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(54) Title: COMPOUNDS AND USES THEREOF

(57) Abstract: The present disclosure features compounds useful for the treatment of BAF complex-related disorders.

COMPOUNDS AND USES THEREOF

Background

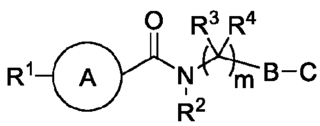
The invention relates to compounds useful for modulating BRG1- or BRM-associated factors (BAF) complexes. In particular, the invention relates to compounds useful for treatment of disorders associated with BAF complex function.

Chromatin regulation is essential for gene expression, and ATP-dependent chromatin remodeling is a mechanism by which such gene expression occurs. The human Switch/Sucrose Non-Fermentable (SWI/SNF) chromatin remodeling complex, also known as BAF complex, has two SWI2-like ATPases known as BRG1 (Brahma-related gene-1) and BRM (Brahma). The transcription activator BRG1, also known as ATP-dependent chromatin remodeler SMARCA4, is encoded by the SMARCA4 gene on chromosome 19. BRG1 is overexpressed in some cancer tumors and is needed for cancer cell proliferation. BRM, also known as probable global transcription activator SNF2L2 and/or ATP-dependent chromatin remodeler SMARCA2, is encoded by the SMARCA2 gene on chromosome 9 and has been shown to be essential for tumor cell growth in cells characterized by loss of BRG1 function mutations. Deactivation of BRG and/or BRM results in downstream effects in cells, including cell cycle arrest and tumor suppression.

Summary

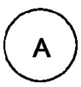
The present invention features compounds useful for modulating a BAF complex. In some embodiments, the compounds are useful for the treatment of disorders associated with an alteration in a BAF complex, e.g., a disorder associated with an alteration in one or both of the BRG1 and BRM proteins. The compounds of the invention, alone or in combination with other pharmaceutically active agents, can be used for treating such disorders.

In an aspect, the invention features a compound having the structure:



Formula I

wherein R^1 is H, optionally substituted C_1-C_6 acyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted amino, or $–SO_2R^5$;



is optionally substituted arylene, optionally substituted 5-membered heteroarylene, or optionally substituted 6-membered heteroarylene;

m is 0, 1, 2, or 3;

B is an optionally substituted 6- to 10-membered bicyclic heteroarylene;

C is optionally substituted 3- to 10-membered cycloalkyl; optionally substituted 6- to 10-membered aryl; optionally substituted 5- to 10-membered heteroaryl; or optionally substituted 5- to 10-membered heterocyclyl;

R^2 is hydrogen or optionally substituted C_1-C_6 alkyl;

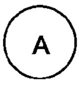
each of R^3 and R^4 is, independently, hydrogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

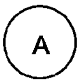
R^5 is optionally substituted C_1-C_6 alkyl or $-NR^6R^7$; and

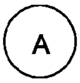
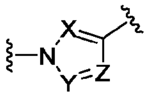
each of R^6 and R^7 is, independently, optionally substituted C_1-C_6 alkyl,

or a pharmaceutically acceptable salt thereof.

In some embodiments, B is a 9- or 10-membered heteroarylene

In some embodiments,  is optionally substituted 6-membered heteroarylene.

In some embodiments,  is optionally substituted 5-membered heteroarylene.

In some embodiments,  is , wherein each X, Y, and Z is, independently, N or CR^8, wherein each R^8 is H, halo, or C_1-C_6 alkyl (e.g., each of X, Y, and Z is CH; X is N, and each of Y and Z is CH; or X is CH, Y is $C(CH_3)$, and Z is CH); or both R^8, together with the carbon atoms to which they are attached, form a 5- or 6-membered ring. In some embodiments, X is N and each of Y and Z is CH. In some embodiments, Z is N and each of X and Y is CH. In some embodiments, Y is N and each of X and Z is CH.

In some embodiments,  is arylene.

In some embodiments, R^2 is hydrogen.

In some embodiments, m is 1.

In some embodiments, R^4 is hydrogen.

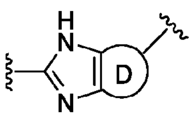
In some embodiments, R^3 is hydrogen.

In some embodiments, R^3 is optionally substituted C_1-C_6 alkyl (e.g., methyl).

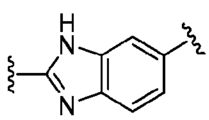
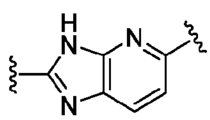
In some embodiments, R^3 is optionally substituted C_1-C_6 heteroalkyl (e.g., is $-CH_2OCH_3$ or $-(CH_2)_2SCH_3$).

In some embodiments, B is optionally substituted 9-membered bicyclic heteroarylene.

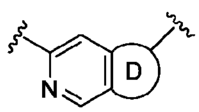
In some embodiments, B has the structure:

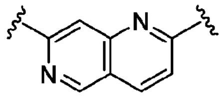
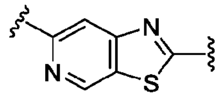


,

wherein D is an optionally substituted 5- or 6-membered heteroaryl or optionally substituted 5- or 6-membered heterocyclyl. In some embodiments, B is  or .

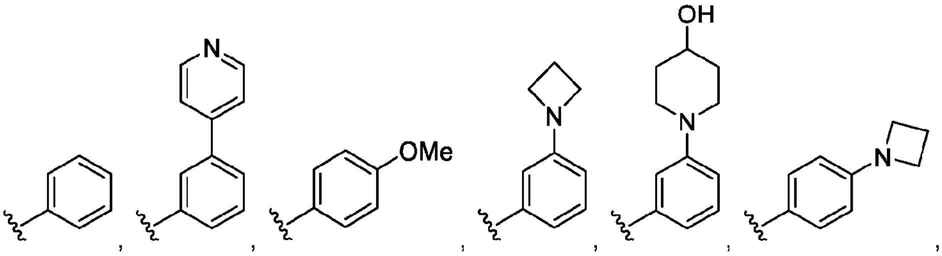
In some embodiments, B has the structure:

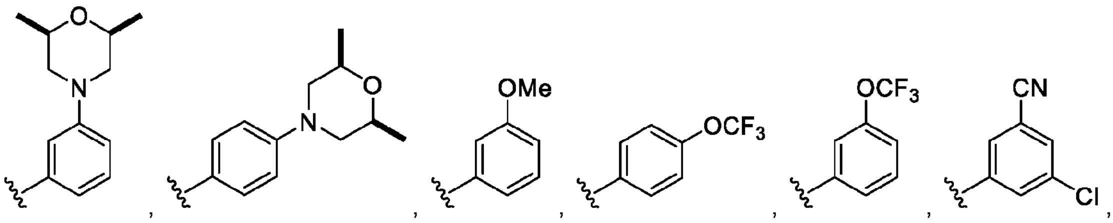


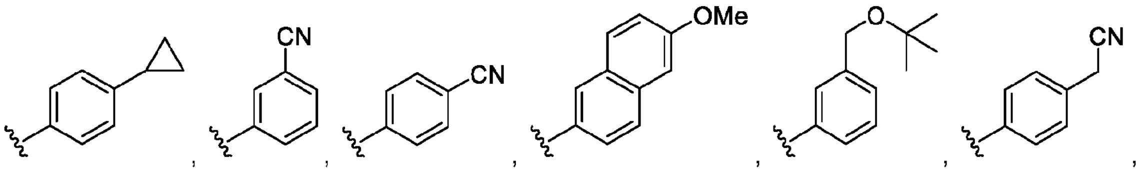
wherein D is an optionally substituted 5- or 6-membered heteroaryl or optionally substituted 5- or 6-membered heterocyclyl. In some embodiments, B is  or .

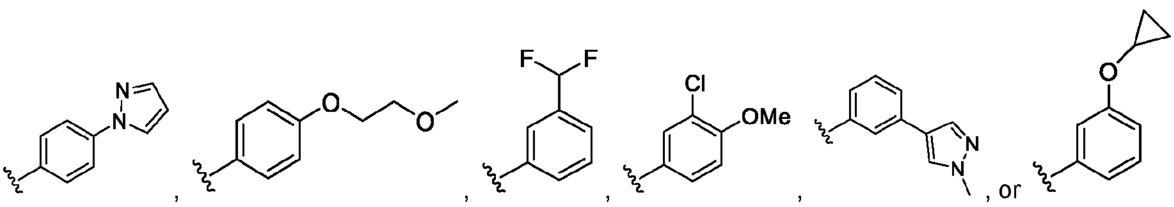
In some embodiments, C is optionally substituted C_3-C_{10} cycloalkyl (e.g., cyclopropyl).

In some embodiments, C is optionally substituted C_6-C_{10} aryl. In some embodiments, C is optionally substituted phenyl (e.g.,



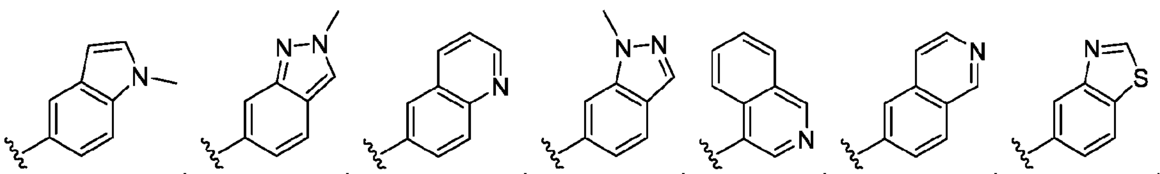


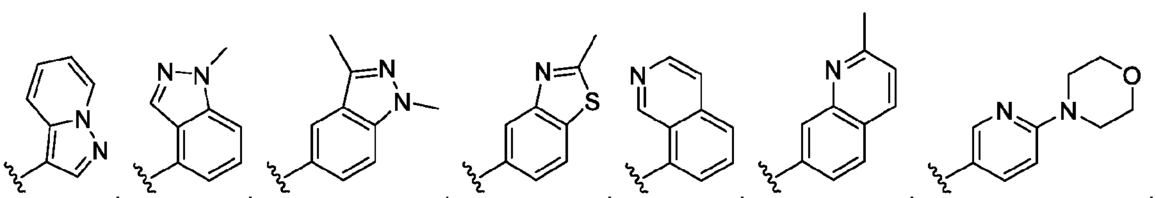


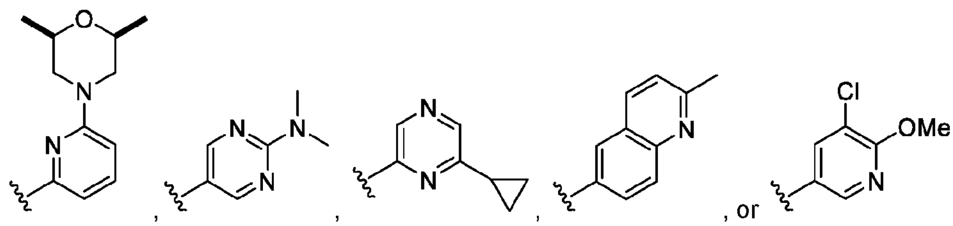


).

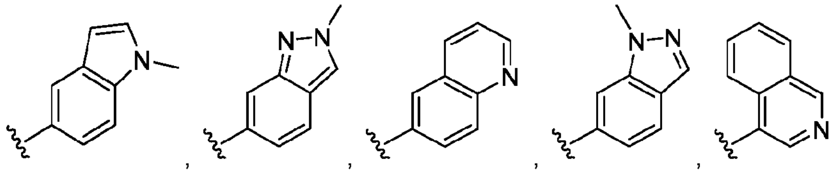
In some embodiments, C is optionally substituted 5- to 10-membered heteroaryl (e.g.,

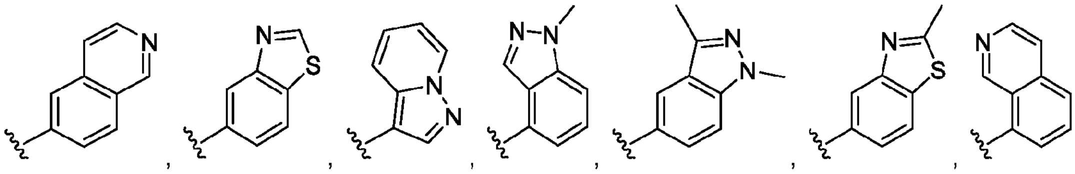


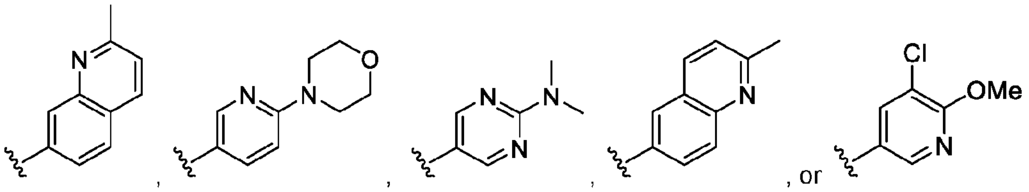




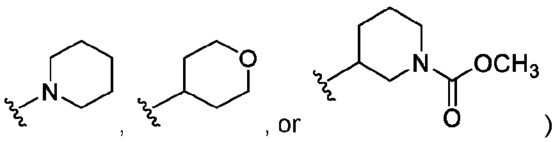
). In some embodiments, C is





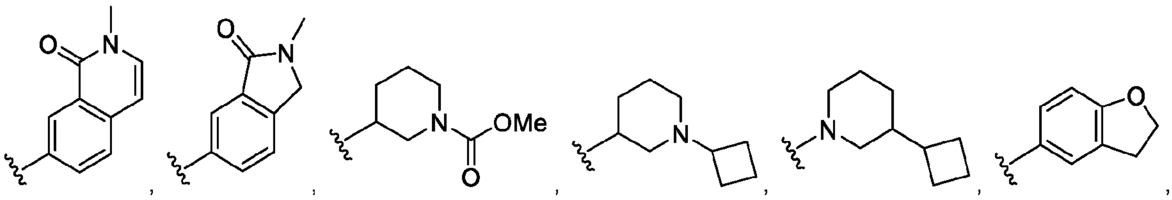


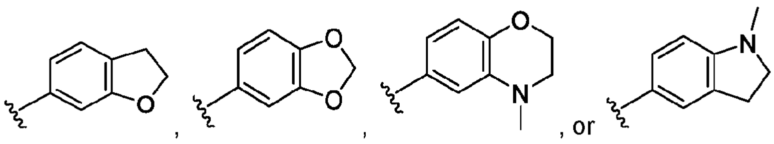
In some embodiments, C is optionally substituted 5- to 10-membered heterocyclyl (e.g., C is



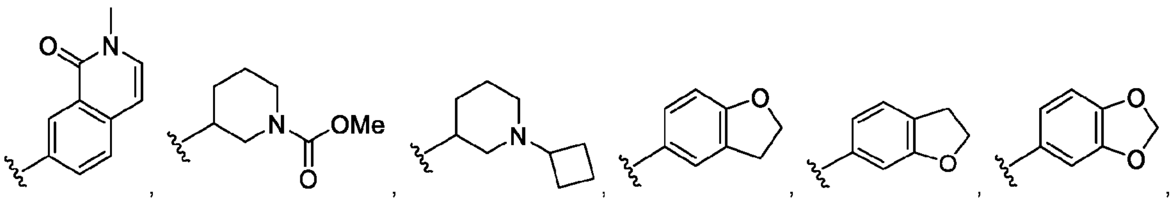
).

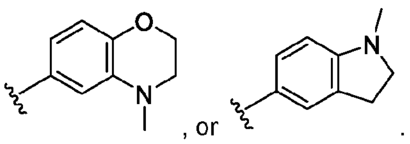
In some embodiments, C is optionally substituted 5- to 10-membered heterocyclyl (e.g.,





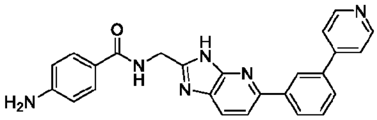
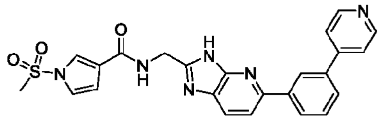
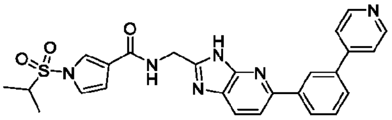
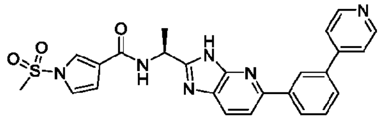
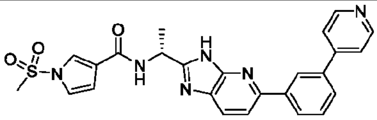
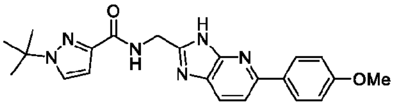
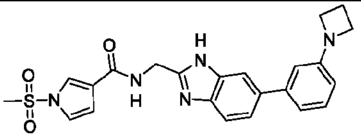
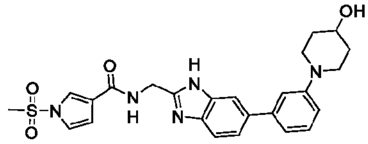
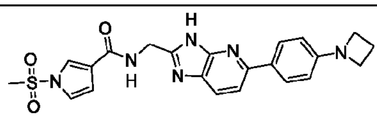
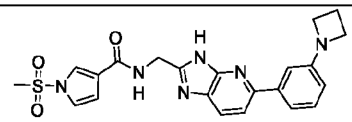
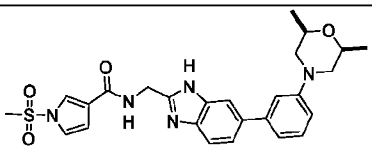
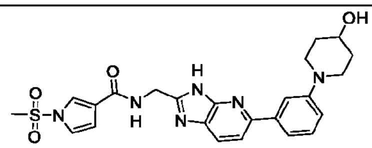
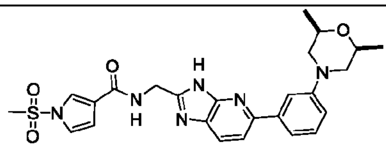
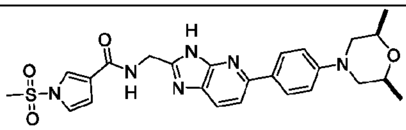
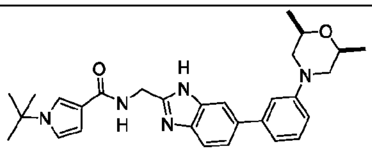
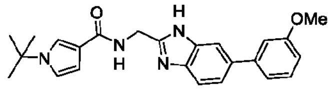
). In some embodiments, C is

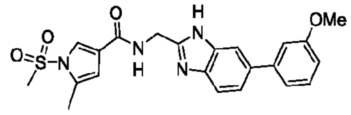
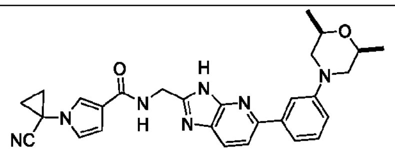
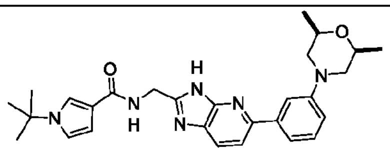
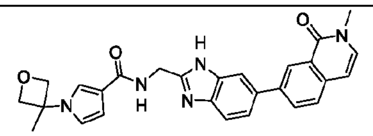
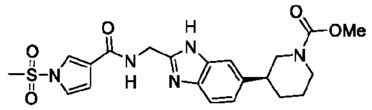
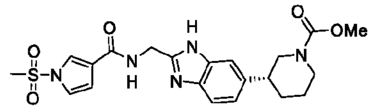
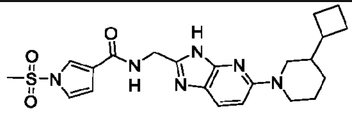
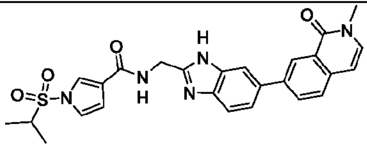
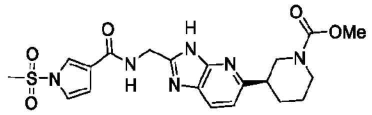
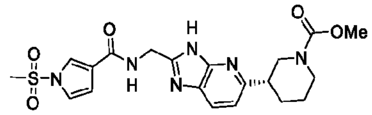
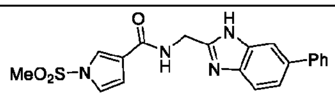
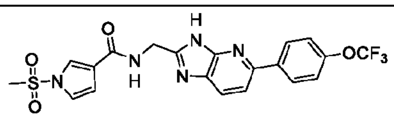
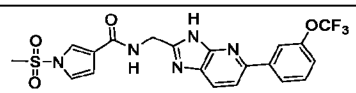
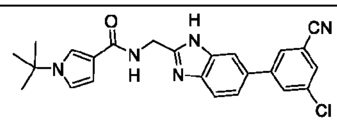
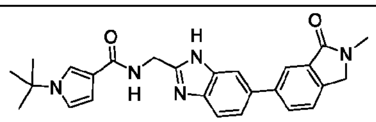
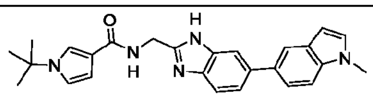
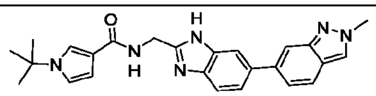
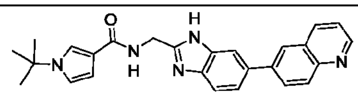
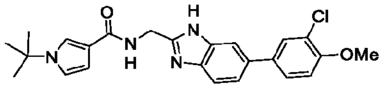
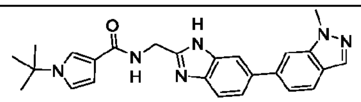




In some embodiments, the compound is any one of compounds 1-82 in Table 1. In some embodiments, the compound is any one of compounds 1-74 in Table 1.

Table 1. Exemplary Compounds of the Invention

#	Compound	#	Compound
1		2	
3		4	
5		6	
7		8	
9		10	
11		12	
13		14	
15		16	

#	Compound	#	Compound
17		18	
19		20	
21		22	
23		24	
25		26	
27		28	
29		30	
31		32	
33		34	
35		36	

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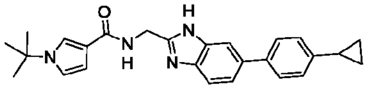
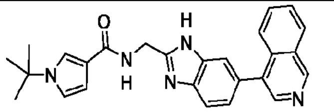
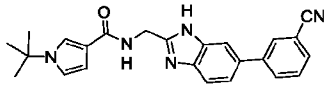
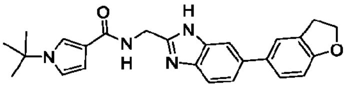
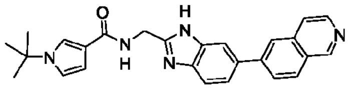
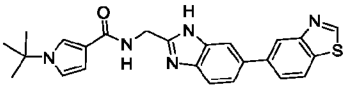
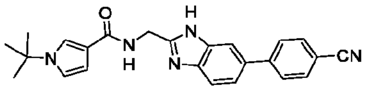
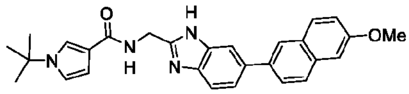
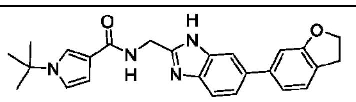
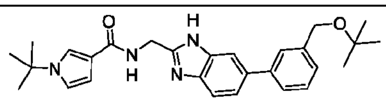
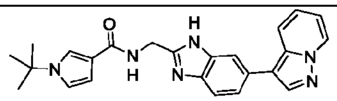
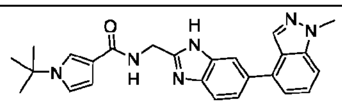
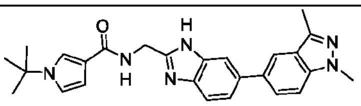
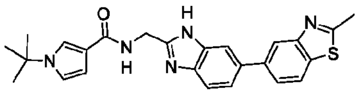
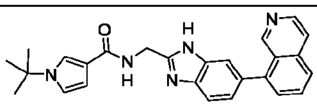
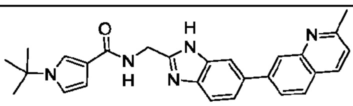
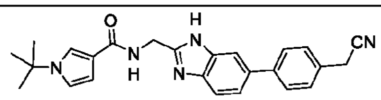
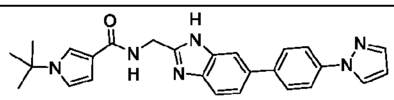
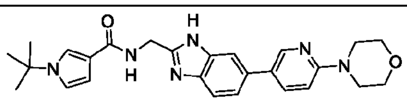
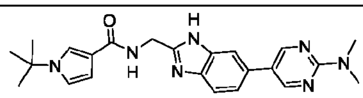
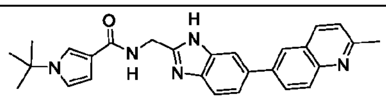
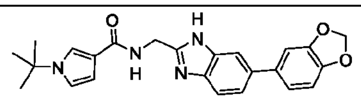
37		38	
39		40	
41		42	
43		44	
45		46	
47		48	
49		50	
51		52	
53		54	
55		56	
57		58	

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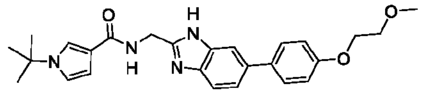
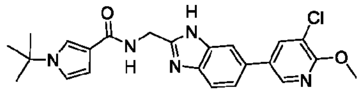
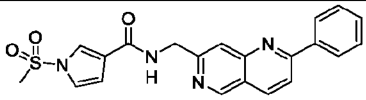
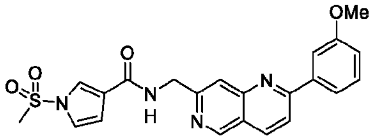
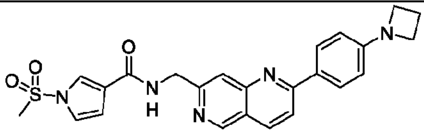
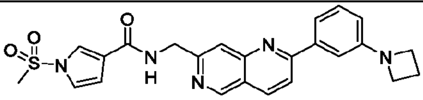
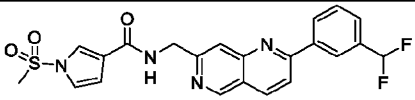
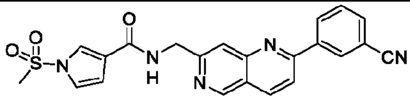
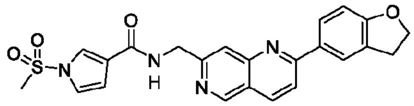
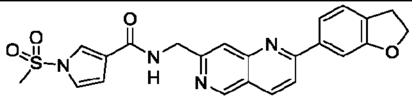
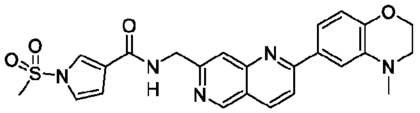
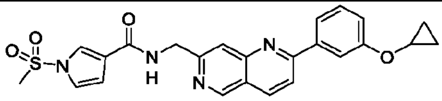
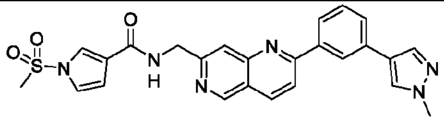
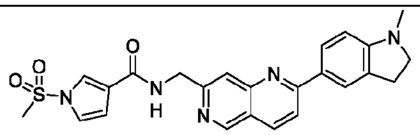
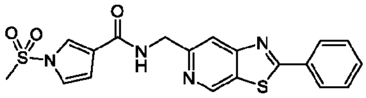
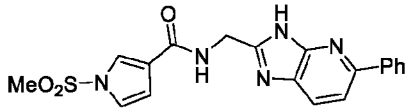
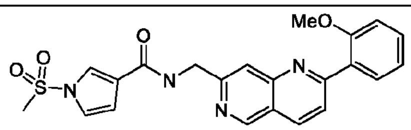
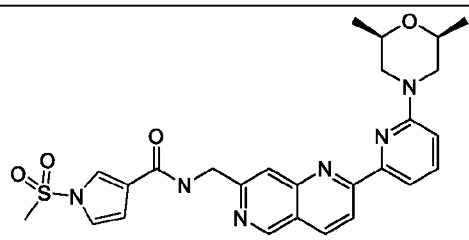
59		60	
61		62	
63		64	
65		66	
67		68	
69		70	
71		72	
73		74	
75		76	

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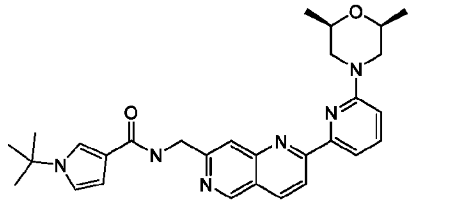
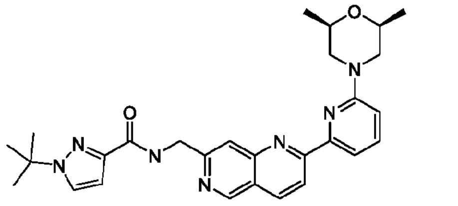
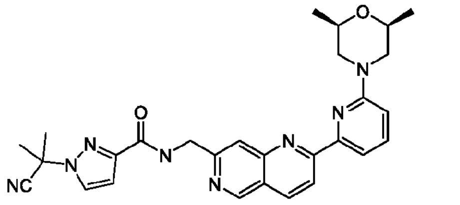
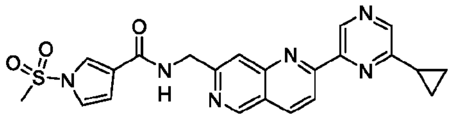
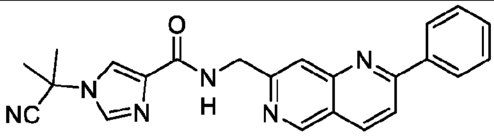
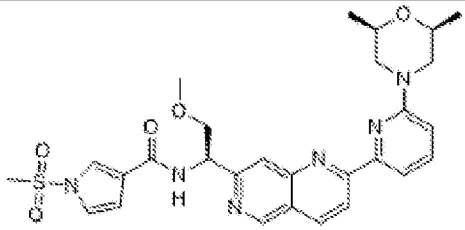
77		78	
79		80	
81		82	

In another aspect, the invention features a pharmaceutical composition including any one of the above compounds and a pharmaceutically acceptable excipient.

In another aspect, the invention features a method of decreasing the activity of a BAF complex in a cell, the method involving contacting the cell with an effective amount of any of the foregoing compounds or a pharmaceutical composition thereof.

In some embodiments, the cell is a cancer cell.

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

In some embodiments, the BAF complex-related disorder is cancer or a viral infection.

In a further aspect, the invention features a method of inhibiting BRM, the method involving contacting a cell with an effective amount of any of the foregoing compounds or a pharmaceutical composition thereof. In some embodiments, the cell is a cancer cell.

In another aspect, the invention features a method of inhibiting BRG1, the method involving contacting the cell with an effective amount of any of the foregoing compounds or a pharmaceutical composition thereof. In some embodiments, the cell is a cancer cell.

In a further aspect, the invention features a method of inhibiting BRM and BRG1, the method involving contacting the cell with an effective amount of any of the foregoing compounds or a pharmaceutical composition thereof. In some embodiments, the cell is a cancer cell.

In another aspect, the invention features a method of treating a disorder related to a BRG1 loss of function mutation in a subject in need thereof, the method involving administering to the subject an effective amount of any of the foregoing compounds or a pharmaceutical composition thereof.

In some embodiments, the disorder related to a BRG1 loss of function mutation is cancer. In other embodiments, the subject is determined to have a BRG1 loss of function disorder, for example, is determined to have a BRG1 loss of function cancer (for example, the cancer has been determined to include cancer cells with loss of BRG1 function).

In another aspect, the invention features a method of inducing apoptosis in a cell, the method involving contacting the cell with an effective amount of any of the foregoing compounds or a pharmaceutical composition thereof. In some embodiments, the cell is a cancer cell.

In a further aspect, the invention features a method of treating cancer in a subject in need thereof, the method including administering to the subject an effective amount of any of the foregoing compounds or a pharmaceutical composition thereof.

In some embodiments of any of the foregoing methods, the cancer is non-small cell lung cancer, colorectal cancer, bladder cancer, cancer of unknown primary, glioma, breast cancer, melanoma, non-melanoma skin cancer, endometrial cancer, esophagogastric cancer, pancreatic cancer, hepatobiliary cancer, soft tissue sarcoma, ovarian cancer, head and neck cancer, renal cell carcinoma, bone cancer, non-Hodgkin lymphoma, small-cell lung cancer, prostate cancer, embryonal tumor, germ cell tumor, cervical cancer, thyroid cancer, salivary gland cancer, gastrointestinal neuroendocrine tumor, uterine sarcoma, gastrointestinal stromal tumor, CNS cancer, thymic tumor, Adrenocortical carcinoma, appendiceal cancer, small bowel cancer, or penile cancer.

In some embodiments of any of the foregoing methods, the cancer is non-small cell lung cancer, colorectal cancer, bladder cancer, cancer of unknown primary, glioma, breast cancer, melanoma, non-melanoma skin cancer, endometrial cancer, or penile cancer.

In some embodiments of any of the foregoing methods, the cancer is a drug resistant cancer or has failed to respond to a prior therapy (e.g., vemurafenib, dacarbazine, a CTLA4 inhibitor, a PD1 inhibitor, interferon therapy, a BRAF inhibitor, a MEK inhibitor, radiotherapy, temozolimide, irinotecan, a CAR-T therapy, herceptin, perjeta, tamoxifen, xeloda, docetaxol, platinum agents such as carboplatin, taxanes such as paclitaxel and docetaxel, ALK inhibitors, MET inihibitors, alimta, abraxane, Adriamycin®, gemcitabine, avastin, halaven, neratinib, a PARP inhibitor, ARN810, an mTOR inhibitor, topotecan, gemzar, a VEGFR2 inhibitor, a folate receptor antagonist, demcizumab, fosbretabulin, or a PDL1 inhibitor).

In some embodiments of any of the foregoing methods, the cancer has or has been determined to have BRG1 mutations. In some embodiments of any of the foregoing methods, the BRG1 mutations are homozygous. In some embodiments of any of the foregoing methods, the cancer does not have, or has been determined not to have, an epidermal growth factor receptor (EGFR) mutation. In some embodiments of any of the foregoing methods, the cancer does not have, or has been determined not to have, an anaplastic lymphoma kinase (ALK) driver mutation. In some embodiments of any of the foregoing methods, the cancer has, or has been determined to have, a KRAS mutation. In some embodiments of any of the foregoing methods, the BRG1 mutation is in the ATPase catalytic domain of the protein. In some embodiments of any of the foregoing methods, the BRG1 mutation is a deletion at the C-terminus of BRG1.

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

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

In another aspect, the invention features a method of treating melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, or a hematologic cancer in a subject in need thereof, the method including administering to the subject an effective amount of any of the foregoing compounds or pharmaceutical compositions thereof.

In another aspect, the invention features a method of reducing tumor growth of melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, or a hematologic cancer in a subject in need thereof, the method including administering to the subject an effective amount of any of the foregoing compounds or pharmaceutical compositions thereof.

In another aspect, the invention features a method of suppressing metastatic progression of melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, or a hematologic cancer in a subject, the method including administering an effective amount of any of the foregoing compounds or pharmaceutical compositions thereof.

In another aspect, the invention features a method of suppressing metastatic colonization of melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, or a hematologic cancer in a subject, the method including administering an effective amount of any of the foregoing compounds or pharmaceutical compositions thereof.

In another aspect, the invention features a method of reducing the level and/or activity of BRG1 and/or BRM in a melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, or hematologic cancer cell, the method including contacting the cell with an effective amount of any of the foregoing compounds or pharmaceutical compositions thereof.

In some embodiments of any of the above aspects, the melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, or hematologic cell is in a subject.

In some embodiments of any of the above aspects, the effective amount of the compound reduces the level and/or activity of BRG1 by at least 5% (e.g., 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) as compared to a reference. In some embodiments, the effective amount of the compound that reduces the level and/or activity of BRG1 by at least 50% (e.g., 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) as compared to a reference. In some embodiments, the effective amount of the compound that reduces the level and/or activity of BRG1 by at least 90% (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%).

In some embodiments, the effective amount of the compound reduces the level and/or activity of BRG1 by at least 5% (e.g., 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) as compared to a reference for at least 12 hours (e.g., 14 hours, 16 hours, 18 hours, 20 hours, 22 hours, 24 hours, 30 hours, 36 hours, 48 hours, 72 hours, or more). In some embodiments, the effective amount of the compound that reduces the level and/or activity of BRG1 by at least 5% (e.g., 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) as compared to a reference for at least 4 days (e.g., 5 days, 6 days, 7 days, 14 days, 28 days, or more).

In some embodiments of any of the above aspects, the effective amount of the compound reduces the level and/or activity of BRM by at least 5% (e.g., 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) as compared to a reference. In some embodiments, the effective amount of the compound that reduces the level and/or activity of BRM by at least 50% (e.g., 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) as compared to a reference. In some embodiments, the effective amount of the compound that reduces the level and/or activity of BRM by at least 90% (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%).

In some embodiments, the effective amount of the compound reduces the level and/or activity of BRM by at least 5% (e.g., 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) as compared to a reference for at least 12 hours (e.g., 14 hours, 16 hours, 18 hours, 20 hours, 22 hours, 24 hours, 30 hours, 36 hours, 48 hours, 72 hours, or more). In some embodiments, the effective amount of the compound that reduces the level and/or activity of BRM by at least 5% (e.g., 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) as compared to a reference for at least 4 days (e.g., 5 days, 6 days, 7 days, 14 days, 28 days, or more).

In some embodiments, the subject has cancer. In some embodiments, the cancer expresses BRG1 and/or BRM protein and/or the cell or subject has been identified as expressing BRG1 and/or BRM. In some embodiments, the cancer expresses BRG1 protein and/or the cell or subject has been identified as expressing BRG1. In some embodiments, the cancer expresses BRM protein and/or the cell or subject has been identified as expressing BRM. In some embodiments, the cancer is melanoma (e.g., uveal melanoma, mucosal melanoma, or cutaneous melanoma). In some embodiments, the cancer is prostate cancer. In some embodiments, the cancer is a hematologic cancer, e.g., multiple myeloma, large cell lymphoma, acute T-cell leukemia, acute myeloid leukemia, myelodysplastic syndrome, immunoglobulin A lambda myeloma, diffuse mixed histiocytic and lymphocytic lymphoma, B-cell lymphoma, acute lymphoblastic leukemia (e.g., T-cell acute lymphoblastic leukemia or B-cell acute lymphoblastic leukemia), diffuse large cell lymphoma, or non-Hodgkin's lymphoma. In some embodiments, the cancer is breast cancer (e.g., an ER positive breast cancer, an ER negative breast cancer, triple positive breast cancer, or triple negative breast cancer). In some embodiments, the cancer is a bone cancer (e.g., Ewing's sarcoma). In some embodiments, the cancer is a renal cell carcinoma (e.g., a Microphthalmia Transcription Factor (MITF) family translocation renal cell carcinoma (tRCC)). In some embodiments, the cancer is metastatic (e.g., the cancer has spread to the liver). The metastatic cancer can include cells exhibiting migration and/or invasion of migrating cells and/or include cells exhibiting endothelial recruitment and/or angiogenesis. In other embodiments, the migrating cancer is a cell migration cancer. In still other embodiments, the cell migration cancer is a non-metastatic cell migration cancer. The metastatic cancer can be a cancer spread via seeding the surface of the peritoneal, pleural, pericardial, or subarachnoid spaces. Alternatively, the metastatic cancer can be a cancer spread via the lymphatic system, or a cancer spread hematogenously. In some embodiments, the effective amount of an agent that reduces the level and/or activity of BRG1 and/or BRM is an amount effective to inhibit metastatic colonization of the cancer to the liver.

In some embodiments the cancer harbors a mutation in GNAQ. In some embodiments the cancer harbors a mutation in GNA11. In some embodiments the cancer harbors a mutation in PLCB4. In some embodiments the cancer harbors a mutation in CYSLTR2. In some embodiments the cancer harbors a mutation in BAP1. In some embodiments the cancer harbors a mutation in SF3B1. In some embodiments the cancer harbors a mutation in EIF1AX. In some embodiments the cancer harbors a TFE3 translocation. In some embodiments the cancer harbors a TFEB translocation. In some embodiments the cancer harbors a MITF translocation. In some embodiments the cancer harbors an EZH2 mutation. In some embodiments the cancer harbors a SUZ12 mutation. In some embodiments the cancer harbors an EED mutation.

In some embodiments of any of the foregoing methods, the method further includes administering to the subject or contacting the cell with an anticancer therapy, e.g., a chemotherapeutic or cytotoxic agent, immunotherapy, surgery, radiotherapy, thermotherapy, or photocoagulation, or a combination thereof. In some embodiments, the anticancer therapy is a chemotherapeutic or cytotoxic agent, e.g., an antimetabolite, antimitotic, antitumor antibiotic, asparagine-specific enzyme, bisphosphonates, antineoplastic, alkylating agent, DNA-Repair enzyme inhibitor, histone deacetylase inhibitor, corticosteroid, demethylating agent, immunomodulatory, janus-associated kinase inhibitor, phosphinositide 3-kinase inhibitor, proteasome inhibitor, or tyrosine kinase inhibitor, or a combination thereof.

In some embodiments of any of the foregoing methods, the compound of the invention is used in combination with another anti-cancer therapy used for the treatment of uveal melanoma such as surgery, a MEK inhibitor, and/or a PKC inhibitor. For example, in some embodiments, the method further comprises performing surgery prior to, subsequent to, or at the same time as administration of the compound of the invention. In some embodiments, the method further comprises administration of a MEK inhibitor and/or a PKC inhibitor prior to, subsequent to, or at the same time as administration of the compound of the invention.

In some embodiments, the anticancer therapy and the compound of the invention are administered within 28 days of each other and each in an amount that together are effective to treat the subject.

In some embodiments, the subject or cancer has and/or has been identified as having a BRG1 loss of function mutation. In some embodiments, the subject or cancer has and/or has been identified as having a BRM loss of function mutation.

In some embodiments, the cancer is resistant to one or more chemotherapeutic or cytotoxic agents (e.g., the cancer has been determined to be resistant to chemotherapeutic or cytotoxic agents such as by genetic markers, or is likely to be resistant, to chemotherapeutic or cytotoxic agents such as a cancer that has failed to respond to a chemotherapeutic or cytotoxic agent). In some embodiments, the cancer has failed to respond to one or more chemotherapeutic or cytotoxic agents. In some embodiments, the cancer is resistant or has failed to respond to dacarbazine, temozolomide, cisplatin, treosulfan, fotemustine, IMCgp100, a CTLA-4 inhibitor (e.g., ipilimumab), a PD-1 inhibitor (e.g., Nivolumab or pembrolizumab), a PD-L1 inhibitor (e.g., atezolizumab, avelumab, or durvalumab), a mitogen-activated protein kinase (MEK) inhibitor (e.g., selumetinib, binimetinib, or tametinib), and/or a protein kinase C (PKC) inhibitor (e.g., sotrastaurin or IDE196).

In some embodiments, the cancer is resistant to or failed to respond to a previously administered therapeutic used for the treatment of uveal melanoma such as a MEK inhibitor or PKC inhibitor. For example, in some embodiments, the cancer is resistant to or failed to respond to a mitogen-activated protein kinase (MEK) inhibitor (e.g., selumetinib, binimetinib, or tametinib), and/or a protein kinase C (PKC) inhibitor (e.g., sotrastaurin or IDE196).

Chemical Terms

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

For any of the following chemical definitions, a number following an atomic symbol indicates that total number of atoms of that element that are present in a particular chemical moiety. As will be understood, other atoms, such as H atoms, or substituent groups, as described herein, may be present, as necessary, to satisfy the valences of the atoms. For example, an unsubstituted C_2 alkyl group has the formula $-CH_2CH_3$. When used with the groups defined herein, a reference to the number of carbon atoms includes the divalent carbon in acetal and ketal groups but does not include the carbonyl carbon in acyl, ester, carbonate, or carbamate groups. A reference to the number of oxygen, nitrogen, or sulfur atoms in a heteroaryl group only includes those atoms that form a part of a heterocyclic ring.

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

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

The term “alkenyl,” as used herein, alone or in combination with other groups, refers to a straight chain or branched hydrocarbon residue having a carbon-carbon double bond and having 2 to 20 carbon atoms (e.g., 2 to 16 carbon atoms, 2 to 10 carbon atoms, 2 to 6 carbon atoms, or 2 carbon atoms).

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

The term “amino,” as used herein, represents $–N(R^{N1})_2$, wherein each R^{N1} is, independently, H, OH, NO_2, $N(R^{N2})_2$, SO_2OR^{N2}, SO_2R^{N2}, SOR^{N2}, an *N*-protecting group, alkyl, alkoxy, aryl, arylalkyl, cycloalkyl, acyl (e.g., acetyl, trifluoroacetyl, or others described herein), wherein each of these recited R^{N1} groups can be optionally substituted; or two R^{N1} combine to form an alkylene or heteroalkylene, and wherein each R^{N2} is, independently, H, alkyl, or aryl. The amino groups of the invention can be an unsubstituted amino (i.e., $–NH_2$) or a substituted amino (i.e., $–N(R^{N1})_2$).

The term “aryl,” as used herein, refers to an aromatic mono- or polycarbocyclic radical of 6 to 12 carbon atoms having at least one aromatic ring. Examples of such groups include, but are not limited to, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, 1,2-dihydronaphthyl, indanyl, and 1H-indenyl. An “arylene” is a divalent aryl group.

The term “arylalkyl,” as used herein, represents an alkyl group substituted with an aryl group. Exemplary unsubstituted arylalkyl groups are from 7 to 30 carbons (e.g., from 7 to 16 or from 7 to 20 carbons, such as C_1-C_6 alkyl C_6-C_{10} aryl, C_1-C_{10} alkyl C_6-C_{10} aryl, or C_1-C_{20} alkyl C_6-C_{10} aryl), such as, benzyl and phenethyl. In some embodiments, the alkyl and the aryl each can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective groups.

The term “azido,” as used herein, represents a $–N_3$ group.

The term “cyano,” as used herein, represents a –CN group.

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

The term “halo,” as used herein, means a fluorine (fluoro), chlorine (chloro), bromine (bromo), or iodine (iodo) radical.

The term “heteroalkyl,” as used herein, refers to an alkyl group, as defined herein, in which one or more of the constituent carbon atoms have been replaced by nitrogen, oxygen, or sulfur. In some embodiments, the heteroalkyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkyl groups. Examples of heteroalkyl groups are an “alkoxy” which, as used herein, refers alkyl–O– (e.g., methoxy and ethoxy). A “heteroalkylene” is a divalent heteroalkyl group.

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

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

The term "heterocyclyl," as used herein, refers to a mono- or polycyclic radical having 3 to 12 atoms having at least one non-aromatic ring containing 1, 2, 3, or 4 ring atoms selected from N, O or S and no aromatic ring containing any N, O, or S atoms. Examples of heterocyclyl groups include, but are not limited to, morpholinyl, thiomorpholinyl, furyl, piperazinyl, piperidinyl, pyranyl, pyrrolidinyl, tetrahydropyranyl, tetrahydrofuranyl, and 1,3-dioxanyl.

The term "heterocyclylalkyl," as used herein, represents an alkyl group substituted with a heterocyclyl group. Exemplary unsubstituted heterocyclylalkyl groups are from 7 to 30 carbons (e.g., from 7 to 16 or from 7 to 20 carbons, such as C_1-C_6 alkyl C_2-C_9 heterocyclyl, C_1-C_{10} alkyl C_2-C_9 heterocyclyl, or C_1-C_{20} alkyl C_2-C_9 heterocyclyl). In some embodiments, the alkyl and the heterocyclyl each can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective groups.

The term "hydroxyalkyl," as used herein, represents alkyl group substituted with an –OH group.

The term "hydroxyl," as used herein, represents an –OH group.

The term "*N*-protecting group," as used herein, represents those groups intended to protect an amino group against undesirable reactions during synthetic procedures. Commonly used *N*-protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis," 3rd Edition (John Wiley & Sons, New York, 1999). *N*-protecting groups include, but are not limited to, acyl, aryloyl, or carbamyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, α-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and chiral auxiliaries such as protected or unprotected D, L, or D, L-amino acids such as alanine, leucine, and phenylalanine; sulfonyl-containing groups such as benzenesulfonyl, and p-toluenesulfonyl; carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4- 20 dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxy carbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2,-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxy carbonyl, fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, and phenylthiocarbonyl, arylalkyl groups such as benzyl, triphenylmethyl, and benzyloxymethyl, and silyl groups, such as trimethylsilyl. Preferred *N*-protecting groups are alloc, formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, alanyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc), and benzyloxycarbonyl (Cbz).

The term "nitro," as used herein, represents an $-NO_2$ group.

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

The term "thiol," as used herein, represents an –SH group.

The alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl (e.g., cycloalkyl), aryl, heteroaryl, and heterocyclyl groups may be substituted or unsubstituted. When substituted, there will generally be 1 to 4 substituents present, unless otherwise specified. Substituents include, for example: alkyl (e.g., unsubstituted and substituted, where the substituents include any group described herein, e.g., aryl, halo, hydroxy), aryl (e.g., substituted and unsubstituted phenyl), carbocyclyl (e.g., substituted and unsubstituted cycloalkyl), halo (e.g., fluoro), hydroxyl, heteroalkyl (e.g., substituted and unsubstituted methoxy, ethoxy, or thioalkoxy), heteroaryl, heterocyclyl, amino (e.g., NH_2 or mono- or dialkyl amino), azido, cyano, nitro, oxo, acyl, or thiol. Aryl, carbocyclyl (e.g., cycloalkyl), heteroaryl, and heterocyclyl groups may also be substituted with alkyl (unsubstituted and substituted such as arylalkyl (e.g., substituted and unsubstituted benzyl)).

Compounds of the invention can have one or more asymmetric carbon atoms and can exist in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, or mixtures of diastereoisomeric racemates. The optically active forms can be obtained for example by resolution of the racemates, by asymmetric synthesis or asymmetric chromatography (chromatography with a chiral adsorbent or eluant). That is, certain of the disclosed compounds may exist in various stereoisomeric forms. Stereoisomers are compounds that differ only in their spatial arrangement. Enantiomers are pairs of stereoisomers whose mirror images are not superimposable, most commonly because they contain an asymmetrically substituted carbon atom that acts as a chiral center. "Enantiomer" means one of a pair of molecules that are mirror images of each other and are not superimposable. Diastereomers are stereoisomers that are not related as mirror images, most commonly because they contain two or more asymmetrically substituted carbon atoms and represent the configuration of substituents around one or more chiral carbon atoms. Enantiomers of a compound can be prepared, for example, by separating an enantiomer from a racemate using one or more well-known techniques and methods, such as, for example, chiral chromatography and separation methods based thereon. The appropriate technique and/or method for separating an enantiomer of a compound described herein from a racemic mixture can be readily determined by those of skill in the art. "Racemate" or "racemic mixture" means a compound containing two enantiomers, wherein such mixtures exhibit no optical activity; i.e., they do not rotate the plane of polarized light. “Geometric isomer" means isomers that differ in the orientation of substituent atoms in relationship to a carbon-carbon double bond, to a cycloalkyl ring, or to a bridged bicyclic system. Atoms (other than H) on each side of a carbon- carbon double bond may be in an E (substituents are on opposite sides of the carbon- carbon double bond) or Z (substituents are oriented on the same side) configuration. "R," "S," "S*," "R*," "E," "Z," "cis," and "trans," indicate configurations relative to the core molecule. Certain of the disclosed compounds may exist in atropisomeric forms. Atropisomers are stereoisomers resulting from hindered rotation about single bonds where the steric strain barrier to rotation is high enough to allow for the isolation of the conformers. The compounds of the invention may be prepared as individual isomers by either isomer-specific synthesis or resolved from an isomeric mixture. Conventional resolution techniques include forming the salt of a free base of each isomer of an isomeric pair using an optically active acid (followed by fractional crystallization and regeneration of the free base), forming the salt of the acid form of each isomer of an isomeric pair using an optically active amine (followed by fractional crystallization and regeneration of the free acid), forming an ester or amide of each of the isomers of an isomeric pair using an optically pure acid, amine or alcohol (followed by chromatographic separation and removal of the chiral auxiliary), or resolving an isomeric mixture of either a starting material or a final product using various well known chromatographic methods. When the stereochemistry of a disclosed compound is named or depicted by structure, the named or depicted stereoisomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by weight relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by weight optically pure. When a single diastereomer is named or depicted by structure, the depicted or named diastereomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by weight pure. Percent optical purity is the ratio of the weight of the enantiomer or over the weight of the enantiomer plus the weight of its optical isomer. Diastereomeric purity by weight is the ratio of the weight of one diastereomer or over the weight of all the diastereomers. When the stereochemistry of a disclosed compound is named or depicted by structure, the named or depicted stereoisomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by mole fraction pure relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by mole fraction pure. When a single diastereomer is named or depicted by structure, the depicted or named diastereomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by mole fraction pure. Percent purity by mole fraction is the ratio of the moles of the enantiomer or over the moles of the enantiomer plus the moles of its optical isomer. Similarly, percent purity by moles fraction is the ratio of the moles of the diastereomer or over the moles of the diastereomer plus the moles of its isomer. When a disclosed compound is named or depicted by structure without indicating the stereochemistry, and the compound has at least one chiral center, it is to be understood that the name or structure encompasses either enantiomer of the compound free from the corresponding optical isomer, a racemic mixture of the compound, or mixtures enriched in one enantiomer relative to its corresponding optical isomer. When a disclosed compound is named or depicted by structure without indicating the stereochemistry and has two or more chiral centers, it is to be understood that the name or structure encompasses a diastereomer free of other diastereomers, a number of diastereomers free from other diastereomeric pairs, mixtures of diastereomers, mixtures of diastereomeric pairs, mixtures of diastereomers in which one diastereomer is enriched relative to the other diastereomer(s), or mixtures of diastereomers in which one or more diastereomer is enriched relative to the other diastereomers. The invention embraces all of these forms.

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

Unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. Exemplary isotopes that can be incorporated into compounds of the present invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{32}P, ^{33}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I and ^{125}I. Isotopically-labeled compounds (e.g., those labeled with ^{3}H and ^{14}C) can be useful in compound or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes can be useful for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements). In some embodiments, one or more hydrogen atoms are replaced by ^{2}H or ^{3}H, or one or more carbon atoms are replaced by ^{13}C- or ^{14}C-enriched carbon. Positron emitting isotopes such as ^{15}O, ^{13}N, ^{11}C, and ^{18}F are useful for positron emission tomography (PET) studies to examine substrate receptor occupancy. Preparations of isotopically labelled compounds are known to those of skill in the art. For example, isotopically labeled compounds can generally be prepared by following procedures analogous to those disclosed for compounds of the present invention described herein, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

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

Definitions

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

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

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

As used herein, the term “BAF complex” refers to the BRG1- or HBRM-associated factors complex in a human cell.

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

As used herein, the term “BRG1 loss of function mutation” refers to a mutation in BRG1 that leads to the protein having diminished activity (e.g., at least 1% reduction in BRG1 activity, for example 2%, 5%, 10%, 25%, 50%, or 100% reduction in BRG1 activity). Exemplary BRG1 loss of function mutations include, but are not limited to, a homozygous BRG1 mutation and a deletion at the C-terminus of BRG1.

As used herein, the term “BRG1 loss of function disorder” refers to a disorder (e.g., cancer) that exhibits a reduction in BRG1 activity (e.g., at least 1% reduction in BRG1 activity, for example 2%, 5%, 10%, 25%, 50%, or 100% reduction in BRG1 activity).

The term “cancer” refers to a condition caused by the proliferation of malignant neoplastic cells, such as tumors, neoplasms, carcinomas, sarcomas, leukemias, and lymphomas.

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

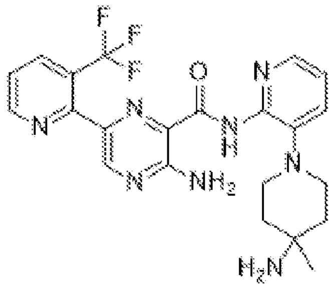
By "determining the level" of a protein or RNA is meant the detection of a protein or an RNA, by methods known in the art, either directly or indirectly. "Directly determining" means performing a process (e.g., performing an assay or test on a sample or "analyzing a sample" as that term is defined herein)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

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

By “decreasing the activity of a BAF complex” is meant decreasing the level of an activity related to a BAF complex, or a related downstream effect. A non-limiting example of decreasing an activity of a BAF complex is Sox2 activation. The activity level of a BAF complex may be measured using any method known in the art, e.g., the methods described in Kadoch et al. Cell, 2013, 153, 71-85, the methods of which are herein incorporated by reference.

As used herein, the term “inhibiting BRM” refers to blocking or reducing the level or activity of the ATPase catalytic binding domain or the bromodomain of the protein. BRM inhibition may be determined using methods known in the art, e.g., a BRM ATPase assay, a Nano DSF assay, or a BRM Luciferase cell assay.

As used herein, the term “LXS196,” also known as IDE196, refers to the PKC inhibitor having the structure:



,

or a pharmaceutically acceptable salt thereof.

The term “pharmaceutical composition,” as used herein, represents a composition containing a compound described herein formulated with a pharmaceutically acceptable excipient and appropriate for administration to a mammal, for example a human. Typically, a pharmaceutical composition is manufactured or sold with the approval of a governmental regulatory agency as part of a therapeutic regimen for the treatment of disease in a mammal. Pharmaceutical compositions can be formulated, for example, for oral administration in unit dosage form (e.g., a tablet, capsule, caplet, gelcap, or syrup); for topical administration (e.g., as a cream, gel, lotion, or ointment); for intravenous administration (e.g., as a sterile solution free of particulate emboli and in a solvent system suitable for intravenous use); or in any other pharmaceutically acceptable formulation.

A “pharmaceutically acceptable excipient,” as used herein, refers to any ingredient other than the compounds described herein (for example, a vehicle capable of suspending or dissolving the active compound) and having the properties of being substantially nontoxic and non-inflammatory in a patient. Excipients may include, for example: antiadherents, antioxidants, binders, coatings, compression aids, disintegrants, dyes (colors), emollients, emulsifiers, fillers (diluents), film formers or coatings, flavors, fragrances, glidants (flow enhancers), lubricants, preservatives, printing inks, sorbents, suspensing or dispersing agents, sweeteners, and waters of hydration. Exemplary excipients include, but are not limited to: butylated hydroxytoluene (BHT), calcium carbonate, calcium phosphate (dibasic), calcium stearate, croscarmellose, crosslinked polyvinyl pyrrolidone, citric acid, crospovidone, cysteine, ethylcellulose, gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, maltitol, mannitol, methionine, methylcellulose, methyl paraben, microcrystalline cellulose, polyethylene glycol, polyvinyl pyrrolidone, povidone, pregelatinized starch, propyl paraben, retinyl palmitate, shellac, silicon dioxide, sodium carboxymethyl cellulose, sodium citrate, sodium starch glycolate, sorbitol, starch (corn), stearic acid, sucrose, talc, titanium dioxide, vitamin A, vitamin E, vitamin C, and xylitol.

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

The compounds of the invention may have ionizable groups so as to be capable of preparation as pharmaceutically acceptable salts. These salts may be acid addition salts involving inorganic or organic acids or the salts may, in the case of acidic forms of the compounds of the invention be prepared from inorganic or organic bases. Frequently, the compounds are prepared or used as pharmaceutically acceptable salts prepared as addition products of pharmaceutically acceptable acids or bases. Suitable pharmaceutically acceptable acids and bases and methods for preparation of the appropriate salts are well-known in the art. Salts may be prepared from pharmaceutically acceptable non-toxic acids and bases including inorganic and organic acids and bases.

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

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

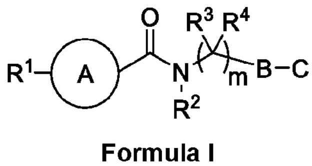
As used herein, the terms "treat," "treated," or "treating" mean therapeutic treatment or any measures whose object is to slow down (lessen) an undesired physiological condition, disorder, or disease, or obtain beneficial or desired clinical results. Beneficial or desired clinical results include, but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

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

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

Detailed Description

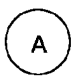
The present disclosure features compounds useful for the inhibition of BRG1 and/or BRM. These compounds may be used to modulate the activity of a BAF complex, for example, for the treatment of a BAF-related disorder, such as cancer. Exemplary compounds described herein include compounds having a structure according to **Formula I**:



Formula I

wherein

R^1 is H, optionally substituted C_1-C_6 acyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted amino, or $–SO_2R^6$;

 is optionally substituted arylene, optionally substituted 5-membered heteroarylene, or optionally substituted 6-membered heteroarylene;

m is 0, 1, 2, or 3;

B is an optionally substituted 9- or 10-membered bicyclic heteroarylene;

C is optionally substituted 3- to 10-membered cycloalkyl; optionally substituted 6- to 10-membered aryl; optionally substituted 5- to 10-membered heteroaryl; or optionally substituted 5- to 10-membered heterocyclyl;

R^2 is hydrogen or optionally substituted C_1-C_6 alkyl;

each of R^3 and R^4 is, independently, hydrogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

R^5 is optionally substituted C_1-C_6 alkyl or $-NR^6R^7$;

and

each of R^6 and R^7 is, independently, optionally substituted C_1-C_6 alkyl,

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound, or pharmaceutically acceptable salt thereof, has the structure of any one of Compounds 1-82 in Table 1.

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

Pharmaceutical Uses

The compounds described herein are useful in the methods of the invention and, while not bound by theory, are believed to exert their ability to modulate the level, status, and/or activity of a BAF complex, i.e., by inhibiting the activity of the BRG1 and/or BRM proteins within the BAF complex in a mammal. BAF complex-related disorders include, but are not limited to, BRG1 loss of function mutation-related disorders.

An aspect of the present invention relates to methods of treating disorders related to BRG1 loss of function mutations such as cancer (e.g., non-small cell lung cancer, colorectal cancer, bladder cancer, cancer of unknown primary, glioma, breast cancer, melanoma, non-melanoma skin cancer, endometrial cancer, or penile cancer) in a subject in need thereof. In some embodiments, the present invention relates to methods of treating melanoma (e.g., uveal melanoma), prostate cancer, breast cancer, bone cancer, renal cell carcinoma, or a hematologic cancer.

In some embodiments, the compound is administered in an amount and for a time effective to result in one or more (e.g., two or more, three or more, four or more) of: (a) reduced tumor size, (b) reduced rate of tumor growth, (c) increased tumor cell death (d) reduced tumor progression, (e) reduced number of metastases, (f) reduced rate of metastasis, (g) decreased tumor recurrence (h) increased survival of subject, (i) increased progression free survival of subject.

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

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

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

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

Treating cancer can also result in a decrease in the mortality rate of a population of treated subjects in comparison to an untreated population. For example, the mortality rate is decreased by more than 2% (e.g., more than 5%, 10%, or 25%). A decrease in the mortality rate of a population of treated subjects may be measured by any reproducible means, for example, by calculating for a population the average number of disease-related deaths per unit time following initiation of treatment with a pharmaceutically acceptable salt of the invention. A decrease in the mortality rate of a population may also be measured, for example, by calculating for a population the average number of disease-related deaths per unit time following completion of a first round of treatment with a pharmaceutically acceptable salt of the invention.

Exemplary cancers that may be treated by the invention include, but are not limited to, non-small cell lung cancer, small-cell lung cancer, colorectal cancer, bladder cancer, glioma, breast cancer, melanoma, non-melanoma skin cancer, endometrial cancer, esophagogastric cancer, pancreatic cancer, hepatobiliary cancer, soft tissue sarcoma, ovarian cancer, head and neck cancer, renal cell carcinoma, bone cancer, non-Hodgkin lymphoma, prostate cancer, embryonal tumor, germ cell tumor, cervical cancer, thyroid cancer, salivary gland cancer, gastrointestinal neuroendocrine tumor, uterine sarcoma, gastrointestinal stromal tumor, CNS cancer, thymic tumor, Adrenocortical carcinoma, appendiceal cancer, small bowel cancer, hematologic cancer, and penile cancer.

Combination Formulations and Uses Thereof

The compounds of the invention can be combined with one or more therapeutic agents. In particular, the therapeutic agent can be one that treats or prophylactically treats any cancer described herein.

Combination Therapies

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

In some embodiments, the second therapeutic agent is a chemotherapeutic agent (e.g., a cytotoxic agent or other chemical compound useful in the treatment of cancer). These include alkylating agents, antimetabolites, folic acid analogs, pyrimidine analogs, purine analogs and related inhibitors, vinca alkaloids, epipodopyyllotoxins, antibiotics, L-Asparaginase, topoisomerase inhibitors, interferons, platinum coordination complexes, anthracenedione substituted urea, methyl hydrazine derivatives, adrenocortical suppressant, adrenocorticosteroides, progestins, estrogens, antiestrogen, androgens, antiandrogen, and gonadotropin-releasing hormone analog. Also included is 5-fluorouracil (5-FU), leucovorin (LV), irenotecan, oxaliplatin, capecitabine, paclitaxel and doxetaxel. Non-limiting examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclosphosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethiylenethiophosphoramide and trimethylolomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analogue topotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimnustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, especially calicheamicin gammall and calicheamicin omegall (see, e.g., Agnew, Chem. Intl. Ed Engl. 33:183-186 (1994)); dynemicin, including dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antiobiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, caminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, Adriamycin® (doxorubicin, including morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5- FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfomithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, Oreg.); razoxane; rhizoxin; sizofuran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2''-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxoids, e.g., Taxol® paclitaxel (Bristol-Myers Squibb Oncology, Princeton, N.J.), ABraxane®, cremophor-free, albumin-engineered nanoparticle formulation of paclitaxel (American Pharmaceutical Partners, Schaumberg, Ill.), and Taxotere® doxetaxel (Rhone-Poulenc Rorer, Antony, France); chloranbucil; Gemzar® gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum coordination complexes such as cisplatin, oxaliplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; Navelbine® vinorelbine; novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeloda; ibandronate; irinotecan (e.g., CPT-11); topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above. Two or more chemotherapeutic agents can be used in a cocktail to be administered in combination with the first therapeutic agent described herein. Suitable dosing regimens of combination chemotherapies are known in the art and described in, for example, Saltz et al. (1999) Proc ASCO 18:233a and Douillard et al. (2000) Lancet 355:1041-7.

In some embodiments, the second therapeutic agent is a therapeutic agent which is a biologic such a cytokine (e.g., interferon or an interleukin (e.g., IL-2)) used in cancer treatment. In some embodiments the biologic is an anti-angiogenic agent, such as an anti-VEGF agent, e.g., bevacizumab (Avastin®). In some embodiments the biologic is an immunoglobulin-based biologic, e.g., a monoclonal antibody (e.g., a humanized antibody, a fully human antibody, an Fc fusion protein or a functional fragment thereof) that agonizes a target to stimulate an anti-cancer response, or antagonizes an antigen important for cancer. Such agents include Rituxan (Rituximab); Zenapax (Daclizumab); Simulect (Basiliximab); Synagis (Palivizumab); Remicade (Infliximab); Herceptin (Trastuzumab); Mylotarg (Gemtuzumab ozogamicin); Campath (Alemtuzumab); Zevalin (Ibritumomab tiuxetan); Humira (Adalimumab); Xolair (Omalizumab); Bexxar (Tositumomab-I-131); Raptiva (Efalizumab); Erbitux (Cetuximab); Avastin (Bevacizumab); Tysabri (Natalizumab); Actemra (Tocilizumab); Vectibix (Panitumumab); Lucentis (Ranibizumab); Soliris (Eculizumab); Cimzia (Certolizumab pegol); Simponi (Golimumab); Ilaris (Canakinumab); Stelara (Ustekinumab); Arzerra (Ofatumumab); Prolia (Denosumab); Numax (Motavizumab); ABThrax (Raxibacumab); Benlysta (Belimumab); Yervoy (Ipilimumab); Adcetris (Brentuximab Vedotin); Perjeta (Pertuzumab); Kadcyla (Ado-trastuzumab emtansine); and Gazyva (Obinutuzumab). Also included are antibody-drug conjugates.

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

The second agent may be a checkpoint inhibitor. In one embodiment, the inhibitor of checkpoint is an inhibitory antibody (e.g., a monospecific antibody such as a monoclonal antibody). The antibody may be, e.g., humanized or fully human. In some embodiments, the inhibitor of checkpoint is a fusion protein, e.g., an Fc-receptor fusion protein. In some embodiments, the inhibitor of checkpoint is an agent, such as an antibody, that interacts with a checkpoint protein. In some embodiments, the inhibitor of checkpoint is an agent, such as an antibody, that interacts with the ligand of a checkpoint protein. In some embodiments, the inhibitor of checkpoint is an inhibitor (e.g., an inhibitory antibody or small molecule inhibitor) of CTLA-4 (e.g., an anti-CTLA4 antibody such as ipilimumab/Yervoy or tremelimumab). In some embodiments, the inhibitor of checkpoint is an inhibitor (e.g., an inhibitory antibody or small molecule inhibitor) of PD-1 (e.g., nivolumab/Opdivo®; pembrolizumab/Keytruda®; pidilizumab/CT-011). In some embodiments, the inhibitor of checkpoint is an inhibitor (e.g., an inhibitory antibody or small molecule inhibitor) of PDL1 (e.g., MPDL3280A/RG7446; MEDI4736; MSB0010718C; BMS 936559). In some embodiments, the inhibitor of checkpoint is an inhibitor (e.g., an inhibitory antibody or Fc fusion or small molecule inhibitor) of PDL2 (e.g., a PDL2/Ig fusion protein such as AMP 224). In some embodiments, the inhibitor of checkpoint is an inhibitor (e.g., an inhibitory antibody or small molecule inhibitor) of B7-H3 (e.g., MGA271), B7-H4, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD160, CGEN-15049, CHK1, CHK2, A2aR, B-7 family ligands, or a combination thereof.

In some embodiments, the compound of the invention is used in combination with another anti-cancer therapy used for the treatment of uveal melanoma such as surgery, a MEK inhibitor, and/or a PKC inhibitor, or a combination thereof. For example, in some embodiments, the method further comprises performing surgery prior to, subsequent to, or at the same time as administration of the compound of the invention. In some embodiments, the method further comprises administration of a MEK inhibitor (e.g., selumetinib, binimetinib, or tametinib) and/or a PKC inhibitor (e.g., sotrastaurin or IDE196) prior to, subsequent to, or at the same time as administration of the compound of the invention.

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

Pharmaceutical Compositions

The compounds of the invention are preferably formulated into pharmaceutical compositions for administration to a mammal, preferably, a human, in a biologically compatible form suitable for administration in vivo. Accordingly, in an aspect, the present invention provides a pharmaceutical composition comprising a compound of the invention in admixture with a suitable diluent, carrier, or excipient.

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

A compound of the invention may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard- or soft-shell gelatin capsules, or it may be compressed into tablets, or it may be incorporated directly with the food of the diet. For oral therapeutic administration, a compound of the invention may be incorporated with an excipient and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, and wafers.

A compound of the invention may also be administered parenterally. Solutions of a compound of the invention can be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, DMSO, and mixtures thereof with or without alcohol, and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms. Conventional procedures and ingredients for the selection and preparation of suitable formulations are described, for example, in Remington's Pharmaceutical Sciences (2003, 20th ed.) and in The United States Pharmacopeia: The National Formulary (USP 24 NF19), published in 1999. The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that may be easily administered via syringe.

A compound described herein may be administered intratumorally, for example, as an intratumoral injection. Intratumoral injection is injection directly into the tumor vasculature and is specifically contemplated for discrete, solid, accessible tumors. Local, regional, or systemic administration also may be appropriate. A compound described herein may advantageously be contacted by administering an injection or multiple injections to the tumor, spaced for example, at approximately, 1 cm intervals. In the case of surgical intervention, the present invention may be used preoperatively, such as to render an inoperable tumor subject to resection. Continuous administration also may be applied where appropriate, for example, by implanting a catheter into a tumor or into tumor vasculature.

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

Dosages

The dosage of the compounds of the invention, and/or compositions comprising a compound of the invention, can vary depending on many factors, such as the pharmacodynamic properties of the compound; the mode of administration; the age, health, and weight of the recipient; the nature and extent of the symptoms; the frequency of the treatment, and the type of concurrent treatment, if any; and the clearance rate of the compound in the animal to be treated. One of skill in the art can determine the appropriate dosage based on the above factors. The compounds of the invention may be administered initially in a suitable dosage that may be adjusted as required, depending on the clinical response. In general, satisfactory results may be obtained when the compounds of the invention are administered to a human at a daily dosage of, for example, between 0.05 mg and 3000 mg (measured as the solid form).

Alternatively, the dosage amount can be calculated using the body weight of the patient. For example, the dose of a compound, or pharmaceutical composition thereof, administered to a patient may range from 0.1-100 mg/kg.

Examples

Definitions used in the following Schemes and elsewhere herein are:

ACN	acetonitrile
AcOH or HOAc	acetic acid
aq.	aqueous
Boc	tert-butoxycarbonyl
B_2pin_2	4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane
t-BuONa or NaOt-Bu	sodium tert-butoxide
Cbz	benzyloxy carbonyl
DCE	dichloroethane
DCM	dichloromethane
DIBAL-H	diisobutylaluminum hydride
DIEA or DIPEA	N,N-diisopropylethylamine
DMA	N,N-dimethylacetamide
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
EDCI or EDCI•HCl	1-ethyl-(3-dimethylaminopropyl)carbodiimide hydrochloride
ES	electrospray ionization
Et_3N or TEA	triethylamine
EtOAc	ethyl acetate
EtOH	ethyl alcohol
FA	formic acid
h	hour
HATU	2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium
HBTU	N,N,N′,N′-tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate
HCl	hydrochloric acid
HOAc	acetic acid
HOBt or HOBT	hydroxybenzotriazole hydrate
KOAc	potassium acetate
KHMDS	potassium hexamethyldisilazide
LED	light-emitting diode
Me	methyl
MeOH	methyl alcohol
MsCl	methanesulfonyl chloride

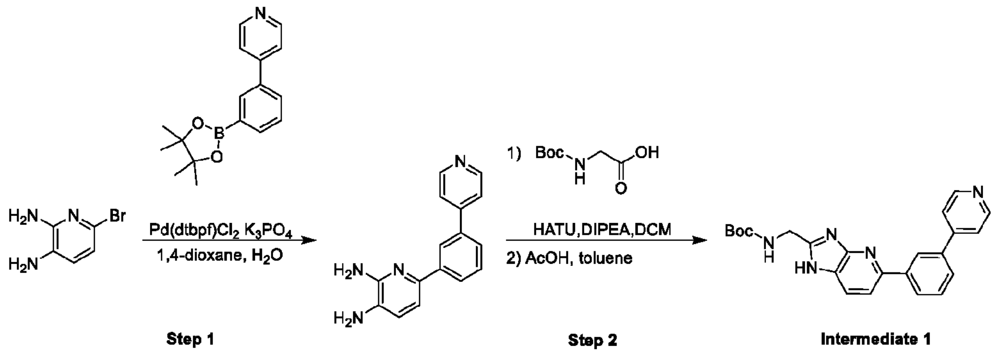
NaHMDS	sodium hexamethyldisilazide
NIS	N-iodosuccinimide
OAc	acetate
Pd/C	palladium on carbon
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium(0)
$Pd(dppf)Cl_2$ or $(DPPF)PdCl_2$	[1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
$Pd(dtbpf)Cl_2$	dichloro[1,1'-bis(di-t-butylphosphino)ferrocene]palladium(II)
Ph	phenyl
PhMe	toluene
PTFE	poly(tetrafluoroethylene)
SFC	supercritical fluid chromatography
SPhos Pd G3	(2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl) [2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate
THF	tetrahydrofuran
Xantphos	9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene

Materials

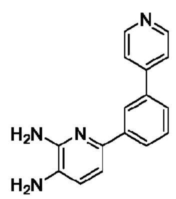
Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. All reactions involving air- or moisture-sensitive reagents were performed under a nitrogen atmosphere.

Example 1. Preparation of tert-butyl ((5-(3-(pyridine-4-yl)phenyl-1H-imiadzo[4,5-b]pyridine-2-yl)methyl)carbamate, (S)-tert-butyl (1-(5-(3-(pyridin-4-yl)phenyl)-1H-imidazo[4,5-b]pyridin-2-yl)ethyl)carbamate, and (R)-tert-butyl (1-(5-(3-(pyridin-4-yl)phenyl)-1H-imidazo[4,5-b]pyridin-2-yl)ethyl)carbamate (Intermediate 1-3)

Intermediate 1: tert-butyl ((5-(3-(pyridine-4-yl)phenyl-1H-imiadzo[4,5-b]pyridine-2-yl)methyl)carbamate

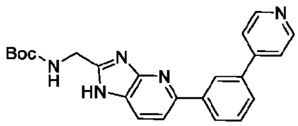


Step 1: Preparation of 6-(3-(pyridin-4-yl)phenyl)pyridine-2,3-diamine



To a solution of 6-bromopyridine-2,3-diamine (500 mg, 2.66 mmol) in 1,4-dioxane (4 mL) was added water (1 mL), 4-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyridine (2.24 g, 7.98 mmol), K_3PO_4 (1.69 g, 7.98 mmol) and [1,1'-bis(di-tert-butylphosphino)ferrocene]dichloropalladium (173 mg, 0.266 mmol). After stirring at 120 °C for 17 h, the reaction mixture was poured into water, then extracted four times with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give residue. The residue was purified by reversed-phase prep-HPLC (NH_3•H_2O) to afford the title compound (470 mg, 1.68 mmol, 63.3% yield) as a white solid. LCMS (ESI) m/z: $[M+H]^+$ = 263.3. ^1H NMR (400 MHz, DMSO-d_6) δ 8.68 - 8.61 (m, 2H), 8.26 - 8.25 (m, 1H), 7.96 - 7.95 (m, 1H), 7.77 - 7.70 (m, 2H), 7.65 - 7.60 (m, 1H), 7.54 - 7.47 (m, 1H), 7.13 (d, J = 7.6 Hz, 1H), 6.80 (d, J = 7.6 Hz, 1H), 5.53 (s, 2H), 4.90 (s, 2H).

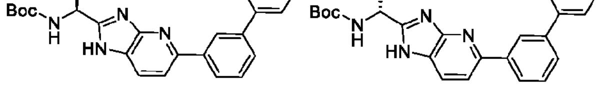
Step 2: Preparation of tert-butyl ((5-(3-(pyridine-4-yl)phenyl-1H-imiadzo[4,5-b]pyridine-2-yl)methyl)carbamate (Intermediate 1)



Intermediate 1

To a solution of 2-(tert-butoxycarbonylamino)acetic acid (330 mg, 1.88 mmol) in DMF (5 mL) was added HATU (1.02 g, 2.69 mmol), DIPEA (695 mg, 5.38 mmol) and 6-(3-(pyridin-4-yl)phenyl)pyridine-2,3-diamine (470 mg, 1.79 mmol). After stirring at room temperature for 0.5 h, the reaction mixture was poured into water, then extracted twice with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give residue. The residue was purified by reversed-phase prep-HPLC (NH_3•H_2O) to afford an intermediate (600 mg, 1.40 mmol, 78.2% yield) as a white solid. The solid was dissolved in toluene (6 mL) and acetic acid (85.9 mg, 1.43 mmol) was added to the mixture. After stirring at 120 °C for 12 h, the reaction mixture was poured into water, then extracted three times with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to afford **Intermediate 1** (500 mg, 1.15 mmol, 80.1% yield) as yellow oil. LCMS (ESI) m/z: $[M+H]^+$ = 402.4. ^1H NMR (400 MHz, DMSO-d_6) δ 13.10 - 12.46 (m, 1H), 8.69 (d, J = 6.0 Hz, 2H), 8.47 (s, 1H), 8.21 (d, J = 8.0 Hz, 1H), 8.05 (br d, J = 8.0 Hz, 1H), 7.95 (br s, 2H), 7.85 - 7.80 (m, 3H), 7.69 - 7.59 (m, 1H), 4.41 (br s, 2H), 1.43 (s, 9H).

Intermediates 2 and 3: (S)-tert-butyl (1-(5-(3-(pyridin-4-yl)phenyl)-1H-imidazo[4,5-b]pyridin-2-yl)ethyl)carbamate and (R)-tert-butyl (1-(5-(3-(pyridin-4-yl)phenyl)-1H-imidazo[4,5-b]pyridin-2-yl)ethyl)carbamate



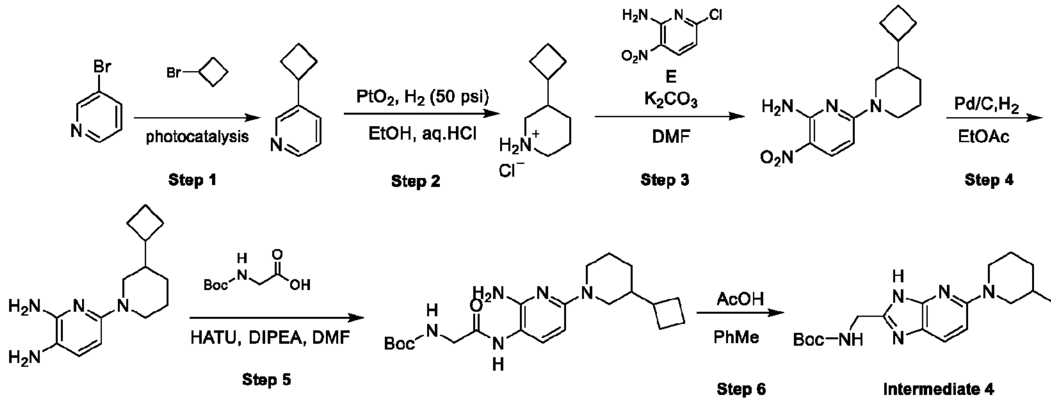
Intermediate 2 **Intermediate 3**

Intermediates 2 and **3** were synthesized starting from the common intermediate 6-(3-(pyridin-4-yl)phenyl)pyridine-2,3-diamine and corresponding racemic N-Boc amino acid utilizing the above-described synthetic protocol for preparing Intermediate 1, followed by a chiral SFC separation.

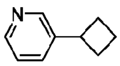
Intermediate 2: LCMS (ESI) m/z: [M+H]+ = 416.1.

Intermediate 3: LCMS (ESI) m/z: [M+H]+ = 416.2.

Example 2. Preparation of tert-butyl ((5-(3-cyclobutylpiperidin-1-yl)-3H-imidazo[4,5-b]pyridin-2-yl)methyl)carbamate (Intermediate 4)

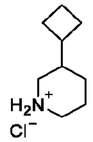


Step 1: Preparation of 3-cyclobutylpyridine



To a vial was added 3-bromopyridine (6.10 mL, 63.3 mmol), bromocyclobutane (7.77 mL, 82.3 mmol), (4,4'-di-t-butyl-2,2'-bipyridine)bis[3,5-difluoro-2-[5-trifluoromethyl-2-pyridinyl-κN)phenyl-κC]iridium(III) hexafluorophosphate (710 mg, 0.633 mmol), nickel(II) chloride, dimethoxyethane adduct (69.5 mg, 0.316 mmol), 4-tert-butyl-2-(4-tert-butyl-2-pyridyl)pyridine (102 mg, 0.380 mmol), bis(trimethylsilyl)silyl-trimethyl-silane (19.5 mL, 63.3 mmol) and K_2CO_3 (17.5 g, 127 mmol) in acetonitrile (240 mL). The vial was sealed and placed under a nitrogen atmosphere and irradiated with a 34 W blue LED lamp (7 cm away) at room temperature. After 14 h, the reaction mixture was diluted with water and extracted three times with ethyl acetate, and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to afford a yellow oil. The oil was purified by flash silica gel chromatography (0-50% ethyl acetate / petroleum ether gradient) to afford the title compound (1.6 g, 12.0 mmol, 17.1% yield) as a yellow oil. LCMS (ESI) m/z: $[M+H]^+$ = 134.1. ^1H NMR (400 MHz, $CDCl_3$) δ 8.36 - 8.31 (m, 2H), 7.45 - 7.42 (m, 1H), 7.13 - 7.10 (m, 1H), 3.50 - 3.41 (m, 1H), 2.44 - 2.26 (m, 2H), 2.06 - 1.96 (m, 3H), 1.86 - 1.81 (m, 1H).

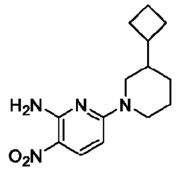
Step 2: Preparation of methyl 3-cyclobutylpiperidin-1-ium chloride



To a mixture of 3-cyclobutylpyridine (1.6 g, 12.0 mmol) in ethanol (16 mL) was added PtO_2 (327 mg, 1.44 mmol) and an aqueous concentrated HCl solution (1.60 mL) at room temperature. The mixture was degassed and purged with H_2 three times, then stirred at 60 °C under H_2 atmosphere (50 psi). After 18 h, the reaction mixture was diluted with methanol and filtered. The filtrate was concentrated to afford the title compound (2.00 g, 11.4 mmol, 94.2% yield) as a yellow oil. LCMS (ESI) m/z: $[M+H]^+$ = 140.3. ^1H

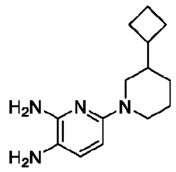
NMR (400 MHz, DMSO-d_6) δ 9.20 (br s, 1H), 8.98 (s, 1H), 3.11 - 3.01 (m, 2H), 2.72 - 2.63 (m, 1H), 2.40 - 2.31 (m, 1H), 2.06 - 2.02 (m, 1H), 1.95 - 1.90 (m, 2H), 1.79 - 1.58 (m, 8H), 1.01 - 0.91 (m, 1H).

Step 3: Preparation of 6-(3-cyclobutylpiperidin-1-yl)-3-nitropyridin-2-amine



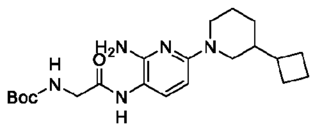
To a mixture of methyl 3-cyclobutylpipderdin-1-ium chloride (2 g, 11.4 mmol) and K_2CO_3 (6.29 g, 45.5 mmol) in DMF (20 mL) was added 6-chloro-3-nitro-pyridin-2-amine (2.17 g, 12.5 mmol) at room temperature. After stirring at 80 °C for 2 h, the reaction mixture was diluted with water and extracted three times with ethyl acetate; the combined organic layers were concentrated to afford a yellow oil. The oil was purified by reversed-phase prep-HPLC (NH_3•H_2O), concentrated to remove acetonitrile and the mixture was extracted twice with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the title compound (2.2 g, 7.96 mmol, 69.8% yield) as a yellow solid. LCMS (ESI) m/z: $[M+H]^+$ = 277.2. ^1H NMR (400 MHz, DMSO-d_6) δ 8.05 - 7.68 (m, 3H), 6.34 (d, J = 9.6 Hz, 1H), 4.25 - 4.16 (m, 1H), 3.15 - 3.09 (m, 1H), 2.76 - 2.75 (m, 1H), 2.07 - 2.03 (m, 2H), 1.99 - 1.95 (m, 1H), 1.80 - 1.72 (m, 6H), 1.43 - 1.40 (m, 3H), 1.15 - 1.10 (m, 1H).

Step 4: Preparation of 6-(3-cyclobutylpiperidin-1-yl)pyridine-2,3-diamine



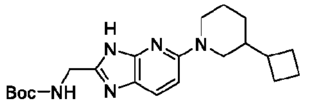
A mixture of 6-(3-cyclobutylpiperidin-1-yl)-3-nitro-pyridine-2-diamine (500 mg, 1.81 mmol) and 10% Pd/C (250 mg, 1.81 mmol) in ethyl acetate (5 mL) was degassed and purged with H_2 (15 psi) three times. After stirring at room temperature under a H_2 atmosphere for 12 h, the reaction mixture was filtered and the filtrate was concentrated under vacuum to afford the title compound (420 mg, 1.70 mmol, 94.2% yield) as a black oil which was used to the next step without further purification. LCMS (ESI) m/z; $[M+H]^+$ = 247.3. ^1H NMR (400 MHz, DMSO-d_6) δ 6.68 (d, J = 8.0 Hz, 1H), 5.80 (d, J = 8.0 Hz, 1H), 5.09 (s, 2H), 3.93 (br s, 2H), 3.84 - 3.77 (m, 2H), 2.47 - 2.44 (m, 1H), 2.06 - 2.06 (m, 1H), 2.05 - 1.93 (m, 3H), 1.86 - 1.61 (m, 6H), 1.47 - 1.37 (m, 2H), 0.91 - 0.86 (m, 1H).

Step 5: Preparation of tert-butyl (2-((2-amino-6-(3-cyclobutylpiperidin-1-yl)pyridin-3-yl)amino)-2-oxoethyl)carbamate



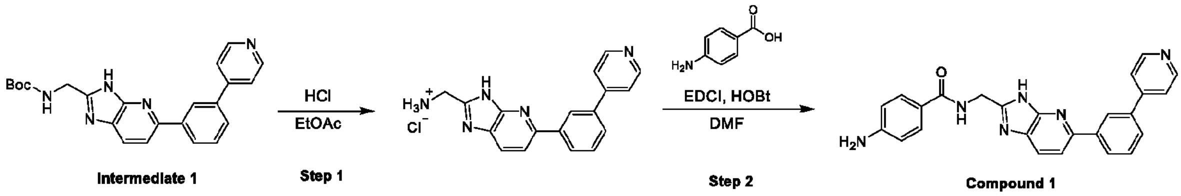
To a mixture of 2-(tert-butoxycarbonylamino)acetic acid (219 mg, 1.25 mmol) and HATU (713 mg, 1.88 mmol) in DMF (4 mL) was added DIPEA (0.653 mL, 3.75 mmol). After stirring at room temperature for 15 minutes, 6-(3-cyclobutylpiperidin-1-yl)pyridine-2,3-diamine (370 mg, 1.50 mmol) was added the mixture. After stirring an addition 2 h, the reaction mixture was diluted with water and extracted three times with ethyl acetate; the combined organic layers were concentrated to afford a black brown oil. The oil was purified by flash silica gel chromatography (0-80% ethyl acetate / petroleum ether gradient) to afford the title compound (280 mg, 694 μmol, 55.5% yield) as a black oil. LCMS (ESI)m/z: $[M+H]^+$ = 404.1. ^1H NMR (400 MHz, DMSO-d_6) δ 8.84 (s, 1H), 7.13 (d, J = 8.4 Hz, 1H), 7.01 - 8.98 (m, 1H), 5.92 (d, J = 8.4 Hz, 1H), 5.33 (s, 2H), 3.97 - 3.94 (m, 1H), 3.68 (br d, J = 5.6 Hz, 2H), 2.69 - 2.67 (m, 1H), 2.34 - 2.31 (m, 1H), 2.14 - 2.00 (m, 2H), 1.97 - 1.96 (m, 1H), 1.74 - 1.59 (m, 7H), 1.39 (s, 11H), 0.98 - 0.97 (m, 1H).

Step 6: Preparation of tert-butyl ((5-(3-cyclobutylpiperidin-1-yl)-3H-imidazo[4,5-b]pyridin-2-yl)methyl)carbamate (Intermediate 4)

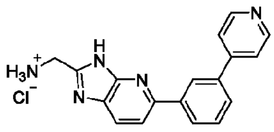


To a mixture of tert-butyl (2-((2-amino-6-(3-cyclobutylpiperidin-1-yl)pyridin-3-yl)amino)-2-oxoethyl)carbamate (280 mg, 694 μmol) in toluene (3 mL) was added acetic acid (0.061 mL, 1.07 mmol) at room temperature. After stirring at 100 °C for 12 h, the reaction mixture was diluted with water and extracted four times with ethyl acetate; the combined organic layers were concentrated to afford a black brown oil. The oil was purified by silica gel flash chromatography (0-100% ethyl acetate / petroleum ether gradient) to afford **Intermediate 4** (130 mg, 0.337 mmol, 48.6% yield) as a brown oil. LCMS (ESI) m/z: $[M+H]^+$ = 386.2. ^1H NMR (400 MHz, DMSO-d_6) δ 12.26 (s, 1H), 7.67 - 7.65 (m, 1H), 7.23 - 7.21 (m, 1H), 6.68 - 6.64 (m, 1H), 4.24 (d, J = 5.6 Hz, 2H), 4.09 (d, J = 1.6 Hz, 1H), 2.79 - 2.77 (m, 1H), 2.41 - 2.38 (m, 1H), 2.08 - 2.02 (m, 3H), 1.82 - 1.65 (m, 7H), 1.39 (s, 11H), 1.02 - 0.96 (m, 1H).

Example 3. Preparation of 4-amino-N-((5-(3-(pyridin-4-yl)phenyl)-3H-imidazo[4,5-b]pyridin-2-yl)methyl)benzamide (Compound 1)

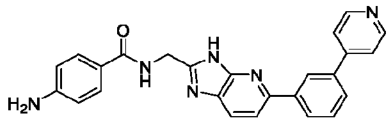


Step 1: Preparation of (5-(3-(pyridin-4-yl)phenyl)-3H-imidazo[4,5-b]pyridin-2-yl)methanaminium chloride



A solution of **Intermediate 1** (500 mg, 1.25 mmol) in a solution of 4 M HCl in ethyl acetate (10 mL, 40 mmol) was stirred at room temperature. After 1 h, the reaction mixture was concentrated to afford the title compound (400 mg, 1.13 mmol, 91.0% yield) as a gray solid, which was used for next step without further purification. LCMS (ESI) m/z: $[M+H]^+$ = 302.1. ^1H NMR (400 MHz, DMSO-d_6) δ 9.03 (br d, J=6.6 Hz, 3H), 8.96 (br s, 2H), 8.68 (s, 1H), 8.56 (d, J=6.6 Hz, 2H), 8.39 (br d, J=7.8 Hz, 1H), 8.25-8.18 (m, 1H), 8.17-8.07 (m, 2H), 7.85-7.71 (m, 1H), 4.43 (br s, 2H).

Step 2: Preparation of 4-amino-N-((5-(3-(pyridin-4-yl)phenyl)-3H-imidazo[4,5-b]pyridin-2-yl)methyl)benzamide (Compound 1)



Compound 1

To a solution of (5-(3-(pyridin-4-yl)phenyl)-3H-imidazo[4,5-b]pyridin-2-yl)methanaminium chloride (60 mg, 0.178 mmol), 4-aminobenzoic acid (24.4 mg, 0.178 mmol), EDCI (68.1 mg, 0.355 mmol), HOBt (48.0 mg, 0.355 mmol) in dichloromethane (1 mL) was added DIPEA (0.155 mL, 0.888 mmol). After stirring at room temperature for 16 h, the reaction mixture was concentrated to afford the crude product. The crude product was purified by reversed-phase prep-HPLC (water:ACN;FA) to afford **Compound 1** (7.98 mg, 17.11 μmol, 9.63% yield, formic acid salt) as a yellow solid. LCMS (ESI) m/z: $[M+H]^+$ = 421.2. ^1H NMR (400 MHz, DMSO-d_6) δ 8.92 (br d, J = 4.6 Hz, 2H), 8.85 (s, 1H), 8.61 (s, 1H), 8.38-8.26 (m, 3H), 8.13 (d, J = 4.8 Hz, 2H), 8.02 (br d, J = 7.6 Hz, 1H), 7.80-7.64 (m, 3H), 6.63 (d, J = 8.4 Hz, 2H), 4.77 (br d, J = 5.4 Hz, 2H).

Example 4. Preparation of Compounds 2 to 5 and 23

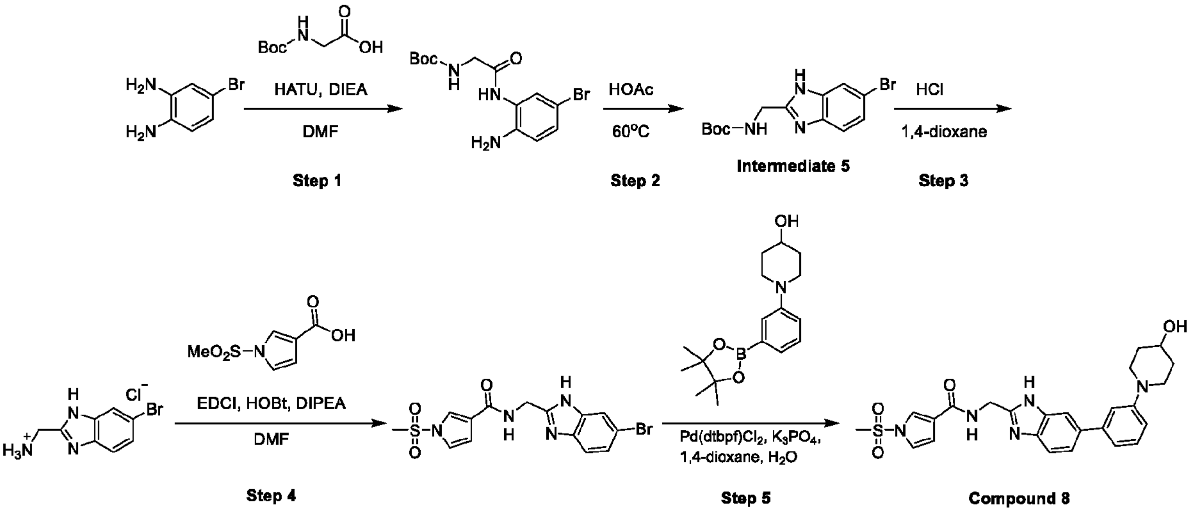
Compounds 2 to 5 and 23, shown in Table 2 below, were each synthesized from **Intermediate 1**, **2**, **3**, or **4** and the corresponding carboxylic acid following the synthetic protocol described in Example 3.

Table 2

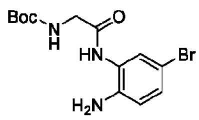
#	LC-MS (m/z)	^1H NMR
2	473.1	^1H NMR (400 MHz, DMSO-d_6) δ 9.02-9.01 (m, 1H), 8.89 (br d, J = 5.6 Hz, 2H), 8.60 (s, 1H), 8.31 (br d, J = 8.0 Hz, 1H), 8.25 (br d, J=6.0 Hz, 2H), 8.09-8.08 (m, 2H), 7.99 (br d, J = 7.6 Hz, 1H), 7.89 (s, 1H), 7.75-7.74 (m, 1H), 7.34 (br s, 1H), 6.82 (br d, J = 1.2 Hz, 1H), 4.73 (br d, J = 5.6 Hz, 2H), 3.58 (s, 3H)
3	501.2	^1H NMR (400 MHz, DMSO-d_6) δ 8.99 (br s, 1H), 8.69 (d, J = 4.8 Hz, 2H), 8.48 (s, 1H), 8.21 (d, J = 7.6 Hz, 1H), 8.09-7.93 (m, 2H), 7.89-7.76 (m, 4H), 7.66-7.65 (m, 1H), 7.30 (d, J = 2.0 Hz, 1H), 6.91-6.77 (m, 1H), 4.69 (br d, J = 5.6 Hz, 2H), 3.96-3.80 (m, 1H), 1.24 (d, J = 6.8 Hz, 6H)
4	487.2	^1H NMR (400 MHz, DMSO-d_6) δ 8.90 (d, J = 6.8 Hz, 2H), 8.82 (d, J = 7.2 Hz, 1H), 8.62-8.61 (m, 1H), 8.33-8.29 (m, 3H), 8.10-8.04 (m, 2H), 8.00-7.98 (m, 1H), 7.96-7.95 (m, 1H), 7.75-7.71 (m, 1H), 7.32-7.31 (m, 1H), 6.81-6.80 (m, 1H), 5.40-5.33 (m, 1H), 3.56 (s, 3H), 1.65 (d, J = 7.2 Hz, 3H)
5	487.2	^1H NMR (400 MHz, DMSO-d_6) δ 8.91 (br d, J = 4.4 Hz, 2H), 8.80 (br d, J = 7.2 Hz, 1H), 8.61 (s, 1H), 8.33-8.31 (m, 3H), 8.10-8.04 (m, 2H), 8.00 (br d, J = 7.6 Hz, 1H), 7.96-7.95 (m, 1H), 7.75-7.71 (m, 1H), 7.31-7.30 (m, 1H), 6.81-6.80 (m, 1H), 5.40-5.33 (m, 1H), 3.56 (s, 3H), 1.65 (d, J = 7.2 Hz, 3H)

#	LC-MS (m/z)	^{1}H NMR
23	457.1	^{1}H NMR (400 MHz, methanol-d$_4$) δ 7.83 - 7.82 (m, 1H), 7.68 (d, J = 8.8 Hz, 1H), 7.25 - 7.24 (m, 1H), 6.80 - 6.79 (m, 1H), 6.73 (d, J = 8.8 Hz, 1H), 4.69 (s, 2H), 4.17 - 4.09 (m, 2H), 3.35 (s, 3H), 2.90 - 2.86 (m, 1H), 2.46 - 2.43 (m, 1H), 2.15 - 2.00 (m, 3H), 1.92 - 1.71 (m, 6H), 1.60 - 1.45 (m, 2H), 1.09 - 0.99 (m, 1H)

Example 5. Preparation of N-((6-(3-(4-hydroxypiperidin-1-yl)phenyl)-1H-benzo[d]imidazol-2-yl)methyl)-1-(methylsulfonyl)-1H-pyrrole-3-carboxamide (Compound 8)

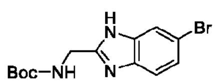


Step 1: Preparation of tert-butyl (2-((2-amino-5-bromophenyl)amino)-2-oxoethyl)carbamate



To a solution of 4-bromo-1,2-benzenediamine (2.0 g, 10.6 mmol), N-(tert-butoxycarbonyl)glycine (1.5 g, 8.8 mmol) and HATU (3.4 g, 8.8 mmol) in DMF (100 mL) was added DIPEA (3.5 mL, 35.3 mmol). After stirring overnight at room temperature, the reaction was quenched with saturated aqueous sodium bicarbonate resulting in a light brown precipitate. The precipitate was filtered off and washed with a small amount of water. The precipitate was collected and dried in vacuo, affording the title compound as a light brown powder (2.3 g, 76% yield) and used without further purification.

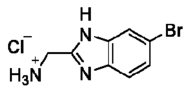
Step 2: Preparation of tert-butyl ((6-bromo-1H-benzo[d]imidazole-2-yl)methyl)carbamate (Intermediate 5)



Intermediate 5

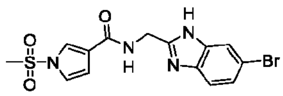
tert-Butyl (2-((2-amino-5-bromophenyl)amino)-2-oxoethyl)carbamate (2.0 g, 5.81 mmol) was dissolved in acetic acid (20 mL) and the reaction solution was heated at 60 °C. After 1.5 h, the reaction was cooled to room temperature and concentrated in vacuo resulting in a dark red solid. The crude product was dissolved in ethyl acetate and washed with saturated aqueous sodium bicarbonate and brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo affording **Intermediate 5** as a light brown powder (1.9 g, 5.82 mmol, 100%).

Step 3: Preparation of (6-bromo-1H-benzo[d]imidazol-2-yl)methanaminium chloride



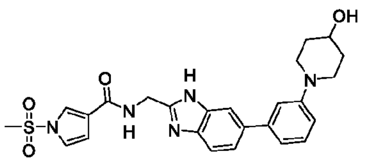
tert-Butyl ((6-bromo-1H-benzo[d]imidazole-2-yl)methyl)carbamate (1.9 g, 5.8 mmol) was suspended in a solution of 4 N HCl in 1,4-dioxane (14.5 mL, 58 mmol). After stirring overnight at room temperature, the reaction mixture was diluted with ether resulting in a white precipitate. The precipitate was filtered off and dried in vacuo affording the title compound as a white powder (1.6 g, 5.8 mmol, 100%).

Step 4: Preparation of N-((6-bromo-1H-benzo[d]imidazol-2-yl)methyl)-1-(methylsulfonyl)-1H-pyrrole-3-carboxamide



To a solution of 1-methylsulfonylpyrrole-3-carboxylic acid (216 mg, 1.14 mmol), EDCI (438 mg, 2.29 mmol), HOBt (309 mg, 2.29 mmol) and DIPEA (0.995 mL, 5.71 mmol) in DMF (3 mL) was added (6-bromo-1H-benzo[d]imidazol-2-yl)methanaminium chloride (300 mg, 1.14 mmol). After stirring at room temperature for 3 h, the reaction mixture was diluted with water and extracted three times with ethyl acetate; the combined organic layers were concentrated to afford a yellow oil. The oil was purified by reversed-phase HPLC to afford the title compound (280 mg, 658 μmol, 57.6% yield) as a white solid. LCMS (ESI) m/z: $[M+H]^+$ = 397.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.45 - 12.37 (m, 1H), 8.95 - 8.93 (m, 1 H), 7.86 - 7.85 (m, 1 H), 7.73 - 7.61 (m, 1 H), 7.51 - 7.40 (m, 1 H), 7.32 - 7.25 (m, 2 H), 6.80 - 6.79 (m, 1 H), 4.62 (d, J=5.2 Hz, 2 H), 3.56 (s, 3 H).

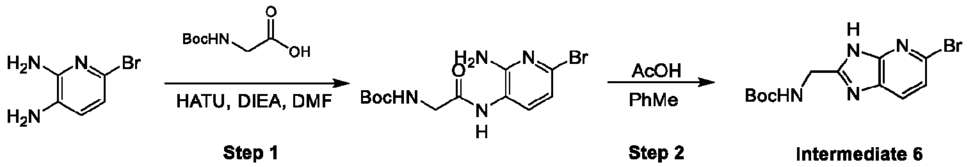
Step 5: Preparation of N-((6-(3-(4-hydroxypiperidin-1-yl)phenyl)-1H-benzo[d]imidazol-2-yl)methyl)-1-(methylsulfonyl)-1H-pyrrole-3-carboxamide (Compound 8)



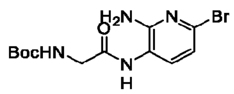
Compound 8

To a solution of N-((6-bromo-1H-benzo[d]imidazole-2-yl)methyl)-1-(methylsulfonyl)-1H-pyrrole-3-carboxamide (60 mg, 0.151 mmol), 1-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidin-4-ol (55.0 mg, 0.181 mmol) and K_3PO_4 (96.2 mg, 0.453 mmol,) in 1,4-dioxane (0.4 mL) and water (0.1 mL) was added [1,1′-bis(di-tert-butylphosphino)ferrocene]dichloropalladium (9.84 mg, 0.0151 μmol) at room temperature. After stirring at 80 °C for 2 h, the reaction mixture was diluted with water and extracted three times with ethyl acetate, the combined organic layers were concentrated to afford a black brown residue. The residue was purified by reversed-phase prep-HPLC to afford **Compound 8** (41.36 mg, 74.16 µmol, 49.10% yield, formic acid salt) as an off-white solid. LCMS (ESI) m/z: $[M+H]^+$=494.3. ^1H NMR (400 MHz, DMSO-d_6) δ 12.26 - 12.19 (m, 1 H), 8.93 - 8.90 (m, 1 H), 7.87 (s, 1 H), 7.75 - 7.61 (m, 1 H), 7.57 - 7.47 (m, 1 H), 7.42 - 7.41 (m, 1 H), 7.32 - 7.23 (m, 1 H), 7.27 - 7.23 (m, 1 H), 7.13 (s, 1 H), 7.02 (d, J = 7.2 Hz, 1 H), 6.90- 6.88 (m, 1 H), 6.81 (d, J = 2.4 Hz, 1 H), 4.65 (d, J = 5.6 Hz, 2 H), 3.63 - 3.58 (m, 3 H), 3.55 (s, 3 H), 2.92 - 2.87 (m, 2 H), 1.84 - 1.81 (m, 2 H), 1.53 - 1.44 (m, 2 H).

Example 6. Preparation of tert-butyl ((5-bromo-3H-imidazo[4,5-b]pyridin-2-yl)methyl)carbamate (Intermediate 6)

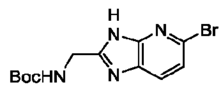


Step 1: Preparation of tert-butyl (2-((2-amino-6-bromopyridin-3-yl)amino)-2-oxoethyl)carbamate



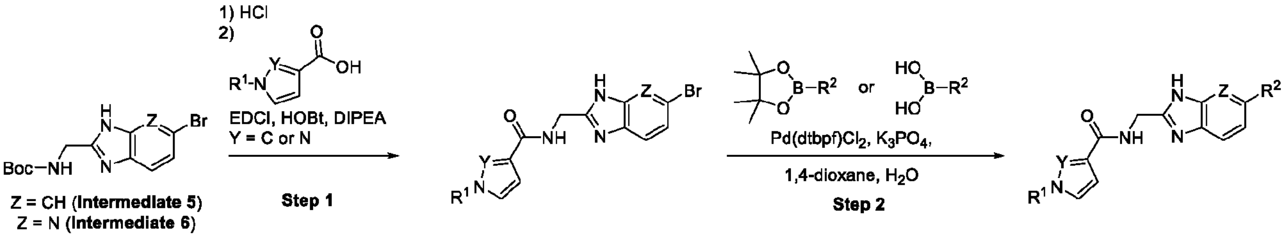
To a mixture of 2-(tert-butoxycarbonylamino)acetic acid (9.32 g, 53.2 mmol) in DMF (100 mL) was added HATU (30.3 g, 79.8 mmol), DIPEA (13.9 mL, 79.8 mmol) followed by 6-bromopyridine-2,3-diamine (10 g, 53.2 mmol). After stirring at room temperature for 2 h, the reaction mixture was added to water, and then extracted three times with ethyl acetate. The combined organic layers were washed twice with brine, filtered and concentrated under reduced pressure to give a residue. The residue was dissolved in ethyl acetate and recrystallized with petroleum ether at room temperature and washed with petroleum ether: ethyl acetate (5:1) to afford the title compound (11 g, 31.8 mmol, 59.8% yield) as a light yellow solid. LCMS (ESI) m/z: $[^{79}BrM+H]^+$ = 345.1. ^1H NMR (400 MHz, DMSO-d_6) δ 9.15 (s, 1H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.07 - 7.03 (m, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 6.27 (s, 2H), 3.73 (d, *J* = 6.0 Hz, 2H), 1.38 (s, 9H).

Step 2: Preparation of tert-butyl ((5-bromo-3H-imidazo[4,5-b]pyridin-2-yl)methyl)carbamate (Intermediate 6)



To a solution of tert-butyl (2-((2-amino-6-bromopyridin-3-yl)amino)-2-oxoethyl)carbamate (11 g, 31.9 mmol) in toluene (110 mL) was added acetic acid (40 mL). After stirring at 100 °C for 12 h, the reaction mixture was quenched by the addition of water at room temperature and extracted three times with ethyl acetate. The combined organic layers were washed twice with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a residue. The residue was purified by flash silica gel chromatography (50-100% ethyl acetate / petroleum ether gradient) to afford **Intermediate 5** (5 g, 15.3 mmol, 48.0% yield) as a yellow solid. LCMS (ESI) m/z: $[^{79}BrM+H]^+$ = 327.1. ^1H NMR (400 MHz, DMSO-d_6) δ 13.16 - 12.65 (m, 1H), 7.86 (d, *J* = 6.0 Hz, 1H), 7.48 (s, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 4.39 (d, *J* = 5.2 Hz, 2H), 1.41 (s, 9H).

Example 7: Preparation of Compounds 6, 7, 9, 10, 11, 15, and 30-60



Compounds 6, 7, 9, 10, 11, 15, and 30-60, shown in Table 3 below, were synthesized starting from **Intermediate 5 or 6**, the corresponding carboxylic acid, and the corresponding boronic acid or ester utilizing the synthetic protocol shown the scheme above.

Table 3

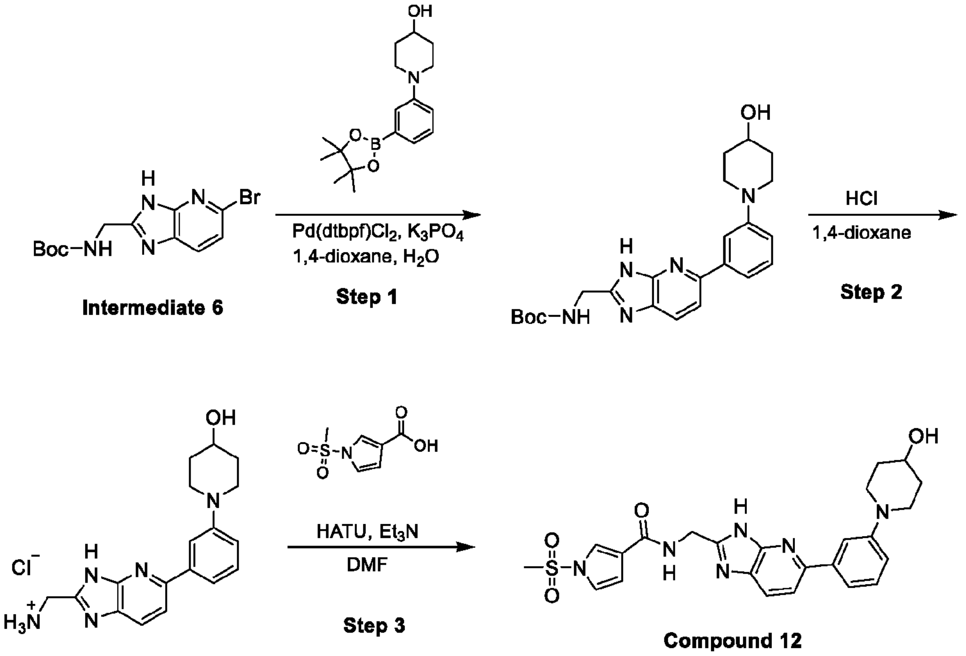
#	LC-MS (m/z)	^{1}H NMR
6	403.7	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 12.17 (br s, 1H), 8.55 (br t, 1H), 7.92 (d, J = 2.4 Hz, 1H), 7.60 – 7.54 (m, 3H), 7.46 (d, J = 8.2 Hz, 1H), 7.40 – 7.33 (m, 1H), 7.02 – 6.97 (m, 2H), 6.67 (d, J = 2.4Hz, 1H), 4.65, (d, J = 5.9 Hz, 2H), 3.77 (s, 3H), 1.56, (s, 9H)
7	450.3	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 12.28 - 12.24 (m, 1 H), 8.93 - 8.90 (m, 1 H), 7.87 (s, 1 H), 7.80 - 7.62 (m, 1 H), 7.59 - 7.48 (m, 1 H), 7.41 - 7.39 (m, 1 H), 7.32 - 7.30 (m, 1 H), 7.24 - 7.20 (m, 1 H), 8.95 (d, J = 7.6 Hz, 1 H), 6.81 (d, J = 1.2 Hz, 1 H), 6.61 (s, 1 H), 6.38 (d, J = 8.0 Hz, 1 H), 4.64 (d, J = 5.6 Hz, 2 H), 3.86 - 3.83 (m, 4 H), 3.56 (s, 3 H), 2.35 - 2.28 (m, 2 H)
9	451.0	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 13.27 - 12.10 (m, 1H), 9.05 - 8.80 (m, 1H), 7.99 - 7.83 (m, 4H), 7.64 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 2.8 Hz, 1H), 6.81 (s, 1H), 6.50 (d, J = 8.8 Hz, 2H), 4.64 (s, 2H), 3.87 (d, J = 7.2 Hz, 4H), 3.57 (s, 3H), 2.37 - 2.31 (m, 2H)
10	451.0	^{1}H NMR (400 MHz, DMSO-d$_6$, 80 °C) δ 8.61 - 8.46 (m, 1H), 7.99 - 7.83 (m, 2H), 7.69 (d, J = 8.4 Hz, 1H), 7.41 - 7.22 (m, 3H), 7.14 (s, 1H), 6.86 - 6.76 (m, 1H), 6.51 - 6.38 (m, 1H), 4.70 (d, J = 5.6 Hz, 2H), 3.91 (d, J = 7.2 Hz, 3H), 3.87 - 3.74 (m, 1H), 3.49 (s, 3H), 2.42 - 2.30 (m, 2H) ppm
11	508.3	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.21 - 9.19 (m, 1 H), 7.91 - 7.90 (m, 2 H), 7.77 (s, 2 H), 7.37 - 7.32 (m, 2 H), 7.21 (s, 1 H), 7.12 (d, J = 7.6 Hz, 1 H), 7.01 - 6.98 (m, 1 H), 6.81 - 6.80 (m, 1 H), 4.86 (d, J = 4.8 Hz, 2 H), 3.74 - 3.68 (m, 4 H), 3.59 (s, 3 H), 2.33 - 2.27 (m, 2 H), 1.17 (d, J = 6.0 Hz, 6 H)
15	486.2	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.47 - 8.43 (m, 1H), 7.72 (s, 1H), 7.58 - 7.52 (m, 2H), 7.45 - 7.41 (m, 1H), 7.31 - 7.26 (m, 1H), 7.17 (s, 1H), 7.07 (d, J = 8.0 Hz, 1H), 7.00 - 6.97 (m, 1H), 6.93 - 6.90 (m, 1H), 6.54 - 6.52 (m, 1H), 4.61 (d, J = 5.6 Hz, 2H), 3.75 - 3.66 (m, 4H), 2.34 - 2.27 (m, 2H), 1.49 (s, 9H), 1.17 (d, J = 6.4 Hz, 6H)
30	432.1	

#	LC-MS (m/z)	^{1}H NMR
31	442.2	
32	426.2	
33	427.2	
34	424.2	
35	437.2	
36	427.2	
37	413.2	
38	424.3	
39	398.2	
40	415.2	
41	424.2	

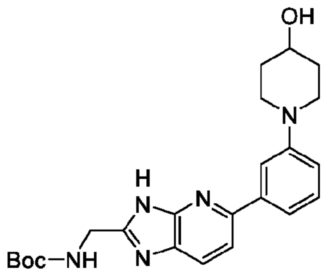
#	LC-MS (m/z)	^{1}H NMR
42	430.2	
43	398.2	
44	453.2	
45	415.2	
46	459.3	
47	413.2	
48	427.2	
49	441.2	
50	444.2	
51	424.2	
52	438.2	

#	LC-MS (m/z)	^{1}H NMR
53	412.2	
54	439.2	
55	459.3	
56	418.2	
57	438.2	
58	417.2	
59	447.2	
60	438.1	

Example 8. Preparation of N-((5-(3-(4-hydroxypiperidin-1-yl)phenyl)-3H-imidazo[4,5-b]pyridin-2-yl)methyl)-1-(methylsulfonyl)-1H-pyrrole-3-carboxamide (Compound 12)

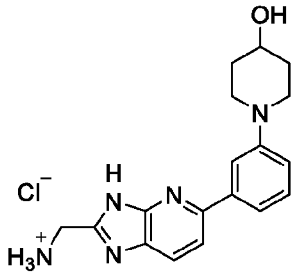


Step 1: Preparation of tert-butyl ((5-(3-(4-hydroxypiperidin-1-yl)phenyl)-3H-imidazo[4,5-b]pyridin-2-yl)methyl)carbamate



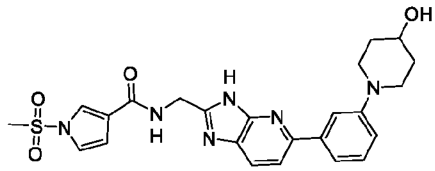
To a mixture of **Intermediate 6** (200 mg, 0.611 mmol) and 1-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidin-4-ol (204 mg, 0.672 mmol) in 1,4-dioxane (3 mL) and water (0.5 mL) was added K_3PO_4 (324 mg, 1.53 mmol) and [1,1'-bis(di-tert-butylphosphino)ferrocene]dichloropalladium (199 mg, 0.305 mmol) at 10 °C. After stirring at 80 °C for 15 h, the mixture was added to water and then extracted three times with ethyl acetate; the combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to get the crude product. The crude product was purified by reversed-phase prep-HPLC (0.1% FA condition). The solution was concentrated to afford the title compound (90 mg, 162 μmol, 26.4% yield) as a white solid. LCMS (ESI) m/z: $[M+H]^+$ = 424.2. ^1H NMR (400 MHz, Methanol-d_4) δ 7.97 - 7.95 (m, 1H), 7.78 - 7.67 (m, 2H), 7.47-7.45 (m, 1H), 7.35 - 7.33 (m, 1H), 7.05 - 7.03 (m, 1H), 4.54 (s, 2H), 3.83 - 3.75 (m, 1H), 3.68 - 3.65 (m, 2H), 3.03 - 2.90 (m, 2H), 2.07 - 1.93 (m, 2H), 1.77 - 1.61 (m,2H), 1.48 (s, 9H).

Step 2: Preparation of (5-(3-(4-hydroxypiperidin-1-yl)phenyl)-3H-imidazo[4,5-b]pyridin-2-yl)methanaminium chloride



A mixture of tert-butyl ((5-(3-(4-hydroxypiperidin-1-yl)phenyl)-3H-imidazo[4,5-b]pyridin-2-yl)methyl)carbamate (90 mg, 0.213 mmol) in a solution of 4 M HCl in 1,4-dioxane (2 mL, 8 mmol) was stirred at 15 °C. After 2 h, the mixture was concentrated to afford the title compound (60 mg) as a brown solid. LCMS (ESI) m/z: $[M+H]^+$ = 324.1.

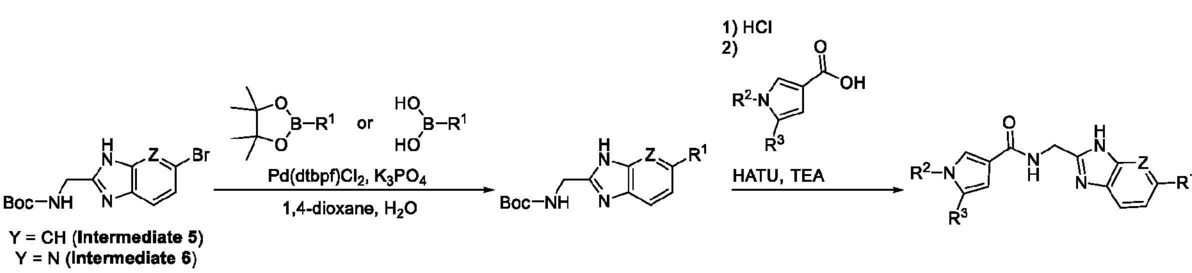
Step 3: Preparation of N-((5-(3-(4-hydroxypiperidin-1-yl)phenyl)-3H-imidazo[4,5-b]pyridin-2-yl)methyl)-1-(methylsulfonyl)-1H-pyrrole-3-carboxamide (Compound 12)



Compound 12

A mixture of 1-methylsulfonylpyrrole-3-carboxylic acid (35 mg, 0.185 mmol), HATU (106 mg, 0.278 mmol), and Et_3N (0.0773 mL , 0.555 mmol) in DMF (1 mL) was stirred at 10 °C. After 10 min, (5-(3-(4-hydroxypiperidin-1-yl)phenyl)-3H-imidazo[4,5-b]pyridin-2-yl)methanaminium chloride (60 mg) was added to the reaction mixture. After stirring at at 15 °C for 2 h, the mixture was filtered off and the filtrate was purified by reversed-phase prep-HPLC (water:ACN:FA) to afford **Compound 12** (22.1 mg, 40.8 μmol, 22.1% yield, formic acid salt) as a white solid. LCMS (ESI) m/z: $[M+H]^+$ = 495.2 ^1H NMR (400 MHz, DMSO-d_6) δ 8.91 (br s, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.87 - 7.86 (m, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.66 (s, 1H), 7.44 (d, J = 6.8 Hz, 1H), 7.34 - 7.24 (m, 2H), 6.98 (d, J = 7.2 Hz, 1H), 6.80 - 6.79 (m, 1H), 4.66 (d, J = 5.6 Hz, 2H), 3.68 - 3.53 (m, 6H), 2.94 - 2.89 (m, 2H), 1.86 - 1.83 (m, 2H), 1.58 - 1.43 (m, 2H).

Example 9. Preparation of Compounds 13, 14, and 16-19

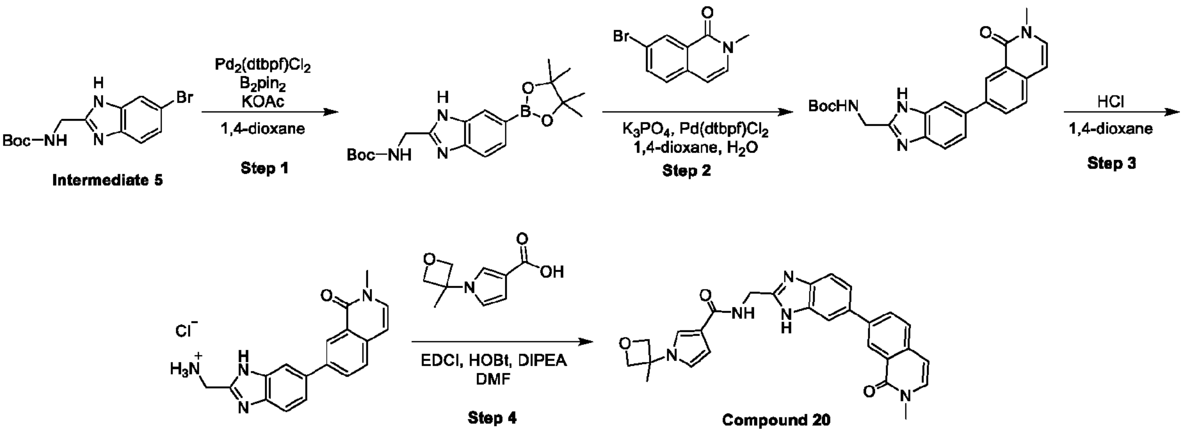


Compounds 13, 14, and 16 to 19, shown in Table 4 below, were synthesized starting from **Intermediate 5** or **6**, the appropriate boronic ester, and the corresponding carboxylic acid utilizing the synthetic protocol shown in the scheme above.

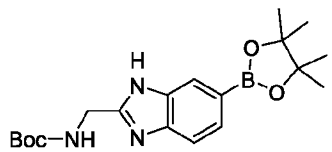
Table 4

#	LC-MS (m/z)	^{1}H NMR
13	509.2	1H NMR (400 MHz, DMSO-d_6) δ 8.95 (s, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.89 - 7.88 (m, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.65 (s, 1H),7.50 (d, J = 7.6 Hz, 1H), 7.38 - 7.29 (m, 2H), 7.02 (d, J = 8.0 Hz, 1H), 6.81 - 6.80 (m, 1H), 4.69 (d, J = 5.6 Hz, 2H), 3.77 - 3.71 (m, 2H), 3.69 - 3.66 (m, 2H), 3.57 (s, 3H), 2.35 - 2.30 (m, 2H), 1.19 - 1.18 (m, 6H)
14	509.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.96 (br s, 1H), 8.91 (s, 1H), 7.97 (d, J = 8.8 Hz, 2H), 7.89 - 7.88 (m, 2H), 7.69 (d, J = 8.4 Hz, 1H), 7.38 - 7.29 (m, 1H), 7.04 (d, J = 8.8 Hz, 2H), 6.82 - 6.81 (m, 1H), 4.65 (d, J = 5.6 Hz, 2H), 3.75 - 3.65 (m, 4H), 3.60 - 3.56 (m, 3H), 2.31 - 2.29 (m, 2H), 1.18 (d, J = 6.0 Hz, 6H)
16	403.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.19 (s, 1H), 8.47 - 8.43 (m, 1H), 7.81 - 7.65 (m, 1H), 7.60 - 7.43 (m, 3H), 7.39 - 7.34 (m, 1H), 7.25 - 7.18 (m, 2H), 6.99 - 6.97 (m, 1H), 6.92 - 6.89 (m, 1H), 6.54 - 6.52 (m, 1H), 4.62 (d, J = 6.0 Hz, 2H), 3.83 (s, 3H), 1.49 (s, 9H)
17	439.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.36 - 12.23 (m, 1H), 8.86 - 8.85 (m, 1H), 7.77 - 7.73 (m, 2H), 7.56 (d, J = 7.2 Hz, 1H), 7.46 - 7.43 (m, 1H), 7.38 - 7.34 (m, 1H), 7.23 - 7.17 (m, 2H), 6.91 - 6.88 (m, 1H), 6.52 (s, 1H), 4.62 (d, J = 5.6 Hz, 2H), 3.82 (s, 3H), 3.52 (s, 3H), 2.40 (s, 3H)
18	496.2	^{1}H NMR (400 MHz, methanol-d_4) δ 7.96 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.68 (s, 1H), 7.59 - 7.58 (m, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.35 - 7.34 (m, 1H), 7.05 - 6.98 (m, 2H), 6.65 - 6.64 (m, 1H), 4.81 (s, 2H), 3.88 - 3.78 (m, 2H), 3.63 (d, J = 10.8 Hz, 2H), 2.42 - 2.37 (m, 2H), 1.82 - 1.72 (m, 4H), 1.25 (d, J = 6.0 Hz, 6H)
19	487.2	^{1}H NMR (400 MHz, methanol-d_4) δ 7.96 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.68 (d, *J* = 1.6 Hz, 1H), 7.60 - 7.59 (m, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.35 - 7.34 (m, 1H), 7.02 - 7.01 (m, 1H), 6.95 - 6.93 (m, 1H), 6.59 - 6.58 (m, 1H), 4.80 (s, 2H), 3.89 - 3.77 (m, 2H), 3.63 (d, *J* = 10.8 Hz, 2H), 2.44 - 2.35 (m, 2H), 1.55 (s, 9H), 1.25 (d, *J* = 6.4 Hz, 6H)

Example 10. Preparation of N-((6-(2-methyl-1-oxo-1,2-dihydroisoquinolin-7-yl)-1H-benzo[d]imidazol-2-yl)methyl)-1-(3-methyloxetan-3-yl)-1H-pyrrole-3-carboxamide (Compound 20)

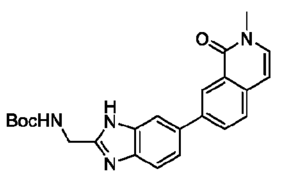


Step 1: Preparation of tert-butyl N-[[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzimidazol-2-yl]methyl]carbamate



To a mixture of tert-butyl ((6-bromo-1H-benzo[d]imidazol-2-yl)methyl)carbamate (5 g, 15.33 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (9.73 g, 38.3 mmol) in 1,2-dimethoxyethane (100 mL) was added Pd(dppf)Cl_2 (2.80 g, 3.83 mmol) and KOAc (4.51 g, 46.0 mmol) at room temperature and the mixture was stirred at 100 °C. After 15 h, the mixture was added to water and then extracted three times with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford the crude product. The residue was purified by silica gel column chromatography (petroleum ether / ethyl acetate = 5/1 to 1/1) to afford the title compound (5.5 g, 11.2 mmol, 73.1% yield) as a yellow solid. LCMS (ESI) m/z: $[M+H]^+$ = 374.1.

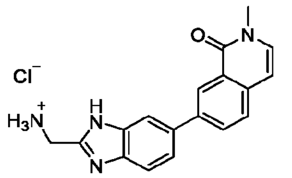
Step 2: Preparation of tert-butyl ((6-(2-methyl-1-oxo-1,2-dihydroisoquinolin-7-yl)-1H-benzo[d]imidazol-2-yl)methyl)carbamate



A mixture of 7-bromo-2-methyl-1(2H)-isoquinolinone (1 g, 4.20 mmol), tert-butyl ((6-(2-methyl-1-oxo-1,2-dihydroisoquinolin-7-yl)-1H-benzo[d]imidazol-2-yl)methyl)carbamate (1.57 g, 4.20 mmol), K_3PO_4 (2.67 g, 12.6 mmol) and [1,1′-bis(di-tert-butylphosphino)ferrocene]dichloropalladium (274 mg, 0.420 mmol) in 1,4-dioxane (10 mL) and water (4 mL) was stirred at 80 °C under a N_2 atmosphere. After 12 h, the reaction mixture was poured into water and extracted three times with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (0-44% methanol / ethyl acetate) to afford the title compound (800 mg, 1.98 mmol, 47.1% yield) as a yellow solid. LCMS

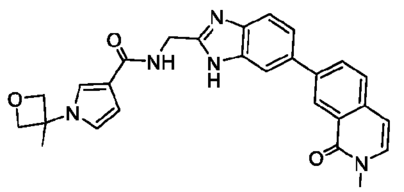
(ESI) m/z: $[M+H]^+$ = 405.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.25 (d, J = 6.4 Hz, 1H), 8.42 (s, 1H), 8.03 - 7.99 (m, 1H), 7.84 - 7.69 (m, 2H), 7.63 - 7.47 (m, 2H), 7.46 - 7.43 (m, 2H), 6.64 - 6.61 (m, 1H), 4.35 (d, J = 6.0 Hz, 2H), 3.50 (s, 3H), 1.39 (s, 9H).

Step 3: Preparation of (6-(2-methyl-1-oxo-1,2-dihydroisoquinolin-7-yl)-1H-benzo[d]imidazol-2-yl)methanaminium chloride



To a mixture of tert-butyl ((6-(2-methyl-1-oxo-1,2-dihydroisoquinolin-7-yl)-1H-benzo[d]imidazol-2-yl)methyl)carbamate (800 mg, 1.98 mmol) in 1,4-dioxane (8 mL) was added a solution of 4 M HCl in 1,4-dioxane (8 mL, 32 mmol). After stirring at room temperature for 12 h, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was poured into dimethyl sulfoxide, stirred for 30 min and filtered to afford the title compound (450 mg, 1.32 mmol, 66.8% yield) as a yellow solid. LCMS (ESI) m/z: $[M+H]^+$ = 305.1.

Step 4: Preparation of N-((6-(2-methyl-1-oxo-1,2-dihydroisoquinolin-7-yl)-1H-benzo[d]imidazol-2-yl)methyl)-1-(3-methyloxetan-3-yl)-1H-pyrrole-3-carboxamide (Compound 20)



Compound 20

A mixture of (6-(2-methyl-1-oxo-1,2-dihydroisoquinolin-7-yl)-1H-benzo[d]imidazol-2-yl)methanaminium chloride (50 mg, 0.147 mmol), 1-(3-methyloxetan-3-yl)pyrrole-3-carboxylic acid (26.6 mg, 0.147 mmol), HOBt (29.7 mg, 0.220 mmol), EDCI (42.2 mg, 0.220 mmol) and DIPEA (0.128 mL, 0.734 mmol) in DMF (1 mL) was stirred at room temperature. After 12 h, the mixture was poured into water and methanol. The solution was purified by reversed-phase prep-HPLC (water:ACN:NH_4OH) to afford **Compound 20** (23.2 mg, 0.0497 mmol, 33.9% yield) as a colorless oil. LCMS (ESI) m/z: $[M+H]^+$ = 468.0. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.27 (s, 1H), 8.58 - 8.55 (m, 1H), 8.46 (d, J = 2.0 Hz, 1H), 8.07 - 8.02 (m, 1H), 7.89 - 7.73 (m, 2H), 7.65 - 7.52 (m, 3H), 7.50 - 7.47 (m, 1H), 7.04 - 7.02 (m, 1H), 6.66 (d, J = 7.2 Hz, 1H), 6.63 - 6.61 (m, 1H), 4.84 (d, J = 6.4 Hz, 2H), 4.66 - 4.62 (m, 4H), 3.54 (s, 3H), 1.79 (s, 3H).

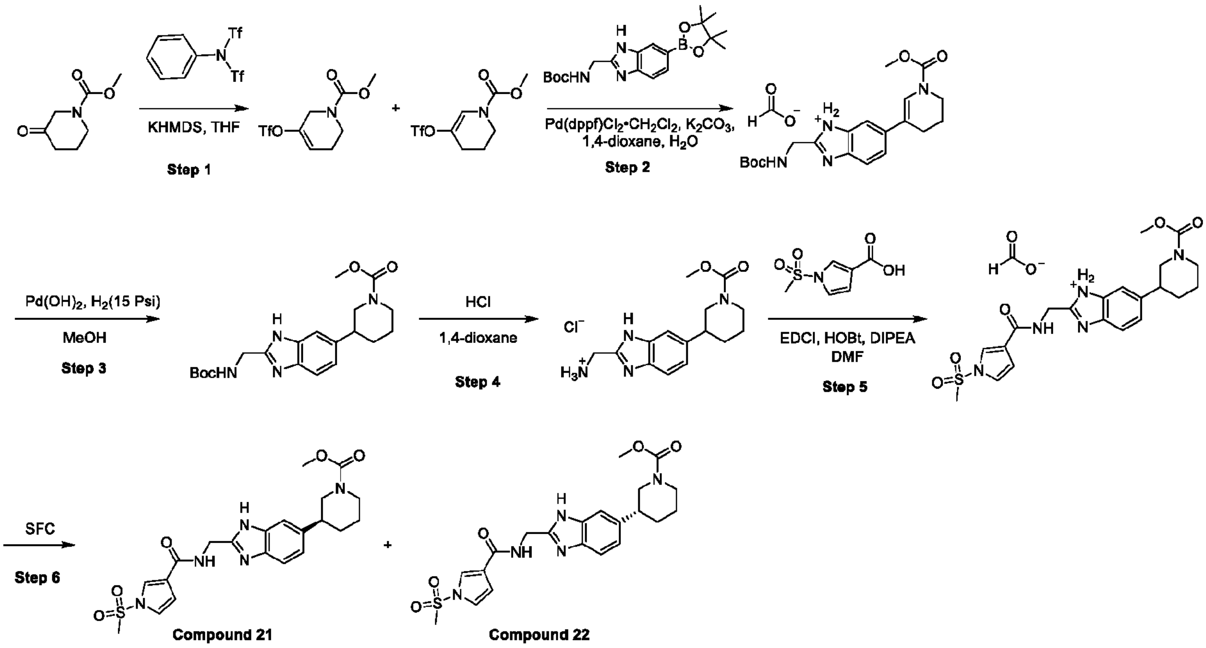
Example 11. Preparation of Compound 24

Compound 24, shown in Table 5 below, was synthesized starting from the appropriate common intermediate (6-(2-methyl-1-oxo-1,2-dihydroisoquinolin-7-yl)-1H-benzo[d]imidazol-2-yl)methanaminium chloride and 1-(isopropylsulfonyl)-1H-pyrrole-3-carboxylic acid utilizing the synthetic protocol described in Example 10 above.

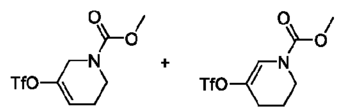
Table 5

#	LC-MS (m/z)	¹H NMR
24	504.0	¹H NMR (400 MHz, DMSO-d_6) δ 12.41 - 12.32 (m, 1H), 8.99 - 8.96 (m, 1H), 8.45 (d, J = 2.0 Hz, 1H), 8.16 (s, 1H), 8.06 - 8.03 (m, 1H), 7.86 - 7.73 (m, 3H), 7.63 - 7.60 (m, 1H), 7.58 - 7.53 (m, 1H), 7.48 (d, J = 7.2 Hz, 1H), 7.29 - 7.28 (m, 1H), 6.84 - 6.83 (m, 1H), 6.65 (d, J = 7.2 Hz, 1H), 4.67 (d, J = 6.0 Hz, 2H), 3.90 - 3.83 (m, 1H), 3.54 (s, 3H), 1.24 - 1.21 (m, 6H)

Example 12: Preparation of (S)-methyl 3-(2-((1-(methylsulfonyl)-1H-pyrrole-3-carboxamido)methyl)-1H-benzo[d]imidazol-6-yl)piperidine-1-carboxylate (Compound 21) and (R)-methyl 3-(2-((1-(methylsulfonyl)-1H-pyrrole-3-carboxamido)methyl)-1H-benzo[d]imidazol-6-yl)piperidine-1-carboxylate (Compound 22)



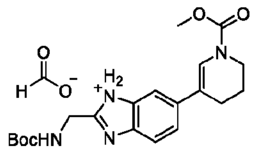
Step 1: methyl 5-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate and methyl 5-(((trifluoromethyl)sulfonyl)oxy)-3,4-dihydropyridine-1(2H)-carboxylate



To a cooled solution (-78 °C) of 1 M KHMDS (350 mL, 350 mmol) in THF (400 mL) was added a solution of methyl 3-oxopiperidine-1-carboxylate (44 g, 280 mmol) dissolved in THF(400 mL) dropwise. After stirring at -78 °C for 0.5 h, a solution of 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)-methanesulfonamide (125 g, 350 mmol) dissolved in THF (500 mL) was added drop wise to the reaction mixture and the mixture was warmed to room temperature. After 2 h, the mixture was washed with water and extracted three times with dichloromethane. The combined organic phase was washed three times with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether / ethyl acetate =

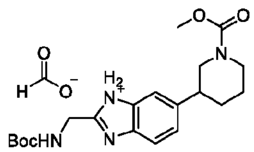
20/1 to 10/1) to afford a mixture of title compounds (80.4 g, 144 mmol, 51.6% yield, 52% purity) as a yellow oil. LCMS (ESI) m/z: $[M+H]^+$ = 290.0.

Step 2: Preparation of 2-(((tert-butoxycarbonyl)amino)methyl)-6-(1-(methoxycarbonyl)-1,4,5,6-tetrahydropyridin-3-yl)-1H-benzo[d]imidazol-1-ium formate



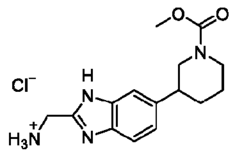
A mixture of methyl 5-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate and methyl 5-(((trifluoromethyl)sulfonyl)oxy)-3,4-dihydropyridine-1(2H)-carboxylate (1.12 g, 2.01 mmol), tert-butyl N-[[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzimidazol-2-yl]methyl]carbamate (500 mg, 1.34 mmol), K_2CO_3 (555 mg, 4.02 mmol) and bis(diphenylphosphino)ferrocene palladium dichloromethane (109 mg, 0.134 mmol) in 1,4-dioxane (10 mL) and water (2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C under a N_2 atmosphere. After for 12 h, the reaction mixture was poured into water and extracted three times with ethyl acetate. The combined organic layers dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (0-20% methanol/dichloromethane). The crude product was further purified by reversed phase chromatography and concentrated under reduced pressure to remove acetonitrile. The solution was extracted three times with ethyl acetate and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the title compound (150 mg, 0.347 mmol, 25.9% yield) as a black brown oil. LCMS (ESI) m/z: $[M+H]^+$ = 387.1. ^1H NMR (400 MHz, DMSO-d_6) δ 12.91 - 12.48 (m, 1H), 8.13 (s, 1H), 7.49 - 7.42 (m, 3H), 7.30 - 7.21 (m, 1H), 6.25 (s, 1H), 4.37 - 4.30 (m, 4H), 3.65 (s, 3H), 3.55 - 3.51 (m, 2H), 2.29 (d, J = 3.6 Hz, 2H), 1.42 (s, 9H).

Step 3: Preparation of 2-(((tert-butoxycarbonyl)amino)methyl)-6-(1-(methoxycarbonyl) -piperidin-3-yl)-1H-benzo[d]imidazol-1-ium formate



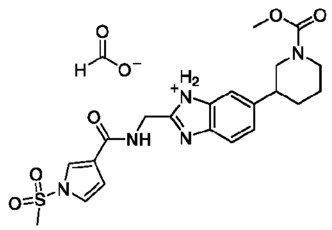
To a solution of 2-(((tert-butoxycarbonyl)amino)methyl)-6-(1-(methoxycarbonyl)-1,4,5,6-tetrahydropyridin-3-yl)-1H-benzo[d]imidazol-1-ium formate (130 mg, 0.301 mmol) in methanol (0.5 mL) was added 50% $Pd(OH)_2$ (50 mg, 0.178 mmol) under N_2. The suspension was degassed under vacuum and purged with H_2 several times and stirred under H_2 (15 psi) at room temperature. After 16 h, the mixture combined with another batch was filtered with celatom and washed three times with methanol and ethyl acetate. The filtrate was concentrated under reduced pressure to afford the title compound (130 mg) as a brown solid. LCMS (ESI) m/z: $[M+H]^+$ = 389.1. ^1H NMR (400 MHz, DMSO-d_6) δ 12.66 - 12.61 (m, 1H), 8.13 (s, 1H), 7.52 - 7.38 (m, 2H), 7.36 (s, 1H), 7.18 - 7.04 (m, 1H), 4.33 (d, J = 6.0 Hz, 2H), 4.10 - 3.71 (m, 3H), 3.67 - 3.56 (m, 4H), 2.71 - 2.66 (m, 1H), 1.92 (d, J = 10.8 Hz, 1H), 1.76 - 1.68 (m, 2H), 1.56 - 1.46 (m, 1H), 1.44 - 1.39 (m, 9H).

Step 4: Preparation of (6-(1-(methoxycarbonyl)piperidin-3-yl)-1H-benzo[d]imidazol-2-yl)-methanaminium chloride



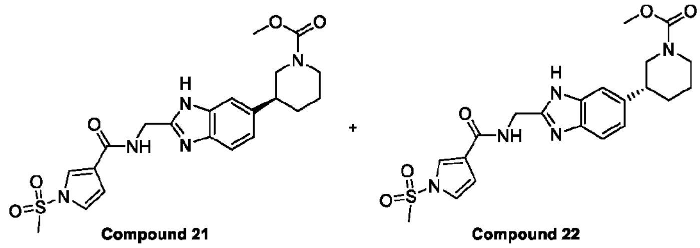
A mixture of **2-(((tert-butoxycarbonyl)amino)methyl)-6-(1-(methoxycarbonyl)piperidin-3-yl)-1H-benzo[d]imidazol-1-ium formate** (110 mg, 0.253 mmol) in a solution of 4 M HCl in 1,4-dioxane (2 mL, 8 mmol) was stirred at room temperature. After 0,5 h, the reaction mixture concentrated under reduced pressure to afford the title compound (110 mg) as a yellow solid which was used in the next step directly. LCMS (ESI) m/z: $[M+H]^+$ = 289.1.

Step 5: Preparation of 6-(1-(methoxycarbonyl)piperidin-3-yl)-2-((1-(methylsulfonyl)-1H-pyrrole-3-carboxamido)methyl)-1H-benzo[d]imidazol-1-ium formate



A mixture of (6-(1-(methoxycarbonyl)piperidin-3-yl)-1H-benzo[d]imidazol-2-yl)-methanaminium chloride (110 mg, 0.339 mmol), 1-methylsulfonylpyrrole-3-carboxylic acid (70.5 mg, 0.373 mmol), EDCI (130 mg, 0.677 mmol), HOBt (91.5 mg, 0.677 mmol) and DIPEA (177 µL , 1.02 mmol) in DMF (2 mL) was stirred at room temperature. After 2 h, the reaction mixture was partitioned between ethyl acetate and water. The organic phase was separated, washed three times with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by reversed-phase prep-HPLC (water:ACN:FA) to afford the title compound (37.4 mg, 74.0 µmol, 21.9% yield, formic acid salt) as a white solid. LCMS (ESI) m/z: $[M+H]^+$ = 459.9. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.26 - 8.16 (m, 1H), 7.88 - 7.82 (m, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.42 (s, 1H), 7.27 - 7.26 (m, 1H), 7.16 (d, J = 8.0 Hz, 1H), 6.82 - 6.81 (m, 1H), 4.77 (s, 2H), 4.25 - 4.10 (m, 2H), 3.70 (s, 3H), 3.37 (s, 3H), 3.00 - 2.82 (m, 2H), 2.77 (s, 1H), 2.09 - 1.99 (m, 1H), 1.88 - 1.72 (m, 2H), 1.61 (d, J = 12.0 Hz, 1H).

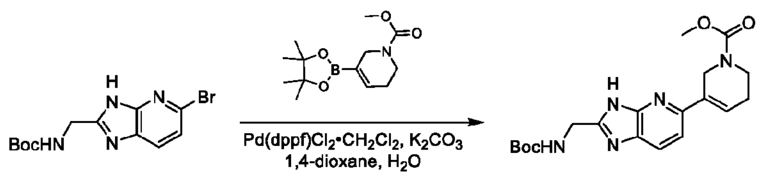
Step 6: Preparation of (S)-methyl 3-(2-((1-(methylsulfonyl)-1H-pyrrole-3-carboxamido)methyl)-1H-benzo[d]imidazol-6-yl)piperidine-1-carboxylate (Compound 21) and (R)-methyl 3-(2-((1-(methylsulfonyl)-1H-pyrrole-3-carboxamido)methyl)-1H-benzo[d]imidazol-6-yl)piperidine-1-carboxylate (Compound 22)



Compound 21 Compound 22

6-(1-(methoxycarbonyl)piperidin-3-yl)-2-((1-(methylsulfonyl)-1H-pyrrole-3-carboxamido)methyl)-1H-benzo[d]imidazol-1-ium formate (37.4 mg, 0.0740 mmol) was subjected to chiral SFC to afford **Compound 21** (10.2 mg, 0.0220 mmol) as an off-white solid and **Compound 22** (10.5 mg, 0.0228 mmol) as an off-white solid. **Compound 21**: LCMS (ESI) m/z: $[M+H]^+$ = 460.4; ^{1}H NMR (400 MHz, methanol-d_4) δ 7.85 - 7.84 (m, 1H), 7.57 - 7.34 (m, 2H), 7.27 - 7.26 (m, 1H), 7.15 (d, J = 8.0 Hz, 1H), 6.83 - 6.82 (m, 1H), 4.76 (s, 2H), 4.26 - 4.09 (m, 2H), 3.70 (s, 3H), 3.37 (s, 3H), 2.98 - 2.83 (m, 2H), 2.82 - 2.71 (m, 1H), 2.09 - 1.99 (m, 1H), 1.87 - 1.74 (m, 2H), 1.68 - 1.53 (m, 1H). **Compound 22**: LCMS (ESI) m/z: $[M+H]^+$ = 460.4; ^{1}H NMR (400 MHz, methanol-d_4) δ 7.86 - 7.85 (m, 1H), 7.56 - 7.32 (m, 2H), 7.27 - 7.26 (m, 1H), 7.16 (d, J = 8.0 Hz, 1H), 6.83 - 6.82 (m, 1H), 4.77 (s, 2H), 4.19 - 4.15 (m, 2H), 3.70 (s, 3H), 3.37 (s, 3H), 2.99 - 2.82 (m, 2H), 2.81 - 2.72 (m, 1H), 2.09 - 2.00 (m, 1H), 1.88 - 1.75 (m, 2H), 1.68 - 1.56 (m, 1H).

Example 13. Preparation of methyl 3-(2-(((tert-butoxycarbonyl)amino)methyl)-3H-imidazo[4,5-b]pyridin-5-yl)-5,6-dihydropyridine-1(2H)-carboxylate



Intermediate 6

A mixture of Intermediate 6 (500 mg, 1.53 mmol), methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro-2H-pyridine-1-carboxylate (449 mg, 1.68 mmol), dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium dichloromethane (125 mg, 0.153 mmol), and K_2CO_3 (634 mg, 4.58 mmol) in 1,4-dioxane (5 mL) and water (1 mL) was degassed and purged with N_2 three times, and then stirred at 80 °C for under a N_2 atmosphere. After 12 h, the reaction mixture was diluted with water and extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (0-100% ethyl acetate / petroleum ether) to afford the title compound (140 mg, 0.361 mmol, 23.7% yield) as a colorless oil. LCMS (ESI) m/z: $[M+H]^+$ = 388.3. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.18 - 12.05 (m, 1H), 7.96 - 7.76 (m, 1H), 7.53 (d, J = 8.4 Hz, 2H), 6.79 - 6.64 (m, 1H), 4.46 (s, 2H), 4.46 - 4.34 (m, 2H), 3.70 - 3.62 (m, 3H), 3.54 (d, J = 5.6 Hz, 2H), 2.39 - 2.30 (m, 2H), 1.42 (d, J = 4.0 Hz, 9H).

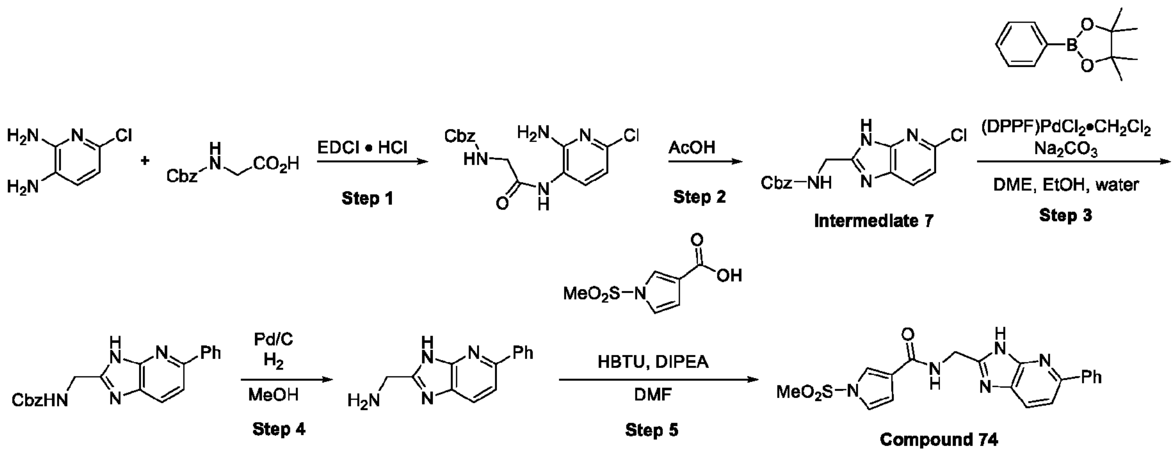
Example 14. Preparation of Compounds 25 and 26

Compounds 25 and 26, shown in Table 6, below were synthesized starting from intermediate 6 and the corresponding cyclohexenes utilizing the synthetic protocol described in Example 12 above.

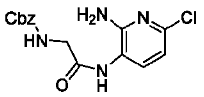
Table 6

#	LC-MS (m/z)	^{1}H NMR
25	461.1	^{1}H NMR (400 MHz, methanol-d$_4$) δ 7.87 (d, *J* = 2.0 Hz, 2H), 7.30 - 7.28 (m, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 6.84 - 6.83 (m, 1H), 4.81 (s, 2H), 4.35 - 4.07 (m, 2H), 3.71 (s, 3H), 3.39 (s, 3H), 3.25 - 3.05 (m, 1H), 2.98 - 2.92 (m, 2H), 2.18 - 2.03 (m, 1H), 1.98 - 1.74 (m, 2H), 1.65 - 1.61 (m, 1H)
26	461.1	^{1}H NMR (400 MHz, methanol-d$_4$) δ 7.85 (s, 2H), 7.27 (s, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 6.82 (s, 1H), 4.81 (s, 2H), 4.36 - 4.04 (m, 2H), 3.71 (s, 3H), 3.39 (s, 3H), 3.19 - 3.02 (m, 1H), 2.99 - 2.79 (m, 2H), 2.15 - 1.99 (m, 1H), 1.96 - 1.74 (m, 2H), 1.71 - 1.52 (m, 1H)

Example 15. Preparation of 1-(methylsulfonyl)-N-((5-phenyl-3H-imidazo[4,5-b]pyridin-2-yl)methyl)-1H-pyrrole-3-carboxamide (Compound 74)

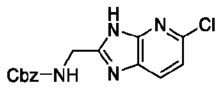


Step 1: Preparation of benzyl (2-((2-amino-6-chloropyridin-3-yl)amino)-2-oxoethyl)carbamate



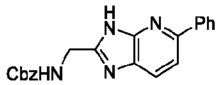
To a solution of 6-chloropyridine-2,3-diamine (2.0 g, 13.9 mmol) and ((benzyloxy)carbonyl)glycine (2.9 g, 13.9 mmol) in pyridine (46.3 mL) was added N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (7.99 g, 41.7 mmol). After stirring at room temperature overnight, the reaction mixture was diluted with water and ethyl acetate. The organic layer was washed twice with water and brine and dried with anhydrous sodium sulfate. Salts were removed via vacuum filtration and volatile material were removed using a rotary evaporator. The residue was triturated with dichloromethane to afford the title compound (3.49 g, 10.4 mmol, 75% yield). LCMS (ESI) m/z: [M+H]$^+$ = 334.6.

Step 2: Preparation of benzyl ((5-chloro-3H-imidazo[4,5-b]pyridin-2-yl)methyl)carbamate (Intermediate 7)



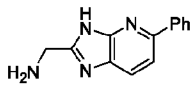
A suspension of benzyl (2-((2-amino-6-chloropyridin-3-yl)amino)-2-oxoethyl)carbamate (2.53 g, 7.55 mmol) in acetic acid (15.1 mL) was irradiated at 150 °C in a microwave reactor. After 1 h, the resulting solution was poured into water and the precipitate was collected via vacuum filtration. The off-white/pink solid was washed with water, dichloromethane and acetonitrile and dried vacuum to afford the title compound (1.65 g, 5.22 mmol, 69% yield). LCMS $(M+H)^+$ = 316.6.

Step 3: Preparation of benzyl ((5-phenyl-3H-imidazo[4,5-b]pyridin-2-yl)methyl)carbamate



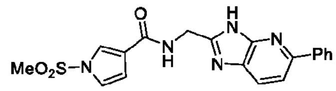
To a microwave reaction vial containing benzyl ((5-chloro-3H-imidazo[4,5-b]pyridin-2-yl)methyl)carbamate (300 mg, 0.947 mmol), phenylboronic acid pinacol ester (250 mg, 1.22 mmol), dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium dichloromethane adduct (154 mg, 0.189 mmol), and sodium carbonate (200 mg, 1.89 mmol) was added degassed 1,2-dimethoxyethane (12 mL), ethanol (4 mL) and water (1 mL). The reaction mixture was irradiated at 120 °C in a microwave reactor. After 3 h, the reaction mixture was diluted with water and ethyl acetate and filtered through a pad of Celite. The layers were separated, and the organic layer was washed with brine and the brine layer was extracted once with ethyl acetate. The combined organic layers were dried with anhydrous sodium sulfate and salts were removed via vacuum filtration. Volatile materials were removed using a rotary evaporator. The resulting residue was purified via silica gel flash chromatography (15% to 50% ethyl acetate in dichloromethane) to yield the title compound (162 mg, 0.430 mmol, 45.4% yield). LCMS (ESI) m/z: $[M+H]^+$ = 358.6.

Step 4: Preparation of (5-phenyl-3H-imidazo[4,5-b]pyridin-2-yl)methanamine



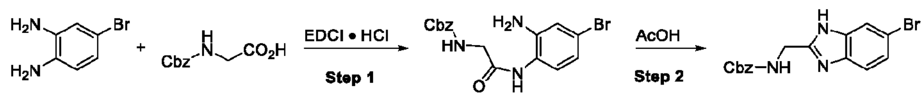
To a mixture of benzyl ((5-phenyl-3H-imidazo[4,5-b]pyridin-2-yl)methyl)carbamate (153 mg, 0.426 mmol) in methanol (5.3 mL) was added 10% Pd/C (9.0 mg, 0.0284 mmol). After the suspension was stirred under a balloon of hydrogen at room temperature overnight, the reaction mixture was filtered through a pad of Celite. Volatile materials were removed using a rotary evaporator to afford the crude title product (51.6 mg, 66.4% yield), which was used without further purification. LCMS (ESI) m/z: $[M+H]^+$= 171.9.

Step 5: Preparation of 1-(methylsulfonyl)-N-((5-phenyl-3H-imidazo[4,5-b]pyridin-2-yl)methyl)-1H-pyrrole-3-carboxamide (Compound 74)



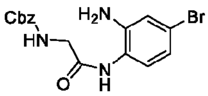
To a solution of (5-phenyl-3H-imidazo[4,5-b]pyridin-2-yl)methanamine (35.1 mg, 0.157 mmol) and 1-(methylsulfonyl)-1H-pyrrole-3-carboxylic acid (44.4 mg, 0.235 mmol) in DMF (2 mL) was added DIPEA (0.082 mL, 0.471 mmol) and HBTU (89.1 mg, 0.235 mmol). After stirring overnight at room temperature, the reaction mixture was diluted with water and ethyl acetate. The layers were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed twice with water and once with brine. The organic layers were dried with anhydrous sodium sulfate and salts were removed via vacuum filtration. Volatile materials were removed using a rotary evaporator. The resulting residue was purified via an automated reversed-phase prep-HPLC to yield **Compound 74** (12.1 mg, 0.0307 mmol, 19.5% yield) as a white powder. LCMS (ESI) m/z: $[M+H]^+$ = 395.6. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.93 (s, 1H), 8.12 – 8.05 (m, 2H), 7.98 (t, J = 2.0 Hz, 1H), 7.88 (t, J = 2.0 Hz, 1H), 7.78 (d, J = 8.3 Hz, 1H), 7.48 (dd, J = 8.4, 6.9 Hz, 2H), 7.42 – 7.35 (m, 1H), 7.32 (dd, J = 3.3, 2.3 Hz, 1H), 6.81 (dd, J = 3.4, 1.6 Hz, 1H), 4.67 (d, J = 5.6 Hz, 2H), 3.56 (s, 3H).

Example 16. Preparation of benzyl ((6-bromo-1H-benzo[d]imidazol-2-yl)methyl)carbamate (Intermediate 8)



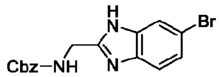
Intermediate 8

Step 1: Preparation of benzyl (2-((2-amino-4-bromophenyl)amino)-2-oxoethyl)carbamate



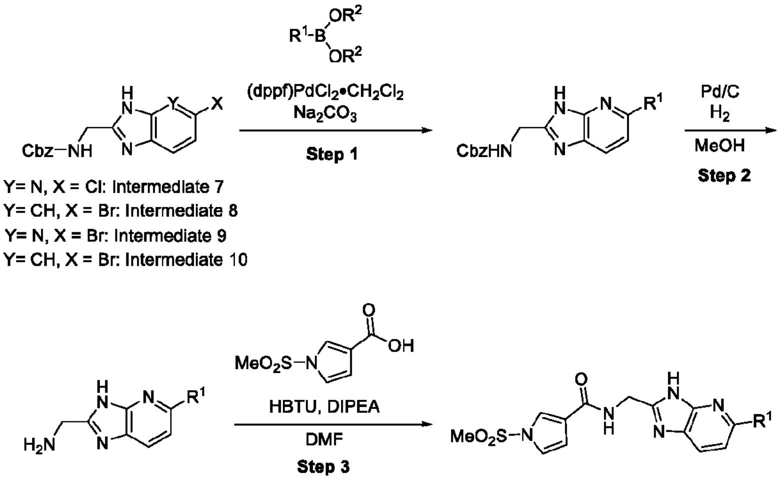
To a solution of 6-chloropyridine-2,3-diamine (2.0 g, 13.9 mmol) and ((benzyloxy)carbonyl)glycine (2.9 g, 13.9 mmol) in pyridine (46.3 mL) was added N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (7.99 g, 41.7 mmol). After stirring overnight at room temperature, the reaction mixture was diluted with water and ethyl acetate. The organic layer was washed twice with water and diluted with brine. The resulting emulsion was filtered through a pad of Celite and the organic layer was dried with anhydrous sodium sulfate. Salts were removed via vacuum filtration and volatile material was removed using a rotary evaporator. The residue was purified by silica gel flash chromatography (20% to 100% ethyl acetate in dichloromethane). The residue was suspended in methanol and solids were removed via vacuum filtration. The filtrate was concentrated to afford the title compound (1.31 g, 3.46 mmol, 32.7% yield). LCMS (ESI) m/z: $[M+H]^+$= 377.6 and 378.4.

Step 2: Preparation of benzyl ((6-bromo-1H-benzo[d]imidazol-2-yl)methyl)carbamate (Intermediate 8)



A suspension of benzyl (2-((2-amino-4-bromophenyl)amino)-2-oxoethyl)carbamate (2.53 g, 7.55 mmol) in acetic acid (15.1 mL) was irradiated at 150 °C in a microwave reactor. After 1 h, the resulting solution was diluted with water and ethyl acetate. To this mixture was slowly added sodium carbonate (10 g). The layers were separated, and the organic layer was washed with saturated aqueous sodium bicarbonate, brine and dried with anhydrous sodium sulfate. Volatile materials were removed using a rotary evaporator. The resulting residue was purified via silica gel flash chromatography (0% to 4% methanol in dichloromethane) to afford **Intermediate 8** (967 mg, 2.68 mmol). LCMS $(M+H)^+$: 359.6 and 361.6.

Example 17. Preparation of Compounds 27 to 29



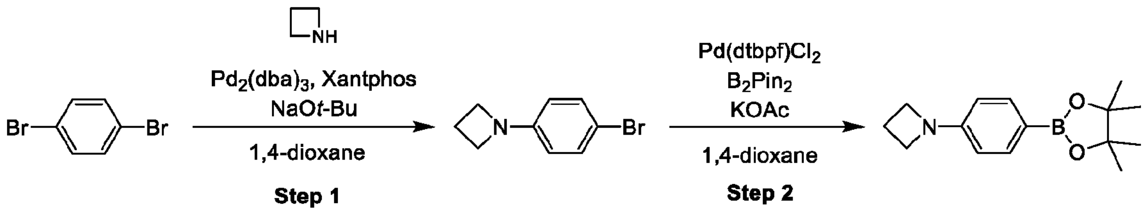
Compounds 27 to 29, shown in Table 7 below, were each synthesized starting from the **Intermediates 7**, **8**, **9**, or **10**, and the appropriate boronic acid using the synthetic protocol shown in the scheme above.

Table 7

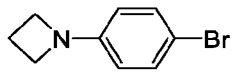
#	LC-MS (m/z)	^{1}H NMR
27	395.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.94 (t, *J* = 5.8 Hz, 1H), 8.20 (d, *J* = 1.1 Hz, 1H), 7.88 (t, *J* = 2.0 Hz, 1H), 7.73 (s, 1H), 7.68 – 7.63 (m, 2H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.51 – 7.42 (m, 3H), 7.35 – 7.27 (m, 2H), 6.82 (dd, *J* = 3.3, 1.6 Hz, 1H), 4.65 (d, *J* = 5.7 Hz, 2H), 3.56 (s, 3H)
28	480.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.14 (s, 1H), 12.60 (s, 1H), 8.94 (dt, *J* = 37.4, 5.7 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 8.07 (s, 1H), 7.99 (dd, *J* = 41.8, 8.4 Hz, 1H), 7.91 – 7.84 (m, 2H), 7.62 (td, *J* = 8.0, 2.6 Hz, 1H), 7.40 (d, *J* = 5.8 Hz, 1H), 7.32 (ddd, *J* = 5.7, 3.2, 2.3 Hz, 1H), 6.81 (ddd, *J* = 7.1, 3.3, 1.7 Hz, 1H), 4.68 (dd, *J* = 14.1, 5.7 Hz, 2H), 3.57 (d, *J* = 1.6 Hz, 3H)

#	LC-MS (m/z)	^{1}H NMR
29	480.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.09 (s, 1H), 12.57 (s, 1H), 8.93 (dt, *J* = 38.3, 5.7 Hz, 1H), 8.21 (dd, *J* = 8.8, 3.2 Hz, 2H), 7.98 (dd, *J* = 41.7, 8.3 Hz, 1H), 7.88 (dt, *J* = 4.2, 2.0 Hz, 1H), 7.82 (dd, *J* = 8.3, 5.2 Hz, 1H), 7.47 (dd, *J* = 8.8, 2.9 Hz, 2H), 7.32 (ddd, *J* = 5.7, 3.1, 2.2 Hz, 1H), 6.81 (ddd, *J* = 7.1, 3.4, 1.6 Hz, 1H), 4.67 (dd, *J* = 13.7, 5.7 Hz, 2H), 3.56 (s, 3H)

Example 18. Preparation of 1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]azetidine

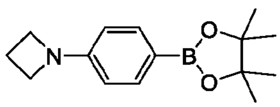


Step 1: Preparation of 1-(4-bromophenyl)azetidine



To a mixture of azetidine (0.0944 mL, 1.40 mmol), 1,4-dibromobenzene (0.163 mL, 1.27 mmol), (5-diphenylphosphanyl-9,9-dimethyl-xanthen-4-yl)-diphenyl-phosphane (147 mg, 0.254 mmol) and tris(dibenzylideneacetone)dipalladium(0) (116 mg, 0.127 mmol) in 1,4-dioxane (3 mL) was added *t*-BuONa (367 mg, 3.82 mmol) under a N_2 atmosphere. After stirring at 60 °C for 2 h, the reaction mixture was diluted with methanol, filtered and concentrated under reduced pressure to afford a residue. The residue was purified by silica gel flash chromatography (0-50% ethyl acetate / petroleum ether gradient) to afford the title compound (200 mg, 0.943 mmol, 74.2% yield) as a yellow solid. LCMS (ESI) m/z: $[M+H]^+$ = 211.8. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 - 7.05 (m, 2H), 6.37 - 6.12 (m, 2H), 3.77 (d, J = 7.2 Hz, 4H), 2.32 - 2.25 (m, 2H).

Step 2: Preparation of 1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]azetidine

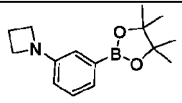
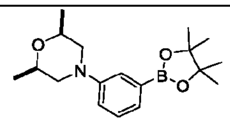
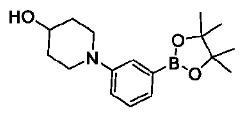
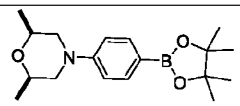


A mixture of 1-(4-bromophenyl)azetidine (150 mg, 0.707 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (180 mg, 0.707 mmol), KOAc (208 mg, 2.12 mmol) and [1,1′-bis(di-tert-butylphosphino)ferrocene]dichloropalladium(II) (46.1 mg, 0.0707 mmol) in 1,4-dioxane (1 mL) was degassed and purged with N_2 three times. After stirring at 80 °C for 2 h under a N_2 atmosphere, the reaction mixture was diluted with water and extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a residue. The residue was purified by silica gel flash chromatography (0-30% ethyl acetate / petroleum ether gradient) to afford the title compound (150 mg, 0.579 mmol, 81.8% yield) as a yellow solid. LCMS (ESI) m/z: $[M+H]^+$ = 260.0. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.4 Hz, 2H), 6.40 - 6.29 (m, 2H), 3.84 (d, *J* = 7.2 Hz, 4H), 2.34 - 2.26 (m, 2H), 1.25 (s, 12H).

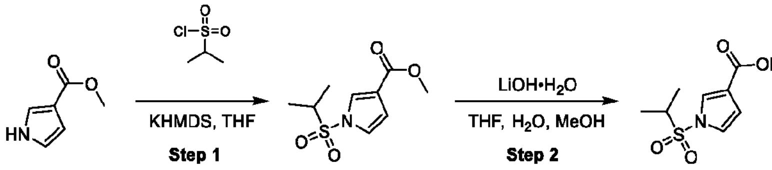
Example 19. Preparation of 1-(3-(4,4,5,5,-tetramethyl-1,3,2-dioxaboronlan-2-yl)phenyl)azetidine, (2S,6R)-2,6-dimethyl-4-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholine, 1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidin-4-ol, and (2S,6R)-2,6-dimethyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholine

The compounds shown in Table 8 below were each synthesized utilizing the synthetic protocol described in Example 18 above from the appropriate dibromobenzene and azetidine, 2,6-dimethylmorpholine, or 4-hydroxypiperidine.

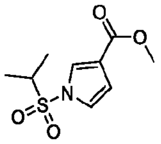
Table 8

Structure	LC-MS (m/z)	^{1}H NMR
 1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaboronlan-2-yl)phenyl)azetidine	260.0	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 - 7.09 (m, 2H), 6.81 (d, J = 2.4 Hz, 1H), 6.50 - 6.47 (m, 1H), 3.82 (d, J = 7.2 Hz, 4H), 2.34 - 2.21 (m, 2H), 1.27 (s, 12H)
 (2S,6R)-2,6-dimethyl-4-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholine	318.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 - 7.26 (m, 3H), 7.06 - 6.99 (m, 1H), 3.87 - 3.75 (m, 2H), 3.55 - 3.46 (m, 2H), 2.50 - 2.36 (m, 2H), 1.36 (s, 12H), 1.29 - 1.28 (m, 6H)
 1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidin-4-ol	304.1	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 2.0 Hz, 1H), 7.32 - 7.23 (m, 2H), 7.09 - 7.02 (m, 1H), 3.88 - 3.78 (m, 1H), 3.64 - 3.53 (m, 2H), 2.98 - 2.87 (m, 2H), 2.04 - 1.98 (m, 2H), 1.75 - 1.64 (m, 2H), 1.34 (s, 12H)
 (2S,6R)-2,6-dimethyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholine	318.2	

Example 20. Preparation of 1-(isopropylsulfonyl)-1H-pyrrole-3-carboxylic acid

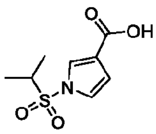


Step 1: Preparation of methyl 1-(isopropylsulfonyl)-1H-pyrrole-3-carboxylate



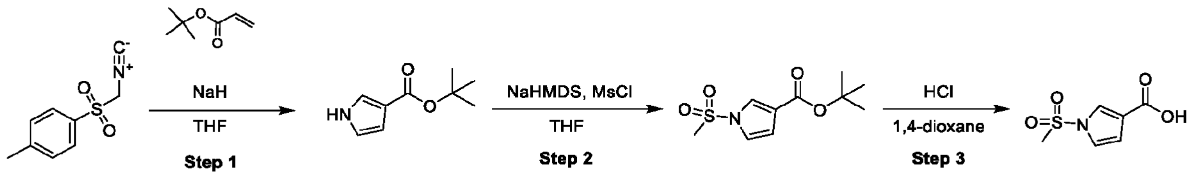
To a cooled solution (0 °C) of methyl 1H-pyrrole-3-carboxylate (2 g, 16.0 mmol) in THF (20 mL) was added a 1 M solution of KHMDS (32.0 mL, 32 mL). After stirring at 0 °C for 30 min, propane-2-sulfonyl chloride (1.96 mL, 17.6 mmol) was added to the reaction mixture and the mixture was warmed to room temperature. After 15.5 h, the reaction mixture was poured into water slowly and extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford a residue. The residue was purified by silica gel flash chromatography (0-30% ethyl acetate / petroleum ether gradient) to afford the title compound (1.2 g, 5.19 mmol, 32.5% yield) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 - 7.69 (m, 1H), 7.07 - 7.06 (m, 1H), 6.75 - 6.73 (m, 1H), 3.85 (s, 3H), 3.49 - 3.39 (m, 1H), 1.35 (d, J = 6.8 Hz, 6H).

Step 2: Preparation of 1-(isopropylsulfonyl)-1H-pyrrole-3-carboxylic acid

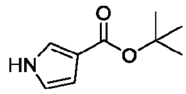


To a mixture of methyl 1-(isopropylsulfonyl)-1H-pyrrole-3-carboxylate (500 mg, 2.16 mmol) in THF (10 mL) and methanol (5 mL) was added a solution of $LiOH•H_2O$ (272 mg, 6.49 mmol) dissolved in water (5 mL). After stirring at room temperature for 2 h, the reaction mixture was acidified with 1 N HCl to pH = 3 and extracted three times with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by reversed phase chromatography and concentrated under reduced pressure to remove acetonitrile. The solution was extracted three times with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the title compound (400 mg, 1.84 mmol, 85.2% yield) as a white solid. LCMS (ESI) m/z: $[M+H]^+$ = 218.0. ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 - 7.78 (m, 1H), 7.11 - 7.09 (m, 1H), 6.80 - 6.78 (m, 1H), 3.50 - 3.43 (m, 1H), 1.37 (d, J = 6.8 Hz, 6H).

Example 21. Preparation of 1-(methylsulfonyl)-1H-pyrrole-3-carboxylic acid

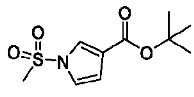


Step 1: Preparation of tert-butyl 1H-pyrrole-3-carboxylate



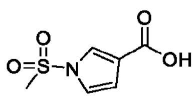
To a mixture of tert-butyl prop-2-enoate (78.6 mL, 542 mmol) and 1-(isocyanomethylsulfonyl)-4-methylbenzene (106 g, 542 mmol) in THF (1300 mL) was added 60% NaH in mineral oil (25.97 g, 649 mmol) slowly at 30 °C over 1 h and then heated to 70 °C. After 2 h, the reaction mixture was poured into saturated aqueous NH_4Cl solution and extracted three times with ethyl acetate. The combined organic phase was washed twice with brine, dried over anhydrous Na_2SO_4,,filtered and concentrated under reduced pressure to afford a residue. The residue was purified by silica gel column chromatography (petroleum ether / ethyl acetate =20:1-3:1) to afford the title compound (41.5 g, 236 mmol, 43% yield) as a yellow solid. LCMS (ESI) m/z $[M+Na]^+$ = 180.4. ^1H NMR (400 MHz, $CDCl_3$) δ 8.36 (br s, 1H), 7.35 - 7.25 (m, 1H), 6.71 - 6.62 (m, 1H), 6.59 - 6.49 (m, 1H), 1.48 (s, 9H).

Step 2: Preparation of tert-butyl 1-methylsulfonylpyrrole-3-carboxylate



To a cooled solution (0 °C) of tert-butyl 1H-pyrrole-3-carboxylate (40.5 g, 242 mmol) in THF (1500 mL) was added a 1 M solution of NaHMDS (484 mL, 484 mmol). After stirring at 0 °C for 30 min, methanesulfonyl chloride (28.1 mL, 363 mmol) slowly and the mixture was warmed to 30 °C. After 16 h, the reaction mixture was slowly poured into saturated aqueous NH_4Cl solution and extracted three times with ethyl acetate. The combined organic layers were washed twice with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford a residue. The residue was purified by silica gel chromatography (petroleum ether / ethyl acetate = 10/1) to afford a yellow solid. The yellow solid was triturated with methyl tert-butyl ether at room temperature for 20 min, filtered and dried in vacuum to afford the title compound (25.7 g, 105 mmol, 43 % yield) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.66-7.64 (m, 1H), 7.10-7.08 (m, 1H), 6.73-6.71 (m, 1H), 3.21 (s, 3H), 1.56 (s, 9H).

Step 3: Preparation of 1-methylsulfonylpyrrole-3-carboxylic acid



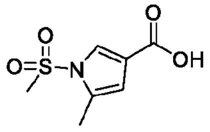
To a mixture of tert-butyl 1-methylsulfonylpyrrole-3-carboxylate (25.7 g, 105 mmol) in 1,4-dioxane (100 mL) was added a 4 M solution of HCl in 1,4-dioxane (400 mL, 1.6 mol) at 15 °C. After stirring at 15 °C for 14 h, the reaction mixture was concentrated under reduced pressure to afford a residue. The residue was triturated with methyl tert-butyl ether at 15 °C for 16 h. The mixture was filtered and dried in vacuum to afford the title compound (18.7 g, 98.8 mmol, 94 % yield) as a white solid. LCMS (ESI) m/z

$[M+H]^+$ = 189.8. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.78-7.77 (m, 1H), 7.25-7.23 (m, 1H), 6.72-6.70 (m, 1H), 3.37 (s, 3H).

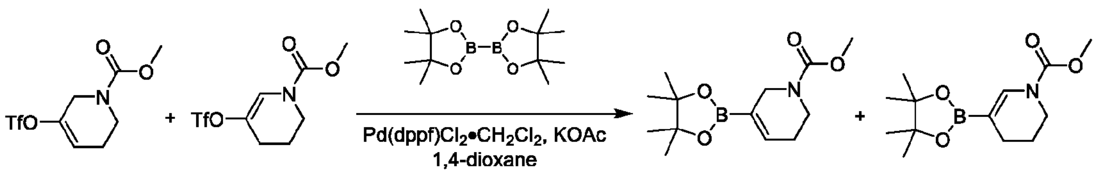
Example 22. Preparation of 5-methyl-1-(methylsulfonyl)-1H-pyrrole-3-carboxylic acid

The compound shown in Table 9 below was synthesized using an analogous method to the method described in Example 21 above.

Table 9

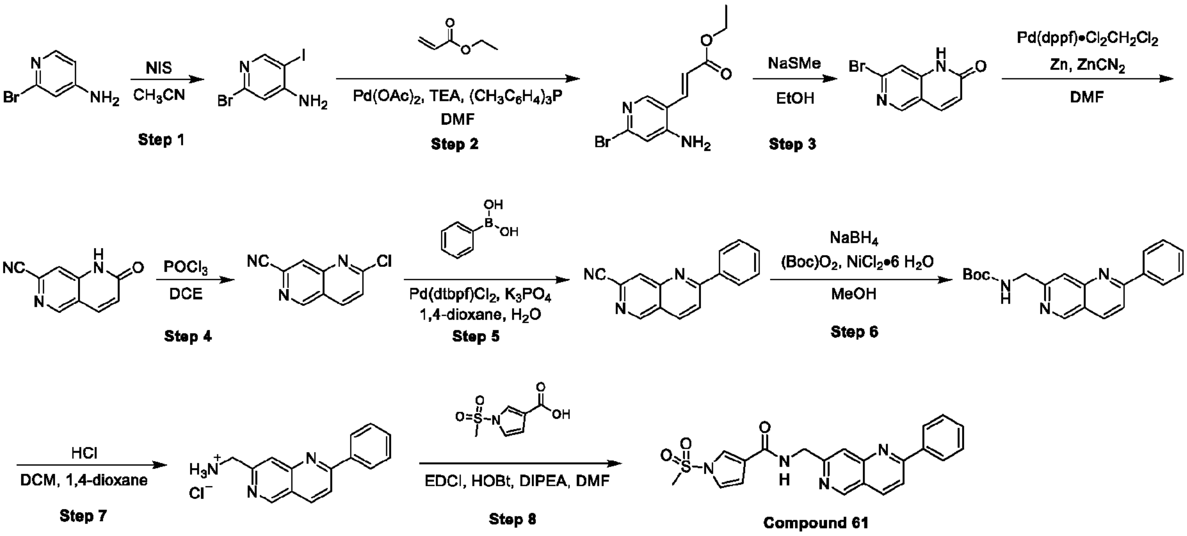
Structure	LC-MS (m/z)	^{1}H NMR
	204.1	^{1}H NMR (400 MHz, methanol-d_4) δ 7.69 (d, *J* = 1.6 Hz, 1H), 6.41 (s, 1H), 3.35 (s, 3H), 2.44 (d, *J* = 0.8 Hz, 3H)

Example 23. Preparation of methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate and methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydropyridine-1(2H)-carboxylate



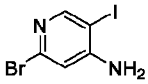
To a mixture of methyl 3-(((trifluoromethyl)sulfonyl)oxy)-5,6-dihydropyridine-1(2H)-carboxylate (75 g, 135 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (37.7 g, 148 mmol) in 1,4-dioxane (600 mL) was added KOAc (39.7 g, 405 mmol) and Pd(dppf)Cl_2•CH_2Cl_2 (5.51 g, 6.74 mmol) at room temperature under a N_2 atmosphere. After stirring at 80 °C for 3 h, the reaction mixture was diluted with water and extracted three times with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel flash chromatography (0-30% ethyl acetate / petroleum ether gradient) to give methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (13 g, 48.7 mmol, 36.1% yield) as a white solid and methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydropyridine-1(2H)-carboxylate (9.2 g, 34.4 mmol, 25.5% yield) as a yellow oil.

Example 24. Preparation of 1-(methylsulfonyl)-N-((2-phenyl-1,6-naphthyridin-7-yl)methyl)-1H-pyrrole-3-carboxamide (Compound 61)



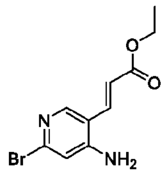
Compound 61

Step 1: Preparation of 2-bromo-5-iodopyridin-4-amine



To a solution of 2-bromopyridin-4-amine (80 g, 347mmol) in acetonitrile (2000 mL) was added NIS (125 g, 555 mmol) at 80 °C. After stirring at 80 °C for 16 h, additional NIS (52.0 g, 231 mmol) was added to the reaction and stirred at 80 °C. After 4 h, additional NIS (52.0 g, 231 mmol) was added to the mixture was stirred at 80 °C. After stirring an additional 16 h, the reaction mixture was concentrated under reduced pressure. The residue was diluted with saturated aqueous Na_2SO_3 and extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether / ethyl acetate = 20:3) to afford the title compound (75 g, 251 mmol, 54.3% yield) as a light yellow solid. LCMS (ESI) m/z: $[^{79}BrM+H]^+$ = 299.0. ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 6.78 (s, 1H), 4.75 (br s, 2H).

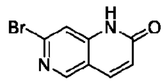
Step 2: Preparation of (E)-ethyl 3-(4-amino-6-bromopyridin-3-yl)acrylate



To a solution of 2-bromo-5-iodopyridin-4-amine (120 g, 401 mmol) in DMF (1200 mL) was added ethyl prop-2-enoate (87.3 mL, 803 mmol), TEA (83.82 mL, 602 mmol), $Pd(OAc)_2$ (4.51 g, 20.1 mmol) and tri-o-tolylphosphine (12.2 g, 40.2 mmol) under N_2. The mixture was stirred at 100 °C under N_2. After 3 h, the reaction mixture was diluted with water and extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether / ethyl acetate = 20:3) to afford the title compound (100 g, 369 mmol, 91.9% yield) as a light yellow solid. LCMS (ESI) m/z:

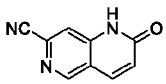
[^{79}BrM+H]$^+$ = 271.0. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 1H), 7.73 (d, *J* = 16.0 Hz, 1H), 6.90 - 6.67 (m, 3H), 6.52 (d, *J* = 16.0 Hz, 1H), 4.20 - 4.15 (m, 2H), 1.26 - 1.23 (m, 3H).

Step 3: Preparation of 7-bromo-1,6-naphthyridin-2(1H)-one



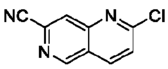
To a solution of (E)-ethyl 3-(4-amino-6-bromopyridin-3-yl)acrylate (90 g, 332 mmol) in ethanol (450 mL) was added NaSMe (59.0 g, 855.38 mmol) and the mixture was stirred at 60 °C. After 2 h, the reaction mixture was diluted with water and neutralized with 1 N HCl to pH 7.0. The mixture was filtered and the filter cake was washed with methyl tert-butyl ether and dried under reduced pressure to afford the title compound (60 g, 264 mmol, 79.5% yield) as a brown solid. LCMS (ESI) m/z: [^{79}BrM+H]$^+$ = 225. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.09 (br s, 1H), 8.65 (s, 1H), 7.99 (d, *J* = 9.6 Hz, 1H), 7.36 (s, 1H), 6.62 (d, *J* = 9.6 Hz, 1H).

Step 4: Preparation of 2-oxo-1,2-dihydro-1,6-naphthyridine-7-carbonitrile



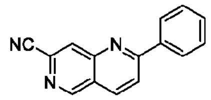
To a solution of 7-bromo-1,6-naphthyridin-2(1H)-one (50 g, 222 mmol), Pd(dppf)Cl_2•CH_2Cl_2 (5.01 g, 6.13 mmol) and $Zn(CN)_2$ (39.1 g, 333 mmol) in DMF (1000 mL) was added Zn powder (2.91 g, 44.4 mmol) under N_2. The mixture was degassed and purged with N_2 for 3 times and stirred at 85 °C under N_2 atmosphere. After 2 h, the reaction mixture was diluted with water and extracted seven times with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was triturated with methanol. The suspension was filtered, and the filter cake was washed with methyl tert-butyl ether and dried under reduced pressure to afford the title compound (32 g, 187 mmol, 84.2% yield) as an off-white solid. LCMS (ESI) m/z: [M+H]$^+$ = 172.2. ^{1}H NMR (400 MHz, DMSO-d6) δ 12.36 (br s, 1H), 8.96 (s, 1H), 8.08 (d, *J* = 9.6 Hz, 1H), 7.66 (s, 1H), 6.76 (d, *J* = 9.6 Hz, 1H).

Step 5: Preparation of 2-chloro-1,6-naphthyridine-7-carbonitrile



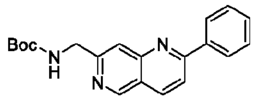
To a solution of 2-oxo-1,2-dihydro-1,6-naphthyridine-7-carbonitrile (28 g, 164 mmol) in 1,2-dichloroethane (700 mL) was added $POCl_3$ (76.0 mL, 818 mmol) and the mixture was stirred at 60 °C. After 14 h, additional of $POCl_3$ (150 mL, 1.61 mol) was added to the reaction mixture. After stirring at 60 °C for an additional 2 h, the reaction mixture was added into ice water drop wise. The resulting mixture was basified with solid $NaHCO_3$ to pH = 7.0 and filtered to give a filter cake. The solid was triturated with ethyl acetate. The solid was collected with filtered and dried under reduced pressure to afford the title compound (23 g, 119 mmol, 73.0% yield) as an off-white solid. LCMS (ESI) m/z: [M+H]$^+$ = 190.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.57 (s, 1H), 8.79 (d, *J* = 8.8 Hz, 1H), 8.68 (s, 1H), 7.99 (d, *J* = 8.8 Hz, 1H).

Step 6: Preparation of 2-phenyl-1,6-naphthyridine-7-carbonitrile



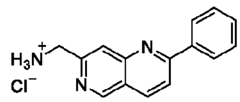
A mixture of 2-chloro-1,6-naphthyridine-7-carbonitrile (300 mg, 1.58 mmol), phenylboronic acid (289 mg, 2.37 mmol), [1,1'-bis(di-tert-butylphosphino)ferrocene]dichloropalladium (103 mg, 0.158 mmol) and K_3PO_4 (1.01 g, 4.75 mmol) in dioxane (9 mL) and H_2O (1.8 mL) was degassed and purged with N_2 for 3 times, and then stirred at 60 °C under N_2 atmosphere. After 3 h, water was added to the mixture, and then extracted three times with ethyl acetate. The combined organic layer was dried over Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by silica gel flash chromatography (0-50% ethyl acetate / petroleum ether gradient) to afford the title compound (395 mg, 1.54 mmol, 97.2% yield) as an off-white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.30 (d, J = 0.8 Hz, 1H), 8.47 - 8.39 (m, 2H), 8.28 - 8.15 (m, 3H), 7.63 - 7.54 (m, 3H).

Step 7: Preparation of tert-butyl ((2-phenyl-1,6-naphthyridin-7-yl)methyl)carbamate



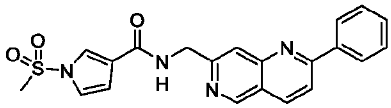
To a cooled solution (-10 °C) of 2-phenyl-1,6-naphthyridine-7-carbonitrile (300 mg, 1.30 mmol), $(Boc)_2O$ (849 mg, 3.89 mmol) and $NiCl_2 \cdot 6H_2O$ (61.7 mg, 0.259 mmol) in MeOH (45 mL) was added $NaBH_4$ (491 mg, 13.0 mmol). After stirring at room temperature for 16 h, the reaction mixture was concentrated under reduced pressure. The residue was diluted with saturated aqueous NH_4Cl and extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a residue. The residue was purified by silica gel flash chromatography (0-60% ethyl acetate / petroleum ether gradient) to afford the title compound (150 mg, 0.403 mmol, 31.0% yield) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.33 (d, J = 8.8 Hz, 1H), 8.22 - 8.12 (m, 2H), 8.03 - 7.91 (m, 2H), 7.59 - 7.50 (m, 3H), 5.50 (s, 1H), 4.68 (d, J = 5.2 Hz, 2H), 1.50 (s, 9H).

Step 8: Preparation of (2-phenyl-1,6-naphthyridin-7-yl)methanaminium chloride



To a cooled solution (0 °C) of tert-butyl ((2-phenyl-1,6-naphthyridin-7-yl)methyl)carbamate (190 mg, 0.566 mmol) in dichloromethane (6 mL) was added solution of 4 M HCl in 1,4-dioxane (1.9 mL, 7.6 mmol). After stirring at room temperature for 1 h, the reaction mixture was concentrated to afford the title compound (190 mg) as a light yellow solid, which was used without further purification. LCMS (ESI) m/z: $[M+H]^+$ = 236.1.

Step 9: Preparation of 1-(methylsulfonyl)-N-((2-phenyl-1,6-naphthyridin-7-yl)methyl)-1H-pyrrole-3-carboxamide (Compound 61)



Compound 61

To a solution of 1-methylsulfonylpyrrole-3-carboxylic acid (63.4 mg, 0.335 mmol), EDCI (98.8 mg, 0.515 mmol), HOBt (69.6 mg, 0.515 mmol) and DIPEA (0.224 mL, 1.29 mmol) in DMF (1 mL) was added (2-phenyl-1,6-naphthyridin-7-yl)methanaminium chloride (70 mg, 0.258 mmol). After stirring at room temperature for 3 h, the reaction mixture was diluted with water and extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by reversed-phase prep-HPLC (water:ACN:FA) to afford **Compound 61** (43.4 mg, 0.107 mmol, 41.4% yield) as a white solid. LCMS (ESI) m/z: $[M+H]^+$ =407.0. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.37 (d, *J* = 0.6 Hz, 1H), 9.06 - 8.97 (m, 1H), 8.68 - 8.63 (m, 1H), 8.33 - 8.25 (m, 3H), 7.94 - 7.89 (m, 1H), 7.79 - 7.75 (m, 1H), 7.61 - 7.51 (m, 3H), 7.36 - 7.31 (m, 1H), 6.88 - 6.82 (m, 1H), 4.73 (d, *J* = 6.0 Hz, 2H), 3.59 (s, 3H).

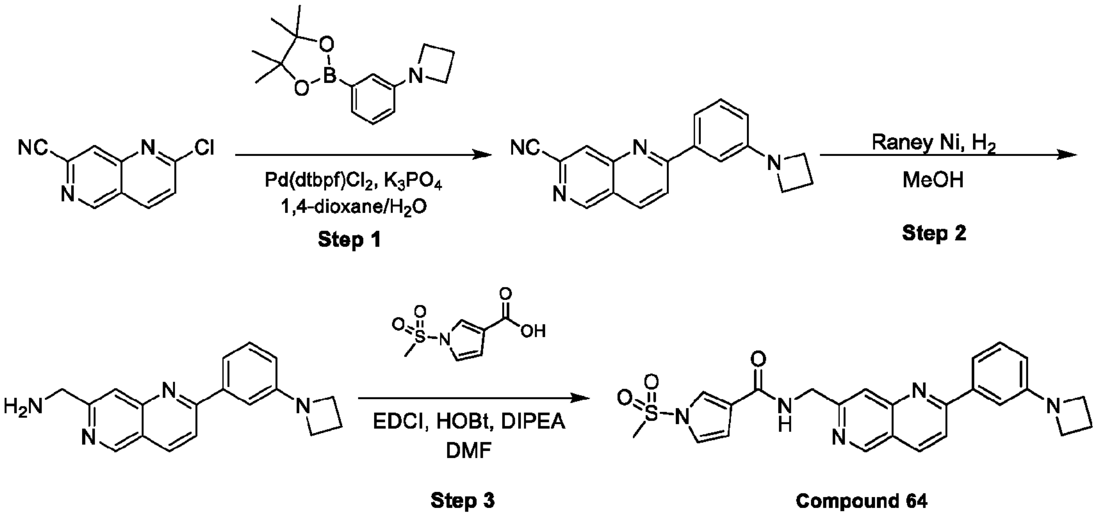
Example 25. Preparation of Compounds 62 and 63

Compounds 62 and 63, shown in Table 10 below, were synthesized starting from 2-chloro-1,6-naphthyridine-7-carbonitrile and the corresponding boronic acid or boronic ester utilizing the synthetic protocol described in Example 24 above.

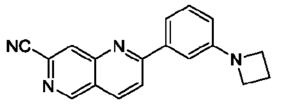
Table 10

#	LC-MS (m/z)	^{1}H NMR
62	437.0	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.37 (s, 1H), 9.01-8.98 (m, 1H), 8.64 (d, *J* = 9.2 Hz, 1H), 8.28 (d, *J* = 8.8 Hz, 1H),7.91-7.90 (m, 1H), 7.87-7.82 (m, 2H), 7.78 (s, 1H), 7.50-7.46 (m, 1H), 7.34 - 7.32 (m, 1H), 7.13-7.11 (m, 1H), 6.85-6.84 (m, 1H), 4.72 (d, *J* = 5.6 Hz, 2H), 3.86 (s, 3H), 3.58 (s, 3H)
63	462.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (s, 1H), 8.98 - 8.97 (m, 1H), 8.47 (d, *J* = 8.8 Hz, 1H), 8.17 - 8.12 (m, 3H), 7.91 - 7.90 (m, 1H), 7.65 (s, 1H), 7.34 - 7.32 (m, 1H), 6.85 - 6.84 (m, 1H), 6.51 (d, *J* = 9.2 Hz, 2H), 4.69 (br d, *J* = 5.6 Hz, 2H), 3.94 - 3.91 (m, 4H), 3.58 (s, 3H), 2.39 - 3.35 (m, 2H)

Example 26. Preparation of N-[[2-[3-(azetidin-1-yl)phenyl]-1,6-naphthyridin-7-yl]methyl]-1-methylsulfonyl-pyrrole-3-carboxamide (Compound 64)

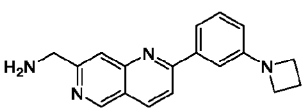


Step 1: Preparation of 2-[3-(azetidin-1-yl)phenyl]-1,6-naphthyridine-7-carbonitrile



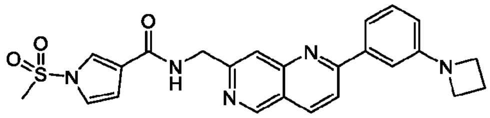
A mixture of 1-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]azetidine (1.8 g, 3.30 mmol), 2-chloro-1,6-naphthyridine-7-carbonitrile (626 mg, 3.30 mmol) and K_3PO_4 (2.10 g, 9.90 mmol) in 1,4-dioxane (18 mL) and H_2O (1.8 mL) was added [1,1'-bis(di-tert-butylphosphino)ferrocene]dichloropalladium (215 mg, 0.330 mol). After stirring at 80 °C for 12 h, the reaction mixture was poured into water and extracted three times with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford a residue. The residue was purified by silica gel flash chromatography (0-48% ethyl acetate / petroleum ether gradient) to afford the title compound (900 mg, 3.05 mmol, 92.3% yield) as a red solid. LCMS (ESI) m/z: $[M+H]^+$ = 287.2. ^{1}HNMR (400 MHz, DMSO-d_6) δ 9.48 (s, 1H), 8.73 (d, J = 8.4 Hz, 1H), 8.64 (s, 1H), 8.44 (d, J = 8.8 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.39 - 7.34 (m, 1H), 7.29 - 7.27 (m, 1H), 6.62 - 6.59 (m, 1H), 3.92 - 3.88 (m, 4H), 2.37 - 2.33 (m, 2H).

Step 2: Preparation of [2-[3-(azetidin-1-yl)phenyl]-1,6-naphthyridin-7-yl]methanamine



A mixture of 2-[3-(azetidin-1-yl)phenyl]-1,6-naphthyridine-7-carbonitrile (800 mg, 2.79 mmol) and Raney-Ni (400 mg, 4.67 mmol) in methanol (8 mL) was degassed and purged with H_2 (15 psi). After stirring at room temperature for 12 h, the reaction mixture was filtered, and the filtrate was concentrated to afford the title compound (700 mg, 1.90 mmol, 68.1% yield) as a brown oil. LCMS (ESI) m/z: $[M+H]^+$ = 291.

Step 5: Preparation of N-[[2-[3-(azetidin-1-yl)phenyl]-1,6-naphthyridin-7-yl]methyl]-1-methylsulfonyl-pyrrole-3-carboxamide (Compound 64)



Compound 64

To a mixture of 1-methylsulfonylpyrrole-3-carboxylic acid (32.6 mg, 0.172 mmol), EDCI (49.5 mg, 0.258 mmol), HOBt (34.9 mg, 0.258 mmol) and DIPEA (150 µL, 0.861 mmol) in DMF (1 mL) was added [2-[3-(azetidin-1-yl)phenyl]-1,6-naphthyridin-7-yl]methanamine (50 mg, 0.172 mmol). After stirring at room temperature for 8 h, the reaction mixture was diluted with water and extracted four times with ethyl acetate. The combined organic layers were concentrated and the resulting residue was purified by reversed-phase prep-HPLC (water:ACN:NH_4OH) to afford **Compound 64** (11.0 mg, 0.0235 mmol, 13.6% yield) as a yellow solid. LCMS (ESI) m/z: $[M+H]^+$ = 462.2. ^{1}HNMR (400 MHz, DMSO-d_6) δ 9.35 (s, 1H), 9.00 - 8.99 (m, 1H), 8.61 (d, *J* = 8.8 Hz, 1H), 8.22 (d, *J* = 8.8 Hz, 1H), 7.92 - 7.91 (m, 1H), 7.76 (s, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.39 - 7.32 (m, 2H), 7.27 - 7.26 (m, 1H), 6.85 - 6.84 (m, 1H), 6.59 - 6.58 (m, 1H), 4.72 (d, *J* = 5.2 Hz, 2H), 3.91 - 3.88 (m, 4H), 3.58 (s, 3H), 2.35 - 2.32 (m, 2H).

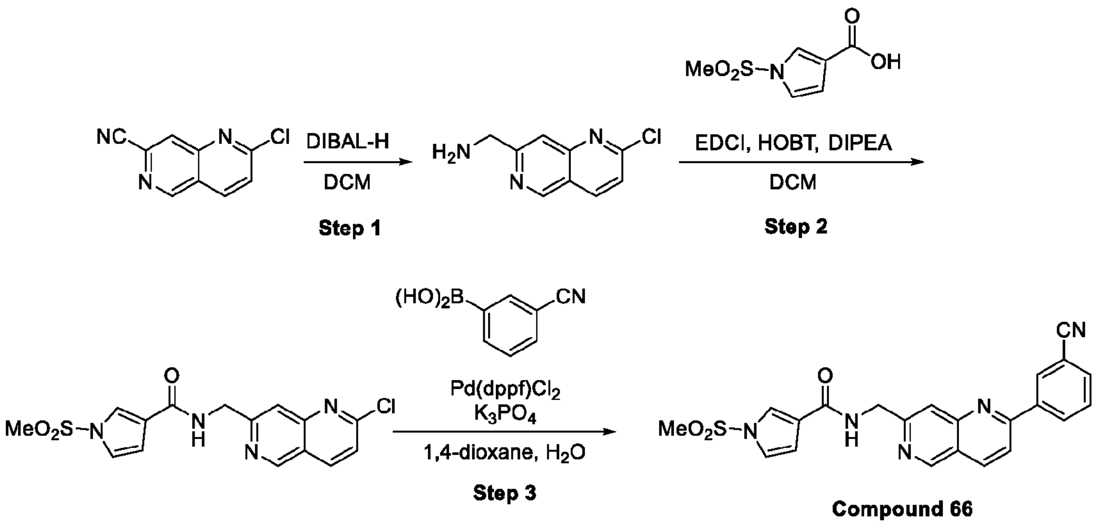
Example 27. Preparation of Compound 65

Compound 65, shown in Table 11 below, was synthesized from 2-chloro-1,6-naphthyridine-7-carbonitrile and 2-(3-(difluoromethyl)phenyl)-4,4,5,5,-tetramethyl-1,3,2-dioxaborolane utilizing the synthetic protocol described in Example 26 above.

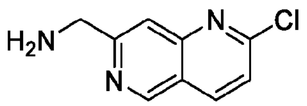
Table 11

#	LC-MS (m/z)	^{1}H NMR
65	457.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.41 (s, 1H), 9.02 (t, J = 6.0 Hz, 1H), 8.71 (d, J = 8.8 Hz, 1H), 8.52 (s, 1H), 8.47 (d, J = 7.2 Hz, 1H), 8.35 (d, J = 8.8 Hz, 1H), 7.93 (t, J = 2.0 Hz, 1H), 7.86 - 7.66 (m, 3H), 7.40 - 7.01 (m, 2H), 6.86 - 6.85 (m, 1H), 4.74 (d, J = 6.0 Hz, 2H), 3.60 (s, 3H)

Example 28. Preparation of N-((2-(3-cyanophenyl)-1,6-naphthyridin-7-yl)methyl)-1-(methylsulfonyl)-1H-pyrrole-3-carboxamide (Compound 66)

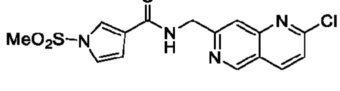


Step 1: Preparation of (2-chloro-1,6-naphthyridin-7-yl)methanamine



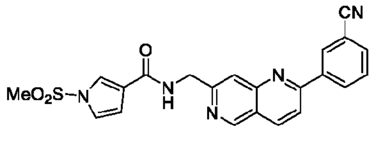
To a cooled suspension (-78 °C) of 2-chloro-1,6-naphthyridine-7-carbonitrile (0.500 g, 2.63 mmol) in dichloromethane (21 mL) was added a solution of 1 M DIBAL-H in toluene (6.57 mL, 6.57 mmol) over 5 min. After stirring at -78 °C for 1 h, the reaction mixture was quenched with saturated aqueous potassium sodium tartrate tetrahydrate and warmed to room temperature. The mixture was diluted with 10% methanol in dichloromethane and the resulting emulsion was filtered through a Celite pad. The layers of the resulting filtrate were separated, and the aqueous layer was extracted twice with 10% methanol in dichloromethane. The solid residue and Celite were suspended in 10% methanol in dichloromethane and saturated aqueous potassium sodium tartrate tetrahydrate and stirred for 45 min. The resulting mixture was filtered via vacuum filtration and the layers of the resulting filtrate was extracted twice with 10% methanol in dichloromethane. The combined organic layers were washed with brine and dried with anhydrous sodium sulfate. Salts were removed via vacuum filtration and volatile materials were removed using a rotary evaporator to afford the title compound as a brown solid (513 mg, 2.64 mmol, quantitative yield), which was used without further purification. LCMS (ESI) m/z: $[M+H]^+$ = 194.1.

Step 2: Preparation of N-((2-chloro-1,6-naphthyridin-7-yl)methyl)-1-(methylsulfonyl)-1H-pyrrole-3-carboxamide



To a suspension of (2-chloro-1,6-naphthyridin-7-yl)methanamine (512 mg, 2.64 mmol) and 1-(methylsulfonyl)-1H-pyrrole-3-carboxylic acid (548 mg, 2.90 mmol) in dichloromethane (13.2 mL) was added DIPEA (1.81 mL, 10.5 mmol) followed by 1-hydroxybenzotriazole hydrate (426 mg, 3.16 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (612 mg, 3.16 mmol). After stirring at room temperature for 3 days, the mixture was diluted with water and ethyl acetate. The layers were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine and dried with anhydrous sodium sulfate. Salts were removed via vacuum filtration and volatile materials were removed using a rotary evaporator. The resulting mixture was purified via silica gel flash chromatography (0% to 5% MeOH in DCM and 99:0:1 to 96:3:1 DCM:MeOH:TEA) to afford the title compound (342 mg, 0.937 mmol, 35.5% yield, 67% purity) as an orange/beige solid. LCMS (ESI) m/z: $[M+H]^+$ = 365.0

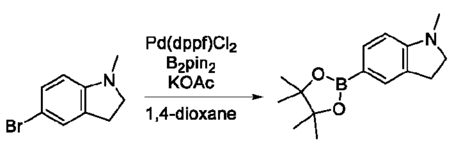
Step 3: Preparation of N-((2-(3-cyanophenyl)-1,6-naphthyridin-7-yl)methyl)-1-(methylsulfonyl)-1H-pyrrole-3-carboxamide (Compound 66)



Compound 66

In a vial were combined N-((2-chloro-1,6-naphthyridin-7-yl)methyl)-1-(methylsulfonyl)-1H-pyrrole-3-carboxamide (45 mg, 0.123 mmol), 3-cyanophenylboronic acid (27 mg, 0.184 mmol), potassium phosphate (78.3 mg, 0.369 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (17.8 mg, 0.0245 μmol). The vial was purged with nitrogen and sealed with PTFE lined septum. To the resulting mixture was added 1,4-dioxane (1.1 mL) and water (0.3 mL) and heated to 80 °C. After 1 h, the reaction mixture was cooled to room temperature and diluted with water and ethyl acetate. The layers were separated the and aqueous layers was extracted twice with ethyl acetate. The combined organic layers were washed with brine and the resulting emulsion was filtered through a Celite plug. The layers were separated the and organic layer was dried with anhydrous sodium sulfate. Salts were removed via vacuum filtration and volatile materials were removed using a rotary evaporator. The resulting residue was purified via automated silica gel flash chromatography (0% to 4% MeOH in DCM) and by reversed-phase prep-HPLC to afford **Compound 66** (12.4 mg, 0.0288 mmol, 23.5% yield) as a white powder. LCMS (ESI) m/z: $[M+H]^+$ = 432.3. ^1H NMR (500 MHz, DMSO-d_6) δ 9.41 (d, J = 0.9 Hz, 1H), 9.02 (t, J = 6.0 Hz, 1H), 8.76 – 8.70 (m, 2H), 8.65 (dt, J = 8.0, 1.5 Hz, 1H), 8.39 (d, J = 8.6 Hz, 1H), 8.02 (dt, J = 7.7, 1.4 Hz, 1H), 7.94 – 7.87 (m, 1H), 7.81 (t, J = 0.9 Hz, 1H), 7.78 (t, J = 7.8 Hz, 1H), 7.34 (dd, J = 3.2, 2.3 Hz, 1H), 6.85 (dd, J = 3.3, 1.7 Hz, 1H), 4.74 (d, J = 5.9 Hz, 2H), 3.59 (s, 3H).

Example 29. Preparation of 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indoline



In a vial were combined 5-bromo-2,3-dihydro-1-methyl-1H-indole (90 mg, 0.424 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (161 mg, 0.636 mmol), potassium acetate (124 mg, 1.27 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (30.8 mg, 0.0424 mmol). The vial was purged with nitrogen and sealed with PTFE lined septum. To the resulting mixture was added 1,4-dioxane (1.2 mL) and the vial was heated at 80 °C. After 3 h, the reaction mixture was cooled to room temperature and diluted with water and ethyl acetate. The layers were separated, and the aqueous layers was extracted twice with ethyl acetate. The combined organic layers were washed with brine and dried with anhydrous sodium sulfate. Salts were removed via vacuum filtration and volatile materials were removed using a rotary evaporator. The resulting mixture was purified via silica gel flash chromatography (10% to 30% ethyl acetate in heptane) to afford the title compound (61.6 mg, 0.237 mmol, 56.5% yield) as a white solid. LCMS (ESI) m/z: $[M+H]^+$ = 260.1.

Example 30. Preparation of Compounds 67 to 72

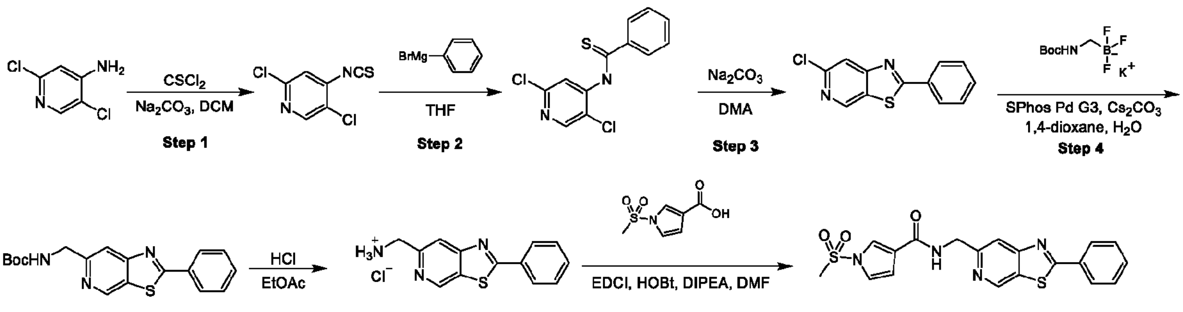
Compounds 67 to 72, shown in Table 12 below, were each synthesized from 2-chloro-1,6-naphthyridine-7-carbonitrile and the corresponding boronic acid or boronic ester utilizing the synthetic protocol described in Example 28 above.

Table 12

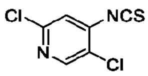
#	LC-MS (m/z)	^{1}H NMR
67	449.1	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.29 (d, *J* = 0.9 Hz, 1H), 8.99 (t, *J* = 6.0 Hz, 1H), 8.55 (dd, *J* = 8.7, 0.9 Hz, 1H), 8.23 (q, *J* = 1.4 Hz, 1H), 8.19 (d, *J* = 8.7 Hz, 1H), 8.10 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.94 – 7.89 (m, 1H), 7.70 (d, *J* = 1.0 Hz, 1H), 7.34 (dd, *J* = 3.2, 2.3 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.85 (dd, *J* = 3.3, 1.7 Hz, 1H), 4.71 (d, *J* = 6.0 Hz, 2H), 4.63 (t, *J* = 8.7 Hz, 2H), 3.59 (s, 3H), 3.28 (t, *J* = 8.9 Hz, 2H).
68	449.3	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.34 (d, *J* = 0.9 Hz, 1H), 8.99 (t, *J* = 6.0 Hz, 1H), 8.60 (dd, *J* = 8.8, 0.9 Hz, 1H), 8.23 (d, *J* = 8.7 Hz, 1H), 7.91 (t, *J* = 2.0 Hz, 1H), 7.80 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.75 (d, *J* = 1.0 Hz, 1H), 7.67 (d, *J* = 1.6 Hz, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.33 (dd, *J* = 3.3, 2.3 Hz, 1H), 6.85 (dd, *J* = 3.3, 1.7 Hz, 1H), 4.72 (d, *J* = 5.9 Hz, 2H), 4.60 (t, *J* = 8.7 Hz, 2H), 3.59 (s, 3H), 3.26 (t, *J* = 8.7 Hz, 2H).
69	478.2	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.29 (s, 1H), 8.97 (t, *J* = 6.0 Hz, 1H), 8.53 (d, *J* = 8.7 Hz, 1H), 8.21 (d, *J* = 8.7 Hz, 1H), 7.91 (t, *J* = 2.0 Hz, 1H), 7.72 (s, 1H), 7.62 (d, *J* = 2.1 Hz, 1H), 7.56 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.33 (dd, *J* = 3.2, 2.3 Hz, 1H), 6.84 (dd, *J* = 3.2, 1.7 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 4.71 (d, *J* = 5.9 Hz, 2H), 4.31 (dd, *J* = 5.3, 3.5 Hz, 2H), 3.58 (s, 3H), 3.31 – 3.27 (m, 2H), 2.96 (s, 3H).
70	463.3	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.37 (d, *J* = 0.9 Hz, 1H), 8.99 (t, *J* = 6.0 Hz, 1H), 8.66 – 8.61 (m, 1H), 8.27 (d, *J* = 8.6 Hz, 1H), 7.92 (dt, *J* = 12.4, 2.0 Hz, 2H), 7.88 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.78 (s, 1H), 7.49 (t, *J* = 7.9 Hz, 1H), 7.33 (dd, *J* = 3.2, 2.2 Hz, 1H), 7.24 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 6.84 (dd, *J* = 3.3, 1.7 Hz, 1H), 4.73 (d, *J* = 5.9 Hz, 2H), 3.99 (tt, *J* = 6.0, 3.0 Hz, 1H), 3.58 (s, 3H), 0.88 – 0.79 (m, 2H), 0.74 – 0.63 (m, 2H).
71	487.1	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.38 (d, *J* = 0.9 Hz, 1H), 9.01 (t, *J* = 6.0 Hz, 1H), 8.67 (dd, *J* = 8.7, 0.9 Hz, 1H), 8.43 (t, *J* = 1.8 Hz, 1H), 8.36 (d, *J* = 8.7 Hz, 1H), 8.30 (s, 1H), 8.11 (dt, *J* = 7.8, 1.4 Hz, 1H), 8.00 (d, *J* = 0.8 Hz, 1H), 7.92 (t, *J* = 2.0 Hz, 1H), 7.80 (s, 1H), 7.74 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.54 (t, *J* = 7.7 Hz, 1H), 7.34 (dd, *J* = 3.3, 2.3 Hz, 1H), 6.85 (dd, *J* = 3.3, 1.7 Hz, 1H), 4.74 (d, *J* = 5.9 Hz, 2H), 3.89 (s, 3H), 3.59 (s, 3H).

#	LC-MS (m/z)	^{1}H NMR
72	462.2	^{1}H NMR (500 MHz, DMSO-*d*6) δ 9.21 (d, *J* = 0.9 Hz, 1H), 8.97 (t, *J* = 6.0 Hz, 1H), 8.44 (dd, *J* = 8.9, 0.9 Hz, 1H), 8.12 (d, *J* = 8.8 Hz, 1H), 8.03 (d, *J* = 7.3 Hz, 2H), 7.91 (t, *J* = 2.0 Hz, 1H), 7.63 (t, *J* = 1.0 Hz, 1H), 7.34 (dd, *J* = 3.3, 2.3 Hz, 1H), 6.85 (dd, *J* = 3.3, 1.7 Hz, 1H), 6.58 (d, *J* = 9.0 Hz, 1H), 4.68 (d, *J* = 5.9 Hz, 2H), 3.59 (s, 3H), 3.42 (t, *J* = 8.4 Hz, 2H), 3.00 (t, *J* = 8.3 Hz, 2H), 2.81 (s, 3H).
75	437.4	^{1}H NMR (400 MHz, DMSO-*d*6) δ 9.35 (s, 1H), 8.98 (t, *J* = 6.0 Hz, 1H), 8.53 (d, *J* = 8.6 Hz, 1H), 8.05 (d, *J* = 8.6 Hz, 1H), 7.90 (d, *J* = 2.3 Hz, 1H), 7.79 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.75 (s, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 2.9 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 6.87 – 6.81 (m, 1H), 4.72 (d, *J* = 5.9 Hz, 2H), 3.87 (s, 3H), 3.57 (s, 3H).

Example 31. Preparation of 1-methylsulfonyl-N-[(2-phenylthiazolo[5,4-c]pyridin-6-yl)methyl]pyrrole-3-carboxamide (Compound 73)

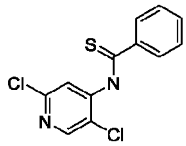


Step 1: Preparation of 2,5-dichloro-4-isothiocyanato-pyridine



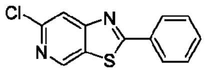
Thiocarbonyl dichloride (0.942 mL, 12.3 mmol) was added to a solution of 2,5-dichloropyridin-4-amine (1 g, 6.13 mmol) and Na_2CO_3 (2.60 g, 24.5 mmol) in dichloromethane (15 mL). After stirring at room temperature for 15 h, the reaction mixture was filtered, and the filtrate was concentrated to get the crude product. The residue was purified by silica gel column chromatography (petroleum ether / ethyl acetate = 10/1 to 5/1) to afford the title compound (750 mg, 3.66 mmol, 59.6% yield) as a brown solid. ^{1}HNMR (400 MHz, DMSO-d6) δ 8.63 (s, 1H), 7.85 - 7.76 (m, 1H).

Step 2: Preparation of N-(2,5-dichloro-4-pyridyl)benzenecarbothioamide



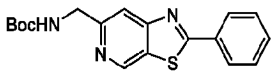
To a cooled mixture (-40 °C) of 2,5-dichloro-4-isothiocyanato-pyridine (650 mg, 3.17 mmol) in THF (8 mL) was added a solution of 3 M bromo(phenyl)magnesium (1.58 mL, 4.74 mmol), after addition. After stirring at -40 °C for 30 min, the reaction was warmed to room temperature. After 2 h, the mixture was added into water, and then extracted with ethyl acetate; the organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to get the crude product. The residue was purified by silica gel column chromatography (petroleum ether / ethyl acetate = 10/1-5/1) to afford the title compound (650 mg, 2.30 mmol, 72.4% yield) as a white solid. ^{1}HNMR (400 MHz, methanol-d_4) δ 8.55 - 8.51 (m, 1H), 8.08 - 8.03 (m, 1H), 7.97 - 7.90 (m, 2H), 7.60 - 7.53 (m, 1H), 7.50 - 7.43 (m, 2H).

Step 3: Preparation of 6-chloro-2-phenyl-thiazolo[5,4-c]pyridine



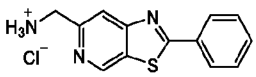
To a mixture of N-(2,5-dichloro-4-pyridyl)benzenecarbothioamide (550 mg, 1.94 mmol) in DMA (8 mL) was added Na_2CO_3 (412 mg, 3.88 mmol) at room temperature. After heating at 120 °C for 3 h, the mixture was quenched with water, and then extracted three times with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to get the crude product. The residue was purified by silica gel column chromatography (petroleum ether / ethyl acetate = 10/1 to 5/1) to afford the title compound (250 mg, 1.01 mmol, 52.2% yield) as a yellow solid. LCMS (ESI) m/z: $[M+H]^+$ = 247.0. ^{1}HNMR (400 MHz, DMSO-d_6) δ 9.25 (d, J = 0.4 Hz, 1H), 8.21 - 8.16 (m, 3H), 7.70 - 7.59 (m, 3H).

Step 4: Preparation of tert-butyl N-[(2-phenylthiazolo[5,4-c]pyridin-6-yl)methyl]carbamate



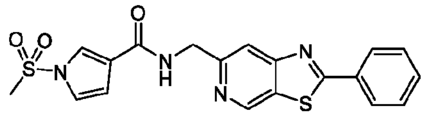
To a mixture of 6-chloro-2-phenyl-thiazolo[5,4-c]pyridine (80 mg, 0.324 mmol) and potassium N-Boc-aminomethyltrifluoroborate (122 mg, 0.486 mmol) in 1,4-dioxane (3 mL) and water (0.5 mL) was added (2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl) [2-(2'-amino-1,1'-biphenyl)]palladium methanesulfonate (25.3 mg, 0.0324 mmol), Cs_2CO_3 (211 mg, 649 μmol) at room temperature. After stirring at 100 °C for 15 h under a N_2 atmosphere, the mixture was filtered, and the filtrate was concentrated to give the crude product. The residue was purified by silica gel column chromatography (petroleum ether / ethyl acetate = 5/1 to 3/1) to afford the title compound (60 mg, 0.176 mmol, 54.2% yield) as a white solid. LCMS (ESI) m/z: $[M+H]^+$ = 342.1. ^{1}HNMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.15 - 8.13 (m, 2H), 7.94 (s, 1H), 7.62 - 7.49 (m, 4H), 5.50 (s, 1H), 4.62 (d, J = 5.2 Hz, 2H), 1.49 (s, 9H).

Step 5: Preparation of (2-phenylthiazolo[5,4-c]pyridin-6-yl)methanaminium chloride



A mixture of tert-butyl N-[(2-phenylthiazolo[5,4-c]pyridin-6-yl)methyl]carbamate (60 mg, 0.176 mmol) in a solution of 4 M HCl in 1,4-dioxane (2 mL, 8 mmol) was stirred at room temperature. After 2 h, the mixture was concentrated to afford the title compound (30 mg, 0.108 mmol, 61.5% yield) as a white solid which was used in the next step directly. LCMS (ESI) m/z: $[M+H]^+$ = 242.1.

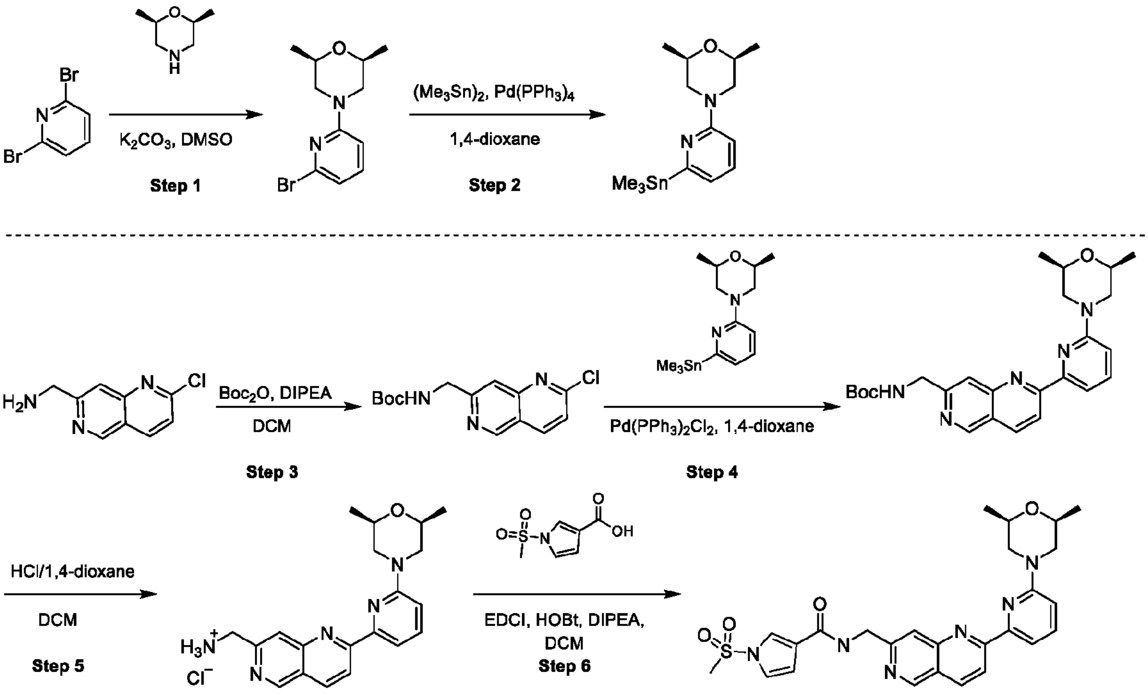
Step 6: Preparation of 1-methylsulfonyl-N-[(2-phenylthiazolo[5,4-c]pyridin-6-yl)methyl]pyrrole-3-carboxamide (Compound 73)



Compound 73

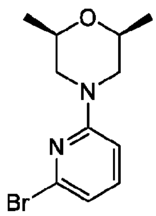
To a mixture **of (2-phenylthiazolo[5,4-c]pyridin-6-yl)methanaminium chloride** (15 mg, 0.0540 mmol) and 1-methylsulfonylpyrrole-3-carboxylic acid (10.2 mg, 0.0540 µmol) in DMF (1 mL) was added EDCI (20.7 mg, 0.108 mmol), HOBt (14.6 mg, 0.108 mmol) and DIPEA (0.047 mL, 0.270 mmol) at room temperature. After 15 h, water was added to the mixture, then extracted three times with ethyl acetate; the combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to get the crude product. The crude product was purified by reversed-phase prep-HPLC (water:ACN:FA) to afford **Compound 73** (1.98 mg, 0.00470 mmol, 8.71% yield) as a white solid. LCMS (ESI) m/z: $[M+H]^+$ = 413.0. ^{1}HNMR (400 MHz, DMSO-d_6) δ 9.34 (d, J = 0.8 Hz, 1H), 8.96 - 8.93 (m, 1H), 8.21 - 8.13 (m, 2H), 7.93 - 7.86 (m, 2H), 7.70 - 7.57 (m, 3H), 7.33-7.31 (m, 1H), 6.83 - 6.81 (m, 1H), 4.67 (d, J = 6.0 Hz, 2H), 3.58 (s, 3H).

Example 32: Preparation of N-((2-(6-(cis-2,6-dimethylmorpholino)pyridin-2-yl)-1,6-naphthyridin-7-yl)methyl)-1-(methylsulfonyl)-1H-pyrrole-3-carboxamide (Compound 76)



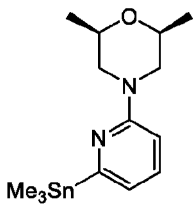
76

Step 1: Preparation of cis-4-(6-bromo-2-pyridyl)-2,6-dimethyl-morpholine



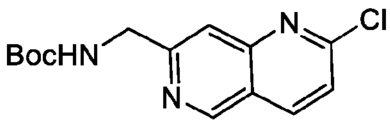
To a solution of 2,6-dibromopyridine (50 g, 211 mmol) and cis-2,6-dimethylmorpholine (36.5 g, 317 mmol) in DMSO (500 mL) was added K_2CO_3 (87.5 g, 633 mmol). After stirring at 80 °C for 16 h, the reaction mixture was poured into water. The solution was extracted three times with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 10/1-1/1), the solution was concentrated to give cis-4-(6-bromo-2-pyridyl)-2,6-dimethyl-morpholine (54 g, 199 mmol, 94.4% yield) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.31 - 7.27 (m, 1H), 6.76 (d, J = 7.6 Hz, 1H), 6.50 (d, J = 8.0 Hz, 1H), 4.03 - 3.99 (m, 2H), 3.69 - 3.66 (m, 2H), 2.55 - 2.49 (m, 2H), 1.28 - 1.25 (m , 6H).

Step 2: Preparation of [6-[cis-2,6-dimethylmorpholin-4-yl]-2-pyridyl]-trimethyl-stannane



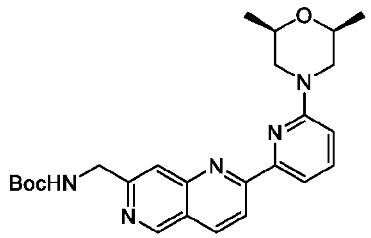
To a solution of cis-4-(6-bromo-2-pyridyl)-2,6-dimethyl-morpholine (20 g, 73.8 mmol) and trimethyl(trimethylstannyl)stannane (29.0 g, 88.5 mmol) in 1,4-dioxane (200 mL) was added $Pd(PPh_3)_4$ (4.26 g, 3.69 mmol). The mixture was stirred at 100 °C for 2 h under a N_2 atmosphere. The reaction mixture was poured into water and the resulting solution was extracted three times with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to give [6-[cis-2,6-dimethylmorpholin-4-yl]-2-pyridyl]-trimethyl-stannane (26.1 g, crude) as a brown oil, which was used for the next step directly.

Step 3: Preparation of tert-butyl N-[(2-chloro-1,6-naphthyridin-7-yl)methyl]carbamate



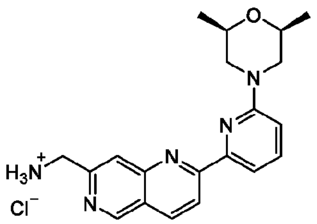
To a solution of (2-chloro-1,6-naphthyridin-7-yl)methanamine (51 g, 263 mmol) in DCM (1500 mL) was added $(Boc)_2O$ (172 g, 790 mmol) and DIPEA (102 g, 790 mmol). The mixture was stirred at 25 °C for 16 h. The reaction mixture was diluted with water and then filtered. The filtrate was extracted with three times with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether / ethyl acetate = 10/1 to 2/1 to 1/3) to afford tert-butyl N-[(2-chloro-1,6-naphthyridin-7-yl)methyl]carbamate (21 g, 64.3 mmol, 24.4% yield) as a light yellow solid. LCMS (ESI) m/z: $[M+H]^+$ = 293.9. ^1H NMR (400 MHz, DMSO-d_6) δ 9.37 (s, 1H), 8.62 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.58 - 7.53 (m, 2H), 4.39 (d, *J* = 6.4 Hz, 2H), 4.20 – 4.25 (m, 2H), 1.41 (s, 9H).

Step 4: Preparation of tert-butyl N-[[2-[6-[(2S,6R)-2,6-dimethylmorpholin-4-yl]-2-pyridyl]-1,6-naphthyridin-7-yl]methyl]carbamate



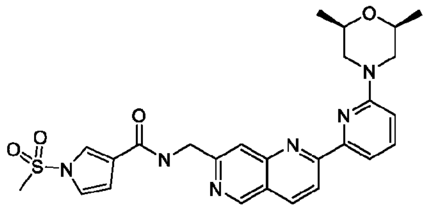
A mixture of [6-[cis-2,6-dimethylmorpholin-4-yl]-2-pyridyl]-trimethyl-stannane (26 g, 73.2 mmol) and tert-butyl N-[(2-chloro-1,6-naphthyridin-7-yl)methyl]carbamate (10.8 g, 36.6 mmol) in 1,4-dioxane (120 mL) was added $Pd(PPh_3)_2Cl_2$ (2.57 g, 3.66 mmol) was stirred at 100 °C for 2 h under a N_2 atmostphere. The reaction mixture was concentrated to give a residue. The residue was purified by silica gel column chromatography (petroleum ether / ethyl acetate = 1:1 - 0:1) to afford N-[[2-[6-[(2S,6R)-2,6-dimethylmorpholin-4-yl]-2-pyridyl]-1,6-naphthyridin-7-yl]methyl]carbamate (15 g, 32.8 mmol, 89.5% yield) as a yellow solid. LCMS (ESI) m/z: $[M+H]^+$ = 450.2. ^1H NMR (400 MHz, DMSO-d_6) δ 9.35 (s, 1H), 8.66 - 8.59 (m, 2H), 7.93 (d, *J* = 7.2 Hz, 1H), 7.79 - 7.74 (m, 2H), 7.62 (7.63-7.61, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 4.45 (br d, *J* = 6.0 Hz, 2H), 4.32 (br d, *J* = 11.2 Hz, 2H), 3.69 – 3.65 (m , 2H), 2.52 (br s, 2H), 1.44 - 1.36 (m, 9H), 1.22 (d, *J* = 6.0 Hz, 6H)

Step 5: Preparation of (2-(6-(cis-2,6-dimethylmorpholino)pyridin-2-yl)-1,6-naphthyridin-7-yl)methanaminium chloride



To a solution of HCl (4 M in 1,4-dioxane, 200 mL) was added a solution of N-[[2-[6-[(2S,6R)-2,6-dimethylmorpholin-4-yl]-2-pyridyl]-1,6-naphthyridin-7-yl]methyl]carbamate (15 g, 33.4 mmol) in DCM (200 mL). The mixture was stirred at 30 °C for 2 h. The reaction mixture was concentrated and the resulting residue was poured into MTBE. The solution was filtered and the filter cake was dried in vacuum to give (2-(6-(cis-2,6-dimethylmorpholino)pyridin-2-yl)-1,6-naphthyridin-7-yl)methanaminium chloride (15.5 g, crude) as a yellow solid. LCMS (ESI) m/z: $[M+H]^+$ = 350.1. ^1H NMR (400 MHz, DMSO-d_6) δ 9.56 (s, 1H), 8.82 - 8.70 (m, 5H), 8.21 (s, 1H), 7.94 (d, *J* = 7.6 Hz, 1H), 7.82 – 7.78 (m, 1H), 7.08 (d, *J* = 8.4 Hz, 1H), 4.42 - 4.31 (m, 4H), 3.70 - 3.65 (m, 2H), 2.54 - 2.52 (m, 2H), 1.22 – 1.16 (m, 6H).

Step 6: preparation of N-((2-(6-(cis-2,6-dimethylmorpholino)pyridin-2-yl)-1,6-naphthyridin-7-yl)methyl)-1-(methylsulfonyl)-1H-pyrrole-3-carboxamide (Compound 76)



76

To a solution of 1-methylsulfonylpyrrole-3-carboxylic acid (17.1 mg, 0.0906 mmol) and (2-(6-(cis-2,6-dimethylmorpholino)pyridin-2-yl)-1,6-naphthyridin-7-yl)methanaminium chloride (35.0 mg, 0.0906 mmol) in DCM (0.36 mL) was added DIPEA (0.079 mL, 0.453 mmol) followed by EDCI (20.7 mg, 0.108 mmol) and HOBt (14.5 mg, 0108 mmol). The resulting mixture was stirred overnight at room temperature. The mixture was dilute with water and ethyl acetate. The layers were separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by C18 prep-HPLC (H_2O:ACN:FA) to give compound 76 (14.3 mg, 0.0274 mmol, 30.1% yield) as a yellow powder. LCMS (ESI) m/z: $[M+H]^+$ = 521.3. ^1H NMR (400 MHz, DMSO-d_6) δ 9.38 (d, J = 1.0 Hz, 1H), 8.99 (t, J = 6.0 Hz, 1H), 8.70 – 8.58 (m, 2H), 7.92 (dt, J = 4.8, 2.2 Hz, 2H), 7.81 – 7.71 (m, 2H), 7.34 (td, J = 2.8, 2.2, 1.2 Hz, 1H), 7.03 (d, J = 8.5 Hz, 1H), 6.85 (dt, J = 3.1, 1.4 Hz, 1H), 4.73 (d, J = 5.9 Hz, 2H), 4.31 (dt, J = 12.7, 1.7 Hz, 2H), 3.74 – 3.62 (m, 2H), 3.59 (s, 3H), 2.63 – 2.40 (m, 2H), 1.22 (d, J = 6.3 Hz, 6H).

Example 33. Preparation of compounds of the invention

The compounds in Table 13 below were synthesized starting from the appropriate common intermediate (2-(6-(cis-2,6-dimethylmorpholino)pyridin-2-yl)-1,6-naphthyridin-7-yl)methanaminium chloride and corresponding carboxylic acid utilizing the synthetic protocol described in Example 32.

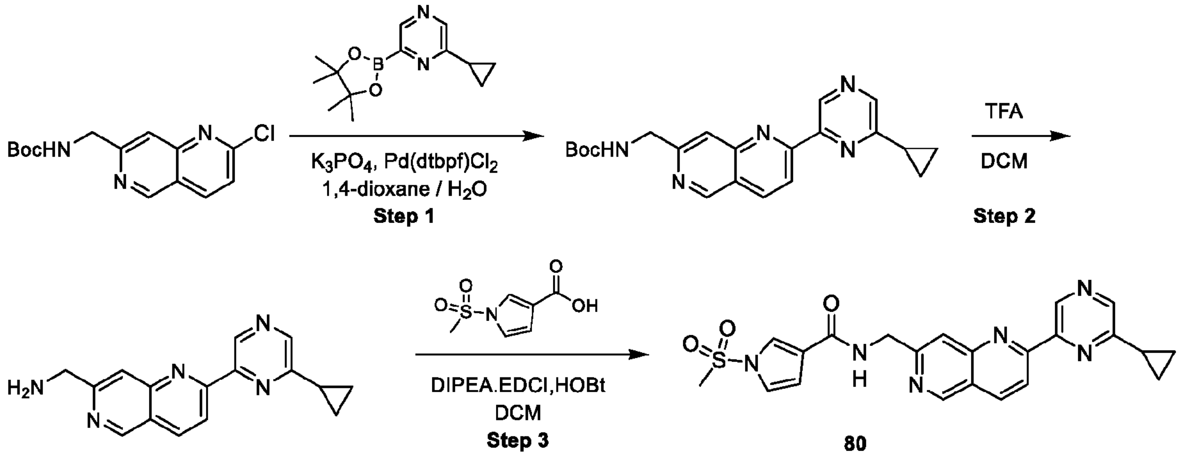
Table 13

#	LC-MS (m/z)	^1H NMR
77	499.4	^1H NMR (400 MHz, DMSO-d_6) δ 9.37 (s, 1H), 8.69 – 8.58 (m, 2H), 8.53 (t, J = 6.0 Hz, 1H), 7.91 (d, J = 7.7 Hz, 1H), 7.77 – 7.68 (m, 2H), 7.58 (t, J = 2.0 Hz, 1H), 7.07 – 6.96 (m, 2H), 6.57 (dt, J = 2.9, 1.4 Hz, 1H), 4.70 (d, J = 6.0 Hz, 2H), 4.31 (d, J = 13.1 Hz, 2H), 3.74 – 3.62 (m, 2H), 2.57 – 2.43 (m, 2H), 1.51 (s, 9H), 1.21 (d, J = 6.2 Hz, 6H)
78	500.3	^1H NMR (400 MHz, DMSO-d_6) δ 9.38 (s, 1H), 8.75 (t, J = 6.1 Hz, 1H), 8.69 – 8.58 (m, 2H), 7.96 (dd, J = 2.4, 0.9 Hz, 1H), 7.91 (d, J = 7.4 Hz, 1H), 7.78 – 7.70 (m, 2H), 7.03 (d, J = 8.5 Hz, 1H), 6.72 – 6.66 (m, 1H), 4.75 (d, J = 6.1 Hz, 2H), 4.31 (d, J = 11.2 Hz, 2H), 3.74 – 3.63 (m, 2H), 2.61 – 2.40 (m, 2H), 1.60 (s, 9H), 1.22 (d, J = 6.1 Hz, 6H)

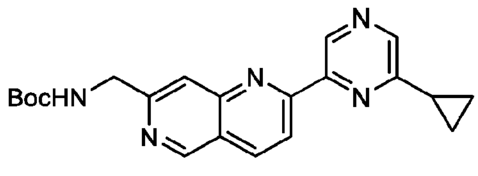
#	LC-MS (m/z)	[1]H NMR
79	511.4	[1]H NMR (400 MHz, DMSO-d_6) δ 9.39 (s, 1H), 8.95 (t, *J* = 6.1 Hz, 1H), 8.70 – 8.59 (m, 2H), 8.18 (dd, *J* = 2.6, 0.9 Hz, 1H), 7.91 (d, *J* = 7.4 Hz, 1H), 7.77 (s, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.03 (d, *J* = 8.5 Hz, 1H), 6.85 (dd, *J* = 2.6, 0.9 Hz, 1H), 4.77 (d, *J* = 6.0 Hz, 2H), 4.31 (d, *J* = 12.5 Hz, 2H), 3.74 – 3.60 (m, 2H), 2.56 – 2.45 (m, 2H), 2.06 (s, 6H), 1.22 (d, *J* = 6.2 Hz, 6H)
82*	565.3	[1]H NMR (400 MHz, DMSO-d6) δ 9.40 (s, 1H), 8.76 (d, *J* = 8.2 Hz, 1H), 8.70 - 8.58 (m, 2H), 8.46 (br d, *J* = 3.1 Hz, 1H), 8.04 (t, *J* = 2.0 Hz, 1H), 7.99 - 7.85 (m, 2H), 7.80 - 7.68 (m, 1H), 7.31 (dd, *J* = 2.3, 3.2 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.84 (dd, *J* = 1.7, 3.2 Hz, 1H), 5.60 - 5.44 (m, 1H), 4.32 (br d, *J* = 11.2 Hz, 2H), 3.94 - 3.81 (m, 2H), 3.68 (ddd, *J* = 2.3, 6.2, 10.3 Hz, 2H), 3.58 (s, 3H), 3.32 (s, 3H), 2.53 (br d, *J* = 2.9 Hz, 2H), 1.21 (d, *J* = 6.2 Hz, 6H)

* formate salt of compound 82

Example 34: Preparation of N-[[2-(6-cyclopropylpyrazin-2-yl)-1,6-naphthyridin-7-yl]methyl]-1-methylsulfonyl-pyrrole-3-carboxamide (Compound 80)

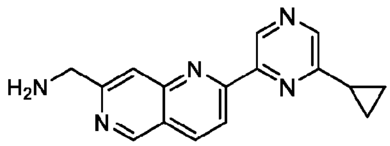


Step 1: Preparation of tert-butyl N-[[2-(6-cyclopropylpyrazin-2-yl)-1,6-naphthyridin-7-yl]methyl]carbamate



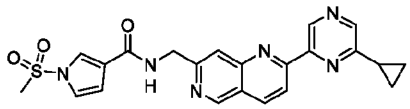
To a solution of tert-butyl N-[(2-chloro-1,6-naphthyridin-7-yl)methyl]carbamate (270 mg, 0.919 mmol) and 2-cyclopropyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazine (679 mg, 2.76 mmol) in 1,4-dioxane / H_2O (4/1, 5 mL) was added K_3PO_4 (585 mg, 2.76 mmol) and Pd(dtbpf)Cl_2 (59.9 mg, 0.0919 mmol) at 25 °C. The mixture was stirred at 80 °C for 2 h under a N_2 atmosphere. The reaction mixture was diluted with H_2O and extracted twice with DCM. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to afford the residue. The residue was purified by silica gel column chromatography (Petroleum ether / Ethyl acetate, 1/0 to 0/1) to afford tert-butyl N-[[2-(6-cyclopropylpyrazin-2-yl)-1,6-naphthyridin-7-yl]methyl]carbamate (210 mg, 0.0556 mmol, 60.5% yield) as a yellow solid. LCMS (ESI) m/z: $[M+H]^+$ = 378.2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (s, 1H), 9.25(s, 1H), 8.60 (s, 1H), 8.58(d, *J* = 8.8 Hz, 1H), 8.38 (d, *J* = 8.4 Hz, 1H), 7.96 (s, 1H), 4.69 (d, *J* = 5.6 Hz, 2H), 2.21-2.17 (m, 1H), 1.24 (s, 9H), 1.23 - 1.22 (m, 2H), 1.18-1.15(m, 2H).

Step 2: Preparation of Intermediate 8 [2-(6-cyclopropylpyrazin-2-yl)-1,6-naphthyridin-7-yl]methanamine



To a solution of tert-butyl N-[[2-(6-cyclopropylpyrazin-2-yl)-1,6-naphthyridin-7-yl]methyl]carbamate (210 mg, 0.556 mmol) in DCM (3 mL) was added TFA (0.6 mL, 8.10 mmol). The mixture was stirred at 25 °C for 1 h. To the reaction mixture was added to sat. aqueous $NaHCO_3$ and the mixture was extracted twice with DCM. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to afford the product [2-(6-cyclopropylpyrazin-2-yl)-1,6-naphthyridin-7-yl]methanamine (130 mg, 0.469 mmol, 84.3% yield) as a yellow solid which was used directly in the next step. LCMS (ESI) m/z: $[M+H]^+$ = 278.3.

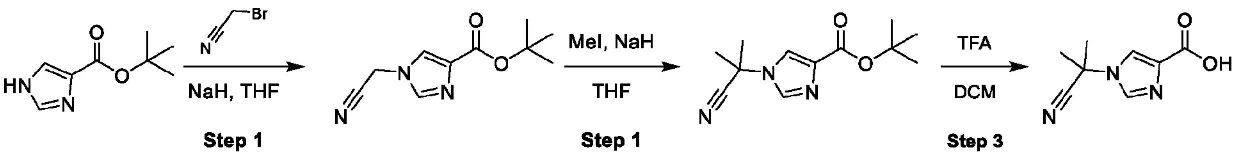
Step 3: Preparation of N-[[2-(6-cyclopropylpyrazin-2-yl)-1,6-naphthyridin-7-yl]methyl]-1-methylsulfonyl-pyrrole-3-carboxamide (Compound 80)



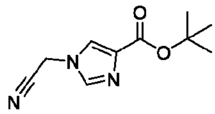
80

To a mixture of 1-(methylsulfonyl)-1H-pyrrole-3-carboxylic acid (20.5 mg, 0.108 mmol) and [2-(6-cyclopropylpyrazin-2-yl)-1,6-naphthyridin-7-yl]methanamine (25 mg, 0.0902 mmol) in DCM (1 mL) was added DIPEA (46.60 mg, 0.361 mmol), EDCI (25.92 mg, 0.135 mmol), and HOBt (18.27 mg, 0.135 mmol). The mixture was stirred at 25 °C for 1 h. The mixture was poured into water and extracted three times with ethyl acetate. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, and filtered; the filtrate was evaporated to dryness. The residue was purified by prep-HPLC to afford compound 80 (30.9 mg, 0.0647 mmol, 71.8% yield) as a yellow solid. LCMS (ESI) m/z $[M+H]^+$ = 449.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.45 - 9.43 (m, 2H), 9.04-9.01 (m, 1H), 8.78 (s, 1H), 8.74 (d, J = 8.0 Hz, 1H), 8.55 (d, J = 8.4 Hz, 1H), 7.92 - 7.91 (m, 1H), 7.83 (s, 1H), 7.34-7.33 (m, 1H), 6.85-6.84 (m, 1H), 4.74 (d, J = 5.6 Hz, 2H), 3.60 - 3.59 (m, 3H), 2.38 - 2.34 (m, 1H), 1.16 - 1.14 (m, 4H).

Example 35. Preparation of 1-(1-cyano-1-methyl-ethyl)imidazole-4-carboxylic acid

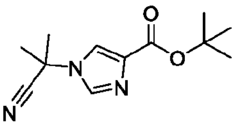


Step 1: Preparation of tert-butyl 1-(cyanomethyl)imidazole-4-carboxylate



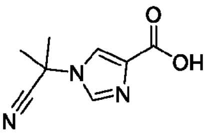
To a cooled (15 °C) solution of tert-butyl 1H-imidazole-5-carboxylate (0.550 g, 3.27 mmol) in THF (10 mL) was added NaH (0.157 g, 3.92 mmol, 60% purity). After 30 min, 2-bromoacetonitrile (0.262 mL, 3.92 mmol) was added. The mixture was warmed to room temperature and stirred for 2 h. The reaction was diluted with water and extracted three times with ethyl acetate. The combined the organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (petroleum ether / ethyl acetate = 10/1 to 3/1) to give tert-butyl 1-(cyanomethyl)imidazole-4-carboxylate (0.520 g, 2.51 mmol, 76.7% yield) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 - 7.61 (m, 2H), 5.03 - 5.00 (m, 2H), 1.58 (s, 9H).

Step 2: Preparation of tert-butyl 1-(1-cyano-1-methyl-ethyl)imidazole-4-carboxylate



To a cooled (0 °C) solution of tert-butyl 1-(cyanomethyl)imidazole-4-carboxylate (0.400 g, 1.93 mmol) in THF (8 mL) was added NaH (0.386 g, 9.65 mmol, 60% purity) in portion. The mixture was stirred at 25 °C for 1 h, followed by addition of MeI (0.721 mL, 11.6 mmol). After 12 h, the reaction was slowly poured into saturated aqueous NH_4Cl and extracted three times with ethyl acetate. The combined the organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether / ethyl acetate = 10/1 to 1/1) to give tert-butyl 1-(1-cyano-1-methyl-ethyl)imidazole-4-carboxylate (0.100 g, 0.397 mmol, 20.5% yield) as a yellow solid. LCMS (ESI) m/z: $[M+H]^+$ = 236.1; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 - 7.64 (m, 2H), 1.94 (s, 6H), 1.52 (s, 9H).

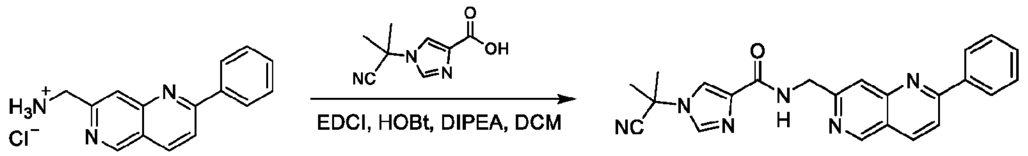
Step 3: Preparation of 1-(1-cyano-1-methyl-ethyl)imidazole-4-carboxylic acid



To a solution of tert-butyl 1-(1-cyano-1-methyl-ethyl)imidazole-4-carboxylate (0.050 g, 0.213 mmol) in dichloromethane (0.7 mL) was added TFA (0.157 mL, 2.13 mmol) and stirred at for 2 h. The mixture was concentrated to afford 1-(1-cyano-1-methyl-ethyl)imidazole-4-carboxylic acid (0.034 g, 0.190

mmol, 89.29% yield) as a yellow solid which was used into the next step without further purification. LCMS (ESI) m/z: $[M+H]^+$ = 180.0.

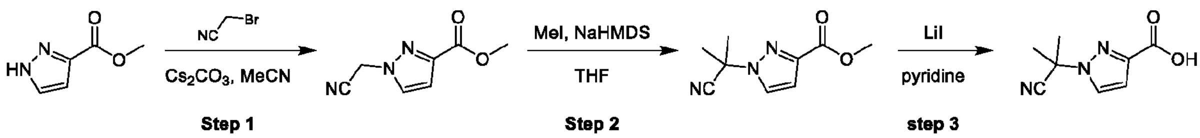
Example 36: Preparation of 1-(2-cyanopropan-2-yl)-N-((2-phenyl-1,6-naphthyridin-7-yl)methyl)-1H-imidazole-4-carboxamide (Compound 81)



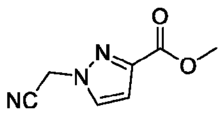
81

Compound 81 was prepared according the procedure in example 34 beginning with (2-phenyl-1,6-naphthyridin-7-yl)methanaminium chloride and 1-(1-cyano-1-methyl-ethyl)imidazole-4-carboxylic acid to afford compound 81. LCMS (ESI) m/z: $[M+H]^+$ = 397.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.36 (s, 1H), 8.86 (t, *J* = 6.2 Hz, 1H), 8.64 (d, *J* = 8.6 Hz, 1H), 8.33 – 8.22 (m, 3H), 8.14 (dd, *J* = 17.6, 1.5 Hz, 2H), 7.73 (d, *J* = 1.2 Hz, 1H), 7.56 (dd, *J* = 5.2, 1.9 Hz, 3H), 4.75 (d, *J* = 6.2 Hz, 2H), 2.04 (s, 6H).

Example 37: Preparation of 1-(1-cyano-1-methyl-ethyl)pyrazole-3-carboxylic acid

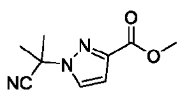


Step 1: Preparation of 3 methyl 1-(cyanomethyl)pyrazole-3-carboxylate



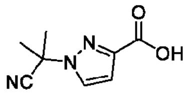
To a solution of methyl 1H-pyrazole-3-carboxylate (50 g, 396 mmol) in MeCN (500 mL) was added bromoacetonitrile (39.6 mL, 595 mmol) and Cs_2CO_3 (194 g, 595 mmol). The reaction mixture was stirred at 60 °C for 2 h under a N_2 atmosphere. The reaction mixture was diluted with water and extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by silica gel column chromatography (Petroleum ether / Ethyl acetate = 20/1 to 1/1) to give 3 methyl 1-(cyanomethyl)pyrazole-3-carboxylate (30 g, 180 mmol, 45.4% yield) as a yellow solid. LCMS (ESI) m/z: $[M+H]^+$ = 166.0. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (d, *J* = 2.4 Hz, 1H), 6.83 (d, *J* = 2.4 Hz, 1H), 5.60 (s, 2H), 3.81 (s, 3H).

Step 2: Preparation of methyl 1-(1-cyano-1-methyl-ethyl)pyrazole-3-carboxylate



To a solution of 3 methyl 1-(cyanomethyl)pyrazole-3-carboxylate (12 g, 72.7 mmol) and MeI (27.1 mL, 436 mmol) in THF (150 mL) was added NaHMDS (1 M, 291 mL, 291 mmol) in 0 °C. The reaction mixture was stirred at 25 °C for 2 h under a N_2 atmostphere. The reaction mixture was quenched with saturated aq. NH_4Cl and extracted three times with ethyl acetate. The organic layer was concentrated under vacuum. The residue was purified by silica gel flash chromatography (Ethyl acetate / Petroleum ether, 0-50%) to afford methyl 1-(1-cyano-1-methyl-ethyl)pyrazole-3-carboxylate (3 g, 14.3 mmol, 19.7% yield) as a yellow oil. LCMS (ESI) m/z: $[M+H]^+$ = 194.2. ^1H NMR (400 MHz, DMSO-d_6) δ 8.19 (d, *J* = 2.8 Hz, 1H), 6.89 (d, *J* = 2.8 Hz, 1H), 3.82 (s, 3H), 2.00 (s, 6H).

Step 3: Preparation of 1-(1-cyano-1-methyl-ethyl)pyrazole-3-carboxylic acid



To a solution of methyl 1-(1-cyano-1-methyl-ethyl)pyrazole-3-carboxylate (2 g, 10.4 mmol) in pyridine (20 mL) was added LiI (13.9 g, 104 mmol) at 25 °C. The reaction was stirred at 135 °C for 12 h under a N_2 atmosphere. The mixture was concentrated under vacuum. The residue was washed with water and extracted three times with ethyl acetate. The aqueous phase was adjusted to pH~3 by 1 M HCl solution and extracted three times with ethyl acetate. The combined organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to afford 1-(1-cyano-1-methyl-ethyl)pyrazole-3-carboxylic acid (1.2 g, crude) as a yellow solid. LCMS (ESI) m/z: $[M+H]^+$ = 180.1. ^1H NMR (400 MHz, DMSO-d_6) δ 12.96 (br s, 1H), 8.14 (s, 1H), 6.82 (s, 1H), 2.00 (s, 6H).

Example 38. Assay for ATPase catalytic activity of BRM and BRG-1

The ATPase catalytic activity of BRM or BRG-1 was measured by an in vitro biochemical assay using ADP-Glo™ (Promega, V9102). The ADP-Glo™ kinase assay is performed in two steps once the reaction is complete. The first step is to deplete any unconsumed ATP in the reaction. The second step is to convert the reaction product ADP to ATP, which will be utilized by the luciferase to generate luminesce and be detected by a luminescence reader, such as Envision.

The assay reaction mixture (10 µL) contains 30 nM of BRM or BRG-1, 20 nM salmon sperm DNA (from Invitrogen, UltraPure™ Salmon Sperm DNA Solution, cat# 15632011), and 400 µM of ATP in the ATPase assay buffer, which comprises of 20 mM Tris, pH 8, 20 mM $MgCl_2$, 50 mM NaCl, 0.1% Tween-20, and 1 mM fresh DTT (Pierce™ DTT (Dithiothreitol), cat# 20290). The reaction is initiated by the addition of the 2.5 µL ATPase solution to 2.5 µL ATP/DNA solution on low volume white Proxiplate-384 plus plate (PerkinElmer,cat # 6008280) and incubates at room temperature for 1 hour. Then following addition of 5 µL of ADP-Glo™ Reagent provided in the kit, the reaction incubates at room temperature for 40 minutes. Then 10 µL of Kinase Detection Reagent provided in the kit is added to convert ADP to ATP, and the reaction incubates at room temperature for 60 minutes. Finally, luminescence measurement is collected with a plate-reading luminometer, such as Envision.

BRM and BRG-1 were synthesized from High Five insect cell lines with a purity of greater than 90%. IC_{50} data for Compounds 1-83 from the ATPase catalytic activity assay described herein are shown in Table 14 below.

Table 14. BRM and BRG-1 Inhibition Data for Compounds of the Invention

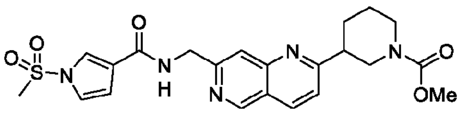
Compound #	BRM ATPase: IC_{50} (μM)	BRG1 ATPase: IC_{50} (μM)
1	++	++
2	+++	+++
3	+++	++
4	+++	+++
5	++	++
6	++	++
7	++	++
8	+++	++
9	+++	+++
10	+++	++
11	+++	+++
12	++	++
13	+++	+++
14	++	++
15	++	++
16	++	++
17	+++	+++
18	++	++
19	++	++
20	++	++
21	++	++
22	++	+
23	++	++
24	++	++
25	++	++
26	++	+
27	++	++
28	+++	+++
29	++	++
30	+++	++
31	+++	+++
32	+++	+++
33	+++	+++
34	+++	+++
35	+++	++
36	++	++
37	++	++
38	++	++

Compound #	BRM ATPase: IC_{50} (µM)	BRG1 ATPase: IC_{50} (µM)
39	++	++
40	++	++
41	+++	+++
42	+++	+++
43	++	++
44	+++	+++
45	+++	++
46	+++	++
47	+++	+++
48	+++	+++
49	+++	+++
50	+++	++
51	+++	++
52	+++	+++
53	++	++
54	++	++
55	++	++
56	+++	+++
57	+++	+++
58	+++	++
59	++	++
60	+++	++
61	++	++
62	++	++
63	++	++
64	+++	++
65	++	++
66	+	+
67	++	++
68	++	++
69	+++	++
70	++	++
71	+++.	++
72	++	++
73	++	++
75	+++	++
76	++++	+++
77	+++	+++
78	+++	++

Compound #	BRM ATPase: IC_{50} (μM)	BRG1 ATPase: IC_{50} (μM)
79	+++	+++
80	+++	++
81	-	-
82	+++	++
83	-	-

"+" indicates inhibitory effect of > 1 μM; "++" indicates inhibitory effect of 0.1-1 μM; "+++" indicates inhibitory effect of 0.01-0.1 μM, "++++" indicates inhibitory effect of < 0.01 μM

In Table 14, compound 83 is a control compound of the following structure:



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83

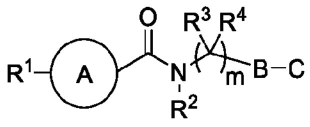
Other Embodiments

While the invention has been described in connection with specific embodiments thereof, it will be understood that invention is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure that come within known or customary practice within the art to which the invention pertains and may be applied to the essential features hereinbefore set forth, and follows in the scope of the claims.

Other embodiments are in the claims.

CLAIMS

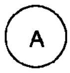
1. A compound having the structure:



Formula I

wherein

R^1 is H, optionally substituted C_1-C_6 acyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted amino, or $-SO_2R^5$;

 is optionally substituted arylene, optionally substituted 5-membered heteroarylene, or optionally substituted 6-membered heteroarylene;

m is 0, 1, 2, or 3;

B is an optionally substituted 6- to 10-membered bicyclic heteroarylene;

C is optionally substituted 3- to 10-membered cycloalkyl; optionally substituted 6- to 10-membered aryl; optionally substituted 5- to 10-membered heteroaryl; or optionally substituted 5- to 10-membered heterocyclyl;

R^2 is hydrogen or optionally substituted C_1-C_6 alkyl;

each of R^3 and R^4 is, independently, hydrogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

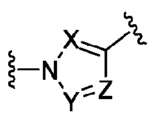
R^5 is optionally substituted C_1-C_6 alkyl or $-NR^6R^7$; and

each of R^6 and R^7 is, independently, optionally substituted C_1-C_6 alkyl,

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein  is optionally 6-membered heteroarylene.

3.. The compound of claim 1, wherein  is optionally substituted 5-membered heteroarylene.

4. The compound of claim 3, wherein  is 

, wherein each X, Y, and Z is, independently, N or CR^8, wherein R^8 is H or C_1-C_6 alkyl.

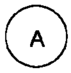
5. The compound of claim 4, wherein each of X, Y, and Z is CH.

6. The compound of claim 4, wherein X is N and each of Y and Z is CH.

7. The compound of claim 4, wherein Z is N and each of X and Y is CH.

8. The compound of claim 4, wherein Y is N and each of X and Z is CH.

9. The compound of claim 4, wherein each of X and Z is CH and Y is $C(CH_3)$.

10. The compound of claim 1, where 

is arylene.

11. The compound of any one of claims 1 to 10, wherein R^2 is hydrogen.

12. The compound of any one of claims 1 to 11, wherein m is 1.

13. The compound of any one of claims 1 to 12, wherein R^4 is hydrogen.

14. The compound of any one of claims 1 to 13, wherein R^3 is hydrogen.

15. The compound of any one of claims 1 to 13, wherein R^3 is optionally substituted C_1-C_6 alkyl.

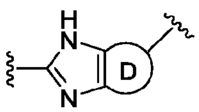
16. The compound of claim 15, wherein R^3 is methyl.

17. The compound of any one of claims 1 to 13, wherein R^3 is optionally substituted C_1-C_6 heteroalkyl.

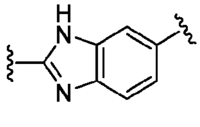
18. The compound of claim 17, wherein R^3 is $-CH_2OCH_3$.

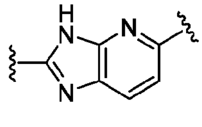
19. The compound of any one of claims 1 to 18, wherein B is a 9- or 10-membered heteroarylene.

20. The compound of claim 19, wherein B has the structure:



wherein D is an optionally substituted 5- or 6-membered heteroaryl or optionally substituted 5- or 6-membered heterocyclyl.

21. The compound of claim 20, wherein B is 

or 

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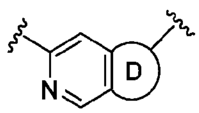
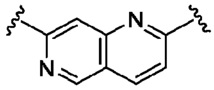
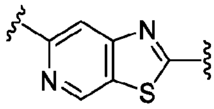
22. The compound of claim 19, wherein B has the structure:



wherein D is an optionally substituted 5- or 6-membered heteroaryl or optionally substituted 5- or 6-membered heterocyclyl.

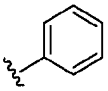
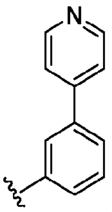
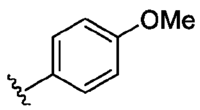
23. The compound of claim 22, wherein B is  or .

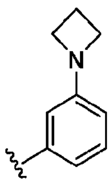
24. The compound of any one of claims 1 to 23, wherein C is optionally substituted C_3-C_{10} cycloalkyl.

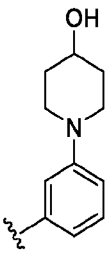
25. The compound of claim 24, wherein C is cyclopropyl.

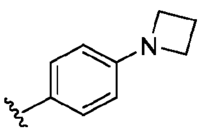
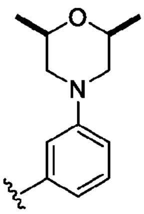
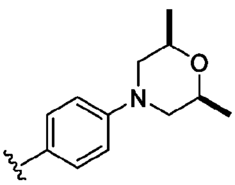
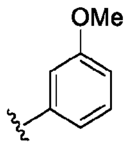
26. The compound of any one of claims 1 to 23, wherein C is optionally substituted C_6-C_{10} aryl.

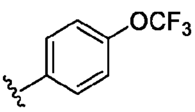
27. The compound of claim 26, wherein C is optionally substituted phenyl.

28. The compound of claim 27, wherein C is , , 

, ,



, , , , 

, 

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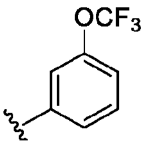
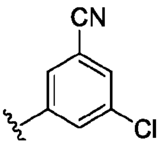
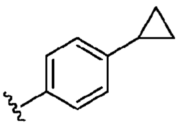
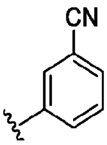
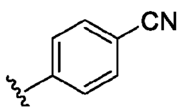
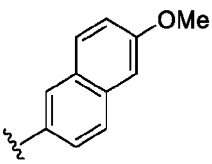


, 

, , 

, 

, 

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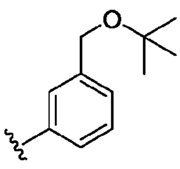
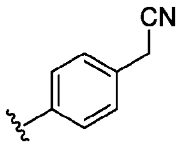
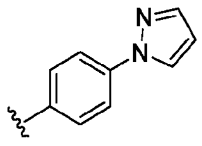
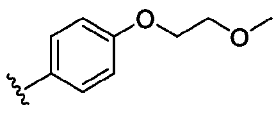
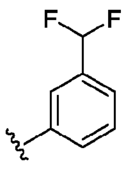
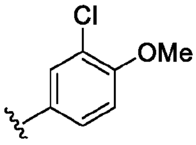
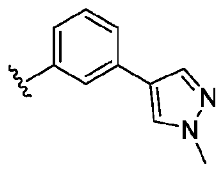
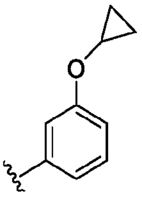
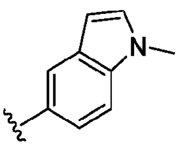
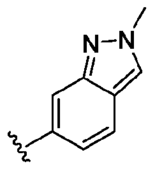
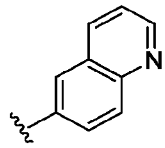
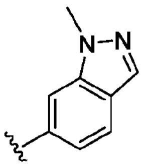
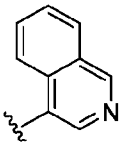
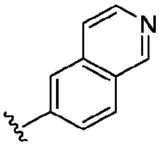
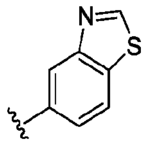
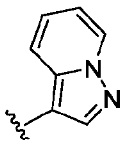
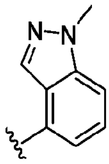
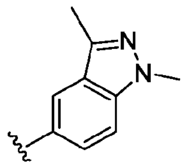
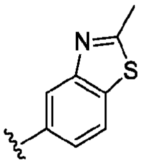
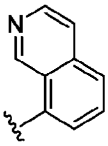
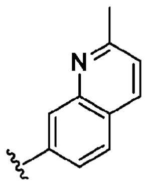
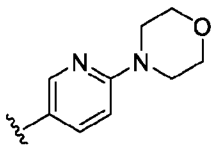
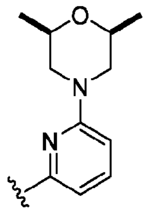
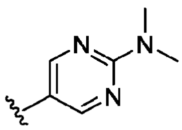
, , , , ,

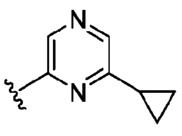
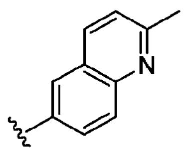
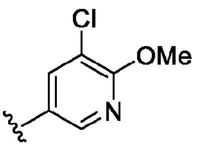
, , or .

29. The compound of any one of claims 1 to 23, wherein C is optionally substituted 5- to 10-membered heteroaryl.

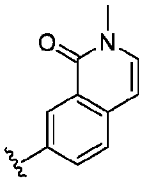
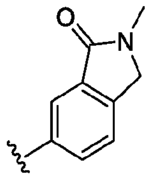
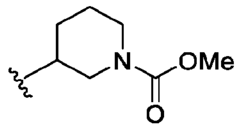
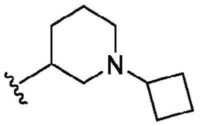
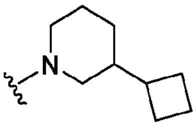
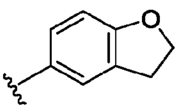
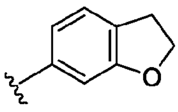
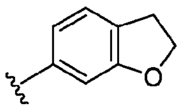
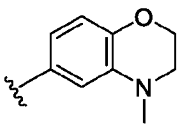
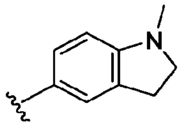
30. The compound of claim 29, wherein C is , , ,

, , , , , , ,

, , , , , ,

, , or .

31. The compound of any one of claims 1 to 23, wherein C is optionally substituted 5- to 10-membered heterocyclyl.

32. The compound of claim 31, wherein C is , , , , , , , , , or .

33. The compound of claim 1, wherein the compound is any one of Compounds 1-82 in Table 1.

34. A pharmaceutical composition comprising a compound of any one of claims 1 to 33 and a pharmaceutically acceptable excipient.

35. A method of decreasing the activity of a BAF complex in a cell, the method comprising contacting the cell with an effective amount of a compound of any one of claims 1 to 33 or a pharmaceutical composition of claim 34.

36. The method of claim 35, wherein the BAF complex is in a cancer cell.

37. A method of treating a BAF complex-related disorder in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of any one of claims 1 to 33 or a pharmaceutical composition of claim 34.

38. The method of claim 37, wherein the BAF complex-related disorder is cancer or a viral infection.

39. A method of inhibiting BRM, the method comprising contacting a cell with an effective amount of a compound of any one of claims 1 to 33 or a pharmaceutical composition of claim 34.

40. The method of claim 39, wherein the cell is a cancer cell.

41. A method of treating a disorder related to a BRG1 loss of function mutation in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of any one of claims 1 to 33 or a pharmaceutical composition of claim 34.

42. The method of claim 41, wherein the disorder related to a BRG1 loss of function mutation is cancer.

43. A method of inducing apoptosis in a cell, the method comprising contacting the cell with an effective amount of a compound of any one of claims 1 to 33 or a pharmaceutical composition of claim 34.

44. The method of claim 43, wherein the cell is a cancer cell.

45. A method of treating cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of any one of claims 1 to 33 or a pharmaceutical composition of claim 34.

46. The method of claim 45, wherein the cancer is non-small cell lung cancer, colorectal cancer, bladder cancer, cancer of unknown primary, glioma, breast cancer, melanoma, non-melanoma skin cancer, endometrial cancer, esophagogastric cancer, pancreatic cancer, hepatobiliary cancer, soft tissue sarcoma, ovarian cancer, head and neck cancer, renal cell carcinoma, bone cancer, non-Hodgkin lymphoma, small-cell lung cancer, prostate cancer, embryonal tumor, germ cell tumor, cervical cancer, thyroid cancer, salivary gland cancer, gastrointestinal neuroendocrine tumor, uterine sarcoma, gastrointestinal stromal tumor, CNS cancer, thymic tumor, Adrenocortical carcinoma, appendiceal cancer, small bowel cancer, or penile cancer.

47. The method of claim 46, wherein the cancer is non-small cell lung cancer, colorectal cancer, bladder cancer, cancer of unknown primary, glioma, breast cancer, melanoma, non-melanoma skin cancer, endometrial cancer, soft tissue sarcoma, or penile cancer.

48. The method of claim 47, wherein the cancer is non-small cell lung cancer.

49. The method of claim 48, wherein the cancer is soft tissue sarcoma.

50. A method of treating a viral infection in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of any one of claims 1 to 33 or a pharmaceutical composition of claim 34.

51. The method of claim 50, wherein the viral infection is an infection with a virus of the Retroviridae family, Hepadnaviridae family, Flaviviridae family, Adenoviridae family, Herpesviridae family, Papillomaviridae family, Parvoviridae family, Polyomaviridae family, Paramyxoviridae family, or Togaviridae family.

52. A method of treating melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, or a hematologic cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of any one of claims 1 to 33 or a pharmaceutical composition of claim 34.

53. A method of reducing tumor growth of melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, or a hematologic cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of any one of claims 1 to 33 or a pharmaceutical composition of claim 34.

54. A method of suppressing metastatic progression of melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, or a hematologic cancer in a subject, the method comprising administering an effective amount of a compound of any one of claims 1 to 33 or a pharmaceutical composition of claim 34.

55. A method of suppressing metastatic colonization of melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, or a hematologic cancer in a subject, the method comprising administering an effective amount of a compound of any one of claims 1 to 33 or a pharmaceutical composition of claim 34.

56. A method of reducing the level and/or activity of BRG1 and/or BRM in a melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, or hematologic cancer cell, the method comprising contacting the cell with an effective amount a compound of any one of claims 1 to 33 or a pharmaceutical composition of claim 34.

57. The method of claim 56, wherein the cell is in a subject.

58. The method of any one of claims 52 to 57, wherein the melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, or hematologic cancer is metastatic.

59. The method of any one of claims 52 to 58, wherein the method further comprises administering to the subject or contacting the cell with an anticancer therapy.

60. The method of claim 59, wherein the anticancer therapy is a chemotherapeutic or cytotoxic agent, immunotherapy, surgery, radiotherapy, thermotherapy, or photocoagulation, or a combination thereof.

61. The method of claim 59, wherein the anticancer therapy is surgery.

62. The method of claim 59, wherein the anticancer therapy is a chemotherapeutic or cytotoxic agent.

63. The method of claim 62, wherein the chemotherapeutic or cytotoxic agent is an antimetabolite, antimitotic, antitumor antibiotic, asparagine-specific enzyme, bisphosphonates, antineoplastic, alkylating agent, DNA-Repair enzyme inhibitor, histone deacetylase inhibitor, corticosteroid, demethylating agent, immunomodulatory, janus-associated kinase inhibitor,

phosphinositide 3-kinase inhibitor, proteasome inhibitor, or tyrosine kinase inhibitor, or a combination thereof.

64. The method of claim 62 or 63, wherein the one or more chemotherapeutic or cytotoxic agent is dacarbazine, temozolomide, cisplatin, treosulfan, fotemustine, IMCgp100, a CTLA-4 inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a mitogen-activated protein kinase inhibitor, and/or a protein kinase C inhibitor.

65. The method of any one of claims 59 to 64, wherein the anticancer therapy and the compound of any one of claims 1 to 32 or a pharmaceutical composition of claim 31 are administered within 28 days of each other and each in an amount that together are effective to treat the subject.

66. The method of any one of claims 52 to 65, wherein the subject or cancer has and/or has been identified as having a BRG1 loss of function mutation.

67. The method of any one of claims 52 to 65, wherein the subject or cancer has and/or has been identified as having a BRM loss of function mutation.

68. The method of any one of claims 52 to 67, wherein the melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, or hematologic cancer has failed to respond to or progressed after administration of one or more chemotherapeutic or cytotoxic agents.

69. The method of any one of claims 52 to 68, wherein the melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, or hematologic cancer is resistant to, or predicted to be resistant to one or more chemotherapeutic agents.

70. The method of claim 68 or 69, wherein the one or more chemotherapeutic or cytotoxic agents is dacarbazine, temozolomide, cisplatin, treosulfan, fotemustine, IMCgp100, a CTLA-4 inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a mitogen-activated protein kinase inhibitor, and/or a protein kinase C inhibitor.

71. The method of any one of claims 52 to 70, wherein the melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, or hematologic cancer is melanoma.

72. The method of claim 71, wherein the melanoma is uveal melanoma.

73. The method of claim 71, wherein the melanoma is mucosal melanoma.

74. The method of claim 71, wherein the melanoma is cutaneous melanoma.

75. The method of any one of claims 52 to 70, wherein the melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, or hematologic cancer is a hematologic cancer.

76. The method of claim 75, wherein the hematologic cancer is multiple myeloma, large cell lymphoma, acute T-cell leukemia, acute myeloid leukemia, myelodysplastic syndrome, immunoglobulin A lambda myeloma, diffuse mixed histiocytic and lymphocytic lymphoma, B-cell lymphoma, acute lymphoblastic leukemia, diffuse large cell lymphoma, or non-Hodgkin's lymphoma.

77. The method of claim 75, wherein the hematologic cancer is acute myeloid leukemia.

78. The method of any one of claims 52 to 70, wherein the melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, or hematologic cancer is prostate cancer.

79. The method of any one of claims 52 to 70, wherein the melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, or hematologic cancer is breast cancer.

80. The method of claim 79, wherein the breast cancer is an ER positive breast cancer, an ER negative breast cancer, triple positive breast cancer, or triple negative breast cancer.

81. The method of any one of claims 52 to 70, wherein the melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, or hematologic cancer is bone cancer.

82. The method of claim 81, wherein the bone cancer is Ewing's sarcoma.

83. The method of any one of claims 52 to 71, wherein the melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, or hematologic cancer is renal cell carcinoma.

84. The method of claim 83, wherein the renal cell carcinoma is Microphthalmia Transcription Factor (MITF) family translocation renal cell carcinoma.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/15878

A. CLASSIFICATION OF SUBJECT MATTER
IPC - A61K 31/495 (2021.01)

CPC - A61K 31/495; A61P 1/14; A61P 11/00; A61P 15/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PubChem-SID-172131678, Modify Date: 9 December 2014 (09.12.2014), pg 2, Fig.	1,10-11
A	US 2010/0048565 A1 (FRENKEL et al.) 25 February 2010 (25.02.2010), especially: Fig. 1d, formula 16.	1,10-11
A	US 2018/0105500 A1 (DUKE UNIVERSITY) 19 April 2018 (19.04.2018), entire document.	1,10-11

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 May 2021	JUN 04 2021
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Lee Young Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/15878

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 12-32 and 34-84
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
(see extra sheet)

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1 and 10-11

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

--BOX III - LACK OF UNITY--

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I+: Claims 1-11 and 33 directed to a compound of Formula I or a pharmaceutically acceptable salt thereof. The compound of Formula I will be searched to the extent that it encompasses the first species of claim 1, wherein R1 is H; A is unsubstituted arylene; m is 0; B is unsubstituted 9-membered bicyclic heteroarylene; C is unsubstituted 3-membered cycloalkyl; R2 is hydrogen; wherein B is the first species of claim 21 (benzimidazole). It is believed that claims 1 and 10-11 encompass this first named invention, and thus these claims will be searched without fee to the extent that they encompass the first species of claim 1. Applicant is invited to elect additional compounds of Formula I, wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be a compound of claim 1, wherein R1 is H; A is unsubstituted 6-membered heteroarylene; m is 0; B is unsubstituted 9-membered bicyclic heteroarylene; C is unsubstituted 3-membered cycloalkyl; R2 is hydrogen; wherein B is the first species of claim 21 (benzimidazole, i.e. claims 1-2 and 11).

The groups of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group I+ includes the technical feature of a unique compound of Formula I, which is not required by any other invention of Group I+.

Common technical features:

The inventions of Groups I+ share the technical feature of a compound having the structure of Formula I.

These shared technical features, however, do not provide a contribution over the prior art, as being anticipated by US 2010/0048565 A1 to Frenkel et al. (hereinafter 'FRENKEL').

Frenkel teaches a compound having the structure of Formula I wherein R1 is H; A is nitro substituted arylene; m is 0; B is fluoro substituted 9-membered bicyclic heteroarylene; C is hydroxyl substituted 6-membered cycloalkyl; R2 is hydrogen (Fig. 1d, formula 16; see also instant specification pg 16, ln 39 to pg 17, ln 6, The alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl (e.g., cycloalkyl) aryl, heteroaryl, and heterocyclyl groups may be substituted or unsubstituted... Substituents include... halo (e.g., fluoro), hydroxyl... nitro).

As said compound was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the inventions of Group I+.

The inventions of Group I+ thus lack unity under PCT Rule 13.

Notes:

Claims 12-32 and 34-84 are unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).