[19] Patents Registry
The Hong Kong Special Administrative Region
香港特別行政區
專利註冊處

[11] 40045602 B
EP 3837256 B1

[12] **STANDARD PATENT (R) SPECIFICATION**
轉錄標準專利說明書

[21] Application no. 申請編號
62021035121.4

[22] Date of filing 提交日期
16.07.2021

[51] Int. Cl.
C07D 417/12 (2006.01) A61P 35/00 (2006.01)
A61K 31/4439 (2006.01)

[54] UREA COMPOUNDS AND COMPOSITIONS AS SMARCA2/BRM-ATPASE INHIBITORS
作為 SMARCA2/BRM-ATP 酶抑制劑的脲化合物和組合物

[30] Priority 優先權
17.08.2018 US 62/765,138

[43] Date of publication of application 申請發表日期
22.10.2021

[45] Date of publication of grant of patent 批予專利的發表日期
11.08.2023

[86] International application no. 國際申請編號
PCT/IB2019/056847

[87] International publication no. and date 國際申請發表編號及日期
WO2020/035779 20.02.2020

EP Application no. & date 歐洲專利申請編號及日期
EP 19779145.2 12.08.2019

EP Publication no. & date 歐洲專利申請發表編號及日期
EP 3837256 23.06.2021

Date of grant in designated patent office 指定專利當局批予專利日期
08.03.2023

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(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) **EP 3 837 256 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
08.03.2023 Bulletin 2023/10

(21) Application number: **19779145.2**

(22) Date of filing: **12.08.2019**

(51) International Patent Classification (IPC):
C07D 417/12 *(2006.01)* ***A61P 35/00*** *(2006.01)*
A61K 31/4439 *(2006.01)*

(52) Cooperative Patent Classification (CPC):
C07D 417/12; A61P 35/00

(86) International application number:
PCT/IB2019/056847

(87) International publication number:
WO 2020/035779 (20.02.2020 Gazette 2020/08)

(54) UREA COMPOUNDS AND COMPOSITIONS AS SMARCA2/BRM-ATPASE INHIBITORS

HARNSTOFFVERBINDUNGEN UND ZUSAMMENSETZUNGEN ALS SMARCA2/BRM-ATPASE-HEMMER

COMPOSÉS URÉIQUES ET COMPOSITIONS UTILISÉS EN TANT QU'INHIBITEURS DE SMARCA2/BRM-ATPASE

(84) Designated Contracting States:
AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR

(30) Priority: **17.08.2018 US 201862765138 P**

(43) Date of publication of application:
23.06.2021 Bulletin 2021/25

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- **JULIEN P. N. PAPILLON ET AL: "Discovery of Orally Active Inhibitors of Brahma Homolog (BRM)/SMARCA2 ATPase Activity for the Treatment of Brahma Related Gene 1 (BRG1)/SMARCA4-Mutant Cancers", JOURNAL OF MEDICINAL CHEMISTRY, vol. 61, no. 22, 19 October 2018 (2018-10-19), pages 10155-10172, XP055619669, US ISSN: 0022-2623, DOI: 10.1021/acs.jmedchem.8b01318**

Remarks:
The complete document including Reference Table(s) and the Sequence Listing(s) can be downloaded from the EPO website

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Description

SEQUENCE LISTING

[0001] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on November 30, 2016, is named PAT057524-US-PSP_SL.txt and is 31,078 bytes in size.

FIELD OF THE INVENTION

[0002] The present disclosure relates to compounds, compositions comprising such compounds, and their use for the treatment of BRM-mediated and/or BRG1-mediated disorders or diseases including BRG1/SMARCA4-mutant cancers.

BACKGROUND OF THE INVENTION

[0003] The mammalian SWI/SNF (mSWI/SNF) multi-protein complexes regulate chromatin structure through ATP-dependent nucleosome remodeling and thereby control many key cellular processes. Several subunits of the mSWI/SNF complexes have roles as tumor suppressors, and recent genomic studies revealed recurrent mutations in several of these subunits, with a collective mutation frequency of approximately 20% across all cancers. The catalytic SWI/SNF subunit BRG1, also known as SMARCA4, is frequently mutated in lung adenocarcinomas and other cancer types.

[0004] BRM (also known as SMARCA2) is the paralog of BRG1 (or BRM/SWI2-related gene 1, also known as SMARCA4), and these two proteins function as mutually exclusive ATP-dependent subunits within the mammalian SWI/SNF chromatin remodeling complex. Either BRM or BRG1 is required for cells to assemble a catalytically active SWI/SNF complex. Multiple variants of the SWI/SNF complex have been characterized with differing subunit composition, but only one catalytic subunit (BRM or BRG1) is present in each complex.

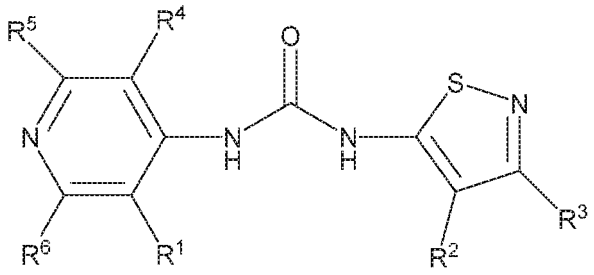
[0005] BRG1 has been shown to function as a tumor suppressor and is significantly mutated in human cancers. Evidence for the tumor suppressive function of BRG1 has been demonstrated by re-expression of wild type BRG1 in *BRG1*-mutant cell lines, resulting in differentiation and cell cycle arrest. Brg1 +/- mice develop mammary carcinoma with a 10% incidence in one year. Loss-of-function mutations in *BRG1* have been identified in ~30% of established non-small-cell lung cancer lines, and silencing of BRG1 is found in many other cancer cell lines and tumor samples, including lung, pancreatic, and ovarian cancers, melanomas, and pediatric rhabdoid sarcomas. Importantly, recent results from the Cancer Genome Atlas (TCGA) project identified *BRG1* mutations as a prominently mutated gene in tumor samples from patients with lung adenocarcinoma, occurring in ~10% of all tumor samples (a rate similar to other well characterized oncogenes and tumor suppressors such as *EGFR* and *LKB1*). The TCGA project has likewise identified BRM mutations and deletions in various cancers including that from lung.

[0006] Insights into therapeutic targeting of SWI/SNF mutant cancers have come from studies showing that residual SWI/SNF complexes play a role in the survival of cancers with SWI/SNF mutations. In particular, a synthetic lethal relationship was discovered between BRM and BRG1, the two ATPases of the complex, whereby loss of one leads to a dependency on the other. For example, BRM depletion was demonstrated to induce growth inhibition in BRG1-mutant cancer cells. Additionally, other studies have shown that SNF5-deficient tumor cells (SNF5 is a subunit of the SWI/SNF complex) are dependent on BRG1. Finally, certain cancers lacking SWI/SNF mutations have also been reported to be sensitive to BRG1 inhibition such as in acute myeloid leukemia (AML). Hence, the inhibition of certain SWI/SNF subunits, including BRG1 and BRM, presents opportunities for the development of novel therapeutic agents for the treatment of human diseases, including cancers.

SUMMARY OF THE INVENTION

[0007] The invention is defined in the appended claims. Also, for the avoidance of doubt, any references to methods of treatment in the subsequent paragraphs of this description are to be interpreted as references to the compounds, pharmaceutical compositions and medicaments of the present invention for use in a method for treatment of the human or animal body by therapy. There remains a need for new treatments and therapies for BRM-mediated and/or BRG1-mediated disorders or diseases. The present disclosure provides compounds, pharmaceutically acceptable salts thereof, pharmaceutical compositions thereof and combinations thereof, which compounds are BRM and/or BRG1 inhibitors. The present disclosure further provides method of treating BRM-mediated and/or BRG1-mediated disorders or diseases, comprising administering to a subject in need thereof an effective amount of a BRM and/or BRG1 inhibitor (e.g., compounds of the present disclosure).

[0008] One aspect of the present disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein R^1-R^6 are as defined herein.



Formula (I)

[0009] Another aspect of the present disclosure provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers.

[0010] In yet another aspect of the present disclosure, a pharmaceutical combination is provided which comprises a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and one or more therapeutically active agents.

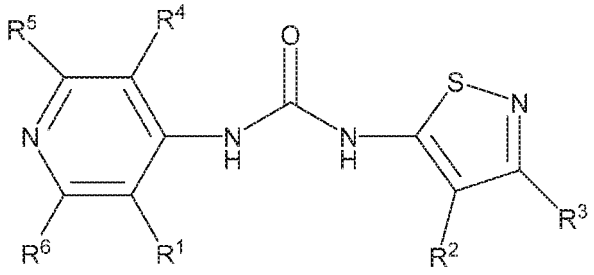
[0011] In yet another aspect of the present disclosure, a method is provided for treating BRM-mediated and/or BRG1-mediated disorders or diseases, which comprises administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0012] In yet another aspect of the present disclosure, processes are provided for preparing compounds of Formula (I), or a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION

[0013] Various (enumerated) embodiments of the disclosure are described herein. It will be recognized that features specified in each embodiment may be combined with other specified features to provide further embodiments of the present disclosure.

[0014] Embodiment 1: A compound of Formula (I)

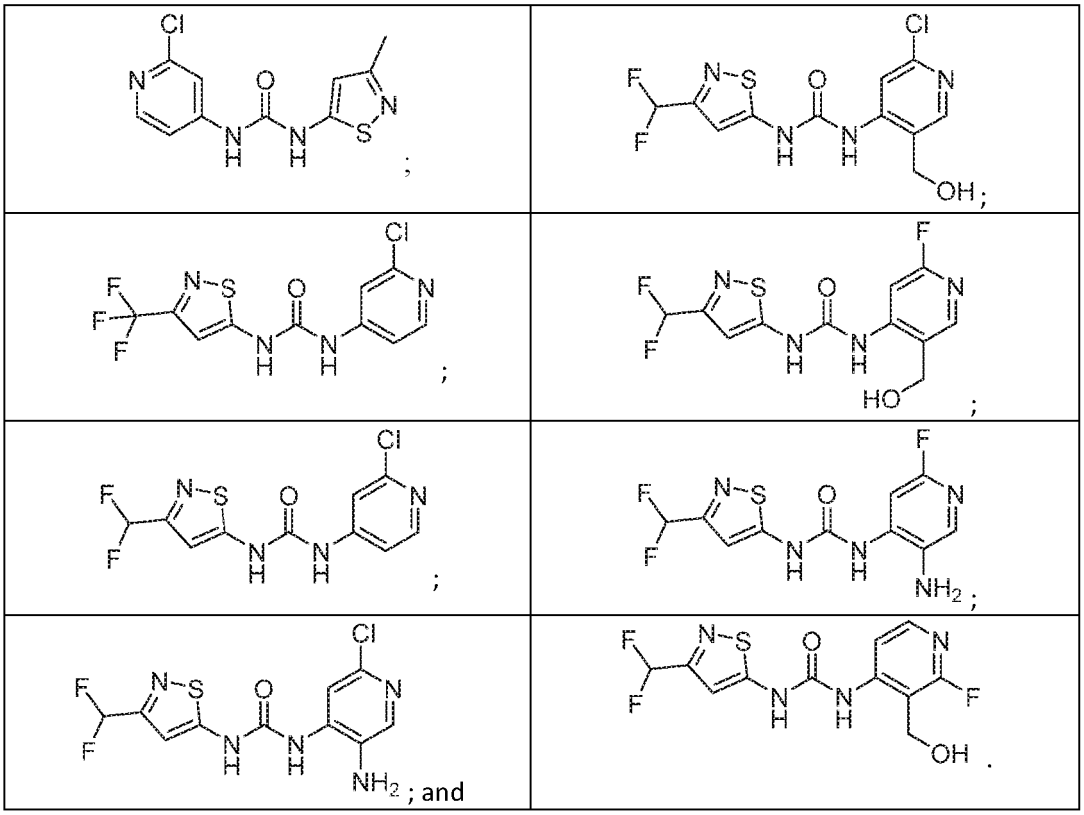


Formula (I)

or a pharmaceutically acceptable salt thereof, in which: R^1 is selected from hydrogen, amino and hydroxy-substituted $C_{1\text{-}2}$alkyl; R^2 is hydrogen; R^3 is selected from $C_{1\text{-}2}$alkyl and halo-substituted-$C_{1\text{-}2}$alkyl; R^4 is hydrogen; R^5 is selected from hydrogen and halo; and R^6 is selected from hydrogen and halo.

[0015] Embodiment 2: A compound or a pharmaceutically acceptable salt thereof according to Embodiment 1, in which: R^1 is selected from hydrogen, amino and hydroxy-methyl; R^2 is hydrogen; R^3 is selected from methyl, difluoromethyl and trifluoromethyl; R^4 is hydrogen; R^5 is selected from hydrogen, chloro and fluoro; and R^6 is selected from hydrogen and fluoro.

[0016] Embodiment 3: A compound or a pharmaceutically acceptable salt thereof according to Embodiment 1 selected from:



[0017] Embodiment 4: A pharmaceutical composition, comprising a therapeutically effective amount of a compound of according to any one of Embodiments 1 to 3 or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers.

[0018] Embodiment 5: A pharmaceutical combination, comprising a therapeutically effective amount of a compound according to any one of Embodiments 1 to 4 or a pharmaceutically acceptable salt thereof, and one or more therapeutically active agents.

[0019] Embodiment 6: A pharmaceutical combination according to Embodiment 5, where said one or more therapeutically active agents are independently selected from anti-cancer agents, anti-allergic agents, anti-emetics, pain relievers, immunomodulators and cytoprotective agents.

[0020] Embodiment 7: A method of treating a BRM-mediated and/or a BRG1-mediated disorder or disease, comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any one of Embodiments 1 to 27 or a pharmaceutically acceptable salt thereof.

[0021] Embodiment 8: A method according to Embodiment 7, wherein said disorder or disease is malignancy which is characterized by BRG1-deficiency and/or BRM-deficiency.

[0022] Embodiment 9: A method according to Embodiment 7 or 8, wherein said disorder or disease is malignancy which is characterized by BRG1 mutation and/or BRM mutation.

[0023] Embodiment 10: A method according to any one of Embodiments 7-9, wherein said disorder or disease is solid tumor, leukemia or lymphoma.

[0024] Embodiment 11: A method according to any one of Embodiments 7-10, wherein said disorder or disease is selected from the group consisting of non-small cell lung carcinoma, lung adenocarcinoma, lung carcinoma, large cell lung carcinomas, non-small cell lung carcinoma, lung squamous cell carcinoma, small cell lung cancer, skin cutaneous melanoma, desmoplastic melanoma, uveal melanoma, small cell carcinoma of the ovary (hypercalcemic type), ovarian rhabdoid tumor, cutaneous squamous cell carcinoma, glioma, uterine carcinosarcoma, uterine corpus endometrial carcinoma, ovarian serous cystadenocarcinoma, bladder urothelial carcinoma, primary central nervous system lymphoma, esophageal carcinoma, bladder cancer, bladder cancer plasmacytoid variant, stomach adenocarcinoma, adenoid cystic carcinoma, lymphoid neoplasm diffuse large B-cell lymphoma, pancreatic cancer, colorectal adenocarcinoma, cholangiocarcinoma, sarcoma, head and neck cancers, cervical and endocervical cancers, medulloblastoma, cutaneous T cell lymphoma, liver hepatocellular carcinoma, kidney renal papillary cell carcinoma, breast cancer, mantle cell lymphoma, gallbladder carcinoma, testicular germ cell cancers, kidney renal cell clear cell carcinoma, prostate cancer, pediatric ewing sarcoma, thymoma, kidney chromophobe, renal non-clear cell carcinoma, pheochromocytoma and paraganglio-

ma, thyroid cancers, malignant peripheral nerve sheath tumor, neuroendocrine prostate cancer, head and neck squamous cell carcinoma, adrenocortical carcinoma, cervical and endocervical cancers, cutaneous squamous cell carcinoma, testicular germ cell cancer, glioblastoma, glioblastoma multiforme, Ewing's sarcoma, clear cell renal cell carcinoma, neuroblastoma, diffuse large B cell lymphoma, acute myeloid leukemia, chronic lymphocytic leukemia, multiple myeloma, malignant rhabdoid tumors, epithelioid sarcomas, familial schwannomatosis, renal medullary carcinomas, synovial sarcoma, and meningiomas.

[0025] Embodiment 12: A method according to any one of Embodiments 7-11, wherein said disorder or disease is selected from the group consisting of non-small cell lung carcinoma, lung adenocarcinoma, lung carcinoma, large cell lung carcinomas, non-small cell lung carcinoma, lung squamous cell carcinoma, small cell lung cancer, skin cutaneous melanoma, desmoplastic melanoma and uveal melanoma.

[0026] Embodiment 13: A method according to Embodiment 7 or 8, wherein said disorder or disease is malignancy which is characterized by BRG1-deficiency.

[0027] Embodiment 14: A method according to any one of Embodiments 7, 8 or 13, wherein said disorder or disease is malignancy which is characterized by BRG1 mutation.

[0028] Embodiment 15: A method according to any one of Embodiments 7, 8, 13 and 14, wherein said disorder or disease is selected from the group consisting of non-small cell lung carcinoma, lung adenocarcinoma, lung carcinoma, large cell lung carcinomas, non-small cell lung carcinoma, lung squamous cell carcinoma, small cell lung cancer, skin cutaneous melanoma, desmoplastic melanoma, uveal melanoma, small cell carcinoma of the ovary, cutaneous squamous cell carcinoma, glioma, uterine carcinosarcoma, uterine corpus endometrial carcinoma, ovarian serous cystadenocarcinoma, bladder urothelial carcinoma, primary central nervous system lymphoma, esophageal carcinoma, bladder cancer, bladder cancer plasmacytoid variant, stomach adenocarcinoma, adenoid cystic carcinoma, lymphoid neoplasm diffuse large B-cell lymphoma, pancreatic cancer, colorectal adenocarcinoma, cholangiocarcinoma, sarcoma, head and neck cancers, cervical and endocervical cancers, medulloblastoma, cutaneous T cell lymphoma, liver hepatocellular carcinoma, kidney renal papillary cell carcinoma, breast cancer, mantle cell lymphoma, gallbladder carcinoma, testicular germ cell cancers, kidney renal cell clear cell carcinoma, prostate cancer, pediatric ewing sarcoma, thymoma, kidney chromophobe, renal non-clear cell carcinoma, pheochromocytoma and paraganglioma and thyroid cancers.

[0029] Embodiment 16: A method according to any one of Embodiments 7, 8 and 13-15, wherein said disorder or disease is selected from the group consisting of non-small cell lung carcinoma, lung adenocarcinoma, lung carcinoma, large cell lung carcinomas, non-small cell lung carcinoma, lung squamous cell carcinoma, small cell lung cancer, skin cutaneous melanoma, desmoplastic melanoma and uveal melanoma.

[0030] Embodiment 17: A method according to Embodiment 7 or 8, wherein said disorder or disease is malignancy which is characterized by BRM-deficiency.

[0031] Embodiment 18: A method according to any one of Embodiments 7, 8 and 17, wherein said disorder or disease is malignancy which is characterized by BRM mutation.

[0032] Embodiment 19: A method according to any one of Embodiments 7, 8 and 17-18, wherein said disorder or disease is selected from the group consisting of malignant peripheral nerve sheath tumor, neuroendocrine prostate cancer, breast cancer, bladder urothelial carcinoma, adenoid cystic carcinoma, stomach adenocarcinoma, breast carcinomas, ovarian serous cystadenocarcinoma, uterine carcinosarcoma, esophageal carcinoma, head and neck squamous cell carcinoma, non-small cell lung carcinomas, lung adenocarcinoma, lung squamous cell carcinoma, small cell lung cancer, pancreatic cancer, adrenocortical carcinoma, skin cutaneous melanoma, sarcoma, colorectal adenocarcinoma, cervical and endocervical cancers, liver hepatocellular carcinoma, cutaneous squamous cell carcinoma, testicular germ cell cancer, glioblastoma, glioblastoma multiforme, cholangiocarcinoma, Ewing's sarcoma, clear cell renal cell carcinoma, neuroblastoma, acute myeloid leukemia and diffuse large B-cell lymphoma.

[0033] Embodiment 20: A method according to any one of Embodiments 7-8 and 17-19, wherein said disorder or disease is selected from the group consisting of non-small cell lung carcinoma, lung adenocarcinoma, lung carcinoma, large cell lung carcinomas, non-small cell lung carcinoma, lung squamous cell carcinoma, small cell lung cancer, skin cutaneous melanoma, desmoplastic melanoma and uveal melanoma.

[0034] Embodiment 21: A method according to Embodiment 7, wherein said disorder or disease is malignancy which is characterized by mutations in SWI/SNF subunits other than BRM or BRG1.

[0035] Embodiment 22: A method according to Embodiment 7 or 21, wherein said disorder or disease is solid tumor, leukemia or lymphoma.

[0036] Embodiment 23: A method according to any one of Embodiments 7, 21 and 22, wherein said disorder or disease is selected from the group consisting of malignant rhabdoid tumors (characterized by deficiency in SNF5/SMARCB1), epithelioid sarcomas, familial schwannomatosis, renal medullary carcinomas, Ewing sarcomas, synovial sarcoma, uterine corpus endometrial carcinoma, stomach adenocarcinoma, bladder urothelial carcinoma, bladder cancer, adenoid cystic carcinoma, cholangiocarcinoma, desmoplastic melanoma, cutaneous squamous cell carcinoma, pancreatic cancer, liver hepatocellular carcinoma, melanoma, diffuse large B-cell lymphoma, breast cancers, colorectal cancer, ovarian clear cell carcinoma, neuroblastoma, esophageal carcinoma, lung cancers, kidney renal clear cell carcinoma, mesothe-

lioma, adenoid cystic carcinoma of the breast, adenoid cystic carcinoma, thyroid cancers, meningiomas, uveal melanomas and acute myeloid leukemias.

[0037] Embodiment 24: A method according to any one of Embodiments 7, 21, 22 and 23, wherein said disorder or disease is selected from the group consisting of malignant rhabdoid tumors, breast cancers, pancreatic cancers, ovarian cancers, ovarian clear cell carcinomas, bladder cancers, renal clear cell carcinomas, colorectal cancer, gastric cancers, liver cancer, melanoma, glioma, acute myeloid leukemia and lung cancers.

[0038] Embodiment 25: A compound according to any one of the Embodiments 1-3, or a pharmaceutically acceptable salt thereof, for use as a medicament.

[0039] Other features of the present disclosure should become apparent in the course of the above descriptions of exemplary embodiments that are given for illustration of the disclosure and are not intended to be limiting thereof.

DEFINITIONS

[0040] For purposes of interpreting this specification, the following definitions will apply, and whenever appropriate, terms used in the singular will also include the plural. Terms used in the specification have the following meanings unless the context clearly indicates otherwise.

[0041] All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (*e.g.* "such as") provided herein is intended merely to better illuminate the present disclosure and does not pose a limitation on the scope of the present disclosure otherwise claimed.

[0042] The term "a," "an," "the" and similar terms used in the context of the present disclosure (especially in the context of the claims) are to be construed to cover both the singular and plural unless otherwise indicated herein or clearly contradicted by the context.

[0043] As used herein, the terms "alkyl" refers to a hydrocarbon radical of the general formula C_nH_{2n+1}. The alkane radical may be straight or branched. For example, the term "C_1-C_6 alkyl" or "C_1 to C_6 alkyl" refers to a monovalent, straight, or branched aliphatic group containing 1 to 6 carbon atoms (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, neopentyl, 3,3-dimethylpropyl, hexyl, 2-methylpentyl, and the like). When an alkyl is substituted with one more substituents, the substitutents can be substituted on any carbon atoms of the alkyl.

[0044] "Halogen" or "halo" may be fluorine, chlorine, bromine or iodine (preferred halogens as substituents are fluorine and chlorine).

[0045] "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with one or more halogens. Thus, "C_1-C_6 haloalkyl" or "C_1 to C_6 haloalkyl" is intended to include, but not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, trichloromethyl, pentafluoroethyl, pentachloroethyl, 2,2,2-trifluoroethyl, heptafluoropropyl, and heptachloropropyl.

[0046] As referred to herein, the term "substituted" means that at least one hydrogen atom is replaced with a non-hydrogen group, provided that normal valencies are maintained and that the substitution results in a stable compound. When a substituent is keto (*i.e.*, =O), then 2 hydrogens on the atom are replaced. Keto substituents are not present on aromatic moieties.

[0047] The phrase "pharmaceutically acceptable" indicates that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

[0048] Unless specified otherwise, the term "compounds of the present disclosure" refers to compounds of Formula (I) as well as isomers, such as stereoisomers (including diastereoisomers, enantiomers and racemates), geometrical isomers, conformational isomers (including rotamers and astropisomers), tautomers, isotopically labeled compounds (including deuterium substitutions), and inherently formed moieties (e.g., polymorphs, solvates and/or hydrates). When a moiety is present that is capable of forming a salt, then salts are included as well, in particular pharmaceutically acceptable salts.

[0049] Depending on the process conditions the end products of the present disclosure are obtained either in free (neutral) or salt form. Both the free form and the salts of these end products are within the scope of the present disclosure. If so desired, one form of a compound may be converted into another form. A free base or acid may be converted into a salt; a salt may be converted into the free compound or another salt; a mixture of isomeric compounds of the present disclosure may be separated into the individual isomers.

[0050] Pharmaceutically acceptable salts are preferred. However, other salts may be useful, *e.g.,* in isolation or purification steps which may be employed during preparation, and thus, are contemplated within the scope of the present disclosure.

[0051] As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. For example, pharmaceutically acceptable salts

include, but are not limited to, acetate, ascorbate, adipate, aspartate, benzoate, besylate, bromide/hydrobromide, bicarbonate/carbonate, bisulfate/sulfate, camphorsulfonate, caprate, chloride/hydrochloride, chlortheophyllonate, citrate, ethandisulfonate, fumarate, gluceptate, gluconate, glucuronate, glutamate, glutarate, glycolate, hippurate, hydroiodide/iodide, isethionate, lactate, lactobionate, laurylsulfate, malate, maleate, malonate/hydroxymalonate, mandelate, mesylate, methylsulphate, mucate, naphthoate, napsylate, nicotinate, nitrate, octadecanoate, oleate, oxalate, palmitate, pamoate, phenylacetate, phosphate/hydrogen phosphate/dihydrogen phosphate, polygalacturonate, propionate, salicylates, stearate, succinate, sulfamate, sulfosalicylate, tartrate, tosylate, trifluoroacetate or xinafoate salt form.

[0052] Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, sulfosalicylic acid, and the like.

[0053] Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, ammonium salts and metals from columns I to XII of the periodic table. In certain embodiments, the salts are derived from sodium, potassium, ammonium, calcium, magnesium, iron, silver, zinc, and copper; particularly suitable salts include ammonium, potassium, sodium, calcium and magnesium salts. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like. Certain organic amines include isopropylamine, benzathine, cholinate, diethanolamine, diethylamine, lysine, meglumine, piperazine and tromethamine.

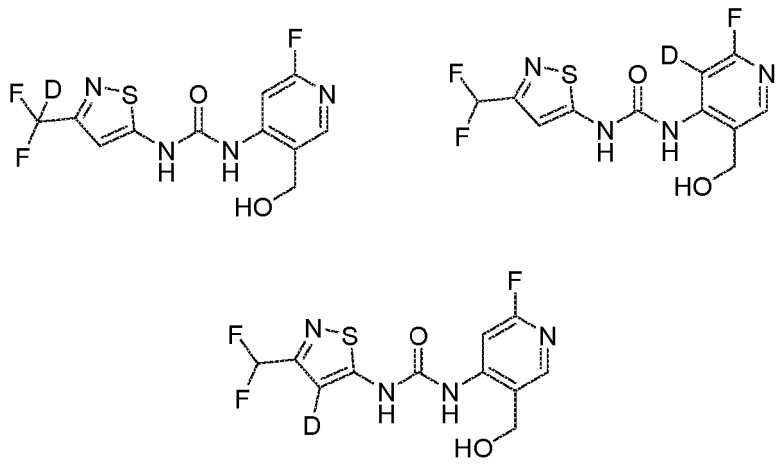
[0054] The pharmaceutically acceptable salts of the present disclosure can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Allen, L.V., Jr., ed., Remington: The Science and Practice of Pharmacy, 22nd Edition, Pharmaceutical Press, London, UK (2012).

[0055] Compounds of the present disclosure that contain groups capable of acting as donors and/or acceptors for hydrogen bonds may be capable of forming co-crystals with suitable co-crystal formers. These co-crystals may be prepared from compounds of the present disclosure by known co-crystal forming procedures. Such procedures include grinding, heating, co-subliming, co-melting, or contacting in solution compounds of the present disclosure with the co-crystal former under crystallization conditions and isolating co-crystals thereby formed. Suitable co-crystal formers include those described in WO 2004/078163. Hence the present disclosure further provides co-crystals comprising a compound of the present disclosure.

[0056] Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the present disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine and iodine such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F ^{31}P, ^{32}P, ^{35}S, ^{36}Cl, ^{123}I , ^{124}I , ^{125}I respectively. The present disclosure includes various isotopically labeled compounds as defined herein, for example those into which radioactive isotopes, such as ^{3}H and ^{14}C, or those into which non-radioactive isotopes, such as ^{2}H and ^{13}C are present. Such isotopically labelled compounds are useful in metabolic studies (with ^{14}C), reaction kinetic studies (with, for example ^{2}H or ^{3}H), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F or labeled compound may be particularly desirable for PET or SPECT studies.

[0057] Further, substitution with heavier isotopes, particularly deuterium (i.e., ^{2}H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index. It is understood that deuterium in this context is regarded as a substituent of a compound of the present disclosure. The concentration of such a heavier isotope, specifically deuterium, may be defined by the isotopic enrichment factor. The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope. If a substituent in a compound of this present disclosure is denoted deuterium, such compound has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

[0058] For example, a deuterated compound can be:



[0059] Isotopically labeled compounds of this present disclosure can generally be prepared by conventional techniques known to those skilled in the art or by processes disclosed in the schemes or in the examples and preparations described below (or analogous process to those described herein), by substituting an appropriate or readily available isotopically labeled reagent for a non-isotopically labeled reagent otherwise employed. Such compounds have a variety of potential uses, e.g., as standards and reagents in determining the ability of a potential pharmaceutical compound to bind to target proteins or receptors, or for imaging compounds of this disclosure bound to biological receptors *in vivo* or *in vitro.*

[0060] The term "solvate" means a physical association of a compound of this disclosure with one or more solvent molecules, whether organic or inorganic. This physical association includes hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. The solvent molecules in the solvate may be present in a regular arrangement and/or a non-ordered arrangement. The solvate may comprise either a stoichiometric or nonstoichiometric amount of the solvent molecules. "Solvate" encompasses both solution-phase and isolable solvates. Exemplary solvates include, but are not limited to, hydrates, ethanolates, methanolates, and isopropanolates. Methods of solvation are generally known in the art.

[0061] As used herein, "polymorph(s)" refer to crystalline form(s) having the same chemical structure/composition but different spatial arrangements of the molecules and/or ions forming the crystals. Compounds of the present disclosure can be provided as amorphous solids or crystalline solids. Lyophilization can be employed to provide the compounds of the present disclosure as a solid.

[0062] "BRM" and "BRG1" refer to two paralogs of the ATPase subunit in the SWI/SNF complex, also known as SMARCA2 and SMARCA4, respectively. Unless specifically stated otherwise, BRM, as used herein, refers to human BRM (Entrez Gene 6595), whose protein sequence has Swiss-Prot accession number P51531.2; and BRG1, as used herein, refers to human BRG1 (Entrez Gene 6597), whose protein sequence has Swiss-Prot: accession numbers P51532.2. BRM, BRG1, and the SWI/SNF complex is described in detail in such reviews as Wilson, BG, et al. Nat Rev Cancer. 2011 Jun 9;11(7):481-92. The BRG1 (SMARCA4) genomic sequence has NCBI Reference Sequence: NG_011556.1; its mRNAs result from a variety of splice forms (i.e., transcript variants), including NCBI Reference numbers NM_001128844.1, NM_001 128849.1, NM_001 128845.1, NM_001128846.1, NM_001 128847.1, NM_001128848.1, and NM_003072.3. The BRM (SMARCA2) genomic sequence has NCBI Reference Sequence: NC_000009.11, it's mRNAs result from two splice forms (i.e., transcript variants), including NCBI Reference numbers NM_003070.3 and NM_139045.2.

[0063] The term "BRM mediated disorder or disease" refers to any disorder or disease which is directly or indirectly regulated by BRM. The term "BRG1 mediated disorder or disease" refers to any disorder or disease which is directly or indirectly regulated by BRG1. A BRM mediated or BRG1 mediated disorder or disease may be characterized by BRG1 deficiency and/or BRM deficiency. A BRM mediated or BRG1 mediated disorder or disease may be characterized by mutations in SWI/SNF subunits other than BRM/SMARCA2 or BRG1/SMARCA4, e.g., mutations in ARID1A, ARID1B, ARID2, PBRM1, SMARCB1/SNF5, SMARCE1, SMARCC1, SMARCC2, PHF10, DPF1, DPF3, DPF2, ACTL6A, ACTL6B, SMARCD2, SMARCD3, SMARCD1, BCL11A, BCL11B, BCL7A, BCL7B, BCL7C, BRD9, BRD7, SS18 and ACTB. A BRM mediated or BRG1 mediated disorder or disease may be characterized by dependency on BRM, BRG1 or other SWI/SNF subunits as described above where said dependency is not related to mutations of BRM, BRG1 or other SWI/SNF subunits.

[0064] The terms "BRG1 deficient" and "BRG1 deficiency" refer to cells (including, but not limited to, cancer cells, cell lines, tissues, tissue types, tumors, etc.) that have mutation or deletion of the BRG1 gene, or have a significant reduction in production, expression, level, stability and/or activity of BRG1 relative to that in a control, e.g., reference or normal or non-cancerous cells. The reduction can be at least about 20%, 30%, 40%, 50%, 60%, 70%, 80% or 90%. In some

embodiments, the reduction is at least 20%. In some embodiments, the reduction is at least 50%. Mutations in the BRG1 gene that lead to loss of function in which mutations may be of the type that are nonsense, insertions/deletions resulting in frameshift, or missense mutations. The BRG1 deficient cells include those wherein the BRG1 gene has been mutated or deleted.

[0065] The terms "BRM-deficient" and "BRM-deficiency" refer to cells (including, but not limited to, cancer cells, cell lines, tissues, tissue types, tumors, etc.) that have a loss-of-function ("LOF") mutation or deletion of the BRM gene, or have a significant reduction in production, expression, level, stability and/or activity of BRM relative to that in a control, e.g., reference or normal or non-cancerous cells. The reduction can be at least about 20%, 30%, 40%, 50%, 60%, 70%, 80% or 90%. In some embodiments, the reduction is at least 20%. In some embodiments, the reduction is at least 50%. The BRM deficient cells include those wherein the BRM gene has been mutated or deleted.

[0066] The term "BRG1 deficiency related disorder or disease" or "disorder or disease characterized by BRG1 deficiency" refers to a disorder or disease wherein cells are BRG1deficient. For example, in a BRG1 deficiency related disorder or disease, one or more disease cells can have a mutation or deletion of the BRG1 gene, or have a significant reduction in production, expression, level, stability and/or activity of BRG1. In a patient afflicted with a BRG1 deficiency related disorder or disease, it is possible that some disease cells (e.g., cancer cells) can be BRG1 deficient while others are not.

[0067] The term "BRM deficiency related disorder or disease" or "disorder or disease characterized by BRM deficiency" refers to a disorder or disease wherein cells are BRM deficient. For example, in a BRM deficiency related disorder or disease, one or more disease cells can have a mutation or deletion of the BRM gene, or have a significant reduction in production, expression, level, stability and/or activity of BRM. In a patient afflicted with a BRM deficiency related disorder or disease, it is possible that some disease cells (e.g., cancer cells) can be BRM deficient while others are not.

[0068] The term "malignancy", also called cancer, refers to diseases in which abnormal cells divide without control and can invade nearby tissues. Malignant cells can also spread to other parts of the body through the blood and lymph systems. There are several main types of malignancy. Carcinoma is a malignancy that begins in the skin or in tissues that line or cover internal organs. Sarcoma is a malignancy that begins in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue. Leukemia is a malignancy that starts in blood-forming tissue, such as the bone marrow, and causes large numbers of abnormal blood cells to be produced and enter the blood. Lymphoma and multiple myeloma are malignancies that begin in the cells of the immune system. Central nervous system cancers are malignancies that begin in the tissues of the brain and spinal cord.

[0069] The term "solid tumor" refers to malignancies/cancers formed of abnormal masses of tissue that usually do not contain cysts or liquid areas. Solid tumors are named/classified according to the tissue/cells of origin. Examples include, but are not limited to, sarcomas and carcinomas.

[0070] The term "leukemia" refers to hematologic or blood cell malignancies/cancers that begin in blood-forming tissue, such as the bone marrow. Examples include, but are not limited to, acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphocytic leukemia (ALL) and chronic lymphocytic leukemia (CLL).

[0071] The term "lymphoma" refers to lymphatic cell malignancies/cancers that begin in the cells of the immune system. Examples include, but are not limited to, Non-Hodgkin Lymphoma and Multiple Myeloma.

[0072] As used herein, the term "patient" encompasses all mammalian species.

[0073] As used herein, the term "subject" refers to an animal. Typically the animal is a mammal. A subject also refers to for example, primates (*e.g.,* humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, fish, birds and the like. In certain embodiments, the subject is a primate. In yet other embodiments, the subject is a human. Exemplary subjects include human beings of any age with risk factors for cancer disease.

[0074] As used herein, a subject is "in need of" a treatment if such subject would benefit biologically, medically or in quality of life from such treatment (preferably, a human).

[0075] As used herein, the term "inhibit", "inhibition" or "inhibiting" refers to the reduction or suppression of a given condition, symptom, or disorder, or disease, or a significant decrease in the baseline activity of a biological activity or process.

[0076] As used herein, the term "treat', "treating" or "treatment" of any disease/ disorder refers the treatment of the disease/disorder in a mammal, particularly in a human, and include: (a) ameliorating the disease/disorder, (*i.e.,* slowing or arresting or reducing the development of the disease/disorder, or at least one of the clinical symptoms thereof); (b) relieving or modulating the disease/disorder, (*i.e.,* causing regression of the disease/disorder), either physically, (*e.g.,* stabilization of a discernible symptom), physiologically, (*e.g.*, stabilization of a physical parameter), or both); (c) alleviating or ameliorating at least one physical parameter including those which may not be discernible by the subject; and/or (d) preventing or delaying the onset or development or progression of the disease or disorder from occurring in a mammal, in particular, when such mammal is predisposed to the disease or disorder but has not yet been diagnosed as having it.

[0077] The term "a therapeutically effective amount" of a compound of the present disclosure refers to an amount of the compound of the present disclosure that will elicit the biological or medical response of a subject, for example, reduction or inhibition of an enzyme or a protein activity, or ameliorate symptoms, alleviate conditions, slow or delay

disease progression, or prevent a disease, etc. In one non-limiting embodiment, the term "a therapeutically effective amount" refers to the amount of the compound of the present disclosure that, when administered to a subject, is effective to (1) at least partially alleviate, inhibit, prevent and/or ameliorate a condition, or a disorder or a disease mediated by BRM and/or BRG1; or (2) reducing or inhibiting the activity of BRM and/or BRG1.

[0078] In another non-limiting embodiment, the term "a therapeutically effective amount" refers to the amount of the compound of the present disclosure that, when administered to a cell, or a tissue, or a non-cellular biological material, or a medium, is effective to at least partially reducing or inhibiting the activity of BRM and/or BRG1; or at least partially reducing or inhibiting the expression of BRM and/or BRG1.

[0079] The effective amount can vary depending on such factors as the size and weight of the subject, the type of illness, or the particular compound of the present disclosure. One of ordinary skill in the art would be able to study the factors contained herein and make the determination regarding the effective amount of the compounds of the present disclosure without undue experimentation.

[0080] The regimen of administration can affect what constitutes an effective amount. The compound of the present disclosure can be administered to the subject either prior to or after the onset of a BRM and/or BRG1 mediated condition. Further, several divided dosages, as well as staggered dosages, can be administered daily or sequentially, or the dose can be continuously infused, or can be a bolus injection. Further, the dosages of the compound(s) of the present disclosure can be proportionally increased or decreased as indicated by the exigencies of the therapeutic or prophylactic situation.

PREPARATION OF COMPOUNDS

[0081] The compounds of the present disclosure can be prepared in a number of ways known to one skilled in the art of organic synthesis in view of the methods, reaction schemes and examples provided herein. The compounds of the present disclosure can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or by variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. The reactions are performed in a solvent or solvent mixture appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the disclosure

[0082] The starting materials are generally available from commercial sources such as Sigma Aldrich or other commercial vendors, or are prepared as described in this disclosure, or are readily prepared using methods well known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, Reagents for Organic Synthesis, v. 1-19, Wiley, New York (1967-1999 ed.), Larock, R.C., Comprehensive Organic Transformations, 2nd-ed., Wiley-VCH Weinheim, Germany (1999), or Beilsteins Handbuch der organischen Chemie, 4, Aufl. ed. Springer-Verlag, Berlin, including supplements (also available via the Beilstein online database)).

[0083] For illustrative purposes, the reaction schemes depicted below provide potential routes for synthesizing the compounds of the present disclosure as well as key intermediates. For a more detailed description of the individual reaction steps, see the Examples section below. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the inventive compounds. Although specific starting materials and reagents are depicted in the schemes and discussed below, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art.

[0084] In the preparation of compounds of the present disclosure, protection of remote functionality of intermediates may be necessary. The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. The need for such protection is readily determined by one skilled in the art. For a general description of protecting groups and their use, see Greene, T.W. et al., Protecting Groups in Organic Synthesis, 4th Ed., Wiley (2007). Protecting groups incorporated in making of the compounds of the present disclosure, such as the trityl protecting group, may be shown as one regioisomer but may also exist as a mixture of regioisomers.

[0085] The following abbreviations used herein below have the corresponding meanings: (app) apparent; (br) broad; (BSA) bovine serum albumin; (d) doublet; (dd) doublet of doublets; (DCM) dichloromethane; (DIPEA) diisopropylethylamine; (DMF) N,N-dimethylformamide; (DMSO) dimethylsulfoxide; (ESI) electrospray ionization; (Et) ethyl; (EtOAc) ethyl acetate; (h) hour(s); (HPLC) high pressure liquid chromatography; (LAH) lithium aluminum hydride; (LCMS) liquid chromatography and mass spectrometry; (LHMDS) lithium hexamethyldisilazide; (MTBE) Methyl tert-butyl ether; (MeCN) acetonitrile; (MeOH) methanol; (MHz) mega hertz; (MS) mass spectrometry; (m) multiplet; (mg) milligram; (min) minutes; (mL) milliliter; (mmol) millimol; (m/z) mass to charge ratio; (NMR) nuclear magnetic resonance; (Ph) phenyl; (ppm) parts per million; (q) quartet; (Rt) retention time; (RT) room temperature; (s) singlet; (t) triplet; (TBDMS) t-butyldimethylsilyl; (tert) tertiary; (TFA) trifluoroacetic acid; (THF) tetrahydrofuran; (TMAF) tetramethyl ammonium fluoride: (TMS) trimethylsilyl.

LC/MS Methods Employed in Characterization of Examples

[0086] LC/MS data were recorded using Agilent 1100 HPLC systems with Waters Micromass ZQ, or Waters ACQUITY UPLC with Waters SQ detector or with Waters 25 ACQUITY Qda detector. The methods used to acquire all LCMS data are described below.

LCMS method 1

[0087]

Column	Sunfire C18 3.0x30 mm, 3.5 μm
Column Temperature	40 °C
Eluents	A: H_2O containing 0.05% TFA, B: MeCN
Flow Rate	2.0 mL/min
Gradient	5% to 95% B in 1.7 min, 0.3 min 95% B

LCMS method 2

[0088]

Column	XBridge C18 3.0x30 mm, 3.5 μm
Column Temperature	40 °C
Eluents	A: H_2O + 5 mM ammonium hydroxide, B: MeCN
Flow Rate	2.0 mL/min
Gradient	5% to 95% B in 1.7 min, 0.3 min 95% B

LCMS method 3

[0089]

Column	AcQuity UPLC BEH C18 2.1x30 mm, 1.7 μm
Column Temperature	50 °C
Eluents	A: 0.1% formic acid in water, B: 0.1% formic acid in MeCN
Flow Rate	1.0 mL/min
Gradient	2% to 98% B in 1.5 min, 0.3 min 98% B

LCMS method 4

[0090]

Column	AcQuity UPLC BEH C18 2.1x30 mm, 1.7 μm
Column Temperature	50 °C
Eluents	A: 5 mM NH_4OH in water, B: 5 mM NH_4OH in MeCN
Flow Rate	1.0 mL/min
Gradient	1% to 30% B in 1.2 min, 30% to 98%B in 0.95 min

NMR Employed in Characterization of Examples

[0091] ^1H NMR spectra were obtained with Bruker Fourier transform spectrometers operating at frequencies as follows: ^1H NMR: 400 MHz (Bruker). Spectra data are reported in the format: chemical shift (multiplicity, number of hydrogens). Chemical shifts are specified in ppm downfield of a tetramethylsilane internal standard (δ units, tetramethylsilane = 0 ppm) and/or referenced to solvent peaks, which in ^1H NMR spectra appear at 2.50 ppm for CDsSOCDs, 3.31 ppm for CD_3OD, 1.94 ppm for CD_3CN, 4.79 ppm for D_2O, 5.32 ppm for CD_2Cl_2, and 7.26 ppm for $CDCl_3$.

Methods Employed in the Purification of the Examples

[0092] Purification of intermediates and final products was carried out via either normal, reverse phase chromatography or supercritical fluid chromatography (SFC). Normal phase chromatography was carried out using prepacked SiO_2 cartridges (e.g., RediSep® Rf columns from Teledyne Isco, Inc.) eluting with gradients of appropriate solvent systems (e.g., heptane and ethyl acetate; DCM and MeOH; or unless otherwise indicated). Reverse phase preparative HPLC was carried out using the methods described below:

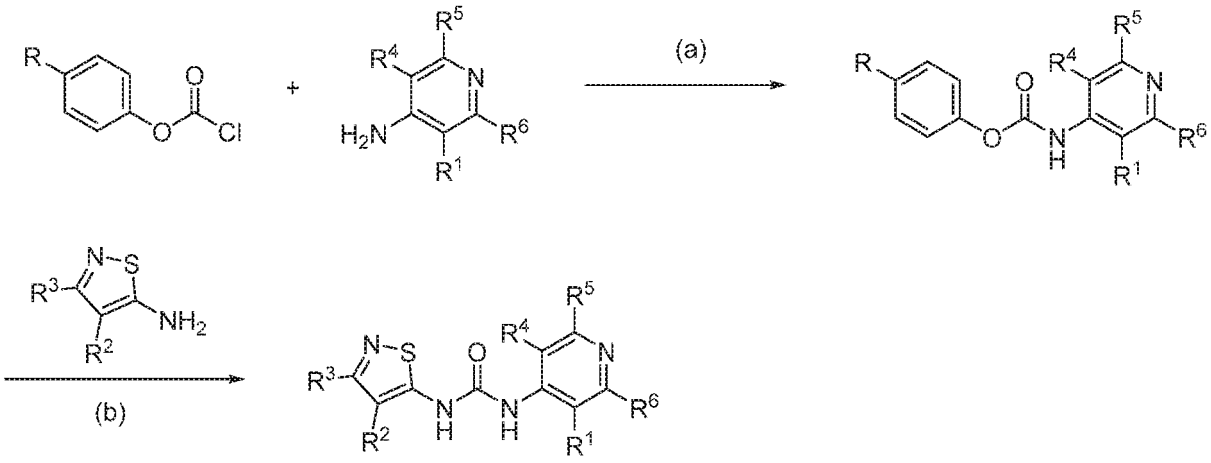
(1) Basic method: XBridge 5 μm column, 5mM NH_4OH in acetonitrile and water.
(2) Formic acid method: XBridge 5 μm column; 0.1% formic acid in acetonitrile and water.

The above HPLC methods run a focused gradient from 15 % acetonitrile to 40 % acetonitrile.

GENERAL SYNTHETIC SCHEMES

[0093] Schemes 1 and 2 (shown below) describe potential routes for preparing the compounds of the present disclosure which include compounds of Formula (I) wherein R^1-R^6 are as defined in the Summary of the Invention. The starting materials for the below reaction scheme are commercially available or can be prepared according to methods known to one skilled in the art or by methods disclosed herein. Compounds of Formula (I) can be made substantially optically pure by either using substantially optically pure starting material or by separation chromatography, recrystallization or other separation techniques well-known in the art. For a more detailed description, see the Example section below.

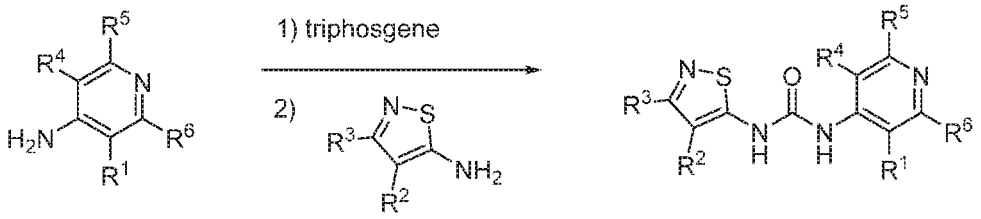
Scheme 1



[0094] Step (a) involves reaction of (un)substituted phenyl chloroformate (for example, R can be H or nitro group) and (un)substituted 4-aminopyridine in a suitable solvent such as DCM or dioxane with a suitable base such as pyridine at a suitable temperature such as RT.

[0095] Step (b) involves reaction of substituted 5-aminoisothiazole (or substituted 3-aminobenzothiazoles) and the carbamate intermediate obtained in Step (a) in a suitable solvent such as THF or dioxane with a suitable base such as diisopropylethylamine at a suitable temperature such as 60 °C. Alternatively, the substituted 5-aminoisothiazole (or substituted 3-aminobenzothiazoles) may be deprotonated by a suitable base such as LHMDS first, followed by reaction with the carbamate intermediate obtained in Step (a). Following the formation of the urea, R^1-R^6 groups may undergo further transformations as needed to provide the desired products.

Scheme 2



[0096] Formation of urea product involves reaction of (un)substituted 4-aminopyridine with triphosgene, followed by substituted 5-aminoisothiazole, in a suitable solvent such as THF with a suitable base such as triethylamine at a suitable temperature such as RT. Following the formation of the urea, R^1-R^6 groups may undergo further transformations as needed to provide the desired products.

EXAMPLES

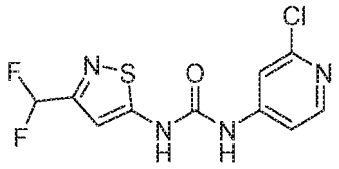
[0097] The following Examples have been prepared, isolated and characterized using the methods disclosed herein. The following examples demonstrate a partial scope of the disclosure and are not meant to be limiting of the scope of the disclosure.

[0098] Unless specified otherwise, starting materials are generally available from a non-limiting commercial sources such as TCI Fine Chemicals (Japan), Aurora Fine Chemicals LLC (San Diego, CA), FCH Group (Ukraine), Aldrich Chemicals Co. (Milwaukee, Wis.), Acros Organics (Fairlawn, N.J.), Maybridge Chemical Company, Ltd. (Cornwall, England), Matrix Scientific (USA), Enamine Ltd (Ukraine), Combi-Blocks, Inc. (San Diego, USA), Oakwood Products, Inc. (USA), Apollo Scientific Ltd. (UK).

Example 1

1-(2-chloropyridin-4-yl)-3-(3-(difluoromethyl)isothiazol-5-yl)urea

[0099]

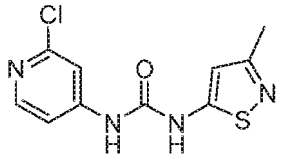


[0100] To a mixture of 2-chloro-4-aminopyridine (1.57 g, 12.25 mmol) and pyridine (1.38 mL, 17.05 mmol) in DCM (100 mL) at 0 °C was added 4-nitrophenyl chloroformate (2.6 g, 12.89 mmol). The mixture was maintained at 0 °C for 2 min, then warmed up at rt. After another 20 min, the mixture was concentrated in vacuo to give a residue, which was taken up in dioxane (80 mL). A solution of 3-(difluoromethyl)isothiazol-5-amine (Intermediate 1) (1.60 g, 10.66 mmol) in dioxane (10 mL) was rapidly added, followed by DIPEA (6.51 mL, 37.3 mmol). The mixture was heated to 60 °C. After 3 h, the mixture was cooled to RT, then water and EtOAc were added. The organic layer was washed repeatedly with water, saturated aqueous sodium bicarbonate and brine. The organic phase was dried over sodium sulfate, filtered and concentrated in vacuo to obtain a residue which was purified by flash chromatography (EtOH/EtOAc/heptane). The partially purified residue was triturated with ether, and the obtained solid was taken up in water. Lyophilization removed residual ether to give the title compound. ^{1}H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 10.15 (s, 1H), 8.26 (d, J = 4 Hz, 1H), 7.68 (d, J = 2 Hz, 1H), 7.46 (dd, J = 4, 2 Hz, 1H), 7.15 (s, 1H), 6.97 (t, J = 52 Hz, 1H). MS (ESI) m/z 305.1 [M + H]$^+$. LCMS: Rt = 1.25 min, m/z 305.1 (M+H) (LCMS method 1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.08 (s, 1H), 10.15 (s, 1H), 8.26 (d, J = 4 Hz, 1H), 7.68 (d, J = 2 Hz, 1H), 7.46 (dd, J = 4, 2 Hz, 1H), 7.15 (s, 1H), 6.97 (t, J = 52 Hz, 1H).

Example 2

1-(2-chloropyridin-4-vl)-3-(3-methylisothiazol-5-vl)urea

[0101]

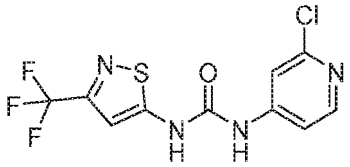


[0102] A solution of 2-chloro-4-aminopyridine (101 mg, 0.786 mmol) in THF (2 mL) was added slowly to a solution of triphosgene (101 mg, 0.340 mmol) in THF (2 mL) at RT. Triethylamine (0.11 mL, 0.790 mmol) was then added. After the mixture was stirred at RT for 20 min, a mixture of 3-methyl-5-aminoisothiazole hydrochloride (120 mg, 0.797 mmol) and triethylamine (0.12 mL, 0.863 mmol) in THF (2 mL) was added. The mixture was stirred at RT for 18 h and partitioned between EtOAc and aqueous KOH. The combined organic extract was dried over $MgSO_4$ and concentrated. The residue was purified by HPLC (basic method) to give the title compound. LCMS: Rt = 0.85 min, m/z 269.0 (M+H) (LCMS method 2). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.78 (s, 1H), 9.87 (s, 1H), 8.24 (d, J = 4 Hz, 1H), 7.66 (s, 1H), 7.43 (d, J = 4 Hz, 1H), 6.73 (s, 1H), 2.30 (s, 3H).

Example 3

1-(2-chloropvridin-4-vl)-3-(3-(trifluoromethyl)isothiazol-5-vl)urea

[0103]

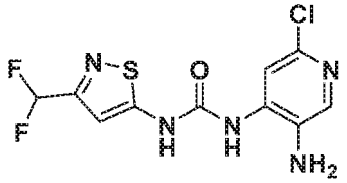


[0104] To an ice-cold mixture of 3-(trifluoromethyl)isothiazol-5-amine (Intermediate 2) (70 mg, 0.41 mmol), and phenyl (2-chloropyridin-4-yl)carbamate (Intermediate 3) (104 mg, 0.41 mmol) in DMF (1.2 mL) was added a solution of LHMDS (1M in THF, 0.41 mL, 0.41 mmol). The mixture was allowed to warm to RT and stirred for 16 h. The mixture was concentrated in vacuo, then purified by HPLC (basic method) to obtain the title compound. LCMS: Rt = 1.38 min, m/z 323 (M+H) (LCMS method 1). ^{1}H NMR (400 MHz, DMSO-d6) δ 11.21 (br s, 1H), 10.18 (br s, 1H), 8.23 (d, J = 5.6 Hz, 1H), 7.69 (d, J = 1.8 Hz, 1H), 7.46 (dd, J = 5.7, 1.9 Hz, 1H), 7.22 (s, 1H).

Example 4

1-(5-amino-2-chloropyridin-4-yl)-3-(3-(difluoromethyl)isothiazol-5-yl)urea

[0105]

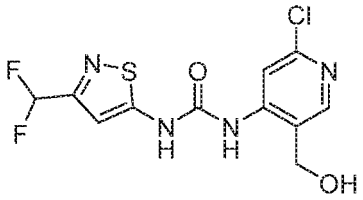


[0106] A mixture of 1-(5-nitro-2-chloropyridin-4-yl)-3-(3-(difluoromethyl)isothiazol-5-yl)urea (Intermediate 5) (7.63 g, 21.82 mmol), iron (4.87 g, 87 mmol) and ammonium chloride (9.34 g, 175 mmol) in ethanol (84 mL) and water (25 mL) was heated for 1 h at 50 °C. The mixture was filtered over Celite, the filter cake was rinsed with MeOH, and the filtrate was concentrated in vacuo. The residue was taken up in EtOAc and washed with brine. The organic fraction was dried over magnesium sulfate and concentrated in vacuo to give a residue which was purified by silica gel chromatography (EtOAc/heptane) followed by purification using ISCO reverse phase purification on a C18 column eluting with water + 0.1% formic acid and acetonitrile + 0.1% formic acid. LCMS: Rt = 0.76 min, m/z = 320.2 (M+H) (LCMS method 2). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.88 (s, 1H), 7.84 (s, 1H), 6.99 (s, 1H), 6.66 (t, J = 54.9 Hz, 1H).

Example 5

1-(2-chloro-5-(hydroxymethyl)pyridin-4-yl)-3-(3-(difluoromethyl)isothiazol-5-yl)urea

[0107]



Step 1: Synthesis of 1-(5-(((tert-butyldimethylsilyl)oxy)methyl)-2-chloropyridin-4-yl)-3-(3-(difluoromethyl)isothiazol-5-yl)urea

[0108] LHMDS (1M in THF, 9.2 mL, 9.2 mmol) was added dropwise to a solution of phenyl (5-(((tert-butyldimethylsilyl)oxy)methyl)-2-chloropyridin-4-yl)carbamate (Intermediate 6) (3.46 g, 8.81 mmol) and 3-(difluoromethyl)isothiazol-5-amine (Intermediate 1) (1.15 g, 7.66 mmol) in DMF (30 mL), and the reaction was stirred at RT for 30 min. The reaction was quenched with MeOH (10 mL) and volatiles were removed in vacuo. The residue was taken up in 1:1 EtOAc/saturated aqueous NH_4Cl and the layers were separated. The aqueous layer was extracted with EtOAc. The organics were combined, dried with Na_2SO_4, filtered, and volatiles were removed in vacuo. The crude residue was purified by silica gel chromatography (EtOAc/heptane). LCMS: Rt= 1.79 min, m/z = 449.2 (M+H) (LCMS method 1). ^{1}H NMR (400 MHz, DMSO-d6) δ 11.39 (s, 1H), 8.93 (s, 1H), 8.29 (s, 1H), 8.14 (s, 1H), 7.19 (s, 1H), 6.96 (t, J = 54.5 Hz, 1H), 4.79 (s, 2H), 0.86 (s, 9H), 0.07 (s, 6H).

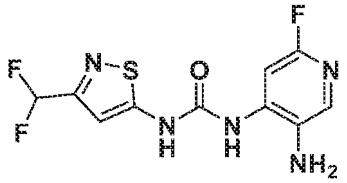
Step 2: Synthesis of 1-(2-chloro-5-(hydroxymethyl)pyridin-4-yl)-3-(3-(difluoromethyl)isothiazol-5-yl)urea

[0109] TBAF (1M in THF, 2.45 mL, 2.45 mmol) was added to a solution of 1-(5-(((tertbutyldimethylsilyl)oxy)methyl)-2-chloropyridin-4-yl)-3-(3-(difluoromethyl)isothiazol-5-yl)urea (obtained in step 1 above) (1.1 g, 2.45 mmol) and in THF (8 mL), and the mixture was stirred at RT for 2 h. The reaction mixture was poured into water, and product was extracted with EtOAc. The organic extract was combined, dried with Na_2SO_4, filtered, and volatiles were removed in vacuo. The crude product was purified by silica gel chromatography (MeOH / DCM) to give the title compound. LCMS: Rt = 0.78 min, m/z = 335.2 (M+H) (LCMS method 2). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.75 (s, 1H), 9.22 (s, 1H), 8.23 (s, 1H), 8.15 (s, 1H), 7.20 (s, 1H), 6.97 (t, J = 56 Hz, 1H), 5.79 (t, J = 5 Hz, 1H), 4.59 (d, J = 5 Hz, 2H).

Example 6

1-(5-amino-2-fluoropyridin-4-yl)-3-(3-(difluoromethyl)isothiazol-5-yl)urea

[0110]



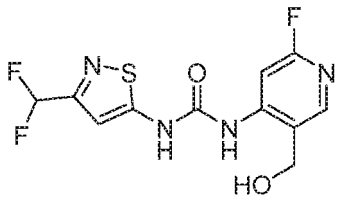
[0111] A mixture of 1-(5-nitro-2-chloropyridin-4-yl)-3-(3-(difluoromethyl)isothiazol-5-yl)urea (Intermediate 5) (3.77 g, 8.62 mmol), TMAF (3.61 g, 38.8 mmol) and DMF (83 mL) was heated at 75 °C for 1 h. The reaction was quenched with water and extracted with EtOAc. The combined organic fractions were washed with water, brine, then dried with sodium sulfate, filtered and concentrated in vacuo. The residue was then purified by flash chromatography (EtOAc/heptane) to give partially purified product (2.73 g) which was taken up in ethanol (100 mL) and water (20 mL). Ammonium chloride (2.13 g, 39.8 mmol) and iron (1.91 g, 34.2 mmol) were added and the mixture was heated to 45 °C for 30 min. The reaction mixture was then filtered on a short pad of celite, which was washed with MeOH. The filtrate was concentrated down, and then diluted with EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic

fractions were washed with brine, then dried with sodium sulfate, filtered and concentrated in vacuo. The residue was sequentially purified by silica gel chromatography (EtOAc/heptane), followed by ISCO reverse phase purification on a C18 column eluting with water + 0.1% formic acid and acetonitrile + 0.1% formic acid. A small number of impure fractions were finally purified by HPLC (formic acid method) and the combined fractions afforded the title compound. LCMS: Rt = 1.12 min, m/z 304.2 (M+H) (LCMS method 1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.15 (s, 1H), 8.92 (s, 1H), 7.63 (d, J = 0.9 Hz, 1H), 7.46 (d, J = 0.8 Hz, 1H), 7.14 (s, 1H), 6.95 (t, J = 54.5 Hz, 1H), 4.82 (s, 2H).

Example 7

1-(3-(difluoromethyl)isothiazol-5-yl)-3-(2-fluoro-5-(hydroxymethyl)pyridin-4-yl)urea

[0112]



Step 1: Synthesis of 1-(5-(((tert-butyldimethylsilyl)oxy)methyl)-2-fluoropyridin-4-yl)-3-(3-(difluoromethyl)isothiazol-5-yl)urea.

[0113] To a solution of 3-(difluoromethyl)isothiazol-5-amine (Intermediate 1) (48 mg, 0.323 mmol), and phenyl (5-(((tert-butyldimethylsilyl)oxy)methyl)-2-fluoropyridin-4-yl)carbamate (Intermediate 7) (135 mg, 0.323 mmol) in DMF (2 mL) was added LHMDS (1M in THF, 0.484 mL, 0.484 mmol) and the resulting mixture was stirred at RT for 30 min. The mixture was concentrated *in vacuo* and the product purified by silica gel chromatography (EtOAc / heptane) to give the title compound. LCMS: Rt = 1.76 min, m/z 433.2 (M+H) (LCMS method 1

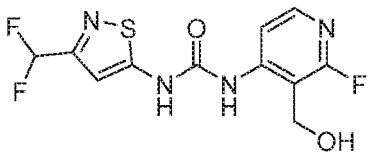
Step 2: Synthesis of 1-(3-(difluoromethyl)isothiazol-5-yl)-3-(2-fluoro-5-(hydroxymethyl)pyridin-4-yl)urea.

[0114] To a solution of 1-(5-(((tert-butyldimethylsilyl)oxy)methyl)-2-fluoropyridin-4-yl)-3-(3-(difluoromethyl)isothiazol-5-yl)urea (119 mg, 0.275 mmol) in THF (5 mL) was added TBAF (1M in THF, 0.275 mL, 0.275 mmol) and the resulting mixture was allowed to stir at RT for 2 h. The mixture was concentrated *in vacuo* and purified by silica gel chromatography (MeOH / DCM with ammonium hydroxide as the modifier) to give the title compound. LCMS: Rt = 1.16 min, m/z 337 (M+H) (LCMS method 1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.76 (s, 1H), 9.26 (s, 1H), 8.06 (s, 1H), 7.77 (s, 1H), 7.22 - 6.70 (m, 2H), 5.73 (t, J = 5.4 Hz, 1H), 4.59 (d, J = 5.1 Hz, 2H).

Example 8

1-(3-(difluoromethyl)isothiazol-5-yl)-3-(2-fluoro-3-(hydroxymethyl)pyridin-4-yl)urea

[0115]



Step 1: Synthesis of 1-(3-(((tert-butyldimethylsilyl)oxy)methyl)-2-fluoropyridin-4-yl)-3-(3-(difluoromethyl)isothiazol-5-yl)urea

[0116] To a solution of 3-(difluoromethyl)isothiazol-5-amine (Intermediate 1) (1.04 g, 6.93 mmol), and phenyl (3-(((tert-butyldimethylsilyl)oxy)methyl)-2-fluoropyridin-4-yl)carbamate (Intermediate 8) (3.39 g, 9.00 mmol) in DMF (35 mL) was added LHMDS (1M in THF, 13.8 mL, 13.8 mmol) at 0 °C. The cooling bath was removed and the resulting mixture was stirred at RT for 45 min. The mixture was concentrated *in vacuo* and the product purified by silica gel chromatography

(EtOAc / heptane) to give the title compound. LCMS: Rt = 1.74 min, m/z 433.3 (M+H) (LCMS method 1).

Step 2: Synthesis of 1-(3-(difluoromethyl)isothiazol-5-yl)-3-(2-fluoro-3-(hydroxymethyl)pyridin-4-yl)urea

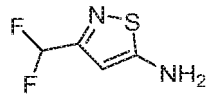
[0117] To a solution of 1-(3-(((tert-butyldimethylsilyl)oxy)methyl)-2-fluoropyridin-4-yl)-3-(3-(difluoromethyl)isothiazol-5-yl)urea (2.19 g, 5.06 mmol) in THF (40 mL) was added TBAF (1M in THF, 6.6 mL, 6.6 mmol) and the resulting mixture was allowed to stir at RT for 30 min. The reaction was quenched with water, then diluted with EtOAc. The aqueous layer was extracted with EtOAc. The combined organic fractions were combined, washed with brine, then dried with sodium sulfate, filtered and concentrated in vacuo. The crude mixture was purified by flash chromatography (MeOH/DCM) to give the title compound. LCMS: Rt = 1.12 min, m/z 319.2 (M+H) (LCMS method 1). 1H NMR (400 MHz, DMSO-d6) δ 11.89 (s, 1H), 9.44 (s, 1H), 8.10 - 8.02 (m, 2H), 7.05 (s, 1H), 6.95 (t, J = 54.5 Hz, 1H), 5.83 (s, 1H), 4.62 (s, 2H).

INTERMEDIATES

Intermediate 1

3-(Difluoromethyl)isothiazol-5-amine

[0118]



Step 1: 3-methyl-5-nitroisothiazole

[0119] Cu powder (96 g, 1.5 mol) was placed in a 5 L reactor. Water (1 L) was added followed by $NaNO_2$ (104 g, 1.5 mol). Aqueous HCl (12 M, 1.5 mL, 18 mmol) was added, and the reaction mixture was stirred for 20 min. A solution of 3-methyl-5-aminoisothiazole hydrochloride (58 g, 507 mmol) in 500 mL of water and aqueous HCl (12 M, 65 mL, 0.78 mol) was added dropwise via addition funnel maintaining the temperature below 30 °C. An additional 100 mL of water was added. The reaction mixture was allowed to stir for 3 h after addition. The reaction mixture was filtered through Celite with water and MTBE. The filtrate was transferred to the reactor and the layers were separated. The aqueous layer was washed twice with MTBE. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give the title compound. 1H NMR (400 MHz, DMSO-d6) δ 8.12 (s, 1H), 2.50 (s, 3H).

Step 2: 5-nitroisothiazole-3-carboxylic acid

[0120] To a 1L 3-neck round bottom flask in a water bath equipped with a mechanical stirrer and a temperature monitor was added 3-methyl-5-nitroisothiazole (26.5 g, 184 mmol), then H_2SO_4 (350 mL) at a rate to keep the temperature below 30 °C. CrO_3 (55.1 g, 552 mmol) was added in 6 portions every 20 min, ensuring the temperature remained below 24 °C. The reaction was left stirring in the presence of the water bath for 3 days. The reaction mixture was poured into ice water (total of 1.4 L) and was extracted 3 times with Et_2O (1 L). The combined organic layers were washed with brine, then dried over $MgSO_4$, filtered and concentrated to provide a yellow solid. The solid was taken up in heptane (80 mL) and Et_2O (20 mL) and triturated. After 2 min of vigorous stirring, the mixture was filtered, and then rinsed with a 5:1 heptane/ether mixture (minimal amount) to provide the title compound. 1H NMR (400 MHz, DMSO-d6) δ 9.89 (s, 1H), 8.57 (s, 1H).

Step 3: (5-Nitroisothiazol-3-yl)methanol

[0121] A flask was charged with 5-nitroisothiazole-3-carboxylic acid (3.0 g, 17.2 mmol) in THF (50 mL), cooled on an ice bath, then borane tetrahydrofuran complex (1M in THF) (22.4 mL, 22.4 mmol) was added dropwise over 30 min and the reaction was allowed to warm overnight. The reaction mixture was re-cooled to 0 °C, then methanol (20 mL) was added dropwise. The reaction was vigorously stirred at 0 °C for 5 min, then allowed to warm to RT and stirred for another 15 min. The reaction mixture was concentrated in vacuo to half volume, then was diluted with EtOAc (100 mL), saturated aqueous NH_4Cl (50 mL) and water (50 mL). The layers were separated and the aqueous portion was extracted with EtOAc (2x100 mL). The organic fractions were combined and washed with brine, then dried over sodium sulfate, filtered and concentrated in vacuo. Purification via silica gel chromatography (EtOAc/DCM) gavethe title compound. 1H NMR

(400 MHz, DMSO-d6) δ 8.09 (s, 1H), 5.77 (t, J = 6.1 Hz, 1H), 4.58 (d, J = 6.1 Hz, 2H). MS (ESI) m/z 161.0 $[M + H]^+$.

Step 4: Synthesis of 5-nitroisothiazole-3-carbaldehyde

[0122] Dess-Martin periodinane (2.23 g, 5.27 mmol) was added in small portions over 5 min to (5-nitroisothiazol-3-yl)methanol (767 mg, 4.79 mmol) in DCM (25 mL) at 0 °C. The mixture was stirred at 0 °C for 10 min, warmed to RT and stirred at RT for 20 min. The mixture was diluted with DCM. Saturated aqueous $NaHCO_3$ and saturated aqueous sodium thiosulfate were added. The mixture was vigorously stirred for 10 min, and then two layers were separated. The aqueous layer was extracted with DCM. The combined organic extract was washed with brine, dried over sodium sulfate and concentrated in vacuo to give the title compound. The product was used directly in the next step without purification. ^1H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 8.58 (s, 1H).

Step 5: Synthesis of 3-(difluoromethyl)-5-nitroisothiazole

[0123] DAST (0.201 mL, 1.518 mmol) was added at 0 °C in a dropwise fashion to a solution of 5-nitroisothiazole-3-carbaldehyde (obtained in step 1 above) (80 mg, 0.506 mmol) in DCM (3.5 mL). The mixture was stirred at 0 °C for 25 min, warmed to RT and stirred at RT for 2 h. The mixture was quenched at 0 °C with saturated aqueous $NaHCO_3$, and diluted with DCM. The mixture was vigorously stirred for 1 min, and the two layers were separated. The aqueous layer was extracted with DCM. The combined organic extract was washed with brine, dried over sodium sulfate and concentrated in vacuo to give the title compound. The product was used immediately in the next step without purification. ^1H NMR (400 MHz, DMSO-d_6) δ 8.54 (s, 1H), 7.16 (t, J = 52 Hz, 1H).

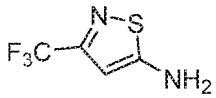
Step 6: Synthesis of 3-(difluoromethyl)isothiazol-5-amine

[0124] A mixture of 3-(difluoromethyl)-5-nitroisothiazole (49 mg, 0.27 mmol), iron powder (46 mg, 0.81 mmol) and acetic acid (1.5 mL) was heated to 50 °C for 2 h. The mixture was diluted with ethyl acetate and basified with 30 % ammonium hydroxide. The organic layer was separated and concentrated in vacuo, then purified by silica gel chromatography (EtOAc/heptane) to obtain the title compound . LCMS: Rt = 0.42 min; m/z 151.2 (M+H) (LCMS method 2); ^1H NMR (400 MHz, methanol-d4) δ 6.46 (t, J = 55.0 Hz, 1H), 6.39 (s, 1H). ^{19}F NMR (376 MHz, MeOD) δ -116.06.

Intermediate 2

3-(trifluoromethyl)isothiazol-5-amine

[0125]



Step 1: Synthesis of 4,4,4-trifluoro-3-oxobutanenitrile

[0126] A dry 100 mL flask was charged with KOt-Bu (1M in THF, 85 mL, 85 mmol) and cooled down on ice. After 30 min, a mixture of ethyl trifluoroacetate (7.27 mL, 60.9 mmol) and acetonitrile (3.18 mL, 60.9 mmol) was added over 3 min. The reaction mixture became a suspension. The mixture was allowed to slowly warm up to RT and stirred for 24 h. The mixture was quenched with 1M HCl, and the crude product was extracted with ether and washed with water. The organic layer was separated, dried over magnesium sulfate, filtered and concentrated in vacuo to furnish the title compound, which was used in the next step without purification. LCMS: Rt = 0.22 min, m/z 136.1 (M-1) (LCMS method 4). ^1H NMR (400 MHz, DMSO-d_6) δ 2.99 (s, 2H).

Step 2: Synthesis of (Z)-3-amino-4,4,4-trifluorobut-2-enenitrile

[0127] A mixture of 4,4,4-trifluoro-3-oxobutanenitrile (prepared in step 1) (1.1 g, 8.03 mmol), ammonium formate (1.518 g, 24.08 mmol) and acetic acid (0.046 mL, 0.803 mmol) in toluene (100 mL) was heated to 120 °C under zeotropic conditions for 18 h. The mixture was concentrated in vacuo and used in the next step without further purification.

Step 3: Synthesis of (Z)-3-amino-4,4,4-trifluorobut-2-enethioamide

[0128] A mixture of (Z)-3-amino-4,4,4-trifluorobut-2-enenitrile (prepared in step 2) (1.00 g, 7.35 mmol), $MgCl_2$ (0.70 g, 7.35 mmol) and NaSH (0.824 g, 14.70 mmol) in DMF (20 mL) was allowed to stir at RT for 24 h. The mixture was partitioned between ethyl acetate and water. The combined organic extract was dried over magnesium sulfate, filtered and concentrated in vacuo to furnish the title compound. LCMS: Rt = 0.81 min, m/z 171 (M+H) (LCMS method 1).

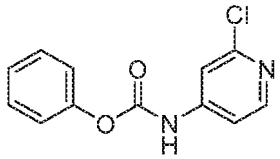
Step 4: Synthesis of 3-(trifluoromethyl)isothiazol-5-amine

[0129] To a mixture of (Z)-3-amino-4,4,4-trifluorobut-2-enethioamide (prepared in step 3) (1.2 g, 7.05 mmol) in pyridine (24 mL) was added H_2O_2 (3 mL, 29.4 mmol) at 0 - 5 °C, and the mixture was allowed to warm up to RT and stirred for 2 h. The mixture was concentrated in vacuo, and the residue was chromatographed on silica gel (ethyl acetate / heptane) to give the title compound. LCMS: Rt = 0.97 min, m/z 169 (M+H) (LCMS method 1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.21 (s, 2H), 6.44 (s, 1H).

Intermediate 3

Phenyl (2-chloropyridin-4-yl)carbamate

[0130]

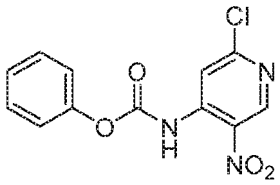


[0131] To a solution of 2-chloropyridin-4-amine (12.9 g, 101 mmol) and pyridine (8.13 mL, 101 mmol) in DCM (315 mL) at 0 °C was added phenyl chloroformate (13.3 mL, 106 mmol). The mixture was allowed to warm to RT over 2 h and concentrated in vacuo. Water was added, and the mixture was stirred at RT. The solid was filtered over a fritted plastic funnel, rinsed with water and dried under high vacuum at 40 °C for 24 h to give the title compound. LCMS: Rt = 1.20 min, m/z = 249.2 (M+H) (LCMS method 2).

Intermediate 4

Phenyl (2-chloro-5-nitropyridin-4-yl)carbamate

[0132]

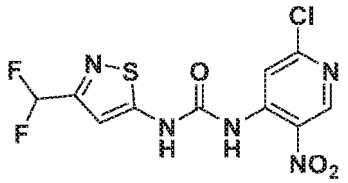


[0133] To a solution of 4-amino-2-chloro-5-nitropyridine (150 mg, 0.864 mmol) and pyridine (0.070 mL, 0.86 mmol) in dioxane (4 mL) at 0 °C was phenyl chloroformate (0.114 mL, 0.907 mmol). The mixture was heated at 80 °C for 18 h, cooled to RT and poured into water. The product was extracted with EtOAc. The combined organic extract was dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by silica gel chromatography (EtOAc / heptane) to give the title compound. LCMS: Rt = 1.51 min, m/z = 294.1 (M+H) (LCMS method 1).

Intermediate 5

1-(5-nitro-2-chloropyridin-4-yl)-3-(3-(difluoromethyl)isothiazol-5-yl)urea

[0134]

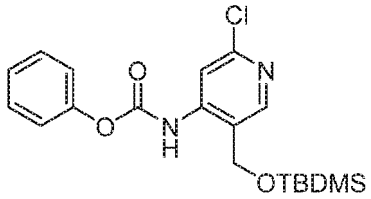


[0135] A solution of phenyl (2-chloro-5-nitropyridin-4-yl)carbamate (Intermediate 4) (4.50 g, 15.32 mmol), 3-(difluoromethyl)isothiazol-5-amine (Intermediate 1) (2.0 g, 13.32 mmol) and DIPEA (5.8 mL, 33.3 mmol) in dioxane (59 mL) was heated at 85 °C for 16 h. The mixture was concentrated in vacuo and the residue was purified by silica gel chromatography (EtOAc/heptane) to give the title compound. LCMS: Rt = 1.43 min, m/z = 350.1 (M+H) (LCMS method 1).

Intermediate 6

Phenyl (5-(((tert-butyldimethylsilyl)oxy)methyl)-2-chloropyridin-4-yl)carbamate

[0136]



Step 1: Synthesis of methyl 6-chloro-4-((4-methoxybenzyl)amino)nicotinate

[0137] A mixture of p-methoxybenzylamine (19.0 mL, 146 mmol), methyl 4,6-dichloronicotinate (25 g, 121 mmol), triethylamine (20.3 mL, 146 mmol) in MeCN (60 mL) was stirred at RT for 24 h. More 4-methoxybenzylamine (2.5 mL) was added, and the mixture was stirred at RT for 72 h. The mixture was concentrated, and the residue was partitioned between EtOAc and aqueous saturated NH_4Cl. The organic extract was combined, dried with Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (EtOAc / heptane) to give the title compound. LCMS: Rt = 1.42 min, m/z = 307.1 (M+H) (LCMS method 1).

Step 2: Synthesis of (6-chloro-4-((4-methoxybenzyl)amino)pyridin-3-yl)methanol

[0138] To a solution of LAH (2M in THF, 21.52 mL, 43.0 mmol) in THF (150 mL) stirring at 0 °C was added a solution of methyl 6-chloro-4-((4-methoxybenzyl)amino)nicotinate (prepared in step 1) (12 g, 39.1 mmol) in THF (100 mL) dropwise. The reaction was allowed to warm to RT and was stirred for 30 min. The reaction was quenched with slow addition of EtOAc in an ice bath, followed by Steinhardt conditions for quenching LAH (2 mL H_2O, followed by 2 mL of 15% NaOH and 6 mL of H_2O). The resulting solution was stirred for 15 min and was allowed to warm to RT. The mixture was filtered over Celite and the filtrate was transferred to a separatory funnel. The product was further diluted with water and then extracted with EtOAc. The organics were combined, dried with Na_2SO_4, filtered, and volatiles were removed in vacuo to give the title compound. LCMS: Rt = 0.84 min, m/z = 279.3 (M+H) (LCMS 1 method 1).

Step 3: Synthesis of (4-amino-6-chloropyridin-3-yl)methanol

[0139] A solution of (6-chloro-4-((4-methoxybenzyl)amino)pyridin-3-yl)methanol (prepared in step 2) (9.82 g, 35.2 mmol) in TFA (2.71 mL, 35.2 mmol) was heated at 60 °C for 18 h. The reaction was neutralized with 10% aqueous K_2CO_3 to pH ~7. The mixture was then transferred to a separatory funnel and was extracted with DCM. The organics were combined, dried with Na_2SO_4, filtered, and volatiles were removed in vacuo to give a portion of the title compound. The aqueous layer was concentrated in vacuo, and the resulting solid was diluted in isopropanol. Insoluble salts were filtered off, and the solution was cooled on ice. Additional salts that precipitated out were filtered off. Volatiles were removed in vacuo to give more amount of the title compound. LCMS: Rt = 0.26 min, m/z = 159.1 (M+H) (LCMS method 2).

Step 4: Synthesis of 5-(((tert-butyldimethylsilyl)oxy)methyl)-2-chloropyridin-4-amine

[0140] A mixture of (4-amino-6-chloropyridin-3-yl)methanol (prepared in step 3) (5 g, 32 mmol), TBDMSCl (5.23 g, 34.7 mmol) and imidazole (5.37 g, 79 mmol) in DMF (10 mL) was stirred at RT for 1 h. The reaction mixture was poured into water and was extracted with EtOAc. The organics were combined, dried with Na_2SO_4, filtered, and volatiles were removed in vacuo. The crude residue was purified by silica gel chromatography (EtOAc / heptane) to give the title compound. LCMS: Rt = 1.52 min, m/z = 273.2 (M+H) (LCMS method 2).

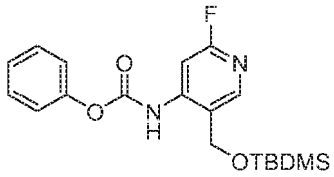
Step 5: Synthesis of Phenyl (5-(((tert-butyldimethylsilyl)oxy)methyl)-2-chloropyridin-4-yl)carbamate

[0141] To a solution of 5-(((tert-butyldimethylsilyl)oxy)methyl)-2-chloropyridin-4-amine (prepared in step 4) (5.55 g, 20.3 mmol) and pyridine (1.8 mL, 22.4 mmol) in DCM (75 mL) stirring at RT was added phenyl chloroformate (2.68 mL, 21.4 mmol). The reaction was allowed to warm to RT over 2 h. Volatiles were removed in vacuo, and the residue was diluted with EtOAc and saturated aqueous $NaHCO_3$. The mixture was then extracted with EtOAc. The organics were combined, dried with Na_2SO_4, filtered, and volatiles were removed in vacuo. The crude residue was purified by silica gel chromatography (EtOAc / heptane) to give the title compound. LCMS: Rt = 1.94 min, m/z = 393.3 (M+H) (LCMS method 1).

Intermediate 7

Phenyl (5-(((tert-butyldimethylsilyl)oxy)methyl)-2-fluoropyridin-4-yl)carbamate

[0142]



Step 1: Synthesis of methyl 4-amino-6-fluoronicotinate.

[0143] To a 500 mL flask containing methyl-4,6-dichloronicotinate (6.75 g, 32.8 mmol) and TMAF (8.0 g, 86 mmol) was added DMF (100 mL) and the mixture was stirred at RT for 1.5 h until complete formation of intermediate methyl-4,6-difluoronicotinate was identified by LCMS. To this reaction mixture was then added a solution of 2M ammonia in isopropanol (35 mL, 70 mmol) and stirred at RT for 20 h. Complete formation of the title compound was identified by LCMS. The reaction mixture was quenched with water, and the crude product was extracted with EtOAc. The organic layer was washed with brine, then dried over sodium sulfate, filtered and concentrated *in vacuo.* The residue was purified by silica gel chromatography (EtOAc / heptane) to obtain the title compound. LCMS: Rt = 0.97 min, m/z 174 (M+H) (LCMS method 1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 (s, 1H), 7.52 (s, 2H), 6.30 (s, 1H), 3.82 (s, 3H).

Step 2: Synthesis of (4-amino-6-fluoropyridin-3-yl)methanol.

[0144] To an ice-cold (0 °C) solution of LAH (2M in THF, 24.8 mL, 49.6 mmol) diluted further with THF (200 mL) was added, via addition funnel over 45 min, a solution of methyl 4-amino-6-fluoronicotinate (4.22 g, 24.8 mmol) in THF (100 mL) resulting in a suspension. The mixture was allowed to warm to RT for 2 h after which the reaction was judged complete by LCMS. The reaction mixture was diluted with THF (200 mL) and cooled on ice. Sodium sulfate decahydrate was added in portions to the mixture until the bubbling ceased. The mixture was stirred for 18 h, then filtered and concentrated *in vacuo.* The resulting residue was purified by silica gel chromatography (EtOAc / heptane) to obtain the title compound. LCMS : Rt = 0.27 min, m/z 143 (M+H) (LCMS method 3). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63 (s, 1H), 6.20 (s, 2H), 6.09 (s, 1H), 5.04 (t, J = 5.5 Hz, 1H), 4.35 (d, J = 5.5 Hz, 2H).

Step 3: Synthesis of 5-(((tert-butyldimethylsilyl)oxy)methyl)-2-fluoropyridin-4-amine.

[0145] A mixture of (4-amino-6-fluoropyridin-3-yl)methanol (1.52 g, 10.7 mmol), TBDMSCl (1.77 g, 11.8 mmol), and imidazole (1.82 g, 26.7 mmol) in DMF (50 mL) was stirred at RT for 1 h, after which the reaction was judged complete by TLC, 100% EtOAc. The reaction mixture was concentrated *in vacuo,* then purified by silica gel chromatography

(EtOAc / heptane) to obtain the title compound. LCMS: Rt= 1.46 min, m/z 257 (M+H) (LCMS method 1). ^{1}H NMR (400 MHz, DMSO-d6) δ 7.60 (s, 1H), 6.11 (s, 2H), 6.04 (s, 1H), 4.50 (s, 2H), 0.81 (s, 9H), 0.00 (s, 6H).

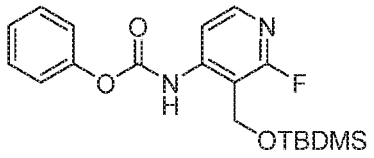
Step 4: Synthesis of phenyl (5-(((tert-butyldimethylsilyl)oxy)methyl)-2-fluoropyridin-4-yl) carbamate.

[0146] To a mixture of (4-amino-6-fluoropyridin-3-yl)methanol (1.45 g, 5.66 mmol) and pyridine (0.46 mL, 5.66 mmol) in dioxane (30 mL) was added phenyl chloroformate (0.710 mL, 5.66 mmol) and the resulting mixture was stirred for 1 h. The mixture was then diluted with EtOAc, then washed with sodium bicarbonate followed by water. The organic portion was dried over sodium sulfate and concentrated *in vacuo.* The residue was purified by silica gel chromatography (EtOAc / heptane) to obtain the title compound. LCMS: Rt = 1.89 min, m/z 377 (M+H) (LCMS method 1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.66 (s, 1H), 8.03 (s, 1H), 7.41 (s, 1H), 7.39 - 7.31 (m, 2H), 7.16 - 7.09 (m, 2H), 6.74 - 6.52 (m, 1H), 4.78 (s, 2H), 0.80 (s,9 H), 0.00 (s, 6H).

Intermediate 8

Phenyl (3-(((tert-butyldimethylsilyl)oxy)methyl)-2-fluoropyridin-4-yl)carbamate

[0147]



Step 1: Synthesis of methyl 2,4-difluoronicotinate

[0148] A solution of 2,4-difluoropyridine (5 g, 43.4 mmol) in THF (120 mL) was added dropwise to a stirring solution of lithium diisopropylamide (2M in THF/heptane/ethylbenzene, 26.1 mL, 52.1 mmol) at -78 °C. After stirring for 1 h, the reaction was transferred to a stirring solution of methyl chloroformate (5.05 mL, 65.2 mmol) in THF (120 mL) at -78 °C via cannula. The reaction mixture was allowed to warm to RT over 30 min. The reaction was quenched slowly with water (100 mL) and was extracted with EtOAc (3×100mL). The organics were combined, dried with Na_2SO_4, filtered, and volatiles were removed in vacuo. The product was purified by silica gel chromatography (EtOAc / heptane) to give the title compound. LCMS: Rt = 0.94 min, m/z 174.1 (M+H) (LCMS method 1).

Step 2: Synthesis of methyl 4-amino-2-fluoronicotinate

[0149] To a solution of methyl 2,4-difluoronicotinate (prepared in step 1) (2 g, 11.55 mmol) in dioxane (40 mL) was added ammonia in dioxane (0.5M, 46.2 mL, 23.11 mmol). The reaction was stirred at 60 °C for 18 h. The reaction was poured into saturated $NaHCO_{3(aq)}$ and was extracted with EtOAc (3×100mL). The organics were combined, dried with Na_2SO_4, filtered, and volatiles were removed in vacuo. The product was purified by silica gel chromatography (EtOAc / heptane) to give the title compound. LCMS: Rt = 0.77 min, m/z 171.1 (M+H) (LCMS method 1).

Step 3: Synthesis of (4-amino-2-fluoropyridin-3-yl)methanol

[0150] To a solution of methyl 4-amino-2-fluoronicotinate (2.02 g, 11.87 mmol) in THF (70 mL) stirring in an ice bath was added LAH (2M in THF, 7.1 mL, 14.2 mmol) dropwise. The reaction was stirred at 0 °C for 30 min and the reaction was quenched by slowly adding sodium sulfate decahydrate (3.5 g). The mixture was stirred for 15 min, before anhydrous Na_2SO_4 was added. The mixture was filtered over Celite and the volatiles were removed in vacuo. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.56 (d, J = 5.7 Hz, 1H), 6.47 (dd, J = 5.7, 1.2 Hz, 1H), 6.29 (s, 2H), 4.96 (t, J = 5.4 Hz, 1H), 4.40 (d, J = 5.4 Hz, 2H).

Step 4: Synthesis of 3-(((tert-butyldimethylsilyl)oxy)methyl)-2-fluoropyridin-4-amine

[0151] A mixture of (4-amino-2-fluoropyridin-3-yl)methanol (1.57 g, 11.05 mmol), TBDMSCl (2.00 g, 13.26 mmol) and imidazole (1.88 g, 27.6 mmol) was stirred in DMF (30 mL) at RT. After 90 min, the reaction was quenched with sat.aq. $NaHCO_3$, then diluted with EtOAc. The aqueous layer was extracted with EtOAc. The organic fractions were combined, washed with brine, then dried with sodium sulfate, filtered and concentrated in vacuo. The crude mixture was purified

by flash chromatography (EtOAc/heptane). LCMS: Rt = 1.47 min, m/z 257.3 (M+H) (LCMS method 1).

Step 5: Synthesis of phenyl (3-(((tert-butyldimethylsilyl)oxy)methyl)-2-fluoropyridin-4-yl)carbamate

[0152] To a solution of 3-(((tert-butyldimethylsilyl)oxy)methyl)-2-fluoropyridin-4-amine (2.36 g, 9.20 mmol) and pyridine (0.89 mL, 11.0 mmol) in dioxane (40 mL) was added phenyl chloroformate (1.21 mL, 9.7 mmol) at RT. After 2.5 h the reaction was quenched with saurated aqueous $NaHCO_3$, then diluted with EtOAc. The aqueous layer was extracted with EtOAc. The organic fractions were combined, washed with brine, then dried with sodium sulfate, filtered and concentrated in vacuo.

[0153] The crude mixture was purified by flash chromatography (EtOAc/heptane) to give the title compound. LCMS: Rt = 1.91 min, m/z 377.4 (M+H) (LCMS method 1). 1H NMR (400 MHz, DMSO-d6) δ 9.92 (s, 1H), 8.11 (d, J = 5.7 Hz, 1H), 7.78 (d, J = 5.7 Hz, 1H), 7.52 - 7.42 (m, 2H), 7.36 - 7.26 (m, 1H), 7.26 - 7.19 (m, 2H), 4.90 (s, 2H), 0.87 (s, 9H), 0.08 (s, 6H).

PHARMACEUTICAL COMPOSITIONS AND COMBINATIONS

[0154] The compounds of the present disclosure are typically used as a pharmaceutical composition (e.g., a compound of the present disclosure and at least one pharmaceutically acceptable carrier). A "pharmaceutically acceptable carrier (diluent or excipient)" refers to media generally accepted in the art for the delivery of biologically active agents to animals, in particular, mammals, including, generally recognized as safe (GRAS) solvents, dispersion media, coatings, surfactants, antioxidants, preservatives (*e.g.*, antibacterial agents, antifungal agents), isotonic agents, absorption delaying agents, salts, preservatives, drug stabilizers, binders, buffering agents (e.g., maleic acid, tartaric acid, lactic acid, citric acid, acetic acid, sodium bicarbonate, sodium phosphate, and the like), disintegration agents, lubricants, sweetening agents, flavoring agents, dyes, and the like and combinations thereof, as would be known to those skilled in the art (see, for example, Allen, L.V., Jr. et al., *Remington: The Science and Practice of Pharmacy* (2 Volumes), 22nd Edition, Pharmaceutical Press (2012).

[0155] In one aspect, the present disclosure provides a pharmaceutical composition comprising a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In a further embodiment, the composition comprises at least two pharmaceutically acceptable carriers, such as those described herein. For purposes of the present disclosure, unless designated otherwise, solvates and hydrates are generally considered compositions. Preferably, pharmaceutically acceptable carriers are sterile. The pharmaceutical composition can be formulated for particular routes of administration such as oral administration, parenteral administration, and rectal administration, etc. In addition, the pharmaceutical compositions of the present disclosure can be made up in a solid form (including without limitation capsules, tablets, pills, granules, powders or suppositories), or in a liquid form (including without limitation solutions, suspensions or emulsions). The pharmaceutical compositions can be subjected to conventional pharmaceutical operations such as sterilization and/or can contain conventional inert diluents, lubricating agents, or buffering agents, as well as adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers and buffers, etc. Typically, the pharmaceutical compositions are tablets or gelatin capsules comprising the active ingredient together with one or more of:

a) diluents, *e.g.*, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine;
b) lubricants, *e.g.,* silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also
c) binders, *e.g.,* magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone; if desired
d) disintegrants, *e.g.,* starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and
e) absorbents, colorants, flavors and sweeteners.

[0156] Tablets may be either film coated or enteric coated according to methods known in the art.

[0157] Suitable compositions for oral administration include an effective amount of a compound of the disclosure in the form of tablets, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use are prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions can contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets may contain the active ingredient in admixture with nontoxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients are, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example, starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets are

uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed. Formulations for oral use can be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

[0158] Certain injectable compositions are aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions. Said compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. Said compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1-75%, or contain about 1-50%, of the active ingredient.

[0159] Suitable compositions for transdermal application include an effective amount of a compound of the disclosure with a suitable carrier. Carriers suitable for transdermal delivery include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound of the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

[0160] Suitable compositions for topical application, *e.g.,* to the skin and eyes, include aqueous solutions, suspensions, ointments, creams, gels or sprayable formulations, *e.g.,* for delivery by aerosol or the like. Such topical delivery systems will in particular be appropriate for dermal application, *e.g.,* for the treatment of skin cancer, *e.g.,* for prophylactic use in sun creams, lotions, sprays and the like. They are thus particularly suited for use in topical, including cosmetic, formulations well-known in the art. Such may contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

[0161] As used herein a topical application may also pertain to an inhalation or to an intranasal application. They may be conveniently delivered in the form of a dry powder (either alone, as a mixture, for example a dry blend with lactose, or a mixed component particle, for example with phospholipids) from a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray, atomizer or nebuliser, with or without the use of a suitable propellant.

[0162] The present disclosure further provides anhydrous pharmaceutical compositions and dosage forms comprising the compounds of the present disclosure as active ingredients, since water may facilitate the degradation of certain compounds.

[0163] Anhydrous pharmaceutical compositions and dosage forms of the disclosure can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. An anhydrous pharmaceutical composition may be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (*e. g*., vials), blister packs, and strip packs.

[0164] The present disclosure further provides pharmaceutical compositions and dosage forms that comprise one or more agents that reduce the rate by which the compound of the present invention as an active ingredient will decompose. Such agents, which are referred to herein as "stabilizers," include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers, etc.

[0165] The compound of the present disclosure is typically formulated into pharmaceutical dosage forms to provide an easily controllable dosage of the drug and to give the patient an elegant and easily handleable product. The dosage regimen for the compounds of the present disclosure will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient, and the effect desired. Compounds of this disclosure may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

[0166] In certain instances, it may be advantageous to administer the compound of the present disclosure in combination with one or more therapeutically active agents independently selected from anti-cancer agents, anti-allergic agents, anti-emetics, pain relievers, immunomodulators and cytoprotective agents.

[0167] The term "combination therapy" refers to the administration of two or more therapeutic agents to treat a therapeutic disease, disorder or condition described in the present disclosure. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients. Alternatively, such administration encompasses co-administration in multiple, or in separate containers (e.g., capsules, powders, and liquids) for each active ingredient. The compound of the present disclosure and additional therapeutic agents can be administered via the same administration route or via different administration routes. Powders and/or liquids may be reconstituted or diluted to a desired dose prior to administration. In addition, such

administration also encompasses use of each type of therapeutic agent in a sequential manner, either at approximately the same time or at different times. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the diseases, conditions or disorders described herein.

[0168] General Chemotherapeutic agents considered for use in combination therapies include capecitabine (Xeloda®), N4-pentoxycarbonyl-5-deoxy-5-fluorocytidine, carboplatin (Paraplatin®), cisplatin (Platinol®), cladribine (Leustatin®), cyclophosphamide (Cytoxan® or Neosar®), cytarabine, cytosine arabinoside (Cytosar-U®), cytarabine liposome injection (DepoCyt®), dacarbazine (DTIC-Dome®), doxorubicin hydrochloride (Adriamycin®, Rubex®), fludarabine phosphate (Fludara®), 5-fluorouracil (Adrucil®, Efudex®), Gemcitabine (difluorodeoxycitidine), irinotecan (Camptosar®), L-asparaginase (ELSPAR®), 6-mercaptopurine (Purinethol®), methotrexate (Folex®), pentostatin, 6-thioguanine, thiotepa, and topotecan hydrochloride for injection (Hycamptin®).

[0169] Anti-cancer agents of particular interest for combinations with the compounds of the present disclosure include: Phosphoinositide 3-kinase (PI3K) inhibitors: 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 09/036082 and WO 09/055730); 4-(trifluoromethyl)-5-(2,6-dimorpholinopyrimidin-4-yl)pyridin-2-amine (also known as BKM120 or NVP-BKM120, and described in PCT Publication No. WO2007/084786); Alpelisib (BYL719): (5Z)-5-[[4-(4-Pyridinyl)-6-quinolinyl]methylene]-2,4-thiazolidinedione (GSK1059615, CAS 958852-01-2); 5-[8-methyl-9-(1-methylethyl)-2-(4-morpholinyl)-9H-purin-6-yl]-2-pyrimidinamine (VS-5584, CAS 1246560-33-7) and everolimus (AFINITOR®).

[0170] Mitogen-activated protein kinase (MEK) inhibitors: XL-518 (also known as GDC-0973, Cas No. 1029872-29-4, available from ACC Corp.); Selumetinib (5-[(4-bromo-2-chlorophenyl)amino]-4-fluoro-N-(2-hydroxyethoxy)-1-methyl-1H-benzimidazole-6-carboxamide, also known as AZD6244 or ARRY 142886, described in PCT Publication No. WO2003077914); 2-[(2-Chloro-4-iodophenyl)amino]-N-(cyclopropylmethoxy)-3,4-difluoro-benzamide (also known as CI-1040 or PD184352 and described in PCT Publication No. WO2000035436); N-[(2R)-2,3-Dihydroxypropoxy]-3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]- benzamide (also known as PD0325901 and described in PCT Publication No. WO2002006213); 2,3-Bis[amino[(2-aminophenyl)thio]methylene]-butanedinitrile (also known as U0126 and described in US Patent No. 2,779,780); N-[3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]-6-methoxyphenyl]-1-[(2R)-2,3-dihydroxypropyl]- cyclopropanesulfonamide (also known as RDEA119 or BAY869766 and described in PCT Publication No. WO2007014011); (3S,4R,5Z,8S,9S,11E)-14-(Ethylamino)-8,9,16-trihydroxy-3,4-dimethyl-3,4,9, 19-tetrahydro-1H-2-benzoxacyclotetradecine-1,7(8H)-dione] (also known as E6201 and described in PCT Publication No. WO2003076424); 2'-Amino-3'-methoxyflavone (also known as PD98059 available from Biaffin GmbH & Co., KG, Germany); (R)-3-(2,3-Dihydroxypropyl)-6-fluoro-5-(2-fluoro-4-iodophenylamino)-8-methylpyrido[2,3-d]pyrimidine-4,7(3H,8H)-dione (TAK-733, CAS 1035555-63-5); Pimasertib (AS-703026, CAS 1204531-26-9); Trametinib dimethyl sulfoxide (GSK-1120212, CAS 1204531-25-80); 2-(2-Fluoro-4-iodophenylamino)-N-(2-hydroxyethoxy)-1,5-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide (AZD 8330); 3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]-N-(2-hydroxyethoxy)-5-[(3-oxo-[1,2]oxazinan-2-yl)methyl]benzamide (CH 4987655 or Ro 4987655); (); and 5-[(4-Bromo-2-fluorophenyl)amino]-4-fluoro-N-(2-hydroxyethoxy)-1-methyl-1H-Benzimidazole-6-carboxamide (MEK162).

[0171] Epidermal growth factor receptor (EGFR) inhibitors: Erlotinib hydrochloride (Tarceva®), Gefitnib (Iressa®); Dacomitinib (PF299804); N-[4-[(3-Chloro-4-fluorophenyl)amino]-7-[[(3"S")-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4(dimethylamino)-2-butenamide, Tovok®); Vandetanib (Caprelsa®); Lapatinib (Tykerb®); (3R,4R)-4-Amino-1-((4-((3-methoxyphenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-5-yl)methyl)piperidin-3-ol (BMS690514); Canertinib dihydrochloride (CI-1033); 6-[4-[(4-Ethyl-1-piperazinyl)methyl]phenyl]-*N*-[(1*R*)-1-phenylethyl]-7*H*-Pyrrolo[2,3-*d*]pyrimidin-4-amine (AEE788, CAS 497839-62-0); Mubritinib (TAK165); Pelitinib (EKB569); Afatinib (BIBW2992); Neratinib (HKI-272); *N*-[4-[[1-[(3-Fluorophenyl)methyl]-1*H*-indazol-5-yl]amino]-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl]-carbamic acid, (3*S*)-3-morpholinylmethyl ester (BMS599626); *N*-(3,4-Dichloro-2-fluorophenyl)-6-methoxy-7-[[(3aα,5β,6aα)-octahydro-2-methylcyclopenta[*c*]pyrrol-5-yl]methoxy]-4-quinazolinamine (XL647, CAS 781613-23-8); and 4-[4-[[(1R)-1-Phenylethyl]amino]-7*H*-pyrrolo[2,3-d]pyrimidin-6-yl]-phenol (PKI166, CAS 187724-61-4).

[0172] EGFR antibodies: Cetuximab (Erbitux®); Panitumumab (Vectibix®); Matuzumab (EMD-72000); Trastuzumab (Herceptin®); Nimotuzumab (hR3); Zalutumumab; TheraCIM h-R3; MDX0447 (CAS 339151-96-1); and ch806 (mAb-806, CAS 946414-09-1).

[0173] MAPK inhibitors: Vemurafinib (Zelboraf®), Sorafinib (Nexavar®), Dabrefinib (Tafinlar®), Trametinib (Mekinist®) and Selumetinib (AZD6244, ARRY-142886)

[0174] EED/EZH2 inhibitors: tazemetostat (EPZ-6438), GSK2816126 (CAS 1346574-57-9), CPI-1205 (CAS 1621862-70-1) and DS-3201 (also known as DS-3201b, Daiichi Sankyo, Inc).

[0175] Immune checkpoint modulators: Pembrolizumab (Keytruda®), Nivolumab (Opdivo®), Atezolizumab (Tecentriq®) and Ipilumumab (Yervoy®).

[0176] Some patients may experience allergic reactions to the compounds of the present disclosure and/or other anti-cancer agent(s) during or after administration; therefore, anti-allergic agents are often administered to minimize the risk of an allergic reaction. Suitable anti-allergic agents include corticosteroids (Knutson, S., et al., PLoS One, DOI:10.1371/journal.pone.0111840 (2014)), such as dexamethasone (e.g., Decadron®), beclomethasone (e.g., Beclo-

vent®), hydrocortisone (also known as cortisone, hydrocortisone sodium succinate, hydrocortisone sodium phosphate, and sold under the tradenames Ala-Cort®, hydrocortisone phosphate, Solu-Cortef®, Hydrocort Acetate® and Lanacort®), prednisolone (sold under the tradenames Delta-Cortel®, Orapred®, Pediapred® and Prelone®), prednisone (sold under the tradenames Deltasone®, Liquid Red®, Meticorten® and Orasone®), methylprednisolone (also known as 6-methylprednisolone, methylprednisolone acetate, methylprednisolone sodium succinate, sold under the tradenames Duralone®, Medralone®, Medrol®, M-Prednisol® and Solu-Medrol®); antihistamines, such as diphenhydramine (e.g., Benadryl®), hydroxyzine, and cyproheptadine; and bronchodilators, such as the beta-adrenergic receptor agonists, albuterol (e.g., Proventil®), and terbutaline (Brethine®).

[0177] Some patients may experience nausea during and after administration of the compound of the present disclosure and/or other anti-cancer agent(s); therefore, anti-emetics are used in preventing nausea (upper stomach) and vomiting. Suitable anti-emetics include aprepitant (Emend®), ondansetron (Zofran®), granisetron HCl (Kytril®), lorazepam (Ativan®, dexamethasone (Decadron®), prochlorperazine (Compazine®), casopitant (Rezonic® and Zunrisa®), and combinations thereof.

[0178] Medication to alleviate the pain experienced during the treatment period is often prescribed to make the patient more comfortable. Common over-the-counter analgesics, such Tylenol®, are often used. However, opioid analgesic drugs such as hydrocodone/paracetamol or hydrocodone/acetaminophen (e.g., Vicodin®), morphine (e.g., Astramorph® or Avinza®), oxycodone (e.g., OxyContin® or Percocet®), oxymorphone hydrochloride (Opana®), and fentanyl (e.g., Duragesic®) are also useful for moderate or severe pain.

[0179] Immunomodulators of particular interest for combinations with the compounds of the present disclosure include: Afutuzumab (available from Roche®); Pegfilgrastim (Neulasta®); Lenalidomide (CC-5013, Revlimid®); Thalidomide (Thalomid®), Actimid (CC4047); and IRX-2 (mixture of human cytokines including interleukin 1, interleukin 2, and interferon γ, CAS 951209-71-5, available from IRX Therapeutics).

[0180] In an effort to protect normal cells from treatment toxicity and to limit organ toxicities, cytoprotective agents (such as neuroprotectants, free-radical scavengers, cardioprotectors, anthracycline extravasation neutralizers, nutrients and the like) may be used as an adjunct therapy. Suitable cytoprotective agents include Amifostine (Ethyol®), glutamine, dimesna (Tavocept®), mesna (Mesnex®), dexrazoxane (Zinecard® or Totect®), xaliproden (Xaprila®), and leucovorin (also known as calcium leucovorin, citrovorum factor and folinic acid).

[0181] The structure of the active compounds identified by code numbers, generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Patents International (e.g. IMS World Publications).

[0182] In one embodiment, the present disclosure provides pharmaceutical compositions comprising at least one compound of the present disclosure or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier suitable for administration to a human or animal subject, either alone or together with other anti-cancer agents.

[0183] In another embodiment, the present disclosure provides methods of treating human or animal subjects suffering from a cellular proliferative disease, such as malignancy. The present disclosure provides methods of treating a human or animal subject in need of such treatment, comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof, either alone or in combination with other anti-cancer agents.

[0184] In particular, compositions will either be formulated together as a combination therapeutic or administered separately.

[0185] In one embodiment, the present disclosure provides a pharmaceutical combination comprising a compound of the present disclosure or a pharmaceutically acceptable salt thereof, and one or more therapeutically active agents selected from the group consisting of Abitrexate (Methotrexate), Abraxane (Paclitaxel Albumin-stabilized Nanoparticle Formulation), Afatinib Dimaleate, Afinitor (Everolimus), Alecensa (Alectinib), Alectinib, Alimta (Pemetrexed Disodium), Avastin (Bevacizumab), Bevacizumab, Carboplatin, Ceritinib, Crizotinib, Cyramza (Ramucirumab), Docetaxel, Erlotinib Hydrochloride, Everolimus, Folex (Methotrexate), Folex PFS (Methotrexate), Gefitinib, Gilotrif (Afatinib Dimaleate), Gemcitabine Hydrochloride, Gemzar (Gemcitabine Hydrochloride), Iressa (Gefitinib), Keytruda (Pembrolizumab), Mechlorethamine Hydrochloride, Methotrexate, Methotrexate LPF (Methotrexate), Mexate (Methotrexate), Mexate-AQ (Methotrexate), Mustargen (Mechlorethamine Hydrochloride), Navelbine (Vinorelbine Tartrate), Necitumumab, Nivolumab, Opdivo (Nivolumab), Osimertinib, Paclitaxel, Paclitaxel Albumin-stabilized Nanoparticle Formulation, Paraplat (Carboplatin), Paraplatin (Carboplatin), Pembrolizumab, Pemetrexed Disodium, Portrazza (Necitumumab), Ramucirumab, Tagrisso (Osimertinib), Tarceva (Erlotinib Hydrochloride), Taxol (Paclitaxel), Taxotere (Docetaxel), Vinorelbine Tartrate, Xalkori (Crizotinib), Zykadia (Ceritinib), CARBOPLATIN-TAXOL and GEMCITABINE-CISPLATIN, for the treatment of lung carcinoma (including, but not limited to, non-small cell lung carcinoma, lung adenocarcinoma, lung carcinoma, large cell lung carcinomas, non-small cell lung carcinoma, lung squamous cell carcinoma, small cell lung cancer).

[0186] In another embodiment, the present disclosure provides a pharmaceutical combination comprising a compound of the present disclosure or a pharmaceutically acceptable salt thereof, and one or more therapeutically active agents

selected from the group consisting of Aldesleukin, Cobimetinib, Cotellic (Cobimetinib), Dabrafenib, Dacarbazine, DTIC-Dome (Dacarbazine), IL-2 (Aldesleukin), ImLygic (Talimogene Laherparepvec), Interleukin-2 (Aldesleukin), Intron A (Recombinant Interferon Alfa-2b), Ipilimumab, Keytruda (Pembrolizumab), Mekinist (Trametinib), Nivolumab, Opdivo (Nivolumab), Peginterferon Alfa-2b, PEG-Intron (Peginterferon Alfa-2b), Pembrolizumab, Proleukin (Aldesleukin), Recombinant Interferon Alfa-2b, Sylatron (Peginterferon Alfa-2b), Tafinlar (Dabrafenib), Talimogene Laherparepvec, Trametinib, Vemurafenib, Yervoy (Ipilimumab) and Zelboraf (Vemurafenib), for the treatment of melanoma (including, but not limited to, skin cutaneous melanoma, desmoplastic melanoma and uveal melanoma).

[0187] In combination therapy for treatment of a malignancy, the compound of the present disclosure and other anti-cancer agent(s) may be administered simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the two compounds in the body of the subject.

[0188] In a preferred embodiment, the compound of the present disclosure and the other anti-cancer agent(s) is generally administered sequentially in any order by infusion or orally. The dosing regimen may vary depending upon the stage of the disease, physical fitness of the patient, safety profiles of the individual drugs, and tolerance of the individual drugs, as well as other criteria well-known to the attending physician and medical practitioner(s) administering the combination. The compound of the present disclosure and other anti-cancer agent(s) may be administered within minutes of each other, hours, days, or even weeks apart depending upon the particular cycle being used for treatment. In addition, the cycle could include administration of one drug more often than the other during the treatment cycle and at different doses per administration of the drug.

[0189] In another aspect of the present disclosure, a kit comprising two or more separate pharmaceutical compositions, at least one of which contains a compound of the present disclosure is provided. In one embodiment, the kit comprises means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is a blister pack, as typically used for the packaging of tablets, capsules and the like.

[0190] The kit of the present disclosure may be used for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit of the present disclosure typically comprises directions for administration.

[0191] A compound of the present disclosure may also be used to advantage in combination with known therapeutic processes, for example, the administration of hormones or especially radiation. A compound of the present disclosure may in particular be used as a radiosensitizer, especially for the treatment of tumors which exhibit poor sensitivity to radiotherapy.

[0192] In the combination therapies of the present disclosure, the compound of the present disclosure and the other therapeutic agent may be manufactured and/or formulated by the same or different manufacturers. Moreover, the compound of the present disclosure and the other therapeutic (or pharmaceutical agent) may be brought together into a combination therapy: (i) prior to release of the combination product to physicians (*e.g.* in the case of a kit comprising the compound of the present disclosure and the other therapeutic agent); (ii) by the physician themselves (or under the guidance of the physician) shortly before administration; (iii) in the patient themselves, *e.g.* during sequential administration of the compound of the present disclosure and the other therapeutic agent.

[0193] The pharmaceutical composition (or formulation) for application may be packaged in a variety of ways depending upon the method used for administering the drug. Generally, an article for distribution includes a container having deposited therein the pharmaceutical formulation in an appropriate form. Suitable containers are well-known to those skilled in the art and include materials such as bottles (plastic and glass), sachets, ampoules, plastic bags, metal cylinders, and the like. The container may also include a tamper-proof assemblage to prevent indiscreet access to the contents of the package. In addition, the container has deposited thereon a label that describes the contents of the container. The label may also include appropriate warnings.

[0194] The pharmaceutical composition or combination of the present disclosure can be in unit dosage of about 1-1000 mg of active ingredient(s) for a subject of about 50-70 kg, or about 1-500 mg or about 1-250 mg or about 1-150 mg or about 0.5-100 mg, or about 1-50 mg of active ingredients. The therapeutically effective dosage of a compound, the pharmaceutical composition, or the combinations thereof, is dependent on the species of the subject, the body weight, age and individual condition, the disorder or disease or the severity thereof being treated. A physician, clinician or veterinarian of ordinary skill can readily determine the effective amount of each of the active ingredients necessary to prevent, treat or inhibit the progress of the disorder or disease.

[0195] The above-cited dosage properties may be demonstrable *in vitro* and *in vivo* tests using advantageously mammals, e.g., mice, rats, dogs, monkeys or isolated organs, tissues and preparations thereof. The compounds of the present disclosure can be applied *in vitro* in the form of solutions, e.g., aqueous solutions, and *in vivo* either enterally, parenterally, advantageously intravenously, e.g., as a suspension or in aqueous solution. The dosage *in vitro* may range between about 10^{-3} molar and 10^{-9} molar concentrations. A therapeutically effective amount *in vivo* may range depending on the route of administration, between about 0.1-500 mg/kg, or between about 1-100 mg/kg.

PHARMACOLOGY AND UTILITY

[0196] Mutations in SWI/SNF chromatin remodeling complexes are highly prevalent in cancers, occurring at a frequency of approximately 20% (Kadoch, C., Hargreaves, D. C., et al. 2013 Nat Genet. 45: 592-601) (Shain, A.H., and Pollack, J.R. 2013 PLoS ONE 8(1): e55119). SWI/SNF complexes consist of multiple subunits, and function in ATP-dependent remodeling of chromatin to control key cellular events such as regulation of gene expression. The catalytic ATPase subunits within the SWI/SNF complex consist of either BRM/SMARCA2 or BRG1/SMARCA4, and are thus mutually exclusive (Hodges, C., Kirkland, J.G., et al. 2016 Cold Spring Harb Persp Med 6(8)). Functional genomics screening via shRNAs, has revealed a compelling synthetic lethal relationship between these two SWI/SNF ATPases, BRM and BRG1 (Hoffman, G.R; Rahal, R et al. 2014 PNAS 111(8): 3128-33; Wilson, B.G., Helming, K.C., et al. 2014 Molecular and Cellular Biology 34(6): 1136-44). In particular, cancer cells lacking functional BRG1, such as through loss of function mutations or deletions, are exquisitely sensitive to depletion of BRM via shRNA mediated knockdown, resulting in growth inhibition (Hoffman, G.R., Rahal, R et al., 2014 PNAS 111(8): 3128-33; Oike, T., Ogiwara, H., et al. 2013 Cancer Research 73(17): 5508-5518); and Vangamudi, B., Paul, T.A., et al. 2015 Cancer Research 75(18): 3865-3878). Therefore, these studies reveal that in the absence of one of the SWI/SNF ATPases, cancer cells can become highly dependent on the remaining ATPase for survival, uncovering a vulnerability that can be exploited for targeted therapy. Genetic lesions in BRG1 have indeed been identified in various cancers, predominantly in non-small cell lung cancers at approximately 10%, but also in other cancer types such as liver, pancreatic, melanomas etc. (Imielinski, M., A. H. Berger, et al. (2012) Cell 150(6): 1107-1120); The Cancer Genome Atlas (TCGA) Data Portal, and the cBioPortal for Cancer Genomics). As such, these constitute highly significant patient populations with clear unmet medical need, and would be predicted to benefit from therapeutic inhibition of BRM. Just as certain cancer cells are dependent on BRM due to loss of BRG1 function, interestingly, other cancer types have been reported to be BRG1-dependent potentially occurring through various mechanisms including mutations in other subunits of the SWI/SNF complex (Shi, J; Whyte, W.A., et al. 2013 Genes and Development 27(24): 2648-2662; Xi, W., Sansam, C.G., et al. 2009 Cancer Research 69(20): 8094-8101; and Zuber, J., Shi, J., et al. 2011 Nature 478(7370), 524-528). In addition, SWI/SNF activity has also been reported to be altered in other disease settings, making it an attractive therapeutic target in other diseases besides cancer (Han, P., Li, W., et al. 2014 Nature 514(7520): 102-06). Therefore, the potential to inhibit either ATPase or both can have multiple applications in treating different types of cancers and diseases.

[0197] *BRG1* mutations, deletions or loss of expression that can lead to loss of function can occur in various types of cancers (The Cancer Genome Atlas (TCGA) Data Portal; the cBioPortal for Cancer Genomics; Becker, T. M., S. Haferkamp, et al. (2009) Mol Cancer 8: 4.; Matsubara, D., Kishaba, Y., et al. 2013 Cancer Science 104(2): 266-273; and Yoshimoto, T., Matsubara, D., et al. 2015 Pathology International 65(11): 595-602). Examples of specific types of cancers with *BRG1* mutation, deletions, or loss of expression include, but are not limited to non-small cell lung carcinoma, lung adenocarcinoma, lung carcinoma, large cell lung carcinomas, non-small cell lung carcinoma, lung squamous cell carcinoma, small cell lung cancer, skin cutaneous melanoma, desmoplastic melanoma, uveal melanoma, small cell carcinoma of the ovary, cutaneous squamous cell carcinoma, glioma, uterine carcinosarcoma, uterine corpus endometrial carcinoma, ovarian serous cystadenocarcinoma, bladder urothelial carcinoma, primary central nervous system lymphoma, esophageal carcinoma, bladder cancer, bladder cancer plasmacytoid variant, stomach adenocarcinoma, adenoid cystic carcinoma, lymphoid neoplasm diffuse large B-cell lymphoma, pancreatic cancer, colorectal adenocarcinoma, cholangiocarcinoma, sarcoma, head and neck cancers, cervical and endocervical cancers, medulloblastoma, cutaneous T cell lymphoma, liver hepatocellular carcinoma, kidney renal papillary cell carcinoma, breast cancer, mantle cell lymphoma, gallbladder carcinoma, testicular germ cell cancers, kidney renal cell clear cell carcinoma, prostate cancer, pediatric ewing sarcoma, thymoma, kidney chromophobe, renal non-clear cell carcinoma, pheochromocytoma and paraganglioma, thyroid cancers.

[0198] *SMARCB1*/*SNF5*-mutant cancers including malignant rhabdoid tumors in which BRG1-dependency has been demonstrated (Xi, W., Sansam, C.G., et al. 2009 Cancer Research 69(20): 8094-8101), but also SMARCB1/SNF-mutant epithelioid sarcomas, familial schwannomatosis, renal medullary carcinomas and Ewing sarcomas (Jahromi, M.S; Putnam, A.R, et al. 2012 Cancer Genetics 205(7-8): 391-404; Prensner, J.R., Iyer, M.K., et al. 2013 Nature Genetics 45(11): 1392-8; and Roberts, C.W.M., and Biegel, J.A., 2009 Cancer Biology and Thereapy 8(5): 412-416) and cancers in which SNF5 is deficient in the SWI/SNF complex not arising through mutations, such as in synovial sarcomas (Kadoch, C., and Crabtree, G.R., 2013 Cell 153(1): 71-85) as well as BRG1-dependent hematopoietic malignancies such as acute myeloid leukemias (AML) (Shi, J., Whyte, W.A., et al. 2013 Genes and Development 27(24): 2648-2662; and Zuber, J., Shi, J., et al. 2011 Nature 478(7370), 524-528). BRM-mutant (including deleted) or SNF5/SMARCB1 mutant (including deleted) cancers (The Cancer Genome Atlas (TCGA) Data Portal, and the cBioPortal for Cancer Genomics) include but not limited to malignant peripheral nerve sheath tumor, neuroendocrine prostate cancer, breast cancer, bladder urothelial carcinoma, adenoid cystic carcinoma, stomach adenocarcinoma,ovarian serous cystadenocarcinoma, uterine carcinosarcoma, esophageal carcinoma, head and neck squamous cell carcinoma, non-small cell lung carcinomas, lung adenocarcinoma, lung squamous cell carcinoma, small cell lung cancer, pancreatic cancer, adrenocortical carcinoma,

skin cutaneous melanoma, sarcoma, colorectal adenocarcinoma, cervical and endocervical cancers, liver hepatocellular carcinoma, cutaneous squamous cell carcinoma, testicular germ cell cancer, glioblastoma, glioblastoma multiforme, cholangiocarcinoma, Ewing's sarcoma, clear cell renal cell carcinoma, neuroblastoma, thymoma, diffuse large B cell lymphoma, acute myeloid leukemia, chronic lymphocytic leukemia, medulloblastoma, pheochromocytoma and paraganglioma and multiple myeloma.

[0199] Dual inhibitors in which there is a benefit of either BRM, BRG1, or BRM and BRG1 inhibition may also be applicable in cancers containing mutations or deficiencies in SWI/SNF subunits other than BRG1/SMARCA4, BRM/SMARCA2, or SNF5/SMARCB1 as detailed above, such as ARID1A, ARID1B, ARID2, PBRM1, SMARCE1, SMARCC1, SMARCC2, PHF10, DPF1, DPF3, DPF2, ACTL6A, ACTL6B, SMARCD2, SMARCD3, SMARCD1, BCL11A, BCL11B, BCL7A, BCL7B, BCL7C, BRD9 and ACTB. In other cases, dependency on BRM/BRG1 ATPases may arise from mechanisms other than SWI/SNF mutations.

[0200] Compounds of the present disclosure have favorable therapeutic benefits for BRM-mediated and/or BRG1-mediated disorders or diseases. The compounds of present disclosure in free form or in pharmaceutically acceptable salt form, exhibit valuable pharmacological properties, which can be demonstrated at least by using any one of the following test procedures. Compounds of the present disclosure were assessed for their ability to inhibit BRM and BRG1 activity in biochemical assays.

BRM ATPase Inhibition Assay

I. Isolation of the Recombinant BRM ATPase Domain

A. Cloning of His_{10}-ZZ-HCV3C-BRM(636-1331) into pFastBac1

[0201] Sequences encoding a His_{10} tag (SEQ ID NO: 1), the immunoglobulin G (IgG) binding ZZ domain of protein A (*Staphylococcus aureus*) and a human rhinovirus 3C protease site were fused upstream of BRM residues 636-1331 using standard DNA synthesis methods. The synthesized construct was cloned into the MCS of pFastBac1 (Life Technologies) by PCR amplification using the following 5' and 3' primers: 5'-GACCGAACTAGTATGGCTTCTCACCACCAT-3' (SEQ ID NO: 2) and 5'-AGCGTTAAGCTTTTAATCCTCGATGGCGCG-3' (SEQ ID NO: 3) to include a stop codon and ligated into SpeI and HindIII sites using standard molecular biology techniques. The final recombinant vector, pFB1-His_{10}-ZZ-HCV3C-BRM (636-1331), results in the expression of a HCV3C protease-cleavable His_{10}-ZZ tag (underlined) upstream of native BRM sequences encoding the ATPase and SnAC domains.

MASHHHHHHHHHHAQHDEAVDNKFNKEQQNAFYEILHLPNLNEEQRNAFIQSLKDDPSQSAN
LLAEAKKLNDAQAPKVDNKFNKEQQNAFYEILHLPNLNEEQRNAFIQSLKDDPSQSANLLAEAK
KLNDAQAPKVDANGGGGSGGGGSLEVLFQGPEESDSDYEEEDEEEESSRQETEEKILLDPNS
EEVSEKDAKQIIETAKQDVDDEYSMQYSARGSQSYYTVAHAISERVEKQSALLINGTLKHYQLQ
GLEWMVSLYNNNLNGILADEMGLGKTIQTIALITYLMEHKRLNGPYLIIVPLSTLSNWTYEFDKW
APSVVKISYKGTPAMRRSLVPQLRSGKFNVLLTTYEYIIKDKHILAKIRWKYMIVDEGHRMKNHH
CKLTQVLNTHYVAPRRILLTGTPLQNKLPELWALLNFLLPTIFKSCSTFEQWFNAPFAMTGERV
DLNEEETILIIRRLHKVLRPFLLRRLKKEVESQLPEKVEYVIKCDMSALQKILYRHMQAKGILLTDG
SEKDKKGKGGAKTLMNTIMQLRKICNHPYMFQHIEESFAEHLGYSNGVINGAELYRASGKFELL
DRILPKLRATNHRVLLFCQMTSLMTIMEDYFAFRNFLYLRLDGTTKSEDRAALLKKFNEPGSQY
FIFLLSTRAGGLGLNLQAADTVVIFDSDWNPHQDLQAQDRAHRIGQQNEVRVLRLCTVNSVEE
KILAAAKYKLNVDQKVIQAGMFDQKSSSHERRAFLQAILEHEEENEEEDEVPDDETLNQMIARR
EEEFDLFMRMDMDRRREDARNPKRKPRLMEEDELPWIIKDDAEVERLTCEEEEEKIFGRGSRQ
RRDVDYSDALTEKQWLRAIED (SEQ ID NO: 4)

B. Expression of BRM (636-1331)

[0202] The recombinant vector generated above was used to make recombinant bacmid by transforming to DH10Bac

cells using standard protocols as detailed by the manufacturer (Life Technologies). High titer P3 virus was generated by transfecting the bacmid to Spodoptera frugiperda 9 (Sf9) cells and amplifying the virus using standard methods as detailed by Life Technologies. His_{10}-ZZ-HCV3C-BRM (636-1331) was expressed from 25L of Sf9 cells in log phase growth (1.5×10^6 cells/mL) in a WAVE bioreactor (GE Healthcare Life Sciences) at a 1:100 v/v of virus. The infection was allowed to proceed on the rocking incubator at 27 °C and harvested three days post infection after cell viability had dropped to 80% with an increase in the overall cell diameter consistent with infection. Cells were harvested @ 4,000xg for 20 min, flash frozen and stored at -80 °C until use.

C. Purification of BRM (636-1331)

[0203] Sf9 cells expressing recombinant His_{10}-ZZ-HCV3C-BRM(636-1331) were lysed in 50 mM Tris (8.0), 300 mM NaCl, 10% glycerol and 2 mM TCEP supplemented with a protease inhibitor cocktail (Roche cOmplete), using 7.5 mL lysis buffer per gram of cell paste. Cells were lysed upon thawing, homogenized and subsequently clarified in a JA25.50 rotor @ 50,000xg for 30 min to remove insoluble material. The clarified lysate was applied to a 5 mL His-Trap HP column (GE Healthcare Life Sciences), washed rigorously in lysis buffer without protease inhibitors supplemented with 25 mM imidazole. Bound protein was eluted over a fifteen column volume gradient against lysis buffer supplemented with 500 mM imidazole. Fractions containing His_{10}-ZZ-HCV3C-BRM (636-1331) were pooled and dialyzed overnight against 50 mM Tris (8.0), 300 mM NaCl, 10% glycerol and 2 mM TCEP supplemented with HCV3C protease to effect removal of the His_{10}-ZZ tag. Cleavage was monitored by coomassie-stained SDS/PAGE and LC/MS. The intact mass was consistent with BRM residues 636-1331 proceeded by two non-native amino acids, Gly-Pro, a residual of the HCV3C cleavage site. The expected mass was 160 Da greater than predicted, consistent with two phosphorylation sites.

[0204] The cleaved product was diluted in dialysis buffer not supplemented with salt to a final NaCl concentration of 100 mM, passed thru a 0.2 μm syringe filter and immediately loaded to a 1 mL HiTrap Q HP column (GE Health Biosciences) previously equilibrated in 50 mM Tris (8.0), 100 mM NaCl, 10% glycerol & 1 mM TCEP. Following capture, the bound protein was competed against the same buffer supplemented with 1 M NaCl. Fractions containing BRM (636-1331) were pooled and loaded to a S200 16/60 size exclusion column equilibrated in 50 mM Tris (8.0), 200 mM NaCl, 10% glycerol & 2 mM TCEP. The purified construct was concentrated to 2.5 mg/mL, flash frozen and stored @ -80 °C until used in downstream assays.

II. Brm ATPase inhibition activity

[0205] Compound inhibition of ATPase activity of Brm ATPase-SnAC (636-1331) was measured by using the ADP-Glo assay kit from Promega (V6930). 120 nL of compound in 100% DMSO were transferred to a white 384 well microtiter assay plate using an ATS Acoustic Transfer System from EDC Biosystems. All subsequent reagent additions were performed using a MultiFlo FX Multi-Mode Dispenser. Assay buffer was 20mM HEPES pH 7.5, 1 mM $MgCl_2$, 20 mM KCl, 1mM DTT, 0.01% BSA, 0.005% Tween 20. 4 μL of 7.5 nM Brm ATPase-SnAC in assay buffer was added to the assay plate and incubated at RT for 5 min with compound. 2 μL of 255 μM ATP and 6 nM pCMV-dR8.91 plasmid in assay buffer was added to assay plate to initiate the reaction. The final concentrations of reagents were 5nM BRM ATPase-SnAC, 85 μM ATP, and 2 nM pCMV-dR8.91 plasmid. The ATPase reaction was incubated at RT for 60 min. 3 μL of ADP-Glo reagent was added to stop the reaction and was incubated for 30 min at RT. 3 μL of Kinase detection reagent was added to the assay plate which was incubated for 90 min at RT. Plates were read with a 2103 Multilabel Envision reader using ultrasensitive luminescence detection. IC_{50} values were determined from the average of duplicate data points by non-linear regression analysis of percent inhibition values plotted versus compound concentration.

BRG1 ATPase Inhibition Assay

I. Isolation of the Recombinant BRG1 ATPase Domain

A. Cloning of BRG1(658-1361)-His_6 into pDEST8

[0206] The construct BRG1(658-1361)-His_6 for expression in insect cells was sub-cloned from a full length BRG1 plasmid, pDONR221-BRG1-His_6 (OPS7173) by PCR as follows. An ATTB flanked PCR fragment encoding BRG1(658-1361)-His_6 was generated using the following primers: Forward, ATTB1 BRG1(658-x) 5'-GGGGACAAGTTTGTACAAAAAAGCAGGCTTCGAAGGAGATAGAACCATGGA AGAAAGTGGCTCAGAAGAAGAG-GAAG (SEQ ID NO: 5); Reverse, BRG1(x-1361)HISstpATTB2rev, 5'-GGGGACCACTTTGTACAAGAAAGCTGGGTCT-CAGTGATGATGATGATGATGCTCCTCGATG GCCTTGAGCCACTGC (SEQ ID NO: 6). This PCR fragment was re-combined into the vector pDEST8 using the Gateway® method following the manufacturer's protocol (Life Technologies). The insertion was confirmed by sequencing and entered into the OPS database (OPS8023) before proceeding to bacmid

generation.

MEESGSEEEE EEEEEEQPQA AQPPTLPVEE KKKIPDPDSD DVSEVDARHI IENAKQDVDD EYGVSQALAR GLQSYYAVAH AVTERVDKQS ALMVNGVLKQ YQIKGLEWLV SLYNNNLNGI LADEMGLGKT IQTIALITYL MEHKRINGPF LIIVPLSTLS NWAYEFDKWA PSVVKVSYKG SPAARRAFVP QLRSGKFNVL LTTYEYIIKD KHILAKIRWK YMIVDEGHRM KNHHCKLTQV LNTHYVAPRR LLLTGTPLQN KLPELWALLN FLLPTIFKSC STFEQWFNAP FAMTGEKVDL NEEETILIIR RLHKVLRPFL LRRLKKEVEA QLPEKVEYVI KCDMSALQRV LYRHMQAKGV LLTDGSEKDK KGKGGTKTLM NTIMQLRKIC NHPYMFQHIE ESFSEHLGFT GGIVQGLDLY

RASGKFELLD RILPKLRATN HKVLLFCQMT SLMTIMEDYF AYRGFKYLRL DGTTKAEDRG MLLKTFNEPG SEYFIFLLST RAGGLGLNLQ SADTVIIFDS DWNPHQDLQA QDRAHRIGQQ NEVRVLRLCT VNSVEEKILA AAKYKLNVDQ KVIQAGMFDQ KSSSHERRAF LQAILEHEEQ DEEEDEVPDD ETVNQMIARH EEEFDLFMRM DLDRRREEAR NPKRKPRLME EDELPSWIIK DDAEVERLTC EEEEEKMFGR GSRHRKEVDY SDSLTEKQWL KAIEEHHHHH H (SEQ ID NO: 7)

B. Expression of BRG1(658-1361)-His_6

[0207] The recombinant vector generated above was used to make recombinant bacmid by transforming to DH10Bac cells using standard protocols as detailed by the manufacturer (Life Technologies). High titer P3 virus was generated by transfecting the bacmid to Spodoptera frugiperda 9 (Sf9) cells and amplifying the virus using standard methods as detailed by Life Technologies. BRG1 (658-1361)-His_6 was expressed from Sf9 cells in log phase growth (1.5-3.9$\times 10^6$ cells/mL) at a 15 virus/cell. The infection was allowed to proceed on the rocking incubator at 27 °C and harvested three days post infection after cell viability had dropped to 80% with an increase in the overall cell diameter consistent with infection. Cells were harvested @ 4,000xg for 20 min, flash frozen and stored at -80 °C until use.

C. Purification of BRG1(658-1361)-His_6

[0208] Sf9 cells expressing recombinant BRG1(658-1361)-His_6 were lysed in 50 mM Tris (8.0), 300 mM NaCl, 5% glycerol and 1 mM TCEP supplemented with a protease inhibitor cocktail (Roche cOmplete) , using 7.5 mL lysis buffer per gram of cell paste. Cells were lysed upon thawing, homogenized and subsequently clarified in a JA25.50 rotor @ 50,000xg for 30 min to remove insoluble material. The clarified lysate was applied to a 5 mL His-Trap HP column (GE Healthcare Life Sciences), washed rigorously in lysis buffer without protease inhibitors supplemented with 20 mM imidazole. Bound protein was eluted over a ten column volume gradient against lysis buffer supplemented with 250 mM imidazole. Fractions containing BRG1(658-1361)-His_6 were pooled and diluted till conductivity reached about 6 mS/cm (~60mM NaCl) using 50mM Tris pH 8.0, 5% glycerol, and 1mM TCEP, passed thru a .2μ filter and immediately loaded to a 5 mL HiTrap Q HP column (GE Health Biosciences) previously equilibrated in 50 mM Tris (pH8.0), 100 mM NaCl, 5% glycerol, and 1 mM TCEP. Following capture, the bound protein was competed against the same buffer supplemented with 1 M NaCl. Fractions containing BRG1(658-1361)-His_6 were pooled and loaded to a S200 16/60 size exclusion column equilibrated in 50 mM Tris (8.0), 200 mM NaCl, 5% glycerol, and 1 mM TCEP. The purified construct was concentrated to 1 to 2.5 mg/mL, flash frozen and stored @ -80 °C until used in downstream assays.

BRG1 ATPase inhibition activity

[0209] Compound inhibition of ATPase activity of Brg1 ATPase-SnAC (658-1361) was measured by using the ADP-Glo assay kit from Promega (V6930). 120 nL of compound in 100% DMSO were transferred to a white 384 well microtiter assay plate using an ATS Acoustic Transfer System from EDC Biosystems. All subsequent reagent additions were performed using a MultiFlo FX Multi-Mode Dispenser. Assay buffer was 20 mM HEPES pH 7.5, 1 mM $MgCl_2$, 20 mM KCl, 1 mM DTT, 0.01% BSA, 0.005% Tween 20. 4 μL of 7.5 nM Brg1 ATPase-SnAC in assay buffer was added to the

assay plate and incubated at RT for 5 min with compound. 2 μL of 195 μM ATP and 6 nM pCMV-dR8.91 plasmid in assay buffer was added to assay plate to initiate the reaction. The final concentrations of reagents were 5 nM Brg1 ATPase-SnAC, 65 μM ATP, and 2 nM pCMV-dR8.91 plasmid. The ATPase reaction was incubated at RT for 60 min. 3 μL of ADP-Glo reagent was added to stop the reaction and was incubated for 30 min at RT. 3 μL of Kinase detection reagent was added to the assay plate which was incubated for 90 min at RT. Plates were read with a 2103 Multilabel Envision reader using ultrasensitive luminescence detection. IC_{50} values were determined from the average of duplicate data points by non-linear regression analysis of percent inhibition values plotted versus compound concentration.

pCMV-dR8.91 plasmid used for BRM / BRG1 ATPase Inhibition assays:

[0210] The plasmid template pCMV-dR8.91 (see sequence below) is propagated using One Shot Stbl3 Chemically Competent E. coli (Catalog Number C73C7303, Invitrogen/Thermo Fisher Scientific) following the transformation protocol provided with the reagent. Transformed bacterial colonies are then selected on LB agar plates containing ampicillin/carbenicllin antibiotic selection medium (Catalog Number L1010, Teknova). Bacterial colonies are grown in LB liquid broth (Catalog number 10855001, Invitrogen) containing ampicillin at 100 micrograms/mL and plasmid DNA isolated according to required scale according to the manufacturers protocol provided with the Qiagen Plasmid Isolation Kits (Maxi prep, Product Id Number 10063).

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gaagtagtgaggaggctttttggaggcctaggcttttgcaaaaagcttggacacaagacaggcttgcgagatatgtttgagaatacca
ctttatcccgcgtcagggagaggcagtgcgtaaaaagacgcggactcatgtgaaatactggtttttagtgcgccagatctctataatctc
gcgcaacctattttcccctcgaacacttttaagccgtagataaacaggctgggacacttcacatgagcgaaaaatacatcgtcacctg
gacatgttgcagatccatgcacgtaaactcgcaagccgactgatgccttctgaacaatggaaaggcattattgccgtaagccgtggc
ggtctgtaccgggtgcgttactggcgcgtgaactgggtattcgtcatgtcgataccgtttgtatttccagctacgatcacgacaaccagcg
cgagcttaaagtgctgaaacgcgcagaaggcgatggcgaaggcttcatcgttattgatgacctggtggataccggtggtactgcggtt
gcgattcgtgaaatgtatccaaaagcgcactttgtcaccatcttcgcaaaaccggctggtcgtccgctggttgatgactatgttgttgatat
cccgcaagatacctggattgaacagccgtgggatatgggcgtcgtattcgtcccgccaatctccggtcgctaatcttttcaacgcctggc
actgccgggcgttgttcttttaacttcaggcgggttacaatagtttccagtaagtattctggaggctgcatccatgacacaggcaaacctg
agcgaaaccctgttcaaaccccgctttaaacatcctgaaacctcgacgctagtccgccgctttaatcacggcgcacaaccgcctgtgc
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atcctcgacgtccaggcacgtattgtgatgagcgatgccgaacgtaccgacgatgatttatacgatacggtgattggctaccgtggcgg
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aagctctaaggtaaatataaaatttttaacccggatctttgtgaaggaaccttacttctgtggtgtgacataattggacaaactacctacag
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ctgctgactctcaacattctactcctccaaaaaagaagagaaaggtagaagaccccaaggactttccttcagaattgctaagttttttga
gtcatgctgtgtttagtaatagaactcttgcttgctttgctatttacaccacaaaggaaaaagctgcactgctatacaagaaaattatggaa
aaatattctgtaacctttataagtaggcataacagttataatcataacatactgttttttcttactccacacaggcatagagtgtctgctattaa
taactatgctcaaaaattgtgtacctttagctttttaatttgtaaaggggttaataaggaatatttgatgtatagtgccttgactagagatcata
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ttgttgttgggctgcaggaattaattcgagctcgcccgaca (SEQ ID NO: 8)

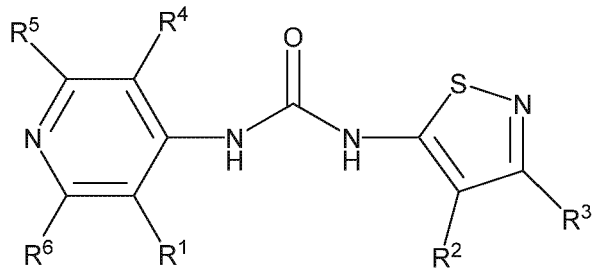
[0211] The inhibitory activity data of representative compounds of the present disclosure from the two assays described above (e.g., the BRM ATPase Inhibition Assay; and the BRG1 ATPase Inhibition Assay) are provided in the following Table 1.

Table 1

Example No	BRM IC_{50} (μM)	BRG1 IC_{50} (μM)
1	0.005	0.006
2	0.033	0.03
3	0.010	0.010
4	<0.005	<0.005
5	<0.005	<0.005
6	<0.005	<0.005
7	<0.005	<0.005
8	0.09	0.019

Claims

1. A compound, or a pharmaceutically acceptable salt thereof, of formula I:



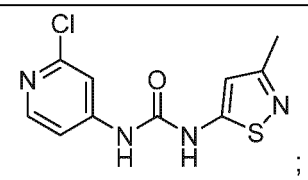
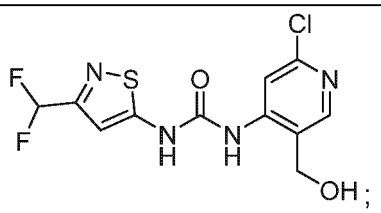
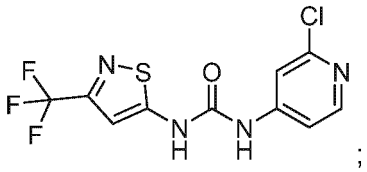
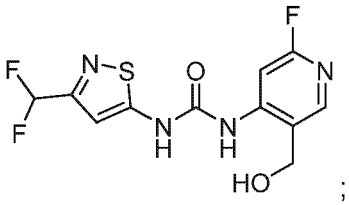
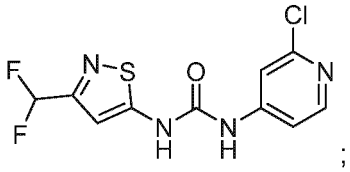
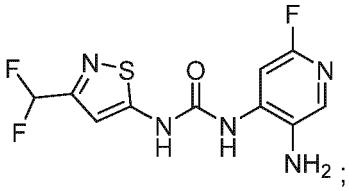
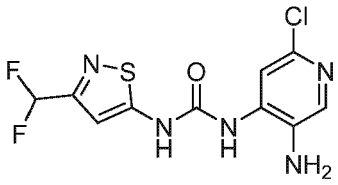
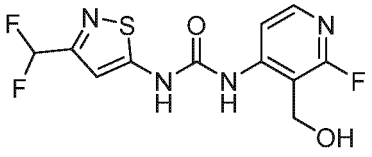
in which:

R^1 is selected from hydrogen, amino and hydroxy-substituted C_{1-2}alkyl;
R^2 is hydrogen;
R^3 is selected from C_{1-2}alkyl and halo-substituted-C_{1-2}alkyl;
R^4 is hydrogen;
R^5 is selected from hydrogen and halo; and
R^6 is selected from hydrogen and halo.

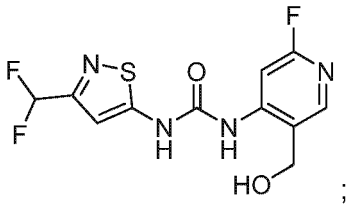
2. The compound, or a pharmaceutically acceptable salt thereof, of claim 1 in which:

R^1 is selected from hydrogen, amino and hydroxy-methyl;
R^2 is hydrogen;
R^3 is selected from methyl, difluoromethyl and trifluoromethyl;
R^4 is hydrogen;
R^5 is selected from hydrogen, chloro and fluoro; and
R^6 is selected from hydrogen and fluoro.

3. The compound of claim 2, or a pharmaceutically acceptable salt thereof, selected from:

 ;	 ;
 ;	 ;
 ;	 ;
 ; and	 .

4. A compound according to claim 3 having the structure:

 ;

or a pharmaceutically acceptable salt thereof

5. A pharmaceutical composition, comprising a compound according to any one of claims 1 to 4 or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers.

6. A pharmaceutical combination, comprising a compound according to any one of claims 1 to 4 or a pharmaceutically acceptable salt thereof, and one or more therapeutically active agents.

7. A pharmaceutical combination of claim 6, wherein said one or more therapeutically active agents are independently selected from anti-cancer agents, anti-allergic agents, anti-emetics, pain relievers, immunomodulators and cytoprotective agents.

8. A compound according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, for use as a medicament.

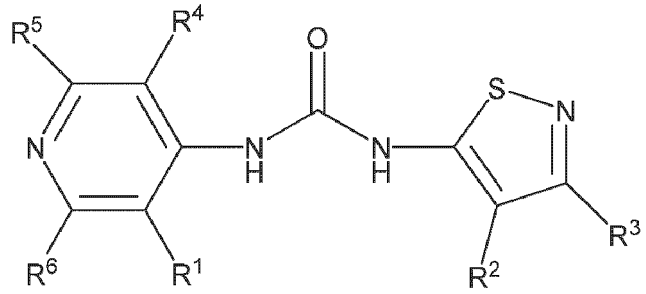
9. A compound according to any one of claims 1 to 4 or a pharmaceutically acceptable salt thereof, for use in the

treatment of a BRM mediated and/or a BRG1 mediated disorder or disease, wherein the BRM mediated and/or BRG1 mediated disorder or disease is a solid tumor, leukemia or lymphoma.

10. A compound for use according to claim 9, wherein said disorder or disease is selected from non-small cell lung carcinoma, lung adenocarcinoma, lung carcinoma, large cell lung carcinomas, non-small cell lung carcinoma, lung squamous cell carcinoma, small cell lung cancer, skin cutaneous melanoma, desmoplastic melanoma, uveal melanoma, small cell carcinoma of the ovary (hypercalcemic type), ovarian rhabdoid tumor, cutaneous squamous cell carcinoma, glioma, uterine carcinosarcoma, uterine corpus endometrial carcinoma, ovarian serous cystadenocarcinoma, bladder urothelial carcinoma, primary central nervous system lymphoma, esophageal carcinoma, bladder cancer, bladder cancer plasmacytoid variant, stomach adenocarcinoma, adenoid cystic carcinoma, lymphoid neoplasm diffuse large B-cell lymphoma, pancreatic cancer, colorectal adenocarcinoma, cholangiocarcinoma, sarcoma, head and neck cancers, cervical and endocervical cancers, medulloblastoma, cutaneous T cell lymphoma, liver hepatocellular carcinoma, kidney renal papillary cell carcinoma, breast cancer, mantle cell lymphoma, gallbladder carcinoma, testicular germ cell cancers, kidney renal cell clear cell carcinoma, prostate cancer, pediatric ewing sarcoma, thymoma, kidney chromophobe, renal non-clear cell carcinoma, pheochromocytoma and paraganglioma, thyroid cancers, malignant peripheral nerve sheath tumor, neuroendocrine prostate cancer, head and neck squamous cell carcinoma, adrenocortical carcinoma, cutaneous squamous cell carcinoma, testicular germ cell cancer, glioblastoma, glioblastoma multiforme, Ewing's sarcoma, clear cell renal cell carcinoma, neuroblastoma, diffuse large B cell lymphoma, acute myeloid leukemia, chronic lymphocytic leukemia, multiple myeloma, malignant rhabdoid tumors, epithelioid sarcomas, familial schwannomatosis, renal medullary carcinomas, synovial sarcoma, and meningiomas.

Patentansprüche

1. Verbindung, oder ein pharmazeutisch annehmbares Salz davon, der Formel 1:



,

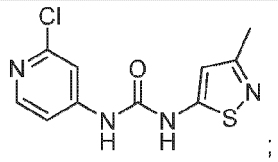
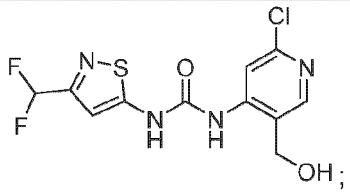
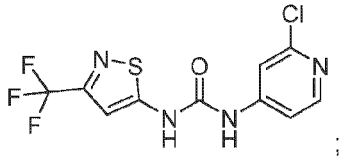
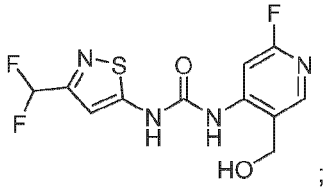
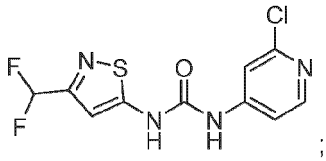
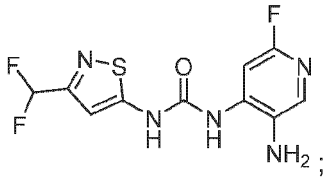
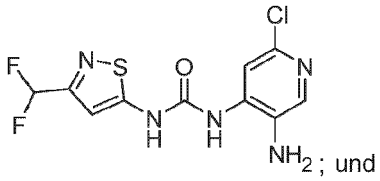
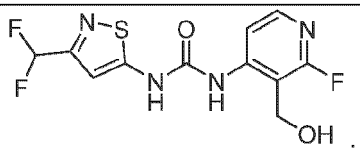
wobei:

R^1 aus Wasserstoff, Amino und hydroxysubstituiertem C_{1-2}-Alkyl ausgewählt ist;
R^2 Wasserstoff ist;
R^3 aus C_{1-2}-Alkyl und halogensubstituiertem C_{1-2}-Alkyl ausgewählt ist;
R^4 Wasserstoff ist;
R^5 aus Wasserstoff und Halogen ausgewählt ist; und
R^6 aus Wasserstoff und Halogen ausgewählt ist.

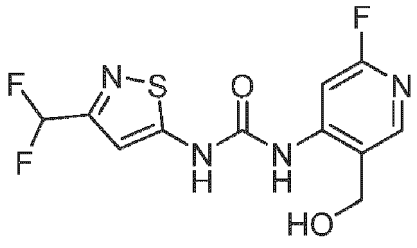
2. Verbindung, oder ein pharmazeutisch annehmbares Salz davon, nach Anspruch 1, wobei:

R^1 aus Wasserstoff, Amino und Hydroxymethyl ausgewählt ist;
R^2 Wasserstoff ist;
R^3 aus Methyl, Difluormethyl und Trifluormethyl ausgewählt ist;
R^4 Wasserstoff ist;
R^5 aus Wasserstoff, Chlor und Fluor ausgewählt ist; und
R^6 aus Wasserstoff und Fluor ausgewählt ist.

3. Verbindung nach Anspruch 2, oder ein pharmazeutisch annehmbares Salz davon, ausgewählt aus:

 ;	 ;
 ;	 ;
 ;	 ;
 ; und	 .

4. Verbindung nach Anspruch 3 mit der Struktur:

 ;

oder ein pharmazeutisch annehmbares Salz davon.

5. Pharmazeutische Zusammensetzung, umfassend eine Verbindung nach einem der Ansprüche 1 bis 4, oder ein pharmazeutisch annehmbares Salz davon, und einen oder mehrere pharmazeutisch annehmbare Träger.

6. Pharmazeutische Kombination, umfassend eine Verbindung nach einem der Ansprüche 1 bis 4, oder ein pharmazeutisch annehmbares Salz davon, und ein oder mehrere therapeutische Wirkstoffe.

7. Pharmazeutische Kombination nach Anspruch 6, wobei der eine oder die mehreren therapeutischen Wirkstoffe unabhängig aus Antikrebsmitteln, Antiallergika, Antiemetika, Schmerzmitteln, Immunmodulatoren und Zytoprotektiva ausgewählt sind.

8. Verbindung nach einem der Ansprüche 1 bis 4, oder ein pharmazeutisch annehmbares Salz davon, zur Verwendung als Medikament.

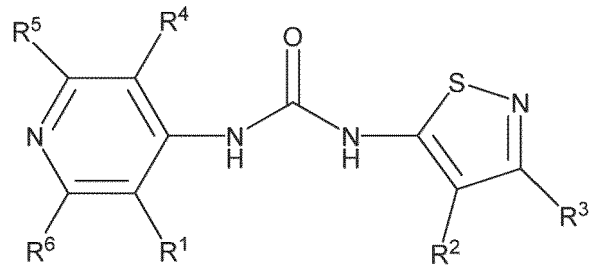
9. Verbindung nach einem der Ansprüche 1 bis 4, oder ein pharmazeutisch annehmbares Salz davon, zur Verwendung

bei der Behandlung einer BRM-vermittelten und/oder einer BRG1-vermittelten Krankheit oder Erkrankung, wobei es sich bei der BRM-vermittelten und/oder BRG1-vermittelten Krankheit oder Erkrankung um einen soliden Tumor, Leukämie oder Lymphom handelt.

10. Verbindung zur Verwendung nach Anspruch 9, wobei die Krankheit oder Erkrankung ausgewählt ist aus nichtkleinzelligem Lungenkarzinom, Lungenadenokarzinom, Lungenkarzinom, großzelligen Lungenkarzinomen, nichtkleinzelligem Lungenkarzinom, Lungenplattenepitelkarzinom, kleinzelligem Lungenkrebs, kutanem Hautmelanom, desmoplastischem Melanom, Aderhautmelanom, kleinzelligem Karzinom des Ovars (hyperkalzämischer Typ), rhabdoidem Ovarialtumor, kutanem Plattenepithelkarzinom, Gliom, Uterus-Karzinosarkom, Uterus- oder Korpus-Endometriumkarzinom, serösem Zystadenokarzinom des Ovars, Blasenurothelkarzinom, primärem Lymphom des zentralen Nervensystems, Ösophaguskarzinom, Blasenkrebs, plasmazytoider Variante von Blasenkrebs, Magenadenokarzinom, adenoid-zystischem Karzinom, lymphatischer Neoplasie in Form von diffusem großzelligem B-Zell-Lymphom, Bauchspeicheldrüsenkrebs, kolorektalem Adenokarzinom, Cholangiokarzinom, Sarkom, Kopf-Hals-Krebserkrankungen, Zervix- und Endozervix-Krebserkrankungen, Medulloblastom, kutanem T-Zell-Lymphom, hepatozellulärem Leberkarzinom, papillärem Nierenzellkarzinom, Brustkrebs, Mantelzelllymphom, Gallenblasenkarzinom, testikulären Keimzell-Krebserkrankungen, klarzelligem Nierenzellkarzinom, Prostatakrebs, pädiatrischem Ewing-Sarkom, Thymom, chromophobem nicht-klarzelligem Nierenzellkarzinom, Phäochromozytom und Paragangliom, Schilddrüsenkrebserkrankungen, malignem peripherem Nervenscheidentumor, neuroendokrinem Prostatakrebs, Kopf- und Hals-Plattenepithelkarzinom, adrenokortikalem Karzinom, kutanem Plattenepithelkarzinom, testikulärem Keimzellkrebs, Glioblastom, Glioblastoma multiforme, Ewing-Sarkom, klarzelligem Nierenzellkarzinom, Neuroblastom, diffusem großzelligem B-Zell-Lymphom, akuter myeloischer Leukämie, chronischer lymphatischer Leukämie, multiplem Myelom, malignen rhabdoiden Tumoren, epithelioiden Sarkomen, familiärer Schwannomatose, medullären Nierenkarzinomen, Synovialsarkom und Meningiomen.

Revendications

1. Composé, ou sel pharmaceutiquement acceptable de celui-ci, de formule 1 :



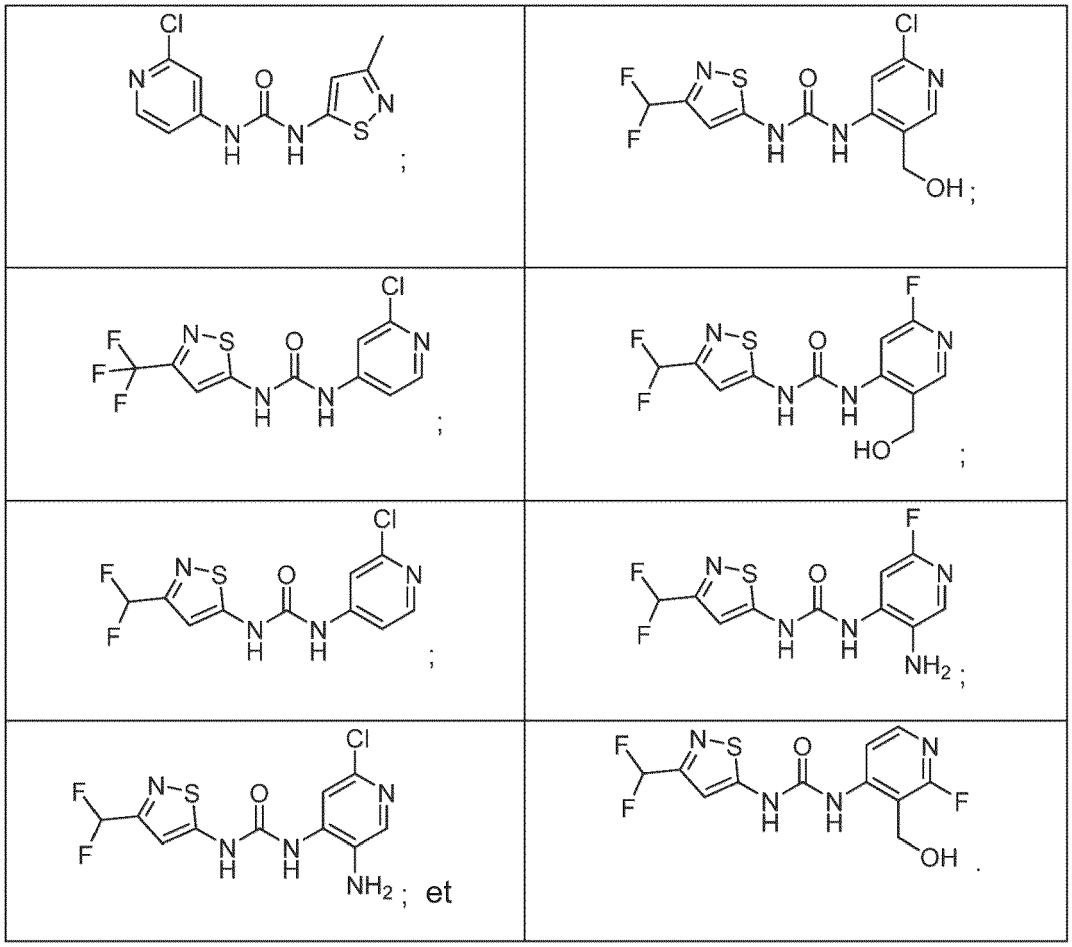
dans laquelle :

R^1 est choisi parmi hydrogène, amino et alkyle en C_{1-2} substitué par hydroxy ;
R^2 est hydrogène ;
R^3 est choisi parmi alkyle en C_{1-2} et alkyle en C_{1-2} substitué par halogène ;
R^4 est hydrogène ;
R^5 est choisi parmi hydrogène et halogéno ; et
R^6 est choisi parmi hydrogène et halogéno.

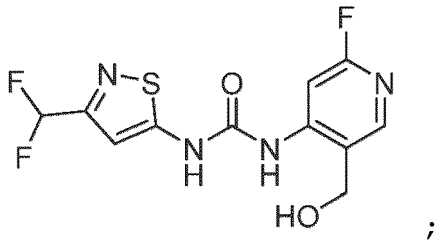
2. Composé, ou sel pharmaceutiquement acceptable de celui-ci, selon la revendication 1 dans lequel :

R^1 est choisi parmi hydrogène, amino et hydroxy-méthyle ;
R^2 est hydrogène ;
R^3 est choisi parmi méthyle, difluorométhyle et trifluorométhyle ;
R^4 est hydrogène ;
R^5 est choisi parmi hydrogène, chloro et fluoro ; et
R^6 est choisi parmi hydrogène et fluoro.

3. Composé selon la revendication 2, ou sel pharmaceutiquement acceptable de celui-ci, choisi parmi :



4. Composé selon la revendication 3 ayant la structure :



ou sel pharmaceutiquement acceptable de celui-ci.

5. Composition pharmaceutique, comprenant un composé selon l'une quelconque des revendications 1 à 4 ou un sel pharmaceutiquement acceptable de celui-ci, et un ou plusieurs véhicules pharmaceutiquement acceptables.

6. Combinaison pharmaceutique, comprenant un composé selon l'une quelconque des revendications 1 à 4 ou un sel pharmaceutiquement acceptable de celui-ci, et un ou plusieurs agents thérapeutiquement actifs.

7. Combinaison pharmaceutique selon la revendication 6, dans laquelle lesdits un ou plusieurs agents thérapeutiquement actifs sont indépendamment choisis parmi des agents anticancéreux, des agents antiallergiques, des antiémétiques, des antalgiques, des immunomodulateurs et des agents cytoprotecteurs.

8. Composé selon l'une quelconque des revendications 1 à 4, ou sel pharmaceutiquement acceptable de celui-ci, pour utilisation en tant que médicament.

9. Composé selon l'une quelconque des revendications 1 à 4 ou sel pharmaceutiquement acceptable de celui-ci, pour utilisation dans le traitement d'un trouble ou d'une maladie médié(e) par BRM et/ou d'un trouble ou d'une maladie médié(e) par BRG1, le trouble ou la maladie médié(e) par BRM et/ou médié(e) par BRG1 étant une tumeur solide, une leucémie ou un lymphome.

10. Composé pour utilisation selon la revendication 9, ledit trouble ou ladite maladie étant choisi(e) parmi un carcinome pulmonaire non à petites cellules, un adénocarcinome pulmonaire, un carcinome pulmonaire, des carcinomes pulmonaires à grandes cellules, un carcinome pulmonaire non à petites cellules, un carcinome épidermoïde pulmonaire, un cancer du poumon à petites cellules, un mélanome cutané, un mélanome desmoplasique, un mélanome uvéal, un carcinome de l'ovaire à petites cellules (type hypercalcémique), une tumeur rhabdoïde ovarienne, un carcinome épidermoïde cutané, un gliome, un carcinosarcome utérin, un carcinome de l'endomètre du corps utérin, un cystadénocarcinome séreux ovarien, un carcinome urothélial de la vessie, un lymphome du système nerveux central primitif, un carcinome de l'œsophage, un cancer de la vessie, un variant plasmacytoïde du cancer de la vessie, un adénocarcinome de l'estomac, un carcinome adénoïde kystique, un néoplasme lymphoïde, un lymphome diffus à grandes cellules B, un cancer du pancréas, un adénocarcinome colorectal, un cholangiocarcinome, un sarcome, des cancers de la tête et du cou, des cancers du col de l'utérus et endocervical, un médulloblastome, un lymphome T cutané, un carcinome hépatocellulaire du foie, un carcinome du rein à cellules papillaires rénales, un cancer du sein, un lymphome à cellules du manteau, un carcinome de la vésicule biliaire, des cancers des cellules germinales testiculaires, un carcinome du rein à cellules rénales claires, un cancer de la prostate, un sarcome d'Ewing pédiatrique, un thymome, un carcinome rénal à cellules chromophobes, un carcinome à cellules rénales non claires, un phéochromocytome et un paragangliome, des cancers de la thyroïde, une tumeur maligne de la gaine de nerf périphérique, un cancer neuroendocrinien de la prostate, un carcinome épidermoïde de la tête et du cou, un carcinome corticosurrénalien, un carcinome épidermoïde cutané, un cancer des cellules germinales testiculaires, un glioblastome, un glioblastome multiforme, un sarcome d'Ewing, un carcinome à cellules rénales claires, un neuroblastome, un lymphome diffus à grandes cellules B, une leucémie aiguë myéloïde, une leucémie lymphoïde chronique, un myélome multiple, des tumeurs rhabdoïdes malignes, des sarcomes épithélioïdes, la schwannomatose familiale, des carcinomes médullaires rénaux, un sarcome synovial et des méningiomes.

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