gene fusions in prostate cancer,” Cancer Res. 68(1):73-80 (2008). cited by applicant
Herrero-Martin et al., “Stable interference of EWS-FLI1 in an Ewing sarcoma cell line impairs IGF-1/IGF-1R signalling and reveals TOPK as a new target,” Br J Cancer 101(1):80-90 (Jul. 7, 2009). cited by applicant
Ho et al., “An embryonic stem cell chromatin remodeling complex, esBAF, is essential for embryonic stem cell self-renewal and pluripotency,” Proc Natl Acad Sci U S A. 106(13):5181-6 (2009). cited by applicant
Houghten et al., “The use of synthetic peptide combinatorial libraries for the identification of bioactive peptides,” Biotechniques. 13(3):412-21 (1992). cited by applicant
Ichikawa et al., “An RNA-binding protein gene, TLS/FUS, is fused to ERG in human myeloid leukemia with t(16;21) chromosomal translocation,” Cancer Res. 54(11):2865-8 (1994). cited by applicant
International Preliminary Report on Patentability for International Application No. PCT/US2016/062911 issued May 22, 2018 (13 pages). cited by applicant
International Preliminary Report on Patentability for International Application No. PCT/US2019/015722, issued Aug. 4, 2020 (6 pages). cited by applicant
International Preliminary Report on Patentability for International Application No. PCT/US2019/056312, mailed Apr. 14, 2021 (10 pages). cited by applicant
International Preliminary Report on Patentability for International Application No. PCT/US2020/033829, issued Nov. 17, 2022 (6 pages). cited by applicant
International Preliminary Report on Patentability for International Application No. PCT/US2022/019506, issued Sep. 12, 2023 (6 pages). cited by applicant
International Preliminary Report on Patentability for International Application No. PCT/US2022/020943, issued Sep. 12, 2023 (5 pages). cited by applicant
International Search Report and Written Opinion for International Application No. PCT/US18/000339 dated Jan. 28, 2019 (13 pages). cited by applicant
International Search Report and Written Opinion for International Application No. PCT/US19/15722, mailed May 31, 2019 (12 pages). cited by applicant
International Search Report and Written Opinion for International Application No. PCT/US19/56312, dated Jan. 14, 2020 (14 pages). cited by applicant
International Search Report and Written Opinion for International Application No. PCT/US19/56365 dated Jan. 30, 2020 (8 pages). cited by applicant
International Search Report and Written Opinion for International Application No. PCT/US2016/062911 dated Mar. 3, 2017 (16 pages). cited by applicant
International Search Report and Written Opinion for International Application No. PCT/US2020/015605, mailed Jun. 16, 2020 (15 pages). cited by applicant
International Search Report and Written Opinion for International Application No. PCT/US2020/015723, mailed Jul. 2, 2020 (15 pages). cited by applicant
International Search Report and Written Opinion for International Application No. PCT/US2020/033829, mailed Aug. 17, 2020 (14 pages). cited by applicant
International Search Report and Written Opinion for International Application No. PCT/US2022/019506, dated Jun. 7, 2022 (9 pages). cited by applicant
International Search Report and Written Opinion for International Application No. PCT/US2023/017839, mailed Sep. 6, 2023 (11 pages). cited by applicant
International Search Report and Written Opinion for International Application No. PCT/US2023/077088, mailed Mar. 4, 2024 (17 pages). cited by applicant
International Search Report and Written Opinion for International Application No. PCT/US21/15876, mailed on Apr. 7, 2021 (23 pages). cited by applicant
International Search Report and Written Opinion for International Application No. PCT/US21/15878, mailed Jun. 4, 2021 (10 pages). cited by applicant
International Search Report and Written Opinion for International Application No. PCT/US23/17821, mailed Jun. 30, 2023 (9 pages). cited by applicant

International Search Report and Written Opinion for International Application No. PCT/US23/17829, mailed Aug. 23, 2023 (15 pages). cited by applicant
International Search Report and Written Opinion for International Patent Application No. PCT/US2019/062525, mailed Feb. 18, 2020 (14 pages). cited by applicant
International Search Report and Written Opinion for PCT/US2022/020943, mailed Jun. 14, 2022 (17 pages). cited by applicant
Karim et al., "The ETS-domain: a new DNA-binding motif that recognizes a purine-rich core DNA sequence," Genes Dev. 4(9):1451-3 (1990). cited by applicant
Kedage et al., "An Interaction with Ewing's Sarcoma Breakpoint Protein EWS Defines a Specific Oncogenic Mechanism of ETS Factors Rearranged in Prostate Cancer," Cell Rep. 17(5):1289-301 (Oct. 25, 2016) (14 pages). cited by applicant
Klezovitch et al., "A causal role for ERG in neoplastic transformation of prostate epithelium," Proc Natl Acad Sci U S A. 105(6):2105-10 (2008). cited by applicant
Kumar-Sinha et al., "Recurrent gene fusions in prostate cancer," available in PMC Jul. 16, 2009. Published in final edited form as: Nat Rev Cancer. 8(7):497-511 (2008) (29 pages). cited by applicant
Kunderfranco et al., "ETS transcription factors control transcription of EZH2 and epigenetic silencing of the tumor suppressor gene Nkx3.1 in prostate cancer," PLoS One. 5(5):e10547 (2010) (17 pages). cited by applicant
Lam et al., "A new type of synthetic peptide library for identifying ligand-binding activity," Nature. 354(6348):82-84 (1991). cited by applicant
Lam, "Application of combinatorial library methods in cancer research and drug discovery," Anticancer Drug Des. 12(3):145-67 (1997). cited by applicant
Langmead et al., "Fast gapped-read alignment with Bowtie 2," available in PMC Apr. 1, 2013. Published in final edited form as: Nat Methods. 9(4):357-9 (2012) (8 pages). cited by applicant
Link et al., "Targeting the BAF57 SWI/SNF subunit in prostate cancer: a novel platform to control androgen receptor activity," Cancer Res. 68(12):4551-8 (2008). cited by applicant
Love et al., "Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2," Genome Biol. 15(12):550 (2014) (21 pages). cited by applicant
Lupien et al., "FoxA1 translates epigenetic signatures into enhancer-driven lineage-specific transcription," Cell. 132(6):958-70 (2008). cited by applicant
Machanick et al., "MEME-ChIP: motif analysis of large DNA datasets," Bioinformatics. 27(12):1696-7 (2011). cited by applicant
Mackereth et al., "Diversity in structure and function of the Ets family PNT domains," J Mol Biol. 342(4):1249-64 (2004). cited by applicant
Madura et al., "N-recognin/Ubc2 interactions in the N-end rule pathway," J Biol Chem. 268(16): 12046-54 (1993). cited by applicant
Melé et al., "The human transcriptome across tissues and individuals," available in PMC Aug. 24, 2015. Published in final edited form as: Science. 348(6235):660-5 (2015) (12 pages). cited by applicant
Mill et al., "RUNX1-targeted therapy for AML expressing somatic or germline mutation in RUNX1," Blood 134(1):59-73 (Jul. 4, 2019). cited by applicant
Mounir et al., "ERG signaling in prostate cancer is driven through PRMT5-dependent methylation of the Androgen Receptor," Elife. 5:e13964 (2016) (19 pages). cited by applicant
Nagaich et al., "Rapid periodic binding and displacement of the glucocorticoid receptor during chromatin remodeling," Mol Cell. 14(2):163-74 (2004). cited by applicant
Nam et al., "Expression of the TMPRSS2:ERG fusion gene predicts cancer recurrence after surgery for localised prostate cancer," Br J Cancer. 97(12):1690-5 (2007). cited by applicant
Office Action for Chinese Patent Application No. 201980023925.9, dated Apr. 20, 2022 (13 pages). cited by applicant
Ong et al., "A practical recipe for stable isotope labeling by amino acids in cell culture (SILAC)," Nat Protoc. 1(6):2650-60 (2006). cited by applicant
Papillon et al., "Discovery of Orally Active Inhibitors of Brahma Homolog (BRM)/SMARCA2 ATPase Activity for the Treatment of Brahma Related Gene 1 (BRG1)/SMARCA4-Mutant Cancers," J Med

Chem. 61(22): 10155-72 (Nov. 2018). cited by applicant
Partial Supplementary European Search Report for European Patent Application No. 19887386.1, dated Jul. 20, 2022 (23 pages). cited by applicant
Partial Supplementary European Search Report for European Patent Application No. 20936213.6, dated Feb. 8, 2024 (20 pages). cited by applicant
Paulo et al., "FLII is a novel ETS transcription factor involved in gene fusions in prostate cancer," Genes Chromosomes Cancer. 51(3):240-9 (2012). cited by applicant
Petrovics et al., "Frequent overexpression of ETS-related gene-1 (ERG1) in prostate cancer transcriptome," Oncogene. 24(23):3847-52 (2005). cited by applicant
Pomerantz et al., "The androgen receptor cistrome is extensively reprogrammed in human prostate tumorigenesis," available in PMC May 1, 2016. Published in final edited form as: Nat Genet. 47(11):1346-51 (2015) (17 pages). cited by applicant
Prensner et al., "The long noncoding RNA SChLAP1 promotes aggressive prostate cancer and antagonizes the SWI/SNF complex," available in PMC May 1, 2014. Published in final edited form as: Nat Genet. 45(11):1392-8 (2013) (26 pages). cited by applicant
PubChem CID 117640569, "N-[2-[[4-(4-Methoxyphenyl)-1,3-thiazol-2-yl]amino]-2-oxoethyl]-1,3-thiazole-5-carboxamide," https://pubchem.ncbi.nlm.nih.gov/compound/117640569, created Feb. 23, 2016 (9 pages). cited by applicant
PubChem CID 56442706, "1-(4-Methoxyphenyl)-N-[2-oxo-2-[4-(1,2,4-triazol-1-yl)anilino]ethyl]pyrazole-3-carboxamide," https://pubchem.ncbi.nlm.nih.gov/compound/56442706, created Jan. 25, 2012 (8 pages). cited by applicant
PubChem CID 91946137, "N-[2-[(1-Ethylpyrazol-3-yl)amino]-2-oxoethyl]-1-methylpyrazole-3-carboxamide," https://pubchem.ncbi.nlm.nih.gov/compound/91946137, created Oct. 22, 2015 (8 pages). cited by applicant
PubChem Compound Summary for CID 155037309, dated Dec. 19, 2020 (9 pages). cited by applicant
PubChem Compound Summary for CID No. 136572628, "4-Chloro-N-[2-(cyclopentylamino)-2-oxoethyl]-5-nitro-1H-pyrazole-3-carboxamide," created Jan. 24, 2019, <https://pubchem.ncbi.nlm.nih.gov/compound/136572628>, (7 pages). cited by applicant
PubChem Compound Summary for CID No. 49726797, "N-Methyl-N-(2-oxo-2-((4-(pyridin-3-yl) thiazol-2-yl)amino)ethyl)-1H-indole-3-carboxamide," created Nov. 27, 2010, <https://pubchem.ncbi.nlm.nih.gov/compound/49726797>, (8 pages). cited by applicant
PubChem Compound Summary for CID No. 91945707, "N-[2-[(4,5-Dimethyl-1,3-thiazol-2-yl) amino]-2-oxoethyl]-1-methylpyrazole-3-carboxamide," created Oct. 22, 2015 <https://pubchem.ncbi.nlm.nih.gov/compound/91945707>, (8 pages). cited by applicant
PubChem Compound Summary for PubChem CID 49726798, "N-(2-((4-(Furan-2-yl)thiazol-2-yl)amino)-2-oxoethyl)-N-methyl-1H-indole-3-carboxamide," created Nov. 27, 2010 <https://pubchem.ncbi.nih.gov/compound/49726798> (8 pages). cited by applicant
PubChem Compound Summary for SID 172131678, dated Dec. 9, 2014 (8 pages). cited by applicant
Pubchem, "Compound Summary for CID 108452511," <https://pubchem.ncbi.nlm.nih.gov/compound/108452511>, created Jan. 15, 2016, retrieved Jan. 4, 2021 (7 pages). cited by applicant
Pubchem, "Compound Summary for CID 2955118," <https://pubchem.ncbi.nlm.nih.gov/compound/2955118>, created Jul. 29, 2005, retrieved Mar. 22, 2017 (13 pages). cited by applicant
Pubchem, "Compound Summary for CID 7325930," <https://pubchem.ncbi.nlm.nih.gov/compound/7325930>, created Jul. 29, 2006, retrieved Mar. 22, 2017 (11 pages). cited by applicant
Pubchem, "Compound Summary for CID 970466," <https://pubchem.ncbi.nlm.nih.gov/compound/970466>, created Jul. 9, 2005, retrieved Mar. 22, 2017 (11 pages). cited by applicant
Quinlan et al., "BEDTools: a flexible suite of utilities for comparing genomic features," Bioinformatics. 26(6):841-2 (2010). cited by applicant

Rajput et al., “Frequency of the TMPRSS2:ERG gene fusion is increased in moderate to poorly differentiated prostate cancers,” J Clin Pathol. 60(11):1238-43 (2007). cited by applicant
Ramos et al., “Current Approaches in the Treatment of Relapsed and Refractory Acute Myeloid Leukemia,” J Clin Med. 4(4):665-95 (Apr. 2015). cited by applicant
Rappsilber et al., “Protocol for micro-purification, enrichment, pre-fractionation and storage of peptides for proteomics using StageTips,” Nat Protoc. 2(8):1896-906 (2007). cited by applicant
Riggi et al., “EWS-FLI1 utilizes divergent chromatin remodeling mechanisms to directly activate or repress enhancer elements in Ewing sarcoma,” Cancer Cell 26(5):668-81 (Nov. 10, 2014) (28 pages). cited by applicant
Sankar et al., “Promiscuous partnerships in Ewing's sarcoma,” Cancer Genet. 204(7):351-65 (Jul. 2011) (28 pages). cited by applicant
Scott et al., “Searching for peptide ligands with an epitope library,” Science. 249(4967):386-390 (1990). cited by applicant
Shen et al., “The SWI/SNF ATPase Brm is a gatekeeper of proliferative control in prostate cancer,” Cancer Res. 68(24):10154-62 (Dec. 2008). cited by applicant
Shi et al., “Role of SWI/SNF in acute leukemia maintenance and enhancer-mediated Myc regulation,” Genes Dev. 27(24):2648-62 (Dec. 2013). cited by applicant
Siegel et al., “Cancer statistics, 2015,” CA Cancer J Clin. 65(1):5-29 (2015). cited by applicant
STN Registry Database, RN 1010893-05-6, entered Mar. 30, 2008 (2 pages). cited by applicant
STN Registry Database, RN 1049271-26-2, entered Sep. 14, 2008 (2 pages). cited by applicant
STN Registry Database, RN 1081662-32-9, entered Dec. 8, 2008 (2 pages). cited by applicant
STN Registry Database, RN 1209112-42-4, entered Mar. 12, 2010 (2 pages). cited by applicant
STN Registry Database, RN 1246047-75-5, entered Oct. 12, 2010 (2 pages). cited by applicant
STN Registry Database, RN 1308280-67-2, entered Jun. 9, 2011 (2 pages). cited by applicant
STN Registry Database, RN 1351682-19-3, entered Dec. 22, 2011 (2 pages). cited by applicant
STN Registry Database, RN 1401558-47-1, entered Oct. 22, 2012 (2 pages). cited by applicant
STN Registry Database, RN 1455783-72-8, entered Oct. 6, 2013 (2 pages). cited by applicant
STN Registry Database, RN 1576383-94-2, entered Mar. 31, 2014 (2 pages). cited by applicant
Takigami et al., “Synthetic siRNA targeting the breakpoint of EWS/Fli-1 inhibits growth of Ewing sarcoma xenografts in a mouse model,” Int J Cancer 128(1):216-26 (Jan. 1, 2011). cited by applicant
Wu et al., “Targeting the chromatin remodeling enzyme BRG1 increases the efficacy of chemotherapy drugs in breast cancer cells,” Oncotarget 7(19):27158-75 (May 10, 2016). cited by applicant
U.S. Appl. No. 18/292,426-A1, Chen et al. cited by applicant
U.S. Appl. No. 18/292,508, Huang, Liyue. cited by applicant
U.S. Appl. No. 62/798,374, Ruppel et al. cited by applicant
U.S. Appl. No. 62/881,195, Ruppel et al. cited by applicant
U.S. Appl. No. 62/985,774, Nasveschuk et al. cited by applicant
U.S. Appl. No. 63/061,659, Nasveschuk et al. cited by applicant
Brien et al., “Targeted degradation of BRD9 reverses oncogenic gene expression in synovial sarcoma,” eLife. 7:e41305 (Nov. 15, 2018) (26 pages). cited by applicant
Communication Pursuant to Rule 164(1) for European Patent Application 19746772.3, dated Oct. 7, 2021 (13 pages). cited by applicant
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). cited by applicant
Decision Denying Institution of Post-Grant Review of U.S. Pat. No. 11,414,416 dated Sep. 12, 2023 (4 Pages). cited by applicant
Decision Denying Institution of Post-Grant Review of U.S. Pat. No. 11,560,381, dated Jan. 23, 2024 (4 Pages). cited by applicant
Declaration of Christopher G. Nasveschuk, Ph.D. Under 37 C.F.R. §1.68 and §42.53(a), dated Oct. 19, 2023 (24 pages). cited by applicant
Declaration of Kevin T. Sprott, Ph.D., Under 37 C.F.R. §1.68 and §42.53(a), dated Oct. 19, 2023 (74 pages). cited by applicant

Declaration of Stevan W. Djuric, Ph.D. Under 37 C.F.R. §1.68 and §42.53(a), dated Oct. 19, 2023 (202 pages). cited by applicant
Del Gaudio et al., "BRD9 binds cell type-specific chromatin regions regulating leukemic cell survival via STAT5 inhibition," Cell Death Dis. 10(5):338 (Apr. 2019) doi: 10.1038/s41419-019-1570-9 (14 pages). cited by applicant
Extended European Search Report for European Application No. 19746772.3, dated Feb. 7, 2022 (15 pages). cited by applicant
Extended European Search Report for European Application No. 20748462.7, dated Jan. 2, 2023 (10 pages). cited by applicant
Hay et al., "Design and synthesis of potent and selective inhibitors of BRD7 and BRD9 bromodomains," Med. Chem. Commun. 6:1381-86 (2015). cited by applicant
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). cited by applicant
International Preliminary Report on Patentability for International Application No. PCT/2020/015744, mailed Aug. 12, 2021 (8 pages). cited by applicant
International Search Report and Written Opinion for International Application No. PCT/2020/015744, mailed Jun. 26, 2020 (16 pages). cited by applicant
International Search Report and Written Opinion for International Patent Application No. PCT/US2019/015733, dated Jul. 1, 2019 (17 pages). cited by applicant
International Search Report and Written Opinion for PCT/US2020/015746, mailed May 18, 2020 (11 pages). cited by applicant
K. Luby-Phelps, "Cytoarchitecture and Physical Properties of Cytoplasm: Volume, Viscosity, Diffusion, Intracellular Surface Area," Int Rev Cytol. 192:189-221 (2000). cited by applicant
Kadoch et al., "Mammalian SWI/SNF chromatin remodeling complexes and cancer: Mechanistic insights gained from human genomics," Sci Adv. 1(5):e1500447 (2015) (17 pages). cited by applicant
Kadoch 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). cited by applicant
Kadoch et al., "Reversible Disruption of mSWI/SNF (BAF) Complexes by the SS18-SSX Oncogenic Fusion in Synovial Sarcoma," Cell. 153(1):71-85 (2013). cited by applicant
Martin et al., "Structure-Based Design of an in Vivo Active Selective BRD9 Inhibitor," J Med Chem. 59(10):4462-75 (2016). cited by applicant
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). cited by applicant
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). cited by applicant
Munoz et al. "CRISPR Screens Provide a Comprehensive Assessment of Cancer Vulnerabilities but Generate False-Positive Hits for Highly Amplified Genomic Regions," Cancer Discov. 6(8):900-13 (Aug. 2016) (14 pages). cited by applicant
Nasir, M.S. et al., "Fluorescence Polarization: An analytical tool for Immunoassay and Drug Discovery," Comb. Chem High Throughput Screen. 2(4):177-190 (Aug. 1999). cited by applicant
Pan et al., "A major chromatin regulator determines resistance of tumor cells to T cell-mediated killing," Science. 359(6377):770-75 (Jan. 2018) (11 pages). cited by applicant
Petition for Post Grant Review of U.S. Pat. No. 11,414,416 filed May 1, 2023 (133 Pages). cited by applicant
Petition for Post Grant Review of U.S. Pat. No. 11,560,381 filed Oct. 23, 2023 (163 Pages). cited by applicant
Picaud et al., "9H-purine scaffold reveals induced-fit pocket plasticity of the BRD9 bromodomain," J Med Chem. 58(6):2718-36 (2015). cited by applicant
PubChem CID 118028040, "6-Ethyl-4-(2-methoxy-5-methylsulfonylphenyl)-2-methyl-7,8-dihydro-5H-2,6-naphthyridin-1-one," created Feb. 23, 2020, retrieved Jun. 11, 2020 <https://pubchem.ncbi.nlm.nih/gov/compound/118028040> (10 pages). cited by applicant

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). cited by applicant
Sender et al., “Revised Estimates for the No. of Human and Bacteria Cells in the Body,” PLoS Biol. 14(8):e1002533 (Aug. 19, 2016) (14 pages). cited by applicant
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). cited by applicant
Teuscher et al., “A Versatile Method to Determine the Cellular Bioavailability of Small-Molecule Inhibitors,” J Med Chem. 60(1): 157-169 (2017). cited by applicant
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). cited by applicant
Tsherniak et al. “Defining a Cancer Dependency Map,” available in PMC Jul. 27, 2018, published in final edited form as: Cell. 170(3):564-576 (Jul. 2017) (40 pages). cited by applicant
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). cited by applicant
Wang et al., “NMR Fragment Screening Hit Induces Plasticity of BRD7/9 Bromodomains,” Chembiochem. 17(15):1456-63 (2016). cited by applicant
Z.X. Wang, “An exact mathematical expression for describing competitive binding of two different ligands to a protein molecule,” FEBS Lett. 360(2):111-114 (Feb. 1995). cited by applicant
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). cited by applicant

---

Primary Examiner: Alstrum-Acevedo; James H

Assistant Examiner: Sanchez; Justin Christopher

Attorney, Agent or Firm: Clark & Elbing LLP

Background/Summary

BACKGROUND

(1) 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

(2) 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.

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

(4) In an aspect, the disclosure features a compound having the structure of Formula I:
(5) ##STR00001## where R.sup.1 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.10 carbocyclyl; Z.sup.1 is CR.sup.2 or N; R.sup.2 is H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, or optionally substituted C.sub.2-C.sub.9 heteroaryl;
(6) ##STR00002## X.sup.1 is a bond, O, NR.sup.3a,
(7) ##STR00003## or CR.sup.4aR.sup.5a; X.sup.2 is O, NR.sup.3b,
(8) ##STR00004## or CR.sup.4bR.sup.5b; X.sup.3 is O, NR.sup.3c,
(9) ##STR00005## or CR.sup.4cR.sup.5c; X.sup.4 is a bond, O, NR.sup.3d,
(10) ##STR00006## or CR.sup.4dR.sup.5d; X.sup.5 is O or NR.sup.3e and X.sup.6 is CR.sup.4fR.sup.5f, or X.sup.5 is CR.sup.4eR.sup.5e and X.sup.6 is O or NR.sup.3f; X.sup.7 is O, NR.sup.3g, or CR.sup.4gR.sup.5g; X.sup.8 is O, NR.sup.3h, or CR.sup.4hR.sup.5h; each of R.sup.3a, R.sup.3b, R.sup.3c, and R.sup.3d is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted C.sub.1-C.sub.6 acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R.sup.3a and R.sup.4b, R.sup.4a and R.sup.3b, R.sup.4b and R.sup.4a, R.sup.3b and R.sup.4c, R.sup.4b and R.sup.4c, R.sup.3c and R.sup.4b, R.sup.3c and R.sup.4d, R.sup.4c and R.sup.4d, and/or R.sup.3d and R.sup.4c, together with the atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heterocyclyl; each of R.sup.4a, R.sup.4b, R.sup.4c, and R.sup.4d is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted C.sub.1-C.sub.6 acyl, thiol, optionally substituted sulfone, or optionally substituted amino, or R.sup.3a and R.sup.4b, R.sup.4a and R.sup.3b, R.sup.4b and R.sup.4a, R.sup.3b and R.sup.4c, R.sup.4b and R.sup.4c, R.sup.3c and R.sup.4b, R.sup.3c and R.sup.4d, R.sup.4c and R.sup.4d, and/or R.sup.3d and R.sup.4c, together with the atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heterocyclyl; each of R.sup.5a, R.sup.5b, R.sup.5c, and R.sup.5d is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; each of R.sup.3e, R.sup.3f, R.sup.3g, and R.sup.3h is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted C.sub.1-C.sub.6 acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R.sup.3e and R.sup.4f or R.sup.4e and R.sup.3f, together with the atoms to which each is attached, combine to form optionally substituted heterocyclycl; each of R.sup.4e, R.sup.4f, R.sup.4g, and R.sup.4h is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted C.sub.1-C.sub.6 acyl, thiol,

optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R.sup.3e and R.sup.4f or R.sup.4e and R.sup.3f, together with the atoms to which each is attached, combine to form optionally substituted heterocyclycl; each of R.sup.5e, R.sup.5f, R.sup.5g, and R.sup.5h is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; and G is optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or C.sub.2-C.sub.9 heterocyclyl, or a pharmaceutically acceptable salt thereof.

(11) In some embodiments,

(12) ##STR00007##

In some embodiments,

(13) ##STR00008##

In some embodiments,

(14) ##STR00009##

In some embodiments, is

(15) ##STR00010##

(16) In another aspect, the disclosure features a compound having the structure of Formula I:

(17) ##STR00011## where R.sup.1 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.10 carbocyclyl; Z.sup.1 is CR.sup.2 or N; R.sup.2 is H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, or optionally substituted C.sub.2-C.sub.9 heteroaryl;

(18) ##STR00012## X.sup.1 is a bond, O, NR.sup.3a, or CR.sup.4aR.sup.5a; X.sup.2 is O, NR.sup.3b, or CR.sup.4bR.sup.5b; X.sup.3 is O, NR.sup.3c, or CR.sup.4cR.sup.5c; X.sup.4 is a bond, O, NR.sup.3d, or CR.sup.4dR.sup.5d; each of R.sup.3a, R.sup.3b, R.sup.3c, and R.sup.3d is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted C.sub.1-C.sub.6 acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R.sup.3a and R.sup.4b, R.sup.4a and R.sup.3b, R.sup.4b and R.sup.4a, R.sup.3b and R.sup.4c, R.sup.4b and R.sup.4c, R.sup.3c and R.sup.4b, R.sup.3c and R.sup.4d, R.sup.4c and R.sup.4d, and/or R.sup.3d and R.sup.4c, together with the atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heterocyclyl; each of R.sup.4a, R.sup.4b, R.sup.4c, and R.sup.4d is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted C.sub.1-C.sub.6 acyl, thiol, optionally substituted sulfone, or optionally substituted amino, or R.sup.3a and R.sup.4b, R.sup.4a and R.sup.3b, R.sup.4b and R.sup.4a, R.sup.3b and R.sup.4c, R.sup.4b and R.sup.4c, R.sup.3c and R.sup.4b, R.sup.3c and R.sup.4d, R.sup.4c and R.sup.4d, and/or R.sup.3d and R.sup.4c, together with the atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heterocyclyl; each of R.sup.5a, R.sup.5b, R.sup.5c, and R.sup.5d is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl,

optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; and G is optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or C.sub.2-C.sub.9 heterocyclyl, or a pharmaceutically acceptable salt thereof.

(19) In some embodiments, R.sup.1 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.10 carbocyclyl. In some embodiments, R.sup.1 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.2-C.sub.6 alkenyl, or optionally substituted C.sub.3-C.sub.10 carbocyclyl. In some embodiments, R.sup.1 is H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.3-C.sub.10 carbocyclyl.

(20) In some embodiments, R.sup.1 is H. In some embodiments, R.sup.1 is optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, R.sup.1 is optionally substituted C.sub.2-C.sub.6 alkenyl. In some embodiments, R.sup.1 is optionally substituted C.sub.3-C.sub.10 carbocyclyl.

(21) In some embodiments, optionally substituted C.sub.1-C.sub.6 alkyl is C.sub.1-C.sub.6 perfluoroalkyl.

(22) In some embodiments, R.sup.1 is

(23) ##STR00013##

(24) In some embodiments, R.sup.1 is

(25) ##STR00014##

(26) In some embodiments, R.sup.1 is

(27) ##STR00015##

(28) In some embodiments, R.sup.1 is H,

(29) ##STR00016##

In some embodiments, R.sup.1 is

(30) ##STR00017##

In some embodiments, R.sup.1 is H,

(31) ##STR00018##

(32) In some embodiments, R.sup.1 is H,

(33) ##STR00019##

(34) In some embodiments, R.sup.1 is H,

(35) ##STR00020##

(36) In some embodiments, R.sup.1 is H or

(37) ##STR00021##

(38) In some embodiments, R.sup.1 is H. In some embodiments, R.sup.1 is

(39) ##STR00022##

(40) In some embodiments, Z.sup.1 is CR.sup.2. In some embodiments, Z.sup.1 is N.

(41) In some embodiments, R.sup.2 is H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, or optionally substituted C.sub.6-C.sub.10 aryl.

(42) In some embodiments, R.sup.2 is H, halogen, or optionally substituted C.sub.1-C.sub.6 alkyl.

(43) In some embodiments, R.sup.2 is H, F, or

(44) ##STR00023##

(45) In some embodiments, R.sup.2 is H. In some embodiments, R.sup.2 is F. In some embodiments, R.sup.2 is

(46) ##STR00024##

(47) In some embodiments, X.sup.1 is a bond, O, NR.sup.3a, or CR.sup.4aR.sup.5a; X.sup.2 is O, NR.sup.3b, or CR.sup.4bR.sup.5b; X.sup.3 is O, NR.sup.3c, or CR.sup.4cR.sup.5c; and X.sup.4 is a bond, O, NR.sup.3d, or CR.sup.4dR.sup.5d.

(48) In some embodiments, X.sup.1 is a bond. In some embodiments, X.sup.1 is O, NR.sup.3a, or CR.sup.4aR.sup.5a. In some embodiments, X.sup.1 is O or NR.sup.3a. In some embodiments, X.sup.1 is NR.sup.3a or CR.sup.4aR.sup.5a In some embodiments, X.sup.2 is O or NR.sup.3b. In some embodiments, X.sup.2 is CR.sup.4bR.sup.5b. In some embodiments, X.sup.2 is NR.sup.3b or CR.sup.4bR.sup.5b.

(49) In some embodiments, X.sup.3 is O or NR.sup.3c. In some embodiments, X.sup.3 is CR.sup.4cR.sup.5c. In some embodiments, X.sup.3 is NR.sup.3c or CR.sup.4cR.sup.5c.
(50) In some embodiments, X.sup.4 is a bond. In some embodiments, X.sup.4 is O, NR.sup.3d, or CR.sup.4dR.sup.5d. In some embodiments, X.sup.4 is O or NR.sup.3d. In some embodiments, X.sup.4 is NR.sup.3d or CR.sup.4dR.sup.5d.
(51) In some embodiments, X.sup.1 is O, NR.sup.3a, or CR.sup.4aR.sup.5a; X.sup.2 is O, NR.sup.3b, or CR.sup.4bR.sup.5b; X.sup.3 is O, NR.sup.3c, or CR.sup.4cR.sup.5c; and X.sup.4 is O, NR.sup.3d, or CR.sup.4dR.sup.5d.
(52) In some embodiments, X.sup.1 is CR.sup.4aR.sup.5a; X.sup.2 is NR.sup.3b; X.sup.3 is CR.sup.4cR.sup.5c; and X.sup.4 is CR.sup.4dR.sup.5d. In some embodiments, X.sup.1 is CR.sup.4aR.sup.5a; X.sup.2 is CR.sup.4bR.sup.5b; X.sup.3 is NR.sup.3c; and X.sup.4 is CR.sup.4dR.sup.5d. In some embodiments, X.sup.1 is O or NR.sup.3a; X.sup.2 is CR.sup.4bR.sup.5b; X.sup.3 is CR.sup.4cR.sup.5c; and X.sup.4 is O or NR.sup.3d. In some embodiments, X.sup.1 is a bond; X.sup.2 is CR.sup.4bR.sup.5b; X.sup.3 is O or NR.sup.3c; and X.sup.4 is CR.sup.4dR.sup.5d. In some embodiments, X.sup.1 is CR.sup.4aR.sup.5a; X.sup.2 is CR.sup.4bR.sup.5b; X.sup.3 is CR.sup.4cR.sup.5c; and X.sup.4 is CR.sup.4dR.sup.5d. In some embodiments, X.sup.5 is NR.sup.3e and X.sup.6 is CR.sup.4fR.sup.5f.
(53) In some embodiments, each of R.sup.3a, R.sup.3b, R.sup.3c, and R.sup.3d is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.1-C.sub.6 acyl, optionally substituted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R.sup.3a, R.sup.3b, R.sup.3c, and R.sup.3d is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R.sup.3a, R.sup.3b, R.sup.3c, and R.sup.3d is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 acyl, optionally substituted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R.sup.3a, R.sup.3b, R.sup.3c, and R.sup.3d is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 acyl.
(54) In some embodiments, each of R.sup.3a, R.sup.3b, R.sup.3c, and R.sup.3d is, independently, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.1-C.sub.6 acyl, optionally substituted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R.sup.3a, R.sup.3b, R.sup.3c, and R.sup.3d is, independently, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 acyl, optionally substituted sulfone, or optionally substituted sulfonamide.
(55) In some embodiments, each of R.sup.3a, R.sup.3b, R.sup.3c, and R.sup.3d is, independently, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.1-C.sub.6 acyl. In some embodiments, each of R.sup.3a, R.sup.3b, R.sup.3c, and R.sup.3d is, independently, optionally substituted C.sub.1-C.sub.6 alkyl or optionally substituted C.sub.1-C.sub.6 heteroalkyl. In some embodiments, each of R.sup.3a, R.sup.3b, R.sup.3c, and R.sup.3d is, independently, optionally substituted C.sub.1-C.sub.6 alkyl or optionally substituted C.sub.1-C.sub.6 acyl. In some embodiments, each of R.sup.3a, R.sup.3b, R.sup.3c, and R.sup.3d is, independently, optionally substituted C.sub.1-C.sub.6 acyl. In some embodiments, each of R.sup.3a, R.sup.3b, R.sup.3c, and R.sup.3d is, independently, optionally substituted sulfone or optionally substituted sulfonamide.
(56) In some embodiments, each of R.sup.3a, R.sup.3b, R.sup.3c, and R.sup.3d is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl,
(57) ##STR00025## where R.sup.5 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, or optionally substituted C.sub.6-C.sub.10 aryl; W.sup.1 is O or S; W.sup.2 is NR.sup.7 or O; R.sup.7 is H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl; R.sup.8 is optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, or optionally substituted C.sub.6-

C.sub.10 aryl; and R.sup.9 is H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl.
(58) In some embodiments, each of R.sup.3a, R.sup.3b, R.sup.3c, and R.sup.3d is, independently, C.sub.1-C.sub.6 alkyl,
(59) ##STR00026##
In some embodiments, each of R.sup.3a, R.sup.3b, R.sup.3c, and R.sup.3d is, independently, C.sub.1-C.sub.6 alkyl. In some embodiments, each of R.sup.3a, R.sup.3b, R.sup.3c, and R.sup.3d is, independently,
(60) ##STR00027##
In some embodiments, each of R.sup.3a, R.sup.3b, R.sup.3c, and R.sup.3d is, independently,
(61) ##STR00028##
In some embodiments, each of R.sup.3a, R.sup.3b, R.sup.3c, and R.sup.3d is, independently,
(62) ##STR00029##
In some embodiments, each of R.sup.3a, R.sup.3b, R.sup.3c, and R.sup.3d is, independently,
(63) ##STR00030##
In some embodiments, each of R.sup.3a, R.sup.3b, R.sup.3c, and R.sup.3d is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl,
(64) ##STR00031##
In some embodiments, each of R.sup.3a, R.sup.3b, R.sup.3c, and R.sup.3d is, independently, H, C.sub.1-C.sub.6 alkyl,
(65) ##STR00032##
In some embodiments, each of R.sup.3a, R.sup.3b, R.sup.3c, and R.sup.3d is, independently, H, C.sub.1-C.sub.6 alkyl, or
(66) ##STR00033##
In some embodiments, each of R.sup.3a, R.sup.3b, R.sup.3c, and R.sup.3d is, independently, C.sub.1-C.sub.6 alkyl
(67) ##STR00034##
In some embodiments, each of R.sup.3a, R.sup.3b, R.sup.3c, and R.sup.3d is, independently, H, methyl, or
(68) ##STR00035##
In some embodiments, each of R.sup.3a, R.sup.3b, R.sup.3c, and R.sup.3d is, independently, optionally substituted C.sub.1-C.sub.6 alkyl.
(69) In some embodiments, each of R.sup.4a, R.sup.4b, R.sup.4c, and R.sup.4d is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.1-C.sub.6 acyl, optionally substituted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R.sup.4a, R.sup.4b, R.sup.4c, and R.sup.4d is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R.sup.4a, R.sup.4b, R.sup.4c, and R.sup.4d is H. In some embodiments, each of R.sup.4a, R.sup.4b, R.sup.4c, and R.sup.4d is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 acyl, optionally substituted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R.sup.4a, R.sup.4b, R.sup.4c, and R.sup.4d is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 acyl.
(70) In some embodiments, each of R.sup.4a, R.sup.4b, R.sup.4c, and R.sup.4d is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl,
(71) ##STR00036## where R.sup.6 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, or optionally substituted C.sub.6-C.sub.10 aryl; W.sup.1 is O or S; W.sup.2 is NR.sup.7 or O; R.sup.7 is H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl; R.sup.8 is optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, or optionally substituted C.sub.6-

C.sub.10 aryl; and R.sup.9 is H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl.
(72) In some embodiments, each of R.sup.4a, R.sup.4b, R.sup.4c, and R.sup.4d is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl,
(73) ##STR00037##
In some embodiments, each of R.sup.4a, R.sup.4b, R.sup.4c, and R.sup.4d is, independently, H or optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, each of R.sup.4a, R.sup.4b, R.sup.4c, and R.sup.4d is, independently, H.
(74) In some embodiments, W.sup.1 is O. In some embodiments, W.sup.1 is S.
(75) In some embodiments, W.sup.2 is O. In some embodiments, W.sup.2 is NR.sup.7.
(76) In some embodiments, R.sup.6 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.10 carbocyclyl. In some embodiments, R.sup.6 is H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl. In some embodiments, R.sup.6 is H, optionally substituted C.sub.3-C.sub.10 carbocyclyl, or optionally substituted C.sub.6-C.sub.10 aryl. In some embodiments, R.sup.6 is optionally substituted C.sub.1-C.sub.6 alkyl or optionally substituted C.sub.1-C.sub.6 heteroalkyl. In some embodiments, R.sup.6 is optionally substituted C.sub.3-C.sub.10 carbocyclyl or optionally substituted C.sub.6-C.sub.10 aryl
(77) In some embodiments, R.sup.6 is H, methyl, ethyl
(78) ##STR00038##
In some embodiments, R.sup.6 is H. In some embodiments, R.sup.6 is methyl, ethyl,
(79) ##STR00039##
In some embodiments, R.sup.6 is
(80) ##STR00040##
In some embodiments, R.sup.6 is H, methyl, ethyl,
(81) ##STR00041##
(82) In some embodiments, R.sup.7 is H or optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, R.sup.7 is H or methyl.
(83) In some embodiments, each of R.sup.3a, R.sup.3b, R.sup.3c, and R.sup.3d is, independently, H, methyl,
(84) ##STR00042##
(85) In some embodiments, each of R.sup.3a, R.sup.3b, R.sup.3c, and R.sup.3d is, independently, H, methyl,
(86) ##STR00043##
(87) In some embodiments, R.sup.3a is H, methyl,
(88) ##STR00044##
In some embodiments, R.sup.3b is H, methyl,
(89) ##STR00045##
In some embodiments, R.sup.3c is H, methyl,
(90) ##STR00046##
In some embodiments, R.sup.3d is H, methyl,
(91) ##STR00047##
(92) In some embodiments, R.sup.3a and R.sup.4b, R.sup.4a and R.sup.3b, R.sup.4b and R.sup.4a, R.sup.3b and R.sup.4c, R.sup.4b and R.sup.4c, R.sup.3c and
(93) R.sup.4b, R.sup.3c and R.sup.4d, R.sup.4c and R.sup.4d, and/or R.sup.3d and R.sup.4c, together with the atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heterocyclyl.
(94) In some embodiments, R.sup.3a and R.sup.4b, R.sup.4b and R.sup.4a, R.sup.4b and R.sup.4c, R.sup.3c and R.sup.4b, R.sup.3c and R.sup.4d, and/or R.sup.3d and R.sup.4c, together with the atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heterocyclyl.
(95) In some embodiments, each of R.sup.5a, R.sup.5b, R.sup.5c, and R.sup.5d is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl. In

some embodiments, each of R.sup.5a, R.sup.5b, R.sup.5c, and R.sup.5d is H.
(96) In some embodiments, each of R.sup.3e, R.sup.3f, R.sup.3g, and R.sup.3h is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.1-C.sub.6 acyl, optionally substituted sulfone, or optionally substituted sulfonamide.
(97) In some embodiments, each of R.sup.4e, R.sup.4f, R.sup.4g, and R.sup.4h is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.1-C.sub.6 acyl, optionally substituted sulfone, or optionally substituted sulfonamide.
(98) In some embodiments, each of R.sup.5e, R.sup.5f, R.sup.5g, and R.sup.5h is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl. In some embodiments, each of R.sup.5e, R.sup.5f, R.sup.5g, and R.sup.5h is H.
(99) In some embodiments, G is optionally substituted C.sub.3-C.sub.10 carbocyclyl or optionally substituted C.sub.2-C.sub.9 heterocyclyl. In some embodiments, G is optionally substituted C.sub.6-C.sub.10 aryl or optionally substituted C.sub.2-C.sub.9 heteroaryl.
(100) In some embodiments, G is optionally substituted C.sub.3-C.sub.10 carbocyclyl. In some embodiments, G is optionally substituted C.sub.6-C.sub.10 aryl. In some embodiments, G is optionally substituted C.sub.2-C.sub.9 heterocyclyl. In some embodiments, G is optionally substituted C.sub.2-C.sub.9 heteroaryl.
(101) In some embodiments, G is
(102) ##STR00048## where each of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G1 and R.sup.G2, R.sup.G2 and R.sup.G3, R.sup.G3 and R.sup.G4, and/or R.sup.G4 and R.sup.G5, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or optionally substituted C.sub.2-C.sub.9 heterocyclyl.
(103) In some embodiments, each of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G1 and R.sup.G2, R.sup.G2 and R.sup.G3, R.sup.G3 and R.sup.G4, and/or R.sup.G4 and R.sup.G5, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or optionally substituted C.sub.2-C.sub.9 heterocyclyl.
(104) In some embodiments, each of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, or optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl; or R.sup.G1 and R.sup.G2, R.sup.G2 and R.sup.G3, R.sup.G3 and R.sup.G4, and/or R.sup.G4 and R.sup.G5, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heteroaryl or optionally substituted C.sub.2-C.sub.9 heterocyclyl.
(105) In some embodiments, each of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is,

independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, or optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl.
(106) In some embodiments, each of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is, independently, H, F, Cl,
(107) ##STR00049##
(108) In some embodiments, each of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is, independently, H, F,
(109) ##STR00050##
(110) In some embodiments, each of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is, independently, H, F, Cl,
(111) ##STR00051##
(112) In some embodiments, R.sup.G1 is H; R.sup.G2 is
(113) ##STR00052##
R.sup.G3 is
(114) ##STR00053##
R.sup.G4 is
(115) ##STR00054##
and R.sup.G5 is H. In some embodiments, R.sup.G1 is H; R.sup.G2 is
(116) ##STR00055##
R.sup.G3 is
(117) ##STR00056##
R.sup.G4 is H; and R.sup.G5 is
(118) ##STR00057##
In some embodiments, R.sup.G1 is H; R.sup.G2 is
(119) ##STR00058##
R.sup.G3 is
(120) ##STR00059##
R.sup.G4 is Cl or F; and R.sup.G5 is H. In some embodiments, R.sup.G1 is H; R.sup.G2 is
(121) ##STR00060##
R.sup.G3 is
(122) ##STR00061##
R.sup.G4 is H; and R.sup.G5 is H. In some embodiments, R.sup.G1 is H; R.sup.G2 is
(123) ##STR00062##
R.sup.G3 is
(124) ##STR00063##
R.sup.G4 is
(125) ##STR00064##
and R.sup.G5 is H.
(126) In some embodiments, R.sup.G1 and R.sup.G2, R.sup.G2 and R.sup.G3, R.sup.G3 and R.sup.G4, and/or R.sup.G4 and R.sup.G5, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heteroaryl or optionally substituted C.sub.2-C.sub.9 heterocyclyl.
(127) In some embodiments, R.sup.G1 and R.sup.G2, R.sup.G2 and R.sup.G3, R.sup.G3 and R.sup.G4, and/or R.sup.G4 and R.sup.G5, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heterocyclyl. In some embodiments, R.sup.G1 and R.sup.G2, R.sup.G2 and R.sup.G3, R.sup.G3 and R.sup.G4, and/or R.sup.G4 and R.sup.G5, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heteroaryl.
(128) In some embodiments, G is
(129) ##STR00065## where R.sup.G6 is H or optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, G is

(130) ##STR00066##
where R.sup.G6 is H or optionally substituted C.sub.1-C.sub.6 alkyl.
(131) In some embodiments, R.sup.G1 and R.sup.G2, R.sup.G2 and R.sup.G3, R.sup.G3 and R.sup.G4, and/or R.sup.G4 and R.sup.G5, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heterocyclyl or optionally substituted C.sub.2-C.sub.9 heteroaryl.
(132) In some embodiments, G is
(133) ##STR00067##
where R.sup.G6 is H or optionally substituted C.sub.1-C.sub.6 alkyl.
(134) In some embodiments, R.sup.G6 is H,
(135) ##STR00068##
(136) In some embodiments, R.sup.G6 is H or
(137) ##STR00069##
(138) In some embodiments, R.sup.G6 is H.
(139) In some embodiments, R.sup.G1 is H, F,
(140) ##STR00070##
In some embodiments, R.sup.G1 is H.
(141) In some embodiments, R.sup.G2 is H, F,
(142) ##STR00071##
In some embodiments, R.sup.G2 is H.
(143) In some embodiments, R.sup.G3 is H, F,
(144) ##STR00072##
In some embodiments, R.sup.G3 is H.
(145) In some embodiments, R.sup.G4 is H, F,
(146) ##STR00073##
In some embodiments, R.sup.G4 is H.
(147) In some embodiments, R.sup.G5 is H, F,
(148) ##STR00074##
In some embodiments, R.sup.G5 is H.
(149) In some embodiments, one or more of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is H. In some embodiments, two or more of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is H. In some embodiments, three or more of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is H. In some embodiments, each of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is H.
(150) In some embodiments, G is
(151) ##STR00075## where each of R.sup.G7, R.sup.G8, R.sup.G9, R.sup.G10, and R.sup.G11 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G7 and R.sup.G8, R.sup.G8 and R.sup.G9, R.sup.G9 and R.sup.G10, and/or R.sup.G10 and R.sup.G11, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or C.sub.2-C.sub.9 heterocyclyl.
(152) In some embodiments, each of R.sup.G7, R.sup.G8, R.sup.G9, R.sup.G10, and R.sup.G11 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G7 and R.sup.G8,

R.sup.G8 and R.sup.G9, R.sup.G9 and R.sup.G10, and/or R.sup.G10 and R.sup.G11, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or C.sub.2-C.sub.9 heterocyclyl.
(153) In some embodiments, each of R.sup.G7, R.sup.G8, R.sup.G9, R.sup.G10, and R.sup.G11 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, or optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl; or R.sup.G7 and R.sup.G8, R.sup.G8 and R.sup.G9, R.sup.G9 and R.sup.G10, and/or R.sup.G10 and R.sup.G11, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or C.sub.2-C.sub.9 heterocyclyl.
(154) In some embodiments, each of R.sup.G7, R.sup.G8, R.sup.G9, R.sup.G10, and R.sup.G11 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, or optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl.
(155) In some embodiments, each of R.sup.G7, R.sup.G8, R.sup.G9, R.sup.G10, and R.sup.G11 is, independently, H, F, Cl,
(156) ##STR00076##
In some embodiments, R.sup.G8 is
(157) ##STR00077##
(158) In some embodiments, G is
(159) ##STR00078##
(160) In some embodiments, R.sup.G7 is H; R.sup.G8 is
(161) ##STR00079##
R.sup.G9 is H; and R.sup.G11 is H.
(162) In some embodiments, G is
(163) ##STR00080## where each of R.sup.G12, R.sup.G13, and R.sup.G14 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G12 and R.sup.G14, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or optionally substituted C.sub.2-C.sub.9 heterocyclyl.
(164) In some embodiments, each of R.sup.G12, R.sup.G13, and R.sup.G14 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G12 and R.sup.G14, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or optionally substituted C.sub.2-C.sub.9 heterocyclyl.
(165) In some embodiments, the structure of Formula I has the structure of Formula Ia:
(166) ##STR00081##
or a pharmaceutically acceptable salt thereof.
(167) In some embodiments, the structure of Formula I has the structure of Formula Ib:
(168) ##STR00082##

or a pharmaceutically acceptable salt thereof.
(169) In some embodiments, the structure of Formula I has the structure of Formula Ic:
(170) ##STR00083##
or a pharmaceutically acceptable salt thereof.
(171) In some embodiments, the structure of Formula I has the structure of Formula Id:
(172) ##STR00084##
or a pharmaceutically acceptable salt thereof.
(173) In some embodiments, the structure of Formula I has the structure of Formula Ie:
(174) ##STR00085##
or a pharmaceutically acceptable salt thereof.
(175) In some embodiments, the structure of Formula I has the structure of Formula If:
(176) ##STR00086##
or a pharmaceutically acceptable salt thereof.
(177) In some embodiments, the structure of Formula I has the structure of Formula Ig:
(178) ##STR00087##
or a pharmaceutically acceptable salt thereof.
(179) In some embodiments, the structure of Formula I has the structure of Formula Ih:
(180) ##STR00088##
or a pharmaceutically acceptable salt thereof.
(181) In some embodiments, the structure of Formula I has the structure of Formula Ii:
(182) ##STR00089##
or a pharmaceutically acceptable salt thereof.
(183) In some embodiments, the structure of Formula I has the structure of Formula Ij:
(184) ##STR00090##
or a pharmaceutically acceptable salt thereof.
(185) In some embodiments, the compound has the structure of any one of compounds B1-B21 in Table 1A, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound has the structure of any one of compounds B22-B24 in Table 1B, or a pharmaceutically acceptable salt thereof.
(186) In an aspect, the disclosure features a compound having the structure of any one of compounds B1-B21 in Table 1A, or a pharmaceutically acceptable salt thereof.
(187) In another aspect, the disclosure features a compound having the structure of any one of compounds B22-B24 in Table 1B, or a pharmaceutically acceptable salt thereof.
(188) TABLE-US-00001 TABLE 1A Compounds B1-B21 of the Disclosure Compound No. Structure B1  B2  B3  B4  B5  B6  B7  B8  B9  B10 00  B11 01  B12 02  B13 03  B14 04  B15 05  B16 06  B17 07  B18 08  B19 09  B20 0  B21 
(189) TABLE-US-00002 TABLE 1B Compounds B22-B24 of the Disclosure Compound No. Structure B22  B23  B24 
(190) In another aspect, the disclosure features a compound having the structure of Formula II: A-L-B Formula II, where B is a degradation moiety, L is a linker, and A has the structure of Formula III:
(191) ##STR00115## where R.sup.1 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.10 carbocyclyl; Z.sup.1 is CR.sup.2 or N; R.sup.2 is H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, or optionally substituted C.sub.2-C.sub.9 heteroaryl;
(192) ##STR00116## X.sup.1′ is a bond, O, NR.sup.3a′, or CR.sup.4a′R.sup.5a′; X.sup.2′ is O, NR.sup.3b′, or CR.sup.4b′R.sup.5b′; X.sup.3′ is O, NR.sup.3c′, or CR.sup.4c′R.sup.5c′; X.sup.4′ is a

bond, O, NR.sup.3d′, or CR.sup.4d′R.sup.5d′; X.sup.5′ is O, NR.sup.3e′, or CR.sup.4e′R.sup.5e′; X.sup.6′ is O, NR.sup.3f′, or CR.sup.4f′R.sup.5f′; X.sup.7′ is O, NR.sup.3g′, or CR.sup.4g′R.sup.5g′; each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently, H,

(193) ##STR00117## halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted C.sub.1-C.sub.6 acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R.sup.3a′ and R.sup.4b′, R.sup.4a′ and R.sup.3b′, R.sup.4b′ and R.sup.4a′, R.sup.3b′ and R.sup.4c′, R.sup.4b′ and R.sup.4c′, R.sup.3c′ and R.sup.4b′, R.sup.3c′ and R.sup.4d′, R.sup.4c′ and R.sup.4d′, and/or R.sup.3d′ and R.sup.4c′, together with the atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heterocyclyl; R.sup.3′ is absent, optionally substituted C.sub.1-C.sub.6 alkylene, optionally substituted C.sub.1-C.sub.6 heteroalkylene, optionally substituted C.sub.3-C.sub.10 carbocyclylene, optionally substituted C.sub.2-C.sub.9 heterocyclylene, optionally substituted C.sub.6-C.sub.10 arylene, optionally substituted C.sub.2-C.sub.9 heteroarylene, optionally substituted C.sub.2-C.sub.6 alkenylene, optionally substituted C.sub.2-C.sub.6 heteroalkenylene, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino; each of R.sup.4a′, R.sup.4b′, R.sup.4c′, and R.sup.4d′ is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, thiol, optionally substituted sulfone, or optionally substituted amino, or R.sup.3a′ and R.sup.4b′, R.sup.4a′ and R.sup.3b′, R.sup.4b′ and R.sup.4a′, R.sup.3b′ and R.sup.4c′, R.sup.4b′ and R.sup.4c′, R.sup.3c′ and R.sup.4b′, R.sup.3c′ and R.sup.4d′, R.sup.4c′ and R.sup.4d′, and/or R.sup.3d′ and R.sup.4c′, together with the atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heterocyclyl; each of R.sup.5a′, R.sup.5b′, R.sup.5′, and R.sup.5d′ is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; each of R.sup.3e′, R.sup.3f′, and R.sup.3g′ is, independently, H,

(194) ##STR00118## halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted C.sub.1-C.sub.6 acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R.sup.3e and R.sup.4f or R.sup.4e and R.sup.3f, together with the atoms to which each is attached, combine to form optionally substituted heterocyclycl; each of R.sup.4e′, R.sup.4f′, and R.sup.4g′ is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted C.sub.1-C.sub.6 acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R.sup.3e′ and R.sup.4f′ or R.sup.4e′ and R.sup.3f′, together with the atoms to which each is attached, combine to form optionally substituted heterocyclycl; each of R.sup.5e′, R.sup.5f′, and R.sup.5g′ is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9

heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; G″ is
(195) ##STR00119## optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or C.sub.2-C.sub.9 heterocyclyl; G′ is optionally substituted C.sub.3-C.sub.10 carbocyclylene, C.sub.2-C.sub.9 heterocyclylene, optionally substituted C.sub.6-C.sub.10 arylene, or optionally substituted C.sub.2-C.sub.9 heteroarylene; and A.sup.1 is a bond between A and the linker, where one of R.sup.3a′, R.sup.3b′, R.sup.3c′, R.sup.3d′, R.sup.3e′, R.sup.3f′, and R.sup.3g′ is
(196) ##STR00120## or G is
(197) ##STR00121## or a pharmaceutically acceptable salt thereof.
(198) In some embodiments,
(199) ##STR00122##
In some embodiments,
(200) ##STR00123##
is
(201) ##STR00124##
In some embodiments,
(202) ##STR00125##
(203) In another aspect, the disclosure features a compound having the structure of Formula II:
A-L-B Formula II, where B is a degradation moiety, L is a linker, and A has the structure of Formula III:
(204) ##STR00126## where R.sup.1 is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.10 carbocyclyl; Z.sup.1 is CR.sup.2 or N; R.sup.2 is H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, or optionally substituted C.sub.2-C.sub.9 heteroaryl;
(205) ##STR00127## X.sup.1′ is a bond, O, NR.sup.3a′, or CR.sup.4a′R.sup.5a′; X.sup.2′ is O, NR.sup.3b′, or CR.sup.4b′R.sup.5b′; X.sup.3′ is O, NR.sup.3c′, or CR.sup.4c′R.sup.5c′; X.sup.4′ is a bond, O, NR.sup.3d′, or CR.sup.4d′R.sup.5d′; each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently, H,
(206) ##STR00128## halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted C.sub.1-C.sub.6 acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R.sup.3a′ and R.sup.4b, R.sup.4a′ and R.sup.3b′, R.sup.4b′ and R.sup.4a′, R.sup.3b′ and R.sup.4c′, R.sup.4b′ and R.sup.4c′, R.sup.3c′ and R.sup.4b′, R.sup.3c′ and R.sup.4d′, R.sup.4c′ and R.sup.4d′, and/or R.sup.3d′ and R.sup.4c′, together with the atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heterocyclyl; R.sup.3′ is absent, optionally substituted C.sub.1-C.sub.6 alkylene, optionally substituted C.sub.1-C.sub.6 heteroalkylene, optionally substituted C.sub.3-C.sub.10 carbocyclylene, optionally substituted C.sub.2-C.sub.9 heterocyclylene, optionally substituted C.sub.6-C.sub.10 arylene, optionally substituted C.sub.2-C.sub.9 heteroarylene, optionally substituted C.sub.2-C.sub.6 alkenylene, optionally substituted C.sub.2-C.sub.6 heteroalkenylene, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino; each of R.sup.4a′, R.sup.4b′, R.sup.4c′, and R.sup.4d′ is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally

substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, thiol, optionally substituted sulfone, or optionally substituted amino, or R.sup.3a′ and R.sup.4b, R.sup.4a′ and R.sup.3b′, R.sup.4b′ and R.sup.4a′, R.sup.3b′ and R.sup.4c′, R.sup.4b′ and R.sup.4c′, R.sup.3c′ and R.sup.4b′, R.sup.3c′ and R.sup.4d′, R.sup.4c′ and R.sup.4d′, and/or R.sup.3d′ and R.sup.4c′, together with the atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heterocyclyl; each of R.sup.5a′, R.sup.5b′, R.sup.5c′, and R.sup.5d′ is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; G″ is

(207) ##STR00129## optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or C.sub.2-C.sub.9 heterocyclyl; G′ is optionally substituted C.sub.3-C.sub.10 carbocyclylene, C.sub.2-C.sub.9 heterocyclylene, optionally substituted C.sub.6-C.sub.10 arylene, or optionally substituted C.sub.2-C.sub.9 heteroarylene; and A.sup.1 is a bond between A and the linker, where one of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is

(208) ##STR00130## or G is

(209) ##STR00131## or a pharmaceutically acceptable salt thereof.

(210) In some embodiments, R.sup.1 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.10 carbocyclyl. In some embodiments, R.sup.1 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.2-C.sub.6 alkenyl, or optionally substituted C.sub.3-C.sub.10 carbocyclyl. In some embodiments, R.sup.1 is H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.3-C.sub.10 carbocyclyl.

(211) In some embodiments, R.sup.1 is H. In some embodiments, R.sup.1 is optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, R.sup.1 is optionally substituted C.sub.2-C.sub.6 alkenyl. In some embodiments, R.sup.1 is optionally substituted C.sub.3-C.sub.10 carbocyclyl.

(212) In some embodiments, optionally substituted C.sub.1-C.sub.6 alkyl is C.sub.1-C.sub.6 perfluoroalkyl.

(213) In some embodiments, R.sup.1 is

(214) ##STR00132##

(215) In some embodiments, R.sup.1 is

(216) ##STR00133##

(217) In some embodiments, R.sup.1 is

(218) ##STR00134##

(219) In some embodiments, R.sup.1 is H,

(220) ##STR00135##

In some embodiments, R.sup.1 is

(221) ##STR00136##

In some embodiments, R.sup.1 is H,

(222) ##STR00137##

(223) In some embodiments, R.sup.1 is H,

(224) ##STR00138##

(225) In some embodiments, R.sup.1 is H,

(226) ##STR00139##

(227) In some embodiments, R.sup.1 is H or

(228) ##STR00140##

(229) In some embodiments, R.sup.1 is H. In some embodiments, R.sup.1 is

(230) ##STR00141##

(231) In some embodiments, Z.sup.1 is CR.sup.2. In some embodiments, Z.sup.1 is N.

(232) In some embodiments, R.sup.2 is H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl,

optionally substituted C.sub.3-C.sub.10 carbocyclyl, or optionally substituted C.sub.6-C.sub.10 aryl.
(233) In some embodiments, R.sup.2 is H, halogen, or optionally substituted C.sub.1-C.sub.6 alkyl.
(234) In some embodiments, R.sup.2 is H, F, or
(235) ##STR00142##
(236) In some embodiments, R.sup.2 is H. In some embodiments, R.sup.2 is F. In some embodiments, R.sup.2 is
(237) ##STR00143##
(238) In some embodiments, X.sup.1′ is a bond. In some embodiments, X.sup.1 is O, NR.sup.3a′, or CR.sup.4a′R.sup.5a′. In some embodiments, X.sup.1′ is O or NR.sup.3a′. In some embodiments, X.sup.1′ is NR.sup.3a′ or CR.sup.4a′R.sup.5a′.
(239) In some embodiments, X.sup.2′ is O or NR.sup.3b′. In some embodiments, X.sup.2′ is CR.sup.4b′R.sup.5b′. In some embodiments, X.sup.2′ is NR.sup.3b′ or CR.sup.4b′R.sup.5b′.
(240) In some embodiments, X.sup.3′ is O or NR.sup.3c′. In some embodiments, X.sup.3′ is CR.sup.4c′R.sup.5c′. In some embodiments, X.sup.3′ is NR.sup.3c′ or CR.sup.4c′R.sup.5c′.
(241) In some embodiments, X.sup.4′ is a bond. In some embodiments, X.sup.4′ is O, NR.sup.3d′, or CR.sup.4d′R.sup.5d′. In some embodiments, X.sup.4′ is O or NR.sup.3d′. In some embodiments, X.sup.4′ is NR.sup.3d′ or CR.sup.4d′R.sup.5d′.
(242) In some embodiments, X.sup.1′ is O, NR.sup.3a′, or CR.sup.4a′R.sup.5a′; X.sup.2′ is O, NR.sup.3b′, or CR.sup.4b′R.sup.5b′; X.sup.3′ is O, NR.sup.3c′, or CR.sup.4c′R.sup.5c′; and X.sup.4′ is O, NR.sup.3d′, or CR.sup.4d′R.sup.5d′.
(243) In some embodiments, X.sup.1′ is CR.sup.4a‘R.sup.5a’; X.sup.2′ is NR.sup.3b′; X.sup.3′ is CR.sup.4c′R.sup.5c′; and X.sup.4′ is CR.sup.4d′R.sup.5d′.
(244) In some embodiments, X.sup.1′ is CR.sup.4a′R.sup.5a′; X.sup.2′ is CR.sup.4b′R.sup.5b′; X.sup.3′ is NR.sup.3c′; and X.sup.4′ is CR.sup.4d′R.sup.5d′.
(245) In some embodiments, X.sup.1′ is O or NR.sup.3a′; X.sup.2′ is CR.sup.4b′R.sup.5b′; X.sup.3′ is CR.sup.4c′R.sup.5c′; and X.sup.4′ is O or NR.sup.3d′.
(246) In some embodiments, X.sup.1′ is a bond; X.sup.2′ is CR.sup.4b′R.sup.5b′; X.sup.3′ is O or NR.sup.3c′; and X.sup.4′ is CR.sup.4d′R.sup.5d′.
(247) In some embodiments, X.sup.1′ is CR.sup.4a′R.sup.5a′; X.sup.2′ is CR.sup.4b′R.sup.5b′; X.sup.3′ is CR.sup.4c′R.sup.5c′; and X.sup.4′ is CR.sup.4d′R.sup.5d′.
(248) In some embodiments, X.sup.5′ is CR.sup.4e′R.sup.5e′ and X.sup.6′ is NR.sup.3f′.
(249) In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently, H,
(250) ##STR00144##
optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.1-C.sub.6 acyl, optionally substituted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently, H,
(251) ##STR00145##
optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently, H,
(252) ##STR00146##
optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 acyl, optionally substituted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently, H,
(253) ##STR00147##
optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 acyl.
(254) In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently,
(255) ##STR00148##
(256) optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.1-C.sub.6 acyl, optionally substituted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is,

independently,
(257) ##STR00149##
optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 acyl, optionally substituted sulfone, or optionally substituted sulfonamide.
(258) In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently,
(259) ##STR00150##
optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.1-C.sub.6 acyl. In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently,
(260) ##STR00151##
optionally substituted C.sub.1-C.sub.6 alkyl or optionally substituted C.sub.1-C.sub.6 heteroalkyl. In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently,
(261) ##STR00152##
optionally substituted C.sub.1-C.sub.6 alkyl or optionally substituted C.sub.1-C.sub.6 acyl. In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently,
(262) ##STR00153## or optionally substituted C.sub.1-C.sub.6 acyl. In some embodiments, each of R.sup.3a′, R.sup.3c′, R.sup.3c′, and R.sup.3d′ is, independently,
(263) ##STR00154##
optionally substituted sulfone, or optionally substituted sulfonamide.
(264) In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently, H,
(265) ##STR00155##
optionally substituted C.sub.1-C.sub.6 alkyl,
(266) ##STR00156## where R.sup.6 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, or optionally substituted C.sub.6-C.sub.10 aryl; W.sup.1 is O or S; W.sup.2 is NR.sup.7 or O; R.sup.7 is H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl; R.sup.8 is optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, or optionally substituted C.sub.6-C.sub.10 aryl; and R.sup.9 is H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl.
(267) In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently,
(268) ##STR00157##
C.sub.1-C.sub.6 alkyl,
(269) ##STR00158##
In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently,
(270) ##STR00159## or C.sub.1-C.sub.6 alkyl. In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently
(271) ##STR00160##
In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently,
(272) ##STR00161##
In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d is, independently,
(273) ##STR00162##
In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently,
(274) ##STR00163##
In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently, H,
(275) ##STR00164##
optionally substituted C.sub.1-C.sub.6 alkyl,
(276) ##STR00165##
In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently, H,
(277) ##STR00166##
C.sub.1-C.sub.6 alkyl,
(278) ##STR00167##

In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently, H,
(279) ##STR00168##
C.sub.1-C.sub.6 alkyl, or
(280) ##STR00169##
In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently,
(281) ##STR00170##
C.sub.1-C.sub.6 alkyl, or
(282) ##STR00171##
In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently, H,
(283) ##STR00172##
methyl, or
(284) ##STR00173##
(285) In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently
(286) ##STR00174## or optionally substituted C.sub.1-C.sub.6 alkyl.
(287) In some embodiments, each of R.sup.4a′, R.sup.4b′, R.sup.4c′, and R.sup.4d′ is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.1-C.sub.6 acyl, optionally substituted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R.sup.4a′, R.sup.4b′, R.sup.4c′, and R.sup.4d′ is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R.sup.4a, R.sup.4b′, R.sup.4c′, and R.sup.4d′ is H. In some embodiments, each of R.sup.4a′, R.sup.4b′, R.sup.4c′, and R.sup.4d′ is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 acyl, optionally substituted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R.sup.4a′, R.sup.4b′, R.sup.4c′, and R.sup.4d′ is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 acyl.
(288) In some embodiments, each of R.sup.4a′, R.sup.4b′, R.sup.4c′, and R.sup.4d′ is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl,
(289) ##STR00175## where R.sup.6 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, or optionally substituted C.sub.6-C.sub.10 aryl; W.sup.1 is O or S; W.sup.2 is NR.sup.7 or O; R.sup.7 is H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl; R.sup.8 is optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, or optionally substituted C.sub.6-C.sub.10 aryl; and R.sup.9 is H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl.
(290) In some embodiments, each of R.sup.4a′, R.sup.4b′, R.sup.4c′, and R.sup.4d′ is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl,
(291) ##STR00176##
In some embodiments, each of R.sup.4a′, R.sup.4b′, R.sup.4c′, and R.sup.4d′ is, independently, H or optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, each of R.sup.4a′, R.sup.4b′, R.sup.4c′, and R.sup.4d′ is, independently, H.
(292) In some embodiments, W.sup.1 is O. In some embodiments, W.sup.1 is S.
(293) In some embodiments, W.sup.2 is O. In some embodiments, W.sup.2 is NR.sup.7.
(294) In some embodiments, R.sup.6 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.10 carbocyclyl. In some embodiments, R.sup.6 is H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl. In some embodiments, R.sup.6 is H, optionally substituted C.sub.3-C.sub.10 carbocyclyl, or optionally substituted C.sub.6-C.sub.10 aryl. In some embodiments, R.sup.6 is optionally substituted C.sub.1-C.sub.6 alkyl or optionally substituted C.sub.1-C.sub.6 heteroalkyl. In some embodiments, R.sup.6 is optionally substituted C.sub.3-C.sub.10 carbocyclyl or optionally substituted C.sub.6-C.sub.10 aryl

(295) In some embodiments, R.sup.6 is H, methyl, ethyl,
(296) ##STR00177##
In some embodiments, R.sup.6 is H or
(297) ##STR00178##
In some embodiments, R.sup.6 is methyl, ethyl,
(298) ##STR00179##
In some embodiments, R.sup.6 is or
(299) ##STR00180##
In some embodiments, R.sup.6 is H. In some embodiments, R.sup.6 is H, methyl, ethyl,
(300) ##STR00181##
(301) In some embodiments, R.sup.7 is H or optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, R.sup.7 is H or methyl.
(302) In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently, H,
(303) ##STR00182##
methyl,
(304) ##STR00183##
(305) In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently, H,
(306) ##STR00184##
methyl,
(307) ##STR00185##
(308) In some embodiments, R.sup.3a′ is H,
(309) ##STR00186##
methyl
(310) ##STR00187##
In some embodiments, R.sup.3b′ is H,
(311) ##STR00188##
methyl,
(312) ##STR00189##
In some embodiments, R.sup.3c′ is H
(313) ##STR00190##
methyl,
(314) ##STR00191##
In some embodiments, R.sup.3d′ is H,
(315) ##STR00192##
methyl,
(316) ##STR00193##
(317) In some embodiments, one of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is
(318) ##STR00194##
(319) In some embodiments, R.sup.3b′ is
(320) ##STR00195##
In some embodiments, R.sup.3c′ is
(321) ##STR00196##
(322) In some embodiments, R.sup.3′ is absent.
(323) In some embodiments, R.sup.3a′ and R.sup.4b′, R.sup.4a′ and R.sup.3b′, R.sup.4b′ and R.sup.4a′, R.sup.3b′ and R.sup.4c′, R.sup.4b′ and R.sup.4c′, R.sup.3c′ and R.sup.4b′, R.sup.3c′ and R.sup.4d′, R.sup.4c′ and R.sup.4d′, and/or R.sup.3d′ and R.sup.4c′, together with the atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heterocyclyl.
(324) In some embodiments, R.sup.3a′ and R.sup.4b′, R.sup.4a′ and R.sup.3b′, R.sup.3b′ and R.sup.4c′, R.sup.4b′ and R.sup.3c′, R.sup.3c′ and R.sup.4d′, and/or R.sup.4c′ and R.sup.3d′, together with the atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heterocyclyl.
(325) In some embodiments, each of R.sup.5a, R.sup.5b, R.sup.5c, and R.sup.5d is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl. In

some embodiments, each of R.sup.5a, R.sup.5b, R.sup.5c, and R.sup.5d is H.
(326) In some embodiments, each of R.sup.3e′, R.sup.3f′, and R.sup.3g′ is, independently H,
(327) ##STR00197##
optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.1-C.sub.6 acyl, optionally substituted sulfone, or optionally substituted sulfonamide.
(328) In some embodiments, each of R.sup.4e′, R.sup.4f′, and R.sup.4g′ is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.1-C.sub.6 acyl, optionally substituted sulfone, or optionally substituted sulfonamide.
(329) In some embodiments, each of R.sup.5e′, R.sup.5f′, and R.sup.5g′ is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl. In some embodiments, each of R.sup.5e′, R.sup.5f′, and R.sup.5g′ is H.
(330) In some embodiments, G″ is optionally substituted C.sub.3-C.sub.10 carbocyclyl or optionally substituted C.sub.2-C.sub.9 heterocyclyl. In some embodiments, G″ is optionally substituted C.sub.6-C.sub.10 aryl or optionally substituted C.sub.2-C.sub.9 heteroaryl.
(331) In some embodiments, G″ is optionally substituted C.sub.3-C.sub.10 carbocyclyl. In some embodiments, G is optionally substituted C.sub.6-C.sub.10 aryl. In some embodiments, G is optionally substituted C.sub.2-C.sub.9 heterocyclyl. In some embodiments, G″ is optionally substituted C.sub.2-C.sub.9 heteroaryl.
(332) In some embodiments, G″ is
(333) ##STR00198## where each of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G1 and R.sup.G2, R.sup.G2 and R.sup.G3, R.sup.G3 and R.sup.G4, and/or R.sup.G4 and R.sup.G5, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or optionally substituted C.sub.2-C.sub.9 heterocyclyl.
(334) In some embodiments, each of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G1 and R.sup.G2, R.sup.G2 and R.sup.G3, R.sup.G3 and R.sup.G4, and/or R.sup.G4 and R.sup.G5, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or optionally substituted C.sub.2-C.sub.9 heterocyclyl.
(335) In some embodiments, each of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, or optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl; or R.sup.G1 and R.sup.G2, R.sup.G2 and R.sup.G3, R.sup.G3 and R.sup.G4, and/or R.sup.G4 and R.sup.G5, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heteroaryl or optionally substituted C.sub.2-C.sub.9 heterocyclyl.
(336) In some embodiments, each of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is,

independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, or optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl.
(337) In some embodiments, each of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is, independently, H, F, Cl,
(338) ##STR00199##
(339) In some embodiments, each of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4 and R.sup.G5 is, independently, H, F
(340) ##STR00200##
(341) In some embodiments, each of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is, independently, H, F, Cl,
(342) ##STR00201##
(343) In some embodiments, R.sup.G1 is H; R.sup.G2 is
(344) ##STR00202##
R.sup.G3 is
(345) ##STR00203##
R.sup.G4 is
(346) ##STR00204##
and R.sup.G5 is H. In some embodiments, R.sup.G1 is H; R.sup.G2 is
(347) ##STR00205##
R.sup.G3 is
(348) ##STR00206##
R.sup.G4 is H; and R.sup.G5 is
(349) ##STR00207##
In some embodiments, R.sup.G1 is H; R.sup.G2 is
(350) ##STR00208##
R.sup.G3 is
(351) ##STR00209##
R.sup.G4 is Cl or F; and R.sup.G5 is H. In some embodiments, R.sup.G1 is H; R.sup.G2 is
(352) ##STR00210##
R.sup.G3 is
(353) ##STR00211##
R.sup.G4 is H; and R.sup.G5 is H. In some embodiments, R.sup.G1 is H; R.sup.G2 is
(354) ##STR00212##
R.sup.G3 is
(355) ##STR00213##
R.sup.G4 is
(356) ##STR00214##
and R.sup.G5 is H.
(357) In some embodiments, R.sup.G1 and R.sup.G2, R.sup.G2 and R.sup.G3, R.sup.G3 and R.sup.G4, and/or R.sup.G4 and R.sup.G5, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heteroaryl or optionally substituted C.sub.2-C.sub.9 heterocyclyl.
(358) In some embodiments, R.sup.G1 and R.sup.G2, R.sup.G2 and R.sup.G3, R.sup.G3 and R.sup.G4, and/or R.sup.G4 and R.sup.G5, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heterocyclyl. In some embodiments, R.sup.G1 and R.sup.G2, R.sup.G2 and R.sup.G3, R.sup.G3 and R.sup.G4, and/or R.sup.G4 and R.sup.G5, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heteroaryl.
(359) In some embodiments, R.sup.G1 and R.sup.G2, R.sup.G2 and R.sup.G3, R.sup.G3 and R.sup.G4, and/or R.sup.G4 and R.sup.G5, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heterocyclyl. In some embodiments, R.sup.G1 and

R.sup.G2, R.sup.G2 and R.sup.G3, R.sup.G3 and R.sup.G4, and/or R.sup.G4 and R.sup.G5, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heteroaryl.

(360) In some embodiments, G″ is

(361) ##STR00215##

where R.sup.G6 is H or optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, G″ is

(362) ##STR00216##

where R.sup.G6 is H or optionally substituted C.sub.1-C.sub.6 alkyl.

(363) In some embodiments, G″ is

(364) ##STR00217##

where R.sup.G6 is H or optionally substituted C.sub.1-C.sub.6 alkyl.

(365) In some embodiments, R.sup.G6 is H,

(366) ##STR00218##

(367) In some embodiments, R.sup.G6 is H or

(368) ##STR00219##

(369) In some embodiments, R.sup.G6 is H.

(370) In some embodiments, R.sup.G1 is H, F,

(371) ##STR00220##

In some embodiments, R.sup.G1 is H.

(372) In some embodiments, R.sup.G2 is H, F,

(373) ##STR00221##

In some embodiments, R.sup.G2 is H.

(374) In some embodiments, R.sup.G3 is H, F,

(375) ##STR00222##

In some embodiments, R.sup.G3 is H.

(376) In some embodiments, R.sup.G4 is H, F,

(377) ##STR00223##

In some embodiments, R.sup.G4 is H.

(378) In some embodiments, R.sup.G5 is H, F,

(379) ##STR00224##

In some embodiments, R.sup.G5 is H.

(380) In some embodiments, one or more of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is H. In some embodiments, two or more of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is H. In some embodiments, three or more of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is H. In some embodiments, each of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is H.

(381) In some embodiments, G″ is

(382) ##STR00225## where each of R.sup.G7, R.sup.G8, R.sup.G9, R.sup.G10, and R.sup.G11 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G7 and R.sup.G8, R.sup.G8 and R.sup.G9, R.sup.G9 and R.sup.G10, and/or R.sup.G10 and R.sup.G11, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or C.sub.2-C.sub.9 heterocyclyl.

(383) In some embodiments, each of R.sup.G7, R.sup.G8, R.sup.G9, R.sup.G10, and R.sup.G11 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-

C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G7 and R.sup.G8, R.sup.G8 and R.sup.G9, R.sup.G9 and R.sup.G10, and/or R.sup.G10 and R.sup.G11, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or C.sub.2-C.sub.9 heterocyclyl.

(384) In some embodiments, each of R.sup.G7, R.sup.G8, R.sup.G9, R.sup.G10, and R.sup.G11 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, or optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl; or R.sup.G7 and R.sup.G8, R.sup.G8 and R.sup.G9, R.sup.G9 and R.sup.G10, and/or R.sup.G10 and R.sup.G11, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or C.sub.2-C.sub.9 heterocyclyl.

(385) In some embodiments, each of R.sup.G7, R.sup.G8, R.sup.G9, R.sup.G10, and R.sup.G11 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, or optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl.

(386) In some embodiments, each of R.sup.G7, R.sup.G8, R.sup.G9, R.sup.G10, and R.sup.G11 is, independently, H, F, Cl,

(387) ##STR00226##

In some embodiments, R.sup.G8 is

(388) ##STR00227##

(389) In some embodiments, G″ is

(390) ##STR00228##

(391) In some embodiments, R.sup.G7 is H; R.sup.G8 is

(392) ##STR00229##

R.sup.G9 is H; and R.sup.G11 is H.

(393) In some embodiments, G″ is

(394) ##STR00230## where each of R.sup.G12, R.sup.G13, and R.sup.G14 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G12 and R.sup.G14, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or optionally substituted C.sub.2-C.sub.9 heterocyclyl.

(395) In some embodiments, each of R.sup.G12, R.sup.G13, and R.sup.G14 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G12 and R.sup.G14, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or optionally substituted C.sub.2-C.sub.9 heterocyclyl.

(396) In some embodiments, G″ is

(397) ##STR00231##

(398) In some embodiments, G′ is optionally substituted C.sub.3-C.sub.10 carbocyclylene or optionally

substituted C.sub.2-C.sub.9 heterocyclylene. In some embodiments, G′ is optionally substituted C.sub.6-C.sub.10 arylene or optionally substituted C.sub.2-C.sub.9 heteroarylene.
(399) In some embodiments, G′ is optionally substituted C.sub.3-C.sub.10 carbocyclylene. In some embodiments, G′ is optionally substituted C.sub.6-C.sub.10 arylene. In some embodiments, G′ is optionally substituted C.sub.2-C.sub.9 heterocyclylene. In some embodiments, G′ is optionally substituted C.sub.2-C.sub.9 heteroarylene.
(400) In some embodiments, G′ is
(401) ##STR00232## where each of R.sup.G1′, R.sup.G2′, R.sup.G3′, R.sup.G4′, and R.sup.G5′ is, independently, H, A.sup.1, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G1′ and R.sup.G2′, R.sup.G2′ and R.sup.G3′, R.sup.G3′ and R.sup.G4′, and/or R.sup.G4′ and R.sup.G5′, together with the carbon atoms to which each is attached, combine to form  custom character; and  custom character is optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or optionally substituted C.sub.2-C.sub.9 heterocyclyl, any of which is optionally substituted with A.sup.1, where one of R.sup.G1′, R.sup.G2′, R.sup.G3′, R.sup.G4′, and R.sup.G5′ is A.sup.1, or  custom character is substituted with A.sup.1.
(402) In some embodiments, each of R.sup.G1′, R.sup.G2′, R.sup.G3′, R.sup.G4′, and R.sup.G5′ is, independently, H, A.sup.1, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G1′ and R.sup.G2′, R.sup.G2′ and R.sup.G3′, R.sup.G3′ and R.sup.G4′, and/or R.sup.G4′ and R.sup.G5′, together with the carbon atoms to which each is attached, combine to form  custom character; and  custom character is optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or optionally substituted C.sub.2-C.sub.9 heterocyclyl, any of which is optionally substituted with A.sup.1, where one of R.sup.G1′, R.sup.G2′, R.sup.G3′, R.sup.G4′, and R.sup.G5′ is A.sup.1, or  custom character is substituted with A.sup.1.
(403) In some embodiments, each of R.sup.G1′, R.sup.G2′, R.sup.G3′, R.sup.G4′, and R.sup.G5′ is, independently, H, A.sup.1, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, or optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl; or R.sup.G1′ and R.sup.G2′, R.sup.G2′ and R.sup.G3′, R.sup.G3′ and R.sup.G4′, and/or R.sup.G4′ and R.sup.G5′, together with the carbon atoms to which each is attached, combine to form  custom character; and  custom character is optionally substituted C.sub.2-C.sub.9 heteroaryl or optionally substituted C.sub.2-C.sub.9 heterocyclyl, any of which is optionally substituted with A.sup.1, where one of R.sup.G1′, R.sup.G2′, R.sup.G3′, R.sup.G4′, and R.sup.G5′ is A.sup.1, or  custom character is substituted with A.sup.1.
(404) In some embodiments, each of R.sup.G1′, R.sup.G2′, R.sup.G3′, R.sup.G4′, and R.sup.G5′ is, independently, H, A.sup.1, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, or optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl.
(405) In some embodiments, each of R.sup.G1′, R.sup.G2′, R.sup.G3′, R.sup.G4′, and R.sup.G5′ is, independently, H, A.sup.1, F, Cl,

(406) ##STR00233##
(407) In some embodiments, each of R.sup.G1′, R.sup.G2′, R.sup.G3′, R.sup.G4′, and R.sup.G5′ is, independently, H, A.sup.1, F,
(408) ##STR00234##
(409) In some embodiments, each of R.sup.G1′, R.sup.G2′, R.sup.G3′, R.sup.G4′, and R.sup.G5′ is, independently, H, A.sup.1, F, Cl,
(410) ##STR00235##
(411) In some embodiments, R.sup.G3′ is A.sup.1.
(412) In some embodiments, R.sup.G1′ is H; R.sup.G2′ is
(413) ##STR00236##
R.sup.G3′ is A.sup.1; R.sup.G4′ is
(414) ##STR00237##
and R.sup.G5′ is H. In some embodiments, R.sup.G1′ is H; R.sup.G2′ is
(415) ##STR00238##
R.sup.G3′ is A; R.sup.G4′ is H; and R.sup.G5′ is
(416) ##STR00239##
In some embodiments, R.sup.G1′ is H; R.sup.G2′ is
(417) ##STR00240##
R.sup.G3′ is A.sup.1; R.sup.G4′ is Cl or F; and R.sup.G5′ is H. In some embodiments, R.sup.G1′ is H; R.sup.G2′ is
(418) ##STR00241##
R.sup.G3′ is A.sup.1; R.sup.G4′ is H; and R.sup.G5′ is H. In some embodiments, R.sup.G1′ is H; R.sup.G2′ is
(419) ##STR00242##
R.sup.G3′ is A.sup.1; R.sup.G4′ is
(420) ##STR00243##
and R.sup.G5′ is H.
(421) In some embodiments, R.sup.G1′ and R.sup.G2′, R.sup.G2′ and R.sup.G3′, R.sup.G3′ and R.sup.G4, and/or R.sup.G4′ and R.sup.G5′, together with the carbon atoms to which each is attached, combine to form custom character; and custom character is optionally substituted C.sub.2-C.sub.9 heterocyclyl, which is optionally substituted with A.sup.1, where one of R.sup.G1′, R.sup.G2′, R.sup.G3′, R.sup.G4′ and R.sup.G5′ is A.sup.1, or custom character is substituted with A.sup.1. In some embodiments, R.sup.G1′ and R.sup.G2′, R.sup.G2′ and R.sup.G3′, R.sup.G3′, and R.sup.G4′, and/or R.sup.G4′ and R.sup.G5′, together with the carbon atoms to which each is attached, combine to form custom character; and custom character is optionally substituted C.sub.2-C.sub.9 heteroaryl, which is optionally substituted with A.sup.1, where one of R.sup.G1′, R.sup.G2′, R.sup.G3′, R.sup.G4′, and R.sup.G5′ is A.sup.1, or custom character is substituted with A.sup.1.
(422) In some embodiments, G′ is
(423) ##STR00244##
where R.sup.G6′ is H, A.sup.1, or optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, G′ is
(424) ##STR00245##
where R.sup.G6′ is H, A.sup.1, or optionally substituted C.sub.1-C.sub.6 alkyl.
(425) In some embodiments, R.sup.G1′ and R.sup.G2′, R.sup.G2′ and R.sup.G3′, R.sup.G3′ and R.sup.G4′, and/or R.sup.G4′ and R.sup.G5′, together with the carbon atoms to which each is attached, combine to form custom character; and custom character is optionally substituted C.sub.2-C.sub.9 heterocyclyl or optionally substituted C.sub.2-C.sub.9 heteroaryl, any of which is optionally substituted with A.sup.1, where one of R.sup.G1′, R.sup.G2′, R.sup.G3′, R.sup.G4′, and R.sup.G5′ is A.sup.1, or custom character is substituted with A.sup.1.
(426) In some embodiments, G′ is
(427) ##STR00246## where R.sup.G6′ is H, A.sup.1, or optionally substituted C.sub.1-C.sub.6 alkyl.
(428) In some embodiments, R.sup.G6′ is H, A.sup.1,

(429) ##STR00247##
(430) In some embodiments, R.sup.G6′ is H, A.sup.1, or
(431) ##STR00248##
(432) In some embodiments, R.sup.G6′ is H or A.sup.1.
(433) In some embodiments, R.sup.G6′ is H. In some embodiments, R.sup.G6′ is A.sup.1.
(434) In some embodiments, R.sup.G1′ is H, A.sup.1, F,
(435) ##STR00249##
In some embodiments, R.sup.G1′ is H.
(436) In some embodiments, R.sup.G2′ is H, A.sup.1, F,
(437) ##STR00250##
In some embodiments, R.sup.G2′ is H.
(438) In some embodiments, R.sup.G3′ is H, A.sup.1, F,
(439) ##STR00251##
In some embodiments, R.sup.G3′ is H.
(440) In some embodiments, R.sup.G4′ is H, A.sup.1, F,
(441) ##STR00252##
In some embodiments, R.sup.G4′ is H.
(442) In some embodiments, R.sup.G5′ is H, A.sup.1, F,
(443) ##STR00253##
In some embodiments, R.sup.G5′ is H.
(444) In some embodiments, one or more of R.sup.G1′, R.sup.G2′, R.sup.G3′, R.sup.G4′, and R.sup.G5′ is H. In some embodiments, two or more of R.sup.G1′, R.sup.G2′, R.sup.G3′, R.sup.G4′, and R.sup.G5′ is H. In some embodiments, three or more of R.sup.G1′, R.sup.G2′, R.sup.G3′, R.sup.G4′, and R.sup.G5′ is H.
(445) In some embodiments, R.sup.G1′ is A.sup.1. In some embodiments, R.sup.G2′ is A.sup.1. In some embodiments, R.sup.G3′ is A.sup.1. In some embodiments, R.sup.G4′ is A.sup.1. In some embodiments, R.sup.G5′ is A.sup.1. In some embodiments,  custom character is substituted with A.sup.1.
(446) In some embodiments, G′ is
(447) ##STR00254## where each of R.sup.G7′, R.sup.G8′, R.sup.G9′, R.sup.G10′, and R.sup.G11′ is, independently, H, A.sup.1, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G7′ and R.sup.G8′, R.sup.G8′ and R.sup.G9′, R.sup.G9′ and R.sup.G10′, and/or R.sup.G10′ and R.sup.G11′, together with the carbon atoms to which each is attached, combine to form  custom character; and  custom character is optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or C.sub.2-C.sub.9 heterocyclyl, any of which is optionally substituted with A.sup.1, where one of R.sup.G7′, R.sup.G8′, R.sup.G9′, R.sup.G10′, and R.sup.G11′ is A.sup.1; or  custom character is substituted with A.sup.1.
(448) In some embodiments, each of R.sup.G7′, R.sup.G8′, R.sup.G9′, R.sup.G10′, and R.sup.G11′ is, independently, H, A.sup.1, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G7′ and R.sup.G8′, R.sup.G8′ and R.sup.G9′, R.sup.G9′ and R.sup.G10′, and/or R.sup.G10′ and

R.sup.G11′, together with the carbon atoms to which each is attached, combine to form  custom character; and  custom character is optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or C.sub.2-C.sub.9 heterocyclyl, any of which is optionally substituted with A.sup.1, where one of R.sup.G7′, R.sup.G8′, R.sup.G9′, R.sup.G10′, and R.sup.G11′ is A.sup.1; or  custom character is substituted with A.sup.1.

(449) In some embodiments, each of R.sup.G7′, R.sup.G8′, R.sup.G9′, R.sup.G10′, and R.sup.G11′ is, independently, H, A.sup.1, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, or optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl; or R.sup.G7′ and R.sup.G8′, R.sup.G8′ and R.sup.G9′, R.sup.G9′ and R.sup.G10′, and/or R.sup.G10′ and R.sup.G11′, together with the carbon atoms to which each is attached, combine to form  custom character; and custom character is optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or C.sub.2-C.sub.9 heterocyclyl, any of which is optionally substituted with A.sup.1, where one of R.sup.G7′, R.sup.G8′, R.sup.G9′, R.sup.G10′, and R.sup.G11′ is A.sup.1; or  custom character is substituted with A.sup.1.

(450) In some embodiments, each of R.sup.G7′, R.sup.G8′, R.sup.G9′, R.sup.G10′, and R.sup.G11′ is, independently, H, A.sup.1, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, or optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl.

(451) In some embodiments, each of R.sup.G7′, R.sup.G8′, R.sup.G9′, R.sup.G10′, and R.sup.G11′ is, independently, H, A.sup.1, F, Cl,

(452) ##STR00255##

In some embodiments, R.sup.G8′ is

(453) ##STR00256##

(454) In some embodiments, G′ is

(455) ##STR00257##

(456) In some embodiments, R.sup.G7′ is H; R.sup.G8′ is

(457) ##STR00258##

R.sup.G9′ is A.sup.1; and R.sup.G11′ is H.

(458) In some embodiments, G′ is

(459) ##STR00259## where each of R.sup.G12′, R.sup.G13′, and R.sup.G14′ is, independently, H, A.sup.1, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G12′ and R.sup.G14′ together with the carbon atoms to which each is attached, combine to form  custom character; and  custom character is optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or optionally substituted C.sub.2-C.sub.9 heterocyclyl, any of which is optionally substituted with A.sup.1, where one of R.sup.G12′, R.sup.G13′, and R.sup.G14′ is A.sup.1; or  custom character is substituted with A.sup.1.

(460) In some embodiments, each of R.sup.G12′, R.sup.G13′, and R.sup.G14′ is, independently, H, A.sup.1, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-

C.sub.2-C.sub.5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G12′ and R.sup.G14′, together with the carbon atoms to which each is attached, combine to form custom character; and custom character is optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or optionally substituted C.sub.2-C.sub.9 heterocyclyl, any of which is optionally substituted with A.sup.1, where one of R.sup.G12′, R.sup.G13′, and R.sup.G14′ is A.sup.1; or custom character is substituted with A.sup.1.

(461) In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.1-C.sub.6 acyl, optionally substituted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R.sup.3a′ R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 acyl, optionally substituted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 acyl.

(462) In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.1-C.sub.6 acyl, optionally substituted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c, and R.sup.3d′ is, independently, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 acyl, optionally substituted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.1-C.sub.6 acyl. In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently, optionally substituted C.sub.1-C.sub.6 alkyl or optionally substituted C.sub.1-C.sub.6 heteroalkyl. In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently, optionally substituted C.sub.1-C.sub.6 alkyl or optionally substituted C.sub.1-C.sub.6 acyl. In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently, or optionally substituted C.sub.1-C.sub.6 acyl. In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently, optionally substituted sulfone, or optionally substituted sulfonamide.

(463) In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl,

(464) ##STR00260## where R.sup.6 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, or optionally substituted C.sub.6-C.sub.10 aryl; W.sup.1 is O or S; W.sup.2 is NR.sup.7 or O; R.sup.7 is H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl; R.sup.8 is optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, or optionally substituted C.sub.6-C.sub.10 aryl; and R.sup.9 is H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl.

(465) In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently, C.sub.1-C.sub.6 alkyl,

(466) ##STR00261##

In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently, or C.sub.1-C.sub.6 alkyl. In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently,

(467) ##STR00262##

In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently,

(468) ##STR00263##

In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently,
(469) ##STR00264##
In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently,
(470) ##STR00265##
In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl,
(471) ##STR00266##
In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c, and R.sup.3d′ is, independently, H, C.sub.1-C.sub.6 alkyl,
(472) ##STR00267##
In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently, H, C.sub.1-C.sub.6 alkyl, or
(473) ##STR00268##
In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently, C.sub.1-C.sub.6 alkyl or
(474) ##STR00269##
In some embodiments, each of R.sup.3a, R.sup.3b, R.sup.3c, and R.sup.3d is, independently, H, methyl, or
(475) ##STR00270##
(476) In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently, optionally substituted C.sub.1-C.sub.6 alkyl.
(477) In some embodiments, W.sup.1 is O. In some embodiments, W.sup.1 is S.
(478) In some embodiments, W.sup.2 is O. In some embodiments, W.sup.2 is NR.sup.7.
(479) In some embodiments, R.sup.6 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.10 carbocyclyl. In some embodiments, R.sup.6 is H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl. In some embodiments, R.sup.6 is H, optionally substituted C.sub.3-C.sub.10 carbocyclyl, or optionally substituted C.sub.6-C.sub.10 aryl. In some embodiments, R.sup.6 is optionally substituted C.sub.1-C.sub.6 alkyl or optionally substituted C.sub.1-C.sub.6 heteroalkyl. In some embodiments, R.sup.6 is optionally substituted C.sub.3-C.sub.10 carbocyclyl or optionally substituted C.sub.6-C.sub.10 aryl
(480) In some embodiments, R.sup.6 is H, methyl, ethyl,
(481) ##STR00271##
In some embodiments, R.sup.6 is H or
(482) ##STR00272##
In some embodiments, R.sup.6 is methyl, ethyl,
(483) ##STR00273##
In some embodiments, R.sup.6 is or
(484) ##STR00274##
In some embodiments, R.sup.6 is H. In some embodiments, R.sup.6 is H, methyl, ethyl,
(485) ##STR00275##
(486) In some embodiments, R.sup.7 is H or optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, R.sup.7 is H or methyl.
(487) In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c, and R.sup.3d′ is, independently, H, methyl,
(488) ##STR00276##
(489) In some embodiments, each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently, H, methyl,
(490) ##STR00277##
(491) In some embodiments, R.sup.3a′ is H, methyl,
(492) ##STR00278##
(493) In some embodiments, R.sup.3b′ is H, methyl,

(494) ##STR00279##
In some embodiments, R.sup.3c′ is H, methyl,
(495) ##STR00280##
In some embodiments, R.sup.3d′ is H, methyl,
(496) ##STR00281##
(497) In some embodiments, A has the structure of Formula IIIa:
(498) ##STR00282##
or a pharmaceutically acceptable salt thereof.
(499) In some embodiments, A has the structure of Formula IIIb:
(500) ##STR00283##
or a pharmaceutically acceptable salt thereof.
(501) In some embodiments, A has the structure of Formula IIIc:
(502) ##STR00284##
or a pharmaceutically acceptable salt thereof.
(503) In some embodiments, A has the structure of Formula IIId:
(504) ##STR00285##
or a pharmaceutically acceptable salt thereof.
(505) In some embodiments, A has the structure of Formula IIIe:
(506) ##STR00286##
or a pharmaceutically acceptable salt thereof.
(507) In some embodiments, A has the structure of Formula IIIf:
(508) ##STR00287##
or a pharmaceutically acceptable salt thereof.
(509) In some embodiments, A has the structure of Formula IIIg:
(510) ##STR00288##
or a pharmaceutically acceptable salt thereof.
(511) In some embodiments, A has the structure of Formula IIIh:
(512) ##STR00289##
or a pharmaceutically acceptable salt thereof.
(513) In some embodiments, A has the structure of Formula IIIi:
(514) ##STR00290##
or a pharmaceutically acceptable salt thereof.
(515) In some embodiments, A has the structure of Formula IIIj:
(516) ##STR00291##
or a pharmaceutically acceptable salt thereof.
(517) In some embodiments, A has the structure of Formula IIIk:
(518) ##STR00292##
or a pharmaceutically acceptable salt thereof.
(519) In some embodiments, A has the structure of Formula IIIm:
(520) ##STR00293##
or a pharmaceutically acceptable salt thereof.
(521) In some embodiments, A has the structure of Formula IIIn:
(522) ##STR00294##
or a pharmaceutically acceptable salt thereof.
(523) In some embodiments, A has the structure of Formula IIIo:
(524) ##STR00295##
or a pharmaceutically acceptable salt thereof.
(525) In some embodiments, A has the structure of Formula IIIp:
(526) ##STR00296##
or a pharmaceutically acceptable salt thereof.
(527) In some embodiments, A has the structure of Formula IIIq:
(528) ##STR00297##

or a pharmaceutically acceptable salt thereof.
(529) In some embodiments, A has the structure of Formula IIIr:
(530) ##STR00298##
or a pharmaceutically acceptable salt thereof.
(531) In some embodiments, A has the structure of Formula IIIs:
(532) ##STR00299##
or a pharmaceutically acceptable salt thereof.
(533) In some embodiments, the degradation moiety is a ubiquitin ligase binding moiety.
(534) 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.
(535) In some embodiments, the degradation moiety is a ubiquitin ligase binding moiety.
(536) 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.
(537) In some embodiments, the degradation moiety includes the structure of Formula Y:
(538) ##STR00300## where A.sup.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.sup.1 is a bond or
(539) ##STR00301## T.sup.2 is
(540) ##STR00302## R.sup.5A is H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl; each R.sup.J1 is, independently, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl; and J is absent, optionally substituted C.sub.3-C.sub.10 carbocyclylene, optionally substituted C.sub.6-C.sub.10 arylene, optionally substituted C.sub.2-C.sub.9 heterocyclylene, or optionally substituted C.sub.2-C.sub.9 heteroarylene, or a pharmaceutically acceptable salt thereof.
(541) In some embodiments, T.sup.1 is a bond. In some embodiments, T.sup.1 is
(542) ##STR00303##
(543) In some embodiments, T.sup.2 is
(544) ##STR00304##
In some embodiments, T.sup.2 is or
(545) ##STR00305##
In some embodiments, T.sup.2 is
(546) ##STR00306##
(547) In some embodiments, the structure of Formula Y has the structure of Formula Y1:
(548) ##STR00307##
or a pharmaceutically acceptable salt thereof.
(549) In some embodiments, the structure of Formula Y has the structure of Formula Y2:
(550) ##STR00308##
or a pharmaceutically acceptable salt thereof.
(551) In some embodiments, the structure of Formula Y has the structure of Formula Z:
(552) ##STR00309##
or a pharmaceutically acceptable salt thereof.
(553) In some embodiments, u1 is 1. In some embodiments, u1 is 2. In some embodiments u1 is 3.
(554) In some embodiments, the structure of Formula Z has the structure of Formula AA:
(555) ##STR00310##
or a pharmaceutically acceptable salt thereof.
(556) In some embodiments, the structure of Formula Z has the structure of Formula AB:
(557) ##STR00311##
or a pharmaceutically acceptable salt thereof.
(558) In some embodiments, the structure of Formula Z has the structure of Formula AC:
(559) ##STR00312##
or a pharmaceutically acceptable salt thereof.

(560) 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.
(561) In some embodiments, the structure of Formula AA has the structure of Formula AA1:
(562) ##STR00313##
or a pharmaceutically acceptable salt thereof.
(563) In some embodiments, the structure of Formula AB has the structure of Formula AB1:
(564) ##STR00314##
or a pharmaceutically acceptable salt thereof.
(565) In some embodiments, the structure of Formula AC has the structure of Formula AC1:
(566) ##STR00315##
or a pharmaceutically acceptable salt thereof.
(567) In some embodiments, J is absent. In some embodiments, J is optionally substituted C.sub.3-C.sub.10 carbocyclylene or optionally substituted C.sub.6-C.sub.10 arylene. In some embodiments, J is optionally substituted C.sub.2-C.sub.9 heterocyclylene or optionally substituted C.sub.2-C.sub.9 heteroarylene.
(568) In some embodiments, J is optionally substituted heterocyclylene. In some embodiments, J is optionally substituted C.sub.6-C.sub.10 arylene.
(569) In some embodiments, the structure of Formula AA has the structure of Formula AA2:
(570) ##STR00316##
or a pharmaceutically acceptable salt thereof.
(571) In some embodiments, the structure of Formula AA has the structure of Formula AA3:
(572) ##STR00317##
or a pharmaceutically acceptable salt thereof.
(573) In some embodiments, the structure of Formula AA has the structure of Formula AA4:
(574) ##STR00318##
or a pharmaceutically acceptable salt thereof.
(575) In some embodiments, R.sup.AS is H or optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, R.sup.A5 is H or methyl. In some embodiments, R.sup.A5 is H. In some embodiments, R.sup.A5 is methyl.
(576) In some embodiments, the structure of Formula AA has the structure of Formula A:
(577) ##STR00319## where Y.sup.1 is
(578) ##STR00320## R.sup.A5 is H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl; R.sup.A6 is H or optionally substituted C.sub.1-C.sub.6 alkyl; and R.sup.A7 is H or optionally substituted C.sub.1-C.sub.6 alkyl; or R.sup.A6 and R.sup.A7, together with the carbon atom to which each is bound, combine to form optionally substituted C.sub.3-C.sub.6 carbocyclyl or optionally substituted C.sub.2-C.sub.5 heterocyclyl; or R.sup.A6 and R.sup.A7, together with the carbon atom to which each is bound, combine to form optionally substituted C.sub.3-C.sub.6 carbocyclyl or optionally substituted C.sub.2-C.sub.5 heterocyclyl; R.sup.A8 is H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl; each of R.sup.A1, R.sup.A2, R.sup.A3, and R.sup.A4 is, independently, H, A.sup.2, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.A1 and R.sup.A2, R.sup.A2 and R.sup.A3, and/or R.sup.A3 and R.sup.A4, together with the carbon atoms to which each is attached, combine to form custom character; and custom character is optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or C.sub.2-C.sub.9 heterocyclyl, any of which is optionally substituted with A.sup.2, where one of R.sup.A1, R.sup.A2, R.sup.A3, and R.sup.A4 is A.sup.2, or custom character is substituted with A.sup.2, or a pharmaceutically acceptable salt thereof.
(579) In some embodiments, each of R.sup.A1, R.sup.A2, R.sup.A3, and R.sup.A4 is, independently, H,

A.sup.2, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.A1 and R.sup.A2, R.sup.A2 and R.sup.A3, and/or R.sup.A3 and R.sup.A4, together with the carbon atoms to which each is attached, combine to form custom character; and custom character is optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or C.sub.2-C.sub.9 heterocyclyl, any of which is optionally substituted with A.sup.2, where one of R.sup.A1, R.sup.A2, R.sup.A3, and R.sup.A4 is A.sup.2, or custom character is substituted with A.sup.2, or a pharmaceutically acceptable salt thereof.

(580) In some embodiments, each of R.sup.A1, R.sup.A2, R.sup.A3, and R.sup.A4 is, H, A.sup.2, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, hydroxyl, optionally substituted amino; or R.sup.A1 and R.sup.A2, R.sup.A2 and R.sup.A3, or R.sup.A3 and R.sup.A4, together with the carbon atoms to which each is attached, combine to form custom character; and custom character is optionally substituted C.sub.2-C.sub.9 heterocyclyl, which is optionally substituted with A.sup.2, where one of R.sup.A1, R.sup.A2, R.sup.A3, and R.sup.A4 is A.sup.2, or custom character is substituted with A.sup.2.

(581) In some embodiments, each of R.sup.A1, R.sup.A2, R.sup.A3, and R.sup.A4 is, independently, H, A.sup.2, F,

(582) ##STR00321## or R.sup.A1 and R.sup.A2, R.sup.A2 and R.sup.A3, or R.sup.A3 and R.sup.A4, together with the carbon atoms to which each is attached, combine to form custom character; and custom character is optionally substituted C.sub.2-C.sub.9 heterocyclyl, which is optionally substituted with A.sup.2, where one of R.sup.A1, R.sup.A2, R.sup.A3, and R.sup.A4 is A.sup.2, or custom character is substituted with A.sup.2.

(583) In some embodiments, R.sup.A1 is A.sup.2. In some embodiments, R.sup.A2 is A.sup.2. In some embodiments, R.sup.A3 is A.sup.2. In some embodiments, R.sup.A4 is A.sup.2. In some embodiments, R.sup.A5 is A.sup.2.

(584) In some embodiments, R.sup.A5 is H or optionally substituted C.sub.1-C.sub.6 alkyl.

(585) In some embodiments, R.sup.A5 is H or

(586) ##STR00322##

In some embodiments, R.sup.A5 is H. In some embodiments, R.sup.A5 is

(587) ##STR00323##

(588) In some embodiments, Y.sup.1 is

(589) ##STR00324##

In some embodiments, Y.sup.1 is

(590) ##STR00325##

In some embodiments, Y.sup.1 is

(591) ##STR00326##

(592) In some embodiments, each of R.sup.A6 and R.sup.A7 is, independently, H, F,

(593) ##STR00327##

or R.sup.A6 and R.sup.A7, together with the carbon atom to which each is bound, combine to form

(594) ##STR00328##

(595) In some embodiments, Y.sup.1 is

(596) ##STR00329##

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

(598) ##STR00330##

or a pharmaceutically acceptable salt thereof.

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

(600) ##STR00331##

or a pharmaceutically acceptable salt thereof.

(601) In some embodiments, the structure of Formula A has the structure of Formula A3:
(602) ##STR00332##
or a pharmaceutically acceptable salt thereof.
(603) In some embodiments, the structure of Formula A has the structure of Formula A4:
(604) ##STR00333##
or a pharmaceutically acceptable salt thereof.
(605) In some embodiments, the structure of Formula A has the structure of Formula A5:
(606) ##STR00334##
or a pharmaceutically acceptable salt thereof.
(607) In some embodiments, the structure of Formula A has the structure of Formula A6:
(608) ##STR00335##
or a pharmaceutically acceptable salt thereof.
(609) In some embodiments, the structure of Formula A has the structure of Formula A7:
(610) ##STR00336##
or a pharmaceutically acceptable salt thereof.
(611) In some embodiments, the structure of Formula A has the structure of Formula A8:
(612) ##STR00337##
or a pharmaceutically acceptable salt thereof.
(613) In some embodiments, the structure of Formula A has the structure of Formula A9:
(614) ##STR00338##
or a pharmaceutically acceptable salt thereof.
(615) In some embodiments, the structure of Formula A has the structure of Formula A10:
(616) ##STR00339##
or a pharmaceutically acceptable salt thereof.
(617) In some embodiments, wherein the structure of Formula A is
(618) ##STR00340## ##STR00341##
or derivative or analog thereof.
(619) In some embodiments, the structure of Formula A is
(620) ##STR00342##
(621) In some embodiments, the structure of Formula A is
(622) ##STR00343##
or derivative or analog thereof.
(623) In some embodiments,
(624) ##STR00344##
where R.sup.A9 is H, A.sup.2, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl.
(625) In some embodiments, the structure of Formula A is
(626) ##STR00345##
(627) In some embodiments, R.sup.A9 is H, A.sup.2, or optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, R.sup.A9 is H, A.sup.2, or methyl. In some embodiments, R.sup.9A is H. In some embodiments, R.sup.9A is methyl. In some embodiments, R.sup.A9 is A.sup.2.
(628) In some embodiments, the structure of Formula A is
(629) ##STR00346##
(630) In some embodiments, the structure of Formula AA has the structure of Formula B:
(631) ##STR00347## where R.sup.A5 is H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl; each of R.sup.A1, R.sup.A2, R.sup.A3, and R.sup.A4 is, independently, H, A.sup.2, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.A1 and R.sup.A2, R.sup.A2 and R.sup.A3, and/or

R.sup.A3 and R.sup.A4, together with the carbon atoms to which each is attached, combine to form custom character; and custom character is optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or C.sub.2-C.sub.9 heterocyclyl, any of which is optionally substituted with A.sup.2, where one of R.sup.A1, R.sup.A2, R.sup.A3, and R.sup.A4 is A.sup.2, or custom character is substituted with A.sup.2, or a pharmaceutically acceptable salt thereof.

(632) In some embodiments, each of R.sup.A1, R.sup.A2, R.sup.A3, and R.sup.A4 is, H, A.sup.2, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, hydroxyl, optionally substituted amino; or R.sup.A1 and R.sup.A2, R.sup.A2 and R.sup.A3, or R.sup.A3 and R.sup.A4, together with the carbon atoms to which each is attached, combine to form custom character; and custom character is optionally substituted C.sub.2-C.sub.9 heterocyclyl, which is optionally substituted with A.sup.2, where one of R.sup.A1, R.sup.A2, R.sup.A3, and R.sup.A4 is A.sup.2, or custom character is substituted with A.sup.2.

(633) In some embodiments, each of R.sup.A1, R.sup.A2, R.sup.A3, and R.sup.A4 is, independently, H, A.sup.2, F,

(634) ##STR00348## or R.sup.A1 and R.sup.A2, R.sup.A2 and R.sup.A3, or R.sup.A3 and R.sup.A4, together with the carbon atoms to which each is attached, combine to form custom character; and custom character is optionally substituted C.sub.2-C.sub.9 heterocyclyl, which is optionally substituted with A.sup.2, where one of R.sup.A1, R.sup.A2, R.sup.A3, and R.sup.A4 is A.sup.2, or custom character is substituted with A.sup.2.

(635) In some embodiments, R.sup.A1 is A.sup.2. In some embodiments, R.sup.A2 is A.sup.2. In some embodiments, R.sup.A3 is A.sup.2. In some embodiments, R.sup.A4 is A.sup.2. In some embodiments, R.sup.A5 is A.sup.2.

(636) In some embodiments, R.sup.A5 is H or optionally substituted C.sub.1-C.sub.6 alkyl.

(637) In some embodiments, R.sup.A5 is H or

(638) ##STR00349##

In some embodiments, R.sup.A5 is H. In some embodiments, R.sup.A5 is

(639) ##STR00350##

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

(641) ##STR00351##

or a pharmaceutically acceptable salt thereof.

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

(643) ##STR00352##

or a pharmaceutically acceptable salt thereof.

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

(645) ##STR00353##

or a pharmaceutically acceptable salt thereof.

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

(647) ##STR00354##

or a pharmaceutically acceptable salt thereof.

(648) In some embodiments, the structure of Formula B is

(649) ##STR00355##

In some embodiments, the structure of Formula B is

(650) ##STR00356##

In some embodiments, the structure of Formula B is

(651) ##STR00357##

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

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

(654) ##STR00358##

or derivative or analog thereof.

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

(656) ##STR00359## where R.sup.B1 is H, A.sup.2, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl; R.sup.B2 is H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl; R.sup.B3 is A.sup.2, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.1-C.sub.6 alkyl C.sub.3-C.sub.10 carbocyclyl, or optionally substituted C.sub.1-C.sub.6 alkyl C.sub.6-C.sub.10 aryl; R.sup.B4 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.1-C.sub.6 alkyl C.sub.3-C.sub.10 carbocyclyl, or optionally substituted C.sub.1-C.sub.6 alkyl C.sub.6-C.sub.10 aryl; R.sup.B5 is H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl; v2 is 0, 1, 2, 3, or 4; each R.sup.B6 is, independently, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino; and each of R.sup.B7 and R.sup.B8 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.6-C.sub.10 aryl, where one of R.sup.B1 and R.sup.B3 is A.sup.2, or a pharmaceutically acceptable salt thereof.

(657) In some embodiments, the structure of Formula C is

(658) ##STR00360##

or derivative or analog thereof.

(659) In some embodiments, the structure of Formula C is

(660) ##STR00361##

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

(662) ##STR00362## where A.sup.2 is a bond between B and the linker; each of R.sup.C1, R.sup.C2, and R.sup.C7 is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl; R.sup.C3 is optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.1-C.sub.6 alkyl C.sub.3-C.sub.10 carbocyclyl, or optionally substituted C.sub.1-C.sub.6 alkyl C.sub.6-C.sub.10 aryl; R.sup.C5 is optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.1-C.sub.6 alkyl C.sub.3-C.sub.10 carbocyclyl, or optionally substituted C.sub.1-C.sub.6 alkyl C.sub.6-C.sub.10 aryl; v3 is 0, 1, 2, 3, or 4; each R.sup.C8 is, independently, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino; v4 is 0, 1, 2, 3, or 4; and each R.sup.C9 is, independently, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino, or a pharmaceutically acceptable salt thereof.

(663) In some embodiments, the structure of Formula D is

(664) ##STR00363##

or derivative or analog thereof.

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

(666) ##STR00364## where A.sup.2 is a bond between B and the linker; each of R.sup.C10 and R.sup.C11 is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted

C.sub.1-C.sub.6 alkyl C.sub.3-C.sub.10 carbocyclyl, or optionally substituted C.sub.1-C.sub.6 alkyl C.sub.6-C.sub.10 aryl; v5 is 0, 1, 2, 3, or 4; each R.sup.C12 is, independently, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino; v6 is 0, 1, 2, 3, or 4; and each R.sup.21 is, independently, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino, or a pharmaceutically acceptable salt thereof.

(667) In some embodiments, the structure of Formula E is

(668) ##STR00365##

or derivative or analog thereof.

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

(670) ##STR00366## where

(671) ##STR00367##

or a bicyclic moiety which is substituted with A.sup.2 and substituted with one or more groups independently selected from H, R.sup.FF1, and oxo; custom character is a single bond or a double bond; u2 is 0, 1, 2, or 3; A.sup.2 is a bond between the degrader and the linker; Y.sup.Fa is CR.sup.FbR.sup.Fc, C═O, C═S, C═CH.sub.2, SO.sub.2, S(O), P(O)Oalkyl, P(O)NHalkyl, P(O)N(alkyl).sub.2, P(O)alkyl, P(O)OH, P(O)NH.sub.2; Y.sup.Fb is NH, NR.sup.FF1, CH.sub.2, CHR.sup.FF1, C(R.sup.FF1).sub.2, O, or S; Y.sup.Fc is CR.sup.FdR.sup.Fe, C═O, C═S, C═CH.sub.2, SO.sub.2, S(O), P(O)Oalkyl, P(O)NHalkyl, P(O)N(alkyl).sub.2, P(O)alkyl, P(O)OH, P(O)NH.sub.2; each of R.sup.Fb, R.sup.Fc, R.sup.Fd, and R.sup.Fe is, independently, H, alkyl, aliphatic, heteroaliphatic, aryl, heteroaryl, carbocyclyl, hydroxyl, alkoxy, amino, —NHalkyl, or —Nalkyl.sub.2; or R.sup.Fb and R.sup.Fc, together with the carbon atom to which each is attached, combine to form a 3-, 4-, 5-, or 6-membered spirocarbocyclylene, or a 4-, 5-, or 6-membered spiroheterocyclylene comprising 1 or 2 heteroatoms selected from N and O; or R.sup.Fd and R.sup.Fe, together with the carbon atom to which each is attached, combine to form a 3-, 4-, 5-, or 6-membered spirocarbocyclylene, or a 4-, 5-, or 6-membered spiroheterocyclylene comprising 1 or 2 heteroatoms selected from N and O; and or R.sup.Fd and R.sup.Fb, 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.sup.Fd and Y.sup.Ff is, independently, CH.sub.2, CHR.sup.FF2, C(R.sup.FF2).sub.2, C(O), N, NH, NR.sup.FF3, O, S, or S(O); Y.sup.Fe is a bond or a divalent moiety attached to Y.sup.Fd and Y.sup.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.sup.2 and the others are substituted with one or more groups independently selected from H and R.sup.FF1; and wherein the contiguous atoms of Y.sup.Fe can be attached through a single or double bond; each R.sup.FF1 is, independently, H, alkyl, alkenyl, alkynyl, aliphatic, heteroaliphatic, carbocyclyl, halogen, hydroxyl, amino, cyano, alkoxy, aryl, heteroaryl, heterocyclyl, alkylamino, alkylhydroxyl, or haloalkyl; each R.sup.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.sub.2alkyl, —N(alkyl)SO.sub.2alkyl, —NHSO.sub.2aryl, —N(alkyl)SO.sub.2aryl, —NHSO.sub.2alkenyl, —N(alkyl)SO.sub.2alkenyl, —NHSO.sub.2alkynyl, —N(alkyl)SO.sub.2alkynyl, aliphatic, heteroaliphatic, aryl, heteroaryl, hetercyclic, carbocyclic, cyano, nitro, nitroso, —SH, —Salkyl, or haloalkyl; and R.sup.FF3 is alkyl, alkenyl, alkynyl, —C(O)H, —C(O)OH, —C(O)alkyl, or —C(O)Oalkyl, wherein if Y.sup.Fd or Y.sup.Ff is substituted with A.sup.2, then Y.sup.Fe is a bond, or a pharmaceutically acceptable salt thereof.

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

(673) ##STR00368##
or a pharmaceutically acceptable salt thereof.
(674) In some embodiments, the degradation moiety includes the structure of Formula FB:
(675) ##STR00369## where
(676) ##STR00370##
or a bicyclic moiety which is substituted with A.sup.2 and substituted with one or more groups independently selected from H, R.sup.FF1, and oxo; A.sup.2 is a bond between the degrader and the linker; Y.sup.Fa is CR.sup.FbR.sup.Fc, C═O, C═S, C═CH.sub.2, SO.sub.2, S(O), P(O)Oalkyl, P(O)NHalkyl, P(O)N(alkyl).sub.2, P(O)alkyl, P(O)OH, P(O)NH.sub.2; each of Y.sup.Fb and Y.sup.Fg is, independently, NH, NR.sup.FF1, CH.sub.2, CHR.sup.FF1, C(R.sup.FF1).sub.2, O, or S; Y.sup.Fc is CR.sup.FdR.sup.Fe, C═O, C═S, C═CH.sub.2, SO.sub.2, S(O), P(O)Oalkyl, P(O)NHalkyl, P(O)N(alkyl).sub.2, P(O)alkyl, P(O)OH, P(O)NH.sub.2; each of R.sup.Fb, R.sup.Fc, R.sup.Fd, R.sup.Fe, R.sup.Ff, and R.sup.Fg is, independently, H, alkyl, aliphatic, heteroaliphatic, aryl, heteroaryl, carbocyclyl, hydroxyl, alkoxy, amino, —NHalkyl, or —Nalkyl.sub.2; or R.sup.Fb and R.sup.Fc, together with the carbon atom to which each is attached, combine to form a 3-, 4-, 5-, or 6-membered spirocarbocyclylene, or a 4-, 5-, or 6-membered spiroheterocyclylene comprising 1 or 2 heteroatoms selected from N and O; or R.sup.Fd and R.sup.Fe, together with the carbon atom to which each is attached, combine to form a 3-, 4-, 5-, or 6-membered spirocarbocyclylene, or a 4-, 5-, or 6-membered spiroheterocyclylene comprising 1 or 2 heteroatoms selected from N and O; or R.sup.Ff and R.sup.Fg, together with the carbon atom to which each is attached, combine to form a 3-, 4-, 5-, or 6-membered spirocarbocyclylene, or a 4-, 5-, or 6-membered spiroheterocyclylene comprising 1 or 2 heteroatoms selected from N and O; or R.sup.Fd and R.sup.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.sup.Fd and R.sup.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.sup.Fb and R.sup.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.sup.Fd and Y.sup.Ff is, independently, CH.sub.2, CHR.sup.FF2, C(R.sup.FF2).sub.2, C(O), N, NH, NR.sup.FF3, O, S, or S(O); Y.sup.Fe is a bond or a divalent moiety attached to Y.sup.Fd and Y.sup.Ff that contains 1 to 5 contiguous carbon atoms that form a 3 to 3-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.sup.2 and the others are substituted with one or more groups independently selected from H and R.sup.FF1; and wherein the contiguous atoms of Y.sup.Fe can be attached through a single or double bond; each R.sup.FF1 is, independently, H, alkyl, alkenyl, alkynyl, aliphatic, heteroaliphatic, carbocyclyl, halogen, hydroxyl, amino, cyano, alkoxy, aryl, heteroaryl, heterocyclyl, alkylamino, alkylhydroxyl, or haloalkyl; each R.sup.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.sub.2alkyl, —N(alkyl)SO.sub.2alkyl, —NHSO.sub.2aryl, —N(alkyl)SO.sub.2aryl, —NHSO.sub.2alkenyl, —N(alkyl)SO.sub.2alkenyl, —NHSO.sub.2alkynyl, —N(alkyl)SO.sub.2alkynyl, aliphatic, heteroaliphatic, aryl, heteroaryl, hetercyclic, carbocyclic, cyano, nitro, nitroso, —SH, —Salkyl, or haloalkyl; and R.sup.FF3 is alkyl, alkenyl, alkynyl, —C(O)H, —C(O)OH, —C(O)alkyl, or —C(O)Oalkyl, wherein if Y.sup.Fd or is substituted with A.sup.2, then Y.sup.Fe is a bond, or a pharmaceutically acceptable salt thereof.
(677) In some embodiments, the compound of Formula FB has the structure of Formula FB1:
(678) ##STR00371##
or a pharmaceutically acceptable salt thereof.
(679) In some embodiments, the degradation moiety includes the structure of Formula F1:
(680) ##STR00372##
where A.sup.2 is a bond between the degrader and the linker; and R.sup.F1 is absent or O, or a pharmaceutically acceptable salt thereof.
(681) In some embodiments, R.sup.F1 is absent. In some embodiments, R.sup.F1 is O.
(682) In some embodiments, the structure of Formula F1 is
(683) ##STR00373##

(684) In some embodiments, the degradation moiety includes the structure Formula F2:
(685) ##STR00374##
where A.sup.2 is a bond between the degrader and the linker; and Y.sup.2 is CH.sub.2 or NH, or a pharmaceutically acceptable salt thereof.
(686) In some embodiments, Y.sup.2 is NH. In some embodiments, Y.sup.2 is CH.sub.2.
(687) In some embodiments, structure of Formula F2 is
(688) ##STR00375##
(689) In some embodiments, the degradation moiety includes the structure Formula G:
(690) ##STR00376##
where A.sup.2 is a bond between the degrader and the linker; and Y.sup.3 is CH.sub.2 or NH, or a pharmaceutically acceptable salt thereof.
(691) In some embodiments, Y.sup.3 is NH. In some embodiments, Y.sup.3 is CH.sub.2.
(692) In some embodiments, structure of Formula G is
(693) ##STR00377##
(694) 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.
(695) In some embodiments, the linker has the structure of Formula IV:
A.sup.1-(B.sup.1).sub.f—(C.sup.1).sub.g—(B.sup.2).sub.h-(D)-(B.sup.3).sub.i—(C.sup.2).sub.j—(B.sup.4).sub.k-A.sup.2 Formula IV where A.sup.1 is a bond between the linker and A; A.sup.2 is a bond between B and the linker; each of B.sup.1, B.sup.2, B.sup.3, and B.sup.4 is, independently, optionally substituted C.sub.1-C.sub.2 alkylene, optionally substituted C.sub.1-C.sub.3 heteroalkylene, O, S, S(O).sub.2, or NR.sup.N; each R.sup.N is, independently, H, optionally substituted C.sub.1-4 alkyl, optionally substituted C.sub.2-4 alkenyl, optionally substituted C.sub.2-4 alkynyl, optionally substituted C.sub.2-6 heterocyclyl, optionally substituted C.sub.6-12 aryl, or optionally substituted C.sub.1-7 heteroalkyl; each of C.sup.1 and C.sup.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.sub.1-10 alkylene, optionally substituted C.sub.2-10 alkenylene, optionally substituted C.sub.2-10 alkynylene, optionally substituted C.sub.2-6 heterocyclylene, optionally substituted C.sub.6-12 arylene, optionally substituted C.sub.2-C.sub.10 polyethylene glycol, or optionally substituted C.sub.1-10 heteroalkylene, or a chemical bond linking A.sup.1-(B.sup.1).sub.f—(C.sup.1).sub.g—(B.sup.2).sub.h— to —(B.sup.3).sub.i—(C.sup.2).sub.j—(B.sup.4).sub.k-A.sup.2.
(696) In some embodiments, each of B.sup.1, B.sup.2, B.sup.3, and B.sup.4 is, independently, optionally substituted C.sub.1-C.sub.4 alkylene, optionally substituted C.sub.1-C.sub.4 heteroalkylene, or NR.sup.N.
(697) In some embodiments, each R.sup.N is, independently, H or optionally substituted C.sub.1-C.sub.4 alkylene.
(698) In some embodiments, each R.sup.N is, independently, H or methyl.
(699) In some embodiments, each of B.sup.1 and B.sup.4 is, independently,
(700) ##STR00378##
(701) In some embodiments, B.sup.1 is
(702) ##STR00379##
(703) In some embodiments, each of C.sup.1 and C.sup.2 is, independently
(704) ##STR00380##
(705) In some embodiments, C.sup.1 is
(706) ##STR00381##
(707) In some embodiments, B.sup.2 is NR.sup.N. In some embodiments, B.sup.2 is optionally substituted C.sub.1-C.sub.4 alkylene.
(708) 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.
(709) In some embodiments, the linker has the structure of

(710) ##STR00382## wherein x is 1, 2, 3, 4, 5, 6, 7, or 8; y is 1, 2, 3, or 4; R.sup.x is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.6 carbocyclyl; R.sup.y is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.6 carbocyclyl; and W is O or NR.sup.w, wherein R.sup.w is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.6 carbocyclyl.
(711) In some embodiments, the linker has the structure of
(712) ##STR00383##
(713) In some embodiments, R.sup.x is H or me optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, R.sup.y is H or optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, R.sup.w is H or optionally substituted C.sub.1-C.sub.6 alkyl.
(714) In some embodiments, R.sup.x is H or methyl. In some embodiments, RY is H or methyl. In some embodiments, R.sup.w is H or methyl.
(715) In some embodiments, the linker has the structure of
(716) ##STR00384## ##STR00385## ##STR00386##
(717) In some embodiments, the linker has the structure of
(718) ##STR00387##
(719) In some embodiments, the linker has the structure of
(720) ##STR00388##
(721) In some embodiments, the linker has the structure of Formula V:
A.sup.1-(E.sup.1)-(F.sup.1)—(C.sup.3).sub.m-(E.sup.3).sub.n-(F.sup.2).sub.o1—(F.sup.3).sub.o2-(E.sup.2).sub.p-A.sup.2, Formula V where A.sup.1 is a bond between the linker and A; A.sup.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.sup.1 and E.sup.2 is, independently, O, S, NR.sup.N, optionally substituted C.sub.1-10 alkylene, optionally substituted C.sub.2-10 alkenylene, optionally substituted C.sub.2-10 alkynylene, optionally substituted C.sub.2-C.sub.10 polyethylene glycol, or optionally substituted C.sub.1-10 heteroalkylene; E.sup.3 is optionally substituted C.sub.1-C.sub.6 alkylene, optionally substituted C.sub.1-C.sub.6 heteroalkylene, O, S, or NR.sup.N; each R.sup.N is, independently, H, optionally substituted C.sub.1-4 alkyl, optionally substituted C.sub.2-4 alkenyl, optionally substituted C.sub.2-4 alkynyl, optionally substituted C.sub.2-6 heterocyclyl, optionally substituted C.sub.6-12 aryl, or optionally substituted C.sub.1-7 heteroalkyl; C.sup.3 is carbonyl, thiocarbonyl, sulphonyl, or phosphoryl; and each of F.sup.1, F.sup.2, and F.sup.3 is, independently, optionally substituted C.sub.3-C.sub.10 carbocyclylene, optionally substituted C.sub.2-10 heterocyclylene, optionally substituted C.sub.6-C.sub.10 arylene, or optionally substituted C.sub.2-C.sub.9 heteroarylene.
(722) In some embodiments, the linker has the structure of Formula Va:
A.sup.1-(E.sup.1)-(F.sup.1)—(C.sup.3).sub.m-(E.sup.2).sub.p-A.sup.2. Formula Va
(723) In some embodiments, the linker has the structure of Formula Vb:
A.sup.1-(E.sup.1)-(F.sup.1)-(E.sup.2).sub.p-A.sup.2. Formula Vb
(724) In some embodiments, the linker has the structure of Formula Vc:
A.sup.1-(E.sup.1)-(F.sup.1)-A.sup.2. Formula Vc
(725) In some embodiments, the linker has the structure of Formula Vd:
A.sup.1-(E.sup.1)-(F.sup.1)—(C.sup.3).sub.m—(F.sup.2).sub.o1-A.sup.2. Formula Vd
(726) In some embodiments, the linker has the structure of Formula Ve:
A.sup.1-(E.sup.1)-(F.sup.1)-(E.sup.3).sub.n-(F.sup.2).sub.o1-(E.sup.2).sub.p-A.sup.2. Formula Ve
(727) In some embodiments, the linker has the structure of Formula Vf:
A.sup.1-(E.sup.1)-(F.sup.1)—(C.sup.3).sub.m-(E.sup.3)n-(F.sup.2).sub.o1-(E.sup.2).sub.p-A.sup.2. Formula Vf
(728) In some embodiments, the linker has the structure of Formula Vg:
A.sup.1-(E.sup.1)-(F.sup.1)—(C.sup.3).sub.m-(E.sup.3).sub.n-(F.sup.2).sub.o1—(F.sup.3).sub.o2-(E.sup.2).sub.p-A.sup.2, Formula Vg
(729) In some embodiments, each of E.sup.1 and E.sup.2 is, independently, NR.sup.N, optionally

substituted C.sub.1-10 alkyl, optionally substituted C.sub.2-C.sub.10 polyethylene glycol, or optionally substituted C.sub.1-10 heteroalkyl.
(730) In some embodiments, E.sup.3 is optionally substituted C.sub.1-C.sub.6 alkylene, O, S, or NR.sup.N;
(731) In some embodiments, E.sup.3 is optionally substituted C.sub.1-C.sub.6 alkylene. In some embodiments, E.sup.3 is optionally substituted C.sub.1-C.sub.3 alkylene. In some embodiments, E.sup.3 is O, S, or NR.sup.N.
(732) In some embodiments, E.sup.3 is C.sub.1-C.sub.6 alkylene. In some embodiments, E.sup.3 is C.sub.1-C.sub.3 alkylene. In some embodiments, E.sup.3 is O.
(733) In some embodiments, E.sup.3 is
(734) ##STR00389##
where a is 0, 1, 2, 3, 4, or 5.
(735) In some embodiments, E.sup.3 is
(736) ##STR00390##
(737) In some embodiments, each R.sup.N is, independently, H or optionally substituted C.sub.1-4 alkyl.
(738) In some embodiments, each R.sup.N is, independently, H or methyl.
(739) In some embodiments, E.sup.1 is
(740) ##STR00391##
where a is 0, 1, 2, 3, 4, or 5.
(741) In some embodiments, E.sup.1 is
(742) ##STR00392##
where a is 0, 1, 2, 3, 4, or 5.
(743) In some embodiments, E.sup.1 is
(744) ##STR00393##
(745) In some embodiments, E.sup.1 is
(746) ##STR00394##
(747) In some embodiments, E.sup.1 is
(748) ##STR00395## ##STR00396## where b is 0, 1, 2, 3, 4, 5, or 6; R.sup.a is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.6 carbocyclyl; R.sup.b is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.6 carbocyclyl; and R.sup.c is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.6 carbocyclyl.
(749) In some embodiments, E.sup.1 is
(750) ##STR00397## ##STR00398##
(751) In some embodiments, E.sup.1 is
(752) ##STR00399##
(753) In some embodiments, E.sup.1 is
(754) ##STR00400##
(755) In some embodiments, R.sup.a is H or optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, R.sup.b is H or optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, R.sup.c is H or optionally substituted C.sub.1-C.sub.6 alkyl.
(756) In some embodiments, R.sup.a is H or methyl. In some embodiments, R.sup.b is H or methyl. In some embodiments, R.sup.c is H or methyl.
(757) 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.
(758) In some embodiments, E.sup.1 is
(759) ##STR00401##
(760) In some embodiments, E.sup.1 is
(761) ##STR00402##
(762) In some embodiments, E.sup.1 is
(763) ##STR00403##

(764) In some embodiments, E.sup.1 is
(765) ##STR00404##
(766) In some embodiments, E.sup.1 is
(767) ##STR00405##
(768) In some embodiments, E.sup.1 is
(769) ##STR00406##
(770) In some embodiments, E.sup.2 is O, NR.sup.w,
(771) ##STR00407## 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.sup.d is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.6 carbocyclyl; R.sup.e is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.6 carbocyclyl; R.sup.f is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.6 carbocyclyl; R.sup.g is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.6 carbocyclyl; and W is O or NR.sup.w, wherein R.sup.w is H or optionally substituted C.sub.1-C.sub.6 alkyl.
(772) In some embodiments, E.sup.2 is O, NR.sup.w,
(773) ##STR00408##
(774) In some embodiments, R.sup.d is H or optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, R.sup.e is H or optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, R.sup.f is H or optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, R.sup.g is H or optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, R.sup.w is H or optionally substituted C.sub.1-C.sub.6 alkyl.
(775) In some embodiments, R.sup.d is H or methyl. In some embodiments, R.sup.e is H or methyl. In some embodiments, R.sup.f is H or methyl. In some embodiments, R.sup.g is H or methyl. In some embodiments, R.sup.w is H or methyl.
(776) In some embodiments, E.sup.2 is
(777) ##STR00409##
(778) In some embodiments, E.sup.2 is O,
(779) ##STR00410##
(780) In some embodiments, each of F.sup.1, F.sup.2, or F.sup.3 is, independently, optionally substituted C.sub.3-C.sub.10 carbocyclylene.
(781) In some embodiments, the C.sub.3-C.sub.10 carbocyclylene is monocyclic. In some embodiments, the C.sub.3-C.sub.10 carbocyclylene is polycyclic.
(782) In some embodiments, the C.sub.3-C.sub.10 carbocyclylene is bicyclic.
(783) In some embodiments, the C.sub.3-C.sub.10 carbocyclylene is bridged. In some embodiments, the C.sub.3-C.sub.10 carbocyclylene is fused. In some embodiments, the C.sub.3-C.sub.10 carbocyclylene is spirocyclic.
(784) In some embodiments, the C.sub.3-C.sub.10 carbocyclylene is
(785) ##STR00411##
(786) In some embodiments, F.sup.2 is
(787) ##STR00412##
(788) In some embodiments, the C.sub.3-C.sub.10 carbocyclylene is
(789) ##STR00413##
(790) In some embodiments, F.sup.1 is
(791) ##STR00414##
(792) In some embodiments, each of F.sup.1, F.sup.2, or F.sup.3 is, independently, optionally substituted C.sub.2-C.sub.9 heterocyclylene.
(793) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is monocyclic. In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is polycyclic.
(794) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is bicyclic.
(795) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is bridged. In some embodiments, the

C.sub.2-C.sub.9 heterocyclylene is fused. In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is spirocyclic.
(796) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene includes a quaternary amine.
(797) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is
(798) ##STR00415## ##STR00416## 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.sup.h is, independently, .sup.2H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, OR.sup.i2, or NR.sup.i3R.sup.i4; or two R.sup.h groups, together with the carbon atom to which each is attached, combine to form optionally substituted C.sub.3-C.sub.10 carbocyclyl or optionally substituted C.sub.2-C.sub.9 heterocyclyl; or two R.sup.h groups, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.3-C.sub.10 carbocyclyl or optionally substituted C.sub.2-C.sub.9 heterocyclyl; R.sup.i1 is H or optionally substituted C.sub.1-C.sub.6 alkyl; R.sup.i2 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.6 carbocyclyl; R.sup.i3 is H or optionally substituted C.sub.1-C.sub.6 alkyl; and R.sup.i4 is H or optionally substituted C.sub.1-C.sub.6 alkyl.
(799) In some embodiments, each R.sup.h is, independently, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, OR.sup.i2, or NR.sup.i3R.sup.i4. In some embodiments, R.sup.i1 is H or optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, R.sup.i2 is H or optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, R.sup.i3 is H or optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, R.sup.i4 is H or optionally substituted C.sub.1-C.sub.6 alkyl.
(800) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is
(801) ##STR00417##
(802) In some embodiments, each R.sup.h is, independently, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, OR.sup.i2, or NR.sup.i3R.sup.i4. In some embodiments, each R.sup.h is, independently, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, or NR.sup.i3R.sup.i4.
(803) In some embodiments, each R.sup.h is, independently, .sup.2H, halogen, cyano, optionally substituted C.sub.1-C.sub.6 alkyl, OR.sup.i2, or NR.sup.i3R.sup.i4. In some embodiments, two R.sup.h groups, together with the carbon atom to which each is attached, combine to form optionally substituted C.sub.3-C.sub.10 carbocyclyl or optionally substituted C.sub.2-C.sub.9 heterocyclyl. In some embodiments, two R.sup.h groups, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.3-C.sub.10 carbocyclyl or optionally substituted C.sub.2-C.sub.9 heterocyclyl.
(804) In some embodiments, each R.sup.h is, independently, H, .sup.2H, F, methyl,
(805) ##STR00418##
(806) In some embodiments, each R.sup.h is, independently, F, methyl, or NR.sup.i3R.sup.i4.
(807) In some embodiments, q1 is 0, 1, or 2. In some embodiments, q1 is 0. In some embodiments, q1 is 1. In some embodiments, q1 is 2.
(808) In some embodiments, q2 is 0, 1, or 2. In some embodiments, q2 is 0. In some embodiments, q2 is 1. In some embodiments, q2 is 2.
(809) In some embodiments, q3 is 0, 1, or 2. In some embodiments, q3 is 0. In some embodiments, q3 is 1. In some embodiments, q3 is 2.
(810) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is
(811) ##STR00419## ##STR00420## ##STR00421## ##STR00422## ##STR00423##
(812) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is
(813) ##STR00424## ##STR00425##
(814) In some embodiments, F.sup.1 is
(815) ##STR00426##
(816) In some embodiments, F.sup.1 is
(817) ##STR00427##
(818) In some embodiments, F.sup.2 is
(819) ##STR00428##
(820) In some embodiments, F.sup.3 is
(821) ##STR00429##

(822) In some embodiments, R.sup.i1 is H or methyl. In some embodiments, R.sup.i2 is H or methyl. In some embodiments, R.sup.i3 is H or methyl. In some embodiments, R.sup.i4 is H or methyl.
(823) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is
(824) ##STR00430##
(825) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is
(826) ##STR00431##
(827) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is
(828) ##STR00432## ##STR00433##
(829) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is
(830) ##STR00434##
(831) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is
(832) ##STR00435##
(833) In some embodiments, F.sup.1 is
(834) ##STR00436##
(835) In some embodiments, F.sup.1 is
(836) ##STR00437##
(837) In some embodiments, F.sup.1 is
(838) ##STR00438##
(839) In some embodiments, F.sup.2 is
(840) ##STR00439##
(841) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is
(842) ##STR00440## ##STR00441##
(843) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is
(844) ##STR00442## ##STR00443##
(845) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is
(846) ##STR00444##
(847) In some embodiments, F.sup.1 is
(848) ##STR00445##
(849) In some embodiments, F.sup.1 is
(850) ##STR00446##
(851) In some embodiments, F.sup.1 is
(852) ##STR00447##
(853) In some embodiments, F.sup.1 is
(854) ##STR00448##
(855) In some embodiments, F.sup.2 is
(856) ##STR00449##
(857) In some embodiments, F.sup.2 is
(858) ##STR00450##
(859) In some embodiments, F.sup.2 is
(860) ##STR00451##
(861) In some embodiments, each of F.sup.1, F.sup.2, or F.sup.3 is, independently, optionally substituted C.sub.6-C.sub.10 arylene.
(862) In some embodiments, the C.sub.6-C.sub.10 arylene is
(863) ##STR00452##
(864) In some embodiments, each of F.sup.1, F.sup.2, or F.sup.3 is, independently, optionally substituted C.sub.2-C.sub.9 heteroarylene.
(865) In some embodiments, the C.sub.2-C.sub.9 heteroarylene is
(866) ##STR00453##
(867) In some embodiments, F.sup.2 is
(868) ##STR00454##
In some embodiments, F.sup.2 is
(869) ##STR00455##

(870) In some embodiments, C.sup.3 is
(871) ##STR00456##
In some embodiments, C.sup.3 is
(872) ##STR00457##
(873) In some embodiments, m is 1. In some embodiments, p is 1.
(874) In some embodiments, the linker has the structure of
(875) ##STR00458## ##STR00459## ##STR00460## ##STR00461## ##STR00462## ##STR00463## ##STR00464## ##STR00465## ##STR00466## ##STR00467##
(876) In some embodiments, the linker has the structure of
(877) ##STR00468## ##STR00469## ##STR00470## ##STR00471## ##STR00472## ##STR00473## ##STR00474## ##STR00475## ##STR00476## ##STR00477## ##STR00478## ##STR00479## ##STR00480## ##STR00481##
(878) In some embodiments, the linker has the structure of:
(879) ##STR00482## ##STR00483## ##STR00484## ##STR00485##
In some embodiments, the linker is a bond.
(880) In some embodiments, the linker is optionally substituted C.sub.3-C.sub.10 carbocyclylene, optionally substituted C.sub.2-10 heterocyclylene, optionally substituted C.sub.6-C.sub.10 arylene, or optionally substituted C.sub.2-C.sub.9 heteroarylene.
(881) In some embodiments, the linker is optionally substituted C.sub.3-C.sub.10 carbocyclylene or optionally substituted C.sub.2-10 heterocyclylene. In some embodiments, the linker is optionally substituted C.sub.6-C.sub.10 arylene or optionally substituted C.sub.2-C.sub.9 heteroarylene.
(882) In some embodiments, the linker is optionally substituted C.sub.2-10 heterocyclylene.
(883) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is monocyclic. In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is polycyclic.
(884) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is bicyclic.
(885) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is bridged. In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is fused. In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is spirocyclic.
(886) In some embodiments, the linker has the structure of
(887) ##STR00486##
(888) In some embodiments, the linker has the structure of
(889) ##STR00487##
(890) In some embodiments, the compound has the structure of any one of compounds D1-D38 in Table 2A, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound has the structure of any one of compounds D1-D33 in Table 2A, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound has the structure of any one of compounds D34-D38 in Table 2A, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound has the structure of any one of compounds D39-D302 in Table 2B, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound has the structure of any one of compounds D303-D375 in Table 2C, or a pharmaceutically acceptable salt thereof.
(891) In some embodiments, the compound has the structure of any one of compounds D9, D22, D25, D28, or D29 in Table 2A, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound has the structure of any one of compounds D39-D49, D51, D52, D55, D56, D58, D58, D63, D64, D68, D69, D71-D73, D76, D78, D80-89, D91, D93, D95-107, D109, D110, D112-119, D121, D123-D1256, D127, D128, D130-D136, D138-D143, D145-D147, D149, D151, D152, D154-D166, D169-D174, D178-D183, D195-D201, D222, D224, D227, D231, D246, D251, D253-256, D283, or D299-302 in Table 2B, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound has the structure of any one of compounds D303, D304, D306-D312, D314, D315, D317-D327, D329, D330, D332-336, D338-D342, D344-D348, D350, OR D353-D373, or a pharmaceutically acceptable salt thereof.
(892) In an aspect, the disclosure features compounds D1-D38 in Table 2A, or a pharmaceutically acceptable salt thereof.

(893) In another aspect, the disclosure features compounds D1-D33 in Table 2A, or a pharmaceutically acceptable salt thereof.
(894) In another aspect, the disclosure features compounds D39-D302 in Table 2B, or a pharmaceutically acceptable salt thereof.
(895) In yet another aspect, the disclosure features compounds D303-D375 in Table 2C, or a pharmaceutically acceptable salt thereof.
(896) TABLE-US-00003 TABLE 2A Compounds D1-D38 of the Disclosure Compound No. Structure D1  D2  D3 0  D4  D5  D6  D7  D8  D9  D10  D11  D12  D13 00  D14 01  D15 02  D16 03  D17 04  D18 05  D19 06 D20 07  D21 08  D22 09  D23 0  D24  D25  D26  D27  D28  D29  D30  D31  D32  D33 0  D34  D35  D36  D37  D38 
(897) TABLE-US-00004 TABLE 2B Compounds D39-D302 of the Disclosure Com- pound No. Structure D39  D40  D41 D42 D43 0 D44 D45 D46 D47 D48 D49 D50 D51 D52 D53 0 D54 D55 D56 D57 D58 D59 D60 D61 D62 D63 0 D64 D65 D66 D67 D68 D69 D70 D71 D72 D73 0 D74 D75 D76 D77 D78 D79 D80 D81 D82 D83 0 D84 D85 D86 D87 D88 D89 D90 D91 D92 D93 0 D94 D95 D96 D97 D98 D99 D100 D101 D102 D103 0 D104 D105 D106 D107 D109 D110 D111 D112 D113 D114 00 D115 01 D116 02 D117 03 D118 04 D119 05 D120 06 D121 07 D122 08 D123 09 D124 0 D125 D126 D127 D128 D129 D130 D131 D132 D133 D134 0 D135 D136 D137 D138 D139 D140 D141 D142 D143 D144 0 D145 D146 D147 D148 D149 D150 D151 D152 D153 D154 0 D155 D156 D157 D158 D159 D161 D162 D163 D164 D165 0 D166 D167 D168 D169 D170 D171 D172 D173 D174

(898) TABLE-US-00005 TABLE 2C Compounds D303-D375 of the Disclosure Compound No. Structure D303

D373 embedded image D374 embedded image D375 0embedded image
(899) In an aspect, the disclosure features a compound having the structure of DD1, or a pharmaceutically acceptable salt thereof.
(900) ##STR00861##
(901) 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.
(902) 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.
(903) 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.
(904) In some embodiments, the cell is a cancer cell.
(905) 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.
(906) 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 pharmaceutically 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.
(907) 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.
(908) 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.
(909) 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, oligodendrogliomas, ependymomas, gliobastomas, 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 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 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, oligodendroglioma, 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, 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.

(910) 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.

(911) 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.

(912) 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, oligodendrogliomas, ependymomas,

gliobastomas, 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 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 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, oligodendroglioma, 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, 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.

(913) 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.

(914) 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), 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), Togaviridae family (e.g. Rubella virus).

(915) 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).

(916) 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.

(917) 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

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

(919) 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 C.sub.2 alkyl group has the formula —CH.sub.2CH.sub.3. 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.

(920) 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.

(921) 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 C.sub.1-C.sub.2, C.sub.1-C.sub.3, C.sub.1-C.sub.4, C.sub.1-C.sub.5, or C.sub.1-C.sub.6. 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 C.sub.1-C.sub.6 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 C.sub.1-C.sub.4 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.

(922) 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.

(923) 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.

(924) 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.

(925) 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 “alkenylene” is a divalent alkenyl group.

(926) 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.

(927) The term “amino,” as used herein, represents —N(R.sup.N1).sub.2, wherein each R.sup.N1 is, independently, H, OH, NO.sub.2, N(R.sup.N2).sub.2, SO.sub.2OR.sup.N2, SO.sub.2R.sup.N2, SOR.sup.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.sup.N1 groups can be optionally substituted; or two R.sup.N1 combine to form an alkylene or heteroalkylene, and wherein each R.sup.N2 is, independently, H, alkyl, or aryl. The amino groups of the compounds described herein can be an unsubstituted amino (i.e., —NH.sub.2) or a substituted amino (i.e., —N(R.sup.N1).sub.2).

(928) The term “aryl,” as used herein, refers to an aromatic mono- or polycarbocyclic 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.

(929) 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 C.sub.1-C.sub.6 alkyl C.sub.6-C.sub.10 aryl, C.sub.1-C.sub.10 alkyl C.sub.6-C.sub.10 aryl, or C.sub.1-C.sub.20 alkyl C.sub.6-C.sub.10 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.

(930) The term “azido,” as used herein, represents a —N.sub.3 group.

(931) 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).

(932) The term “cyano,” as used herein, represents a —CN group.

(933) The term “carbocyclyl,” as used herein, refers to a non-aromatic C.sub.3-C.sub.12, 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 “carbocyclylene” is a divalent carbocyclyl group.

(934) 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.
(935) The terms “halo” or “halogen,” as used herein, mean a fluorine (fluoro), chlorine (chloro), bromine (bromo), or iodine (iodo) radical.
(936) 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 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.sup.Na, where R.sup.Na is H or alkyl (e.g., methylamino). A “heteroalkylene” is a divalent heteroalkyl group.
(937) 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.
(938) 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.
(939) 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, benzooxazolyl, benzoimidazolyl, benzothiazolyl, imidazolyl, oxaxolyl, and thiazolyl. A “heteroarylene” is a divalent heteroaryl group.
(940) 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 C.sub.1-C.sub.6 alkyl C.sub.2-C.sub.9 heteroaryl, C.sub.1-C.sub.10 alkyl C.sub.2-C.sub.9 heteroaryl, or C.sub.1-C.sub.20 alkyl C.sub.2-C.sub.9 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.
(941) 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.
(942) 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 C.sub.1-C.sub.6 alkyl C.sub.2-C.sub.9 heterocyclyl, C.sub.1-C.sub.10 alkyl C.sub.2-C.sub.9 heterocyclyl, or C.sub.1-C.sub.20 alkyl C.sub.2-C.sub.9 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.
(943) The term “hydroxyalkyl,” as used herein, represents alkyl group substituted with an —OH group.
(944) The term “hydroxyl,” as used herein, represents an —OH group.
(945) The term “imine,” as used herein, represents ═NR.sup.N group, where R.sup.N is, e.g., H or alkyl.
(946) 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, aryloyl, or carbamyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, 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 benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-20 dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxy carbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2,-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxy carbonyl, fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, and phenylthiocarbonyl, arylalkyl groups such as benzyl, triphenylmethyl, and benzyloxymethyl, and silyl groups, such as trimethylsilyl. Preferred N-protecting groups are alloc, formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, alanyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc), and benzyloxycarbonyl (Cbz).

(947) The term “nitro,” as used herein, represents an —NO.sub.2 group.

(948) The term “oxo,” as used herein, represents an ═O group.

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

(950) 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., NH.sub.2 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)).

(951) 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.

(952) 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.

(953) 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 .sup.2H, .sup.3H, .sup.11C, .sup.13C, .sup.14C, .sup.13N, .sup.15N, .sup.15O, .sup.17O, .sup.18O, .sup.32P, .sup.33P, .sup.35S, .sup.18F,

.sup.36Cl, .sup.123I and .sup.125I. Isotopically-labeled compounds (e.g., those labeled with .sup.3H and .sup.14C) can be useful in compound or substrate tissue distribution assays. Tritiated (i.e., .sup.3H) and carbon-14 (i.e., .sup.14C) isotopes can be useful for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., .sup.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 .sup.2H or .sup.3H, or one or more carbon atoms are replaced by .sup.13C- or .sup.14C-enriched carbon. Positron emitting isotopes such as .sup.15O, .sup.13N, .sup.11C, and .sup.18F 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 the present invention described herein, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

(954) 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.

(955) 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

(956) 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.

(957) 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.

(958) 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.

(959) 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.

(960) 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 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.
(961) 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.
(962) 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.
(963) As used herein, the term “BAF complex” refers to the BRG1- or HRBM-associated factors complex in a human cell.
(964) 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.
(965) 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.
(966) As used herein, the term “BRD9” refers to bromodomain-containing protein 9, 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 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%, 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.
(967) 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.
(968) 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.

(969) 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 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.

(970) 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.

(971) 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.

(972) 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.

(973) 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 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.

(974) 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).

(975) 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.

(976) 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, μg/mL, ng/mL) or percentage relative to total protein or mRNA in a sample.

(977) 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-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).
(978) 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.
(979) "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 multiplied by (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.
(980) 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, printing inks, sorbents, suspensing or dispersing agents, 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 methylcellulose, 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.
(981) 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.

(982) 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-hydroxy-ethanesulfonate, 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.

(983) 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 (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.

(984) 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.

(985) 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.

(986) 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.

(987) 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).

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

(989) 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.

(990) 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.

(991) 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.

(992) 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.

(993) 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.

Description

BRIEF DESCRIPTION OF THE DRAWINGS

(1) 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 show with BRD9 PFAM domains annotated from the PFAM database.
(2) 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.
(3) 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.
(4) 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.
(5) 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.
(6) 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.
(7) 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.
(8) 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.
(9) 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.
(10) 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 μM for 8 or 13 days.
(11) 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 μM, or lenalidomide at 200 nM for 8 days. Numerical values corresponding to each contour plot are found in the table below.
(12) 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 μM, or lenalidomide at 200 nM for 13 days. Numerical values corresponding to each contour plot are found in the table below.
(13) 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 μM, or lenalidomide at 200 nM for 8 days. Numerical values corresponding to each contour plot are found in the table below.
(14) FIG. **14** is a graph illustrating the proteins present in BAF complexes including the SS18-SSX fusion protein.

DETAILED DESCRIPTION

(15) 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.

(16) Compounds

(17) 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.

(18) Formula I is:

(19) ##STR00862## where R.sup.1 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.10 carbocyclyl; Z.sup.1 is CR.sup.2 or N; R.sup.2 is H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, or optionally substituted C.sub.2-C.sub.9 heteroaryl;

(20) ##STR00863## X.sup.1 is a bond, O, NR.sup.3a,

(21) ##STR00864## or CR.sup.4aR.sup.5a; X.sup.2 is O, NR.sup.3b,

(22) ##STR00865## or CR.sup.4bR.sup.5b; X.sup.3 is O, NR.sup.3c,

(23) ##STR00866## or CR.sup.4cR.sup.5c; X.sup.4 is a bond, O, NR.sup.3d,
(24) ##STR00867## or CR.sup.4dR.sup.5d; X.sup.5 is O or NR.sup.3e and X.sup.6 is CR.sup.4fR.sup.5f, or X.sup.5 is CR.sup.4eR.sup.5e and X.sup.6 is O or NR.sup.3f; X.sup.7 is O, NR.sup.3g, or CR.sup.4gR.sup.5g; X.sup.8 is O, NR.sup.3h, or CR.sup.4hR.sup.5h; each of R.sup.3a, R.sup.3b, R.sup.3c, and R.sup.3d is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted C.sub.1-C.sub.6 acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R.sup.3a and R.sup.4b, R.sup.4a and R.sup.3b, R.sup.4b and R.sup.4a, R.sup.3b and R.sup.4c, R.sup.4b and R.sup.4c, R.sup.3c and R.sup.4b, R.sup.3c and R.sup.4d, R.sup.4c and R.sup.4d, and/or R.sup.3d and R.sup.4c, together with the atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heterocyclyl; each of R.sup.4a, R.sup.4b, R.sup.4c, and R.sup.4d is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted C.sub.1-C.sub.6 acyl, thiol, optionally substituted sulfone, or optionally substituted amino, or R.sup.3a and R.sup.4b, R.sup.4a and R.sup.3b, R.sup.4b and R.sup.4a, R.sup.3b and R.sup.4c, R.sup.4b and R.sup.4c, R.sup.3c and R.sup.4b, R.sup.3c and R.sup.4d, R.sup.4c and R.sup.4d, and/or R.sup.3d and R.sup.4c, together with the atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heterocyclyl; each of R.sup.5a, R.sup.5b, R.sup.5c, and R.sup.5d is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; each of R.sup.3e, R.sup.3f, R.sup.3g, and R.sup.3h is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted C.sub.1—C.sub.6 acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R.sup.3e and R.sup.4f or R.sup.4e and R.sup.3f, together with the atoms to which each is attached, combine to form optionally substituted heterocyclycl; each of R.sup.4e, R.sup.4f, R.sup.4g, and R.sup.4h is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted C.sub.1-C.sub.6 acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R.sup.3e and R.sup.4f or R.sup.4e and R.sup.3f, together with the atoms to which each is attached, combine to form optionally substituted heterocyclycl; each of R.sup.5e, R.sup.5f, R.sup.5g, and R.sup.5h is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; and G is optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or C.sub.2-C.sub.9 heterocyclyl, or a

pharmaceutically acceptable salt thereof.
Formula II is:
A-L-B Formula II, where B is a degradation moiety, L is a linker, and A has the structure of Formula III:
(25) ##STR00868## where R.sup.1 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.10 carbocyclyl; Z.sup.1 is CR.sup.2 or N; R.sup.2 is H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, or optionally substituted C.sub.2-C.sub.9 heteroaryl;
(26) ##STR00869## X.sup.1′ is a bond, O, NR.sup.3a′, or CR.sup.4a′R.sup.5a′; X.sup.2′ is O, NR.sup.3b′, or CR.sup.4b′R.sup.5b′; X.sup.3′ is O, NR.sup.3c′, or CR.sup.4c′R.sup.5c′; X.sup.4′ is a bond, O, NR.sup.3d′, or CR.sup.4d′R.sup.5d′; X.sup.5′ is O, NR.sup.3e′, or CR.sup.4e′R.sup.5e′; X.sup.6′ is O, NR.sup.3f′, or CR.sup.4f′R.sup.5f′; X.sup.7′ is O, NR.sup.3g′, or CR.sup.4g′R.sup.59′; each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently, H,
(27) ##STR00870## halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted C.sub.1-C.sub.6 acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R.sup.3a′ and R.sup.4b′, R.sup.4a′ and R.sup.3b′, R.sup.4b′ and R.sup.4a′, R.sup.3b′ and R.sup.4c′, R.sup.4b′ and R.sup.4c′, R.sup.3c′ and R.sup.4b′, R.sup.3c′ and R.sup.4d′, R.sup.4c′ and R.sup.4d′, and/or R.sup.3d′ and R.sup.4c′, together with the atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heterocyclyl; R.sup.3′ is absent, optionally substituted C.sub.1-C.sub.6 alkylene, optionally substituted C.sub.1-C.sub.6 heteroalkylene, optionally substituted C.sub.3-C.sub.10 carbocyclylene, optionally substituted C.sub.2-C.sub.9 heterocyclylene, optionally substituted C.sub.6-C.sub.10 arylene, optionally substituted C.sub.2-C.sub.9 heteroarylene, optionally substituted C.sub.2-C.sub.6 alkenylene, optionally substituted C.sub.2-C.sub.6 heteroalkenylene, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino; each of R.sup.4a′, R.sup.4b′, R.sup.4c′, and R.sup.4d′ is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, thiol, optionally substituted sulfone, or optionally substituted amino, or R.sup.3a′ and R.sup.4b, R.sup.4a′ and R.sup.3b′, R.sup.4b′ and R.sup.4a′, R.sup.3b′ and R.sup.4c′, R.sup.4b′ and R.sup.4c′, R.sup.3c′ and R.sup.4b′, R.sup.3c′ and R.sup.4d′, R.sup.4c′ and R.sup.4d′, and/or R.sup.3d′ and R.sup.4c′, together with the atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heterocyclyl; each of R.sup.5a′, R.sup.5b′, R.sup.5c′, and R.sup.5d′ is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; each of R.sup.3e′, R.sup.3f′, and R.sup.3g′ is, independently, H,
(28) ##STR00871## halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted C.sub.1-C.sub.6 acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R.sup.3e and

R.sup.4f or R.sup.4e and R.sup.3f, together with the atoms to which each is attached, combine to form optionally substituted heterocyclycl; each of R.sup.4e′, R.sup.4f′, and R.sup.4g′ is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted C.sub.1-C.sub.6 acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R.sup.3e′ and R.sup.4f′ or R.sup.4e′ and R.sup.3f′, together with the atoms to which each is attached, combine to form optionally substituted heterocyclycl; each of R.sup.5e′, R.sup.5f′, and R.sup.5g′ is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; G″ is

(29) ##STR00872## optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or C.sub.2-C.sub.9 heterocyclyl; G′ is optionally substituted C.sub.3-C.sub.10 carbocyclylene, C.sub.2-C.sub.9 heterocyclylene, optionally substituted C.sub.6-C.sub.10 arylene, or optionally substituted C.sub.2-C.sub.9 heteroarylene; and A.sup.1 is a bond between A and the linker, where one of R.sup.3a′, R.sup.3b′, R.sup.3c′, R.sup.3d′, R.sup.3e′, R.sup.3f′, and R.sup.3g′ is

(30) ##STR00873## or G is

(31) ##STR00874## or a pharmaceutically acceptable salt thereof.

(32) In some embodiments, the compound has the structure of any one of compounds D1-D38 in Table 2A, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound has the structure of any one of compounds D39-D302 in Table 2B, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound has the structure of any one of compounds D303-D375 in Table 2C, or a pharmaceutically acceptable salt thereof.

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

(34) Pharmaceutical Uses

(35) 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.

(36) 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.

(37) 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.

(38) 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×, 3×, 4×, 5×, 10×, or 50×).

(39) 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×, 10×, or 50×).

(40) 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.

(41) 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 reproducible 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.

(42) Combination Therapies

(43) 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. 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.

(44) 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). These include alkylating agents, antimetabolites, folic acid analogs, pyrimidine analogs, purine analogs and related inhibitors, vinca alkaloids, epipodopyyllotoxins, antibiotics, L-Asparaginase, topoisomerase inhibitors, interferons, platinum coordination complexes, anthracenedione substituted urea, methyl hydrazine derivatives, adrenocortical suppressant, adrenocorticosteroides, progestins, estrogens, antiestrogen, androgens, antiandrogen, and gonadotropin-releasing hormone analog. Also included is 5-fluorouracil (5-FU), leucovorin (LV), irenotecan, oxaliplatin, capecitabine, paclitaxel, and doxetaxel. Non-limiting examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclosphosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethiylenethiophosphoramide and trimethylolomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analogue topotecan); bryostatin; callystatin; 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, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimnustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, especially calicheamicin gammaII and calicheamicin omegaII (see, e.g., *Agnew, Chem. Intl. 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 antiobiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, caminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, ADRIAMYCIN® (doxorubicin, including morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, 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, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfomithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; 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), ABRAXANE®, cremophor-free, albumin-engineered nanoparticle formulation of paclitaxel (American Pharmaceutical Partners, Schaumberg, IL), and TAXOTERE® doxetaxel (Rhone-Poulenc Rorer, Antony, France); chloranbucil; 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).

(45) In some embodiments, the second therapeutic agent is a therapeutic agent which is a biologic such 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.
(46) 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.
(47) 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/RG7446; 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.
(48) 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 number 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.
(49) 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 hours 16, 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.
(50) Pharmaceutical Compositions
(51) 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.
(52) 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.

(53) 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 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.

(54) 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.

(55) Dosages

(56) 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.

(57) 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).

(58) Kits

(59) 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

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

(61) 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 (Tsherniak 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.

(62) 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.

(63) TABLE-US-00006 TABLE 3 BRD9 sgRNA Library SEQ ID NO. Nucleic Acid Sequence 203 CAAGAAGCACAAGAAGCACA 204 CTTGTGCTTCTTGCCCATGG 205 CTTCTTGTGCTTCTTGCCCA 206 ACAAGAAGCACAAGGCCGAG 207 CTCGTAGGACGAGCGCCACT 208 CGAGTGGCGCTCGTCCTACG 209 GAGTGGCGCTCGTCCTACGA 210 AGGCTTCTCCAGGGGCTTGT 211 AGATTATGCCGACAAGCCCC 212 ACCTTCAGGACTAGCTTTAG 213 AGCTTTAGAGGCTTCTCCAG 214 CTAGCTTTAGAGGCTTCTCC 215 TAGCTTTAGAGGCTTCTCCA 216 CTAAAGCTAGTCCTGAAGGT 217 GCCTCTAAAGCTAGTCCTGA 218 CTTCACTTCCTCCGACCTTC 219

AAGCTAGTCCTGAAGGTCGG 220 AGTGAAGTGACTGAACTCTC 221
GTGACTGAACTCTCAGGATC 222 ATAGTAACTGGAGTCGTGGC 223
CATCATAGTAACTGGAGTCG 224 TGACCTGTCATCATAGTAAC 225
ACTCCAGTTACTATGATGAC 226 CTTTGTGCCTCTCTCGCTCA 227
GGTCAGACCATGAGCGAGAG 228 GAAGAAGAAGAAGTCCGAGA 229
GTCCAGATGCTTCTCCTTCT 230 GTCCGAGAAGGAGAAGCATC 231
GGAGAAGCATCTGGACGATG 232 TGAGGAAAGAAGGAAGCGAA 233
ATCTGGACGATGAGGAAAGA 234 AGAAGAAGCGGAAGCGAGAG 235
GAAGAAGCGGAAGCGAGAGA 236 CCGCCCAGGAAGAGAAGAAG 237
AGAGAGGGAGCACTGTGACA 238 AGGGAGCACTGTGACACGGA 239
GAGGGAGCACTGTGACACGG 240 GCACTGTGACACGGAGGGAG 241
GAGGCTGACGACTTTGATCC 242 AGGCTGACGACTTTGATCCT 243
TCCACCTCCACCTTCTTCCC 244 CGACTTTGATCCTGGGAAGA 245
CTTTGATCCTGGGAAGAAGG 246 TGATCCTGGGAAGAAGGTGG 247
TCCTGGGAAGAAGGTGGAGG 248 CGGACTGGCCGATCTGGGGG 249
ACGCTCGGACTGGCCGATCT 250 AGGTGGAGCCGCCCCCAGAT 251
CGCTCGGACTGGCCGATCTG 252 GCTCGGACTGGCCGATCTGG 253
CACGCTCGGACTGGCCGATC 254 TGTGTCCGGCACGCTCGGAC 255
CTGGCTGTGTCCGGCACGCT 256 ATCGGCCAGTCCGAGCGTGC 257
CACCCTTGCCTGGCTGTGTC 258 CGAGCGTGCCGGACACAGCC 259
TGTTCCAGGAGTTGCTGAAT 260 CACACCTATTCAGCAACTCC 261
GCTGGCGGAGGAAGTGTTCC 262 TTTACCTCTGAAGCTGGCGG 263
CCCCGGTTTACCTCTGAAGC 264 ACTTCCTCCGCCAGCTTCAG 265
CAGGAAAAGCAAAAAATCCA 266 GCTTTCAGAAAAGATCCCCA 267
AGGAAAAGCAAAAAATCCAT 268 GGAAAAGCAAAAAATCCATG 269
GGAGCAATTGCATCCGTGAC 270 GTCACGGATGCAATTGCTCC 271
TTTATTATCATTGAATATCC 272 AATGATAATAAAACATCCCA 273
ATAAAACATCCCATGGATTT 274 TTCATGGTGCCAAAATCCAT 275
TTTCATGGTGCCAAAATCCA 276 TAATGAATACAAGTCAGTTA 277
CAAGTCAGTTACGGAATTTA 278 ATAATGCAATGACATACAAT 279
AACTTGTAGTACACGGTATC 280 CTTCGCCAACTTGTAGTACA 281
AGATACCGTGTACTACAAGT 282 GCGAAGAAGATCCTTCACGC 283
TCATCTTAAAGCCTGCGTGA 284 TTCTCAGCAGGCAGCTCTTT 285
CAATGAAGATACAGCTGTTG 286 ACTGGTACAACTTCAGGGAC 287
CTTGTACTGGTACAACTTCA 288 ACTTGTACTGGTACAACTTC 289
TTGGCAGTTTCTACTTGTAC 290 TACCTGATAACTTCTCTACT 291
AGCCGAGTAGAGAAGTTATC 292 AGCTGCATGTTTGAGCCTGA 293
GCTGCATGTTTGAGCCTGAA 294 AAGCTGCAGGCATTCCCTTC 295
GGTACTGTCCGTCAAGCTGC 296 AGGGAATGCCTGCAGCTTGA 297
CTTGACGGACAGTACCGCAG 298 CGCCAGCACGTGCTCCTCTG 299
TACCGCAGAGGAGCACGTGC 300 AGAGGAGCACGTGCTGGCGC 301
GGAGCACGTGCTGGCGCTGG 302 AGCACGCAGCTGACGAAGCT 303
GCACGCAGCTGACGAAGCTC 304 CAGCTGACGAAGCTCGGGAC 305
AAGCTCGGGACAGGATCAAC 306 CCTTGCCGCCTGGGAGGAAC 307
AGGATCAACCGGTTCCTCCC 308 ATCAACCGGTTCCTCCCAGG 309
GCACTACCTTGCCGCCTGGG 310 AGAGCACTACCTTGCCGCCT 311
CCGGTTCCTCCCAGGCGGCA 312 TCCTCTTCAGATAGCCCATC 313
ATGGGCTATCTGAAGAGGAA 314 GGGCTATCTGAAGAGGAACG 315
TGGGCTATCTGAAGAGGAAC 316 TATCTGAAGAGGAACGGGGA 317
ATCTGAAGAGGAACGGGGAC 318 TGTTGACCACGCTGTAGAGC 319
GCTCTACAGCGTGGTCAACA 320 CGGGAGCCTGCTCTACAGCG 321
CGTGGTCAACACGGCCGAGC 322 CCCACCATCAGCGTCCGGCT 323

ACGGCCGAGCCGGACGCTGA 324 GGGCACCCACCATCAGCGTC 325
GCCGAGCCGGACGCTGATGG 326 CCATGTCCGTGTTGCAGAGG 327
CCGAGCCGGACGCTGATGGT 328 CGAGCTCAAGTCCACCGGGT 329
GCGAGCTCAAGTCCACCGGG 330 AGAGCGAGCTCAAGTCCACC 331
GAGAGCGAGCTCAAGTCCAC 332 GAAGCCTGGGAGTAGCTTAC 333
CTCTCCAGTAAGCTACTCCC 334 AGCCCAGCGTGGTGAAGCCT 335
AAGCCCAGCGTGGTGAAGCC 336 ACTCCCAGGCTTCACCACGC 337
CTCCCAGGCTTCACCACGCT 338 CTCGTCTTTGAAGCCCAGCG 339
CACTGGAGAGAAAGGTGACT 340 GCACTGGAGAGAAAGGTGAC 341
AGTAGTGGCACTGGAGAGAA 342 CGAAAGCGCAGTAGTGGCAC 343
CTGCATCGAAAGCGCAGTAG 344 ATGCAGAATAATTCAGTATT 345
AGTATTTGGCGACTTGAAGT 346 CGACTTGAAGTCGGACGAGA 347
GAGCTGCTCTACTCAGCCTA 348 CACGCCTGTCTCATCTCCGT 349
TCAGCCTACGGAGATGAGAC 350 CAGGCGTGCAGTGTGCGCTG 351
CCGCGGCCCCTCTAGCCTGC 352 CATCCTTCACAAACTCCTGC 353
TAGCCTGCAGGAGTTTGTGA 354 CAGGAGTTTGTGAAGGATGC 355
AGGAGTTTGTGAAGGATGCT 356 TGGGAGCTACAGCAAGAAAG 357
GAGCTACAGCAAGAAAGTGG 358 GAAAGTGGTGGACGACCTCC 359
CGCCTGTGATCTGGTCCAGG 360 CTCCGCCTGTGATCTGGTCC 361
GACCTCCTGGACCAGATCAC 362 CTCCTGGACCAGATCACAGG 363
GCTGGAAGAGCGTCCTAGAG 364 TGCAGCCCACCTGCTTCAGC 365
GACGCTCTTCCAGCTGAAGC 366 CTCTTCCAGCTGAAGCAGGT 367
GCTCTTCCAGCTGAAGCAGG 368 CCTCCAGATGAAGCCAAGGT 369
GCTTCATCTGGAGGCTTCAT 370 GGCTTCATCTGGAGGCTTCA 371
CTTACCTTGGCTTCATCTGG 372 AAACTTACCTTGGCTTCATC 373
GAAGCCTCCAGATGAAGCCA 374 TCCTAGGGTGTCCCCAACCT 375
CCTAGGGTGTCCCCAACCTG 376 GTGTCTGTCTCCACAGGTTG 377
TGTGTCTGTCTCCACAGGTT 378 CCACAGGTTGGGGACACCCT 379
AGAGCTGCTGCTGTCTCCTA 380 CAGAGCTGCTGCTGTCTCCT 381
AGACAGCAGCAGCTCTGTTC 382 ATCCACAGAAACGTCGGGAT 383
GAGATATCCACAGAAACGTC 384 GGAGATATCCACAGAAACGT 385
GTCCTATCCCGACGTTTCTG 386 TCTCCATGCTCAGCTCTCTG 387
CTCACCCAGAGAGCTGAGCA 388 ATCTCCATGCTCAGCTCTCT 389
TATCTCCATGCTCAGCTCTC 390 ATGTCCTGTTTACACAGGGA 391
TTACACAGGGAAGGTGAAGA 392 AGTTCAAATGGCTGTCGTCA 393
TGACGACAGCCATTTGAACT 394 AAGTTCAAATGGCTGTCGTC 395
TCGTCTCATCCAAGTTCAAA 396 TGAGACGACGAAGCTCCTGC 397
GTGCTTCGTGCAGGTCCTGC 398 GCAGGACCTGCACGAAGCAC 399
GCTCCGCCTGTGCTTCGTGC 400 GGACCTGCACGAAGCACAGG 401
CACGAAGCACAGGCGGAGCG 402 AGGCGGAGCGCGGCGGCTCT 403
AGGGAGCTGAGGTTGGACGA 404 GTTGGACAGGGAGCTGAGGT 405
AGGCGTTGGACAGGGAGCTG 406 CCCTCTCGGAGGCGTTGGAC 407
CCTCTCGGAGGCGTTGGACA 408 CTGGTCCCTCTCGGAGGCGT 409
CCCTGTCCAACGCCTCCGAG 410 CCTGTCCAACGCCTCCGAGA 411
GTGGTGCTGGTCCCTCTCGG 412 CAGGTGGTGCTGGTCCCTCT 413
GCATCTCACCCAGGTGGTGC 414 CGAGAGGGACCAGCACCACC 415
GAGAGGGACCAGCACCACCT 416 GTGGGGGCATCTCACCCAGG 417
CCCCGACACTCAGGCGAGAA 418 TCCCCGACACTCAGGCGAGA 419
AGCCCTTCTCGCCTGAGTGT 420 CTGGCTGCTCCCCGACACTC 421
CCCTTCTCGCCTGAGTGTCG 422 GCCCTTCTCGCCTGAGTGTC 423
TAGGGGTCGTGGGTGACGTC 424 AAGAAACTCATAGGGGTCGT 425
GAAGAAACTCATAGGGGTCG 426 GAGACTGAAGAAACTCATAG 427

GGAGACTGAAGAAACTCATA 428 TGGAGACTGAAGAAACTCAT 429
TCTTCAGTCTCCAGAGCCTG 430 TTGGCAGAGGCCGCAGGCTC 431
TAGGTCTTGGCAGAGGCCGC 432 CTAGAGTTAGGTCTTGGCAG 433
GGTGGTCTAGAGTTAGGTCT

(64) TABLE-US-00007 TABLE 4 Control sgRNA Library SEQ ID Nucleic Acid NO. gRNA Label Gene Sequence 434 1|sg_Non_Targeting_Human_0001| Non_Targeting_Human GTAGCGAACGTGTCCGGCGT Non_Targeting_Human 435 1|sg_Non_Targeting_Human_0002| Non_Targeting_Human GACCGGAACGATCTCGCGTA Non_Targeting_Human 436 1|sg_Non_Targeting_Human_0003| Non_Targeting_Human GGCAGTCGTTCGGTTGATAT Non_Targeting_Human 437 1|sg_Non_Targeting_Human_0004| Non_Targeting_Human GCTTGAGCACATACGCGAAT Non_Targeting_Human 438 1|sg_Non_Targeting_Human_0005| Non_Targeting_Human GTGGTAGAATAACGTATTAC Non_Targeting_Human 439 1|sg_Non_Targeting_Human_0006| Non_Targeting_Human GTCATACATGGATAAGGCTA Non_Targeting_Human 440 1|sg_Non_Targeting_Human_0007| Non_Targeting_Human GATACACGAAGCATCACTAG Non_Targeting_Human 441 1|sg_Non_Targeting_Human_0008| Non_Targeting_Human GAACGTTGGCACTACTTCAC Non_Targeting_Human 442 1|sg_Non_Targeting_Human_0009| Non_Targeting_Human GATCCATGTAATGCGTTCGA Non_Targeting_Human 443 1|sg_Non_Targeting_Human_0010| Non_Targeting_Human GTCGTGAAGTGCATTCGATC Non_Targeting_Human 444 1|sg_Non_Targeting_Human_0011| Non_Targeting_Human GTTCGACTCGCGTGACCGTA Non_Targeting_Human 445 1|sg_Non_Targeting_Human_0012| Non_Targeting_Human GAATCTACCGCAGCGGTTCG Non_Targeting_Human 446 1|sg_Non_Targeting_Human_0013| Non_Targeting_Human GAAGTGACGTCGATTCGATA Non_Targeting_Human 447 1|sg_Non_Targeting_Human_0014| Non_Targeting_Human GCGGTGTATGACAACCGCCG Non_Targeting_Human 448 1|sg_Non_Targeting_Human_0015| Non_Targeting_Human GTACCGCGCCTGAAGTTCGC Non_Targeting_Human 449 1|sg_Non_Targeting_Human_0016| Non_Targeting_Human GCAGCTCGTGTGTCGTACTC Non_Targeting_Human 450 1|sg_Non_Targeting_Human_0017| Non_Targeting_Human GCGCCTTAAGAGTACTCATC Non_Targeting_Human 451 1|sg_Non_Targeting_Human_0018| Non_Targeting_Human GAGTGTCGTCGTTGCTCCTA Non_Targeting_Human 452 1|sg_Non_Targeting_Human_0019| Non_Targeting_Human GCAGCTCGACCTCAAGCCGT Non_Targeting_Human 453 1|sg_Non_Targeting_Human_0020| Non_Targeting_Human GTATCCTGACCTACGCGCTG Non_Targeting_Human 454 1|sg_Non_Targeting_Human_0021| Non_Targeting_Human GTGTATCTCAGCACGCTAAC Non_Targeting_Human 455 1|sg_Non_Targeting_Human_0022| Non_Targeting_Human GTCGTCATACAACGGCAACG Non_Targeting_Human 456 1|sg_Non_Targeting_Human_0023| Non_Targeting_Human GTCGTGCGCTTCCGGCGGTA Non_Targeting_Human 457 1|sg_Non_Targeting_Human_0024| Non_Targeting_Human GCGGTCCTCAGTAAGCGCGT Non_Targeting_Human 458 1|sg_Non_Targeting_Human_0025| Non_Targeting_Human GCTCTGCTGCGGAAGGATTC Non_Targeting_Human 459 1|sg_Non_Targeting_Human_0026| Non_Targeting_Human GCATGGAGGAGCGTCGCAGA Non_Targeting_Human 460 1|sg_Non_Targeting_Human_0027| Non_Targeting_Human GTAGCGCGCGTAGGAGTGGC Non_Targeting_Human 461 1|sg_Non_Targeting_Human_0028| Non_Targeting_Human GATCACCTGCATTCGTACAC Non_Targeting_Human 462 1|sg_Non_Targeting_Human_0029| Non_Targeting_Human GCACACCTAGATATCGAATG Non_Targeting_Human 463 1|sg_Non_Targeting_Human_0030| Non_Targeting_Human GTTGATCAACGCGCTTCGCG Non_Targeting_Human 464 1|sg_Non_Targeting_Human_0031| Non_Targeting_Human GCGTCTCACTCACTCCATCG Non_Targeting_Human 465 1|sg_Non_Targeting_Human_0032| Non_Targeting_Human GCCGACCAACGTCAGCGGTA Non_Targeting_Human 466 1|sg_Non_Targeting_Human_0033| Non_Targeting_Human GGATACGGTGCGTCAATCTA Non_Targeting_Human 467 1|sg_Non_Targeting_Human_0034| Non_Targeting_Human GAATCCAGTGGCGGCGACAA Non_Targeting_Human 468 1|sg_Non_Targeting_Human_0035| Non_Targeting_Human GCACTGTCAGTGCAACGATA Non_Targeting_Human 469

1|sg_Non_Targeting_Human_0036| Non_Targeting_Human GCGATCCTCAAGTATGCTCA Non_Targeting_Human 470 1|sg_Non_Targeting_Human_0037| Non_Targeting_Human GCTAATATCGACACGGCCGC Non_Targeting_Human 471 1|sg_Non_Targeting_Human_0038| Non_Targeting_Human GGAGATGCATCGAAGTCGAT Non_Targeting_Human 472 1|sg_Non_Targeting_Human_0039| Non_Targeting_Human GGATGCACTCCATCTCGTCT Non_Targeting_Human 473 1|sg_Non_Targeting_Human_0040| Non_Targeting_Human GTGCCGAGTAATAACGCGAG Non_Targeting_Human 474 1|sg_Non_Targeting_Human_0041| Non_Targeting_Human GAGATTCCGATGTAACGTAC Non_Targeting_Human 475 1|sg_Non_Targeting_Human_0042| Non_Targeting_Human GTCGTCACGAGCAGGATTGC Non_Targeting_Human 476 1|sg_Non_Targeting_Human_0043| Non_Targeting_Human GCGTTAGTCACTTAGCTCGA Non_Targeting_Human 477 1|sg_Non_Targeting_Human_0044| Non_Targeting_Human GTTCACACGGTGTCGGATAG Non_Targeting_Human 478 1|sg_Non_Targeting_Human_0045| Non_Targeting_Human GGATAGGTGACCTTAGTACG Non_Targeting_Human 479 1|sg_Non_Targeting_Human_0046| Non_Targeting_Human GTATGAGTCAAGCTAATGCG Non_Targeting_Human 480 1|sg_Non_Targeting_Human_0047| Non_Targeting_Human GCAACTATTGGAATACGTGA Non_Targeting_Human 481 1|sg_Non_Targeting_Human_0048| Non_Targeting_Human GTTACCTTCGCTCGTCTATA Non_Targeting_Human 482 1|sg_Non_Targeting_Human_0049| Non_Targeting_Human GTACCGAGCACCACAGGCCG Non_Targeting_Human 483 1|sg_Non_Targeting_Human_0050| Non_Targeting_Human GTCAGCCATCGGATAGAGAT Non_Targeting_Human 484 1|sg_Non_Targeting_Human_0051| Non_Targeting_Human GTACGGCACTCCTAGCCGCT Non_Targeting_Human 485 1|sg_Non_Targeting_Human_0052| Non_Targeting_Human GGTCCTGTCGTATGCTTGCA Non_Targeting_Human 486 1|sg_Non_Targeting_Human_0053| Non_Targeting_Human GCCGCAATATATGCGGTAAG Non_Targeting_Human 487 1|sg_Non_Targeting_Human_0054| Non_Targeting_Human GCGCACGTATAATCCTGCGT Non_Targeting_Human 488 1|sg_Non_Targeting_Human_0055| Non_Targeting_Human GTGCACAACACGATCCACGA Non_Targeting_Human 489 1|sg_Non_Targeting_Human_0056| Non_Targeting_Human GCACAATGTTGACGTAAGTG Non_Targeting_Human 490 1|sg_Non_Targeting_Human_0057| Non_Targeting_Human GTAAGATGCTGCTCACCGTG Non_Targeting_Human 491 1|sg_Non_Targeting_Human_0058| Non_Targeting_Human GTCGGTGATCCAACGTATCG Non_Targeting_Human 492 1|sg_Non_Targeting_Human_0059| Non_Targeting_Human GAGCTAGTAGGACGCAAGAC Non_Targeting_Human 493 1|sg_Non_Targeting_Human_0060| Non_Targeting_Human GTACGTGGAAGCTTGTGGCC Non_Targeting_Human 494 1|sg_Non_Targeting_Human_0061| Non_Targeting_Human GAGAACTGCCAGTTCTCGAT Non_Targeting_Human 495 1|sg_Non_Targeting_Human_0062| Non_Targeting_Human GCCATTCGGCGCGGCACTTC Non_Targeting_Human 496 1|sg_Non_Targeting_Human_0063| Non_Targeting_Human GCACACGACCAATCCGCTTC Non_Targeting_Human 497 1|sg_Non_Targeting_Human_0064| Non_Targeting_Human GAGGTGATCGATTAAGTACA Non_Targeting_Human 498 1|sg_Non_Targeting_Human_0065| Non_Targeting_Human GTCACTCGCAGACGCCTAAC Non_Targeting_Human 499 1|sg_Non_Targeting_Human_0066| Non_Targeting_Human GCGCTACGGAATCATACGTT Non_Targeting_Human 500 1|sg_Non_Targeting_Human_0067| Non_Targeting_Human GGTAGGACCTCACGGCGCGC Non_Targeting_Human 501 1|sg_Non_Targeting_Human_0068| Non_Targeting_Human GAACTGCATCTTGTTGTAGT Non_Targeting_Human 502 1|sg_Non_Targeting_Human_0069| Non_Targeting_Human GATCCTGATCCGGCGGCGCG Non_Targeting_Human 503 1|sg_Non_Targeting_Human_0070| Non_Targeting_Human GGTATGCGCGATCCTGAGTT Non_Targeting_Human 504 1|sg_Non_Targeting_Human_0071| Non_Targeting_Human GCGGAGCTAGAGAGCGGTCA Non_Targeting_Human 505 1|sg_Non_Targeting_Human_0072| Non_Targeting_Human GAATGGCAATTACGGCTGAT Non_Targeting_Human 506 1|sg_Non_Targeting_Human_0073| Non_Targeting_Human GTATGGTGAGTAGTCGCTTG Non_Targeting_Human 507 1|sg_Non_Targeting_Human_0074| Non_Targeting_Human GTGTAATTGCGTCTAGTCGG Non_Targeting_Human 508

1|sg_Non_Targeting_Human_0075| Non_Targeting_Human GGTCCTGGCGAGGAGCCTTG
Non_Targeting_Human 509 1|sg_Non_Targeting_Human_0076| Non_Targeting_Human
GAAGATAAGTCGCTGTCTCG Non_Targeting_Human 510 1|sg_Non_Targeting_Human_0077|
Non_Targeting_Human GTCGGCGTTCTGTTGTGACT Non_Targeting_Human 511
1|sg_Non_Targeting_Human_0078| Non_Targeting_Human GAGGCAAGCCGTTAGGTGTA
Non_Targeting_Human 512 1|sg_Non_Targeting_Human_0079| Non_Targeting_Human
GCGGATCCAGATCTCATTCG Non_Targeting_Human 513 1|sg_Non_Targeting_Human_0080|
Non_Targeting_Human GGAACATAGGAGCACGTAGT Non_Targeting_Human 514
1|sg_Non_Targeting_Human_0081| Non_Targeting_Human GTCATCATTATGGCGTAAGG
Non_Targeting_Human 515 1|sg_Non_Targeting_Human_0082| Non_Targeting_Human
GCGACTAGCGCCATGAGCGG Non_Targeting_Human 516 1|sg_Non_Targeting_Human_0083|
Non_Targeting_Human GGCGAAGTTCGACATGACAC Non_Targeting_Human 517
1|sg_Non_Targeting_Human_0084| Non_Targeting_Human GCTGTCGTGTGGAGGCTATG
Non_Targeting_Human 518 1|sg_Non_Targeting_Human_0085| Non_Targeting_Human
GCGGAGAGCATTGACCTCAT Non_Targeting_Human 519 1|sg_Non_Targeting_Human_0086|
Non_Targeting_Human GACTAATGGACCAAGTCAGT Non_Targeting_Human 520
1|sg_Non_Targeting_Human_0087| Non_Targeting_Human GCGGATTAGAGGTAATGCGG
Non_Targeting_Human 521 1|sg_Non_Targeting_Human_0088| Non_Targeting_Human
GCCGACGGCAATCAGTACGC Non_Targeting_Human 522 1|sg_Non_Targeting_Human_0089|
Non_Targeting_Human GTAACCTCTCGAGCGATAGA Non_Targeting_Human 523
1|sg_Non_Targeting_Human_0090| Non_Targeting_Human GACTTGTATGTGGCTTACGG
Non_Targeting_Human 524 1|sg_Non_Targeting_Human_0091| Non_Targeting_Human
GTCACTGTGGTCGAACATGT Non_Targeting_Human 525 1|sg_Non_Targeting_Human_0092|
Non_Targeting_Human GTACTCCAATCCGCGATGAC Non_Targeting_Human 526
1|sg_Non_Targeting_Human_0093| Non_Targeting_Human GCGTTGGCACGATGTTACGG
Non_Targeting_Human 527 1|sg_Non_Targeting_Human_0094| Non_Targeting_Human
GAACCAGCCGGCTAGTATGA Non_Targeting_Human 528 1|sg_Non_Targeting_Human_0095|
Non_Targeting_Human GTATACTAGCTAACCACACG Non_Targeting_Human 529
1|sg_Non_Targeting_Human_0096| Non_Targeting_Human GAATCGGAATAGTTGATTCG
Non_Targeting_Human 530 1|sg_Non_Targeting_Human_0097| Non_Targeting_Human
GAGCACTTGCATGAGGCGGT Non_Targeting_Human 531 1|sg_Non_Targeting_Human_0098|
Non_Targeting_Human GAACGGCGATGAAGCCAGCC Non_Targeting_Human 532
1|sg_Non_Targeting_Human_0099| Non_Targeting_Human GCAACCGAGATGAGAGGTTC
Non_Targeting_Human 533 1|sg_Non_Targeting_Human_0100| Non_Targeting_Human
GCAAGATCAATATGCGTGAT Non_Targeting_Human 534 1|sg_Non_Targeting_Human_GA_0101|
Non_Targeting_Human ACGGAGGCTAAGCGTCGCAA Non_Targeting_Human 535
1|sg_Non_Targeting_Human_GA_0102| Non_Targeting_Human CGCTTCCGCGGCCCGTTCAA
Non_Targeting_Human 536 1|sg_Non_Targeting_Human_GA_0103| Non_Targeting_Human
ATCGTTTCCGCTTAACGGCG Non_Targeting_Human 537 1|sg_Non_Targeting_Human_GA_0104|
Non_Targeting_Human GTAGGCGCGCCGCTCTCTAC Non_Targeting_Human 538
1|sg_Non_Targeting_Human_GA_0105| Non_Targeting_Human CCATATCGGGGCGAGACATG
Non_Targeting_Human 539 1|sg_Non_Targeting_Human_GA_0106| Non_Targeting_Human
TACTAACGCCGCTCCTACAG Non_Targeting_Human 540 1|sg_Non_Targeting_Human_GA_0107|
Non_Targeting_Human TGAGGATCATGTCGAGCGCC Non_Targeting_Human 541
1|sg_Non_Targeting_Human_GA_0108| Non_Targeting_Human GGGCCCGCATAGGATATCGC
Non_Targeting_Human 542 1|sg_Non_Targeting_Human_GA_0109| Non_Targeting_Human
TAGACAACCGCGGAGAATGC Non_Targeting_Human 543 1|sg_Non_Targeting_Human_GA_0110|
Non_Targeting_Human ACGGGCGGCTATCGCTGACT Non_Targeting_Human 544
1|sg_Non_Targeting_Human_GA_0111| Non_Targeting_Human CGCGGAAATTTTACCGACGA
Non_Targeting_Human 545 1|sg_Non_Targeting_Human_GA_0112| Non_Targeting_Human
CTTACAATCGTCGGTCCAAT Non_Targeting_Human 546 1|sg_Non_Targeting_Human_GA_0113|
Non_Targeting_Human GCGTGCGTCCCGGGTTACCC Non_Targeting_Human 547

1|sg_Non_Targeting_Human_GA_0114| Non_Targeting_Human CGGAGTAACAAGCGGACGGA Non_Targeting_Human 548 1|sg_Non_Targeting_Human_GA_0115| Non_Targeting_Human CGAGTGTTATACGCACCGTT Non_Targeting_Human 549 1|sg_Non_Targeting_Human_GA_0116| Non_Targeting_Human CGACTAACCGGAAACTTTTT Non_Targeting_Human 550 1|sg_Non_Targeting_Human_GA_0117| Non_Targeting_Human CAACGGGTTCTCCCGGCTAC Non_Targeting_Human 551 1|sg_Non_Targeting_Human_GA_0118| Non_Targeting_Human CAGGAGTCGCCGATACGCGT Non_Targeting_Human 552 1|sg_Non_Targeting_Human_GA_0119| Non_Targeting_Human TTCACGTCGTCTCGCGACCA Non_Targeting_Human 553 1|sg_Non_Targeting_Human_GA_0120| Non_Targeting_Human GTGTCGGATTCCGCCGCTTA Non_Targeting_Human 554 1|sg_Non_Targeting_Human_GA_0121| Non_Targeting_Human CACGAACTCACACCGCGCGA Non_Targeting_Human 555 1|sg_Non_Targeting_Human_GA_0122| Non_Targeting_Human CGCTAGTACGCTCCTCTATA Non_Targeting_Human 556 1|sg_Non_Targeting_Human_GA_0123| Non_Targeting_Human TCGCGCTTGGGTTATACGCT Non_Targeting_Human 557 1|sg_Non_Targeting_Human_GA_0124| Non_Targeting_Human CTATCTCGAGTGGTAATGCG Non_Targeting_Human 558 1|sg_Non_Targeting_Human_GA_0125| Non_Targeting_Human AATCGACTCGAACTTCGTGT Non_Targeting_Human 559 1|sg_Non_Targeting_Human_GA_0126| Non_Targeting_Human CCCGATGGACTATACCGAAC Non_Targeting_Human 560 1|sg_Non_Targeting_Human_GA_0127| Non_Targeting_Human ACGTTCGAGTACGACCAGCT Non_Targeting_Human 561 1|sg_Non_Targeting_Human_GA_0128| Non_Targeting_Human CGCGACGACTCAACCTAGTC Non_Targeting_Human 562 1|sg_Non_Targeting_Human_GA_0129| Non_Targeting_Human GGTCACCGATCGAGAGCTAG Non_Targeting_Human 563 1|sg_Non_Targeting_Human_GA_0130| Non_Targeting_Human CTCAACCGACCGTATGGTCA Non_Targeting_Human 564 1|sg_Non_Targeting_Human_GA_0131| Non_Targeting_Human CGTATTCGACTCTCAACGCG Non_Targeting_Human 565 1|sg_Non_Targeting_Human_GA_0132| Non_Targeting_Human CTAGCCGCCCAGATCGAGCC Non_Targeting_Human 566 1|sg_Non_Targeting_Human_GA_0133| Non_Targeting_Human GAATCGACCGACACTAATGT Non_Targeting_Human 567 1|sg_Non_Targeting_Human_GA_0134| Non_Targeting_Human ACTTCAGTTCGGCGTAGTCA Non_Targeting_Human 568 1|sg_Non_Targeting_Human_GA_0135| Non_Targeting_Human GTGCGATGTCGCTTCAACGT Non_Targeting_Human 569 1|sg_Non_Targeting_Human_GA_0136| Non_Targeting_Human CGCCTAATTTCCGGATCAAT Non_Targeting_Human 570 1|sg_Non_Targeting_Human_GA_0137| Non_Targeting_Human CGTGGCCGGAACCGTCATAG Non_Targeting_Human 571 1|sg_Non_Targeting_Human_GA_0138| Non_Targeting_Human ACCCTCCGAATCGTAACGGA Non_Targeting_Human 572 1|sg_Non_Targeting_Human_GA_0139| Non_Targeting_Human AAACGGTACGACAGCGTGTG Non_Targeting_Human 573 1|sg_Non_Targeting_Human_GA_0140| Non_Targeting_Human ACATAGTCGACGGCTCGATT Non_Targeting_Human 574 1|sg_Non_Targeting_Human_GA_0141| Non_Targeting_Human GATGGCGCTTCAGTCGTCGG Non_Targeting_Human 575 1|sg_Non_Targeting_Human_GA_0142| Non_Targeting_Human ATAATCCGGAAACGCTCGAC Non_Targeting_Human 576 1|sg_Non_Targeting_Human_GA_0143| Non_Targeting_Human CGCCGGGCTGACAATTAACG Non_Targeting_Human 577 1|sg_Non_Targeting_Human_GA_0144| Non_Targeting_Human CGTCGCCATATGCCGGTGGC Non_Targeting_Human 578 1|sg_Non_Targeting_Human_GA_0145| Non_Targeting_Human CGGGCCTATAACACCATCGA Non_Targeting_Human 579 1|sg_Non_Targeting_Human_GA_0146| Non_Targeting_Human CGCCGTTCCGAGATACTTGA Non_Targeting_Human 580 1|sg_Non_Targeting_Human_GA_0147| Non_Targeting_Human CGGGACGTCGCGAAAATGTA Non_Targeting_Human 581 1|sg_Non_Targeting_Human_GA_0148| Non_Targeting_Human TCGGCATACGGGACACACGC Non_Targeting_Human 582 1|sg_Non_Targeting_Human_GA_0149| Non_Targeting_Human AGCTCCATCGCCGCGATAAT Non_Targeting_Human 583 1|sg_Non_Targeting_Human_GA_0150| Non_Targeting_Human ATCGTATCATCAGCTAGCGC Non_Targeting_Human 584 1|sg_Non_Targeting_Human_GA_0151| Non_Targeting_Human TCGATCGAGGTTGCATTCGG Non_Targeting_Human 585 1|sg_Non_Targeting_Human_GA_0152| Non_Targeting_Human CTCGACAGTTCGTCCCGAGC Non_Targeting_Human 586

1|sg_Non_Targeting_Human_GA_0153| Non_Targeting_Human CGGTAGTATTAATCGCTGAC Non_Targeting_Human 587 1|sg_Non_Targeting_Human_GA_0154| Non_Targeting_Human TGAACGCGTGTTTCCTTGCA Non_Targeting_Human 588 1|sg_Non_Targeting_Human_GA_0155| Non_Targeting_Human CGACGCTAGGTAACGTAGAG Non_Targeting_Human 589 1|sg_Non_Targeting_Human_GA_0156| Non_Targeting_Human CATTGTTGAGCGGGCGCGCT Non_Targeting_Human 590 1|sg_Non_Targeting_Human_GA_0157| Non_Targeting_Human CCGCTATTGAAACCGCCCAC Non_Targeting_Human 591 1|sg_Non_Targeting_Human_GA_0158| Non_Targeting_Human AGACACGTCACCGGTCAAAA Non_Targeting_Human 592 1|sg_Non_Targeting_Human_GA_0159| Non_Targeting_Human TTTACGATCTAGCGGCGTAG Non_Targeting_Human 593 1|sg_Non_Targeting_Human_GA_0160| Non_Targeting_Human TTCGCACGATTGCACCTTGG Non_Targeting_Human 594 1|sg_Non_Targeting_Human_GA_0161| Non_Targeting_Human GGTTAGAGACTAGGCGCGCG Non_Targeting_Human 595 1|sg_Non_Targeting_Human_GA_0162| Non_Targeting_Human CCTCCGTGCTAACGCGGACG Non_Targeting_Human 596 1|sg_Non_Targeting_Human_GA_0163| Non_Targeting_Human TTATCGCGTAGTGCTGACGT Non_Targeting_Human 597 1|sg_Non_Targeting_Human_GA_0164| Non_Targeting_Human TACGCTTGCGTTTAGCGTCC Non_Targeting_Human 598 1|sg_Non_Targeting_Human_GA_0165| Non_Targeting_Human CGCGGCCCACGCGTCATCGC Non_Targeting_Human 599 1|sg_Non_Targeting_Human_GA_0166| Non_Targeting_Human AGCTCGCCATGTCGGTTCTC Non_Targeting_Human 600 1|sg_Non_Targeting_Human_GA_0167| Non_Targeting_Human AACTAGCCCGAGCAGCTTCG Non_Targeting_Human 601 1|sg_Non_Targeting_Human_GA_0168| Non_Targeting_Human CGCAAGGTGTCGGTAACCCT Non_Targeting_Human 602 1|sg_Non_Targeting_Human_GA_0169| Non_Targeting_Human CTTCGACGCCATCGTGCTCA Non_Targeting_Human 603 1|sg_Non_Targeting_Human_GA_0170| Non_Targeting_Human TCCTGGATACCGCGTGGTTA Non_Targeting_Human 604 1|sg_Non_Targeting_Human_GA_0171| Non_Targeting_Human ATAGCCGCCGCTCATTACTT Non_Targeting_Human 605 1|sg_Non_Targeting_Human_GA_0172| Non_Targeting_Human GTCGTCCGGGATTACAAAAT Non_Targeting_Human 606 1|sg_Non_Targeting_Human_GA_0173| Non_Targeting_Human TAATGCTGCACACGCCGAAT Non_Targeting_Human 607 1|sg_Non_Targeting_Human_GA_0174| Non_Targeting_Human TATCGCTTCCGATTAGTCCG Non_Targeting_Human 608 1|sg_Non_Targeting_Human_GA_0175| Non_Targeting_Human GTACCATACCGCGTACCCTT Non_Targeting_Human 609 1|sg_Non_Targeting_Human_GA_0176| Non_Targeting_Human TAAGATCCGCGGGTGGCAAC Non_Targeting_Human 610 1|sg_Non_Targeting_Human_GA_0177| Non_Targeting_Human GTAGACGTCGTGAGCTTCAC Non_Targeting_Human 611 1|sg_Non_Targeting_Human_GA_0178| Non_Targeting_Human TCGCGGACATAGGGCTCTAA Non_Targeting_Human 612 1|sg_Non_Targeting_Human_GA_0179| Non_Targeting_Human AGCGCAGATAGCGCGTATCA Non_Targeting_Human 613 1|sg_Non_Targeting_Human_GA_0180| Non_Targeting_Human GTTCGCTTCGTAACGAGGAA Non_Targeting_Human 614 1|sg_Non_Targeting_Human_GA_0181| Non_Targeting_Human GACCCCCGATAACTTTTGAC Non_Targeting_Human 615 1|sg_Non_Targeting_Human_GA_0182| Non_Targeting_Human ACGTCCATACTGTCGGCTAC Non_Targeting_Human 616 1|sg_Non_Targeting_Human_GA_0183| Non_Targeting_Human GTACCATTGCCGGCTCCCTA Non_Targeting_Human 617 1|sg_Non_Targeting_Human_GA_0184| Non_Targeting_Human TGGTTCCGTAGGTCGGTATA Non_Targeting_Human 618 1|sg_Non_Targeting_Human_GA_0185| Non_Targeting_Human TCTGGCTTGACACGACCGTT Non_Targeting_Human 619 1|sg_Non_Targeting_Human_GA_0186| Non_Targeting_Human CGCTAGGTCCGGTAAGTGCG Non_Targeting_Human 620 1|sg_Non_Targeting_Human_GA_0187| Non_Targeting_Human AGCACGTAATGTCCGTGGAT Non_Targeting_Human 621 1|sg_Non_Targeting_Human_GA_0188| Non_Targeting_Human AAGGCGCGCGAATGTGGCAG Non_Targeting_Human 622 1|sg_Non_Targeting_Human_GA_0189| Non_Targeting_Human ACTGCGGAGCGCCCAATATC Non_Targeting_Human 623 1|sg_Non_Targeting_Human_GA_0190| Non_Targeting_Human CGTCGAGTGCTCGAACTCCA Non_Targeting_Human 624 1|sg_Non_Targeting_Human_GA_0191| Non_Targeting_Human TCGCAGCGGCGTGGGATCGG Non_Targeting_Human 625

1|sg_Non_Targeting_Human_GA_0192| Non_Targeting_Human ATCTGTCCTAATTCGGATCG
Non_Targeting_Human 626 1|sg_Non_Targeting_Human_GA_0193| Non_Targeting_Human
TGCGGCGTAATGCTTGAAAG Non_Targeting_Human 627 1|sg_Non_Targeting_Human_GA_0194|
Non_Targeting_Human CGAACTTAATCCCGTGGCAA Non_Targeting_Human 628
1|sg_Non_Targeting_Human_GA_0195| Non_Targeting_Human GCCGTGTTGCTGGATACGCC
Non_Targeting_Human 629 1|sg_Non_Targeting_Human_GA_0196| Non_Targeting_Human
TACCCTCCGGATACGGACTG Non_Targeting_Human 630 1|sg_Non_Targeting_Human_GA_0197|
Non_Targeting_Human CCGTTGGACTATGGCGGGTC Non_Targeting_Human 631
1|sg_Non_Targeting_Human_GA_0198| Non_Targeting_Human GTACGGGGCGATCATCCACA
Non_Targeting_Human 632 1|sg_Non_Targeting_Human_GA_0199| Non_Targeting_Human
AAGAGTAGTAGACGCCCGGG Non_Targeting_Human 633 1|sg_Non_Targeting_Human_GA_0200|
Non_Targeting_Human AAGAGCGAATCGATTTCGTG Non_Targeting_Human 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 ACAAAGGTTGGAACAGAACC 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 CGTTGGCGATGATCTCCACG 643 3|sg_hHSPA5_CC_2|HSPA5
HSPA5 TGGCCTTTTCTACCTCGCGC 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
AGGCTGCGGCGCCCACGAGA 648 3|sg_hHSPA9_CC_3|HSPA9 HSPA9
ACTTTGACCAGGCCTTGCTA 649 3|sg_hHSPA9_CC_4|HSPA9 HSPA9
ACCTTCCATAACTGCCACGC 650 3|sg_hPAFAH1B1_CC_1|PAFAH1B1 PAFAH1B1
CGAGGCGTACATACCCAAGG 651 3|sg_hPAFAH1B1_CC_2|PAFAH1B1 PAFAH1B1
ATGGTACGGCCAAATCAAGA 652 3|sg_hPAFAH1B1_CC_3|PAFAH1B1 PAFAH1B1
TCTTGTAATCCCATACGCGT 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
GCAGTAGCGCTTCAGGCCCA 662 3|sg_hRPL9_CC_1|RPL9 RPL9
CAAATGGTGGGGTAACAGAA 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
TGAGGAGAAGGAACGGCTCA 667 3|sg_hSF3A3_CC_2|SF3A3 SF3A3
GGAAGAATGCAGAGTATAAG 668 3|sg_hSF3A3_CC_3|SF3A3 SF3A3
GGAATTTGAGGAACTCCTGA 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
GAATGAGTACACAGAACGGA 673 3|sg_hSF3B3_CC_4|SF3B3 SF3B3
GGAGCAGGACAAGGTCGGGG

Example 2—BRD9 Degrader Depletes BRD9 Protein

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

(66) 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.

(67) ##STR00875##

(68) 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 min, 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**).

(69) 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

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

(71) Procedures:

(72) 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 confluency over time using an IncuCyte live cell analysis system (FIG. **5**). Growth medium and compounds were refreshed every 3-4 days.

(73) 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.

(74) ##STR00876##

(75) 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 dH20 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**).

(76) 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 degarder, Compound 1, at indicated doses (FIG. **3**C). Media and compounds were changed every 5 d and cell colonies were imaged at day 14.

(77) 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).

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

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

(79) 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 μL 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.

(80) 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

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

(82) Procedure: SYO1 cells were treated for 8 or 13 days with DMSO, a BRD9 degrader (Compound 1) at 200 nM or 1 μM, 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.

(83) 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

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

(85) 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.

(86) 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).

Example 7—Preparation of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2,9-dimethyl-5H,6H,10H,11H, 11aH-pyrimido[4,3-a] 2,7-naphthyridine-1,8-dione (Compound B1)

(87) ##STR00877## ##STR00878##

Step 1: Preparation of 6-bromo-3-methyl-[1,2,4]triazolo[4,3-a]pyridin-8-amine (i-2)

(88) ##STR00879##

(89) A solution of 2-chloro-4-methylpyridine-3-carbonitrile (3.00 g, 19.662 mmol, 1.00 equiv) in DMF-DMA (120.00 mL, 896.257 mmol, 45.58 equiv) was stirred for 6 hours at 110° C. The resulting mixture was concentrated. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:1). This resulted in 3.4 g (83.27%) of 2-chloro-4-[(E)-2-(dimethylamino)ethenyl]pyridine-3-carbonitrile as a light yellow solid. LCMS (ESI) m/z: [M+H]+=208.

Step 2: Preparation of 8-chloro-1,2-dihydro-2,7-naphthyridin-1-one (i-3)

(90) ##STR00880##

(91) Into a 250-mL round-bottom flask, was placed 2-chloro-4-[(E)-2-(dimethylamino)ethenyl]pyridine-3-carbonitrile (3.40 g, 16.373 mmol, 1.00 equiv), H.sub.2SO.sub.4 (100.00 mL). The resulting solution was stirred for 2 hours at 110° C. The reaction was then quenched by the addition of 100 mL of water/ice. The pH of the solution was adjusted to pH>7 by addition of aqueous (aq.) K.sub.2CO.sub.3. The resulting solution was extracted with ethyl acetate (3×300 mL) and the organic layers combined and concentrated. This resulted in 2.7 g (91.32%) of 8-chloro-1,2-dihydro-2,7-naphthyridin-1-one as a light yellow solid. LCMS (ESI) m/z: [M+H]+=181.

Step 3: Preparation of 8-chloro-1,2-dihydro-2,7-naphthyridin-1-one (i-4)

(92) ##STR00881##
(93) To a solution of 8-chloro-1,2-dihydro-2,7-naphthyridin-1-one (2.20 g, 12.182 mmol, 1.00 equiv) in THE (120.00 mL) was added NaH (321.00 mg, 13.376 mmol, 1.10 equiv) and Mel (3.45 g, 24.306 mmol, 2.00 equiv). The resulting solution was stirred for 2 hours at room temperature. The reaction was then quenched by the addition of 100 mL of water and extracted with ethyl acetate (3×250 mL), and the organic layers were combined and concentrated. This resulted in 2 g (84.36%) of 8-chloro-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one as a light yellow solid. LCMS (ESI) m/z: [M+H]+=195.
Step 4: Preparation of 8-ethenyl-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (i-5)
(94) ##STR00882##
(95) To a solution of 8-chloro-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (2.0 g, 10.276 mmol, 1.00 equiv) in 1,4-dioxane (72.00 mL) and H.sub.2O (24.00 mL), was added Cs.sub.2CO.sub.3 (10.0 g, 30.727 mmol, 2.99 equiv) and 2-ethenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.2 g, 20.758 mmol, 2.02 equiv), Pd(dppf)Cl.sub.2.Math.CH.sub.2Cl.sub.2 (1.68 g, 2.055 mmol, 0.20 equiv) at 25° C. The resulting solution was stirred for 2 hours at 80° C. The resulting mixture was concentrated. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:1). This resulted in 980 mg (51.21%) of 8-ethenyl-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one as a light yellow solid. LCMS (ESI) m/z: [M+H]+=187.
Step 5: Preparation of 2-methyl-8-[2-(methylamino)ethyl]-1,2-dihydro-2,7-naphthyridin-1-one (i-6)
(96) ##STR00883##
(97) To a solution of 8-ethenyl-2-methyl-1, 2-dihydro-2, 7-naphthyridin-1-one (580 mg, 2.67 mmol, 1.00 equiv) in THE (2.00 mL) was added 4 M MeNH.sub.2 THF solution (20 mL) dropwise at 25° C. The resulting solution was stirred for 5 hours at 90° C. The reaction was cooled and concentrated, the crude product was purified by Flash-Prep-HPLC (Conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, acetonitrile (MeCN or ACN) in water, 10% to 50% gradient in 10 minutes; detector, UV 254 nm). This resulted in 480 mg (71.0%) of 2-methyl-8-[2-(methylamino) ethyl]-1, 2-dihydro-2, 7-naphthyridin-1-one as light yellow oil. LCMS (ESI) m/z: [M+H]+=218.
Step 6: Preparation of 2-methyl-8-[2-(methylamino)ethyl]-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (i-7)
(98) ##STR00884##
(99) To a solution of 2-methyl-8-[2-(methylamino)ethyl]-1,2-dihydro-2,7-naphthyridin-1-one (480.00 mg, 2.201 mmol, 1.00 equiv) in MeOH (10.00 mL) was added PtO.sub.2 (386.71 mg, 1.703 mmol, 0.74 equiv) under high pressure of H.sub.2 (22.0 atm) atmosphere at 25° C. The resulting solution was stirred for 12 hours at room temperature. The solids were filtered out. The filtrate was concentrated. This resulted in 350 mg crude of 2-methyl-8-[2-(methylamino)ethyl]-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one as light yellow oil, that was used directly without further purification. LCMS (ESI) m/z: [M+H]+=222.
Step 7: Preparation of 2,9-dimethyl-1H,2H,5H,6H,8H,9H,10H,11H,11aH-pyrimido[4,3-a]2,7-naphthyridine-1,8-dione (i-8)
(100) ##STR00885##
(101) To a solution of 2-methyl-8-[2-(methylamino)ethyl]-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (350.00 mg, 1.576 mmol, 1.00 equiv) in THE (3.00 mL) was added CDI (1,1′-carbonyldiimidazole) (511.0 mg, 3.153 mmol, 2.00 equiv) at room temperature. The resulting solution was stirred for 6 hours at 70° C. The mixture was concentrated. This resulted in 340 mg crude of 2,9-dimethyl-1H,2H,5H,6H,8H,9H,10H,11H,11 aH-pyrimido[4,3-a]2,7-naphthyridine-1,8-dione as light yellow oil, that was used directly without further purification. LCMS (ESI) m/z: [M+H]+=248.
Step 8: Preparation of 4-bromo-2,9-dimethyl-1H,2H,5H,6H,8H,9H,10H,11H,11aH-pyrimido[4,3-a]2,7-naphthyridine-1,8-dione (i-9)
(102) ##STR00886##
(103) To a solution of 2,9-dimethyl-1H,2H,5H,6H,8H,9H,1 OH, 11H,11 aH-pyrimido[4,3-a]2,7-naphthyridine-1,8-dione (340.00 mg, 1.371 mmol, 1.00 equiv) in HOAc (20.00 mL) was added NBS (732.1 mg, 4.113 mmol, 2.99 equiv) at room temperature. The resulting solution was stirred for 12 hours at room temperature. The mixture was concentrated. The crude product was purified by Flash-Prep-

HPLC (conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, MeCN/H.sub.2O=0 increasing to MeCN/H.sub.2O=100 within 30 minutes; Detector, 254 nm. This resulted in 385 mg of 4-bromo-2,9-dimethyl-1H,2H,5H,6H,8H,9H,10H,11H,11 aH-pyrimido[4,3-a]2,7-naphthyridine-1,8-dione as a light yellow solid. LCMS (ESI) m/z: [M+H]+=326.

Step 9: Preparation of 4-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-2,9-dimethyl-5,6,9,10,11,11a-hexahydro-1H-pyrimido[6,1-a][2,7]naphthyridine-1,8 (2H)-dione (Compound B1)

(104) ##STR00887##

(105) To a solution of 4-bromo-2,9-dimethyl-5H,6H,10H,11H,11 aH-pyrimido[4,3-a]2,7-naphthyridine-1,8-dione (110.00 mg, 0.337 mmol, 1.00 equiv) in Dioxane (4.00 mL) and H.sub.2O (1.00 mL) was added 4-[(dimethylamino)methyl]-3,5-dimethoxyphenylboronic acid (161.25 mg, 0.674 mmol, 2.00 equiv), Cs.sub.2CO.sub.3 (329.62 mg, 1.012 mmol, 3.00 equiv) and Pd(dppf)Cl.sub.2 (49.35 mg, 0.067 mmol, 0.20 equiv) at 25° C. The resulting solution was stirred for 12 hours at 80° C. The solids were filtered out. The filtrate was concentrated. The crude product was purified by Prep-HPLC with the following conditions: Column, SunFire Prep C18 OBD Column, 19, 150 mm 5 μm 10 nm; mobile phase, Water (0.1% FA) and ACN (3% Phase B up to 10% in 35 minutes); Detector, UV. This resulted in 12 mg (7.31%) of 4-(4-((dimethylamino) methyl)-3,5-dimethoxyphenyl)-2,9-dimethyl-5,6,9,10,11,11a-hexahydro-1H-pyrimido[6,1-a][2,7]naphthyridine-1,8 (2H)-dione formate as a light yellow semi-solid. .sup.1H NMR (300 MHz, Methanol-d4) δ 8.51 (s, 1.35H, FA), 7.66 (s, 1H), 6.74 (s, 2H), 4.75-4.46 (m, 2H), 4.38 (s, 2H), 3.96 (s, 6H), 3.64 (s, 3H), 3.61-3.50 (m, 1H), 3.29 (dd, J=5.3, 1.8 Hz, 1H), 2.99 (s, 4H), 2.89 (s, 6H), 2.85-2.73 (m, 1H), 2.70-2.54 (m, 1H), 2.39 (d, J=16.7 Hz, 1H), 1.73-1.49 (m, 1H). LCMS (ESI) m/z: [M+H]+=441.30.

Example 8—Preparation 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-3-carboxylic acid (Compound B2)

(106) ##STR00888## ##STR00889##

Step 1: Preparation of 5-bromo-2-chloro-N-methylpyridine-4-carboxamide (i-11)

(107) ##STR00890##

(108) To a solution of 5-bromo-2-chloropyridine-4-carboxylic acid (10 g, 42.292 mmol, 1 equiv) and methanamine (1.58 g, 50.751 mmol, 1.2 equiv) in solvent DCM (100 mL) was added HATU (24.12 g, 63.438 mmol, 1.5 equiv) and DIEA (27.33 g, 211.461 mmol, 5 equiv), The resulting solution was stirred at 25° C. for 2 hours. The resulting mixture was diluted with H.sub.2O (50 mL) and extracted with DCM (3×50 ml). The organic layers were dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (5:1) to afford 5-bromo-2-chloro-N-methylpyridine-4-carboxamide (8.3 g, 78.66%) as a white solid. LCMS (ESI) m/z: [M+H]+=248.9, 250.9.

Step 2: Preparation of 2-chloro-5-[(E)-2-ethoxyethenyl]-N-methylpyridine-4-carboxamide (i-12)

(109) ##STR00891##

(110) To a solution of 5-bromo-2-chloro-N-methylpyridine-4-carboxamide (8.00 g, 32.065 mmol, 1.00 equiv) and 2-[(E)-2-ethoxyethenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6.35 g, 32.065 mmol, 1.0 equiv) in dioxane (50.00 mL) and H.sub.2O (5.00 mL) was added Pd(dppf)Cl.sub.2 (2.35 g, 3.207 mmol, 0.1 equiv) and Cs.sub.2CO.sub.3 (20.90 g, 64.131 mmol, 2.0 equiv). The resulting solution was stirred at 90° C. for 2 hours under N.sub.2 atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (4:1) to afford 2-chloro-5-[(E)-2-ethoxyethenyl]-N-methylpyridine-4-carboxamide (5.4 g, 69.97%) as a yellow solid. LCMS (ESI) m/z: [M+H]+=241.1.

Step 3: Preparation of 7-chloro-2-methyl-1,2-dihydro-2,6-naphthyridin-1-one (i-13)

(111) ##STR00892##

(112) To a solution of 2-chloro-5-[(E)-2-ethoxyethenyl]-N-methylpyridine-4-carboxamide (5.40 g, 22.435 mmol, 1.00 equiv) in solvent TFA (20.00 mL) was refluxed at 100° C. for 3 hours. The mixture was basified with sodium bicarbonate saturated solution to pH 9. The resulting mixture was extracted with DCM (3×30 mL). The combined organic layers were washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA

(5:1) to afford 7-chloro-2-methyl-1,2-dihydro-2,6-naphthyridin-1-one (3.2 g, 73.29%) as a yellow solid. LCMS (ESI) m/z: [M+H]+=195.0.
Step 4: Preparation of methyl 6-methyl-5-oxo-5,6-dihydro-2,6-naphthyridine-3-carboxylate (i-14)
(113) ##STR00893##
(114) To a solution of 7-chloro-2-methyl-1,2-dihydro-2,6-naphthyridin-1-one (3.20 g, 16.442 mmol, 1.00 equiv) and Pd(dppf)Cl.sub.2 (2.41 g, 3.288 mmol, 0.2 equiv) in MeOH (30.00 mL) and TEA (5 mL) was refluxed at 100° C. for 15 hours under 20 atm CO atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (4:1) to afford methyl 6-methyl-5-oxo-5,6-dihydro-2,6-naphthyridine-3-carboxylate (1.8 g, 50.17%) as a yellow solid. LCMS (ESI) m/z: [M+H]+=219.1.
Step 5: Preparation of methyl 6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-3-carboxylate (i-15)
(115) ##STR00894##
(116) A solution of methyl 6-methyl-5-oxo-5,6-dihydro-2,6-naphthyridine-3-carboxylate (1.80 g, 8.249 mmol, 1.00 equiv) and PtO.sub.2 (0.94 g, 0.004 mmol, 0.5 equiv) in EtOH (20 mL) was stirred at 25° C. for 15 hours under 20 atm H.sub.2 atmosphere. The resulting mixture was concentrated under reduced pressure then purified by silica gel column chromatography, eluted with DCM/MeOH (10/1) to afford methyl 6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-3-carboxylate (960 mg, 52.37%) as a yellow solid. LCMS (ESI) m/z: [M+H]+=223.1.
Step 6: Preparation of 2-tert-butyl 3-methyl 6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-2,3-dicarboxylate (i-16)
(117) ##STR00895##
(118) A solution of methyl 6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-3-carboxylate (900.00 mg, 4.050 mmol, 1.00 equiv) and (Boc).sub.2O (2.65 g, 12.149 mmol, 3.0 equiv) in DCM (30.00 mL) was stirred at 25° C. for 1 hour. The resulting mixture was concentrated under reduced pressure then purified by silica gel column chromatography, eluted with PE/EA (5/1) to afford 2-tert-butyl 3-methyl 6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-2,3-dicarboxylate (760 mg, 58.22%) as a yellow solid. LCMS (ESI) m/z: [M+H]+=323.2.
Step 7: Preparation of 2-tert-butyl 3-methyl 8-bromo-6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-2,3-dicarboxylate (i-17)
(119) ##STR00896##
(120) A solution of 2-tert-butyl 3-methyl 6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-2,3-dicarboxylate (760.00 mg, 2.358 mmol, 1.00 equiv) and NBS (503.54 mg, 2.829 mmol, 1.20 equiv) in DCM (10.00 mL) was stirred at 25° C. for 2 hours. The resulting mixture was extracted with DCM (20 mL×3). The combined organic layers were washed with H.sub.2O and then dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure and purified by silica gel column chromatography, eluted with PE/EA (4/1) to afford 2-tert-butyl 3-methyl 8-bromo-6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-2,3-dicarboxylate (680 mg, 71.88%) as a yellow solid. LCMS (ESI) m/z: [M+H]+=401.1, 403.1.
Step 8: Preparation of 2-tert-butyl 3-methyl 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-2,3-dicarboxylate (i-18)
(121) ##STR00897##
(122) To a solution of 2-tert-butyl 3-methyl 8-bromo-6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-2,3-dicarboxylate (680.00 mg, 1.695 mmol, 1.00 equiv) and [4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl] boronic acid (607.74 mg, 2.542 mmol, 1.50 equiv) in dioxane (10.00 mL) and H.sub.2O (2.00 mL) was added Pd(dppf)Cl.sub.2 (248.00 mg, 0.339 mmol, 0.20 equiv) and Cs.sub.2CO.sub.3 (1656.48 mg, 5.084 mmol, 3.00 equiv). The resulting solution was stirred at 90° C. for 2 hours. The resulting mixture was concentrated under reduced pressure then purified by silica gel column chromatography, eluted with DCM/MeOH (10/1) to afford 2-tert-butyl 3-methyl 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-2,3-dicarboxylate (480 mg, 54.93%) as a yellow solid. LCMS (ESI) m/z: [M+H]+=516.3.

Step 9: Preparation of 2-[(tert-butoxy)carbonyl]-8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-3-carboxylic acid (i-19)
(123) ##STR00898##
(124) A solution of 2-tert-butyl 3-methyl 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-2,3-dicarboxylate (480.00 mg, 0.931 mmol, 1.00 equiv) and LiOH (44.59 mg, 1.862 mmol, 2.00 equiv) in solvent EtOH (20.00 mL) was stirred at 25° C. for 2 hours. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 10% to 20% gradient in 8 minutes; detector, UV 254 nm to afford 2-[(tert-butoxy)carbonyl]-8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-1,2,3,4, 5,6-hexahydro-2,6-naphthyridine-3-carboxylic acid (210 mg, 44.97%) as a yellow solid. LCMS (ESI) m/z: [M+H]+=502.2.
Step 10: Preparation of 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-3-carboxylic acid (Compound B2)
(125) ##STR00899##
(126) 2-[(tert-butoxy)carbonyl]-8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-3-carboxylic acid (30.00 mg, 0.060 mmol, 1.00 equiv) was added to 4 M HCl 1,4-dioxane solution (5.00 mL), and the resulting solution was stirred at 25° C. for 1 hour. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 10% to 50% gradient in 30 minutes; detector, UV 254 nm to afford 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-3-carboxylic acid (18 mg, 74.96%) as a yellow solid. .sup.1H NMR (400 MHz, Methanol-d4) δ 7.71 (s, 1H), 6.74 (s, 2H), 4.55-4.26 (m, 4H), 4.07 (d, J=16.9 Hz, 1H), 3.96 (s, 6H), 3.66 (s, 3H), 3.47-3.34 (m, 1H), 2.90 (m, 7H). LCMS (ESI) m/z: [M+H]+=402.25.
Example 9—Preparation of and 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N,6-dimethyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-3-carboxamide and 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-3-carboxamide (Compounds B3 and B4)
(127) ##STR00900##
Preparation of 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N,6-dimethyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-3-carboxamide (Compound B3)
(128) ##STR00901##
(129) 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-3-carboxylic acid (30.00 mg, 0.075 mmol, 1.00 equiv), HATU (42.62 mg, 0.112 mmol, 1.50 equiv), and methyl amine (4.64 mg, 0.149 mmol, 2.00 equiv), and diisopropylethylamine (57.9 mg, 0.448 mmol, 6.00 equiv) were dissolved in DCM (5.0 mL). The resulting solution was stirred at 25° C. for 3 hours. The crude product was purified by Prep-HPLC (conditions: C18 silica gel; mobile phase, MeCN in water, 10% to 50% gradient in 30 minutes; detector, UV 254 nm) to afford 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N,6-dimethyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-3-carboxamide (6.8 mg, 22%) as a yellow solid. .sup.1H NMR (400 MHz, Methanol-d4) δ 7.50 (s, 1H), 6.62 (s, 2H), 3.88 (s, 6H), 3.85-3.69 (m, 4H), 3.63 (s, 3H), 3.52 (dd, J=10.4, 4.8 Hz, 1H), 2.96 (dd, J=17.5, 4.7 Hz, 1H), 2.81 (s, 3H), 2.55 (dd, J=17.7, 10.4 Hz, 1H), 2.42 (s, 6H). LCMS (ESI) m/z: [M+H]+=415.30.
Preparation of 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-3-carboxamide (Compound B4)
(130) ##STR00902##
(131) 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-3-carboxylic acid (30.00 mg, 0.075 mmol, 1.00 equiv), HATU (42.62 mg, 0.112 mmol and 1.50 equiv), DIEA (57.95 mg, 0.448 mmol, 6.00 equiv) were dissolved in DCM (5.00 mL). Then NH.sub.3 (2.55 mg, 0.149 mmol, 2.00 equiv) in DCM was added to the reaction, and the resulting solution was stirred at 25° C. for 3 hours. The crude product (30 mg) was purified by Prep-HPLC (conditions: C18 silica gel; mobile phase, MeCN in water, 10% to 50% gradient in 30 minutes; detector, UV 254 nm) to afford 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-1,2,3,4,5,6-

hexahydro-2,6-naphthyridine-3-carboxamide (4.7 mg, 15.71%) as a yellow solid. .sup.1H NMR (400 MHz, Methanol-d4) δ 7.50 (s, 1H), 6.59 (s, 2H), 3.86 (s, 6H), 3.83-3.66 (m, 4H), 3.63 (s, 3H), 3.57 (dd, J=10.4, 4.8 Hz, 1H), 3.05-2.94 (m, 1H), 2.58 (dd, J=17.8, 10.3 Hz, 1H), 2.32 (s, 6H). LCMS (ESI) m/z: [M+H]+=401.30.

Example 10—Preparation of 5-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-N-ethyl-7-methyl-8-oxo-3,4,7,8-tetrahydro-2,7-naphthyridine-2 (1H)-carboxamide (Compound B5)

(132) ##STR00903##

(133) Using the same procedure as for the synthesis of Compound B9 and substituting with ethyl isocyanate afforded 5-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-N-ethyl-7-methyl-8-oxo-3,4,7,8-tetrahydro-2,7-naphthyridine-2 (1H)-carboxamide (18.8 mg, 521% yield) as a white solid. .sup.1H NMR (400 MHz, DMSO-d6) δ 7.61 (s, 1H), 6.61 (t, J=5.4 Hz, 1H), 6.55 (s, 2H), 4.19 (s, 2H), 3.75 (s, 5H), 3.47 (s, 3H), 3.43-3.34 (m, 4H), 3.11-2.97 (m, 2H), 2.09 (s, 6H), 1.00 (t, J=7.1 Hz, 3H). LCMS (ESI) m/z: [M+H].sup.+=429.2.

Example 11—Preparation of 5-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-N,N,7-trimethyl-8-oxo-3,4,7,8-tetrahydro-2,7-naphthyridine-2 (1H)-carboxamide (Compound B6)

(134) ##STR00904##

(135) To a solution of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (30 mg, 83.9 μmol, 1 equiv) in DCM (1 mL) was added triethylamine (15.1 μL, 109 μmol, 1.3 equiv) and N,N-dimethylcarbamoyl chloride (8.48 μL, 92.2 μmol, 1.1 equiv) at RT. The reaction was stirred at RT for 2 hours. The reaction mixture was concentrated in vacuo. The crude was purified by flash chromatography eluting with 0-15% MeOH with 0.1% NH.sub.4OH in DCM to afford 5-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-N,N,7-trimethyl-8-oxo-3,4,7,8-tetrahydro-2,7-naphthyridine-2 (1H)-carboxamide (5.2 mg, 14.5 yield) as a white solid. .sup.1H NMR (400 MHz, Chloroform-d) δ 7.14 (s, 1H), 6.40 (s, 2H), 4.33 (s, 2H), 3.83 (s, 6H), 3.58 (s, 3H), 3.58 (m, 2H), 3.37 (t, J=5.6 Hz, 2H), 2.89 (s, 5H), 2.63-2.52 (m, 2H), 1.25 (s, 6H). LCMS (ESI) m/z: [M+H].sup.+=429.2.

Example 12—Preparation of N-butyl-5-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-7-methyl-8-oxo-3,4,7,8-tetrahydro-2,7-naphthyridine-2 (1H)-carboxamide (Compound B7

(136) ##STR00905##

(137) Using the same procedure as for the synthesis of Compound B9 and substituting with 1-isocyanatobutane afforded N-butyl-5-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-7-methyl-8-oxo-3,4,7,8-tetrahydro-2,7-naphthyridine-2 (1H)-carboxamide (18.8 mg, 49% yield) as a white solid. .sup.1H NMR (400 MHz, Chloroform-d) δ 7.18 (s, 1H), 6.37 (s, 2H), 4.68 (t, J=5.5 Hz, 1H), 4.28 (s, 2H), 3.82 (s, 6H), 3.61 (s, 3H), 3.61 (m, 2H), 3.53 (s, 1H), 3.28 (td, J=7.1, 5.3 Hz, 2H), 2.57 (t, J=5.6 Hz, 2H), 2.30 (s, 6H), 1.59-1.45 (m, 9H), 1.43-1.30 (m, 2H), 0.93 (t, J=7.3 Hz, 3H). LCMS (ESI) m/z: [M+H].sup.+=457.2.

Example 13—Preparation of N-cyclopropyl-5-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-7-methyl-8-oxo-3,4,7,8-tetrahydro-2,7-naphthyridine-2 (1H)-carboxamide (Compound B8)

(138) ##STR00906##

(139) Using the same procedure as for the synthesis of Compound B9 and substituting with cyclopropyl isocyanate afforded N-cyclopropyl-5-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-7-methyl-8-oxo-3,4,7,8-tetrahydro-2,7-naphthyridine-2 (1H)-carboxamide (7.8 mg, 21% yield) as a white solid. .sup.1H NMR (400 MHz, Chloroform-d) δ 7.18 (s, 1H), 6.37 (s, 2H), 4.93 (d, J=1.9 Hz, 1H), 4.23 (s, 2H), 3.82 (s, 6H), 3.60 (d, J=2.2 Hz, 5H), 3.54 (s, 2H), 2.70 (ddd, J=6.9, 4.6, 2.7 Hz, 1H), 2.56 (t, J=5.7 Hz, 2H), 2.31 (s, 6H), 1.25 (s, 6H), 0.79-0.69 (m, 2H), 0.56-0.38 (m, 2H). LCMS (ESI) m/z: [M+H].sup.+=441.2.

Example 14—Preparation of 5-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4,7,8-tetrahydro-2,7-naphthyridine-2 (1H)-carboxamide (Compound B9)

(140) ##STR00907##

(141) To a solution of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (20 mg, 55.9 μmol, 1 equiv) in anhydrous DCM (1 mL) was added N-methyl-1H-imidazole-1-carboxamide (7.7 mg, 61.4 μmol, 1.1 equiv) and triethylamine (10 μL, 72.6

μmol, 1.3 equiv). The reaction mixture was stirred at room temperature for 3 hours and concentrated in vacuo. The crude was purified by flash chromatography eluting with 0-15% MeOH w 0.1% NH.sub.4OH in DCM to afford 5-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4,7,8-tetrahydro-2,7-naphthyridine-2 (1H)-carboxamide (4.0 mg, 18% yield) as a white solid. .sup.1H NMR (400 MHz, DMSO-d6) δ 7.60 (s, 1H), 6.55 (s, 2H), 6.54 (bs, 1H), 4.19 (s, 2H), 3.75 (s, 6H), 3.47 (s, 3H), 3.39 (dd, J=12.4, 7.0 Hz, 4H), 2.57 (d, J=4.3 Hz, 3H), 2.48 (m, 2H), 2.10 (s, 6H). LCMS (ESI) m/z: [M+H].sup.+=415.3.

Example 15—Preparation of N-(6-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-3-methyl-[1,2,4]triazolo[4,3-a]pyridin-8-yl)acetamide (Compound B10)

(142) ##STR00908##

Step 1: Preparation of 4-bromo-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (i-21)

(143) ##STR00909##

(144) To a solution of 4-bromo-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (238 mg, 0.996 mmol, 1 equiv) in AcOH (2.0 mL) was added NaBH.sub.4 (263.64 mg, 6.969 mmol, 7 equiv). The mixture was stirred at 0° C. for 1 hour. Ammonium hydroxide was added to the resulting mixture until pH above 7, and then the resulting mixture was extracted with DCM (30 mL×3). The combined organic layers were dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (10:1) to afford 4-bromo-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (180 mg, 74.38%) as a white solid. LCMS (ESI) m/z: [M+H].sup.+=243.

Step 2: Preparation of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (i-22)

(145) ##STR00910##

(146) To a solution of 4-bromo-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (242 mg, 0.995 mmol, 1 equiv) and [4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]boronic acid (237.99 mg, 0.995 mmol, 1 equiv) in dioxane (5 mL) and H.sub.2O (0.5 mL) was added Pd(dppf)Cl.sub.2 (72.84 mg, 0.100 mmol, 0.1 equiv) and Cs.sub.2CO.sub.3 (973.02 mg, 2.986 mmol, 3.0 equiv). The resulting solution was stirred at 90° C. for 2 hours under N.sub.2. The mixture was diluted with 50 mL of H.sub.2O, and the resulting mixture was extracted with DCM (30 mL×3). The combined organic layers were dried over sodium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (10:1) to afford 4-[4-[(dimethylamino) methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (200 mg, 56.21%) as a yellow solid. LCMS (ESI) m/z: [M+H].sup.+=358.

Step 3: Preparation of 7-[2-[(tert-butyldimethylsilyl)oxy]ethyl]-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (i-23)

(147) ##STR00911##

(148) To a solution of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (200 mg, 0.560 mmol, 1 equiv) and 2-[(tert-butyldimethylsilyl)oxy]acetaldehyde (146.30 mg, 0.839 mmol, 1.5 equiv) in MeOH (5 mL) was added NaBH.sub.3CN (105.48 mg, 1.679 mmol, 3.0 equiv). The mixture was stirred at 25° C. for 1 hour. Then the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:1) to afford 7-[2-[(tert-butyldimethylsilyl)oxy]ethyl]-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (224 mg, 77.5%) as a brown oil. LCMS (ESI) m/z: [M+H].sup.+=516.

Step 4: Preparation of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-(2-hydroxyethyl)-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (Compound B10)

(149) ##STR00912##

(150) To a solution of 7-[2-[(tert-butyldimethylsilyl)oxy]ethyl]-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (90 mg, 0.174 mmol, 1 equiv) was dissolved in ACN (2.0 mL) was added TBAF (91.25 mg, 0.349 mmol, 2.0 equiv). The resulting solution was stirred at 25° C. for 1 hour. The mixture was concentrated under reduced pressure. The residue was purified by Prep-(conditions: column, Xselect Peptide CSH 19*150 mm 5 μm; Mobile

Phase A: Water (0.1% FA), Mobile Phase B: MeOH-HPLC; Flow rate: 25 mL/minute; Gradient: 15% B to 15% B in 12 minutes; 220 nm; R.sub.t: 9.51 minutes; detector, UV 254 nm) to afford gave 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-(2-hydroxyethyl)-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (10 mg, 14.27%) as a yellow solid. .sup.1H NMR (300 MHz, Methanol-d4) δ 7.51 (s, 1H), 6.61 (s, 2H), 3.87 (s, 6H), 3.83-3.72 (m, 4H), 3.60 (d, J=14.7 Hz, 5H), 2.79-2.68 (m, 6H), 2.37 (s, 6H). LCMS (ESI) m/z: [M+H]+=402.40.

Example 16—Preparation of Ethyl 5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-1,2,3,4,7,8-hexahydro-2,7-naphthyridine-2-carboxylate (Compound B11)

(151) ##STR00913##

Step 1: Preparation of 4-Bromo-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (i-25)

(152) ##STR00914##

(153) To a solution of 4-bromo-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (500 mg, 2.091 mmol, 1 equiv) in AcOH (4.20 mL) was added NaBH.sub.4 (553.87 mg, 14.640 mmol, 7 equiv) at 0° C. The resulting solution was stirred at 0° C. for 1 hour. Ammonia was added to the resulting mixture until pH above 7. Then the mixture was diluted with water (10 mL) and extracted with DCM (30 mL×3). The combined organic layers were dried over saturated sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (10:1) to afford 4-bromo-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (520 mg, 74.38%) as a white solid. LCMS (ESI) m/z: [M+H].sup.+=243.

Step 2: Preparation of ethyl 5-bromo-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxylate (i-26)

(154) ##STR00915##

(155) To a solution of 4-bromo-2-methyl-5,6,7,8-tetrahydro-2,7-naphthyridin-1-one (100.00 mg, 0.411 mmol, 1.00 equiv) in (5.00 mL) was added NaH (19.74 mg, 0.494 mmol, 1.20 equiv, 60%). Then ethyl chloroformate (66.96 mg, 0.617 mmol, 1.50 equiv) was added at 0° C. The resulting mixture was stirred for 2 hours at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EtOAc 5:1) to afford ethyl 5-bromo-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxylate (120 mg, 92.56%) as a yellow solid. LCMS (ESI) m/z: [M+H].sup.+=315.

Step 3: Preparation of ethyl 5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-1,2,3,4,7,8-hexahydro-2,7-naphthyridine-2-carboxylate (Compound B11)

(156) ##STR00916##

(157) To a solution of ethyl 5-bromo-7-methyl-8-oxo-1,2,3,4,7,8-hexahydro-2,7-naphthyridine-2-carboxylate (96 mg, 0.305 mmol, 1 equiv) and [4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]boronic acid (72.82 mg, 0.305 mmol, 1 equiv) in dioxane (2 mL) and H.sub.2O (0.5 mL) was added Cs.sub.2CO.sub.3 (297.73 mg, 0.914 mmol, 3 equiv) and Pd(dppf)Cl.sub.2 (33.43 mg, 0.046 mmol, 0.15 equiv). The resulting solution was stirred at 90° C. for 2 hours (under N.sub.2 atmosphere). The resulting mixture was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (conditions: XBridge Shield RP18 OBD Column, 5 μm, 19*150 mm; Mobile Phase A: Water (0.05% NH.sub.3/H.sub.2O), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 24% B to 37% B in 8 minutes; 220 nm; Rt: 7.9 minutes) to afford ethyl 5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-1,2,3,4,7,8-hexahydro-2,7-naphthyridine-2-carboxylate (8.2 mg, 6.09%) as a light brown solid. .sup.1H NMR (300 MHz, Methanol-d4) δ 7.56 (s, 1H), 6.61 (s, 2H), 4.47 (s, 2H), 4.20 (q, J=7.1 Hz, 2H), 3.87 (s, 6H), 3.71 (s, 2H), 3.62 (d, J=8.9 Hz, 5H), 2.65 (t, J=5.8 Hz, 2H), 2.34 (s, 6H), 1.31 (t, J=7.1 Hz, 3H). LCMS (ESI) m/z: [M+H].sup.+=430.20.

Example 17—Preparation of 4-(3,5-dimethoxy-4-methylphenyl)-2-methyl-7-propanoyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (Compound B12)

(158) ##STR00917##

Step 1: Preparation of 4-bromo-2-methyl-7-propanoyl-6,8-dihydro-5H-2,7-naphthyridin-1-one (i-28)

(159) ##STR00918##

(160) To a stirred mixture of 4-bromo-2-methyl-5,6,7,8-tetrahydro-2,7-naphthyridin-1-one (500.00 mg,

2.057 mmol, 1.00 equiv) and propanoic acid (182.83 mg, 2.468 mmol, 1.20 equiv) in DCM (25.00 mL) was added DIEA (79.75 mg, 0.617 mmol, 3.00 equiv). The mixture was stirred at room temperature for 5 minutes, then HATU (938.44 mg, 2.468 mmol, 1.20 equiv) was added. The mixture was stirred for 2 hours at room temperature, and the resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH.sub.2Cl.sub.2/MeOH (20:1) to afford 4-bromo-2-methyl-7-propanoyl-6,8-dihydro-5H-2,7-naphthyridin-1-one (502 mg, 78.88%) as a white solid.

Step 2: Preparation of 4-(3,5-dimethoxy-4-methylphenyl)-2-methyl-7-propanoyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (Compound B12)

(161) ##STR00919##

(162) To a solution of 4-bromo-2-methyl-7-propanoyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (200 mg, 0.669 mmol, 1 equiv) and [4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]boronic acid (191.80 mg, 0.802 mmol, 1.20 equiv) in dioxane (10 mL) and H.sub.2O (1 mL) was added Cs.sub.2CO.sub.3 (653.45 mg, 2.006 mmol, 3.00 equiv) and Pd(dppf)Cl.sub.2.Math.CH.sub.2Cl.sub.2 (49.13 mg, 0.060 mmol, 0.09 equiv). After stirring for 2 hours at 90° C. under a nitrogen atmosphere, the resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (10/1) to afford 4-(3,5-dimethoxy-4-methylphenyl)-2-methyl-7-propanoyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (130 mg, 51.44%). .sup.1H NMR (400 MHz, Methanol-d4) δ 7.61 (d, J=10.5 Hz, 1H), 6.75 (d, J=6.3 Hz, 2H), 4.56 (d, J=14.2 Hz, 1H), 4.39 (s, 2H), 3.96 (d, J=2.6 Hz, 6H), 3.76-3.57 (m, 5H), 2.90 (s, 6H), 2.72 (d, J=6.1 Hz, 1H), 2.64 (s, 1H), 2.53 (dq, J=15.0, 7.5 Hz, 1H), 1.31 (s, 1H), 1.17 (td, J=7.5, 3.8 Hz, 3H). LCMS (ESI) m/z: [M+H]+=414.30.

Example 18—Preparation of 7-acetyl-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (Compound B13)

(163) ##STR00920##

(164) To a stirred solution of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (45.4 mg, 0.127 mmol, 1 equiv) in DCM (3 mL) was added isocyanatotrimethylsilane (29.26 mg, 0.254 mmol, 2 equiv) and TEA (38.56 mg, 0.381 mmol, 3 equiv). The resulting mixture was stirred for 2 hours at room temperature. The crude product was purified by Prep-HPLC (conditions: XBridge Prep Phenyl OBD Column 5 μm, 19*250 mm; Mobile Phase A: Water (10 mmol/L NH.sub.4HCO.sub.3), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 14% B to 20% B in 8 minutes; 254 nm; R.sub.t: 7.18 minutes) to afford 5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-1,2,3,4,7,8-hexahydro-2,7-naphthyridine-2-carboxamide (6.6 mg, 12.35%) as a white solid. .sup.1H NMR (400 MHz, MeOD) δ 7.57 (s, 1H), 6.61 (s, 2H), 4.41 (s, 2H), 3.87 (s, 6H), 3.68 (s, 2H), 3.64 (s, 3H), 3.55 (t, 2H), 2.68-2.65 (m, 2H), 2.31 (s, 6H). LCMS (ESI) m/z: [M+H]+=401.4.

Example 19—Preparation of 7-acetyl-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (Compound B14)

(165) ##STR00921##

(166) To the solution of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (35.7 mg, 0.100 mmol, 1 equiv) in DCM (3 mL) was added acetic acid (7.20 mg, 0.120 mmol, 1.2 equiv), HATU (56.96 mg, 0.150 mmol, 1.5 equiv), and DIEA (38.72 mg, 0.300 mmol, 3 equiv). The resulting solution was stirred at room temperature for 1 hour. The resulting solution was concentrated. The crude product was purified by Prep-HPLC (conditions: XBridge Shield RP18 OBD Column, 5 μm, 19*150 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 0% B to 15% B in 8 minutes; 254/220 nm; R.sub.t: 7.03 minutes) to afford 7-acetyl-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (7.3 mg, 17.64%) as a white solid. .sup.1H NMR (400 MHz, MeOD) δ 7.58 (d, 1H), 6.61 (d, 2H), 4.55 (d, 2H), 3.87 (d, 6H), 3.75-3.67 (m, 3H), 3.64 (d, 4H), 2.74 (t, 1H), 2.64 (t, 1H), 2.33 (d, 6H), 2.22 (d, 3H). LCMS (ESI) m/z: [M+H]+=400.25.

Example 20—Preparation of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-ethyl-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one formic acid (Compound B15 formic acid)

(167) ##STR00922##
(168) To the solution of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (20 mg, 0.056 mmol, 1 equiv) in MeOH (2 mL) was added acetaldehyde (24.65 mg, 0.560 mmol, 10 equiv) and NaBH.sub.3CN (10.55 mg, 0.168 mmol, 3 equiv). The resulting solution was stirred at room temperature for 1 hour. The resulting solution was concentrated. The crude product was purified by Prep-HPLC (conditions: XBridge Shield RP18 OBD Column, 5 μm, 19*150 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 0% B to 15% B in 8 minutes; 254/220 nm; R.sub.t: 7.03 minutes) to afford 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-ethyl-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one formic acid (10.1 mg) as a white oil. .sup.1H NMR (400 MHz, Methanol-d4) δ 8.47 (s, 1H), 7.59 (s, 1H), 6.73 (s, 2H), 4.38 (s, 2H), 3.96 (s, 6H), 3.74 (s, 2H), 3.64 (s, 3H), 2.89 (s, 1 OH), 2.76 (t, J=5.8 Hz, 2H), 1.31 (t, J=7.2 Hz, 3H). LCMS (ESI) m/z: [M+H].sup.+=386.30.
Example 21—Preparation of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2,7-dimethyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one formic acid (Compound B16 formic acid)
(169) ##STR00923##
(170) To the solution of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (20 mg, 0.056 mmol, 1 equiv) in MeOH (2 mL) was added formaldehyde (16.80 mg, 0.560 mmol, 10 equiv), NaBH.sub.3CN (10.55 mg, 0.168 mmol, 3 equiv). The resulting solution was stirred at room temperature for 1 hour. The resulting solution was concentrated. The crude product was purified by Prep-HPLC (conditions: XBridge Shield RP18 OBD Column, 5 μm, 19*150 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 0% B to 15% B in 8 minutes; 254/220 nm; R.sub.t: 7.12 minutes) to afford 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2,7-dimethyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one formic acid (10.8 mg) as a white oil. .sup.1H NMR (400 MHz, Methanol-d4) δ 8.48 (s, 1H), 7.58 (s, 1H), 6.73 (s, 2H), 4.38 (s, 2H), 3.96 (s, 6H), 3.67 (s, 2H), 3.63 (s, 3H), 2.89 (s, 6H), 2.84 (t, J=5.7 Hz, 2H), 2.75 (d, J=5.8 Hz, 2H), 2.66 (s, 3H). LCMS (ESI) m/z: [M+H].sup.+=372.25.
Example 22—Preparation of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (Compound B17)
(171) ##STR00924##
Step 1: Preparation of 2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-2,7-naphthyridin-1-one (i-30)
(172) ##STR00925##
(173) To the solution of 4-bromo-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (2.7 g, 11.294 mmol, 1 equiv) in dioxane (15 mL) was added 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (3.44 g, 13.552 mmol, 1.2 equiv), Pd(dppf)Cl.sub.2 (0.83 g, 1.129 mmol, 0.1 equiv), and AcOK (3.33 g, 33.881 mmol, 3 equiv). The resulting solution was stirred at 90° C. for 2 hours under nitrogen atmosphere. The resulting solution was concentrated. The residue was purified by Flash column chromatography with EtOAc/PE (0-100%) to afford 2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-2,7-naphthyridin-1-one (1.62 g, 50.13%) as light yellow solid. LCMS (ESI) m/z: [M+H]+=287.
Step 2: Preparation of 2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzaldehyde (i-31)
(174) ##STR00926##
(175) To the solution of 2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-2,7-naphthyridin-1-one (1.62 g, 5.662 mmol, 1 equiv) in dioxane (30 mL) was added 4-bromo-2,6-dimethoxybenzaldehyde (1.39 g, 5.662 mmol, 1 equiv), Pd(dppf)Cl.sub.2 (414.26 mg, 0.566 mmol, 0.1 equiv), Cs.sub.2CO.sub.3 (5.53 g, 16.985 mmol, 3 equiv), H.sub.2O (3 mL). The resulting solution was stirred at 90° C. for 2 hours under nitrogen atmosphere. The solution was concentrated. The residue was purified by Flash column chromatography with EtOAc/PE (0-100%) to give compound 2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzaldehyde (1.02 g, 55.55%) as yellow solid. LCMS (ESI) m/z: [M+H]+=325.
Step 3: Preparation of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2-dihydro-2,7-

naphthyridin-1-one (i-32)
(176) ##STR00927##
(177) To the solution of 2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzaldehyde (1.20 g, 3.700 mmol, 1.00 equiv) in MeOH (10.00 mL) was added dimethylamine (362.02 mg, 4.440 mmol, 1.20 equiv) and NaBH.sub.3CN (697.52 mg, 11.100 mmol, 3.00 equiv). The resulting solution was stirred at room temperature for 2 hours. The residue was purified by silica gel column chromatography, eluted with CH.sub.2Cl.sub.2/MeOH (20:1) to afford 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (1 g, 76.48%) as a yellow solid. LCMS (ESI) m/z: [M+H]+=354.
Step 4: Preparation of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (Compound B17)
(178) ##STR00928##
(179) To a stirred solution of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (1 g, 2.829 mmol, 1 equiv) in MeOH (15 mL) was added PtO.sub.2 (1 g, 4.404 mmol, 1.56 equiv). The resulting mixture was stirred for 6 hours at room temperature under hydrogen atmosphere. The resulting mixture was filtered, the filter cake was washed with methanol (3×100 mL). The filtrate was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (conditions: XBridge 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: 15% B to 35% B in 8 minutes; 254/220 nm; R.sub.t: 5.35 minutes) to afford 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (27.2 mg, 2.59%) as a light yellow solid. .sup.1H NMR (400 MHz, DMSO-d6) δ 7.54 (s, 1H), 6.55 (s, 2H), 3.77 (s, 6H), 3.60 (s, 2H), 3.46 (s, 3H), 3.36 (s, 3H), 2.80 (s, 2H), 2.40 (s, 2H), 2.11 (s, 6H). LCMS (ESI) m/z: [M+H].sup.+=358.30.
Example 23—Preparation of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (Compound B17)
(180) ##STR00929##
Step 1: Preparation of 4-bromo-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (i-34)
(181) ##STR00930##
(182) To a solution of 4-bromo-1,2-dihydro-2,7-naphthyridin-1-one (4.96 g, 22.040 mmol, 1 equiv) and NaH (0.74 g, 30.856 mmol, 1.40 equiv) in DMF (30 mL, 387.653 mmol, 17.59 equiv) was added iodomethane (8.95 g, 63.035 mmol, 2.86 equiv). The resulting solution was stirred at 0° C. for 2 hours under N.sub.2 atmosphere. The resulting mixture was filtered, and the filter cake was washed with ice water to afford 4-bromo-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (4.5 g, 76.86%), which was used directly without further purification. LCMS (ESI) m/z: [M+H]+=239.0, 241.0.
Step 2: Preparation of 4-bromo-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (i-35)
(183) ##STR00931##
(184) NaBH.sub.4 (4.43 g, 117.120 mmol, 7 equiv) was slowly added to a solution of 4-bromo-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (4.00 g, 16.731 mmol, 1.00 equiv) in AcOH (20.00 mL). The resulting solution was stirred at 0° C. for 1 hour. Ammonia was added to the resulting mixture until pH above 7. Then the resulting mixture was extracted with DCM (3×30 mL). The combined organic layers were dried over by saturated sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (10:1) to afford 4-bromo-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (2.2 g, 52.64%) as a yellow solid. LCMS (ESI) m/z: [M+H]+=243.0, 245.0.
Step 3: Preparation of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (Compound B17)
(185) ##STR00932##
(186) To a solution of 4-bromo-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (2.00 g, 8.227 mmol, 1.00 equiv) and [4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]boronic acid (1.97 g, 8.227 mmol, 1.00 equiv) in dioxane (30 mL) and H.sub.2O (6 mL) was added Pd(dppf)Cl.sub.2 (0.60 g, 0.823 mmol, 0.1 equiv) and Cs.sub.2CO.sub.3 (8.04 g, 24.681 mmol, 3.0 equiv). The resulting solution was stirred at 90° C. for 2 hours under N.sub.2 atmosphere. The residue was purified by reverse flash

chromatography (conditions: column, C18 silica gel; mobile phase, MeOH in water, 10% to 50% gradient in 30 minutes; detector, UV 254 nm) to afford 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (1.54 g, 52.21%) as a yellow solid. .sup.1H NMR (300 MHz, Methanol-d4) δ 7.50 (s, 1H), 6.59 (s, 2H), 3.88 (s, 1H), 3.86 (s, 6H), 3.81 (s, 2H), 3.64 (d, J=14.9 Hz, 5H), 3.63 (s, 1H), 3.55 (s, 1H), 2.99 (dt, J=25.5, 5.8 Hz, 2H), 2.60 (dt, J=27.3, 5.7 Hz, 2H), 2.30 (s, 6H). LCMS (ESI) m/z: [M+H]+=358.25.

Example 24—Preparation of 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N,6-dimethyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide (Compound B18)

(187) ##STR00933##

Step 1: Preparation of 4-bromo-2H-2,6-naphthyridin-1-one (i-37)

(188) ##STR00934##

(189) To a stirred solution of 2H-2,6-naphthyridin-1-one (584.00 mg, 3.996 mmol, 1.00 equiv) in DCM (10.00 mL) was added NBS (640.09 mg, 3.596 mmol, 0.9 equiv) in portions at room temperature under air atmosphere. The mixture was stirred for another 1 hour. The reaction mixture was concentrated and purified by silica gel column chromatography, eluted with CH.sub.2Cl.sub.2/MeOH (10:1) to afford 4-bromo-2H-2,6-naphthyridin-1-one (1.2 g, 86.74%) as a light yellow solid. LCMS (ESI) m/z: [M+H]+=225, 227.

Step 2: Preparation of 4-bromo-2-methyl-2,6-naphthyridin-1-one (i-38)

(190) ##STR00935##

(191) To a stirred solution of 4-bromo-2H-2,6-naphthyridin-1-one (600.00 mg, 2.666 mmol, 1.00 equiv) in DMF (15.00 mL) was added NaH (127.96 mg, 5.332 mmol, 2 equiv) in portions at 0° C. under nitrogen atmosphere. Then MeI (1513.71 mg, 10.665 mmol, 4 equiv) was added drop-wise. The mixture was stirred for another 1 hour at room temperature and quenched with water at 0° C. The product was precipitated by the addition of water. The precipitated solids were collected by filtration and washed with water (2×20 mL). The crude product 4-bromo-2-methyl-2,6-naphthyridin-1-one (369 mg, 57.89%) was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H]+=239, 241.

Step 3: Preparation of 4-bromo-2-methyl-5,6,7,8-tetrahydro-2,6-naphthyridin-1-one (i-39)

(192) ##STR00936##

(193) To a stirred solution of 4-bromo-2-methyl-2,6-naphthyridin-1-one (119.50 mg, 0.500 mmol, 1.00 equiv) in AcOH (5.00 mL) was added NaBH.sub.4 (132.38 mg, 3.499 mmol, 7.00 equiv) in portions at 0° C. under nitrogen atmosphere. The resulting mixture was stirred for 5 minutes at room temperature. Then, the mixture was poured into ice water, basified with ammonium hydroxide, and extracted with CH.sub.2Cl.sub.2 (3×50 mL). The combined organic layers were concentrated under reduced pressure and the resulting crude product 4-bromo-2-methyl-5, 6, 7, 8-tetrahydro-2,6-naphthyridin-1-one (128 mg, 87.43%) was used directly in the next step. LCMS (ESI) m/z: [M+H]+=243, 245.

Step 4: Preparation of 8-bromo-N,6-dimethyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide (i-40)

(194) ##STR00937##

(195) To a stirred solution of 4-bromo-2-methyl-5,6,7,8-tetrahydro-2,6-naphthyridin-1-one (128.00 mg, 0.527 mmol, 1.00 equiv) and N-methylimidazole-1-carboxamide (79.06 mg, 0.632 mmol, 1.20 equiv) in DCM (2.00 mL) was added Et.sub.3N (532.79 mg, 5.265 mmol, 10 equiv). The resulting mixture was stirred for 2 hours at room temperature under air atmosphere. The mixture was concentrated and purified by silica gel column chromatography, eluted with CH.sub.2Cl.sub.2/MeOH (12:1) to afford 8-bromo-N,6-dimethyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide (153 mg, 80.35%). LCMS (ESI) m/z: [M+H]+=300, 302.

Step 5: Preparation of 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N,6-dimethyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide (Compound B18)

(196) ##STR00938##

(197) To a solution of 8-bromo-N,6-dimethyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide (153.00 mg, 0.510 mmol, 1.00 equiv) and [[2,6-dimethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl]dimethylamine (163.74 mg, 0.510 mmol, 1 equiv) in dioxane (5.00 mL) and H.sub.2O (1.00 mL) was added Cs.sub.2CO.sub.3 (498.25 mg, 1.529 mmol, 3 equiv) and

Pd(dppf)Cl.sub.2.Math.CH.sub.2Cl.sub.2 (41.63 mg, 0.051 mmol, 0.1 equiv). After stirring for 1.5 hours at 100° C. under a nitrogen atmosphere, the resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH.sub.2Cl.sub.2/MeOH (12:1) to afford a crude product, and the crude was further purified by Prep-HPLC (conditions: Xselect CSH F-Phenyl OBD column, 19*250, 5 μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 4 B to 22 B in 8 minutes; 254/220 nm; R.sub.T1:6.32 minutes) to afford 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N,6-dimethyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide (49 mg, 23.19%) as a white solid. .sup.1H NMR (300 MHz, Methanol-d4) δ 8.56 (brs, 0.5H, FA), 7.52 (s, 1H), 6.74 (s, 2H), 4.39 (s, 2H), 4.28 (s, 2H), 3.96 (s, 6H), 3.67-3.59 (m, 5H), 2.81 (s, 6H), 2.75-2.67 (m, 5H). LCMS (ESI) m/z: [M+H]+=415.35.

Example 25—Preparation of N-butyl-5-{4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl}-7-methyl-8-oxo-1,2,3,4,7,8-hexahydro-2,7-naphthyridine-2-sulfonamide (compound B19)

(198) ##STR00939##

Step 1: Preparation of N-butyl-2-oxo-1,3-oxazolidine-3-sulfonamide (i-41)

(199) ##STR00940##

(200) To a solution of chlorosulfonyl isocyanate (539 μL, 6.21 mmol, 1.00 equiv) in dry dichloromethane (8.8 mL) at 0° C. under nitrogen atmosphere was added a solution of 2-chloroethanol (416 μL, 6.21 mmol, 1.00 equiv) in dry dichloromethane (2.6 mL) dropwise over 30 minutes. The reaction mixture was then stirred at 0° C. for an additional 30 minutes. A solution of butylamine (674 μL, 6.83 mmol, 1.10 equiv) and triethylamine (1.88 mL, 13.6 mmol, 2.20 equiv) in dry dichloromethane (5.2 mL) was then added dropwise and the reaction mixture was warmed to room temperature and stirred for 2 hours. Then 1 N aqueous hydrochloric acid was added to adjust the pH to 2. The organic layer was separated and washed with 1 N aqueous hydrochloric acid (1×7 mL) then water (1×7 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford N-butyl-2-oxo-1,3-oxazolidine-3-sulfonamide (1.49 g, 100%) as a white solid. The crude product was used in the next step without further purification.

Step 2: Preparation of N-butyl-5-{4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl}-7-methyl-8-oxo-1,2,3,4,7,8-hexahydro-2,7-naphthyridine-2-sulfonamide (compound B19)

(201) ##STR00941##

(202) To a mixture of 4-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-2-methyl-5,6,7,8-tetrahydro-2,7-naphthyridin-1 (2H)-one (48.0 mg, 134.6 μmol, 1.50 equiv) and N-butyl-2-oxo-1,3-oxazolidine-3-sulfonamide (20 mg, 89.8 μmol, 1.00 equiv) in dry acetonitrile (0.44 mL) at room temperature was added triethylamine (33.6 μL, 242 μmol, 2.70 equiv). The reaction mixture was stirred at 80° C. for 6 hours. The reaction mixture was then cooled down to room temperature and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography, elution gradient 0 to 100% dichloromethane/methanol/ammonium hydroxide (90:10:1) in dichloromethane. Fractions containing the expected product were evaporated to dryness to afford 15.9 mg of impure product. Purification by Prep-HPLC (conditions: waters Xterra C18 Column, 19*100 mm, 10 μm particles; mobile phase A=0.1% ammonium hydroxide in water, mobile phase B=acetonitrile; flow Rate=40 mL/minute; gradient: 40-82% B in 6 minutes, then a 2 minutes hold at 98% B; wavelength=215 and 254 nm) afforded N-butyl-5-{4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl}-7-methyl-8-oxo-1,2,3,4,7,8-hexahydro-2,7-naphthyridine-2-sulfonamide (3.5 mg, 7.9%) as a white solid. .sup.1H NMR (400 MHz, DMSO-d6) δ 7.64 (s, 1H), 7.36 (s, 1H), 6.57 (s, 2H), 4.00 (s, 2H), 3.77 (s, 6H), 3.49 (s, 3H), 3.40 (s, 2H), 3.23 (t, J=5.6 Hz, 2H), 2.89 (t, J=7.0 Hz, 2H), 2.63 (t, J=5.4 Hz, 2H), 2.10 (s, 6H), 1.46-1.37 (m, 2H), 1.34-1.25 (m, 2H), 0.85 (t, J=7.3 Hz, 3H). LCMS (ESI) m/z: [M+H]+=493.6.

Example 26—Preparation of N-butyl-5-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-7-methyl-8-oxo-3,4,7,8-tetrahydro-2,7-naphthyridine-2 (1H)-carbothioamide (compound B20)

(203) ##STR00942##

(204) 4-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-2-methyl-5,6,7,8-tetrahydro-2,7-naphthyridin-1 (2H)-one (25 mg, 0.069 mmol, 1.00 equiv) was dissolved in dichloromethane. Diisopropylethylamine (0.0126 mL, 0.104 mmol, 1.50 equiv) was then added followed by 1-isothiocyanatobutane (0.0133 ml, 0.0768 mmol, 1.10 equiv). The reaction was allowed to stir at room

temperature for 1 hour. The solvent was removed under reduced pressure and the resulting oil was purified by prep-HPLC to obtain N-butyl-5-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-7-methyl-8-oxo-3,4,7,8-tetrahydro-2,7-naphthyridine-2 (1H)-carbothioamide (30 mg, 47%). .sup.1H NMR (400 MHz, DMSO-d6) δ 8.16 (s, 1H), 7.80 (t, J=5.3 Hz, 1H), 7.65 (s, 1H), 6.59 (s, 2H), 4.59 (s, 2H), 3.87 (q, J=5.1, 4.7 Hz, 2H), 3.77 (s, 6H), 3.51 (d, J=15.7 Hz, 7H), 3.15 (s, 1H), 2.57 (t, J=5.6 Hz, 2H), 2.19 (s, 6H), 1.52 (tt, J=8.0, 6.6 Hz, 2H), 1.27 (h, J=7.3 Hz, 2H), 0.87 (t, J=7.3 Hz, 3H). LCMS (ESI) m/z: [M+H]+=473.4.

Example 27—Preparation of 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N,N,6-trimethyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide (compound B21)

(205) ##STR00943##

Step 1:preparation of 8-bromo-N,N,6-trimethyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide (i-42)

(206) ##STR00944##

(207) Using the same procedure as described in Example 24, step 4 and substituting with dimethylcarbamyl chloride (25.8 mg, 0.240 mmol, 1.20 equiv) afforded 8-bromo-N,N,6-trimethyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide (73 mg, 94%) as an off-white solid. LCMS (ESI) m/z: [M+H]+=314.

Step 2: Preparation of 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N,N,6-trimethyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide (compound B21)

(208) ##STR00945##

(209) Using the same procedure as described in Example 23, step 2 and substituting with 8-bromo-N,N,6-trimethyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide (64.2 mg, 0.204 mmol, 1.00 equiv) afforded 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N,N,6-trimethyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide (26.1 mg, 29%) as an off-white solid. .sup.1H NMR (400 MHz, DMSO-d6) δ 7.57 (s, 1H), 6.60 (s, 2H), 4.00 (s, 2H), 3.78 (s, 6H), 3.48 (s, 3H), 3.46 (s, 2H), 3.37 (t, J=5.9 Hz, 2H), 2.70 (s, 6H), 2.57 (t, J=6.0 Hz, 2H), 2.14 (s, 6H). LCMS (ESI) m/z: [M+H]+=429.35

(210) Compound B22: LCMS 482.2.

(211) Compound B23: LCMS 511.2; .sup.1H NMR (400 MHz, DMSO-d6) δ 7.60 (s, 1H), 6.55 (s, 3H), 4.19 (s, 2H), 4.06 (d, J=5.3 Hz, 1H), 3.75 (s, 7H), 3.48 (d, J=8.1 Hz, 6H), 3.38 (t, J=5.5 Hz, 2H), 3.24 (s, 1H), 3.15 (d, J=4.6 Hz, 2H), 2.96 (s, 0H), 2.57 (d, J=4.2 Hz, 3H), 2.37 (s, 4H), 2.13 (s, 4H).

Example 28—Preparation of 5-(4-[[4-(4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]butanoyl)piperazin-1-yl]methyl]-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (Compound D1)

(212) ##STR00946##

(213) Compound D1 was prepared in a similar manner to the preparation of compound D2. PyBOP in step 3 was substituted with HATU. 5-(4-[[4-(4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]butanoyl)piperazin-1-yl]methyl]-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (21.2 mg) was obtained as a white solid. .sup.1H NMR (300 MHz, Methanol-d4) δ 7.80 (t, J=7.9 Hz, 1H), 7.57 (s, 1H), 7.48 (d, J=7.8 Hz, 2H), 6.64 (s, 2H), 5.11 (dd, J=12.1, 5.4 Hz, 1H), 4.36 (s, 2H), 4.30 (t, J=5.7 Hz, 2H), 4.00 (s, 2H), 3.88 (s, 6H), 3.80-3.69 (m, 4H), 3.64 (s, 3H), 3.53 (d, J=5.7 Hz, 2H), 2.94-2.81 (m, 5H), 2.78 (s, 4H), 2.72 (t, J=7.1 Hz, 3H), 2.67-2.59 (m, 2H), 2.22-2.09 (m, 3H). LCMS (ESI) m/z: [M+H]+=798.40.

Example 29—Preparation of 5-(4-[[4-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]acetyl)piperazin-1-yl]methyl]-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (Compound D2)

(214) ##STR00947##

Step 1: Preparation of tert-butyl4-([2,6-dimethoxy-4-[2-methyl-7-(methylcarbamoyl)-1-oxo-6,8-dihydro-5H-2,7-naphthyridin-4-yl]phenyl]methyl)piperazine-1-carboxylate (i-44)

(215) ##STR00948##

(216) A mixture of 5-(4-formyl-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (400.00 mg, 1.038 mmol, 1.00 equiv) and tert-butyl piperazine-1-carboxylate (193.30 mg, 1.038 mmol, 1.00 equiv) in MeOH (2 mL) was stirred for 30 minutes at room

temperature under air atmosphere. To the above mixture was added NaBH(AcO).sub.3 (439.92 mg, 2.076 mmol, 2.00 equiv) in portions for 2 hours at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by reverse flash chromatography (conditions: column, C18 silica gel; mobile phase, MeOH in water, 10% to 50% gradient in 50 minutes; detector, UV 254 nm). This resulted in tert-butyl4-([2,6-dimethoxy-4-[2-methyl-7-(methylcarbamoyl)-1-oxo-6,8-dihydro-5H-2,7-naphthyridin-4-yl]phenyl]methyl)piperazine-1-carboxylate (300 mg, 52.02%) as a yellow oil. LCMS (ESI) m/z: [M+H]+=556.

Step 2: Preparation of 5-[3,5-dimethoxy-4-(piperazin-1-ylmethyl)phenyl]-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (i-45)

(217) ##STR00949##

(218) A solution of TFA (1.00 mL) and tert-butyl 4-([2,6-dimethoxy-4-[2-methyl-7-(methylcarbamoyl)-1-oxo-6,8-dihydro-5H-2,7-naphthyridin-4-yl]phenyl]methyl)piperazine-1-carboxylate (10.00 mg, 0.018 mmol, 1.00 equiv) in DCM (2.00 mL) was stirred for 1 hour at room temperature under air atmosphere. The reaction mixture was concentrated under vacuum. The crude product mixture was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H]+=456.

Step 3: 5-(4-[[4-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]acetyl)piperazin-1-yl]methyl]-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (Compound D2)

(219) ##STR00950##

(220) A mixture of [[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]acetic acid (36.47 mg, 0.110 mmol, 1.00 equiv), DIEA (70.93 mg, 0.549 mmol, 5.00 equiv), PyBOP (114.23 mg, 0.220 mmol, 2.00 equiv), and [[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]acetic acid (36.47 mg, 0.110 mmol, 1.00 equiv) in DMF (2 mL) was stirred for 2 hours at room temperature under air atmosphere. 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 (0.1% FA), Mobile Phase B:ACN; Flow rate: 25 mL/minute; Gradient: 7 B to 20 B in 12 minutes; 254 nm; R.sub.t:10.95 minutes) to afford 5-(4-[[4-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]acetyl)piperazin-1-yl]methyl]-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (21.2 mg) as a white solid. .sup.1H NMR (300 MHz, Methanol-d4) δ 7.85-7.72 (m, 1H), 7.61-7.49 (m, 2H), 7.48-7.35 (m, 1H), 6.74 (s, 2H), 5.13 (dd, J=12.2, 5.4 Hz, 3H), 5.04 (d, J=4.2 Hz, 1H), 4.66-4.42 (m, 3H), 4.40-4.18 (m, 3H), 3.96 (s, 6H), 3.72-3.62 (m, 4H), 3.61-3.45 (m, 5H), 2.96-2.70 (m, 7H), 2.69-2.57 (m, 2H), 2.22-2.09 (m, 1H). LCMS (ESI) m/z: [M+H].sup.+=770.55.

Example 30—Preparation of 5-(4-[[4-(4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]butanoyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl]methyl]-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (Compound D3)

(221) ##STR00951##

(222) Compound D3 was prepared in a similar manner to the preparation of compound D4. Compound D3 (19 mg, 19.2%) was obtained as an off-white solid. .sup.1H NMR (300 MHz, Methanol-d4) δ 7.84-7.76 (m, 1H), 7.60 (d, J=7.8 Hz, 1H), 7.51-7.43 (m, 2H), 6.71 (d, J=5.0 Hz, 2H), 5.17-5.06 (m, 1H), 4.41-4.20 (m, 6H), 3.99-3.86 (m, 6H), 3.83-3.67 (m, 4H), 3.66-3.62 (m, 3H), 3.59-3.46 (m, 4H), 2.96-2.69 (m, 8H), 2.69-2.51 (m, 3H), 2.43-1.91 (m, 6H), 1.88-1.61 (m, 2H). LCMS (ESI) m/z: [M+H]+=868.80.

Example 31—Preparation of 5-(4-[[4-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]pentanoyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl]methyl]-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid (Compound D4)

(223) ##STR00952##

Step 1: Preparation of tert-butyl 9-([2,6-dimethoxy-4-[2-methyl-7-(methylcarbamoyl)-1-oxo-6,8-dihydro-5H-2,7-naphthyridin-4-yl]phenyl]methyl)-1-oxa-4,9-diazaspiro[5.5]undecane-4-carboxylate (i-47)

(224) ##STR00953##

(225) Using a similar procedure as described in Example 29, step 1 and substituting with tert-butyl1-

oxa-4,9-diazaspiro[5.5]undecane-4-carboxylate (93.1 mg, 0.363 mmol, 1 equiv afforded tert-butyl9-([2,6-dimethoxy-4-[2-methyl-7-(methylcarbamoyl)-1-oxo-6,8-dihydro-5H-2,7-naphthyridin-4-yl]phen yl]methyl)-1-oxa-4,9-diazaspiro[5.5]undecane-4-carboxylate (290 mg, 93.1%) as a light brown oil. LCMS (ESI) m/z: [M+H]+=626.

Step 2: Preparation of 5-(3, 5-dimethoxy-4-[1-oxa-4,9-diazaspiro[5.5]undecan-9-ylmethyl]phenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (i-48)

(226) ##STR00954##

(227) Using a similar procedure as described in Example 29, step 2 afforded 5-(3,5-dimethoxy-4-[1-oxa-4,9-diazaspiro[5.5]undecan-9-ylmethyl]phenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (114 mg, 46.8%) as a light brown solid. LCMS (ESI) m/z: [M+H]+=526.

Step 3: Preparation of 5-(4-[[4-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]pentanoyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl]methyl]-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid (Compound D4)

(228) ##STR00955##

(229) Using a similar procedure as described in Example 29, step 3 and substituting with 5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]pentanoic acid (28.5 mg, 0.076 mmol, 1.00 equiv) and 5-(3,5-dimethoxy-4-[1-oxa-4,9-diazaspiro[5.5]undecan-9-ylmethyl]phenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (40 mg, 0.076 mmol, 1.00 equiv) afforded 5-(4-[[4-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]pentanoyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl]methyl]-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid (23 mg, 32.6%) as an off-white solid. .sup.1H NMR (300 MHz, Methanol-d4) δ 8.55 (brs, 0.6H, formic acid), 7.79 (t, J=7.9 Hz, 1H), 7.58 (s, 1H), 7.46 (d, J=8.7 Hz, 2H), 6.70 (d, J=5.7 Hz, 2H), 5.15-5.07 (m, 1H), 4.39-4.25 (m, 6H), 3.93 (d, J=5.5 Hz, 6H), 3.82-3.72 (m, 2H), 3.64 (s, 5H), 3.59-3.50 (m, 4H), 3.31-3.05 (m, 4H), 2.93-2.83 (m, 1H), 2.78 (s, 3H), 2.77-2.56 (m, 6H), 2.21-2.03 (m, 3H), 2.01-1.68 (m, 6H). LCMS (ESI) m/z: [M+H]+=882.60.

Example 32—Preparation of 5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N-[2-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1-oxo-3H-isoindol-4-yl]amino]ethoxy)ethoxy]ethyl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid (Compound D5 formic acid)

(230) ##STR00956##

(231) Compound D5 was prepared in a similar manner to the preparation of compound D21. Compound D5 formic acid (12.8 mg, 21.5%) was obtained as a green solid. .sup.1H NMR (300 MHz, Methanol-d4) δ 8.56 (brs, 1.7H, FA), 7.55 (s, 1H), 7.24 (t, J=7.7 Hz, 1H), 7.09 (d, J=7.6 Hz, 1H), 6.91 (d, J=7.9 Hz, 1H), 6.71 (s, 2H), 5.19 (dd, J=13.4, 5.1 Hz, 1H), 4.39-4.27 (m, 5H), 4.09-3.98 (m, 2H), 3.94 (s, 6H), 3.67-3.50 (m, 14H), 3.40 (t, J=5.4 Hz, 2H), 3.04-2.91 (m, 2H), 2.85 (s, 6H), 2.61 (s, 2H), 2.53-2.39 (m, 1H), 2.24-2.12 (m, 1H). LCMS (ESI) m/z: [M−H].sup.+=774.37.

Example 33—Preparation of 5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N-[2-[(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethyl)(methyl)amino]ethyl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (Compound D6)

(232) ##STR00957##

(233) Compound D6 was prepared in a similar manner to the preparation of compound D21. Compound D6 (2.1 mg, 3.45%) was obtained as a green solid. .sup.1H NMR (300 MHz, Acetonitrile-d3) δ 9.17 (s, 1H), 7.58 (t, J=7.7 Hz, 1H), 7.43 (s, 1H), 7.15 (d, J=8.4 Hz, 1H), 7.06 (d, J=7.0 Hz, 1H), 6.67-6.47 (m, 4H), 4.95 (dd, J=12.2, 5.2 Hz, 1H), 4.35-4.17 (m, 4H), 3.87 (s, 6H), 3.77 (d, J=5.8 Hz, 2H), 3.55 (s, 4H), 3.44-3.24 (m, 5H), 2.92 (s, 3H), 2.77 (s, 6H), 2.73-2.60 (m, 3H), 2.54 (s, 2H), 2.30-2.22 (m, 1H), 2.14-2.02 (m, 1H). LCMS (ESI) m/z: [M−H].sup.+=757.36.

Example 34—Preparation of 5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethanesulfonyl)ethyl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid (Compound D7 formic acid)

(234) ##STR00958##

(235) Compound D7 was prepared in a similar manner to the preparation of compound D21. Compound D7 formic acid (13.1 mg, 22.5%) was obtained as a green solid. .sup.1H NMR (300 MHz, Methanol-d4) δ 8.56 (brs, 1H, FA), 7.66-7.54 (m, 2H), 7.12 (dd, J=17.2, 7.8 Hz, 2H), 6.69 (s, 2H), 5.05 (dd, J=12.6,

5.4 Hz, 1H), 4.35 (s, 2H), 4.24 (s, 2H), 3.94 (s, 6H), 3.89 (t, J=6.4 Hz, 2H), 3.70 (t, J=6.3 Hz, 2H), 3.63 (s, 3H), 3.49 (t, J=6.3 Hz, 4H), 3.42-3.37 (m, 2H), 2.86-2.68 (m, 9H), 2.67-2.60 (m, 3H), 2.13-2.01 (m, 1H). LCMS (ESI) m/z: [M+H]+=792.45.

Example 35—Preparation of N-(2-[[2-(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carbonylamino)ethyl](methyl)amino]ethyl)-2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]acetamide formic acid (Compound D8 formic acid)

(236) ##STR00959##

(237) Compound D7 was prepared in a similar manner to the preparation of compound D21. Compound D8 formic acid (10.9 mg, 19.24%) was obtained as a white solid. .sup.1H NMR (300 MHz, Methanol-d4) δ 8.42 (brs, 2H, FA), 7.72-7.63 (m, 1H), 7.51 (s, 1H), 7.43-7.37 (m, 2H), 6.67 (s, 2H), 5.12 (dd, J=12.7, 5.4 Hz, 1H), 4.81 (s, 2H), 4.39 (s, 2H), 4.15 (s, 2H), 3.98 (s, 6H), 3.63-3.55 (m, 5H), 3.42 (s, 3H), 2.97-2.85 (m, 11H), 2.82-2.63 (m, 3H), 2.59 (s, 3H), 2.54-2.39 (m, 2H), 2.21-2.09 (m, 1H). LCMS (ESI) m/z: [M+H]+=815.36.

Example 36—Preparation of 5-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-N-(8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)amino)octyl)-7-methyl-8-oxo-3,4,7,8-tetrahydro-2,7-naphthyridine-2 (1H)-carboxamide formic acid (Compound D9 formic acid)

(238) ##STR00960##

(239) Compound D9 was prepared in a similar manner to the preparation of compound D21. Compound D9 formic acid (9.7 mg, 23.93%) was obtained as a light yellow solid. LCMS (ESI) m/z: [M+H].sup.+=784.60. .sup.1H NMR (300 MHz, Methanol-d4) δ 8.56 (br s, 1H, FA), 7.61-7.50 (m, 2H), 6.96 (d, J=2.1 Hz, 1H), 6.82 (dd, J=8.4, 2.1 Hz, 1H), 6.69 (s, 2H), 5.05 (dd, J=12.4, 5.5 Hz, 1H), 4.36 (s, 2H), 4.21 (s, 2H), 3.93 (s, 6H), 3.63 (s, 3H), 3.54 (t, J=5.6 Hz, 2H), 3.25-3.15 (m, 4H), 2.96-2.81 (m, 1H), 2.75 (s, 8H), 2.63 (t, J=5.2 Hz, 2H), 2.15-2.03 (m, 1H), 1.73-1.61 (m, 2H), 1.60-1.49 (m, 2H), 1.48-1.33 (m, 8H).

Example 37—Preparation of 5-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-N-(8-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetamido)octyl)-7-methyl-8-oxo-3,4,7,8-tetrahydro-2,7-naphthyridine-2 (1H)-carboxamide formic acid (Compound D10 formic acid)

(240) ##STR00961##

(241) Compound D10 was prepared in a similar manner to the preparation of compound D21. Compound D10 formic acid (8.5 mg, 21.8%) was obtained as a white solid. LCMS (ESI) m/z: [M+H].sup.+=842.65. .sup.1H NMR (300 MHz, Methanol-d4) δ 8.56 (br s, 0.6H, FA), 7.82 (dd, J=8.4, 7.4 Hz, 1H), 7.61-7.52 (m, 2H), 7.44 (d, J=8.4 Hz, 1H), 6.71 (s, 2H), 5.15 (dd, J=12.4, 5.5 Hz, 1H), 4.77 (s, 2H), 4.36 (s, 2H), 4.27 (s, 2H), 3.94 (s, 6H), 3.64 (s, 3H), 3.54 (t, J=5.6 Hz, 2H), 3.30 (s, 2H), 3.19 (t, J=7.0 Hz, 2H), 2.98-2.83 (m, 1H), 2.83-2.70 (m, 8H), 2.64 (t, J=5.4 Hz, 2H), 2.22-2.10 (m, 1H), 1.65-1.47 (m, 4H), 1.36 (s, 8H).

Example 38—Preparation of 5-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-N-(5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)pentyl)-7-methyl-8-oxo-3,4,7,8-tetrahydro-2,7-naphthyridine-2 (1H)-carboxamide formic acid (Compound D11 formic acid)

(242) ##STR00962##

(243) Compound D11 was prepared in a similar manner to the preparation of compound D21. Compound D11 formic acid (8.7 mg, 20.7%) was obtained as a light yellow solid. .sup.1H NMR (300 MHz, Methanol-d4) δ 8.56 (br s, 1H, FA), 7.60-7.52 (m, 2H), 7.04 (dd, J=9.4, 7.8 Hz, 2H), 6.71 (s, 2H), 5.04 (dd, J=12.2, 5.4 Hz, 1H), 4.36 (s, 2H), 4.26 (s, 2H), 3.94 (s, 6H), 3.64 (s, 3H), 3.53 (t, J=5.6 Hz, 2H), 3.36 (t, J=6.8 Hz, 2H), 3.25 (t, J=6.8 Hz, 2H), 2.87-2.72 (m, 8H), 2.70-2.59 (m, 3H), 2.15-2.03 (m, 1H), 1.78-1.66 (m, 2H), 1.66-1.56 (m, 2H), 1.56-1.45 (m, 2H). LCMS (ESI) m/z: [M+H].sup.+=742.55.

Example 39—Preparation of 5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N-[2-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethoxy]ethyl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid (Compound D12 formic acid)

(244) ##STR00963##

(245) Compound D12 was prepared in a similar manner to the preparation of compound D21. Compound D12 formic acid (100 mg, 17.1%) was obtained as a yellow solid. .sup.1H NMR (300 MHz, Methanol-d4) δ 8.56 (br s, 0.9H, FA), 7.54 (s, 1H), 7.48 (dd, J=8.6, 7.1 Hz, 1H), 7.06 (d, J=8.5 Hz, 1H),

6.99 (d, J=7.1 Hz, 1H), 6.69 (s, 2H), 5.03 (dd, J=12.5, 5.4 Hz, 1H), 4.34 (s, 2H), 4.30 (s, 2H), 3.95 (s, 6H), 3.79 (t, J=5.2 Hz, 2H), 3.72-3.65 (m, 4H), 3.64-3.58 (m, 5H), 3.56-3.46 (m, 4H), 3.41 (t, J=5.4 Hz, 2H), 2.89-2.79 (m, 7H), 2.77-2.64 (m, 2H), 2.63-2.52 (m, 2H), 2.16-2.05 (m, 1H). LCMS (ESI) m/z: [M+H]+=812.45.

Example 40—Preparation of 5-(4-[[([[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]ethoxy)ethyl] carbamoyl]methyl)(methyl)amino]methyl]-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (Compound D13)

(246) ##STR00964##

Step 1: Preparation of 2,6-dimethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (i-51)

(247) ##STR00965##

(248) To a stirred solution of bis(pinacolato)diboron (7.62 g, 29.991 mmol, 1.50 equiv) and bis(pinacolato)diboron (7.62 g, 29.991 mmol, 1.50 equiv) in dioxane (70.00 mL) was added Pd(dppf)Cl.sub.2.Math.CH.sub.2Cl.sub.2 (1.63 g, 1.999 mmol, 0.10 equiv) and AcOK (5.89 g, 59.982 mmol, 3.00 equiv). The resulting mixture was stirred for 1 hour at 90° C. under nitrogen atmosphere. Then the reaction was concentrated and purified by silica gel column chromatography, eluted with PE/EtOAc (10:1) to afford 2,6-dimethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (6.3 g, 92.76%) as an orange solid. LCMS (ESI) m/z: [M+H]+=293.

Step 2: Preparation of 5-(4-formyl-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (i-43)

(249) ##STR00966##

(250) To a stirred solution of 2,6-dimethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (291.99 mg, 0.999 mmol, 1.00 equiv) and 5-bromo-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (300.00 mg, 0.999 mmol, 1.00 equiv) in dioxane (5.00 mL) and H.sub.2O (0.60 mL) was added Cs.sub.2CO.sub.3 (976.95 mg, 2.998 mmol, 3.00 equiv) and Pd(dppf)Cl.sub.2.Math.CH.sub.2Cl.sub.2 (81.62 mg, 0.100 mmol, 0.1 equiv). After stirring for 3 hours at 100° C. under a nitrogen atmosphere, the resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH.sub.2Cl.sub.2/MeOH (19:1) to afford 5-(4-formyl-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (257 mg, 66.72%) as a brown semi-solid. LCMS (ESI) m/z: [M+H]+=386.

Step 3: Preparation of tert-butyl2-[([2,6-dimethoxy-4-[2-methyl-7-(methylcarbamoyl)-1-oxo-6,8-dihydro-5H-2,7-naphthyridin-4-yl]phenyl]methyl)(methyl)amino]acetate (i-53)

(251) ##STR00967##

(252) To a stirred solution of 5-(4-formyl-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (222.00 mg, 0.576 mmol, 1.00 equiv) and tert-butyl 2-(methylamino)acetate hydrochloride (104.64 mg, 0.576 mmol, 1 equiv) in MeOH (5.00 mL) was added NaBH.sub.3CN (72.39 mg, 1.152 mmol, 2 equiv) in portions. The resulting mixture was stirred for 1 hour at room temperature under air atmosphere. Then the reaction mixture was concentrated, and the resulting residue was purified by silica gel column chromatography, eluted with CH.sub.2Cl.sub.2/MeOH (19:1) to afford tert-butyl 2-[([2,6-dimethoxy-4-[2-methyl-7-(methylcarbamoyl)-1-oxo-6,8-dihydro-5H-2,7-naphthyridin-4-yl]phenyl]methyl)(methyl)amino] acetate (268 mg, 90.41%) as a light yellow solid. LCMS (ESI) m/z: [M+H]+=515.

Step 4: Preparation of [([2,6-dimethoxy-4-[2-methyl-7-(methylcarbamoyl)-1-oxo-6,8-dihydro-5H-2,7-naphthyridin-4-yl]phenyl]methyl)(methyl)amino]acetic acid (i-54)

(253) ##STR00968##

(254) A solution of tert-butyl 2-[([2,6-dimethoxy-4-[2-methyl-7-(methylcarbamoyl)-1-oxo-6,8-dihydro-5H-2,7-naphthyridin-4-yl]phenyl]methyl)(methyl)amino]acetate (268.00 mg, 0.521 mmol, 1.00 equiv) and TFA (2.00 mL, 26.926 mmol, 51.70 equiv) in DCM (3 mL) was stirred for 1 hour at room temperature under air atmosphere. The reaction mixture was concentrated, and the resulting residue was purified by reverse flash chromatography (conditions: C18 silica gel column; mobile phase, MeCN in water, 10% to 50% gradient in 10 minutes; detector, UV 254 nm) to afford [([2,6-dimethoxy-4-[2-

methyl-7-(methylcarbamoyl)-1-oxo-6,8-dihydro-5H-2,7-naphthyridin-4-yl]phenyl]methyl)(methyl)amino]acetic acid (135 mg, 56.54%) as a light yellow oil. LCMS (ESI) m/z: [M+H]+=459.
Step 5: Preparation of 5-(4-[[([[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]ethoxy)ethyl]carbamoyl]methyl)(methyl)amino] methyl]-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (Compound D13)
(255) ##STR00969##
(256) To a stirred solution of [([2,6-dimethoxy-4-[2-methyl-7-(methylcarbamoyl)-1-oxo-6,8-dihydro-5H-2,7-naphthyridin-4-yl]phenyl]methyl)(methyl)amino]acetic acid (70.00 mg, 0.153 mmol, 1.00 equiv) and 4-[2-(2-aminoethoxy)ethoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (55.17 mg, 0.153 mmol, 1.00 equiv) in DMF (1.00 mL) was added DIEA (98.66 mg, 0.763 mmol, 5.00 equiv) and HATU (116.10 mg, 0.305 mmol, 2.00 equiv). The resulting mixture was stirred for 1 hour at room temperature. Then the solution was directly 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 25% B in 12 minutes; 254 nm; R.sub.t: 10.82 minutes) to afford 5-(4-[[([[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]ethoxy)ethyl]carbamoyl]methyl)(methyl)amino] methyl]-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (23 mg, 18.79%) as a yellow solid. .sup.1H NMR (300 MHz, Methanol-d4) δ 8.52 (br s, 0.4H, FA), 7.66-7.57 (m, 1H), 7.54 (s, 1H), 7.30 (d, J=7.2 Hz, 1H), 7.16 (d, J=8.4 Hz, 1H), 6.63 (s, 2H), 5.11 (dd, J=12.8, 5.4 Hz, 1H), 4.32 (s, 2H), 4.10-3.93 (m, 4H), 3.90 (s, 6H), 3.65-3.48 (m, 1 OH), 3.42-3.37 (m, 3H), 2.88 (dd, J=12.6, 4.6 Hz, 2H), 2.77 (s, 3H), 2.65 (d, J=18.1 Hz, 3H), 2.55-2.48 (m, 3H), 2.07-2.12 (s, 1H). LCMS (ESI) m/z: [M+H]+=802.55.
Example 41—Preparation of 5-[4-[(dimethylamino)methyl]-2,5-dimethoxyphenyl]-N-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethyl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid (Compound D14 formic acid)
(257) ##STR00970##
(258) To a stirred solution of triphosgene (13.2 mg, 0.044 mmol, 0.40 equiv) in DCM (1 mL) was added a solution of 4-[[2-(2-aminoethoxy)ethyl]amino]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (40.0 mg, 0.111 mmol, 1.00 equiv) and TEA (50 uL) in DCM (0.6 mL) dropwise at 0° C. After 2 minutes, additional TEA (30 uL) was added dropwise. The resulting mixture was stirred for additional 10 minutes at 0° C. 4-[4-[(dimethylamino)methyl]-2,5-dimethoxyphenyl]-2-methyl-5,6,7,8-tetrahydro-2,7-naphthyridin-1-one (39.7 mg, 0.111 mmol, 1.00 equiv) was then added in one portion. The reaction was stirred for additional 5 minutes at 0° C. and then warmed to room temperature for 25 minutes. The reaction solution was concentrated under vacuum. 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 (0.1% FA), Mobile Phase B:ACN; Flow rate: 25 mL/minute; Gradient: 9 B to 19 B in 14 minutes; 254 nm; RT: 15.53 minutes) to afford 5-[4-[(dimethylamino)methyl]-2,5-dimethoxyphenyl]-N-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethyl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid (5.9 mg, 6%) as a yellow solid. .sup.1H NMR (400 MHz, Methanol-d4) δ 8.56 (s, 0.4H, FA), 7.56 (dd, J=8.6, 7.1 Hz, 1H), 7.44 (s, 1H), 7.11 (d, J=9.3 Hz, 2H), 7.03 (d, J=7.0 Hz, 1H), 6.95 (s, 1H), 5.04 (dd, J=12.4, 5.4 Hz, 1H), 4.36 (br s, 2H), 4.09 (s, 2H), 3.89 (s, 3H), 3.81-3.70 (m, 6H), 3.66-3.56 (m, 6H), 3.51 (t, J=5.2 Hz, 2H), 3.43 (t, J=5.3 Hz, 2H), 2.89-2.62 (m, 9H), 2.53 (br s, 1H), 2.32 (br s, 1H), 2.11-2.02 (m, 1H). LCMS (ESI) m/z: [M+H]+=744.50.
Example 42—Preparation of 5-(4-[[3-(6-[[2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]hexanamido)azetidin-1-yl]methyl]-2,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid (Compound D15 formic acid)
(259) ##STR00971##
Step 1: Preparation of 4-Formyl-2,5-dimethoxyphenylboronic acid (i-58)
(260) ##STR00972##
(261) To a stirred solution of 4-bromo-2,5-dimethoxybenzaldehyde (200.00 mg, 0.816 mmol, 1.00 equiv) and bis(pinacolato)diboron (248.68 mg, 0.979 mmol, 1.2 equiv) in dioxane (2 mL) was added KOAc (160.19 mg, 1.632 mmol, 2 equiv) and Pd(dppf)Cl.sub.2 (59.71 mg, 0.082 mmol, 0.1 equiv). The mixture was stirred at 90° C. for 1 hour (under N.sub.2 atmosphere). The resulting mixture was

concentrated under reduced pressure to afford 4-formyl-2,5-dimethoxyphenylboronic acid (400 mg, crude) as a brown solid. The crude product was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H]+=211.3.
Step 2: Preparation of 5-(4-Formyl-2,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (i-59)
(262) ##STR00973##
(263) To a stirred solution of 4-formyl-2,5-dimethoxyphenylboronic acid (107.00 mg, 0.510 mmol, 1.00 equiv) and 5-bromo-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (152.94 mg, 0.510 mmol, 1.00 equiv) in dioxane (1.00 mL) and H.sub.2O (5.00 mL) was added CS.sub.2CO.sub.3 (332.04 mg, 1.019 mmol, 2 equiv) and Pd(dppf)Cl.sub.2 (37.28 mg, 0.051 mmol, 0.1 equiv). The mixture was stirred at 90° C. for 1 hour (under N.sub.2 atmosphere). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH.sub.2Cl.sub.2/MeOH (10:1) to afford 5-(4-formyl-2,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (247 mg, crude) as a brown solid. LCMS (ESI) m/z: [M+H]+=386.2.
Step 3: Preparation of tert-Butyl N-[1-([2,5-dimethoxy-4-[2-methyl-7-(methylcarbamoyl)-1-oxo-6,8-dihydro-5H-2,7-naphthyridin-4-yl]phenyl]methyl)azetidin-3-yl]carbamate (i-60)
(264) ##STR00974##
(265) To a stirred solution of 5-(4-formyl-2,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (100.00 mg, 0.259 mmol, 1.00 equiv) and tert-butyl N-(azetidin-3-yl)carbamate (44.69 mg, 0.259 mmol, 1 equiv) in MeOH (2.00 mL) was added NaBH(OAc).sub.3 (109.98 mg, 0.519 mmol, 2 equiv). The mixture was stirred at room temperature for 1 h. The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (CH.sub.2Cl.sub.2/MeOH 10:1) to afford tert-butyl N-[1-([2,5-dimethoxy-4-[2-methyl-7-(methylcarbamoyl)-1-oxo-6,8-dihydro-5H-2,7-naphthyridin-4-yl]phenyl]methyl)azetidin-3-yl]carbamate (100 mg, 71.16%) as a brown solid. LCMS (ESI) m/z: [M+H]+=542.2
Step 4: Preparation of afford 5-[4-[(3-Aminoazetidin-1-yl)methyl]-2,5-dimethoxyphenyl]-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (i-61)
(266) ##STR00975##
(267) To a stirred solution of tert-butyl N-[1-([2,5-dimethoxy-4-[2-methyl-7-(methylcarbamoyl)-1-oxo-6,8-dihydro-5H-2,7-naphthyridin-4-yl]phenyl]methyl)azetidin-3-yl]carbamate (100.00 mg, 0.185 mmol, 1.00 equiv) in DCM (2.00 mL) was added TFA (0.40 mL). The resulting mixture was concentrated under reduced pressure to afford 5-[4-[(3-aminoazetidin-1-yl)methyl]-2,5-dimethoxyphenyl]-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (80 mg, 98.14%) as a yellow solid. The crude product was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H]+=442.2.
Step 5: Preparation of afford 5-(4-[[3-(6-[[2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]hexanamido)azetidin-1-yl]methyl]-2,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid (Compound D15 formic acid)
(268) ##STR00976##
(269) To a solution of 5-[4-[(3-aminoazetidin-1-yl)methyl]-2,5-dimethoxyphenyl]-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (70.00 mg, 0.159 mmol, 1.00 equiv) and 6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]hexanoic acid (61.57 mg, 0.159 mmol, 1.00 equiv) in DMF (1 mL) was added DIEA (102.45 mg, 0.793 mmol, 5.00 equiv) and HATU (90.42 mg, 0.238 mmol, 1.50 equiv). The resulting solution was stirred at room temperature for 1 hour. Without 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 23 B in 14 minutes; 254 nm; R.sub.t: 14.33 minutes) to give 5-(4-[[3-(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]hexanamido)azetidin-1-yl]methyl]-2,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid (9.7 mg, 6.84%) as a white solid. .sup.1H NMR (400 MHz, Methanol-d4) δ 8.49 (br s, 1H, FA), 7.78 (dd, J=8.4, 7.4 Hz, 1H), 7.49-7.41 (m, 3H), 7.06 (s, 1H), 6.88 (s, 1H), 5.10 (dd, J=12.5, 5.5 Hz, 1H),

4.55-4.44 (m, 1H), 4.34 (s, 2H), 4.25 (t, J=6.1 Hz, 2H), 4.11 (s, 2H), 4.06 (t, J=8.5 Hz, 2H), 3.86 (s, 3H), 3.76 (s, 3H), 3.74-3.64 (m, 3H), 3.61 (s, 3H), 2.95-2.65 (m, 6H), 2.52 (s, 2H), 2.29 (t, J=7.3 Hz, 2H), 2.18-2.07 (m, 1H), 1.96-1.85 (m, 2H), 1.81-1.69 (m, 2H), 1.66-1.54 (m, 2H). LCMS (ESI) m/z: [M+H]+=812.45.

Example 43—Preparation of 5-(4-[[3-(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]hexanamido)azetidin-1-yl]methyl]-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid (Compound D16 formic acid)

(270) ##STR00977##

(271) Compound D16 was prepared in a similar manner to the preparation of compound D21. 15 Compound D16 formic acid (15 mg, 40.8%) was obtained as a white solid. .sup.1H NMR (400 MHz, Methanol-d4) δ 8.52 (br s, 1H, FA), 7.78 (dd, J=8.4, 7.3 Hz, 1H), 7.56 (s, 1H), 7.45 (dd, J=7.8, 2.7 Hz, 2H), 6.68 (s, 2H), 5.10 (dd, J=12.4, 5.5 Hz, 1H), 4.55-4.46 (m, 1H), 4.41-4.32 (m, 4H), 4.25 (t, J=6.1 Hz, 2H), 4.19 (s, 2H), 3.92 (s, 7H), 3.64 (s, 3H), 3.54 (t, J=5.6 Hz, 2H), 2.89-2.66 (m, 6H), 2.62 (t, J=5.6 Hz, 2H), 2.29 (t, J=7.3 Hz, 2H), 2.17-2.08 (m, 1H), 1.94-1.85 (m, 2H), 1.79-1.71 (m, 2H), 1.66-1.55 (m, 2H). LCMS (ESI) m/z: [M+H]+=812.45.

Example 44—Preparation of 5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethyl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid (Compound D17 Formic Acid)

(272) ##STR00978##

(273) Compound D17 formic acid was prepared in a similar manner to the preparation of compound D21. Compound D17 formic acid (75.8 mg, 22%) was obtained as a yellow solid. .sup.1H NMR (300 MHz, Methanol-d4) δ 8.57 (s, 0.1H, FA), 7.62-7.50 (m, 2H), 7.11 (d, J=8.5 Hz, 1H), 7.03 (d, J=7.1 Hz, 1H), 6.72 (s, 2H), 5.03 (dd, J=12.3, 5.3 Hz, 1H), 4.38 (s, 2H), 4.27 (s, 2H), 3.94 (s, 6H), 3.74 (t, J=5.0 Hz, 2H), 3.67-3.61 (m, 5H), 3.51 (q, J=4.9 Hz, 4H), 3.44 (t, J=5.3 Hz, 2H), 2.80 (s, 7H), 2.78-2.56 (m, 4H), 2.13-2.00 (m, 1H). LCMS (ESI) m/z: [M+H]+=744.45.

Example 45—Preparation of 5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]pentyl)-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (Compound D18)

(274) ##STR00979##

(275) Compound D18 was prepared in a similar manner to the preparation of compound D21. Compound D18 (5 mg, 12.10%) was obtained as a yellow solid. .sup.1H NMR (300 MHz, Methanol-d4) δ 7.78 (dd, J=8.5, 7.2 Hz, 1H), 7.59 (s, 1H), 7.46 (d, J=1.7 Hz, 1H), 7.43 (s, 1H), 6.74 (s, 2H), 5.12 (dd, J=12.3, 5.4 Hz, 1H), 4.38 (s, 4H), 4.26 (t, J=6.1 Hz, 2H), 3.96 (s, 6H), 3.63 (s, 3H), 3.54 (d, J=5.6 Hz, 2H), 3.27 (t, J=6.6 Hz, 1H), 2.89 (s, 7H), 2.90-2.79 (m, 1H), 2.79-2.59 (m, 3H), 2.18-2.05 (m, 1H), 1.97-1.86 (m, 2H), 1.65 (s, 5H). LCMS (ESI) m/z: [M+H].sup.+=743.65.

Example 46—Preparation of 4-[[9-(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-1,2,3,4,7,8-hexahydro-2,7-naphthyridin-2-yl)-9-oxononyl]amino]-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione (Compound D19)

(276) ##STR00980##

(277) To a stirred solution of 9-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]nonanoic acid (100 mg, 0.233 mmol, 1 equiv) in DMF (2 mL) was added HATU (115.02 mg, 0.303 mmol, 1.3 equiv) and DIEA (150.46 mg, 1.164 mmol, 5.0 equiv). The mixture was stirred at 25° C. for 30 minutes, and then 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (83.23 mg, 0.233 mmol, 1 equiv) was added. The mixture was stirred at 25° C. for 2 hours. Then the mixture was diluted with water (20 mL) and extracted with DCM (20 mL×3). The organic layers were combined and washed with saturated sodium chloride (20 mL), then dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude product. The residue was purified by Prep-HPLC (condition: 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 40% B in 8 minutes; 254/220 nm; R.sub.t: 7.08 minutes; Detector, 254 nm) to give 4-[[9-(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-1,2,3, 4,7,8-hexahydro-2,7-naphthyridin-2-yl)-9-oxononyl]amino]-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione

(25 mg, 32.5 μmol, 13.96%) as a yellow solid. .sup.1H NMR (400 MHz, Methanol-d4) δ 7.64-7.51 (m, 2H), 7.04 (dd, J=7.9, 6.2 Hz, 2H), 6.72 (d, J=5.9 Hz, 2H), 5.12-5.01 (m, 1H), 4.62 (s, 2H), 4.55 (d, J=5.5 Hz, 2H), 4.33 (d, J=11.1 Hz, 2H), 3.95 (d, J=1.9 Hz, 6H), 3.75-3.63 (m, 5H), 2.86 (d, J=2.3 Hz, 7H), 2.80-2.68 (m, 3H), 2.67-2.59 (m, 1H), 2.50 (dt, J=17.8, 7.6 Hz, 2H), 2.17-2.08 (m, 1H), 1.67 (dd, J=13.6, 6.8 Hz, 4H), 1.45-1.31 (m, 8H). LCMS (ESI) m/z: [M+H]+=769.70.

Example 47—Preparation of ([4-[7-(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]oxy]hexanoyl)-2-methyl-1-oxo-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)(methyl)aminyl (Compound D20)

(278) ##STR00981##

(279) Compound D20 was prepared in a similar manner to the preparation of compound D19 and by substituting the carboxylic acid i-36 with 6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]oxy]hexanoic acid (130 mg, 0.336 mmol, 1.20 equiv) in dimethylformamide (3.0 mL). Compound D20 (7.8 mg, 3.74%) was obtained as a white solid. .sup.1H NMR (400 MHz, Methanol-d4) δ 8.56 (s, 1H), 7.76 (td, J=7.9, 3.5 Hz, 1H), 7.59 (d, J=12.7 Hz, 1H), 7.43 (q, J=5.8 Hz, 2H), 6.71 (s, 2H), 5.08 (dd, J=12.6, 5.5 Hz, 1H), 4.55 (s, 2H), 4.25 (dt, J=6.5, 3.2 Hz, 4H), 3.93 (d, J=4.5 Hz, 6H), 3.70 (dt, J=10.4, 5.6 Hz, 2H), 3.63 (d, J=2.9 Hz, 3H), 2.78 (d, J=6.0 Hz, 7H), 2.66 (s, 2H), 2.77-2.51 (m, 4H), 2.11 (tdd, J=10.7, 5.9, 3.1 Hz, 1H), 1.91 (h, J=6.4 Hz, 2H), 1.76 (p, J=7.5 Hz, 2H), 1.70-1.57 (m, 2H). LCMS (ESI) m/z: [M+H].sup.+=728.50.

Example 48—Preparation of 5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]amino]ethoxy)ethyl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid (Compound D21 formic acid)

(280) ##STR00982##

Step 1: Preparation of tert-butyl N-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]amino]ethoxy) ethyl]carbamate (i-65)

(281) ##STR00983##

(282) To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-5-fluoroisoindole-1,3-dione (1.00 g, 3.620 mmol, 1.00 equiv) and tert-butyl N-[2-(2-aminoethoxy)ethyl]carbamate (1.48 g, 7.241 mmol, 2.00 equiv) in NMP (10 mL) was added DIEA (935.79 mg, 7.241 mmol, 2.00 equiv) at room temperature. The resulting mixture was stirred for 4 hours at 90° C. under nitrogen atmosphere. The residue was purified by reverse flash chromatography (conditions: column, C18 silica gel; mobile phase, ACN in water, 0% to 50% gradient in 20 minutes; detector, UV 254 nm). This resulted in tert-butyl N-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]amino]ethoxy)ethyl]carbamate (430 mg, 25.79%) as a yellow oil. LCMS (ESI) m/z: [M+H]+=461.20.

Step 2: Preparation of 5-[[2-(2-aminoethoxy)ethyl]amino]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (i-66)

(283) ##STR00984##

(284) A solution of tert-butyl N-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]amino]ethoxy)ethyl] carbamate (400.00 mg, 0.869 mmol, 1.00 equiv) and TFA (1.00 mL) in DCM was stirred for 2 hours at room temperature. The resulting mixture was concentrated under vacuum. This resulted in 5-[[2-(2-aminoethoxy)ethyl]amino]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (220 mg, 70.28%) as a brown solid. LCMS (ESI) m/z: [M+H]+=361.14.

Step 3: Preparation of 5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]amino]ethoxy)ethyl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid (Compound D21 formic acid)

(285) ##STR00985##

(286) A solution of 5-[[2-(2-aminoethoxy)ethyl]amino]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (60.00 mg, 0.166 mmol, 1.00 equiv) and CDI (29.70 mg, 0.183 mmol, 1.10 equiv) in acetonitrile (1.5 mL) and DMF (0.3 mL) was stirred for 2 hours at room temperature. Then 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-5,6,7,8-tetrahydro-2,7-naphthyridin-1-one (119.03 mg, 0.333 mmol, 2.00 equiv) and TEA (33.70 mg, 0.333 mmol, 2.00 equiv) was added to the reaction mixture. The resulting mixture was stirred for overnight at room temperature. The crude product was purified by Prep-HPLC (conditions: SunFire C18 OBD Prep Column, 100 Å, 5 μm, 19

mm×250 mm; mobile phase, Water (0.05% TFA) and ACN (12% Phase B up to 26% in 15 minutes); Detector, UV). This resulted in 5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]amino]ethoxy)ethyl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (4 mg, 3.23%) as a green semi-solid. .sup.1H NMR (400 MHz, Acetonitrile-d3) δ 9.31 (s, 1H), 9.03 (brs, 1.0H, FA), 7.51 (d, J=8.3 Hz, 1H), 7.40 (s, 1H), 7.00 (d, J=2.1 Hz, 1H), 6.91 (dd, J=8.3, 2.2 Hz, 1H), 6.60 (s, 2H), 6.18 (s, 1H), 5.67 (t, J=5.7 Hz, 1H), 4.92 (dd, J=12.5, 5.4 Hz, 1H), 4.28 (d, J=4.8 Hz, 4H), 3.85 (s, 6H), 3.71 (t, J=5.0 Hz, 2H), 3.58-3.49 (m, 7H), 3.39 (q, J=5.3 Hz, 2H), 3.34 (t, J=5.0 Hz, 2H), 2.77 (s, 6H), 2.75-2.65 (m, 2H), 2.57 (t, J=5.6 Hz, 2H), 1.35-1.24 (m, 1H). LCMS (ESI) m/z: [M+H].sup.+=744.50.

Example 49—Preparation of 5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]pentyl)-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid (Compound D22 formic acid)

(287) ##STR00986##

(288) Compound D22 formic acid was prepared in a similar manner to the preparation of compound D21. Compound D22 formic acid (8.7 mg, 20.8%) was obtained as a light yellow solid. .sup.1H NMR (400 MHz, Methanol-d4) δ 8.57 (brs, 0.7H, FA), 7.79 (d, J=8.3 Hz, 1H), 7.58 (s, 1H), 7.37 (d, J=2.2 Hz, 1H), 7.31 (dd, J=8.3, 2.3 Hz, 1H), 6.66 (s, 2H), 5.10 (dd, J=12.6, 5.4 Hz, 1H), 4.36 (s, 2H), 4.17 (t, J=6.3 Hz, 2H), 4.10 (s, 2H), 3.91 (s, 6H), 3.64 (s, 3H), 3.54 (t, J=5.6 Hz, 2H), 3.27 (t, J=6.6 Hz, 2H), 2.93-2.70 (m, 3H), 2.70-2.58 (m, 8H), 2.17-2.07 (m, 1H), 1.89 (p, J=6.5 Hz, 2H), 1.70-1.52 (m, 4H). LCMS (ESI) m/z: [M+H].sup.+=743.35.

Example 50—Preparation of 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N-[2-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethoxy]ethyl]-6-methyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide formic acid (Compound D23 formic acid)

(289) ##STR00987##

Step 1: Preparation of 4-bromo-2H-2,6-naphthyridin-1-one (i-68)

(290) ##STR00988##

(291) To a stirred solution of 2H-2,6-naphthyridin-1-one (584.00 mg, 3.996 mmol, 1.00 equiv) in DCM (10.00 mL) was added NBS (640.09 mg, 3.596 mmol, 0.9 equiv) in portions at room temperature under air atmosphere. The mixture was stirred for another 1 hour. The reaction mixture was concentrated and purified by silica gel column chromatography, eluted with CH.sub.2Cl.sub.2/MeOH (12:1) to afford 4-bromo-2H-2,6-naphthyridin-1-one (1.18 g, 85.29%) as a light yellow solid. LCMS (ESI) m/z: [M+H]+=225, 227.

Step 2: Preparation of 4-bromo-2-methyl-2,6-naphthyridin-1-one (i-69)

(292) ##STR00989##

(293) To a stirred solution of 4-bromo-2H-2,6-naphthyridin-1-one (1.18 g, 5.243 mmol, 1.00 equiv) in Mel (2.98 g, 20.974 mmol, 4.00 equiv) was added NaH (0.25 g, 10.487 mmol, 2.00 equiv) in portions at 0° C. under nitrogen atmosphere. Then Mel (1513.71 mg, 10.665 mmol, 4 equiv) was added drop-wise. The mixture was stirred for another 1 hour at room temperature and quenched with water at 0° C. The product was precipitated by the addition of water. The precipitated solids were collected by filtration and washed with water (2×20 mL). The crude product 4-bromo-2-methyl-2, 6-naphthyridin-1-one (568 mg, 45.31%) was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H]+=239, 241.

Step 3: Preparation of 4-bromo-2-methyl-5,6,7,8-tetrahydro-2,6-naphthyridin-1-one (i-70)

(294) ##STR00990##

(295) To a stirred solution of 4-bromo-2-methyl-2, 6-naphthyridin-1-one (239.10 mg, 1.000 mmol, 1.00 equiv) in AcOH (5.00 mL) was added NaBH.sub.4 (264.86 mg, 7.001 mmol, 7.00 equiv) in portions at 0° C. under nitrogen atmosphere. The resulting mixture was stirred for 5 minutes at room temperature. Then, the mixture was poured into ice water, basified with ammonium hydroxide, and extracted with CH.sub.2Cl.sub.2 (3×50 mL). The combined organic layers were concentrated under reduced pressure and the resulting crude product 4-bromo-2-methyl-5,6,7,8-tetrahydro-2,6-naphthyridin-1-one (237 mg, 80.91%) was used directly in the next step. LCMS (ESI) m/z: [M+H]+=243, 245.

Step 4: Preparation of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-5,6,7,8-

tetrahydro-2,6-naphthyridin-1-one (i-72)
(296) ##STR00991##
(297) To a solution of 4-bromo-2-methyl-5,6,7,8-tetrahydro-2,6-naphthyridin-1-one (237.00 mg, 0.975 mmol, 1.00 equiv) and [[2,6-dimethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl]dim ethylamine (313.15 mg, 0.975 mmol, 1 equiv) in dioxane (5.00 mL) and H.sub.2O (1.00 mL) was added Cs.sub.2CO.sub.3 (952.92 mg, 2.925 mmol, 3 equiv) and Pd(dppf)Cl.sub.2.Math.CH.sub.2Cl.sub.2 (79.61 mg, 0.097 mmol, 0.1 equiv). After stirring for 1.5 h at 100° C. under a nitrogen atmosphere, the resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH.sub.2Cl.sub.2/MeOH (12:1) to afford the crude product, 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-5,6,7,8-tetrahydro-2,6-naphthyridin-1-one (524 mg, 79.69%) as a dark brown solid. LCMS (ESI) m/z: [M+H]+=358.
Step 5: Preparation of 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N-[2-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethoxy]ethyl]-6-methyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide formic acid (Compound D23 formic acid)
(298) ##STR00992##
(299) To a stirred solution of 4-([2-[2-(2-aminoethoxy)ethoxy]ethyl]amino)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione trifluoroacetic acid salt (40.40 mg, 0.078 mmol, 1.00 equiv) in DMF (0.30 mL) and MeCN (0.90 mL) was added CDI (13.90 mg, 0.086 mmol, 1.10 equiv). The mixture was stirred for 2 hours at room temperature under air atmosphere. Then 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-5,6,7,8-tetrahydro-2,6-naphthyridin-1-one (41.78 mg, 0.117 mmol, 1.50 equiv) and Et.sub.3N (23.66 mg, 0.234 mmol, 3.00 equiv) was added, and the final reaction mixture was stirred for overnight at room temperature under air atmosphere. Without any additional work-up, the resulting mixture was purified by Prep-HPLC (conditions: Xselect CSH F-Phenyl OBD Column 19*150 mm 5 μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 9 B to 20 B in 10 minutes; 254 nm; R.sub.t1:9.75 minutes) to afford 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N-[2-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethoxy]ethyl]-6-methyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide (21 mg, 33.49%) as a yellow solid. .sup.1H NMR (300 MHz, Methanol-d4) δ 8.57 (brs, 0.7H, FA), 7.58-7.48 (m, 2H), 7.07 (dd, J=14.0, 7.8 Hz, 2H), 6.71 (s, 2H), 5.03 (dd, J=12.4, 5.4 Hz, 1H), 4.36 (s, 2H), 4.19 (s, 2H), 3.94 (s, 6H), 3.73 (t, J=5.2 Hz, 2H), 3.68-3.57 (m, 9H), 3.57-3.47 (m, 4H), 3.35 (s, 1H), 2.92-2.75 (m, 2H), 2.74 (s, 6H), 2.71-2.58 (m, 4H), 2.14-2.04 (m, 1H). LCMS (ESI) m/z: [M+H]+=788.50.
Example 51—Preparation of 8-(4-(((2-((2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)ethoxy)ethyl)amino)-2-oxoethyl)(methyl)amino)methyl)-3,5-dimethoxyphenyl)-N,6-dimethyl-5-oxo-3,4,5,6-tetrahydro-2,6-naphthyridine-2 (1H)-carboxamide (Compound D24)
(300) ##STR00993##
(301) Compound D24 was prepared in a similar manner to the preparation of compound D13 and compound D23.
Example 52—Preparation of 5-[4-[(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]-N-methylhexanamido)methyl]-3,5-dimethoxyphenyl]-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (Compound D25)
(302) ##STR00994##
Step 1: Preparation of 5-bromo-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (1-75)
(303) ##STR00995##
(304) Using a similar procedure as described in Example 24, step 4 and substituting with 4-bromo-2-methyl-5,6,7,8-tetrahydro-2,7-naphthyridin-1-one (243 mg, 1.000 mmol) afforded 5-bromo-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (348 mg, 98.6%) as a light yellow solid. LCMS (ESI) m/z: [M+H]+=300, 302.
Step 2: Preparation of 5-(4-formyl-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (i-76)

(305) ##STR00996##
(306) Using a similar procedure as described in Example 23, step 3 and substituting with 5-bromo-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (100 mg, 0.333 mmol, 1.00 equiv) and 2,6-dimethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (97.3 mg, 0.333 mmol, 1.00 equiv) afforded 5-(4-formyl-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (132 mg, 91.5%) as a light yellow solid. LCMS (ESI) m/z: [M+H]+=386.
Step 3: Preparation of 5-[3,5-dimethoxy-4-[(methylamino)methyl]phenyl]-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (i-77)
(307) ##STR00997##
(308) To a stirred solution of 5-(4-formyl-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (100 mg, 0.259 mmol, 1.00 equiv) and triethylamine (78.76 mg, 0.778 mmol, 3.00 equiv) in methanol (1.00 mL) was added sodium cyanoborohydride (32.6 mg, 0.519 mmol, 2.00 equiv) in portions at room temperature. Solvent was then evaporated under reduced pressure and the residue was purified by silica gel column chromatography, eluted with dichloromethane/methanol (12:1) to afford 5-[3,5-dimethoxy-4-[(methylamino)methyl] phenyl]-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (71 mg, 68.3%) as a yellow solid. LCMS (ESI) m/z: [M+H]+=400.
Step 4: Preparation of 5-[4-[(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]-N-methylhexanamido)methyl]-3,5-dimethoxyphenyl]-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (Compound D25)
(309) ##STR00998##
(310) Using a similar procedure as described in Example 46 and substituting with 5-[3,5-dimethoxy-4-[(methylamino)methyl]phenyl]-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (60 mg, 0.150 mmol, 1.00 equiv) and 6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]hexanoic acid (58.2 mg, 0.150 mmol, 1.00 equiv) afforded 5-[4-[(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]-N-methylhexanamido)methyl]-3,5-dimethoxyphenyl]-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (30 mg, 25.5%) as an off-white solid. .sup.1H NMR (300 MHz, Methanol-d4) δ 7.76 (dd, J=8.6, 7.2 Hz, 1H), 7.55 (d, J=2.8 Hz, 1H), 7.49-7.37 (m, 2H), 6.60 (d, J=14.9 Hz, 2H), 5.08 (dd, J=12.3, 5.5 Hz, 1H), 4.76-4.57 (m, 2H), 4.35 (s, 2H), 4.25 (t, J=6.1 Hz, 2H), 3.85 (d, J=11.5 Hz, 6H), 3.63 (d, J=3.6 Hz, 3H), 3.52 (q, J=5.2 Hz, 2H), 2.83 (d, J=2.0 Hz, 4H), 2.77 (d, J=6.8 Hz, 4H), 2.72-2.55 (m, 4H), 2.51-2.39 (m, 1H), 2.20-2.00 (m, 1H), 1.87 (d, J=7.8 Hz, 2H), 1.66 (dd, J=21.4, 2.6 Hz, 4H). LCMS (ESI) m/z: [M+H]+=771.40.
Example 53—Preparation of 5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N-[1-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]ethyl)piperidin-4-yl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid (Compound D26 formic acid)
(311) ##STR00999##
(312) Compound D26 was prepared in a similar manner to the preparation of compound D21. Compound D26 formic acid (4.5 mg, 4.68%) was obtained as a white solid. .sup.1H NMR (300 MHz, Methanol-d4) δ 8.48 (brs, 1.6H, FA), 7.85 (d, J=8.3 Hz, 1H), 7.60 (s, 1H), 7.49 (d, J=2.2 Hz, 1H), 7.39 (dd, J=8.3, 2.3 Hz, 1H), 6.74 (s, 2H), 5.13 (dd, J=12.3, 5.4 Hz, 1H), 4.39 (d, J=3.8 Hz, 6H), 3.95 (s, 6H), 3.78-3.68 (m, 1H), 3.64 (s, 3H), 3.56 (t, J=5.5 Hz, 2H), 3.29-3.22 (m, 2H), 3.13 (s, 2H), 2.89 (s, 6H), 2.86-2.71 (m, 3H), 2.69-2.54 (m, 4H), 2.22-2.09 (m, 1H), 2.01 (d, J=13.0 Hz, 2H), 1.81-1.64 (m, 2H). LCMS (ESI) m/z: [M+H].sup.+=784.45.
Example 54—Preparation of 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethyl]-6-methyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide formic acid (Compound D27 formic acid)
(313) ##STR01000##
(314) Compound D27 was prepared in a similar manner to the preparation of compound D23. Compound D27 formic acid (21 mg, 35.8%) was obtained as a yellow solid. .sup.1H NMR (300 MHz, DMSO-d6) δ 11.09 (s, 1H), 8.19 (brs, 0.4H, FA), 7.63-7.52 (m, 2H), 7.13 (d, J=8.6 Hz, 1H), 7.04 (d, J=7.1 Hz, 1H), 6.73-6.54 (m, 4H), 5.06 (dd, J=12.8, 5.3 Hz, 1H), 4.26 (s, 2H), 3.80 (s, 6H), 3.64-3.51 (m, 7H), 3.47 (s, 3H), 3.45-3.41 (m, 5H), 3.20-3.12 (m, 3H), 2.96-2.83 (m, 1H), 2.61 (s, 1H), 2.27 (s,

6H), 2.07-1.97 (m, 1H). LCMS (ESI) m/z: [M+H]+=744.35
Example 55—Preparation of 5-(4-[[4-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethyl)piperidin-1-yl]methyl]-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid (Compound D28 formic acid)
(315) ##STR01001##
(316) Using a similar procedure as described in Example 29, step 1 and substituting with 2-(2,6-dioxopiperidin-3-yl)-5-[4-[2-(piperidin-4-yl)ethyl]piperazin-1-yl]isoindole-1,3-dione (40 mg, 0.088 mmol, 1.00 equiv) in DMF (2 ml) and 5-(4-formyl-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (34 mg, 0.088 mmol, 1.00 equiv) afforded 5-(4-[[4-(2-[4-[2-(2,6-dioxo piperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethyl)piperidin-1-yl]methyl]-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid (11.1 mg, 15.3%) as a yellow solid. .sup.1H NMR (400 MHz, Methanol-d4) δ 8.34 (brs, 2.4H, FA), 7.72 (d, J=8.5 Hz, 1H), 7.58 (s, 1H), 7.40 (d, J=1.9 Hz, 1H), 7.27 (d, J=10.4 Hz, 1H), 6.73 (s, 2H), 5.09 (dd, J=12.5, 5.4 Hz, 1H), 4.36 (s, 4H), 3.96 (s, 7H), 3.64 (s, 3H), 3.57-3.49 (m, 8H), 3.20-3.04 (m, 2H), 2.96-2.82 (m, 2H), 2.78 (s, 4H), 2.76-2.67 (m, 6H), 2.67-2.60 (m, 2H), 2.59-2.52 (m, 2H), 2.14 (s, 1H), 2.01 (s, 2H), 1.77-1.48 (m, 5H). LCMS (ESI) m/z: [M+H]+=823.45.
Example 56—Preparation of 5-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-N-(8-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)amino)octyl)-7-methyl-8-oxo-3,4,7,8-tetrahydro-2,7-naphthyridine-2 (1H)-carboxamide formic acid (Compound D29 formic acid)
(317) ##STR01002##
(318) Compound D29 was prepared in a similar manner to the preparation of compound D21. Compound D29 formic acid (2.4 mg, 4.9%) was obtained as a white solid. .sup.1H NMR (300 MHz, Methanol-d4) δ 8.57 (brs, 0.8H, FA), 7.57 (s, 1H), 7.32 (t, J=7.8 Hz, 1H), 7.07 (d, J=7.4 Hz, 1H), 6.82 (d, J=7.9 Hz, 1H), 6.69 (s, 2H), 5.17 (dd, J=13.3, 5.2 Hz, 1H), 4.36 (s, 2H), 4.29 (d, J=3.2 Hz, 2H), 4.18 (s, 2H), 3.92 (s, 6H), 3.64 (s, 3H), 3.53 (t, J=5.8 Hz, 2H), 3.21 (q, J=7.3 Hz, 4H), 2.97-2.80 (m, 2H), 2.73 (s, 6H), 2.67-2.60 (m, 2H), 2.49 (dd, J=13.1, 4.8 Hz, 1H), 2.26-2.15 (m, 1H), 1.74-1.62 (m, 2H), 1.60-1.50 (m, 2H), 1.49-1.35 (m, 8H). LCMS (ESI) m/z: [M+H].sup.+=770.25.
Example 57—Preparation of 5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N-(2-[[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]ethoxy)ethyl](methyl)amino]ethyl)-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid (Compound D30 formic acid)
(319) ##STR01003##
(320) Compound D30 was prepared in a similar manner to the preparation of compound D21. Compound D30 formic acid (3 mg, 3.1%) was obtained as an off-white solid. .sup.1H NMR (400 MHz, Methanol-d4) δ 8.55 (brs, 2.6H, FA), 7.70 (dd, J=8.5, 7.2 Hz, 1H), 7.57 (s, 1H), 7.44 (d, J=8.5 Hz, 1H), 7.36 (d, J=7.3 Hz, 1H), 5.10 (dd, J=12.7, 5.5 Hz, 1H), 4.42 (t, J=4.1 Hz, 2H), 4.37 (s, 2H), 4.21 (s, 2H), 4.04-3.98 (m, 4H), 3.97 (s, 6H), 3.63 (s, 3H), 3.55-3.45 (m, 3H), 3.44-3.35 (m, 3H), 3.26 (s, 2H), 2.93-2.82 (m, 1 OH), 2.79-2.65 (m, 2H), 2.63-2.48 (m, 2H), 2.19-2.10 (m, 1H). LCMS (ESI) m/z: [M+H].sup.+=802.30.
Example 58—Preparation of 5-(4-((4-(5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)pentanoyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4,7,8-tetrahydro-2,7-naphthyridine-2 (1H)-carboxamide formic acid (Compound D31 Formic Acid)
(321) ##STR01004##
(322) Compound D31 was prepared in a similar manner to the preparation of compound D4. Compound D31 formic acid (3.6 mg, 9.4%) was obtained as a white solid. .sup.1H NMR (400 MHz, Methanol-d4) δ 8.55 (brs, 0.8H, FA), 7.81 (dd, J=8.3, 5.2 Hz, 1H), 7.59 (s, 1H), 7.41 (d, J=2.3 Hz, 1H), 7.33 (dd, J=8.4, 2.2 Hz, 1H), 6.70 (d, J=4.2 Hz, 2H), 5.12 (dd, J=12.6, 5.4 Hz, 1H), 4.36 (s, 2H), 4.34-4.26 (m, 2H), 4.24-4.18 (m, 2H), 3.93 (d, J=3.0 Hz, 6H), 3.81-3.71 (m, 2H), 3.67-3.59 (m, 5H), 3.57-3.47 (m, 4H), 3.30-3.12 (m, 4H), 2.96-2.82 (m, 2H), 2.78 (s, 3H), 2.76-2.72 (m, 1H), 2.66-2.47 (m, 4H), 2.19-2.02 (m, 3H), 1.97-1.74 (m, 6H). LCMS (ESI) m/z: [M+H].sup.+=882.25.
Example 59—Preparation of 5-[4-[(dimethylamino)methyl]-2,5-dimethoxyphenyl]-N-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]amino]ethoxy)ethyl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-

naphthyridine-2-carboxamide formic acid (Compound D32 Formic Acid)
(323) ##STR01005##
(324) Compound D32 was prepared in a similar manner to the preparation of compound D21. Compound D32 formic acid (24.2 mg, 19.5%) was obtained as a green solid. .sup.1H NMR (400 MHz, Methanol-d4) δ 8.55 (brs, 0.7H, FA), 7.51 (d, J=8.3 Hz, 1H), 7.43 (s, 1H), 7.07 (s, 1H), 7.03 (d, J=2.2 Hz, 1H), 6.91-6.87 (m, 2H), 5.03 (dd, J=12.6, 5.4 Hz, 1H), 4.33 (s, 2H), 4.06-3.93 (m, 2H), 3.86 (s, 3H), 3.73 (s, 6H), 3.61 (s, 6H), 3.45-3.38 (m, 4H), 2.90-2.84 (m, 1H), 2.78-2.69 (m, 2H), 2.69-2.47 (m, 8H), 2.11-2.04 (m, 1H).LCMS (ESI) m/z: [M+H]+=744.33.
Example 60—Preparation of 8-(4-(((2-(2-(4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)piperazin-1-yl)ethoxy)ethyl)(methyl)amino)methyl)-3,5-dimethoxyphenyl)-N,N,6-trimethyl-5-oxo-3,4,5,6-tetrahydro-2,6-naphthyridine-2 (1H)-carboxamide formic acid (Compound D33 formic acid)
(325) ##STR01006##
Step 1: Preparation of 8-(4-formyl-3,5-dimethoxyphenyl)-N,N,6-trimethyl-5-oxo-3,4,5,6-tetrahydro-2,6-naphthyridine-2 (1H)-carboxamide (i-81)
(326) ##STR01007##
(327) Using a similar procedure as described in Example 23, step 3 and substituting with 8-bromo-N,N,6-trimethyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide (200 mg, 0.637 mmol, 1.00 equiv) and 4-formyl-3,5-dimethoxyphenylboronic acid (200.5 mg, 0.955 mmol, 1.50 equiv) afforded 8-(4-formyl-3,5-dimethoxyphenyl)-N,N,6-trimethyl-5-oxo-3,4,5,6-tetrahydro-2,6-naphthyridine-2 (1H)-carboxamide (200.0 mg, 78.7%) as a yellow oil. LCMS (ESI) m/z: [M+H].sup.+=400.
Step 2: Preparation of 8-(4-(((2-(2-(4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)piperazin-1-yl)ethoxy)ethyl)(methyl)amino)methyl)-3,5-dimethoxyphenyl)-N,N,6-trimethyl-5-oxo-3,4,5,6-tetrahydro-2,6-naphthyridine-2 (1H)-carboxamide formic acid (Compound D33 formic acid)
(328) ##STR01008##
(329) Using a similar procedure as described in Example 52, step 3 and substituting with 8-(4-formyl-3,5-dimethoxyphenyl)-N,N,6-trimethyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide (30.0 mg, 0.075 mmol, 1.00 equiv) and 2-(2,6-dioxopiperidin-3-yl)-5-(4-[2-[2-(methylamino)ethoxy]ethyl]piperazin-1-yl)isoindole-1,3-dione (33.3 mg, 0.075 mmol, 1.00 equiv) afforded 8-[4-([[2-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethoxy)ethyl](methyl)amino]methyl)-3,5-dimethoxyphenyl]-N,N,6-trimethyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide formic acid (7.6 mg, 11.2%) as a yellow green solid. .sup.1H-NMR (400 MHz, Methanol-d4) δ 8.47 (brs, 1.4H, FA), 7.69 (d, J=8.5 Hz, 1H), 7.50 (s, 1H), 7.34 (d, J=2.3 Hz, 1H), 7.24 (dd, J=8.6, 2.3 Hz, 1H), 6.77 (s, 2H), 5.08 (dd, J=12.4, 5.5 Hz, 1H), 4.50 (s, 2H), 4.09 (s, 2H), 3.97 (s, 6H), 3.92-3.87 (m, 2H), 3.76 (t, J=5.2 Hz, 2H), 3.61 (s, 3H), 3.51-3.45 (m, 8H), 2.90-2.86 (m, 4H), 2.83 (s, 6H), 2.79-2.71 (m, 1 OH), 2.17-2.07 (m, 1H). LCMS (ESI) m/z: [M+H].sup.+=827.50.
Example 61—Preparation of (2S,4R)-1-[(2S)-2-(2-[2-[2-(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carbonylamino)ethoxy]ethoxy]acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-[[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide formic acid (Compound D34 formic acid)
(330) ##STR01009##
(331) To a stirred mixture of CDI (9.29 mg, 0.057 mmol, 1.10 equiv) in ACN (0.50 mL) and DMF (0.10 mL) was added (2S,4R)-1-[(2S)-2-[2-[2-(2-aminoethoxy)ethoxy]acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-[[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide (30 mg, 0.052 mmol, 1.00 equiv) and ACN (0.30 mL) dropwise at room temperature under nitrogen atmosphere. After 3 hours, 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-5,6,7,8-tetrahydro-2,7-naphthyridin-1-one (22.35 mg, 0.063 mmol, 1.20 equiv) and TEA (15.82 mg, 0.156 mmol, 3.00 equiv) were added. The resulting mixture was stirred at room temperature for 12 hours under nitrogen atmosphere. Without any additional work-up, the mixture was purified by Prep-HPLC (conditions: Gemini-NX C18 AXAI Packed, 21.2*150 mm, 5 μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 10% B to 25% B in 12 minutes; 254/220 nm; RT: 12.30 minutes). This resulted in (2S,4R)-1-[(2S)-2-(2-[2-[2-(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-

carbonylamino)ethoxy]ethoxy]acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-[[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide formic acid (13.9 mg, 26.23%) as a white solid. .sup.1H NMR (400 MHz, Methanol-d4) δ 8.88 (s, 1H), 8.56 (brs, 1.0H, FA), 7.56 (s, 1H), 7.49-7.38 (m, 4H), 6.67 (s, 2H), 4.84-4.75 (m, 2H), 4.67-4.59 (m, 1H), 4.52 (s, 1H), 4.48-4.26 (m, 5H), 4.03-3.83 (m, 1 OH), 3.77-3.61 (m, 7H), 3.59 (s, 3H), 3.55-3.48 (m, 1H), 3.43-3.34 (m, 2H), 2.84 (s, 6H), 2.69-2.52 (m, 2H), 2.48 (s, 3H), 2.31 (dd, J=13.1, 7.7 Hz, 1H), 2.18-2.07 (m, 1H), 1.08 (s, 9H). LCMS (ESI) m/z: [M+H].sup.+=959.55.

Example 62—Preparation of (2R,4S)-1-[(2R)-2-[2-(2-[2-[2-(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carbonylamino)ethoxy]ethoxy]ethoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-[[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide (Compound D35)

(332) ##STR01010##

(333) Compound D35 was prepared in a similar manner to the preparation of compound D34. Compound D35 (24.3 mg, 29.8%) was obtained as an off-white solid. .sup.1H NMR (300 MHz, DMSO-d6) δ 8.98 (s, 1H), 8.59 (s, 1H), 8.17 (brs, 0.4H, FA), 7.64 (s, 1H), 7.40 (s, 5H), 6.66 (d, J=18.5 Hz, 3H), 5.15 (s, 1H), 4.63-4.53 (m, 1H), 4.51-4.32 (m, 3H), 4.31-4.17 (m, 3H), 3.97 (s, 2H), 3.81 (s, 7H), 3.72 (s, 2H), 3.63-3.47 (m, 12H), 3.40 (s, 4H), 3.20 (s, 2H), 2.44 (s, 6H), 2.35 (s, 5H), 2.13-2.00 (m, 1H), 1.98-1.82 (m, 1H), 0.95 (s, 9H). LCMS (ESI) m/z: [M+H].sup.+=1003.60.

Example 63—Preparation of (2S,4R)-1-[(2S)-2-[6-(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carbonylamino)hexanamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-[[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide (Compound D36)

(334) ##STR01011##

(335) Compound D36 was prepared in a similar manner to the preparation of compound D34. Compound D36 formic acid (13.3 mg, 24.6%) was obtained as a white solid. .sup.1H NMR (400 MHz, DMSO-d6) δ 9.05 (brs, 0.7H, FA), 8.99 (s, 1H), 8.56 (t, J=6.0 Hz, 1H), 7.83 (d, J=9.3 Hz, 1H), 7.66 (s, 1H), 7.41 (q, J=8.2 Hz, 4H), 6.73 (s, 2H), 6.65 (t, J=5.4 Hz, 1H), 6.51 (s, 0.3H, FA), 5.12 (d, J=3.6 Hz, 1H), 4.55 (d, J=9.4 Hz, 1H), 4.47-4.39 (m, 2H), 4.35 (s, 1H), 4.23 (s, 5H), 3.87 (s, 6H), 3.71-3.62 (m, 2H), 3.51 (s, 3H), 3.41 (t, J=5.5 Hz, 2H), 3.30-3.26 (m, 2H), 3.08-2.98 (m, 2H), 2.74 (s, 6H), 2.45 (s, 3H), 2.31-2.22 (m, 1H), 2.17-2.00 (m, 2H), 1.95-1.87 (m, 1H), 1.55-1.38 (m, 4H), 1.29-1.20 (m, 2H), 0.93 (s, 9H). LCMS (ESI) m/z: [M+H]+=927.55.

Example 64—Preparation of (2S,4R)-1-[(2S)-2-[8-(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carbonylamino)octanamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-[[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide formic acid (Compound D37)

(336) ##STR01012##

(337) Compound D37 was prepared in a similar manner to the preparation of compound D34. Compound D37 formic acid (19.9 mg, 37.9%) was obtained as a white solid. .sup.1H NMR (400 MHz, Methanol-d4) δ 8.89 (s, 1H), 8.57 (brs, 0.6H, FA), 7.58 (s, 1H), 7.51-7.40 (m, 4H), 6.69 (s, 2H), 4.66 (s, 1H), 4.62-4.49 (m, 3H), 4.38 (d, J=12.6 Hz, 3H), 4.16 (s, 2H), 3.92 (s, 6H), 3.90 (s, 1H), 3.82 (dd, J=11.0, 3.9 Hz, 1H), 3.64 (s, 3H), 3.53 (t, J=5.5 Hz, 2H), 3.20 (t, J=7.1 Hz, 2H), 2.71 (s, 6H), 2.63 (t, J=5.2 Hz, 2H), 2.49 (s, 3H), 2.36-2.19 (m, 3H), 2.15-2.05 (m, 1H), 1.63 (t, J=6.8 Hz, 2H), 1.54 (t, J=7.0 Hz, 2H), 1.36 (s, 6H), 1.05 (s, 9H). LCMS (ESI) m/z: [M+H]+=955.55.

Example 65—Preparation of (2S,4R)-1-[(2S)-2-[10-(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carbonylamino)decanamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-[[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide (Compound D38)

(338) ##STR01013##

(339) Compound D35 was prepared in a similar manner to the preparation of compound D34. Compound D35 formic acid (15.3 mg, 29.6%) was obtained as a white solid. .sup.1H NMR (400 MHz, Methanol-d4) δ 8.90 (s, 1H), 8.57 (brs, 0.5H, FA), 7.59 (s, 1H), 7.52-7.41 (m, 4H), 6.69 (s, 2H), 4.65 (s, 1H), 4.62-4.49 (m, 3H), 4.40-4.34 (m, 3H), 4.14 (s, 2H), 3.92 (s, 7H), 3.82 (dd, J=10.9, 3.9 Hz, 1H),

3.64 (s, 3H), 3.54 (t, J=5.6 Hz, 2H), 3.20 (t, J=7.2 Hz, 2H), 2.69 (s, 6H), 2.63 (t, J=5.1 Hz, 2H), 2.49 (s, 3H), 2.37-2.19 (m, 3H), 2.14-2.05 (m, 1H), 1.68-1.48 (m, 4H), 1.34 (s, 1 OH), 1.05 (s, 9H). LCMS (ESI) m/z: [M+H].sup.+=983.65.

Example 66—Preparation of Compounds D39-D302 and DD1

(340) In analogy to the procedures described in the examples above, compounds D39-D302 and DD1 were prepared using the appropriate starting materials

(341) TABLE-US-00008 Compound No. LCMS .sup.1H NMR D39 LCMS (ESI) .sup.1H NMR (400 MHz, Methanol-d4) δ 8.39 (s, 2H, FA), 7.66-7.61 (m, m/z: [M + H]+ = 1H), 7.59 (s, 1H), 7.09 (d, J = 7.9 Hz, 2H), 6.72 (s, 2H), 5.11 (dd, J = 795.6 13.3, 5.2 Hz, 1H), 4.40 (d, J = 6.8 Hz, 2H), 4.35 (d, J = 7.5 Hz, 4H), 3.95 (s, 8H), 3.64 (s, 3H), 3.55 (t, J = 5.6 Hz, 2H), 3.32-3.17 (m, 4H), 2.99-2.69 (m, 11H), 2.69-2.60 (m, 2H), 2.49 (td, J = 13.1, 4.8 Hz, 1H), 2.41 (d, J = 7.0 Hz, 2H), 2.16 (dtd, J = 12.8, 5.3, 2.4 Hz, 1H), 1.91 (d, J = 13.4 Hz, 2H), 1.84 (d, J = 3.6 Hz, 1H), 1.40-1.26 (m, 2H). D40 LCMS (ESI) .sup.1H NMR (400 MHz, Methanol-d4) δ 8.52 (s, 1H, FA), 7.58 (s, 1H), 7.45 m/z: [M + H]+ = (d, J = 8.4 Hz, 1H), 7.38-7.29 (m, 2H), 6.70 (s, 2H), 5.15 (dd, J = 795.6 13.3, 5.1 Hz, 1H), 4.48-4.39 (m, 2H), 4.36 (s, 2H), 4.23 (s, 2H), 3.93 (s, 6H), 3.82-3.74 (m, 2H), 3.64 (s, 3H), 3.55 (t, J = 5.6 Hz, 2H), 3.18 (s, 4H), 2.92 (ddd, J = 18.3, 13.5, 5.4 Hz, 2H), 2.86-2.59 (m, 11H), 2.49 (td, J = 13.2, 4.7 Hz, 1H), 2.40 (d, J = 7.1 Hz, 2H), 2.19 (ddd, J = 10.0, 5.2, 2.6 Hz, 1H), 1.93 (d, J = 13.0 Hz, 2H), 1.77 (s, 1H), 1.45- 1.33 (m, 2H). D41 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.09 (s, 1H), 7.70-7.64 (m, 2H), m/z: [M + H]+ = 7.33 (d, J = 2.3 Hz, 1H), 7.29-7.22 (m, 1H), 6.69 (s, 2H), 6.58 (d, J = 837.5 5.0 Hz, 1H), 5.07 (dd, J = 12.9, 5.4 Hz, 1H), 4.62-4.46 (m, 2H), 4.07 (d, J = 13.0 Hz, 3H), 3.89-3.80 (m, 1H), 3.85 (s, 6H), 3.60-3.30 (m, 9H), 3.14-2.82 (m, 8H), 2.78 (d, J = 4.8 Hz, 1H), 2.63-2.52 (m, 5H), 2.17 (d, J = 17.0 Hz, 1H), 2.06-1.98 (m, 1H), 1.76 (d, J = 12.7 Hz, 2H), 1.60-1.52 (m, 3H), 1.27-1.13 (m, 2H), 0.86 (d, J = 6.7 Hz, 3H). D42 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.09 (s, 1H), 8.14 (s, 0H), 7.64 (d, m/z: [M + H]+ = J = 9.1 Hz, 2H), 7.31 (d, J = 2.2 Hz, 1H), 7.27-7.18 (m, 1H), 6.60 (d, 851.75 J = 5.7 Hz, 3H), 5.07 (dd, J = 12.9, 5.4 Hz, 1H), 4.21 (s, 2H), 4.05 (d, J J = 12.6 Hz, 2H), 3.79 (s, 6H), 3.66-3.46 (m, 5H), 3.41 (dd, J = 8.1, 2.8 Hz, 2H), 3.31 (s, 4H), 3.00-2.90 (m, 4H), 2.92-2.81 (m, 3H), 2.63-2.55 (m, 4H), 2.09-1.94 (m, 3H), 1.76 (d, J = 12.5 Hz, 2H), 1.63-1.33 (m, 3H), 1.30-1.13 (m, 3H), 1.10-0.95 (m, 6H). D43 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.09 (s, 1H), 8.16 (s, FA, 1H), 7.67- m/z: [M + H]+ = 7.62 (m, 2H), 7.30 (d, J = 2.3 Hz, 1H), 7.23 (dd, J = 8.8, 2.3 Hz, 1H), 867.35 6.71 (t, J = 5.5 Hz, 1H), 6.59 (s, 2H), 5.07 (dd, J = 12.9, 5.4 Hz, 1H), 4.22 (s, 2H), 4.03 (d, J = 13.0 Hz, 2H), 3.78 (s, 6H), 3.53 (s, 2H), 3.50 (s, 3H), 3.45-3.31 (m, 8H), 3.24 (s, 3H), 3.24-3.16 (m, 2H), 2.98- 2.82 (m, 3H), 2.63-2.53 (m, 2H), 2.43 (s, 5H), 2.35-2.30 (m, 3H), 2.04-1.97 (m, 1H), 1.74 (d, J = 12.7 Hz, 2H), 1.57 (s, 1H), 1.40-1.37 (m, 2H), 1.23-1.10 (m, 2H). D44 LCMS (ESI) .sup.1H NMR (400 MHz, MeOD) δ 8.49 (s, 2FA, 2H), 7.82 (d, J = 8.3 Hz, m/z: [M + H]+ = 1H), 7.58 (s, 1H), 7.29 (d, J = 2.2 Hz, 1H), 7.25 (dd, J = 8.3, 2.3 Hz, 867.75 1H), 6.72 (s, 2H), 5.13 (dd, J = 12.6, 5.5 Hz, 1H), 4.38-4.30 (m, 3H), 3.95 (s, 5H), 3.90-3.81 (m, 1H), 3.80-3.62 (m, 1H), 3.58-3.50 (m, 3H), 3.52-3.45 (m, 1H), 3.15-3.04 (m, 2H), 2.78 (s, 4H), 2.77-2.74 (m, 1H), 2.73-2.68 (m, 1H), 2.67-2.57 (m, 3H), 2.56-2.50 (m, 4H), 2.25-2.09 (m, 1H), 2.09-1.97 (m, 6H), 1.88-1.79 (m, 4H), 1.58- 1.53 (m, 2H), 1.38-1.29 (m, 3H). D45 LCMS (ESI) .sup.1H NMR (400 MHz, MeOD) δ 8.49 (s, 2FA, 2H), 7.82 (d, J = 8.3 Hz, m/z: [M + H]+ = 1H), 7.58 (s, 1H), 7.29 (d, J = 2.2 Hz, 1H), 7.25 (dd, J = 8.3, 2.3 Hz, 826.35 1H), 6.72 (s, 2H), 5.13 (dd, J = 12.6, 5.5 Hz, 1H), 4.38-4.30 (m, 3H), 3.95 (s, 5H), 3.90-3.81 (m, 1H), 3.80-3.62 (m, 1H), 3.58-3.50 (m, 3H), 3.52-3.45 (m, 1H), 3.15-3.04 (m, 2H), 2.78 (s, 4H), 2.77-2.74 (m, 1H), 2.73-2.68 (m, 1H), 2.67-2.57 (m, 3H), 2.56-2.50 (m, 4H), 2.25-2.09 (m, 1H), 2.09-1.97 (m, 6H), 1.88-1.79 (m, 4H), 1.58- 1.53 (m, 2H), 1.38-1.29 (m, 3H). D46 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO) δ 11.09 (s, 1H), 8.20 (s, FA, 1H), 7.68- m/z: [M + H]+ = 7.61 (m, 2H), 7.30 (d, J = 2.2 Hz, 1H), 7.22 (dd, J = 8.7, 2.3 Hz, 1H), 873.75 7.13 (t, J = 5.7, 5.7 Hz, 1H), 6.59 (s, 2H), 6.15-5.81 (m, 1H), 5.07 (dd, J = 12.9, 5.4 Hz, 1H), 4.26 (s, 2H), 4.03 (d, J = 12.9 Hz, 2H), 3.78 (s, 6H), 3.55-3.48 (m, 5H), 3.47-3.36 (m, 5H), 2.99-2.83 (m, 3H), 2.63-2.52 (m, 4H), 2.44-2.38 (m, 5H), 2.35-2.26 (m, 4H), 2.04- 1.97 (m, 1H), 1.78-1.70 (m, 2H), 1.65-1.47 (m, 1H), 1.40-1.32 (m, 2H), 1.26-1.11 (m, 2H). D47 LCMS (ESI) .sup.1H NMR (400 MHz, MeOD) δ 8.51 (s, 1H), 7.81 (d, J = 8.2 Hz, 1H), m/z: [M + H]+ = 7.58 (s, 1H), 7.32-7.20 (m, 2H), 6.72 (s, 2H), 5.12 (dd, J = 12.6, 5.4 867.55 Hz, 1H), 4.41-4.31 (m, 4H), 3.95 (s, 6H), 3.64 (s, 3H), 3.59-3.45 (m, 5H), 3.11-3.07 (m, 2H), 2.92-2.82 (m, 1H), 2.81-2.69 (m, 5H), 2.67-2.59 (m,

3H), 2.53-2.57 (m, 4H), 2.20-2.09 (m, 1H), 2.08- 1.96 (m, 5H), 1.87-1.78 (m, 4H), 1.68-1.43 (m, 2H). D48 LCMS (ESI) .sup.1H NMR (400 MHz, MeOD) δ 7.68 (d, J = 8.5 Hz, 1H), 7.57 (s, 1H), m/z: [M + H]+ = 7.36 (d, J = 2.3 Hz, 1H), 7.23 (dd, J = 8.6, 2.3 Hz, 1H), 6.73 (s, 2H), 826.55 5.08 (dd, J = 12.5, 5.5 Hz, 1H), 4.48-4.43 (m, 2H), 4.36 (s, 2H), 4.07 (d, J = 13.1 Hz, 2H), 3.94 (s, 6H), 3.64 (s, 4H), 3.58-3.50 (m, 9H), 3.22-3.17 (m, 2H), 3.01 (t, J = 12.4, 12.4 Hz, 2H), 2.93-2.83 (m, 1H), 2.80-2.70 (m, 2H), 2.69-2.59 (m, 2H), 2.18-2.06 (m, 1), 1.88 (d, J = 12.9 Hz, 2H), 1.74-1.68 (m, 3H), 1.44-1.34 (m, 2H). D49 LCMS (ESI) .sup.1H NMR (400 MHz, Methanol-d4)6 7.61-7.50 (m, 2H), 7.18 (d, J = m/z: [M + H]+ = 8.3 Hz, 1H), 6.73 (s, 2H), 5.13 (dd, J = 13.3, 5.2 Hz, 1H), 4.54-4.45 839.31 (m, 2H), 4.38-4.34 (m, 4H), 3.95 (s, 9H), 3.65-3.61 (m, 4H), 3.59- 3.51 (m, 4H), 3.37-3.32 (m, 2H), 3.18-3.08 (m, 2H), 3.04-2.98 (m, 4H), 2.96-2.86 (m, 1H), 2.86-2.80 (m, 2H), 2.79-2.74 (m, 5H), 2.64 (t, J = 5.7 Hz, 2H), 2.59-2.44 (m, 1H), 2.25-2.11 (m, 1H), 2.07- 1.95 (m, 2H), 1.80-1.47 (m, 5H). LCMS (ESI) .sup.1H NMR (400 MHz, Methanol-d4) δ 7.56 (s, 1H), 6.77-6.64 (m, 3H), D50 m/z: [M + H]+ = 6.57 (s, 1H), 5.04 (dd, J = 13.2, 5.4 Hz, 1H), 4.48-4.28 (m, 6H), 4.17- 839.35 3.98 (m, 2H), 3.98-3.86 (m, 10H), 3.76-3.45 (m, 10H), 3.28- 3.20 (m, 3H), 3.16-3.01 (m, 2H), 2.94-2.81 (m, 1H), 2.81-2.71 (m, 4H), 2.66-2.56 (m, 2H), 2.43 (qd, J = 13.0, 4.7 Hz, 1H), 2.19- 2.07 (m, 1H), 2.06-1.87 (m, 3H), 1.86-1.69 (m, 3H), 1.67-1.48 (m, 2H). D51 LCMS (ESI) .sup.1H NMR (400 MHz, Methanol-d4) δ 7.66-7.52 (m, 2H), 6.72 (s, 2H), m/z: [M + H]+ = 6.57 (d, J = 8.1 Hz, 2H), 5.11 (dd, J = 13.3, 5.1 Hz, 1H), 4.70-4.09 821.40 (m, 10H), 3.96 (s, 6H), 3.91-3.73 (m, 4H), 3.64 (s, 3H), 3.55 (t, J = 5.6 Hz, 2H), 3.34 (s, 4H), 3.25-3.10 (m, 1H), 3.08-3.00 (m, 1H), 2.98-2.84 (m, 1H), 2.84-2.72 (m, 4H), 2.62 (t, J = 5.3 Hz, 2H), 2.58- 2.40 (m, 1H), 2.35-2.06 (m, 5H), 1.38 (d, J = 6.4 Hz, 3H). D52 LCMS (ESI) .sup.1H NMR (400 MHz, Methanol-d4) δ 7.57 (s, 1H), 7.42 (d, J = 8.2 Hz, m/z: [M + H]+ = 1H), 6.88 (d, J = 2.3 Hz, 1H), 6.80 (dd, J = 8.2, 2.3 Hz, 1H), 6.73 (s, 821.55 2H), 5.14 (dd, J = 13.3, 5.2 Hz, 1H), 4.60-4.45 (m, 2H), 4.43-4.31 (m, 5H), 4.31-4.10 (m, 3H), 3.97 (s, 6H), 3.89-3.70 (m, 5H), 3.64 (s, 3H), 3.55 (t, J = 5.6 Hz, 2H), 3.32 (s, 4H), 3.17-3.00 (m, 1H), 2.99- 2.85 (m, 1H), 2.85-2.80 (m, 1H), 2.78 (s, 3H), 2.62 (t, J = 5.5 Hz, 2H), 2.57-2.42 (m, 1H), 2.39-2.05 (m, 5H), 1.39 (d, J = 6.6 Hz, 3H). D53 LCMS (ESI) .sup.1H NMR (400 MHz, Methanol-d4) δ 7.58 (s, 1H), 7.53 (dd, J = 8.4, 2.0 m/z: [M + H]+ = Hz, 1H), 7.24 (dd, J = 8.4, 2.4 Hz, 1H), 7.13 (dd, J = 8.1, 2.3 Hz, 1H), 698.50 6.73 (d, J = 6.8 Hz, 2H), 5.15 (dd, J = 13.3, 5.1 Hz, 1H), 4.61 (s, 1H), 4.57-4.46 (m, 3H), 4.46-4.33 (m, 5H), 4.33-4.26 (m, 1H), 4.23- 4.14 (m, 1H), 3.97 (s, 2H), 3.91 (s, 4H), 3.64 (s, 3H), 3.54 (t, J = 5.5 Hz, 2H), 2.98 (d, J = 2.8 Hz, 3H), 2.98-2.86 (m, 1H), 2.82 (dd, J = 4.8, 2.5 Hz, 1H), 2.78 (s, 3H), 2.62 (s, 2H), 2.51 (qd, J = 13.2, 4.7 Hz, 1H), 2.19 (ddd, J = 10.6, 5.3, 2.9 Hz, 1H). D54 LCMS (ESI) .sup.1H NMR (300 MHz, Methanol-d4) δ 8.46 (s, 2H, FA), 7.68-7.56 (m, m/z: [M + H]+ = 2H), 7.07 (d, J = 9.3 Hz, 1H), 6.75-6.65 (m, 3H), 4.37 (s, 4H), 3.96 (s, 835.25 7H), 3.65 (s, 3H), 3.60-3.50 (m, 4H), 3.50-3.40 (m, 4H), 3.20-3.10 (m, 2H), 2.80-2.50 (m, 13H), 2.10-1.90 (m, 3H), 1.80-1.40 (m, 10H). D55 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 10.96 (s, 1H), 7.66 (s, 1H), 7.52 (d, m/z: [M + H]+ = J = 8.7 Hz, 1H), 7.15-6.99 (m, 4H), 6.62 (s, 1H), 5.15-4.98 (m, 1H), 813.35 4.40-4.13 (m, 4H), 3.99-3.72 (m, 7H), 3.61-3.31 (m, 7H), 3.23- 2.94 (m, 5H), 2.95-2.69 (m, 3H), 2.66-2.56 (m, 4H), 2.45-2.22 (m, 6H), 2.05-1.88 (m, 1H), 1.75 (d, J = 12.3 Hz, 2H), 1.67-1.46 (m, 3H), 1.37-1.11 (m, 2H). D56 LCMS (ESI) .sup.1H NMR (300 MHz, MeOD) δ 8.45 (s, 2FA, 2H), 7.60 (d, J = 9.4 Hz, m/z: [M + H]+ = 2H), 6.73 (s, 2H), 6.55 (d, J = 7.4 Hz, 2H), 5.10 (dd, J = 13.2, 5.1 Hz, 835.85 1H), 4.37 (d, J = 4.4 Hz, 6H), 3.95 (s, 6H), 3.74 (s, 4H), 3.64 (s, 3H), 3.55 (t, J = 5.2, 5.2 Hz, 4H), 3.20-3.06 (m, 2H), 2.97-2.77 (m, 1H), 2.81-2.75 (m, 5H), 2.73-2.59 (m, 5H), 2.51-2.45 (m, 3H), 2.23- 1.88 (m, 8H), 1.56 (s, 2H). D57 LCMS (ESI) .sup.1H NMR (400 MHz, Methanol-d4) δ 7.58 (s, 1H), 7.35 (dd, J = 10.1, m/z: [M + H]+ = 2.2 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.22 (dd, J = 10.1, 4.0 Hz, 1H), 811.30 6.77-6.71 (m, 2H), 5.36 (dd, J = 12.6, 5.3 Hz, 1H), 4.37 (d, J = 6.9 Hz, 4H), 4.04-3.87 (m, 6H), 3.65 (d, J = 6.4 Hz, 5H), 3.60-3.52 (m, 4H), 3.36-3.43 (m, 2H), 3.28 (d, J = 10.1 Hz, 3H), 3.18-3.05 (m, 2H), 2.93 (d, J = 5.0 Hz, 1H), 2.90 (d, J = 5.2 Hz, 1H), 2.86 (d, J = 4.0 Hz, 1H), 2.80-2.84 (m, 1H), 2.79 (s, 3H), 2.70 (dd, J = 13.0, 4.7 Hz, 1H), 2.63 (s, 3H), 2.33 (t, J = 5.0 Hz, 1H), 2.02 (t, J = 15.9 Hz, 3H), 1.80 (t, J = 8.2 Hz, 2H), 1.65-1.48 (m, 2H). D58 825.5 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.96 (s, 1H), 8.14 (s, 1H, FA), 7.89 (q, J = 4.2 Hz, 1H), 7.69 (s, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.13-7.03 (m, 2H), 6.73 (s, 2H), 5.06 (dd, J = 13.2, 5.1 Hz, 1H), 4.59 (s, 2H), 4.34 (d, J = 17.0 Hz, 1H), 4.21 (d, J = 17.0 Hz, 1H), 4.16 (s, 2H), 3.93 (t, J = 5.5 Hz, 2H), 3.87 (s, 6H), 3.53 (s, 3H), 3.48-3.40 (m, 6H), 3.01-2.84 (m, 6H), 2.69-2.55 (m, 7H), 2.47-2.30 (m, 3H), 2.01-1.92 (m, 1H), 1.84 (d, J = 13.0 Hz, 2H), 1.68-

1.29 (m, 5H). D59 LCMS (ESI) .sup.1H NMR (300 MHz, Methanol-d4) δ 8.44 (s, 3H, FA), 7.59 (s, 1H), 7.40 m/z: [M + H]+ = (d, J = 8.2 Hz, 1H), 6.88-6.69 (m, 4H), 5.21-5.04 (m, 2H), 4.43- 821.55 4.34 (m, 4H), 4.10-3.87 (m, 9H), 3.76-3.61 (m, 8H), 3.56 (s, 2H), 3.19-3.05 (m, 1H), 2.96-2.83 (m, 1H), 2.79 (s, 3H), 2.77-2.71 (m, 3H), 2.68-2.46 (m, 7H), 2.20 (s, 1H), 1.91 (s, 4H), 1.55 (d, J = 6.6 Hz, 3H). D60 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 11.01 (s, 1H), 8.14 (s, 1H, FA), 7.65 m/z: [M + H]+ = (s, 1H), 7.30 (s, 1H), 7.22 (s, 1H), 6.65-6.57 (m, 3H), 5.19 (dd, J = 633.30 11.6, 4.5 Hz, 1H), 4.22 (s, 2H), 3.81 (s, 6H), 3.67 (s, 2H), 3.50 (s, 3H), 3.43-3.31 (m, 6H), 2.96-2.70 (m, 6H), 2.67-2.56 (m, 6H), 2.19- 2.11 (m, 1H). D61 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 7.79 (d, J = 7.6 Hz, 1H), 7.62 (s, 1H), m/z: [M + H]+ = 6.75-6.63 (m, 3H), 6.28 (d, J = 1.6 Hz, 1H), 5.23 (dd, J = 12.5, 5.3 Hz, 700.25 1H), 4.31 (s, 2H), 4.22 (s, 2H), 3.94-3.87 (m, 2H), 3.87 (s, 6H), 3.50 (s, 3H), 3.4-3.36 (m, 4H), 3.32-3.10 (m, 4H), 2.94-2.81 (m, 1H), 2.70-2.60 (m, 1H), 2.59 (s, 3H), 2.58-2.50 (m, 2H), 2.49-2.42 (m, 1H), 2.22-2.08 (m, 1H). D62 LCMS (ESI) .sup.1H NMR (400 MHz, Methanol-d4) δ 8.54 (s, 0.3H, FA), 7.56 (s, 1H), m/z: [M + H]+ = 6.62 (s, 2H), 5.05 (dd, J = 12.6, 5.3 Hz, 1H), 4.37 (s, 2H), 3.88 (s, 6H), 664.40 3.84 (s, 2H), 3.64 (s, 3H), 3.54 (t, J = 5.6 Hz, 2H), 3.23 (s, 3H), 3.18 (d, J = 5.3 Hz, 4H), 2.93-2.72 (m, 9H), 2.65 (t, J = 5.6 Hz, 2H), 2.62- 2.49 (m, 1H), 2.25-2.12 (m, 1H). D63 839.7 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.09 (s, 1H), 8.21 (s, 1H, FA), 7.86 (d, J = 4.4 Hz, 1H), 7.68 (t, J = 4.3 Hz, 2H), 7.33 (d, J = 2.2 Hz, 1H), 7.25 (dd, J = 8.7, 2.3 Hz, 1H), 6.61 (s, 2H), 5.07 (dd, J = 12.7, 5.4 Hz, 1H), 4.60 (s, 2H), 3.98-3.85 (m, 2H), 3.79 (s, 6H), 3.78 (s, 1H), 3.58 (s, 3H), 3.51 (s, 3H), 3.47-3.38 (m, 4H), 2.98-2.82 (m, 6H), 2.65- 2.54 (m, 3H), 2.49-2.44 (m, 3H), 2.33 (t, J = 7.3 Hz, 2H), 2.19-1.95 (m, 3H), 1.63 (d, J = 12.0 Hz, 2H), 1.48-1.02 (m, 5H). D64 824.7 1HNMR (300 MHz, DMSO-d6) δ 11.09 (s, 1H), 8.15 (s, 0.4H, FA), 7.74-7.63 (m, 2H), 7.36 (d, J = 2.2 Hz, 1H), 7.28 (dd, J = 8.6, 2.2 Hz, 1H), 6.73 (s, 2H), 5.08 (dd, J = 12.7, 5.4 Hz, 1H), 4.29 (s, 2H), 4.17 (s, 2H), 3.87 (s, 6H), 3.66 (s, 3H), 3.54-3.44 (m, 11H), 3.07- 2.79 (m, 4H), 2.64-2.53 (m, 7H), 2.49-2.40 (m, 2H), 2.09-1.97 (m, 1H), 1.85 (d, J = 13.0 Hz, 2H), 1.66-1.53 (m, 1H), 1.45 (s, 4H). D65 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 7.73-7.52 (m, 3H), 7.40 (d, J = 2.6 m/z: [M + H]+ = Hz, 1H), 6.71 (d, J = 2.0 Hz, 2H), 5.23 (dd, J = 11.4, 5.7 Hz, 1H), 4.20 836.65 (d, J = 8.2 Hz, 4H), 3.94 (s, 2H), 3.86 (s, 6H), 3.67-3.62 (m, 1H), 3.51 (s, 4H), 3.45-3.30 (m, 4H), 3.28-3.08 (m, 6H), 3.07-2.92 (m, 3H), 2.93-2.75 (m, 1H), 2.68-2.55 (m, 9H), 2.23-2.08 (m, 1H), 1.92-1.70 (m, 3H), 1.68-1.52 (m, 2H), 1.52-1.28 (m, 2H). D66 752.3 1H NMR (300 MHz, Methanol-d4) δ 7.41 (d, J = 8.2 Hz, 1H), 7.23 (s, 1H), 6.88 (d, J = 2.2 Hz, 1H), 6.86 (s, 2H), 6.80 (dd, J = 8.2, 2.3 Hz, 1H), 5.14 (dd, J = 13.3, 5.1 Hz, 1H), 4.48 (s, 2H), 4.35 (dd, J = 27.7, 5.0 Hz, 6H), 4.13 (d, J = 10.3 Hz, 2H), 3.96 (s, 6H), 3.77 (d, J = 17.5 Hz, 4H), 3.63 (s, 3H), 3.49 (dd, J = 10.8, 6.4 Hz, 7H), 3.10 (d, J = 1.7 Hz, 2H), 2.99-2.84 (m, 1H), 2.79 (dd, J = 13.0, 2.7 Hz, 1H), 2.60- 2.41 (m, 1H), 2.32-2.02 (m, 4H). D67 706.52 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.81 (s, 1H), 8.17 (s, 2H), 7.60 (s, 1H), 6.56 (s, 3H), 5.73 (s, 1H), 4.19 (s, 2H), 3.76 (s, 6H), 3.51 (s, 2H), 3.47 (s, 3H), 3.38 (t, J = 5.5 Hz, 2H), 3.26-3.08 (m, 1H), 3.07-2.92 (m, 2H), 2.81 (d, J = 11.5 Hz, 2H), 2.57 (d, J = 4.2 Hz, 3H), 2.28 (t, J = 7.4 Hz, 3H), 2.04 (s, 1H), 1.57 (d, J = 12.0 Hz, 2H), 1.15 (s, 3H), 1.05 (d, J = 11.4 Hz, 2H). D68 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 11.00 (s, 1H), 8.23 (s, 2H, FA), 7.69- m/z: 7.62 (m, 2H), 7.49 (s, 1H), 7.40 (d, J = 7.9 Hz, 1H), 6.61 (s, 3H), [M + H]+ = 808.43. 5.11 (dd, J = 13.2, 5.1 Hz, 1H), 4.46-4.26 (m, 3H), 4.22 (s, 2H), 3.80 (s, 6H), 3.64 (s, 2H), 3.50 (s, 3H), 3.44-3.36 (m, 2H), 3.05 (d, J = 10.6 Hz, 2H), 2.92 (d, J = 10.4 Hz, 3H), 2.67-2.57 (m, 5H), 2.49- 2.30 (m, 3H), 2.29-2.06 (m, 4H), 2.04-1.94 (m, 1H), 1.87-1.57 (m, 6H), 1.40 (s, 2H), 1.34-1.07 (m, 3H). D69 LCMS (ESI) .sup.1H NMR (400 MHz, Methanol-d4) δ 7.67-7.48 (m, 2H), 7.45-7.32 m/z: [M + H]+ = (m, 2H), 6.73 (d, J = 6.3 Hz, 2H), 5.25-5.09 (m, 1H), 4.52-4.42 (m, 809.40 2H), 4.37 (d, J = 3.6 Hz, 3H), 3.96 (s, 2H), 3.95 (s, 6H), 3.75 (d, J = 13.9 Hz, 2H), 3.64 (s, 3H), 3.60 (d, J = 12.7 Hz, 2H), 3.54 (d, J = 5.6 Hz, 2H), 3.32-3.25 (m, 3H), 3.19 (s, 1H), 3.18-3.05 (m, 2H), 2.98- 2.86 (m, 1H), 2.82 (dd, J = 4.8, 2.5 Hz, 1H), 2.78 (s, 3H), 2.64 (t, J = 5.6 Hz, 2H), 2.51 (qd, J = 13.2, 4.7 Hz, 1H), 2.24-2.14 (m, 1H), 2.04 (d, J = 13.9 Hz, 2H), 2.00-1.86 (m, 1H), 1.86-1.70 (m, 3H), 1.68- 1.51 (m, 2H). D70 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 8.15 (s, 1H, FA), 7.73 (d, J = 8.5 Hz, m/z: 1H), 7.66-7.49 (m, 3H), 7.38 (d, J = 2.2 Hz, 1H), 7.33-7.23 (m, 2H), [M + H]+ = 824.35. 6.62-6.54 (m, 3H), 4.22 (s, 2H), 4.07 (d, J = 13.1 Hz, 2H), 3.78 (s, 6H), 3.55-3.49 (m, 5H), 3.44-3.39 (m, 4H), 2.97 (t, J = 12.5 Hz, 3H), 2.60 (d, J = 4.2 Hz, 4H), 2.44-2.31 (m, 8H), 1.76 (d, J = 12.9 Hz, 2H), 1.65-1.52 (m, 1H), 1.42-1.30 (m, 2H), 1.25-1.13 (m, 2H). D71 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 7.86-7.52 (m, 4H), 6.73 (s, 2H), m/z: 5.10

(dd, J = 13.2, 5.2 Hz, 1H), 4.51-4.28 (m, 2H), 4.24 (d, J = 9.8 [M + H]+ = 809.43. Hz, 4H), 3.88 (s, 6H), 3.67-3.58 (m, 2H), 3.51 (s, 3H), 3.43-3.28 (m, 6H), 3.22-2.99 (m, 6H), 2.96-2.72 (m, 4H), 2.67-2.53 (m, 8H), 2.48-2.33 (m, 2H), 2.10-1.95 (m, 4H). D72 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 7.73 (d, J = 7.9 Hz, 1H), 7.62 (s, 1H), m/z: 7.53-7.41 (m, 2H), 6.73 (s, 2H), 5.10 (dd, J = 13.2, 5.1 Hz, 1H), 4.50- [M + H]+ = 809.43. 4.29 (m, 2H), 4.24 (d, J = 10.0 Hz, 4H), 3.87 (s, 6H), 3.67-3.54 (m, 5H), 3.44-3.28 (m, 6H), 3.19-2.86 (m, 8H), 2.79-2.72 (m, 2H), 2.67-2.52 (m, 8H), 2.47-2.31 (m, 2H), 2.06-1.95 (m, 4H). D73 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 11.1 (br s, 1H), 8.26 (s, 2H, FA), m/z: [M + H]+ = 7.64 (s, 1H), 7.55 (d, J = 8.9 Hz, 3H), 6.61 (s, 3H), 5.11 (dd, J = 13.2, 808.43 5.1 Hz, 1H), 4.42 (d, J = 17.1 Hz, 1H), 4.28 (d, J = 17.2 Hz, 1H), 4.22 (s, 2H), 3.80 (s, 6H), 3.62 (s, 2H), 3.50 (s, 3H), 3.40 (t, J = 5.9 Hz, 2H), 3.05 (d, J = 10.7 Hz, 2H), 2.90 (d, J = 12.0 Hz, 3H), 2.71-2.54 (m, 5H), 2.42 (s, 4H), 2.46-2.35 (m, 3H), 2.16 (q, J = 12.1 Hz, 4H), 2.05-1.93 (m, 1H), 1.82-1.58 (m, 6H), 1.41 (s, 2H), 1.32-1.12 (m, 3H). D74 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 8.15 (s, 1H, FA), 7.64 (s, 1H), 6.68 m/z: (s, 2H), 6.64-6.57 (m, 1H), 4.22 (s, 2H), 3.95 (s, 2H), 3.84 (s, 6H), [M + H]+ = 701.50. 3.51 (s, 4H), 3.44-3.39 (m, 5H), 3.19-3.08 (m, 3H), 2.86 (s, 4H), 2.70-2.57 (m, 7H), 2.46-2.41 (m, 2H), 2.10 (s, 3H), 1.74 (s, 7H), 1.67-1.55 (m, 6H), 1.45-1.26 (m, 5H). D75 LCMS (ESI) .sup.1H NMR (400 MHz, Methanol-d4) δ 8.22 (s, 1H, FA), 7.58 (s, 1H), 7.38 m/z: (d, J = 6.1 Hz, 1H), 6.73 (s, 2H), 5.12 (dd, J = 12.7, 5.4 Hz, 1H), 4.36 [M + H]+ = 859.50. (s, 4H), 3.95 (s, 6H), 3.64 (s, 3H), 3.55 (t, J = 5.6 Hz, 4H), 3.50 (t, J = 4.7 Hz, 4H), 3.18-3.06 (m, 2H), 2.98 (s, 4H), 2.90-2.69 (m, 8H), 2.64 (t, J = 5.7 Hz, 2H), 2.19-2.11 (m, 1H), 2.02 (d, J = 13.8 Hz, 2H), 1.80-1.46 (m, 5H). D76 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.07 (s, 1H), 8.19 (s, 2H, FA), 8.09 m/z: (s, 1H), 7.82 (s, 1H), 7.63 (s, 1H), 7.42 (d, J = 8.7 Hz, 2H), 6.93 (d, J = [M + H]+ = 820.55. 8.7 Hz, 2H), 6.58 (s, 3H), 5.36 (dd, J = 11.9, 5.1 Hz, 1H), 4.21 (s, 2H), 3.78 (s, 6H), 3.52 (s, 2H), 3.50 (s, 3H), 3.42-3.39 (m, 6H), 3.14- 3.11 (m, 4H), 2.86-2.79 (m, 3H), 2.60 (d, J = 4.3 Hz, 4H), 2.49- 2.44 (m, 5H), 2.29-2.22 (m, 1H), 2.08-2.00 (m, 2H), 1.65-1.58 (m, 2H), 1.40-1.34 (m, 2H), 1.29-1.22 (m, 1H), 1.18-1.08 (m, 2H). D77 LCMS (ESI) .sup.1H NMR (300 MHz, Methanol-d4) δ 8.41 (s, 1H, FA), 7.72 (d, J = 7.8 m/z: Hz, 1H), 7.58 (s, 1H), 6.73 (s, 3H), 6.17 (s, 1H), 5.27 (dd, J = 12.3, 5.3 [M + H]+ = 811.55 Hz, 1H), 4.36 (s, 4H), 3.95 (s, 6H), 3.64 (s, 3H), 3.60-3.49 (m, 4H), 3.43 (s, 4H), 3.13-3.04 (m, 1H), 2.92-2.76 (m, 9H), 2.72-2.54 (m, 6H), 2.36-2.24 (m, 1H), 2.08-1.95 (m, 2H), 1.78-1.44 (m, 5H). D78 LCMS (ESI) .sup.1H NMR (400 MHz, Methanol-d4) δ 8.50 (s, 2H, FA), 7.58 (s, 1H), 7.51 m/z: [M + H]+ = (d, J = 9.6 Hz, 1H), 6.73 (s, 2H), 5.12 (dd, J = 12.8, 5.4 Hz, 1H), 4.36 858.50 (s, 4H), 3.96 (s, 6H), 3.64 (s, 4H), 3.55 (t, J = 5.6 Hz, 3H), 3.44 (s, 4H), 3.14-3.07 (m, 1H), 2.97-2.83 (m, 2H), 2.78 (s, 4H), 2.76- 2.69 (m, 5H), 2.66-2.57 (m, 4H), 2.17-2.11 (m, 1H), 2.06-1.98 (m, 2H), 1.75-1.49 (m, 5H). D79 793.47 D80 826.37 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.05 (s, 1H), 8.13 (s, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.61 (s, 1H), 7.31 (d, J = 2.2 Hz, 1H), 7.23 (dd, J = 8.7, 2.3 Hz, 1H), 6.61 (s, 1H), 4.19 (s, 2H), 3.79 (s, 6H), 3.76 (s, 2H), 3.48 (s, 3H), 3.30 (s, 6H), 2.99 (t, J = 10.0 Hz, 2H), 2.57 (d, J = 4.1 Hz, 2H), 2.36-2.28 (m, 2H), 1.98 (d, J = 12.8 Hz, 1H), 1.37 (s, 3H), 1.80- 1.61 (m, 2H), 1.32-1.18 (m, 2H). D81 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.15 (s, 2H, FA), 7.69 m/z: (d, J = 8.5 Hz, 1H), 7.63 (s, 1H), 7.34 (s, 1H), 7.26 (d, J = 8.8 Hz, 1H), [M + H]+ = 849.25. 6.75 (s, 1H), 6.64 (s, 2H), 5.07 (dd, J = 12.9, 5.3 Hz, 1H), 4.20 (s, 2H), 3.82 (s, 10H), 3.50 (s, 5H), 3.45-3.41 (m, 8H), 3.05-2.87 (m, 4H), 2.63-2.58 (m, 3H), 2.41-2.26 (m, 3H), 2.06-1.95 (m, 1H), 1.79- 1.66 (m, 2H), 1.45-1.36 (m, 3H), 1.33-1.21 (m, 2H), 0.57-0.51 (m, 2H), 0.45-0.39 (m, 2H). D82 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 7.70 (d, J = 8.5 Hz, 1H), 7.64 (s, 1H), m/z: [M + H]+ = 7.35 (d, J = 2.2 Hz, 1H), 7.27 (d, J = 8.9 Hz, 1H), 6.68-6.56 (m, 3H), 939. 5.72-5.59 (m, 2H), 5.27 (dd, J = 13.0, 5.3 Hz, 1H), 4.77 (p, J = 6.2 Hz, 1H), 4.22 (s, 2H), 3.82 (s, 8H), 3.50 (s, 3H), 3.47-3.38 (m, 8H), 3.16-2.96 (m, 4H), 2.90-2.66 (m, 2H), 2.65-2.53 (m, 7H), 2.40- 2.26 (m, 3H), 2.14-2.03 (m, 1H), 1.72 (d, J = 12.3 Hz, 2H), 1.47- 1.35 (m, 3H), 1.31-1.19 (m, 8H). D83 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 10.98 (s, 1H), 8.16 (s, 2H, FA), 7.64 m/z: (s, 1H), 7.44 (d, J = 11.8 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 6.65-6.52 [M + H]+ = 827.45. (m, 3H), 5.09 (dd, J = 13.4, 5.0 Hz, 1H), 4.41-4.19 (m, 5H), 3.80 (s, 7H), 3.65 (s, 4H), 3.50 (s, 5H), 3.41 (s, 2H), 3.04 (s, 4H), 2.98-2.87 (m, 3H), 2.61-2.58 (m, 4H), 2.44-2.30 (m, 4H), 2.07-1.93 (m, 1H), 1.72-1.59 (m, 2H), 1.47-1.10 (m, 6H). D84 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 10.98 (s, 1H), 8.16 (s, 2H, FA), 7.64 m/z: (s, 1H), 7.43 (d, J = 11.6 Hz, 1H), 7.23 (d, J = 7.5 Hz, 1H), 6.66-6.56 [M + H]+ = 827.35. (m, 3H), 5.08 (dd, J = 13.2, 5.1 Hz, 1H), 4.40-4.25 (m, 2H), 4.22 (s, 2H), 3.88-3.74

(m, 9H), 3.50 (s, 4H), 3.45-3.38 (m, 5H), 3.11 (s, 4H), 3.06-2.85 (m, 4H), 2.65-2.57 (m, 5H), 2.41-2.32 (m, 4H), 2.04-1.93 (m, 1H), 1.71 (d, J = 12.4 Hz, 2H), 1.44-1.24 (m, 5H). D85 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 10.95 (s, 1H), 8.18 (s, 2H, FA), 7.64 m/z: (s, 1H), 7.55-7.48 (m, 1H), 7.06 (d, J = 7.9 Hz, 2H), 6.65-6.56 (m, [M + H]+ = 809.80. 3H), 5.05 (dd, J = 13.3, 5.1 Hz, 1H), 4.33 (d, J = 16.9 Hz, 1H), 4.26- 4.17 (m, 3H), 3.81 (s, 6H), 3.71 (s, 2H), 3.50 (s, 3H), 3.41 (t, J = 5.6 Hz, 3H), 3.30-3.24 (m, 5H), 3.02-2.85 (m, 4H), 2.63-2.52 (m, 6H), 2.43-2.23 (m, 6H), 2.00-1.92 (m, 1H), 1.68 (d, J = 12.5 Hz, 2H), 1.44-1.30 (m, 3H), 1.29-1.16 (m, 2H). D86 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.10 (s, 1H), 8.16 (s, 1H, FA), 7.64 m/z: (s, 1H), 7.24 (s, 1H), 7.05 (d, J = 13.2 Hz, 1H), 6.66 (s, 2H), 6.60 (d, [M + H]+ = 840.40. J = 4.6 Hz, 1H), 5.07 (dd, J = 12.8, 5.4 Hz, 1H), 4.22 (s, 2H), 3.87 (s, 2H), 3.83 (s, 6H), 3.53-3.44 (m, 8H), 3.43-3.38 (m, 3H), 3.09 (d, J = 11.4 Hz, 2H), 2.94-2.83 (m, 1H), 2.63-2.54 (m, 6H), 2.49-2.41 (m, 5H), 2.37-2.30 (m, 2H), 2.06-1.97 (m, 1H), 1.73 (d, J = 12.6 Hz, 2H), 1.47-1.36 (m, 3H), 1.35-1.22 (m, 2H). D87 LCMS (ESI) ..sup.1H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.16 (s, 1H, FA), 7.67- m/z: 7.61 (m, 2H), 7.37 (t, J = 7.7 Hz, 1H), 6.66-6.55 (m, 3H), 5.10 (dd, [M + H]+ = 840.95. J = 12.8, 5.4 Hz, 1H), 4.22 (s, 2H), 3.81 (s, 6H), 3.74 (s, 2H), 3.50 (s, 4H), 3.41 (t, J = 5.5 Hz, 5H), 3.22 (t, J = 4.8 Hz, 5H), 2.99 (d, J = 11.2 Hz, 2H), 2.94-2.78 (m, 2H), 2.64-2.56 (m, 5H), 2.40-2.31 (m, 4H), 2.07-1.97 (m, 1H), 1.69 (d, J = 12.5 Hz, 2H), 1.38 (s, 3H), 1.29- 1.16 (m, 2H). D88 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6, D20) δ 7.80 (d, J = 11.1 Hz, 1H), m/z: 8.14(s, 0H, FA), 7.64 (s, 1H), 7.56 (s, 1H), 6.73 (s, 2H), 5.12 (dd, J = [M + H]+ = 841.55. 12.8, 5.4 Hz, 1H), 4.31-4.14 (m, 4H), 3.87 (s, 6H), 3.51 (s, 3H), 3.48- 3.39 (m, 6H), 3.31-3.06 (m, 4H), 3.06-2.80 (m, 4H), 2.66-2.56 (m, 5H), 2.56-2.53 (m, 4H), 2.10-1.99 (m, 1H), 1.91-1.82 (m, 2H), 1.81-1.15 (m, 6H). D89 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 11.02 (s, 1H), 8.27 (s, 1H, FA), 7.67- m/z: 7.55 (m, 1H), 7.28 (t, J = 7.7 Hz, 1H), 6.92 (d, J = 7.4 Hz, 1H), 6.73 [M + H]+ = 782.65. (d, J = 8.1 Hz, 1H), 6.67-6.62 (m, 1H), 6.59 (s, 2H), 5.56 (t, J = 5.0 Hz, 1H), 5.11 (dd, J = 13.2, 5.1 Hz, 1H), 4.27-4.06 (m, 5H), 3.83- 3.73 (m, 7H), 3.65 (s, 2H), 3.50 (s, 3H), 3.40 (t, J = 5.4 Hz, 2H), 3.28 (t, J = 7.1 Hz, 3H), 3.14-3.00 (m, 4H), 2.97-2.86 (m, 1H), 2.67- 2.53 (m, 2H), 2.34-2.25 (m, 1H), 2.09-1.98 (m, 1H), 1.98-1.84 (m, 2H), 1.63-1.50 (m, 2H), 1.43-1.21 (m, 10H). D90 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.18(s, 0H, FA), 7.83 m/z: (d, J = 8.3 Hz, 1H), 7.64 (s, 1H), 7.43 (d, J = 2.2 Hz, 1H), 7.35 (dd, J = [M + H]+ = 755.65. 8.3, 2.3 Hz, 1H), 6.69 (t, J = 5.4 Hz, 1H), 6.64 (s, 2H), 5.12 (dd, J = 12.9, 5.3 Hz, 1H), 4.19 (dd, J = 13.5, 7.1 Hz, 4H), 3.91 (s, 2H), 3.82 (s, 6H), 3.65-3.55 (m, 4H), 3.50 (s, 3H), 3.41 (t, J = 5.3 Hz, 4H), 3.13- 3.04 (m, 2H), 2.96-2.83 (m, 1H), 2.66-2.55 (m, 2H), 2.15-2.00 (m, 3H), 1.85-1.68 (m, 2H), 1.57-1.37 (m, 4H). D91 LCMS (ESI) .sup.1H NMR (300 MHz, Methanol-d4) δ 8.54 (br s, 1H, FA), 7.72 (d, J = m/z: [M + H]+ = 8.4 Hz, 1H), 7.61 (s, 1H), 7.41 (d, J = 2.1 Hz, 1H), 7.28 (d, J = 8.7 Hz, 811.70 1H), 6.98-6.87 (m, 2H), 5.10 (dd, J = 12.3, 5.3 Hz, 1H), 4.39-4.33 (m, 4H), 3.99 (s, 3H), 3.64 (s, 4H), 3.55 (s, 8H), 3.09 (t, J = 12.1 Hz, 2H), 2.92-2.80 (m, 5H), 2.80-2.71 (m, 5H), 2.64 (d, J = 5.9 Hz, 4H), 2.14 (s, 1H), 2.00 (s, 1H), 1.78-1.45 (m, 5H). D92 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 11.09 (s, 1H), 8.16 (s, 2H, FA), 8.08 m/z: (d, J = 1.7 Hz, 1H), 7.73-7.64 (m, 2H), 7.42 (d, J = 1.8 Hz, 1H), 7.34 [M + H]+ = 794.80. (d, J = 2.2 Hz, 1H), 7.26 (dd, J = 8.7, 2.3 Hz, 1H), 6.61 (q, J = 4.4 Hz, 1H), 5.08 (dd, J = 12.8, 5.4 Hz, 1H), 4.22 (s, 2H), 3.85 (s, 3H), 3.69 (s, 2H), 3.50 (s, 3H), 3.46-3.40 (m, 8H), 2.98-2.83 (m, 3H), 2.64- 2.55 (m, 5H), 2.45-2.25 (m, 5H), 2.17 (t, J = 11.4 Hz, 2H), 2.06- 1.98 (m, 1H), 1.65 (d, J = 11.8 Hz, 2H), 1.44-1.09 (m, 6H D93 848.51 D94 863.63 D95 863.56 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.03 (s, 1H), 8.14 (s, 1H), 7.62 (d, J = 8.6 Hz, 2H), 7.27 (d, J = 2.3 Hz, 1H), 7.20 (dd, J = 8.6, 2.4 Hz, 1H), 6.56 (s, 3H), 5.03 (dd, J = 13.0, 5.4 Hz, 1H), 4.19 (s, 2H), 4.10-3.91 (m, 3H), 3.76 (s, 6H), 3.51 (s, 2H), 3.47 (s, 3H), 3.37 (d, J = 5.8 Hz, 1H), 3.15 (d, J = 2.4 Hz, 2H), 2.92 (t, J = 12.1 Hz, 2H), 2.89-2.80 (m, 1H), 2.65 (q, J = 1.9 Hz, 1H), 2.57 (d, J = 4.3 Hz, 3H), 2.34-2.23 (m, 4H), 1.99 (d, J = 14.8 Hz, 3H), 1.77-1.67 (m, 2H), 1.59 (s, 5H), 1.28 (d, J = 7.0 Hz, 1H), 1.24-1.08 (m, 1H). D96 835.56 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.03 (s, 1H), 8.16 (s, 1H), 7.70- 7.49 (m, 2H), 7.28 (d, J = 2.3 Hz, 1H), 7.20 (dd, J = 8.7, 2.4 Hz, 1H), 6.55 (s, 2H), 5.04 (dd, J = 12.8, 5.4 Hz, 1H), 4.19 (s, 2H), 4.01 (d, J = 13.0 Hz, 2H), 3.75 (s, 5H), 3.73-3.59 (m, 2H), 3.47 (s, 3H), 3.38 (t, J = 5.5 Hz, 2H), 3.15 (s, 2H), 2.99-2.88 (m, 2H), 2.88-2.79 (m, 1H), 2.57 (d, J = 4.3 Hz, 3H), 2.43-2.12 (m, 3H), 2.03-1.93 (m, 1H), 1.74 (d, J = 12.8 Hz, 2H), 1.62 (s, 1H), 1.43 (t, J = 7.1 Hz, 1H), 1.24- 1.12 (m, 2H), 0.43 (q, J = 4.8 Hz, 1H), 0.22-0.03 (m, 1H). D97 890.39 D98 865.52 D99 837.59 D100 837.59 D101 850.44 D102 851.59 D103 867.5 D104 873.43 D105 831.57 D106

LCMS (ESI) .sup.1H NMR (400 MHz, Methanol-d4) δ 7.56 (s, 1H), 6.77-6.64 (m, 3H), m/z: [M + H]+ = 6.57 (s, 1H), 5.04 (dd, J = 13.2, 5.4 Hz, 1H), 4.48-4.28 (m, 6H), 4.17- 878.55 3.98 (m, 2H), 3.98-3.86 (m, 10H), 3.76-3.45 (m, 10H), 3.28- 3.20 (m, 3H), 3.16-3.01 (m, 2H), 2.94-2.81 (m, 1H), 2.81-2.71 (m, 4H), 2.66-2.56 (m, 2H), 2.43 (qd, J = 13.0, 4.7 Hz, 1H), 2.19- 2.07 (m, 1H), 2.06-1.87 (m, 3H), 1.86-1.69 (m, 3H), 1.67-1.48 (m, 2H). D107 LCMS (ESI) .sup.1H NMR (300 MHz, Methanol-d4) δ 8.45 (br s, 1H, FA), 7.64 (d, J = m/z: 8.3 Hz, 1H), 7.58 (s, 1H), 6.82 (d, J = 2.0 Hz, 1H), 6.73 (s, 2H), 6.66 [M + H]+ = 835.45. (dd, J = 8.3, 2.1 Hz, 1H), 5.07 (dd, J = 12.3, 5.4 Hz, 1H), 4.46 (s, 2H), 4.36 (s, 2H), 4.21-4.08 (m, 3H), 3.99-3.85 (m, 7H), 3.78 (s, 4H), 3.64 (s, 3H), 3.55 (t, J = 5.4 Hz, 2H), 2.97 (s, 2H), 2.91-2.68 (m, 6H), 2.66-2.58 (m, 4H), 2.51-2.41 (m, 2H), 2.19-2.01 (m, 1H), 1.97- 1.75 (m, 4H), 0.98 (d, J = 5.0 Hz, 3H). D109 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.07 (s, 1H), 8.19 (s, 1H, FA), 7.64 m/z: (d, J = 8.3 Hz, 2H), 6.77 (d, J = 2.1 Hz, 1H), 6.65 (dd, J = 8.4, 2.1 Hz, [M + H]+ = 821.50. 1H), 6.62-6.57 (m, 3H), 5.05 (dd, J = 12.9, 5.4 Hz, 1H), 4.22 (s, 2H), 3.80 (s, 6H), 3.73 (s, 4H), 3.70 (s, 2H), 3.50 (s, 4H), 3.48-3.45 (m, 6H), 3.09-3.01 (m, 3H), 2.92-2.87 (m, 1H), 2.60 (d, J = 4.3 Hz, 4H), 2.45-2.40 (m, 2H), 2.28 (s, 4H), 2.05-1.97 (m, 1H), 1.78-1.69 (m, 4H). D110 LCMS (ESI) m/z: [M + H]+ = 794.30 D111 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.06 (s, 1H), 7.60 (s, 1H), 7.55 (d, J = m/z: 8.4 Hz, 1H), 7.22-7.14 (m, 2H), 6.98 (dd, J = 8.5, 2.1 Hz, 1H), 6.64 [M + H]+ = 643.25. (s, 2H), 6.58 (d, J = 4.6 Hz, 1H), 5.02 (dd, J = 13.0, 5.3 Hz, 1H), 4.32 (d, J = 5.3 Hz, 2H), 4.21 (s, 2H), 3.86 (s, 6H), 3.49 (s, 3H), 3.41 (d, J = 5.5 Hz, 3H), 2.95-2.81 (m, 1H), 2.59 (d, J = 4.3 Hz, 3H), 2.54 (s, 3H), 1.99 (d, J = 12.5 Hz, 1H). D112 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.06 (s, 1H), 7.63 (t, J = 4.3 Hz, m/z: 2H), 7.31 (d, J = 2.4 Hz, 1H), 7.11-7.01 (m, 1H), 6.64 (s, 2H), 6.58 [M + H]+ = 657.10. (d, J = 4.5 Hz, 1H), 5.04 (dd, J = 12.9, 5.3 Hz, 1H), 4.64 (s, 2H), 4.20 (s, 2H), 3.85 (s, 6H), 3.48 (s, 3H), 3.09 (s, 3H), 2.86 (d, J = 12.5 Hz, 1H), 2.68 (p, J = 1.8 Hz, 3H), 2.59 (s, 3H), 2.58 (s, 6H), 2.00 (d, J = 12.5 Hz, 1H). D113 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.18 (s, 1H), 7.86 (d, m/z: [M + H]+ = J = 7.7 Hz, 1H), 7.81-7.74 (m, 2H), 7.64 (s, 1H), 6.62 (s, 2H), 6.60- 822.70 6.57 (m, 1H), 5.14 (dd, J = 12.9, 5.4 Hz, 1H), 4.22 (s, 2H), 3.80 (s, 6H), 3.67 (s, 2H), 3.50 (s, 4H), 3.41 (t, J = 5.6 Hz, 4H), 3.03 (d, J = 10.9 Hz, 2H), 2.97-2.88 (m, 3H), 2.77 (t, J = 12.2 Hz, 1H), 2.63- 2.58 (m, 4H), 2.43-2.36 (m, 2H), 2.30-2.21 (m, 2H), 2.12-2.02 (m, 3H), 1.86-1.79 (m, 2H), 1.78-1.63 (m, 4H), 1.43-1.28 (m, 3H), 1.25-1.14 (m, 2H). D114 LCMS (ESI) 1HNMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.24 (s, 1H, TFA), 8.32 m/z: (s, 1H, TFA), 7.86 (d, J = 8.2 Hz, 1H), 7.64 (s, 1H), 7.35-7.26 (m, [M + H]+ = 892.45. 2H), 6.75 (s, 2H), 6.62 (d, J = 4.6 Hz, 1H), 5.13 (dd, J = 12.8, 5.4 Hz, 1H), 5.09-5.00 (m, 1H), 4.27-4.10 (m, 4H), 3.89 (d, J = 2.4 Hz, 6H), 3.52 (s, 3H), 3.43-3.41 (m, 4H), 3.24-3.16 (m, 1H), 3.08-2.81 (m, 5H), 2.75-2.69 (m, 1H), 2.66-2.52 (m, 8H), 2.43-2.39 (m, 1H), 2.17-1.96 (m, 6H), 1.94-1.81 (m, 4H), 1.73-1.61 (m, 2H), 1.24 (s, 6H). D115 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.18 (s, 1H, FA), 7.68 m/z: (d, J = 8.5 Hz, 1H), 7.63 (s, 1H), 7.34 (d, J = 2.2 Hz, 1H), 7.26 (dd, J = [M + H]+ = 809.35. 8.8, 2.3 Hz, 1H), 6.64 (s, 2H), 6.59 (q, J = 4.4 Hz, 1H), 5.07 (dd, J = 12.9, 5.4 Hz, 1H), 4.21 (s, 2H), 3.90 (s, 2H), 3.82 (s, 6H), 3.50 (s, 3H), 3.44-3.39 (m, 8H), 3.37-3.28 (m, 5H), 3.08 (t, J = 8.9 Hz, 2H), 2.94- 2.80 (m, 3H), 2.62-2.56 (m, 4H), 2.30 (t, J = 7.2 Hz, 2H), 2.21- 2.13 (m, 1H), 2.06-1.94 (m, 2H), 1.61-1.49 (m, 2H), 1.48-1.39 (m, 1H). D116 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.19 (s, 2H, FA), 7.86- m/z: 7.80 (m, 1H), 7.64 (s, 1H), 7.30-7.23 (m, 2H), 6.60 (s, 3H), 5.12 [M + H]+ = 699.40. (dd, J = 12.8, 5.4 Hz, 1H), 4.94 (t, J = 5.5 Hz, 1H), 4.21 (s, 2H), 3.78 (s, 6H), 3.72-3.65 (m, 5H), 3.50 (s, 3H), 3.40 (s, 3H), 3.13-3.08 (m, 2H), 2.91-2.86 (m, 1H), 2.63-2.57 (m, 5H), 2.09-2.00 (m, 1H). D117 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 11.15 (s, 1H), 9.47 (s, 1H, TFA), m/z: 7.93 (d, J = 7.7 Hz, 1H), 7.87 (s, 1H), 7.83-7.77 (m, 1H), 7.64 (s, [M + H]+ = 823.55. 1H), 6.74 (s, 2H), 6.63 (s, 1H), 5.16 (dd, J = 12.8, 5.4 Hz, 1H), 4.24 (d, J = 7.7 Hz, 4H), 3.88 (s, 6H), 3.62 (d, J = 10.7 Hz, 2H), 3.52 (s, 3H), 3.44-3.31 (m, 6H), 3.21-3.00 (m, 7H), 2.98-2.72 (m, 4H), 2.66- 2.58 (m, 4H), 2.50-2.42 (m, 4H), 2.15-1.93 (m, 5H). D118 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 11.09 (s, 1H), 8.18 (s, 2H, FA), 7.69 m/z: (d, J = 8.5 Hz, 1H), 7.34 (d, J = 2.8 Hz, 2H), 7.26 (dd, J = 8.7, 2.2 Hz, [M + H]+ = 849.50. 1H), 6.68-6.56 (m, 3H), 5.08 (dd, J = 12.8, 5.3 Hz, 1H), 4.23 (s, 2H), 3.82 (s, 9H), 3.49-3.30 (m, 10H), 3.07 (d, J = 11.1 Hz, 3H), 2.97-2.73 (m, 3H), 2.63-2.55 (m, 6H), 2.40-2.30 (m, 2H), 2.08-1.97 (m, 1H), 1.73 (d, J = 12.2 Hz, 2H), 1.51-1.18 (m, 5H), 1.00 (s, 2H), 0.95-0.86 (m, 2H). D119 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.06 (s, 1H), 8.95 (s, 1H), 7.73- m/z: [M + H]+ = 7.61 (m, 2H), 6.94 (d, J = 2.2 Hz, 1H), 6.86 (dd, J =

8.6, 2.1 Hz, 1H), 766.25 6.74 (s, 2H), 6.70 (d, J = 7.2 Hz, 1H), 5.06 (dd, J = 12.8, 5.4 Hz, 1H), 4.28 (s, 2H), 4.22 (s, 2H), 3.88 (s, 7H), 3.59 (t, J = 9.6 Hz, 1H), 3.55- 3.48 (m, 5H), 3.45 (t, J = 5.5 Hz, 2H), 3.28-3.23 (m, 1H), 2.97-2.82 (m, 2H), 2.75 (s, 6H), 2.71-2.65 (m, 1H), 2.62-2.53 (m, 3H), 2.13- 1.94 (m, 3H), 1.71-1.59 (m, 1H), 1.55-1.41 (m, 1H). D120 LCMS (ESI) m/z: [M + H]+ = 810.20 D121 LCMS (ESI) m/z: [M + H]+ = 810.45 D122 LCMS (ESI) m/z: [M + H]+ = 780.35 D123 LCMS (ESI) m/z: [M + H]+ = 780.25 D124 LCMS (ESI) .sup.1H NMR (300 MHz, Methanol-d4) δ 7.65 (d, J = 8.3 Hz, 1H), 7.57 (s, m/z: 1H), 6.83 (d, J = 2.0 Hz, 1H), 6.73 (s, 2H), 6.66 (dd, J = 8.4, 2.1 Hz, [M + H]+ = 849.30. 1H), 5.07 (dd, J = 12.2, 5.5 Hz, 1H), 4.38 (d, J = 15.8 Hz, 4H), 4.02 (d, J = 9.2 Hz, 4H), 3.97 (s, 6H), 3.79 (s, 3H), 3.67-3.63 (m, 4H), 3.55 (t, J = 5.5 Hz, 2H), 2.92-2.69 (m, 7H), 2.67-2.54 (m, 6H), 2.16-2.08 (m, 1H), 1.89 (s, 4H), 1.15 (s, 6H). D125 .sup.1H NMR (300 MHz, DMSO-d6, D20) δ 7.91-7.80 (m, 1H), 7.59 (s, 1H), 7.36-7.25 (m, 2H), 6.70 (s, 2H), 5.11 (dd, J = 12.8, 5.4 Hz, 1H), 4.75 (t, J = 6.8 Hz, 1H), 4.30-4.09 (m, 4H), 3.85 (s, 6H), 3.61-3.60 (m, 5H), 3.47-3.35 (m, 5H), 3.19-2.77 (m, 8H), 2.66-2.57 (m, 5H), 2.12-1.74 (m, 5H), 1.55-1.34 (m, 2H), 1.32-1.16 (m, 6H), 1.05 (t, J = 7.0 Hz, 1H). D126 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 11.14 (s, 1H), 8.25 (s, 1H, FA), 7.91 m/z: (d, J = 8.1 Hz, 1H), 7.88-7.80 (m, 2H), 7.61 (s, 1H), 6.57 (s, 3H), [M + H]+ = 818.45. 5.17 (dd, J = 12.9, 5.4 Hz, 1H), 4.21 (s, 2H), 3.77 (s, 6H), 3.62 (s, 3H), 3.49 (s, 4H), 3.42-3.39 (d, J = 5.5 Hz, 6H), 3.01 (s, 3H), 2.93-2.70 (m, 2H), 2.59 (d, J = 4.1 Hz, 5H), 2.14-2.00 (m, 1H), 1.64 (s, 4H), 1.41 (s, 6H). D127 LCMS (ESI) .sup.1H NMR (400 MHz, Methanol-d4) δ 8.49 (s, 2H), 7.72 (d, J = 8.4 Hz, m/z: 1H), 7.58 (s, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.27 (dd, J = 8.5, 2.4 Hz, [M + H]+ = 821.50. 1H), 6.73 (s, 2H), 5.61-5.54 (m, 1H), 5.09 (dd, J = 12.5, 5.4 Hz, 1H), 4.36 (s, 4H), 3.95 (s, 6H), 3.64 (s, 4H), 3.56-3.49 (m, 6H), 3.28-3.22 (m, 2H), 3.18-3.13 (m, 2H), 2.91-2.83 (m, 1H), 2.78 (s, 4H), 2.75-2.40 (m, 12H), 2.16-2.08 (m, 1H). D128 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.10 (s, 1H), 8.16 (s, 1H, FA), 7.83 m/z: (d, J = 8.1 Hz, 1H), 7.63 (s, 1H), 7.31-7.25 (m, 2H), 6.63 (s, 2H), [M + H]+ = 878.44. 6.58 (q, J = 4.4 Hz, 1H), 5.12 (dd, J = 12.9, 5.4 Hz, 1H), 4.98 (p, J = 6.7 Hz, 1H), 4.22 (s, 2H), 3.81 (s, 6H), 3.74 (s, 2H), 3.50 (s, 3H), 3.41 (t, J = 5.6 Hz, 7H), 3.01 (d, J = 10.0 Hz, 2H), 2.94-2.86 (m, 1H), 2.62- 2.57 (m, 4H), 2.46-2.38 (m, 3H), 2.31-2.13 (m, 4H), 2.09-2.00 (m, 1H), 1.96-1.87 (m, 1H), 1.84-1.75 (m, 2H), 1.68-1.47 (m, 5H), 1.41-1.29 (m, 1H), 1.25-1.08 (m, 2H), 0.84 (d, J = 6.4 Hz, 3H). D129 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.09 (s, 1H), 8.27 (s, 1H, FA), 7.69 m/z: (d, J = 8.5 Hz, 1H), 7.64 (s, 1H), 7.34 (d, J = 2.3 Hz, 1H), 7.26 (dd, J = [M + H]+ = 821.35. 8.7, 2.2 Hz, 1H), 6.69-6.58 (m, 3H), 5.08 (dd, J = 12.9, 5.4 Hz, 1H), 4.22 (s, 2H), 3.96-3.87 (m, 2H), 3.83 (s, 8H), 3.50 (s, 3H), 3.46-3.39 (m, 8H), 3.14-2.98 (m, 2H), 2.94-2.74 (m, 3H), 2.60 (d, J = 4.2 Hz, 3H), 2.57-2.54 (m, 2H), 2.46-2.41 (m, 2H), 2.38-2.29 (m, 2H), 2.20 (s, 1H), 2.06-1.98 (m, 1H), 1.85-1.78 (m, 1H), 1.76- 1.68 (m, 1H), 1.57-1.48 (m, 1H), 1.43-1.32 (m, 1H). D130 LCMS (ESI) .sup.1H NMR (300 MHz, Methanol-d4) δ 7.63 (d, J = 8.5 Hz, 1H), 7.43 (d, m/z: [M + H]+ = J = 2.6 Hz, 1H), 7.28 (dd, J = 5.9, 2.1 Hz, 2H), 7.20 (d, J = 8.4 Hz, 1H), 823.25 6.56 (s, 2H), 5.09 (dd, J = 12.3, 5.4 Hz, 1H), 4.68-4.57 (m, 1H), 4.41- 4.14 (m, 2H), 3.88 (d, J = 1.1 Hz, 6H), 3.72-3.60 (m, 3H), 3.59- 3.49 (m, 4H), 3.30-3.18 (m, 4H), 3.06-2.86 (m, 4H), 2.90-2.76 (m, 5H), 2.78-2.36 (m, 10H), 2.30-2.11 (m, 2H), 2.07-1.76 (m, 3H), 1.44-1.28 (m, 1H). D131 712.49 D132 767.52 D133 746.3 D134 774.3 1H NMR (400 MHz, DMSO-d6) δ 11.10 (s, 1H), 8.13 (s, 1H), 7.95- 7.84 (m, 2H), 7.83 (s, 2H), 7.60 (s, 1H), 6.56 (s, 3H), 5.73 (s, 2H), 5.13 (dd, J = 12.7, 5.4 Hz, 1H), 4.19 (s, 2H), 3.47 (s, 4H), 3.38 (t, J = 5.6 Hz, 2H), 3.30 (d, J = 8.7 Hz, 1H), 3.28 (s, 4H), 2.87 (td, J = 16.8, 15.2, 5.3 Hz, 1H), 2.57 (d, J = 4.2 Hz, 4H), 2.51 (s, 1H), 2.18 (t, J = 10.0 Hz, 2H), 2.05 (dd, J = 10.4, 4.7 Hz, 1H), 1.94-1.84 (m, 2H), 1.54 (d, J = 5.9 Hz, 4H). D135 762.4 1H NMR (400 MHz, DMSO-d6) δ 11.10 (s, 1H), 8.12 (s, 1H), 7.95- 7.84 (m, 1H), 7.82 (dd, J = 7.4, 3.8 Hz, 2H), 7.60 (d, J = 7.0 Hz, 1H), 6.68 (s, 1H), 6.61 (d, J = 1.8 Hz, 2H), 6.56 (d, J = 4.3 Hz, 1H), 5.73 (s, 1H), 5.13 (dd, J = 12.8, 5.3 Hz, 1H), 4.19 (s, 2H), 3.86-3.78 (m, 7H), 3.48 (t, J = 3.1 Hz, 3H), 3.39 (t, J = 5.6 Hz, 2H), 3.24 (dd, J = 16.5, 8.3 Hz, 1H), 2.93-2.80 (m, 3H), 2.73 (s, 1H), 2.57 (dd, J = 4.2, 1.5 Hz, 4H), 2.38 (dt, J = 26.0, 9.7 Hz, 2H), 2.19 (dt, J = 20.1, 9.5 Hz, 2H), 2.08-2.00 (m, 1H), 1.95 (dd, J = 13.3, 7.0 Hz, 2H). D136 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.21 (s, 2H, FA), 7.64 m/z: (t, J = 4.1 Hz, 2H), 6.78 (d, J = 2.1 Hz, 1H), 6.68-6.57 (m, 4H), 5.05 [M + H].sup.+ = 849.60. (dd, J = 12.9, 5.4 Hz, 1H), 4.22 (s, 2H), 3.81 (s, 6H), 3.77-3.68 (m, 6H), 3.50 (s, 3H), 3.41 (t, J = 5.6 Hz, 2H), 2.98 (s, 2H), 2.94-2.83 (m, 1H), 2.63-2.52 (m, 7H), 2.47-2.19 (m, 6H), 2.10 (d, J = 7.0 Hz, 2H), 2.04-1.95 (m, 1H), 1.80-1.72 (m, 4H), 1.68 (d, J = 12.7 Hz, 2H), 1.61-1.50 (m, 1H), 1.23-1.10 (m, 2H).

D137 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.15 (s, 1H), 8.21 (s, 1H FA), 7.91 m/z: (dd, J = 7.6, 0.9 Hz, 1H), 7.88-7.81 (m, 2H), 7.63 (s, 1H), 6.66-6.51 [M + H]+ = 832.40. (m, 3H), 5.17 (dd, J = 12.8, 5.4 Hz, 1H), 4.21 (s, 2H), 3.77 (s, 6H), 3.40 (t, J = 5.5 Hz, 4H), 2.94-2.85 (m, 1H), 2.77 (t, J = 6.8 Hz, 2H), 2.63-2.54 (m, 7H), 2.42 (s, 4H), 2.12-2.00 (m, 1H), 1.62-1.44 (m, 6H), 1.41 (s, 6H). D138 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.09 (s, 1H), 8.25 (s, 1H, FA), 7.69 m/z: (d, J = 8.6 Hz, 1H), 7.64 (s, 1H), 7.35 (d, J = 2.3 Hz, 1H), 7.27 (dd, J = [M + H]+ = 835.41. 8.7, 2.3 Hz, 1H), 6.65 (s, 2H), 6.61 (q, J = 4.4 Hz, 1H), 5.08 (dd, J = 12.9, 5.3 Hz, 1H), 4.22 (s, 2H), 4.00-3.92 (m, 1H), 3.92-3.78 (m, 8H), 3.50 (s, 5H), 3.47-3.38 (m, 9H), 3.13-3.05 (m, 1H), 2.94- 2.82 (m, 2H), 2.63-2.55 (m, 5H), 2.44-2.24 (m, 4H), 2.07-1.99 (m, 1H), 1.95-1.72 (m, 3H), 1.66-1.49 (m, 3H), 1.41-1.30 (m, 1H). D139 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.18 (s, 2H, FA), 7.71- m/z: 7.60 (m, 2H), 7.34 (d, J = 2.1 Hz, 1H), 7.29-7.22 (m, 1H), 6.62- [M + H]+ = 824.50. 6.55 (m, 3H), 5.07 (dd, J = 12.6, 5.3 Hz, 1H), 4.22 (s, 2H), 3.78 (s, 6H), 3.56-3.49 (m, 6H), 3.45-3.38 (m, 8H), 2.93-2.82 (m, 1H), 2.66-2.53 (m, 8H), 2.47-2.31 (m, 12H), 2.06-1.98 (m, 1H). D140 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.15 (s, 1H, FA), 7.72- m/z: 7.62 (m, 2H), 7.34 (d, J = 2.2 Hz, 1H), 7.26 (d, J = 8.8 Hz, 1H), 6.67- [M + H]+ = 908.55. 6.56 (m, 3H), 5.07 (dd, J = 12.7, 5.3 Hz, 1H), 4.22 (s, 2H), 3.84- 3.73 (m, 8H), 3.60 (s, 2H), 3.50 (s, 3H), 3.46-3.38 (m, 9H), 2.95- 2.83 (m, 1H), 2.76-2.65 (m, 3H), 2.64-2.53 (m, 9H), 2.40-2.23 (m, 6H), 2.17 (s, 2H), 2.08-1.98 (m, 1H), 1.91-1.80 (m, 2H), 1.67- 1.51 (m, 4H). D141 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.04 (s, 1H), 8.18 (s, 2H), 7.74- m/z: [M + H]+ = 7.47 (m, 2H), 7.26 (d, J = 2.2 Hz, 1H), 7.19 (dd, J = 8.7, 2.3 Hz, 1H), 851.51 6.54 (s, 3H), 5.03 (dd, J = 12.9, 5.4 Hz, 1H), 4.19 (s, 2H), 3.99 (d, J = 13.0 Hz, 2H), 3.81 (s, 2H), 3.74 (s, 6H), 3.46 (s, 3H), 3.37 (d, J = 5.7 Hz, 2H), 2.95-2.85 (m, 3H), 2.57 (d, J = 4.3 Hz, 3H), 2.14 (t, J = 7.5 Hz, 2H), 2.03-1.95 (m, 1H), 1.75-1.64 (m, 4H), 1.07 (d, J = 5.7 Hz, 7H), 1.00 (d, J = 6.6 Hz, 2H). D142 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.10 (s, 1H), 8.14 (s, 1H), 7.91- m/z: [M + H]+ = 7.81 (m, 2H), 7.60 (s, 1H), 6.56 (d, J = 3.9 Hz, 3H), 5.13 (dd, J = 12.7, 707.34 5.4 Hz, 1H), 4.19 (s, 2H), 3.77 (s, 5H), 3.55 (s, 2H), 3.48 (d, J = 10.1 Hz, 5H), 3.37 (t, J = 5.7 Hz, 3H), 3.19-3.14 (m, 2H), 2.87 (ddd, J = 16.7, 13.6, 5.4 Hz, 1H), 2.67-2.59 (m, 1H), 2.57 (d, J = 4.2 Hz, 3H), 2.11-1.98 (m, 1H). D143 LCMS (ESI) m/z: [M + H]+ = 735.38 D144 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.22 (s, 1H, FA), 7.70- m/z: [M + H]+ = 7.59 (m, 2H), 6.91 (d, J = 2.1 Hz, 1H), 6.81 (dd, J = 8.6, 2.2 Hz, 1H), 821.5 6.63-6.53 (m, 3H), 5.06 (dd, J = 12.6, 5.4 Hz, 1H), 4.21 (s, 2H), 4.00 (q, J = 8.5 Hz, 2H), 3.88-3.81 (m, 2H), 3.78 (s, 6H), 3.68-3.57 (m, 3H), 3.54-3.45 (m, 8H), 3.25-3.16 (m, 4H), 3.10 (q, J = 7.3 Hz, 2H), 2.95-2.81 (m, 1H), 2.62-2.55 (m, 6H), 2.26-2.17 (m, 2H), 2.07- 1.96 (m, 1H). D145 LCMS (ESI) .sup.1H NMR (300 MHz, Methanol-d4) δ 7.82-7.76 (m, 1H), 7.58 (s, 1H), m/z: 7.51 (d, J = 2.3 Hz, 1H), 7.38 (dd, J = 8.5, 2.2 Hz, 1H), 6.73 (s, 2H), [M + H]+ = 851.65. 5.11 (dd, J = 12.4, 5.4 Hz, 1H), 4.37 (d, J = 4.6 Hz, 4H), 4.25 (d, J = 13.6 Hz, 2H), 3.96 (d, J = 3.5 Hz, 6H), 3.75-3.60 (m, 6H), 3.60- 3.52 (m, 3H), 3.51-3.41 (m, 2H), 3.24-3.07 (m, 4H), 2.92-2.70 (m, 6H), 2.63 (s, 2H), 2.18-1.85 (m, 4H), 1.84-1.58 (m, 4H), 1.57- 1.48 (m, 6H). D146 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.17 (s, 1H, FA), 7.68 m/z: (d, J = 8.5 Hz, 1H), 7.63 (s, 1H), 7.34 (d, J = 2.2 Hz, 1H), 7.25 (dd, J = [M + H]+ = 807.55. 8.7, 2.3 Hz, 1H), 6.66-6.56 (m, 3H), 5.07 (dd, J = 12.9, 5.4 Hz, 1H), 4.22 (s, 2H), 3.84 (s, 2H), 3.82 (s, 6H), 3.59 (s, 2H), 3.50 (s, 4H), 3.48 (s, 2H), 3.43-3.39 (m, 8H), 2.93-2.84 (m, 1H), 2.62-2.58 (m, 4H), 2.58-2.55 (m, 1H), 2.35 (t, J = 4.9 Hz, 4H), 2.27-2.19 (m, 2H), 2.06- 1.99 (m, 1H), 1.95 (t, J = 10.1 Hz, 2H). D147 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.09 (s, 1H), 8.15 (s, 1H, FA), 7.68 m/z: (d, J = 8.4 Hz, 1H), 7.64 (s, 1H), 7.34 (s, 1H), 7.25 (dd, J = 8.9, 2.3 [M + H]+ = 827.35. Hz, 1H), 6.59 (s, 3H), 5.07 (dd, J = 12.8, 5.4 Hz, 1H), 4.22 (s, 2H), 3.79 (s, 6H), 3.57 (s, 2H), 3.50 (s, 3H), 3.46-3.37 (m, 10H), 2.94- 2.82 (m, 1H), 2.65-2.55 (m, 11H), 2.38-2.30 (m, 2H), 2.06-1.98 (m, 1H), 1.81 (t, J = 12.2 Hz, 2H), 1.74-1.54 (m, 2H). D148 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.18 (s, 1H, FA), 7.68 m/z: (d, J = 8.5 Hz, 1H), 7.63 (s, 1H), 7.34 (d, J = 2.2 Hz, 1H), 7.26 (dd, J = [M + H]+ = 809.35. 8.8, 2.3 Hz, 1H), 6.64 (s, 2H), 6.59 (q, J = 4.4 Hz, 1H), 5.07 (dd, J = 12.9, 5.4 Hz, 1H), 4.21 (s, 2H), 3.90 (s, 2H), 3.82 (s, 6H), 3.50 (s, 3H), 3.44-3.39 (m, 8H), 3.37-3.28 (m, 5H), 3.08 (t, J = 8.9 Hz, 2H), 2.94- 2.80 (m, 3H), 2.62-2.56 (m, 4H), 2.30 (t, J = 7.2 Hz, 2H), 2.21- 2.13 (m, 1H), 2.06-1.94 (m, 2H), 1.61-1.49 (m, 2H), 1.48-1.39 (m, 1H). D149 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.23 (s, 2H, FA), 7.83 m/z: [M + H]+ = (dd, J = 8.2, 2.8 Hz, 1H), 7.63 (s, 1H), 7.34-7.23 (m, 2H), 6.66-6.57

824.75 (m, 3H), 5.12 (dd, J = 12.9, 5.4 Hz, 1H), 4.98-4.90 (m, 1H), 4.69 (p, J = 7.1 Hz, 1H), 4.22 (s, 2H), 3.80 (d, J = 4.7 Hz, 6H), 3.71 (s, 2H), 3.50 (s, 3H), 3.40 (t, J = 5.5 Hz, 2H), 3.01-2.92 (m, 2H), 2.92-2.84 (m, 1H), 2.74-2.68 (m, 1H), 2.65-2.57 (m, 4H), 2.56-2.52 (m, 2H), 2.42-2.25 (m, 3H), 2.22-2.14 (m, 1H), 2.10-1.98 (m, 6H), 1.93- 1.57 (m, 4H), 1.49 (s, 1H), 1.25-1.07 (m, 2H). D150 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.09 (s, 1H), 8.21 (s, 2H, FA), 7.68 m/z: [M + H]+ = (d, J = 8.5 Hz, 1H), 7.64 (s, 1H), 7.34 (d, J = 2.2 Hz, 1H), 7.26 (dd, J = 769.45 8.7, 2.3 Hz, 1H), 6.66 (t, J = 5.5 Hz, 1H), 6.60 (s, 2H), 5.08 (dd, J = 12.9, 5.4 Hz, 1H), 4.23 (s, 2H), 3.79 (s, 6H), 3.54 (s, 2H), 3.50 (s, 3H), 3.46-3.39 (m, 7H), 3.22 (q, J = 6.5 Hz, 3H), 2.93-2.83 (m, 1H), 2.64-2.53 (m, 6H), 2.43 (t, J = 7.1 Hz, 2H), 2.21 (s, 6H), 2.06-1.98 (m, 1H). D151 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.15 (s, 2H), 7.68 (d, m/z: [M + H]+ = J = 8.5 Hz, 1H), 7.63 (s, 1H), 7.34 (d, J = 2.2 Hz, 1H), 7.25 (dd, J = 8.6, 839.55 2.2 Hz, 1H), 6.59 (s, 3H), 5.08 (dd, J = 12.7, 5.3 Hz, 1H), 4.21 (s, 2H), 3.79 (s, 6H), 3.76-3.67 (m, 1H), 3.52 (s, 2H), 3.49 (s, 5H), 3.48- 3.35 (m, 10H), 2.98-2.80 (m, 1H), 2.75-2.55 (m, 7H), 2.50-2.43 (m, 2H), 2.36-2.26 (m, 2H), 2.19-1.97 (m, 2H), 1.85 (t, J = 10.7 Hz, 1H), 1.61-1.32 (m, 4H). D152 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.14 (s, 1H, FA), 7.68 m/z: (d, J = 8.5 Hz, 1H), 7.63 (s, 1H), 7.35 (s, 1H), 7.26 (dd, J = 8.7, 2.3 [M + H]+ = 825.70. Hz, 1H), 6.62 (s, 2H), 6.61-6.57 (m, 1H), 5.08 (dd, J = 12.9, 5.3 Hz, 1H), 4.21 (s, 2H), 3.81 (s, 6H), 3.78-3.73 (m, 1H), 3.65 (s, 2H), 3.50 (s, 4H), 3.47-3.42 (m, 6H), 3.42-3.37 (m, 5H), 2.95-2.82 (m, 2H), 2.74-2.69 (m, 1H), 2.60 (d, J = 4.3 Hz, 5H), 2.58-2.54 (m, 4H), 2.31-2.21 (m, 1H), 2.12-1.97 (m, 2H), 1.68-1.51 (m, 2H). D153 LCMS (ESI) .sup.1H NMR (400 MHz, Methanol-d4) δ 8.49 (s, 2H, FA), 7.74 (dd, J = m/z: 16.5, 8.4 Hz, 1H), 7.57 (s, 1H), 7.27 (s, 1H), 7.13 (d, J = 8.8 Hz, 1H), [M + H]+ = 835.60. 6.70 (s, 2H), 5.11 (dd, J = 12.7, 5.4 Hz, 1H), 4.34 (d, J = 11.5 Hz, 4H), 4.05-3.88 (m, 8H), 3.78 (d, J = 12.0 Hz, 2H), 3.71-3.61 (m, 5H), 3.57-3.40 (m, 5H), 3.12-2.99 (m, 2H), 2.89-2.68 (m, 9H), 2.62 (s, 3H), 2.18-2.09 (m, 1H), 1.93 (d, J = 13.8 Hz, 2H), 1.84-1.78 (m, 1H), 1.73-1.63 (m, 1H), 1.52 (s, 3H), 1.39-1.27 (m, 1H). D154 LCMS (ESI) .sup.1H NMR (300 MHz, Methanol-d4) δ 8.51 (s, 2H), 7.70 (d, J = 8.5 Hz, m/z: 1H), 7.57 (s, 1H), 7.37 (d, J = 2.2 Hz, 1H), 7.25 (dd, J = 8.6, 2.3 Hz, [M + H]+ = 859.75. 1H), 6.72 (s, 2H), 5.09 (dd, J = 12.3, 5.4 Hz, 1H), 4.37 (d, J = 9.4 Hz, 4H), 3.95 (s, 6H), 3.70-3.62 (m, 4H), 3.60-3.45 (m, 7H), 3.18 (t, J = 12.6 Hz, 2H), 2.95-2.69 (m, 12H), 2.68-2.59 (m, 2H), 2.58-2.46 (m, 1H), 2.19-2.07 (m, 3H), 2.03-1.86 (m, 2H). D155 LCMS (ESI) .sup.1H NMR (300 MHz, Methanol-d4) δ 7.79 (d, J = 8.4 Hz, 1H), 7.59 (s, m/z: 1H), 7.50 (d, J = 2.1 Hz, 1H), 7.41-7.34 (m, 1H), 6.75 (s, 2H), 5.12 [M + H]+ = 859.50. (dd, J = 12.4, 5.4 Hz, 1H), 4.50 (s, 2H), 4.36 (s, 2H), 3.96 (s, 6H), 3.94- 3.74 (m, 3H), 3.70-3.62 (m, 5H), 3.61-3.39 (m, 8H), 3.39-3.35 (m, 2H), 3.23-3.19 (m, 1H), 2.87-2.71 (m, 6H), 2.68-2.61 (m, 2H), 2.40-2.21 (m, 3H), 2.18-2.09 (m, 1H), 1.96-1.80 (m, 2H). D156 737.88 D157 723.39 D158 738.37 D159 751.46 D161 751.39 NA D162 751.32 NA D163 765.39 NA D164 766.4 1H NMR (400 MHz, DMSO-d6) δ 11.04 (s, 1H), 8.13 (s, 1H), 7.65- 7.57 (m, 2H), 6.75 (d, J = 2.1 Hz, 1H), 6.61 (dd, J = 8.4, 2.1 Hz, 1H), 6.56 (s, 2H), 6.54 (d, J = 4.5 Hz, 1H), 5.03 (dd, J = 12.9, 5.4 Hz, 1H), 4.19 (s, 2H), 4.05 (t, J = 7.7 Hz, 2H), 3.80 (dd, J = 8.9, 4.9 Hz, 2H), 3.76 (s, 5H), 3.54 (s, 2H), 3.47 (s, 3H), 3.37 (s, 1H), 3.25 (q, J = 5.9 Hz, 1H), 3.15 (s, 1H), 2.86 (ddd, J = 17.6, 13.9, 5.4 Hz, 1H), 2.61-2.50 (m, 4H), 2.47-2.42 (m, 4H), 2.34-2.29 (m, 4H), 1.99 (dp, J = 12.2, 4.6, 4.0 Hz, 1H). D165 737.4 1H NMR (400 MHz, DMSO-d6) δ 11.03 (s, 1H), 8.15 (s, 1H), 7.61 (d, J = 8.8 Hz, 2H), 6.76 (d, J = 2.1 Hz, 1H), 6.62 (dd, J = 8.4, 2.1 Hz, 1H), 6.57 (s, 2H), 6.54 (dd, J = 5.8, 3.3 Hz, 1H), 5.03 (dd, J = 12.9, 5.4 Hz, 1H), 4.19 (s, 2H), 3.90 (q, J = 8.4 Hz, 4H), 3.77 (s, 6H), 3.47 (s, 3H), 3.38 (t, J = 5.5 Hz, 2H), 3.15 (s, 1H), 3.10 (s, 0H), 2.86 (ddd, J = 17.4, 13.9, 5.5 Hz, 1H), 2.77 (s, 2H), 2.61-2.48 (m, 6H), 2.05-1.93 (m, 3H). D166 737.4 1H NMR (400 MHz, DMSO-d6) δ 11.04 (s, 1H), 8.13 (s, 1H), 7.65- 7.58 (m, 2H), 6.80 (d, J = 2.0 Hz, 1H), 6.72 (dd, J = 8.3, 2.0 Hz, 1H), 6.56 (d, J = 12.0 Hz, 3H), 5.03 (dd, J = 12.9, 5.4 Hz, 1H), 4.28 (dt, J = 8.3, 4.2 Hz, 1H), 4.19 (s, 2H), 3.77 (s, 6H), 3.78-3.66 (m, 2H), 3.47 (s, 3H), 3.38 (t, J = 5.6 Hz, 2H), 3.15 (s, 1H), 2.96-2.79 (m, 2H), 2.72 (s, 1H), 2.57 (d, J = 4.3 Hz, 4H), 2.51 (s, 1H), 2.45 (s, 0H), 2.03-1.85 (m, 2H). D167 LCMS .sup.1H NMR (300 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.24 (s, 2H, FA), 7.69- (ESI) m/z: 7.59 (m, 2H), 6.89 (d, J = 2.1 Hz, 1H), 6.80 (dd, J = 8.6, 2.2 Hz, 1H), [M + H]+ = 807. 6.60 (s, 3H), 5.05 (dd, J = 12.5, 5.4 Hz, 1H), 4.21 (s, 2H), 3.79 (s, 6H), 3.70-3.63 (m, 4H), 3.54-3.47 (m, 7H), 3.43-3.37 (m, 6H), 3.18- 3.10 (m, 4H), 3.04 (s, 2H), 2.91-2.82 (m, 1H), 2.63-2.56 (m, 5H), 2.39-2.31 (m, 1H), 2.15 (t, J = 6.8 Hz, 2H), 2.06-1.95 (m, 1H). D168 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.09 (s, 1H), 7.69 (d, J = 8.5 Hz, m/z: 1H), 7.64 (s, 1H), 7.35 (d, J = 2.3

Hz, 1H), 7.26 (dd, J = 8.7, 2.3 Hz, [M + H]+ = 981.35. 1H), 6.69 (s, 2H), 6.60 (q, J = 4.4 Hz, 1H), 5.08 (dd, J = 12.9, 5.4 Hz, 1H), 4.22 (s, 2H), 4.14 (s, 2H), 4.00-3.91 (m, 2H), 3.86 (s, 6H), 3.70- 3.56 (m, 2H), 3.50 (s, 3H), 3.45-3.39 (m, 6H), 2.94-2.83 (m, 2H), 2.63-2.56 (m, 6H), 2.50-2.42 (m, 7H), 2.06-1.97 (m, 1H). D169 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.21 (s, 1H, FA), 7.68 m/z: (d, J = 8.5 Hz, 1H), 7.63 (s, 1H), 7.34 (d, J = 2.3 Hz, 1H), 7.26 (dd, J = [M + H]+ = 795.35. 8.7, 2.3 Hz, 1H), 6.64-6.54 (m, 3H), 5.07 (dd, J = 12.9, 5.4 Hz, 1H), 4.22 (s, 2H), 3.80 (s, 6H), 3.73 (s, 2H), 3.50 (s, 4H), 3.45-3.37 (m, 8H), 2.95-2.79 (m, 2H), 2.66-2.56 (m, 6H), 2.49-2.44 (m, 3H), 2.40-2.32 (m, 3H), 2.31-2.26 (m, 2H), 2.07-1.96 (m, 1H), 1.91- 1.81 (m, 1H), 1.46-1.34 (m, 1H). D170 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.19 (s, 1H, FA), 7.68- m/z: 7.61 (m, 2H), 7.32 (d, J = 2.3 Hz, 1H), 7.24 (dd, J = 8.7, 2.3 Hz, 1H), [M + H]+ = 795.35. 6.58 (s, 3H), 5.07 (dd, J = 12.9, 5.4 Hz, 1H), 4.21 (s, 2H), 4.04 (d, J = 12.7 Hz, 2H), 3.77 (s, 6H), 3.51 (d, J = 11.7 Hz, 6H), 3.40 (t, J = 5.6 Hz, 4H), 2.98-2.86 (m, 3H), 2.63-2.55 (m, 5H), 2.48-2.37 (m, 8H), 2.06-1.97 (m, 1H), 1.83 (d, J = 12.1 Hz, 2H), 1.43 (q, J = 11.7, 11.0 Hz, 2H). D171 LCMS (ESI) .sup.1H NMR (300 MHz, Methanol-d4) δ 7.73 (d, J = 8.2 Hz, 1H), 7.57 (s, m/z: 1H), 6.96 (d, J = 2.1 Hz, 1H), 6.81 (dd, J = 8.2, 2.1 Hz, 1H), 6.73 (d, [M + H]+ = 823.55 J = 4.1 Hz, 2H), 5.09 (dd, J = 12.3, 5.4 Hz, 1H), 4.50-4.20 (m, 9H), 3.96 (d, J = 4.8 Hz, 6H), 3.64 (s, 3H), 3.62-3.52 (m, 4H), 3.25-3.02 (m, 4H), 2.96-2.82 (m, 4H), 2.81-2.69 (m, 5H), 2.67-2.60 (m, 2H), 2.18-1.86 (m, 4H), 1.80-1.52 (m, 4H). D172 LCMS (ESI) .sup.1H NMR (300 MHz, Methanol-d4) δ 8.45 (s, 2H, FA), 7.68 (d, J = 8.4 m/z: [M + H]+ = Hz, 1H), 7.58 (s, 1H), 7.09 (d, J = 2.1 Hz, 1H), 6.94 (dd, J = 8.5, 2.2 835.80. Hz, 1H), 6.71 (s, 2H), 5.08 (dd, J = 12.4, 5.4 Hz, 1H), 4.74 (s, 1H), 4.35 (s, 4H), 4.14 (s, 1H), 3.93 (s, 6H), 3.71-3.60 (m, 5H), 3.58- 3.44 (m, 4H), 3.24 (d, J = 10.4 Hz, 1H), 3.16-3.01 (m, 3H), 2.97- 2.70 (m, 8H), 2.63 (t, J = 5.7 Hz, 2H), 2.28-2.07 (m, 3H), 1.96 (d, J = 13.4 Hz, 2H), 1.75-1.49 (m, 5H). D173 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.20 (s, 2H, FA), 7.69- m/z: 7.61 (m, 2H), 7.27 (d, J = 2.2 Hz, 1H), 7.21 (dd, J = 8.8, 2.4 Hz, 1H), [M + H]+ = 851.40. 6.69-6.54 (m, 3H), 5.07 (dd, J = 12.9, 5.4 Hz, 1H), 4.22 (s, 2H), 4.03-3.93 (m, 3H), 3.79 (s, 7H), 3.63 (s, 3H), 3.50 (s, 3H), 3.40 (t, J = 5.5 Hz, 2H), 2.99-2.84 (m, 5H), 2.59 (d, J = 4.3 Hz, 3H), 2.58-2.53 (m, 4H), 2.25 (s, 3H), 2.23-2.15 (m, 2H), 2.06-1.97 (m, 1H), 1.88- 1.71 (m, 2H), 1.63 (d, J = 12.5 Hz, 2H), 1.56-1.43 (m, 2H), 1.31 (s, 3H), 1.21-1.07 (m, 2H). D174 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 11.09 (s, 1H), 8.18 (s, 1H, FA), 7.68 m/z: (d, J = 8.5 Hz, 1H), 7.62 (s, 1H), 7.34 (d, J = 2.2 Hz, 1H), 7.25 (dd, J = [M + H]+ = 849.35. 8.7, 2.0 Hz, 1H), 6.59 (s, 3H), 5.07 (dd, J = 12.8, 5.4 Hz, 1H), 4.21 (s, 2H), 3.78 (s, 6H), 3.60-3.37 (m, 15H), 2.96-2.80 (m, 4H), 2.63- 2.53 (m, 6H), 2.20 (s, 2H), 2.13-1.95 (m, 3H), 1.60-1.50 (m, 2H), 1.45-1.31 (m, 2H), 1.28-1.13 (m, 1H), 0.39 (s, 2H), 0.17 (s, 2H). D175 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.19 (s, 1H, FA), 7.70- m/z: 7.66 (m, 1H), 7.63 (d, J = 2.7 Hz, 1H), 7.35 (s, 1H), 7.26 (t, J = 7.9 [M + H]+ = 922.35. Hz, 1H), 6.62-6.56 (m, 3H), 5.07 (dd, J = 13.0, 5.4 Hz, 1H), 4.21 (s, 2H), 3.77 (d, J = 2.7 Hz, 6H), 3.61 (s, 2H), 3.57-3.52 (m, 4H), 3.50- 3.47 (m, 4H), 3.44-3.40 (m, 7H), 3.34-3.30 (m, 3H), 2.94-2.84 (m, 1H), 2.63-2.58 (m, 6H), 2.57-2.54 (m, 5H), 2.48-2.41 (m, 3H), 2.41-2.23 (m, 2H), 2.06-1.97 (m, 1H), 1.72-1.58 (m, 2H), 1.56- 1.41 (m, 2H). D176 792.29 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.10 (d, J = 15.8 Hz, 1H), 8.14 (s, 2H), 7.78 (d, J = 16.8 Hz, 2H), 7.60 (s, 1H), 6.57 (d, J = 15.8 Hz, 3H), 5.20-4.89 (m, 2H), 4.19 (s, 2H), 3.96 (s, 3H), 3.79 (d, J = 3.5 Hz, 7H), 3.48 (s, 3H), 2.57 (d, J = 4.2 Hz, 3H), 1.88-1.64 (m, 1H), 1.45- 1.24 (m, 2H). D177 764.92 D178 794.46 D179 LCMS (ESI) m/z: [M + H]+ = 780.46 D180 LCMS (ESI) m/z: [M + H]+ = 766.39 D181 LCMS (ESI) m/z: [M + H]+ = 820.5 D182 LCMS (ESI) m/z: [M + H]+ = 792.91 D183 LCMS (ESI) m/z: [M + H]+ = 767.92 D184 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 11.06 (s, 1H), 8.20 (s, 2H, FA), 7.79- m/z: [M + H]+ = 7.50 (m, 2H), 6.76 (d, J = 2.0 Hz, 1H), 6.67 (d, J = 7.8 Hz, 1H), 6.62 781.45 (s, 2H), 5.05 (dd, J = 12.6, 5.4 Hz, 1H), 4.88 (t, J = 5.4 Hz, 1H), 4.24 (s, 2H), 4.21-4.10 (m, 1H), 4.00 (d, J = 9.7 Hz, 1H), 3.80 (s, 6H), 3.75-3.59 (m, 4H), 3.51 (s, 4H), 3.46-3.37 (m, 3H), 3.20 (d, J = 6.2 Hz, 2H), 3.08 (t, J = 8.0 Hz, 1H), 2.98-2.80 (m, 1H), 2.71-2.59 (m, 3H), 2.58-2.54 (m, 2H), 2.29 (s, 6H), 2.08-1.91 (m, 2H), 1.76 (d, J = 12.4 Hz, 1H). D185 LCMS (ESI) m/z: [M + H]+ = 795.25 D186 LCMS (ESI) m/z: [M + H]+ = 867.6 D187 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 11.06 (s, 1H), 8.22 (s, 3H, FA), 7.66- m/z: [M + H]+ = 7.58 (m, 2H), 6.83 (d, J = 2.0 Hz, 1H), 6.74 (dd, J = 8.3, 2.1 Hz, 1H), 795.55 6.64-6.56 (m, 3H), 5.05 (dd, J = 12.8, 5.4 Hz, 1H), 4.40-4.31 (m, 1H), 4.22 (s, 2H), 3.80 (s, 8H), 3.62 (s, 2H), 3.50 (s, 3H), 3.41 (t, J = 5.5 Hz, 2H), 3.20 (d, J = 6.7 Hz, 2H), 2.96-2.77 (m, 3H), 2.63-2.53 (m, 6H), 2.44 (t,

J = 6.5 Hz, 3H), 2.31-2.25 (m, 6H), 2.07-1.90 (m, 3H). D188 LCMS (ESI) m/z: [M + H]+ = 809.65 D189 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 11.06 (s, 1H), 8.23 (s, 3H, FA), 7.76- m/z: [M + H]+ = 7.55 (m, 2H), 6.79 (d, J = 2.1 Hz, 1H), 6.71-6.60 (m, 2H), 6.60 (s, 795.6 2H), 5.06 (dd, J = 12.7, 5.3 Hz, 1H), 4.23 (s, 2H), 4.06-3.87 (m, 4H), 3.79 (s, 6H), 3.51 (s, 5H), 3.47-3.37 (m, 2H), 3.24-3.13 (m, 2H), 2.98-2.75 (m, 4H), 2.68-2.51 (m, 7H), 2.19 (s, 6H), 2.04 (q, J = 12.6, 9.6 Hz, 3H). D190 LCMS (ESI) m/z: [M + H]+ = 809.65 D191 LCMS (ESI) m/z: [M + H]+ = 809.45 D192 LCMS (ESI) m/z: [M + H]+ = 781.7 D193 LCMS (ESI) m/z: [M + H]+ = 936.55 D194 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 11.10 (s, 1H), 8.19 (s, 2H, FA), 7.83 m/z: [M + H]+ = (d, J = 8.3 Hz, 1H), 7.64 (s, 1H), 7.42 (d, J = 2.2 Hz, 1H), 7.34 (dd, J = 824.35 8.3, 2.3 Hz, 1H), 6.68 (t, J = 5.7 Hz, 1H), 6.61 (s, 2H), 5.12 (dd, J = 12.9, 5.4 Hz, 1H), 4.25-4.13 (m, 4H), 3.80 (s, 6H), 3.63 (s, 3H), 3.50 (s, 4H), 3.40 (t, J = 5.5 Hz, 2H), 3.30 (s, 2H), 3.24 (s, 2H), 3.03 (t, J = 6.2 Hz, 2H), 2.96-2.81 (m, 1H), 2.66-2.55 (m, 4H), 2.28 (s, 7H), 2.15-2.03 (m, 3H), 1.86-1.71 (m, 4H) D195 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 11.07 (s, 1H), 8.15 (s, 1H), 7.67 (d, m/z: J = 8.5 Hz, 1H), 7.63 (s, 1H), 7.32 (d, J = 2.2 Hz, 1H), 7.25 (dd, J = 8.6, [M + H]+ = 837.65. 2.3 Hz, 1H), 6.69 (s, 2H), 6.59 (q, J = 4.4 Hz, 1H), 5.06 (dd, J = 12.8, 5.4 Hz, 1H), 4.22 (s, 2H), 4.16-4.00 (m, 4H), 3.85 (s, 6H), 3.54- 3.48 (m, 7H), 3.03-2.89 (m, 4H), 2.86-2.67 (m, 4H), 2.63-2.57 (m, 4H), 2.31-2.25 (m, 2H), 2.21 (s, 3H), 2.10-1.95 (m, 2H), 1.85-1.71 (m, 4H), 1.69-1.59 (m, 1H), 1.54-1.40 (m, 2H), 1.37-1.23 (m, 2H). D196 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 11.07 (s, 1H), 8.18 (s, 2H, FA), 7.69- m/z: 7.61 (m, 2H), 6.95 (d, J = 2.1 Hz, 1H), 6.86 (dd, J = 8.6, 2.2 Hz, 1H), [M + H]+ = 849.60. 6.64-6.55 (m, 3H), 5.06 (dd, J = 12.6, 5.4 Hz, 1H), 4.21 (s, 2H), 3.79 (s, 6H), 3.70-3.61 (m, 4H), 3.50 (s, 3H), 3.40 (t, J = 5.6 Hz, 2H), 3.30 (dd, J = 11.0, 2.6 Hz, 2H), 3.00-2.91 (m, 4H), 2.91-2.76 (m, 2H), 2.65-2.52 (m, 10H), 2.44-2.38 (m, 2H), 2.32-2.23 (m, 2H), 2.04- 1.94 (m, 1H), 1.63 (d, J = 12.2 Hz, 2H), 1.38-1.12 (m, 5H). D197 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 11.06 (s, 1H), 8.19 (s, 2H, FA), 7.68- m/z: 7.61 (m, 2H), 6.95 (d, J = 2.1 Hz, 1H), 6.87-6.81 (m, 1H), 6.59 (s, [M + H]+ = 837.42. 3H), 5.06 (dd, J = 12.4, 5.4 Hz, 1H), 4.22 (s, 2H), 3.78 (s, 6H), 3.66- 3.53 (m, 5H), 3.50 (s, 4H), 3.41 (s, 2H), 3.21-3.10 (m, 4H), 2.90- 2.80 (m, 3H), 2.60 (d, J = 4.2 Hz, 3H), 2.43-2.39 (m, 2H), 2.18 (s, 3H), 2.13-1.98 (m, 4H), 1.90-1.79 (m, 1H), 1.62 (d, J = 11.9 Hz, 2H), 1.38-1.04 (m, 6H). D198 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.07 (s, 1H), 8.20 (s, 2H, FA), 7.66- m/z: 7.61 (m, 2H), 7.11 (d, J = 2.3 Hz, 1H), 7.03 (dd, J = 8.8, 2.4 Hz, 1H), [M + H]+ = 837.65. 6.63-6.57 (m, 3H), 5.06 (dd, J = 12.9, 5.4 Hz, 1H), 4.22 (s, 2H), 3.79 (s, 6H), 3.69-3.59 (m, 7H), 3.50 (s, 3H), 3.40 (t, J = 5.5 Hz, 2H), 2.99- 2.80 (m, 4H), 2.73 (t, J = 5.1 Hz, 2H), 2.62-2.54 (m, 6H), 2.44 (t, J = 7.2 Hz, 2H), 2.19 (t, J = 11.0 Hz, 2H), 2.06-1.95 (m, 1H), 1.85 (p, J = 6.2, 5.6 Hz, 2H), 1.59 (d, J = 11.9 Hz, 2H), 1.38-1.01 (m, 6H). D199 LCMS (ESI) .sup.1H NMR (300 MHz, Methanol-d4) δ 8.54 (s, 1H), 7.66 (d, J = 8.3 Hz, m/z: [M + H]+ = 1H), 7.58 (s, 1H), 6.84 (d, J = 2.1 Hz, 1H), 6.74-6.66 (m, 3H), 5.07 835.60 (dd, J = 12.3, 5.4 Hz, 1H), 4.36 (s, 2H), 4.33 (s, 2H), 4.17 (s, 4H), 3.95 (s, 6H), 3.71-3.62 (m, 4H), 3.60-3.52 (m, 6H), 3.51-3.42 (m, 2H), 3.12-2.99 (m, 2H), 2.88-2.71 (m, 6H), 2.68-2.59 (m, 4H), 2.17- 2.07 (m, 1H), 1.95 (d, J = 13.5 Hz, 2H), 1.73-1.53 (m, 2H), 1.46-1.36 (m, 2H). D200 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 11.06 (s, 1H), 8.16 (s, 1H, FA), 7.69- m/z: 7.60 (m, 2H), 7.32 (d, J = 2.2 Hz, 1H), 7.25 (dd, J = 8.7, 2.3 Hz, 1H), [M + H]+ = 851.95. 6.64-6.54 (m, 3H), 5.07 (dd, J = 12.7, 5.4 Hz, 1H), 4.22 (s, 2H), 4.10 (d, J = 13.0 Hz, 2H), 3.80 (s, 6H), 3.69 (s, 2H), 3.50 (s, 3H), 3.44- 3.37 (m, 5H), 3.00-2.87 (m, 5H), 2.84-2.66 (m, 2H), 2.63-2.56 (m, 4H), 2.47-2.44 (m, 1H), 2.30-2.17 (m, 5H), 2.06-1.98 (m, 1H), 1.79 (d, J = 12.3 Hz, 2H), 1.65 (d, J = 12.3 Hz, 2H), 1.55-1.41 (m, 2H), 1.39-1.16 (m, 5H). D201 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 11.07 (s, 1H), 8.19 (s, 1H, FA), 7.67 m/z: [M + H]+ = (d, J = 8.5 Hz, 1H), 7.63 (s, 1H), 7.33 (d, J = 2.1 Hz, 1H), 7.24 (dd, J = 795.75 8.7, 2.3 Hz, 1H), 6.62-6.54 (m, 3H), 5.07 (dd, J = 12.7, 5.3 Hz, 1H), 4.22 (s, 2H), 3.79 (s, 6H), 3.53-3.49 (m, 6H), 3.43-3.39 (m, 8H), 2.93-2.82 (m, 3H), 2.60 (d, J = 4.3 Hz, 8H), 2.25-2.16 (m, 1H), 2.10-1.98 (m, 3H), 1.71 (d, J = 11.9 Hz, 2H), 1.47-1.31 (m, 2H). D202 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.14 (s, 1H, FA), 7.70 m/z: (d, J = 8.5 Hz, 1H), 7.64 (s, 1H), 7.35 (d, J = 2.3 Hz, 1H), 7.27 (dd, J = [M + H]+ = 894.55. 8.8, 2.2 Hz, 1H), 6.72 (s, 2H), 6.60 (q, J = 4.2 Hz, 1H), 5.08 (dd, J = 12.7, 5.4 Hz, 1H), 4.28-4.11 (m, 4H), 3.87 (s, 6H), 3.64 (s, 2H), 3.51 (s, 3H), 3.49-3.40 (m, 9H), 3.15-3.00 (m, 4H), 2.97-2.82 (m, 2H), 2.65-2.54 (m, 10H), 2.47-2.28 (m, 6H), 2.12-1.96 (m, 3H), 1.85- 1.54 (m, 2H). D203 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 11.11 (s, 1H), 8.17 (s, 1H FA), 7.84 m/z: (dd, J = 8.4, 4.2 Hz, 1H), 7.63 (d, J = 3.5 Hz,

1H), 7.43 (s, 1H), 7.36 [M + H]+ = 868.50. (d, J = 8.4 Hz, 1H), 6.65-6.53 (m, 3H), 5.12 (dd, J = 12.9, 5.4 Hz, 1H), 4.25-4.15 (m, 4H), 3.79 (d, J = 3.3 Hz, 6H), 3.69-3.54 (m, 5H), 3.50 (s, 3H), 3.45-3.29 (m, 8H), 2.97-2.83 (m, 1H), 2.65-2.54 (m, 7H), 2.47-2.32 (m, 3H), 2.07-1.93 (m, 3H), 1.75-1.60 (m, 2H), 1.59-1.44 (m, 2H). D204 853.65 D205 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.19 (s, 2H, FA), 7.68- m/z: [M + H]+ = 7.62 (m, 2H), 7.31 (d, J = 2.2 Hz, 1H), 7.23 (dd, J = 8.7, 2.3 Hz, 1H), 837.75 6.66 (t, J = 5.1 Hz, 1H), 6.60 (s, 2H), 5.07 (dd, J = 12.7, 5.4 Hz, 1H), 4.22 (s, 2H), 4.12-4.01 (m, 2H), 3.79 (s, 6H), 3.59 (s, 2H), 3.50 (s, 3H), 3.41 (t, J = 5.4 Hz, 4H), 3.22-3.13 (m, 4H), 2.95-2.81 (m, 4H), 2.65-2.55 (m, 3H), 2.25 (s, 8H), 2.05-1.96 (m, 1H), 1.89-1.67 (m, 4H), 1.53-1.36 (m, 2H), 1.27-1.12 (m, 2H). D206 LCMS (ESI) m/z: [M + H]+ = 867.65 D207 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 11.06 (s, 1H), 8.24 (s, 2H, FA), 7.64 m/z: [M + H]+ = (d, J = 5.9 Hz, 2H), 6.96-6.41 (m, 5H), 5.20-4.86 (m, 1H), 4.46- 809.7 4.12 (m, 2H), 3.96 (t, J = 6.6 Hz, 6H), 3.79 (s, 6H), 3.65-3.30 (m, 9H), 3.11 (d, J = 6.9 Hz, 2H), 2.77 (s, 4H), 2.23 (s, 6H), 2.15-1.92 (m, 3H), 1.75-1.55 (m, 2H), 1.25-0.97 (m, 3H). D208 LCMS (ESI) m/z: [M + H]+ = 823.6 D209 LCMS (ESI) m/z: [M + H]+ = 823.45 D210 LCMS (ESI) m/z: [M + H]+ = 809.45 D211 LCMS (ESI) m/z: [M + H]+ = 795.55 D212 LCMS (ESI) m/z: [M + H]+ = 809.35 D213 LCMS (ESI) m/z: [M + H]+ = 840.4 D214 LCMS (ESI) m/z: [M + H]+ = 920.4 D215 LCMS (ESI) m/z: [M + H]+ = 824.4 D216 LCMS (ESI) m/z: [M + H]+ = 920.4 D217 LCMS (ESI) m/z: [M + H]+ = 950.5 D218 LCMS (ESI) m/z: [M + H]+ = 934.55 D219 LCMS (ESI) m/z: [M + H]+ = 906.5 D220 LCMS (ESI) .sup.1H NMR (300 MHz, Methanol-d4) δ 8.47 (s, 2H, FA), 7.71-7.57 (m, m/z: [M + H]+ = 2H), 7.36 (s, 1H), 7.24 (d, J = 8.6 Hz, 1H), 6.71 (s, 2H), 5.07 (dd, J = 920.5 12.3, 5.4 Hz, 1H), 4.38 (s, 4H), 4.10 (t, J = 9.0 Hz, 1H), 3.95 (s, 6H), 3.63 (s, 4H), 3.51 (s, 5H), 3.45-3.39 (m, 1H), 3.23-3.04 (m, 4H), 3.01-2.81 (m, 8H), 2.80-2.60 (m, 8H), 2.58-2.50 (m, 2H), 2.36- 2.22 (m, 1H), 2.20-2.03 (m, 3H), 2.00-1.76 (m, 6H), 1.75-1.58 (m, 3H). D221 LCMS (ESI) m/z: [M + H]+ = 906.5 D222 NA .sup.1H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.15 (s, 2H, FA), 7.84 (d, J = 8.3 Hz, 1H), 7.64 (s, 1H), 7.43 (d, J = 2.3 Hz, 1H), 7.35 (dd, J = 8.4, 2.3 Hz, 1H), 6.67-6.56 (m, 3H), 5.12 (dd, J = 12.9, 5.3 Hz, 1H), 4.39-4.35 (m, 1H), 4.25-4.17 (m, 4H), 3.81 (s, 6H), 3.59 (t, J = 4.2 Hz, 2H), 3.50 (s, 4H), 3.41-3.38 (m, 3H), 2.94-2.85 (m, 1H), 2.67- 2.57 (m, 7H), 2.37-2.25 (m, 5H), 2.18 (s, 2H), 2.10-2.01 (m, 1H), 1.90-1.73 (m, 4H), 1.63-1.51 (m, 4H), 1.46-1.39 (m, 2H). D223 LCMS (ESI) m/z: [M + H]+ = 881.4 D224 LCMS (ESI) m/z: [M + H]+ = 824.4 D225 LCMS (ESI) m/z: [M + H]+ = 824.4 D226 LCMS (ESI) m/z: [M + H]+ = 906.45 D227 LCMS (ESI) .sup.1H NMR (300 MHz, Methanol-d4) δ 8.55 (s, 2H, FA), 7.66 (d, J = 8.5 m/z: [M + H]+ = Hz, 1H), 7.61 (s, 1H), 7.33 (d, J = 2.1 Hz, 1H), 7.22 (dd, J = 8.7, 2.2 851.6 Hz, 1H), 6.72 (s, 2H), 5.08 (dd, J = 12.3, 5.4 Hz, 1H), 4.44-4.34 (m, 4H), 4.13-4.00 (m, 2H), 3.95 (s, 6H), 3.64 (s, 3H), 3.57 (t, J = 5.4 Hz, 3H), 3.47-3.34 (m, 4H), 3.22 (t, J = 7.0 Hz, 2H), 3.13-2.94 (m, 3H), 2.88 (s, 7H), 2.78-2.62 (m, 4H), 2.24 (s, 2H), 2.16-2.07 (m, 1H), 2.03-1.77 (m, 5H), 1.62 (s, 1H), 1.46-1.29 (m, 2H). D228 LCMS (ESI) m/z: [M + H]+ = 810.7 D229 LCMS (ESI) m/z: [M + H]+ = 881.6 D230 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.17 (s, 2H, FA), 7.69 m/z: [M + H]+ = (d, J = 8.5 Hz, 1H), 7.65 (s, 1H), 7.35 (s, 1H), 7.31-7.23 (m, 1H), 892.5 6.82 (d, J = 7.4 Hz, 1H), 6.63 (s, 2H), 5.08 (dd, J = 12.8, 5.2 Hz, 1H), 4.22 (s, 2H), 4.03 (q, J = 7.9 Hz, 1H), 3.81 (s, 6H), 3.77-3.70 (m, 4H), 3.61 (s, 2H), 3.50 (s, 3H), 3.47-3.38 (m, 10H), 2.94-2.76 (m, 3H), 2.60-2.54 (m, 2H), 2.45-2.29 (m, 12H), 2.15 (t, J = 10.2 Hz, 2H), 2.08-1.97 (m, 1H), 1.51-1.33 (m, 4H). D231 LCMS (ESI) m/z: [M + H]+ = 809.45 D232 LCMS (ESI) m/z: [M + H]+ = 920.45 D233 LCMS (ESI) m/z: [M + H]+ = 868.45 D234 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.07 (s, 1H), 8.18 (s, 1H, FA), 7.67- m/z: [M + H]+ = 7.59 (m, 2H), 6.93-6.85 (m, 2H), 6.77-6.71 (m, 1H), 6.60 (s, 2H), 823.45 5.04 (dd, J = 12.8, 5.4 Hz, 1H), 4.23 (s, 2H), 4.14-4.04 (m, 1H), 3.79 (s, 6H), 3.59 (s, 2H), 3.53-3.47 (m, 5H), 3.45-3.41 (m, 3H), 3.41 (s, 2H), 3.13-3.04 (m, 3H), 2.94-2.83 (m, 1H), 2.74-2.69 (m, 1H), 2.62-2.57 (m, 1H), 2.47-2.34 (m, 3H), 2.25 (s, 6H), 2.15 (t, J = 10.9 Hz, 1H), 2.05-1.89 (m, 4H), 1.79-1.68 (m, 2H), 1.65-1.56 (m, 2H). D235 LCMS (ESI) m/z: [M + H]+ = 852.45 D236 LCMS (ESI) m/z: [M + H]+ = 837.45 D237 LCMS (ESI) m/z: [M + H]+ = 838.4 D238 LCMS (ESI) m/z: [M + H]+ = D239 823.45 m/z: [M + H]+ = 824.85 D240 LCMS (ESI) m/z: [M + H]+ = 920.5 D241 LCMS (ESI) m/z: [M + H]+ = 795.4 D242 LCMS (ESI) m/z: [M + H]+ = 838.45 D243 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.27 (s, 2H, FA), 7.68 m/z: [M + H]+ = (d, J = 8.5 Hz, 1H), 7.64 (s, 1H), 7.34 (s, 1H), 7.26 (d, J = 8.7 Hz, 1H), 892.45 6.77 (s, 1H), 6.58 (s, 2H), 5.08 (dd, J = 12.8, 5.5 Hz, 1H), 4.28 (d, J = 5.9 Hz, 2H), 4.02-3.94 (m, 1H), 3.78 (s,

6H), 3.61-3.50 (m, 4H), 3.50-3.42 (m, 12H), 2.95-2.85 (m, 2H), 2.79-2.67 (m, 3H), 2.64- 2.56 (m, 3H), 2.40-2.25 (m, 4H), 2.14 (s, 6H), 2.05-1.81 (m, 3H), 1.76-1.67 (m, 1H), 1.63-1.47 (m, 5H). D244 LCMS (ESI) m/z: [M + H]+ = 824.45 D245 LCMS (ESI) m/z: [M + H]+ = 906.45 D246 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 11.08 (s, 1H), 9.37 (s, 1H, TFA), m/z: [M + H]+ = 9.04 (s, 1H), 7.69 (t, J = 4.1 Hz, 2H), 6.93 (s, 1H, TFA), 6.75 (d, J = 823.45 13.2 Hz, 3H), 6.65 (d, J = 8.3 Hz, 1H), 5.06 (dd, J = 12.8, 5.3 Hz, 1H), 4.31-4.09 (m, 4H), 3.89 (d, J = 6.6 Hz, 8H), 3.83 (s, 2H), 3.52 (s, 3H), 3.45 (s, 4H), 3.25-2.79 (m, 8H), 2.76 (d, J = 4.8 Hz, 6H), 2.66- 2.60 (m, 3H), 2.16 (d, J = 13.7 Hz, 2H), 1.95 (dd, J = 34.7, 19.8 Hz, 5H). D247 LCMS (ESI) m/z: [M + H]+ = 892.6 D248 LCMS (ESI) m/z: [M + H]+ = 810.4 D249 LCMS (ESI) m/z: [M + H]+ = 796.35 D250 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 8.42 (s, 2H, FA), 7.90 (d, J = 8.2 Hz, m/z: 1H), 7.67 (s, 1H), 7.50 (d, J = 2.2 Hz, 1H), 7.39 (dd, J = 8.3, 2.3 Hz, [M + H]+ = 838.35 1H), 6.78 (s, 2H), 6.59 (d, J = 7.1 Hz, 1H), 5.13 (dd, J = 12.9, 5.4 Hz, 1H), 4.48 (s, 2H), 4.31 (t, J = 5.7 Hz, 2H), 4.25 (s, 2H), 4.06 (q, J = 7.5 Hz, 1H), 3.88 (s, 6H), 3.52 (s, 6H), 3.46-3.39 (m, 2H), 3.11-3.05 (m, 2H), 3.01 (s, 6H), 2.93 (s, 2H), 2.92-2.80 (m, 1H), 2.63 (s, 1H), 2.61-2.53 (m, 2H), 2.35 (s, 2H), 2.10-2.04 (m, 1H), 1.94-1.83 (m, 2H), 1.70 (t, J = 6.8 Hz, 3H), 1.60-1.44 (m, 3H). D251 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.17 (s, 1H, FA), 7.83 m/z: (d, J = 8.2 Hz, 1H), 7.63 (s, 1H), 7.33-7.25 (m, 2H), 6.65-6.57 (m, [M + H]+ = 878.85 3H), 5.12 (dd, J = 12.8, 5.4 Hz, 1H), 4.98 (q, J = 6.8 Hz, 1H), 4.22 (s, 2H), 3.79 (s, 6H), 3.63 (s, 2H), 3.50 (s, 3H), 3.41 (t, J = 5.5 Hz, 3H), 2.95-2.84 (m, 3H), 2.64-2.56 (m, 6H), 2.48-2.34 (m, 8H), 2.26-2.15 (m, 2H), 2.09-2.00 (m, 1H), 1.87-1.78 (m, 2H), 1.70-1.55 (m, 6H), 1.42-1.32 (m, 2H), 1.31-1.10 (m, 3H). D252 LCMS (ESI) m/z: [M + H]+ = 838.35 D253 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.17 (s, 1H, FA), 7.83 m/z: (d, J = 8.1 Hz, 1H), 7.64 (s, 1H), 7.35-7.23 (m, 2H), 6.68-6.55 (m, [M + H].sup.+ = 864.85. 3H), 5.12 (dd, J = 12.9, 5.4 Hz, 1H), 5.04-4.93 (m, 1H), 4.22 (s, 2H), 3.81 (s, 6H), 3.73 (s, 2H), 3.50 (s, 3H), 3.43-3.41 (m, 3H), 3.01- 2.93 (m, 2H), 2.92-2.77 (m, 2H), 2.64-2.56 (m, 6H), 2.45-2.26 (m, 7H), 2.15-1.99 (m, 3H), 1.86-1.76 (m, 2H), 1.71-1.53 (m, 7H), 1.26-1.08 (m, 2H). D254 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.21 (s, 1H, FA), 7.84 m/z: (d, J = 8.3 Hz, 1H), 7.63 (s, 1H), 7.34-7.26 (m, 2H), 6.65-6.56 (m, [M + H]+ = 878.65. 3H), 5.12 (dd, J = 12.8, 5.4 Hz, 1H), 5.03 (t, J = 6.9 Hz, 1H), 4.22 (s, 2H), 3.78 (s, 6H), 3.53-3.49 (m, 6H), 3.43-3.39 (m, 6H), 2.96- 2.78 (m, 4H), 2.64-2.56 (m, 5H), 2.47-2.44 (m, 1H), 2.15-2.00 (m, 4H), 1.92-1.82 (m, 2H), 1.67-1.43 (m, 9H). D255 LCMS (ESI) 1H-NMR (400 MHz, DMSO-d6) δ 11.09 (s, 1H), 8.15 (s, 1H, FA), 7.69 m/z: (d, J = 8.5 Hz, 1H), 7.64 (s, 1H), 7.35 (d, J = 2.2 Hz, 1H), 7.27 (dd, J = [M + H]+ = 835.45. 8.7, 2.3 Hz, 1H), 6.69 (s, 2H), 6.61 (q, J = 4.3 Hz, 1H), 5.08 (dd, J = 12.9, 5.4 Hz, 1H), 4.22 (s, 2H), 4.04 (s, 2H), 3.86 (s, 6H), 3.51 (s, 3H), 3.48-3.38 (m, 7H), 3.10-2.83 (m, 5H), 2.73 (t, J = 7.6 Hz, 1H), 2.64- 2.53 (m, 6H), 2.39 (s, 4H), 2.08-1.95 (m, 3H), 1.76 (s, 2H), 1.73- 1.57 (m, 4H). D256 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO) δ 11.08 (s, 1H), 8.20 (d, FA, 2H), 7.73- m/z: 7.61 (m, 2H), 7.39-7.18 (m, 2H), 6.60 (d, 3H), 5.07 (dd, 1H), 4.22 (s, [M + H]+ = 809. 2H), 3.80 (s, 7H), 3.63 (d, 3H), 3.50 (s, 3H), 3.42 (d, 6H), 2.98-2.80 (m, 3H), 2.60 (d, 4H), 2.51-2.39 (m, 5H), 2.22-2.12 (m, 4H), 2.16- 1.95 (m, 1H), 1.69 (d, 2H), 1.60-1.45 (m, 1H), 1.22-1.05 (m, 2H); D257 LCMS (ESI) .sup.1H NMR (400 MHz, Methanol-d4) δ 8.49 (s, 3H, FA), 7.81 (d, J = 8.4 m/z: Hz, 1H), 7.56-7.48 (m, 2H), 7.39 (d, J = 8.6 Hz, 1H), 6.64 (s, 2H), [M + H]+ = 809.50. 5.12 (dd, J = 12.6, 5.4 Hz, 1H), 4.35 (s, 2H), 4.10-4.02 (m, 3H), 3.90 (s, 6H), 3.89-3.85 (m, 3H), 3.84-3.62 (m, 9H), 3.55-3.48 (m, 3H), 3.08-3.01 (m, 1H), 2.98-2.83 (m, 2H), 2.78 (s, 3H), 2.76-2.70 (m, 2H), 2.64-2.57 (m, 2H), 2.44 (s, 1H), 2.17-1.98 (m, 4H), 1.39- 1.27 (m, 2H). D258 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 8.37 (s, 1H, FA), 7.79 m/z: (d, J = 8.3 Hz, 1H), 7.56 (d, J = 30.9 Hz, 2H), 7.47-7.31 (m, 1H), [M + H]+ = 795.40. 6.61 (d, J = 5.4 Hz, 3H), 5.10 (dd, J = 13.0, 5.4 Hz, 1H), 4.21 (s, 2H), 3.91 (d, J = 8.9 Hz, 1H), 3.81 (s, 10H), 3.76-3.57 (m, 12H), 3.40 (t, J = 5.6 Hz, 4H), 3.26 (t, J = 10.7 Hz, 2H), 2.98-2.82 (m, 1H), 2.71 (s, 1H), 2.66-2.54 (m, 5H), 2.28-2.20 (m, 1H), 2.09-1.98 (m, 1H), 1.84-1.79 (s, 1H). D259 LCMS (ESI) .sup.1H NMR (300 MHz, Methanol-d4) δ 8.48 (s, 1H, FA), 7.84 (d, J = 8.3 m/z: [M + H]+ = Hz, 1H), 7.60 (s, 1H), 7.46 (s, 1H), 7.40-7.34 (m, 1H), 6.72 (s, 2H), 854.4 5.13 (dd, J = 12.4, 5.4 Hz, 1H), 4.44-4.35 (m, 6H), 4.19-4.09 (m, 1H), 3.95 (s, 6H), 3.69-3.48 (m, 8H), 3.43-3.38 (m, 1H), 3.18-3.11 (m, 2H), 2.92-2.72 (m, 13H), 2.65 (s, 2H), 2.21-2.10 (m, 1H), 1.98 (dd, J = 12.8, 7.2 Hz, 1H), 1.82-1.71 (m, 4H), 1.58-1.47 (m, 1H). D260 LCMS (ESI) m/z: [M + H]+ = 795.4 D261 LCMS (ESI) m/z: [M + H]+ = 809.45 D262 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 8.43 (s, 2H, FA), 7.90 (d, J =

8.4 Hz, m/z: [M + H]+ = 1H), 7.68 (s, 1H), 7.50 (d, J = 2.2 Hz, 1H), 7.39 (dd, J = 8.4, 2.3 Hz, 824.4 1H), 6.88 (d, J = 6.7 Hz, 1H), 6.77 (s, 2H), 5.14 (dd, J = 12.8, 5.4 Hz, 1H), 4.48 (s, 2H), 4.31 (t, J = 5.2 Hz, 4H), 4.25 (s, 2H), 4.13 (dq, J = 16.8, 8.2 Hz, 1H), 3.88 (s, 6H), 3.52 (s, 6H), 3.42 (t, J = 4.7 Hz, 2H), 3.01 (s, 6H), 2.96-2.84 (m, 4H), 2.63 (d, J = 3.8 Hz, 1H), 2.61-2.53 (m, 3H), 2.40-2.33 (m, 1H), 2.27-1.96 (m, 6H), 1.87-1.82 (m, 1H), 1.81-1.74 (m, 1H). D263 LCMS (ESI) m/z: [M + H]+ = 810.45 D264 LCMS (ESI) m/z: [M + H]+ = 796.7 D265 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6 with a drop of D.sub.2O) δ 8.40 (s, 2H, FA), m/z: [M + H]+ = 7.88 (d, J = 8.3 Hz, 1H), 7.66 (s, 1H), 7.48 (d, J = 2.3 Hz, 1H), 7.39 838.45 (dd, J = 8.4, 2.3 Hz, 1H), 6.74 (s, 2H), 5.12 (dd, J = 12.8, 5.4 Hz, 1H), 4.47 (s, 2H), 4.30 (t, J = 6.1 Hz, 2H), 4.23 (s, 2H), 3.86 (s, 6H), 3.55- 3.48 (m, 5H), 3.41 (s, 2H), 3.25 (s, 1H), 3.07-2.97 (m, 9H), 2.96- 2.81 (m, 3H), 2.75-2.70 (m, 1H), 2.66-2.55 (m, 5H), 2.34 (s, 1H), 2.24-2.14 (m, 1H), 2.09-1.94 (m, 3H), 1.52-1.42 (m, 2H), 1.03- 0.97 (m, 1H). D266 LCMS (ESI) m/z: [M + H]+ = 824.4 D267 LCMS (ESI) m/z: [M + H]+ = 838.4 D268 LCMS (ESI) m/z: [M + H]+ = 810.7 D269 LCMS (ESI) .sup.1H NMR (400 MHz, Methanol-d4) δ 8.51 (s, 2H, FA), 7.81 (d, J = 8.2 m/z: [M + H]+ = Hz, 1H), 7.60 (s, 1H), 7.46 (s, 1H), 7.37 (d, J = 8.2 Hz, 1H), 6.71 (s, 824.45 2H), 5.12 (dd, J = 12.4, 5.4 Hz, 1H), 4.49 (s, 2H), 4.37 (d, J = 2.8 Hz, 4H), 3.95 (s, 6H), 3.63 (s, 3H), 3.58-3.52 (m, 2H), 3.37 (s, 2H), 3.27 (d, J = 7.3 Hz, 2H), 3.15 (s, 4H), 2.88 (s, 7H), 2.80-2.58 (m, 4H), 2.17-2.07 (m, 1H), 1.97-1.55 (m, 4H), 1.18-1.06 (m, 1H), 0.70- 0.60 (m, 1H), 0.37 (t, J = 5.1 Hz, 1H). D270 LCMS (ESI) m/z: [M + H]+ = 810.4 D271 LCMS (ESI) m/z: [M + H]+ = 810.45 D272 LCMS (ESI) m/z: [M + H]+ = 824.4 D273 LCMS (ESI) m/z: [M + H]+ = 810.4 D274 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.18 (s, 2H, FA), 7.84 m/z: [M + H]+ = (d, J = 8.3 Hz, 1H), 7.64 (s, 1H), 7.46 (dd, J = 4.0, 2.2 Hz, 1H), 7.37 796.35 (dt, J = 8.3, 2.3 Hz, 1H), 6.63 (s, 2H), 6.58 (d, J = 4.9 Hz, 1H), 5.12 (dd, J = 12.9, 5.4 Hz, 1H), 4.26 (d, J = 11.7 Hz, 4H), 3.89 (s, 1H), 3.80 (d, J = 1.9 Hz, 6H), 3.74-3.54 (m, 4H), 3.50 (s, 3H), 3.44 (d, J = 5.7 Hz, 2H), 3.18-3.10 (m, 2H), 3.03-2.98 (m, 1H), 2.92-2.84 (m, 3H), 2.74-2.69 (m, 1H), 2.32 (s, 5H), 2.22 (d, J = 13.6 Hz, 2H), 2.09- 2.04 (s, 2H), 1.80 (t, J = 11.3 Hz, 1H), 1.74-1.61 (m, 2H), 1.46 (d, J = 10.2 Hz, 1H). LCMS (ESI) m/z: [M + H]+ = 796.35 D275 LCMS (ESI) .sup.1H NMR (400 MHz, Methanol-d4) δ 8.56 (br s, 1H, FA), 7.82 (d, J = m/z: 8.3 Hz, 1H), 7.58 (s, 1H), 7.30 (s, 1H), 7.25 (dd, J = 8.2, 2.2 Hz, 1H), [M + H]+ = 864.45. 6.72 (s, 2H), 5.12 (dd, J = 12.7, 5.4 Hz, 1H), 4.97 (t, J = 6.6 Hz, 1H), 4.47 (s, 2H), 4.36 (s, 2H), 4.25 (t, J = 9.5 Hz, 2H), 4.01-3.90 (m, 8H), 3.64 (s, 3H), 3.60-3.49 (m, 5H), 3.47-3.42 (m, 1H), 3.23-3.17 (m, 1H), 2.95-2.82 (m, 3H), 2.80-2.67 (m, 5H), 2.64-2.54 (m, 4H), 2.18-2.10 (m, 1H), 2.03 (dd, J = 12.7, 6.2 Hz, 2H), 1.80-1.60 (m, 4H). D276 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 7.84 (d, J = 8.3 Hz, m/z: 1H), 7.70 (t, J = 5.8 Hz, 1H), 7.62 (s, 1H), 7.44 (d, J = 2.3 Hz, 1H), [M + H]+ = 852.39. 7.36 (dd, J = 8.3, 2.3 Hz, 1H), 6.62-6.57 (m, 1H), 6.56 (s, 2H), 5.12 (dd, J = 12.9, 5.4 Hz, 1H), 4.19 (dd, J = 13.0, 6.6 Hz, 4H), 3.77 (s, 6H), 3.50 (s, 3H), 3.44 (s, 2H), 3.40 (t, J = 5.5 Hz, 2H), 3.40-3.35 (m, 2H), 3.07 (q, J = 6.5 Hz, 2H), 2.95-2.84 (m, 1H), 2.63-2.54 (m, 5H), 2.09-1.97 (m, 4H), 1.90 (s, 6H), 1.81-1.71 (m, 2H), 1.54-1.35 (m, 4H). D277 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.23 (s, 1H, FA), 7.84 m/z: (d, J = 8.3 Hz, 1H), 7.61 (s, 1H), 7.43 (d, J = 2.2 Hz, 1H), 7.35 (dd, J = [M + H]+ = 820.55. 8.3, 2.3 Hz, 1H), 7.25 (t, J = 5.8 Hz, 1H), 6.64-6.54 (m, 3H), 5.13 (dd, J = 12.9, 5.4 Hz, 1H), 4.25-4.15 (m, 4H), 4.02-3.85 (m, 2H), 3.77 (s, 6H), 3.57 (s, 2H), 3.49 (s, 3H), 3.43-3.38 (m, 6H), 3.11 (q, J = 6.5 Hz, 2H), 2.96-2.82 (m, 1H), 2.66-2.52 (m, 6H), 2.10-1.99 (m, 1H), 1.97-1.85 (m, 2H). D278 LCMS (ESI) .sup.1H NMR (400 MHz, Methanol-d4) δ 8.48 (s, 1H, FA), 7.80 (d, J = 8.3 m/z: Hz, 1H), 7.55 (s, 1H), 7.40 (d, J = 2.3 Hz, 1H), 7.32 (dd, J = 8.4, 2.3 [M + H]+ = 834.15 Hz, 1H), 6.63 (s, 2H), 5.11 (dd, J = 12.5, 5.4 Hz, 1H), 4.35 (s, 2H), 4.20 (t, J = 6.2 Hz, 2H), 4.16-4.06 (m, 1H), 4.02 (s, 2H), 3.88 (s, 6H), 3.88-3.83 (m, 4H), 3.63 (s, 3H), 3.53 (t, J = 5.6 Hz, 2H), 3.14 (t, J = 6.9 Hz, 2H), 2.95-2.83 (m, 1H), 2.80-2.67 (m, 5H), 2.65-2.60 (m, 2H), 2.18-2.09 (m, 1H), 1.97-1.86 (m, 2H), 1.80-1.67 (m, 2H). D279 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 7.86 (d, J = 8.3 Hz, m/z: 1H), 7.61 (s, 1H), 7.51 (s, 1H), 7.46 (d, J = 2.3 Hz, 1H), 7.37 (dd, J = [M + H]+ = 806.45. 8.3, 2.3 Hz, 1H), 6.62-6.53 (m, 3H), 5.13 (dd, J = 12.9, 5.3 Hz, 1H), 4.24-4.16 (m, 4H), 4.04 (s, 1H), 3.78 (s, 6H), 3.59 (s, 2H), 3.49 (s, 3H), 3.47-3.36 (m, 7H), 3.31 (s, 1H), 2.95-2.83 (m, 1H), 2.64- 2.53 (m, 7H), 2.10-2.02 (m, 1H). D280 LCMS (ESI) .sup.1H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 7.83 (dd, J = 8.5, 7.2 m/z: Hz, 1H), 7.62 (s, 1H), 7.53 (d, J = 8.5 Hz, 1H), 7.47 (d, J = 7.2 Hz, [M + H]+ = 820.60. 1H), 6.75-6.58 (m, 3H), 5.09 (dd, J = 12.8, 5.4 Hz, 1H), 4.28-4.19 (m, 4H), 3.96-3.61 (m, 8H), 3.50 (s,

3H), 3.40 (t, J = 5.5 Hz, 2H), 3.38 (s, 6H), 3.24-3.14 (m, 2H), 2.97-2.82 (m, 1H), 2.64-2.54 (m, 6H), 2.09-1.88 (m, 3H). D281 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 10.08 (s, 1H, TFA), m/z: 7.83 (dd, J = 8.5, 7.2 Hz, 1H), 7.69 (s, 1H), 7.64 (s, 1H), 7.53 (d, J = [M + H]+ = 834.10 8.5 Hz, 1H), 7.47 (d, J = 7.3 Hz, 1H), 6.71 (s, 2H), 6.61 (q, J = 4.3 Hz, 1H), 5.09 (dd, J = 12.7, 5.5 Hz, 1H), 4.66-4.29 (m, 5H), 4.26-4.14 (m, 5H), 3.86 (s, 6H), 3.51 (s, 3H), 3.44-3.39 (m, 4H), 3.11-3.01 (m, 2H), 2.94-2.81 (m, 1H), 2.64-2.53 (m, 6H), 2.07-1.98 (m, 1H), 1.85-1.76 (m, 2H), 1.70-1.60 (m, 2H). D282 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 7.84 (t, J = 7.8 Hz, m/z: [M + H]+ = 1H), 7.62 (s, 1H), 7.55 (d, J = 8.6 Hz, 1H), 7.50 (d, J = 7.2 Hz, 1H), 806.60. 6.69-6.53 (m, 3H), 5.11 (dd, J = 12.8, 5.4 Hz, 1H), 4.49-4.00 (m, 7H), 3.79 (s, 7H), 3.56-3.47 (m, 4H), 3.44-3.37 (m, 5H), 2.94- 2.83 (m, 1H), 2.59 (d, J = 4.2 Hz, 4H), 2.57-2.53 (m, 4H), 2.07- 1.98 (m, 1H). D283 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 7.82 (dd, J = 8.5, 7.3 m/z: Hz, 1H), 7.69 (t, J = 5.8 Hz, 1H), 7.62 (s, 1H), 7.53 (d, J = 8.6 Hz, 1H), [M + H]+ = 852.39. 7.45 (d, J = 7.2 Hz, 1H), 6.59 (d, J = 4.4 Hz, 1H), 6.56 (s, 2H), 5.08 (dd, J = 12.9, 5.4 Hz, 1H), 4.24-4.17 (m, 4H), 3.77 (s, 6H), 3.50 (s, 3H), 3.44 (s, 2H), 3.40 (t, J = 5.6 Hz, 2H), 3.37 (s, 2H), 3.11-3.03 (m, 2H), 2.93-2.81 (m, 1H), 2.61-2.55 (m, 5H), 2.07-1.98 (m, 4H), 1.90 (s, 6H), 1.81-1.73 (m, 2H), 1.54-1.38 (m, 4H). D284 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.09 (s, 1H), 8.15 (s, 1H, FA), 7.67 m/z: (d, J = 8.5 Hz, 1H), 7.63 (s, 1H), 7.33 (d, J = 2.3 Hz, 1H), 7.25 (dd, J = [M + H]+ = 813.45 8.7, 2.3 Hz, 1H), 6.61 (d, J = 6.9 Hz, 3H), 5.07 (dd, J = 12.9, 5.4 Hz, 1H), 4.21 (s, 2H), 3.84-3.77 (m, 7H), 3.71 (s, 2H), 3.64-3.53 (m, 5H), 3.52-3.46 (m, 4H), 3.43-3.38 (m, 7H), 2.95-2.83 (m, 1H), 2.72 (s, 2H), 2.60-2.53 (m, 9H), 2.28 (s, 3H), 2.06-1.97 (m, 1H). D285 LCMS (ESI) .sup.1H NMR (300 MHz, Methanol-d4) δ 8.56 (br s, 1.7H, FA), 7.55 (s, 1H), m/z: 7.24 (t, J = 7.7 Hz, 1H), 7.09 (d, J = 7.6 Hz, 1H), 6.91 (d, J = 7.9 Hz, [M − H]+ = 774.37. 1H), 6.71 (s, 2H), 5.19 (dd, J = 13.4, 5.1 Hz, 1H), 4.39-4.27 (m, 5H), 4.09-3.98 (m, 2H), 3.94 (s, 6H), 3.67-3.50 (m, 14H), 3.40 (t, J = 5.4 Hz, 2H), 3.04-2.91 (m, 2H), 2.85 (s, 6H), 2.61 (s, 2H), 2.53-2.39 (m, 1H), 2.24-2.12 (m, 1H). D286 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.18 (s, 1.0H, FA), m/z: 7.83 (d, J = 8.3 Hz, 1H), 7.68-7.62 (m, 2H), 7.43 (d, J = 2.3 Hz, 1H), [M + H]+ = 866.30. 7.35 (dd, J = 8.3, 2.3 Hz, 1H), 6.62-6.56 (m, 3H), 5.12 (dd, J = 12.9, 5.4 Hz, 1H), 4.25-4.13 (m, 4H), 3.78 (s, 6H), 3.54 (s, 2H), 3.50 (s, 3H), 3.42-3.38 (m, 3H), 3.05 (q, J = 6.6 Hz, 2H), 2.94-2.84 (m, 1H), 2.64-2.53 (m, 6H), 2.48 (s, 2H), 2.11 (s, 3H), 2.08-2.01 (m, 1H), 1.85 (s, 6H), 1.80-1.71 (m, 2H), 1.51-1.35 (m, 4H). D287 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.16 (s, 0.7H, FA), m/z: 7.68 (d, J = 8.5 Hz, 1H), 7.61 (s, 1H), 7.35 (d, J = 2.3 Hz, 1H), 7.26 [M + H]+ = 874.35. (dd, J = 8.6, 2.3 Hz, 1H), 7.08 (t, J = 5.8 Hz, 1H), 6.58 (s, 3H), 5.07 (dd, J = 12.9, 5.3 Hz, 1H), 4.21 (s, 2H), 4.07-3.95 (m, 1H), 3.78 (s, 6H), 3.58 (s, 2H), 3.49 (s, 3H), 3.47-3.34 (m, 14H), 3.08 (q, J = 6.5 Hz, 2H), 2.94-2.82 (m, 1H), 2.59 (d, J = 4.2 Hz, 5H), 2.54 (s, 2H), 2.42 (t, J = 6.7 Hz, 2H), 2.07-1.99 (m, 1H). D288 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.14 (s, 1H), 8.19 (s, 0.9H, FA), m/z: 7.81 (dd, J = 8.6, 7.3 Hz, 1H), 7.68-7.61 (m, 2H), 7.52 (d, J = 8.6 Hz, [M + H]+ = 866.25. 1H), 7.45 (d, J = 7.2 Hz, 1H), 6.64-6.54 (m, 3H), 5.08 (dd, J = 12.9, 5.4 Hz, 1H), 4.26-4.13 (m, 4H), 3.78 (s, 6H), 3.55-3.47 (m, 6H), 3.40 (t, J = 5.5 Hz, 2H), 3.08-3.01 (m, 2H), 2.93-2.82 (m, 1H), 2.63- 2.52 (m, 6H), 2.47 (s, 2H), 2.10 (s, 3H), 2.06-1.99 (m, 1H), 1.84 (s, 6H), 1.81-1.73 (m, 2H), 1.51-1.39 (m, 4H). D289 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.19 (s, 0.9H, FA), m/z: 7.83 (d, J = 8.3 Hz, 1H), 7.63 (s, 1H), 7.44 (d, J = 2.3 Hz, 1H), 7.36 (d, [M + H]+ = 854.70. J = 8.4 Hz, 1H), 6.58 (s, 3H), 5.12 (dd, J = 12.9, 5.4 Hz, 1H), 4.33- 4.26 (m, 2H), 4.21 (s, 2H), 3.97-3.89 (m, 1H), 3.76 (s, 8H), 3.70- 3.67 (m, 2H), 3.59 (s, 3H), 3.49 (s, 4H), 2.95-2.76 (m, 5H), 2.63- 2.52 (m, 10H), 2.29-2.19 (m, 1H), 2.18-2.10 (m, 1H), 2.09-1.99 (m, 1H), 1.52-1.28 (m, 2H). D290 LCMS (ESI) .sup.1H NMR (400 MHz, DMSO-d6, D2O) δ 8.53 (t, J = 5.8 Hz, TFA salt), m/z: 7.84 (d, J = 8.3 Hz, 1H), 7.66 (s, 1H), 7.46 (d, J = 2.3 Hz, 1H), 7.40 [M + H]+ = 815.50. (dd, J = 8.3, 2.3 Hz, 1H), 6.68 (s, 2H), 5.11 (dd, J = 12.9, 5.4 Hz, 1H), 4.77 (s, 2H), 4.22 (d, J = 4.7 Hz, 4H), 3.86 (s, 6H), 3.58-3.52 (m, 2H), 3.50 (s, 3H), 3.44-3.14 (m, 8H), 2.94-2.83 (m, 4H), 2.75 (s, 6H), 2.65-2.53 (m, 4H), 2.08-1.96 (m, 1H). D291 LCMS (ESI) 1H-NMR (400 MHz, DMSO-d6) δ 11.01 (s, 1H), 8.31 (t, J = 5.3 Hz, m/z: 1H), 8.22 (s, 0.8H, FA), 7.64 (s, 1H), 7.48 (t, J = 8.1 Hz, 1H), 6.68- [M + H]+ = 797.55. 6.59 (m, 4H), 6.49 (d, J = 8.3 Hz, 1H), 5.18 (dd, J = 11.5, 5.6 Hz, 1H), 4.22 (s, 2H), 3.79 (s, 6H), 3.62 (s, 2H), 3.50 (s, 3H), 3.40 (t, J = 5.5 Hz, 2H), 3.14 (q, J = 6.6 Hz, 2H), 3.03 (q, J = 6.5 Hz, 2H), 2.90-2.76 (m, 1H), 2.70-2.58 (m, 2H), 2.58-2.52 (m, 5H), 2.27 (s, 6H), 2.20- 2.08 (m, 1H), 1.65-1.54 (m, 2H), 1.44-1.38 (m, 2H), 1.37-1.18 (m, 8H).

D292 LCMS (ESI) 1H-NMR (400 MHz, Methanol-d4) δ 8.55 (brs, 0.9H, FA), 7.53 (s, 1H), m/z: 7.43 (t, J = 8.1 Hz, 1H), 6.70-6.63 (m, 3H), 6.51 (d, J = 8.3 Hz, 1H), [M + H]+ = 801.50. 5.20-5.13 (m, 1H), 4.41-4.25 (m, 4H), 3.94 (s, 6H), 3.82-3.77 (m, 2H), 3.68 (s, 4H), 3.62-3.57 (m, 5H), 3.56-3.35 (m, 6H), 2.93- 2.79 (m, 8H), 2.78-2.69 (m, 1H), 2.62 (s, 3H), 2.58-2.50 (m, 2H), 2.23-2.14 (m, 1H). D293 764.3 .sup.1H NMR (400 MHz, DMSO-d6) δ 7.72 (s, 1H), 7.41 (d, J = 8.6 Hz, 1H), 6.75-6.62 (m, 4H), 5.06 (dd, J = 13.2, 5.0 Hz, 1H), 4.35 (t, J = 18.7 Hz, 4H), 4.27-4.16 (m, 3H), 4.11-3.98 (m, 3H), 3.88 (s, 6H), 3.75- 3.62 (m, 5H), 3.53 (s, 3H), 3.31-3.12 (m, 3H), 3.05-2.82 (m, 8H), 2.81-2.73 (m, 1H), 2.70-2.56 (m, 3H), 2.42-2.32 (m, 1H), 2.18- 2.05 (m, 2H), 2.04-1.84 (m, 3H). D294 866.45 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.13 (s, 1H), 8.20 (s, 0.9H, FA), 7.81 (dd, J = 8.5, 7.2 Hz, 1H), 7.64 (t, J = 5.8 Hz, 1H), 7.58-7.49 (m, 2H), 7.44 (d, J = 7.2 Hz, 1H), 6.58 (s, 2H), 6.54 (q, J = 4.3 Hz, 1H), 5.08 (dd, J = 12.9, 5.4 Hz, 1H), 4.26 (s, 2H), 4.20 (t, J = 6.4 Hz, 2H), 3.79 (s, 6H), 3.56-3.49 (m, 4H), 3.47 (s, 3H), 3.05 (q, J = 6.4 Hz, 2H), 2.88 (ddd, J = 17.3, 14.1, 5.4 Hz, 1H), 2.63-2.55 (m, 1H), 2.55- 2.51 (m, 4H), 2.50-2.46 (m, 4H), 2.11 (s, 3H), 2.07-1.99 (m, 1H), 1.85 (s, 6H), 1.77 (t, J = 6.9 Hz, 2H), 1.50-1.39 (m, 4H). D295 854.7 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.15 (s, 0.7H, FA), 7.83 (d, J = 8.3 Hz, 1H), 7.56 (s, 1H), 7.45 (d, J = 2.2 Hz, 1H), 7.36 (dd, J = 8.3, 2.3 Hz, 1H), 6.61 (s, 2H), 6.55 (q, J = 4.4 Hz, 1H), 5.12 (dd, J = 12.9, 5.4 Hz, 1H), 4.31-4.27 (m, 2H), 4.25 (s, 2H), 3.94- 3.88 (m, 1H), 3.79 (s, 8H), 3.75 (s, 2H), 3.72-3.68 (m, 3H), 3.47 (s, 4H), 3.10-3.01 (m, 2H), 2.99-2.81 (m, 3H), 2.69-2.52 (m, 10H), 2.41-2.32 (m, 1H), 2.31-2.21 (m, 1H), 2.08-1.97 (m, 1H), 1.64- 1.39 (m, 2H). D296 813.45 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.16 (s, 1.1H, FA), 7.67 (d, J = 8.5 Hz, 1H), 7.56 (s, 1H), 7.34 (d, J = 2.3 Hz, 1H), 7.25 (dd, J = 8.7, 2.3 Hz, 1H), 6.63 (s, 2H), 6.54 (d, J = 4.5 Hz, 1H), 5.07 (dd, J = 12.9, 5.4 Hz, 1H), 4.27 (s, 2H), 3.82 (s, 6H), 3.73 (s, 2H), 3.63- 3.55 (m, 4H), 3.52 (t, J = 5.9 Hz, 2H), 3.46 (s, 3H), 3.45-3.38 (m, 8H), 2.94-2.84 (m, 1H), 2.75 (s, 2H), 2.64-2.54 (m, 9H), 2.35- 2.25 (m, 3H), 2.08-1.97 (m, 1H). D297 802.55 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.10 (s, 1H), 8.19 (s, 0.8H, FA), 7.82-7.72 (m, 2H), 7.54 (s, 1H), 7.48 (d, J = 8.6 Hz, 1H), 7.43 (d, J = 7.2 Hz, 1H), 6.57 (s, 2H), 6.56-6.51 (m, 1H), 5.08 (dd, J = 12.9, 5.4 Hz, 1H), 4.37-4.29 (m, 2H), 4.25 (s, 2H), 3.85-3.77 (m, 8H), 3.59 (t, J = 5.7 Hz, 2H), 3.54-3.50 (m, 4H), 3.46 (s, 3H), 3.34 (q, J = 5.9 Hz, 4H), 2.94 (s, 2H), 2.91-2.83 (m, 1H), 2.62-2.52 (m, 5H), 2.10 (s, 3H), 2.05-1.96 (m, 1H). D298 827.5 1H-NMR (400 MHz, Methanol-d4) δ 8.47 (brs, 1.4H, FA), 7.69 (d, J = 8.5 Hz, 1H), 7.50 (s, 1H), 7.34 (d, J = 2.3 Hz, 1H), 7.24 (dd, J = 8.6, 2.3 Hz, 1H), 6.77 (s, 2H), 5.08 (dd, J = 12.4, 5.5 Hz, 1H), 4.50 (s, 2H), 4.09 (s, 2H), 3.97 (s, 6H), 3.92-3.87 (m, 2H), 3.76 (t, J = 5.2 Hz, 2H), 3.61 (s, 3H), 3.51-3.45 (m, 8H), 2.90-2.86 (m, 4H), 2.83 (s, 6H), 2.79-2.71 (m, 10H), 2.17-2.07 (m, 1H). D299 809.94 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.04 (s, 1H), 8.13 (s, 2H), 7.87 (s, 1H), 7.65 (d, J = 8.5 Hz, 1H), 7.31 (d, J = 2.3 Hz, 1H), 7.23 (dd, J = 8.7, 2.3 Hz, 1H), 6.68 (s, 2H), 6.33 (d, J = 4.5 Hz, 1H), 5.05 (dd, J = 12.9, 5.4 Hz, 1H), 3.81 (s, 5H), 3.65 (d, J = 3.1 Hz, 2H), 3.52 (s, 3H), 3.39 (d, J = 5.4 Hz, 4H), 3.15 (s, 2H), 2.97-2.78 (m, 3H), 2.58 (d, J = 4.3 Hz, 3H), 2.00 (dd, J = 9.2, 4.2 Hz, 1H), 1.64 (d, J = 12.6 Hz, 2H), 1.35 (s, 1H). D300 738.82 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.03 (s, 1H), 8.14 (s, 1H), 7.85 (d, J = 11.1 Hz, 1H), 7.60 (d, J = 8.3 Hz, 1H), 6.70-6.56 (m, 3H), 5.02 (dd, J = 12.9, 5.4 Hz, 1H), 4.68-4.54 (m, 2H), 4.38 (s, 2H), 3.80 (s, 6H), 3.73 (d, J = 19.6 Hz, 4H), 3.52 (s, 3H), 3.47 (s, 2H), 2.93-2.74 (m, 1H), 2.58 (dd, J = 4.4, 2.9 Hz, 4H), 2.37 (s, 4H), 2.05-1.91 (m, 1H), 1.69 (s, 4H). D301 749.15 .sup.1H NMR (400 MHz, Methanol-d4) δ 7.41 (d, J = 7.8 Hz, 2H), 6.88 (d, J = 2.2 Hz, 1H), 6.80 (dd, J = 8.2, 2.2 Hz, 1H), 6.70 (s, 2H), 5.14 (dd, J = 13.3, 5.2 Hz, 1H), 4.51 (s, 2H), 4.47-4.20 (m, 4H), 4.15 (s, 2H), 3.95 (s, 6H), 3.77 (s, 4H), 3.61 (s, 3H), 3.55-3.35 (m, 5H), 3.15 (s, 1H), 3.29-3.01 (m, 1H), 2.98-2.85 (m, 1H), 2.80 (d, J = 17.6 Hz, 1H), 2.60 (t, J = 6.4 Hz, 2H), 2.51-2.47 (m, 3H), 2.25-2.04 (m, 5H), 1.85-1.79 (m, 2H), 1.72-1.67 (m, 2H). D302 737.4 1H NMR (400 MHz, Methanol-d4) δ 8.33 (s, 2H, FA), 7.91 (s, 1H), 7.39 (d, J = 8.2 Hz, 1H), 6.85 (d, J = 2.2 Hz, 1H), 6.81-6.74 (m, 3H), 5.23 (t, J = 3.4 Hz, 2H), 5.14 (dd, J = 13.3, 5.2 Hz, 1H), 5.07 (t, J = 3.4 Hz, 2H), 4.45 (s, 2H), 4.42 (d, J = 16.5 Hz, 1H), 4.36 (d, J = 16.5 Hz, 1H), 4.22 (t, J = 9.4 Hz, 2H), 3.98 (s, 6H), 3.95 (d, J = 10.0 Hz, 2H), 3.71 (s, 3H), 3.68 (s, 4H), 3.20-3.10 (m, 1H), 2.98-2.86 (m, 1H), 2.84-2.69 (m, 3H), 2.61-2.42 (m, 5H), 2.23-2.13 (m, 1H), 1.94- 1.90 (m, 4H). DD1 LCMS (ESI) .sup.1H NMR (400 MHz, Methanol-d4) δ 8.56 (s, 1H, FA), 7.55 (s, 1H), 7.49 m/z: (td, J = 8.6, 5.9 Hz, 1H), 7.28-7.20 (m, 1H), 7.19-7.12 (m, 1H), [M + H]+ = 878.5. 6.63 (s, 2H), 4.36 (s, 2H), 3.96-3.82 (m, 8H), 3.64 (s, 3H), 3.59-3.49 (m, 4H), 3.31-3.24(m, 2H), 2.94-2.74 (m, 8H), 2.69-2.45 (m, 7H), 1.79 (d, J = 10.9 Hz, 2H), 1.62-1.46 (m, 5H).

Example 67—Preparation of Compounds D303-D375

(342) In analogy to the procedures described in the examples above, compounds D303-D375 were prepared using the appropriate starting materials

(343) TABLE-US-00009 Compound No. LCMS .sup.1H NMR D303 669.2 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.07 (s, 1H), 7.67 (d, J = 8.3 Hz, 1H), 7.60 (s, 1H), 6.82 (d, J = 2.1 Hz, 1H), 6.73-6.66 (m, 1H), 6.63-6.53 (m, 3H), 5.06 (dd, J = 12.9, 5.4 Hz, 1H), 4.44-4.36 (m, 3H), 4.20 (s, 2H), 4.16 (s, 2H), 3.73 (s, 6H), 3.48 (s, 3H), 3.42-3.35 (m, 2H), 2.95-2.81 (m, 1H), 2.63-2.57 (m, 4H), 2.57-2.51 (m, 3H), 2.07-1.96 (m, 1H). D304 752.45 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.97 (s, 1H), 7.65 (s, 1H), 7.38 (d, J = 8.2 Hz, 1H), 6.69 (d, J = 7.5 Hz, 2H), 6.61 (d, J = 5.1 Hz, 3H), 5.08 (dd, J = 13.2, 5.1 Hz, 1H), 4.39-4.11 (m, 4H), 3.81 (s, 6H), 3.79-3.53 (m, 4H), 3.54-3.44 (m, 5H), 3.47-3.36 (m, 3H), 3.00-2.80 (m, 1H), 2.72-2.51 (m, 6H), 2.50-2.10 (m, 4H), 2.05-1.61 (m, 4H), 0.95 (d, J = 6.7 Hz, 3H). D305 823.45 .sup.1H NMR (400 MHz, DMSO-d6) δ 8.14 (s, 1H, FA), 7.62 (s, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.26 (dd, J = 8.4, 2.4 Hz, 1H), 7.16 (d, J = 2.3 Hz, 1H), 6.67-6.58 (m, 2H), 6.54 (s, 1H), 5.16 (dd, J = 13.5, 5.1 Hz, 1H), 4.37-4.16 (m, 4H), 3.84-3.70 (m, 10H), 3.50 (s, 3H), 3.40 (t, J = 5.7 Hz, 2H), 3.31 (s, 3H), 3.07-2.92 (m, 5H), 2.82-2.66 (m, 8H), 2.63-2.58 (m, 4H), 2.38 (dd, 2H), 2.05-1.93 (m, 1H), 1.75 (d, J = 12.5 Hz, 2H), 1.48 (s, 3H), 1.35-1.12 (m, 3H). D306 774.4 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.98 (s, 1H), 7.65 (s, 1H), 7.42 (d, J = 8.6 Hz, 1H), 6.75-6.65 (m, 4H), 6.61 (s, 1H), 5.08 (dd, J = 13.3, 5.0 Hz, 1H), 4.38-4.15 (m, 5H), 3.92 (s, 3H), 3.86 (s, 7H), 3.75 (s, 3H), 3.51 (s, 3H), 2.98-2.83 (m, 2H), 2.60 (s, 7H), 2.43-2.34 (m, 3H), 2.25-2.07 (m, 2H), 2.02-1.92 (m, 1H). D307 693.2 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.97 (s, 1H), 7.65 (s, 1H), 7.36 (d, J = 9.2 Hz, 1H), 7.17-7.07 (m, 3H), 6.65-6.60 (m, 2H), 6.23-5.73 (m, 1H), 5.08 (dd, J = 13.3, 5.1 Hz, 1H), 4.50 (s, 2H), 4.36-4.12 (m, 4H), 3.83 (s, 6H), 3.49 (s, 3H), 3.43 (d, J = 5.0 Hz, 4H), 2.90 (s, 4H), 2.62 (s, 2H), 2.44- 2.29 (m, 2H), 1.98 (d, J = 12.6 Hz, 1H). D308 738.45 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1H), 8.18 (s, 1H, FA), 7.65 (s, 1H), 7.37 (d, J = 8.1 Hz, 1H), 6.77-6.65 (m, 2H), 6.63-6.53 (m, 3H), 5.08 (m, J = 13.3, 5.1 Hz, 1H), 4.39-4.12 (m, 4H), 3.79 (s, 6H), 3.57 (s, 4H), 3.50 (d, J = 4.1 Hz, 4H), 3.41 (m, J = 4.9 Hz, 4H), 2.91 (m, J = 17.6, 13.6, 5.3 Hz, 1H), 2.59 (d, J = 4.2 Hz, 6H), 2.44-2.33 (m, 4H), 2.03- 1.95 (m, 1H), 1.71 (m, J = 5.3 Hz, 4H). D309 837.6 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 7.63 (s, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.26 (dd, J = 8.5, 2.4 Hz, 1H), 7.15 (d, J = 2.3 Hz, 1H), 6.76- 6.50 (m, 3H), 5.10 (dd, J = 13.3, 5.1 Hz, 1H), 4.39-4.14 (m, 4H), 3.98- 3.66 (m, 8H), 3.50 (s, 3H), 3.45-3.38 (m, 2H), 3.33-3.26 (m, 4H), 3.00- 2.82 (m, 2H), 2.81-2.64 (m, 3H), 2.64-2.56 (m, 5H), 2.56-2.52 (m, 2H), 2.49-2.27 (m, 3H), 2.20 (s, 1H), 2.06-1.90 (m, 1H), 1.83-1.67 (m, 2H), 1.62-1.35 (m, 5H), 1.35-0.94 (m, 6H). D310 835.5 .sup.1H NMR (400 MHz, Methanol-d4) δ 7.68-7.61 (m, 1H), 7.54 (s, 1H), 7.10 (d, J = 8.0 Hz, 2H), 6.61 (s, 2H), 5.12 (dd, J = 13.3, 5.1 Hz, 1H), 4.63 (s, 1H), 4.49-4.38 (m, 2H), 4.36 (s, 2H), 4.22 (s, 1H), 3.97 (d, J = 12.8 Hz, 2H), 3.87 (s, 7H), 3.63 (s, 4H), 3.53 (t, J = 5.6 Hz, 3H), 3.23 (s, 2H), 3.09 (s, 2H), 2.99-2.86 (m, 3H), 2.85-2.71 (m, 5H), 2.62 (d, J = 6.1 Hz, 2H), 2.54-2.41 (m, 1H), 2.22-2.13 (m, 1H), 1.89 (d, J = 12.5 Hz, 2H), 1.79- 1.71 (m, 2H), 1.66 (s, 1H), 1.44 (q, J = 11.2 Hz, 2H), 1.09-0.87 (m, 2H), 0.80 (s, 2H). D311 885.45 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.96 (s, 1H), 8.20 (s, 1H, FA), 7.61 (s, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.13 (t, J = 5.8 Hz, 1H), 7.08-6.99 (m, 2H), 6.55 (s, 2H), 6.17-5.76 (m, 1H), 5.05 (dd, J = 13.3, 5.1 Hz, 1H), 4.39- 4.11 (m, 5H), 3.87 (d, J = 12.3 Hz, 2H), 3.76 (s, 8H), 3.49 (s, 4H), 3.47- 3.33 (m, 6H), 2.98-2.76 (m, 4H), 2.73-2.69 (m, 2H), 2.66-2.54 (m, 3H), 2.57-2.52 (m, 1H), 2.41-2.32 (m, 1H), 2.00-1.92 (m, 1H), 1.76 (d, J = 12.5 Hz, 2H), 1.63-1.39 (m, 3H), 1.30-1.17 (m, 2H), 0.68-0.63 (m, 2H), 0.48 (s, 2H). D312 885.45 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.96 (s, 1H), 8.21 (s, 2H, TFA), 7.62 (s, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.26 (dd, J = 8.6, 2.4 Hz, 1H), 7.18-7.09 (m, 2H), 6.55 (s, 2H), 6.17-5.79 (m, 1H), 5.10 (dd, J = 13.3, 5.1 Hz, 1H), 4.45-4.13 (m, 5H), 3.86-3.66 (m, 10H), 3.55-3.48 (m, 5H), 3.48- 3.41 (m, 4H), 3.40-3.36 (m, 1H), 2.98-2.85 (m, 1H), 2.76-2.66 (m, 6H), 2.65-2.55 (m, 3H), 2.45-2.34 (m, 1H), 2.03-1.96 (m, 1H), 1.77 (d, J = 12.3 Hz, 2H), 1.51-1.47 (m, 3H), 1.28 (d, J = 11.7 Hz, 2H), 0.69- 0.65 (m, 2H), 0.51 (s, 2H). D313 887.65 .sup.1H NMR (400 MHz, Methanol-d4) δ 7.81 (s, 1H), 7.71 (s, 2H), 7.58 (s, 1H), 6.73 (s, 2H), 5.90 (tt, J = 56.7, 4.2 Hz, 1H), 5.18 (dd, J = 13.3, 5.2 Hz, 1H), 4.77-4.45 (m, 3H), 4.41 (s, 2H), 4.30-4.01 (m, 1H), 3.95 (s, 6H), 3.80 (d, J = 12.1 Hz, 2H), 3.65 (s, 3H), 3.62-3.49 (m, 4H), 3.42 (s, 2H), 3.16 (br s, 1H), 3.00-2.76 (m, 3H), 2.75-2.61 (m, 5H), 2.61-2.42 (m, 2H), 2.26-2.16 (m, 1H), 2.08 (d, J = 13.6 Hz, 2H), 1.82 (s, 1H), 1.67 (s, 10H). D314 835.5 .sup.1H NMR (400 MHz, Methanol-d4) δ 7.54 (s, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.39-7.30

(m, 2H), 6.61 (s, 2H), 5.15 (dd, J = 13.3, 5.2 Hz, 1H), 4.63 (s, 1H), 4.50-4.35 (m, 2H), 4.36 (s, 2H), 4.23 (s, 1H), 4.02-3.85 (m, 7H), 3.81 (d, J = 12.3 Hz, 2H), 3.66-3.61 (m, 4H), 3.56-3.51 (m, 3H), 3.34- 3.20 (m, 2H), 3.09 (s, 2H), 2.96-2.77 (m, 4H), 2.80-2.76 (m, 4H), 2.61 (s, 2H), 2.58-2.45 (m, 1H), 2.24-2.15 (m, 1H), 1.92 (d, J = 12.4 Hz, 2H), 1.77 (s, 2H), 1.61 (s, 1H), 1.50 (q, J = 10.8 Hz, 2H), 1.10 (s, 1H), 0.94- 0.73 (m, 3H). D315 871.6 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.98 (s, 1H), 8.18 (s, 1H, FA), 7.64 (s, 1H), 7.41 (d, J = 8.8 Hz, 1H), 6.76-6.68 (m, 2H), 6.63-6.58 (m, 3H), 5.10 (dd, 1H), 4.39-4.13 (m, 4H), 3.89 (d, J = 7.9 Hz, 2H), 3.79 (s, 6H), 3.69 (d, J = 8.0 Hz, 2H), 3.60 (s, 2H), 3.50 (s, 3H), 3.41 (s, 2H), 3.40 (s, 2H), 2.98-2.82 (m, 3H), 2.59 (d, J = 4.2 Hz, 5H), 2.44-2.34 (m, 4H), 2.18 (d, J = 7.2 Hz, 4H), 2.00 (s, 3H), 1.63 (d, J = 12.6 Hz, 2H), 1.50 (s, 1H), 1.17-1.02 (m, 2H). D316 862.5 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 7.63 (s, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.26 (dd, J = 8.5, 2.4 Hz, 1H), 7.15 (dd, J = 9.2, 4.1 Hz, 2H), 6.64 (s, 2H), 5.99 (t, J = 4.2 Hz, 1H), 5.09 (dd, J = 13.3, 5.1 Hz, 1H), 4.43- 4.10 (m, 5H), 3.78 (d, J = 27.4 Hz, 9H), 3.61 (s, 1H), 3.11 (s, 6H), 2.92 (s, 2H), 2.98-2.85 (m, 4H), 2.72 (d, J = 11.9 Hz, 2H), 2.62 (s, 3H), 2.55 (s, 3H), 2.46-2.30 (m, 3H), 2.06-1.89 (m, 1H), 1.82-1.68 (m, 2H), 1.53 (d, J = 40.7 Hz, 3H), 1.35-1.20 (m, 2H),. D317 862.35 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.95 (s, 1H), 8.16 (s, 1H, FA), 7.65 (s, 1H), 7.49 (d, J = 8.6 Hz, 1H), 7.13 (t, J = 5.7 Hz, 1H), 7.04 (s, 2H), 6.59 (s, 2H), 6.15-5.81 (m, 1H), 5.09-4.99 (m, 1H), 4.37-4.12 (m, 4H), 3.85 (d, J = 12.6 Hz, 2H), 3.78 (s, 6H), 3.53 (s, 2H), 3.49-3.39 (m, 6H), 2.95- 2.74 (m, 1H), 2.71-2.63 (m, 2H), 2.63-2.57 (m, 1H), 2.57-2.54 (m, 3H), 2.47-2.40 (m, 3H), 2.40-2.37 (m, 1H), 2.37-2.28 (m, 4H), 2.03- 1.88 (m, 1H), 1.73 (d, J = 13.8 Hz, 2H), 1.50(s, 1H), 1.42-1.31 (m, 2H), 1.27-1.12 (m, 2H),. D318 840.55 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.96 (s, 1H), 8.22 (s, 1H, FA), 7.63 (s, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.12-6.99 (m, 2H), 6.65-6.58 (m, 1H), 6.56 (s, 2H), 5.05 (dd, J = 13.2, 5.1 Hz, 1H), 4.38-4.12 (m, 4H), 3.92-3.81 (m, 4H), 3.78 (s, 6H), 3.49-3.34 (m, 4H), 3.00-2.70 (m, 5H), 2.65-2.54 (m, 4H), 2.41-2.15 (m, 5H), 2.14-1.91 (m, 3H), 1.80-1.67 (m, 2H), 1.60- 1.45 (m, 1H), 1.43-1.30 (m, 2H), 1.28-1.17 (m, 2H), 1.16-1.06 (m, 6H). D319 840.55 .sup.1H NMR (300 MHz, Methanol-d4) δ 7.80-7.53 (m, 4H), 6.75 (s, 2H), 5.18 (dd, J = 13.3, 5.1 Hz, 1H), 4.62-4.42 (m, 4H), 4.36 (s, 2H), 3.98 (s, 6H), 3.93-3.72 (m, 5H), 3.61-3.50 (m, 3H), 3.29-3.21 (m, 3H), 3.02-2.81 (m, 4H), 2.78 (s, 4H), 2.69-2.60 (m, 2H), 2.57-2.44 (m, 1H), 2.30-2.15 (m, 1H), 2.12-1.97 (m, 2H), 1.91-2.69 (m, 4H), 1.66-1.51 (m, 7H). D320 887.45 .sup.1H NMR (400 MHz, Methanol-d4) δ 7.68 (d, J = 9.2 Hz, 1H), 7.58 (s, 1H), 7.20-7.17 (m, 2H), 6.73 (s, 2H), 5.90 (tt, J = 56.6, 4.2 Hz, 1H), 5.13 (dd, J = 13.3, 5.1 Hz, 1H), 4.62 (s, 1H), 4.53-4.33 (m, 4H), 4.13 (s, 1H), 3.95 (s, 7H), 3.92 (s, 1H), 3.64 (s, 3H), 3.60-3.54 (m, 3H), 3.53-3.49 (m, 1H), 3.47 (s, 2H), 3.15 (s, 1H), 3.05-2.93 (m, 3H), 2.96-2.86 (m, 1H), 2.85-2.75 (m, 4H), 2.64 (t, J = 5.2 Hz, 3H), 2.48 (qd, J = 13.2, 4.7 Hz, 1H), 2.23-2.12 (m, 1H), 1.90 (d, J = 12.6 Hz, 2H), 1.68 (s, 7H), 1.66- 1.59 (m, 2H), 1.51-1.37 (m, 2H). D321 849.55 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.96 (s, 1H), 7.62 (s, 1H), 7.54 (d, J = 8.3 Hz, 1H), 7.11 (s, 2H), 6.72 (s, 2H), 5.04 (dd, J = 13.2, 5.1 Hz, 1H), 4.58 (s, 1H), 4.38-4.14 (m, 4H), 3.97 (s, 3H), 3.89 (s, 7H), 3.62-3.57 (m, 4H), 3.51 (s, 3H), 3.41 (t, J = 5.6 Hz, 2H), 3.34-3.15 (m, 4H), 2.97- 2.78 (m, 3H), 2.67-2.55 (m, 6H), 2.56-2.50 (m, 2H), 2.45-2.29 (m, 1H), 2.22 (s, 1H), 2.03-1.81 (m, 3H), 1.82-1.68 (m, 4H), 1.64-1.55 (m, 1H), 1.31 (q, J = 10.7 Hz, 2H). D322 899.5 .sup.1H NMR (300 MHz, Methanol-d4) δ 7.69 (d, J = 9.1 Hz, 1H), 7.59 (s, 1H), 7.20 (d, J = 7.1 Hz, 2H), 6.74 (s, 2H), 6.16-5.65 (m, 1H), 5.12 (dd, J = 13.2, 5.1 Hz, 1H), 4.58-4.26 (m, 6H), 4.06-3.86 (m, 9H), 3.76-3.65 (m, 4H), 3.67-3.46 (m, 7H), 3.40 (s, 2H), 3.24 (s, 2H), 3.03 (t, J = 12.2 Hz, 2H), 2.94-2.78 (m, 2H), 2.78-2.69 (m, 2H), 2.67-2.61 (m, 2H), 2.57-2.34 (m, 2H), 2.22-2.02 (m, 3H), 1.94 (d, J = 12.5 Hz, 2H), 1.74 (d, J = 33.3 Hz, 3H), 1.61-1.38 (m, 2H). D323 840.5 .sup.1H NMR (300 MHz, Methanol-d4) δ 8.49 (s, 2H, FA), 7.58 (s, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.37-7.30 (m, 2H), 6.73 (s, 2H), 5.15 (dd, J = 13.3, 5.1 Hz, 1H), 4.54-4.46 (m, 1H), 4.43-4.29 (m, 5H), 3.96 (s, 6H), 3.84- 3.68 (m, 4H), 3.64 (s, 3H), 3.55 (t, J = 5.3 Hz, 2H), 3.37 (s, 1H), 2.96- 2.72 (m, 6H), 2.64 (s, 3H), 2.58-2.44 (m, 3H), 2.24-2.12 (m, 1H), 1.95- 1.83 (m, 2H), 1.62-1.42 (m, 9H), 1.42-1.22 (m, 2H). D324 840.5 .sup.1H NMR (400 MHz, Methanol-d4) δ 7.68 (d, J = 9.3 Hz, 1H), 7.58 (s, 1H), 7.20-7.17 (m, 2H), 6.74 (s, 2H), 5.13 (dd, J = 13.3, 5.1 Hz, 1H), 4.59 (d, J = 13.5 Hz, 1H), 4.50-4.41 (m, 3H), 4.36 (s, 2H), 4.04-3.88 (m, 10H), 3.64 (s, 4H), 3.55 (t, J = 5.6 Hz, 2H), 3.37 (s, 1H), 3.24-3.13 (m, 1H), 3.08-2.84 (m, 6H), 2.83-2.75 (m, 1H), 2.68-2.59 (m, 2H), 2.52-2.41 (m, 1H), 2.23-2.12 (m, 1H), 1.91 (d, J = 12.9 Hz, 2H), 1.77-1.67 (m, 3H), 1.61 (d, J = 6.6 Hz, 6H), 1.52-1.40 (m, 2H). D325 837.4 .sup.1H NMR (400 MHz, Methanol-d4) δ 8.57 (s, 1H, FA), 7.63 (d, J = 8.6 Hz, 1H), 7.57 (s, 1H), 7.11-7.05 (m, 2H), 6.72 (s, 2H), 5.11 (dd, J = 13.3,

5.1 Hz, 1H), 4.94-4.89 (m, 1H), 4.46 (s, 1H), 4.46-4.37 (m, 2H), 4.36 (s, 3H), 3.97-3.91 (m, 8H), 3.73-3.66 (m, 1H), 3.64 (s, 3H), 3.55 (t, J = 5.6 Hz, 2H), 3.00-2.89 (m, 1H), 2.89-2.80 (m, 3H), 2.78 (s, 5H), 2.63 (t, J = 5.6 Hz, 3H), 2.60-2.39 (m, 4H), 2.21-2.10 (m, 1H), 1.92-1.83 (m, 2H), 1.65 (s, 1H), 1.58-1.48 (m, 8H), 1.44-1.29 (m, 3H). D326 837.45 .sup.1H NMR (400 MHz, Methanol-d4) δ 8.57 (s, 1H, FA), 7.58 (s, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.39-7.26 (m, 2H), 6.73 (s, 2H), 5.15 (dd, J = 13.3, 5.1 Hz, 1H), 4.49-4.34 (m, 3H), 4.36 (s, 3H), 3.96 (s, 6H), 3.77 (d, J = 12.3 Hz, 2H), 3.74-3.66 (m, 1H), 3.64 (s, 3H), 3.55 (t, J = 5.6 Hz, 2H), 3.01- 2.86 (m, 2H), 2.86-2.76 (m, 6H), 2.75 (s, 1H), 2.64 (t, J = 5.7 Hz, 3H), 2.60-2.42 (m, 4H), 2.26-2.13 (m, 1H), 1.89 (s, 2H), 1.52 (d, J = 6.6 Hz, 9H), 1.48-1.35 (m, 3H). D327 807.55 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.99 (s, 1H), 8.19 (s, 1H), 7.61 (s, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.25 (d, J = 8.1 Hz, 1H), 7.15 (s, 1H), 6.76 (s, 2H), 6.60 (d, J = 4.2 Hz, 1H), 5.10 (dd, J = 13.2, 4.8 Hz, 1H), 4.33 (d, J = 17.1 Hz, 1H), 4.25-4.14 (m, 3H), 3.90-3.70 (m, 7H), 3.49 (s, 3H), 3.39 (s, 4H), 2.99-2.84 (m, 2H), 2.78-2.65 (m, 4H), 2.65-2.55 (m, 4H), 2.44- 2.30 (m, 10H), 2.04-1.93 (m, 1H), 1.75 (d, J = 11.7 Hz, 2H), 1.55-1.35 (m, 3H), 1.35-1.12 (m, 5H). D328 876.3 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.09 (s, 1H), 7.65 (t, J = 4.3 Hz, 2H), 7.32-7.09 (m, 3H), 6.58 (s, 2H), 5.99 (tt, J = 56.7, 4.3 Hz, 1H), 5.07 (dd, J = 12.8, 5.4 Hz, 1H), 4.26 (s, 2H), 4.03 (d, J = 12.7 Hz, 2H), 3.77 (s, 6H), 3.51 (s, 2H), 3.46 (m, 2H), 3.44 (m, 2H), 3.43 (m, 2H), 2.91 (q, J = 14.2, 13.3 Hz, 4H), 2.61 (d, J = 3.6 Hz, 1H), 2.35 (d, J = 30.3 Hz, 10H), 2.01 (d, J = 11.0 Hz, 1H), 1.74 (d, J = 12.6 Hz, 2H), 1.57 (s, 1H), 1.35 (d, J = 7.3 Hz, 2H), 1.19 (dd, J = 20.1, 9.1 Hz, 2H). D329 853.4 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.96 (s, 1H), 7.63 (s, 1H), 7.52 (d, J = 8.5 Hz, 1H), 7.10-7.04 (m, 2H), 6.70 (s, 2H), 6.62 (s, 1H), 5.05 (dd, J = 13.3, 5.1 Hz, 1H), 4.32 (d, J = 16.9 Hz, 1H), 4.25-4.15 (m, 4H), 3.85- 3.83 (m, 2H), 3.81-3.73 (m, 8H), 3.72-3.58 (m, 4H), 3.51 (s, 4H), 3.42 (s, 6H), 3.27-2.99 (m, 5H), 2.98-2.84 (m, 4H), 2.64-2.56 (m, 4H), 2.45- 2.28 (m, 1H), 2.02-1.89 (m, 1H), 1.75 (d, J = 12.4 Hz, 2H), 1.65-1.48 (m, 3H), 1.33-1.17 (m, 2H). D330 845.4 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.96 (s, 1H), 8.24 (s, 2H, FA), 7.64 (s, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.17-7.06 (m, 2H), 6.59 (s, 3H), 5.05 (dd, J = 13.2, 5.0 Hz, 1H), 4.37-4.29 (m, 1H), 4.25-4.19 (m, 3H), 4.11-4.07 (m, 1H), 3.90-3.86 (m, 2H), 3.78 (s, 6H), 3.54-3.47 (m, 5H), 3.40 (t, J = 5.6 Hz, 3H), 3.24 (dd, J = 30.5, 13.2 Hz, 2H), 3.05-2.84 (m, 2H), 2.64- 2.57 (m, 4H), 2.47-2.26 (m, 10H), 2.15-2.06 (m, 1H), 2.01-1.81 (m, 3H), 1.53-1.40 (m, 1H), 1.37-1.18 (m, 1H). D331 655.4 1H NMR (400 MHz, DMSO-d6) δ 10.94 (s, 1H), 7.60 (s, 1H), 7.51 (d, J = 8.3 Hz, 1H), 6.64-6.49 (m, 5H), 5.04 (dd, J = 13.3, 5.1 Hz, 1H), 4.36- 4.28 (m, 4H), 4.24-4.15 (m, 3H), 4.03-3.97 (m, 2H), 3.73 (s, 6H), 3.48 (s, 3H), 3.38 (t, J = 5.5 Hz, 2H), 2.97-2.83 (m, 1H), 2.63-2.53 (m, 6H), 2.42-2.27 (m, 1H), 1.99-1.92 (m, 1H). D332 849.5 1H NMR (400 MHz, DMSO-d6) δ 10.99 (s, 1H), 7.62 (s, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.38 (dd, J = 8.5, 2.3 Hz, 1H), 7.32 (d, J = 2.3 Hz, 1H), 6.73 (s, 2H), 5.09 (dd, J = 13.3, 5.1 Hz, 1H), 4.65-4.43 (m, 1H), 4.44-4.15 (m, 4H), 3.89 (s, 6H), 3.81-3.76 (m, 4H), 3.57-3.31 (m, 4H), 3.41-3.30 (m, 3H), 3.24-3.06 (m, 5H), 2.94-2.84 (m, 4H), 2.75-2.63 (m, 5H), 2.61-2.57 (m, 3H), 2.56-2.52 (m, 1H), 2.14-2.05 (m, 1H), 2.04- 1.96 (m, 1H), 1.96-1.79 (m, 4H), 1.74-1.69 (m, 2H), 1.60-1.56 (m, 1H), 1.46-1.36 (m, 2H). D333 899.5 .sup.1H NMR (300 MHz, Methanol-d4) δ 7.72-7.56 (m, 4H), 6.74 (s, 2H), 6.16- 5.60 (m, 1H), 5.24-5.08 (m, 1H), 4.62-4.22 (m, 6H), 3.97 (s, 6H), 3.80 (d, J = 12.0 Hz, 2H), 3.70-3.46 (m, 8H), 3.44-3.33 (m, 4H), 3.29- 3.16 (m, 4H), 3.06 (s, 2H), 2.96-2.68 (m, 2H), 2.68-2.59 (m, 4H), 2.57- 2.46 (m, 1H), 2.41 (s, 1H), 2.12 (dt, J = 45.4, 6.8 Hz, 5H), 1.83-1.47 (m, 5H). D334 875.4 .sup.1H NMR (300 MHz, Methanol-d4) δ 7.59 (s, 1H), 7.39 (d, J = 8.2 Hz, 1H), 7.04-6.67 (m, 4H), 5.14 (dd, J = 13.1, 5.1 Hz, 1H), 4.66-4.48 (m, 2H), 4.45-4.31 (m, 4H), 4.31-4.12 (m, 4H), 3.97 (s, 6H), 3.93-3.89 (m, 2H), 3.87-3.57 (m, 9H), 3.55 (t, J = 5.6 Hz, 3H), 2.98-2.80 (m, 3H), 2.78 (s, 3H), 2.76-2.66 (m, 2H), 2.66-2.60 (m, 2H), 2.57-2.43 (m, 1H), 2.26-2.13 (m, 1H), 2.11-1.98 (m, 1H), 1.93-1.70 (m, 3H). D335 868.55 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.98 (s, 1H), 8.14 (s, 0.4H, FA), 7.65 (s, 1H), 7.39 (d, J = 8.3 Hz, 1H), 7.33-7.25 (m, 1H), 7.20 (d, J = 8.0 Hz, 1H), 6.73-6.64 (m, 2H), 6.57 (s, 2H), 5.39 (d, J = 8.0 Hz, 1H), 5.08 (dd, J = 13.3, 5.1 Hz, 1H), 4.61 (s, 2H), 4.36-4.16 (m, 2H), 3.80 (s, 6H), 3.72- 3.57 (m, 6H), 3.48 (s, 3H), 3.14-2.81 (m, 5H), 2.70-2.56 (m, 5H), 2.49- 2.30 (m, 4H), 2.27-2.05 (m, 3H), 2.04-1.58 (m, 6H), 1.51-1.32 (m, 1H). D336 885.4 .sup.1H NMR (400 MHz, MeOD) δ 8.47 (s, 2FA, 2H), 7.59 (s, 1H), 7.40 (d, J = 8.2 Hz, 1H), 6.86 (d, J = 2.2 Hz, 1H), 6.78 (dd, J = 8.2, 2.2 Hz, 1H), 6.73 (s, 2H), 6.07-5.71 (m, 1H), 5.14 (dd, J = 13.3, 5.1 Hz, 1H), 4.47-4.32 (m, 6H), 3.95 (s, 6H), 3.67 (d, J = 18.9 Hz, 7H), 3.61-3.48 (m, 6H), 3.15- 3.10 (m, 2H), 2.98-2.57 (m, 8H), 2.56-2.42 (m, 3H), 2.21-2.14 (m, 1H), 2.09-2.0 (m, 3H), 1.99-1.93 (m, 5H), 1.58-1.53 (m, 2H). D337 837.5 .sup.1H

NMR (300 MHz, DMSO-d6) δ 7.65 (d, J = 8.5 Hz, 1H), 7.29-7.16 (m, 2H), 6.50 (s, 2H), 4.99 (dd, J = 12.7, 5.5 Hz, 1H), 4.19 (d, J = 16.7 Hz, 4H), 3.96 (s, 3H), 3.77 (s, 6H), 3.50 (s, 4H), 3.34 (s, 8H), 3.10 (s, 2H), 2.94 (t, J = 12.3 Hz, 2H), 2.84-2.72 (m, 1H), 2.63 (d, J = 3.4 Hz, 1H), 2.55 (s, 3H), 2.4-2.5 (m, 1H), 2.18 (s, 2H), 2.10 (s, 3H), 2.06-1.96 (m, 1H), 1.73 (d, J = 12.4 Hz, 2H), 1.57 (s, 3H), 1.17 (d, J = 12.4 Hz, 2H). D338 900.45 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.13 (s, 1H), 8.03 (t, 1H), 7.86-7.71 (m, 1H), 7.57 (s, 1H), 7.35-7.21 (m, 2H), 6.73-6.59 (m, 3H), 5.12 (dd, J = 12.8, 5.4 Hz, 1H), 4.98 (t, J = 6.8 Hz, 1H), 4.25 (s, 2H), 3.79 (s, 6H), 3.59 (s, 3H), 3.42 (t, J = 5.5 Hz, 3H), 2.99-2.81 (m, 3H), 2.66-2.57 (m, 5H), 2.46-2.37 (m, 2H), 2.37-1.98 (m, 9H), 1.80 (dd, J = 12.3, 6.3 Hz, 2H), 1.70-1.59 (m, 4H), 1.56 (t, J = 5.1 Hz, 2H), 1.48 (s, 1H), 1.17-0.98 (m, 2H). D339 871.5 .sup.1H NMR (400 MHz, Methanol-d4) δ 8.53 (s, 1H, FA), 7.65-7.54 (m, 2H), 6.70 (s, 2H), 6.61-6.51 (m, 2H), 5.09 (dd, J = 13.2, 5.1 Hz, 1H), 4.61 (s, 2H), 4.47-4.27 (m, 6H), 4.05 (d, J = 7.9 Hz, 2H), 3.93 (s, 6H), 3.74 (d, J = 8.0 Hz, 2H), 3.63 (s, 3H), 3.53 (t, J = 5.6 Hz, 4H), 3.17-3.01 (m, 2H), 2.95-2.85 (m, 1H), 2.82-2.73 (m, 4H), 2.72-2.58 (m, 3H), 2.57-2.39 (m, 3H), 2.37-2.27 (m, 2H), 2.18-2.07 (m, 3H), 2.05-1.97 (m, 2H), 1.96-1.83 (m, 1H), 1.51-1.40(m, 1H). D340 853.4 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.99 (s, 1H), 7.63 (s, 1H), 7.44 (d, J = 8.5 Hz, 1H), 7.33-7.26 (m, 1H), 7.20 (s, 1H), 6.70 (s, 2H), 6.62 (s, 1H), 5.10 (dd, J = 13.3, 5.1 Hz, 1H), 4.34 (d, J = 16.8 Hz, 1H), 4.25-4.17 (m, 4H), 3.81-3.77 (m, 8H), 3.76-3.72 (m, 6H), 3.51 (s, 3H), 3.40 (s, 6H), 3.24-3.00 (m, 4H), 2.98-2.85 (m, 3H), 2.76 (t, J = 11.9 Hz, 3H), 2.65- 2.52 (m, 4H), 2.43-2.34 (m, 1H), 2.04-1.94 (m, 1 H), 1.78 (d, J = 12.3 Hz, 2H), 1.66-1.45 (m, 3H), 1.39-1.23 (m, 2H). D341 812.45 .sup.1H NMR (300 MHz, MeOD) δ 8.52 (s, FA, 1H), 7.57 (s, 1H), 7.45 (d, J = 8.3 Hz, 1H), 7.38-7.27 (m, 2H), 6.68 (s, 2H), 5.15 (dd, J = 13.2, 5.1 Hz, 1H), 4.51-4.33 (m, 4H), 4.11 (s, 2H), 3.91 (s, 6H), 3.77 (d, J = 12.2 Hz, 2H), 3.64 (s, 3H), 3.54 (t, J = 5.7, 5.7 Hz, 2H), 3.15-3.03 (m, 4H), 3.00- 2.85 (m, 4H), 2.85-2.68 (m, 6H), 2.66-2.61 (m, 2H), 2.59-2.42 (m, 1H), 2.23-2.13 (m, 1H), 1.87 (d, J = 12.3 Hz, 2H), 1.64-1.55 (m, 3H), 1.51-1.38 (m, 2H). D342 850.35 .sup.1H NMR (400 MHz, Methanol-d4) δ 8.53 (s, 2H, FA), 8.10-7.81 (m,, 3H), 7.59 (s, 1H), 6.73 (s, 2H), 5.16 (dd, J = 12.6, 5.4 Hz, 1H), 4.37 (d, J = 3.4 Hz, 4H), 4.26-4.09 (m, 1 H), 3.95 (s, 6H), 3.80-3.65 (m, 4H), 3.59-3.36 (m, 6H), 3.11 (s, 3H), 2.90 (ddd, J = 17.6, 14.3, 5.1 Hz, 1H), 2.83-2.69 (m, 5H), 2.64 (t, J = 5.5 Hz, 2H), 2.30 (t, J = 13.5 Hz, 1H), 2.21-2.09 (m, 2H), 2.04 (d, J = 12.7 Hz, 3H), 1.96 (s, 1H), 1.78 (s, 3H), 1.65 (s, 2H), 1.58- 1.49 (m, 3H), 1.45 (d, J = 6.2 Hz, 3H). D343 932.4 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.19 (s, FA, 1H), 7.82 (d, J = 8.2 Hz, 1H), 7.62 (s, 1H), 7.32-7.24 (m, 2H), 6.64-6.55 (m, 3H), 5.12 (dd, J = 12.8, 5.4 Hz, 1H), 5.01-4.94 (m, 1H), 4.21 (s, 2H), 3.86-3.71 (m, 8H), 3.54-3.47 (m, 5H), 3.05-2.90 (m, 2H), 2.90-2.76 (m, 5H), 2.73-2.68 (m, 1H), 2.64-2.55 (m, 5H), 2.45-2.40 (m, 4H), 2.07-1.96 (m, 3H), 1.92-1.75 (m, 3H), 1.64-1.45 (m, 6H), 1.32-1.11 (m, 2H). D344 859.45 .sup.1H NMR (400 MHz, Methanol-d4) δ 7.69 (d, J = 2.1 Hz, 1H), 7.66-7.57 (m, 3H), 6.74 (s, 2H), 6.13-5.65 (m, 1H), 5.22-5.13 (m, 1H), 4.62- 4.37 (m, 6H), 3.95 (s, 6H), 3.88-3.74 (m, 3H), 3.65 (s, 3H), 3.60-3.55 (m, 7H), 3.53-3.49 (m, 1H), 3.44 (s, 3H), 3.27-3.20 (m, 2H), 3.19-3.09 (m, 2H), 2.99-2.85 (m, 1H), 2.81-2.76 (m, 1H), 2.66 (t, J = 5.6 Hz, 2H), 2.59-2.44 (m, 1H), 2.25-2.15(m, 1H), 2.03 (d, J = 13.2 Hz, 2H), 1.77- 1.73 (m, 3H), 1.68-1.58 (m, 2H). D345 918.45 .sup.1H NMR (400 MHz, Methanol-d4) δ 7.58 (s, 1H), 7.48 (d, J = 8.3 Hz, 1H), 7.20 (d, J = 2.5 Hz, 1H), 7.15 (dd, J = 8.3, 2.4 Hz, 1H), 6.74 (d, J = 4.1 Hz, 2H), 5.16 (dd, J = 13.3, 5.1 Hz, 1H), 4.79 (t, J = 6.7 Hz, 1H), 4.50-4.42 (m, 2H), 4.36 (s, 4H), 3.96 (s, 6H), 3.69-3.59 (m, 5H), 3.55 (t, J = 5.6 Hz, 2H), 3.38-3.35 (m, 1H), 3.20-3.08 (m, 2H), 3.00-2.84 (m, 4H), 2.84- 2.81 (m, 1H), 2.78 (s, 3H), 2.68-2.58 (m, 3H), 2.57-2.45 (m, 4H), 2.37 (d, J = 14.8 Hz, 1H), 2.24-2.01 (m, 4H), 1.96-1.87 (m, 2H), 1.74-1.52 (m, 6H). D346 845.4 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.99 (s, 1H), 8.36 (s, 3H, FA), 7.64 (s, 1H), 7.44 (d, J = 8.3 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.20 (s, 1H), 6.58 (s, 3H), 5.10 (dd, J = 13.4, 4.9 Hz, 1H), 4.40-4.31 (m, 1H), 4.25-4.16 (m, 3H), 4.02-3.89 (m, 3H), 3.78 (s, 6H), 3.52-3.49 (m, 5H), 3.42- 3.37 (m, 3H), 3.23-3.14 (m, 1H), 3.14-3.05 (m, 1H), 2.97-2.84 (m, 2H), 2.62-2.56 (m, 4H), 2.44-2.28 (m, 10H), 2.05-1.94 (m, 2H), 1.92- 1.72 (m, 2H), 1.57-1.44 (m, 1H), 1.36-1.22 (m, 1H). D347 882.4 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.14 (s, 1H), 9.21 (d, J = 73.7 Hz, TFA 2H), 7.86 (d, J = 8.3 Hz, 1H), 7.77 (s, 1H), 7.34 (d, J = 2.3 Hz, 1H), 7.30 (d, J = 8.3 Hz, 1H), 6.77 (s, 2H), 6.66 (d, J = 4.5 Hz, 1H), 6.13 (s, 1H), 5.96 (s, 1H), 5.13 (dd, J = 12.9, 5.3 Hz, 1H), 5.05-4.97 (m, 1H), 4.23 (d, J = 14.7 Hz, 4H), 3.88 (s, 6H), 3.18 (s, 2H), 3.07-2.78 (m, 7H), 2.60 (d, J = 4.1 Hz, 8H), 2.18-1.69 (m, 11H), 1.63-1.39 (m, 2H). D348 737.4 1H), 7.61-7.55 (m, 2H), 7.51 (dd, J = 8.4, 2.2 Hz, 1H), 6.80 (s, 2H), 5.17 (dd, J = 13.3, 5.2 Hz, 1H), 4.54-4.43 (m, 2H),

4.40 (s, 2H), 3.97 (s, 6H), 3.79 (d, J = 12.1 Hz, 2H), 3.67 (s, 3H), 3.48-3.42 (m, 5H), 3.32-3.24 (m, 3H), 3.15-3.01 (m, 6H), 2.92-2.84 (m, 3H), 2.84-2.74 (m, 1H), 2.60- 2.42 (m, 1H), 2.24-2.07 (m, 3H), 2.03-1.94 (m, 2H), 1.75-1.67 (m, 3H), 1.60-1.50 (m, 2H). D349 796.25 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 10.30-9.27 (m, 2H, TFA), 7.63 (d, J = 7.4 Hz, 1H), 7.41 (d, J = 8.8 Hz, 1H), 6.80-6.67 (m, 4H), 5.07 (dd, J = 13.2, 5.1 Hz, 1H), 4.43-4.26 (m, 6H), 4.24-4.18 (m, 2H), 4.10- 3.94 (m, 3H), 3.89 (d, J = 3.2 Hz, 6H), 3.76-3.70 (m, 2H), 3.69-3.59 (m, 5H), 3.51 (s, 3H), 3.27-3.08 (m, 2H), 3.05-2.84 (m, 3H), 2.70-2.56 (m, 4H), 2.45-2.36 (m, 1H), 2.17-2.06 (m, 2H), 2.03-1.88 (m, 3H). D350 736.25 .sup.1H NMR (300 MHz, DMSO-d6) δ 7.68 (s, 1H), 7.41 (d, J = 8.8 Hz, 1H), 6.79-6.66 (m, 4H), 5.04 (dd, J = 13.2, 5.1 Hz, 1H), 4.34 (dd, J = 17.0, 5.4 Hz, 3H), 4.25-4.14 (m, 3H), 4.04-3.92 (m, 2H), 3.89 (s, 6H), 3.71 (s, 2H), 3.57-3.49 (m, 3H), 3.42 (s, 5H), 3.36 (s, 3H), 3.26-3.10 (m, 1H), 3.05-2.92 (m, 3H), 2.82 (q, J = 11.6, 9.6 Hz, 2H), 2.60 (d, J = 16.7 Hz, 1H), 2.36 (dt, J = 13.5, 6.6 Hz, 1H), 2.11 (d, J = 13.7 Hz, 2H), 1.93 (td, J = 17.8, 16.9, 9.8 Hz, 3H). D351 695.25 .sup.1H NMR (400 MHz, Methanol-d4) δ 8.56 (s, 1H, FA), 7.66 (d, J = 8.2 Hz, 1H), 6.88 (s, 1H), 6.86 (d, J = 2.1 Hz, 1H), 6.69 (dd, J = 8.4, 2.1 Hz, 1H), 6.65 (s, 2H), 5.08 (dd, J = 12.5, 5.4 Hz, 1H), 4.10-3.98 (m, 2H), 3.98- 3.88 (m, 6H), 3.89-3.80 (m, 4H), 3.62 (s, 3H), 3.40 (t, J = 5.6 Hz, 2H), 3.05-2.81 (m, 4H), 2.81-2.68 (m, 3H), 2.56 (t, J = 6.2 Hz, 2H), 2.19- 1.97 (m, 5H), 1.85 (q, J = 5.9 Hz, 2H). D352 750.3 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1H), 8.21 (s, 2H, FA), 7.47 (s, 1H), 7.37 (d, J = 8.0 Hz, 1H), 6.68 (d, J = 10.2 Hz, 2H), 6.63 (s, 2H), 5.08 (dd, J = 13.3, 5.1 Hz, 1H), 4.38-4.14 (m, 2H), 3.81 (s, 7H), 3.57 (s, 6H), 3.40 (d, J = 16.8 Hz, 4H), 3.29 (dd, J = 6.9, 4.7 Hz, 1H), 3.15 (s, 3H), 2.98- 2.84 (m, 1H), 2.77-2.68 (m, 2H), 2.59 (d, J = 16.1 Hz, 2H), 2.42 (d, J = 6.8 Hz, 2H), 2.39 (s, 3H), 2.28 (s, 4H), 1.98 (d, J = 12.0 Hz, 1H), 1.72 (t, J = 5.3 Hz, 4H). D353 763.6 .sup.1H NMR (300 MHz, MeOD) δ 7.71 (s, 1H), 7.42 (d, J = 8.2 Hz, 1H), 6.88 (d, J = 2.2 Hz, 1H), 6.80 (d, J = 3.3 Hz, 3H), 5.14 (dd, J = 13.2, 5.1 Hz, 1H), 4.53-4.31 (m, 4H), 3.98 (d, J = 3.5 Hz, 6H), 3.78 (d, J = 23.5 Hz, 4H), 3.70-3.58 (m, 7H), 3.31-3.25 (m, 1H), 3.24-2.96 (m, 7H), 2.96-2.74 (m, 4H), 2.59-2.42 (m, 1H), 2.34-2.00 (m, 10H), 1.78-1.55 (m, 2H). D354 807.45 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 8.87 (s, 1H), 8.23 (s, 2H, FA), 7.64-7.47 (m, 2H), 7.07-6.92 (m, 2H), 6.59 (s, 2H), 5.07 (dd, J = 13.4, 5.1 Hz, 1H), 4.86-4.78 (m, 1H), 4.38 (d, J = 17.2 Hz, 1H), 4.25 (d, J = 17.3 Hz, 1H), 3.79 (s, 6H), 3.55 (s, 3H), 3.53 (s, 2H), 2.93-2.77 (m, 5H), 2.64-2.59 (m, 1H), 2.45-2.36 (m, 5H), 2.29-2.17 (m, 4H), 2.08- 1.99 (m, 5H), 1.80-1.75 (m, 2H), 1.61-1.51 (m, 6H), 1.45-1.41 (m, 1H), 1.07-0.99 (m, 2H). D355 868.55 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.98 (s, 1H), 8.14 (s, 0.4H, FA), 7.65 (s, 1H), 7.39 (d, J = 8.3 Hz, 1H), 7.33-7.25 (m, 1H), 7.20 (d, J = 8.0 Hz, 1H), 6.73-6.64 (m, 2H), 6.57 (s, 2H), 5.39 (d, J = 8.0 Hz, 1H), 5.08 (dd, J = 13.3, 5.1 Hz, 1H), 4.61 (s, 2H), 4.36-4.16 (m, 2H), 3.80 (s, 6H), 3.72- 3.57 (m, 6H), 3.48 (s, 3H), 3.14-2.81 (m, 5H), 2.70-2.56 (m, 5H), 2.49- 2.30 (m, 4H), 2.27-2.05 (m, 3H), 2.04-1.58 (m, 6H), 1.51-1.32 (m, 1H). D356 666.4 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.98 (s, 1H), 8.20 (s, 1H, FA), 7.76 (s, 1H), 7.37 (d, J = 8.1 Hz, 1H), 6.73-6.62 (m, 4H), 5.08 (dd, J = 13.2, 5.0 Hz, 1H), 4.38-4.12 (m, 2H), 3.82 (s, 6H), 3.56 (s, 3H), 3.53-3.47 (m, 6H), 3.02-2.82 (m, 3H), 2.72 (t, J = 7.5 Hz, 2H), 2.65-2.56 (m, 1H), 2.45- 2.27 (m, 5H), 2.05-1.94 (m, 3H), 1.81-1.63 (m, 4H). D357 668.25 .sup.1H NMR (300 MHz, DMSO-d6) δ 8.24 (s, 1H, FA), 7.98 (s, 1H), 7.37 (d, J = 8.1 Hz, 1H), 6.73-6.62 (m, 4H), 5.20 (s, 2H), 5.06 (dd, J = 13.2, 5.1 Hz, 1H), 4.93 (s, 2H), 4.38-4.12 (m, 2H), 3.82 (s, 6H), 3.60-3.51 (m, 9H), 2.98-2.80 (m, 1H), 2.65-2.53 (m, 3H), 2.42-2.26 (m, 3H), 2.03-1.93 (m, 1H), 1.79-1.69 (m, 4H). D358 682.25 .sup.1H NMR (300 MHz, DMSO-d6) δ 8.22 (s, 1H, FA), 7.98 (s, 1H), 7.62 (d, J = 8.2 Hz, 1H), 6.76 (d, J = 2.0 Hz, 1H), 6.64 (s, 3H), 5.20 (s, 2H), 5.04 (dd, J = 12.8, 5.3 Hz, 1H), 4.93 (s, 2H), 3.81 (s, 6H), 3.72 (s, 4H), 3.56 (s, 3H), 3.53 (s, 2H), 2.90-2.78 (m, 1H), 2.64-2.52 (m, 2H), 2.47-2.35 (m, 4H), 2.05-1.95 (m, 1H), 1.76-1.70 (m, 4H). D359 668.25 .sup.1H NMR (300 MHz, DMSO-d6) δ 8.22 (s, 1H, FA), 7.98 (s, 1H), 7.48 (d, J = 8.2 Hz, 1H), 6.65 (s, 2H), 6.54-6.43 (m, 2H), 5.20 (s, 2H), 5.01 (dd, J = 13.3, 5.0 Hz, 1H), 4.92 (s, 2H), 4.36-4.02 (m, 2H), 3.82 (s, 6H), 3.61 (s, 9H), 2.88 (t, J = 14.3 Hz, 1H), 2.68-2.50 (m, 5H), 2.40-2.29 (m, 1H), 2.00-1.91 (m, 1H), 1.79-1.73 (m, 4H). D360 681.4 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.95 (s, 1H), 8.14 (s, 0.2H, FA), 7.50 (d, J = 8.2 Hz, 1H), 6.90 (s, 1H), 6.64 (s, 2H), 6.57-6.45 (m, 2H), 5.49 (s, 1H), 5.04 (dd, J = 13.3, 5.1 Hz, 1H), 4.35-4.16 (m, 2H), 4.10-3.78 (m, 8H), 3.69 (s, 4H), 3.48 (s, 3H), 3.26 (s, 3H), 3.01-2.79 (m, 3H), 2.65- 2.55 (m, 2H), 2.48-2.43 (m, 2H), 2.41-2.35 (m, 1H), 2.05-1.77 (m, 5H), 1.69 (s, 2H), D361 681.35 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 8.15 (s, 0.2H, FA), 7.39 (d, J = 8.1 Hz, 1H), 6.90 (s, 1H), 6.69 (d, J = 7.6 Hz, 2H), 6.66-6.52 (m, 2H), 5.47 (d, J = 2.8 Hz, 1H), 5.08 (dd,

J = 13.3, 5.1 Hz, 1H), 4.35-4.16 (m, 2H), 3.91-3.74 (m, 8H), 3.62 (s, 4H), 3.48 (s, 3H), 3.26 (s, 4H), 2.96- 2.87 (m, 1H), 2.85-2.70 (m, 2H), 2.64-2.55 (m, 1H), 2.50-2.45 (m, 2H), 2.43-2.33 (m, 1H), 2.03-1.94 (m, 1H), 1.84 (s, 4H), 1.70 (s, 2H). D362 627.2 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 7.88-7.80 (m, 1H), 7.76 (s, 1H), 7.27 (d, J = 7.4 Hz, 2H), 6.67 (s, 2H), 5.12 (dd, J = 12.8, 5.3 Hz, 1H), 4.97 (s, 1H), 3.81 (s, 9H), 3.51 (s, 3H), 3.28-3.12 (m, 3H), 3.01- 2.80 (m, 3H), 2.70 (d, J = 7.6 Hz, 2H), 2.60 (d, J = 13.7 Hz, 2H), 2.00 (q, J = 7.5 Hz, 3H). D363 680.2 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.18 (s, 1H, FA), 7.76 (s, 1H), 7.63 (d, J = 8.3 Hz, 1H), 6.78 (d, J = 2.1 Hz, 1H), 6.69-6.60 (m, 3H), 5.05 (dd, J = 12.8, 5.3 Hz, 1H), 3.81 (s, 6H), 3.73 (s, 3H), 3.51 (s, 5H), 2.96 (t, J = 7.5 Hz, 3H), 2.90-2.80 (m, 1H), 2.78-2.55 (m, 4H), 2.41 (s, 4H), 1.99 (t, J = 7.7 Hz, 3H), 1.72 (s, 4H). D364 626.25 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.98 (s, 1H), 7.77 (s, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.29-7.20 (m, 1H), 7.13 (d, J = 2.3 Hz, 1H), 6.67 (s, 2H), 5.09 (dd, J = 13.2, 5.1 Hz, 1H), 4.39-4.13 (m, 2H), 3.83 (s, 6H), 3.60 (s, 2H), 3.51 (s, 3H), 3.16 (s, 4H), 3.01-2.83 (m, 3H), 2.70 (d, J = 7.4 Hz, 2H), 2.58 (s, 5H), 2.41-2.30 (m, 1H), 1.98 (d, J = 8.4 Hz, 3H). D365 621.35 .sup.1H NMR (400 MHz, Methanol-d4) δ 8.53 (s, 1H, FA), 7.83 (s, 1H), 7.76- 7.66 (m, 2H), 7.60 (d, J = 7.9 Hz, 1H), 6.79 (s, 2H), 5.17 (dd, J = 13.3, 5.2 Hz, 1H), 4.60-4.45 (m, 2H), 4.41-4.27 (m, 4H), 4.10 (q, J = 7.6 Hz, 2H), 3.97 (s, 6H), 3.85 (q, J = 8.2 Hz, 1H), 3.66 (s, 3H), 3.06-2.75 (m, 6H), 2.51 (qd, J = 13.2, 4.7 Hz, 1H), 2.24-2.18 (m, 1H), 2.15-2.02 (m, 2H). D366 640.3 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.09 (s, 1H), 7.76 (s, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.32 (s, 1H), 7.23 (d, J = 8.6 Hz, 1H), 6.68 (s, 2H), 5.07 (dd, J = 13.1, 5.3 Hz, 1H), 3.83 (s, 6H), 3.67-3.57 (m, 2H), 3.51 (s, 3H), 3.40 (s, 5H), 2.96 (t, J = 7.3 Hz, 2H), 2.86 (d, J = 14.5 Hz, 1H), 2.70 (d, J = 7.5 Hz, 2H), 2.63-2.55 (m, 5H), 1.98 (q, J = 8.7, 7.2 Hz, 3H). D367 623.15 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.02 (s, 1H), 8.14 (s, 0.4H, FA), 8.01 (s, 1H), 7.74-7.58 (m, 3H), 6.69 (s, 2H), 5.20 (t, J = 3.5 Hz, 2H), 5.11 (dd, J = 13.2, 5.1 Hz, 1H), 4.92 (t, J = 3.4 Hz, 2H), 4.57-4.30 (m, 2H), 4.02- 3.89 (m, 4H), 3.86 (s, 6H), 3.67-3.53 (m, 6H), 3.01-2.83 (m, 1H), 2.67- 2.55 (m, 1H), 2.49-2.30 (m, 1H), 2.08-1.96 (m, 1H). D368 623.2 .sup.1H NMR (300 MHz, DMSO-d6 with a drop of D2O) δ 8.17 (s, 0.4H, FA), 7.96 (s, 1H), 7.70 (dd, J = 7.9, 0.7 Hz, 1H), 7.64 (t, J = 1.1 Hz, 1H), 7.52 (dd, J = 7.9, 1.4 Hz, 1H), 6.64 (s, 2H), 5.17 (d, J = 3.5 Hz, 2H), 5.08 (dd, J = 13.2, 5.1 Hz, 1H), 4.92 (d, J = 3.3 Hz, 2H), 4.50-4.19 (m, 2H), 3.82 (s, 6H), 3.71-3.61 (m, 4H), 3.55 (s, 3H), 3.40 (q, J = 7.2 Hz, 1H), 3.29 (t, J = 7.0 Hz, 2H), 2.98-2.80 (m, 1H), 2.67-2.55 (m, 1H), 2.48-2.27 (m, 1H), 2.06-1.96 (m, 1H). D369 621.3 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.02 (s, 1H), 10.1 (d, 2H, TFA), 7.77 (dd, J = 11.4, 7.3 Hz, 2H), 7.69 (s, 1H), 7.58 (d, J = 7.9 Hz, 1H), 6.78 (d, J = 3.3 Hz, 2H), 5.13 (dd, J = 13.2, 5.1 Hz, 1H), 4.53-4.08 (m, 9H), 3.90 (s, 6H), 3.51 (s, 3H), 2.93 (q, J = 9.5 Hz, 3H), 2.77-2.56 (m, 3H), 2.40- 2.24 (m, 1H), 1.99 (q, J = 7.5 Hz, 3H). D370 651.3 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.01 (s, 1H), 8.15 (.1.0 FA, s, 1H), 7.99 (s, 1H), 7.73-7.54 (m, 3H), 6.67 (s, 2H), 5.32-5.05 (m, 3H), 5.00-4.86 (m, 2H), 4.58-4.27 (m, 2H), 3.84 (s, 6H), 3.67 (s, 2H), 3.56 (s, 3H), 3.01- 2.79 (m, 3H), 2.75-2.55 (m, 2H), 2.47-2.20 (m, 3H), 2.11-1.95 (m, 1H), 1.95-1.80 (m, 2H), 1.76-1.53 (m, 2H). D371 649.35 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.01 (s, 1H), 8.19 (.1.0 FA, s, 1H), 7.75 (s, 1H), 7.68-7.55 (m, 3H), 6.66 (s, 2H), 5.11 (dd, J = 13.2, 5.1 Hz, 1H), 4.59-4.25 (m, 2H), 3.81 (s, 6H), 3.54 (s, 2H), 3.51 (s, 3H), 3.01-2.87 (m, 3H), 2.82-2.67 (m, 4H), 2.67-2.54 (m, 2H), 2.48-2.34 (m, 1H), 2.34-2.17 (m, 2H), 2.08-1.91 (m, 3H), 1.91-1.77 (m, 2H), 1.69-1.50 (m, 2H). D372 765.6 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.97 (s, 1H), 8.17 (s, FA, 1H), 7.99 (s, 1H), 7.37 (d, J = 8.2 Hz, 1H), 6.67 (s, 4H), 5.21 (s, 2H), 5.08 (dd, J = 13.2, 5.0 Hz, 1H), 4.94 (s, 2H), 4.35-4.14 (m, 2H), 3.83 (s, 6H), 3.67 (s, 2H), 3.57 (d, J = 3.8 Hz, 7H), 3.05-2.79 (m, 4H), 2.64-2.55 (m, 1H), 2.42- 2.17 (m, 6H), 2.17-2.06 (m, 2H), 2.04-1.91 (m, 1H), 1.84-1.58 (m, 6H), 1.58-1.47 (m, 1H), 1.28-0.95 (m, 2H). D373 642.2 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.09 (s, 1H), 8.14 (s, FA, 0.2H), 8.00 (s, 1H), 7.68 (d, J = 8.5 Hz, 1H), 7.38-7.17 (m, 2H), 6.68 (s, 2H), 5.21 (s, 2H), 5.07 (dd, J = 12.7, 5.4 Hz, 1H), 4.93 (s, 2H), 3.85 (s, 6H), 3.56 (s, 5H), 3.50-3.38 (m, 4H), 2.97-2.80 (m, 1H), 2.69-2.54 (m, 4H), 2.50- 2.40 (m, 2H), 2.11-1.95 (m, 1H). D374 528.1 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.00 (s, 1H), 7.82 (s, 1H), 7.67-7.42 (m, 3H), 6.78 (s, 2H), 5.13 (dd, 1H), 4.53-4.29 (m, 2H), 3.73 (s, 6H), 3.53 (s, 3H), 3.08-2.99 (m, 2H), 2.69 (d, 4H), 2.28 (s, 1H), 2.13-1.96 (m, 3H). D375 612.25 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.28 (s, 1H), 8.22 (s, 2H, FA), 7.74 (s, 1H), 7.14 (t, J = 8.0 Hz, 1H), 6.64 (s, 2H), 6.58 (d, J = 7.9 Hz, 1H), 6.35 (s, 1H), 6.28 (d, J = 8.4 Hz, 1H), 3.80 (s, 6H), 3.72 (t, J = 6.7 Hz, 2H), 3.50 (d, J = 3.4 Hz, 6H), 2.96 (t, J = 7.5 Hz, 2H), 2.81-2.66 (m, 5H), 2.66-2.59 (m, 1H), 2.40 (s, 4H), 2.03-1.92 (m, 3H), 1.69 (t, J = 5.5 Hz, 4H).

Example 68—BRD9 bromodomain TR-FRET Competition Binding Assay

(344) This example demonstrates the ability of the compounds of the disclosure to biochemically inhibit BRD9 bromodomain in a competition binding assay.

(345) Procedure: His-Flag-BRD9 (P133-K239; Swiss Prot Q9H8M2; SEQ ID NO:1 mgsshhhhhhenlyfq/gdykddddkgslevlfqg/PAENESTPIQQLLEHFLRQLQRKDPHGFFAFPVTDAIAPGYSMII KHPMDFGTMKDKIVANEYKSVTEFKADFKLMCDNAMTYNRPDTVYYKLAKKILHAGFKMMSK) 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.

(346) 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.

(347) 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 IC.sub.50 (μM) as shown in Table 5. As shown by the results in Table 5, a number of compounds of the present disclosure exhibit an IC.sub.50 value of <1 μM for BRD9 binding, indicating their affinity for targeting BRD9.

(348) TABLE-US-00010 TABLE 5 Bromodomain TR-FRET Binding Compound No. Bromodomain TR-FRET BRD9 IC.sub.50 (nM) B1 NT B2 + B3 + B4 + B5 ++++ B6 ++ B7 ++++ B8 +++ B9 ++++ B10 + B11 + B12 + B13 +++ B14 + B15 + B16 + B17 + B18 +++ B19 +++ B20 +++ B21 ++ D1 NT D2 NT D3 NT D4 NT D5 NT D6 NT D7 NT D8 NT D9 NT D10 NT D11 NT D12 NT D13 NT D14 +++ D15 +++ D16 NT D17 +++ D18 +++ D19 + D20 + D21 +++ D22 ++++ D23 ++ D24 ++ D25 NT D26 ++++ D27 ++ D28 ++++ D29 ++++ D30 ++ D31 ++++ D32 ++ D33 +++ D34 +++ D35 +++ D36 +++ D37 ++++ D38 ++++ “+” 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

Example 69—SYO1 BRD9 NanoLuc Degradation Assay

(349) This example demonstrates the ability of the compounds of the disclosure to degrade a Nanoluciferase-BRD9 fusion protein in a cell-based degradation assay.

(350) Procedure: A stable SYO-1 cell line expressing 3×FLAG-NLuc-BRD9 was generated. On day 0 cells were seeded in 30 μL 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 μM 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 μL of freshly prepared Nano-Glo Luciferase Assay Reagent (Promega N1130), shaking the plates for 10 minutes and reading the bioluminescence using an EnVision reader.

(351) Results: The Inhibition % was calculated using the following formula: % Inhibition=100×(Lum.sub.HC−Lum.sub.Sample)/(Lum.sub.HC−Lum.sub.LC). DMSO treated cells are employed as High Control (HC) and 1 μM 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 calculate IC.sub.50 (μM) 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 IC.sub.50 value of <1 μM 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.

(352) TABLE-US-00011 TABLE 6A SYO1 BRD9-NanoLuc Degradation Compound No. SYO1 BRD9-

NanoLuc degradation IC.sub.50 (nM) 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 NT D27 NT D28 ++++ D29 ++++ D30 + D31 +++ D32 ++ D33 + D34 NT D35 NT D36 NT D37 +++ D38 +++ "+" 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

(353) TABLE-US-00012 TABLE 6B SYO1 BRD9-NanoLuc Degradation Compound SYO1 BRD9-NanoLuc No. degradation IC.sub.50 (nM) B22 + B23 + B24 NT D39 ++++ D40 ++++ D41 ++++ D42 ++++ D43 ++++ D44 ++++ D45 ++++ D46 ++++ D47 ++++ D48 ++++ D49 ++++ D50 +++ 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 ++++ D81 ++++ D82 ++++ D83 ++++ D84 ++++ D85 ++++ D86 ++++ D87 ++++ D88 ++++ D89 ++++ D90 +++ D91 ++++ D92 +++ D93 ++++ D94 NT D95 ++++ D96 ++++ D97 ++++ D98 ++++ D99 ++++ D100 ++++ D101 ++++ D102 ++++ D103 ++++ D104 ++++ D105 ++++ D106 ++++ D107 ++++ D109 ++++ D110 ++++ D111 +++ D112 ++++ D113 ++++ D114 ++++ D115 ++++ D116 ++++ D117 ++++ D118 ++++ D119 ++++ D120 ++ D121 ++++ D122 +++ D123 ++++ D124 ++++ D125 ++++ 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 ++++ D161 ++++ D162 ++++ D163 ++++ D164 ++++ D165 ++++ D166 ++++ D167 +++ D168 +++ D169 ++++ D170 ++++ D171 ++++ D172 ++++ D173 ++++ D174 ++++ D175 ++ D176 +++ D177 +++ D178 ++++ D179 ++++ D180 ++++ D181 ++++ D182 ++++ D183 ++++ D184 +++ 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 +++ 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 NT D286 ++ D287 ++ D288 ++ D289 +++ D290 + D291 +++ D292 ++ D293 ++ D294 + D295 ++ D296 + D297 + D298 + D299 ++++ D300 ++++ D301 ++++ D302 ++++ DD1 ++++ "+" 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

(354) TABLE-US-00013 TABLE 6C SYO1 BRD9-NanoLuc Degradation Compound SYO1 BRD9-NanoLuc No. degradation IC.sub.50 (nM) D303 ++++ D304 ++++ D305 + D306 ++++ D307 ++++ D308 ++++ D309 ++++ D310 ++++ D311 ++++ D312 ++++ D313 + D314 ++++ D315 ++++ D316 + D317 ++++ D318 ++++ D319 ++++ D320 ++++ D321 ++++ D322 ++++ D323 ++++ D324 ++++ D325 ++++ D326 ++++ D327 ++++ D328 + D329 ++++ D330 ++++ D331 +++ D332 ++++ D333 ++++ D334 ++++ D335 ++++ D336 ++++ D337 + D338 ++++ D339 ++++ D340 ++++ D341 ++++ D342 ++++ D343 + D344 ++++ D345 ++++ D346 ++++ D347 ++++ D348 ++++ D349 +++ D350 ++++ D351 +++ D352 +++ D353 ++++ D354 ++++ D355 ++++ D356 ++++ D357 ++++ D358 ++++ D359 ++++ D360 ++++ D361 ++++ D362 ++++ D363 ++++ D364 ++++ D365 ++++ D366 ++++ D367 ++++ D368 ++++ D369 ++++ D370 ++++ D371 ++++ D372 ++++ D373 ++++ D374 ++++ D375 + "+" 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

(355) 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.
(356) While the invention has been described in connection with specific embodiments thereof, it will be understood that 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 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.
(357) Other embodiments are in the claims.

Claims

1. A compound having the structure of Formula I: ##STR01014## wherein R.sup.1 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.10 carbocyclyl; Z.sup.1 is CR.sup.2 or N; R.sup.2 is H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, or optionally substituted C.sub.2-C.sub.9 heteroaryl; ##STR01015## X.sup.1 is a bond, O, NR.sup.3a, ##STR01016## or CR.sup.4aR.sup.5a; X.sup.2 is O, NR.sup.3b, ##STR01017## or CR.sup.4bR.sup.5b; X.sup.3 is O, NR.sup.3c, ##STR01018## or CR.sup.4cR.sup.5c; X.sup.4 is a bond, O, NR.sup.3d, ##STR01019## or CR.sup.4dR.sup.5d; X.sup.5 is O or NR.sup.3e and X.sup.6 is CR.sup.4fR.sup.5f, or X.sup.5 is CR.sup.4eR.sup.5e and X.sup.6 is O or NR.sup.3f; X.sup.7 is O, NR.sup.3g, or CR.sup.4gR.sup.5g; X.sup.8 is O, NR.sup.3h, or CR.sup.4hR.sup.5h; each of R.sup.3a, R.sup.3b, R.sup.3c, and R.sup.3d is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted C.sub.1-C.sub.6 acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R.sup.3a and R.sup.4b, R.sup.4a and R.sup.3b, R.sup.4b and R.sup.4a, R.sup.3b and R.sup.4c, R.sup.4b and R.sup.4c, R.sup.3c and R.sup.4b, R.sup.3c and R.sup.4d, R.sup.4c and R.sup.4d, and/or R.sup.3d and R.sup.4c, together with the atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heterocyclyl; each of R.sup.4a, R.sup.4b, R.sup.4c, and R.sup.4d is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted C.sub.1-C.sub.6 acyl, thiol, optionally substituted sulfone, or optionally substituted amino, or R.sup.3a and R.sup.4b, R.sup.4a and R.sup.3b, R.sup.4b and R.sup.4a, R.sup.3b and R.sup.4c, R.sup.4b and R.sup.4c, R.sup.3c and R.sup.4b, R.sup.3c and R.sup.4d, R.sup.4c and R.sup.4d, and/or R.sup.3d and R.sup.4c, together with the atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heterocyclyl; each of R.sup.5a, R.sup.5b, R.sup.5c, and R.sup.5d is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; each of R.sup.3e, R.sup.3f, R.sup.3g, and R.sup.3h is, independently, H, halogen, hydroxyl, optionally

substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted C.sub.1-C.sub.6 acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R.sup.3e and R.sup.4f or R.sup.4e and R.sup.3f, together with the atoms to which each is attached, combine to form optionally substituted heterocyclycl; each of R.sup.4e, R.sup.4f, R.sup.4g, and R.sup.4h is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted C.sub.1-C.sub.6 acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R.sup.3e and R.sup.4f or R.sup.4e and R.sup.3f, together with the atoms to which each is attached, combine to form optionally substituted heterocyclycl; each of R.sup.5e, R.sup.5f, R.sup.5g, and R.sup.5h is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; and G is optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or C.sub.2-C.sub.9 heterocyclyl, or a pharmaceutically acceptable salt thereof.

2. A compound having the structure of Formula II:

A-L-B Formula II, where B is a degradation moiety, L is a linker, and A has the structure of Formula III: ##STR01020## where R.sup.1 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.10 carbocyclyl; Z.sup.1 is CR.sup.2 or N; R.sup.2 is H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.1O carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, or optionally substituted C.sub.2-C.sub.9 heteroaryl; ##STR01021## X.sup.1′ is a bond, O, NR.sup.3a′, or CR.sup.4a′R.sup.5a′; X.sup.2′ is O, NR.sup.3b′, or CR.sup.4b′R.sup.5b′; X.sup.3′ is O, NR.sup.3c′, or CR.sup.4c′R.sup.5c′; X.sup.4′ is a bond, O, NR.sup.3d′, or CR.sup.4d′R.sup.5d′; X.sup.5′ is O, NR.sup.3e′, or CR.sup.4e′R.sup.5e′; X.sup.6′ is O, NR.sup.3f′, or CR.sup.4f′R.sup.5f′; X.sup.7′ is O, NR.sup.3g′, or CR.sup.4g′R.sup.5g′; each of R.sup.3a′, R.sup.3b′, R.sup.3c′, and R.sup.3d′ is, independently, H, ##STR01022## halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted C.sub.1-C.sub.6 acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R.sup.3a′ and R.sup.4b′, R.sup.4a′ and R.sup.3b′, R.sup.4b′ and R.sup.4a′, R.sup.3b′ and R.sup.4c′, R.sup.4b′ and R.sup.4c′, R.sup.3c′ and R.sup.4b′, R.sup.3c′ and R.sup.4d′, R.sup.4c′ and R.sup.4d′, and/or R.sup.3d′ and R.sup.4c′, together with the atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heterocyclyl; R.sup.3′ is absent, optionally substituted C.sub.1-C.sub.6 alkylene, optionally substituted C.sub.1-C.sub.6 heteroalkylene, optionally substituted C.sub.3-C.sub.10 carbocyclylene, optionally substituted C.sub.2-C.sub.9 heterocyclylene, optionally substituted C.sub.6-C.sub.10 arylene, optionally substituted C.sub.2-C.sub.9 heteroarylene, optionally substituted C.sub.2-C.sub.6 alkenylene, optionally substituted C.sub.2-C.sub.6 heteroalkenylene, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino; each of R.sup.4a′, R.sup.4b′, R.sup.4c′, and R.sup.4d′ is, independently, H, halogen, hydroxyl, optionally substituted

C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, thiol, optionally substituted sulfone, or optionally substituted amino, or R.sup.3a′ and R.sup.4b′, R.sup.4a′ and R.sup.3b′, R.sup.4b′ and R.sup.4a′, R.sup.3b′ and R.sup.4c′, R.sup.4b′ and R.sup.4c′, R.sup.3c′ and R.sup.4b′, R.sup.3c′ and R.sup.4d′, R.sup.4c′ and R.sup.4d′, and/or R.sup.3d′ and R.sup.4c′, together with the atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heterocyclyl; each of R.sup.5a′, R.sup.5b′, R.sup.5c′, and R.sup.5d′ is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; each of R.sup.3e′, R.sup.3f′, and R.sup.3g′ is, independently, H, ##STR01023## halogen, hydroxyl, optionally substituted C.sub.1-C6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted C.sub.1-C.sub.6 acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R.sup.3e and R.sup.4f or R.sup.4e and R.sup.3f, together with the atoms to which each is attached, combine to form optionally substituted heterocyclycl; each of R.sup.4e′, R.sup.4f′, and R.sup.4g′ is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted C.sub.1-C.sub.6 acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R.sup.3e′ and R.sup.4f′ or R.sup.4e′ and R.sup.3f′, together with the atoms to which each is attached, combine to form optionally substituted heterocyclycl; each of R.sup.5e′, R.sup.5f′, and R.sup.5g′ is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; G″ is ##STR01024## optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or C.sub.2-C.sub.9 heterocyclyl; G′ is optionally substituted C.sub.3-C.sub.10 carbocyclylene, C.sub.2-C.sub.9 heterocyclylene, optionally substituted C.sub.6-C.sub.10 arylene, or optionally substituted C.sub.2-C.sub.9 heteroarylene; and A.sup.1 is a bond between A and the linker, where one of R.sup.3a′, R.sup.3b′, R.sup.3c′, R.sup.3d′, R.sup.3e′, R.sup.3f′, and R.sup.3g′ is ##STR01025## or G″ is ##STR01026## wherein B has the structure of Formula Y: ##STR01027## where A.sup.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.sup.1 is a bond or ##STR01028## T.sup.2 is ##STR01029## R.sup.5A is H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl; each R.sup.J1 is, independently, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl; J.sup.A is absent, O, optionally substituted amino, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl; and J is absent, optionally substituted C.sub.3-C.sub.10 carbocyclylene, optionally substituted C.sub.6-C.sub.10 arylene, optionally substituted C.sub.2-C.sub.9 heterocyclylene, or optionally substituted C.sub.2-C.sub.9 heteroarylene; wherein L has the structure of Formula V:

A.sup.1-(E.sup.1)-(F.sup.1)—(C.sup.3).sub.m-(E.sup.3).sub.n-(F.sup.2).sub.o1—(F.sup.3).sub.o2-(E.sup.2).sub.p-A.sup.2, Formula V wherein A.sup.1 is a bond between the linker and A; A.sup.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.sup.1 and E.sup.2 is, independently, O, S, NR.sup.N, optionally substituted C.sub.1-10 alkylene, optionally substituted C.sub.2-10 alkenylene, optionally substituted C.sub.2-10 alkynylene, optionally substituted C.sub.2-C.sub.10 polyethylene qlycol, or optionally substituted C.sub.1-10 heteroalkylene; E.sup.3 is optionally substituted C.sub.1-C.sub.6 alkylene, optionally substituted C.sub.1-C.sub.6 heteroalkylene, O, S, or NR.sup.N; each R.sup.N is, independently, H, optionally substituted C.sub.1-4 alkyl, optionally substituted C.sub.2-4 alkenyl, optionally substituted C.sub.2-4 alkynyl, optionally substituted C.sub.2-6 heterocyclyl, optionally substituted C.sub.6-12 aryl, or optionally substituted C.sub.1-7 heteroalkyl; C.sup.3 is carbonyl, thiocarbonyl, sulphonyl, or phosphoryl; and each of F.sup.1, F.sup.2, and F.sup.3 is, independently, optionally substituted C.sub.3-C.sub.10 carbocyclylene, optionally substituted C.sub.2-10 heterocyclylene, optionally substituted C.sub.6-C.sub.10 arylene, or optionally substituted C.sub.2-C.sub.9 heteroarylene; or a pharmaceutically acceptable salt thereof.

3. The compound of claim 2, wherein ##STR01030##

4. The compound of claim 3, wherein ##STR01031##

5. The compound of claim 2, wherein the structure of Formula Y has the structure of Formula A: ##STR01032## wherein in Y.sup.1 is ##STR01033## R.sup.A5 is H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl; R.sup.A6 is H or optionally substituted C.sub.1-C.sub.6 alkyl; and R.sup.A7 is H or optionally substituted C.sub.1-C.sub.6 alkyl; or R.sup.A6 and R.sup.A7, together with the carbon atom to which each is bound, combine to form optionally substituted C.sub.3-C.sub.6 carbocyclyl or optionally substituted C.sub.2-C.sub.5 heterocyclyl; or R.sup.A6 and R.sup.A7, together with the carbon atom to which each is bound, combine to form optionally substituted C.sub.3-C.sub.6carbocyclyl or optionally substituted C.sub.2-C.sub.5 heterocyclyl; R.sup.A8 is H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl; each of R.sup.A1, R.sup.A2, R.sup.A3, and R.sup.A4 is, independently, H, A.sup.2, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.A1 and R.sup.A2, R.sup.A2 and R.sup.A3, and/or R.sup.A3 and R.sup.A4, together with the carbon atoms to which each is attached, combine to form {circle around (N)}; and {circle around (N)} is optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or C.sub.2-C.sub.9 heterocyclyl, any of which is optionally substituted with A.sup.2, wherein one of R.sup.A1, R.sup.A2, R.sup.A3, and R.sup.A4 is A.sup.2, or {circle around (N)} is substituted with A.sup.2, or a pharmaceutically acceptable salt thereof.

6. The compound of claim 5, wherein the structure of Formula A is ##STR01034##

7. The compound of claim 2, wherein the degradation moiety comprises the structure of Formula FA: ##STR01035## where ##STR01036## or a bicyclic moiety which is substituted with A.sup.2 and substituted with one or more groups independently selected from H, R.sup.FF1, and oxo; ---- is a single bond or a double bond; u2 is 0, 1, 2, or 3; A.sup.2 is a bond between the degrader and the linker; Y.sup.Fa is CR.sup.FbR.sup.Fc, C═O, C═S, C═CH.sub.2, SO.sub.2, S(O), P(O)Oalkyl, P(O)NHalkyl, P(O)N(alkyl).sub.2, P(O)alkyl, P(O)OH, P(O)NH.sub.2; Y.sup.Fb is NH, NR.sup.FF1, CH.sub.2, CHR.sup.FF1, C(R.sup.FF1).sub.2, O, or S; Y.sup.Fc is CR.sup.FdR.sup.Fe, C═O, C═S, C═CH.sub.2, SO.sub.2, S(O), P(O)Oalkyl, P(O)NHalkyl, P(O)N(alkyl).sub.2, P(O)alkyl, P(O)OH, P(O)NH.sub.2; each of R.sup.Fb, R.sup.Fc, R.sup.Fd, and R.sup.Fe is, independently, H, alkyl, aliphatic, heteroaliphatic, aryl, heteroaryl, carbocyclyl, hydroxyl, alkoxy, amino, —NHalkyl, or —Nalkyl.sub.2; or R.sup.Fb and R.sup.Fc, together with the carbon atom to which each is attached, combine to form a 3-, 4-, 5-, or 6-membered spirocarbocyclylene, or a 4-, 5-, or 6-membered spiroheterocyclylene comprising 1 or 2 heteroatoms selected from N and O; or R.sup.Fd and R.sup.Fe, together with the carbon atom to which each is attached, combine to form a 3-, 4-, 5-, or 6-membered spirocarbocyclylene, or a 4-, 5-, or 6-membered spiroheterocyclylene comprising 1 or 2 heteroatoms selected from N and O; and or

R.sup.Fd and R.sup.Fb, 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.sup.Fd and Y.sup.Ff is, independently, CH.sub.2, CHR.sup.FF2, C(R.sup.FF2).sub.2, C(O), N, NH, NR.sup.FF3, O, S, or S(O); Y.sup.Fe is a bond or a divalent moiety attached to Y.sup.Fd and Y.sup.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.sup.2 and the others are substituted with one or more groups independently selected from H and R.sup.FF1; and wherein the contiguous atoms of Y.sup.Fe can be attached through a single or double bond; each R.sup.FF1 is, independently, H, alkyl, alkenyl, alkynyl, aliphatic, heteroaliphatic, carbocyclyl, halogen, hydroxyl, amino, cyano, alkoxy, aryl, heteroaryl, heterocyclyl, alkylamino, alkylhydroxyl, or haloalkyl; each R.sup.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.sub.2alkyl, —N(alkyl)SO.sub.2alkyl, —NHSO.sub.2aryl, —N(alkyl)SO.sub.2aryl, —NHSO.sub.2alkenyl, —N(alkyl)SO.sub.2alkenyl, —NHSO.sub.2alkynyl, —N(alkyl)SO.sub.2alkynyl, aliphatic, heteroaliphatic, aryl, heteroaryl, hetercyclic, carbocyclic, cyano, nitro, nitroso, —SH, —Salkyl, or haloalkyl; and R.sup.FF3 is alkyl, alkenyl, alkynyl, —C(O)H, —C(O)OH, —C(O)alkyl, or —C(O)Oalkyl, wherein if Y.sup.Fd or Y.sup.Ff is substituted with A.sup.2, then Y.sup.Fe is a bond, or a pharmaceutically acceptable salt thereof.

8. The compound of claim 2, wherein the degradation moiety comprises the structure of Formula FB: ##STR01037## where ##STR01038## or a bicyclic moiety which is substituted with A.sup.2 and substituted with one or more groups independently selected from H, R.sup.FF1, and oxo; A.sup.2 is a bond between the degrader and the linker; Y.sup.Fa is CR.sup.FbR.sup.Fc, C═O, C═S, C═CH.sub.2, SO.sub.2, S(O), P(O)Oalkyl, P(O)NHalkyl, P(O)N(alkyl).sub.2, P(O)alkyl, P(O)OH, P(O)NH.sub.2; each of Y.sup.Fb and Y.sup.Fg is, independently, NH, NR.sup.FF1, CH.sub.2, CHR.sup.FFI, C(R.sup.FF1).sub.2, O, or S; Y.sup.Fc is CR.sup.FdR.sup.Fe, C═O, C═S, C═CH.sub.2, SO.sub.2, S(O), P(O)Oalkyl, P(O)NHalkyl, P(O)N(alkyl).sub.2, P(O)alkyl, P(O)OH, P(O)NH.sub.2; each of R.sup.Fb, R.sup.Fc, R.sup.Fd, R.sup.Fe, R.sup.Ff, and R.sup.Fg is, independently, H, alkyl, aliphatic, heteroaliphatic, aryl, heteroaryl, carbocyclyl, hydroxyl, alkoxy, amino, —NHalkyl, or —Nalkyl.sub.2; or R.sup.Fb and R.sup.Fc, together with the carbon atom to which each is attached, combine to form a 3-, 4-, 5-, or 6-membered spirocarbocyclylene, or a 4-, 5-, or 6-membered spiroheterocyclylene comprising 1 or 2 heteroatoms selected from N and O; or R.sup.Fd and R.sup.Fe, together with the carbon atom to which each is attached, combine to form a 3-, 4-, 5-, or 6-membered spirocarbocyclylene, or a 4-, 5-, or 6-membered spiroheterocyclylene comprising 1 or 2 heteroatoms selected from N and O; or R.sup.Ff and R.sup.Fg, together with the carbon atom to which each is attached, combine to form a 3-, 4-, 5-, or 6-membered spirocarbocyclylene, or a 4-, 5-, or 6-membered spiroheterocyclylene comprising 1 or 2 heteroatoms selected from N and O; or R.sup.Fd and R.sup.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.sup.Fd and R.sup.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.sup.Fb and R.sup.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.sup.Fd and Y.sup.Ff is, independently, CH.sub.2, CHR.sup.FF2, C(R.sup.FF2).sub.2, C(O), N, NH, NR.sup.FF3, O, S, or S(O); Y.sup.Fe is a bond or a divalent moiety attached to Y.sup.Fd and Y.sup.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.sup.2 and the others are substituted with one or more groups independently selected from H and R.sup.FF1; and wherein the contiguous atoms of Y.sup.Fe can be attached through a single or double bond; each R.sup.FF1 is, independently, H, alkyl, alkenyl, alkynyl, aliphatic, heteroaliphatic, carbocyclyl, halogen, hydroxyl, amino, cyano, alkoxy, aryl, heteroaryl, heterocyclyl, alkylamino, alkylhydroxyl, or haloalkyl; each R.sup.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.sub.2alkyl, —N(alkyl)SO.sub.2alkyl, —NHSO.sub.2aryl, —N(alkyl)SO.sub.2aryl, —NHSO.sub.2alkenyl, —N(alkyl)SO.sub.2alkenyl, —

NHSO.sub.2alkynyl, —N(alkyl)SO.sub.2alkynyl, aliphatic, heteroaliphatic, aryl, heteroaryl, hetercyclic, carbocyclic, cyano, nitro, nitroso, —SH, —Salkyl, or haloalkyl; and R.sup.FF3 is alkyl, alkenyl, alkynyl, —C(O)H, —C(O)OH, —C(O)alkyl, or —C(O)Oalkyl, wherein if Y.sup.Fd or Y.sup.Ff is substituted with A.sup.2, then Y.sup.Fe is a bond, or a pharmaceutically acceptable salt thereof.

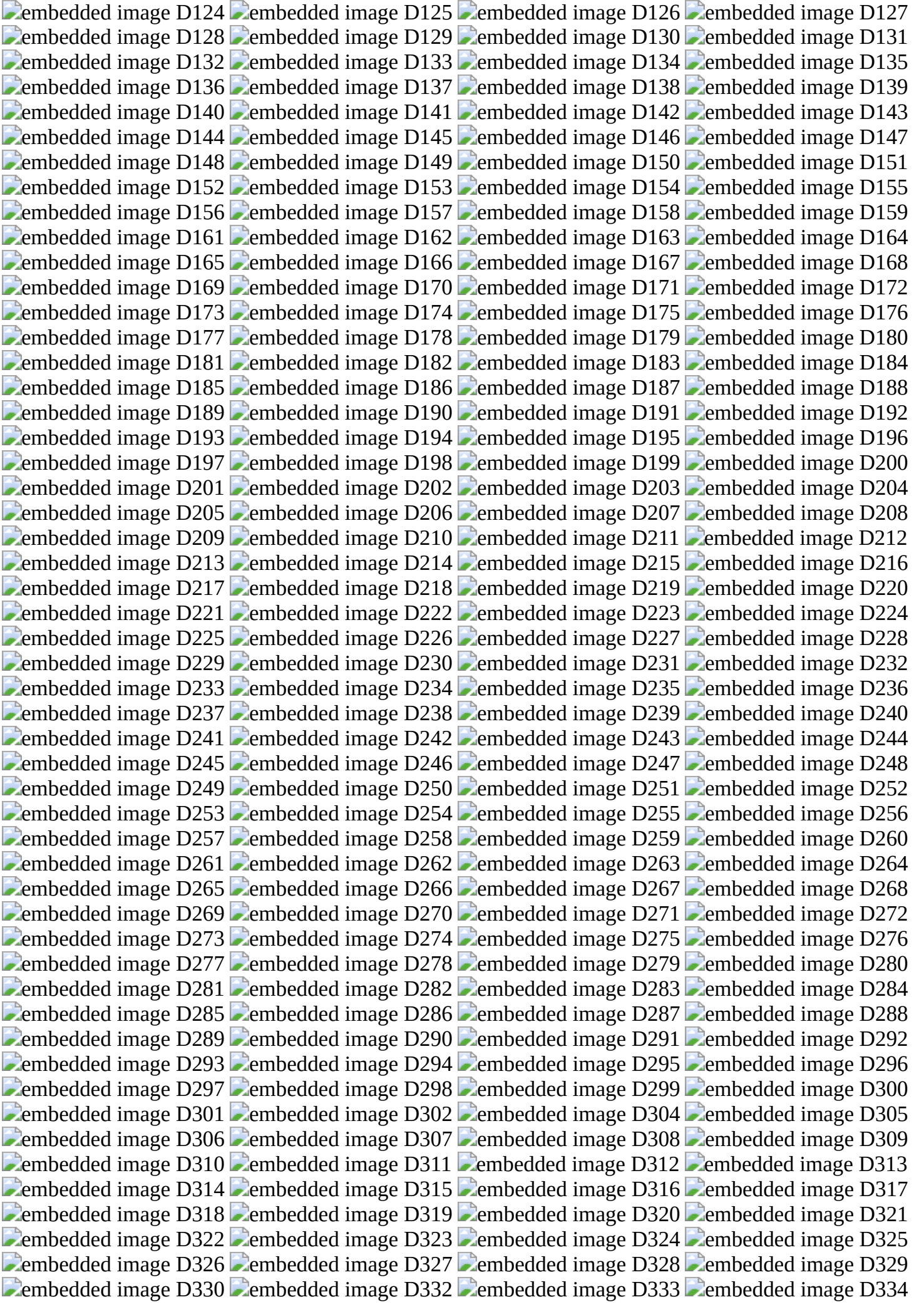
9. The compound of claim 2, wherein the degradation moiety comprises the structure of Formula F1: ##STR01039## wherein A.sup.2 is a bond between the degrader and the linker; and R.sup.F1 is absent or O, or a pharmaceutically acceptable salt thereof.

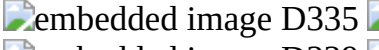
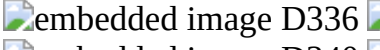
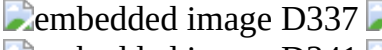
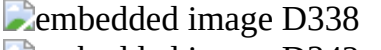
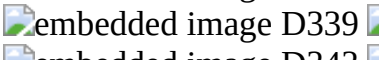
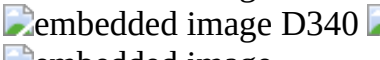
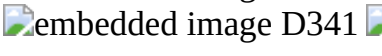
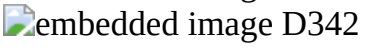
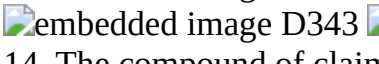
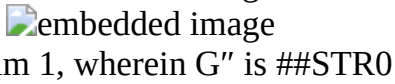
10. The compound of claim 2, wherein the degradation moiety comprises the structure of Formula F2: ##STR01040## wherein A.sup.2 is a bond between the degrader and the linker; and R.sup.F1 is absent or O, or a pharmaceutically acceptable salt thereof.

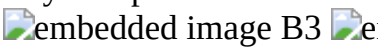
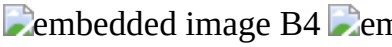
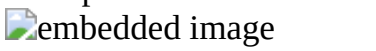
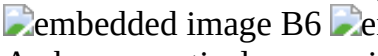
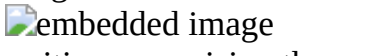
11. The compound of claim 2, wherein the degradation moiety comprises the structure of Formula G: ##STR01041## wherein A.sup.2 is a bond between the degrader and the linker; and R.sup.F1 is absent or O, or a pharmaceutically acceptable salt thereof.

12. The compound of claim 2, wherein the linker has the structure of Formula IV: A.sup.1-(B.sup.1).sub.f—(C.sup.1).sub.g—(B.sup.2).sub.h-(D)-(B.sup.3).sub.i—(C.sup.2).sub.j—(B.sup.4).sub.k-A.sup.2 Formula IV wherein A.sup.1 is a bond between the linker and A; A.sup.2 is a bond between B and the linker; each of B.sup.1, B.sup.2, B.sup.3, and B.sup.4 is, independently, optionally substituted C.sub.1-C.sub.2 alkyl, optionally substituted C.sub.1-C.sub.3 heteroalkyl, O, S, S(O).sub.2, or NR.sup.N; each R.sup.N is, independently, H, optionally substituted C.sub.1-4 alkyl, optionally substituted C.sub.2-4 alkenyl, optionally substituted C.sub.2-4 alkynyl, optionally substituted C.sub.2-6 heterocyclyl, optionally substituted C.sub.6-12 aryl, or optionally substituted C.sub.1-7 heteroalkyl; each of C.sup.1 and C.sup.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.sub.1-10 alkyl, optionally substituted C.sub.2-10 alkenyl, optionally substituted C.sub.2-10 alkynyl, optionally substituted C.sub.2-6 heterocyclyl, optionally substituted C.sub.6-12 aryl, optionally substituted C.sub.2-C.sub.10 polyethylene glycol, or optionally substituted C.sub.1-10 heteroalkyl, or a chemical bond linking A.sup.1-(B.sup.1).sub.f—(C.sup.1).sub.g—(B.sup.2).sub.h— to —(B.sup.3).sub.i—(C.sup.2).sub.j—(B.sup.4).sub.k-A.sup.2.

13. The compound of claim 2, wherein the compound has the structure of A any one of compounds D1-D31, D32-D211, and D212-D343, or a pharmaceutically acceptable salt thereof TABLE-US-00014 Compound No. Structure D1  D2 D3 D4  D15 D16 D26 D28 D31 D39 D40 D41 D42 D43 D44 D45 D46 D47 D48 D49 D50 D51 D52 D53 D54 D55 D56 D57 D58 D59 D60 D61 D62 D63 D64 D65 D66 D67 D68 D69 D70 D71 D72 D73 D75 D76 D77 D78 D79 D81 D82 D83 D84 D85 D86 D87 D88 D89 D90 D91 D92 D93 D94 D95 D96 D97 D98 D99 D100 D101 D102 D103 D104 D106 D107 D109 D110 D113 D114 D115 D116 D117 D118 D119 D120 D121 D122 D123



   
   
 
14. The compound of claim 1, wherein G″ is ##STR01347## wherein each of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G1 and R.sup.G2, R.sup.G2 and R.sup.G3, R.sup.G3 and R.sup.G4, and/or R.sup.G4 and R.sup.G5, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or optionally substituted C.sub.2-C.sub.9 heterocyclyl.

15. The compound of claim 1, wherein the compound has the structure of any one of compounds B1-B6 in the below table, or a pharmaceutically acceptable salt thereof TABLE-US-00015 Compound No. Structure B1  B2  B3  B4 
B5  B6 

16. A pharmaceutical composition comprising the compound of claim 2, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

17. A method of treating a synovial cancer in a subject having synovial cancer the method including administering to the subject having synovial cancer an effective amount of a compound of claim 2 or a pharmaceutically acceptable salt thereof.