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(54) Title: NOVEL COMPOUNDS AS PKMYT1 INHIBITORS AND USE THEREOF

(57) Abstract: Disclosed are compounds or pharmaceutically acceptable salts, stereoisomer, or isotopic variant thereof useful as PKMYT1 inhibitors, pharmaceutical compositions comprising the same, and use thereof in the treatment of PKMYT1-associated diseases or conditions such as cancer.

NOVEL COMPOUNDS AS PKMYT1 INHIBITORS AND USE THEREOF

CROSS-REFERENCE

[0001] This patent application claims the benefit of International Application No. PCT/CN2023/119295, filed September 18, 2023; which is incorporated herein by reference in its entirety.

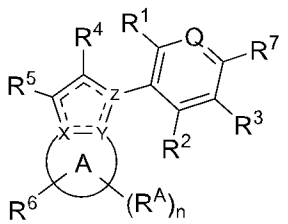
BACKGROUND

[0002] DNA is continuously subjected to both endogenous insults (e.g., stalled replication forks, reactive oxygen species) and exogenous insults (UV, ionizing radiation, chemical) that can lead to DNA damage. As a result, cells have established sophisticated mechanisms to counteract these deleterious events that would otherwise compromise genomic integrity and lead to genomic instability diseases such as tumor. To maintain genomic integrity, two checkpoints of cell cycle allow for efficient repair of DNA damages, one of which is the WEE kinase family. The WEE kinase family consists of three members: WEE1, PKMYT1, and the less important WEE1B. PKMYT1 functions as negative regulators of the cell cycle by inhibiting the CDK1-cyclin B complex. CDK1, a master regulator of the cell cycle, is essential for entry into mitosis, meaning that PKMYT1 might be expected to act as tumor suppressors by preventing CDK1 activation. Studies showed that loss of PKMYT1 interferes with the G2-M checkpoint, driving cells into mitosis prematurely, which results in the accumulation of genetic lesions from unrepaired DNA damage, ultimately leading to apoptosis or mitotic catastrophe. However, the concomitant inhibition of WEE1 and PKMYT1 leads to strong cytotoxic effects. Thus, PKMYT1 is a promising target for anti-cancer therapy. Moreover, PKMYT1 has also been implicated in many cancer types, including gastric cancer, non-small-cell lung cancer, hepatocellular carcinoma, glioblastoma, neuroblastoma, and colorectal cancer, etc., in which overexpression of PKMYT1 generally correlates with poor prognosis and disease progression. Therefore, selective targeting PKMYT1 with small molecules provides new opportunities for cancer therapy.

SUMMARY

[0003] Disclosed herein are novel compounds as PKMYT1 inhibitors. As a result, the compounds of the present disclosure are particularly useful in the modulation of PKMYT1 and thus in the treatment of PKMYT1-associated diseases and conditions.

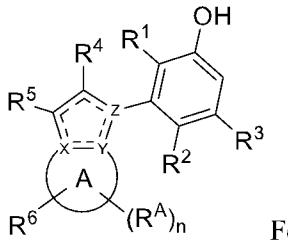
[0004] In one aspect, the present disclosure provides a compound of Formula (V), or a pharmaceutically acceptable salt thereof:



Formula (V),

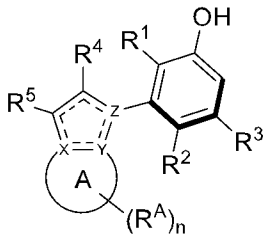
as disclosed herein.

[0005] In one aspect, the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof:



Formula (I), as disclosed herein.

[0006] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, the compound is of Formula (Ia):



Formula (Ia), as disclosed herein.

[0007] Also disclosed herein is a pharmaceutical composition comprising a compound disclosed herein (e.g., a compound of Formula (V), (I), (Ia) or a compound set forth in Table 1 or Table 2), or a pharmaceutically acceptable salt thereof, or stereoisomer thereof, and a pharmaceutically acceptable excipient.

[0008] Also disclosed herein is a method of treating cancer in a subject in need thereof, the method comprising administering to the subject the compound disclosed herein (e.g., a compound of Formula (V), (I), (Ia) or a compound set forth in Table 1 or Table 2), or a pharmaceutically acceptable salt, or stereoisomer thereof, or the pharmaceutical composition disclosed herein.

[0009] Also disclosed herein is a method of modulating PKMYT1 in a subject, the method comprising administering to the subject the compound disclosed herein (e.g., a compound of Formula (V), (I), (Ia) or a compound set forth in Table 1 or Table 2), or a pharmaceutically acceptable salt, or stereoisomer thereof, or the pharmaceutical composition disclosed herein.

[0010] Also disclosed herein is a method of inhibiting PKMYT1 in a subject, the method comprising administering to the subject the compound disclosed herein (e.g., a compound of Formula (V), (I), (Ia) or a compound set forth in Table 1 or Table 2), or a pharmaceutically acceptable salt, or stereoisomer thereof, or the pharmaceutical composition disclosed herein. In some embodiments, the subject has cancer. In some embodiments, the cancer depends on the activity of PKMYT1. In some embodiments, the cancer overexpresses CCNE1. In some embodiments, the cancer has an inactivating mutation in the FBXW7 gene. In some embodiments, the cancer is a solid tumor. In some embodiments, the cancer is breast cancer, colorectal cancer, endometrial cancer, esophageal

cancer, glioblastoma, hepatocellular carcinoma, lung cancer, neuroblastoma, ovarian cancer, prostate cancer, stomach cancer, or uterine cancer.

[0011] Also disclosed herein is a pharmaceutical composition for treating a PKMYT1-associated disease or condition, comprising the compound disclosed herein (e.g., a compound of Formula (V), (I), (Ia) or a compound set forth in Table 1 or Table 2), or a pharmaceutically acceptable salt, or stereoisomer thereof, and a pharmaceutically acceptable excipient.

[0012] Also disclosed herein is use of the compound disclosed herein (e.g., a compound of Formula (V), (I), (Ia) or a compound set forth in Table 1 or Table 2), or a pharmaceutically acceptable salt, or stereoisomer thereof, or the pharmaceutical composition disclosed herein in the manufacture of a medicament for treating a PKMYT1-associated disease or condition, such as cancer.

[0013] A kit for treating a PKMYT1-associated disease or condition such as cancer, comprising the compound disclosed herein (e.g., a compound of Formula (V), (I), (Ia) or a compound set forth in Table 1 or Table 2), or a pharmaceutically acceptable salt, or stereoisomer thereof, or the pharmaceutical composition disclosed herein, a container, and optionally a package insert or label indicating treatment of said disease or condition.

INCORPORATION BY REFERENCE

[0014] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

DETAILED DESCRIPTION

Definitions

[0015] In the following description, certain specific details are set forth in order to provide a thorough understanding of various embodiments. However, one skilled in the art will understand that the invention may be practiced without these details. In other instances, well-known structures have not been shown or described in detail to avoid unnecessarily obscuring descriptions of the embodiments. Unless the context requires otherwise, throughout the specification and claims which follow, the word "comprise" and variations thereof, such as, "comprises" and "comprising" are to be construed in an open, inclusive sense, that is, as "including, but not limited to." Further, headings provided herein are for convenience only and do not interpret the scope or meaning of the claimed invention.

[0016] Reference throughout this specification to "some embodiments" or "an embodiment" means that a particular feature, structure, or characteristic described in connection with the embodiment is included in at least one embodiment. Thus, the appearances of the phrases "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features, structures, or characteristics may be

combined in any suitable manner in one or more embodiments. Also, as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the content clearly dictates otherwise. It should also be noted that the term "or" is generally employed in its sense including "and/or" unless the content clearly dictates otherwise.

[0017] The terms below, as used herein, have the following meanings, unless indicated otherwise.

[0018] Definitions of specific functional groups and chemical terms are described in more detail below. For purposes of this disclosure, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Organic Chemistry, Thomas Sorrell, 2nd Edition, University Science Books, Sausalito, 2006; Smith and March March's Advanced Organic Chemistry, 6th Edition, John Wiley & Sons, Inc., New York, 2007; Larock, Comprehensive Organic Transformations, 3rd Edition, VCH Publishers, Inc., New York, 2018; Carruthers, Some Modern Methods of Organic Synthesis, 4th Edition, Cambridge University Press, Cambridge, 2004; the entire contents of each of which are incorporated herein by reference.

[0019] At various places in the present disclosure, linking substituents are described. Where the structure clearly requires a linking group, the Markush variables listed for that group are understood to be linking groups. For example, if the structure requires a linking group and the Markush group definition for that variable lists "alkyl", then it is understood that the "alkyl" represents a linking alkylene group.

[0020] When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom in the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such formula. Combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

[0021] When any variable (e.g., R^i) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R^i moieties, then the group may optionally be substituted with up to two R^i moieties and R^i at each occurrence is selected independently from the definition of R^i. Also, combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

[0022] As used herein, the term "C_i-C_j" indicates a range of the carbon atoms numbers, wherein i and j are integers and the range of the carbon atoms numbers includes the endpoints (i.e. i and j) and each integer point in between, and wherein j is greater than i. For examples, C_1-C_6 indicates a range of one to six carbon atoms, including one carbon atom, two carbon atoms, three carbon atoms, four

carbon atoms, five carbon atoms and six carbon atoms. In some embodiments, the term "C_{1-12}" indicates 1 to 12, particularly 1 to 10, particularly 1 to 8, particularly 1 to 6, particularly 1 to 5, particularly 1 to 4, particularly 1 to 3 or particularly 1 to 2 carbon atoms.

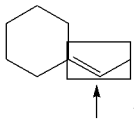
[0023] "Oxo" refers to =O.

[0024] "Amino", whether as part of another term or used independently, refers to the group -NR^aR^b, wherein R^a and R^b are independently selected from groups consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl or other suitable organic groups and each of which may be optionally substituted.

[0025] "Hydroxy" or "hydroxyl", whether as part of another term or used independently, refers to -OH.

[0026] "Alkyl", whether as part of another term or used independently, refers to a straight-chain, or branched-chain saturated hydrocarbon monoradical having from one to about ten carbon atoms, more preferably one to six carbon atoms. Examples include, but are not limited to methyl, ethyl, n-propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, tert-amyl and hexyl, and longer alkyl groups, such as heptyl, octyl and the like. Whenever it appears herein, a numerical range such as "C_1-C_6 alkyl" or "C_{1-6}alkyl", means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated. In some embodiments, the alkyl is a C_{1-10}alkyl. In some embodiments, the alkyl is a C_{1-6}alkyl. In some embodiments, the alkyl is a C_{1-5}alkyl. In some embodiments, the alkyl is a C_{1-4}alkyl. In some embodiments, the alkyl is a C_{1-3}alkyl. Unless stated otherwise specifically in the specification, an alkyl group may be optionally substituted, for example, with one or more substituents, such as oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkyl is optionally substituted with one or more substituents, such as oxo, halogen, -CN, -COOH, -COOMe, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, the alkyl is optionally substituted with one or more substituents, such as halogen, -CN, -OH, or -OMe. In some embodiments, the alkyl is optionally substituted with halogen.

[0027] "Alkylidenyl" is a divalent group formed from alkanes by removal of two hydrogen atoms from the same carbon atom, the free valencies of which are part of a double bond attached to the rest part of the molecule. For example, in the compound below:



the alkylidenyl group is enclosed by the box which is indicated by the arrow.

[0028] "Alkenyl", whether as part of another term or used independently, refers to a straight-chain, or branched-chain hydrocarbon monoradical having one or more carbon-carbon double-bonds and having from two to about ten carbon atoms, more preferably two to about six carbon atoms. The group may be in either the *cis* or *trans* conformation, or alternatively, *E* or *Z* conformation about the double bond(s), and should be understood to include both isomers. Examples include, but are not limited to ethenyl (-CH=CH_2), 1-propenyl (-CH_2CH=CH_2), isopropenyl [-C(CH_3)=CH_2], butenyl, 1,3-butadienyl and the like. Whenever it appears herein, a numerical range such as "C_2-C_6 alkenyl" or "C_{2-6}alkenyl", means that the alkenyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term "alkenyl" where no numerical range is designated. Unless stated otherwise specifically in the specification, an alkenyl group may be optionally substituted, for example, with one or more substituents, such as oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkenyl is optionally substituted with one or more substituents, such as oxo, halogen, -CN, -COOH, -COOMe, -OH, -OMe, -NH_2, or -NO_2. In some embodiments, the alkenyl is optionally substituted with one or more substituents, such as halogen, -CN, -OH, or -OMe. In some embodiments, the alkenyl is optionally substituted with halogen.

[0029] "Alkynyl", whether as part of another term or used independently, refers to a straight-chain or branched-chain hydrocarbon monoradical having one or more carbon-carbon triple-bonds and having from two to about ten carbon atoms, more preferably from two to about six carbon atoms. Examples include, but are not limited to ethynyl, 2-propynyl, 2-butynyl, 1,3-butadiynyl and the like. Whenever it appears herein, a numerical range such as "C_2-C_6alkynyl" or "C_{2-6}alkynyl", means that the alkynyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term "alkynyl" where no numerical range is designated. Unless stated otherwise specifically in the specification, an alkynyl group may be optionally substituted, for example, with one or more substituents, such as oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkynyl is optionally substituted with one or more substituents, such as oxo, halogen, -CN, -COOH, COOMe, -OH, -OMe, -NH_2, or -NO_2. In some embodiments, the alkynyl is optionally substituted with one or more substituents, such as halogen, -CN, -OH, or -OMe. In some embodiments, the alkynyl is optionally substituted with halogen.

[0030] "Alkoxy", whether as part of another term or used independently, refers to a radical of the formula -OR_a where R_a is an alkyl radical as defined. Whenever it appears herein, a numerical range

such as "C_1-C_6 alkoxy" or "C_{1-6}alkoxy", means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term "alkoxy" where no numerical range is designated. In some embodiments, the alkoxy is a C_{1-10}alkoxy. In some embodiments, the alkoxy is a C_{1-6}alkoxy. In some embodiments, the alkoxy is a C_{1-5}alkoxy. In some embodiments, the alkoxy is a C_{1-4}alkoxy. In some embodiments, the alkyl is a C_{1-3}alkoxy. In some embodiments, the alkyl is a C_{1-2}alkoxy. In some embodiments, the alkyl is methoxy. Unless stated otherwise specifically in the specification, an alkoxy group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkoxy is optionally substituted with halogen, -CN, -COOH, COOMe, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, the alkoxy is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkoxy is optionally substituted with halogen.

[0031] "Aryl", whether as part of another term or used independently, refers to a radical derived from a hydrocarbon ring system comprising 6 to 30 carbon atoms and at least one aromatic ring. The aryl radical may be a monocyclic or polycyclic (including but not limited to, bicyclic, tricyclic, or tetracyclic) ring system, which may include fused (for example, fused with a cycloalkyl, heterocycloalkyl or heteroaryl ring, the aryl is bonded through an aromatic ring atom) or bridged ring systems. In some embodiments, the aryl is a 6- to 10-membered aryl. In some embodiments, the aryl is a 6-membered aryl (phenyl). Aryl radicals include, but are not limited to, aryl radicals derived from the hydrocarbon ring systems of anthrylene, naphthylene, phenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, as-indacene, s-indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, pyrene, and triphenylene. Unless stated otherwise specifically in the specification, an aryl may be optionally substituted, for example, with one or more substituents, such as halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the aryl is optionally substituted with one or more substituents, such as halogen, methyl, ethyl, -CN, -COOH, COOMe, $-CF_3$, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, the aryl is optionally substituted with one or more substituents, such as halogen, methyl, ethyl, -CN, $-CF_3$, -OH, or -OMe. In some embodiments, the aryl is optionally substituted with halogen.

[0032] "Aminoalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more aminos. In some embodiments, the alkyl is substituted with one amino. In some embodiments, the alkyl is substituted with one, two, or three aminos. Aminoalkyl include, for example, aminomethyl, aminoethyl, aminopropyl, aminobutyl, or aminopentyl. In some embodiments, the aminoalkyl is aminomethyl.

[0033] "Cycloalkyl", whether as part of another term or used independently, refers to a partially or fully saturated, monocyclic, or polycyclic carbocyclic ring, which may include fused (for example,

fused with a heterocycloalkyl or another cycloalkyl ring), spiro, or bridged ring systems. In some embodiments, the cycloalkyl is fully saturated. In some embodiments, the cycloalkyl is partially saturated. Representative cycloalkyls include, but are not limited to, cycloalkyls having from three to fifteen carbon atoms (C_3-C_{15} cycloalkyl), from three to ten carbon atoms (C_3-C_{10} cycloalkyl), from three to eight carbon atoms (C_3-C_8 cycloalkyl), from three to six carbon atoms (C_3-C_6 cycloalkyl), from three to five carbon atoms (C_3-C_5 cycloalkyl or), or three to four carbon atoms (C_3-C_4 cycloalkyl). Monocyclic cycloalkyls include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyls include, for example, adamantyl, norbornyl, decalinyl, bicyclo[3.3.0]octane, bicyclo[4.3.0]nonane, cis-decalin, trans-decalin, bicyclo[2.1.1]hexane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, and bicyclo[3.3.2]decane, and 7,7-dimethyl-bicyclo[2.2.1]heptanyl. Partially saturated cycloalkyls include, for example cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. Unless stated otherwise specifically in the specification, a cycloalkyl is optionally substituted, for example, with one or more substituents, such as oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a cycloalkyl is optionally substituted with one or more substituents, such as oxo, halogen, methyl, ethyl, -CN, -COOH, COOMe, -CF_3, -OH, -OMe, -NH_2, or -NO_2. In some embodiments, a cycloalkyl is optionally substituted with one or more substituents, such as oxo, halogen, methyl, ethyl, -CN, -CF_3, -OH, or -OMe. In some embodiments, the cycloalkyl is optionally substituted with halogen.

[0034] "Halo" or "halogen" refers to bromo, chloro, fluoro or iodo. In some embodiments, halogen is fluoro or chloro. In some embodiments, halogen is fluoro.

[0035] "Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like.

[0036] "Hydroxyalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more hydroxyls. In some embodiments, the alkyl is substituted with one hydroxyl. In some embodiments, the alkyl is substituted with one, two, or three hydroxyls. Hydroxyalkyl include, for example, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, or hydroxypentyl. In some embodiments, the hydroxyalkyl is hydroxymethyl.

[0037] "Heteroalkyl" refers to an alkyl group in which one or more skeletal atoms of the alkyl are selected from an atom other than carbon, e.g., oxygen, nitrogen (e.g., -NH-, -N(alkyl)-), sulfur, phosphorus, or combinations thereof. A heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. In one aspect, a heteroalkyl is a C_1-C_6 heteroalkyl wherein the heteroalkyl is comprised of 1 to 6 carbon atoms and one or more atoms other than carbon, e.g., oxygen, nitrogen (e.g. -NH-, -N(alkyl)-), sulfur, phosphorus, or combinations thereof wherein the heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. Examples of such heteroalkyl

are, for example, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2CH_2OCH_2CH_2OCH_3$, $-CH(CH_3)OCH_3$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CH_2CH_2NHCH_3$, or $-CH_2CH_2N(CH_3)_2$. Unless stated otherwise specifically in the specification, a heteroalkyl is optionally substituted for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a heteroalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, $-CF_3$, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, a heteroalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, $-CF_3$, -OH, or -OMe. In some embodiments, the heteroalkyl is optionally substituted with halogen.

[0038] "Heteroalkenyl" refers to an alkenyl group in which one or more skeletal atoms of the alkenyl are selected from an atom other than carbon, e.g., oxygen, nitrogen, sulfur, phosphorus, or combinations thereof. A heteroalkenyl is attached to the rest of the molecule at a carbon atom of the heteroalkenyl. In one aspect, a heteroalkenyl is a C_2-C_6 heteroalkenyl wherein the heteroalkenyl is comprised of 2 to 6 carbon atoms and one or more atoms other than carbon, e.g., oxygen, nitrogen, sulfur, phosphorus, or combinations thereof wherein the heteroalkenyl is attached to the rest of the molecule at a carbon atom of the heteroalkenyl. Examples of such heteroalkenyl are, for example, $-CH=CHOCH_3$, $-CH=CHOCH_2CH_2OCH_3$, $-CH_2CH_2OCH=CHOCH_3$, $-C(=CH_2)OCH_3$, $-CH=NCH_3$, $-CH_2N=CH_2$,$-CH=CHNHCH_3$, or $-CH=CHN(CH_3)_2$. Unless stated otherwise specifically in the specification, a heteroalkenyl is optionally substituted for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a heteroalkenyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, $-CF_3$, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, a heteroalkenyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, $-CF_3$, -OH, or -OMe. In some embodiments, the heteroalkenyl is optionally substituted with halogen.

[0039] "Heteroalkynyl" refers to an alkynyl group in which one or more skeletal atoms of the alkynyl are selected from an atom other than carbon, e.g., oxygen, nitrogen, sulfur, phosphorus, or combinations thereof. A heteroalkynyl is attached to the rest of the molecule at a carbon atom of the heteroalkynyl. In one aspect, a heteroalkynyl is a C_2-C_6 heteroalkynyl wherein the heteroalkynyl is comprised of 2 to 6 carbon atoms and one or more atoms other than carbon, e.g., oxygen, nitrogen, sulfur, phosphorus, or combinations thereof wherein the heteroalkynyl is attached to the rest of the molecule at a carbon atom of the heteroalkynyl. Examples of such heteroalkynyl are, for example, $-C\equiv COCH_3$, $-C\equiv COCH_2CH_2OCH_3$, $-CH_2CH_2OC\equiv COCH_3$, $-C\equiv C-NHCH_3$, or $-C\equiv C-N(CH_3)_2$. Unless stated otherwise specifically in the specification, a heteroalkynyl is optionally substituted for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a heteroalkynyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, $-CF_3$, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, a heteroalkynyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, $-CF_3$, -OH, or -OMe. In some embodiments, the heteroalkynyl is optionally substituted with halogen.

[0040] "Heterocycloalkyl", whether as part of another term or used independently, refers to a 3- to 24-membered partially or fully saturated ring radical comprising 2 to 23 carbon atoms and from 1 to 8 heteroatoms selected from the group consisting of nitrogen, oxygen, phosphorous, silicon, and sulfur. In some embodiments, the heterocycloalkyl is fully saturated. In some embodiments, the heterocycloalkyl is partially saturated. In some embodiments, the heterocycloalkyl comprises one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur. In some embodiments, the heterocycloalkyl comprises one to three heteroatoms selected from the group consisting of nitrogen and oxygen. In some embodiments, the heterocycloalkyl comprises one to three nitrogens. In some embodiments, the heterocycloalkyl comprises one or two nitrogens. In some embodiments, the heterocycloalkyl comprises one nitrogen. In some embodiments, the heterocycloalkyl comprises one nitrogen and one oxygen. Unless stated otherwise specifically in the specification, the heterocycloalkyl radical may be a monocyclic or polycyclic (including but not limited to, bicyclic, tricyclic, or tetracyclic) ring system, which may include fused (for example, fused with a cycloalkyl or another heterocycloalkyl ring), spiro, or bridged ring systems; and the nitrogen, carbon, or sulfur atoms in the heterocycloalkyl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. Representative heterocycloalkyls include, but are not limited to, heterocycloalkyls having from two to fifteen carbon atoms (C_2-C_{15} heterocycloalkyl), from two to ten carbon atoms (C_2-C_{10} heterocycloalkyl), from two to eight carbon atoms (C_2-C_8 heterocycloalkyl), from two to seven carbon atoms (C_2-C_7 heterocycloalkyl), from two to six carbon atoms (C_2-C_6 heterocycloalkyl), from two to five carbon atoms (C_2-C_5 heterocycloalkyl), or two to four carbon atoms (C_2-C_4 heterocycloalkyl). Examples of such heterocycloalkyl radicals include, but are not limited to, aziridinyl, azetidinyl, oxetanyl, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, 1,3-dihydroisobenzofuran-1-yl, 3-oxo-1,3-dihydroisobenzofuran-1-yl, methyl-2-oxo-1,3-dioxol-4-yl, and 2-oxo-1,3-dioxol-4-yl. The term heterocycloalkyl also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides, and the oligosaccharides. In some embodiments, heterocycloalkyls have from 2 to 10 carbons in the ring. It is understood that when referring to the number of carbon atoms in a heterocycloalkyl, the number of carbon atoms in the heterocycloalkyl is not the same as the total number of atoms (including the heteroatoms) that make up the heterocycloalkyl (i.e. skeletal atoms of the heterocycloalkyl ring). In some embodiments, the heterocycloalkyl is a 3- to 8-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 3- to 7-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 3- to 6-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 4- to 6-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 5- to 6-

membered heterocycloalkyl. Unless stated otherwise specifically in the specification, a heterocycloalkyl may be optionally substituted as described below, for example, with one or more substituents, such as oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the heterocycloalkyl is optionally substituted with one or more substituents, such as oxo, halogen, methyl, ethyl, -CN, -COOH, -COOMe, $-CF_3$, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, the heterocycloalkyl is optionally substituted with one or more substituents, such as halogen, methyl, ethyl, -CN, $-CF_3$, -OH, or -OMe. In some embodiments, the heterocycloalkyl is optionally substituted with halogen.

[0041] "Heteroaryl", whether as part of another term or used independently, refers to a 5- to 14-membered ring system radical comprising one to thirteen carbon atoms, one to six heteroatoms selected from the group consisting of nitrogen, oxygen, phosphorous, and sulfur, and at least one aromatic ring. In some embodiments, the heteroaryl comprises one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur. In some embodiments, the heteroaryl comprises one to three heteroatoms selected from the group consisting of nitrogen and oxygen. In some embodiments, the heteroaryl comprises one to three nitrogens. In some embodiments, the heteroaryl comprises one or two nitrogens. In some embodiments, the heteroaryl comprises one nitrogen. The heteroaryl radical may be a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may include fused (for example fused with a cycloalkyl, heterocycloalkyl or aryl ring) or bridged ring systems; and the nitrogen, carbon, or sulfur atoms in the heteroaryl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. In some embodiments, the heteroaryl is a 5- to 10-membered heteroaryl. In some embodiments, the heteroaryl is a 5- to 6-membered heteroaryl. In some embodiments, the heteroaryl is a 6-membered heteroaryl. In some embodiments, the heteroaryl is a 5-membered heteroaryl. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[b][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furyl, furanonyl, isothiazolyl, imidazolyl, indazolyl, indolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1H-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, tetrahydroquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl (i.e., thienyl). It should be appreciated that any ring system satisfying Hückel's Rule is considered as aromatic ring. Therefore, "heteroaryl" also includes both tautomers such as hydroxyl pyridyl and

pyridonyl, hydroxyl pyrimidinyl and pyrimidonyl, hydroxyl pyrazinyl and pyrazonyl, and hydroxyl triazinyl and triazonyl, or polycyclic system thereof. Unless stated otherwise specifically in the specification, a heteroaryl may be optionally substituted, for example, with one or more substituents, such as halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the heteroaryl is optionally substituted with one or more substituents, such as halogen, methyl, ethyl, -CN, -COOH, COOMe, $-CF_3$, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, the heteroaryl is optionally substituted with one or more substituents, such as halogen, methyl, ethyl, -CN, $-CF_3$, -OH, or -OMe. In some embodiments, the heteroaryl is optionally substituted with halogen.

[0042] The term "cycloalkyl-alkyl" or "alkyl-cycloalkyl" used interchangeably herein, whether as part of another term or used independently, refers to an alkyl group substituted with one cycloalkyl group on any carbon atom of the alkyl group or a cycloalkyl group substituted with one alkyl group on any carbon atom of the cycloalkyl group. A cycloalkyl-alkyl may be bonded to the rest of a compound via the cycloalkyl moiety or alkyl moiety. Unless stated otherwise specifically in the specification, both the cycloalkyl moiety and alkyl moiety of a cycloalkyl-alkyl may be optionally substituted with one or more groups as described above.

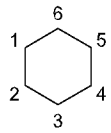
[0043] The term "heterocycloalkyl-alkyl" or "alkyl-heterocycloalkyl" used interchangeably herein, whether as part of another term or used independently, refers to an alkyl group substituted with one heterocycloalkyl group on any carbon atom of the alkyl group or a heterocycloalkyl group substituted with one alkyl group on any carbon atom or heteroatom of the heterocycloalkyl group. A heterocycloalkyl-alkyl may be bonded to the rest of a compound via the heterocycloalkyl moiety or alkyl moiety. Unless stated otherwise specifically in the specification, both the heterocycloalkyl moiety and alkyl moiety of a heterocycloalkyl-alkyl may be optionally substituted with one or more groups as described above.

[0044] The term "arylalkyl" or "alkylaryl" used interchangeably herein, whether as part of another term or used independently, refers to an alkyl group substituted with one aryl group on any carbon atom of the alkyl group or an aryl group substituted with one alkyl group on any carbon atom of the aryl group. An arylalkyl may be bonded to the rest of a compound via the aryl moiety or alkyl moiety. Unless stated otherwise specifically in the specification, both the aryl moiety and alkyl moiety of an arylalkyl may be optionally substituted with one or more groups as described above.

[0045] The term "heteroarylalkyl" or "alkylheteroaryl" used interchangeably herein, whether as part of another term or used independently, refers to an alkyl group substituted with one heteroaryl group on any carbon atom of the alkyl group or an heteroaryl group substituted with one alkyl group on any carbon atom or heteroatom of the heteroaryl group. A heteroarylalkyl may be bonded to the rest of a compound via the heteroaryl moiety or alkyl moiety. Unless stated otherwise specifically in the specification, both the heteroaryl moiety and alkyl moiety of a heteroarylalkyl may be optionally substituted with one or more groups as described above.

[0046] The term "partially saturated" or "partially unsaturated" refers to a radical that includes at least one double or triple bond, and is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aromatic (i.e., fully unsaturated) moieties.

[0047] When two atoms are directly connected via one bond (e.g., a single bond, double bond or triple bond), then these two atoms are "adjacent" to each other. When two atoms are connected via one or more other atoms and two or more bonds (e.g., a single bond, double bond or triple bond), then these two atoms are not adjacent or "non-adjacent" to each other. For example, in the following hexane, Carbon Atom 1 and Carbon Atom 2 or Carbon Atom 1 and Carbon Atom 6 are "adjacent" atoms; whereas Carbon Atom 1 and Carbon Atom 3, Carbon Atom 1 and Carbon Atom 4 or Carbon Atom 1 and Carbon Atom 5 are "non-adjacent" atoms.



Hexane with carbon atom numbers indicated

[0048] The term "optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted alkyl" means either "alkyl" or "substituted alkyl" as defined above. Further, an optionally substituted group may be un-substituted (e.g., $-CH_2CH_3$), fully substituted (e.g., $-CF_2CF_3$), mono-substituted (e.g., $-CH_2CH_2F$) or substituted at a level anywhere in-between fully substituted and mono-substituted (e.g., $-CH_2CHF_2$, $-CH_2CF_3$, $-CF_2CH_3$, $-CFHCHF_2$, etc.). It will be understood by those skilled in the art with respect to any group containing one or more substituents that such groups are not intended to introduce any substitution or substitution patterns that are sterically impractical and/or synthetically non-feasible. Thus, any substituents described should generally be understood as having a maximum molecular weight of about 1,000 daltons, and more typically, up to about 500 daltons.

[0049] The term "one or more" when referring to an optional substituent means that the subject group is optionally substituted with one, two, three, four substituents, or more substituents. In some embodiments, the subject group is optionally substituted with one, two, three, or four substituents. In some embodiments, the subject group is optionally substituted with one, two, or three substituents. In some embodiments, the subject group is optionally substituted with one or two substituents. In some embodiments, the subject group is optionally substituted with one substituent. In some embodiments, the subject group is optionally substituted with two substituents.

[0050] An "effective amount" or "therapeutically effective amount" refers to an amount of a compound administered to a mammalian subject, either as a single dose or as part of a series of doses, which is effective to produce a desired therapeutic effect.

[0051] The terms "treat," "treating" or "treatment," as used herein, include alleviating, abating, or ameliorating at least one symptom of a disease or condition, preventing additional symptoms, inhibiting the disease or condition, e.g., arresting the development of the disease or condition,

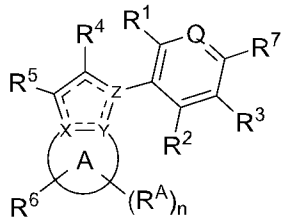
relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition.

[0052] As used herein, a "disease or disorder associated with PKMYT1" or, alternatively, "a PKMYT1-mediated disease or disorder" means any disease or other deleterious condition in which PKMYT1, or a mutant thereof, is known or suspected to play a role.

Compounds

[0053] Described herein are compounds, or pharmaceutically acceptable salts thereof useful in the modulation of PKMYT1 (e.g., inhibiting PKMYT1) and thus in the treatment of PKMYT1-associated diseases and conditions.

[0054] In one aspect, provided herein is a compound of Formula (V):



Formula (V),

or a pharmaceutically acceptable salt thereof, wherein:

each of X, Y and Z is independently N or C;

each of === is a single bond or double bond;

Ring A is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

Q is N or CR^Q;

R^Q is H, OH or NH_2;

or R^Q and R^1 taken together with the atoms to which they are attached form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R;

or R^Q and R^7 taken together with the atoms to which they are attached form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R;

each R^A is independently halogen, cyano, oxo, $-OR^a$, $-SR^a$, $-SO_2R^a$, $-N(R^b)_2$, $-C(O)OR^b$, $-C(O)N(R^b)_2$, $-SO_2N(R^b)_2$, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl-alkyl, heterocycloalkyl-alkyl, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl-alkyl, heterocycloalkyl-alkyl, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally substituted with one or more R;

or two adjacent R^A taken together with the atoms to which they are attached form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R;

R^6 is oxo;

each of R^1 and R^2 is independently hydrogen, halogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the alkyl,

alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally substituted with one or more R;

R^3 is hydrogen, halogen, cyano, $-NO_2$, $-OR^a$, $-SR^a$, $-N(R^b)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^b)_2$, alkyl, alkenyl, alkynyl, cycloalkyl, or heterocycloalkyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, and heterocycloalkyl are optionally substituted with one or more R;

R^4 is hydrogen, halogen, cyano, $-OR^a$, $-SR^a$, $-N(R^b)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^b)_2$, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, whereinthe alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are independently optionally substituted with one or more R;

R^5 is $-C(O)NH(R^a)$, $-C(O)R^a$, or $-SO_2R^a$;

R^7 is hydrogen, halogen, -CN, $-NO_2$, -OH, $-OR^a$, $-N(R^b)_2$, $-C(O)R^a$, $-C(O)OR^b$, $-C(O)N(R^b)_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, or heterocycloalkyl, wherein the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, cycloalkyl, and heterocycloalkyl are optionally substituted with one or more R;

each R is independently halogen, cyano, oxo, $-OR^a$, $-SR^a$, $-SO_2R^a$, $-N(R^b)_2$, $-C(O)N(R^b)_2$, $-SO_2N(R^b)_2$, alkyl, alkenyl, alkylidenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the alkyl, alkenyl, alkylidenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are independently optionally substituted with one or more R';

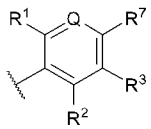
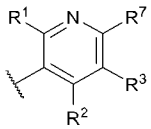
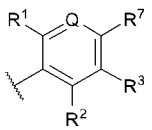
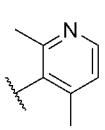
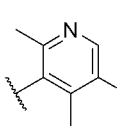
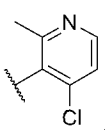
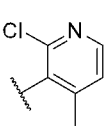
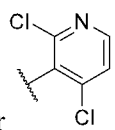
each R' is independently halogen, cyano, oxo, $-OR^a$, $-SR^a$, $-SO_2R^a$, $-N(R^b)_2$, $-C(O)N(R^b)_2$, $-SO_2N(R^b)_2$, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

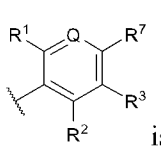
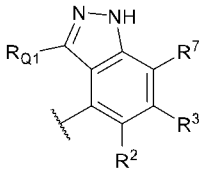
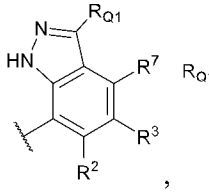
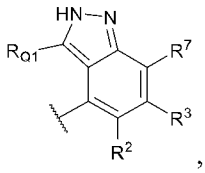
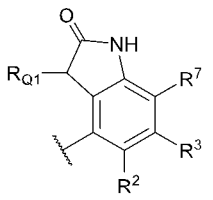
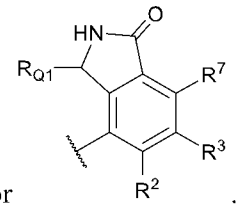
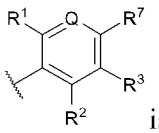
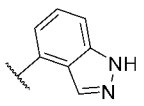
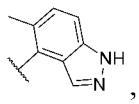
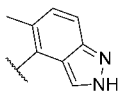
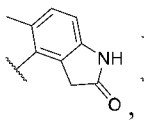
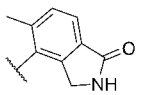
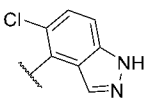
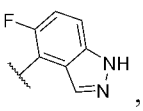
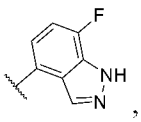
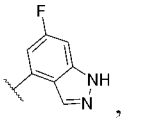
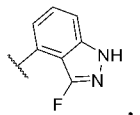
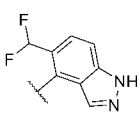
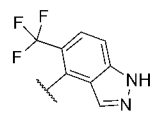
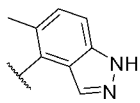
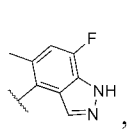
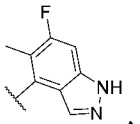
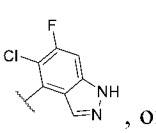
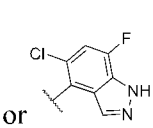
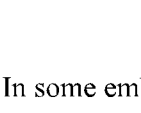
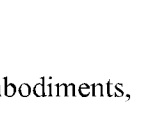
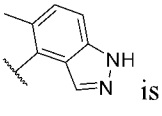
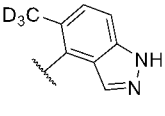
each R^a is independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, hydroxyalkyl, aminoalkyl, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^b is independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, hydroxyalkyl, aminoalkyl, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

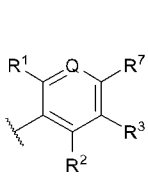
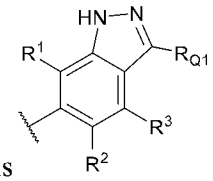
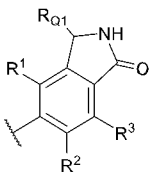
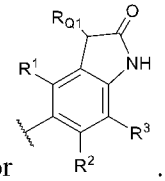
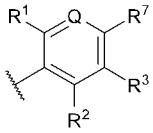
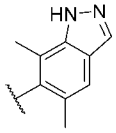
or two R^b taken together with the atom to which they are attached form a heterocycloalkyl; and

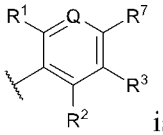
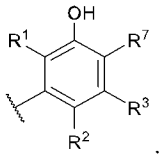
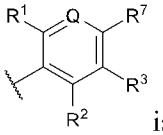
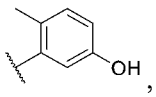
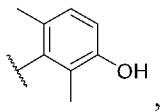
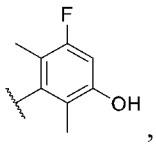
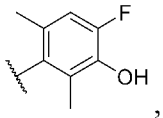
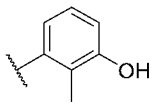
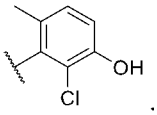
n is an integer of 0-8.

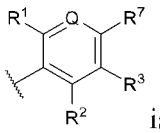
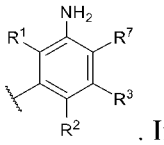
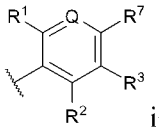
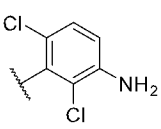
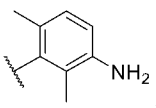
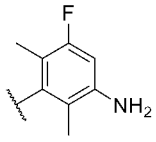
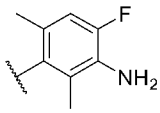
[0055] In some embodiments, Q is N. In some embodiments,  is . In some embodiments,  is , , , , or .

[0056] In some embodiments, Q is CR^Q, and R^Q and R^1 taken together with the atoms to which they are attached form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, each optionally substituted with one or more R. In some embodiments, Q is CR^Q, and R^Q and R^1 taken together with the atoms to which they are attached form a C_{5-6} cycloalkyl, 5- to 6- membered heterocycloalkyl, phenyl, or 5- to 6- membered heteroaryl, each optionally substituted with one or more R. In some embodiments, Q is CR^Q, and R^Q and R^1 taken together with the atoms to which they are attached form a 5- to 6- membered heterocycloalkyl, or 5- to 6- membered heteroaryl, each optionally substituted with one or more R. In some embodiments, Q is CR^Q, and R^Q and R^1 taken together with the atoms to which they are attached form a pyrazolyl, wherein the pyrazolyl is optionally substituted with one or more R. In some embodiments,  is , , , , or . In some embodiments,  is , , , , , , , , , , , , , , , , , , , , , , , , , or . In some embodiments, is .

[0057] In some embodiments, Q is CR^Q, and R^Q and R^7 taken together with the atoms to which they are attached form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, each optionally substituted with one or more R. In some embodiments, Q is CR^Q, and R^Q and R^7 taken together with the atoms to which they are attached form a C_{5-6} cycloalkyl, 5- to 6- membered heterocycloalkyl, phenyl, or 5- to 6- membered heteroaryl, each optionally substituted with one or more R. In some embodiments, Q is CR^Q, and R^Q and R^7 taken together with the atoms to which they are attached form a 5- to 6- membered heterocycloalkyl, or 5- to 6- membered heteroaryl, each optionally substituted with one or more R. In some embodiments, Q is CR^Q, and R^Q and R^7 taken together with the atoms to which they are attached form a pyrazolyl, wherein the pyrazolyl is optionally substituted with one or more R. In

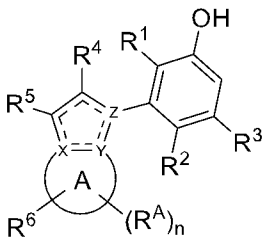
some embodiments,  is , , , or . In some embodiments,  is .

[0058] In some embodiments, Q is CR^Q, and R^Q is OH. In some embodiments,  is . In some embodiments,  is , , , , , or .

[0059] In some embodiments, Q is CR^Q, and R^Q is NH_2. In some embodiments,  is . In some embodiments,  is , , , or .

[0060] In some embodiments, R^7 is hydrogen or halogen. In some embodiments, R^7 is hydrogen or F. In some embodiments, R^7 is hydrogen.

[0061] In one aspect, provided herein is a compound of Formula (I):



Formula (I),

or a pharmaceutically acceptable salt thereof, wherein:

each of X, Y and Z is independently N or C;

each of === is a single bond or double bond;

Ring A is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^A is independently halogen, cyano, oxo, $-OR^a$, $-SR^a$, $-SO_2R^a$, $-N(R^b)_2$, $-C(O)OR^b$, $-C(O)N(R^b)_2$, $-SO_2N(R^b)_2$, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl-alkyl, heterocycloalkyl-alkyl, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl-alkyl, heterocycloalkyl-alkyl, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally substituted with one or more R;

or two adjacent R^A taken together with the atoms to which they are attached form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R;

R^6 is oxo;

each of R^1 and R^2 is independently hydrogen, halogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally substituted with one or more R;

R^3 is hydrogen, halogen, cyano, $-NO_2$, $-OR^a$, $-SR^a$, $-N(R^b)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^b)_2$, alkyl, alkenyl, alkynyl, cycloalkyl, or heterocycloalkyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, and heterocycloalkyl are optionally substituted with one or more R;

R^4 is hydrogen, halogen, cyano, $-OR^a$, $-SR^a$, $-N(R^b)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^b)_2$, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are independently optionally substituted with one or more R;

R^5 is $-C(O)NH(R^a)$, $-C(O)R^a$, or $-SO_2R^a$;

each R is independently halogen, cyano, oxo, $-OR^a$, $-SR^a$, $-SO_2R^a$, $-N(R^b)_2$, $-C(O)N(R^b)_2$, $-SO_2N(R^b)_2$, alkyl, alkenyl, alkylidenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl wherein the alkyl, alkenyl, alkylidenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are independently optionally substituted with one or more R';

each R' is independently halogen, cyano, oxo, $-OR^a$, $-SR^a$, $-SO_2R^a$, $-N(R^b)_2$, $-C(O)N(R^b)_2$, $-SO_2N(R^b)_2$, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^a is independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, hydroxyalkyl, aminoalkyl, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^b is independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, hydroxyalkyl, aminoalkyl, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^b taken together with the atom to which they are attached form a heterocycloalkyl; and

n is an integer of 0-8.

[0062] In some embodiments,

X is C, Y is C and Z is C;

X is C, Y is C and Z is N;

X is N, Y is C and Z is C;

X is N, Y is C and Z is N;

X is C, Y is N and Z is C;

X is C, Y is N and Z is N;

X is N, Y is N and Z is C; or

X is N, Y is N and Z is N.

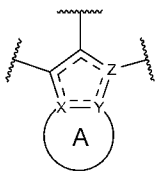
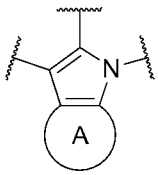
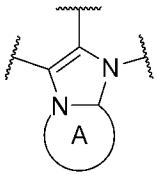
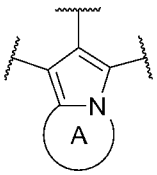
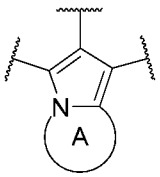
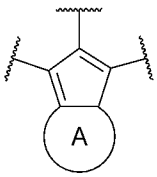
[0063] In some embodiments,

X is C, Y is C and Z is N;

X is N, Y is C and Z is N;

X is C, Y is N and Z is C; or

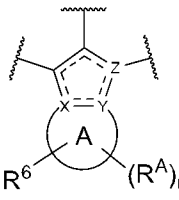
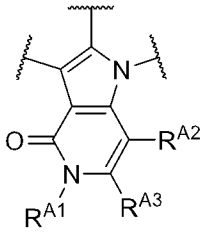
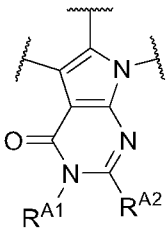
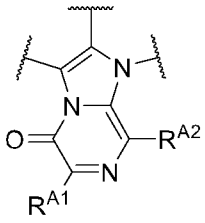
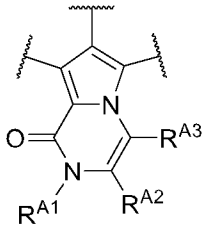
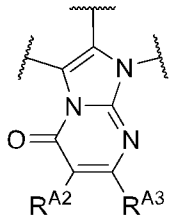
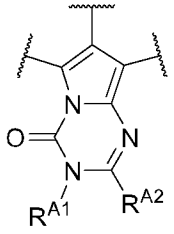
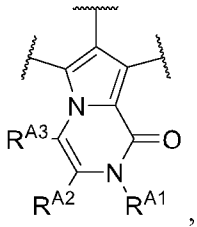
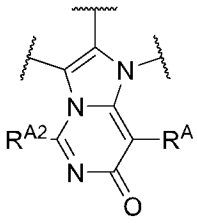
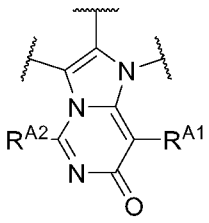
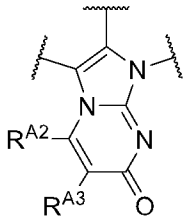
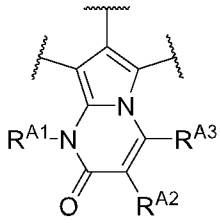
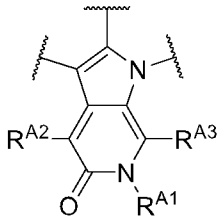
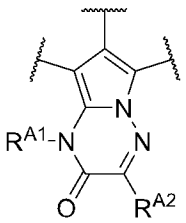
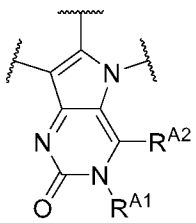
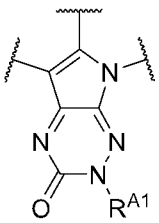
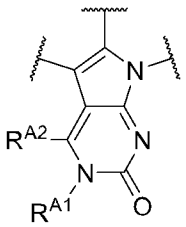
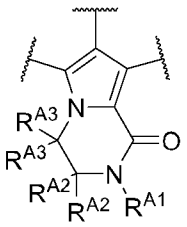
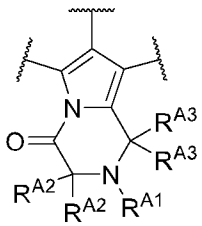
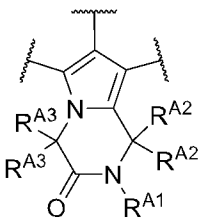
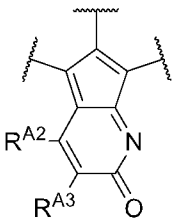
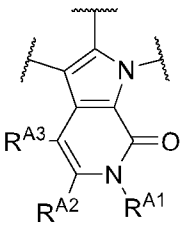
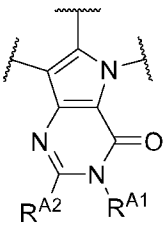
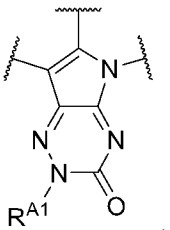
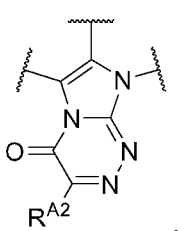
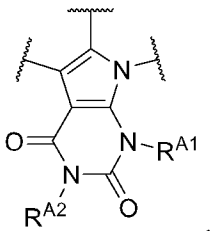
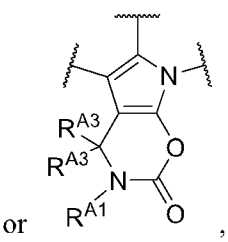
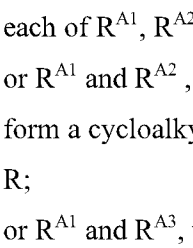
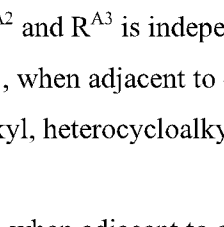
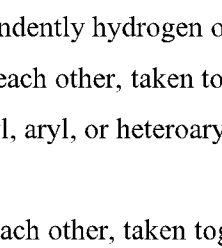
X is N, Y is C and Z is C.

[0064] In some embodiments,  is , , , , or .

[0065] In some embodiments, Ring A is heterocycloalkyl or heteroaryl. In some embodiments, Ring A is heterocycloalkyl or heteroaryl containing at least one N atom.

[0066] In some embodiments, Ring A is 5- to 10-membered heterocycloalkyl, 5- to 9-membered heterocycloalkyl, 5- to 8-membered heterocycloalkyl, 6- to 8-membered heterocycloalkyl or 6- to 7-membered heterocycloalkyl. In some embodiments, Ring A is 10-membered heterocycloalkyl, 9-membered heterocycloalkyl, 8-membered heterocycloalkyl, 7-membered heterocycloalkyl, 6-membered heterocycloalkyl or 5-membered heterocycloalkyl. In some embodiments, Ring A is 5- to 10-membered heteroaryl, 5- to 9-membered heteroaryl, 5- to 8-membered heteroaryl, 6- to 8-membered heteroaryl or 6- to 7-membered heteroaryl. In some embodiments, Ring A is 10-membered heteroaryl, 9-membered heteroaryl, 8-membered heteroaryl, 7-membered heteroaryl, 6-membered heteroaryl or 5-membered heteroaryl.

[0067] In some embodiments, Ring A is 6-membered heterocycloalkyl. In some embodiments, Ring A is 6-membered heteroaryl.

[0068] In some embodiments,  is , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , wherein

each of R^{A1}, R^{A2} and R^{A3} is independently hydrogen or independently selected from R^{A};

or R^{A1} and R^{A2}, when adjacent to each other, taken together with the atoms to which they are attached form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, each optionally substituted with one or more R;

or R^{A1} and R^{A3}, when adjacent to each other, taken together with the atoms to which they are attached form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, each optionally substituted with one or more R;

or R^{A2} and R^{A3} , when adjacent to each other, taken together with the atoms to which they are attached form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, each optionally substituted with one or more R;

or two R^{A2} taken together with the same atom to which they are attached form a cycloalkyl, or heterocycloalkyl, each optionally substituted with one or more R;

or two R^{A3} taken together with the same atom to which they are attached form a cycloalkyl, or heterocycloalkyl, each optionally substituted with one or more R.

[0069] In some embodiments, each of R^{A1}, R^{A2} and R^{A3} is independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxy, cycloalkyl-alkyl, heterocycloalkyl-alkyl, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxy, cycloalkyl-alkyl, heterocycloalkyl-alkyl, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally substituted with one or more R.

[0070] In some embodiments, R^{A1} and R^{A2} taken together with the atoms to which they are attached form a 5- to 6- membered heterocycloalkyl or 5- to 6-membered heteroaryl, each optionally substituted with one or more R.

[0071] In some embodiments, R^{A2} and R^{A3} taken together with the atoms to which they are attached form a C_{5-6} cycloalkyl, 5- to 6- membered heterocycloalkyl, C_6aryl, or 5- to 6- membered heteroaryl, each optionally substituted with one or more R.

[0072] In some embodiments, each R^A is independently $-OR^a$, hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl-alkyl, heterocycloalkyl-alkyl, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl-alkyl, heterocycloalkyl-alkyl, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally substituted with one or more (e.g., two, or three, etc) R.

[0073] In some embodiments, one or more R^A is C_{1-6} alkyl, C_{1-5} alkyl, C_{1-4} alkyl, C_{1-3} alkyl or C_{1-2} alkyl, each optionally substituted with one or more R. In some embodiments, one or more R^A is C_6 alkyl, C_5 alkyl, C_4 alkyl, C_3 alkyl, C_2 alkyl or C_1 alkyl, each optionally substituted with one or more R.

[0074] In some embodiments, one or more R^A is C_{2-6} alkenyl, C_{2-5} alkenyl, C_{2-4} alkenyl or C_{2-3} alkenyl, each optionally substituted with one or more R. In some embodiments, one or more R^A is C_6 alkenyl, C_5 alkenyl, C_4 alkenyl, C_3 alkenyl or C_2 alkenyl, each optionally substituted with one or more (e.g., two, or three, etc) R.

[0075] In some embodiments, one or more R^A is C_{2-6} alkynyl, C_{2-5} alkynyl, C_{2-4} alkynyl or C_{2-3} alkynyl, each optionally substituted with one or more R. In some embodiments, one or more R^A is C_6 alkynyl, C_5 alkynyl, C_4 alkynyl, C_3 alkynyl or C_2 alkynyl, each optionally substituted with one or more (e.g., two, or three, etc) R.

[0076] In some embodiments, one or more R^A is C_{1-6} haloalkyl, C_{1-5} haloalkyl, C_{1-4} haloalkyl, C_{1-3} haloalkyl or C_{1-2} haloalkyl, each optionally substituted with one or more R. In some embodiments, one or more R^A is C_6 haloalkyl, C_5 haloalkyl, C_4 haloalkyl, C_3 haloalkyl, C_2 haloalkyl or C_1 haloalkyl, each optionally substituted with one or more (e.g., two, or three, etc) R.

[0077] In some embodiments, one or more R^A is C_{1-6} hydroxyalkyl, C_{1-5} hydroxyalkyl, C_{1-4} hydroxyalkyl, C_{1-3} hydroxyalkyl or C_{1-2} hydroxyalkyl, each optionally substituted with one or more R. In some embodiments, one or more R^A is C_6 hydroxyalkyl, C_5 hydroxyalkyl, C_4 hydroxyalkyl, C_3 hydroxyalkyl, C_2 hydroxyalkyl or C_1 hydroxyalkyl, each optionally substituted with one or more R.

[0078] In some embodiments, one or more R^A is C_{1-6} aminoalkyl, C_{1-5} aminoalkyl, C_{1-4} aminoalkyl, C_{1-3} aminoalkyl or C_{1-2} aminoalkyl, each optionally substituted with one or more R. In some embodiments, one or more R^A is C_6 aminoalkyl, C_5 aminoalkyl, C_4 aminoalkyl, C_3 aminoalkyl, C_2 aminoalkyl or C_1 aminoalkyl, each optionally substituted with one or more (e.g., two, or three, etc) R.

[0079] In some embodiments, one or more R^A is C_{1-6}alkoxy, C_{1-5}alkoxy, C_{1-4}alkoxy, C_{1-3}alkoxy, or C_{1-2}alkoxy each optionally substituted with one or more R. In some embodiments, one or more R^A is C_6alkoxy, C_5 alkoxy, C_4alkoxy, C_3alkoxy, C_2alkoxy or C_1alkoxy, each optionally substituted with one or more (e.g., two, or three, etc) R.

[0080] In some embodiments, one or more R^A is cycloalkyl-C_{1-6} alkyl, cycloalkyl-C_{1-5} alkyl, cycloalkyl-C_{1-4} alkyl, cycloalkyl-C_{1-3} alkyl or cycloalkyl-C_{1-2} alkyl, each optionally substituted with one or more R. In some embodiments, one or more R^A is cycloalkyl-C_6 alkyl, cycloalkyl-C_5 alkyl, cycloalkyl-C_4 alkyl, cycloalkyl-C_3 alkyl, cycloalkyl-C_2 alkyl or cycloalkyl-C_1 alkyl, each optionally substituted with one or more R. In some embodiments, one or more R^A is C_{3-10} cycloalkyl-C_{1-6} alkyl, C_{3-9} cycloalkyl-C_{1-6} alkyl, C_{3-8} cycloalkyl-C_{1-6} alkyl, C_{3-7} cycloalkyl-C_{1-6} alkyl or C_{3-6} cycloalkyl-C_{1-6} alkyl, each optionally substituted with one or more R. In some embodiments, one or more R^A is C_{3-10} cycloalkyl-C_1 alkyl, C_{3-9} cycloalkyl-C_1 alkyl, C_{3-8} cycloalkyl-C_1 alkyl, C_{3-7} cycloalkyl-C_1 alkyl or C_{3-6} cycloalkyl-C_1 alkyl, each optionally substituted with one or more (e.g., two, or three, etc) R.

[0081] In some embodiments, one or more R^A is heterocycloalkyl-C_{1-6} alkyl, heterocycloalkyl-C_{1-5} alkyl, heterocycloalkyl-C_{1-4} alkyl, heterocycloalkyl-C_{1-3} alkyl or heterocycloalkyl-C_{1-2} alkyl, each optionally substituted with one or more R. In some embodiments, one or more R^A is heterocycloalkyl-C_6 alkyl, heterocycloalkyl-C_5 alkyl, heterocycloalkyl-C_4 alkyl, heterocycloalkyl-C_3 alkyl, heterocycloalkyl-C_2 alkyl or heterocycloalkyl-C_1 alkyl, each optionally substituted with one or more R. In some embodiments, one or more R^A is 4- to 10-membered heterocycloalkyl-C_{1-6} alkyl, 4- to 9-membered heterocycloalkyl-C_{1-6} alkyl, 4- to 8-membered heterocycloalkyl-C_{1-6} alkyl, 4- to 7-membered heterocycloalkyl-C_{1-6} alkyl or 4- to 6-membered heterocycloalkyl-C_{1-6} alkyl, each optionally substituted with one or more R. In some embodiments, one or more R^A is 4- to 10-membered heterocycloalkyl-C_1 alkyl, 4- to 9-membered heterocycloalkyl-C_1 alkyl, 4- to 8-membered heterocycloalkyl-C_1 alkyl, 4- to 7-membered heterocycloalkyl-C_1 alkyl or 4- to 6-membered heterocycloalkyl-C_1 alkyl, each optionally substituted with one or more (e.g., two, or three, etc) R.

[0082] In some embodiments, one or more R^A is aryl-C_{1-6} alkyl, aryl-C_{1-5} alkyl, aryl-C_{1-4} alkyl, aryl-C_{1-3} alkyl or aryl-C_{1-2} alkyl, each optionally substituted with one or more R. In some embodiments, one or more R^A is aryl-C_6 alkyl, aryl-C_5 alkyl, aryl-C_4 alkyl, aryl-C_3 alkyl, aryl-C_2 alkyl or aryl-C_1 alkyl, each optionally substituted with one or more R. In some embodiments, one or more R^A is C_{6-12} aryl-C_{1-6} alkyl, C_{6-11} aryl-C_{1-6} alkyl, C_{6-10} aryl-C_{1-6} alkyl, C_{6-9} aryl-C_{1-6} alkyl or C_{6-8} aryl-C_{1-6} alkyl, each optionally substituted with one or more R. In some embodiments, one or more R^A is C_{6-12} aryl-C_1 alkyl, C_{6-11} aryl-C_1 alkyl, C_{6-10} aryl-C_1 alkyl, C_{6-9} aryl-C_1 alkyl or C_{6-8} aryl-C_1 alkyl, each optionally substituted with one or more (e.g., two, or three, etc) R.

[0083] In some embodiments, one or more R^A is heteroaryl-C_{1-6} alkyl, heteroaryl-C_{1-5} alkyl, heteroaryl-C_{1-4} alkyl, heteroaryl-C_{1-3} alkyl or heteroaryl-C_{1-2} alkyl, each optionally substituted with one or more R. In some embodiments, one or more R^A is heteroaryl-C_6 alkyl, heteroaryl-C_5 alkyl, heteroaryl-C_4 alkyl, heteroaryl-C_3 alkyl, heteroaryl-C_2 alkyl or heteroaryl-C_1 alkyl, each optionally substituted with one or more R. In some embodiments, one or more R^A is 5- to 10-membered heteroaryl-C_{1-6} alkyl, 5- to 9-membered heteroaryl-C_{1-6} alkyl, 5- to 8-membered heteroaryl-C_{1-6} alkyl, 6- to 8-membered heteroaryl-C_{1-6} alkyl or 6- to 7-membered heteroaryl-C_{1-6} alkyl, each optionally substituted with one or more R. In some embodiments, one or more R^A is 5- to 10-membered heteroaryl-C_1 alkyl, 5- to 9-membered heteroaryl-C_1 alkyl, 5- to 8-membered heteroaryl-C_1 alkyl, 6- to 8-membered heteroaryl-C_1 alkyl or 6- to 7-membered heteroaryl-C_1 alkyl, each optionally substituted with one or more (e.g., two, or three, etc) R.

[0084] In some embodiments, one or more R^A is C_{3-10} cycloalkyl, C_{3-9} cycloalkyl, C_{3-8} cycloalkyl, C_{3-7} cycloalkyl, C_{3-6} cycloalkyl or C_{3-5} cycloalkyl, each optionally substituted with one or more R. In some embodiments, one or more R^A is C_{10} cycloalkyl, C_9 cycloalkyl, C_8 cycloalkyl, C_7 cycloalkyl, C_6 cycloalkyl, C_5 cycloalkyl, C_4 cycloalkyl or C_3 cycloalkyl, each optionally substituted with one or more (e.g., two, or three, etc) R.

[0085] In some embodiments, one or more R^A is 4- to 10-membered heterocycloalkyl, 4- to 9-membered heterocycloalkyl, 4- to 8-membered heterocycloalkyl, 5- to 8-membered heterocycloalkyl, 5- to 8-membered heterocycloalkyl or 5- to 7-membered heterocycloalkyl, each optionally substituted with one or more R. In some embodiments, one or more R^A is 10-membered heterocycloalkyl, 9-membered heterocycloalkyl, 8-membered heterocycloalkyl,7-membered heterocycloalkyl, 6-membered heterocycloalkyl, 5-membered heterocycloalkyl or 4-membered heterocycloalkyl, each optionally substituted with one or more (e.g., two, or three, etc) R.

[0086] In some embodiments, one or more R^A is 5- to 10-membered heteroaryl, 5- to 9-membered heteroaryl, 5- to 8-membered heteroaryl, 6- to 8-membered heteroaryl or 6- to 7-membered heteroaryl, each optionally substituted with one or more R. In some embodiments, one or more R^A is 10-membered heteroaryl, 9-membered heteroaryl, 8-membered heteroaryl,7-membered heteroaryl, 6-membered heteroaryl or 5-membered heteroaryl, each optionally substituted with one or more (e. g., two, or three, etc) R.

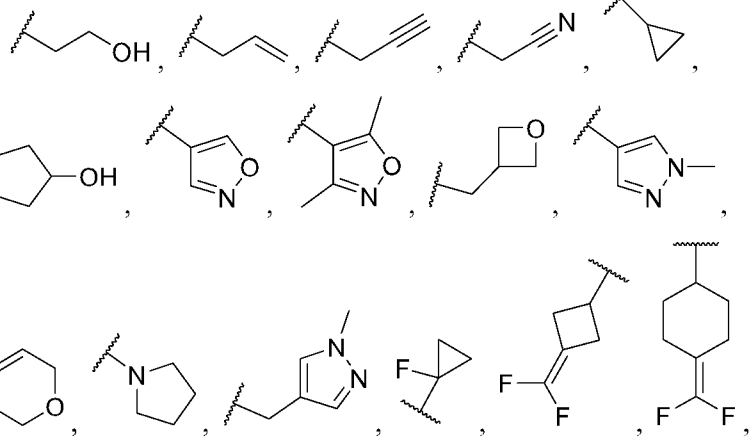
[0087] In some embodiments, one or more R^A is C_{6-12} aryl, C_{6-11} aryl, C_{6-10} aryl, C_{6-9} aryl or C_{6-8} aryl, each optionally substituted with one or more R. In some embodiments, one or more R^A is C_{12} aryl, C_{11} aryl, C_{10} aryl, C_9 aryl, C_8 aryl, C_7 aryl or C_6 aryl, each optionally substituted with one or more (e.g., two, or three, etc) R.

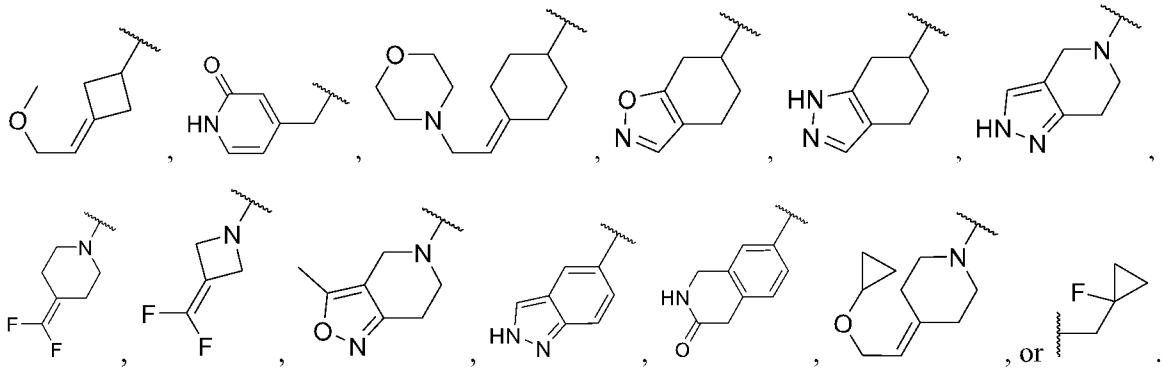
[0088] In some embodiments, one or more R^A is independently $-OR^a$. In some embodiments, R^a is C_{1-6} alkyl, C_{1-5} alkyl, C_{1-4} alkyl, C_{1-3} alkyl or C_{1-2} alkyl. In some embodiments, R^a is C_6 alkyl, C_5 alkyl, C_4 alkyl, C_3 alkyl, C_2 alkyl or C_1 alkyl. In some embodiments, R^a is C_{1-6} haloalkyl, C_{1-5} haloalkyl, C_{1-4} haloalkyl, C_{1-3} haloalkyl or C_{1-2} haloalkyl. In some embodiments, R^a is C_6 haloalkyl, C_5 haloalkyl, C_4 haloalkyl, C_3 haloalkyl, C_2 haloalkyl or C_1 haloalkyl.

[0089] In some embodiments, one or more R^A is $-O-C_{1-6}$ alkyl, $-O-C_{1-5}$ alkyl, $-O-C_{1-4}$ alkyl, $-O-C_{1-3}$ alkyl or $-O-C_{1-2}$ alkyl. In some embodiments, one or more R^A is $-O-C_6$ alkyl, $-O-C_5$ alkyl, $-O-C_4$ alkyl, $-O-C_3$ alkyl, $-O-C_2$ alkyl or $-O-C_1$ alky.

[0090] In some embodiments, one or more R^A is $-O-C_{1-6}$ haloalkyl, $-O-C_{1-5}$ haloalkyl, $-O-C_{1-4}$ haloalkyl, $-O-C_{1-3}$ haloalkyl or $-O-C_{1-2}$ haloalkyl. In some embodiments, one or more R^A is $-O-C_6$ haloalkyl, $-O-C_5$ haloalkyl, $-O-C_4$ haloalkyl, $-O-C_3$ haloalkyl, $-O-C_2$ haloalkyl or $-O-C_1$ haloalkyl.

[0091] In some embodiments, each R is independently halogen, hydroxyl, cyano, alkyl, oxo, or alkylidenyl, wherein the alkyl, and alkylidenyl are independently optionally substituted with one or more R'. In some embodiments, each R is independently -F, hydroxyl, cyano, $-CH_3$ or oxo. In some embodiments, each R is alkylidenyl, wherein the alkylidenyl is independently optionally substituted with halogen, $-OR^a$, or 5- to 6- membered heterocycloalkyl.

[0092] In some embodiments, each R^A is independently $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CH_2F$, $-CHF_2$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-OCH_3$, $-OCF_3$, $-OCH_2F$, $-OCHF_2$, $-OCH_2CH_3$, $-OCH_2CF_3$, $-OCH_2CF_3$, $-OCH_2CHF_2$, $-OCH_2CH_2F$, 



[0093] In some embodiments, R^1 is alkyl optionally substituted with one or more R. In some embodiments, R^1 is C_{1-6} alkyl, C_{1-5} alkyl, C_{1-4} alkyl, C_{1-3} alkyl or C_{1-2} alkyl, each optionally substituted with one or more R. In some embodiments, R^1 is C_6 alkyl, C_5 alkyl, C_4 alkyl, C_3 alkyl, C_2 alkyl or C_1 alkyl, each optionally substituted with one or more R.

[0094] In some embodiments, R^1 is $-CH_3$.

[0095] In some embodiments, R^2 is alkyl optionally substituted with one or more R. In some embodiments, R^2 is C_{1-6} alkyl, C_{1-5} alkyl, C_{1-4} alkyl, C_{1-3} alkyl or C_{1-2} alkyl, each optionally substituted with one or more R. In some embodiments, R^2 is C_6 alkyl, C_5 alkyl, C_4 alkyl, C_3 alkyl, C_2 alkyl or C_1 alkyl, each optionally substituted with one or more R.

[0096] In some embodiments, R^2 is $-CH_3$.

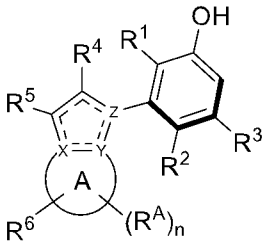
[0097] In some embodiments, R^3 is hydrogen or halogen. In some embodiments, R^3 is hydrogen or -F.

[0098] In some embodiments, R^4 is $-N(R^b)_2$. In some embodiments, each R^b is independently hydrogen or alkyl. In some embodiments, each R^b is independently hydrogen, C_{1-6} alkyl, C_{1-5} alkyl, C_{1-4} alkyl, C_{1-3} alkyl or C_{1-2} alkyl. In some embodiments, each R^b is hydrogen. In some embodiments, R^4 is $-NH_2$.

[0099] In some embodiments, R^5 is $-C(O)NH(R^a)$. In some embodiments, R^a is hydrogen or alkyl. In some embodiments, R^a is hydrogen, C_{1-6} alkyl, C_{1-5} alkyl, C_{1-4} alkyl, C_{1-3} alkyl or C_{1-2} alkyl. In some embodiments, R^a is hydrogen. In some embodiments, R^5 is $-C(O)NH_2$.

[00100] In some embodiments, n is 0, 1, 2, 3, 4, 5, 6, 7 or 8. In some embodiments, n is 0, 1, 2, 3, 4 or 5. In some embodiments, n is 0, 1 or 2.

[00101] In some embodiments, the compound provided herein is of Formula (Ia):



Formula (Ia),

wherein Ring A, X, Y, Z, R^1 to R^6, R^A, and n are as defined herein.

[00102] In some embodiments of a compound disclosed herein, one or more of R, R^1, R^2, R^3, R^4, R^5, R^A, R^a and R^b groups comprise deuterium at a percentage higher than the natural abundance of deuterium.

[00103] In some embodiments of a compound disclosed herein, one or more ^1H are replaced with one or more deuteriums in one or more of the following groups R, R^1, R^2, R^3, R^4, R^5, R^A, R^a and R^b.

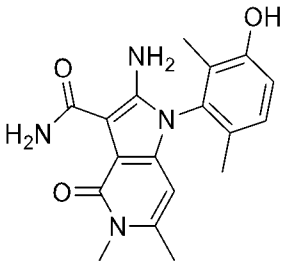
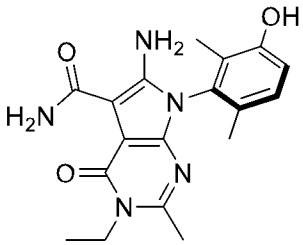
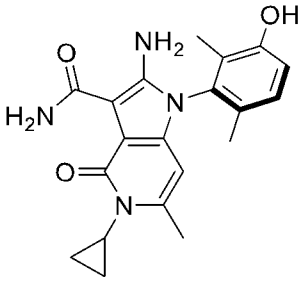
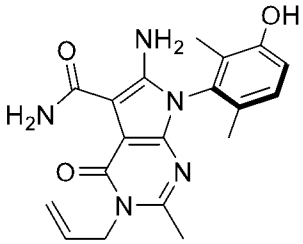
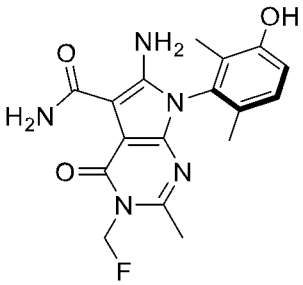
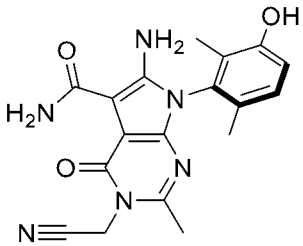
[00104] In some embodiments of a compound disclosed herein, the abundance of deuterium in each of R, R^1, R^2, R^3, R^4, R^5, R^A, R^a and R^b is independently at least 1%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or 100% by molar.

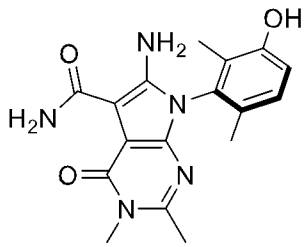
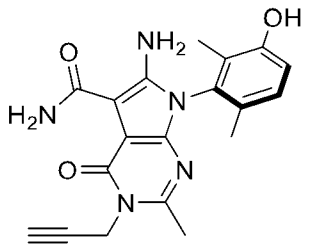
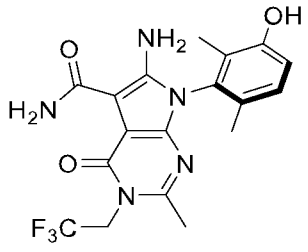
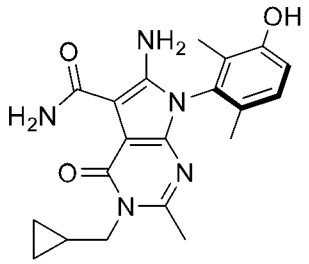
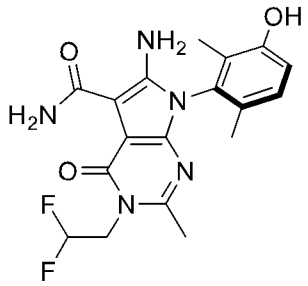
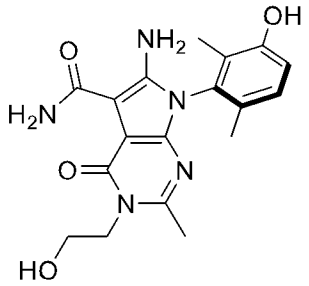
[00105] In some embodiments of a compound disclosed herein, one or more ^1H of Ring A are replaced with one or more deuteriums.

[00106] Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

[00107] In some embodiments, the present disclosure provides a compound selected from any one of the compounds in Table 1, or a pharmaceutically acceptable salt thereof.

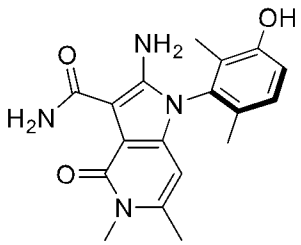
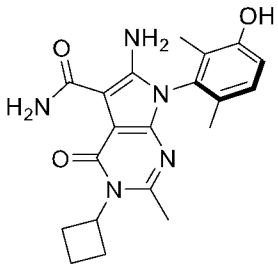
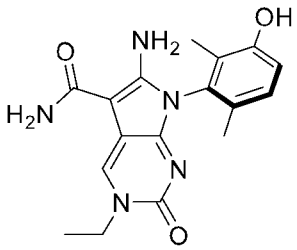
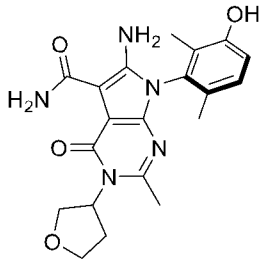
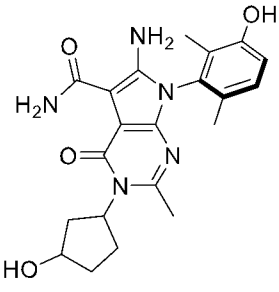
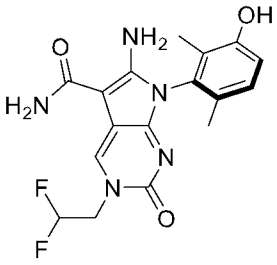
TABLE 1 Exemplary Compounds

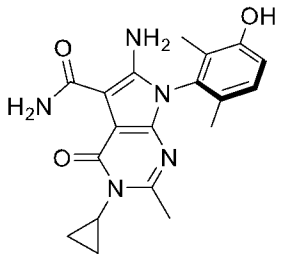
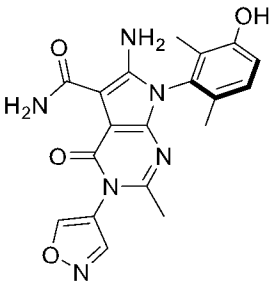
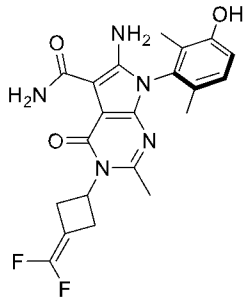
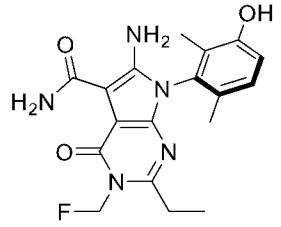
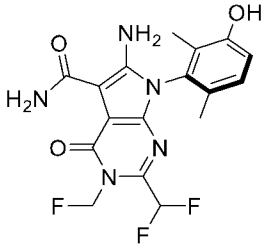
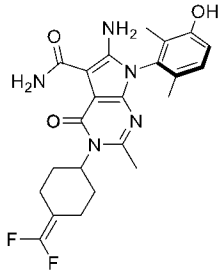
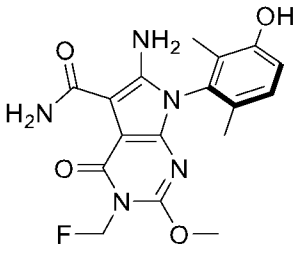
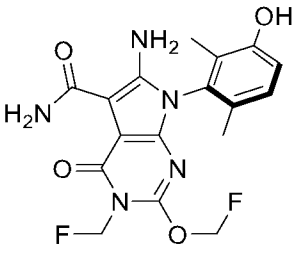
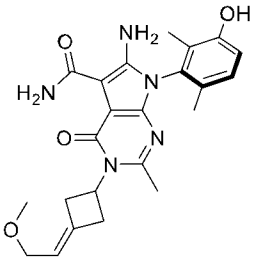
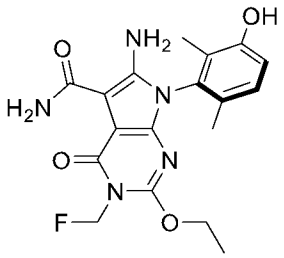
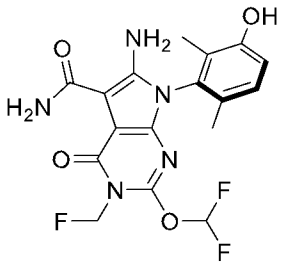
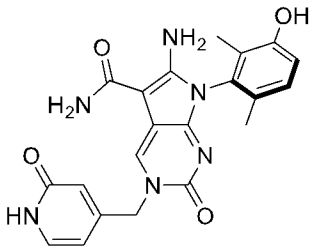
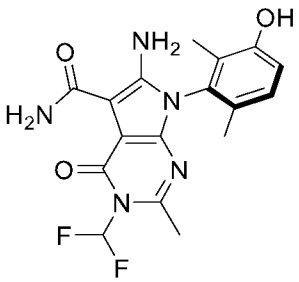
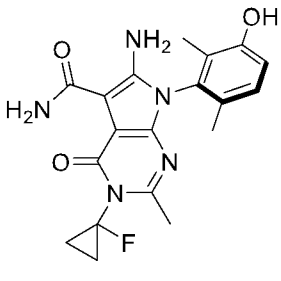
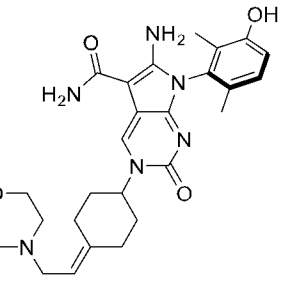
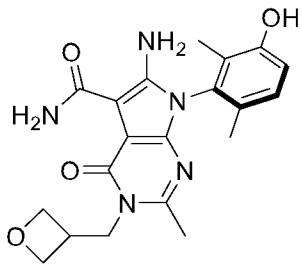
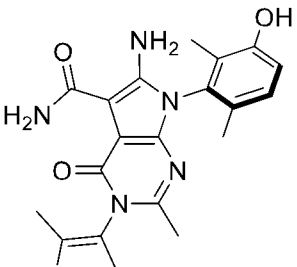
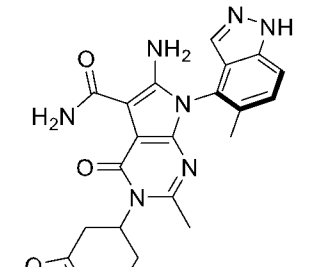
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3		9	

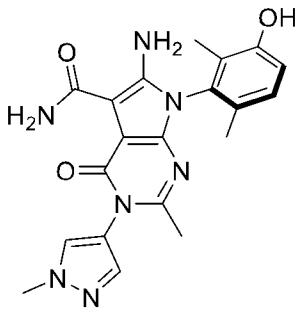
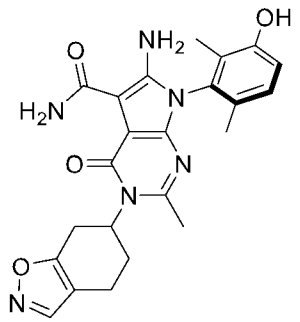
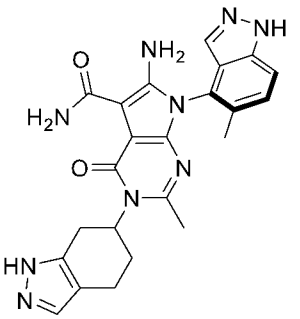
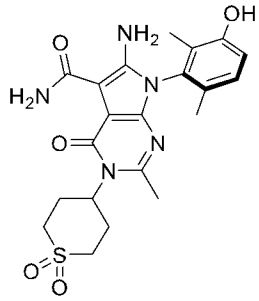
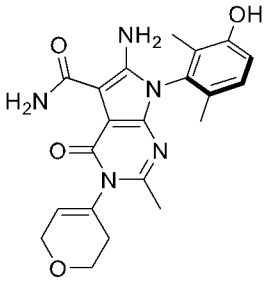
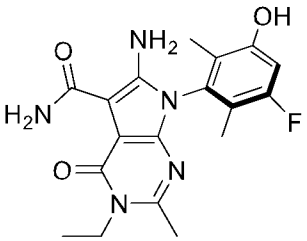
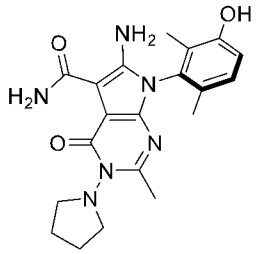
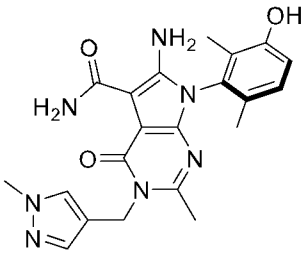
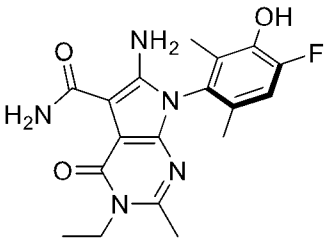
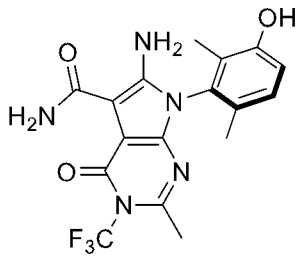
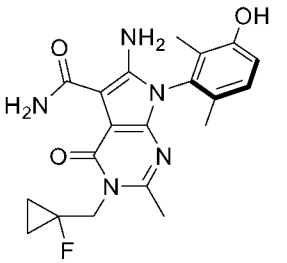
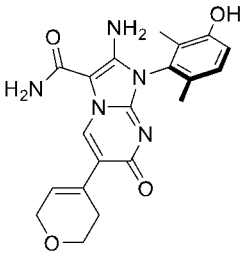
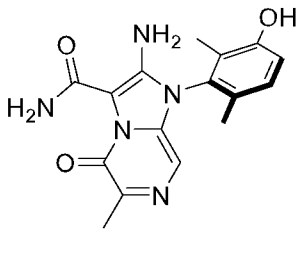
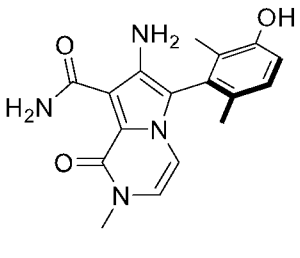
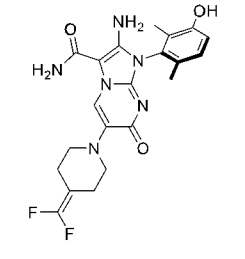
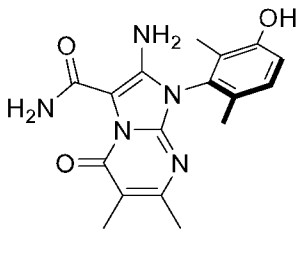
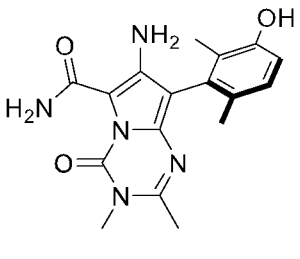
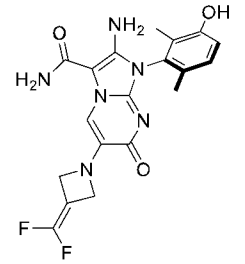
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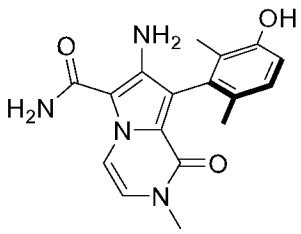
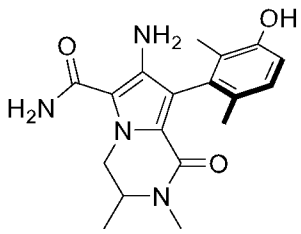
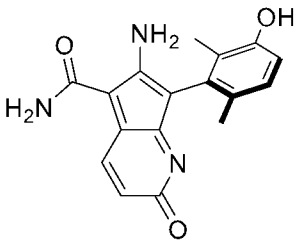
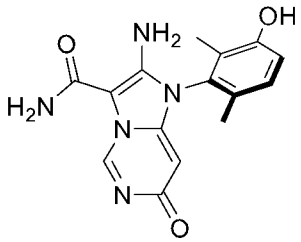
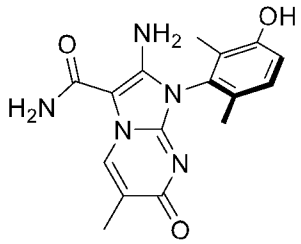
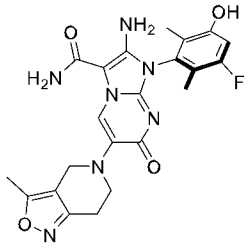
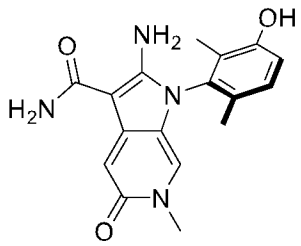
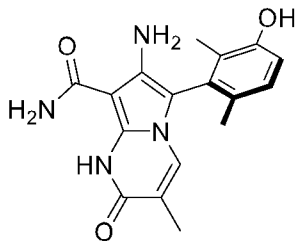
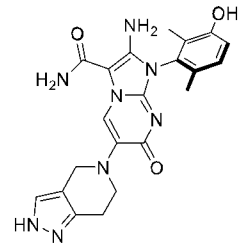
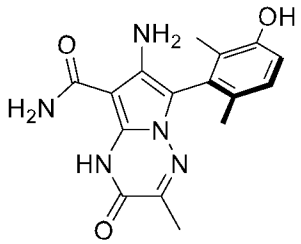
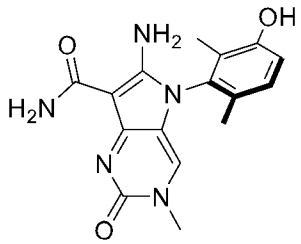
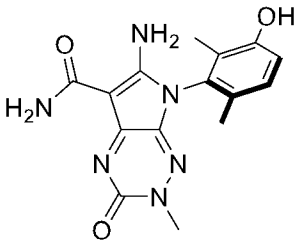
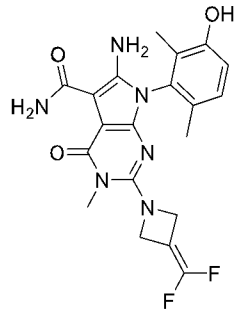
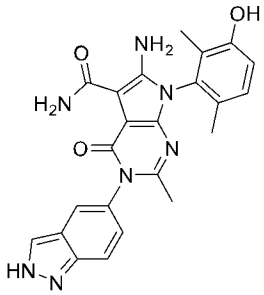
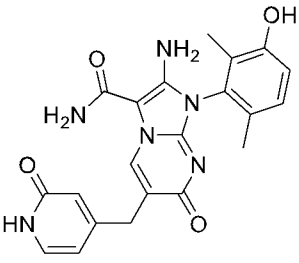
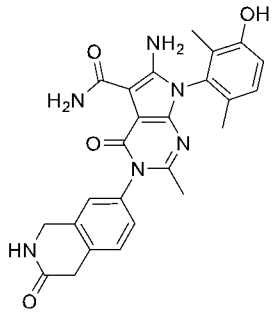
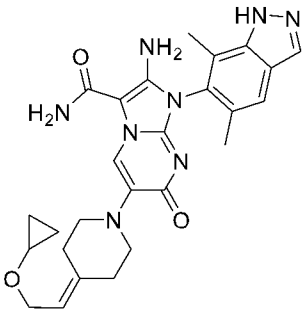
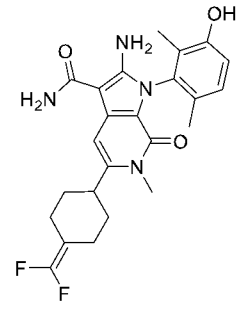
[00108] In some embodiments, the present disclosure provides a compound selected from any one of the compounds in Table 2, or a pharmaceutically acceptable salt thereof.

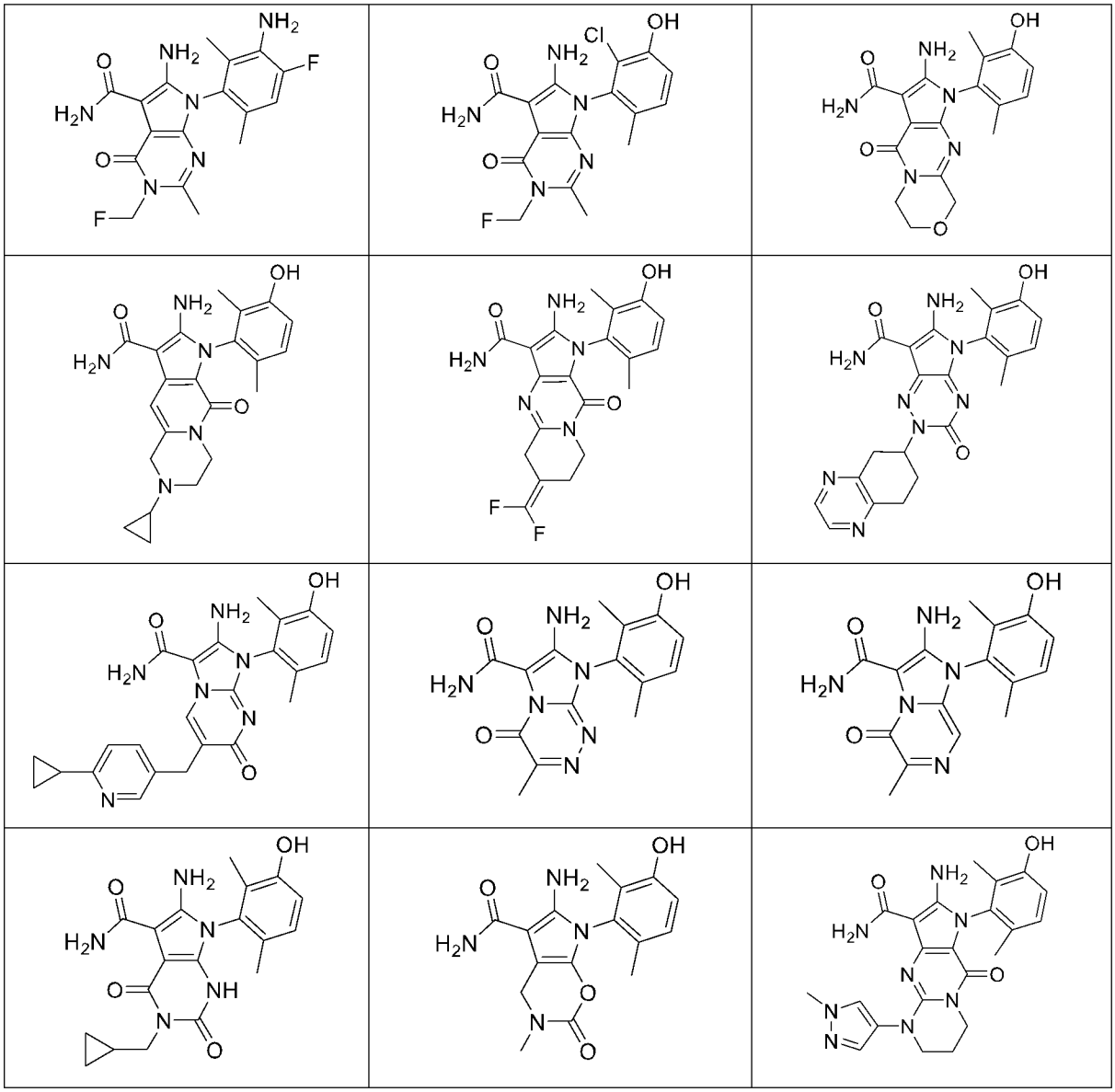
TABLE 2 Exemplary Compounds

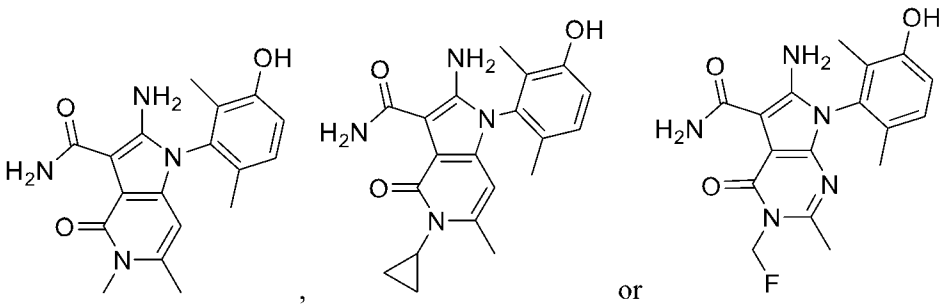
		
		
		
		
		
		



[00109] In some embodiments, the compound disclosed herein is not



, or .

Further Forms of Compounds Disclosed Herein

Isomers/Stereoisomers

[00110] In some embodiments, the compounds described herein exist as geometric isomers. In some embodiments, the compounds described herein possess one or more double bonds. The compounds

presented herein include all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the corresponding mixtures thereof. In some situations, the compounds described herein possess one or more chiral centers and each center exists in the R configuration, or S configuration. The compounds described herein include all diastereomeric, enantiomeric, and epimeric forms as well as the corresponding mixtures thereof. In additional embodiments of the compounds and methods provided herein, mixtures of enantiomers and/or diastereoisomers, resulting from a single preparative step, combination, or interconversion are useful for the applications described herein. In some embodiments, the compounds described herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. In some embodiments, dissociable complexes are preferred. In some embodiments, the diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and are separated by taking advantage of these dissimilarities. In some embodiments, the diastereomers are separated by chiral chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. In some embodiments, the optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization.

Isotopically enriched compounds

[00111] Unless otherwise stated, compounds described herein may exhibit their natural isotopic abundance, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. All isotopic variations of the compounds of the present disclosure, whether radioactive or not, are encompassed within the scope of the present disclosure. For example, hydrogen has three naturally occurring isotopes, denoted ^{1}H (protium), ^{2}H (deuterium), and ^{3}H (tritium). Protium is the most abundant isotope of hydrogen in nature. Enriching for deuterium may afford some therapeutic advantages, such as increased *in vivo* half-life and/or exposure, or may provide a compound useful for investigating *in vivo* routes of drug elimination and metabolism.

[00112] For example, the compounds described herein may be artificially enriched in one or more particular isotopes. In some embodiments, the compounds described herein may be artificially enriched in one or more isotopes that are not predominantly found in nature. In some embodiments, the compounds described herein may be artificially enriched in one or more isotopes selected from deuterium (^{2}H), tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C). In some embodiments, the compounds described herein are artificially enriched in one or more isotopes selected from ^{2}H, ^{11}C, ^{13}C, ^{14}C, ^{15}C, ^{12}N, ^{13}N, ^{15}N, ^{16}N, ^{16}O, ^{17}O, ^{14}F, ^{15}F, ^{16}F, ^{17}F, ^{18}F, ^{33}S, ^{34}S, ^{35}S, ^{36}S, ^{35}Cl, ^{37}Cl, ^{79}Br, ^{81}Br, ^{131}I, and ^{125}I. In some embodiments, the abundance of the enriched isotopes is independently at least 1%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or 100% by molar.

[00113] In some embodiments, the compound is deuterated in at least one position. In some embodiments, the compounds disclosed herein have some or all of the ^{1}H atoms replaced with ^{2}H atoms. In some embodiments, each hydrogen atom of the compounds disclosed herein is independently ^{1}H, ^{2}H (D) or ^{3}H (T). In some embodiments, one or more hydrogen atom of the compounds disclosed herein is ^{2}H (deuterium, or D).

[00114] The methods of synthesis for deuterium-containing compounds are known in the art and include, by way of non-limiting example only, the procedure described in U.S. Patent Nos. 5,846,514 and 6,334,997, and the following synthetic methods. For example, deuterium substituted compounds may be synthesized using various methods such as described in: Dean, Dennis C.; Editor. Recent Advances in the Synthesis and Applications of Radiolabeled Compounds for Drug Discovery and Development. [In: Curr., Pharm. Des., 2000; 6(10)] **2000**, 110 pp; George W.; Varma, Rajender S. The Synthesis of Radiolabeled Compounds via Organometallic Intermediates, Tetrahedron, **1989**, 45(21), 6601-21; and Evans, E. Anthony. Synthesis of radiolabeled compounds, J. Radioanal. Chem., **1981**, 64(1-2), 9-32.

[00115] Deuterated starting materials are readily available and are subjected to the synthetic methods described herein to provide for the synthesis of deuterium-containing compounds. Large numbers of deuterium-containing reagents and building blocks are available commercially from chemical vendors, such as Aldrich Chemical Co.

Pharmaceutically acceptable salts

[00116] In some embodiments, the compounds described herein exist as their pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts as pharmaceutical compositions.

[00117] In some embodiments, the compounds described herein possess acidic or basic groups and therefore react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. In some embodiments, these salts are prepared *in situ* during the final isolation and purification of the compounds disclosed herein, or by separately reacting a purified compound in its free form with a suitable acid or base, and isolating the salt thus formed.

[00118] Examples of pharmaceutically acceptable salts include those salts prepared by reaction of the compounds described herein with a mineral, organic acid or inorganic base, such salts including, acetate, acrylate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, bisulfite, bromide, butyrate, butyn-1,4-dioate, camphorate, camphorsulfonate, caproate, caprylate, chlorobenzoate, chloride, citrate, cyclopentanepropionate, decanoate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hexyne-1,6-dioate, hydroxybenzoate, γ-hydroxybutyrate, hydrochloride, hydrobromide, hydroiodide, 2-

hydroxyethanesulfonate, iodide, isobutyrate, lactate, maleate, malonate, methanesulfonate, mandelate, metaphosphate, methanesulfonate, methoxybenzoate, methylbenzoate, monohydrogenphosphate, 1-napthalenesulfonate, 2-napthalenesulfonate, nicotinate, nitrate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, pyrosulfate, pyrophosphate, propiolate, phthalate, phenylacetate, phenylbutyrate, propanesulfonate, salicylate, succinate, sulfate, sulfite, succinate, suberate, sebacate, sulfonate, tartrate, thiocyanate, tosylate, undecanoate, and xylenesulfonate.

[00119] Further, the compounds described herein can be prepared as pharmaceutically acceptable salts formed by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid, including, but not limited to, inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid metaphosphoric acid, and the like; and organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, p-toluenesulfonic acid, tartaric acid, trifluoroacetic acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, arylsulfonic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1 -carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid and muconic acid. In some embodiments, other acids, such as oxalic, while not in themselves pharmaceutically acceptable, are employed in the preparation of salts useful as intermediates in obtaining the compounds disclosed herein, and their pharmaceutically acceptable acid addition salts.

[00120] In some embodiments, those compounds described herein which comprise a free acid group react with a suitable base, such as the hydroxide, carbonate, bicarbonate, sulfate, of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary, tertiary, or quaternary amine. Representative salts include the alkali or alkaline earth salts, like lithium, sodium, potassium, calcium, and magnesium, and aluminum salts and the like. Illustrative examples of bases include sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate, $N^+(C_{1-4}\ alkyl)_4$, and the like.

[00121] Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like. It should be understood that the compounds described herein also include the quaternization of any basic nitrogen-containing groups they contain. In some embodiments, water or oil-soluble or dispersible products are obtained by such quaternization.

Tautomers

[00122] In some situations, compounds exist as tautomers. The compounds described herein include all possible tautomers within the formulas described herein. Tautomers are compounds that are interconvertible by migration of a hydrogen atom, accompanied by a switch of a single bond and adjacent double bond. In bonding arrangements where tautomerization is possible, a chemical equilibrium of the tautomers will exist. All tautomeric forms of the compounds disclosed herein are contemplated. The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH.

Method of Treatment

[00123] In a further aspect, the present disclosure is directed to a method of treating a PKMYT1-associated disease or condition in a subject in need thereof, which comprises administering to the subject a therapeutically effective amount of the compound of Formula (V), (I) or (Ia) or a pharmaceutically acceptable salt, stereoisomer, or isotopic variant thereof as provided herein, owning to the PKMYT1 inhibitory activity of the compound of the present disclosure. In some embodiments, the compounds of the present disclosure are selective PKMYT1 inhibitors.

[00124] As used herein, the term "subject in need thereof" is a subject having a PKMYT1-associated disease or condition, or a subject having an increased risk of developing PKMYT1-associated disease or condition relative to the population at large. In some embodiments, the subject is a warm-blooded animal. In some embodiments, the warm-blooded animal is a mammal. In some embodiments, the warm-blooded animal is a human.

[00125] PKMYT1 has been implicated as a potentially important cancer target as it is essential in many cancer cells. Overexpression of PKMYT1 has been observed in various cancers including, for example, hepatocellular carcinoma as well as clear-cell renal-cell carcinoma. PKMyt1 downregulation has a minor role in unperturbed cells but has a more prominent role in cells exposed to DNA damage. Additionally, cells that exhibit high levels of replication stress in addition to defective G1 checkpoint regulation may be particularly sensitive to loss of PKMYT1 function, as these cells will be prone to entering mitosis prematurely with compromised genomic material leading to mitotic catastrophe. Inhibitors of PKMYT1, a regulator of G2-M transition, has been found to be particularly useful in the treatment of tumors (e.g., cancers) harboring CCNE1-amplification or FBXW7 loss-of-function mutations using a synthetic lethal therapeutic strategy. Cancers harboring CCNE1-amplification may include, e.g., uterine cancer, ovarian cancer, breast cancer, gastric cancer, esophageal cancer, lung cancer, and endometrial cancer, etc. Cancers harboring FBXW7 loss-of-function may include, e.g., uterine cancer, colorectal cancer, breast cancer, lung cancer, and esophageal cancer, etc. Moreover, PKMYT1 has been implicated in non-small-cell lung cancer, hepatocellular carcinoma, glioblastoma, neuroblastoma, etc.

[00126] In some embodiments, the PKMYT1-associated disease or condition is tumor, and particularly, advanced solid tumor. In some embodiments, the PKMYT1-associated disease or

condition is selected from the group consisting of uterine cancer, ovarian cancer, breast cancer, gastric cancer, esophageal cancer, lung cancer (e.g., non-small-cell lung cancer), endometrial cancer, colorectal cancer, hepatocellular carcinoma, glioblastoma, neuroblastoma, etc.

[00127] The method of treating a PKMYT1-associated disease or condition as described herein may be used as a monotherapy. As used herein, the term "monotherapy" refers to the administration of a single active or therapeutic compound to a subject in need thereof. In some embodiments, monotherapy will involve administration of a therapeutically effective amount of one of the compounds of the present disclosure or a pharmaceutically acceptable salt, stereoisomer, or isotopic variant thereof, to a subject in need of such treatment.

[00128] Depending upon the particular disease or condition to be treated, the method of treating a PKMYT1-associated disease or condition described herein may involve, in addition to administration of the compound of Formula (V), (I) or (Ia), combination therapy of one or more additional therapeutic agent(s), for example, a second therapeutic agent which is an anti-cancer agent. In some embodiments, non-limiting examples of the additional therapeutical agents may include an additional PKMYT1 inhibitor. In some embodiments, one or more additional therapeutic agent(s) may be selected from the group consisting of: a cytotoxic agent; an antimetabolite; an alkylating agent; an anthracycline; an antibiotic; an anti-mitotic agent; a hormone therapy; a signal transduction inhibitor; a gene expression modulator; an apoptosis inducer; an angiogenesis inhibitor; an immunotherapy agent; a DNA damage repair inhibitor; or a combination thereof.

[00129] In a further aspect, the present disclosure provided a method of treating cancer in a subject in need thereof, the method comprising administering to the subject the compound disclosed herein, or a pharmaceutically acceptable salt, or stereoisomer thereof, or the pharmaceutical composition disclosed herein.

[00130] In a further aspect, the present disclosure provided a method of modulating PKMYT1 in a subject, the method comprising administering to the subject the compound disclosed herein, or a pharmaceutically acceptable salt, or stereoisomer thereof, or the pharmaceutical composition disclosed herein.

[00131] In a further aspect, the present disclosure provided a method of inhibiting PKMYT1 in a subject, the method comprising administering to the subject the compound disclosed herein, or a pharmaceutically acceptable salt, or stereoisomer thereof, or the pharmaceutical composition disclosed herein.

[00132] In some embodiments, the subject has cancer. In some embodiments, the cancer depends on the activity of PKMYT1. In some embodiments, the cancer overexpresses CCNE1. In some embodiments, the cancer has an inactivating mutation in the FBXW7 gene. In some embodiments, the cancer is a solid tumor. In some embodiments, the cancer is breast cancer, colorectal cancer, endometrial cancer, esophageal cancer, glioblastoma, hepatocellular carcinoma, lung cancer, neuroblastoma, ovarian cancer, prostate cancer, stomach cancer, or uterine cancer.

[00133] In a further aspect, the present disclosure provided a pharmaceutical composition for treating a PKMYT1-associated disease or condition, comprising the compound disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[00134] In a further aspect, the present disclosure provided use of the compound disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition disclosed herein in the manufacture of a medicament for treating cancer.

[00135] In a further aspect, the present disclosure provided a kit for treating cancer, comprising the compound disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition disclosed herein, a container, and optionally a package insert or label indicating treatment of said disease or condition.

Dosing

[00136] In some embodiments, the compositions containing the compound(s) described herein are administered for therapeutic treatments. In certain therapeutic applications, the compositions are administered to a patient already suffering from a disease or condition, in an amount sufficient to cure or at least partially arrest at least one of the symptoms of the disease or condition. Amounts effective for this use depend on the severity and course of the disease or condition, previous therapy, the patient's health status, weight, and response to the drugs, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation and/or dose ranging clinical trial.

Routes of Administration

[00137] Suitable routes of administration include, but are not limited to, oral, intravenous, rectal, aerosol, parenteral, ophthalmic, pulmonary, transmucosal, transdermal, vaginal, otic, nasal, and topical administration. In addition, by way of example only, parenteral delivery includes intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intralymphatic, and intranasal injections.

[00138] In some embodiments, a compound as described herein is administered in a local rather than systemic manner, for example, via injection of the compound directly into an organ, often in a depot preparation or sustained release formulation. In specific embodiments, long acting formulations are administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Furthermore, in other embodiments, the drug is delivered in a targeted drug delivery system, for example, in a liposome coated with organ specific antibody. In such embodiments, the liposomes are targeted to and taken up selectively by the organ. In yet other embodiments, the compound as described herein is provided in the form of a rapid release formulation, in the form of an extended release formulation, or in the form of an intermediate release formulation.

Pharmaceutical Compositions/Formulations

[00139] The compounds described herein are administered to a subject in need thereof, either alone or in combination with pharmaceutically acceptable carriers, excipients, or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. In some embodiments, the compounds described herein are administered to animals.

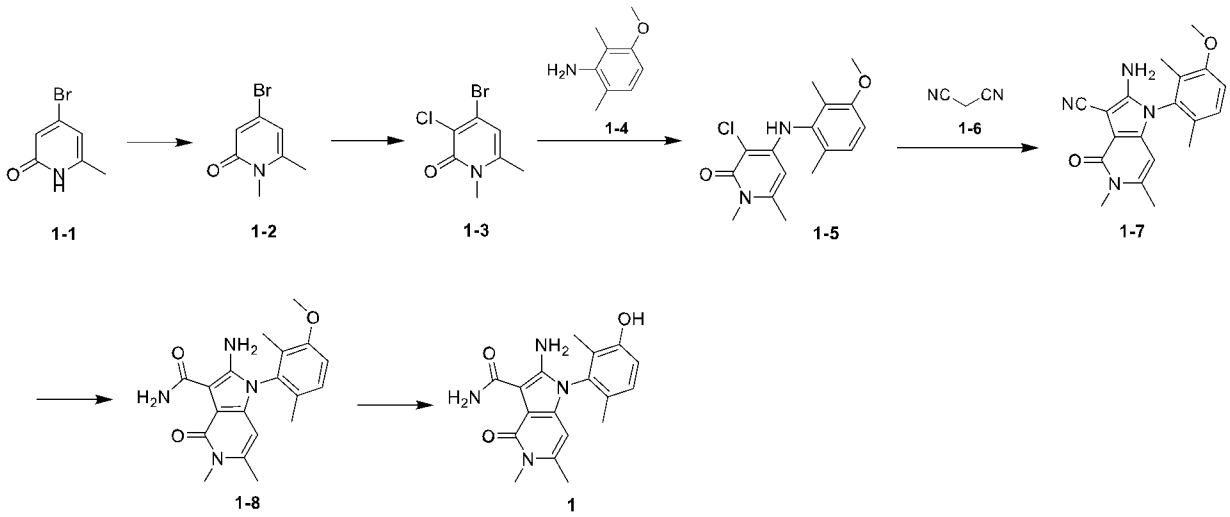
[00140] In another aspect, provided herein are pharmaceutical compositions comprising a compound described herein, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient. Pharmaceutical compositions are formulated in a conventional manner using one or more pharmaceutically acceptable excipients that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. A summary of pharmaceutical compositions described herein can be found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999), herein incorporated by reference for such disclosure.

Examples

[00141] For the purpose of illustration, the following examples are included. The Examples provided herein describe the synthesis of compounds disclosed herein as well as intermediates used to prepare the compounds. However, it is to be understood that these examples do not limit the present disclosure and are only meant to suggest a method of practicing the present disclosure. Persons skilled in the art will recognize that the chemical reactions described may be readily adapted to prepare a number of other compounds of the present disclosure, and alternative methods for preparing the compounds of the present disclosure are deemed to be within the scope of the present disclosure. For example, the synthesis of non-exemplified compounds according to the present disclosure may be successfully performed by modifications apparent to those skilled in the art, e.g., by appropriately protecting interfering groups, by utilizing other suitable reagents and building blocks known in the art other than those described, and/or by making routine modifications of reaction conditions. Besides, persons skilled in the art will also understand that individual steps described herein or in the separate batches of a compound may be combined. Alternatively, other reactions disclosed herein or known in the art will be recognized as having applicability for preparing other compounds of the present disclosure. The following description is, therefore, not intended to limit the scope of the present disclosure, but rather is specified by the claims appended hereto.

Example 1: Synthesis of Exemplary Compounds

Example 1.1:



[00142] Step 1: Preparation of Compound 1-2

[00143] To a solution of compound **1-1** (3.70 g, 19.68 mmol) in THF (10 mL) were added TBAF (78.7 mL, 78.72 mmol) and CH_3I (2.45 mL, 39.36 mmol). The mixture was stirred at 60 ℃ for 16 h. The mixture was cooled to rt, diluted with EA (100 mL), washed with water (100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated, and purified by silica gel column to give compound **1-2** (3.50 g, 88.0%). **LCMS**: 204.0 $[M+H]^+$; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.72 (d, J = 4.0 Hz, 1H), 6.23 (s, 1H), 3.48 (s, 3H), 2.34 (s, 3H).

[00144] Step 2: Preparation of Compound 1-3

[00145] To a solution of compound **1-2** (1.0 g, 4.949 mmol) in DMF (10 mL) was added NCS (726.96 mg, 5.444 mmol). The mixture was stirred at 45 ℃ for 16 h. The reaction mixture was diluted with EA (100 mL), and washed with brine (100 mL ×3). The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column to give compound **1-3** (1.00 g, 85.4%). **LCMS**: 237.9 $[M+H]^+$.

[00146] Step 3: Preparation of Compound 1-5

[00147] To a solution of compound **1-3** (500 mg, 2.114 mmol) in dioxane (10 mL) were added compound **1-4** (352 mg, 2.326 mmol), XantPhos Pd G3 (240.6 mg, 0.254 mmol), and Cs_2CO_3 (2.07 g, 6.343 mmol), and the mixture was stirred at 110 ℃ for 16 h and cooled to rt. The mixture was diluted with EA (100 mL) and water (30 mL). The organic layer was separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified using silica gel column chromatography to afford compound **1-5** (230 mg, 35.5%). **LCMS**: 307.1 $[M+H]^+$.

[00148] Step 4: Preparation of Compound 1-7

[00149] To a solution of compound **1-6** (75.79 mg, 1.147 mmol) in DMF (3 mL) was added NaH (46 mg, 1.147 mmol) at 0 ℃. The mixture was stirred for 0.5 h. Then CuI (4.9 mg, 0.026 mmol),

methyl[(1*S*,2*S*)-2-(methylamino)cyclohexyl]amine (7.42 mg, 0.052 mmol), and compound **1-5** (160 mg, 0.522 mmol) were added. The mixture was stirred at 150 ℃ for 1 h under microwave. The mixture was quenched with water (10 mL) and extracted with EA (10 mL). The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by prep-TLC to afford compound **1-7**. **LCMS**: 337.1 $[M+H]^+$.

[00150] Step 5: Preparation of Compound 1-8

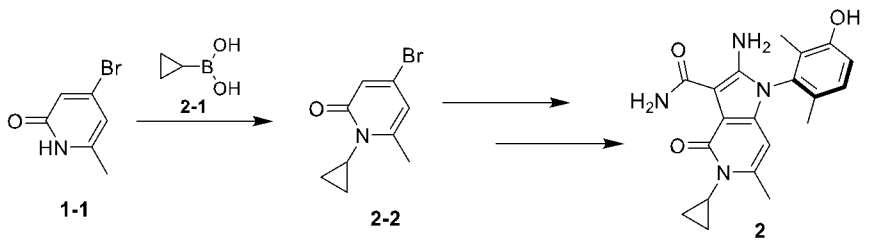
[00151] A mixture of compound **1-7** (50 mg, 0.149 mmol) in H_2SO_4 (2 mL) was stirred at 15 ℃ for 0.5 h. The mixture was quenched with ice-water (15 mL), basified to pH~8 with 2 M NaOH. The mixture was extracted with DCM (20 mL ×3). The organic layers were combined dried over Na_2SO_4, concentrated to dryness. The residue was purified by prep-TLC to afford compound **1-8**. **LCMS**: 355.1 $[M+H]^+$.

[00152] Step 6: Preparation of Compound 1

[00153] To a solution of compound **1-8** (90 mg, 0.277 mmol) in DCM (1 mL) was added BBr_3 (0.3 μL, 0.027 mmol). The mixture was stirred at 15 ℃ for 2 h. The reaction was quenched with MeOH (1mL). The mixture was concentrated and purified by prep-HPLC to afford **Compound 1**. **LCMS**: 341.0 $[M+H]^+$.

[00154] **^{1}H NMR** (400 MHz, DMSO-d_6): δ 10.33 (s, 1H), 9.63 (s, 1H), 7.09 (t, J = 7.8 Hz, 1H), 6.94 (d, J = 8.2 Hz, 1H), 6.64 (s, 1H), 6.45 (s, 1H), 6.27 (s, 1H), 5.67 (s, 1H), 3.49 (s, 3H), 2.30 (s, 3H), 1.78 (s, 3H), 1.69 (s, 3H).

Example 1.2



[00155] Step 1: Preparation of Compound 2-2

[00156] To a solution of compound **1-1** (2.50 g, 13.296 mmol) in toluene (50 mL) were added compound **2-1** (2.28 g, 26.593 mmol), $Cu(OAc)_2$ (2.42 g, 13.296 mmol), pyridine (5.35 mL, 66.482 mmol), and KHMDS (13.3 mL, 13.296 mmol), and the reaction was stirred at 100 ℃ under O_2 overnight. The mixture was cooled to rt, diluted with DCM and water. The organic layer was separated, dried, filtered, and concentrated. The residue was purified using silica gel column chromatography to afford compound **2-2** (1.70 g, 56.1%). **LCMS**: 230.1 $[M+H]^+$.

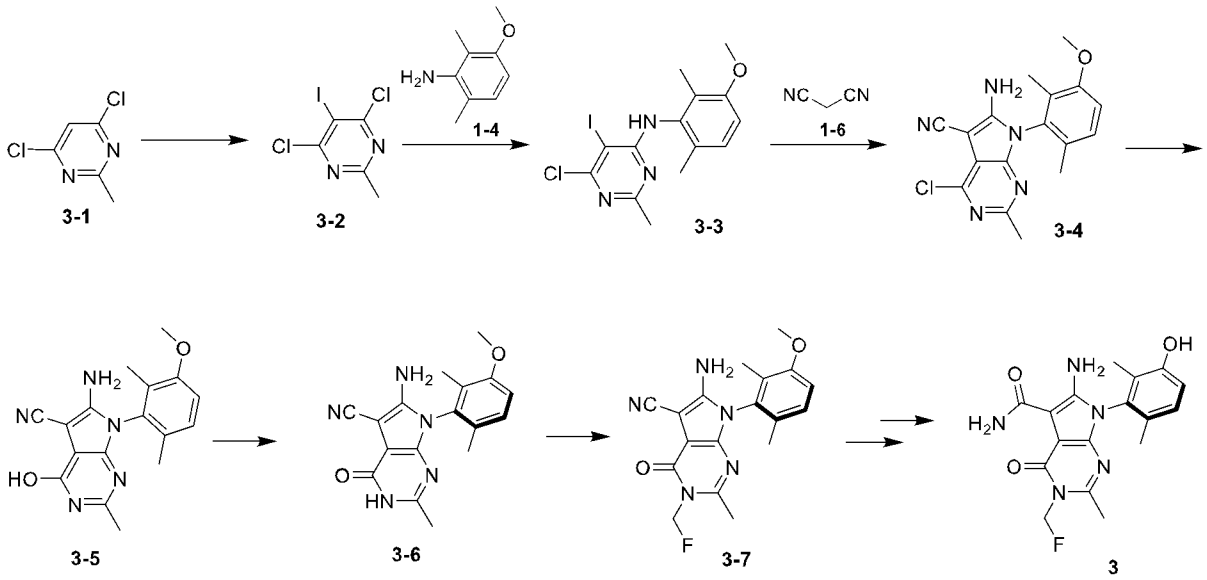
[00157] Step 2: Preparation of Compound 2

[00158] **Compound 2** was prepared from compound **2-2** (1.50 g, 6.576 mmol) in a similar fashion with the synthesis of **Compound 1**, the isomer was separated by SFC. Instrument: Waters SFC 150; Column: Daicelchiralcel®OZ, 250*25 mm 10 μm; Condition: 45% MeOH (+0.1% 7.0mol/L

ammonia in MeOH) with 55% CO_2; Flow rate: 80 mL/min; RT = 2.671 min (the other enantiomer RT = 4.589 min). **LCMS**: 367.3 $[M+H]^+$.

[00159] **^{1}H NMR** (400 MHz, DMSO-d_6): δ 10.26 (s, 1H), 9.63 (s, 1H), 7.09 (d, J = 8.2 Hz, 1H), 6.93 (d, J = 8.2 Hz, 1H), 6.63 (s, 1H), 6.42 (s, 2H), 5.61 (s, 1H), 2.95–2.79 (m, 1H), 2.38 (s, 3H), 1.78 (s, 3H), 1.69 (s, 3H), 1.17–1.12 (m, 2H), 0.85–0.81 (m, 2H).

Example 1.3



[00160] **Step 1: Preparation of Compound 3-2**

[00161] To a solution of compound **3-1** (50 g, 306.748 mmol) in THF (2 L) was added LDA (245.40 mL, 490.798 mmol) at -78 ℃. The mixture was stirred at -78 ℃ for 0.5 h. Then I_2 (217.7 g, 490.798 mmol) in THF (500 mL) was added and stirred at -78 ℃ for 1 h. The reaction was quenched by NH_4Cl (sat.aq, 2 L) under ice-bath, which was extracted with EA (2 L ×3). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by silica gel column chromatography to afford compound **3-2** (25 g, 28.2%). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 2.54 (s, 3H).

[00162] **Step 2: Preparation of Compound 3-3**

[00163] To a solution of compound **3-2** (38 g, 131.533 mmol), compound **1-4** (19.9 g, 131.533 mmol) in THF (1.5 L) was added LiHMDS (1.0 M, 263.07 mL) at 0 ℃ under N_2. The mixture was stirred at 0 ℃ for 1 h. The mixture quenched by NH_4Cl (sat.aq, 1 L) under ice-bath, which was extracted with EA (500 mL ×3). Combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by silica gel column chromatography to afford compound **3-3** (11.5 g, 21.7%). **LCMS:** 404.0 $[M+H]^+$.

[00164] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.08 (d, J = 8.4 Hz, 1H), 6.81–6.77 (m, 2H), 3.84 (s, 3H), 2.36 (s, 3H), 2.13 (s, 3H), 2.06 (s, 3H).

[00165] **Step 3: Preparation of Compound 3-4**

[00166] To a solution of compound **1-6** (245.7 mg, 3.717 mmol) in DME (15 mL) was added NaH (123.9 mg, 3.097 mmol) at 0 ℃. The mixture was stirred at 0 ℃ for 30 min. Then compound **3-3** (500 mg, 1.239 mmol) and XantPhos Pd G3 (176.2 mg, 0.186 mmol) were added. The mixture was stirred at 130 ℃ for 3 h under N_2. The mixture was quenched by H_2O (50 mL), and extracted with EA (30 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel to afford compound **3-4** (70.4 mg, 33.7%). **LCMS:** 342.1 $[M+H]^+$.

[00167] **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.49 (s, 2H), 7.26 (d, J = 8.4 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 3.85 (s, 3H), 2.42 (s, 3H), 1.80 (s, 3H), 1.71 (s, 3H).

[00168] **Step 4: Preparation of Compound 3-5**

[00169] To a solution of compound **3-4** (500 mg, 1.463 mmol) in AcOH (10 mL) was added NaOAc (959.7 mg, 11.704 mmol). The mixture was stirred at 100 ℃ for 24 h. The reaction mixture was carefully added into ice-water (30 mL) while stirring, which was adjusted to pH~8 with NaOH (4 M in water). The mixture was extracted with EA (30 mL ×3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by silica gel column chromatography to afford compound **3-5**. **LCMS:** 324.0 $[M+H]^+$.

[00170] **Step 4: Preparation of Compound 3-6**

[00171] Compound **3-6** was obtained by SFC separation of racemic compound **3-5**. Instrument: Waters SFC150; Column: Daicelchiralpak®AS, 250*25 mm 10 μm; Condition: 25% EtOH (+0.1% 7.0 mol/L Ammonia in MeOH) with Supercritical CO_2; Flow rate: 120 mL/min; RT = 1.654 min (the other enantiomer RT = 2.534 min). **LCMS**: 324.2 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 12.10 (s, 1H), 7.21 (d, J = 8.4 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.39 (s, 2H), 3.83 (s, 3H), 2.17 (s, 3H), 1.82 (s, 3H), 1.72 (s, 3H).

[00172] **Step 5: Preparation of Compound 3-7**

[00173] To a solution of compound **3-6** (500 mg, 1.546 mmol) in ACN (10 mL) and Cs_2CO_3 (756 mg, 2.319 mmol) was added fluoroiodomethane (297 mg, 1.856 mmol). The mixture was stirred at rt for 2 h. The mixture was filtered and concentrated to dryness. The residue was purified by silica gel column chromatography to afford compound **3-7**. **LCMS**: 356.2 $[M+H]^+$.

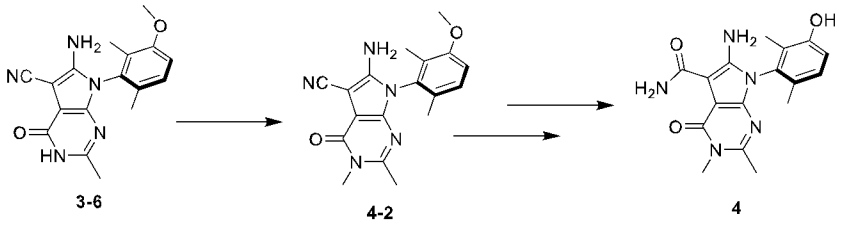
[00174] **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.23 (d, J = 8.4 Hz, 1H), 7.09 (d, J = 8.4 Hz, 1H), 6.59 (s, 2H), 6.17 (d, J = 52.0 Hz, 1H), 3.84 (s, 3H), 2.45 (s, 3H), 1.84 (s, 3H), 1.74 (s, 3H)

[00175] **Step 6: Preparation of Compound 3**

[00176] **Compound 3** was synthesized from compound **3-7** (900 mg, 2.53 mmol) in a similar fashion according to the procedure for **Compound 1.LCMS**: 360.2 $[M+H]^+$.

[00177] **^{1}H NMR** (400 MHz, DMSO-d_6): δ 9.59 (s, 1H), 9.14 (s, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.88 (s, 1H), 6.54 (s, 2H), 6.23 (d, J = 52.0 Hz, 2H), 2.49 (s, 3H), 1.80 (s, 3H), 1.71 (s, 3H).

Example 1.4



[00178] Step 1: Preparation of Compound 4-2

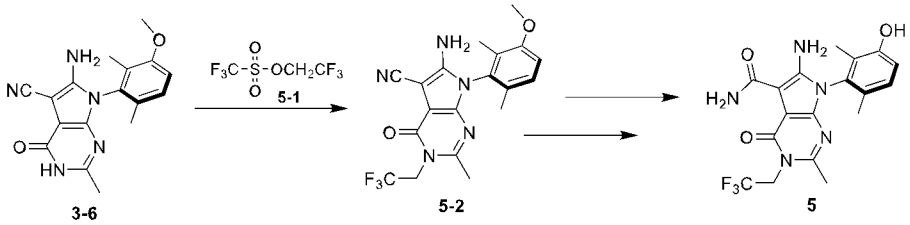
[00179] To a solution of compound **3-6**(70 mg, 0.216 mmol) and Cs_2CO_3 (141.0 mg, 0.433 mmol) in CH_3CN (4 mL) was added MeI (46.1 mg, 0.325 mmol). The mixture was stirred at rt for 2 h. The mixture was diluted with H_2O (10 mL) and extracted with EA (10 mL ×3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel to afford compound **4-2** (50 mg, 68.5%). **LCMS:** 338.2 $[M+H]^+$; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.22 (d, J = 8.4 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 6.44 (s, 2H), 3.83 (s, 3H), 3.47 (s, 3H), 2.37 (s, 3H), 1.82 (s, 3H), 1.73 (s, 3H).

[00180] Step 2: Preparation of Compound 4

[00181] Compound 4 was synthesized from compound **4-2** (40 mg, 0.119 mmol) in a similar fashion according to the procedure for **Compound 1**. **LCMS**: 342.2 $[M+H]^+$.

[00182] ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.54 (s, 1H), 9.50 (s, 1H), 7.05 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 6.75 (s, 1H), 6.45 (s, 2H), 3.52 (s, 3H), 2.40 (s, 3H), 1.78 (s, 3H), 1.69 (s, 3H).

Example 1.5



[00183] Step 1: Preparation of Compound 5-2

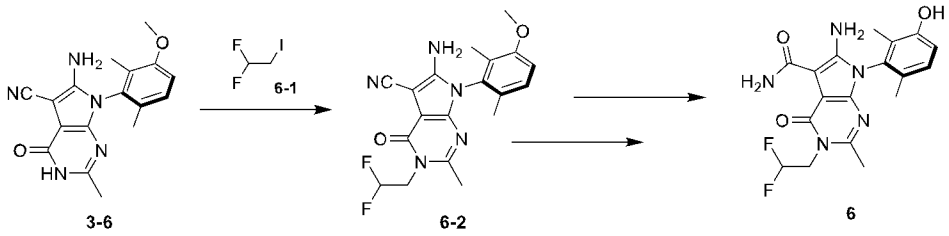
[00184] To a solution of compound **3-6** (150 mg, 0.464 mmol) in ACN (8 mL) were added compound **5-1** (129.2 mg, 0.557 mmol) and Cs_2CO_3 (181.3 mg, 0.557 mmol). The mixture was stirred at rt for 2 h. The reaction mixture was diluted with water (30 mL) and extracted with EA (30 mL ×3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by silica gel column chromatography to afford compound **5-2** (90 mg, 47.9%). **LCMS:** 406.2 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.22 (d, J = 8.4 Hz, 1H), 7.08 (d, J = 8.4 Hz, 1H), 6.59 (s, 2H), 5.05 (q, J = 8.0 Hz, 2H), 3.83 (s, 3H), 2.43 (s, 3H), 1.83 (s, 3H), 1.74 (s, 3H).

[00185] Step 2: Preparation of Compound 5

[00186] **Compound 5** was synthesized from compound **5-2** (80 mg, 0.197 mmol) in a similar fashion according to the procedure for **Compound 1**. **LCMS:** 410.3 $[M+H]^+$.

[00187] **^{1}H NMR** (400 MHz, DMSO-d_6): δ 9.56 (s, 1H), 9.16 (s, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.85 (s, 1H), 6.55 (s, 2H), 5.05 (q, J = 8.0 Hz, 2H), 2.47 (s, 3H), 1.79 (s, 3H), 1.71 (s, 3H).

Example 1.6



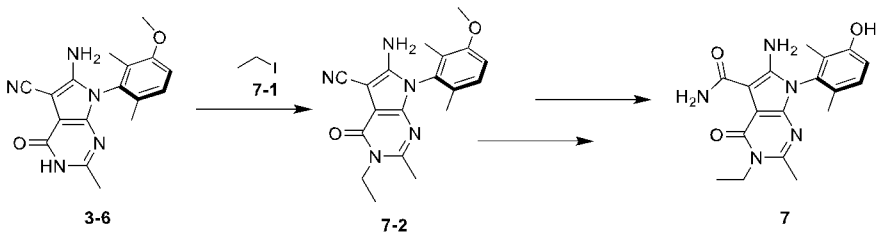
[00188] **Step 1: Preparation of Compound 6-2**

[00189] To a solution of compound **3-6** (150 mg, 0.464 mmol) in ACN (8 mL) were added compound **6-1** (119.2 mg, 0.557 mmol) and Cs_2CO_3 (181.3 mg, 0.557 mmol). The mixture was stirred at rt for 2 h. The mixture was diluted with water (30 mL), which was extracted with EA (30 mL ×3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by silica gel column chromatography to afford compound **6-2** (75 mg, 41.7%). **LCMS:** 388.1 $[M+H]^+$; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.22 (d, J = 8.4 Hz, 1H), 7.08 (d, J = 8.4 Hz, 1H), 6.55 (s, 2H), 6.50–6.20 (m, 1H), 4.52–4.44 (m, 2H), 3.84 (s, 3H), 2.41 (s, 3H), 1.83 (s, 3H), 1.74 (s, 3H).

[00190] **Step 2: Preparation of Compound 6**

[00191] **Compound 6** was synthesized from compound **6-2** (65 mg, 0.168 mmol) in a similar fashion according to the procedure for **Compound 1**. **LCMS**: 392.2 $[M+H]^+$; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 9.62 (s, 1H), 9.25 (s, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 2.8 Hz, 1H), 6.52 (s, 2H), 6.40–6.24 (m, 1H), 4.57–4.49 (m, 2H), 2.45 (s, 3H), 1.79 (s, 3H), 1.70 (s, 3H).

Example 1.7



[00192] **Step 1: Preparation of Compound 7-2**

[00193] To a solution of compound **3-6** (150 mg, 0.464 mmol) in DMF (5 mL) were added iodoethane (86.8 mg, 0.557 mmol) and Cs_2CO_3 (181.3 mg, 0.557 mmol). The mixture was stirred at rt

for 2 h. The reaction mixture was diluted with water (20 mL) and extracted with EA (30 mL ×3). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by silica gel column chromatography to afford compound **7-2** (90 mg, 55.2%). **LCMS**: 352.1 $[M+H]^+$.

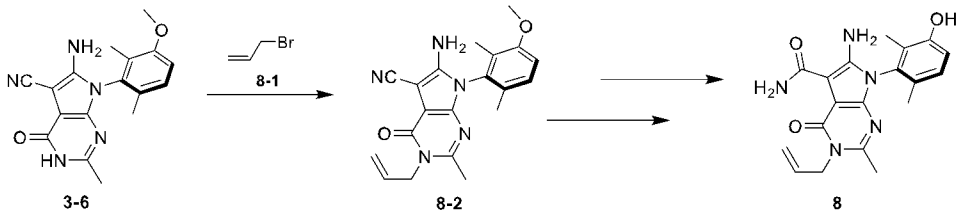
[00194] **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.21 (d, J = 8.4 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 6.43 (s, 2H), 4.06–4.01 (m, 2H), 3.83 (s, 3H), 2.41 (s, 3H), 1.82 (s, 3H), 1.73 (s, 3H), 1.22 (t, J = 7.2 Hz, 3H).

[00195] **Step 2: Preparation of Compound 7**

[00196] **Compound 7** was synthesized from compound **7-2** (70 mg, 0.199 mmol) in a similar fashion according to the procedure for **Compound 1**. **LCMS**: 356.2 $[M+H]^+$.

[00197] **^{1}H NMR** (400 MHz, DMSO-d_6): δ 9.57 (s, 1H), 9.49 (s, 1H), 7.05 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 6.78 (d, J = 3.2 Hz, 1H), 6.46 (s, 2H), 4.08 (q, J = 8.0 Hz, 2H), 2.45 (s, 3H), 1.78 (s, 3H), 1.69 (s, 3H), 1.25 (t, J = 8.0 Hz, 3H).

Example 1.8



[00198] **Step 1: Preparation of Compound 8-2**

[00199] To a solution of compound **3-6** (150 mg, 0.464 mmol) and compound **8-1** (112.2 mg, 0.928 mmol) in DMF (5 mL) was added Cs_2CO_3 (181.3 mg, 0.557 mmol). The solution was stirred at rt for 3 h. The reaction mixture was diluted with water (20 mL), which was extracted with EA (30 mL ×3). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by silica gel column chromatography to afford compound **8-2** (70 mg, 41.5%). **LCMS:** 364.0 $[M+H]^+$.

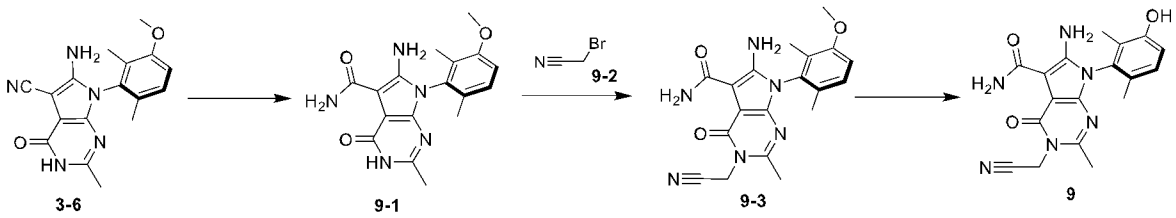
[00200] **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.24 (d, J = 8.4 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 6.48 (s, 2H), 5.98–5.89 (m, 1H), 5.18 (dd, J = 10.4, 0.8 Hz, 1H), 5.11–4.94 (m, 1H), 4.69 (d, J = 4.8 Hz, 2H), 3.84 (s, 3H), 2.36 (s, 3H), 1.84 (s, 3H), 1.74 (s, 3H).

[00201] **Step 2: Preparation of Compound 8**

[00202] **Compound 8** was synthesized from compound **8-2** (80 mg, 0.220 mmol) in a similar fashion according to the procedure for **Compound 1**. **LCMS:** 368.2 $[M+H]^+$.

[00203] **^{1}H NMR** (400 MHz, DMSO-d_6): δ 9.57 (s, 1H), 9.42 (d, J = 3.2 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.80 (d, J = 3.2 Hz, 1H), 6.49 (s, 2H), 5.98–5.91 (m, 1H), 5.19 (dd, J = 10.4, 1.2 Hz, 1H), 5.00 (dd, J = 17.2, 1.2 Hz, 1H), 4.73 (d, J = 5.2 Hz, 2H), 2.40 (s, 3H), 1.79 (s, 3H), 1.70 (s, 3H).

Example 1.9



[00204] Step 1: Preparation of Compound 9-1

[00205] A solution of compound **3-6** (150 mg, 0.464 mmol) in H_2SO_4 (5 mL) was stirred at 40 ℃ for 1 h. The reaction mixture was carefully added into ice-water (20 mL) while stirring and adjusted to pH~8 with NaOH (4 M in water). The mixture was extracted with DCM (30 mL ×3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by silica gel column chromatography to afford compound **9-1** (150 mg, 94.7%). **LCMS:** 342.3 $[M+H]^+$.

[00206] ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.28 (s, 1H), 9.46 (s, 1H), 7.23 (d, J = 8.4 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 6.76 (s, 1H), 6.41 (s, 2H), 3.84 (s, 3H), 2.21 (s, 3H), 1.83 (s, 3H), 1.73 (s, 3H).

[00207] Step 2: Preparation of Compound 9-3

[00208] To a solution of compound **9-1** (150 mg, 0.439 mmol) and compound **9-2** (79.0 mg, 0.659 mmol) in DMF (1 mL) was added K_2CO_3 (182.2 mg, 1.318 mmol). The solution was stirred at 50 ℃ for 3 h. The reaction mixture was diluted with water (20 mL) and extracted with EA (30 mL ×3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by silica gel column chromatography to afford compound **9-3**. **LCMS:** 381.3 $[M+H]^+$.

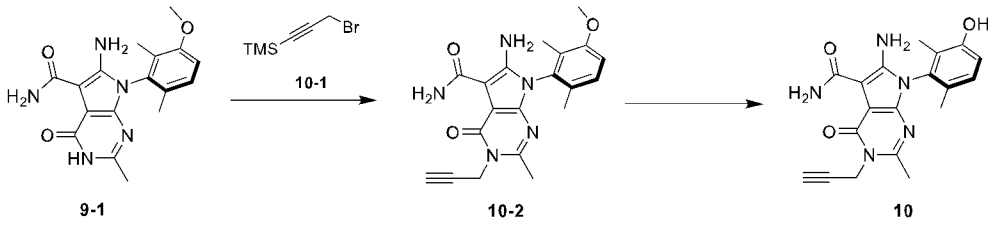
[00209] ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.14 (s, 1H), 7.25 (d, J = 8.4 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 6.91 (s, 1H), 6.61 (s, 2H), 5.22 (s, 2H), 3.85 (s, 3H), 2.50 (s, 3H), 1.85 (s, 3H), 1.75 (s, 3H).

[00210] Step 3: Preparation of Compound 9

[00211] Compound 9 was synthesized from compound **9-3** (60 mg, 0.158 mmol) in a similar fashion according to the procedure for **Compound 1**. **LCMS:** 367.0 $[M+H]^+$.

[00212] ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.58 (s, 1H), 9.12 (s, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.85 (s, 1H), 6.56 (s, 2H), 5.20 (s, 2H), 2.51 (s, 3H), 1.79 (s, 3H), 1.70 (s, 3H).

Example 1.10



[00213] Step 1: Preparation of Compound 10-2

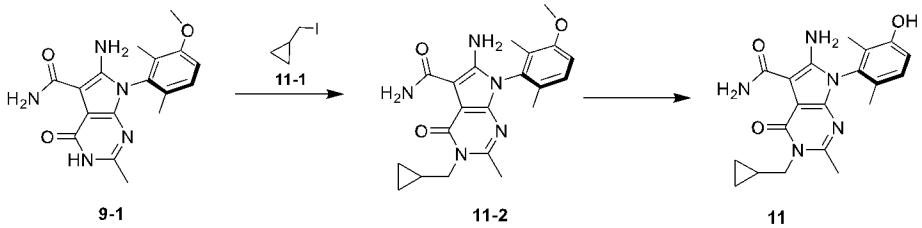
[00214] To a solution of compound **9-1** (100 mg, 0.293 mmol) in DMF (2 mL) were added compound **10-1** (61.6 mg, 0.322 mmol) and Cs_2CO_3 (286.5 mg, 0.879 mmol). The mixture was stirred at rt under N_2 for 2 h. The reaction mixture was diluted with water (20 mL) and extracted with EA (30 mL ×3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by silica gel column chromatography to afford compound **10-2** (90 mg, 81.0%). **LCMS:** 380.0 $[M+H]^+$; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 9.31 (d, J = 2.8 Hz, 1H), 7.24 (d, J = 8.4 Hz, 1H), 7.09 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 2.8 Hz, 1H), 6.56 (s, 2H), 4.94 (d, J = 2.0 Hz, 2H), 3.84 (s, 3H), 3.38 (t, J = 2.0 Hz, 1H), 2.52 (s, 3H), 1.84 (s, 3H), 1.74 (s, 3H).

[00215] Step 2: Preparation of Compound 10

[00216] Compound 10 was synthesized from compound **10-2** (40 mg, 0.105 mmol) in a similar fashion according to the procedure for **Compound 1**. **LCMS:** 366.2 $[M+H]^+$.

[00217] ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.57 (s, 1H), 9.31 (d, J = 2.8 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.83 (d, J = 2.8 Hz, 1H), 6.51 (s, 2H), 4.94 (d, J = 2.0 Hz, 2H), 3.38 (t, J = 2.0 Hz, 1H), 2.52 (s, 3H), 1.79 (s, 3H), 1.70 (s, 3H).

Example 1.11



[00218] Step 1: Preparation of Compound 11-2

[00219] To a solution of compound **9-1** (135 mg, 0.395 mmol) in DMF (3 mL) was added compound **11-1** (86.3 mg, 0.474 mmol) and Cs_2CO_3 (154.4 mg, 0.474 mmol). The mixture was stirred at rt under N_2 for 2 h. The reaction mixture was diluted with water (20 mL) and extracted with EA (30 mL ×3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography to afford compound **11-2** (90 mg, 57.5%). **LCMS**: 396.2 $[M+H]^+$.

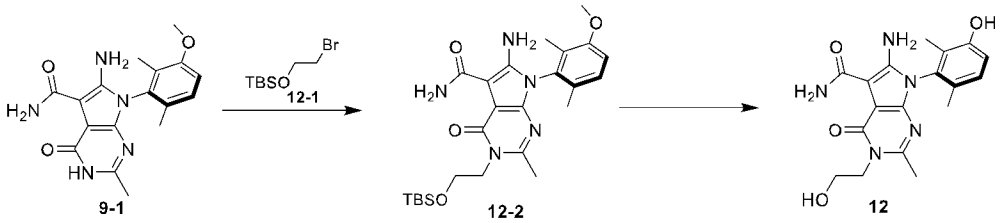
[00220] **^{1}H NMR** (400 MHz, DMSO-d_6): δ 9.49 (d, J = 3.2 Hz, 1H), 7.24 (d, J = 8.4 Hz, 1H), 7.08 (d, J = 8.4 Hz, 1H), 6.78 (d, J = 3.2 Hz, 1H), 6.51 (s, 2H), 4.00 (d, J = 6.8 Hz, 2H), 3.84 (s, 3H), 2.48 (s, 3H), 1.84 (s, 3H), 1.74 (s, 3H), 1.24–1.19 (m, 1H), 0.57–0.37 (m, 4H).

[00221] **Step 2: Preparation of Compound 11**

[00222] **Compound 11** was synthesized from compound **11-2** (110 mg, 0.278 mmol) in a similar fashion according to the procedure for **Compound 1**. **LCMS**: 382.2 $[M+H]^+$.

[00223] **^{1}H NMR** (400 MHz, DMSO-d_6): δ 9.57 (s, 1H), 9.48 (d, J = 3.2 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.76 (d, J = 3.2 Hz, 1H), 6.47 (s, 2H), 4.00 (d, J = 6.8 Hz, 2H), 1.79 (s, 3H), 1.70 (s, 3H), 1.25–1.21 (m, 1H), 0.65–0.35 (m, 4H).

Example 1.12



[00224] **Step 1: Preparation of Compound 12-2**

[00225] A mixture of compound **9-1** (50 mg, 0.146 mmol), compound **12-1** (38.4 mg, 0.161 mmol), Cs_2CO_3 (143.1 mg, 0.439 mmol) in DMF (1 mL) was stirred at 50 ℃ for 3 h. The reaction mixture was diluted with water (10 mL), which was extracted with EA (10 mL ×3). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by prep-TLC to afford compound **12-2** (50 mg, 68.5%). **LCMS**: 500.3 $[M+H]^+$.

[00226] **^{1}H NMR** (400 MHz, DMSO-d_6) : δ 9.59 (s, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 6.92 (s, 1H), 6.62 (s, 2H), 4.32 (t, J = 4.8 Hz, 2H), 4.04 (t, J = 4.8 Hz, 2H), 3.98 (s, 3H), 2.61 (s, 3H), 1.97 (s, 3H), 1.87 (s, 3H), 0.88 (s, 9H), 0.00 (s, 6H).

[00227] **Step 2: Preparation of Compound 12**

[00228] **Compound 12** was synthesized from compound **12-2** (50 mg, 0.100 mmol) in a similar fashion according to the procedure for **Compound 1**. **LCMS**: 372.2 $[M+H]^+$.

[00229] **^{1}H NMR** (400 MHz, DMSO-d_6): δ 9.54 (s, 1H), 9.48 (s, 1H), 7.05 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 6.75 (s, 1H), 6.45 (s, 2H), 4.96 (s, 1H), 4.11 (t, J = 5.4 Hz, 2H), 3.70 (t, J = 5.4 Hz, 2H), 2.49 (s, 3H), 1.79 (s, 3H), 1.70 (s, 3H).

[00230] Other compound disclosed herein can be synthesized with similar methods with modified conditions and different starting materials.

Example 2: Biological Assay

Example 2.1: PKMYT1 HTRF assay

[00231] Test compound serial dilution was performed by Echo, and the final concentrations vary from 10 μM to 0.5 nM. This was filled by the addition of 5 μL /well of Enzyme solution to the assay plate containing the test compound. The plate was centrifuged at 1000 rpm for 1 minute, and incubate 15 minutes at 25 ℃. Then 5 μL /well of tracer solution (Tracer 178) was added to initiate the reaction, and incubate for 60 minutes at 25 °C. Next 5 μL GST-Tb was added into the assay plate, the plate was centrifuged at 1000 rpm for 1 minute, and incubate for 15 minutes at 25 ℃. The assay plate was read on Envision.

Example 2.2: WEE1 ADP-Glo assay

[00232] Test compound serial dilution is performed by Echo, and the final concentrations vary from 10 μM to 0.5 nM. This was filled by the addition of 5 μL /well of Enzyme solution to the assay plate containing the test compound. The plate was centrifuged at 1000 rpm for 1 minute, and incubate 15 minutes at 25 ℃. Then 5 μL /well of substrate solution was added to initiate the reaction, and incubate for 60 minutes at 25 °C. Next 10 μL kinase detection reagent was added into the assay plate, the plate was centrifuged at 1000 rpm for 1 minute, and incubate for 60 minutes at 25 ℃. The assay plate was read on Envision for US LUM as RLU.

[00233] The data for Example 2.1 and Example 2.2 is shown in Table 3, wherein "A" stands for IC_{50} less than or equal to 10 nM; "B" stands for IC_{50} larger than 10 nM but less than or equal to 50 nM; "C" stands for IC_{50} larger than 50 nM but less than or equal to 500 nM; "D" stands for IC_{50} larger than 500 nM but less than or equal to 5000 nM; "E" stands for IC_{50} larger than 5000 nM; and "NT" stands for not tested.

TABLE 3

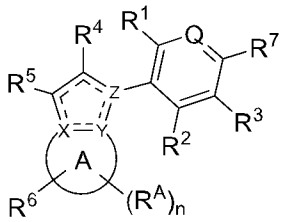
Compound	MYT1 HTRF IC_{50} (nM)	WEE1 ADP-Glo IC_{50} (nM)
1	B	C
2	A	C
3	A	C
4	A	NT
5	A	B
6	A	B
7	A	B
8	A	NT
9	A	NT
10	A	C
11	A	B
12	A	NT

[00234] Other compounds of disclosed herein also show PKMYT1 inhibitory activity.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula (I):



Formula (V),

or a pharmaceutically acceptable salt thereof, wherein:

each of X, Y and Z is independently N or C;

each of ═══ is a single bond or double bond;

Ring A is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

Q is N or CR^Q;

R^Q is H, OH or NH_2;

or R^Q and R^1 taken together with the atoms to which they are attached form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R;

or R^Q and R^7 taken together with the atoms to which they are attached form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R;

each R^A is independently halogen, cyano, oxo, $-OR^a$, $-SR^a$, $-SO_2R^a$, $-N(R^b)_2$, $-C(O)OR^b$, $-C(O)N(R^b)_2$, $-SO_2N(R^b)_2$, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl-alkyl, heterocycloalkyl-alkyl, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl-alkyl, heterocycloalkyl-alkyl, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally substituted with one or more R;

or two adjacent R^A taken together with the atoms to which they are attached form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R;

R^6 is oxo;

each of R^1 and R^2 is independently hydrogen, halogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally substituted with one or more R;

R^3 is hydrogen, halogen, cyano, $-NO_2$, $-OR^a$, $-SR^a$, $-N(R^b)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^b)_2$, alkyl, alkenyl, alkynyl, cycloalkyl, or heterocycloalkyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, and heterocycloalkyl are optionally substituted with one or more R;

R^4 is hydrogen, halogen, cyano, $-OR^a$, $-SR^a$, $-N(R^b)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^b)_2$, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the alkyl, alkenyl, alkynyl,

heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl aare independently optionally substituted with one or more R;

R^5 is -C(O)NH(R^a), -C(O)R^a, or -SO_2R^a;

R^7 is hydrogen, halogen, -CN, -NO_2, -OH, -OR^a, -N(R^b)$_2$, -C(O)R^a, -C(O)OR^b, -C(O)N(R^b)$_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, or heterocycloalkyl, wherein the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, cycloalkyl, and heterocycloalkyl are optionally substituted with one or more R;

each R is independently halogen, cyano, oxo, -OR^a, -SR^a, -SO_2R^a, -N(R^b)$_2$, -C(O)N(R^b)$_2$, -SO_2N(R^b)$_2$, alkyl, alkenyl, alkylidenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the alkyl, alkenyl, alkylidenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are independently optionally substituted with one or more R';

each R' is independently halogen, cyano, oxo, -OR^a, -SR^a, -SO_2R^a, -N(R^b)$_2$, -C(O)N(R^b)$_2$, -SO_2N(R^b)$_2$, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

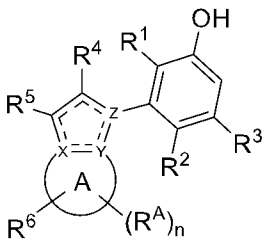
each R^a is independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, hydroxyalkyl, aminoalkyl, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^b is independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, hydroxyalkyl, aminoalkyl, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^b taken together with the atom to which they are attached form a heterocycloalkyl; and

n is an integer of 0-8.

2. A compound of Formula (I):



Formula (I),

or a pharmaceutically acceptable salt thereof, wherein:

each of X, Y and Z is independently N or C;

each of === is a single bond or double bond;

Ring A is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^A is independently halogen, cyano, oxo, -OR^a, -SR^a, -SO_2R^a, -N(R^b)$_2$, -C(O)OR^b, -C(O)N(R^b)$_2$, -SO_2N(R^b)$_2$, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl,

hydroxyalkyl, aminoalkyl, cycloalkyl-alkyl-, heterocycloalkyl-alkyl-, arylalkyl-, heteroarylalkyl-, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl-alkyl-, heterocycloalkyl-alkyl-, arylalkyl-, heteroarylalkyl-, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally substituted with one or more R;

or two adjacent R^A taken together with the atoms to which they are attached form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R;

R^6 is oxo;

each of R^1 and R^2 is independently hydrogen, halogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally substituted with one or more R;

R^3 is hydrogen, halogen, cyano, $-NO_2$, $-OR^a$, $-SR^a$, $-N(R^b)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^b)_2$, alkyl, alkenyl, alkynyl, cycloalkyl, or heterocycloalkyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, and heterocycloalkyl are optionally substituted with one or more R;

R^4 is hydrogen, halogen, cyano, $-OR^a$, $-SR^a$, $-N(R^b)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^b)_2$, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are independently optionally substituted with one or more R;

R^5 is $-C(O)NH(R^a)$, $-C(O)R^a$, or $-SO_2R^a$;

each R is independently halogen, cyano, oxo, $-OR^a$, $-SR^a$, $-SO_2R^a$, $-N(R^b)_2$, $-C(O)N(R^b)_2$, $-SO_2N(R^b)_2$, alkyl, alkenyl, alkylidenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the alkyl, alkenyl, alkylidenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are independently optionally substituted with one or more R';

each R' is independently halogen, cyano, oxo, $-OR^a$, $-SR^a$, $-SO_2R^a$, $-N(R^b)_2$, $-C(O)N(R^b)_2$, $-SO_2N(R^b)_2$, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^a is independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, hydroxyalkyl, aminoalkyl, arylalkyl-, heteroarylalkyl-, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^b is independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, hydroxyalkyl, aminoalkyl, arylalkyl-, heteroarylalkyl-, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^b taken together with the atom to which they are attached form a heterocycloalkyl; and

n is an integer of 0-8.

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein

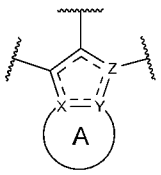
X is C, Y is C and Z is N;

X is N, Y is C and Z is N;

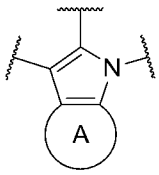
X is C, Y is N and Z is C; or

X is N, Y is C and Z is C.

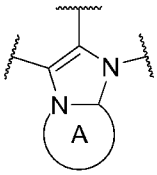
4. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein



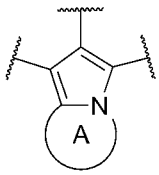
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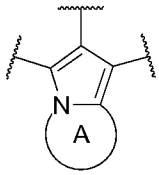
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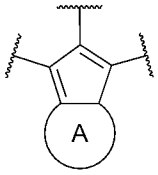
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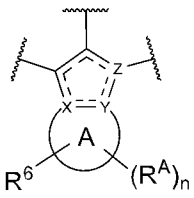


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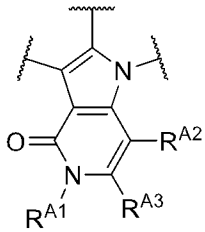
5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein Ring A is heterocycloalkyl or heteroaryl.

6. The compound of claim 5, or a pharmaceutically acceptable salt thereof, wherein Ring A is 6-membered heterocycloalkyl or 6-membered heteroaryl.

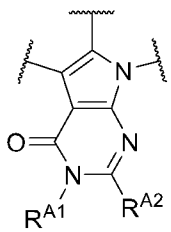
7. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein



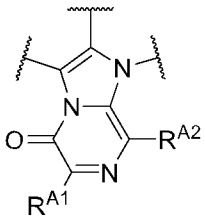
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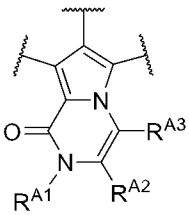
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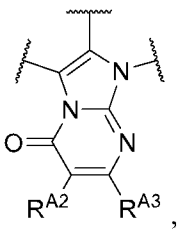
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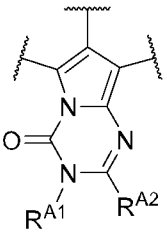
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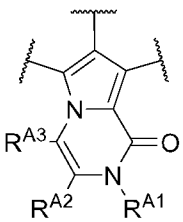
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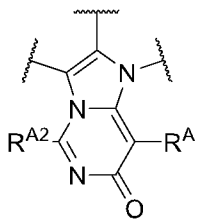
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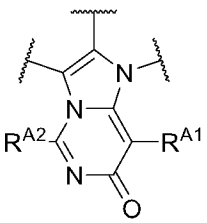
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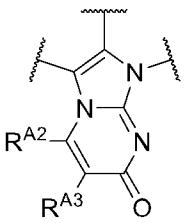
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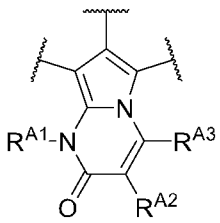
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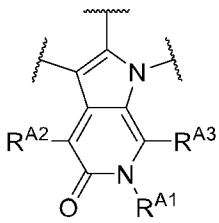
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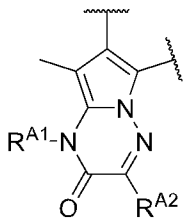
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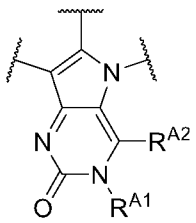
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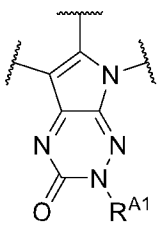
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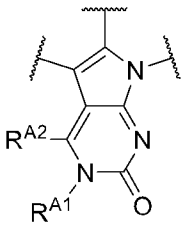
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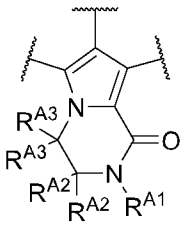
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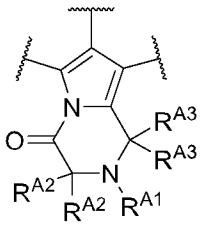
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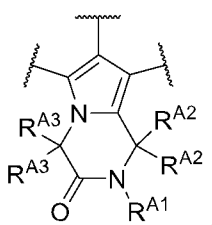
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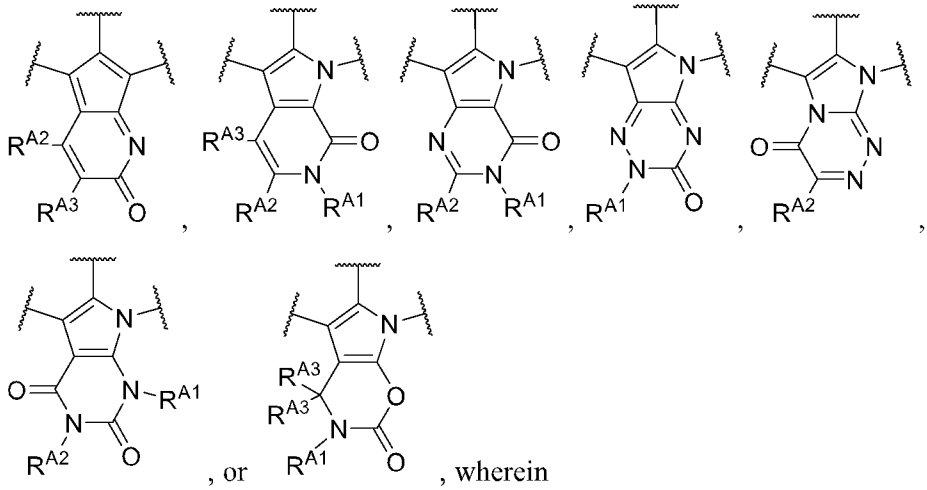
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, wherein

each of R^{A1}, R^{A2} and R^{A3} is independently hydrogen or independently selected from R^A;

or R^{A1} and R^{A2}, when adjacent to each other, taken together with the atoms to which they are attached form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, each optionally substituted with one or more R;

or R^{A1} and R^{A3}, when adjacent to each other, taken together with the atoms to which they are attached form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, each optionally substituted with one or more R;

or R^{A2} and R^{A3}, when adjacent to each other, taken together with the atoms to which they are attached form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, each optionally substituted with one or more R;

or two R^{A2} taken together with the same atom to which they are attached form a cycloalkyl, or heterocycloalkyl, each optionally substituted with one or more R;

or two R^{A3} taken together with the same atom to which they are attached form a cycloalkyl, or heterocycloalkyl, each optionally substituted with one or more R.

8. The compound of claim 7, or a pharmaceutically acceptable salt thereof, each R^A is independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl-alkyl-, heterocycloalkyl-alkyl-, arylalkyl-, heteroarylalkyl-, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl-alkyl-, heterocycloalkyl-alkyl-, arylalkyl-, heteroarylalkyl-, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally substituted with one or more R.

9. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein each R^A is independently $-OR^a$, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl-alkyl-, heterocycloalkyl-alkyl-, arylalkyl-, heteroarylalkyl-, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl-alkyl-, heterocycloalkyl-alkyl-, arylalkyl-, heteroarylalkyl-, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally substituted with one or more R.

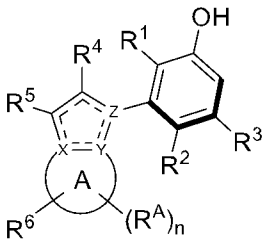
10. The compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein each R is independently halogen, hydroxyl, cyano, alkyl, oxo, or alkylidenyl, wherein the alkyl and alkylidenyl are optionally substituted with one or more R'.

11. The compound of claim 10, or a pharmaceutically acceptable salt thereof, wherein each R^A is independently $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CH_2F$, $-CHF_2$, $-CH_2CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-OCH_3$, $-OCF_3$, $-OCH_2F$, $-OCHF_2$, $-OCH_2CH_3$, $-OCH_2CF_3$, $-OCH_2CF_3$, $-OCH_2CHF_2$, $-OCH_2CH_2F$, , , 

19. The compound of any one of claims 1-18, or a pharmaceutically acceptable salt thereof, wherein R^5 is -C(O)NH(R^a).

20. The compound of claim 19, or a pharmaceutically acceptable salt thereof, wherein R^a is hydrogen.

21. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt thereof, wherein the compound is of Formula (Ia):



Formula (Ia).

22. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from any compound set forth in Table 1 or Table 2.

23. A pharmaceutical composition comprising the compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

24. A method of treating cancer in a subject in need thereof, the method comprising administering to the subject the compound of any one of claims 1-22, or a pharmaceutically acceptable salt, or stereoisomer thereof, or the pharmaceutical composition of claim 23.

25. A method of modulating PKMYT1 in a subject, the method comprising administering to the subject the compound of any one of claims 1-22, or a pharmaceutically acceptable salt, or stereoisomer thereof, or the pharmaceutical composition of claim 23.

26. A method of inhibiting PKMYT1 in a subject, the method comprising administering to the subject the compound of any one of claims 1-22, or a pharmaceutically acceptable salt, or stereoisomer thereof, or the pharmaceutical composition of claim 23.

27. The method of claim 25 or 26, wherein the subject has cancer.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2024/119019

A. CLASSIFICATION OF SUBJECT MATTER

C07D 471/04(2006.01)i; C07D487/04(2006.01)i; C07D487/14(2006.01)i; A61K31/437(2006.01)i; A61K31/407(2006.01)i; A61P35/00(2006.01)i

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)

IPC:C07D; A61K; A61P

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

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

DWPI, CNTXT, REGISTRY(STN), CAPLUS(STN), CNKI, ISI web of science: INSILICO MEDICINE, PKMYT1, MYT1, inhibitor?, dihydropyridin, oxo, one, cancer, tumor, structural search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	CN 117510503 A (CHENGDU HITGEN PHARMACEUTICALS DEVELOPMENT CO., LTD.) 06 February 2024 (2024-02-06) claims 17-20	1-27
PX	WO 2023174329 A1 (INSILICO MEDICINE IP LIMITED) 21 September 2023 (2023-09-21) pages 10-14	1-27
PX	WO 2023198199 A1 (SIMCERE ZAIMING PHARMACEUTICAL CO., LTD.) 19 October 2023 (2023-10-19) pages 8-16, claims 19-24	1-27
PX	WO 2024109942 A1 (SHANGHAI QILU PHARMACEUTICAL RESEARCH AND DEVELOPMENT CENTRE LTD.) 30 May 2024 (2024-05-30) page 176, claims 25-29	1-27
A	WO 2022213204 A1 (REPARE THERAPEUTICS INC. et al.) 13 October 2022 (2022-10-13) pages 1, 29-52	1-27
A	US 2023122909 A1 (REPARE THERAPEUTICS INC.) 20 April 2023 (2023-04-20) pages 1, 16-58	1-27

☐ 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
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"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
29 November 2024	**09 December 2024**

Name and mailing address of the ISA/CN	Authorized officer
CHINA NATIONAL INTELLECTUAL PROPERTY ADMINISTRATION **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088, China**	**WANG,XinYue** Telephone No. **(+86) 010-53962173**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2024/119019

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.: **24-27**
because they relate to subject matter not required to be searched by this Authority, namely:

The subject matter of claims 24-27 relates to methods for the treatment of human body by therapy as defined in PCT Rules 39.1(IV). This report has been carried out on the basis of the subject matter of the use in manufacture of medicaments for treating the alleged diseases.

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.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2024/119019

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
CN 117510503 A	06 February 2024	None	
WO 2023174329 A1	21 September 2023	None	
WO 2023198199 A1	19 October 2023	None	
WO 2024109942 A1	30 May 2024	TW 202430164 A	01 August 2024
WO 2022213204 A1	13 October 2022	EP 4319752 A1	14 February 2024
		US 2024207300 A1	27 June 2024
		JP 2024514844 A	03 April 2024
		WO 2022213204 A9	16 November 2023
		CA 3214900 A1	13 October 2022
US 2023122909 A1	20 April 2023	None	