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Inventor(s)	Parsons; Andrew Thomas et al.

Synthesis of key intermediate of KRAS G12C inhibitor compound

Abstract

The present invention relates to an improved, efficient, scalable process to prepare intermediate compounds, such as compound 5M, having the structure ##STR00001## useful for the synthesis of compounds that target KRAS G12C mutations, such as ##STR00002##

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References Cited

U.S. PATENT DOCUMENTS

Patent No.	Issued Date	Patentee Name	U.S. Cl.	CPC
4232027	12/1979	Turk et al.	N/A	N/A
5100883	12/1991	Schiehser	N/A	N/A
5118677	12/1991	Caufield	N/A	N/A
5118678	12/1991	Kao et al.	N/A	N/A
5120842	12/1991	Failli et al.	N/A	N/A
5151413	12/1991	Caufield et al.	N/A	N/A
5256790	12/1992	Nelson	N/A	N/A
5258389	12/1992	Goulet et al.	N/A	N/A
5521184	12/1995	Zimmerman	N/A	N/A
5650415	12/1996	Tang et al.	N/A	N/A
5656643	12/1996	Spada et al.	N/A	N/A
5712291	12/1997	D'Amato	N/A	N/A
5728813	12/1997	Lyman et al.	N/A	N/A
5747498	12/1997	Schnur et al.	N/A	N/A
5770599	12/1997	Gibson	N/A	N/A
5789427	12/1997	Chen et al.	N/A	N/A
5792783	12/1997	Tang et al.	N/A	N/A
5861510	12/1998	Piscopio et al.	N/A	N/A
5863949	12/1998	Robinson et al.	N/A	N/A
5892112	12/1998	Levy et al.	N/A	N/A
5969110	12/1998	Beckmann et al.	N/A	N/A
5981245	12/1998	Fox et al.	N/A	N/A
5990141	12/1998	Hirth et al.	N/A	N/A
6057124	12/1999	Bartley et al.	N/A	N/A
6111090	12/1999	Gorman et al.	N/A	N/A
6232447	12/2000	Cerretti	N/A	N/A
6235764	12/2000	Larson et al.	N/A	N/A
6258812	12/2000	Bold et al.	N/A	N/A
6413932	12/2001	Cerretti et al.	N/A	N/A
6515004	12/2002	Misra et al.	N/A	N/A
6596852	12/2002	Cerretti et al.	N/A	N/A
6630500	12/2002	Gingrich et al.	N/A	N/A
6656963	12/2002	Firestone et al.	N/A	N/A
6713485	12/2003	Carter et al.	N/A	N/A

6727225	12/2003	Wiley	N/A	N/A
7025962	12/2005	Gorman et al.	N/A	N/A
7358384	12/2007	Morii et al.	N/A	N/A
7361760	12/2007	Sircar et al.	N/A	N/A
7618632	12/2008	Collins et al.	N/A	N/A
7812135	12/2009	Smith et al.	N/A	N/A
7838700	12/2009	Martin et al.	N/A	N/A
8388967	12/2012	Smith et al.	N/A	N/A
8586023	12/2012	Shiku et al.	N/A	N/A
8591886	12/2012	Ponath et al.	N/A	N/A
10519146	12/2018	Lanman et al.	N/A	N/A
10532042	12/2019	Lanman et al.	N/A	N/A
10640504	12/2019	Lanman et al.	N/A	N/A
10988485	12/2020	Minatti et al.	N/A	N/A
11045484	12/2020	Wurz et al.	N/A	N/A
11053226	12/2020	Shin et al.	N/A	N/A
11090304	12/2020	Allen et al.	N/A	N/A
11096939	12/2020	Booker et al.	N/A	N/A
11285135	12/2021	Lanman et al.	N/A	N/A
11299281	12/2021	Parsons et al.	N/A	N/A
11905281	12/2023	Lanman et al.	N/A	N/A
2002/0042368	12/2001	Fanslow, III et al.	N/A	N/A
2003/0105091	12/2002	Riedl et al.	N/A	N/A
2003/0162712	12/2002	Cerretti et al.	N/A	N/A
2009/0012085	12/2008	Baum et al.	N/A	N/A
2014/0288045	12/2013	Ren et al.	N/A	N/A
2015/0239900	12/2014	Li et al.	N/A	N/A
2016/0159738	12/2015	Ren et al.	N/A	N/A
2016/0166571	12/2015	Janes et al.	N/A	N/A
2016/0297774	12/2015	Li et al.	N/A	N/A
2018/0015087	12/2017	Liu et al.	N/A	N/A
2018/0072723	12/2017	Blake et al.	N/A	N/A
2018/0334454	12/2017	Lanman et al.	N/A	N/A
2019/0077801	12/2018	Lanman et al.	N/A	N/A
2019/0336514	12/2018	Wurz et al.	N/A	N/A
2019/0343838	12/2018	Allen et al.	N/A	N/A
2019/0345169	12/2018	Minatti et al.	N/A	N/A
2019/0374542	12/2018	Allen et al.	N/A	N/A
2019/0375749	12/2018	Chen et al.	N/A	N/A
2020/0030324	12/2019	Booker et al.	N/A	N/A
2020/0055845	12/2019	Lanman et al.	N/A	N/A
2020/0069657	12/2019	Lanman et al.	N/A	N/A
2020/0165231	12/2019	Shin et al.	N/A	N/A
2020/0207766	12/2019	Lanman et al.	N/A	N/A
2020/0222407	12/2019	Lipford et al.	N/A	N/A
2020/0360374	12/2019	Henary et al.	N/A	N/A
2020/0369662	12/2019	Chaves et al.	N/A	N/A
2021/0009577	12/2020	Lanman et al.	N/A	N/A
2022/0168280	12/2021	Lanman et al.	N/A	N/A
2023/0192681	12/2022	Lanman et al.	N/A	N/A

2023/0192682	12/2022	Lanman et al.	N/A	N/A
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FOREIGN PATENT DOCUMENTS

Patent No.	Application Date	Country	CPC
101239913	12/2007	CN	N/A
19629652	12/1997	DE	N/A
0090505	12/1982	EP	N/A
0520722	12/1991	EP	N/A
0566226	12/1992	EP	N/A
0606046	12/1993	EP	N/A
0682027	12/1994	EP	N/A
0407122	12/1995	EP	N/A
0770622	12/1996	EP	N/A
0780386	12/1996	EP	N/A
0787772	12/1996	EP	N/A
0818442	12/1997	EP	N/A
0837063	12/1997	EP	N/A
0931788	12/1998	EP	N/A
0970070	12/1999	EP	N/A
1004578	12/1999	EP	N/A
1181017	12/2001	EP	N/A
1786785	12/2006	EP	N/A
1866339	12/2006	EP	N/A
1947183	12/2007	EP	N/A
1446372	12/2008	EP	N/A
3401314	12/2018	EP	N/A
3055290	12/2018	EP	N/A
02233610	12/1989	JP	N/A
2019031476	12/2018	JP	N/A
1990005719	12/1989	WO	N/A
1992005179	12/1991	WO	N/A
1992020642	12/1991	WO	N/A
1993011130	12/1992	WO	N/A
1994002136	12/1993	WO	N/A
1994002485	12/1993	WO	N/A
1994009010	12/1993	WO	N/A
1995009847	12/1994	WO	N/A
1995014023	12/1994	WO	N/A
1995016691	12/1994	WO	N/A
1995019774	12/1994	WO	N/A
1995019970	12/1994	WO	N/A
1996027583	12/1995	WO	N/A
1996030347	12/1995	WO	N/A
1996031510	12/1995	WO	N/A
1996033172	12/1995	WO	N/A
1996033980	12/1995	WO	N/A
1996041807	12/1995	WO	N/A
1997002266	12/1996	WO	N/A
1997013771	12/1996	WO	N/A
1997019065	12/1996	WO	N/A

1997027199	12/1996	WO	N/A
1997030034	12/1996	WO	N/A
1997030044	12/1996	WO	N/A
1997032880	12/1996	WO	N/A
1997032881	12/1996	WO	N/A
1997034895	12/1996	WO	N/A
1997038983	12/1996	WO	N/A
1997038994	12/1996	WO	N/A
1997049688	12/1996	WO	N/A
1998002434	12/1997	WO	N/A
1998002437	12/1997	WO	N/A
1998002438	12/1997	WO	N/A
1998002441	12/1997	WO	N/A
1998003516	12/1997	WO	N/A
1998007697	12/1997	WO	N/A
1998007726	12/1997	WO	N/A
1998014449	12/1997	WO	N/A
1998014450	12/1997	WO	N/A
1998014451	12/1997	WO	N/A
1998017662	12/1997	WO	N/A
1998030566	12/1997	WO	N/A
1998033768	12/1997	WO	N/A
1998033798	12/1997	WO	N/A
1998034915	12/1997	WO	N/A
1998034918	12/1997	WO	N/A
1999007675	12/1998	WO	N/A
1999007701	12/1998	WO	N/A
1999020758	12/1998	WO	N/A
1999029667	12/1998	WO	N/A
1999035132	12/1998	WO	N/A
1999035146	12/1998	WO	N/A
1999040196	12/1998	WO	N/A
1999045009	12/1998	WO	N/A
1999052889	12/1998	WO	N/A
1999052910	12/1998	WO	N/A
1999061422	12/1998	WO	N/A
2000002871	12/1999	WO	N/A
2000012089	12/1999	WO	N/A
2000059509	12/1999	WO	N/A
2001003720	12/2000	WO	N/A
2001014387	12/2000	WO	N/A
2001032651	12/2000	WO	N/A
2001037820	12/2000	WO	N/A
2002055501	12/2001	WO	N/A
2002059110	12/2001	WO	N/A
2002066470	12/2001	WO	N/A
2002068406	12/2001	WO	N/A
2003042132	12/2002	WO	N/A
2004005279	12/2003	WO	N/A
2004007458	12/2003	WO	N/A

2004007481	12/2003	WO	N/A
2004009784	12/2003	WO	N/A
2005005434	12/2004	WO	N/A
2005007190	12/2004	WO	N/A
2005011700	12/2004	WO	N/A
2005016252	12/2004	WO	N/A
2005021546	12/2004	WO	N/A
2005055808	12/2004	WO	N/A
2005115451	12/2004	WO	N/A
2006044453	12/2005	WO	N/A
2006083289	12/2005	WO	N/A
2006121168	12/2005	WO	N/A
2006122806	12/2005	WO	N/A
2007133822	12/2006	WO	N/A
2008070740	12/2007	WO	N/A
2009036082	12/2008	WO	N/A
2009055730	12/2008	WO	N/A
2010003118	12/2009	WO	N/A
2011028683	12/2010	WO	N/A
2011051726	12/2010	WO	N/A
2011090754	12/2010	WO	N/A
2012142498	12/2011	WO	N/A
2013039954	12/2012	WO	N/A
2013155223	12/2012	WO	N/A
2014143659	12/2013	WO	N/A
2014152588	12/2013	WO	N/A
2015001076	12/2014	WO	N/A
2015054572	12/2014	WO	N/A
2015075483	12/2014	WO	N/A
2016044772	12/2015	WO	N/A
2016049524	12/2015	WO	N/A
2016049565	12/2015	WO	N/A
2016049568	12/2015	WO	N/A
2016164675	12/2015	WO	N/A
2016168540	12/2015	WO	N/A
2017015562	12/2016	WO	N/A
2017058728	12/2016	WO	N/A
2017058768	12/2016	WO	N/A
2017058792	12/2016	WO	N/A
2017058805	12/2016	WO	N/A
2017058807	12/2016	WO	N/A
2017058902	12/2016	WO	N/A
2017058915	12/2016	WO	N/A
2017087528	12/2016	WO	N/A
2017100546	12/2016	WO	N/A
2017172979	12/2016	WO	N/A
2017201161	12/2016	WO	N/A
2018064510	12/2017	WO	N/A
2018068017	12/2017	WO	N/A
2018119183	12/2017	WO	N/A

2018140598	12/2017	WO	N/A
2018217651	12/2017	WO	N/A
2018218069	12/2017	WO	N/A
2019051291	12/2018	WO	N/A
2019213516	12/2018	WO	N/A
2019213526	12/2018	WO	N/A
2019217691	12/2018	WO	N/A
2019232419	12/2018	WO	N/A
2019241157	12/2018	WO	N/A
2019243533	12/2018	WO	N/A
2019243535	12/2018	WO	N/A
2020050890	12/2019	WO	N/A
2020102730	12/2019	WO	N/A
2020106640	12/2019	WO	N/A
2020232130	12/2019	WO	N/A
2020236947	12/2019	WO	N/A
2020236948	12/2019	WO	N/A
2021081212	12/2020	WO	N/A
2021097207	12/2020	WO	N/A
2021097212	12/2020	WO	N/A
2021126816	12/2020	WO	N/A
2022-076623	12/2021	WO	N/A
2022/109242	12/2021	WO	N/A
2023/172858	12/2022	WO	N/A

OTHER PUBLICATIONS

Dai et al., "Synthesis of Substituted Pyridines via Formal (3+3) Cycloaddition of Enamines with Unsaturated Aldehydes and Ketones," J. Org. Chem., 87:8437-44 (2022). cited by applicant
Murray et al., "Kinetic and Mechanistic Investigations to Enable a Key Suzuki Coupling for Sotorasib Manufacture_What a Difference a Base Makes," Org. Proc. Res. Dev., 27(1):198-205 (2023). cited by applicant

Notice of Allowance, mailed Aug. 13, 2019, for U.S. Appl. No. 15/984,855, 5 pages. cited by applicant

Notice of Allowance, mailed Oct. 3, 2023, for U.S. Appl. No. 17/031,607, 7 pages. cited by applicant

Non-Final Office Action for U.S. Appl. No. 17/031,607, mailed Mar. 31, 2023, 7 pages. cited by applicant

Restriction Requirement, mailed Apr. 14, 2022, for U.S. Appl. No. 17/031,607, 5 pages. cited by applicant

"A Phase 1, Study Evaluating the Safety, Tolerability, PK, and Efficacy of AMG 510 in Subjects With Solid Tumors With a S Mutation." NCT03600883, comparison of version submitted Oct. 29, 2018 and Oct. 9, 2019 (update posted Oct. 10, 2019), for full history of change see <https://clinicaltrials.gov/ct2/history/NCT03600883> (last accessed Nov. 11, 2020), pp. 1-22. cited by applicant

"Acute Leukemia," *The Merck Manual* (Online Edition), pp. 1-6 (2013). cited by applicant

"KRASG12C Inhibitor," Mirati Therapeutics, retrieved on Nov. 27, 2018, from <https://www.mirati.com/mrtx849/>, 5 pages. cited by applicant

4-Methyl-2-(1-methylethyl)-3-Pyridinamine, STN Registry, CAS RN 1698293-93-4, STN entry date May 5, 2015 (May 5, 2015). cited by applicant

Ahmadian, et al., "Guanosine triphosphatase stimulation of oncogenic Ras mutants," *PNAS*, 96:

7065-7070, 1999. cited by applicant

Airoidi, et al., "Glucose-Derived Ras Pathway Inhibitors: Evidence of Ras-Ligand Binding and Ras-GEF (Cdc25) Interaction Inhibition," *ChemBioChem*, 8: 1376-1379 (2007). cited by applicant
AMG-510; CS-0081316; Source: AbaChemScene (CS-0081316); Deposit Date: May 13, 2019
Available Date: May 13, 2019; SID: 384060804[CID: 137278711] (available at
<https://pubchem.ncbi.nlm.nih.gov/substance/384060804/>). cited by applicant

AMG-510; HY-114277; Source: MedChemexpress MCE (HY-114277); Deposit Date: May 13, 2019
Available Date: May 13, 2019; SID: 384060569[CID: 137278711] (available at
<https://pubchem.ncbi.nlm.nih.gov/substance/384060569/>). cited by applicant

Amgen Press Release, "Amgen Announces New Clinical Data Evaluating Novel Investigational KRAS(G12C) Inhibitor In Larger Patient Group At WCLC 2019," dated Sep. 8, 2019 (last accessed Apr. 13, 2021). cited by applicant

ATTC "Organism: *Mus musculus* (B cell); *Mus musculus* (myeloma), mouse (B cell); mouse (myeloma)," Accession No. HB-8508, retrieved from <https://www.atcc.org/~media/0DF7351153724BD6A3E7D78D5BA2F933.ashx>, on Nov. 29, 2018. cited by applicant

Barnett, et al., "Identification and characterization of pleckstrin-holomogy-domain-dependent and isoenzyme specific Akt inhibitors," *Biochem. J.*, 385 (2): 399-408 (2005). cited by applicant

Beaver, et al., Axial Chirality in the Sotorasib Drug Substance, Part 2: Leveraging a high-Temperature Thermal Racemization to Recycle the Classical Resolution Waste System, *Org. Process res. Dev.* 26: 2636-2645 (2022). cited by applicant

Bhatia, et al., "A Review on Bioisosterism: A Rational Approach for Drug Design and Molecular Modification," *Pharmacologyonline*, 1:272-299 (2011). cited by applicant

Biernacka, et al., "The potential utility of re-mining results of somatic mutation testing: KRAS status in lung adenocarcinoma" in *Cancer Genet*;209:195-8 (2016). cited by applicant

Bull, et al., "Isoquino[2,1-c][1,3,2] Benzodiazaphosphorine Derivatives: New Potential Agents for Cancer Chemotherapy," *Phosphorus, Sulfur, and Silicon*, 162:231-243 (2000). cited by applicant

Campillo, et al., "Novel Bronchodilators: Synthesis, Transamination Reactions, and Pharmacology of a Series of Pyrazino[2,3-c][1,2,6]thiadiazine 2,2-Dioxides," *J. Med. Chem.*, 43: 4219-4227 (2000). cited by applicant

Canon, et al., "The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity," *Nature*, 575(7781): 217-223 (2019). cited by applicant

Canon, et al., "The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity," *Nature*, 575(7781): 217-223 (2019) (Supplementary Material, pp. 1-55). cited by applicant

Cee, et al., "Discovery of AMG 510, a first-in-human covalent inhibitor of KRAS.SUP.G12C for the treatment of solid tumors," Abstract and Presentation, ACS Spring Meeting, Orlando, FL, USA, Mar. 31-Apr. 4, 2019. cited by applicant

Clarke, et al., "Dissecting mechanisms of resistance to targeted drug combination therapy in human colorectal cancer" in *Oncogene* 38:5076-90 (2019). cited by applicant

Cohen, "The development and therapeutic potential of protein kinase inhibitors," *Current Opinion in Chemical Biology*, 3:459-465 (1999). cited by applicant

Cowen Slide deck—Warp Drive Bio, slides 1-32, "Corporate Overview Exploiting the Molecules and Mechanisms of Nature to Create Transformative Medicines"

<http://www.warpdrivebio.com/news/cowen%202016.pdf> (last visited Apr. 2016). cited by applicant

Cox, et al., "Drugging the undruggable RAS: mission possible?" in *Nat Rev Drug Discov* 13:828-51 M(2014). cited by applicant

Dasmahapatra, et al., "In vitro Combination Treatment with Perifosine and UCN-01 Demonstrates Synergism Against Prostate (PC-3) and Lung (A549) Epithelial Adenocarcinoma Cell Lines," *Clin. Cancer Res.* 10(15): 5242-5252 (2004). cited by applicant

Database Registry [Online], Chemical Abstracts Service, Columbus, Ohio, US; Jul. 31, 2017 (Jul. 31, 2017), XP002801805, retrieved from STN Database accession No. 2105944-09-8. cited by

applicant

Del Re, et al., "Implications of KRAS mutations in acquired resistance to treatment in NSCLC" in *Oncotarget* 9:6630-43 (2018). cited by applicant

Dermer, et al., "Another Anniversary for the War on Cancer," *Bio/Technology*, 12: 320 (1994). cited by applicant

Douelle, et al., "Highly Diastereoselective Synthesis of vicinal Quaternary and Tertiary Stereocenters Using the Iodo-aldol Cyclization," *Org. Lett.*, 9 (10): 1931-1934 (2007). cited by applicant

Erkkilä, et al., "Mild Organocatalytic α -Methylenation of Aldehydes," *J. Org. Chem.*, 71 (6), 2538-2541 (2006). cited by applicant

Extended European Search Report for European Patent Application No. 19208193.2, dated Jun. 3, 2020, pp. 1-8. cited by applicant

Fakih, et al., "Phase 1 study evaluating the safety, tolerability, pharmacokinetics (PK), and efficacy of AMG 510, a novel small molecule KRASG12C inhibitor, in advanced solid tumors," *Journal of Clinical Oncology*, 37(15 suppl) (May 20, 2019) 3003, published online May 26, 2019. cited by applicant

Fakih, et al., "Phase 1 study evaluating the safety, tolerability, pharmacokinetics (PK), and efficacy of AMG 510, a novel small molecule KRASG12C inhibitor, in advanced solid tumors,"

Presentation, ASCO, Chicago, IL, USA, May 31-Jun. 4, 2019. cited by applicant

Fiala, et al., "G12V and G12A KRAS mutations are associated with poor outcome in patients with metastatic colorectal cancer treated with bevacizumab" in *Tumour Biol* 37:6823-30 (2016). cited by applicant

Final Office Action for U.S. Appl. No. 15/984,855, mailed Mar. 28, 2019, 7 pages. cited by applicant

Final Office Action for U.S. Appl. No. 16/436,647, mailed Mar. 24, 2021, 7 pages. cited by applicant

Final Office Action for U.S. Appl. No. 16/661,907, mailed Mar. 27, 2020, 29 pages. cited by applicant

Freshney, et al., *Culture of Animal Cells, A Manual of Basic Technique*, Alan R. Liss, Inc, New York, p. 4 (1983). cited by applicant

Gentile, et al., "Discovery and Structural Investigation of Novel Binders to the Ras Switch II Pocket," NCI Initiative Symposium Poster (2015). cited by applicant

Gills and Dennis, "The development of phosphatidylinositol ether lipid analogues as inhibitors of the serine/threonine kinase, Akt," *Expert. Opin. Investig. Drugs*, 13: 787-797 (2004). cited by applicant

Goldberg, et al., "Role of PD-1 and its ligand, B7-H1, in early fate decisions of CD8 T cells," *Blood*, 110(1): 186-192 (2007). cited by applicant

Goldstein, et al., "Biological efficacy of a chimeric antibody to the epidermal growth factor receptor in a human tumor xenograft model," *Clin. Cancer Res.*, 1: 1311-1318 (1995). cited by applicant

Golub, et al., "Molecular Classification of Cancer: Class Discovery and Class Prediction by Gene Expression Monitoring," *Science*, 286: 531-537(1999). cited by applicant

Govindan et al., "OA01.06 Safety, Efficacy, and Pharmacokinetics of AMG 510, a Novel KRAS.SUP.G12C .Inhibitor, in Patients with Non-Small Cell Lung Cancer," *J. Thorac. Oncol.*, 14(11, Supplement 1):S1125-1126 (Nov. 2019). cited by applicant

Govindan, et al., "Safety, Efficacy, and Pharmacokinetics of AMG 510, a Novel KRASG12C Inhibitor, in Patients with Non-Small Cell Lung Cancer," Abstract and Presentation, North American Conference on Lung Cancer (NACLC), Chicago, IL, USA, Oct. 10-12, 2019. cited by applicant

Govindan, et al., "Phase 1 Study of AMG 510, a Novel KRAS G12C Inhibitor, in Advanced Solid

Tumors with KRAS p.G12C Mutation,” Abstract, ESMO Congress, Barcelona, Spain, Sep. 27-Oct. 1, 2019. cited by applicant

Govindan, et al., “Phase 1 Study of AMG 510, a Novel KRAS G12C Inhibitor, in Advanced Solid Tumors with KRAS p.G12C Mutation,” Poster, ESMO Congress, Barcelona, Spain, Sep. 27, 2019-Oct. 1, 2019. cited by applicant

Govindan, et al., “Phase 1 Study of Safety, Tolerability, Pharmacokinetics, and Efficacy of AMG510, a Novel KRASG12C Inhibitor, in Non-Small Cell Lung Cancer,” Abstract and Presentation, World Conference on Lung Cancer (WCLC), Barcelona, Spain, Sep. 7-10, 2019. cited by applicant

Gura, “Cancer Models: Systems for Identifying New Drugs Are Often Faulty,” *Science*, 278(5340):1041-1042 (1997). cited by applicant

Halford, “Amgen unveils its Kras covalent inhibitor AMG 510,” *Chemical & Engineering News* 97(14):4 (2019). cited by applicant

Hallin, et al., “The KRAS.SUP.G12C .Inhibitor MRTX849 Provides Insight toward Therapeutic Susceptibility of KRAS-Mutant Cancers in Mouse Models and Patients,” *Cancer Discov.*, 10: 54-71 (2020). cited by applicant

Hansen, et al., “Abstract 686: Drugging an undruggable pocket: the biochemical mechanism of covalent KRAS.SUP.G12C .inhibitors,” Proceedings of the American Association for Cancer Research Annual Meeting 2018; Apr. 14-18, 2018; Chicago, IL; AACR; *Cancer Res.*, 78(13 Suppl): Abstract 686 (2018). cited by applicant

Hichri, et al., “A Convenient Synthesis of 1,3,2-Benzodiazaphosphorine-2-Oxide,” *Phosphorus, Sulfur, and Silicon*, 190: 29-35 (2015). cited by applicant

Hichri, et al., CAPLUS Abstract, 162:245378 (2015). cited by applicant

Hirayama, “Handbook for Making Crystal of Organic Compound,—Principles and Know-how—”, Maruzen Co., Ltd., Jul. 25, 2008, pp. 57-84 (incl. English translation). cited by applicant

Hocker, et al., “Andrographolide derivatives inhibit guanine nucleotide exchange and abrogate oncogenic Ras function,” *PNAS*, 110(25): 10201-10206 (2013). cited by applicant

Hong, et al., “KRAS.SUP.G12C .Inhibition with Sotorasib in Advanced Solid Tumors,” *N. Engl. Med.*, 383:1207-1217 (2020). cited by applicant

Huang, et al., “Epidermal Growth Factor Receptor Blockade with C225 Modulates Proliferation, Apoptosis, and Radiosensitivity in Squamous Cell Carcinomas of the Head and Neck,” *Cancer Res.*, 59(8): 1935-1940 (1999). cited by applicant

International Search Report and Written Opinion, European Patent Office, PCT/US2021/0538g59, dated Jan. 20, 2022. cited by applicant

International Search Report for PCT/US2017/067801, mailed Jul. 25, 2018, 6 pages. cited by applicant

International Search Report for PCT/US2018/033714, mailed Jul. 17, 2018, 3 pages. cited by applicant

International Search Report for PCT/US2018/050044, mailed Oct. 30, 2018, 7 pages. cited by applicant

International Search Report for PCT/US2019/030593, mailed Aug. 6, 2019, 4 pages. cited by applicant

International Search Report for PCT/US2019/030606, mailed Jul. 23, 2019, 5 pages. cited by applicant

International Search Report for PCT/US2019/031535, mailed Jul. 25, 2019, 7 pages. cited by applicant

International Search Report for PCT/US2019/034974, mailed Aug. 9, 2019, 5 pages. cited by applicant

International Search Report for PCT/US2019/036397, mailed Aug. 26, 2019, 5 pages. cited by applicant

International Search Report for PCT/US2019/036626, mailed Jun. 2, 2020, 5 pages. cited by applicant

International Search Report for PCT/US2019/061815, mailed Mar. 5, 2020, 6 pages. cited by applicant

International Search Report for PCT/US2019/062051, mailed Mar. 2, 2020, 3 pages. cited by applicant

International Search Report for PCT/US2019/62064, mailed Oct. 29, 2020, 9 pages. cited by applicant

International Search Report for PCT/US2020/032686, mailed Aug. 14, 2020, 4 pages. cited by applicant

International Search Report for PCT/US2020/033831, mailed Jul. 9, 2020, 6 pages. cited by applicant

International Search Report for PCT/US2020/033832, mailed Jul. 8, 2020, 4 pages. cited by applicant

International Search Report for PCT/US2020/060415, mailed Feb. 3, 2021, 5 pages. cited by applicant

International Search Report for PCT/US2020/065050, mailed Mar. 29, 2021, 7 pages. cited by applicant

Janes, et al., "Targeting KRAS Mutant Cancers with a Covalent G12C-Specific Inhibitor," *Cell*, 172: 578-589 (2018). cited by applicant

Jarvis, "Notorious KRAS: Taking down cancer researchers' biggest foe," *Chemical & Engineering News*, 97(37), 9 pages (2019). cited by applicant

Jin, et al., "Inhibition of AKT survival pathway by a small molecule inhibitor in human endometrial cancer cells," *Br. J. Cancer*, 91: 1808-1812 (2004). cited by applicant

Johnson et al., "Relationships between drug activity in NCI preclinical in vitro and in vivo models and early clinical trials," *British Journal of Cancer*, 84(10): 1424-1431 (2001). cited by applicant

Kargbo RB. "Inhibitors of G12C mutant Ras proteins for the treatment of cancers" in *ACS Med Chem Lett* 10:10-1 (2018). cited by applicant

Kojima, "Aiming to Improve the Efficiency of Crystallization Selection in Drug Development", *Pharmaceutics*, Sep. 1, 2008, vol. 68, No. 5, pp. 344-349 (incl. English translation). cited by applicant

Lanman, et al., "Abstract 4455: Discovery of AMG 510, a first-in-human covalent inhibitor of KRAS.SUP.G12C .for the treatment of solid tumors," Presentation, American Association for Cancer Research (AACR) Annual Meeting, Atlanta, Ga, USA, Mar. 29-Apr. 3, 2019. cited by applicant

Lanman, et al., "Abstract 4455: Discovery of AMG 510, a first-in-human covalent inhibitor of KRAS.SUP.G12C .for the treatment of solid tumors," Proceedings of the American Association for Cancer Research Annual Meeting 2019; Mar. 29, 2019-Apr. 3; Atlanta, GA, USA, AACR, *Cancer Res.* 79(13 Suppl): Abstract nr 4455 (2019). cited by applicant

Lanman, et al., "Discovery of a Covalent Inhibitor of KRAS.SUP.G12C .(AMG 510) for the Treatment of Solid Tumors," *J. Med. Chem.*, 63: 52-65 (2020). cited by applicant

Lanman, et al., Addressing Atropisomerism in the Development of Sotorasib, a Covalent Inhibitor of KRAS G12C: Structural, Analytical and Synthetic Considerations, *ACS Publications* 55: 289-2903 (2022). cited by applicant

Li, et al., "Targeting Protein-Protein Interaction with Covalent Small-Molecule Inhibitors," *Current Topics in Medicinal Chemistry*, 19(21): 1872-1876 (2019). cited by applicant

Lievre, et al., "KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer" in *Cancer Res* 66:3992-5 (2006). cited by applicant

Lim, et al., "Therapeutic Targeting of Oncogenic K-Ras by a Covalent Catalytic Site Inhibitor," *Angew. Chem. Int. Ed*, 53: 199-204 (2014). cited by applicant

Lipford, et al., "Pre-Clinical Development of AMG 510: The First Inhibitor of KRAS.SUP.G12C .in Clinical Testing," Presentation, American Association for Cancer Research (AACR) Annual Meeting, Atlanta, GA, USA, Mar. 29-Apr. 3, 2019. cited by applicant

Lito, et al., "Allele-specific inhibitors inactivate mutant KRAS G12C by a trapping mechanism" in *Science* 351:604-8 (2016). cited by applicant

Liu, Y., "Session SY28—Transformative Small Molecule Therapies—Targeting KRAS mutant cancers with a covalent G12C-specific inhibitor," Presentation on Apr. 4, 2017, AACR Annual Meeting Presentation, Apr. 1-5, 2017, Washington, D.C. (2017). cited by applicant

Lopez, et al., "Optimization of quinazolinone-based covalent inhibitors of KRAS.SUP.G12C .in the discovery of AMG 510," Abstract and Poster, ACS Fall Meeting, San Diego, CA, USA, Aug. 25-29, 2019. cited by applicant

Lu, et al., "KRAS G12C Drug Development: Discrimination between Switch II Pocket Configurations Using Hydrogen/Deuterium-Exchange Mass Spectrometry," *Structure*, 25: 1-7 (2017). cited by applicant

Massarelli, et al., "KRAS mutation is an important predictor of resistance to therapy with epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancer" in *Clin Cancer Res* 13:2890-6 (2007). cited by applicant

Maurer, et al., "Small-molecule ligands bind to a distinct pocket in Rad and inhibit SOS-mediated nucleotide exchange activity," *PNAS*, 109(14): 5299-5304 (2012). cited by applicant

McCormick F. "K-Ras protein as a drug target" in *J Mol Med (Berl)* 2016;94:253-8; Jones RP, Sutton PA, Evans JP, et al. "Specific mutations in KRAS codon 12 are associated with worse overall survival in patients with advanced and recurrent colorectal cancer" in *Br J Cancer* 116:923-9 (2017). cited by applicant

McGregor, et al., "Expanding the Scope of Electrophiles Capable of Targeting K-Ras Oncogenes," *ACS Bio. Chem.*, 56: 3179-3183 (2017). cited by applicant

Meanwell, "Synopsis of Some Recent Tactical Application of Bioisosteres in Drug Design," *J. Med. Chem.* 54:2529-2591 (2011). cited by applicant

Mirati Therapeutics, "Corporate Presentation Nov. 2017," Slides 1-41 (2017). cited by applicant

Modjtahedi, et al., "The human EGF receptor as a target for cancer therapy: six new rat mAbs AGainst the receptor on the breast carcinoma MDA-MB 468," *Br. J. Cancer*, 67(2): 247-253 (1993). cited by applicant

Morrissey et al., "Immunotherapy and Novel Combinations in Oncology: Current Landscape, Challenges, and Opportunities," *Clin. Transl. Sci.*, 9(2):89-104 (2016). cited by applicant

Nadal E, et al., "KRAS-G12C mutation is associated with poor outcome in surgically resected lung adenocarcinoma" in *J Thorac Oncol* 9:1513-22 (2014). cited by applicant

National Cancer Institute identifier: NSC 154020, retrieved on Nov. 29, 2018, from <https://cactus.nci.nih.gov/ncidb2.2/>. cited by applicant

NCBI Reference Sequence, "GTPase KRas isoform a [*Homo sapiens*]," GenBank Accession No. NM_203524.1, Retrieved on Nov. 29, 2018 from <https://www.ncbi.nlm.nih.gov/protein/15718763?sat=4&satkey=234448549>, 4 pages. cited by applicant

Neumann, et al., "Frequency and type of KRAS mutations in routine diagnostic analysis of metastatic colorectal cancer" in *Pathol Res Pract* 205:858-62 (2009). cited by applicant

Non-Final Office Action (Corrected) for U.S. Appl. No. 16/125,359, mailed Apr. 8, 2019, 13 pages. cited by applicant

Non-Final Office Action for U.S. Appl. No. 15/849,905, mailed Mar. 20, 2019, 18 pages. cited by applicant

Non-Final Office Action for U.S. Appl. No. 15/984,855, mailed Sep. 27, 2018, 25 pages. cited by applicant

Non-Final Office Action for U.S. Appl. No. 16/125,359, mailed Apr. 5, 2019, 13 pages. cited by applicant

Non-Final Office Action for U.S. Appl. No. 16/402,538, mailed Oct. 30, 2019, 12 pages. cited by applicant

Non-Final Office Action for U.S. Appl. No. 16/402,589, mailed Mar. 6, 2020, 17 pages. cited by applicant

Non-Final Office Action for U.S. Appl. No. 16/407,889, mailed Jul. 1, 2020, 6 pages. cited by applicant

Non-Final Office Action for U.S. Appl. No. 16/428,163, mailed Sep. 15, 2020, 6 pages. cited by applicant

Non-Final Office Action for U.S. Appl. No. 16/436,647, mailed Aug. 7, 2020, 19 pages. cited by applicant

Non-Final Office Action for U.S. Appl. No. 16/438,349, mailed Dec. 13, 2019, 15 pages. cited by applicant

Non-Final Office Action for U.S. Appl. No. 16/661,907, mailed Nov. 18, 2019, 20 pages. cited by applicant

Non-Final Office Action for U.S. Appl. No. 16/675,121, mailed Feb. 2, 2021, 10 pages. cited by applicant

Non-Final Office Action for U.S. Appl. No. 16/817,109, mailed Mar. 3, 2021, 12 pages. cited by applicant

Noriyuki, "API Form Screening and Selection at the Drug Discovery Stage", Pharm Stage, vol. 6, No. 10, Jan. 15, 2007, pp. 20-25 (incl. English translation). cited by applicant

Notice of Allowance mailed Jan. 14, 2021 for U.S. Appl. No. 16/402,589, 5 pages. cited by applicant

Notice of Allowance mailed Jul. 24, 2020 for U.S. Appl. No. 16/402,538, 8 pages. cited by applicant

Notice of Allowance mailed Jun. 30, 2021 for U.S. Appl. No. 16/438,349, pp. 1-9. cited by applicant

Notice of Allowance mailed Sep. 16, 2020 for U.S. Appl. No. 16/402,589, 5 pages. cited by applicant

Notice of Allowance mailed Sep. 9, 2020 for U.S. Appl. No. 16/438,349 , 9 pages. cited by applicant

Notice of Allowance, mailed Apr. 19, 2021, for U.S. Appl. No. 16/428,163, 9 pages. cited by applicant

Notice of Allowance, mailed Dec. 21, 2020, for U.S. Appl. No. 16/407,889, 5 pages. cited by applicant

Notice of Allowance, mailed Feb. 18, 2021, for U.S. Appl. No. 16/687,546, 9 pages. cited by applicant

Notice of Allowance, mailed Jan. 26, 2021, for U.S. Appl. No. 16/438,349, 9 pages. cited by applicant

Notice of Allowance, mailed Jan. 27, 2021, for U.S. Appl. No. 16/428,163, 9 pages. cited by applicant

Notice of Allowance, mailed Mar. 30, 2021, for U.S. Appl. No. 16/402,538, 8 pages. cited by applicant

Notice of Allowance, mailed Oct. 20, 2021, for U.S. Appl. No. 16/438,349, 9 pages. cited by applicant

Notice of Allowance, mailed Sep. 22, 2021, for U.S. Appl. No. 16/878,824, 8 pages. cited by applicant

Notice of Allowance, mailed Sep. 9, 2021, for U.S. Appl. No. 16/675,121, 7 pages. cited by applicant

Ostrem, et al., "Development of mutant-specific small molecule inhibitors of K-Ras," Poster, AACR 104th Annual Meeting 2013; Apr. 6-10, 2013; Washington, D.C. (2013). cited by applicant

Ostrem, et al., "Direct small molecule inhibitors of KRAS: from structural insights to mechanism-based design" in *Nat Rev Drug Discov* 15:771-85 (2016). cited by applicant

Ostrem, et al., "K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions," *Nature*, 503: 548-551 (2013). cited by applicant

Querhiani, et al., "The mutational spectrum of HRAS, KRAS, NRAS and FGFR3 genes in bladder cancer" in *Cancer Biomark* 2011-2012; 10:259-66 (2012). cited by applicant

Paez, et al., "EGFR Mutations in Lung Cancer Correlation with Clinical Response to Gefitinib Therapy," *Science*, 304(5676): 1497-500 (2004). cited by applicant

Palmioli, et al., "First experimental identification of Ras-inhibitor binding interface using a water-soluble Ras ligand," *Bioorg. Med. Chem. Lett.*, 19: 4217-4222 (2009). cited by applicant

Parsons, et al., Axial Chirality in the Sotorasib Drug Substance, Part 1: Development of a Classical Resolution to Prepare an Atropisomerically Pure Sotorasib Intermediate, *Org. Process res. Dev.* 26: 2629-2635 (2022). cited by applicant

Patricelli, et al., "Selective Inhibition of Oncogenic KRAS Output with Small Molecules Targeting the Inactive State," *Cancer Discov*, 6 (3): 316-329 (2016). cited by applicant

Pearce, et al., "Failure modes in anticancer drug discovery and development," *Cancer Drug Design and Discovery*, Edited by Stephen Neidle, Chapter 18, pp. 424-435 (2008). cited by applicant

Peri, et al., "Design, Synthesis and Biological Evaluation of Sugar-Derived Ras Inhibitors," *ChemBioChem*, 6: 1839-1848 (2005). cited by applicant

Peri, et al., "Sugar-Derived Ras Inhibitors: Group Epitope Mapping by NMR Spectroscopy and Biological Evaluation," *Eur. J. Org. Chem.*, 16: 3707-3720 (2006). cited by applicant

Peters, et al., "Selective inhibition of K-Ras G12C through allosteric control of GTP affinity and effector interactions," EORTC Poster (2013). cited by applicant

PubChem CID 108190520, 2-isopropyl-4-methylpyridin-3-amine, available at <https://pubchem.ncbi.nlm.nih.gov/compound/108190520> (last accessed Aug. 30, 2021). cited by applicant

Remington's Pharmaceutical Sciences, 1435-1712 (18th ed., Mack Publishing Co, Easton, Pennsylvania, 1990 (Table of Contents Only). cited by applicant

Rex et al., "KRAS—AACR 2018," Amgen Collection of Information published at Proceedings of the American Association for Cancer Research Annual Meeting 2018; Apr. 14-18, 2018; Chicago, IL; AACR; slides 1-24 (2018). cited by applicant

Rex, et al., "Abstract 3090: In vivo characterization of AMG 510—a potent and selective KRAS.SUP.G12C .covalent small molecule inhibitor in preclinical KRAS.SUP.G12C .cancer models," Poster, American Association for Cancer Research (AACR) Annual Meeting, Atlanta, GA, USA, Mar. 29-Apr. 3, 2019. cited by applicant

Rex, et al., "Abstract 3090: In vivo characterization of AMG 510—a potent and selective KRAS.SUP.G12C .covalent small molecule inhibitor in preclinical KRAS.SUP.G12C .cancer models," Proceedings of the American Association for Cancer Research Annual Meeting 2019; Mar. 29, 2019-Apr. 3; Atlanta, GA, USA, AACR, *Cancer Res.* 79(13 Suppl): Abstract nr 3090 (2019). cited by applicant

Saiki, et al., "Abstract 4484: Discovery and in vitro characterization of AMG 510—a potent and selective covalent small-molecule inhibitor of KRAS.SUP.G12C.," Presentation, American Association for Cancer Research (AACR) Annual Meeting, Atlanta, GA, USA, Mar. 29-Apr. 3, 2019. cited by applicant

Saiki, et al., "Abstract 4484: Discovery and in vitro characterization of AMG 510—a potent and selective covalent small-molecule inhibitor of KRAS.SUP.G12C.," Proceedings of the American Association for Cancer Research Annual Meeting 2019; Mar. 29, 2019-Apr. 3; Atlanta, GA, USA, AACR, *Cancer Res.* 79(13 Suppl): Abstract nr 4484 (2019). cited by applicant

Sarkar, et al., "Indole-3-Carbinol and Prostate Cancer.SUP.1,2.," *J. Nutr.*, 134(12 Suppl): 3493S-3498S (2004). cited by applicant

Shibata et al., "A Convenient Synthesis of 3-Cyano-2-methylpyridines under Ultrasonic Irradiation," *Bull. Chem. Soc. Jpn.*, 61:2199-2200 (1988). cited by applicant

Shima, et al., "In silico discovery of small-molecule Ras inhibitors that display antitumor activity by blocking the Ras-effector interaction," *PNAS*, 110(20): 8182-8187 (2013). cited by applicant

Simanshu, et al., "RAS proteins and their regulators in human disease" in *Cell* 170:17-33 (2017). cited by applicant

Simone, "Part XIV Oncology: Introduction," *Cecil Textbook of Medicine*, 20.SUP.th .Edition, 1:1004-1010 (1996). cited by applicant

Singh, et al., "Improving Prospects for Targeting RAS," *J. Clinc. Oncl*, 33(31): 3650-3660 (2015). cited by applicant

Stanetty et al., "Synthesis of Aza Analogs of the Herbicide Sindone B," *Monatshefte Fuer Chemie*, 130:441-450 (1999). cited by applicant

Statsyuk, "Let K-Ras activate its own inhibitor," *Nature Structural & Molecular Biology*, 25:435-439 (2018). cited by applicant

Sun, et al., "Discovery of Small Molecules that Bind to K-Ras and Inhibit Sos-Mediated Activation," *Angew. Chem. Int. Ed.*, 51: 6140-6143 (2012). cited by applicant

Suzawa, et al., "Activation of KRAS mediates resistance to targeted therapy in MET exon 14-mutant non-small cell lung cancer" in *Clin Cancer Res* 2019;25:1248-60 (2019). cited by applicant

Synoradski, et al., Tartaric Acid and Its o-Acyl derivatives. Part 2. Applications of Tartaric Acid and of O-Acyl Tartaric Acids and anhydrides. Resolution of Racemates, *Organic Prep. Proc. Int.* 40(2): 163-200 (2008). cited by applicant

Taveras, et al., "Ras Oncoprotein Inhibitors: The Discovery of Potent, Ras Nucleotide Exchange Inhibitors and the Structural Determination of a Drug-Protein Complex," *Biorg. Med. Chem. Lett.*, 5(1): 125-133 (1997). cited by applicant

Teramoto, et al., 1996, *Cancer* 77 (4):639-645. cited by applicant

The ASCO Post Staff, "AACR-NCI-EORTC: Investigational KRAS G12C Inhibitor for KRAS-Mutant Solid Tumors," *The ASCO Post* (2019). cited by applicant

Third Party Observation filed for PCT/US2020/033831, submitted Jan. 15, 2021, 2 pages. cited by applicant

Thompson, et al., "PD-1 Is Expressed by Tumor-Infiltrating Immune Cells and Is Associated with Poor Outcome for Patients with Renal Cell Carcinoma," *Clin. Cancer Res.*, 13(6): 1757-1761 (2007). cited by applicant

Traxler, "Tyrosine kinase inhibitors in cancer treatment (Part II)," *Exp. Opin. Ther. Patents*, 8(12): 1599-1625 (1998). cited by applicant

U.S. Appl. No. 60/528,340, filed Dec. 9, 2003. cited by applicant

Wang, et al., "Ras inhibition via direct Ras binding—is there a path forward?," *Bioorg. Med. Chem. Lett.*, 22: 5766-5776 (2012). cited by applicant

Written Opinion for PCT/US2017/067801, mailed Jul. 25, 2018, 10 pages. cited by applicant

Written Opinion for PCT/US2018/033714, mailed Jul. 17, 2018, 5 pages. cited by applicant

Written Opinion for PCT/US2018/050044, mailed Oct. 30, 2018, 7 pages. cited by applicant

Written Opinion for PCT/US2019/030593, mailed Aug. 6, 2019, 5 pages. cited by applicant

Written Opinion for PCT/US2019/030606, mailed Jul. 23, 2019, 6 pages. cited by applicant

Written Opinion for PCT/US2019/031535, mailed Jul. 25, 2019, 7 pages. cited by applicant

Written Opinion for PCT/US2019/034974, mailed Aug. 9, 2019, 5 pages. cited by applicant

Written Opinion for PCT/US2019/036397, mailed Aug. 26, 2019, 5 pages. cited by applicant

Written Opinion for PCT/US2019/036626, mailed Jun. 2, 2020, 12 pages. cited by applicant

Written Opinion for PCT/US2019/061815, mailed Mar. 5, 2020, 4 pages. cited by applicant

Written Opinion for PCT/US2019/062051, mailed Mar. 2, 2020, 5 pages. cited by applicant

Written Opinion for PCT/US2019/62064, mailed Oct. 29, 2020, 13 pages. cited by applicant

Written Opinion for PCT/US2020/032686, mailed Aug. 14, 2020, 6 pages. cited by applicant

Written Opinion for PCT/US2020/033831, mailed Jul. 9, 2020, 7 pages. cited by applicant
Written Opinion for PCT/US2020/033832, mailed Jul. 8, 2020, 6 pages. cited by applicant
Written Opinion for PCT/US2020/060415, mailed Feb. 3, 2021, 9 pages. cited by applicant
Written Opinion for PCT/US2020/065050, mailed Mar. 29, 2021, 8 pages. cited by applicant
Xing, et al., An Improved Efficient Process for the Production of highly Pure Dexmethylphenidate Hydrochloride, *J. Heterocyclic Chem.*, 54:1298-1303 (2017). cited by applicant
Xiong, et al., "Covalent Guanosine Mimetic Inhibitors of G12C KRAS," *ACS Med. Chem. Lett.*, 8: 61-66 (2017). cited by applicant
Yan, et al., "Pharmacogenetics and pharmacogenomics in oncology therapeutic antibody development," *BioTechniques*, 29(4): 565-568 (2005). cited by applicant
Yang, et al., "Akt/Protein Kinase B Signaling Inhibitor-2, a Selective Small Molecule Inhibitor of Akt Signaling with Antitumor Activity in Cancer Cells Overexpressing Akt," *Cancer Res.*, 64, 4394-4399 (2004). cited by applicant
Yang, et al., "Eradication of Established Tumors by a Fully Human Monoclonal Antibody to the Epidermal Growth Factor Receptor without Concomitant Chemotherapy," *Cancer Res.*, 59: 1236-1243 (1999). cited by applicant
Zeng, et al., "Potent and Selective Covalent Quinazoline Inhibitors of KRAS G12C," *Cell Chemical Biology*, 24: 1-12 (2017). cited by applicant
Zhang, et al., Development of a Commercial manufacturing Process for Sotorasib a First-in-Class KRAS G12C Inhibitor, *Org. Process Res. Dev.* 26:3115-3125 (2002). cited by applicant
Zimmerman, et al., "Small molecule inhibition of the KRAS-PDE δ interaction impairs oncogenic KRAS signaling," *Nature*, 1-5 (2017). cited by applicant
Restriction Requirement, mailed Sep. 29, 2024 for U.S. Appl. No. 17/689,741, 9 pages. cited by applicant
Restriction Requirement, mailed Feb. 24, 2025 for U.S. Appl. No. 18/987,607, 7 pages. cited by applicant
Non-Final Office Action for U.S. Appl. No. 17/689,741, mailed Apr. 1, 2025, 7 pages. cited by applicant

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Background/Summary

CROSS-REFERENCE TO RELATED APPLICATIONS (1) This application is a divisional of U.S. patent application Ser. No. 17/689,741, filed Mar. 8, 2022, which is a continuation of U.S. patent application Ser. No. 16/685,841, filed on Nov. 15, 2019, which claims the benefit of priority to U.S. Provisional Application No. 62/768,802, filed Nov. 16, 2018. Each of the foregoing applications is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

(1) The present invention relates to an improved, efficient, scalable process to prepare intermediate compounds, such as compound 5M, having the structure

(2) ##STR00003##

useful for the synthesis of compounds that inhibit KRAS G12C mutations.

BACKGROUND

(3) KRAS gene mutations are common in pancreatic cancer, lung adenocarcinoma, colorectal cancer, gall bladder cancer, thyroid cancer, and bile duct cancer. KRAS mutations are also observed

in about 25% of patients with NSCLC, and some studies have indicated that KRAS mutations are a negative prognostic factor in patients with NSCLC. Recently, V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations have been found to confer resistance to epidermal growth factor receptor (EGFR) targeted therapies in colorectal cancer; accordingly, the mutational status of KRAS can provide important information prior to the prescription of TKI therapy. Taken together, there is a need for new medical treatments for patients with pancreatic cancer, lung adenocarcinoma, or colorectal cancer, especially those who have been diagnosed to have such cancers characterized by a KRAS mutation, and including those who have progressed after chemotherapy.

Description

BRIEF DESCRIPTION OF THE FIGURES

- (1) FIG. 1 shows the crystal arrangement of composition 4a.
- (2) FIG. 2-1 shows XRPD overlay of Dione racemate Type A-E.
- (3) FIG. 2-2 shows XRPD overlay of (1S)-(-)-camphanic acid cocrystal.
- (4) FIG. 2-3 shows XRPD overlay of (+)-2,3-dibenzoyl-D-tartaric acid cocrystal.
- (5) FIG. 2-4 shows XRPD overlay of D-(+)-malic acid cocrystal.
- (6) FIG. 2-5 shows XRPD overlay of M-Dione cocrystal at different temperatures.
- (7) FIG. 2-6 shows XRPD overlay of P-Dione cocrystal at different temperatures.
- (8) FIG. 2-7 shows XRPD overlay of M-Dione cocrystal and P-Dione cocrystal mixture at different temperatures.
- (9) FIG. 2-8 shows XRPD Overlay of Dione racemate at different temperatures (I/II).
- (10) FIG. 2-9 shows XRPD overlay of Dione racemate at different temperatures (II/II).
- (11) FIG. 2-10 shows Ternary Phase Diagram of M/P-Dione cocrystals.
- (12) FIG. 2-11 shows Ternary phase diagram of M/P-Dione.
- (13) FIG. 3-1 shows XRPD of Dione racemate Type A.
- (14) FIG. 3-2 shows TGA/DSC overlay of Dione racemate Type A.
- (15) FIG. 3-3 shows ¹H NMR spectrum of Dione racemate Type A.
- (16) FIG. 3-4 shows PLM image of Dione racemate Type A.
- (17) FIG. 3-5 shows XRPD of Dione racemate Type B.
- (18) FIG. 3-6 shows TGA/DSC overlay of Dione racemate Type B.
- (19) FIG. 3-7 shows ¹H NMR spectrum of Dione racemate Type B.
- (20) FIG. 3-8 shows XRPD of Dione racemate Type C.
- (21) FIG. 3-9 shows TGA/DSC overlay of Dione racemate Type C.
- (22) FIG. 3-10 shows ¹H NMR spectrum of Dione racemate Type C.
- (23) FIG. 3-11 shows XRPD of Dione racemate Type D.
- (24) FIG. 3-12 shows TGA/DSC overlay of Dione racemate Type D.
- (25) FIG. 3-13 shows ¹H NMR spectrum of Dione racemate Type D.
- (26) FIG. 3-14 shows XRPD of Dione racemate Type E.
- (27) FIG. 3-15 shows TGA/DSC overlay of Dione racemate Type E.
- (28) FIG. 3-16 shows ¹H NMR spectrum of Dione racemate Type E.
- (29) FIG. 3-17 shows XRPD of M-Dione cocrystal Type A.
- (30) FIG. 3-18 shows TGA/DSC overlay of M-Dione cocrystal Type A.
- (31) FIG. 3-19 shows ¹H NMR spectrum of M-Dione cocrystal Type A.
- (32) FIG. 3-20 shows XRPD of P-Dione cocrystal Type A.
- (33) FIG. 3-21 shows TGA/DSC overlay of P-Dione cocrystal Type A.
- (34) FIG. 3-22 shows ¹H NMR spectrum of P-Dione cocrystal Type A.
- (35) FIG. 3-23 shows XRPD overlay of Dione racemate forms.

- (36) FIG. 3-24 shows XRPD of competitive slurry samples.
- (37) FIG. 3-25 shows XRPD overlay of prepared P-Dione cocrystal.
- (38) FIG. 3-26 shows ¹H NMR spectrum overlay of M/P-Dione cocrystals.
- (39) FIG. 3-27 shows XRPD overlay of prepared P-Dione cocrystal.
- (40) FIG. 4-1 shows Inter-conversion diagram of M-Dione DBTA Cocrystal crystal forms.
- (41) FIG. 5-1 shows XRPD overlay of M-dione DBTA cocrystal crystal forms (Type A~E).
- (42) FIG. 5-2 shows XRPD overlay of M-dione DBTA cocrystal crystal forms (Type F~K).
- (43) FIG. 5-3 shows XRPD overlay of M-dione DBTA cocrystal crystal forms (Type L~Q).
- (44) FIG. 5-4 shows XRPD pattern of Type A.
- (45) FIG. 5-5 shows TGA/DSC curves of Type A.
- (46) FIG. 5-6 shows ¹H NMR of Type A.
- (47) FIG. 5-7 shows XRPD overlay of Type B.
- (48) FIG. 5-8 shows TGA/DSC curves of Type B.
- (49) FIG. 5-9 shows ¹H NMR of Type B.
- (50) FIG. 5-10 shows XRPD pattern of Type C.
- (51) FIG. 5-11 shows TGA/DSC curves of Type C.
- (52) FIG. 5-12 shows ¹H NMR of Type C.
- (53) FIG. 5-13 shows XRPD pattern of Type D.
- (54) FIG. 5-14 shows TGA/DSC curves of Type D.
- (55) FIG. 5-15 shows ¹H NMR of Type D.
- (56) FIG. 5-16 shows XRPD pattern of Type E.
- (57) FIG. 5-17 shows TGA/DSC curves of Type E.
- (58) FIG. 5-18 shows ¹H NMR of Type E.
- (59) FIG. 5-19 shows XRPD pattern of Type F.
- (60) FIG. 5-20 shows TGA/DSC curves of Type F.
- (61) FIG. 5-21 shows ¹H NMR of Type F.
- (62) FIG. 5-22 shows XRPD pattern of Type G.
- (63) FIG. 5-23 shows TGA/DSC curves of Type G.
- (64) FIG. 5-24 shows ¹H NMR of Type G.
- (65) FIG. 5-25 shows XRPD pattern of Type H.
- (66) FIG. 5-26 shows TGA/DSC curves of Type H.
- (67) FIG. 5-27 shows ¹H NMR of Type H.
- (68) FIG. 5-28 shows XRPD pattern of Type I.
- (69) FIG. 5-29 shows TGA/DSC curves of Type I.
- (70) FIG. 5-30 shows ¹H NMR of Type I.
- (71) FIG. 5-31 shows XRPD pattern of Type J.
- (72) FIG. 5-32 shows TGA/DSC curves of Type J.
- (73) FIG. 5-33 shows ¹H NMR of Type J.
- (74) FIG. 5-34 shows XRPD pattern of Type K.
- (75) FIG. 5-35 shows TGA/DSC curves of Type K.
- (76) FIG. 5-36 shows ¹H NMR of Type K.
- (77) FIG. 5-37 shows XRPD pattern of Type L.
- (78) FIG. 5-38 shows TGA/DSC curves of Type L.
- (79) FIG. 5-39 shows ¹H NMR of Type L.
- (80) FIG. 5-40 shows XRPD pattern of Type M.
- (81) FIG. 5-41 shows TGA/DSC curves of Type M.
- (82) FIG. 5-42 shows ¹H NMR of Type M.
- (83) FIG. 5-43 shows XRPD pattern of Type N.
- (84) FIG. 5-44 shows TGA/DSC curves of Type N.
- (85) FIG. 5-45 shows ¹H NMR of Type N.

- (86) FIG. 5-46 shows XRPD pattern of Type O.
(87) FIG. 5-47 shows TGA/DSC curves of Type O.
(88) FIG. 5-48 shows ¹H NMR of Type O.
(89) FIG. 5-49 shows XRPD pattern of Type P.
(90) FIG. 5-50 shows TGA/DSC curves of Type P.
(91) FIG. 5-51 shows ¹H NMR of Type P.
(92) FIG. 5-52 shows XRPD pattern of Type Q.
(93) FIG. 5-53 shows TGA/DSC curves of Type Q.
(94) FIG. 5-54 shows ¹H NMR of Type Q.
(95) FIG. 6-1 shows HPLC of M-5 from resolution with 1,3-diphenyl-3-oxopropanesulfonic acid.
(96) FIG. 6-2 shows HPLC of 5 (P-atropisomer excess) from resolution with 1,3-diphenyl-3-oxopropanesulfonic acid.

SUMMARY

(97) The present invention relates to improved preparation of a compound having the following chemical structure:

(98) ##STR00004##

and key intermediates thereof, i.e., compositions and compounds comprising the following chemical structures:

(99) ##STR00005##

(100) The present invention additional relates to a method of preparing Compound 5M having the following chemical structure

(101) ##STR00006##

(102) The present invention additional relates to a composition comprising a structure

(103) ##STR00007##

DETAILED DESCRIPTION

Definitions

(104) Abbreviations: The following abbreviations may be used herein:

(105) TABLE-US-00001 ACN Acetonitrile AcOH acetic acid aq or aq. Aqueous BOC or Boc tert-butyloxy carbonyl BuOH n-butanol BuOAc Butanol acetate cpme cyclopentyl methyl ether CHCl₃ Trichloromethane DCE 1,2-dichloroethane DABCO 1,4-diazabicyclo[2.2.2]octane DCM Dichloromethane DMA N,N-Dimethylacetamide DMAP 4-dimethylaminopyridine DME 1,2-dimethoxy ethane DMF N,N-dimethylformamide DMSO dimethyl sulfoxide Dppf, DPPF or dppf 1,1'-bis(diphenylphosphino)ferrocene eq or eq. or equiv. Equivalent ESI or ES electrospray ionization Et Ethyl Et₂O diethyl ether EtOAc ethyl acetate EtOH ethanol g Grams h Hour H₂O water HPLC high pressure liquid chromatography iPr Isopropyl IPA Isopropyl alcohol IPAc Isopropyl acetate iPr₂NEt or DIPEA N-ethyl diisopropylamine (Hünig's base) KHMDs potassium hexamethyldisilazide KOAc potassium acetate LDA Lithium diisopropylamide Lawesson's reagent 2,4-bis(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4- dithiadiphosphetane, 2,4-Bis-(4-methoxyphenyl)- 1,3-dithia-2,4-diphosphetane 2,4-disulfide LC MS, LCMS, liquid chromatography mass spectroscopy LC-MS or LC/MS LG Leaving group (e.g., halogen, mesylate, triflate) LHMDs or LiHMDs lithium hexamethyldisilazide m/z mass divided by charge Me Methyl MeCN Acetonitrile MeOH Methanol Met Metal species for cross-coupling (e.g., MgX, ZnX, SnR₃, SiR₃, B(OR)₂) 2-MeTHF 2-Methyltetrahydrofuran mg Milligrams min Minutes MIBK 4-Methyl-2-pentanone mL Milliliters MS mass spectra MTBE Methyl tert-butyl ether n-BuLi n-butyl Lithium NaHMDs sodium hexamethyldisilazide NBS N-bromosuccinimide NCS N-chlorosuccinimide NMR nuclear magnetic resonance Pd₂(dba)₃ tris(dibenzylideneacetone)dipalladium(0) Pd(dppf)Cl₂•DCM [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane Pd(PPh₃)₄ Tetrakis(triphenylphosphine)palladium(0) Ph Phenyl PR or PG or protecting group Prot. group rbf round-bottom flask RP-HPLC reverse phase high pressure liquid

chromatography RT or rt room temperature sat. or satd. saturated SFC supercritical fluid chromatography SPhos Pd G3 or (2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl) SPhos G3 [2-(2'-amino-1, 1'-biphenyl)]palladium(II) methanesulfonate TBAF tetra-n-butylammonium fluoride TBTU N,N,N',N'-Tetramethyl-O-(benzotriazol-1-yl)uronium tetrafluoroborate t-BuOH tert-butanol TEA or Et.sub.3N Trimethylamine TFA trifluoroacetic acid THF Tetrahydrofuran UV Ultraviolet XRPD X-Ray Powder Diffraction

(106) The use of the terms “a,” “an,” “the,” and similar referents in the context of describing the invention (especially in the context of the claims) are to be construed to cover both the singular and the plural, unless otherwise indicated. Recitation of ranges of values herein merely are intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. The use of any and all examples, or exemplary language (e.g., “such as”) provided herein, is intended to better illustrate the invention and is not a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

(107) As used herein, the term “alkyl” refers to straight chained and branched C.sub.1-C.sub.8 hydrocarbon groups, including but not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, sec-butyl, t-butyl, n-pentyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, and 2-ethylbutyl. The term C.sub.m-n means the alkyl group has “m” to “n” carbon atoms. The term “alkylene” refers to an alkyl group having a substituent. An alkyl (e.g., methyl), or alkylene (e.g., —CH.sub.2—), group can be substituted with one or more, and typically one to three, of independently selected, for example, halo, trifluoromethyl, trifluoromethoxy, hydroxy, alkoxy, nitro, cyano, alkylamino, C.sub.1-8alkyl, C.sub.2-8alkenyl, C.sub.2-8alkynyl, —NC, amino, —CO.sub.2H, —CO.sub.2C.sub.1-C.sub.8alkyl, —OCOC.sub.1-C.sub.8alkyl, C.sub.3-C.sub.10 cycloalkyl, C.sub.3-C.sub.10 heterocycloalkyl, C.sub.5-C.sub.10aryl, and C.sub.5-C.sub.10 heteroaryl. The term “haloalkyl” specifically refers to an alkyl group wherein at least one, e.g., one to six, or all of the hydrogens of the alkyl group are substituted with halo atoms.

(108) The terms “alkenyl” and “alkynyl” indicate an alkyl group that further includes a double bond or a triple bond, respectively.

(109) As used herein, the term “halo” refers to fluoro, chloro, bromo, and iodo. The term “alkoxy” is defined as —OR, wherein R is alkyl.

(110) As used herein, the term “amino” or “amine” interchangeably refers to a —NR.sub.2 group, wherein each R is, e.g., H or a substituent. In some embodiments, the amino group is further substituted to form an ammonium ion, e.g., NR.sub.3.sup.+. Ammonium moieties are specifically included in the definition of “amino” or “amine.” Substituents can be, for example, an alkyl, alkoxy, cycloalkyl, heterocycloalkyl, amide, or carboxylate. An R group may be further substituted, for example, with one or more, e.g., one to four, groups selected from halo, cyano, alkenyl, alkynyl, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, urea, carbonyl, carboxylate, amine, and amide. An “amide” or “amido” group interchangeably refers to a group similar to an amine or amino group but further including a C(O), e.g., —C(O) NR.sub.2.

(111) As used herein, the term “aryl” refers to a C.sub.6-14 monocyclic or polycyclic aromatic group, preferably a C.sub.6-10 monocyclic or bicyclic aromatic group, or C.sub.10-14 polycyclic aromatic group. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, fluorenyl, azulenyl, anthryl, phenanthryl, pyrenyl, biphenyl, and terphenyl. Aryl also refers to C.sub.10-14 bicyclic and tricyclic carbon rings, where one ring is aromatic and the others are saturated, partially unsaturated, or aromatic, for example, dihydronaphthyl, indenyl, indanyl, or tetrahydronaphthyl (tetralinyl). Unless otherwise indicated, an aryl group can be unsubstituted or substituted with one or more, and in particular one to four, groups independently selected from, for

example, halo, C.sub.1-8alkyl, C.sub.2-8alkenyl, C.sub.2-8alkynyl, —CF.sub.3, —OCF.sub.3, —NO.sub.2, —CN, —NC, —OH, alkoxy, amino, —CO.sub.2H, —CO.sub.2C.sub.1-C.sub.8alkyl, —OCOC.sub.1-C.sub.8alkyl, C.sub.3-C.sub.10 cycloalkyl, C.sub.3-C.sub.10 heterocycloalkyl, C.sub.5-C.sub.10aryl, and C.sub.5-C.sub.10 heteroaryl.

(112) As used herein, the term “cycloalkyl” refers to a monocyclic or polycyclic non-aromatic carbocyclic ring, where the polycyclic ring can be fused, bridged, or spiro. The carbocyclic ring can have 3 to 10 carbon ring atoms. Contemplated carbocyclic rings include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and cyclononyl.

(113) As used herein, the term “heterocycloalkyl” means a monocyclic or polycyclic (e.g., bicyclic), saturated or partially unsaturated, ring system containing 3 or more (e.g., 3 to 12, 4 to 10, 4 to 8, or 5 to 7) total atoms, of which one to five (e.g., 1, 2, 3, 4, or 5) of the atoms are independently selected from nitrogen, oxygen, and sulfur. Nonlimiting examples of heterocycloalkyl groups are pyrrolidinyl, piperidinyl, piperazinyl, dihydropyrrolyl, morpholinyl, thiomorpholinyl, dihydropyridinyl, oxacycloheptyl, dioxacycloheptyl, thiacycloheptyl, and diazacycloheptyl.

(114) Unless otherwise indicated, a cycloalkyl or heterocycloalkyl group can be unsubstituted or substituted with one or more, and in particular one to four, groups. Some contemplated substituents include halo, C.sub.1-8alkyl, C.sub.2-8alkenyl, C.sub.2-8alkynyl, —OCF.sub.3, —NO.sub.2, —CN, —NC, —OH, alkoxy, amino, —CO.sub.2H, —CO.sub.2C.sub.1-C.sub.8alkyl, —OCOC.sub.1-C.sub.8alkyl, C.sub.3-C.sub.10 cycloalkyl, C.sub.3-C.sub.10 heterocycloalkyl, C.sub.5-C.sub.10aryl, and C.sub.5-C.sub.10 heteroaryl.

(115) As used herein, the term “heteroaryl” refers to a monocyclic or polycyclic ring system (for example, bicyclic) containing one to three aromatic rings and containing one to four (e.g., 1, 2, 3, or 4) heteroatoms selected from nitrogen, oxygen, and sulfur in an aromatic ring. In certain embodiments, the heteroaryl group has from 5 to 20, from 5 to 15, from 5 to 10 ring, or from 5 to 7 atoms. Heteroaryl also refers to C.sub.10-14 bicyclic and tricyclic rings, where one ring is aromatic and the others are saturated, partially unsaturated, or aromatic. Examples of heteroaryl groups include, but are not limited to, furanyl, imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, thiadiazolyl, thiazolyl, thienyl, tetrazolyl, triazinyl, triazolyl, benzofuranyl, benzimidazolyl, benzoisoxazolyl, benzopyranyl, benzothiadiazolyl, benzothiazolyl, benzothienyl, benzothiophenyl, benzotriazolyl, benzoxazolyl, furopyridyl, imidazopyridinyl, imidazothiazolyl, indolizinyl, indolyl, indazolyl, isobenzofuranyl, isobenzothienyl, isoindolyl, isoquinolinyl, isothiazolyl, naphthyridinyl, oxazolopyridinyl, phthalazinyl, pteridinyl, purinyl, pyridopyridyl, pyrrolopyridyl, quinolinyl, quinoxalinyl, quiazolinyl, thiadiazolopyrimidyl, and thienopyridyl. Unless otherwise indicated, a heteroaryl group can be unsubstituted or substituted with one or more, and in particular one to four or one or two, substituents. Contemplated substituents include halo, C.sub.1-8alkyl, C.sub.2-8alkenyl, C.sub.2-8alkynyl, —OCF.sub.3, —NO.sub.2, —CN, —NC, —OH, alkoxy, amino, —CO.sub.2H, —CO.sub.2C.sub.1-C.sub.8alkyl, —OCOC.sub.1-C.sub.8alkyl, C.sub.3-C.sub.10 cycloalkyl, C.sub.3-C.sub.10 heterocycloalkyl, C.sub.5-C.sub.10aryl, and C.sub.5-C.sub.10 heteroaryl.

(116) As used herein, the term Boc refers to the structure

(117) ##STR00008##

EMBODIMENTS

Embodiment 1

(118) In one embodiment of the invention, the present invention comprises a composition, the composition comprising a compound of Formula 4:

(119) ##STR00009##

and a compound of Formula B:

(120) ##STR00010##

Embodiment 2

(121) In another embodiment of the present invention, the present invention comprises the composition of embodiment 1, wherein the compound of Formula 4 is a compound of Formula 5M:

(122) ##STR00011##

Embodiment 3

(123) In another embodiment of the present invention, the present invention comprises the composition of embodiment 1, wherein the compound of Formula 4 is a compound of Formula 5P:

(124) ##STR00012##

Embodiment 4

(125) In another embodiment of the present invention, the present invention comprises the composition of any one of embodiments 1-3, wherein the compound of Formula B is a compound of formula B1:

(126) ##STR00013##

Embodiment 5

(127) In another embodiment of the present invention, the present invention comprises the composition of any one of embodiments 1-3, wherein the compound of Formula B is a compound of formula B2:

(128) ##STR00014##

Embodiment 6

(129) In another embodiment of the present invention, the present invention comprises the composition of any one of embodiments 1-5, wherein the composition comprises a 2 to 1 ratio of the compound of Formula 4 to the compound of Formula B.

Embodiment 7

(130) In another embodiment of the present invention, the present invention comprises the composition of any one of embodiments 1-6, wherein the composition further comprises 2-methyltetrahydrofuran having the formula:

(131) ##STR00015##

Embodiment 8

(132) In another embodiment of the present invention, the present invention comprises the composition of any one of embodiments 1-7, wherein the ratio of the 2-methyltetrahydrofuran to the compound of formula B is 2 to 1.

Embodiment 9

(133) In another embodiment of the present invention, the present invention comprises the composition of embodiment 1, wherein the composition has the formula:

(134) ##STR00016##

Embodiment 10

(135) In another embodiment of the present invention, the present invention comprises the composition of embodiment 9, wherein the composition has the formula:

(136) ##STR00017##

Embodiment 11

(137) In another embodiment of the present invention, the present invention comprises the composition of embodiment 9, wherein the composition has the formula:

(138) ##STR00018##

Embodiment 12

(139) In another embodiment of the present invention, the present invention comprises the composition of embodiment 9, wherein the composition has the formula:

(140) ##STR00019##

Embodiment 13

(141) In another embodiment of the present invention, the present invention comprises the composition of embodiment 9, wherein the composition has the formula:

(142) ##STR00020##

Embodiment 14

(143) In another embodiment of the present invention, the present invention comprises the composition of any one of embodiments 1-13, wherein the composition is in a crystalline state.

Embodiment 15

(144) In another embodiment of the present invention, the present invention comprises a method of making a composition of formula 4a, the method comprising reacting a compound 4, having the following chemical structure:

(145) ##STR00021##

with a compound B1, having the formula:

(146) ##STR00022##

in the presence of 2-methyltetrahydrofuran to form the composition of formula 4a, having the structure:

(147) ##STR00023##

Embodiment 16

(148) In another embodiment of the present invention, the present invention comprises a method of obtaining a compound of formula 5M, having the following chemical structure:

(149) ##STR00024## the method comprising: a) reacting a compound 4, having the following chemical structure:

(150) ##STR00025##

with a compound B1, having the formula:

(151) ##STR00026##

in the presence of 2-methyltetrahydrofuran to form a composition of formula 4a, having the structure:

(152) ##STR00027##

as crystals; b) isolating composition 4a, and c) treating the isolated composition 4a with a base to produce the compound of formula 5M.

Embodiment 17

(153) In another embodiment of the present invention, the present invention comprises the method according to Embodiment 16, wherein the base is Na.sub.2HPO.sub.4.

Embodiment 18

(154) In another embodiment of the present invention, the present invention comprises the method according to Embodiment 16, wherein the base is NaHCO.sub.3.

Embodiment 19

(155) In another embodiment of the present invention, the present invention comprises the composition, the composition comprising a compound of Formula 4:

(156) ##STR00028##

and a compound of Formula 11:

(157) ##STR00029##

Embodiment 20

(158) In another embodiment of the present invention, the present invention comprises the composition of embodiment 19, wherein the compound of Formula 4 is a compound of Formula 5M:

(159) ##STR00030##

Embodiment 21

(160) In another embodiment of the present invention, the present invention comprises the composition of embodiment 19, wherein the compound of Formula 4 is a compound of Formula 5P:

(161) ##STR00031##

Embodiment 22

(162) In another embodiment of the present invention, the present invention comprises the

composition of any one of embodiments 19-21, wherein the compound of Formula 11 is a compound of formula 11a:

(163) ##STR00032##

Embodiment 23

(164) In another embodiment of the present invention, the present invention comprises the composition of any one of embodiments 19-21, wherein the compound of Formula 11 is a compound of formula 11b:

(165) ##STR00033##

Embodiment 24

(166) In another embodiment of the present invention, the present invention comprises the composition of embodiment 19, wherein the composition has the formula:

(167) ##STR00034##

Embodiment 25

(168) In another embodiment of the present invention, the present invention comprises the composition of embodiment 19, wherein the composition has the formula:

(169) ##STR00035##

Embodiment 26

(170) In another embodiment of the present invention, the present invention comprises the composition of embodiment 19, wherein the composition has the formula:

(171) ##STR00036##

Embodiment 27

(172) In another embodiment of the present invention, the present invention comprises the composition of embodiment 19, wherein the composition has the formula:

(173) ##STR00037##

Embodiment 28

(174) In another embodiment of the present invention, the present invention comprises the composition of any one of embodiments 19-27, wherein the composition comprises a 1 to 1 ratio of the compound of Formula 4 to the compound of Formula 11.

Embodiment 29

(175) In another embodiment of the present invention, the present invention comprises the method of embodiment 16, wherein the compound of formula 5M is used as an intermediate to generate a compound having the Formula 9:

(176) ##STR00038##

Embodiment 30

(177) The method of embodiment 29, wherein the method further comprises mixing the compound of Formula 9 with at least one pharmaceutically acceptable excipient to form a pharmaceutical composition.

Compounds of the Disclosure

(178) Provided herein are KRAS inhibitors having structures discussed in more detail below.

(179) The compounds disclosed herein include all pharmaceutically acceptable isotopically-labeled compounds wherein one or more atoms of the compounds disclosed herein are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ²H, ³H, ¹¹C, ¹³C, ¹⁴C, ¹³N, ¹⁵N, ¹⁵O, ¹⁷O, ¹⁸O, ³¹P, ³²P, ³⁵S, ¹⁸F, ³⁶Cl, ¹²³I, and ¹²⁵I, respectively. These radiolabelled compounds could be useful to help determine or measure the effectiveness of the compounds, by characterizing, for example, the site or mode of action, or binding affinity to pharmacologically important site of action. Certain isotopically-labeled compounds of the disclosure, for example, those incorporating a radioactive

isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. ^3H , and carbon-14, i.e. ^{14}C , are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

(180) Substitution with heavier isotopes such as deuterium, i.e. ^2H , may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements, and hence are preferred in some circumstances.

(181) Substitution with positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds of structure (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the Preparations and Examples as set out below using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

(182) Isotopically-labeled compounds as disclosed herein can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying examples and schemes using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

(183) Certain of the compounds as disclosed herein may exist as stereoisomers (i.e., isomers that differ only in the spatial arrangement of atoms) including optical isomers and conformational isomers (or conformers). The compounds disclosed herein include all stereoisomers, both as pure individual stereoisomer preparations and enriched preparations of each, and both the racemic mixtures of such stereoisomers as well as the individual diastereomers and enantiomers that may be separated according to methods that are known to those skilled in the art. Additionally, the compounds disclosed herein include all tautomeric forms of the compounds.

(184) Certain of the compounds disclosed herein may exist as atropisomers, which are conformational stereoisomers that occur when rotation about a single bond in the molecule is prevented, or greatly slowed, as a result of steric interactions with other parts of the molecule. The compounds disclosed herein include all atropisomers, both as pure individual atropisomer preparations, enriched preparations of each, or a non-specific mixture of each. Where the rotational barrier about the single bond is high enough, and interconversion between conformations is slow enough, separation and isolation of the isomeric species may be permitted. For example, groups such as, but not limited to, the following groups

(185) ##STR00039##

may exhibit restricted rotation.

(186) The term “monohydrate” means a salt of Compound 9 having about one associated water molecule. Those skilled in the art appreciate that the exact number of the associated water molecules may vary slightly at any time with variable temperature, pressure, and other environmental influence. All slight variations of the number of the associated water molecules are contemplated to be within the scope of the present invention.

(187) The term “dihydrate” means a salt of Compound 9 having about two associated water molecules. Those skilled in the art appreciate that the exact number of the associated water molecules may vary slightly at any time with variable temperature, pressure, and other environmental influence. All slight variations of the number of the associated water molecules are contemplated to be within the scope of the present invention.

(188) The term “co-crystal” means a crystalline material comprising two or more compounds at ambient temperature (20°C ., to 25°C ., preferably 20°C .), of which at least two are held together by weak interaction, wherein at least one of the compounds is a co-crystal former and the other is Compound 5. Weak interaction is being defined as an interaction which is neither ionic nor covalent and includes for example: hydrogen bonds, van der Waals forces, and π - π interactions.

(189) The term “amorphous form” or “amorphous” means a material that lacks long range order and as such does not show distinct X-ray diffraction peaks, i.e. a Bragg diffraction peak. The

XRPD pattern of an amorphous material is characterized by one or more amorphous halos.

(190) The term “amorphous halo” is an approximately bell-shaped maximum in the X-ray powder pattern of an amorphous substance.

(191) The term “substantially pure” refers to a solid form of Compound 9 having purity greater than about 95%, specifically greater than about 99.5%, more specifically greater than about 99.8% and still more specifically greater than about 99.9%.

(192) The term “patient” means animals, such as dogs, cats, cows, horses, sheep and humans. Particular patients are mammals. The term patient includes males and females.

(193) The terms “treating”, “treat” or “treatment” and the like include preventative (e.g., prophylactic) and palliative treatment.

(194) The term “excipient” means any pharmaceutically acceptable additive, carrier, diluent, adjuvant, or other ingredient, other than the active pharmaceutical ingredient (API), which is typically included for formulation and/or administration to a patient.

(195) Pharmaceutical Compositions, Dosing, and Routes of Administration

(196) Also provided herein are pharmaceutical compositions that include a compound as disclosed herein, together with a pharmaceutically acceptable excipient, such as, for example, a diluent or carrier. Compounds and pharmaceutical compositions suitable for use in the present invention include those wherein the compound can be administered in an effective amount to achieve its intended purpose. Administration of the compound described in more detail below.

(197) Suitable pharmaceutical formulations can be determined by the skilled artisan depending on the route of administration and the desired dosage. See, e.g., Remington's Pharmaceutical Sciences, 1435-712 (18th ed., Mack Publishing Co, Easton, Pennsylvania, 1990). Formulations may influence the physical state, stability, rate of in vivo release and rate of in vivo clearance of the administered agents. Depending on the route of administration, a suitable dose may be calculated according to body weight, body surface areas or organ size. Further refinement of the calculations necessary to determine the appropriate treatment dose is routinely made by those of ordinary skill in the art without undue experimentation, especially in light of the dosage information and assays disclosed herein as well as the pharmacokinetic data obtainable through animal or human clinical trials.

(198) The phrases “pharmaceutically acceptable” or “pharmacologically acceptable” refer to molecular entities and compositions that do not produce adverse, allergic, or other untoward reactions when administered to an animal or a human. As used herein, “pharmaceutically acceptable” includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such excipients for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the therapeutic compositions, its use in therapeutic compositions is contemplated. Supplementary active ingredients also can be incorporated into the compositions. In exemplary embodiments, the formulation may comprise corn syrup solids, high-oleic safflower oil, coconut oil, soy oil, L-leucine, calcium phosphate tribasic, L-tyrosine, L-proline, L-lysine acetate, DATEM (an emulsifier), L-glutamine, L-valine, potassium phosphate dibasic, L-isoleucine, L-arginine, L-alanine, glycine, L-asparagine monohydrate, L-serine, potassium citrate, L-threonine, sodium citrate, magnesium chloride, L-histidine, L-methionine, ascorbic acid, calcium carbonate, L-glutamic acid, L-cystine dihydrochloride, L-tryptophan, L-aspartic acid, choline chloride, taurine, m-inositol, ferrous sulfate, ascorbyl palmitate, zinc sulfate, L-carnitine, alpha-tocopheryl acetate, sodium chloride, niacinamide, mixed tocopherols, calcium pantothenate, cupric sulfate, thiamine chloride hydrochloride, vitamin A palmitate, manganese sulfate, riboflavin, pyridoxine hydrochloride, folic acid, beta-carotene, potassium iodide, phylloquinone, biotin, sodium selenate, chromium chloride, sodium molybdate, vitamin D3 and cyanocobalamin.

(199) The compound can be present in a pharmaceutical composition as a pharmaceutically

acceptable salt. As used herein, "pharmaceutically acceptable salts" include, for example base addition salts and acid addition salts.

(200) Pharmaceutically acceptable base addition salts may be formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Pharmaceutically acceptable salts of compounds may also be prepared with a pharmaceutically acceptable cation. Suitable pharmaceutically acceptable cations are well known to those skilled in the art and include alkaline, alkaline earth, ammonium and quaternary ammonium cations. Carbonates or hydrogen carbonates are also possible. Examples of metals used as cations are sodium, potassium, magnesium, ammonium, calcium, or ferric, and the like. Examples of suitable amines include isopropylamine, trimethylamine, histidine, N,N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine.

(201) Pharmaceutically acceptable acid addition salts include inorganic or organic acid salts. Examples of suitable acid salts include the hydrochlorides, formates, acetates, citrates, salicylates, nitrates, phosphates. Other suitable pharmaceutically acceptable salts are well known to those skilled in the art and include, for example, formic, acetic, citric, oxalic, tartaric, or mandelic acids, hydrochloric acid, hydrobromic acid, sulfuric acid or phosphoric acid; with organic carboxylic, sulfonic, sulfo or phospho acids or N-substituted sulfamic acids, for example acetic acid, trifluoroacetic acid (TFA), propionic acid, glycolic acid, succinic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, fumaric acid, malic acid, tartaric acid, lactic acid, oxalic acid, gluconic acid, glucaric acid, glucuronic acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, salicylic acid, 4-aminosalicylic acid, 2-phenoxy benzoic acid, 2-acetoxy benzoic acid, embonic acid, nicotinic acid or isonicotinic acid; and with amino acids, such as the 20 alpha amino acids involved in the synthesis of proteins in nature, for example glutamic acid or aspartic acid, and also with phenylacetic acid, methanesulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, ethane 1,2-disulfonic acid, benzenesulfonic acid, 4-methylbenzenesulfonic acid, naphthalene 2-sulfonic acid, naphthalene 1,5-disulfonic acid, 2- or 3-phosphoglycerate, glucose 6-phosphate, N-cyclohexylsulfamic acid (with the formation of cyclamates), or with other acid organic compounds, such as ascorbic acid.

(202) Pharmaceutical compositions containing the compounds disclosed herein can be manufactured in a conventional manner, e.g., by conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes. Proper formulation is dependent upon the route of administration chosen.

(203) For oral administration, suitable compositions can be formulated readily by combining a compound disclosed herein with pharmaceutically acceptable excipients such as carriers well known in the art. Such excipients and carriers enable the present compounds to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by adding a compound as disclosed herein with a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include, for example, fillers and cellulose preparations. If desired, disintegrating agents can be added. Pharmaceutically acceptable ingredients are well known for the various types of formulation and may be for example binders (e.g., natural or synthetic polymers), lubricants, surfactants, sweetening and flavoring agents, coating materials, preservatives, dyes, thickeners, adjuvants, antimicrobial agents, antioxidants and carriers for the various formulation types.

(204) When a therapeutically effective amount of a compound disclosed herein is administered orally, the composition typically is in the form of a solid (e.g., tablet, capsule, pill, powder, or troche) or a liquid formulation (e.g., aqueous suspension, solution, elixir, or syrup).

(205) When administered in tablet form, the composition can additionally contain a functional solid and/or solid carrier, such as a gelatin or an adjuvant. The tablet, capsule, and powder can contain

about 1 to about 95% compound, and preferably from about 15 to about 90% compound.

(206) When administered in liquid or suspension form, a functional liquid and/or a liquid carrier such as water, petroleum, or oils of animal or plant origin can be added. The liquid form of the composition can further contain physiological saline solution, sugar alcohol solutions, dextrose or other saccharide solutions, or glycols. When administered in liquid or suspension form, the composition can contain about 0.5 to about 90% by weight of a compound disclosed herein, and preferably about 1 to about 50% of a compound disclosed herein. In one embodiment contemplated, the liquid carrier is non-aqueous or substantially non-aqueous. For administration in liquid form, the composition may be supplied as a rapidly-dissolving solid formulation for dissolution or suspension immediately prior to administration.

(207) When a therapeutically effective amount of a compound disclosed herein is administered by intravenous, cutaneous, or subcutaneous injection, the composition is in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred composition for intravenous, cutaneous, or subcutaneous injection typically contains, in addition to a compound disclosed herein, an isotonic vehicle. Such compositions may be prepared for administration as solutions of free base or pharmacologically acceptable salts in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions also can be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations can optionally contain a preservative to prevent the growth of microorganisms.

(208) Injectable compositions can include sterile aqueous solutions, suspensions, or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions, suspensions, or dispersions. In all embodiments the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must resist the contaminating action of microorganisms, such as bacteria and fungi, by optional inclusion of a preservative. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. In one embodiment contemplated, the carrier is non-aqueous or substantially non-aqueous. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size of the compound in the embodiment of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many embodiments, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

(209) Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the embodiment of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

(210) Slow release or sustained release formulations may also be prepared in order to achieve a controlled release of the active compound in contact with the body fluids in the GI tract, and to provide a substantially constant and effective level of the active compound in the blood plasma. For example, release can be controlled by one or more of dissolution, diffusion, and ion-exchange. In addition, the slow release approach may enhance absorption via saturable or limiting pathways

within the GI tract. For example, the compound may be embedded for this purpose in a polymer matrix of a biological degradable polymer, a water-soluble polymer or a mixture of both, and optionally suitable surfactants. Embedding can mean in this context the incorporation of micro-particles in a matrix of polymers. Controlled release formulations are also obtained through encapsulation of dispersed micro-particles or emulsified micro-droplets via known dispersion or emulsion coating technologies.

(211) For administration by inhalation, compounds of the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant. In the embodiment of a pressurized aerosol, the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, e.g., gelatin, for use in an inhaler or insufflator can be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

(212) The compounds disclosed herein can be formulated for parenteral administration by injection (e.g., by bolus injection or continuous infusion). Formulations for injection can be presented in unit dosage form (e.g., in ampules or in multidose containers), with an added preservative. The compositions can take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing, and/or dispersing agents.

(213) Pharmaceutical formulations for parenteral administration include aqueous solutions of the compounds in water-soluble form. Additionally, suspensions of the compounds can be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils or synthetic fatty acid esters. Aqueous injection suspensions can contain substances which increase the viscosity of the suspension. Optionally, the suspension also can contain suitable stabilizers or agents that increase the solubility of the compounds and allow for the preparation of highly concentrated solutions. Alternatively, a present composition can be in powder form for constitution with a suitable vehicle (e.g., sterile pyrogen-free water) before use.

(214) Compounds disclosed herein also can be formulated in rectal compositions, such as suppositories or retention enemas (e.g., containing conventional suppository bases). In addition to the formulations described previously, the compounds also can be formulated as a depot preparation. Such long-acting formulations can be administered by implantation (e.g., subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds can be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

(215) In particular, a compound disclosed herein can be administered orally, buccally, or sublingually in the form of tablets containing excipients, such as starch or lactose, or in capsules or ovules, either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavoring or coloring agents. Such liquid preparations can be prepared with pharmaceutically acceptable additives, such as suspending agents. A compound also can be injected parenterally, for example, intravenously, intramuscularly, subcutaneously, or intracoronarily. For parenteral administration, the compound is best used in the form of a sterile aqueous solution which can contain other substances, for example, salts, or sugar alcohols, such as mannitol, or glucose, to make the solution isotonic with blood.

(216) For veterinary use, a compound disclosed herein is administered as a suitably acceptable formulation in accordance with normal veterinary practice. The veterinarian can readily determine the dosing regimen and route of administration that is most appropriate for a particular animal.

(217) In some embodiments, all the necessary components for the treatment of KRAS-related disorder using a compound as disclosed herein either alone or in combination with another agent or intervention traditionally used for the treatment of such disease may be packaged into a kit. Specifically, the present invention provides a kit for use in the therapeutic intervention of the

disease comprising a packaged set of medicaments that include the compound disclosed herein as well as buffers and other components for preparing deliverable forms of said medicaments, and/or devices for delivering such medicaments, and/or any agents that are used in combination therapy with the compound disclosed herein, and/or instructions for the treatment of the disease packaged with the medicaments. The instructions may be fixed in any tangible medium, such as printed paper, or a computer readable magnetic or optical medium, or instructions to reference a remote computer data source such as a world wide web page accessible via the internet.

(218) A “therapeutically effective amount” means an amount effective to treat or to prevent development of, or to alleviate the existing symptoms of, the subject being treated. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein. Generally, a “therapeutically effective dose” refers to that amount of the compound that results in achieving the desired effect. For example, in one preferred embodiment, a therapeutically effective amount of a compound disclosed herein decreases KRAS activity by at least 5%, compared to control, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, or at least 90%.

(219) The amount of compound administered can be dependent on the subject being treated, on the subject's age, health, sex, and weight, the kind of concurrent treatment (if any), severity of the affliction, the nature of the effect desired, the manner and frequency of treatment, and the judgment of the prescribing physician. The frequency of dosing also can be dependent on pharmacodynamic effects on arterial oxygen pressures. However, the most preferred dosage can be tailored to the individual subject, as is understood and determinable by one of skill in the art, without undue experimentation. This typically involves adjustment of a standard dose (e.g., reduction of the dose if the patient has a low body weight).

(220) While individual needs vary, determination of optimal ranges of effective amounts of the compound is within the skill of the art. For administration to a human in the curative or prophylactic treatment of the conditions and disorders identified herein, for example, typical dosages of the compounds of the present invention can be about 0.05 mg/kg/day to about 50 mg/kg/day, for example at least 0.05 mg/kg, at least 0.08 mg/kg, at least 0.1 mg/kg, at least 0.2 mg/kg, at least 0.3 mg/kg, at least 0.4 mg/kg, or at least 0.5 mg/kg, and preferably 50 mg/kg or less, 40 mg/kg or less, 30 mg/kg or less, 20 mg/kg or less, or 10 mg/kg or less, which can be about 2.5 mg/day (0.5 mg/kg×5 kg) to about 5000 mg/day (50 mg/kg×100 kg), for example. For example, dosages of the compounds can be about 0.1 mg/kg/day to about 50 mg/kg/day, about 0.05 mg/kg/day to about 10 mg/kg/day, about 0.05 mg/kg/day to about 5 mg/kg/day, about 0.05 mg/kg/day to about 3 mg/kg/day, about 0.07 mg/kg/day to about 3 mg/kg/day, about 0.09 mg/kg/day to about 3 mg/kg/day, about 0.05 mg/kg/day to about 0.1 mg/kg/day, about 0.1 mg/kg/day to about 1 mg/kg/day, about 1 mg/kg/day to about 10 mg/kg/day, about 1 mg/kg/day to about 5 mg/kg/day, about 1 mg/kg/day to about 3 mg/kg/day, about 3 mg/day to about 500 mg/day, about 5 mg/day to about 250 mg/day, about 10 mg/day to about 100 mg/day, about 3 mg/day to about 10 mg/day, or about 100 mg/day to about 250 mg/day. Such doses may be administered in a single dose or it may be divided into multiple doses.

Methods of Using KRAS G12C Inhibitors

(221) The present disclosure provides a method of inhibiting RAS-mediated cell signaling comprising contacting a cell with an effective amount of one or more compounds disclosed herein. Inhibition of RAS-mediated signal transduction can be assessed and demonstrated by a wide variety of ways known in the art. Non-limiting examples include a showing of (a) a decrease in GTPase activity of RAS; (b) a decrease in GTP binding affinity or an increase in GDP binding affinity; (c) an increase in K_{off} of GTP or a decrease in K_{off} of GDP; (d) a decrease in the levels of signaling transduction molecules downstream in the RAS pathway, such as a decrease in pMEK, pERK, or pAKT levels; and/or (e) a decrease in binding of RAS complex to downstream signaling

molecules including but not limited to Raf. Kits and commercially available assays can be utilized for determining one or more of the above.

(222) The disclosure also provides methods of using the compounds or pharmaceutical compositions of the present disclosure to treat disease conditions, including but not limited to conditions implicated by G12C KRAS, HRAS or NRAS mutation (e.g., cancer).

(223) In some embodiments, a method for treatment of cancer is provided, the method comprising administering an effective amount of any of the foregoing pharmaceutical compositions comprising a compound as disclosed herein to a subject in need thereof. In some embodiments, the cancer is mediated by a KRAS, HRAS or NRAS G12C mutation. In various embodiments, the cancer is pancreatic cancer colorectal cancer or lung cancer. In some embodiments, the cancer is gall bladder cancer, thyroid cancer, and bile duct cancer.

(224) In some embodiments the disclosure provides method of treating a disorder in a subject in need thereof, wherein the said method comprises determining if the subject has a KRAS, HRAS or NRAS G12C mutation and if the subject is determined to have the KRAS, HRAS or NRAS G12C mutation, then administering to the subject a therapeutically effective dose of at least one compound as disclosed herein or a pharmaceutically acceptable salt thereof.

(225) The disclosed compounds inhibit anchorage-independent cell growth and therefore have the potential to inhibit tumor metastasis. Accordingly, another embodiment the disclosure provides a method for inhibiting tumor metastasis, the method comprising administering an effective amount a compound disclosed herein.

(226) KRAS, HRAS or NRAS G12C mutations have also been identified in hematological malignancies (e.g., cancers that affect blood, bone marrow and/or lymph nodes). Accordingly, certain embodiments are directed to administration of a disclosed compounds (e.g., in the form of a pharmaceutical composition) to a patient in need of treatment of a hematological malignancy. Such malignancies include, but are not limited to leukemias and lymphomas. For example, the presently disclosed compounds can be used for treatment of diseases such as Acute lymphoblastic leukemia (ALL), Acute myelogenous leukemia (AML), Chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), Chronic myelogenous leukemia (CML), Acute monocytic leukemia (AMoL) and/or other leukemias. In other embodiments, the compounds are useful for treatment of lymphomas such as all subtypes of Hodgkins lymphoma or non-Hodgkins lymphoma. In various embodiments, the compounds are useful for treatment of plasma cell malignancies such as multiple myeloma, mantle cell lymphoma, and Waldenstrom's macroglobulinemia.

(227) Determining whether a tumor or cancer comprises a G12C KRAS, HRAS or NRAS mutation can be undertaken by assessing the nucleotide sequence encoding the KRAS, HRAS or NRAS protein, by assessing the amino acid sequence of the KRAS, HRAS or NRAS protein, or by assessing the characteristics of a putative KRAS, HRAS or NRAS mutant protein. The sequence of wild-type human KRAS, HRAS or NRAS is known in the art, (e.g. Accession No. NP203524).

(228) Methods for detecting a mutation in a KRAS, HRAS or NRAS nucleotide sequence are known by those of skill in the art. These methods include, but are not limited to, polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assays, polymerase chain reaction-single strand conformation polymorphism (PCR-SSCP) assays, real-time PCR assays. PCR sequencing, mutant allele-specific PCR amplification (MASA) assays, direct sequencing, primer extension reactions, electrophoresis, oligonucleotide ligation assays, hybridization assays. TaqMan assays. SNP genotyping assays, high resolution melting assays and microarray analyses. In some embodiments, samples are evaluated for G12C KRAS, HRAS or NRAS mutations by real-time PCR. In real-time PCR, fluorescent probes specific for the KRAS, HRAS or NRAS G12C mutation are used. When a mutation is present, the probe binds and fluorescence is detected. In some embodiments, the KRAS, HRAS or NRAS G12C mutation is identified using a direct sequencing method of specific regions (e.g., exon 2 and/or exon 3) in the KRAS, HRAS or NRAS gene. This technique will identify all possible mutations in the region sequenced.

(229) Methods for detecting a mutation in a KRAS, HRAS or NRAS protein are known by those of skill in the art. These methods include, but are not limited to, detection of a KRAS, HRAS or NRAS mutant using a binding agent (e.g., an antibody) specific for the mutant protein, protein electrophoresis and Western blotting, and direct peptide sequencing.

(230) Methods for determining whether a tumor or cancer comprises a G12C KRAS, HRAS or NRAS mutation can use a variety of samples. In some embodiments, the sample is taken from a subject having a tumor or cancer. In some embodiments, the sample is a fresh tumor/cancer sample. In some embodiments, the sample is a frozen tumor/cancer sample. In some embodiments, the sample is a formalin-fixed paraffin-embedded sample. In some embodiments, the sample is a circulating tumor cell (CTC) sample. In some embodiments, the sample is processed to a cell lysate. In some embodiments, the sample is processed to DNA or RNA.

(231) The disclosure also relates to a method of treating a hyperproliferative disorder in a mammal that comprises administering to said mammal a therapeutically effective amount of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof. In some embodiments, said method relates to the treatment of a subject who suffers from a cancer such as acute myeloid leukemia, cancer in adolescents, adrenocortical carcinoma childhood. AIDS-related cancers (e.g. Lymphoma and Kaposi's Sarcoma), anal cancer, appendix cancer, astrocytomas, atypical teratoid, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer, brain stem glioma, brain tumor, breast cancer, bronchial tumors. Burkitt lymphoma, carcinoid tumor, atypical teratoid, embryonal tumors, germ cell tumor, primary lymphoma, cervical cancer, childhood cancers, chordoma, cardiac tumors, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), chronic myeloproliferative disorders, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T-cell lymphoma, extrahepatic ductal carcinoma in situ (DCIS), embryonal tumors, CNS cancer, endometrial cancer, ependymoma, esophageal cancer, esthesioneuroblastoma, ewing sarcoma, extracranial germ cell tumor, extragonadal germ cell tumor, eye cancer, fibrous histiocytoma of bone, gall bladder cancer, gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumors (GIST), germ cell tumor, gestational trophoblastic tumor, hairy cell leukemia, head and neck cancer, heart cancer, liver cancer. Hodgkin lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumors, pancreatic neuroendocrine tumors, kidney cancer, laryngeal cancer, lip and oral cavity cancer, liver cancer, lobular carcinoma in situ (LCIS), lung cancer, lymphoma, metastatic squamous neck cancer with occult primary, midline tract carcinoma, mouth cancer, multiple endocrine neoplasia syndromes, multiple myeloma/plasma cell neoplasm, mycosis fungoides, myelodysplastic syndromes, myelodysplastic/myeloproliferative neoplasms, multiple myeloma, merkel cell carcinoma, malignant mesothelioma, malignant fibrous histiocytoma of bone and osteosarcoma, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, non-hodgkin lymphoma, non-small cell lung cancer (NSCLC), oral cancer, lip and oral cavity cancer, oropharyngeal cancer, ovarian cancer, pancreatic cancer, papillomatosis, paraganglioma, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pleuropulmonary blastoma, primary central nervous system (CNS) lymphoma, prostate cancer, rectal cancer, transitional cell cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, skin cancer, stomach (gastric) cancer, small cell lung cancer, small intestine cancer, soft tissue sarcoma, T-Cell lymphoma, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, transitional cell cancer of the renal pelvis and ureter, trophoblastic tumor, unusual cancers of childhood, urethral cancer, uterine sarcoma, vaginal cancer, vulvar cancer, or viral-induced cancer. In some embodiments, said method relates to the treatment of a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (e. g., psoriasis), restenosis, or prostate (e. g., benign prostatic hypertrophy (BPH)).

(232) In some embodiments, the methods for treatment are directed to treating lung cancers, the methods comprise administering an effective amount of any of the above described compound (or a pharmaceutical composition comprising the same) to a subject in need thereof. In certain

embodiments the lung cancer is a non-small cell lung carcinoma (NSCLC), for example adenocarcinoma, squamous-cell lung carcinoma or large-cell lung carcinoma. In some embodiments, the lung cancer is a small cell lung carcinoma. Other lung cancers treatable with the disclosed compounds include, but are not limited to, glandular tumors, carcinoid tumors and undifferentiated carcinomas.

(233) The disclosure further provides methods of modulating a G12C Mutant KRAS, HRAS or NRAS protein activity by contacting the protein with an effective amount of a compound of the disclosure. Modulation can be inhibiting or activating protein activity. In some embodiments, the disclosure provides methods of inhibiting protein activity by contacting the G12C Mutant KRAS, HRAS or NRAS protein with an effective amount of a compound of the disclosure in solution. In some embodiments, the disclosure provides methods of inhibiting the G12C Mutant KRAS, HRAS or NRAS protein activity by contacting a cell, tissue, or organ that expresses the protein of interest. In some embodiments, the disclosure provides methods of inhibiting protein activity in subject including but not limited to rodents and mammal (e.g., human) by administering into the subject an effective amount of a compound of the disclosure. In some embodiments, the percentage modulation exceeds 25%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%. In some embodiments, the percentage of inhibiting exceeds 25%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%.

(234) In some embodiments, the disclosure provides methods of inhibiting KRAS, HRAS or NRAS G12C activity in a cell by contacting said cell with an amount of a compound of the disclosure sufficient to inhibit the activity of KRAS, HRAS or NRAS G12C in said cell. In some embodiments, the disclosure provides methods of inhibiting KRAS, HRAS or NRAS G12C activity in a tissue by contacting said tissue with an amount of a compound of the disclosure sufficient to inhibit the activity of KRAS, HRAS or NRAS G12C in said tissue. In some embodiments, the disclosure provides methods of inhibiting KRAS, HRAS or NRAS G12C activity in an organism by contacting said organism with an amount of a compound of the disclosure sufficient to inhibit the activity of KRAS, HRAS or NRAS G12C in said organism. In some embodiments, the disclosure provides methods of inhibiting KRAS, HRAS or NRAS G12C activity in an animal by contacting said animal with an amount of a compound of the disclosure sufficient to inhibit the activity of KRAS, HRAS or NRAS G12C in said animal. In some embodiments, the disclosure provides methods of inhibiting KRAS, HRAS or NRAS G12C activity in a mammal by contacting said mammal with an amount of a compound of the disclosure sufficient to inhibit the activity of KRAS, HRAS or NRAS G12C in said mammal. In some embodiments, the disclosure provides methods of inhibiting KRAS, HRAS or NRAS G12C activity in a human by contacting said human with an amount of a compound of the disclosure sufficient to inhibit the activity of KRAS, HRAS or NRAS G12C in said human. The present disclosure provides methods of treating a disease mediated by KRAS, HRAS or NRAS G12C activity in a subject in need of such treatment.

Combination Therapy

(235) The present disclosure also provides methods for combination therapies in which an agent known to modulate other pathways, or other components of the same pathway, or even overlapping sets of target enzymes are used in combination with a compound of the present disclosure, or a pharmaceutically acceptable salt thereof. In one aspect, such therapy includes but is not limited to the combination of one or more compounds of the disclosure with chemotherapeutic agents, therapeutic antibodies, and radiation treatment, to provide a synergistic or additive therapeutic effect.

(236) Many chemotherapeutics are presently known in the art and can be used in combination with the compounds of the disclosure. In some embodiments, the chemotherapeutic is selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, angiogenesis inhibitors, and anti-androgens. Non-limiting

examples are chemotherapeutic agents, cytotoxic agents, and non-peptide small molecules such as Gleevec® (Imatinib Mesylate), Kyprolis® (carfilzomib), Velcade® (bortezomib), Casodex (bicalutamide), Iressa® (gefitinib), Venclexta™ (venetoclax) and Adriamycin™, (doxorubicin) as well as a host of chemotherapeutic agents. Non-limiting examples of chemotherapeutic agents include alkylating agents such as thiotepe and cyclophosphamide (Cytosan™); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide and trimethylolomelamine; nitrogen mustards such as chlorambucil, chlornaphazine, chlorocyclophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabycin, carminomycin, carzinophilin, Casodex™, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, 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-mercaptapurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, androgens such as calusterone, dromostanolone propionate, epitostanol, mepitostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; bestabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfomithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK; razoxane; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2''-trichlorotriethylamine; urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepe; taxanes, e.g. paclitaxel and docetaxel; retinoic acid; esperamicins; capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above.

(237) Also included as suitable chemotherapeutic cell conditioners are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens including for example tamoxifen, (Nolvadex™), raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, LY 117018, onapristone, and toremifene (Fareston); and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitomycin C; mitoxantrone; vincristine; vinorelbine; navelbine; novantrone; teniposide; daunomycin; aminopterin; xeloda; ibandronate; camptothecin-11 (CPT-11); topoisomerase inhibitor RFS 2000; difluoromethylomithine (DMFO).

(238) Where desired, the compounds or pharmaceutical composition of the present disclosure can be used in combination with commonly prescribed anti-cancer drugs such as Herceptin®, Avastin®, Erbitux®, Rituxan®, Taxol®, Arimidex®, Taxotere®, ABVD, AVICINE, Abagovomab, Acridine carboxamide, Adecatumumab, 17-N-Allylamino-17-demethoxygeldanamycin, Alparadin, Alvocidib, 3-Aminopyridine-2-carboxaldehyde thiosemicarbazone, Amonafide, Anthracenedione, Anti-CD22 immunotoxins, Antineoplastic, Antitumorigenic herbs, Apaziquone, Atiprimod, Azathioprine, Belotecan, Bendamustine, BIBW 2992, Biricodar, Brostallicin, Bryostatin, Buthionine sulfoximine, CBV (chemotherapy), Calyculin, cell-cycle nonspecific

antineoplastic agents, Dichloroacetic acid, Discodermolide, Elsamitucin, Enocitabine, Epothilone, Eribulin, Everolimus, Exatecan, Exisulind, Ferruginol, Forodesine, Fosfestrol, ICE chemotherapy regimen, IT-101, Imexon, Imiquimod, Indolocarbazole, Irofulven, Laniquidar, Larotaxel, Lenalidomide, Lucanthone, Lurtotecan, Mafosfamide, Mitozolomide, Nafoxidine, Nedaplatin, Olaparib, Ortataxel, PAC-1, Pawpaw, Pixantrone, Proteasome inhibitor, Rebeccamycin, Resiquimod, Rubitecan, SN-38, Salinosporamide A, Sapacitabine, Stanford V, Swainsonine, Talaporfin, Tariquidar, Tegafur-uracil, Temodar, Tesetaxel, Triplatin tetranitrate, Tris(2-chloroethyl)amine, Troxacitabine, Uramustine, Vadimezan, Vinflunine, ZD6126 or Zosuquidar.

(239) This disclosure further relates to a method for using the compounds or pharmaceutical compositions provided herein, in combination with radiation therapy for inhibiting abnormal cell growth or treating the hyperproliferative disorder in the mammal. Techniques for administering radiation therapy are known in the art, and these techniques can be used in the combination therapy described herein. The administration of the compound of the disclosure in this combination therapy can be determined as described herein.

(240) Radiation therapy can be administered through one of several methods, or a combination of methods, including without limitation external-beam therapy, internal radiation therapy, implant radiation, stereotactic radiosurgery, systemic radiation therapy, radiotherapy and permanent or temporary interstitial brachytherapy. The term “brachytherapy,” as used herein, refers to radiation therapy delivered by a spatially confined radioactive material inserted into the body at or near a tumor or other proliferative tissue disease site. The term is intended without limitation to include exposure to radioactive isotopes (e.g. At-211, I-131, I-125, Y-90, Re-186, Re-188, Sm-153, Bi-212, P-32, and radioactive isotopes of Lu). Suitable radiation sources for use as a cell conditioner of the present disclosure include both solids and liquids. By way of non-limiting example, the radiation source can be a radionuclide, such as I-125, I-131, Yb-169, Ir-192 as a solid source, I-125 as a solid source, or other radionuclides that emit photons, beta particles, gamma radiation, or other therapeutic rays. The radioactive material can also be a fluid made from any solution of radionuclide(s), e.g., a solution of I-125 or I-131, or a radioactive fluid can be produced using a slurry of a suitable fluid containing small particles of solid radionuclides, such as Au-198, Y-90. Moreover, the radionuclide(s) can be embodied in a gel or radioactive micro spheres.

(241) The compounds or pharmaceutical compositions of the disclosure can be used in combination with an amount of one or more substances selected from anti-angiogenesis agents, signal transduction inhibitors, antiproliferative agents, glycolysis inhibitors, or autophagy inhibitors.

(242) Anti-angiogenesis agents, such as MMP-2 (matrix-metalloproteinase 2) inhibitors, MMP-9 (matrix-metalloproteinase 9) inhibitors, and COX-11 (cyclooxygenase 11) inhibitors, can be used in conjunction with a compound of the disclosure and pharmaceutical compositions described herein. Anti-angiogenesis agents include, for example, rapamycin, temsirolimus (CCI-779), everolimus (RAD001), sorafenib, sunitinib, and bevacizumab. Examples of useful COX-II inhibitors include alecoxib, valdecoxib, and rofecoxib. Examples of useful matrix metalloproteinase inhibitors are described in WO 96/33172 WO 96/27583 European Patent Publication EP0818442, European Patent Publication EP1004578, WO 98/07697, WO 98/03516, WO 98/34918, WO 98/34915, WO 98/33768, WO 98/30566, European Patent Publication 606046, European Patent Publication 931 788, WO 90/05719, WO 99/52910, WO 99/52889, WO 99/29667, WO1999007675, European Patent Publication EP1786785, European Patent Publication No. EP 1181017, United States Publication No. US20090012085, United States Publication U.S. Pat. No. 5,863,949, United States Publication U.S. Pat. No. 5,861,510, and European Patent Publication EP0780386, all of which are incorporated herein in their entireties by reference. Preferred MMP-2 and MMP-9 inhibitors are those that have little or no activity inhibiting MMP-1. More preferred, are those that selectively inhibit MMP-2 and/or AMP-9 relative to the other matrix-metalloproteinases (i. e., MAP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP-7, MMP-8, MMP-10, MMP-11, MMP-12, and MMP-13). Some specific examples of MMP inhibitors useful in the

disclosure are AG-3340, RO 32-3555, and RS 13-0830.

(243) The present compounds may also be used in co-therapies with other anti-neoplastic agents, such as acemannan, aclarubicin, aldesleukin, alemtuzumab, alitretinoin, altretamine, amifostine, aminolevulinic acid, amrubicin, amsacrine, anagrelide, anastrozole, ANCER, ancestim, ARGLABIN, arsenic trioxide, BAM 002 (Novelos), bexarotene, bicalutamide, broxuridine, capecitabine, celmoleukin, cetorelix, cladribine, clotrimazole, cytarabine ocfosfate, DA 3030 (Dong-A), daclizumab, denileukin diftitox, deslorelin, dexrazoxane, dilazep, docetaxel, docosanol, doxercalciferol, doxifluridine, doxorubicin, bromocriptine, carmustine, cytarabine, fluorouracil, HIT diclofenac, interferon alfa, daunorubicin, doxorubicin, tretinoin, edelfosine, edrecolomab, eflomithine, emitefur, epirubicin, epoetin beta, etoposide phosphate, exemestane, exisulind, fadrozole, filgrastim, finasteride, fludarabine phosphate, formestane, fotemustine, gallium nitrate, gemcitabine, gemtuzumab zogamicin, gimeracil/oteracil/tegafur combination, glycopine, goserelin, heptaplatin, human chorionic gonadotropin, human fetal alpha fetoprotein, ibandronic acid, idarubicin, (imiquimod, interferon alfa, interferon alfa, natural, interferon alfa-2, interferon alfa-2a, interferon alfa-2b, interferon alfa-N1, interferon alfa-n3, interferon alfacon-1, interferon alpha, natural, interferon beta, interferon beta-1a, interferon beta-1b, interferon gamma, natural interferon gamma-1a, interferon gamma-1b, interleukin-1 beta, iobenguane, irinotecan, irsogladine, lanreotide, LC 9018 (Yakult), leflunomide, lenograstim, lentinan sulfate, letrozole, leukocyte alpha interferon, leuporelin, levamisole+fluorouracil, liarozole, lobaplatin, lonidamine, lovastatin, masoprolol, melarsoprol, metoclopramide, mifepristone, miltefosine, mirimostim, mismatched double stranded RNA, mitoguazone, mitolactol, mitoxantrone, molgramostim, nafarelin, naloxone+pentazocine, nartogastim, nedaplatin, nilutamide, noscapine, novel erythropoiesis stimulating protein, NSC 631570 octreotide, oprelvekin, osaterone, oxaliplatin, paclitaxel, pamidronic acid, pegaspargase, peginterferon alfa-2b, pentosan polysulfate sodium, pentostatin, picibanil, pirarubicin, rabbit antithymocyte polyclonal antibody, polyethylene glycol interferon alfa-2a, porfimer sodium, raloxifene, raltitrexed, rasburiembodiment, rhenium Re 186 etidronate, RII retinamide, rituximab, romurtide, samarium (153 Sm) lexidronam, sargramostim, sizofiran, sobuzoxane, sonermin, strontium-89 chloride, suramin, tasonermin, tazarotene, tegafur, temoporfin, temozolomide, teniposide, tetrachlorodecaoxide, thalidomide, thymalfasin, thyrotropin alfa, topotecan, toremifene, tositumomab-iodine 131, trastuzumab, treosulfan, tretinoin, trilostane, trimetrexate, triptorelin, tumor necrosis factor alpha, natural, ubenimex, bladder cancer vaccine, Maruyama vaccine, melanoma lysate vaccine, valrubicin, verteporfin, vinorelbine, VIRULIZIN, zinostatin stimalamer, or zoledronic acid; abarelix; AE 941 (Aetema), ambamustine, antisense oligonucleotide, bcl-2 (Genta), APC 8015 (Dendreon), cetuximab, decitabine, dexaminogluthethimide, diaziquone, EL 532 (Elan), EM 800 (Endorecherche), eniluracil, etanidazole, fenretinide, filgrastim SD01 (Amgen), fulvestrant, galocitabine, gastrin 17 immunogen, HLA-B7 gene therapy (Vical), granulocyte macrophage colony stimulating factor, histamine dihydrochloride, ibritumomab tiuxetan, ilomastat, IM 862 (Cytran), interleukin-2, iproxifene, LDI 200 (Milkhaus), leridistim, lintuzumab, CA 125 MAb (Biomira), cancer MAb (Japan Pharmaceutical Development), HER-2 and Fc MAb (Medarex), idiotypic 105AD7 MAb (CRC Technology), idiotypic CEA MAb (Trilex), LYM-1-iodine 131 MAb (Techniclone), polymorphic epithelial mucin-yttrium 90 MAb (Antisoma), marimastat, menogaril, mitumomab, motexafin gadolinium, MX 6 (Galderma), nelarabine, nolatrexed, P 30 protein, pegvisomant, pemetrexed, porfiromycin, prinomastat, RL 0903 (Shire), rubitecan, satraplatin, sodium phenylacetate, sparfosic acid, SRL 172 (SR Pharma), SU 5416 (SUGEN, now Pfizer, Inc.), TA 077 (Tanabe), tetrathiomolybdate, thaliblastine, thrombopoietin, tin ethyl etiopurpurin, tirapazamine, cancer vaccine (Biomira), melanoma vaccine (New York University), melanoma vaccine (Sloan Kettering Institute), melanoma oncolysate vaccine (New York Medical College), viral melanoma cell lysates vaccine (Royal Newcastle Hospital), or valspodar.

(244) The compounds of the invention may further be used with VEGFR inhibitors. Other

compounds described in the following patents and patent applications can be used in combination therapy: U.S. Pat. No. 6,258,812, US 2003/0105091, WO 01/37820, U.S. Pat. No. 6,235,764, WO 01/32651, U.S. Pat. Nos. 6,630,500, 6,515,004, 6,713,485, 5,521,184, 5,770,599, 5,747,498, WO 02/68406, WO 02/66470, WO 02/55501, WO 04/05279, WO 04/07481, WO 04/07458, WO 04/09784, WO 02/59110, WO 99/45009, WO 00/59509, WO 99/61422, U.S. Pat. No. 5,990,141, WO 00/12089, and WO 00/02871.

(245) In some embodiments, the combination comprises a composition of the present invention in combination with at least one anti-angiogenic agent. Agents are inclusive of, but not limited to, in vitro synthetically prepared chemical compositions, antibodies, antigen binding regions, radionuclides, and combinations and conjugates thereof. An agent can be an agonist, antagonist, allosteric modulator, toxin or, more generally, may act to inhibit or stimulate its target (e.g., receptor or enzyme activation or inhibition), and thereby promote cell death or arrest cell growth.

(246) Exemplary anti-angiogenic agents include ERBITUX™ (IMC-C225), KDR (kinase domain receptor) inhibitory agents (e.g., antibodies and antigen binding regions that specifically bind to the kinase domain receptor), anti-VEGF agents (e.g., antibodies or antigen binding regions that specifically bind VEGF, or soluble VEGF receptors or a ligand binding region thereof) such as AVASTIN™ or VEGF-TRAP™, and anti-VEGF receptor agents (e.g., antibodies or antigen binding regions that specifically bind thereto), EGFR inhibitory agents (e.g., antibodies or antigen binding regions that specifically bind thereto) such as Vectibix (panitumumab), IRESSA™ (gefitinib), TARCEVA™ (erlotinib), anti-Ang1 and anti-Ang2 agents (e.g., antibodies or antigen binding regions specifically binding thereto or to their receptors, e.g., Tie2/Tek), and anti-Tie2 kinase inhibitory agents (e.g., antibodies or antigen binding regions that specifically bind thereto). The pharmaceutical compositions of the present invention can also include one or more agents (e.g., antibodies, antigen binding regions, or soluble receptors) that specifically bind and inhibit the activity of growth factors, such as antagonists of hepatocyte growth factor (HGF, also known as Scatter Factor), and antibodies or antigen binding regions that specifically bind its receptor “c-met”.

(247) Other anti-angiogenic agents include Campath, IL-8, B-FGF, Tek antagonists (Ceretti et al., U.S. Publication No. 2003/0162712; U.S. Pat. No. 6,413,932), anti-TWEAK agents (e.g., specifically binding antibodies or antigen binding regions, or soluble TWEAK receptor antagonists; see, Wiley, U.S. Pat. No. 6,727,225), ADAM distintegrin domain to antagonize the binding of integrin to its ligands (Fanslow et al., U.S. Publication No. 2002/0042368), specifically binding anti-eph receptor and/or anti-ephrin antibodies or antigen binding regions (U.S. Pat. Nos. 5,981,245; 5,728,813; 5,969,110; 6,596,852; 6,232,447; 6,057,124 and patent family members thereof), and anti-PDGF-BB antagonists (e.g., specifically binding antibodies or antigen binding regions) as well as antibodies or antigen binding regions specifically binding to PDGF-BB ligands, and PDGFR kinase inhibitory agents (e.g., antibodies or antigen binding regions that specifically bind thereto).

(248) Additional anti-angiogenic/anti-tumor agents include: SD-7784 (Pfizer, USA); cilengitide. (Merck KGaA, Germany, EPO 770622); pegaptanib octasodium, (Gilead Sciences, USA); Alphastatin, (BioActa, UK); M-PGA, (Celgene, USA, U.S. Pat. No. 5,712,291); ilomastat, (Arriva, USA, U.S. Pat. No. 5,892,112); emaxanib, (Pfizer, USA, U.S. Pat. No. 5,792,783); vatalanib, (Novartis, Switzerland); 2-methoxyestradiol, (EntreMed, now CASI Pharmaceuticals, USA); TLC ELL-12, (Elan, Ireland); anecortave acetate, (Alcon, USA); alpha-D148 Mab, (Amgen, USA); CEP-7055, (Cephalon, USA); anti-Vn Mab, (Crucell, Netherlands) DAC:antiangiogenic, (ConjuChem, Canada); Angiocidin, (InKine Pharmaceutical, USA); KM-2550, (Kyowa Hakko, Japan); SU-0879, (Pfizer, USA); CGP-79787, (Novartis, Switzerland, EP 970070); ARGENT technology, (Ariad, USA); YIGSR-Stealth, (Johnson & Johnson, USA); fibrinogen-E fragment, (BioActa, UK); angiogenesis inhibitor, (Trigen, UK); TBC-1635, (Encysive Pharmaceuticals, USA); SC-236, (Pfizer, USA); ABT-567, (Abbott, USA); Metastatin, (EntreMed, USA);

angiogenesis inhibitor, (Tripep, Sweden); maspin, (Sosei, Japan); 2-methoxyestradiol, (Oncotherapy Sciences Corporation, USA); ER-68203-00, (IVAX, USA); Benefin, (Lane Labs, USA); Tz-93, (Tsumura, Japan); TAN-1120, (Takeda, Japan); FR-111142, (Fujisawa, Japan, JP 02233610); platelet factor 4, (RepliGen, USA, EP 407122); vascular endothelial growth factor antagonist, (Boreon, Denmark); bevacizumab (pINN), (Genentech, USA); angiogenesis inhibitors, (SUGEN, USA); XL 784, (Exelixis, USA); XL 647, (Exelixis, USA); MAb, alpha5beta3 integrin, second generation, (Applied Molecular Evolution, USA and MedImmune, USA); gene therapy, retinopathy, (Oxford BioMedica, UK); enzastaurin hydrochloride (USAN), (Lilly, USA); CEP 7055, (Cephalon, USA and Sanofi-Synthelabo, France); BC 1, (Genoa Institute of Cancer Research, Italy); angiogenesis inhibitor, (Alchemia, Australia); VEGF antagonist, (Regeneron, USA); rBPI 21 and BPI-derived antiangiogenic, (XOMA, USA); PI 88, (Progen, Australia); cilengitide (pINN), (Merck KGaA, German; Munich Technical University, Germany, Scripps Clinic and Research Foundation, USA); cetuximab (INN), (Aventis, France); AVE 8062, (Ajinomoto, Japan); AS 1404, (Cancer Research Laboratory, New Zealand); SG 292, (Telios, USA); Endostatin, (Boston Childrens Hospital, USA); ATN 161, (Attenuon, USA); ANGIOSTATIN, (Boston Childrens Hospital, USA); 2-methoxyestradiol, (Boston Childrens Hospital, USA); ZD 6474, (AstraZeneca, UK); ZD 6126, (Angiogene Pharmaceuticals, UK); PPI 2458, (Praecis, USA); AZD 9935, (AstraZeneca, UK); AZD 2171, (AstraZeneca, UK); vatalanib (pINN), (Novartis, Switzerland and Schering AG, Germany); tissue factor pathway inhibitors, (EntreMed, USA); pegaptanib (Pinn), (Gilead Sciences, USA); xanthorrhizol, (Yonsei University, South Korea); vaccine, gene-based, VEGF-2, (Scripps Clinic and Research Foundation, USA); SPV5.2, (Supratek, Canada); SDX 103, (University of California at San Diego, USA); PX 478, (ProlX, USA); METASTATIN, (EntreMed, now CASI Pharmaceuticals, USA); troponin I, (Harvard University, USA); SU 6668, (SUGEN, now Pfizer, Inc., USA); OXI 4503, (OXiGENE, USA); o-guanidines, (Dimensional Pharmaceuticals, USA); motuporamine C, (British Columbia University, Canada); CDP 791, (Celltech Group, UK); atiprimod (pINN), (GlaxoSmithKline, UK); E 7820, (Eisai, Japan); CYC 381, (Harvard University, USA); AE 941, (Aetema, Canada); vaccine, angiogenesis, (EntreMed, now CASI Pharmaceuticals, USA); urokinase plasminogen activator inhibitor, (Dendreon, USA); oglufanide (pINN), (Melmotte, USA); HIF-1alpha inhibitors, (Xenova, UK); CEP 5214, (Cephalon, USA); BAY RES 2622, (Bayer, Germany); Angiocidin, (InKine, USA); A6, (Angstrom, USA); KR 31372, (Korea Research Institute of Chemical Technology, South Korea); GW 2286, (GlaxoSmithKline, UK); EHT 0101, (ExonHit, France); CP 868596, (Pfizer, USA); CP 564959, (OSI, USA); CP 547632, (Pfizer, USA); 786034, (GlaxoSmithKline, UK); KRN 633, (Kirin Brewery, Japan); drug delivery system, intraocular, 2-methoxyestradiol, (EntreMed, USA); anginox, (Maastricht University, Netherlands, and Minnesota University, USA); ABT 510, (Abbott, USA); AAL 993, (Novartis, Switzerland); VEGI, (ProteomTech, USA); tumor necrosis factor-alpha inhibitors, (National Institute on Aging, USA); SU 11248, (Pfizer, USA and SUGEN USA); ABT 518, (Abbott, USA); YH16, (Yantai Rongchang, China); S-3APG, (Boston Childrens Hospital, USA and EntreMed, USA); MAb, KDR, (ImClone Systems, USA); MAb, alpha5 beta1, (Protein Design, USA); KDR kinase inhibitor, (Celltech Group, UK, and Johnson & Johnson, USA); GFB 116, (South Florida University, USA and Yale University, USA); CS 706, (Sankyo, Japan); combretastatin A4 prodrug, (Arizona State University, USA); chondroitinase AC, (IBEX, Canada); BAY RES 2690, (Bayer, Germany); AGM 1470, (Harvard University, USA, Takeda, Japan, and TAP, USA); AG 13925, (Agouron, USA); Tetrathiomolybdate, (University of Michigan, USA); GCS 100, (Wayne State University, USA) CV 247, (Ivy Medical, UK); CKD 732, (Chong Kun Dang, South Korea); MAb, vascular endothelium growth factor, (Xenova, UK); irsogladine (INN), (Nippon Shinyaku, Japan); RG 13577, (Aventis, France); WX 360, (Wilex, Germany); squalamine (pINN), (Genaera, USA); RPI 4610, (Sirna, USA); cancer therapy, (Marinova, Australia); heparanase inhibitors, (InSight, Israel); KL 3106, (Kolon, South Korea); Honokiol, (Emory University, USA); ZK CDK, (Schering AG, Germany); ZK Angio, (Schering

AG, Germany); ZK 229561, (Novartis, Switzerland, and Schering AG, Germany); XMP 300, (XOMA, USA); VEGF receptor modulators, (Pharmacopeia, USA); VE-cadherin-2 antagonists, (ImClone Systems, USA); Vasostatin, (National Institutes of Health, USA); vaccine, Flk-1, (ImClone Systems, USA); TZ 93, (Tsumura, Japan); TumStatin, (Beth Israel Hospital, USA); truncated soluble FLT 1 (vascular endothelial growth factor receptor 1), (Merck & Co, USA); Tie-2 ligands, (Regeneron, USA); and, thrombospondin 1 inhibitor, (Allegheny Health, Education and Research Foundation, USA).

(249) Autophagy inhibitors include, but are not limited to chloroquine, 3-methyladenine, hydroxychloroquine (Plaquenil™), bafilomycin A1, 5-amino-4-imidazole carboxamide riboside (AICAR), okadaic acid, autophagy-suppressive algal toxins which inhibit protein phosphatases of type 2A or type 1, analogues of cAMP, and drugs which elevate cAMP levels such as adenosine, LY204002, N6-mercaptopurine riboside, and vinblastine. In addition, antisense or siRNA that inhibits expression of proteins including but not limited to ATG5 (which are implicated in autophagy), may also be used.

(250) Additional pharmaceutically active compounds/agents that can be used in the treatment of cancers and that can be used in combination with one or more compound of the present invention include: epoetin alfa; darbepoetin alfa; panitumumab; pegfilgrastim; palifermin; filgrastim; denosumab; ancestim; AMG 102; AMG 176; AMG 386; AMG 479; AMG 655; AMG 745; AMG 951; and AMG 706, or a pharmaceutically acceptable salt thereof.

(251) In certain embodiments, a composition provided herein is conjointly administered with a chemotherapeutic agent. Suitable chemotherapeutic agents may include, natural products such as vinca alkaloids (e.g., vinblastine, vincristine, and vinorelbine), paclitaxel, epidipodophyllotoxins (e.g., etoposide and teniposide), antibiotics (e.g., dactinomycin (actinomycin D), daunorubicin, doxorubicin, and idarubicin), anthracyclines, mitoxantrone, bleomycins, plicamycin (mithramycin), mitomycin, enzymes (e.g., L-asparaginase which systemically metabolizes L-asparagine and deprives cells which do not have the capacity to synthesize their own asparagine), antiplatelet agents, antiproliferative/antimitotic alkylating agents such as nitrogen mustards (e.g., mechlorethamine, cyclophosphamide and analogs, melphalan, and chlorambucil), ethylenimines and methylmelamines (e.g., hexaamethylmelaamine and thiotepe), CDK inhibitors (e.g., seliciclib, UCN-01, P1446A-05, PD-0332991, dinaciclib, P27-00, AT-7519, RGB286638, and SCH727965), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine (BCNU) and analogs, and streptozocin), trazesines-dacarbazine (DTIC), antiproliferative/antimitotic antimetabolites such as folic acid analogs (e.g., methotrexate), pyrimidine analogs (e.g., fluorouracil, floxuridine, and cytarabine), purine analogs and related inhibitors (e.g., mercaptopurine, thioguanine, pentostatin and 2-chlorodeoxyadenosine), aromatase inhibitors (e.g., anastrozole, exemestane, and letrozole), and platinum coordination complexes (e.g., cisplatin and carboplatin), procarbazine, hydroxyurea, mitotane, aminoglutethimide, histone deacetylase (HDAC) inhibitors (e.g., trichostatin, sodium butyrate, apicidan, suberoyl anilide hydroamic acid, vorinostat, LBH 589, romidepsin, ACY-1215, and panobinostat), mTor inhibitors (e.g., temsirolimus, everolimus, ridaforolimus, and sirolimus), KSP(Eg5) inhibitors (e.g., Array 520), DNA binding agents (e.g., Zalypsis), PI3K delta inhibitor (e.g., GS-1101 and TGR-1202), P13K delta and gamma inhibitor (e.g., CAL-130), multi-kinase inhibitor (e.g., TG02 and sorafenib), hormones (e.g., estrogen) and hormone agonists such as leutinizing hormone releasing hormone (LHRH) agonists (e.g., goserelin, leuprolide and triptorelin), BAFF-neutralizing antibody (e.g., LY2127399), IKK inhibitors, p38MAPK inhibitors, anti-IL-6 (e.g., CNT0328), telomerase inhibitors (e.g., GRN 163 L), aurora kinase inhibitors (e.g., MLN8237), cell surface monoclonal antibodies (e.g., anti-CD38 (HUMAX-CD38), anti-CS1 (e.g., elotuzumab), HSP90 inhibitors (e.g., 17 AAG and KOS 953), P13K/Akt inhibitors (e.g., perifosine), Akt inhibitor (e.g., GSK-2141795), PKC inhibitors (e.g., enzastaurin), FTIs (e.g., Zarnestra™), anti-CD138 (e.g., BT062), Torcl/2 specific kinase inhibitor (e.g., INK128), kinase inhibitor (e.g., GS-1101), ER/UPR targeting agent (e.g., MKC-3946), cFMS inhibitor (e.g., ARRY-

382), JAK1/2 inhibitor (e.g., CYT387), PARP inhibitor (e.g., olaparib and veliparib (ABT-888)), BCL-2 antagonist. Other chemotherapeutic agents may include mechlorethamine, camptothecin, ifosfamide, tamoxifen, raloxifene, gemcitabine, navelbine, sorafenib, or any analog or derivative variant of the foregoing.

(252) The compounds of the present invention may also be used in combination with radiation therapy, hormone therapy, surgery and immunotherapy, which therapies are well known to those skilled in the art.

(253) In certain embodiments, a pharmaceutical composition provided herein is conjointly administered with a steroid. Suitable steroids may include, but are not limited to, 21-acetoxypregnenolone, alclometasone, algestone, amcinonide, beclomethasone, betamethasone, budesonide, chloroprednisone, clobetasol, clocortolone, cloprednol, corticosterone, cortisone, cortivazol, deflazacort, desonide, desoximetasone, dexamethasone, diflorasone, diflucortolone, difuprednate, enoxolone, fluazacort, flucloronide, flumethasone, flunisolide, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluocortolone, fluorometholone, fluperolone acetate, fluprednidene acetate, fluprednisolone, flurandrenolide, fluticasone propionate, formocortal, halcinonide, halobetasol propionate, halometasone, hydrocortisone, loteprednol etabonate, mazipredone, medrysone, meprednisone, methylprednisolone, mometasone furoate, paramethasone, prednicarbate, prednisolone, prednisolone 25-diethylaminoacetate, prednisolone sodium phosphate, prednisone, prednival, prednylidene, rimexolone, tixocortol, triamcinolone, triamcinolone acetonide, triamcinolone benetonide, triamcinolone hexacetonide, and salts and/or derivatives thereof. In a particular embodiment, the compounds of the present invention can also be used in combination with additional pharmaceutically active agents that treat nausea. Examples of agents that can be used to treat nausea include: dronabinol; granisetron; metoclopramide; ondansetron; and prochlorperazine; or a pharmaceutically acceptable salt thereof.

(254) The compounds of the present invention may also be used in combination with an additional pharmaceutically active compound that disrupts or inhibits RAS-RAF-ERK or PI3K-AKT-TOR signaling pathways. In other such combinations, the additional pharmaceutically active compound is a PD-1 and PD-L1 antagonist. The compounds or pharmaceutical compositions of the disclosure can also be used in combination with an amount of one or more substances selected from EGFR inhibitors, MEK inhibitors, PI3K inhibitors, AKT inhibitors, TOR inhibitors, Mcl-1 inhibitors, BCL-2 inhibitors, SHP2 inhibitors, proteasome inhibitors, and immune therapies, including monoclonal antibodies, immunomodulatory imides (IMiDs), anti-PD-1, anti-PDL-1, anti-CTLA4, anti-LAGI, and anti-OX40 agents, GITR agonists, CAR-T cells, and BiTEs.

(255) EGFR inhibitors include, but are not limited to, small molecule antagonists, antibody inhibitors, or specific antisense nucleotide or siRNA. Useful antibody inhibitors of EGFR include cetuximab (Erbix), panitumumab (Vectibix), zalutumumab, nimotuzumab, and matuzumab. Small molecule antagonists of EGFR include gefitinib, erlotinib (Tarceva), and most recently, lapatinib (TykerB). See e.g., Yan L, et. al., *Pharmacogenetics and Pharmacogenomics In Oncology Therapeutic Antibody Development*, BioTechniques 2005; 39(4): 565-8, and Paez J G, et. al., *EGFR Mutations In Lung Cancer Correlation With Clinical Response To Gefitinib Therapy*, Science 2004; 304(5676): 1497-500.

(256) Non-limiting examples of small molecule EGFR inhibitors include any of the EGFR inhibitors described in the following patent publications, and all pharmaceutically acceptable salts and solvates of said EGFR inhibitors: European Patent Application EP 520722, published Dec. 30, 1992; European Patent Application EP 566226, published Oct. 20, 1993; PCT International Publication WO 96/33980, published Oct. 31, 1996; U.S. Pat. No. 5,747,498, issued May 5, 1998; PCT International Publication WO 96/30347, published Oct. 3, 1996; European Patent Application EP 787772, published Aug. 6, 1997; PCT International Publication WO 97/30034, published Aug. 21, 1997; PCT International Publication WO 97/30044, published Aug. 21, 1997; PCT International Publication WO 97/38994, published Oct. 23, 1997; PCT International Publication

WO 97/49688, published Dec. 31, 1997; European Patent Application EP 837063, published Apr. 22, 1998; PCT International Publication WO 98/02434, published Jan. 22, 1998; PCT International Publication WO 97/38983, published Oct. 23, 1997; PCT International Publication WO 95/19774, published Jul. 27, 1995; PCT International Publication WO 95/19970, published Jul. 27, 1995; PCT International Publication WO 97/13771, published Apr. 17, 1997; PCT International Publication WO 98/02437, published Jan. 22, 1998; PCT International Publication WO 98/02438, published Jan. 22, 1998; PCT International Publication WO 97/32881, published Sep. 12, 1997; German Application DE 19629652, published Jan. 29, 1998; PCT International Publication WO 98/33798, published Aug. 6, 1998; PCT International Publication WO 97/32880, published Sep. 12, 1997; PCT International Publication WO 97/32880 published Sep. 12, 1997; European Patent Application EP 682027, published Nov. 15, 1995; PCT International Publication WO 97/02266, published Jan. 23, 1997; PCT International Publication WO 97/27199, published Jul. 31, 1997; PCT International Publication WO 98/07726, published Feb. 26, 1998; PCT International Publication WO 97/34895, published Sep. 25, 1997; PCT International Publication WO 96/31510', published Oct. 10, 1996; PCT International Publication WO 98/14449, published Apr. 9, 1998; PCT International Publication WO 98/14450, published Apr. 9, 1998; PCT International Publication WO 98/14451, published Apr. 9, 1998; PCT International Publication WO 95/09847, published Apr. 13, 1995; PCT International Publication WO 97/19065, published May 29, 1997; PCT International Publication WO 98/17662, published Apr. 30, 1998; U.S. Pat. No. 5,789,427, issued Aug. 4, 1998; U.S. Pat. No. 5,650,415, issued Jul. 22, 1997; U.S. Pat. No. 5,656,643, issued Aug. 12, 1997; PCT International Publication WO 99/35146, published Jul. 15, 1999; PCT International Publication WO 99/35132, published Jul. 15, 1999; PCT International Publication WO 99/07701, published Feb. 18, 1999; and PCT International Publication WO 92/20642 published Nov. 26, 1992.

Additional non-limiting examples of small molecule EGFR inhibitors include any of the EGFR inhibitors described in Traxler, P., 1998, Exp. Opin. Ther. Patents 8(12):1599-1625.

(257) Antibody-based EGFR inhibitors include any anti-EGFR antibody or antibody fragment that can partially or completely block EGFR activation by its natural ligand. Non-limiting examples of antibody-based EGFR inhibitors include those described in Modjtahedi, H., et al., 1993, Br. J. Cancer 67:247-253; Teramoto, T., et al., 1996, Cancer 77:639-645; Goldstein et al., 1995, Clin. Cancer Res. 1:1311-1318; Huang, S. M., et al., 1999, Cancer Res. 15:59(8):1935-40; and Yang, X., et al., 1999, Cancer Res. 59:1236-1243. Thus, the EGFR inhibitor can be monoclonal antibody Mab E7.6.3 (Yang, 1999 supra), or Mab C225 (ATCC Accession No. HB-8508), or an antibody or antibody fragment having the binding specificity thereof.

(258) The KRAS.sup.G12C inhibitors of the present invention can be used in combination with MEK inhibitors. Particular MEK inhibitors that can be used in the combinations of the present invention include PD-325901, trametinib, pimasertib, MEK162 [also known as binimetinib], TAK-733, GDC-0973 and AZD8330. A particular MEK inhibitor that can be used along with KRAS.sup.G12C inhibitor in the combinations of the present invention is trametinib (tradename: Mekinist®, commercially available from Novartis Pharmaceuticals Corp.). Another particular MEK inhibitor is N-(((2R)-2,3-dihydroxypropyl)oxy)-3,4-difluoro-2-((2-fluoro-4-iodophenyl)amino)benzamide, also known as AMG 1009089, 1009089 or PD-325901. Another particular MEK inhibitor that can be used in the combinations of the present invention includes cobimetinib. MEK inhibitors include, but are not limited to, CI-1040, AZD6244, PD318088, PD98059, PD334581, RDEA119, ARRY-142886, and ARRY-438162.

(259) P13K inhibitors include, but are not limited to, wortmannin, 17-hydroxywortmannin analogs described in WO 06/044453, 4-[2-(1H-Indazol-4-yl)-6-[[4-(methylsulfonyl)piperazin-1-yl]methyl]thieno[3,2-d]pyrimidin-4-yl]morpholine (also known as GDC 0941 and described in PCT Publication Nos. WO 09/036,082 and WO 09/055,730), 2-Methyl-2-[4-[3-methyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydroimidazo[4,5-c]quinolin-1-yl]phenyl]propionitrile (also known as BEZ 235 or NVP-BEZ 235, and described in PCT Publication No. WO 06/122806), (S)-1-(4-((2-(2-

aminopyrimidin-5-yl)-7-methyl-4-morpholinothieno[3,2-d]pyrimidin-6-yl)methyl)piperazin-1-yl)-2-hydroxypropan-1-one (described in PCT Publication No. WO 2008/070740), LY294002 (2-(4-Morpholinyl)-8-phenyl-4H-1-benzopyran-4-one available from Axon Medchem), PI 103 hydrochloride (3-[4-(4-morpholinyl)pyrido-[3',2':4,5]furo[3,2-d]pyrimidin-2-yl]phenol hydrochloride available from Axon Medchem), PIK 75 (N'-[(1E)-(6-bromoimidazo[1,2-a]pyridin-3-yl)methylene]-N,2-dimethyl-5-nitrobenzenesulfono-hydrazide hydrochloride available from Axon Medchem), PIK 90 (N-(7,8-dimethoxy-2,3-dihydro-imidazo[1,2-c]quinazolin-5-yl)-nicotinamide available from Axon Medchem), GDC-0941 bismesylate (2-(1H-Indazol-4-yl)-6-(4-methanesulfonyl-piperazin-1-ylmethyl)-4-morpholin-4-yl-thieno[3,2-d]pyrimidine bismesylate available from Axon Medchem), AS-252424 (5-[1-[5-(4-Fluoro-2-hydroxy-phenyl)-furan-2-yl]-meth-(Z)-ylidene]-thiazolidine-2,4-dione available from Axon Medchem), and TGX-221 (7-Methyl-2-(4-morpholinyl)-9-[1-(phenylamino)ethyl]-4H-pyrido-[1,2-a]pyrimidin-4-one available from Axon Medchem), XL-765, and XL-147. Other P13K inhibitors include demethoxyviridin, perifosine, CAL101, PX-866, BEZ235, SF1126, INK1117, IPI-145, BKM120, XL147, XL765, Palomid 529, GSK1059615, ZSTK474, PWT33597, IC87114, TG100-115, CAL263, PI-103, GNE-477, CUDC-907, and AEZS-136.

(260) AKT inhibitors include, but are not limited to, Akt-1-1 (inhibits Akt1) (Barnett et al. (2005) *Biochem. J.*, 385 (Pt. 2), 399-408); Akt-1-1,2 (inhibits Ak1 and 2) (Barnett et al. (2005) *Biochem. J.* 385 (Pt. 2), 399-408); API-59CJ-Ome (e.g., Jin et al. (2004) *Br. J Cancer* 91, 1808-12); 1-H-imidazo[4,5-c]pyridinyl compounds (e.g., WO05011700); indole-3-carbinol and derivatives thereof (e.g., U.S. Pat. No. 6,656,963; Sarkar and Li (2004) *J Nutr.* 134(12 Suppl), 3493S-3498S); perifosine (e.g., interferes with Akt membrane localization; Dasmahapatra et al. (2004) *Clin. Cancer Res.* 10(15), 5242-52, 2004); phosphatidylinositol ether lipid analogues (e.g., Gills and Dennis (2004) *Expert. Opin. Investig. Drugs* 13, 787-97); and triciribine (TCN or API-2 or NCI identifier: NSC 154020; Yang et al. (2004) *Cancer Res.* 64, 4394-9).

(261) TOR inhibitors include, but are not limited to, AP-23573, CCI-779, everolimus, RAD-001, rapamycin, temsirolimus, ATP-competitive TORC1/TORC2 inhibitors, including PI-103, PP242, PP30 and Torin 1. Other TOR inhibitors in FKBP12 enhancer; rapamycins and derivatives thereof, including: CCI-779 (temsirolimus), RAD001 (Everolimus; WO 9409010) and AP23573; rapalogs, e.g. as disclosed in WO 98/02441 and WO 01/14387, e.g. AP23573, AP23464, or AP23841; 40-(2-hydroxyethyl)rapamycin, 40-[3-hydroxy(hydroxymethyl)methylpropanoate]-rapamycin (also called CC1779), 40-epi-(tetrazolyt)-rapamycin (also called ABT578), 32-deoxorapamycin, 16-pentynyloxy-32(S)-dihydrorapamycin, and other derivatives disclosed in WO 05005434; derivatives disclosed in U.S. Pat. No. 5,258,389, WO 94/090101, WO 92/05179, U.S. Pat. Nos. 5,118,677, 5,118,678, 5,100,883, 5,151,413, 5,120,842, WO 93/111130, WO 94/02136, WO 94/02485, WO 95/14023, WO 94/02136, WO 95/16691, WO 96/41807, WO 96/41807 and U.S. Pat. No. 5,256,790; phosphorus-containing rapamycin derivatives (e.g., WO 05016252); 4H-1-benzopyran-4-one derivatives (e.g., U.S. Provisional Application No. 60/528,340).

(262) MCL-1 inhibitors include, but are not limited to, AMG-176, MIK665, and S63845. The myeloid cell leukemia-1 (MCL-1) protein is one of the key anti-apoptotic members of the B-cell lymphoma-2 (BCL-2) protein family. Over-expression of MCL-1 has been closely related to tumor progression as well as to resistance, not only to traditional chemotherapies but also to targeted therapeutics including BCL-2 inhibitors such as ABT-263.

(263) KRAS.sup.G12C inhibitors can also be used in combination with SHP2 inhibitors in the present invention. SHP2 inhibitors that can be used in the present combinations include, but are not limited to, SHP099, and RMC-4550 or RMC-4630, from Revolutions Medicines in Redwood City, CA.

(264) Proteasome inhibitors include, but are not limited to, Kyprolis®(carfilzomib), Velcade®(bortezomib), and oprozomib.

(265) Immune therapies include, but are not limited to, anti-PD-1 agents, anti-PDL-1 agents, anti-

CTLA-4 agents, anti-LAG3 agents, and anti-OX40 agents.

(266) Monoclonal antibodies include, but are not limited to, Darzalex® (daratumumab), Herceptin® (trastuzumab), Avastin® (bevacizumab), Rituxan® (rituximab), Lucentis® (ranibizumab), and Eylea® (aflibercept).

(267) Immunomodulatory agents (IMiDs) are a class of immunomodulatory drugs (drugs that adjust immune responses) containing an imide group. The IMiD class includes thalidomide and its analogues (lenalidomide, pomalidomide, and apremilast).

(268) Anti-PD-1 inhibitors, including but not limited to antibodies include, but are not limited to, pembrolizumab (Keytruda®) and nivolumab (Opdivo®). Exemplary anti-PD-1 antibodies and methods for their use are described by Goldberg et al., *Blood* 110(1):186-192 (2007), Thompson et al., *Clin. Cancer Res.* 13(6):1757-1761 (2007), and Korman et al., International Application No. PCT/JP2006/309606 (publication no. WO 2006/121168 A1), each of which are expressly incorporated by reference herein. include: Yervoy™ (ipilimumab) or Tremelimumab (to CTLA-4), galiximab (to B7.1), BMS-936558 (to PD-1), MK-3475 (to PD-1), AMP224 (to B7DC), BMS-936559 (to B7-H1), MPDL3280A (to B7-H1), MEDI-570 (to ICOS), AMG557 (to B7H2), MGA271 (to B7H3), IMP321 (to LAG-3), BMS-663513 (to CD137), PF-05082566 (to CD137), CDX-1127 (to CD27), anti-OX40 (Providence Health Services), huMAbOX40L (to OX40 L), Atacicept (to TACI), CP-870893 (to CD40), Lucatumumab (to CD40), Dacetuzumab (to CD40), Muromonab-CD3 (to CD3), Ipilimumab (to CTLA-4). Immune therapies also include genetically engineered T-cells (e.g., CAR-T cells) and bispecific antibodies (e.g., BiTEs).

(269) GITR agonists include, but are not limited to, GITR fusion proteins and anti-GITR antibodies (e.g., bivalent anti-GITR antibodies), such as, a GITR fusion protein described in U.S. Pat. No. 6,111,090box.c, European Patent No.: 090505B1, U.S. Pat. No. 8,586,023, PCT Publication Nos.: WO 2010/003118 and 2011/090754, or an anti-GITR antibody described, e.g., in U.S. Pat. No. 7,025,962, European Patent No.: 1947183B1, U.S. Pat. Nos. 7,812,135, 8,388,967, 8,591,886, European Patent No.: EP 1866339, PCT Publication No.: WO 2011/028683, PCT Publication No.: WO 2013/039954, PCT Publication No.: WO2005/007190, PCT Publication No.: WO 2007/133822, PCT Publication No.: WO2005/055808, PCT Publication No.: WO 99/40196, PCT Publication No.: WO 2001/03720, PCT Publication No.: WO99/20758, PCT Publication No.: WO2006/083289, PCT Publication No.: WO 2005/115451, U.S. Pat. No. 7,618,632, and PCT Publication No.: WO 2011/051726.

(270) The compounds described herein can be used in combination with the agents disclosed herein or other suitable agents, depending on the condition being treated. Hence, in some embodiments the one or more compounds of the disclosure will be co-administered with other agents as described above. When used in combination therapy, the compounds described herein are administered with the second agent simultaneously or separately. This administration in combination can include simultaneous administration of the two agents in the same dosage form, simultaneous administration in separate dosage forms, and separate administration. That is, a compound described herein and any of the agents described above can be formulated together in the same dosage form and administered simultaneously. Alternatively, a compound of the disclosure and any of the agents described above can be simultaneously administered, wherein both the agents are present in separate formulations. In another alternative, a compound of the present disclosure can be administered just followed by and any of the agents described above, or vice versa. In some embodiments of the separate administration protocol, a compound of the disclosure and any of the agents described above are administered a few minutes apart, or a few hours apart, or a few days apart.

(271) As one aspect of the present invention contemplates the treatment of the disease/conditions with a combination of pharmaceutically active compounds that may be administered separately, the invention further relates to combining separate pharmaceutical compositions in kit form. The kit comprises two separate pharmaceutical compositions: a compound of the present invention, and a

second pharmaceutical compound. The kit comprises a container for containing the separate compositions such as a divided bottle or a divided foil packet. Additional examples of containers include syringes, boxes, and bags. In some embodiments, the kit comprises directions for the use of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing health care professional.

(272) All patents and other publications recited herein are hereby incorporated by reference.

(273) The processes presented below illustrate specific embodiments of the present invention.

These processes are meant to be representative and are not intended to limit the scope of the claims in any manner.

Representative Examples of the Invention

(274) The following intermediate compounds of 6-Fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propenyl)-3-pyridinyl)-4-((2S)-2-methyl-4-(2-propenoyl)-1-piperazinyl)pyrido[2,3-d]pyrimidin-2(1H)-one are representative examples of the invention and are not intended to be construed as limiting the scope of the present invention.

(275) A synthesis of Compound 9 and the relevant intermediates is described in U.S. Ser. No. 15/984,855, filed May 21, 2018, which claims priority to and the benefit claims the benefit of U.S. Provisional Application No. 62/509,629, filed on May 22, 2017, which are incorporated herein by reference in their entireties for all purposes. 6-Fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propenyl)-3-pyridinyl)-4-((2S)-2-methyl-4-(2-propenoyl)-1-piperazinyl)pyrido[2,3-d]pyrimidin-2(1H)-one was prepared using the following process, in which the isomers of the final product were isolated via chiral chromatography.

(276) ##STR00040## ##STR00041##

Step 1: 2,6-Dichloro-5-fluoronicotinamide (Intermediate S)

(277) To a mixture of 2,6-dichloro-5-fluoro-nicotinic acid (4.0 g, 19.1 mmol, AstaTech Inc., Bristol, PA) in dichloromethane (48 mL) was added oxalyl chloride (2M solution in DCM, 11.9 mL, 23.8 mmol), followed by a catalytic amount of DMF (0.05 mL). The reaction was stirred at room temperature overnight and then was concentrated. The residue was dissolved in 1,4-dioxane (48 mL) and cooled to 0° C. Ammonium hydroxide solution (28.0-30% NH₃ basis, 3.6 mL, 28.6 mmol) was added slowly via syringe. The resulting mixture was stirred at 0° C. for 30 min and then was concentrated. The residue was diluted with a 1:1 mixture of EtOAc/Heptane and agitated for 5 min, then was filtered. The filtered solids were discarded, and the remaining mother liquor was partially concentrated to half volume and filtered. The filtered solids were washed with heptane and dried in a reduced-pressure oven (45° C.) overnight to provide 2,6-dichloro-5-fluoronicotinamide. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.23 (d, J=7.9 Hz, 1H) 8.09 (br s, 1H) 7.93 (br s, 1H). m/z (ESI, +ve ion): 210.9 (M+H)⁺.

Step 2: 2,6-Dichloro-5-fluoro-N-((2-isopropyl-4-methylpyridin-3-yl)carbamoyl)nicotinamide

(278) To an ice-cooled slurry of 2,6-dichloro-5-fluoronicotinamide (Intermediate S, 5.0 g, 23.9 mmol) in THF (20 mL) was added oxalyl chloride (2 M solution in DCM, 14.4 mL, 28.8 mmol) slowly via syringe. The resulting mixture was heated at 75° C. for 1 h, then heating was stopped, and the reaction was concentrated to half volume. After cooling to 0° C., THF (20 mL) was added, followed by a solution of 2-isopropyl-4-methylpyridin-3-amine (Intermediate R, 3.59 g, 23.92 mmol) in THF (10 mL), dropwise via cannula. The resulting mixture was stirred at 0° C. for 1 h and then was quenched with a 1:1 mixture of brine and saturated aqueous ammonium chloride. The mixture was extracted with EtOAc (3×) and the combined organic layers were dried over anhydrous sodium sulfate and concentrated to provide 2,6-dichloro-5-fluoro-N-((2-isopropyl-4-methylpyridin-3-yl)carbamoyl)nicotinamide. This material was used without further purification in the following step. m/z (ESI, +ve ion): 385.1 (M+H)⁺.

Step 3: 7-Chloro-6-fluoro-1-(2-isopropyl-4-methylpyridin-3-yl)pyrido[2,3-d]pyrimidine-

2,4(1H,3H)-dione

(279) To an ice-cooled solution of 2,6-dichloro-5-fluoro-N-((2-isopropyl-4-methylpyridin-3-yl)carbamoyl)nicotinamide (9.2 g, 24.0 mmol) in THF (40 mL) was added KHMDS (1 M solution in THF, 50.2 mL, 50.2 mmol) slowly via syringe. The ice bath was removed and the resulting mixture was stirred for 40 min at room temperature. The reaction was quenched with saturated aqueous ammonium chloride and extracted with EtOAc (3×). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel chromatography (eluent: 0-50% 3:1 EtOAc-EtOH/heptane) to provide 7-chloro-6-fluoro-1-(2-isopropyl-4-methylpyridin-3-yl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 12.27 (br s, 1H), 8.48-8.55 (m, 2H), 7.29 (d, J=4.8 Hz, 1H), 2.87 (quin, J=6.6 Hz, 1H), 1.99-2.06 (m, 3H), 1.09 (d, J=6.6 Hz, 3H), 1.01 (d, J=6.6 Hz, 3H). ¹⁹F NMR (376 MHz, DMSO-d₆) δ: -126.90 (s, 1F). m/z (ESI, +ve ion): 349.1 (M+H).⁺.
Step 4: 4,7-Dichloro-6-fluoro-1-(2-isopropyl-4-methylpyridin-3-yl)pyrido[2,3-d]pyrimidin-2(1H)-one

(280) To a solution of 7-chloro-6-fluoro-1-(2-isopropyl-4-methylpyridin-3-yl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (4.7 g, 13.5 mmol) and DIPEA (3.5 mL, 20.2 mmol) in acetonitrile (20 mL) was added phosphorus oxychloride (1.63 mL, 17.5 mmol), dropwise via syringe. The resulting mixture was heated at 80° C. for 1 h, and then was cooled to room temperature and concentrated to provide 4,7-dichloro-6-fluoro-1-(2-isopropyl-4-methylpyridin-3-yl)pyrido[2,3-d]pyrimidin-2(1H)-one. This material was used without further purification in the following step. m/z (ESI, +ve ion): 367.1 (M+H).⁺.

Step 5: (S)-tert-Butyl 4-(7-chloro-6-fluoro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydropyrido[2,3-d]pyrimidin-4-yl)-3-methylpiperazine-1-carboxylate

(281) To an ice-cooled solution of 4,7-dichloro-6-fluoro-1-(2-isopropyl-4-methylpyridin-3-yl)pyrido[2,3-d]pyrimidin-2(1H)-one (13.5 mmol) in acetonitrile (20 mL) was added DIPEA (7.1 mL, 40.3 mmol), followed by (S)-4-N-Boc-2-methyl piperazine (3.23 g, 16.1 mmol, Combi-Blocks, Inc., San Diego, CA, USA). The resulting mixture was warmed to room temperature and stirred for 1 h, then was diluted with cold saturated aqueous sodium bicarbonate solution (200 mL) and EtOAc (300 mL). The mixture was stirred for an additional 5 min, the layers were separated, and the aqueous layer was extracted with more EtOAc (1×). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel chromatography (eluent: 0-50% EtOAc/heptane) to provide (S)-tert-butyl 4-(7-chloro-6-fluoro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydropyrido[2,3-d]pyrimidin-4-yl)-3-methylpiperazine-1-carboxylate. m/z (ESI, +ve ion): 531.2 (M+H).⁺.

Step 6: (3S)-tert-Butyl 4-(6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydropyrido[2,3-d]pyrimidin-4-yl)-3-methylpiperazine-1-carboxylate

(282) A mixture of (S)-tert-butyl 4-(7-chloro-6-fluoro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydropyrido[2,3-d]pyrimidin-4-yl)-3-methylpiperazine-1-carboxylate (4.3 g, 8.1 mmol), potassium trifluoro(2-fluoro-6-hydroxyphenyl)borate (Intermediate Q, 2.9 g, 10.5 mmol), potassium acetate (3.2 g, 32.4 mmol) and [1,1'-

bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (661 mg, 0.81 mmol) in 1,4-dioxane (80 mL) was degassed with nitrogen for 1 min. De-oxygenated water (14 mL) was added, and the resulting mixture was heated at 90° C. for 1 h. The reaction was allowed to cool to room temperature, quenched with half-saturated aqueous sodium bicarbonate, and extracted with EtOAc (2×) and DCM (1×). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel chromatography (eluent: 0-60% 3:1 EtOAc-EtOH/heptane) to provide (3S)-tert-butyl 4-(6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydropyrido[2,3-d]pyrimidin-4-yl)-3-methylpiperazine-1-carboxylate. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.19 (br s, 1H), 8.38 (d, J=5.0 Hz, 1H), 8.26 (dd, J=12.5, 9.2 Hz, 1H), 7.23-7.28 (m, 1H), 7.18 (d, J=5.0 Hz,

1H), 6.72 (d, J=8.0 Hz, 1H), 6.68 (t, J=8.9 Hz, 1H), 4.77-4.98 (m, 1H), 4.24 (br t, J=14.2 Hz, 1H), 3.93-4.08 (m, 1H), 3.84 (br d, J=12.9 Hz, 1H), 3.52-3.75 (m, 1H), 3.07-3.28 (m, 1H), 2.62-2.74 (m, 1H), 1.86-1.93 (m, 3H), 1.43-1.48 (m, 9H), 1.35 (dd, J=10.8, 6.8 Hz, 3H), 1.26-1.32 (m, 1H), 1.07 (dd, J=6.6, 1.7 Hz, 3H), 0.93 (dd, J=6.6, 2.1 Hz, 3H). ¹⁹F NMR (376 MHz, DMSO-d₆) δ: -115.65 (s, 1F), -128.62 (s, 1F). m/z (ESI, +ve ion): 607.3 (M+H)⁺.

Step 7: 6-Fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propanyl)-3-pyridinyl)-4-((2S)-2-methyl-4-(2-propenoyl)-1-piperazinyl)pyrido[2,3-d]pyrimidin-2(1H)-one

(283) Trifluoroacetic acid (25 mL, 324 mmol) was added to a solution of (3S)-tert-butyl 4-(6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydropyrido[2,3-d]pyrimidin-4-yl)-3-methylpiperazine-1-carboxylate (6.3 g, 10.4 mmol) in DCM (30 mL). The resulting mixture was stirred at room temperature for 1 h and then was concentrated. The residue was dissolved in DCM (30 mL), cooled to 0° C., and sequentially treated with DIPEA (7.3 mL, 41.7 mmol) and a solution of acryloyl chloride (0.849 mL, 10.4 mmol) in DCM (3 mL; added dropwise via syringe). The reaction was stirred at 0° C. for 10 min, then was quenched with half-saturated aqueous sodium bicarbonate and extracted with DCM (2×). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel chromatography (eluent: 0-100% 3:1 EtOAc-EtOH/heptane) to provide 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propanyl)-3-pyridinyl)-4-((2S)-2-methyl-4-(2-propenoyl)-1-piperazinyl)pyrido[2,3-d]pyrimidin-2(1H)-one. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.20 (s, 1H), 8.39 (d, J=4.8 Hz, 1H), 8.24-8.34 (m, 1H), 7.23-7.32 (m, 1H), 7.19 (d, J=5.0 Hz, 1H), 6.87 (td, J=16.3, 11.0 Hz, 1H), 6.74 (d, J=8.6 Hz, 1H), 6.69 (t, J=8.6 Hz, 1H), 6.21 (br d, J=16.2 Hz, 1H), 5.74-5.80 (m, 1H), 4.91 (br s, 1H), 4.23-4.45 (m, 2H), 3.97-4.21 (m, 1H), 3.44-3.79 (m, 2H), 3.11-3.31 (m, 1H), 2.67-2.77 (m, 1H), 1.91 (s, 3H), 1.35 (d, J=6.8 Hz, 3H), 1.08 (d, J=6.6 Hz, 3H), 0.94 (d, J=6.8 Hz, 3H). ¹⁹F NMR (376 MHz, DMSO-d₆) δ ppm -115.64 (s, 1F), -128.63 (s, 1F). m/z (ESI, +ve ion): 561.2 (M+H)⁺.

(284) The present invention comprises the following steps wherein the resolution of the rac-Dione in Steps 4 and 5 promotes the successful separation of the atropisomers:

(285) ##STR00042## ##STR00043##

Process Description

(286) Step 1

(287) ##STR00044##

(288) TABLE-US-00002 MW Equivalents/ Material CAS # (g/mol) Volumes Moles Theoretical
2,6-dichloro-5-fluoro-3- 82671-06-5 209.99 1.0 equiv. 119.1 25 kg pyridinecarboxylic acid
DCM 74-09-2 84.93 16.51 equiv. 2354.9 200 kg DMF 68-12-2 73.09 0.068 equiv. 8.1 592 g (627 mL)
Oxalyl Chloride 79-37-8 126.93 1.25 equiv. 148.9 18.9 kg Ammonium Hydroxide 1336-21-6 35.05 5 equiv. 595.5 40.2 L Water 7732-18-5 18.02 N/A N/A 261 L

(289) To a solution of 2,6-dichloro-5-fluoro-3-pyridinecarboxylic acid (Compound 1) (25 kg; 119.1 mol) in dichloromethane (167 kg) and DMF (592 g) was added Oxalyl chloride (18.9 kg; 148.9 mol) while maintaining an internal temp between 15-20° C. Additional dichloromethane (33 kg) was added as a rinse and the reaction mixture stirred for 2 h. The reaction mixture is cooled then quenched with ammonium hydroxide (40.2 L; 595.5 mol) while maintaining internal temperature 0±10° C. The resulting slurry was stirred for 90 min then the product collected by filtration. The filtered solids were washed with DI water (3×87 L) and dried to provide 2,6-dichloro-5-fluoronicotinamide (Compound 2).

(290) Step 2

(291) ##STR00045##

(292) TABLE-US-00003 MW Equivalents Material CAS# (g/mol) Volumes Moles Theoretical
Amide 113237-20-0 209.99 1.0 equiv. 77.8 16.27 kg (2,6-dichloro-5- fluoronicotinamide) Oxalyl
Chloride 79-37-8 126.93 1.2 equiv. 93.8 11.9 kg (7.9 L) 730.7 kg Dichloromethane 75-09-2 84.93
N/A N/A (551.5 L) Aniline DCM Solution 1698293-93-4 150.22 1.1 equiv. 85.9 12.9 kg (Aniline

2-isopropyl-4- contained wt) methylpyridin-3- amine

(293) In reactor A, a solution of 2,6-dichloro-5-fluoronicotinamide (Compound 2) (16.27 kg; 77.8 mol) in dichloromethane (359.5 kg) was added oxalyl chloride (11.9 kg; 93.8 mol) while maintaining temp $\leq 25^{\circ}\text{C}$. for 75 min. The resulting solution was then headed to $40^{\circ}\text{C} \pm 3^{\circ}\text{C}$. and aged for 3h. Using vacuum, the solution was distilled to remove dichloromethane until the solution was below the agitator. Dichloromethane (300 kg) was then added and the mixture cooled to $0 \pm 5^{\circ}\text{C}$. To a clean, dry reactor (reactor B) was added, 2-isopropyl-4-methylpyridin-3-amine (ANILINE) (12.9 kg; 85.9 mol) followed by dichloromethane (102.6 kg). The ANILINE solution was azeodried via vacuum distillation while maintaining a internal temperature between $20\text{-}25^{\circ}$), replacing with additional dichloromethane until the solution was dry by KF analysis (limit $\leq 0.05\%$ o). The solution volume was adjusted to approx. 23 L volume with dichloromethane. The dried ANILINE solution was then added to reactor A while maintaining an internal temperature of $0 \pm 5^{\circ}\text{C}$. throughout the addition. The mixture was then heated to 23°C . and aged for 1 h. the solution was polish filtered into a clean reactor to afford 2,6-dichloro-5-fluoro-N-((2-isopropyl-4-methylpyridin-3-yl)carbamoyl)nicotinamide (Compound 3) as a solution in DCM and used directly in the next step.

(294) Step 3

(295) ##STR00046##

(296) TABLE-US-00004 MW Equivalents/ Material CAS # (g/mol) Volumes Moles Theoretical
Urea, solution in DCM N/A 385.22 1.0 equiv. 38.9 208.3 kg 2,6-dichloro-5-fluoro- (15 kg N-{[4-methyl-2- contained weight) (propan-2-yl)pyridin-3- yl]carbamoyl}pyridine- 3-carboxamide 2-methyltetrahydrofuran 96-47-9 86.13 N/A N/A 308 kg (358 L) Sodium tert-butoxide 865-48-5 96.11 2.0 equiv 97.8 9.4 kg Ammonium Chloride 12125-02-9 53.49 N/A 430 23.0 kg Hydrochloric Acid 7467-01-0 36.46 N/A 41 1.6 kg Magnesium Sulfate 7487-88-9 120.37 N/A 195 23.5 kg Sodium Chloride 7647-14-5 58.44 N/A 282 16.5 kg Heptane 142-82-5 100.21 N/A N/A 94 L 10% citric acid 75 kg

(297) A dichloromethane solution of 2,6-dichloro-5-fluoro-N-{[4-methyl-2-(propan-2-yl)pyridin-3-yl]carbamoyl}pyridine-3-carboxamide (UREA(Compound 3)) (15 kg contained; 38.9 mol) was solvent exchanged into 2-MeTHF using vacuum distillation while maintaining internal temperature of $20\text{-}25^{\circ}\text{C}$. The reactor volume was adjusted to 40 L and then additional 2-MeTHF was charged (105.4 kg). Sodium t-butoxide was added (9.4 kg; 97.8 mol) while maintaining $5\text{-}10^{\circ}\text{C}$. The contents where warmed to 23°C . and stirred for 3 h. The contents where then cooled to $0\text{-}5^{\circ}\text{C}$ and ammonium chloride added (23.0 kg; 430 mol) as a solution in 60 L of DI water. The mixture was warmed to 20°C and DI water added (15 L) and further aged for 30 min. Agitation was stopped and the layers separated. The aqueous layer was removed and to the organic layer was added DI water(81.7 L). A mixture of conc HCl (1.5 kg) and water (9 L) was prepared then added to the reactor slowly until pH measured between 4-5. The layers were separated, and the aqueous layer back extracted using 2-MeTHF (42.2 kg). The two organic layers combined and washed with a 10% citric acid solution (75 kg) followed by a mixture of water (81.7 L) and saturated NaCl (19.8 kg). The organic layer was then washed with saturated sodium bicarbonate (75 kg) repeateding if necessary to achieve a target pH of ≥ 7.0 of the aqueous. The organic layer was washed again with brine (54.7 kg) and then dried over magnesium sulfate (5 kg). The mixture was filtered to remove magnesium sulfate rinsing the filtered bed with 2-MeTHF (49.2 kg). The combined filtrate and washes where distilled using vacuum to 40 L volume. The concentrated solution was heated to 55°C . and heptane (10-12 kg) slowly added until cloud point. The solution was cooled to 23°C . over 2h then heptane (27.3 kg) was added over 2 h. The product slurry was aged for 3 h at $20\text{-}25^{\circ}\text{C}$. then filtered and washed with a mixture of 2-MeTHF (2.8 kg) and heptane (9 kg). The product was dried using nitrogen and vacuum to afford solid 7-chloro-6-fluoro-1-(2-isopropyl-4-methylpyridin-3-yl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (rac-DIONE (Compound 4)).

(298) Step 4

(299) ##STR00047##

(300) TABLE-US-00005 MW Equivalents/ Material CAS # (g/mol) Volumes Moles Theoretical
Rac-dione N/A 348.76 1.0 (+)-2,3-dibenzoyl-D- 17026-42-5 358.30 2.0 tartaric acid 2-
methyltetrahydrofuran 96-47-9 86.13 7.0 heptane 142-82-5 100.21 2.0 heptane 142-82-5 100.21
3.0 2-methyltetrahydrofuran 96-47-9 86.13 4.0 heptane 142-82-5 100.21 2.0

(301) To a vessel, an agitated suspension of Compound 4, (1.0 eq.) in 2-methyltetrahydrofuran (7.0 L/kg) was added (+)-2,3-dibenzoyl-D-tartaric acid (2.0 eq.) under an atmosphere of nitrogen. 2-MeTHF is chiral, but it is used as a racemic mixture. The different enantiomers of 2-MeTHF are incorporated randomly into the co-crystal. The resulting suspension was warmed to 75° C. and aged at 75° C. until full dissolution was observed (≤ 30 mins.). The resulting solution was polish filtered at 75° C. into a secondary vessel. To the polish filtered solution was charged n-Heptane (2.0 L/kg) at a rate that maintained the internal temperature above 65° C. The solution was then cooled to 60° C., seeded with crystals (0.01 kg/kg) and allowed to age for 30 minutes. The resulting suspension was cooled to 20° C. over 4 hours and then sampled for chiral purity analysis by HPLC. To the suspension, n-Heptane (3.0 L/kg) was charged and then aged for 4 hours at 20° C. under an atmosphere of nitrogen. The suspension was filtered, and the isolated solids were washed two times with (2:1) n-Heptane:2-methyltetrahydrofuran (3.0 L/kg). The material was dried with nitrogen and vacuum to afford M-Dione:DBTA:Me-THF complex (Compound 4a).

(302) Step 5

(303) ##STR00048##

(304) TABLE-US-00006 MW Equivalents/ Material CAS # (g/mol) Volumes Moles Theoretical M-
Dione/DBTA/Me- N/A 1228.08 1.0 74.2 46.9 kg THF cocrystal (25.9 kg corrected for M- dione)
Methyl tert-butyl ether 1634-04-4 88.15 45.0 17593 2100 L Disodium hydrogen 7558-79-4
141.96 2.0 148.4 21.1 kg phosphate USP purified water As needed Magnesium sulfate 7487-88-9
120.37 N/A N/A 25 kg Heptane 142-82-5 100.20 60.0 19322 2835 L

(305) To vessel A, a suspension of disodium hydrogen phosphate (21.1 kg, 2.0 equiv) in DI water (296.8 L, 6.3 L/kg) was agitated until dissolution was observed (≥ 30 min.). To vessel B, a suspension of the M-Dione:DBTA:Me-THF complex (Composition 4a) [46.9 kg (25.9 kg corrected for M-dione, 1.0 equiv.)] in methyl tert-butyl ether (517.8 L, 11.0 L/kg) was agitated for 15 to 30 minutes. The resulting solution from vessel A was added to vessel B, and then the mixture was agitated for more than 3 hours. The agitation was stopped, and the biphasic mixture was left to separate for more than 30 minutes. The lower aqueous phase was removed and then back extracted with methyl tert-butyl ether (77.7 L, 1.7 L/kg). The organic phases were combined in vessel B and dried with magnesium sulfate (24.8 kg, 0.529 kg/kg). The resulting suspension from vessel B was agitated for more than three hours and then filtered into vessel C. To vessel B, a methyl tert-butyl ether (46.9 L, 1.0 L/kg) rinse was charged and then filtered into vessel C. The contents of vessel C were cooled to 10° C. and then distilled under vacuum while slowly being warmed to 35° C. Distillation was continued until 320-350 kg (6.8-7.5 kg/kg) of methyl tert-butyl ether was collected. After cooling the contents of vessel C to 20° C., n-Heptane (278.7 L, 5.9 L/kg) was charged over one hour and then distilled under vacuum while slowly being warmed to 35° C. Distillation was continued until a 190-200 kg (4.1-4.3 kg/kg) mixture of methyl tert-butyl ether and n-Heptane was collected. After cooling the contents of vessel C to 20° C., n-Heptane (278.7 L, 5.9 L/kg) was charged a second time over one hour and then distilled under vacuum while slowly being warmed to 35° C. Distillation was continued until a 190-200 kg (4.1-4.3 kg/kg) mixture of methyl tert-butyl ether and n-Heptane was collected. After cooling the contents of vessel C to 20° C., n-Heptane (195.9 L, 4.2 L/kg) was charged a third time over one hour and then sampled for solvent composition by GC analysis. The vessel C suspension continued to agitate for more than one hour. The suspension was filtered, and then washed with a n-Heptane (68.6 L, 1.5 L/kg) rinse from vessel C. The isolated solids were dried at 50° C., and a sample was submitted for stock suitability. Afforded 7-chloro-6-fluoro-(1M)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]pyrido[2,3-

d]pyrimidine-2,4(1H,3H)-dione (M-DIONE) Compound 5M.

(306) The first-generation process highlighted above has been successfully scaled on 200+ kg of rac-dione starting material (Compound 5). In this process, seeding the crystallization with the thermodynamically-stable rac-dione crystal form (which exhibits low solubility) would cause a batch failure. Based on our subsequent studies, we found that increasing the DBTA equivalents and lowering the seed temperature by adjusting heptane charge schedule improves robustness of the process. The improved process is resistant to the presence of the thermodynamically-stable rac-dione crystal form and promotes successful separation of atropisomers. Subsequent batches will incorporate the improved process for large scale manufacture.

(307) Step 6

(308) ##STR00049##

(309) TABLE-US-00007 MW Equivalents/ Material CAS # (g/mol) Volumes Moles Theoretical M-DIONE N/A 348.76 1 equiv. 9.8 3.7 kg Toluene 108-88-3 92.14 N/A 375 34.6 kg (40 L) Phosphoryl chloride 10025-87-3 153.33 1.2 equiv. 11.7 1.8 kg (1.1 L) N,N- 7087-68-5 129.24 3.0 equiv. 29.4 3.8 kg (5.1 L) Diisopropylethylamine (s)-1-Boc-3- 147081-29-6 200.28 1.1 equiv. 10.8 2.214 kg methylpiperazine Sodium bicarbonate 144-55-8 84.01 N/A N/A 973 g Dichloromethane 75-09-2 84.93 N/A 871 74 kg (55.6 L) Sodium Chloride 7647-14-5 58.44 N/A 103 6.0 kg Ethyl acetate 141-78-6 88.11 N/A 288 25.4 kg (28.2 L)

(310) 7-chloro-6-fluoro-(1M)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (M-DIONE) (3.7 kg; 9.8 mol) was combined in reactor (A) with 10.5 kg of toluene and distilled down to an oil to remove water while maintaining a set point of 45° C. Toluene (21 kg) was added to the residue and the mixture stirred for 30 min at 40-45° C. The contents were cooled to 22° C. then phosphoryl chloride (1.8 kg; 11.7 mol) added. The mixture was cooled to 0-5° C. before adding N,N-Diisopropylethylamine (2.5 kg; 19.34 mol) while maintaining a temperature <5° C. The solution was aged for 3 h at 22° C. In a separate reactor (B), (s)-1-boc-3-methylpiperazine (2.21 kg; 10.8 mol) and N,N-diisopropylethylamine (1.26 kg; 9.75 mol) were combined in toluene (6 kg) and then charged to reactor (A) while maintaining <25° C. The reaction mixture was aged for 15 min at 22 C then quenched with sodium bicarbonate (973 g) in water (12.9 L) while maintaining a temperature <25 C. The mixture was stirred for 30 min then DCM (36.8 kg) added while continuing to stir for 1 h. The layers were allowed to separate, and the lower organic layer drained to reactor (C). The aqueous layer in reactor (A) was back extracted using DCM (18.4 kg) and the combined organic layers washed with brine solution (6.0 kg NaCl; 16.5 kg DI water). The organic layer was distilled under atmospheric pressure maintaining an internal temperature between 45-55 C. DCM is replaced during the distillation to azeotropically dry the solution. Following the distillation, the solution volume was adjusted to 19 L using DCM. The solution was cooled to 30 C and polish filtered. The filtrate was combined with ethyl acetate (8.5 kg) and then distilled at atmospheric pressure until 11-13 kg is collected in the receiver. The solution was seeded with 30 g of authentic product and aged for 1 h at 25-30° C. then further distilled under atmospheric pressure at 45-55 C internal temperature until 8.2 kg of distillate had been collected. The slurry was cooled to 22° C. and aged overnight then further cooled to 0-5° C. The product was collected by filtration and washed twice using ethyl acetate (4.2 kg each). The cake was dried with nitrogen and vacuum to afford tert-butyl (3S)-4-{7-chloro-6-fluoro-(1M)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]-2-oxo-1,2-dihydropyrido[2,3-d]pyrimidin-4-yl}-3-methylpiperazine-1-carboxylate (Compound 6, PIPAZOLINE).

(311) Step 7

(312) ##STR00050##

(313) TABLE-US-00008 MW Equivalents/ Material CAS # (g/mol) Volumes Moles Theoretical [1,1'- 72287- 731.714 0.020 1.01 0.74 kg Bis(diphenylphosphino) 26-4 ferrocene] dichloropalladium(II) Dichloromethane 75-09-2 84.93 N/A 400 kg 1,4-Dioxane 123-91-1 88.1052 5.0 N/A 168 kg Ethylenediaminetetraacetic 6381-92-6 336.207 1.0 45.2 15.2 kg acid disodium salt

dihydrate Heptane 142-82-5 100.21 200 kg Nitrogen As needed Pipazoline N/A 531.0 1.0 45.2 24.0 kg Potassium acetate 127-08-2 98.1417 5.0 225.99 22.2 kg Potassium trifluoro(2-fluoro- N/A 233.03 1.20 54.24 12.6 kg 6-hydroxyphenyl)borate 2-Propanol 67-63-0 66.10 N/A 850 kg Si-Thiol N/A N/A N/A 13.2 kg Sodium hydroxide 1310-73-2 40.00 6.5 kg USP purified water As needed

(314) To a reactor was added degassed dioxane (74.2 kg), tert-butyl (3S)-4-{7-chloro-6-fluoro-(1M)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]-2-oxo-1,2-dihydropyrido[2,3-d]pyrimidin-4-yl}-3-methylpiperazine-1-carboxylate (Compound 6, Pipazoline) (24.0 kg, 45.2 mol), potassium acetate (22.2 kg, 45.2 mol), and (dppf)PdCl.sub.2 (0.74 kg, 1.01 mol). The reactor was inerted with nitrogen gas. The solution was sparged with nitrogen gas until the oxygen content was <500 mg/L. The reaction was heated to 87.5° C. A solution of potassium trifluoro(2-fluoro-6-hydroxyphenyl)borate (12.6 kg, 54.3 mol) in degassed dioxane (49.4 kg) and degassed water (14.4 kg) with oxygen content <500 mg/L was transferred to the reaction, maintaining an internal temperature of 82.5° C.±7.5° C. The reaction was adjusted to 87.5° C.±1.5° C. and stirred for 75 min 15 min. A 1.0 M EDTA solution (47.3 kg) followed by water (40.1 kg) was charged to the reactor while maintaining an internal temperature of 85° C.±5° C. The reaction was cooled to 20° C.±3° C. over >2 h and then stirred for >16 h. The reaction was filtered and the crude solids were rinsed with water (3×120 kg). The solids were rinsed with a mixture of heptane (28.8 kg) and 2-propanol (33.1 kg) and then dried at <50° C. for >10 h. A clean reactor was loaded with crude solids and dichloromethane (240 kg). The contents were stirred at 20° C.±5° C. for >30 min. To the reactor was added Si-Thiol (144 kg) and dichloromethane (14.9 kg). The reaction was stirred at 20° C.±5° C. for 18 h. The reaction was filtered and rinsed with dichloromethane (84 kg). The solution was distilled and solvent swapped to 2-propanol. The reaction was heated to 60° C.±3° C. and heptane (108 kg) was 20 charged while maintaining a reaction temperature of 60° C.±3° C. The reaction was stirred for 45 min and then cooled and stirred at 20° C.±5° C. for 2.5 h. The reaction was filtered and rinsed with 50% v/v heptane/2-propanol (61.9 kg). The isolated solids were dried at <50° C. for >12 h to afford tert-butyl (3S)-4-{6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-(1M)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]-2-oxo-1,2-dihydropyrido[2,3-d]pyrimidin-4-yl}-3-methylpiperazine-1-carboxylate (Compound 7, BIARYL).

(315) Step 8

(316) ##STR00051##

(317) TABLE-US-00009 MW Equivalents/ Material CAS # (g/mol) Volumes Moles Theoretical
BIARYL 7 NA 606.67 1.0 equiv. 5.27 2.75 kg TFA 76-05-1 114.02 11 equiv. 49.7 5.67 kg DCM
74-09-2 84.93 5 vol NA 13.71 L Methanol 67-56-1 32.04 5 vol NA 13.71 L Water 7732-18-5
18.02 20 vol NA 54.8 L Potassium 584-08-7 138.20 18 equiv. 94.91 11.24 kg Carbonate DCM 74-
09-2 84.93 1 vol NA 2.75 L Water 7732-18-5 18.02 10 vol NA 27.5 L Water 7732-18-5 18.02 10
vol NA 27.5 L

(318) To a reactor was added tert-butyl (3S)-4-{6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-(1M)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]-2-oxo-1,2-dihydropyrido[2,3-d]pyrimidin-4-yl}-3-methylpiperazine-1-carboxylate (Compound 7, BIARYL) (2.75 kg, 5.27 mol), DCM (13.7 L), and TFA (5.67 kg, 49.7 mol). The reaction was stirred for 8-16 h at 20±5° C. To a second reactor was added potassium carbonate (11.24 kg), water (54.8 L), and methanol (13.7 L) to form a homogenous solution. The reaction mixture was added to the potassium carbonate solution over 2 h. The mixture was stirred at 20±5° C. for an additional 12 h. The resulting slurry was filtered and rinsed with water (2×27.5 L). The wet cake was dried for 24 h to give 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-4-[(2S)-2-methylpiperazin-1-yl]-(1M)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]pyrido[2,3-d]pyrimidin-2(1H)-one (Compound 8, DESBOC).

(319) Step 9

(320) ##STR00052##

(321) TABLE-US-00010 MW Equivalents/ Material CAS # (g/mol) Volumes mmol mass volume

Des-BOS NA 506.56 10 equiv. 308.4 156.25 g Acryloyl 814-68-6 90.51 1.3 equiv. 401.0 36.29 g — chloride.sup.1 — NMP 872-50-4 99.13 4 vol NA — 625 mL N-methyl pyrrolidinone.sup.2 Water 7732-18-5 18.02 20 vol NA 3125 g 3125 mL Na.sub.2HPO4.sup.3 7558-79-4 141.96 4 equiv. 1233.6 175.12 g — Water 7732-18-5 18.02 20 vol NA 3125 g 3,125 mL .sup.1acryloyl chloride was added over 7 mins on this scale. Avoid over cooling reaction. Colder reaction temperatures led to slower reaction time leading to higher levels of m/z 1066 impurity as the starting material reacts with the product. Ideal temp range is 22-25 C. .sup.2NMP content of dried cake typically 1-2 wt %. .sup.3Disodium phosphate in table is as anhydrous basis. Hydrate may be used, adjust mass accordingly to obtain desired mmol.

(322) 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-4-[(2S)-2-methylpiperazin-1-yl]-(1M)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]pyrido[2,3-d]pyrimidin-2(1H)-one (Compound 8, DESBOC) (156.25 g) was combined with N-methyl pyrrolidinone (625 mL) and stirred at ambient temperature. To the resulting solution was added acryloyl chloride (36.29 g; 401.0 mmol) while maintaining <30° C. internal temperature. The contents were stirred for 2 h at 25 C. In a separate reactor a solution of disodium phosphate (175.1 g; 1234 mmol) in DI water (3.1 L) was prepared. The crude product solution was then transferred to the reactor containing the disodium phosphate solution over >2 h at 25° C. The slurry was heated to 45° C. midway through the addition and after complete addition, aged for 2 h at the same temperature. The mixture was cooled to 25 C and aged for 4h before collecting the solids by vacuum filtration. The solids were washed twice with water (1.5 L each) and the product dried under nitrogen and vacuum to afford the product 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-(1M)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]-4-[(2S)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]pyrido[2,3-d]pyrimidin-2(1H)-one (crude Compound 9)..sup.4

(323) ##STR00053##

(324) TABLE-US-00011 MW Equivalents/ Material CAS # (g/mol) Volumes mmol mass volume
Crude Compound 9 NA 560.60 1.0 equiv. 253.9 142.33 g — Ethanol (200 proof) 64-17-5 — 7.5 V — — 1067 mL USP Water — 18.02 1.9 V — — 270 mL Acetic acid 64-19-7 60.05 1.5 equiv. 380.8 22.87 g 21.82 mL WFI Water — 18.02 15.5 vol — — 2200 mL Ethanol (for wash) 64-17-5 — 2.5 V — — 356 mL WFI Water (for wash) — — 5.0 V — — 712 mL Compound 9 seed.sup.5 — 560.60 0 — 0.3-0.7 g — .sup.5Seed performs best when reduced in particle size via milling or with other type of mechanical grinding if mill is not available (mortar/pestle). Actual seed utilized will be based on seed availability. 0.25%-0.5% is seed is target amount.

(325) 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-(1M)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]-4-[(2S)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]pyrido[2,3-d]pyrimidin-2(1H)-one (crude Compound 9) (142.33 g; 253.9 mmol) was combined with ethanol (996 mL) and water (270 mL). Acetic acid (21.8 ml; 380.8 mmol) was added and the mixture heated to 75° C. to form a solution which was polish filtered into a clean reactor. The solution was cool to 45° C. and then water (1067 mL) was added while maintaining an internal temperature >40° C. The solution was seeded with authentic Compound 9 and the resulting mixture aged for 30 min. Water (1138 mL) was then added over 2 h. The mixture was cooled to 25° C. and aged for 8h after which the solid was collected by vacuum filtration and washed using a mixture of ethanol (355.8 mL) and water (711.6 mL). The solid was dried using vacuum and nitrogen to obtain 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-(1M)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]-4-[(2S)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]pyrido[2,3-d]pyrimidin-2(1H)-one (Compound 9).

(326) Step A1 Reaction Scheme and Charge Table

(327) ##STR00054##

(328) TABLE-US-00012 MW Equivalents/ Mass Volume Material CAS # (g/mol) Volumes mol (g) (L) 3-Fluoroanisole 456-49-5 126.13 1.0 1.19 150 0.136 n-butyllithium (2.5M 109-72-8 64.06 1.5 1.78 N/A 0.712 in hexane) diisopropylamine 108-18-9 101.19 1.4 1.66 168 0.233 Triethylborate 150-46-9 145.99 2.0 2.38 347.5 0.405 Tetrahydrofuran 109-99-9 72.11 12 vol N/A N/A 1.8 Hydrochloric acid (2N) 7647-01-0 36.46 10 vol N/A N/A 1.5 Methyl tert-butyl ether 1634-04-4

88.15 12 Vol N/A N/A 1.8 Heptane 142-82-5 100.20 10.5 Vol N/A N/A 1.575

Reactor A was charged with THF (6 vol) and Diisopropylamine (1.4 equiv). The resulting solution was cooled to -70°C . and n-BuLi (2.5 M in hexane, 1.5 equiv) was slowly added. After addition is complete, a solution of 3-fluoroanisole (1.0 equiv) in THF (6 vol) was added slowly and kept at -70°C . for 5 min. B(EtO)₃ (2.0 equiv) was added slowly and kept at -70°C . for 10 min. The reaction mixture was quenched with 2N HCl. The quenched reaction mixture was extracted with MTBE (3×4 vol). The combined organic phases were concentrated to 1.5-3 total volumes. Heptane (7-9 vol) was added drop-wise and the mixture was cooled to $0-10^{\circ}\text{C}$. and stirred for 3 h. The mixture was filtrated and rinsed with heptane (1.5 vol). The solid was dried under nitrogen at $<30^{\circ}\text{C}$. to afford (2-fluoro-6-methoxyphenyl)boronic acid.

Step A2 Reaction Scheme and Charge Table

(329) ##STR00055##

(330) TABLE-US-00013 MW Equivalents/ Mass Volume Material CAS # (g/mol) Volumes mol (g) (L) (2-fluoro-6- 78495-63-3 169.95 1.0 0.118 20 N/A methoxyphenyl) boronic acid. Boron tribromide 10294-33-4 250.52 1.5 0.177 44.2 0.017 Dichloromethane 75-09-2 84.93 4 vol N/A N/A 0.080 Water 7732-18-5 18.02 13 vol N/A N/A 0.26 Methyl tert-butyl ether 1634-04-4 88.15 13 Vol N/A N/A 0.26 Heptane 142-82-5 100.20 10 Vol N/A N/A 0.20

Reactor A was charged with dichloromethane (4 vol) and 2-fluoro-6-methoxy-4-methylphenylboronic acid (1 equiv). The reaction mixture was cooled to -30°C . and 1.5 BBr₃ (1.5 equiv) was added dropwise. When the addition completed, the mixture was warmed to 25°C . and stirred 2 h. The reaction mixture was quenched into ice cold ($0-5^{\circ}\text{C}$.) water (10 vol). MTBE (10 vol) was added and the mixture warmed to 25°C . and stirred for 1-2 h or until all solids dissolved. The aqueous phase was separated and extracted with MTBE (3 vol). The combined organic extracts were washed with water (3 vol) and then concentrated to 1 total volumes. Heptane (10 vol) was added to the mixture and stirred for 2 h. The resulting product was isolated by filtration and dried at $<30^{\circ}\text{C}$. to afford (2-fluoro-6-hydroxyphenyl)boronic acid.

Step A3 Reaction Scheme and Charge Table

(331) ##STR00056##

(332) TABLE-US-00014 MW Equivalents/ Mass Volume Material CAS # (g/mol) Volumes mol (kg) (L) (2-fluoro-6- 1256345-60-4 155.92 1.0 89.79 14.00 N/A hydroxyphenyl) boronic acid Citric acid 5949-29-1 210.14 1.64 147.26 30.94 N/A monohydrate Acetonitrile 75-05-8 41.05 21 Vol N/A 220.1 294 Potassium fluoride 7789-23-3 58.10 4.00 359.16 20.87 N/A USP Water 7732-18-5 18.02 2.0 Vol N/A 28.00 28.00 Celite N/A N/A N/A N/A 7.00 N/A 2-Propanol 67-63-0 60.10 25 Vol N/A 275 350

Step A3

(333) Potassium Fluoride (21.0 kg; 20.87 mol) was combined with water (28 L) in a reactor (reactor A) and the contents stirred for 30 min. In a separate reactor (reactor B), (2-fluoro-6-hydroxyphenyl)boronic acid (14.00 kg, 89.79 mol) was charged followed by acetonitrile (206.1 kg) and citric acid (30.94 kg; 147.26 mol) at 25°C . The contents of reactor A was added to reactor B at 25°C and stirred at that temperature for 10 h. The reaction mixture was filtered through a bed of celite (7.0 kg) and rinsed with acetonitrile (42 kg). The filtrate was combined with isopropanol (56 kg) and then distilled under vacuum at a temperature $<35^{\circ}\text{C}$. replacing the distilled volume to the reactor with isopropanol and repeated as needed to complete the solvent swap from acetonitrile to isopropanol. The slurry was cooled to 15°C and aged for 1 h before filtered and washing with 28 kg of isopropanol. The cake was dried using vacuum and nitrogen and packaged to afford Compound A3.

Resolution of the M-Dione Compound 5

(334) Chromatographic Resolution of M-Dione Intermediate

(335) Numerous chiral chromatographic techniques and methods were used to isolate the M-dione from Compound 4. The techniques and stationary phases are well known in the art and are outlined

in Table 1.

(336) ##STR00057##

(337) TABLE-US-00015 TABLE 1 Technique Stationary Phase Mobile Phase Yield.sup.Λ SFC Chiralpak ® AD 40% methanol/60% ~95% CO₂ * HPLC Chiralpak ® AD 90/10/0.1 ethanol/ ~94% methanol/ triethylamine HPLC Chiralpak ® IG 60/40/0.1 ethanol/ ~92% methanol/ Triethylamine Simulated Moving Chiralpak ® IC Acetonitrile ~96% Bed (SMB) .sup.Λ Yield is defined as % of available M-Dione that was recovered at the required purity of >98% ee. * This separation was performed multiple times. For each lot of material, the mobile phase may have been slightly modified to accommodate for variations in the lots. Additional mobile phases used for purification included: 1) 25/75 methanol/CO.sub.2, 2) 30/70 methanol/CO.sub.2, and 3) 50/50 methanol/CO.sub.2. The SFC, HPLC, and SMB techniques are well known in the art and the Chiralpak ® stationary phases are commercially available from commercial sources, such as Fisher Scientific and Daicel Corporation. However, it is desired to develop a more efficient process to isolate the M-Dione (Compound 5).

Classical Resolution

(338) The present invention is directed to the development of a viable classical resolution process for M/P-Dione racemate (Compound 4).

(339) A total of 100 cocrystal screening experiments were performed and three potential cocrystals of Dione were identified. Based on the highest area ratio of M/P-Dione in the residual solid and lowest area ratio in the supernatant, (+)-2, 3-dibenzoyl-D-tartaric acid (DBTA) was selected as the chiral reagent for resolution.

(340) According to the results from 100 cocrystal screening experiments and 20 more solvent screening, 2-MeTHF/n-heptane was found to provide a better resolution result than other solvent systems. Based on the solubility results of M-Dione cocrystal and P-Dione cocrystal in different ratios of 2-MeTHF and n-heptane, 2-MeTHF/n-heptane (1.4:1, v/v) was selected as the optimal solvent composition for resolution.

(341) In order to find out any possible form conversion to Dione racemate or M/P-Dione during crystallization process of chiral resolution, the solubility of M-Dione cocrystal, P-Dione cocrystal, M+P-Dione cocrystal mixture (1:1, w/w), Dione racemate and DBTA were determined at different temperatures in 2-MeTHF/n-heptane (1.4:1, v/v). No form change was observed for M-Dione cocrystal and P-Dione cocrystal at different temperatures for 7 days. However, Dione racemate Type C was obtained after stirring of a mixture of M+P-Dione cocrystal mixture (1:1, w/w) at different temperatures for 7 days. Dione racemate Type D (20 and 30° C.) or Dione racemate Type C (40, 50, 60 and 65° C.) were observed after stirring of Dione racemate at corresponding temperatures for 7 days. A solubility of ~100 mg/mL was observed under all the temperatures for DBTA.

(342) To further optimize the resolution process, the ternary phase diagram of M/P-Dione cocrystal was drawn based on the equilibrium solubility results and no eutectic point was obtained likely because racemate Type C could crystallize out when both M-Dione cocrystal and P-Dione cocrystal were present. Another ternary phase diagram of M/P-Dione was drawn based on the equilibrium solubility results and no eutectic point was obtained likely because Dione racemate Type C or Type D could crystallize out when both M-Dione and P-Dione were present.

(343) In summary, a chiral reagent (DBTA) and a solvent system ((2-MeTHF/n-heptane (1.4:1, v/v)) were identified for resolution of Dione racemate. Small scale crystallization process using the resolving reagent and solvent system could achieve a yield of 39% and ee purity of 99% for M-Dione. In addition, polymorphism of Dione racemate was observed and investigated during screening experiments.

(344) 2 Screening Experiment

(345) 2.1 Cocrystal Screening

(346) A total of 100 cocrystal screening experiments were performed using 20 acids and 5 solvent

systems (Results summarized in Table 2-1). In general, Dione racemate and acid in the molar ratio at 1:1 was mixed and stirred at RT for 3 days before isolation for XRPD. Based on the XRPD results, three potential acids that could form cocrystals of Dione racemate were identified, including (1S)-(-)-camphanic acid (FIG. 2-2), (+)-2, 3-dibenzoyl-D-tartaric acid (FIG. 2-3) and D-(+)-malic acid (FIG. 2-4). Four new freebase crystal forms were also obtained based on XRPD results, which were assigned as Dione racemate Type B-E.

(347) As showed in Table 2-2, the supernatant and residual solid of the three potential cocrystals were further tested by HPLC. The ratio of M-Dione/P-Dione was measured and summarized in Table 2-2. As a result, DBTA cocrystal showed an area ratio of M-Dione/P-Dione at 0.11 in the supernatant and 4.4 in the residual solid, which suggested that M-Dione and P-Dione showed a good resolution after forming cocrystal with DBTA. Thus, DBTA was selected as the chiral reagent for further resolution optimization.

(348) TABLE-US-00016 TABLE 2-1 Summary of cocrystal screening experiments Solvent 2-MeTHF/ MTBE/ H.sub.2O/ACN n-heptane n-heptane Acid Acetone (1:1, v/v) EtOAc (1:1, v/v) (1:1, v/v) blank Type B.sup.+ Type C.sup.+ Type C.sup.+ Type D.sup.+ Type E.sup.+ L-Aspartic acid Type B Type C Type C + acid Type D Type E (R)-1,4-Benzodioxane-2- Type B Type C Type C Type D Type E + acid carboxylic acid (1S)-(-)-Camphanic acid Type B Type C Cocrystal Cocrystal Cocrystal Type A* Type B* Type A* (-)-Camphoric acid Type B Type C + acid Type C + acid Type D Type E + acid (+)-2,3-Dibenzoyl-D-tartaric Type B Type C Amorphous Cocrystal Cocrystal acid Type A.sup.# Type A.sup.# D-Glutamic acid Type B Type C Type C + acid Type D Type E D-(+)-Malic acid Type B Type C Cocrystal Type D Type E Type A.sup.\$ (R)-(-)-Mandelic acid Type B Type C Type C Type D Type E + acid (-)-Menthylxyacetic acid Type B Type C Type C Type D Type E (S)-(+)- α - Type B Type C Type C Type D Type E Methoxyphenylacetic acid (R)-(+)- α -Methoxy- α - Type B Type C Type C Type D Type E trifluoromethylphenylacetic acid (R)-(-)-5-Oxo-2- Type B Type C Type C Type D Type E tetrahydrofurancarboxylic acid (R)-(+)-N-(1- Type B Type C Type C Type D Type E + acid Phenylethyl)succinamic acid (S)-(+)-2-Phenylpropionic Type B Type C Type C Type D Type E acid L-Pyroglutamic acid Type B Type C Type C Type D Type E + acid D-(+)-Quinic acid Type B + Type C Type C + acid Type D + acid Type E + acid acid L-(+)-Tartaric acid Type B Type C Type C Type D Type E L-Ascorbic acid Type Type C Type C+30acid Type D Type E B+acid N,N-Bis[(R)-(-)-1- Type B Type C Type C Type D Type E + acid phenylethyl]phthalamic acid (S)-phenylsuccinic acid Type B Type C Type C + acid Type D Type E + acid .sup.+Denotes crystal form of free rac-dione (no co-crystal formed), *(1S)-(-)-Camphanic acid cociystal, .sup.#(+)-2,3-Dibenzoyl-D-tartaric acid cociystal, .sup.sD-(+)-Malic acid cociystal

(349) TABLE-US-00017 TABLE 2-2 HPLC data summary of three cocrystals Peak area Supernatant Solid P-Dione M-Dione P-Dione M-Dione Sample (area) (area) M/P (area) (area) M/P (1S)-(-)-Camphanic acid cocrystal 9021.4 8274.2 0.9 6418.6 6360.4 1.0 Type A (810465-06-C3) (1S)-(-)-Camphanic acid cocrystal 4673.2 4303.4 0.9 4768.3 4736.9 1.0 Type B (810465-06-D3) DBTA cocrystal Type A 17673.1 1858.6 0.11 1180.2 5249.8 4.4 (810465-06-D5) D-(+)-Malic acid cocrystal Type A 11382.6 10696.5 0.9 6443.3 6366.7 1.0 (810465-06-C7)

2.2 Solvent Screening

(350) To select a suitable solvent to further resolute M-Dione and P-Dione, the area ratio from HPLC of M/P-Dione was collected in 20 more solvent/solvent mixtures. As listed in Table 2-3, 2-MeTHF showed the best resolution with the M-Dione/P-Dione area ratio of 0.7 in the supernatant and 4.1 in the residual solid. However, 2-MeTHF/n-heptane (1:1, v/v) showed a better resolution result during cocrystal screening (Table 2-2), thus 2-MeTHF/n-heptane was selected for further optimization. The area ratio from HPLC of M/P-Dione was collected in different ratios of 2-MeTHF/n-heptane with different acid/base ratios. Results in Table 2-4 showed that higher ratio of acid/FB (2:1 or 1.5:1) in 2-MeTHF/n-heptane (8:1 or 4:1, v/v) is desirable to improve the ratio of M/P-Dione in isolated solids.

(351) The solubility of M-cocrystal and P-cocrystal in different ratios of 2-MeTHF/n-heptane was

also performed at 5 and 25° C., which were summarized in Table 2-5. M-cocrystal was provided by client and P-cocrystal was prepared via reverse anti-solvent and anti-solvent (the experimental details refer to Section 4.3). The solubility result in Table 2-5 showed that the volume ratio of 2-MeTHF/n-heptane at 1.5:1 could afford the best resolution at RT. More resolution experiments were performed by client, from which a volume ratio of 1.4:1 showed the best resolution result. Thus, the volume ratio of 2-MeTHF/n-heptane at 1.4:1 was selected as the solvent system for resolution.

(352) TABLE-US-00018 TABLE 2-3 Solvent screening of Dione racemate DBTA cocrystal (M-Dione/P-Dione area ratio) Solvent Supernatant Solid 2-MeTHF 0.7 4.1 MTBE 0.04 3.5 MeOH 0.9 1.0 IPA 1.0 1.0 EtOH/n-heptane (1:1, v/v) 0.9 1.0 MIBK 0.9 1.0 MEK 1.0 1.0 IPAC 0.9 1.0 THF NA NA NMP NA NA DMSO/n-heptane (1:1, v/v) NA NA DMF/n-heptane (1:1, v/v) 0.9 1.0 Toluene/n-heptane (1:1, v/v) 0.8 1.0 Acetic acid NA NA Formic acid NA NA DCM NA NA Cumene 0.9 1.0 1-Butanol 0.9 1.0 n-Propanol 0.9 1.0 1,3 -Dimethyl-2-imidazolidinone 0.9 1.0 NA: A clear solution was obtained and no solid was isolated.

(353) TABLE-US-00019 TABLE 2-4 Results of acid/base ratio and 2-MeTHF/n-heptane ratio screening with Dione racemate DBTA cocrystal (M-Dione/P-Dione area ratio) Acid/base ratio 2-MeTHF/n-heptane (v/v) Form L S Form L S Form L S Form L S 8:1 CA 0.4 13.4 CA 0.4 8.9 CA 0.5 7.0 CA 0.6 2.6 4:1 CA 0.3 8.7 CA 0.3 6.2 CA 0.4 6.2 CA 0.4 5.7 2:1 CA 0.2 6.0 CA 0.2 5.6 CA 0.2 4.7 CA 0.2 5.2 1:2 CA 0.3 1.2 CA 0.1 1.3 CA 0.1 1.4 CA 0.1 1.7 1:4 DA 1.4 1.0 CA 0.4 1.0 CA + DA 0.1 1.0 CA 0.1 1.0 1:8 CA + DA 0.9 1.0 DA 0.5 1.0 DA 0.3 1.0 DA 0.3 1.0 L: Supernatant, S: Solid, CA: Cocrystal Type A, DA: Dione racemate Type A

(354) TABLE-US-00020 TABLE 2-5 2-MeTHF/n-heptane ratio screening of M/P-Dione cocrystals M-Dione P-Dione cocrystal cocrystal Temperature 2-MeTHF/n-heptane (v/v) Solubility (mg/mL) Solubility (° C.) heptane (mg/mL) XRPD (mg/mL) XRPD 5 1:1 11.3 Type A* 38.5 Type A.sup.# 1.5:1 17.3 Type A* 60.8 Type A.sup.# 2:1 22.2 Type A* 66.9 Type A.sup.# 3:1 28.6 Type A* 86.6 Type A.sup.# 4:1 30.8 Type A* 82.9 Type A.sup.# 6:1 47.1 Type A* 92.1 NA 8:1 55.1 Type A* 90.6 NA 25 1:1 13.4 Type A* 52.9 Type A.sup.# 1.5:1 20.3 Type A* 80.8 Type A.sup.# 2:1 28.1 Type A* 81.7 Type A.sup.# 3:1 39.0 Type A* 87.0 NA 4:1 43.0 Type A* 86.5 NA 6:1 53.2 Type A* 81.9 NA 8:1 65.0 Type A* 89.2 NA *M-cocrystal Type A .sup.#P-cocrystal Type A

2.3 Solubility of Dione DBTA Cocrystal, Dione Racemate and DBTA

(355) The 7-day equilibrium solubility of M-Dione cocrystal, P-Dione cocrystal, M+P-Dione cocrystal mixture (1:1, w/w) and Dione racemate were set up at different temperatures (20, 30, 40, 50, 60, 65, 75 and 80° C.) in 2-MeTHF/n-heptane (1.4:1, v/v). Color change was observed at 75 and 80° C. after 5 days suggestive of degradation, so the solubility was not collected. No form change was observed upon stirring of M-cocrystal and P-cocrystal at different temperatures for 7 days (FIG. 2-5 and FIG. 2-6). Dione racemate Type C was obtained after stirring of a mixture of M-Dione cocrystal and P-Dione cocrystal mixture (1:1, w/w) at different temperatures for 7 days (FIG. 2-7). Dione racemate Type D (20 and 30° C.) and Dione racemate Type C (40, 50, 60 and 65° C.) were observed after stirring of Dione racemate at different temperature for 7 days (FIG. 2-8 and FIG. 2-9).

(356) The 5-day equilibrium solubility of DBTA was set up at different temperatures (20, 30, 40, 50, 60 and 65° C.) in 2-MeTHF/n-heptane (1.4:1, v/v). A solubility of ~100 mg/mL was observed under all the temperatures. No significant difference was observed with varying temperatures (Table 2-7).

(357) TABLE-US-00021 TABLE 2-6 Solubility of Dione DBTA cocrystal, mixture of M/P-Dione cocrystal, Dione reamante in 2-MeTHF/n-heptane (1.4:1, v/v) Temp- Solubility Sample erature (mg/mL) ID Material (° C.) M-Dione P-Dione Crystal Form 1-01-A1 M-Dione 20 13.1 — M-cocrystal Type A 1-01-A2 cocrystal 30 15.8 — M-cocrystal Type A 1-01-A3 40 18.4 — M-cocrystal Type A 1-01-A4 50 17.2 — M-cocrystal Type A 1-01-A5 60 34.6 — M-cocrystal Type A 1-01-A6 65 35.4 — M-cocrystal Type A 1-01-B1 P-Dione, 20 — 39.4 P-cocrystal Type A 1-01-B2

cocrystal 30 — 56.5 P-cocrystal Type A 1-01-B3 40 — 55.8 P-cocrystal Type A 1-01-B4 50 — 79.9 P-cocrystal Type A 1-01-B5 60 — 113.9 P-cocrystal Type A 1-01-B6 65 — 110.0 P-cocrystal Type A 1-01-C1 M + P- 20 7.3 10.4 Dione racemate Dione Type C 1-01-C2 cocrystal 30 9.2 16.0 Dione racemate mixture Type C 1-01-C3 40 9.8 12.2 Dione racemate Type C 1-01-C4 50 12.1 21.9 Dione racemate Type C 1-01-C5 60 18.7 26.7 Dione racemate Type C 1-01-C6 65 13.4* 18.0* Dione racemate Type C 1-01-D1 Dione 20 18.0 15.2 Dione racemate racemate Type C 1-01-D2 30 20.1 17.1 Dione racemate Type C 1-01-D3 40 11.5 9.9 Dione racemate Type C 1-01-D4 50 14.2 11.8 Dione racemate Type C 1-01-D5 60 13.7 11.7 Dione racemate Type C 1-01-D6 65 15.3 13.1 Dione racemate Type C

(358) TABLE-US-00022 TABLE 2-7 Solubility of DBTA in 2-MeTHF/n-heptane (1.4:1, v/v)

Sample ID Temperature (° C.) Solubility (mg/mL) 1-15-A1 20 99.1 1-15-A2 30 100.3 1-15-A3 40 98.9 1-15-A4 50 88.0 1-15-A5 60 105.0 1-15-A6 65 96.1

2.4 Ternary Phase Diagram

2.4.1 M/P-Dione Cocrystals

(359) M-Dione cocrystal and P-Dione cocrystal were weighed as corresponding mass listed in the Table 2-8 and were stirred in 2-MeTHF/n-heptane (1.4:1, v/v) at RT for 72 hours. The ternary phase diagram of M/P-Dione cocrystal was drawn based on 72-hour equilibrium solubility data and no eutectic point was obtained (FIG. 2-10).

(360) TABLE-US-00023 TABLE 2-8 Solubility data summary for M/P-Dione cocrystals Weight of Weight of Supernatant Solid M-cocrystal P-cocrystal de [M] [P] de M P de # (mg) (mg) (%)

mg/mL	mg/mL (%)	[M]/[P]	mg	mg (%)	1	50.7	0	100.0	22.9	0.0	100.0	NA	27.8	0.0	100.0	2	0	99.7
-100.0	0.0	81.2	-100.0	NA	0.0	18.5	-100.0	3	21.1	83.4	-59.6	5.1	59.4	-84.2	11.6	80	16.0	24.0
-20.0	4	41	83.5	-34.1	5.9	45.0	-76.9	7.6	58	35.1	38.5	-4.6	5	84	85	-0.6	11.5	23.7
61.3	8.4	6	167.7	83.1	33.7	12.2	20.8	-26.2	1.7	11	155.5	62.3	42.8	7	49.7	50.4	-0.7	17.5
2.3	31	32.2	9.6	54.1	8	49.7	25	33.1	19.9	21.8	-4.6	1.0	95	29.8	3.2	80.7	9	49.2
37.9	0.4	51	27.9	2.6	82.9													

2.4.2 M/P-Dione

(361) M-Dione and P-Dione were weighed as corresponding mass listed in the Table 2-9 and were stirring in 2-MeTHF/n-heptane (1.4:1, v/v) at RT for 5 days. The ternary phase diagram was drawn based on 5-day equilibrium solubility data in 1.0 mL of 2-MeTHF/n-heptane (1.4:1, v/v) at RT. M-Dione Type A, P-Dione Type A, Dione racemate Type C and Type D were observed in the residual solid of solubility samples. No eutectic points were obtained in the phase diagram (FIG. 2-11).

(362) TABLE-US-00024 TABLE 2-9 Data summary of Ternary Phase Diagram for M/P-Dione

Weight of	Weight of Supernatant Solid M-Dione P-Dione de [M] [P] de M P de # (mg) (mg) (%)
mg/mL	mg/mL (%) [M]/[P] mg mg (%)
XRPD 1	99.3 0 100.0 80.1 0 100.0 NA 19.2 0.0 100.0 A 2
0	100.6 -100.0 0 77.1 -100.0 NA 0.0 23.5 -100.0 A 3 20.2 119.3 -71.0 7.7 50.3 -73.6 0.2 12.5
69.0	-69.2 A + RD 4 89.8 90.3 -0.3 16.2 17.5 -3.9 0.9 73.6 72.8 0.6 RD 5 121.1 40.7 49.7 53.0 1.6
94.2	33.4 68.1 39.1 27.0 A + RC 6 90.2 19.5 64.4 52.6 1.4 94.8 37.6 37.6 18.1 35.0 A + RC 7 41.6
39.9	2.1 9.8 9.0 4.4 1.1 31.8 30.9 1.4 RC 8 39.2 120.3 -50.8 7.6 48.1 -72.8 0.2 31.6 72.2 -39.1 A
+ RD 9	119.1 20.5 70.6 54.1 1.6 94.4 34.5 65.0 18.9 54.9 A + RC RC: Dione racemate Type C; RD: Dione racemate Type D; A: M or P-Dione Type A (the XRPD patterns of M-Dione Type A and P-Dione Type A were same and were not distinguished).

3 Solid State Characterization of Crystal Forms

(363) A total of five Dione racemate crystal forms and two cocrystal forms were obtained. All these forms were characterized by XRPD, TGA, DSC, PLM and .sup.1H NMR and summarized in Table 2-10. The solid state characterization data suggested Dione racemate Type A and Type D were identified as 2-MeTHF solvates, Type B as an acetone solvate, Type C as an anhydrate, and Type E as a MTBE solvate.

(364) Both M-Dione cocrystal Type A and P-Dione cocrystal Type A were found to be as 2-MeTHF solvates. All the characterization data are demonstrated in FIG. 3-1 to FIG. 3-22.

(365) TABLE-US-00025 TABLE 2-10 Summary of crystal forms Endotherm Sample ID Crystal form (peak, ° C.) TGA (wt %) .sup.1H NMR (wt %) 5-05-A Dione racemate Type A 110.2, 248.6, 213.4* 2.5 (150° C.) 2.4 (2-MeTHF) 1-10-A1 Dione racemate Type B 113.4, 126.0, 250.9 9.8 (150° C.) 6.2 (acetone) 1-01-D5 Dione racemate Type C 251.9 3.0 (150° C.) ND.sup.& 1-01-D1 Dione racemate Type D 120.5, 253.3 15.4 (150° C.) 12.0 (2-MeTHF) 1-10-A4 Dione racemate Type E 151.6, 158.6, 248.7 14.7 (160° C.) 7.5 (MTBE) 5-17-A M-Dione cocrystal Type A 109.6, 119.2 6.6 (125° C.) 10.6 (2-MeTHF) 5-16-A P-Dione cocrystal Type A 88.3, 112.3, 132.8 9.2 (140° C.) 10.6 (2-MeTHF) *exothermic peak; .sup.¬ detected.

3.1.1 Competitive Slurry of Dione Racemate Forms

(366) Dione racemate Type B~E were successfully re-produced via slurry of Dione racemate Type A in acetone, H.sub.2O/ACN (1:1, v/v), 2-MeTHF/n-heptane (1.4:1, v/v) and MTBE/n-heptane (1:1, v/v) at RT, respectively.

(367) Around 5 mg of each Dione racemate forms (Type A~E) were weighed into an HPLC vial, 0.3 mL of saturated Dione racemate solution in 2-MeHTF/n-heptane (1.4:1, v/v) was added into the vial and the mixture was then stirred at 20, 30, 40, 50, 60 and 65° C. for 5 days.

(368) All the freebase forms converted to Dione racemate Type C via competitive slurry in 2-MeHTF/n-heptane (1.4:1, v/v) at target temperatures, suggesting Dione racemate Type C is the most thermodynamically stable form in 2-MeHTF/n-heptane (1.4:1, v/v) from 20 to 65° C.

(369) TABLE-US-00026 TABLE 2-11 Competitive slurry results Starting Experiment Temperature Form ID Solvent (° C.) Solid Form Dione 1-16-B1 2-MeTHF/ 20 Dione racemate racemate n-heptane Type C Type 1-16-B2 (1.4:1, v/v) 30 Dione racemate A~E Type C 1-16-B3 40 Dione racemate Type C 1-16-B4 50 Dione racemate Type C 1-16-B5 60 Dione racemate Type C 1-16-B6 65 Dione racemate Type C

3.2 Preparation of P-Dione Cocrystal

3.2.1 Small Scale

(370) 2 g P-dione and 1 g DBTA were dissolved in 18 mL 2-MeTHF at 65° C. to get an almost clear solution. 18 mL heptane was added to this solution in 1 h. The solution was cooled to 20° C. over 4 h and aged overnight. The solution was evaporated using air blow at RT for about 1 h and a yellowish oily-like paste was obtained. Another 54 mL heptane was added to the mixture with stirring for 2 h. The suspension was filtered. The solid sample was assigned as 810465-16-A.

(371) 3.2.2 Large Scale

(372) 10 g P-dione and 5 g DBTA were dissolved in 100 mL 2-MeTHF at 65° C. The solution was filtered by 0.45 m PTFE filter and a clear solution was obtained. The clear solution was added dropwise to a suspension of 400 mL heptane containing ~1 g seeds (810465-16-A) produced from the first run. The suspension was kept stirring at RT for 5 h before isolation. About 10 g of the P-Dione cocrystal (810465-20-A) was produced with a yield of ~66%.

(373) 4 Instruments and Methods

(374) 4.1 XRPD

(375) For XRPD analysis, PANalytical X-ray powder diffract meters were used in reflection mode. The XRPD parameters used are listed in Table 4-1.

(376) TABLE-US-00027 TABLE 4-1 Parameters for XRPD test Parameters PANalytical PANalytical PANalytical Model Empyrean X' Pert.sup.3 X' Pert.sup.3 X-Ray Cu, α , Cu, α , Cu, α wavelength $\text{K}\alpha_1$ (Å): $\text{K}\alpha_1$ (Å): $\text{K}\alpha_1$ (Å): 1.540598, 1.540598, 1.540598, $\text{K}\alpha_2$ (Å): $\text{K}\alpha_2$ (Å): $\text{K}\alpha_2$ (Å): 1.544426 1.544426 1.544426 $\text{K}\alpha_2/\text{K}\alpha_1$ $\text{K}\alpha_2/\text{K}\alpha_1$ $\text{K}\alpha_2/\text{K}\alpha_1$ intensity intensity intensity ratio: 0.50 ratio: 0.50 ratio: 0.50 X-Ray tube 45 kV, 45 kV, 45 kV, setting 40 mA 40 mA 40 mA Divergence Automatic $\frac{1}{8}^\circ$ Fixed $\frac{1}{8}^\circ$ slit Scan mode Continuous Continuous Continuous Scan range 3° - 40° 3° - 40° 3° - 40° ($^\circ 2\text{TH}$) Scan step 17.8 46.7 18.9 time (s) Step size 0.0167 0.0263 0.0131 ($^\circ 2\text{TH}$) Test Time 5 min 30 s 5 min 04 s 4 min 15 s

4.2 TGA and DSC

(377) TGA data were collected using a TA discovery 550, Q500 and Q5000 TGA from TA

Instruments. DSC was performed using Q500, Q5000 and Discovery 2500 DSC from TA Instruments. Detailed parameters used are listed in Table 4-2 4-2.

(378) TABLE-US-00028 TABLE 4-2 Parameters for TGA and DSC tests Parameters TGA DSC Method Ramp Ramp Sample pan Aluminum, open Aluminum, crimped Temperature RT-350° C. 25° C.-300 ° C. Heating rate 10° C./min 10° C./min Purge gas N.sub.2 N.sub.2

4.3 HPLC

(379) Agilent 1100/1260 HPLC was utilized to test solubility, with detailed methods listed in Table 4-3.

(380) TABLE-US-00029 TABLE 4-3 HPLC method for solubility test HPLC Agilent 1100 with DAD detector Column CHIRALPAK IC-3, 4.6 × 100 mm, 3 μm Mobile phase A: n-Heptane B: MeOH/EtOH (1:1, v/v) Isocratic elution A:B = 75:25, 60:40 Run time 10.0 min Post time 0.0 min Flow rate 1.0 mL/min Injection volume 5 μL Detector wavelength UV at 215 nm Column temperature 40° C. Sampler temperature RT Diluent EtOH

(381) TABLE-US-00030 TABLE 4-4 HPLC method for solubility test (DBTA) HPLC Agilent 1260 with DAD detector Column Agilent ZORBAX 300SB-C3, 150 × 4.6 mm, 3.5 μm Mobile phase A: 0.05% TFA in H.sub.2O B: 0.05% TFA in ACN Isocratic elution A:B = 65:35 Run time 5.0 min Post time 0.0 min Flow rate 0.6 mL/min Injection volume 5 μL Detector wavelength UV at 215 nm Column temperature 40° C. Sampler temperature RT Diluent EtOH

4.4 .sup.1H NMR

(382) .sup.1H NMR spectrum was collected on Bruker 400M NMR Spectrometer using DMSO-d.sub.6 as solvent.

(383) 4.5 PLM

(384) Polarized light microscopic picture was captured on Nikon DS-Fi2 upright microscope at room temperature.

(385) Additional Screening of Compound 5 with 1,3-Diphenyl-3-Oxopropanesulfonic Acid 11b.

(386) Due to the low basicity of the pyridine moiety in compound 5 and the limited ‘hits’ in terms of the formation of crystalline salts using the standard screening set, it was chosen to screen racemic compound 4 with 1,3-diphenyl-3-oxopropanesulfonic acid 11b on a 0.06 mmol scale.

(387) ##STR00058##

(388) Gram scale resolution of racemic compound 5: A 250 mL round-bottom flask was charged with 2.0 g racemic compound 4 (5.7 mmol, 1.0 eq.) in 200 mL EtOH:AcOH (90:10 v:v). After the material had dissolved, 832 mg of sulfonic acid 11b (2.9 mmol, 0.5 eq.) was added to the solution. The clear solution was left to stir for 15 hours at a stirring speed of 800 rpm. A white precipitate had formed which was isolated from the mother liquor. The isolated salt was suspended in CH.sub.2Cl.sub.2 which was treated with a concentrated aqueous NaHCO.sub.3 solution using a separatory funnel. The organic layer was isolated and the basic aqueous layer was extracted with CH.sub.2Cl.sub.2 (2×). The organic layers were combined and dried over Na.sub.2SO.sub.3. Evaporation of the solvent yielded 415 mg of (M)-5 (96% ee) (see FIG. 6-1).

(389) The clear mother liquor was evaporated to dryness. The yellow oily material was dissolved in CH.sub.2Cl.sub.2 and treated with a concentrated aqueous NaHCO.sub.3 solution using a separatory funnel. The organic layer was isolated and the basic aqueous layer was extracted with CH.sub.2Cl.sub.2 (2×). The organic layers were combined and dried over Na.sub.2SO.sub.3. Evaporation of the solvent yielded 1579 mg of 5 (23% ee in (P)-atropisomer; FIG. 6-2).

(390) Polymorph Screening on M-Dione DBTA Cocrystal

(391) 5 Characterization of Crystal Forms of M-Dione DBTA Cocrystal

(392) Polymorph screening experiments for the M-Dione were set up under 100 conditions using methods of slurry conversion, slow evaporation, slow cooling, anti-solvent addition, vapor diffusion, temperature cycling, and wet grinding. A total of 17 crystal forms (Type A Q) were obtained from the screening. The form relationship is shown in FIG. 4-1. The detailed characterization data are provided in Table 5-1 and the overlays of XRPD patterns are shown in

FIG. 5-1. Solid state characterization results suggested Type G is a hydrate, while the other Types are solvates.

(393) 5.1 Instruments and Methods

(394) 5.1.1 XRPD

(395) XRPD was performed with a Panalytical X'Pert.sup.3 Powder XRPD on a Si zero-background holder. The 20 position was calibrated against a Panalytical Si reference standard disc. The parameters used are listed in Table 5-a.

(396) TABLE-US-00031 TABLE 5-a Parameters for XRPD test Parameters Reflection Mode X-Ray wavelength Cu, $\text{K}\alpha$ $\text{K}\alpha_1$ (Å): 1.540598, $\text{K}\alpha_2$ (Å): 1.544426, $\text{K}\alpha_2/\text{K}\alpha_1$ intensity ratio: 0.50 X-Ray tube setting 45 kV, 40 mA Divergence slit Fixed $\frac{1}{8}^\circ$ Scan mode Continuous Scan range 3-40 ($^\circ 2\text{TH}$) Scan step time [s] 18.87 Step size 0.0131 ($^\circ 2\text{TH}$) Test Time 4 min 15 s

5.1.2 TGA/DSC

(397) TGA data was collected using a TA Discovery 550 TGA from TA Instrument. DSC was performed using a TA Q2000 DSC from TA Instrument. DSC was calibrated with Indium reference standard and the TGA was calibrated using nickel reference standard. Detailed parameters used are listed in Table 5-b.

(398) TABLE-US-00032 TABLE 5-b Parameters for TGA and DSC test Parameters TGA DSC Method Ramp Ramp Sample pan Platinum, open Aluminum, crimped Temperature RT-desired temperature Heating rate 10°C./min Purge gas N.sub.2

5.2 Polymorph Screening

(399) The solubility of Type A (3-05-A) was estimated at RT. Approximately 2 mg solids were added into a 3-mL glass vial. Solvents in Table 5-c were then added stepwise (50/50/200/700 μL) into the vials until the solids were dissolved or a total volume of 2 mL was reached. Results summarized in Table 5-c were used to guide the solvent selection in polymorph screening.

(400) Polymorph screening experiments were performed using different crystallization or solid transition methods. The methods utilized and crystal types identified are summarized in Table 5-c.

(401) TABLE-US-00033 TABLE 5-c Approximate solubility of starting material (6010013-05-A) at RT Solvent Solubility (mg/mL) Solvent Solubility (mg/mL) MTBE $S < 3.1$ Acetone $S > 52.0$ H.sub.2O $2.4 < S < 8.0$ DMF $S > 40.0$ n-Heptane $3.0 < S < 10.0$ Anisole $S > 40.0$ Toluene $2.7 < S < 9.0$ Acetic acid $S > 40.0$ Hexanes $2.9 < S < 9.7$ THF $S > 50.0$ IPA $26.0 < S < 52.0$ ACN $S > 46.0$ 2-MeTHF $24.0 < S < 48.0$ CHCl_3 $S > 50.0$ 1,4-Dioxane $25.0 < S < 50.0$ EtOAc $S > 72.0$ n-BuOH $23.0 < S < 46.0$ DMSO $S > 72.0$ MIBK $38.0 < S < 76.0$ MeOH $S > 78.0$ BuOAc $S > 28.0$ EtOH $S > 68.0$ IPAc $S > 32.0$ — —

(402) TABLE-US-00034 TABLE 5-d Summary of polymorph screening experiments No. of Method Experiments Crystal Type Slurry at RT/ 5°C . 37 Type A~G, Type J, Type N, Type N Slow Evaporation 16 Type A, Type C, Type D, Type J, Type K, Type L, Type N, Type O Slow Cooling 9 Type C, Type J, Type L, Type O Anti-solvent Addition 9 Type A, Type C, Type H and Type I Liquid Vapor Diffusion 5 Type L, Type M, Type Q Solid Vapor Diffusion 6 Type A and M Temperature Cycling 7 Type A, Type G, Type O Wet Grinding 10 Type A Total 99 Type A~Q

5.2.1 Slurry at RT

(403) Slurry experiments were conducted at RT in different solvent systems. About 20 mg of Type A (3-05-A) was suspended in 0.2 mL of solvent in a 3-mL glass vial. After the suspension was stirred magnetically for 13 days at RT, the remaining solids were isolated for XRPD analysis. Results summarized in Table 5-e indicated that Type A-D and Type J were obtained.

(404) TABLE-US-00035 TABLE 5-e Summary of slurry experiments at RT Experiment ID Solvent (v:v) Solid Form 3-07-A1 MTBE Type B 3-07-A2 H.sub.2O Type A 3-07-A3 n-Heptane Low crystallinity 3-07-A4 Toluene Low crystallinity 3-07-A5 Hexanes Type A 3-07-A6* IPA Type A 3-07-A7* 2-MeTHF Type B 3-07-A8* 1,4-Dioxane Type J 3-07-A9 n-BuOH Low crystallinity 3-07-A10* MIBK Type A 3-07-A11 BuOAc Type C 3-07-A12 IPAc Type D 3-07-A13* Acetone Amorphous 3-07-A14* DMF Type P 3-07-A15 Anisole Type E 3-07-A16 THF/n-Heptane(1:9)

Low crystallinity 3-07-A17 2-MeTHF/n-Heptane(1:9) Type A 3-07-A18 IPA/H₂O(1:9) Type A 3-07-A19 IPAc/H₂O(1:9) Type F 3-07-A20 n-BuOH/H₂O(1:9) Type A 3-07-A21 n-BuOH/MTBE(1:9) Type A 3-07-A22 CHCl₃/MTBE(1:9) Type A 3-07-A23* MeOH/H₂O Amorphous (937:63, aw = 0.2) 3-07-A24* MeOH/H₂O Type N (844:156, aw = 0.4) 3-07-A25* MeOH/H₂O Type G (693:304, aw = 0.6) 3-07-A26 MeOH/H₂O Type G (569:431, aw = 0.8)
*Solid obtained via slow evaporation at RT

5.2.2 Slow Evaporation

(405) Slow evaporation experiments were performed under 16 conditions. Briefly, 20 mg of Type A (3-05-A) was dissolved in 0.2~0.8 mL of solvent in a 20-mL glass vial. If no dissolution was achieved, suspensions were filtered using a PTFE (pore size of 0.2 µm) and the filtrates were used for the following steps. The visually clear solutions were covered by Parafilm® with 5-10 pinholes and subjected to evaporation at RT. The solids were isolated for XRPD analysis. The results summarized in Table 5-f indicated that Type A, Type C, Type D, Type J, Type K, Type L, Type N, Type O were obtained.

(406) TABLE-US-00036 TABLE 5-f Summary of slow evaporation experiments

Experiment ID	Solvent (v:v)	Solid Form
3-08-A1	Acetic acid	Amorphous
3-08-A2	THF	Type J
3-08-A3	ACN	Amorphous
3-08-A4	CHCl ₃	Amorphous
3-08-A5	EtOAc	Type C
3-08-A6	DMSO	Amorphous
3-08-A7	MeOH	Amorphous
3-08-A8	EtOH	Type N
3-08-A9	1,4-Dioxane	Type J
3-08-A10	n-BuOH	Type A
3-08-A11	MIBK	Type O
3-08-A12	BuOAc	Type C
3-08-A13	IPAc	Type D
3-08-A14	Acetone	Type K
3-08-A15	DMF	Gel
3-08-A16	2-MeTHF	Type L

5.2.3 Slow Cooling

(407) Slow cooling experiments were conducted in 9 solvent systems. About 20 mg of Type A (3-05-A) was suspended in 1 mL of solvent in a 3-mL glass vial at RT. The suspension was then heated to 50° C., equilibrated for two hour and filtered using a PTFE membrane (pore size of 0.20 µm). Filtrates were slowly cooled down to 5° C. at a rate of 0.1° C./min. Results summarized in Table 5-g indicated Type C, Type G, Type J, Type L and Type O s were observed.

(408) TABLE-US-00037 TABLE 5-g Summary of slow cooling experiments

Experiment ID	Solvent (v:v)	Solid Form
3-09-A1*	IPA	Type O
3-09-A2	2-MeTHF	Type L
3-09-A3*	1,4-Dioxane	Type J
3-09-A4*	n-BuOH	Type L
3-09-A5*	Acetic acid	Type G (Low crystallinity)
3-09-A6	THF	Type J
3-09-A7*	ACN	Amorphous
3-09-A8	CHCl ₃	Low crystallinity
3-09-A9*	EtOAc	Type C

*Solids obtained from evaporation at RT.

5.2.4 Anti-Solvent Addition

(409) A total of 9 anti-solvent addition experiments were carried out. About 20 mg of starting material (3-05-A) was dissolved in 0.2-1.4 mL solvent to obtain a clear solution. The solution was magnetically stirred followed by addition of 0.2 mL anti-solvent stepwise till precipitate appeared or the total amount of anti-solvent reached 15.0 mL. The obtained precipitate was isolated for XRPD analysis. Results in Table 5-h showed that Type A, Type C, Type H and Type I were obtained.

(410) TABLE-US-00038 TABLE 5-h Summary of anti-solvent addition experiments

Experiment ID	Solvent	Anti-solvent	Solid Form
3-10-A1*	H ₂ O	Acetone	Type H
3-10-A2	THF		Amorphous
3-10-A3*	DMSO		Type I
3-10-A4*	MTBE	EtOH	Type A
3-10-A5*	CHCl ₃		Type A
3-10-A6	EtOAc		Type A
3-10-A7*	Acetone		Type C
3-10-A8*	n-heptane	2-MeTHF	Type A
3-10-A9*	IPAc		Type C

*Solids obtained from evaporation at RT.

5.2.5 Liquid Vapor Diffusion

(411) Five liquid vapor diffusion experiments were conducted. Approximate 20 mg of starting material (3-05-A) was dissolved in appropriate solvent to obtain a clear solution in a 3-mL vial. This solution was then placed into a 20-mL vial with 3 mL of volatile solvents. The 20-mL vial was sealed with a cap and kept at RT allowing sufficient time for organic vapor to interact with the solution. The precipitates were isolated for XRPD analysis. The results summarized in Table 5-i showed that Type L, Type M and Type Q were generated.

(412) TABLE-US-00039 TABLE 5-i Summary of liquid vapor diffusion experiments Experiment ID Solvent Anti-solvent Solid Form 3-11-A1 MIBK n-Heptane Type Q 3-11-A2 EtOAc IPA Type M 3-11-A3 THF MTBE Type L 3-11-A4 2-MeTHF n-Heptane Type L 3-11-A5* DMF Toluene Gel *Solids were obtained via evaporation at RT.

5.2.6 Solid Vapor Diffusion

(413) Solid vapor diffusion experiments were conducted using 6 different solvents. Approximate 10 mg of starting material (3-05-A) was weighed into a 3-mL vial, which was placed into a 20-mL vial with 2 mL of volatile solvent. The 20-mL vial was sealed with a cap and kept at RT for 7 days allowing solvent vapor to interact with sample. The solids were tested by XRPD and the results summarized in Table 51j showed that Type A and Type M were generated.

(414) TABLE-US-00040 TABLE 5-j Summary of solid vapor diffusion experiments Experiment ID Solvent Solid Form 3-12-A1 EtOH Type M 3-12-A2 MTBE Type A 3-12-A3 H₂O Type A 3-12-A4 acetone Amorphous 3-12-A5 2-MeTHF Type A 3-12-A6 IPAc Type A

5.2.7 Temperature Cycling

(415) Temperature cycling experiments were conducted in 7 solvent systems. About 20 mg of starting material (3-05-A) was suspended in 1 mL of solvent in a 3-mL glass vial at RT. The suspension was then heated to 50° C., equilibrated for one hour and filtered using a PTFE membrane (pore size of 0.20 µm). Filtrates were slowly cooled down to 5° C. at a rate of 0.2° C./min and then heat to 50° C. at a rate of 1° C./min. Repeat the cycle one more time and then cooling to 5° C. at a rate of 0.2° C./min. The samples were stored 5° C. before solids were isolated and analyzed using XRPD. Results summarized in Table 5-k indicated Type A, Type G and Type O were observed.

(416) TABLE-US-00041 TABLE 5-k Summary of temperature cycling experiments Experiment ID Solvent (v:v) Solid Form 3-13-A1* 2-MeTHF Type A 3-13-A2* MeOH Type G 3-13-A3* MIBK Type A 3-13-A4* ACN Amorphous 3-13-A5 CHCl₃ Low crystallinity 3-13-A6* Toluene Amorphous 3-13-A7* IPA Type O *Solids obtained from evaporation at RT.

5.2.8 Slurry at 5° C.

(417) Slurry experiments were conducted at 5° C. in different solvent systems. About 20 mg of starting material (3-05-A) was suspended in 0.2 mL of solvent in a 3-mL glass vial. After the suspension was stirred magnetically for 7 days at 5° C., the remaining solids were isolated for XRPD analysis. Results summarized in Table 5-1 indicated that Type A, Type C~Type E and Type J were obtained.

(418) TABLE-US-00042 TABLE 5-l Summary of slurry experiments at 5° C. Experiment ID Solvent (v:v) Solid Form 3-14-A1* BuOAc Type C 3-14-A2* IPAc Type D 3-14-A3* Acetone Low crystallinity 3-14-A4* DMF Gel 3-14-A5 Anisole Type E 3-14-A6* 2MeTHF Type A 3-14-A7* ACN Low crystallinity 3-14-A8* CHCl₃ Low crystallinity 3-14-A9* EtOAc Low crystallinity 3-14-A10* MeOH Type C 3-14-A11* THF Type J *Solids obtained from evaporation at RT.

5.2.9 Wet Grinding

(419) Wet grinding experiments were performed under five conditions. Briefly, 10 mg of Type A (3-05-A) was put in mortar and grinding in ~20 µL of solvent for 5 min. The solids were isolated for XRPD analysis. The results summarized in Table 5-in indicated that Type A was obtained.

(420) TABLE-US-00043 TABLE 5-m Summary of wet grinding experiments Experiment ID Solvent (v:v) Solid Form 3-15-A1 MTBE Amorphous 3-15-A2 H.sub.2O Amorphous 3-15-A3 n-Heptane Amorphous 3-15-A4 Toluene Amorphous 3-15-A5 Hexanes Amorphous 3-15-A6 IPA Amorphous 3-15-A7 2-MeTHF Type A (low crystallinity) 3-15-A8 1,4-Dioxane Type A 3-15-A9 n-BuOH Amorphous 3-15-A10 MIBK Amorphous

(421) TABLE-US-00044 TABLE 5-1 Characterization of M-dione DBTA cocrystal crystal forms Crystal Form Preparation Weight Loss DSC Endo. (Batch No.) Conditions in TGA (%) (Peak, ° C.) Form ID Type A Classic 7.31 up to 109.4 2-MeTHF (3-05-A) resolution with 125° C. 120.0 solvate DBTA (2- MeTHF) Type B Slurry at RT 7.21 up to 115.7 MTBE (3-07-A1) (MTBE) 125° C.

solvate Type C Slow 7.99 up to 92.7 EtOAc (3-08-A5) Evaporation 125° C. 116.4 solvate (EtOAc) Type D Slurry at RT 7.51 up to 75.4, 110.5, IPAc (3-07-A12) (IPAc) 130° C. 148.0, 116.6, solvate 265.9(exo). Type E Slurry at RT 8.63 up to 103.8 119.0 Anisole (3-07-A15) (Anisole) 125° C. Solvate Type F Slurry at RT 6.2 up to 86.5, 107.9 IPAc (3-07-A19) IPAc/H.sub.2O 130° C. solvate (v:v 1:9) Type G Slurry at RT 6.44 up to 86.0 Hydrate (3-07-A26) (MeOH/H.sub.2O 100° C. 127.2 133.1 aw = 0.8) Type H Anti-Solvent 3.58 up to 107.6 Acetone (3-10-A1) (Acetone/H.sub.2O) 130° C. solvate Type I Anti-Solvent 7.26 up to 128.9 DMSO (3-10-A3) (DMSO/H.sub.2O) 150° C. solvate Type J Slow 7.27% by 115.7 THF (3-08-A2) Evaporation 125° C. Solvate (THF) Type K Slow 5.71 up to 96.7, 119.8 Acetone (3-08-A14) Evaporation 150° C. 147.4 solvate (Acetone) 157.4° C.(exo). Type L Liquid Vapor 7.94 up to 126.2 2-MeTHF (3-11-A4) Diffusion 130° C. solvate (2-MeTHF/n- Heptane) Type M Liquid Vapor 3.73 up to 122.6 IPA (3-11-A2) Diffusion 150° C. solvate (EtOAc/IPA) Type N Slow 4.08 up to 85.4, 126.5 EtOH (3-08-A8) Evaporation 150° C. 150.9 solvate (EtOH) Type O Slow 2.03 up to 106.2, 151.2 MIBK (3-08-A11) Evaporation 130° C. solvate (MIBK) Type P Slow 8.33 up to 89.9 DMF (3-07-A14) Evaporation 130° C. solvate (DMF) Type Q Liquid Vapor 6.00 up to 92.9, 148.9 MIBK (3-11-A1) Diffusion 120° C. 170.0 solvate (MIBK/n- Heptane)

5.3 Type A

(422) Type A (3-05-A) was provided by client. The XRPD result showed in FIG. 5-4 suggested crystalline. As shown by TGA and DSC data in FIG. 5-5, a weight loss of 7.3% up to 125° C. and two endotherms at 109.4 and 120.0° C. (peak) were observed. As displayed in FIG. 5-6, the presence of 2-MeTHF was evidenced in .sup.1H NMR spectrum. Based on the results, Type A was considered as a 2-MeTHF solvate.

(423) 5.4 Type B

(424) Type B sample (3-07-A1) was obtained via slurry of Type A in MTBE at RT. XRPD pattern shown in FIG. 5-7 suggested crystalline. As shown by TGA and DSC data in FIG. 5-10, a weight loss of 7.2% up to 125° C. and an endotherm at 115.7° C. (peak) were observed. As displayed in FIG. 5-9, the presence of MTBE was evidenced in .sup.1H NMR spectrum. Based on the results, Type B was likely a MTBE solvate.

(425) 5.5 Type C

(426) Type C sample (3-08-A5) was obtained via slow evaporation in EtOAc at RT. XRPD pattern shown in FIG. 5-10 suggested crystalline. TGA and DSC data displayed in FIG. 5-11 indicated a weight loss of 8.0% up to 125° C. and two endotherms at 92.7° C. and 116.4° C. (peak). As displayed in FIG. 5-12, the presence of EtOAc was evidenced in .sup.1H NMR spectrum. Based on the results, Type C was likely an EtOAc solvate.

(427) 5.6 Type D

(428) Type D (3-07-A12) was obtained by slurry of Type A in IPAc at RT. The XRPD result showed in FIG. 5-13 suggested crystalline. As shown by TGA and DSC data in FIG. 5-14, a weight loss of 7.5% up to 130° C. and endotherms at 75.4° C., 110.5° C., 148.0° C. and 116.6° C. (peak) and an exotherm at 265.9° C. were observed. As displayed in FIG. 5-15, the presence of IPAc was evidenced in .sup.1H NMR spectrum. Based on the results, Type D was likely an IPAc solvate.

(429) 5.7 Type E

(430) Type E (3-07-A15) was obtained via slurry of Type A in anisole at RT. The XRPD result showed in FIG. 5-16 suggested crystalline. As shown by TGA and DSC data in FIG. 5-17, a weight loss of 8.6% up to 125° C. and two endotherms at 103.8° C. and 119.0° C. (peak) were observed. As displayed in FIG. 5-18, the presence of IPAc was evidenced in .sup.1H NMR spectrum. Based on the results, Type E was likely an anisole solvate.

(431) 5.8 Type F

(432) Type F (3-07-A19) was obtained via slurry of Type A in IPAc/H.sub.2O (v:v 1:9) at RT. The XRPD result showed in FIG. 5-19 suggested crystalline. As shown by TGA and DSC data in FIG. 5-20, a weight loss of 6.2% up to 130° C. and two endotherms at 86.5° C. and 107.9° C. (peak)

were observed. As displayed in FIG. 5-18, the presence of IPAc was evidenced in .sup.1H NMR spectrum. Based on the results, Type F was likely an IPAc solvate.

(433) 5.9 Type G

(434) Type G (3-07-A26) was obtained via slurry of Type A in MeOH/H.sub.2O (aw=0.8) at RT. The XRPD result showed in FIG. 5-22 suggested crystalline state. As shown by TGA and DSC data in FIG. 5-23, a weight loss of 6.4% up to 100° C. and endotherms at 86.0° C., 127.2° C. and 133.1° C. (peak) were observed. As displayed in FIG. 5-24, no signal for MeOH or MeTHF was observed in solution .sup.1HNMR spectrum. Based on the results, Type G was likely a hydrate.

(435) 5.10 Type H

(436) Type H (3-10-A1) was obtained via anti-solvent addition using Acetone/H.sub.2O. The XRPD result showed in FIG. 5-25 suggested crystalline. As shown by TGA and DSC data in FIG. 5-26, a weight loss of 3.6% up to 130° C. and an endotherm at 107.6° C. (peak) were observed. As displayed in FIG. 5-27, the presence of acetone was evidenced in .sup.1H NMR spectrum. Based on the results, Type H was likely an acetone solvate.

(437) 5.11 Type I

(438) Type I (3-10-A3) was obtained via anti-solvent addition using DMSO/H.sub.2O. The XRPD result showed in FIG. 5-28 suggested crystalline. As shown by TGA and DSC data in FIG. 5-29, a weight loss of 7.3% up to 150° C. and an endotherm at 128.9° C. (peak) were observed. As displayed in FIG. 5-30, the presence of DMSO was evidenced in .sup.1H NMR spectrum. Based on the results, Type I was likely a DMSO solvate.

(439) 5.12 Type J

(440) Type J (3-08-A2) was obtained via slow evaporation in THF. The XRPD result showed in FIG. 5-31 suggested crystalline. As shown by TGA and DSC data in FIG. 5-32, a weight loss of 7.3% up to 125° C. and an endotherm at 115.7° C. (peak) were observed. As displayed in FIG. 5-33, the presence of THF was evidenced in .sup.1H NMR spectrum. Based on the results, Type J was likely a THF solvate.

(441) 5.13 Type K

(442) Type K (3-08-A14) was obtained via slow evaporation in acetone. The XRPD result showed in FIG. 5-34 suggested crystalline. As shown by TGA and DSC data in FIG. 5-35, a weight loss of 5.7% up to 150° C. and endotherms at 96.7° C., 119.8° C. and 147.4° C. (peak) and an exotherm at 157.4° C. (peak) were observed. As displayed in FIG. 5-36, the presence of acetone was evidenced in .sup.1H NMR spectrum. Based on the results, Type K was likely an acetone solvate.

(443) 5.14 Type L

(444) Type L (3-11-A4) was obtained via liquid vapor diffusion in 2-MeTHF/n-Heptane. The XRPD result showed in FIG. 5-37 suggested crystalline with preferred orientation. As shown by TGA and DSC data in FIG. 5-38, a weight loss of 7.9% up to 130° C. and an endotherm at 126.2° C. (peak) were observed. As displayed in FIG. 5-39, the presence of acetone was evidenced while no signal for n-heptane was observed in .sup.1H NMR spectrum. Based on the results, Type L was likely a 2-MeTHF solvate.

(445) 5.15 Type M

(446) Type M (3-11-A2) was obtained from liquid vapor diffusion in EtOAc/IPA. The XRPD result showed in FIG. 5-40 suggested crystalline. As shown by TGA and DSC data in FIG. 5-41, a weight loss of 3.7% up to 150° C. and an endotherm at 122.6° C. (peak) were observed. As displayed in FIG. 5-42, the presence of IPA was evidenced while no signal for EtOAc was observed in .sup.1H NMR. Based on the results, Type M was likely an IPA solvate.

(447) 5.16 Type N

(448) Type N (3-08-A8) was obtained via slow evaporation in EtOH. The XRPD result showed in FIG. 5-43 suggested crystalline. As shown by TGA and DSC data in FIG. 5-44, a weight loss of 4.1% up to 150° C. and endotherms at 85.4° C., 126.5° C. and 150.9° C. (peak) were observed. As displayed in FIG. 5-45, the presence of EtOH was evidenced in .sup.1H NMR spectrum. Based on

the results, Type N was likely an EtOH solvate.

(449) 5.17 Type O

(450) Type O (3-08-A11) was obtained via slow evaporation in MIBK. The XRPD result showed in FIG. 5-46 suggested crystalline. As shown by TGA and DSC data in FIG. 5-47, a weight loss of 2.0% up to 130° C. and two endotherms at 106.2° C. and 151.2° C. (peak) were observed. As displayed in FIG. 5-48, the presence of MIBK was evidenced in .sup.1H NMR spectrum. Based on the results, Type O was likely a MIBK solvate.

(451) 5.18 Type P

(452) Type P (3-07-A14) was obtained via slow evaporation in DMF. The XRPD result showed in FIG. 5-49 suggested crystalline. As shown by TGA and DSC data in FIG. 5-50, a weight loss of 8.3% up to 130° C. and an endotherm at 89.9° C. (peak) were observed. As displayed in FIG. 5-51, the presence of DMF was evidenced in .sup.1H NMR spectrum. Based on the results, Type P was likely a DMF solvate.

(453) 5.19 Type Q

(454) Type Q (3-11-A1) was obtained via liquid vapor diffusion in MIBK/n-Heptane. The XRPD result showed in FIG. 5-52 suggested crystalline. As shown by TGA and DSC data in FIG. 5-53, a weight loss of 6.0% up to 120° C. and endotherms at 92.9° C., 148.9° C. and 170.0° C. (peak) were observed. As displayed in FIG. 5-54, the presence of MIBK was evidenced while no signal of N-Heptane observed in .sup.1H NMR spectrum. Based on the results, Type Q was likely a MIBK solvate.

(455) 6. Crystal data and Experimental for Composition 4a

(456) Experimental.

(457) Single colourless plate-shaped crystals of (Composition 4a) were used as received. A suitable crystal (0.28×0.18×0.09) mm.sup.3 was selected and mounted on a nylon loop with paratone oil on a Bruker APEX-II CCD diffractometer. The crystal was kept at T=173(2) K during data collection. Using Olex2 (Dolomanov et al., 2009), the structure was solved with the XT (Sheldrick, 2015) structure solution program, using the Intrinsic Phasing solution method. The model was refined with version of XL (Sheldrick, 2008) using Least Squares minimisation.

(458) Crystal Data.

(459) C.sub.65H.sub.72Cl.sub.2F.sub.2N.sub.8O.sub.15, M.sub.r=1314.20, triclinic, P1 (No. 1), a=11.5683(10) Å, b=11.6705(10) Å, c=13.9593(12) Å, α=68.1780(10)°, β=69.4150(10)°, γ=87.7760(10)°, V=1628.7(2) Å.sup.3, T=173(2) K, Z=1, Z'=1, μ(MoK.sub.α)=0.178, 26758 reflections measured, 11949 unique (R.sub.int=0.0528) which were used in all calculations. The final wR.sub.2 was 0.2465 (all data) and R.sub.I was 0.0835 (I>2(I)).p

(460) TABLE-US-00045 TABLE 6-2 Fractional Atomic Coordinates (×10.sup.4) and Equivalent Isotropic Displacement Parameters (Å.sup.2 × 10.sup.3) for COMPOSITION 4A. U.sub.eq is defined as 1/3 of the trace of the orthogonalised U.sub.ij. Atom x y z U.sub.eq O1C 5607(5)

3451(5) 6493(5) 44.9(14) O2C 6723(6) 4580(6) 6921(5) 49.9(15) O3C 3704(5) 3216(6) 5826(5) 45.6(14) O4C 2800(6) 3841(6) 4560(6) 55.9(16) O5C 3369(5) 5630(6) 6567(5) 50.2(15) O6C 3636(5) 3990(6) 7917(5) 50.8(15) O7C 5703(6) 2984(7) 4257(5)

55.4(16) O8C 6595(5) 4867(6) 3832(5) 49.1(15) C1C 5032(7) 4527(8) 6031(7) 41(2)

C2C 4615(7) 4267(8) 5203(7) 39.1(19) C3C 3928(8) 4667(8) 6968(7) 42(2) C4C

5705(8) 3954(9) 4361(7) 42(2) C5C 6393(8) 3601(8) 6961(7) 42(2) C6C 6820(9)

2403(8) 7493(8) 49(2) C7C 7721(15) 2378(12) 7941(13) 98(3) C8C 8179(15) 1311(13)

8410(13) 94(3) C9C 7697(17) 223(14) 8497(14) 107(5) C10C 6708(16) 185(12) 8178(13)

98(3) C11C 6265(15) 1303(12) 7665(13) 94(3) C12C 2953(8) 3028(9) 5341(7) 44(2) C13C

2359(9) 1762(9) 5860(8) 54(2) C14C 1223(9) 1501(10) 5822(8) 56(2) C15C 671(11)

300(12) 6312(10) 75(3) C16C 1261(14) -658(13) 6805(13) 98(5) C17C 2446(14) -407(13)

6720(13) 97(4) C18C 2954(13) 800(12) 6325(12) 87(4) Cl1B 6935(2) 1601(2) 11106(2)

66.0(7) F1B 4643(5) 1859(6) 10647(5) 66.7(16) O1B 8509(6) 7968(6) 7303(6) 58.0(17)

02B 4575(6) 6378(7) 8234(6) 66.1(19) N1B 7896(6) 6005(6) 8607(6) 40.4(16) N2B
 7345(6) 3931(7) 9798(6) 42.2(17) N3B 6567(7) 7139(7) 7745(6) 49.2(18) N4B
 11242(6) 5811(7) 8040(6) 47.4(18) C1B 7710(8) 7096(9) 7832(8) 48(2) C2B 7030(8)
 4974(8) 9152(6) 40(2) C3B 6537(8) 2952(9) 10275(7) 47(2) C4B 5411(8) 2909(8)
 10151(7) 47(2) C5B 5070(8) 3977(10) 9543(7) 49(2) C6B 5884(8) 5054(9) 9031(7)
 44(2) C7B 5584(8) 6210(9) 8328(8) 50(2) C8B 9103(7) 5996(7) 8717(7) 41(2) C9B
 9205(8) 6331(8) 9550(7) 43(2) C10B 10370(9) 6393(9) 9588(7) 49(2) C11B
 11350(8) 6131(8) 8840(7) 44(2) C12B 10113(7) 5734(7) 7981(7) 38.9(19) C13B
 8078(9) 6634(9) 10360(8) 55(2) C14B 10040(9) 5292(9) 7127(8) 54(2) C15B
 10546(10) 4041(10) 7234(10) 65(3) C16B 10688(11) 6301(12) 5939(9) 73(3) C11A
 11316(3) -588(3) 4003(3) 82.7(9) F1A 13799(6) -251(6) 4033(5) 77.9(18) O1A
 12158(6) 6025(6) 1115(6) 57.3(17) O2A 15430(6) 4363(7) 1981(6) 63.4(18) N1A
 11949(6) 3944(6) 2039(6) 38.9(16) N2A 11735(7) 1804(7) 3004(6) 48.6(19) N3A
 13776(6) 5170(7) 1580(6) 45.5(18) N4A 8608(6) 4153(7) 2689(6) 46.4(18) C1A
 12607(8) 5110(9) 1551(7) 47(2) C2A 12449(7) 2876(8) 2555(7) 40(2) C3A
 12216(10) 797(10) 3464(8) 56(2) C4A 13389(10) 813(9) 3546(8) 56(3) C5A 14083(9)
 1886(10) 3114(8) 54(2) C6A 13638(8) 2995(8) 2564(7) 44(2) C7A 14365(8) 4199(9)
 2043(8) 48(2) C8A 10709(7) 3834(8) 2039(6) 37.4(19) C9A 10540(8) 3371(9)
 1305(8) 47(2) C10A 9326(8) 3313(8) 1314(7) 47(2) C11A 8421(8) 3689(8) 2008(7)
 45(2) C12A 9733(7) 4227(7) 2738(7) 39.4(19) C13A 11568(8) 2995(10) 522(8) 55(2)
 C14A 9890(8) 4703(9) 3549(7) 50(2) C15A 9619(11) 6056(11) 3255(11) 71(3) C16A
 9045(10) 3875(11) 4734(8) 64(3) O3S 355(10) 1070(10) 9718(9) 116(3) C11S -300(40)
 -220(40) 11630(40) 142(14) C11T -1050(40) -700(50) 11410(40) 190(20) C12S 160(30)
 -310(30) 10410(20) 180(9) C13S 1360(40) -510(50) 10600(40) 151(11) C13T 1220(40)
 -820(40) 9990(40) 151(11) C14S 2240(20) 280(20) 9240(20) 155(8) C15S 1510(20) 1150(20)
 8834(18) 139(7) O2S 6461(8) -721(8) 5995(7) 83(2) C6S 5780(20) -1920(20) 5275(19)
 145(7) C7S 6000(20) -720(20) 5170(20) 155(8) C8S 7200(30) -180(30) 4150(30) 241(15) C9S
 7990(20) 670(20) 4390(20) 153(7) C10S 7490(30) 340(30) 5490(30) 202(11) O1S 4966(9)
 7468(9) 1097(8) 99(3) C1S 5930(20) 8160(20) 2110(20) 176(9) C2S 5018(15) 7306(16)
 2147(14) 105(5) C3S 3770(20) 7280(20) 2920(20) 146(7) C4S 3200(30) 8270(30) 2170(30)
 207(12) C5S 4180(20) 8430(20) 990(20) 162(8)

(461) TABLE-US-00046 TABLE 6-3 Anisotropic Displacement Parameters ($\times 10^3$)

COMPOSITION 4A. Atom U.sub.11 U.sub.22 U.sub.33 U.sub.23 U.sub.13 U.sub.12 O1C 37 (3)
 57 (4) 52 (3) -27 (3) -25 (3) 9 (3) O2C 47 (4) 54 (4) 52 (4) -21 (3) -21 (3) 4 (3) O3C 33 (3) 63
 (4) 39 (3) -21 (3) -10 (3) -3 (3) O4C 52 (4) 68 (4) 53 (4) -20 (4) -26 (3) 1 (3) O5C 34 (3) 56 (4)
 53 (4) -19 (3) -11 (3) 9 (3) O6C 44 (3) 71 (4) 35 (4) -21 (3) -11 (3) 3 (3) O7C 46 (4) 71 (5) 56 (4)
 -34 (4) -15 (3) 3 (3) O8C 33 (3) 56 (4) 55 (4) -22 (3) -11 (3) 7 (3) C1C 31 (4) 48 (5) 47 (5) -20
 (4) -14 (4) 1 (4) C2C 35 (5) 42 (5) 41 (5) -16 (4) -14 (4) 2 (4) C3C 37 (5) 52 (5) 39 (5) -21 (4)
 -14 (4) 2 (4) C4C 36 (5) 51 (5) 45 (5) -17 (4) -22 (4) 6 (4) C5C 40 (5) 48 (5) 35 (4) -16 (4) -11
 (4) 5 (4) C6C 58 (6) 45 (5) 51 (5) -22 (4) -26 (5) 10 (4) C7C 141 (9) 68 (6) 117 (8) -37 (6) -85
 (8) 23 (6) C8C 124 (9) 77 (6) 120 (8) -41 (6) -86 (7) 41 (6) C9C 155 (14) 87 (10) 133 (13) -53 (9)
 -107 (12) 68 (10) C10C 141 (9) 68 (6) 117 (8) -37 (6) -85 (8) 23 (6) C11C 124 (9) 77 (6) 120 (8)
 -41 (6) -86 (7) 41 (6) C12C 35 (5) 65 (6) 38 (5) -26 (5) -15 (4) 3 (4) C13C 50 (6) 59 (6) 56 (6)
 -23 (5) -23 (5) 6 (5) C14C 47 (6) 71 (7) 58 (6) -31 (5) -22 (5) 1 (5) C15C 54 (6) 101 (10) 73 (8)
 -34 (7) -22 (6) -21 (6) C16C 96 (10) 81 (9) 114 (11) -3 (8) -67 (9) -27 (8) C17C 98 (10) 73 (8)
 110 (11) -10 (8) -51 (9) -2 (7) C18C 88 (9) 77 (8) 102 (10) -20 (7) -56 (8) -9 (7) Cl1B 67.9 (16)
 57.4 (14) 64.2 (16) -10.1 (12) -27.3 (13) -6.4 (12) F1B 67 (4) 76 (4) 55 (3) -19 (3) -22 (3) -23
 (3) O1B 41 (4) 55 (4) 71 (4) -12 (3) -23 (3) -6 (3) O2B 36 (4) 89 (5) 78 (5) -31 (4) -28 (3) 11 (3)
 N1B 23 (3) 42 (4) 51 (4) -12 (3) -13 (3) -6 (3) N2B 33 (4) 54 (5) 35 (4) -14 (3) -10 (3) -5 (3)
 N3B 40 (4) 58 (5) 48 (4) -12 (4) -23 (4) 2 (4) N4B 35 (4) 47 (4) 59 (5) -17 (4) -18 (4) 7 (3) C1B

38 (5) 55 (6) 58 (6) -27 (5) -22 (4) 9 (5) C2B 37 (5) 53 (5) 27 (4) -15 (4) -9 (4) 1 (4) C3B 46 (5) 55 (6) 40 (5) -19 (4) -14 (4) 6 (4) C4B 49 (5) 54 (6) 36 (5) -16 (4) -14 (4) -12 (4) C5B 29 (5) 83 (7) 35 (5) -25 (5) -9 (4) -6 (5) C6B 32 (5) 64 (6) 37 (5) -21 (4) -10 (4) -8 (4) C7B 38 (5) 67 (6) 50 (5) -23 (5) -19 (4) 3 (4) C8B 34 (5) 43 (5) 48 (5) -15 (4) -19 (4) 2 (4) C9B 39 (5) 51 (5) 42 (5) -22 (4) -12 (4) 1 (4) C10B 49 (6) 59 (6) 42 (5) -20 (4) -20 (4) 10 (4) C11B 42 (5) 50 (5) 46 (5) -17 (4) -23 (4) 4 (4) C12B 28 (4) 42 (5) 47 (5) -17 (4) -14 (4) 2 (3) C13B 44 (5) 62 (6) 52 (6) -25 (5) -8 (4) 7 (5) C14B 40 (5) 62 (6) 61 (6) -26 (5) -18 (5) 0 (4) C15B 52 (6) 72 (7) 89 (8) -52 (6) -22 (6) 7 (5) C16B 66 (7) 99 (9) 50 (6) -23 (6) -21 (5) -10 (6) Cl1A 84 (2) 60.8 (16) 85 (2) -4.6 (15) -34.1 (16) -3.2 (14) F1A 89 (5) 73 (4) 76 (4) -21 (3) -45 (4) 31 (3) O1A 45 (4) 60 (4) 64 (4) -17 (4) -23 (3) 1 (3) O2A 42 (4) 87 (5) 76 (5) -38 (4) -33 (3) 8 (3) N1A 26 (3) 53 (4) 37 (4) -16 (3) -12 (3) 1 (3) N2A 41 (4) 59 (5) 37 (4) -13 (4) -9 (3) 0 (4) N3A 31 (4) 58 (4) 51 (4) -27 (4) -12 (3) -4 (3) N4A 36 (4) 59 (5) 40 (4) -16 (4) -12 (3) 1 (3) C1A 44 (5) 57 (6) 41 (5) -21 (4) -16 (4) 2 (5) C2A 30 (4) 65 (6) 33 (4) -26 (4) -13 (4) 12 (4) C3A 61 (6) 65 (6) 48 (6) -20 (5) -28 (5) 6 (5) C4A 57 (6) 55 (6) 60 (6) -29 (5) -19 (5) 18 (5) C5A 54 (6) 79 (7) 48 (5) -36 (5) -27 (5) 18 (5) C6A 34 (5) 59 (6) 45 (5) -26 (4) -15 (4) 13 (4) C7A 35 (5) 72 (6) 47 (5) -34 (5) -13 (4) 5 (5) C8A 32 (4) 46 (5) 30 (4) -10 (4) -12 (4) 6 (4) C9A 33 (5) 61 (6) 48 (5) -18 (4) -16 (4) 5 (4) C10A 38 (5) 59 (6) 46 (5) -17 (4) -18 (4) -5 (4) C11A 30 (5) 59 (6) 38 (5) -14 (4) -8 (4) -1 (4) C12A 31 (4) 47 (5) 34 (4) -9 (4) -10 (4) 3 (4) C13A 39 (5) 91 (7) 41 (5) -34 (5) -10 (4) 12 (5) C14A 36 (5) 73 (6) 46 (5) -31 (5) -12 (4) 5 (4) C15A 64 (7) 81 (8) 78 (8) -44 (6) -22 (6) 6 (6) C16A 58 (6) 96 (8) 39 (5) -21 (5) -25 (5) 16 (6) O3S 113 (8) 120 (8) 98 (7) -25 (6) -37 (6) 19 (7) The anisotropic displacement factor exponent takes the form: $-2\pi \cdot \text{sup.2}[\text{h} \cdot \text{sup.2a}^* \cdot \text{sup.2} \times \text{U} \cdot \text{sub.11} + \dots + 2\text{hka}^* \times \text{b}^* \times \text{U} \cdot \text{sub.12}]$

(462) TABLE-US-00047 TABLE 6-3 Bond Lengths in Å for COMPOSITION 4A. Atom Atom Length/Å

O1C	C1C	1.439(10)	O1C	C5C	1.341(10)	O2C	C5C	1.194(10)	O3C	C2C	1.427(10)
O3C	C12C	1.341(10)	O4C	C12C	1.215(11)	O5C	C3C	1.313(10)	O6C	C3C	1.193(10)
O7C	C4C	1.194(10)	O8C	C4C	1.306(10)	C1C	C2C	1.525(11)	C1C	C3C	1.528(12)
C2C	C4C	1.532(12)	C5C	C6C	1.478(13)	C6C	C7C	1.386(16)	C6C	C11C	1.358(16)
C7C	C8C	1.358(17)	C8C	C9C	1.35(2)	N3B	C1B	1.367(11)	N3B	C7B	1.385(12)
N4B	C11B	1.346(11)	N4B	C12B	1.346(10)	C2B	C6B	1.391(12)	C3B	C4B	1.378(13)
C4B	C5B	1.357(13)	C5B	C6B	1.389(12)	C6B	C7B	1.456(14)	C8B	C9B	1.400(12)
C8B	C12B	1.369(12)	C9B	C10B	1.372(12)	C9B	C13B	1.526(13)	C10B	C11B	1.359(13)
C12B	C14B	1.492(13)	C14B	C15B	1.526(14)	C14B	C16B	1.562(15)	C11A	C3A	1.714(11)
F1A	C4A	1.336(11)	O1A	C1A	1.216(11)	O2A	C7A	1.223(11)	N1A	C1A	1.386(11)
N1A	C2A	1.405(11)	N1A	C8A	1.446(10)	N2A	C2A	1.331(11)	N2A	C3A	1.321(12)
N3A	C1A	1.373(12)	N3A	C7A	1.368(12)	N4A	C11A	1.335(11)	N4A	C12A	1.335(11)
C2A	C6A	1.394(12)	C3S	C4S	1.53(3)	C4S	C5S	1.59(4)	C9C	C10C	1.373(19)
C10C	C11C	1.411(17)	C12C	C13C	1.454(14)	C13C	C14C	1.384(13)	C13C	C18C	1.366(16)
C14C	C15C	1.375(15)	C15C	C16C	1.375(18)	C16C	C17C	1.368(19)	C17C	C18C	1.375(18)
Cl1B	C3B	1.732(10)	F1B	C4B	1.339(10)	O1B	C1B	1.212(11)	O2B	C7B	1.221(11)
N1B	C1B	1.398(12)	N1B	C2B	1.381(10)	N1B	C8B	1.458(10)	N2B	C2B	1.344(11)
N2B	C3B	1.305(11)	C3A	C4A	1.402(14)	C4A	C5A	1.324(14)	C5A	C6A	1.419(13)
C6A	C7A	1.453(13)	C8A	C9A	1.393(12)	C8A	C12A	1.398(12)	C9A	C10A	1.405(12)
C9A	C13A	1.485(13)	C10A	C11A	1.339(13)	C12A	C14A	1.497(12)	C14A	C15A	1.527(16)
C14A	C16A	1.541(14)	O3S	C12S	1.51(3)	O3S	C15S	1.44(2)	C11S	C12S	1.64(5)
C11T	C12S	1.51(3)	C12S	C13S	1.49(5)	C12S	C13T	1.39(5)	C13S	C14S	1.70(5)
C13T	C14S	1.55(5)	C14S	C15S	1.39(3)	O2S	C7S	1.43(2)	O2S	C10S	1.52(3)
C6S	C7S	1.38(3)	C7S	C8S	1.54(4)	C8S	C9S	1.57(4)	C9S	C10S	1.34(3)
O1S	C2S	1.429(18)	O1S	C5S	1.41(2)	C1S	C2S	1.45(3)	C2S	C3S	1.46(3)

(463) TABLE-US-00048 TABLE 6-4 Bond Angles in for COMPOSITION 4A. Atom Atom Atom Angle/°

C5C	O1C	C1C	116.5(6)	C12C	O3C	C2C	117.1(7)	O1C	C1C	C2C	105.3(6)	O1C	C1C	C3C
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108.6(7) C3C C1C C2C 115.5(7) O3C C2C C1C 106.6(6) O3C C2C C4C 120.9(6) C1C C2C C4C
110.9(7) O5C C3C C1C 109.9(7) O6C C3C O5C 126.1(8) O6C C3C C1C 124.0(8) O7C C4C O8C
127.3(8) O7C C4C C2C 122.3(8) O8C C4C C2C 110.4(7) O1C C5C C6C 110.8(8) O2C C5C O1C
124.1(8) O2C C5C C6C 125.1(8) C7C C6C C5C 119.6(9) C11C C6C C5C 121.9(9) C11C C6C
C7C 118.1(10) C8C C7C C6C 122.4(12) C9C C8C C7C 119.1(13) C10C C9C C8C 120.6(12) C9C
C10C C11C 119.5(13) C6C C11C C10C 119.7(12) O3C C12C C13C 112.4(8) O4C C12C O3C
122.7(8) O4C C12C C13C 124.9(8) C14C C13C C12C 120.6(9) C18C C13C C12C 120.4(9) C18C
C13C C14C 118.8(10) C15C C14C C13C 120.1(10) C16C C15C C14C 120.5(10) C15C C16C
C17C 118.7(12) C16C C17C C18C 120.4(14) C13C C18C C17C 120.5(12) C1B N1B C8B
115.5(7) C2B N1B C1B 121.7(7) C2B N1B C8B 122.6(7) C3B N2B C2B 116.6(7) C1B N3B C7B
126.9(8) C12B N4B CHB 118.8(8) O1B C1B N1B 121.2(8) O1B C1B N3B 122.4(9) N3B C1B
N1B 116.3(8) N1B C2B C6B 119.7(8) N2B C2B N1B 117.3(7) N2B C2B C6B 123.1(8) N2B C3B
C11B 116.9(7) N2B C3B C4B 125.0(8) C4B C3B C11B 118.0(7) F1B C4B C3B 121.5(8) F1B
C4B C5B 120.2(8) CSB C4B C3B 118.3(8) C4B CSB C6B 119.2(8) C2B C6B C7B 120.9(8) C5B
C6B C2B 117.7(8) C5B C6B C7B 121.2(8) O2B C7B N3B 121.3(9) O2B C7B C6B 124.9(9) N3B
C7B C6B 113.8(7) C9B C8B N1B 118.0(7) C12B C8B N1B 120.2(7) C12B C8B C9B 121.7(7)
C8B C9B C13B 121.4(8) C10B C9B C8B 116.6(8) C10B C9B C13B 122.0(8) C11B C10B C9B
119.9(8) N4B C11B C10B 123.0(8) N4B C12B C8B 119.9(8) N4B C12B C14B 116.2(7) C8B
C12B C14B 123.8(7) C12B C14B C 15B 113.0(8) C12B C14B C16B 110.5(8) C15B C14B C16B
111.7(9) C1A N1A C2A 121.5(7) C1A N1A C8A 118.9(7) C2A N1A C8A 119.5(7) C3A N2A C2A
116.6(8) C7A N3A C1A 126.9(8) C12A N4A C11A 120.6(7) O1A C1A N1A 120.7(8) O1A C1A
N3A 122.4(8) N3A C1A N1A 116.9(8) N2A C2A N1A 116.6(7) N2A C2A C6A 124.3(8) C6A C2A
N1A 119.1(8) N2A C3A C11A 116.6(7) N2A C3A C4A 123.7(9) C4A C3A C11A 119.7(8) F1A
C4A C3A 119.7(9) C5A C4A F1A 121.1(9) C5A C4A C3A 119.2(9) C4A CSA C6A 119.7(9) C2A
C6A C5A 116.4(9) C2A C6A C7A 121.0(8) C5A C6A C7A 122.6(8) O2A C7A N3A 120.9(9) O2A
C7A C6A 124.4(9) N3A C7A C6A 114.7(8) C9A C8A N1A 118.0(7) C9A C8A C12A 122.2(7)
C12A C8A N1A 119.7(7) C8A C9A C10A 115.9(8) C8A C9A C13A 123.3(8) C10A C9A C13A
120.7(8) C11A C10A C9A 119.5(8) C10A C11A N4A 123.5(8) N4A C12A C8A 118.2(8) N4A
C12A C14A 118.8(7) C8A C12A C14A 123.0(7) C12A C14A C15A 110.2(8) C12A C14A C16A
109.8(8) C15A C14A C16A 111.6(9) C15S O3S C12S 101.0(16) O3S C12S C11S 98(2) C11T
C12S O3S 114(3) C13S C12S O3S 101(3) C13S C12S C11T 119(4) C13T C12S O3S 108(3) C13T
C12S C11S 124(4) C12S C13S C14S 94(3) C12S C13T C14S 106(3) C15S C14S C13S 105(2)
C15S C14S C13T 98(2) C14S C15S O3S 109.6(18) C7S O2S C10S 109.8(17) O2S C7S C8S
98(2) C6S C7S O2S 110(2) C6S C7S C8S 105(2) C7S C8S C9S 108(3) C10S C9S C8S 104(3)
C9S C10S O2S 110(2) C5S O1S C2S 99.3(14) O1S C2S C1S 115.3(16) O1S C2S C3S 109.3(14)
C1S C2S C3S 113.3(18) C2S C3S C4S 102.4(19) C3S C4S C5S 100(2) O1S C5S C4S 110(2)
(464) TABLE-US-00049 TABLE 6-5 Hydrogen Fractional Atomic Coordinates ($\times 10^4$) and
Equivalent Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for COMPOSITION 4A.
U_{sub.eq} is defined as 1/3 of the trace of the orthogonalised U_{sub.ij}. Atom x y z U_{sub.eq} H5C
2738 5676 7079 75 H8C 7257 4612 3523 74 H1C 5642 5286 5648 49 H2C 4246 5000 4813 47
H7C 8030 3133 7918 117 H8CA 8829 1329 8674 113 H9C 8046 -520 8781 129 H10C 6325 -589
8302 117 H11C 5582 1286 7440 113 H14C 824 2153 5456 67 H15C -125 131 6310 90 H16C 854
-1479 7197 118 H17C 2922 -1070 6936 117 H18C 3724 966 6375 104 H3B 6442 7830 7268 59
H5B 4284 3988 9467 59 H10B 10491 6619 10136 58 H11B 12147 6175 8883 53 H13A 7637 7233
9947 82 H13B 8351 6990 10789 82 H13C 7521 5873 10864 82 H14B 9141 5177 7246 64 H15A
11415 4105 7168 98 H15B 10492 3806 6645 98 H15D 10055 3410 7957 98 H16A 10303 7074
5885 109 H16B 10596 6013 5392 109 H16D 11573 6448 5797 109 H3A 14191 5912 1268 55 HSA
14875 1914 3171 65 H10A 9147 3010 831 57 H11A 7601 3622 2016 54 H13D 12178 3715 8 83
H13E 11236 2674 104 83 H13F 11970 2347 938 83 H14A 10773 4660 3501 60 H15E 9817 6386
3737 106 H15F 8738 6107 3360 106 H15G 10127 6543 2480 106 H16E 8174 3966 4816 96 H16F

9227 4126 5267 96 H16G 9198 3006 4874 96 H11D 403 121 11721 212 H11E -600 -1054 12212
 212 H11F -968 318 11703 212 H11G -1060 -259 11882 290 H11H -1114 -1599 11825 290 H11I
 -1750 -509 11154 290 H12S 128 -753 9931 215 H12A -557 -686 10345 215 H13G 1497 -1393
 10872 182 H13H 1451 -115 11089 182 H13I 1087 -1267 9548 182 H13J 1458 -1412 10592 182
 H14D 3019 696 9168 186 H14E 2460 -284 8839 186 H14F 2628 537 9673 186 H14G 2896 104
 8645 186 H15H 1338 997 8243 167 H15I 1947 1996 8512 167 H6SA 6575 -2283 5108 218 H6SB
 5393 -1922 4756 218 H6SC 5233 -2417 6034 218 H7S 5282 -222 5136 186 H8SA 7003 307
 3490 290 H8SB 7680 -861 4007 290 H9SA 8880 527 4152 184 H9SB 7923 1561 4003 184 H10D
 7155 1055 5667 243 H10E 8144 66 5812 243 H1SA 6626 7716 2249 264 H1SB 5541 8496 2685
 264 H1SC 6226 8839 1383 264 H2S 5277 6457 2441 126 H3SA 3789 7506 3528 175 H3 SB 3293
 6455 3231 175 H4SA 3168 9048 2302 249 H4SB 2364 7965 2275 249 H5SA 3745 8410 500 195
 H5SB 4689 9246 647 195

(465) TABLE-US-00050 TABLE 6-4 Hydrogen Bond information for COMPOSITION 4A. D H A
 d (D-H)/Å d (H-A)/Å d (D-A)/Å D-H-A/deg O5C H5C N4B.sup.1 0.84 1.82 2.656(9) 170.9 O8C
 H8C N4A 0.84 1.79 2.624(9) 171.6 N3B H3B O2S.sup.2 0.88 1.94 2.805(12) 168.1 C14B H14B
 N1B 1.00 2.44 2.937(12) 110.1 N3A H3A O1S.sup.3 0.88 1.95 2.798(12) 160.7 .sup.1-1 + x, + y,
 + z; .sup.2+ x, 1 + y, + z; .sup.31 + x, + y, + z

(466) TABLE-US-00051 TABLE 6-5 Atomic Occupancies for all atoms that are not fully occupied
 in COMPOSITION 4A. Atom Occupancy C11S 0.5 H11D 0.5 H11E 0.5 H11F 0.5 CUT 0.5 H11G
 0.5 H11H 0.5 H11I 0.5 H12S 0.5 H12A 0.5 C13S 0.5 H13G 0.5 H13H 0.5 C13T 0.5 H13I 0.5 H13J
 0.5 H14D 0.5 H14E 0.5 H14F 0.5 H14G 0.5

(467) The foregoing is merely illustrative of the invention and is not intended to limit the invention
 to the disclosed uses. Variations and changes, which are routine to one skilled in the art, are
 intended to be within the scope and nature of the invention, which are defined in the appended
 claims. All mentioned references, patents, applications and publications, are hereby incorporated by
 reference in their entirety, as if here written.

Claims

1. A process for preparing a composition of Formula (4a): ##STR00059## comprising reacting a compound of Formula (4) ##STR00060## with a compound of Formula (B1) ##STR00061## in the presence of 2-methyltetrahydrofuran to form the composition of Formula (4a).
2. The process of claim 1, wherein the process comprises preparing a suspension of the compound of Formula (4) in 2-methyltetrahydrofuran.
3. The process of claim 2, wherein the compound of Formula (B1) is added to the suspension of the compound of Formula (4) in 2-methyltetrahydrofuran to provide a mixture of the compound of Formula (4) and the compound of Formula (B1) in 2-methyltetrahydrofuran.
4. The process of claim 3, wherein a solution of Compound (4) and Compound (B1) in 2-methyltetrahydrofuran is prepared by heating the mixture of Compound (4) and Compound (B1) to dissolve any solids in the 2-methyltetrahydrofuran.
5. The process of claim 4, wherein heptane is added to the solution to provide a suspension of the composition of Formula (4a).
6. The process of claim 5, wherein, prior to adding heptane to the solution, the solution is filtered.
7. The process of claim 5, wherein the suspension of the composition of Formula (4a) is filtered to provide the composition of Formula (4a) in a crystalline state.
8. The process of claim 7, wherein the composition of Formula (4a) is treated with a base to produce a compound of Formula (5M): ##STR00062##
9. The process of claim 8, wherein the compound of Formula (5M) is used as an intermediate to generate a compound of Formula (9): ##STR00063##
10. A process for preparing a compound of Formula (5M): ##STR00064## the process comprising:

- a) reacting Compound (4): ##STR00065## with Compound (B1): ##STR00066## in the presence of 2-methyltetrahydrofuran to form a composition of Formula (4a): as crystals; ##STR00067## b) isolating the composition of Formula (4a); and c) treating the isolated composition Formula (4a) with a base to produce the compound of Formula (5M).
11. The process of claim 10, wherein the base is Na.sub.2HPO.sub.4.
12. The process of claim 10, wherein the base is NaHCO.sub.3.
13. The process of claim 10, wherein the compound of Formula (5M) is used as an intermediate to generate a compound having the Formula (9): ##STR00068##
14. The process of claim 13, wherein the method further comprises mixing the compound of Formula (9) with at least one pharmaceutically acceptable excipient to form a pharmaceutical composition.
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