COMPOUNDS AS MODULATORS OF BIS-PHOSPHOGLYCERATE MUTASE FOR THE TREATMENT OF SICKLE CELL DISEASE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit under 35 U.S.C. §119(e) of United States Provisional Application No. 63/077,973, filed September 14, 2020, which is hereby incorporated by reference in its entirety.

FIELD

[0002] The present disclosure relates generally to compounds, compositions, and method for treating sickle cell disease.

BACKGROUND

[0003] Bis-phosphoglycerate mutase (BPGM) is an enzyme in the glucose metabolism pathway that regulates the levels of 2,3-bis-phosphoglycerate (2,3-BPG) inside the red blood cell (RBC). 2,3-BPG is a known allosteric modulator of hemoglobin that stabilizes the de-oxy or "T-State" of hemoglobin that has a tendency to polymerize, resulting in the sickle cell morphology. There is currently a large unmet medical need for safe and effective oral therapies for the treatment of sickle cell disease. BPGM modulators that lower 2,3-BPG levels offer a novel mechanism of action from existing therapies and may significantly reduce sickling in sickle cell disease patients.

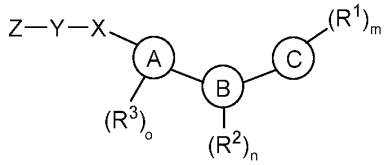
[0004] Accordingly, in one aspect, provided herein are compounds which are modulators of BPGM for use in treating sickle cell disease.

SUMMARY

[0005] Described herein, in certain embodiments, are compounds and compositions thereof for modulating bis-phosphoglycerate mutase (BPGM) for treating sickle cell disease.

[0006] The following embodiments are encompassed.

[0007] Embodiment 1a is a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is a 5-membered heteroarylene containing 1-3 heteroatoms selected from N and S;

Ring B is phenylene or a 5- to 6-membered heteroarylene containing 1-3 heteroatoms selected from N and S;

Ring C is a fused bicyclic 9- to 10-membered heteroaryl or heterocyclyl containing 1-4 heteroatoms selected from N and O, a 5- to 6-membered heteroaryl containing 1-4 nitrogen atoms, or phenyl substituted by one R^4;

each R^1 is independently -OH, halo, oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -CN, -N(H)C(O)R^6, -N(H)SO_2R^6, -$SO_2NR^6R^7$, or -C(O)N(H)SO_2R^6;

each R^2 is independently C_1-C_6 alkyl, C_1-C_6 haloalkyl, or halo;

each R^3 is independently C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_3-C_6 cycloalkyl;

R^4 is -OH, -$OP(O)(OH)_2$, -NO_2, -C(O)N(H)SO_2R^5, 5- to 6-membered heteroaryl or heterocyclyl, or -C(O)N(H)-(5- to 6-membered heteroaryl or heterocyclyl), wherein the heteroaryl and heterocyclyl contain 1-4 heteroatoms selected from N, O, and S, and wherein the heterocyclyl is optionally substituted by 1-2 oxo groups;

m is 0-4;

n is 0-2;

o is 0-2;

R^5 is phenyl or C_1-C_6 alkyl;

X is -CR^6R^7- or a bond;

Y is -O-, -N(H)-, or a bond;

each R^6 and R^7 is independently H or C_1-C_6 alkyl;

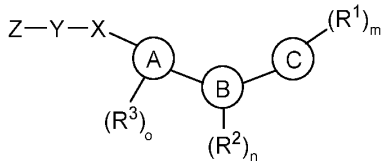
Z is Z^1 or Z^2;

Z^1 is H, C_1-C_6 alkyl, -C(O)(C_1-C_6 alkyl), -CO_2(C_1-C_6 alkyl), -C(O)NR^6R^7, -C(O)NR^6(C_1-C_6 alkylene)NR^6R^7, -CR^6R^7C(O)NR^6R^7, -$CR^6R^7NR^6R^7$, -C(O)(C_1-C_6 alkylene)NR^6R^7, -NR^6C(O)(C_1-C_6 alkyl), -NR^6R^7, -(C_1-C_6 alkyl)-CO_2H, -(C_1-C_6 alkyl)-OH, or -C(NR^6R^7)=N-CN, wherein C_1-C_6 alkylene is optionally substituted by 1-6 halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl;

Z^2 is 5- to 6-membered heteroaryl, -C(O)(5- to 6-membered heteroaryl), -CH_2C(O)(5- to 6-membered heteroaryl), 4- to 6-membered heterocyclyl, -C(O)(4- to 6-membered heterocyclyl), or -CH_2C(O)(4- to 6-membered heterocyclyl), wherein the heteroaryl and heterocyclyl contain 1-3 heteroatoms selected from N and O, and wherein the heteroaryl and heterocyclyl are optionally substituted by 1-3 R^8;

each R^8 is independently halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -NR^6R^7, -OH, oxo, -CO_2H, -O(C_1-C_6 alkyl), -CH_2-O(C_1-C_6 alkyl), or -(C_1-C_6 alkyl)-OH.

[0008] Embodiment 1b is a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is a 5-membered heteroarylene containing 1-3 heteroatoms selected from N and S;

Ring B is phenylene or a 5- to 6-membered heteroarylene containing 1-3 heteroatoms selected from N and S;

Ring C is a fused bicyclic 9- to 10-membered heteroaryl or heterocyclyl containing 1-4 heteroatoms selected from N and O, a 5- to 6-membered heteroaryl containing 1-4 nitrogen atoms, or phenyl substituted by one R^4;

each R^1 is independently -OH, halo, oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -CN, -N(H)C(O)R^6, -N(H)SO_2R^6, -N(H)$SO_2(C_6H_5)$, -$SO_2NR^6R^7$, or -C(O)N(H)SO_2R^6;

each R^2 is independently C_1-C_6 alkyl, C_1-C_6 haloalkyl, or halo;

each R^3 is independently C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_3-C_6 cycloalkyl;

R^4 is -OH, -$OP(O)(OH)_2$, -NO_2, -C(O)N(H)SO_2R^5, 5- to 6-membered heteroaryl or heterocyclyl, or -C(O)N(H)-(5- to 6-membered heteroaryl or heterocyclyl), wherein the heteroaryl and heterocyclyl contain 1-4 heteroatoms selected from N, O, and S, and wherein the heterocyclyl is optionally substituted by 1-2 oxo groups;

m is 0-4;

n is 0-2;

o is 0-2;

R^5 is phenyl or C_1-C_6 alkyl;

X is -CR^6R^7- or a bond;

Y is -O-, -N(H)-, or a bond;

each R^6 and R^7 is independently H or C_1-C_6 alkyl;

Z is Z^1 or Z^2;

Z^1 is H, C_1-C_6 alkyl, -C(O)(C_1-C_6 alkyl), -CO_2(C_1-C_6 alkyl), -C(O)NR^6R^7, -C(O)NR^6(C_1-C_6 alkylene)NR^6R^7, -CR^6R^7C(O)NR^6R^7, -$CR^6R^7NR^6R^7$, -C(O)(C_1-C_6 alkylene)NR^6R^7, -NR^6C(O)(C_1-C_6 alkyl), -NR^6R^7, -(C_1-C_6 alkyl)-CO_2H, -(C_1-C_6 alkyl)-OH, or -C(NR^6R^7)=N-CN, wherein C_1-C_6 alkylene is optionally substituted by 1-6 halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl;

Z^2 is 5- to 6-membered heteroaryl, -C(O)(5- to 6-membered heteroaryl), -CH_2C(O)(5- to 6-membered heteroaryl), 4- to 6-membered heterocyclyl, -C(O)(4- to 6-membered heterocyclyl), or -CH_2C(O)(4- to 6-membered heterocyclyl), wherein the heteroaryl and heterocyclyl contain 1-3 heteroatoms selected from N and O, and wherein the heteroaryl and heterocyclyl are optionally substituted by 1-3 R^8;

each R^8 is independently halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -NR^6R^7, -OH, oxo, -CO_2H, -O(C_1-C_6 alkyl), -CH_2-O(C_1-C_6 alkyl), or -(C_1-C_6 alkyl)-OH.

[0009] Embodiment 2 is the compound of embodiment 1, or a pharmaceutically acceptable salt thereof, wherein:

Ring A is thiazolylene.

[0010] Embodiment 3 is the compound of embodiment 1 or 2, or a pharmaceutically acceptable salt thereof, wherein:

each R^3 is independently C_1-C_3 alkyl or C_3-C_6 cycloalkyl.

[0011] Embodiment 4 is the compound of embodiment 3, or a pharmaceutically acceptable salt thereof, wherein:

each R^3 is independently -CH_3 or cyclopropyl.

[0012] Embodiment 5 is the compound of any one of embodiments 1-4, or a pharmaceutically acceptable salt thereof, wherein:

o is 0 or 1.

[0013] Embodiment 6 is the compound of any one of embodiments 1-5, or a pharmaceutically acceptable salt thereof, wherein:

Ring B is phenylene, pyridinylene, thiazolylene, pyrazolylene, pyrimidinylene, or thienylene.

[0014] Embodiment 7 is the compound of any one of embodiments 1-6, or a pharmaceutically acceptable salt thereof, wherein:

each R^2 is independently C_1-C_3 alkyl or halo.

[0015] Embodiment 8 is the compound of any one of embodiments 1-7, or a pharmaceutically acceptable salt thereof, wherein:

n is 0 or 1.

[0016] Embodiment 9 is the compound of any one of embodiments 1-8, or a pharmaceutically acceptable salt thereof, wherein:

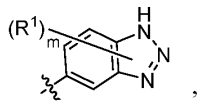
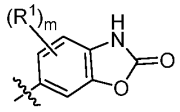
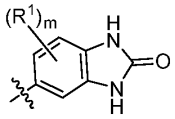
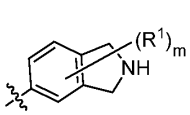
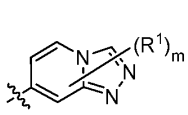
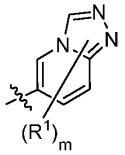
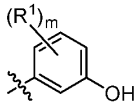
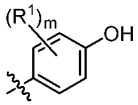
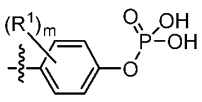
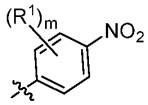
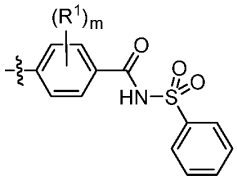
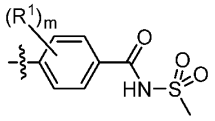
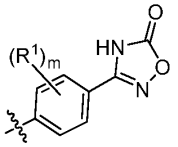
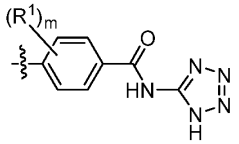
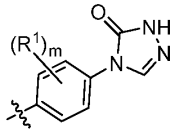
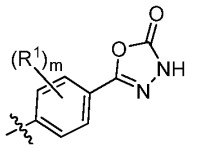
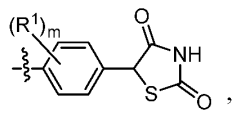
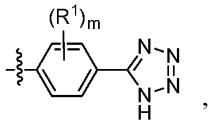
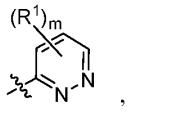
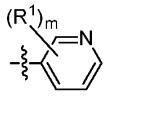
Ring C is a fused bicyclic 9-membered heteroaryl or heterocyclyl containing 1-4 heteroatoms selected from N and O, a 5- to 6-membered heteroaryl containing 1-4 nitrogen atoms, or phenyl substituted by one R^4.

[0017] Embodiment 10 is the compound of any one of embodiments 1-9, or a pharmaceutically acceptable salt thereof, wherein:

R^4 is -OH, -$OP(O)(OH)_2$, -NO_2, -$C(O)N(H)SO_2R^5$, 5- to 6-membered heteroaryl or heterocyclyl, or -C(O)N(H)-(5- to 6-membered heteroaryl or heterocyclyl),
wherein the heteroaryl and heterocyclyl contain 1-4 heteroatoms selected from N, O, and S, and wherein the heterocyclyl is optionally substituted by 1-2 oxo groups; and

R^5 is phenyl or C_1-C_3 alkyl.

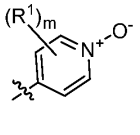
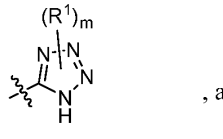
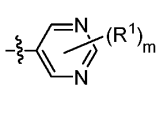
[0018] Embodiment 11 is the compound of any one of embodiments 1-10, or a pharmaceutically acceptable salt thereof, wherein Ring C-$(R^1)_m$ is selected from


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[0019] Embodiment 12a is the compound of any one of embodiments 1-11, or a pharmaceutically acceptable salt thereof, wherein:

each R^1 is independently -OH, halo, oxo, C_1-C_3 alkyl, C_1-C_3 haloalkyl, -CN, -N(H)C(O)R^6, -N(H)SO_2R^6, -$SO_2NR^6R^7$, or -C(O)N(H)SO_2R^6; and

each R^6 and R^7 is independently H or C_1-C_3 alkyl.

[0020] Embodiment 12b is the compound of any one of embodiments 1-11, or a pharmaceutically acceptable salt thereof, wherein:

each R^1 is independently -OH, halo, oxo, C_1-C_3 alkyl, C_1-C_3 haloalkyl, -CN, -N(H)C(O)R^6, -N(H)SO_2R^6, -N(H)$SO_2(C_6H_5)$, -$SO_2NR^6R^7$, or -C(O)N(H)SO_2R^6; and

[0021] each R^6 and R^7 is independently H or C_1-C_3 alkyl.

[0022] Embodiment 13 is the compound of embodiment 12, or a pharmaceutically acceptable salt thereof, wherein:

each R^1 is independently -OH, F, oxo, -CH_3, -CN, -N(H)C(O)CH_3, -N(H)$SO_2(C_6H_5)$, -N(H)SO_2CH_3, -SO_2NH_2, or -C(O)N(H)SO_2CH_3.

[0023] Embodiment 14 is the compound of any one of embodiments 1-13, or a pharmaceutically acceptable salt thereof, wherein:

m is 0-3.

[0024] Embodiment 15 is the compound of any one of embodiments 1-14, or a pharmaceutically acceptable salt thereof, wherein:

X is -CR^6R^7-.

[0025] Embodiment 16 is the compound of embodiment 15, or a pharmaceutically acceptable salt thereof, wherein:

R^6 and R^7 are each H.

[0026] Embodiment 17 is the compound of any one of embodiments 1-14, or a pharmaceutically acceptable salt thereof, wherein:

X is a bond.

[0027] Embodiment 18 is the compound of any one of embodiments 1-17, or a pharmaceutically acceptable salt thereof, wherein:

Y is -O-.

[0028] Embodiment 19 is the compound of any one of embodiments 1-17, or a pharmaceutically acceptable salt thereof, wherein:

Y is -N(H)- or a bond.

[0029] Embodiment 20 is the compound of any one of embodiments 1-19, or a pharmaceutically acceptable salt thereof, wherein:

Z is Z^1.

[0030] Embodiment 21 is the compound of embodiment 20, or a pharmaceutically acceptable salt thereof, wherein:

Z^1 is H, C_1-C_3 alkyl, -C(O)(C_1-C_3 alkyl), -CO_2(C_1-C_3 alkyl), -C(O)NR^6R^7, -C(O)NR^6(C_1-C_3 alkylene)NR^6R^7, -CR^6R^7C(O)NR^6R^7, -$CR^6R^7NR^6R^7$, -C(O)(C_1-C_3 alkylene)NR^6R^7, -NR^6C(O)(C_1-C_3 alkyl), -NR^6R^7, -(C_1-C_3 alkyl)-CO_2H, -(C_1-C_3 alkyl)-OH, or -C(NR^6R^7)=N-CN, wherein C_1-C_3 alkylene is optionally substituted by 1-2 halo, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; and

each R^6 and R^7 is independently H or C_1-C_3 alkyl.

[0031] Embodiment 22 is the compound of embodiment 20 or 21, or a pharmaceutically acceptable salt thereof, wherein:

Z^1 is H, -CO_2CH_3, -$CO_2C(CH_3)_3$, -C(O)CH_3, -C(O)$C(CH_3)_3$, -C($N(CH_3)_2$)=N-CN, -C(O)$N(CH_3)_2$, -CH_3, -CH_2CH_3, -$CH_2C(CH_3)_3$, -CH_2CO_2H, -$CH_2C(CH_3)_2$OH, -C(O)$N(CH_3)CH_2CH_2N(CH_3)_2$, -CH_2C(O)$N(CH_3)_2$, -$CH(CH_3)$C(O)$N(CH_3)_2$, -$N(CH_3)_2$, -$N(CH_3)$C(O)CH_3, or -C(O)$CH(CH_3)CH_2N(CH_3)_2$.

[0032] Embodiment 23 is the compound of any one of embodiments 1-19, or a pharmaceutically acceptable salt thereof, wherein:

Z is Z^2.

[0033] Embodiment 24 is the compound of embodiment 23, or a pharmaceutically acceptable salt thereof, wherein:

Z^2 is 5- to 6-membered heteroaryl, -C(O)(5- to 6-membered heteroaryl), -CH_2C(O)(5- to 6-membered heteroaryl), 4- to 6-membered heterocyclyl, -C(O)(4- to 6-membered heterocyclyl), or -CH_2C(O)(4- to 6-membered heterocyclyl), wherein the heteroaryl and heterocyclyl contain 1-2 heteroatoms selected from N and O, and wherein the heteroaryl and heterocyclyl are optionally substituted by 1-3 R^8.

[0034] Embodiment 25 is the compound of embodiment 23 or 24, or a pharmaceutically acceptable salt thereof, wherein:

Z^2 is pyrimidinyl, pyridazinyl, pyrrolidinyl, piperidinyl, pyridazinyl, -C(O)(tetrahydropyranyl), -C(O)(pyrrolidinyl), -C(O)(pyridazinyl), -C(O)(piperidinyl), -C(O)(azetidinyl), -C(O)(pyrazolyl), -C(O)(piperazinyl), -CH_2C(O)(pyrrolidinyl), -CH_2C(O)(piperidinyl), or -CH_2C(O)(piperazinyl), wherein the heteroaryl and heterocyclyl are optionally substituted by 1-3 R^8.

[0035] Embodiment 26 is the compound of any one of embodiments 1-19 and 23-25, or a pharmaceutically acceptable salt thereof, wherein:

each R^8 is independently halo, C_1-C_3 alkyl, C_1-C_3 haloalkyl, $-NR^6R^7$, -OH, oxo, $-CO_2H$, $-O(C_1$-C_3 alkyl), $-CH_2$-$O(C_1$-C_3 alkyl), or $-(C_1$-C_3 alkyl)-OH; and

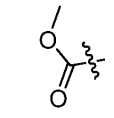
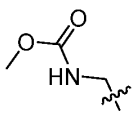
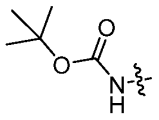
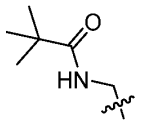
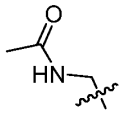
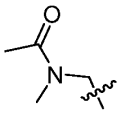
each R^6 and R^7 is independently H or C_1-C_3 alkyl.

[0036] Embodiment 27 is the compound of embodiment 26, or a pharmaceutically acceptable salt thereof, wherein:

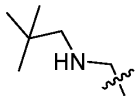
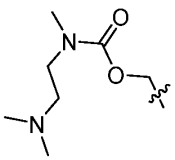
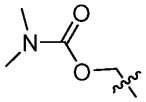
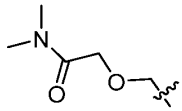
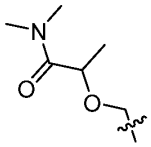
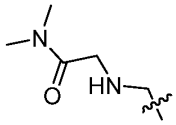
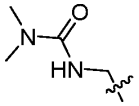
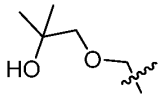
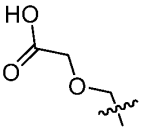
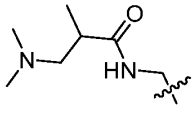
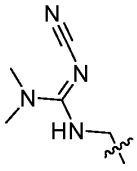
each R^8 is independently $-CH_3$, $-CH_2CH_3$, $-NH_2$, -OH, oxo, $-N(CH_3)_2$, $-OCH_3$, $-CH_2OCH_3$, $-CF_3$, $-CH_2CH_2OH$, $-CO_2H$, or Cl.

[0037] Embodiment 28 is the compound of any one of embodiments 1-22, or a pharmaceutically acceptable salt thereof, wherein:

Z-Y-X- is

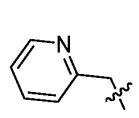
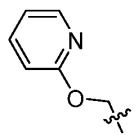
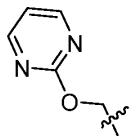
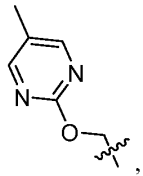

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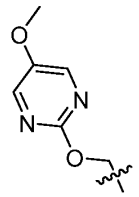
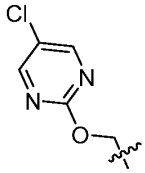
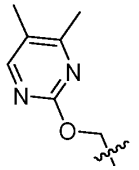
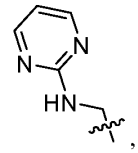
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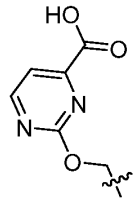
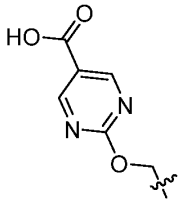
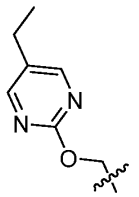
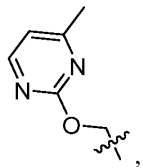
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-CH_2OH
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-OCH_2CH_3
, or
-CH_2OCH_3.

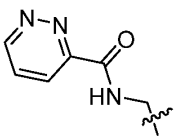
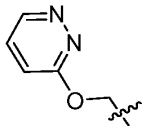
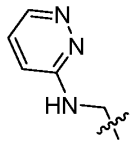
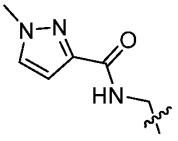
[0038] Embodiment 29 is the compound of any one of embodiments 1-19 and 23-27, or a pharmaceutically acceptable salt thereof, wherein:

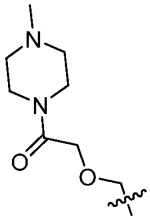
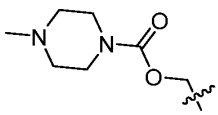
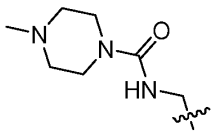
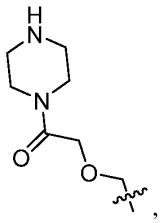
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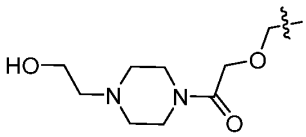
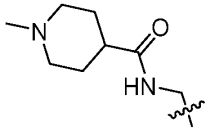
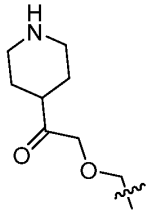
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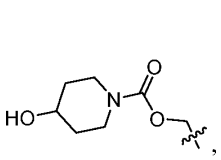
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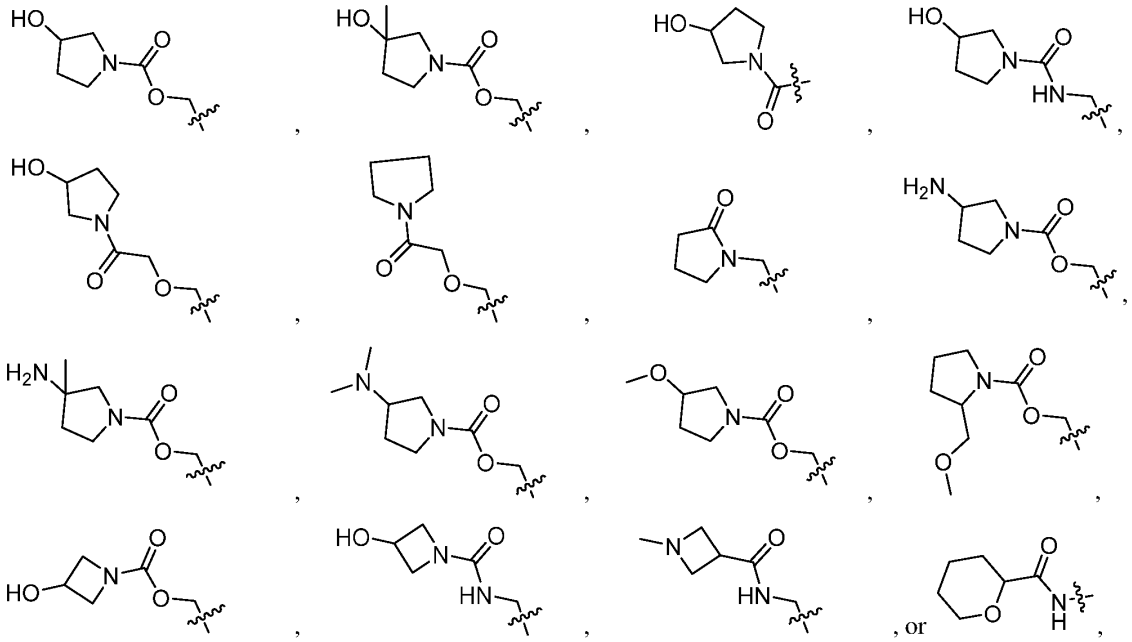
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[0039] Embodiment 30 is a compound selected from the compounds in Table 1, or a pharmaceutically acceptable salt thereof.

[0040] Embodiment 31 is a compound selected from the compounds in Table 2, or a pharmaceutically acceptable salt thereof.

[0041] Embodiment 32 is a pharmaceutical composition comprising the compound of any one of embodiments 1-31, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

[0042] Embodiment 33 is a method of modulating bis-phosphoglycerate mutase (BPGM) comprising contacting an effective amount of the compound of any one of embodiments 1-31, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of embodiment 32, with the BPGM.

[0043] Embodiment 34 is a method of treating sickle cell disease in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the compound of any one of embodiments 1-31, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of embodiment 32.

DETAILED DESCRIPTION

Definitions

[0044] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the claimed subject matter belongs. It is to be understood that the foregoing general description and the following detailed description are exemplary

and explanatory only and are not restrictive of any subject matter claimed. To the extent any material incorporated herein by reference is inconsistent with the express content of this disclosure, the express content controls. In this application, the use of the singular includes the plural unless specifically stated otherwise. It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. In this application, the use of "or" means "and/or" unless stated otherwise. Furthermore, use of the term "including" as well as other forms, such as "include", "includes," and "included," is not limiting.

[0045] Reference in the specification to "some embodiments", "an embodiment", "one embodiment" or "other embodiments" means that a particular feature, structure, or characteristic described in connection with the embodiments is included in at least some embodiments, but not necessarily all embodiments, of the disclosure.

[0046] As used herein, ranges and amounts can be expressed as "about" a particular value or range. About also includes the exact amount. Hence "about 5 μL" means "about 5 μL" and also "5 μL." Generally, the term "about" includes an amount that would be expected to be within experimental error, such as for example, within 15%, 10%, or 5%.

[0047] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[0048] "Alkyl" refers to an unbranched or branched saturated hydrocarbon chain. As used herein, alkyl has 1 to 20 carbon atoms (i.e., C_1-C_{20} alkyl), 1 to 10 carbon atoms (i.e., C_1-C_{10} alkyl), 1 to 6 carbon atoms (i.e., C_1-C_6 alkyl) or 1 to 3 carbon atoms (i.e., C_1-C_3 alkyl). Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl and 3-methylpentyl. When an alkyl residue having a specific number of carbons is named by chemical name or identified by molecular formula, all positional isomers having that number of carbons may be encompassed; thus, for example, "butyl" includes n-butyl (i.e., $-(CH_2)_3CH_3$), isobutyl (i.e., $-CH_2CH(CH_3)_2$), sec-butyl (i.e., $-CH(CH_3)CH_2CH_3$), and tert-butyl (i.e., $-C(CH_3)_3$); and "propyl" includes n-propyl (i.e., $-(CH_2)_2CH_3$) and isopropyl (i.e., $-CH(CH_3)_2$).

[0049] "Alkyl-OH" refers to an refers to an unbranched or branched alkyl group as defined above, wherein one or more hydrogen atoms are replaced by a hydroxyl (-OH). For example, "(C_1-C_6 alkyl)-OH" refers to a C_1-C_6 alkyl which is substituted by one or more hydroxyl groups. A C_1 alkyl-OH refers to a methyl group that may be substituted by 1-3 hydroxyl groups, a C_2 alkyl-OH refers to an ethyl group that may be substituted by 1-5 hydroxyl groups, a C_3 alkyl-OH refers to a propyl group that may be substituted by 1-7 hydroxyl groups, etc. Examples of alkyl-OH include $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH(OH)CH_2(OH)$, and the like.

[0050] "Alkyl-CO_2H" refers to an refers to an unbranched or branched alkyl group as defined above, wherein one or more hydrogen atoms are replaced by a carboxylic acid (-CO_2H). For example, "(C_1-C_6 alkyl)-CO_2H" refers to a C_1-C_6 alkyl which is substituted by one or more carboxylic acid groups. A C_1 alkyl-CO_2H refers to a methyl group that may be substituted by 1-3 carboxylic acid groups, a C_2 alkyl-CO_2H refers to an ethyl group that may be substituted by 1-5 carboxylic acid groups, a C_3 alkyl-CO_2H refers to a propyl group that may be substituted by 1-7 carboxylic acid groups, etc. Examples of alkyl-CO_2H include -CH_2CO_2H, -$CH_2CH_2CO_2H$, -$CH_2CH(CO_2H)CH_3$, -$CH_2CH(CO_2H)CH_2CO_2H$, and the like.

[0051] "Haloalkyl" refers to an unbranched or branched alkyl group as defined above, wherein one or more hydrogen atoms are replaced by a halogen. For example, "C_1-C_6 haloalkyl" refers to a C_1-C_6 alkyl which is substituted by one or more halogen atoms. A C_1 haloalkyl refers to a methyl group that may be substituted by 1-3 halo groups, a C_2 haloalkyl refers to an ethyl group that may be substituted by 1-5 halo groups, a C_3 haloalkyl refers to a propyl group that may be substituted by 1-7 halo groups, etc. Examples of haloalkyl include trifluoromethyl, difluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like. A haloalkyl may contain one or more halo atoms that are the same (i.e., all fluoro) or a mixture of halo atoms (i.e, chloro and fluoro).

[0052] "Cycloalkyl" refers to a saturated or partially unsaturated cyclic alkyl group having a single ring or multiple rings including fused, bridged and spiro ring systems. The term "cycloalkyl" includes cycloalkenyl groups (i.e., the cyclic group having at least one double bond). As used herein, cycloalkyl has from 3 to 20 ring carbon atoms (i.e., C_3-C_{20} cycloalkyl), 3 to 10 ring carbon atoms (i.e., C_3-C_{10} cycloalkyl), or 3 to 6 ring carbon atoms (i.e., C_3-C_6 cycloalkyl). Cycloalkyl also includes "spiro cycloalkyl" when there are two positions for substitution on the same carbon atom. Monocyclic radicals include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. Polycyclic radicals include, for example, adamantyl, norbornyl, decalinyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl and the like. Further, the term cycloalkyl is intended to encompass any non-aromatic ring which may be fused to an aryl ring, regardless of the attachment to the remainder of the molecule.

[0053] "Halogen" or "halo" includes fluoro, chloro, bromo, and iodo.

[0054] "Oxo" refers to the atom (=O) or (O).

[0055] "Heteroaryl" refers to an aromatic group (e.g., a 5-14 membered ring system) having a single ring, multiple rings, or multiple fused rings, with one or more ring heteroatoms independently selected from nitrogen, oxygen and sulfur. As used herein, heteroaryl includes 1 to 10 ring carbon atoms and 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur within the ring. Examples of heteroaryl groups include pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl,

quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, tetrahydroquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl and thiophenyl (i.e., thienyl). A heteroaryl may comprise one or more N-oxide (N-O-) moieties, such as pyridine-N-oxide.

[0056] "Heterocyclyl" refers to a saturated or unsaturated cyclic alkyl group, with one or more ring heteroatoms independently selected from nitrogen, oxygen and sulfur. The term "heterocyclyl" includes heterocycloalkenyl groups (i.e., the heterocyclyl group having at least one double bond), bridged-heterocyclyl groups, fused-heterocyclyl groups and spiro-heterocyclyl groups. A heterocyclyl may be a single ring or multiple rings wherein the multiple rings may be fused, bridged or spiro, and may comprise one or more oxo (C=O) or N-oxide (N-O-) moieties. Any non-aromatic ring containing at least one heteroatom is considered a heterocyclyl, regardless of the attachment (i.e., can be bound through a carbon atom or a heteroatom). Further, the term heterocyclyl is intended to encompass any non-aromatic ring containing at least one heteroatom, which ring may be fused to an aryl or heteroaryl ring, regardless of the attachment to the remainder of the molecule. As used herein, heterocyclyl has 1 to 10 ring carbon atoms, 1 to 8 carbon atoms, 1 to 6 carbon atoms, or 1 to 4 carbon atoms, and 1 to 5 ring heteroatoms, 1 to 4 heteroatoms, 1 to 3 heteroatoms, or 1 to 2 heteroatoms independently selected from nitrogen, sulfur and oxygen. Examples of heterocyclyl groups include 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, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl.

[0057] Certain commonly used alternative chemical names may be used. For example, a divalent group such as a divalent "alkyl" group, a divalent "phenyl" group, a divalent "heteroaryl" group, a divalent "heterocyclyl" group etc., may also be referred to as an "alkylene" group, an "phenylene" group, a "heteroarylene" group, or a "heterocyclylene" group, respectively.

[0058] The terms "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. Also, the term "optionally substituted" refers to any one or more hydrogen atoms on the designated atom or group may or may not be replaced by a moiety other than hydrogen.

[0059] Polymers or similar indefinite structures arrived at by defining substituents with further substituents appended ad infinitum (e.g., a substituted aryl having a substituted alkyl which is itself substituted with a substituted aryl group, which is further substituted by a substituted heteroalkyl group, etc.) are not intended for inclusion herein. Similarly, the above definitions are not intended to include

impermissible substitution patterns (e.g., methyl substituted with 5 fluorines or heteroaryl groups having two adjacent oxygen ring atoms). Such impermissible substitution patterns are well known to the skilled artisan.

[0060] Any compound or Formula described herein is intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I and ^{125}I, respectively. Various isotopically labeled compounds of the present disclosure, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are included in this disclosure. Such isotopically labelled compounds may be useful in metabolic studies, reaction kinetic studies, detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays or in radioactive treatment of patients.

[0061] The disclosure also includes "deuterated analogs" of compounds described herein in which from 1 to n hydrogens attached to a carbon atom is/are replaced by deuterium, in which n is the number of hydrogens in the molecule. Such compounds exhibit increased resistance to metabolism and are thus useful for increasing the half-life of any compound when administered to a mammal, particularly a human. See, for example, Foster, "Deuterium Isotope Effects in Studies of Drug Metabolism," Trends Pharmacol. Sci. 5(12):524-527 (1984). Such compounds are synthesized by means well known in the art, for example by employing starting materials in which one or more hydrogens have been replaced by deuterium.

[0062] "Pharmaceutically acceptable" refers to compounds, salts, compositions, dosage forms and other materials which are useful in preparing a pharmaceutical composition that is suitable for veterinary or human pharmaceutical use.

[0063] The term "pharmaceutically acceptable salt" of a given compound refers to salts that retain the biological effectiveness and properties of the given compound and which are not biologically or otherwise undesirable. "Pharmaceutically acceptable salts" include, for example, salts with inorganic acids and salts with an organic acid. In addition, if the compounds described herein are obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used to prepare nontoxic pharmaceutically

acceptable addition salts. Pharmaceutically acceptable acid addition salts may be prepared from inorganic and organic acids. Salts derived from inorganic acids include hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like. Salts derived from organic acids include acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluene-sulfonic acid, salicylic acid and the like. Likewise, pharmaceutically acceptable base addition salts can be prepared from inorganic and organic bases. Salts derived from inorganic bases include, by way of example only, sodium, potassium, lithium, ammonium, calcium and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary and tertiary amines, such as alkyl amines. Specific examples of suitable amines include, by way of example only, isopropylamine, trimethyl amine, diethyl amine, tri(iso-propyl) amine, tri(n-propyl) amine, ethanolamine, 2-dimethylaminoethanol, piperazine, piperidine, morpholine, N-ethylpiperidine and the like.

[0064] The compounds disclosed herein, or their pharmaceutically acceptable salts, may include an asymmetric center and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)- or, as (D)- or (L)- for amino acids. The disclosure is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optically active (+) and (-), (*R*)- and (*S*)-, or (D)- and (L)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, for example, chromatography and fractional crystallization. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

[0065] "Tautomer" refers to alternate forms of a compound that differ in the position of a proton, such as enol-keto and imine-enamine tautomers, or the tautomeric forms of heteroaryl groups containing a ring atom attached to both a ring -NH-moiety and a ring=N moiety such as pyrazoles, imidazoles, benzimidazoles, triazoles, and tetrazoles. All tautomeric forms of the compounds described herein are intended to be included.

[0066] A "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures, which are not interchangeable. The present disclosure contemplates various stereoisomers and mixtures thereof and includes "enantiomers", which refers to two stereoisomers whose molecules are nonsuperimposable mirror images of one another.

[0067] "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other.

[0068] As used herein, "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" or "excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

[0069] "Effective amount" or dose of a compound or a composition refers to that amount of the compound or the composition that results in an intended result as desired based on the disclosure herein. Effective amounts can be determined by standard pharmaceutical procedures in cell cultures or experimental animals including, without limitation, by determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population).

[0070] "Therapeutically effective amount" or dose of a compound or a compositions refers to that amount of the compound or the composition that results in reduction or inhibition of symptoms or a prolongation of survival in a subject (i.e., a human patient). The results may require multiple doses of the compound or the composition.

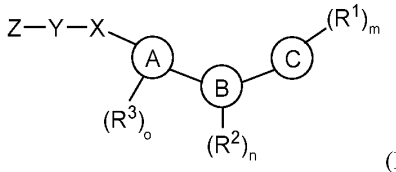
[0071] "Treating" or "treatment" of a disease in a subject refers to 1) preventing the disease from occurring in a patient that is predisposed or does not yet display symptoms of the disease; 2) inhibiting the disease or arresting its development; or 3) ameliorating or causing regression of the disease. As used herein, "treatment" or "treating" is an approach for obtaining beneficial or desired results including clinical results. For the purposes of this disclosures, beneficial or desired results include, but are not limited to, one or more of the following: decreasing one or more symptoms resulting from the disease or disorder, diminishing the extent of the disease or disorder, stabilizing the disease or disorder (e.g., preventing or delaying the worsening of the disease or disorder), delaying the occurrence or recurrence of the disease or disorder, delay or slowing the progression of the disease or disorder, ameliorating the disease or disorder state, providing a remission (whether partial or total) of the disease or disorder, decreasing the dose of one or more other medications required to treat the disease or disorder, enhancing the effect of another medication used to treat the disease or disorder, delaying the progression of the disease or disorder, increasing the quality of life, and/or prolonging survival of a subject. Also encompassed by "treatment" is a reduction of pathological consequence of the disease or disorder. The methods of the disclosure contemplate any one or more of these aspects of treatment.

[0072] As used herein, the terms "individual(s)", "subject(s)" and "patient(s)" mean any mammal. Examples include, but are not limited to, mice, rats, hamsters, guinea pigs, pigs, rabbits, cats, dogs, goats, sheep, cows, and humans. In some embodiments, the mammal is a human.

[0073] Although various features of the disclosure may be described in the context of a single embodiment, the features may also be provided separately or in any suitable combination. Conversely, although the disclosure may be described herein in the context of separate embodiments for clarity, the disclosure may also be implemented in a single embodiment.

Compounds

[0074] In one aspect, provided herein is a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is a 5-membered heteroarylene containing 1-3 heteroatoms selected from N and S;

Ring B is phenylene or a 5- to 6-membered heteroarylene containing 1-3 heteroatoms selected from N and S;

Ring C is a fused bicyclic 9- to 10-membered heteroaryl or heterocyclyl containing 1-4 heteroatoms selected from N and O, a 5- to 6-membered heteroaryl containing 1-4 nitrogen atoms, or phenyl substituted by one R^4;

each R^1 is independently -OH, halo, oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -CN, $-N(H)C(O)R^6$, $-N(H)SO_2R^6$, $-N(H)SO_2(C_6H_5)$, $-SO_2NR^6R^7$, or $-C(O)N(H)SO_2R^6$;

each R^2 is independently C_1-C_6 alkyl, C_1-C_6 haloalkyl, or halo;

each R^3 is independently C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_3-C_6 cycloalkyl;

R^4 is -OH, $-OP(O)(OH)_2$, $-NO_2$, $-C(O)N(H)SO_2R^5$, 5- to 6-membered heteroaryl or heterocyclyl, or -C(O)N(H)-(5- to 6-membered heteroaryl or heterocyclyl),
wherein the heteroaryl and heterocyclyl contain 1-4 heteroatoms selected from N, O, and S, and wherein the heterocyclyl is optionally substituted by 1-2 oxo groups;

m is 0-4;

n is 0-2;

o is 0-2;

R^5 is phenyl or C_1-C_6 alkyl;

X is $-CR^6R^7-$ or a bond;

Y is -O-, -N(H)-, or a bond;

each R^6 and R^7 is independently H or C_1-C_6 alkyl;

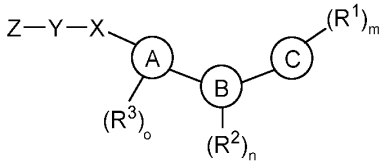
Z is Z^1 or Z^2;

Z^1 is H, C_1-C_6 alkyl, -C(O)(C_1-C_6 alkyl), -CO_2(C_1-C_6 alkyl), -C(O)NR^6R^7, -C(O)NR^6(C_1-C_6 alkylene)NR^6R^7, -CR^6R^7C(O)NR^6R^7, -$CR^6R^7NR^6R^7$, -C(O)(C_1-C_6 alkylene)NR^6R^7, -NR^6C(O)(C_1-C_6 alkyl), -NR^6R^7, -(C_1-C_6 alkyl)-CO_2H, -(C_1-C_6 alkyl)-OH, or -C(NR^6R^7)=N-CN, wherein C_1-C_6 alkylene is optionally substituted by 1-6 halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl;

Z^2 is 5- to 6-membered heteroaryl, -C(O)(5- to 6-membered heteroaryl), -CH_2C(O)(5- to 6-membered heteroaryl), 4- to 6-membered heterocyclyl, -C(O)(4- to 6-membered heterocyclyl), or -CH_2C(O)(4- to 6-membered heterocyclyl), wherein the heteroaryl and heterocyclyl contain 1-3 heteroatoms selected from N and O, and wherein the heteroaryl and heterocyclyl are optionally substituted by 1-3 R^8;

each R^8 is independently halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -NR^6R^7, -OH, oxo, -CO_2H, -O(C_1-C_6 alkyl), -CH_2-O(C_1-C_6 alkyl), or -(C_1-C_6 alkyl)-OH.

[0075] Provided herein is a compound of Formula (I-a):



(I-a)

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is thiazolylene;

Ring B is phenylene or a 5- to 6-membered heteroarylene containing 1-3 heteroatoms selected from N and S;

Ring C is a fused bicyclic 9- to 10-membered heteroaryl or heterocyclyl containing 1-4 heteroatoms selected from N and O, a 5- to 6-membered heteroaryl containing 1-4 nitrogen atoms, or phenyl substituted by one R^4;

each R^1 is independently -OH, halo, oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -CN, -N(H)C(O)R^6, -N(H)SO_2R^6, -$SO_2NR^6R^7$, or -C(O)N(H)SO_2R^6;

each R^2 is independently C_1-C_6 alkyl, C_1-C_6 haloalkyl, or halo;

each R^3 is independently C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_3-C_6 cycloalkyl;

R^4 is -OH, -$OP(O)(OH)_2$, -NO_2, -C(O)N(H)SO_2R^5, 5- to 6-membered heteroaryl or heterocyclyl, or -C(O)N(H)-(5- to 6-membered heteroaryl or heterocyclyl), wherein the heteroaryl and heterocyclyl contain 1-4 heteroatoms selected from N, O, and S, and wherein the heterocyclyl is optionally substituted by 1-2 oxo groups;

m is 0-4;

n is 0-2;

o is 0-2;

R^5 is phenyl or C_1-C_6 alkyl;

X is $-CR^6R^7-$;

Y is -O-, -N(H)-, or a bond;

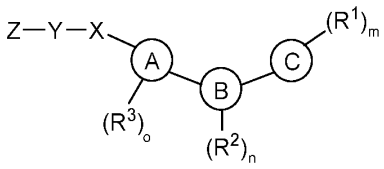
each R^6 and R^7 is independently H or C_1-C_6 alkyl;

Z is Z^2;

Z^2 is 5- to 6-membered heteroaryl, -C(O)(5- to 6-membered heteroaryl), $-CH_2C(O)$(5- to 6-membered heteroaryl), 4- to 6-membered heterocyclyl, -C(O)(4- to 6-membered heterocyclyl), or $-CH_2C(O)$(4- to 6-membered heterocyclyl), wherein the heteroaryl and heterocyclyl contain 1-3 heteroatoms selected from N and O, and wherein the heteroaryl and heterocyclyl are optionally substituted by 1-3 R^8; and

each R^8 is independently halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-NR^6R^7$, -OH, oxo, $-CO_2H$, $-O(C_1$-C_6 alkyl), $-CH_2$-$O(C_1$-C_6 alkyl), or $-(C_1$-C_6 alkyl)-OH.

[0076] Provided herein is a compound of Formula (I-a1):



(I-a1)

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is thiazolylene;

Ring B is a 5- to 6-membered heteroarylene containing 1-3 heteroatoms selected from N and S;

Ring C is a fused bicyclic 9- to 10-membered heteroaryl or phenyl substituted by one R^4;

each R^1 is independently -OH, halo, oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -CN, $-N(H)C(O)R^6$, $-N(H)SO_2R^6$, $-SO_2NR^6R^7$, or $-C(O)N(H)SO_2R^6$;

each R^2 is independently C_1-C_6 alkyl, C_1-C_6 haloalkyl, or halo;

each R^3 is independently C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_3-C_6 cycloalkyl;

R^4 is -OH, $-OP(O)(OH)_2$, $-NO_2$, $-C(O)N(H)SO_2R^5$, 5- to 6-membered heteroaryl or heterocyclyl, or -C(O)N(H)-(5- to 6-membered heteroaryl or heterocyclyl), wherein the heteroaryl and heterocyclyl contain 1-4 heteroatoms selected from N, O, and S, and wherein the heterocyclyl is optionally substituted by 1-2 oxo groups;

m is 0-4;

n is 0-2;

o is 0-2;

R^5 is phenyl or C_1-C_6 alkyl;

X is $-CR^6R^7-$;

Y is -O-, -N(H)-, or a bond;

each R^6 and R^7 is independently H or C_1-C_6 alkyl;

Z is Z^2;

Z^2 is 5- to 6-membered heteroaryl, -C(O)(5- to 6-membered heteroaryl), $-CH_2C(O)$(5- to 6-membered heteroaryl), 4- to 6-membered heterocyclyl, -C(O)(4- to 6-membered heterocyclyl), or $-CH_2C(O)$(4- to 6-membered heterocyclyl), wherein the heteroaryl and heterocyclyl contain 1-3 heteroatoms selected from N and O, and wherein the heteroaryl and heterocyclyl are optionally substituted by 1-3 R^8; and

each R^8 is independently halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-NR^6R^7$, -OH, oxo, $-CO_2H$, $-O(C_1$-C_6 alkyl), $-CH_2-O(C_1$-C_6 alkyl), or $-(C_1$-C_6 alkyl)-OH.

[0077] In some embodiments, Ring A is a 5-membered heteroarylene containing 1-3 heteroatoms selected from N and S. In some embodiments, Ring A is a 5-membered heteroarylene containing 1-2 heteroatoms selected from N and S. In some embodiments, Ring A is a 5-membered heteroarylene containing 1 heteroatom selected from N and S. In some embodiments, Ring A is a 5-membered heteroarylene containing 2 heteroatoms selected from N and S. In some embodiments, Ring A is a 5-membered heteroarylene containing one nitrogen atoms and one sulfur atom. In some embodiments, Ring A is thiazolylene.

[0078] In some embodiments, each R^3 is independently C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_3-C_6 cycloalkyl. In some embodiments, each R^3 is independently C_1-C_3 alkyl or C_3-C_6 cycloalkyl. In some embodiments, R^3 is methyl, ethyl, or propyl. In some embodiments, R^3 is methyl. In some embodiments, R^3 is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some embodiments, R^3 is cyclopropyl. In some embodiments, each R^3 is independently $-CH_3$ or cyclopropyl.

[0079] In some embodiments, o is 0-2. In some embodiments, o is 1-2. In some embodiments, o is 0 or 1. In some embodiments, o is 0. In some embodiments, o is 1. In some embodiments, o is 2.

[0080] In some embodiments, Ring B is phenylene or a 5- to 6-membered heteroarylene containing 1-3 heteroatoms selected from N and S. In some embodiments, Ring B is phenylene. In some embodiments, Ring B is a 5- to 6-membered heteroarylene containing 1-3 heteroatoms selected from N and S. In some embodiments, Ring B is a 5- to 6-membered heteroarylene containing 1-2 heteroatoms selected from N and S. In some embodiments, Ring B is phenylene, pyridinylene, thiazolylene, pyrazolylene, pyrimidinylene, or thienylene.

[0081] In some embodiments, each R^2 is independently C_1-C_6 alkyl, C_1-C_6 haloalkyl, or halo. In some embodiments, each R^2 is independently C_1-C_3 alkyl or halo. In some embodiments, R^2 is methyl, ethyl, or propyl. In some embodiments, R^2 is methyl. In some embodiments, R^2 is F, Cl, or Br.

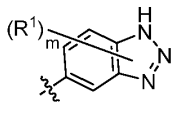
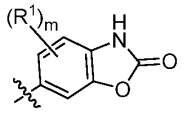
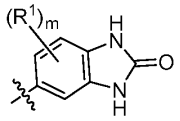
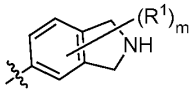
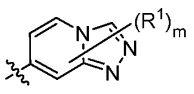
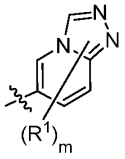
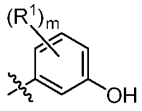
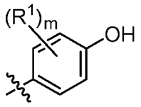
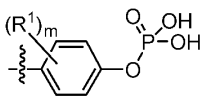
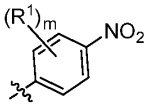
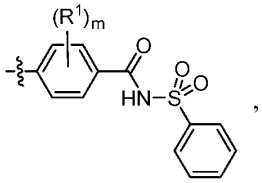
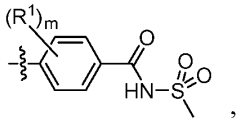
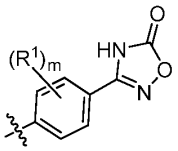
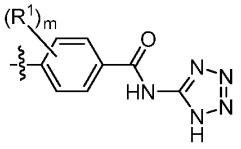
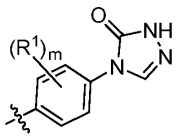
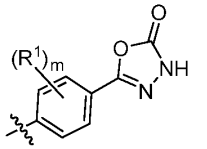
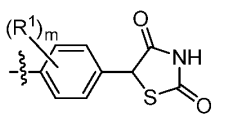
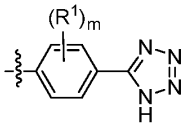
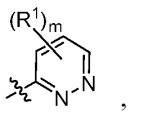
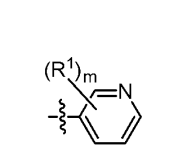
[0082] In some embodiments, n is 0-2. In some embodiments, n is 0 or 1. In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2.

[0083] In some embodiments, Ring C is a fused bicyclic 9- to 10-membered heteroaryl or heterocyclyl containing 1-4 heteroatoms selected from N and O, a 5- to 6-membered heteroaryl containing 1-4 nitrogen atoms, or phenyl substituted by one R^4. In some embodiments, Ring C is a fused bicyclic 9-membered heteroaryl or heterocyclyl containing 1-4 heteroatoms selected from N and O, a 5- to 6-membered heteroaryl containing 1-4 nitrogen atoms, or phenyl substituted by one R^4. In some embodiments, Ring C is a fused bicyclic 9-membered heteroaryl or heterocyclyl containing 1-4 heteroatoms selected from N and O. In some embodiments, Ring C is a fused bicyclic 9-membered heteroaryl containing 1-4 heteroatoms selected from N and O. In some embodiments, Ring C is a fused bicyclic 9-membered heterocyclyl containing 1-4 heteroatoms selected from N and O. In some embodiments, one ring of the fused bicyclic heteroaryl or heterocyclyl is substituted by 0-4 R^1 groups. In some embodiments, both rings of the fused bicyclic heteroaryl or heterocyclyl are together substituted by 0-4 R^1 groups. In some embodiments, Ring C is a 5- to 6-membered heteroaryl containing 1-4 nitrogen atoms. In some embodiments, Ring C is a 5-membered heteroaryl containing 1-4 nitrogen atoms. In some embodiments, Ring C is a 6-membered heteroaryl containing 1-4 nitrogen atoms. In some embodiments, Ring C is phenyl substituted by one R^4.

[0084] In some embodiments, R^4 is -OH, $-OP(O)(OH)_2$, $-NO_2$, $-C(O)N(H)SO_2R^5$, 5- to 6-membered heteroaryl or heterocyclyl, or -C(O)N(H)-(5- to 6-membered heteroaryl or heterocyclyl), wherein the heteroaryl and heterocyclyl contain 1-4 heteroatoms selected from N, O, and S, and wherein the heterocyclyl is optionally substituted by 1-2 oxo groups. In some embodiments, R^4 is -OH. In some embodiments, R^4 is $-OP(O)(OH)_2$. In some embodiments, R^4 is $-NO_2$. In some embodiments, R^4 is $-C(O)N(H)SO_2R^5$. In some embodiments, R^4 is 5- to 6-membered heteroaryl or heterocyclyl, wherein the heteroaryl and heterocyclyl contain 1-4 heteroatoms selected from N, O, and S, and wherein the heterocyclyl is optionally substituted by 1-2 oxo groups. In some embodiments, R^4 is 5- to 6-membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S. In some embodiments, R^4 is 5- to 6-membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, and optionally substituted by 1-2 oxo groups. In some embodiments, R^4 is -C(O)N(H)-(5- to 6-membered heteroaryl or heterocyclyl), wherein the heteroaryl and heterocyclyl contain 1-4 heteroatoms selected from N, O, and S, and wherein the heterocyclyl is optionally substituted by 1-2 oxo groups. In some embodiments, R^4 is -C(O)N(H)-(5- to 6-membered heteroaryl), wherein the heteroaryl contains 1-4 heteroatoms selected from

N, O, and S. In some embodiments, R^4 is -C(O)N(H)-(5- to 6-membered heterocyclyl), wherein the heterocyclyl contains 1-4 heteroatoms selected from N, O, and S, and is optionally substituted by 1-2 oxo groups. In some embodiments, R^4 is -OH, $-OP(O)(OH)_2$, $-NO_2$, $-C(O)N(H)SO_2R^5$, 5- to 6-membered heteroaryl or heterocyclyl, or -C(O)N(H)-(5- to 6-membered heteroaryl or heterocyclyl), wherein the heteroaryl and heterocyclyl contain 1-4 heteroatoms selected from N, O, and S, and wherein the heterocyclyl is optionally substituted by 1-2 oxo groups. In any of these variations, R^5 is phenyl or C_1-C_6 alkyl. In some embodiments, R^5 is phenyl or C_1-C_3 alkyl.

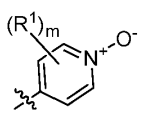
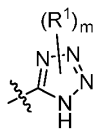
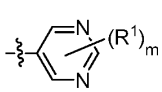
[0085] In some embodiments, Ring C-$(R^1)_m$ is selected from


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[0086] As shown above, certain nitrogen atoms of the heteroaryl and heterocyclyl rings are represented as -NH- in order to complete the valency. However, it is understood that the -NH- group may also be substituted by R^1 (-NR^1-). It is also understood that when –$(R^1)_m$ is drawn through a fused bicyclic heteroaryl or heterocyclyl, then one or both of the fused rings may be substituted by R^1 groups. In some embodiments, only one ring of the fused bicyclic ring is substituted by R^1 groups. In some embodiments, both rings of the fused bicyclic ring are substituted by R^1 groups, such that the total number of R^1 groups substituting the bicyclic ring is 0-4.

[0087] In some embodiments, each R^1 is independently -OH, halo, oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -CN, -N(H)C(O)R^6, -N(H)SO_2R^6, -N(H)$SO_2(C_6H_5)$, -$SO_2NR^6R^7$, or -C(O)N(H)SO_2R^6. In some embodiments, each R^1 is independently -OH, halo, oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -CN, -N(H)C(O)R^6, -N(H)SO_2R^6, -$SO_2NR^6R^7$, or -C(O)N(H)SO_2R^6. In some embodiments, each R^1 is independently -OH, halo, oxo, C_1-C_3 alkyl, C_1-C_3 haloalkyl, -CN, -N(H)C(O)R^6, -N(H)SO_2R^6, -$SO_2NR^6R^7$, or -C(O)N(H)SO_2R^6.

[0088] In some embodiments, R^1 is -OH. In some embodiments, R^1 is halo. In some embodiments, R^1 is F, Cl, or Br. In some embodiments, R^1 is oxo. In some embodiments, R^1 is C_1-C_6 alkyl. In some embodiments, R^1 is C_1-C_3 alkyl. In some embodiments, R^1 is methyl, ethyl, or propyl. In some embodiments, R^1 is C_1-C_6 haloalkyl. In some embodiments, R^1 is C_1-C_3 haloalkyl. In some embodiments, R^1 is -CN. In some embodiments, R^1 is -N(H)C(O)R^6. In some embodiments, R^1 is -N(H)SO_2R^6. In some embodiments, R^1 is -$SO_2NR^6R^7$. In some embodiments, R^1 is -C(O)N(H)SO_2R^6. In some embodiments, each R^1 is independently -OH, halo, oxo, C_1-C_3 alkyl, C_1-C_3 haloalkyl, -CN, -N(H)C(O)R^6, -N(H)SO_2R^6, -$SO_2NR^6R^7$, or -C(O)N(H)SO_2R^6. In any of these variations, each R^6 and R^7 is independently H or C_1-C_6 alkyl. In some embodiments, each R^6 and R^7 is independently H or C_1-C_3 alkyl. In some embodiments, each R^1 is independently -OH, F, oxo, -CH_3, -CN, -N(H)C(O)CH_3, -N(H)$SO_2(C_6H_5)$, -N(H)SO_2CH_3, -SO_2NH_2, or -C(O)N(H)SO_2CH_3.

[0089] In some embodiments, m is 0-4. In some embodiments, m is 0-3. In some embodiments, m is 0. In some embodiments, m is 1-3. In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments, m is 3. In some embodiments, m is 4.

[0090] In some embodiments, R^5 is phenyl or C_1-C_6 alkyl. In some embodiments, R^5 is phenyl or C_1-C_3 alkyl. In some embodiments, R^5 is phenyl. In some embodiments, R^5 is C_1-C_6 alkyl. In some embodiments, R^5 is C_1-C_3 alkyl. In some embodiments, R^5 is methyl, ethyl, or propyl. In some embodiments, R^5 is methyl. In some embodiments, R^5 is phenyl or methyl.

[0091] In some embodiments, X is -CR^6R^7- or a bond. In some embodiments, X is -CR^6R^7-. In some variations, R^6 and R^7 are independently H or C_1-C_6 alkyl. In some variations, R^6 and R^7 are each H, and X is -CH_2-. In some embodiments, X is a bond.

[0092] In some embodiments, Y is -O-, -N(H)-, or a bond. In some embodiments, Y is -O-. In some embodiments, Y is -N(H)-. In some embodiments, Y is a bond.

[0093] In some embodiments, each R^6 and R^7 is independently H or C_1-C_6 alkyl. In some embodiments, each R^6 and R^7 is independently H or C_1-C_3 alkyl. In some embodiments, R^6 and R^7 are each H. In some embodiments, R^6 is H. In some embodiments, R^7 is H. In some embodiments, R^6 is C_1-C_6 alkyl. In some embodiments, R^7 is C_1-C_6 alkyl. In some embodiments, R^6 is H and R^7 is C_1-C_6 alkyl. In some embodiments, R^6 is H and R^7 is C_1-C_3 alkyl. In some embodiments, R^6 and R^7 are each independently C_1-C_6 alkyl. In some embodiments, R^6 and R^7 are each independently C_1-C_3 alkyl. In some embodiments, R^6 and R^7 are each independently methyl, ethyl, or propyl. In some embodiments, R^6 and R^7 are each methyl.

[0094] In some embodiments, Z is Z^1.

[0095] In some embodiments, Z^1 is H, C_1-C_6 alkyl, -C(O)(C_1-C_6 alkyl), -CO_2(C_1-C_6 alkyl), -C(O)NR^6R^7, -C(O)NR^6(C_1-C_6 alkylene)NR^6R^7, -CR^6R^7C(O)NR^6R^7, -$CR^6R^7NR^6R^7$, -C(O)(C_1-C_6 alkylene)NR^6R^7, -NR^6C(O)(C_1-C_6 alkyl), -NR^6R^7, -(C_1-C_6 alkyl)-CO_2H, -(C_1-C_6 alkyl)-OH, or -C(NR^6R^7)=N-CN. In any of these variations, C_1-C_6 alkylene is optionally substituted by 1-6 halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl. In some embodiments, $Z^1$is H, C_1-C_3 alkyl, -C(O)(C_1-C_3 alkyl), -CO_2(C_1-C_3 alkyl), -C(O)NR^6R^7, -C(O)NR^6(C_1-C_3 alkylene)NR^6R^7, -CR^6R^7C(O)NR^6R^7, -$CR^6R^7NR^6R^7$, -C(O)(C_1-C_3 alkylene)NR^6R^7, -NR^6C(O)(C_1-C_3 alkyl), -NR^6R^7, -(C_1-C_3 alkyl)-CO_2H, or -(C_1-C_3 alkyl)-OH, or -C(NR^6R^7)=N-CN. In any of these variations, C_1-C_3 alkylene is optionally substituted by 1-2 halo, C_1-C_3 alkyl, or C_1-C_3 haloalkyl. In some embodiments, each R^6 and R^7 is independently H or C_1-C_3 alkyl. In some embodiments, Z^1 is H, -CO_2CH_3, -$CO_2C(CH_3)_3$, -C(O)CH_3, -C(O)$C(CH_3)_3$, -C($N(CH_3)_2$)=N-CN, -C(O)$N(CH_3)_2$, -CH_3, -CH_2CH_3, -$CH_2C(CH_3)_3$, -CH_2CO_2H, -$CH_2C(CH_3)_2$OH, -C(O)$N(CH_3)CH_2CH_2N(CH_3)_2$, -CH_2C(O)$N(CH_3)_2$, -$CH(CH_3)$C(O)$N(CH_3)_2$, -$N(CH_3)_2$, -$N(CH_3)$C(O)CH_3, or -C(O)$CH(CH_3)CH_2N(CH_3)_2$.

[0096] In some embodiments, if X is a bond and Y is a bond; and $Z^1$is not hydrogen.

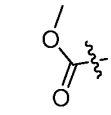
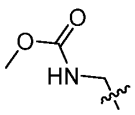
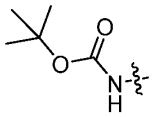
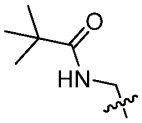
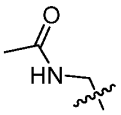
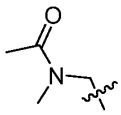
[0097] In some embodiments, Z is Z^2.

[0098] In some embodiments, Z^2 is 5- to 6-membered heteroaryl, -C(O)(5- to 6-membered heteroaryl), -CH_2C(O)(5- to 6-membered heteroaryl), 4- to 6-membered heterocyclyl, -C(O)(4- to 6-membered heterocyclyl), or -CH_2C(O)(4- to 6-membered heterocyclyl), wherein the heteroaryl and heterocyclyl contain 1-3 heteroatoms selected from N and O, and wherein the heteroaryl and heterocyclyl are optionally substituted by 1-3 R^8. In some embodiments, Z^2 is 5- to 6-membered heteroaryl, -C(O)(5- to 6-membered heteroaryl), -CH_2C(O)(5- to 6-membered heteroaryl), 4- to 6-membered heterocyclyl, -C(O)(4- to 6-membered heterocyclyl), or -CH_2C(O)(4- to 6-membered heterocyclyl), wherein the heteroaryl and

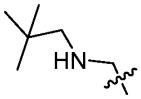
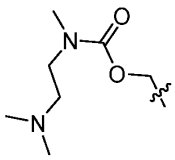
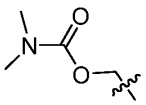
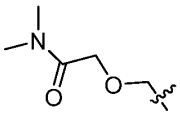
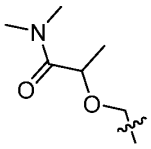
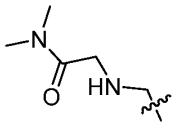
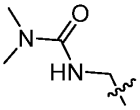
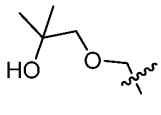
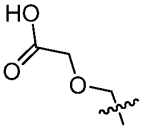
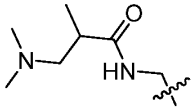
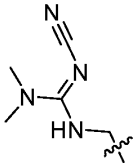
heterocyclyl contain 1-2 heteroatoms selected from N and O, and wherein the heteroaryl and heterocyclyl are optionally substituted by 1-3 R^8. In some embodiments, Z^2 is pyrimidinyl, pyridazinyl, pyrrolidinyl, piperidinyl, pyridazinyl, -C(O)(tetrahydropyranyl), -C(O)(pyrrolidinyl), -C(O)(pyridazinyl), -C(O)(piperidinyl), -C(O)(azetidinyl), -C(O)(pyrazolyl), -C(O)(piperazinyl), -CH_2C(O)(pyrrolidinyl), -CH_2C(O)(piperidinyl), or -CH_2C(O)(piperazinyl), wherein the heteroaryl and heterocyclyl are optionally substituted by 1-3 R^8.

[0099] In some embodiments, each R^8 is independently halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -NR^6R^7, -OH, oxo, -CO_2H, -O(C_1-C_6 alkyl), -CH_2-O(C_1-C_6 alkyl), or -(C_1-C_6 alkyl)-OH. In some embodiments, each R^8 is independently halo, C_1-C_3 alkyl, C_1-C_3 haloalkyl, -NR^6R^7, -OH, oxo, -CO_2H, -O(C_1-C_3 alkyl), -CH_2-O(C_1-C_3 alkyl), or -(C_1-C_3 alkyl)-OH. In some variations, each R^6 and R^7 is independently H or C_1-C_3 alkyl. In some embodiments, each R^8 is independently -CH_3, -CH_2CH_3, -NH_2, -OH, oxo, -$N(CH_3)_2$, -OCH_3, -CH_2OCH_3, -CF_3, -CH_2CH_2OH, -CO_2H, or Cl.

[0100] In some embodiments, Z-Y-X- is

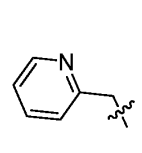
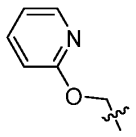
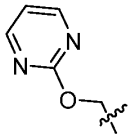
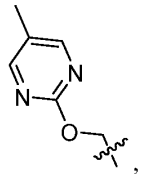
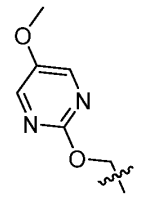
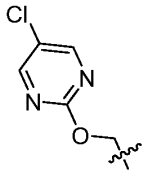
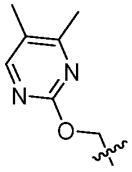
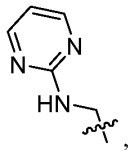
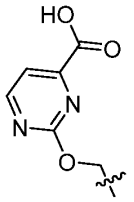
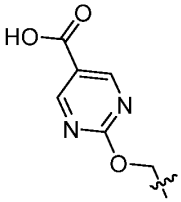
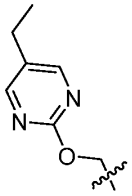
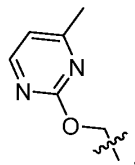
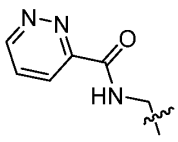
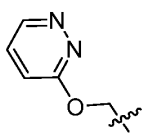
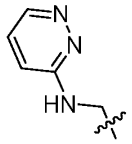
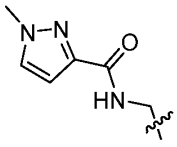
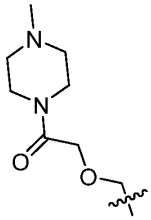
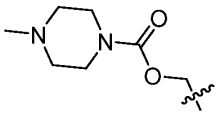
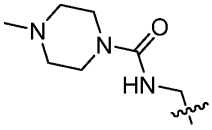
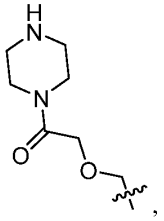
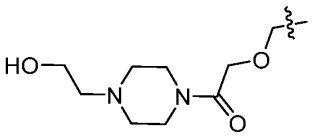
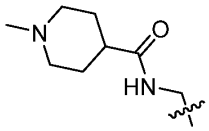
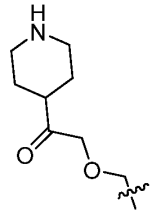
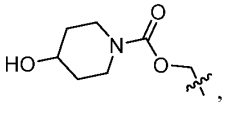
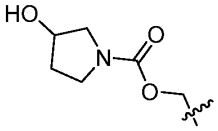
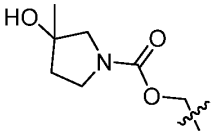
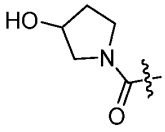
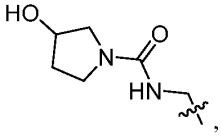

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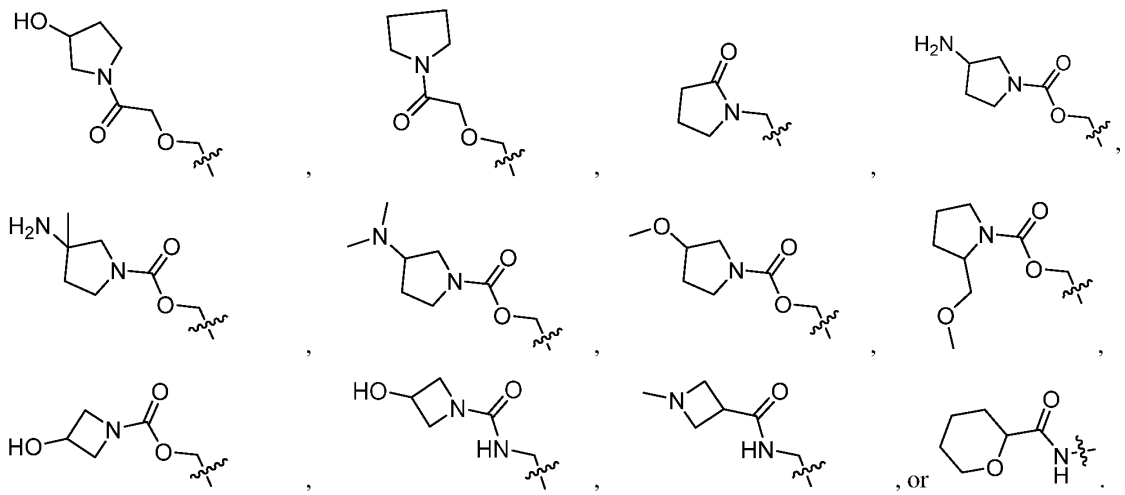
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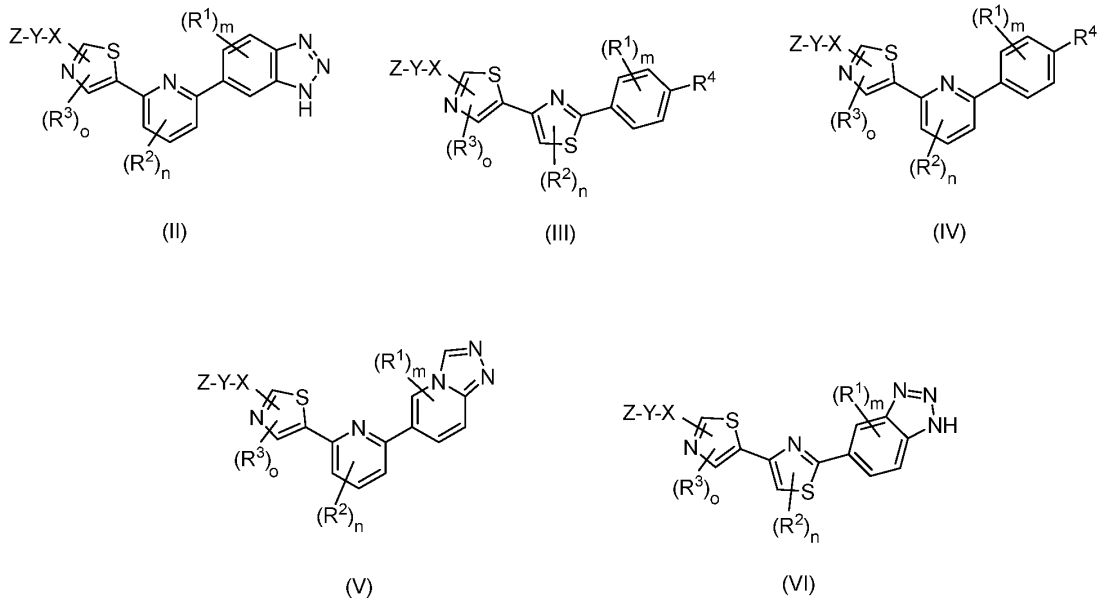
$-CH_2OH$, $-OCH_2CH_3$, or $-CH_2OCH_3$.

[0101] In some embodiments, Z-Y-X- is


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[0102] In some embodiments, the compound of Formula (I) is a compound of Formula (II), (III), (IV), (V), or (VI):



(II) (III) (IV)

(V) (VI)

wherein R^1, m, R^2, n, R^3, o, X, Y, and Z are as described for Formula (I).

[0103] In some embodiments, the compound of Formula (I) is a compound of Formula (II), wherein R^1, m, R^2, n, R^3, o, X, Y, and Z are as described for Formula (I). In some embodiments, the compound of Formula (I) is a compound of Formula (III), wherein R^1, m, R^2, n, R^3, o, X, Y, and Z are as described for Formula (I). In some embodiments, the compound of Formula (I) is a compound of Formula (IV), wherein R^1, m, R^2, n, R^3, o, X, Y, and Z are as described for Formula (I). In some embodiments, the

compound of Formula (I) is a compound of Formula (V), wherein R^1, m, R^2, n, R^3, o, X, Y, and Z are as described for Formula (I). In some embodiments, the compound of Formula (VI) is a compound of Formula (II), wherein R^1, m, R^2, n, R^3, o, X, Y, and Z are as described for Formula (I).

[0104] In some embodiments, the compound is of Formula (II)-(VI) and X is $-CH_2-$. In some embodiments, the compound is of Formula (II)-(VI) and Y is -O- or -N(H)-. In some embodiments, the compound is of Formula (II)-(VI) and R^1 is halo (such as fluoro), -CN, or -OH, and m is 1, 2, or 3. In some embodiments, the compound is of Formula (II)-(VI) and o is 0. In some embodiments, the compound is of Formula (II)-(VI) and o is 1. In some embodiments, the compound is of Formula (II)-(VI) and n is 0. In some embodiments, the compound is of Formula (II)-(VI) and R^3 is C_1-C_6 alkyl (such as methyl), and o is 1. In some embodiments, the compound is of Formula (II)-(VI) and Z is 6-membered heteroaryl (such as pyridazinyl, pyrimidinyl, or pyridinyl) optionally substituted by C_1-C_6 alkyl (such as methyl). In some embodiments, the compound is of Formula (II)-(VI) and Z is $-CO_2(C_1$-C_6 alkyl) (such as $-CO_2CH_3$) or -(C_1-C_6 alkyl)-OH (such as $-CH_2C(CH_3)_2OH$). In some embodiments, the compound is of Formula (II)-(VI) and R^4 is -OH or 6-membered heteroaryl or heterocyclyl (such as tetrazolyl).

[0105] In some embodiments, provided herein is compound of Formula (I) is a compound of Formula (II), wherein X is $-CH_2-$; Y is -O- or -N(H)-; Z is 6-membered heteroaryl optionally substituted by C_1-C_6 alkyl, $-CO_2(C_1$-C_6 alkyl), or -(C_1-C_6 alkyl)-OH; and R^1, m, R^2, n, R^3, and o are as described for Formula (I). In some embodiments, provided herein is compound of Formula (I) is a compound of Formula (III), wherein X is $-CH_2-$; Y is -O- or -N(H)-; Z is 6-membered heteroaryl optionally substituted by C_1-C_6 alkyl, $-CO_2(C_1$-C_6 alkyl), or -(C_1-C_6 alkyl)-OH; and R^1, m, R^2, n, R^3, and o are as described for Formula (I). In some embodiments, provided herein is compound of Formula (I) is a compound of Formula (IV), wherein X is $-CH_2-$; Y is -O- or -N(H)-; Z is 6-membered heteroaryl optionally substituted by C_1-C_6 alkyl, $-CO_2(C_1$-C_6 alkyl), or -(C_1-C_6 alkyl)-OH; and R^1, m, R^2, n, R^3, and o are as described for Formula (I). In some embodiments, provided herein is compound of Formula (I) is a compound of Formula (V), wherein X is $-CH_2-$; Y is -O- or -N(H)-; Z is 6-membered heteroaryl optionally substituted by C_1-C_6 alkyl, $-CO_2(C_1$-C_6 alkyl), or -(C_1-C_6 alkyl)-OH; and R^1, m, R^2, n, R^3, and o are as described for Formula (I). In some embodiments, provided herein is compound of Formula (I) is a compound of Formula (VI), wherein X is $-CH_2-$; Y is -O- or -N(H)-; Z is 6-membered heteroaryl optionally substituted by C_1-C_6 alkyl, $-CO_2(C_1$-C_6 alkyl), or -(C_1-C_6 alkyl)-OH; and R^1, m, R^2, n, R^3, and o are as described for Formula (I).

[0106] In some embodiments, provided herein is compound of Formula (I) is a compound of Formula (II), wherein X is $-CH_2-$; Y is -O- or -N(H)-; Z is 6-membered heteroaryl optionally substituted by C_1-C_6 alkyl; and R^1, m, R^2, n, R^3, and o are as described for Formula (I). In some embodiments, provided herein is compound of Formula (I) is a compound of Formula (III), wherein X is $-CH_2-$; Y is -O- or -N(H)-; Z is 6-membered heteroaryl optionally substituted by C_1-C_6 alkyl; and R^1, m, R^2, n, R^3, and o are as described

for Formula (I). In some embodiments, provided herein is compound of Formula (I) is a compound of Formula (IV), wherein X is -CH_2-; Y is -O- or -N(H)-; Z is 6-membered heteroaryl optionally substituted by C_1-C_6 alkyl; and R^1, m, R^2, n, R^3, and o are as described for Formula (I). In some embodiments, provided herein is compound of Formula (I) is a compound of Formula (V), wherein X is -CH_2-; Y is -O- or -N(H)-; Z is 6-membered heteroaryl optionally substituted by C_1-C_6 alkyl; and R^1, m, R^2, n, R^3, and o are as described for Formula (I). In some embodiments, provided herein is compound of Formula (I) is a compound of Formula (VI), wherein X is -CH_2-; Y is -O- or -N(H)-; Z is 6-membered heteroaryl optionally substituted by C_1-C_6 alkyl; and R^1, m, R^2, n, R^3, and o are as described for Formula (I).

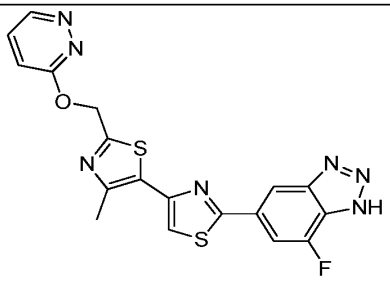
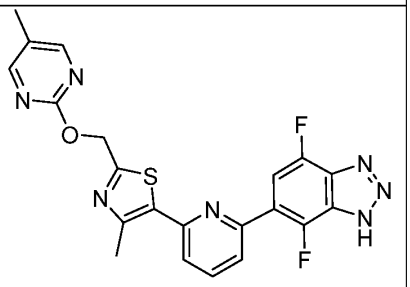
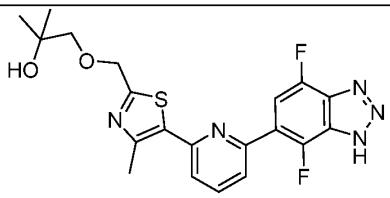
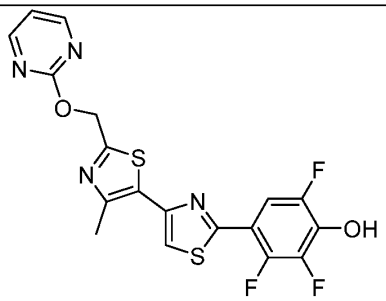
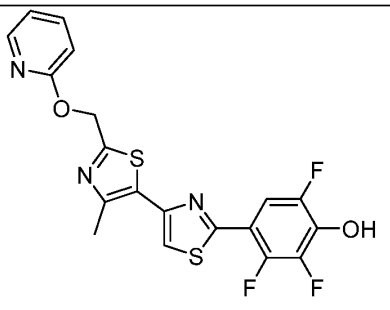
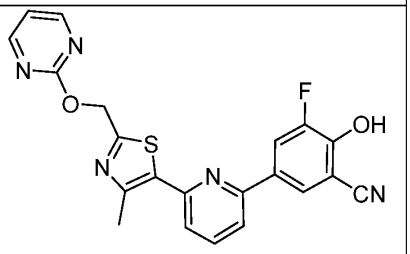
[0107] In some embodiments, provided herein is compound of Formula (I) is a compound of Formula (II), wherein X is -CH_2-; Y is -O- or -N(H)-; Z is -CO_2(C_1-C_6 alkyl) or -(C_1-C_6 alkyl)-OH; and R^1, m, R^2, n, R^3, and o are as described for Formula (I). In some embodiments, provided herein is compound of Formula (I) is a compound of Formula (III), wherein X is -CH_2-; Y is -O- or -N(H)-; Z is -CO_2(C_1-C_6 alkyl) or -(C_1-C_6 alkyl)-OH; and R^1, m, R^2, n, R^3, and o are as described for Formula (I). In some embodiments, provided herein is compound of Formula (I) is a compound of Formula (IV), wherein X is -CH_2-; Y is -O- or -N(H)-; Z is -CO_2(C_1-C_6 alkyl) or -(C_1-C_6 alkyl)-OH; and R^1, m, R^2, n, R^3, and o are as described for Formula (I). In some embodiments, provided herein is compound of Formula (I) is a compound of Formula (V), wherein X is -CH_2-; Y is -O- or -N(H)-; Z is -CO_2(C_1-C_6 alkyl) or -(C_1-C_6 alkyl)-OH; and R^1, m, R^2, n, R^3, and o are as described for Formula (I). In some embodiments, provided herein is compound of Formula (VI) is a compound of Formula (II), wherein X is -CH_2-; Y is -O- or -N(H)-; Z is -CO_2(C_1-C_6 alkyl) or -(C_1-C_6 alkyl)-OH; and R^1, m, R^2, n, R^3, and o are as described for Formula (I).

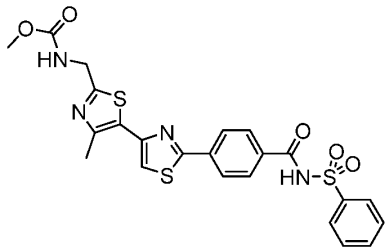
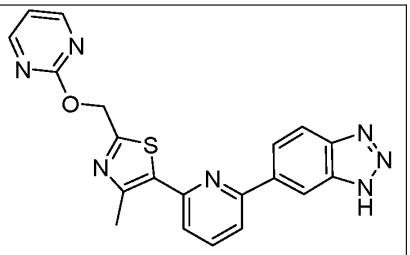
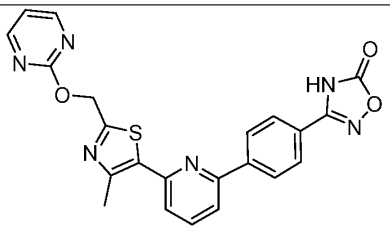
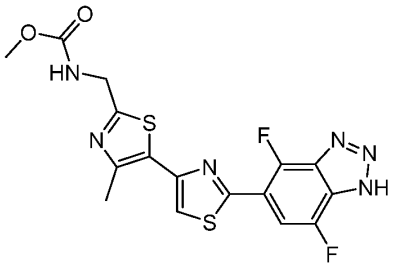
[0108] In the descriptions herein, it is understood that every description, variation, embodiment, or aspect of a moiety may be combined with every description, variation, embodiment, or aspect of other moieties the same as if each and every combination of descriptions is specifically and individually listed. For example, every description, variation, embodiment, or aspect provided herein with respect to L of Formula (I) may be combined with every description, variation, embodiment, or aspect of Ring A, Ring B, Ring C, R^1, R^2, R^3, m, n, o, R^4, R^5, R^6, R^7, X, Y, Z, Z^1, Z^2, and R^8 the same as if each and every combination were specifically and individually listed. It is also understood that all descriptions, variations, embodiments, or aspects of Formula (I), where applicable, apply equally to other formulae detailed herein, and are equally described, the same as if each and every description, variation, embodiment, or aspect were separately and individually listed for all formulae. For example, all descriptions, variations, embodiments, or aspects of Formula (I), where applicable, apply equally to any of the formulae as detailed herein, such as Formulae (II)-(VI), and are equally described, the same as if

each and every description, variation, embodiment, or aspect were separately and individually listed for all formulae.

[0109] In some embodiments, provided is a compound selected from the compounds in Table 1 or a pharmaceutically acceptable salt thereof. In some embodiments, provided is a compound selected from the compounds in Table 2 or a pharmaceutically acceptable salt thereof. Although certain compounds described in the present disclosure, including in Table 1 and Table 2, are presented as specific stereoisomers and/or in a non-stereochemical form, it is understood that any or all stereochemical forms, including any enantiomeric or diastereomeric forms, and any tautomers or other forms of any of the compounds of the present disclosure, including in Table 1 and Table 2, are herein described.

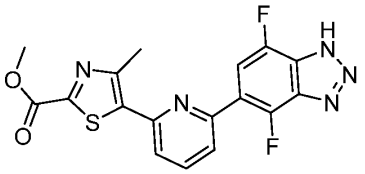
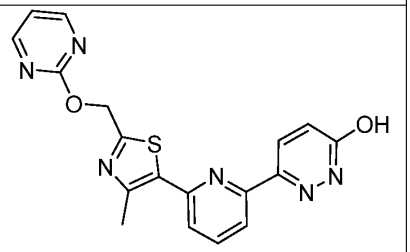
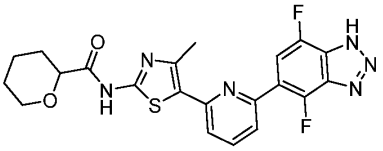
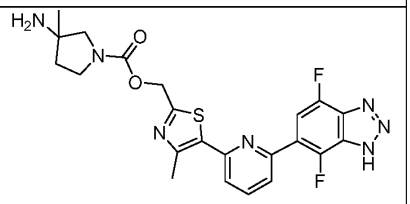
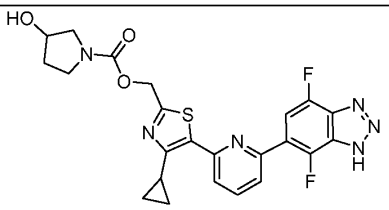
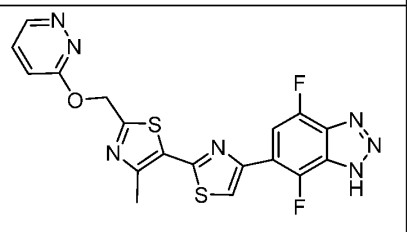
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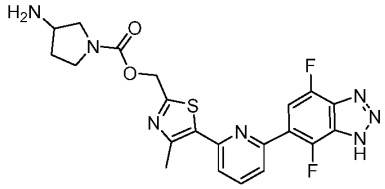
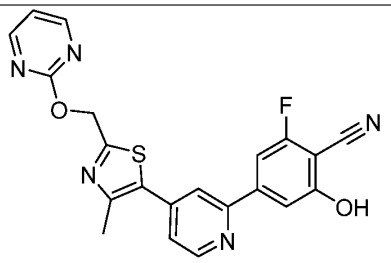
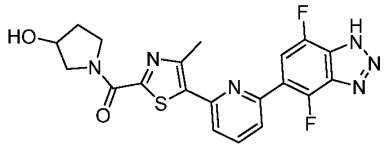
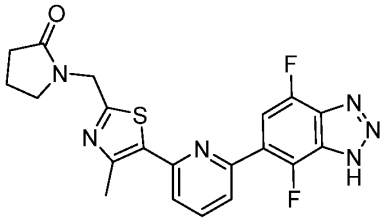
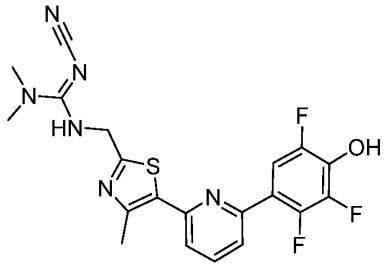
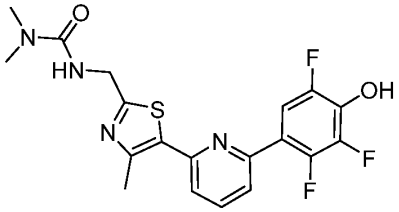
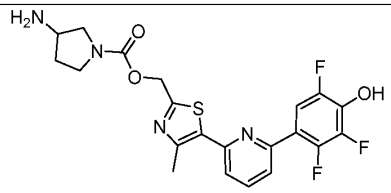
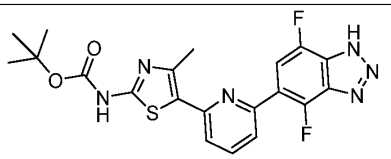
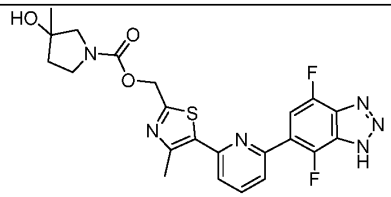
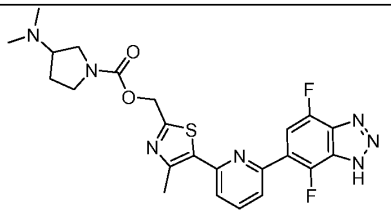
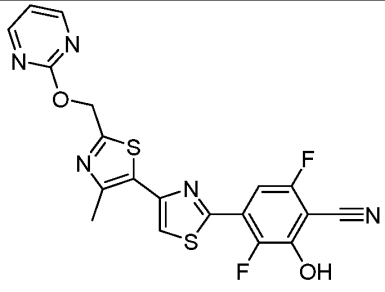
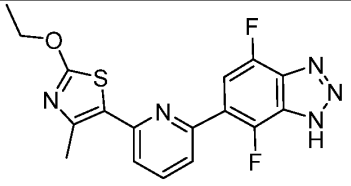
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9		**10**	
11		**12**	

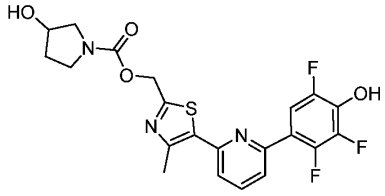
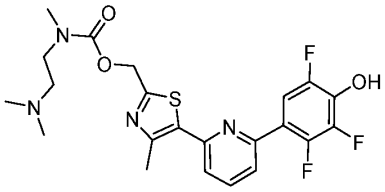
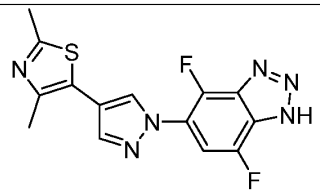
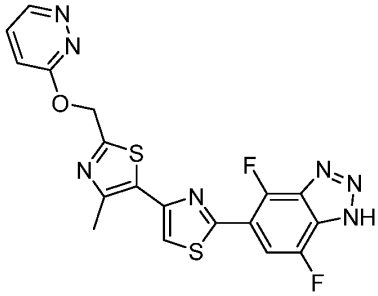
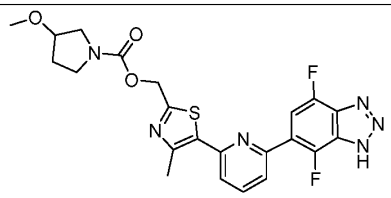
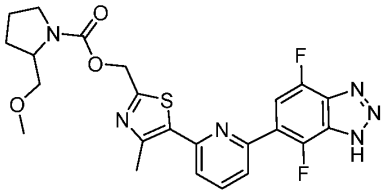
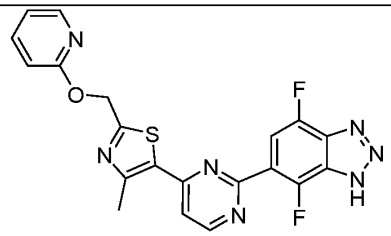
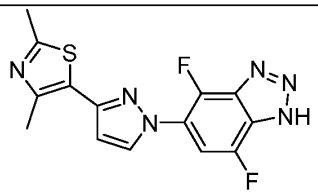
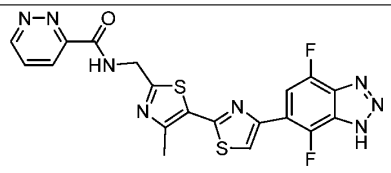
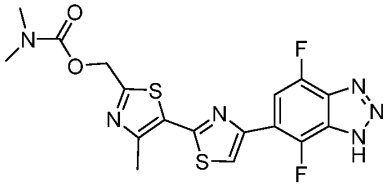
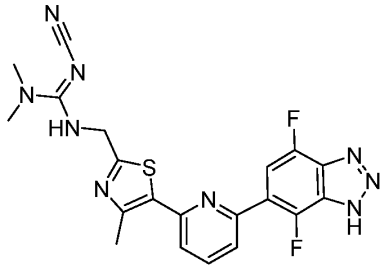
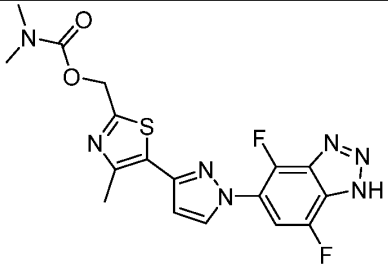
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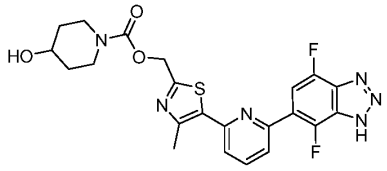
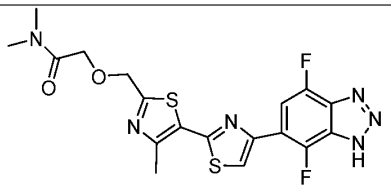
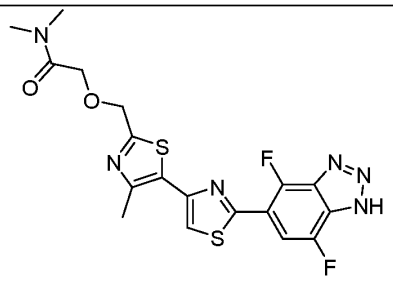
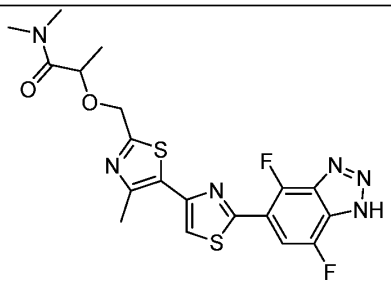
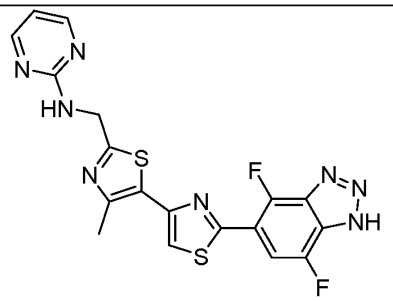
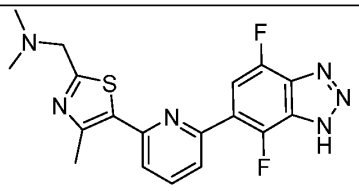
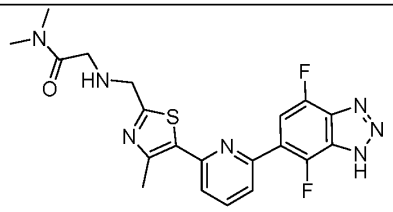
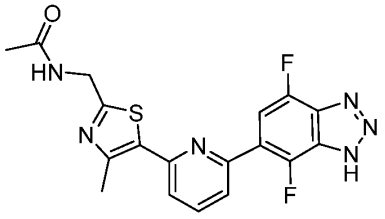
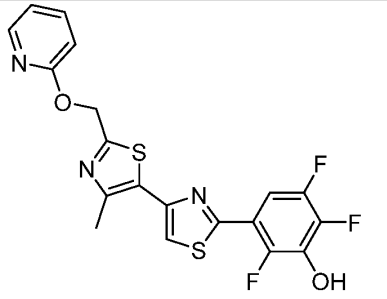
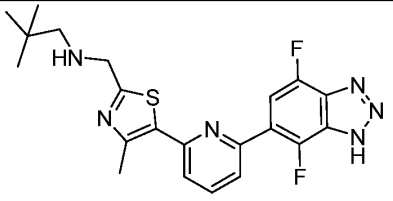
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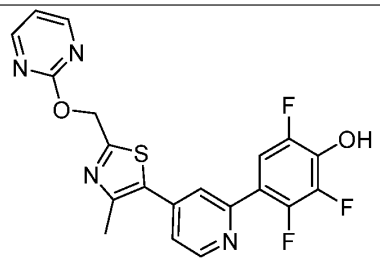
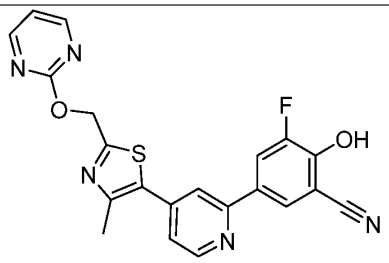
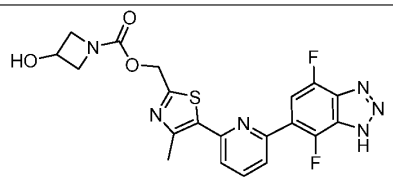
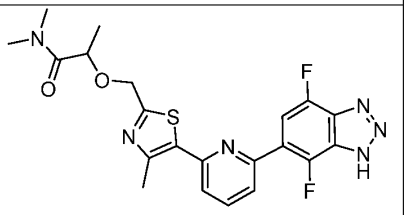
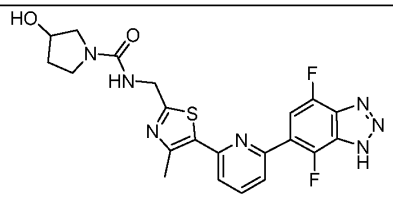
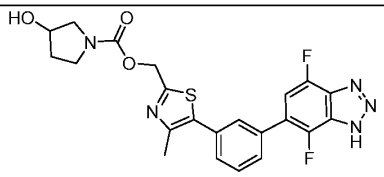
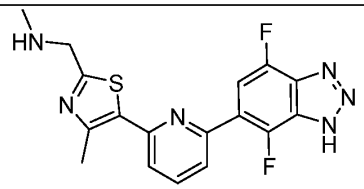
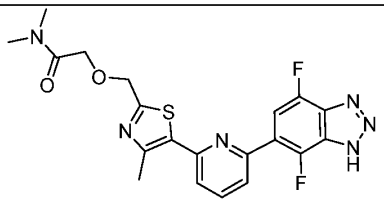
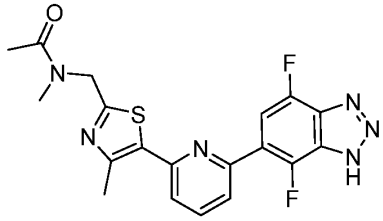
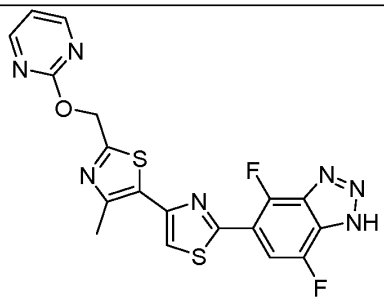
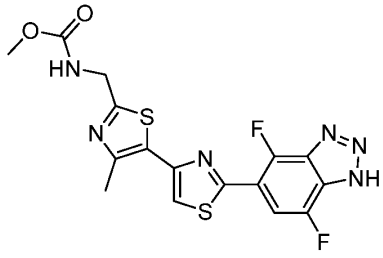
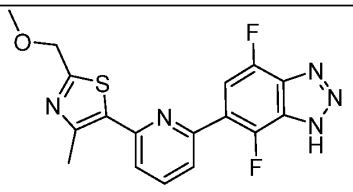
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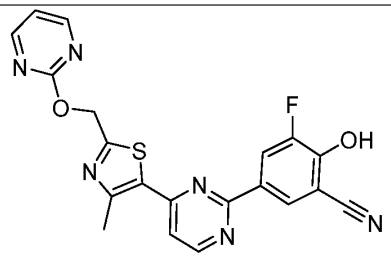
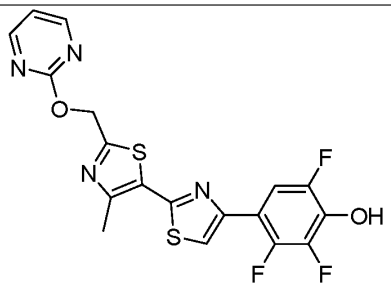
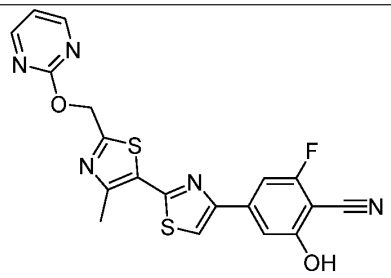
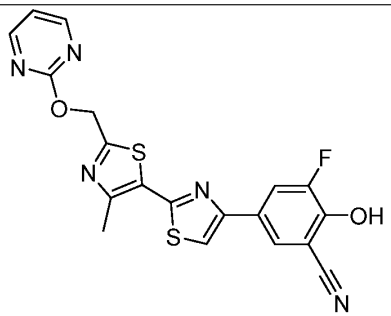
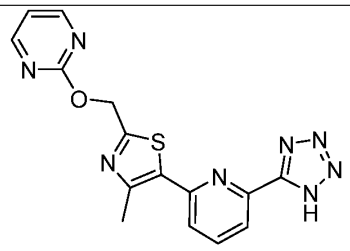
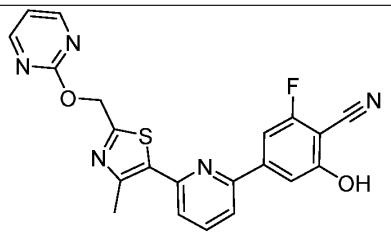
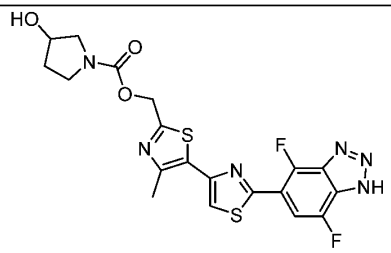
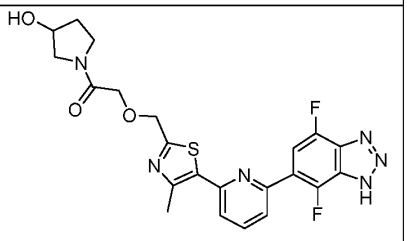
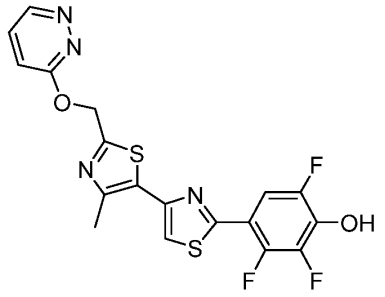
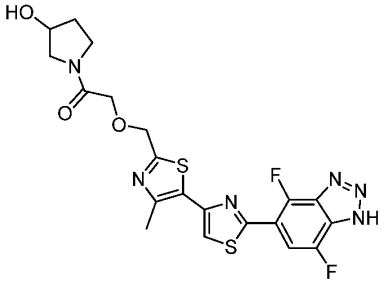
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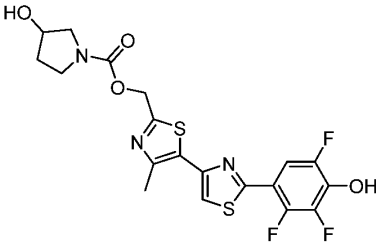
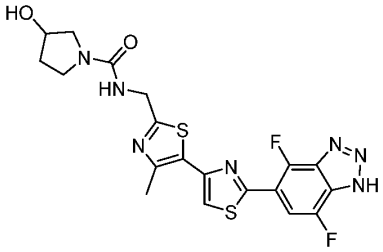
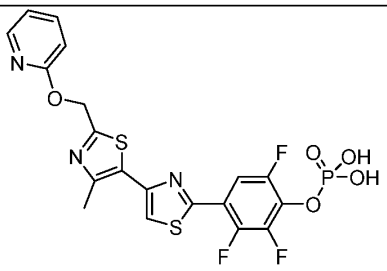
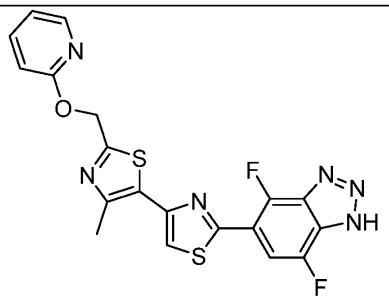
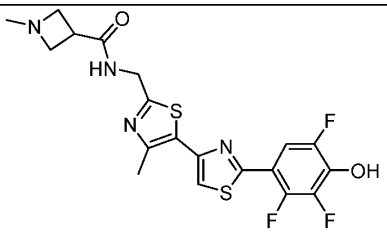
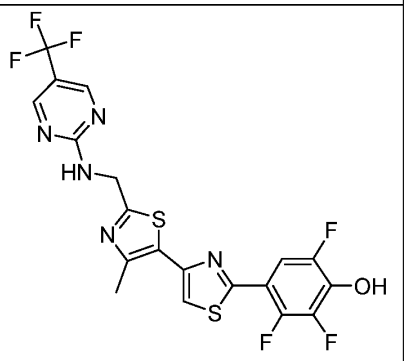
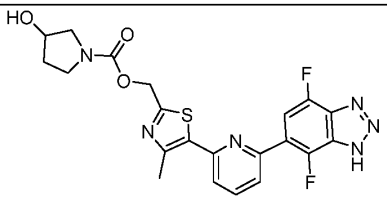
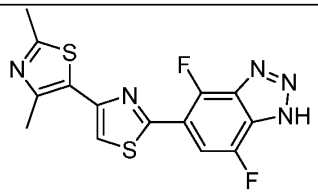
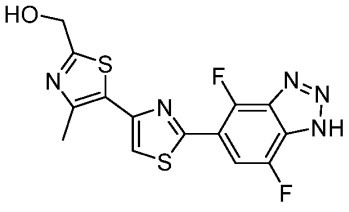
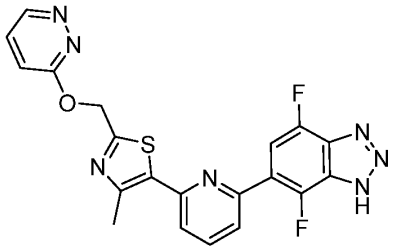
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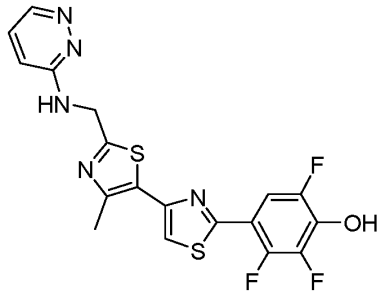
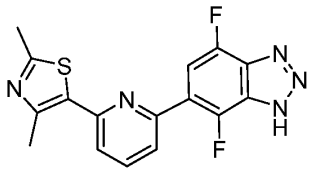
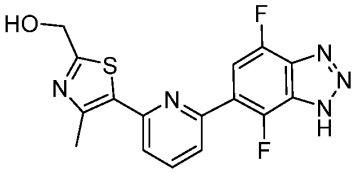
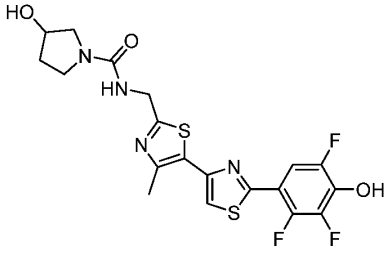
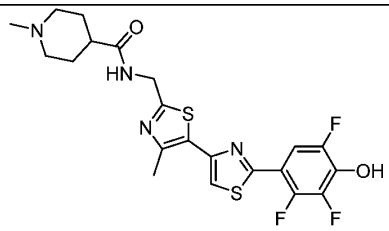
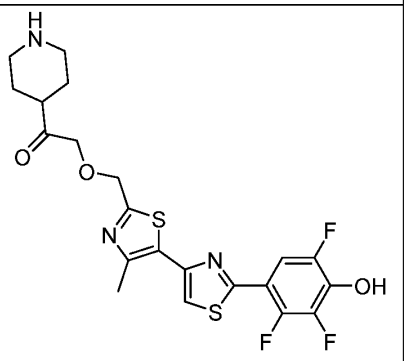
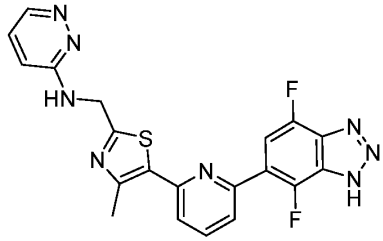
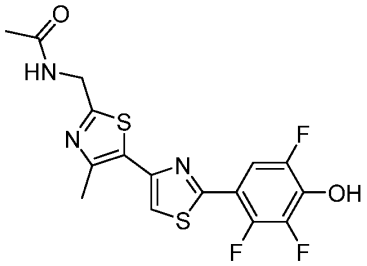
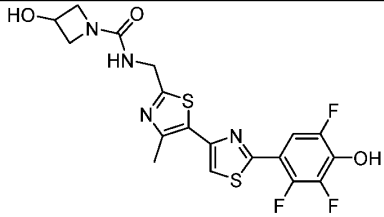
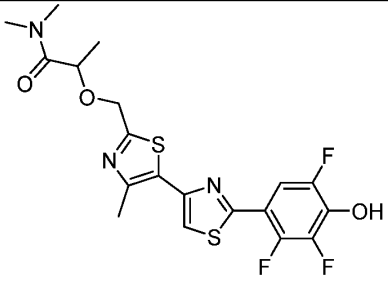
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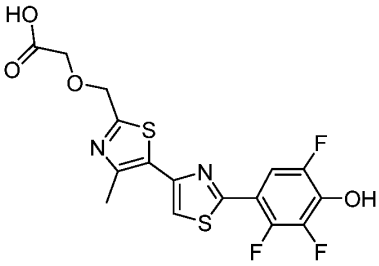
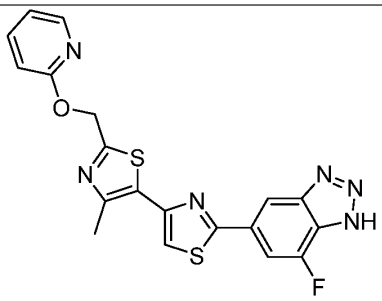
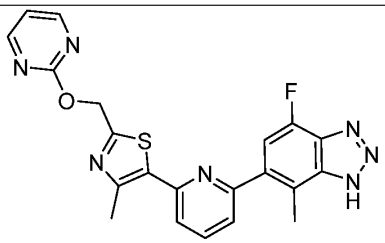
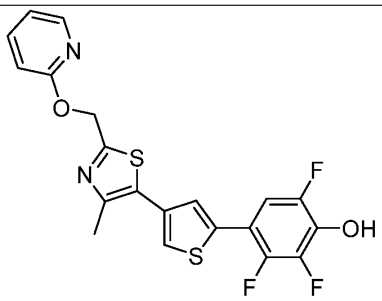
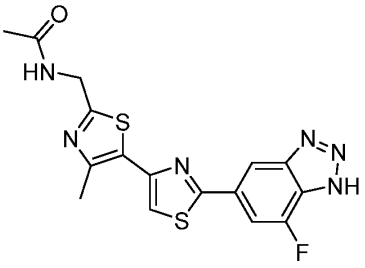
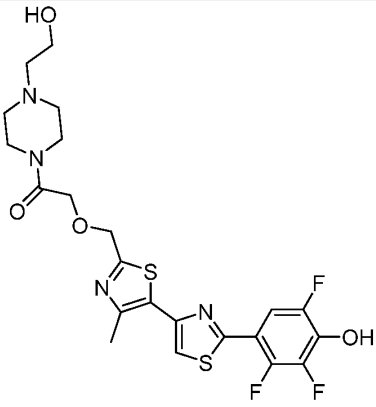
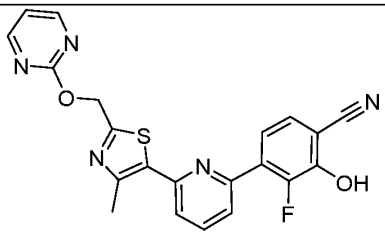
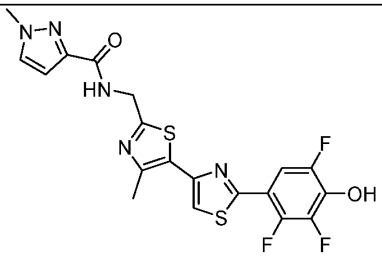
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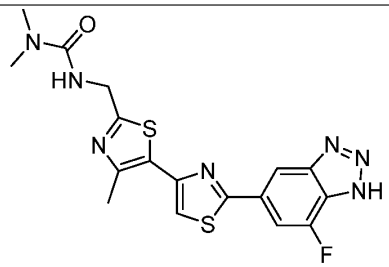
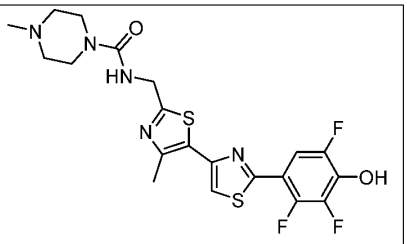
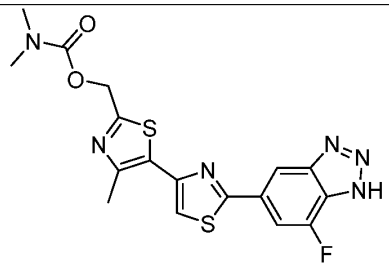
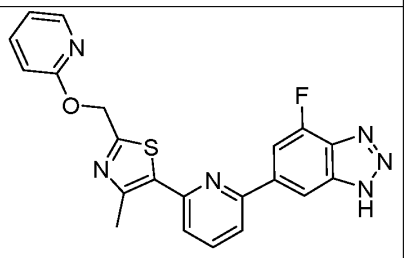
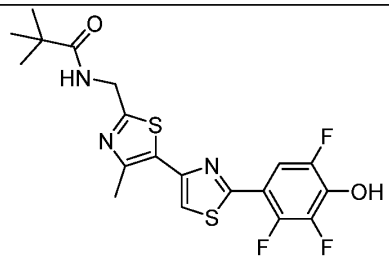
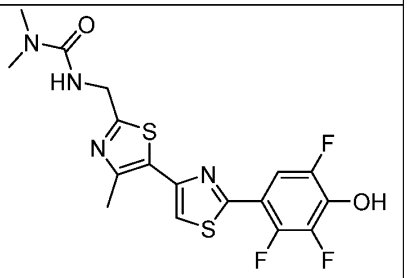
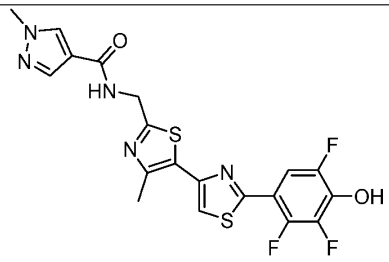
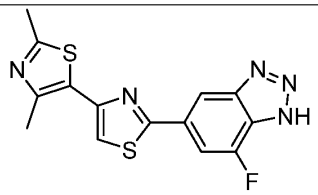
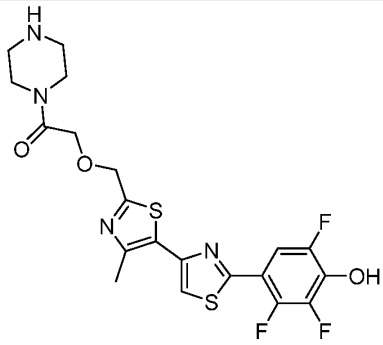
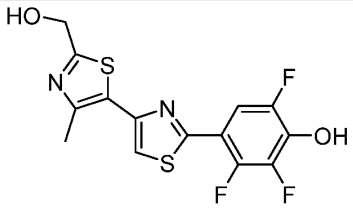
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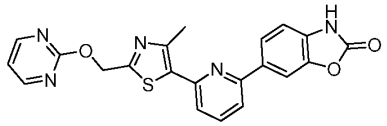
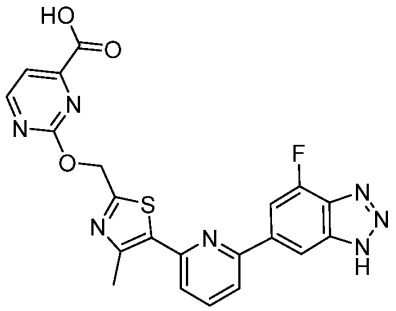
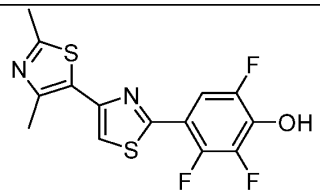
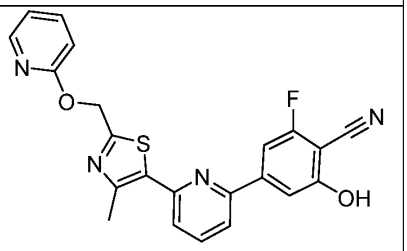
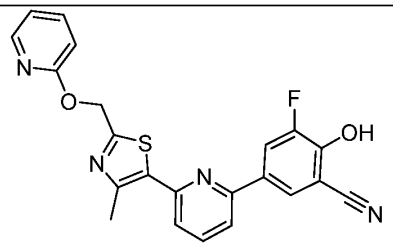
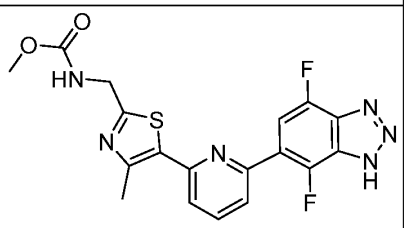
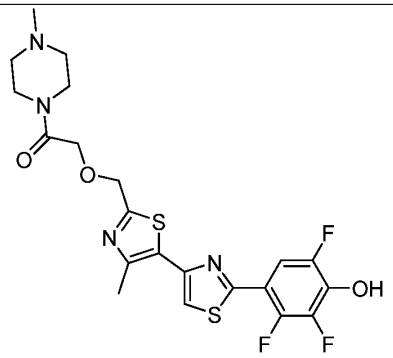
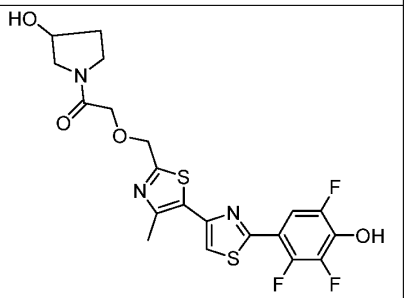
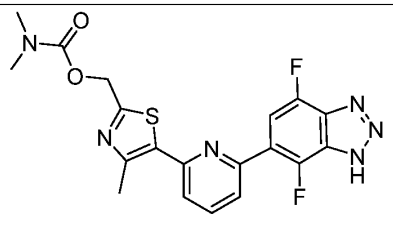
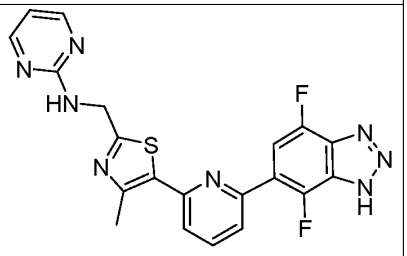
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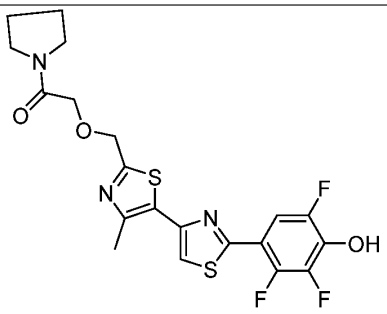
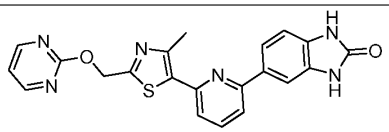
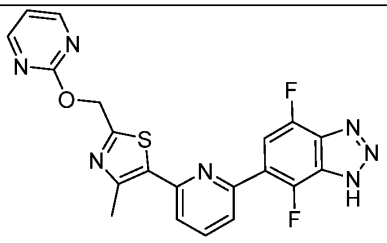
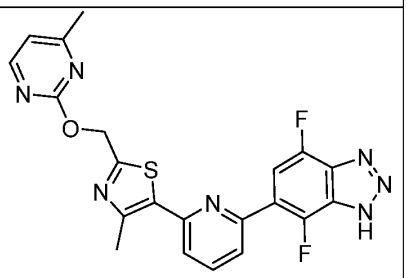
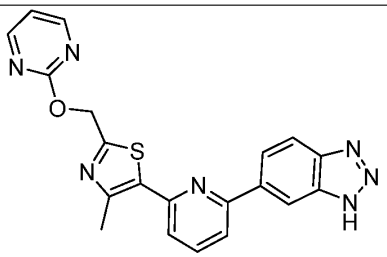
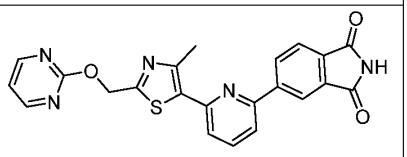
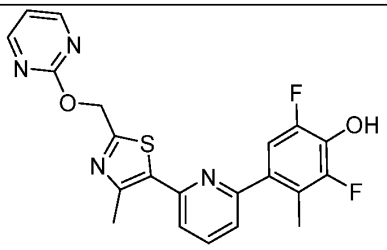
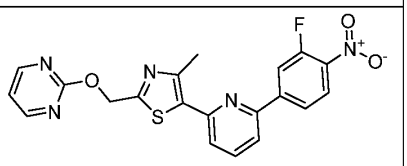
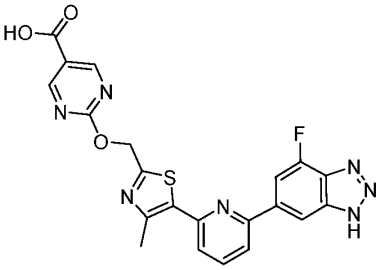
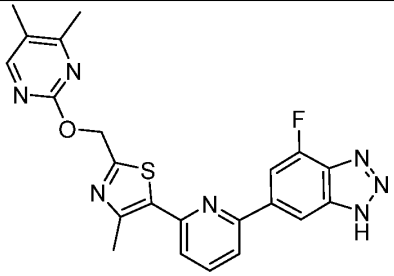
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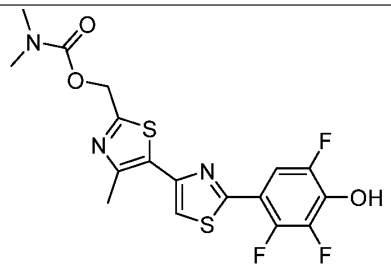
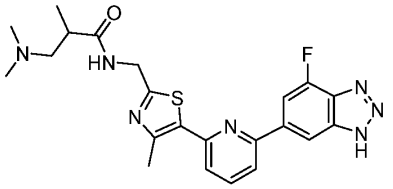
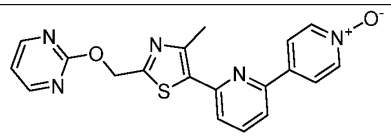
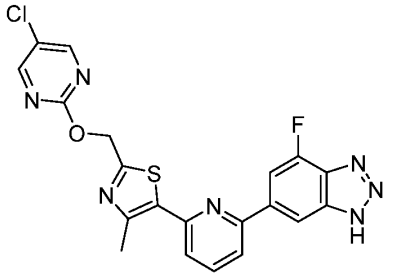
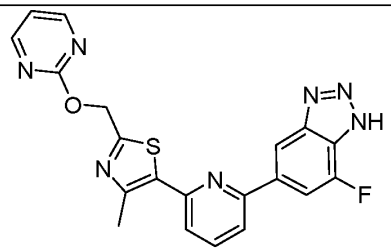
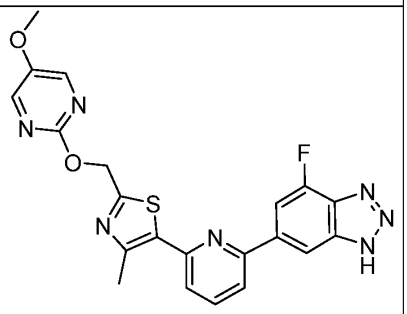
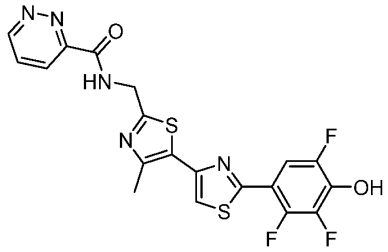
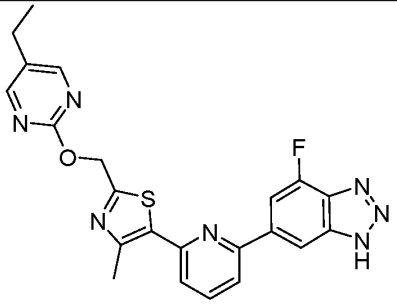
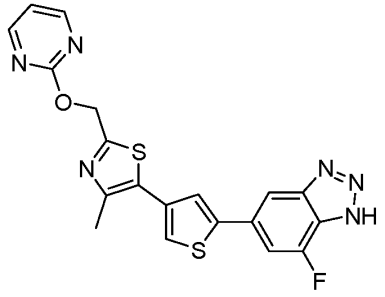
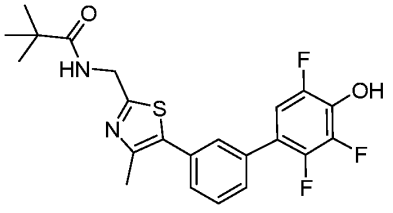
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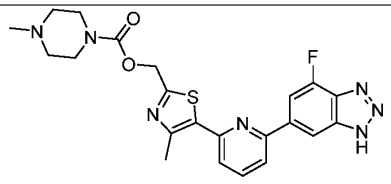
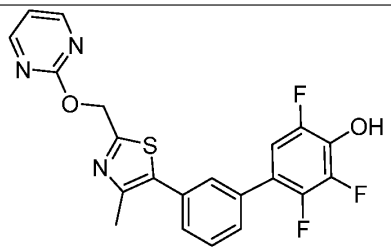
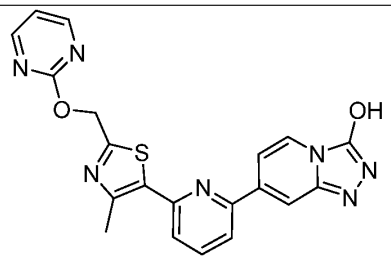
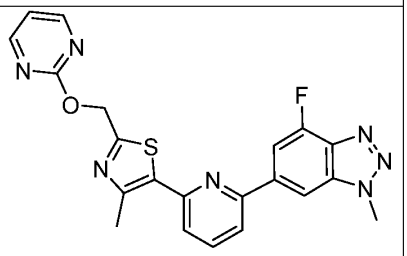
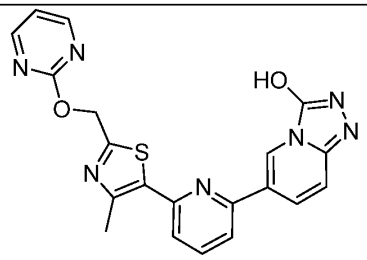
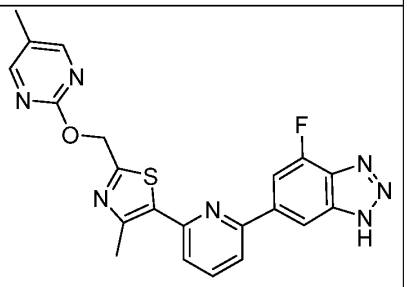
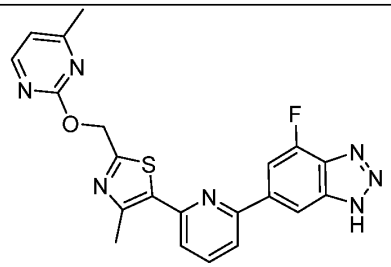
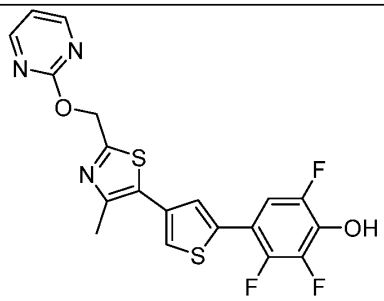
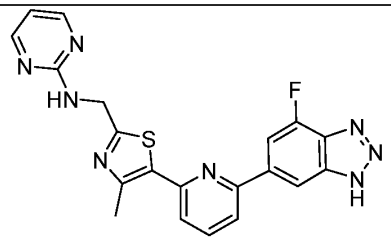
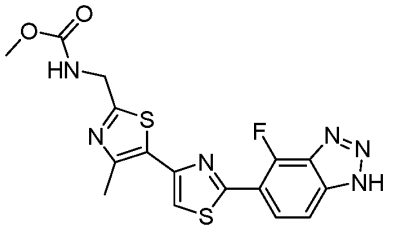
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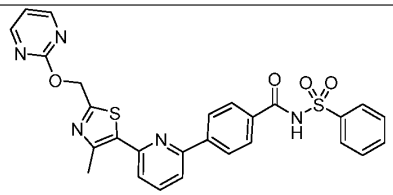
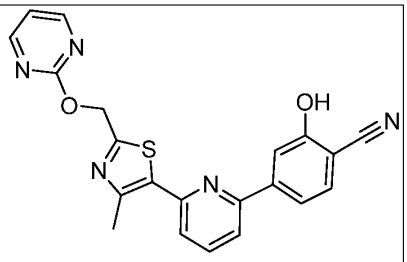
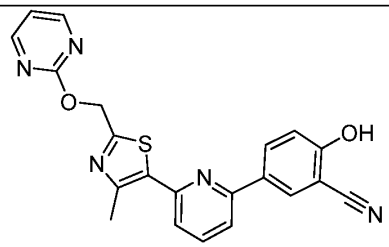
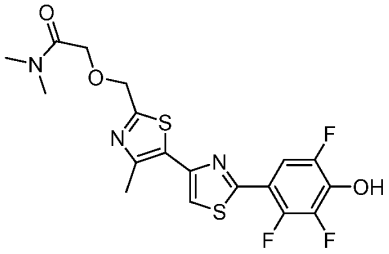
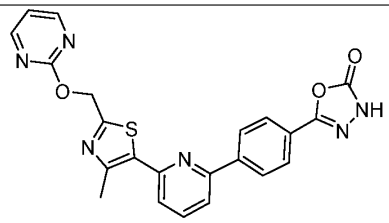
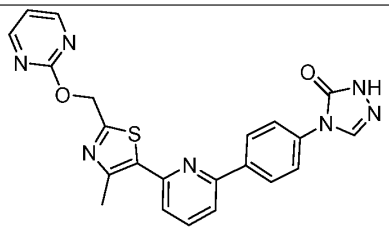
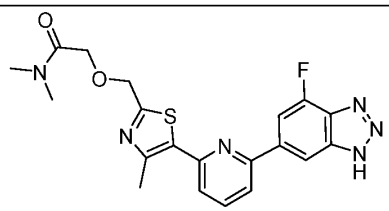
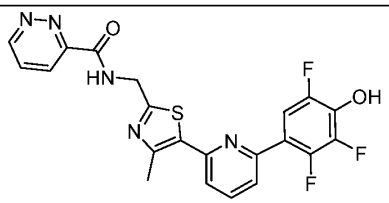
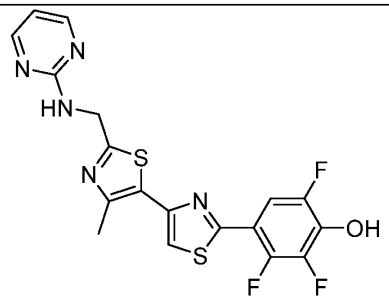
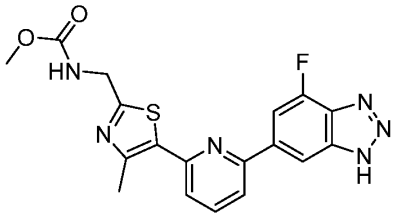
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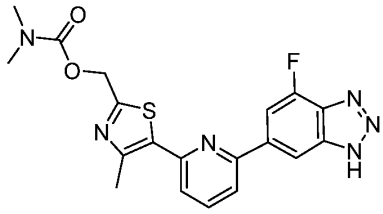
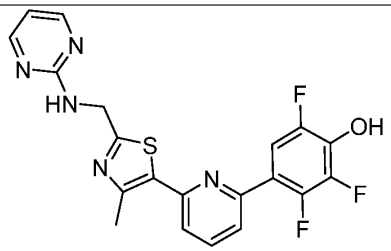
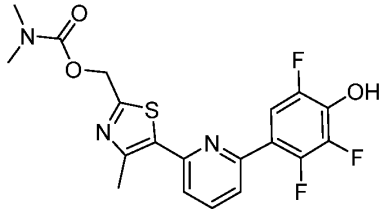
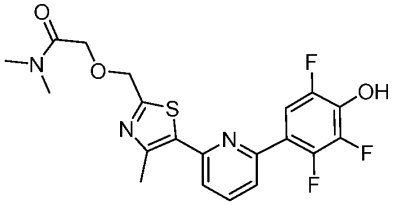
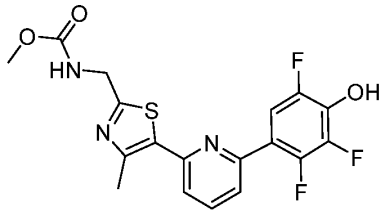
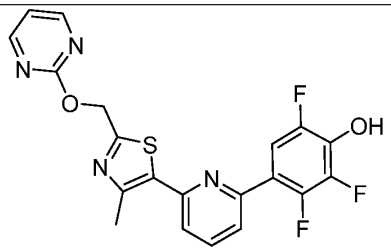
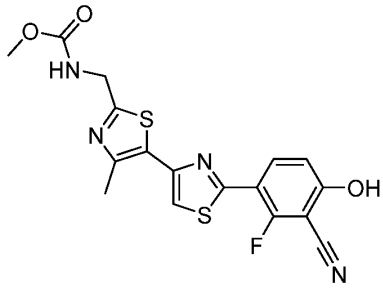
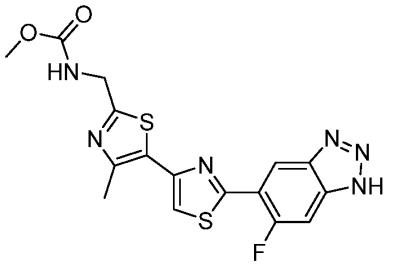
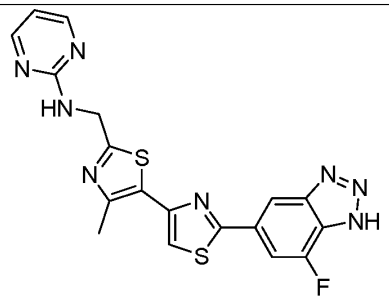
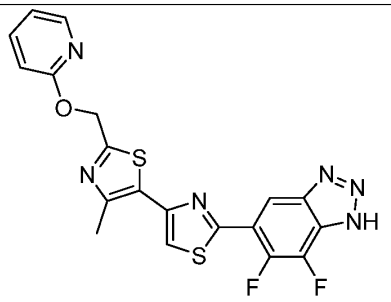
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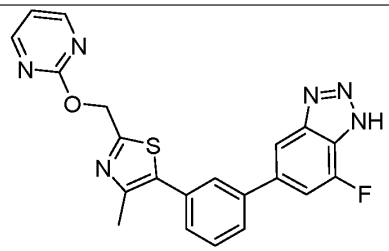
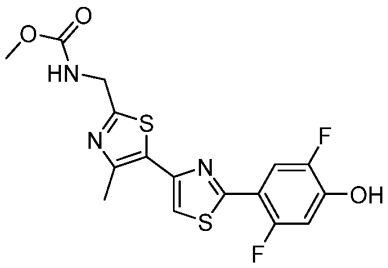
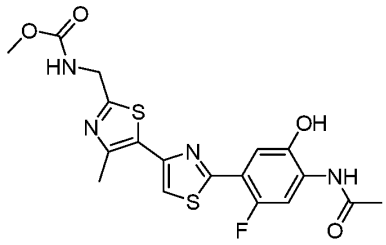
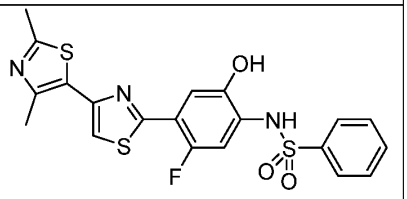
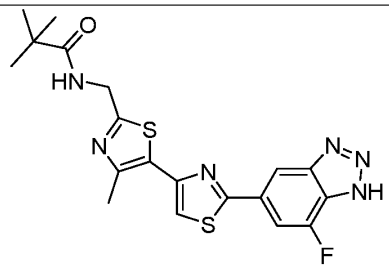
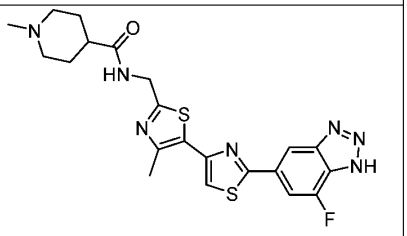
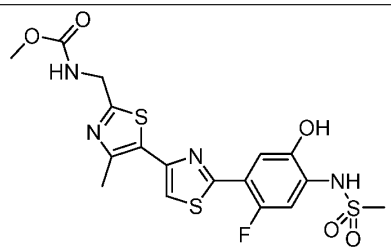
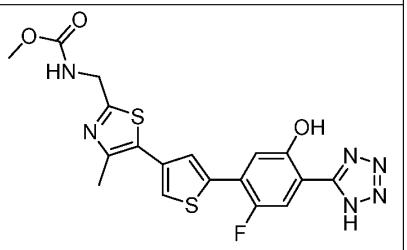
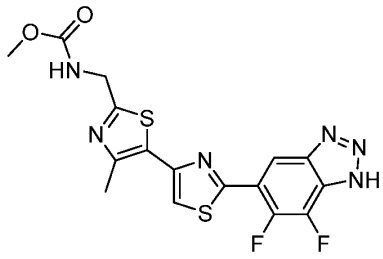
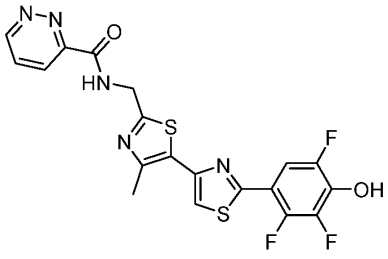
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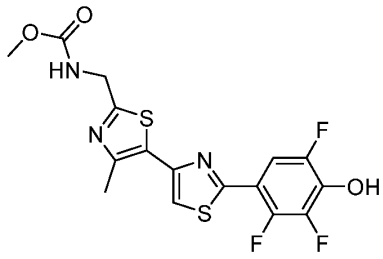
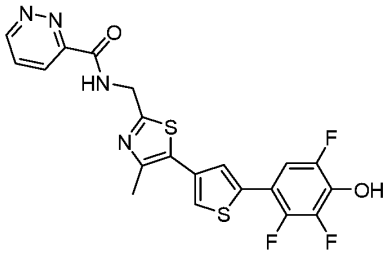
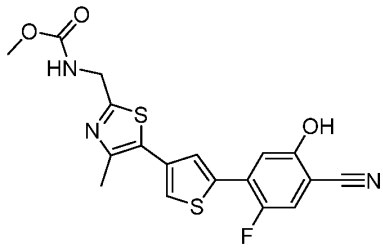
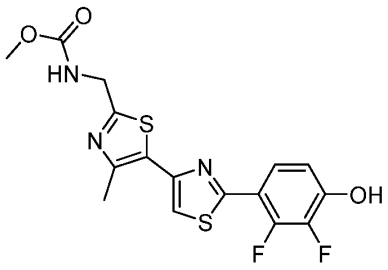
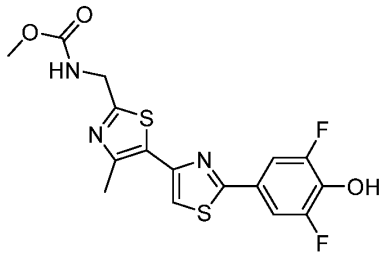
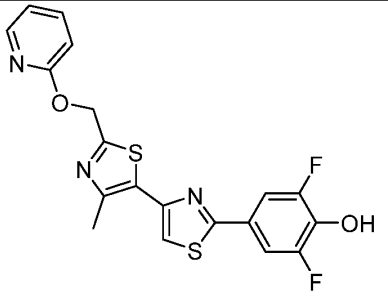
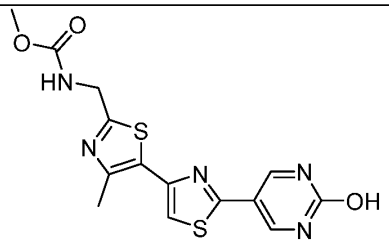
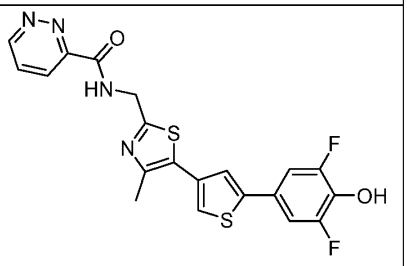
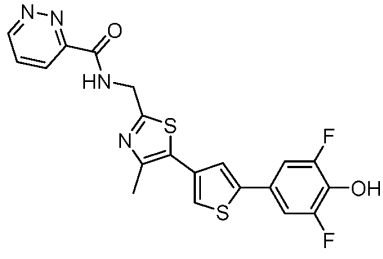
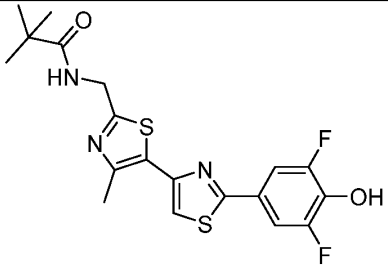
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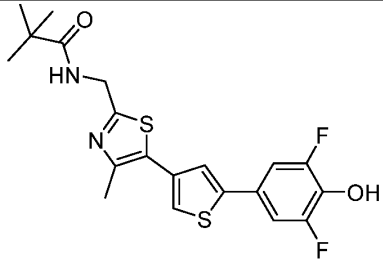
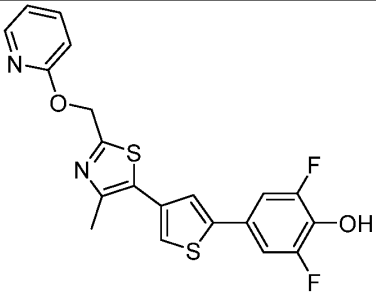
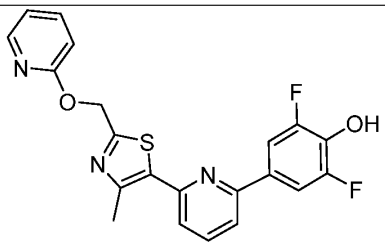
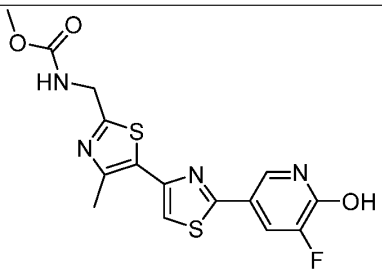
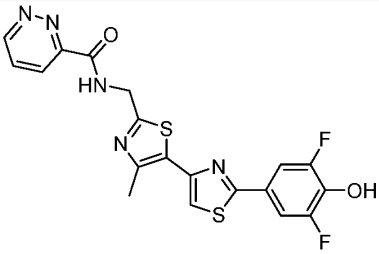
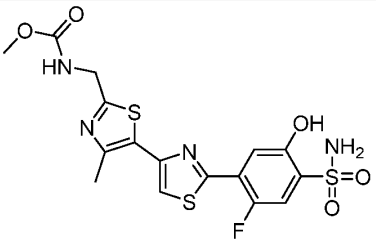
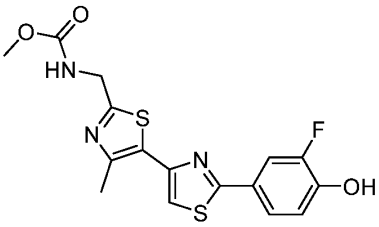
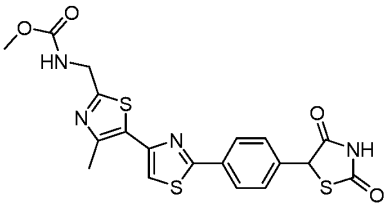
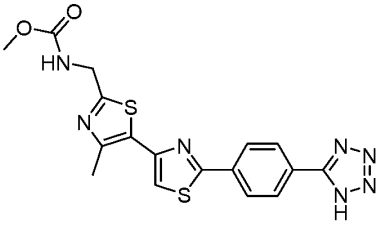
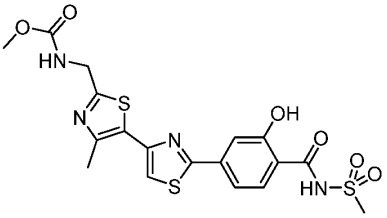
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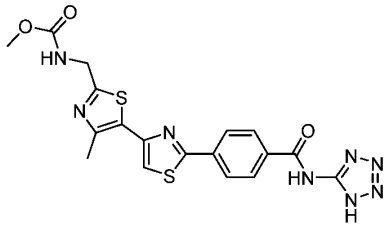
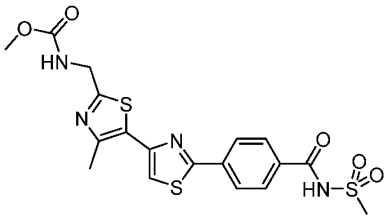
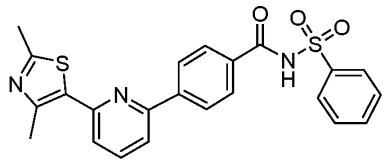
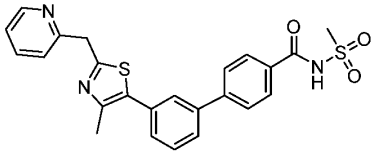
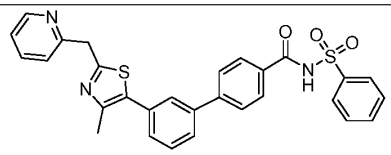
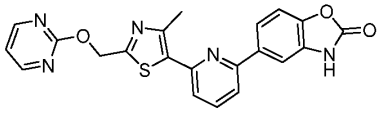
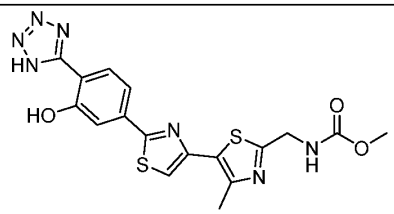
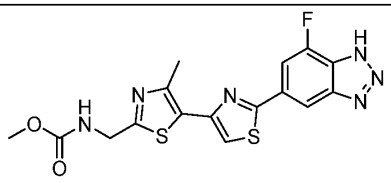
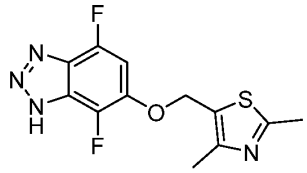
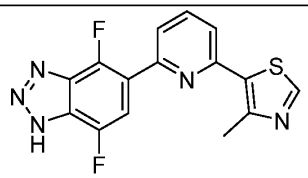
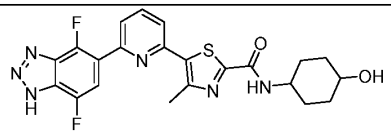
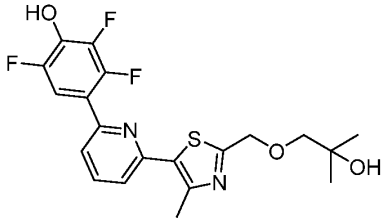
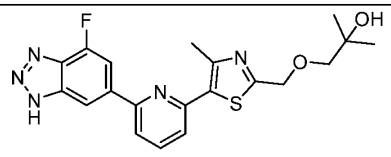
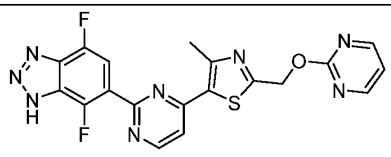
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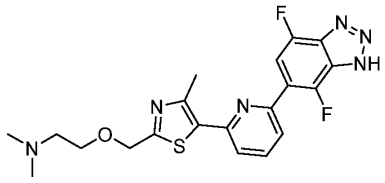
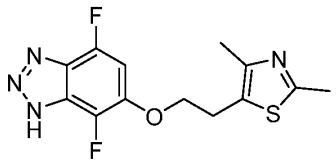
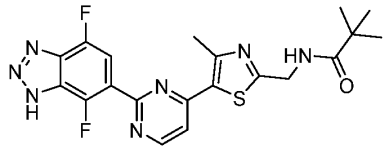
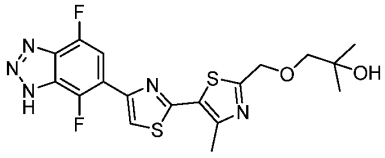
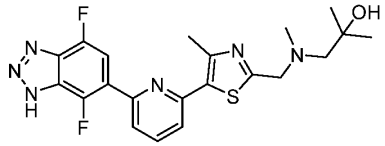
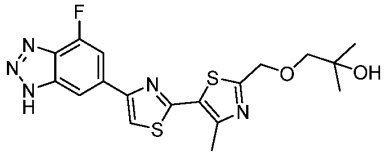
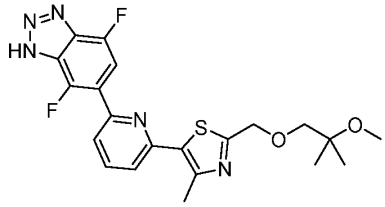
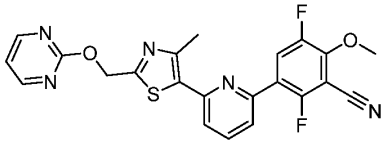
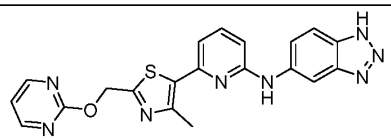
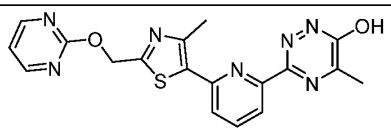
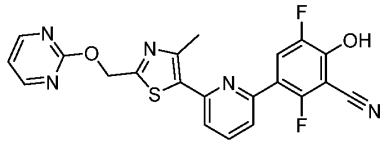
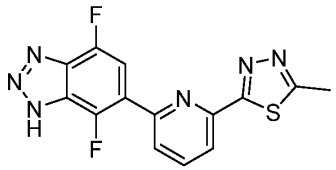
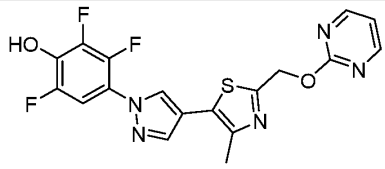
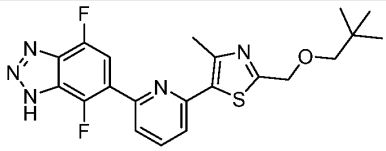
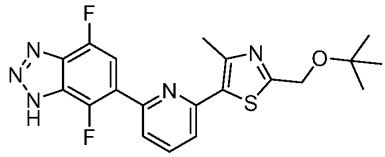
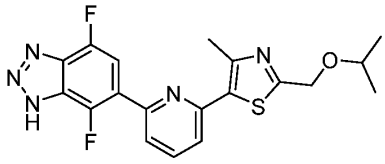
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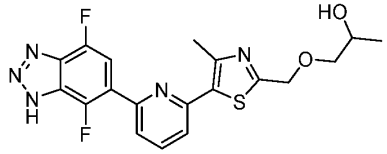
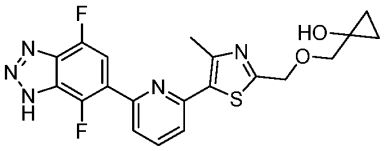
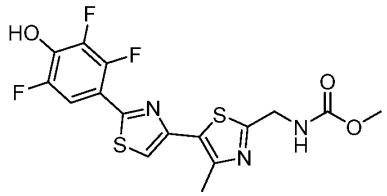
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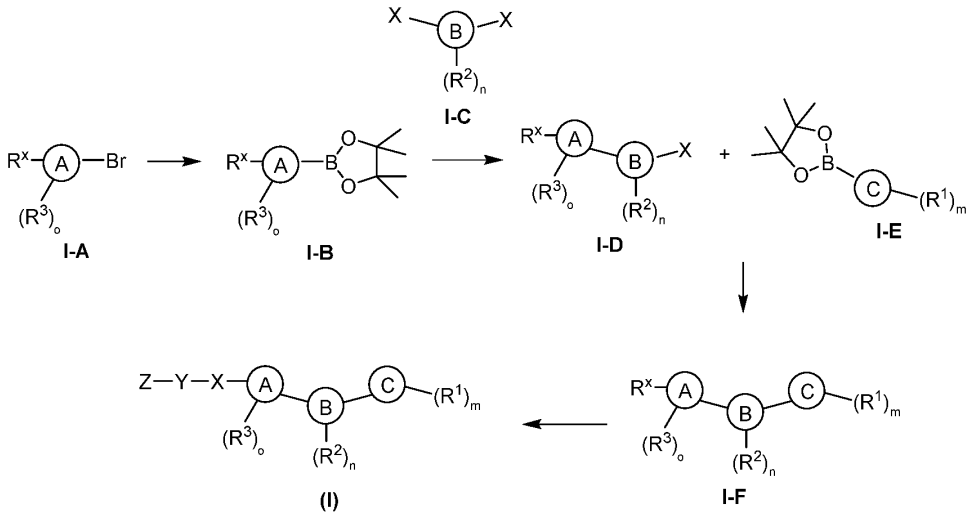
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or a pharmaceutically acceptable salt thereof.

Methods of Synthesis

[0110] Compounds of Formula (I) or any variation thereof may be prepared according to the general reactions shown in Schemes IA, IB, II, and III.

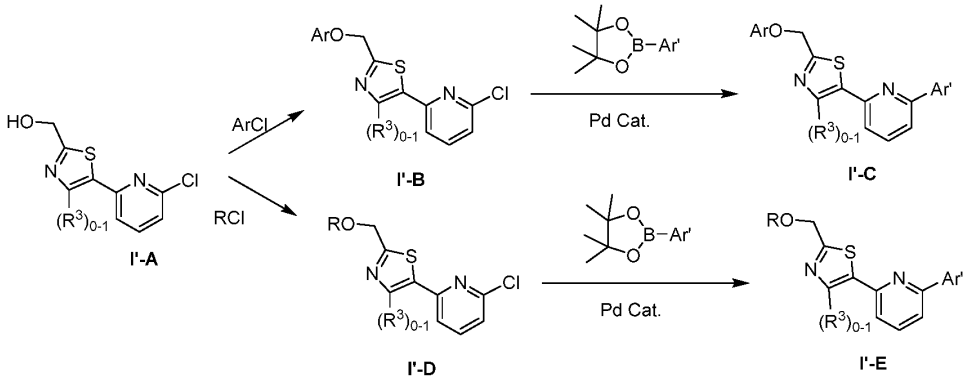
Scheme IA.



[0111] Scheme IA shows an exemplary route for preparing compounds of Formula (I), wherein R^x can be a group useful for conversion to a desired Z-Y-X group (such as shown in the non-limiting examples, Schemes IB, II, and III) and the remaining variables are as described herein. In some embodiments, compound I-A can be derivatized to form compound I-B, which can subsequently be coupled (e.g. under Suzuki coupling conditions) with an appropriate dihalide, compound I-C (wherein X is Cl or Br), to form compound I-D. Compound I-F can be achieved from compound I-D with an appropriate boronic acid ester, compound I-E, and metal catalyst. R^x can subsequently be derivatized to form the desired Z-Y-X group according to methods known in the art. In some embodiments, ring A, B, and C can be connected

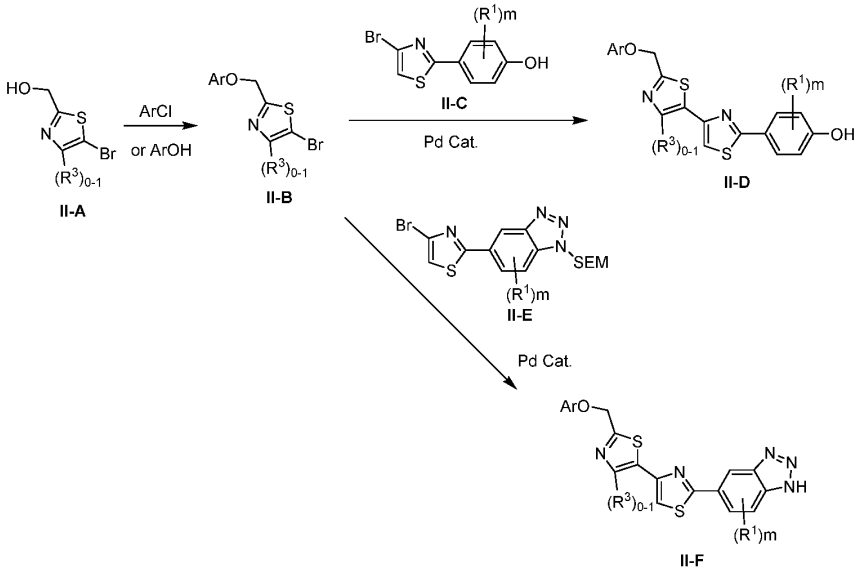
in any order (e.g., ring A and ring B, followed by ring C as shown in Scheme IA; or ring B and ring C, followed by ring A) according to similar methods as described herein.

Scheme IB.



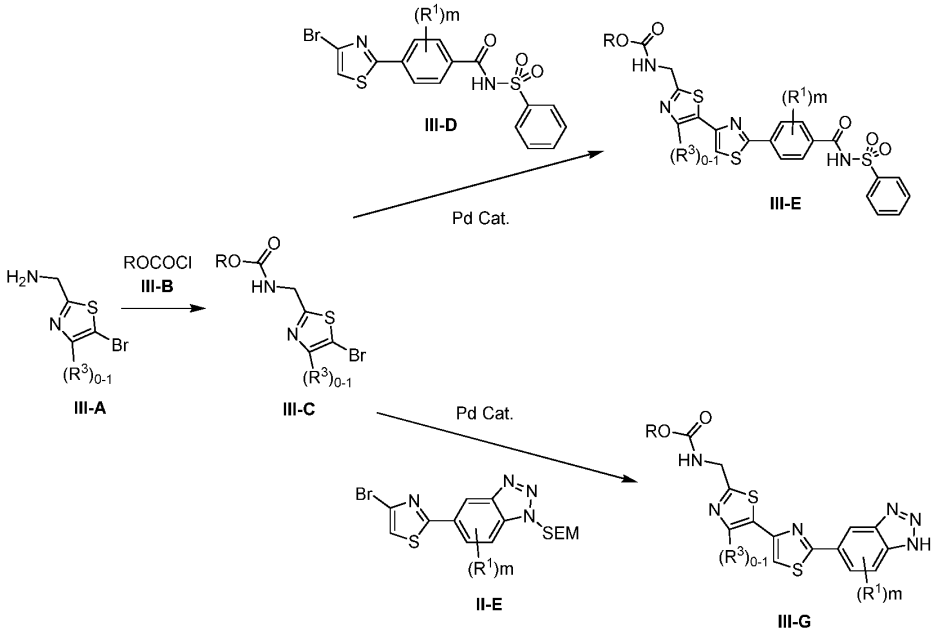
[0112] Scheme IB shows a route for preparing compounds of Formula (I) wherein Ring B is a heteroarylene group such as pyridinylene, Ar and Ar' represent aryl groups, and R is a non-aryl group, such as an alkyl group. In some embodiments, esterification of the hydroxyl group of compound I'-A is achieved under standard conditions, such as in the presence of ArCl to form compound I'-B or in the presence of R-LG (e.g. R-Cl) to form compound I'-D. Suzuki coupling with the appropriate boronic ester in the presence of an appropriate palladium catalyst achieves compound I'-C from compound I'-B or compound I'-E from compound I'-D.

Scheme II.



[0113] Scheme II shows a route for preparing compounds of Formula (I) wherein Rings A and B are each a heteroarylene group such as thiazolylene, Ring C is a phenylene or heteroarylene group, Ar represents an aryl group, and m, R^3, and R^1 are as defined herein. In some embodiments, esterification of compound II-A in the presence of, for example, ArCl or ArOH, under standard conditions achieves compound II-B. Compound II-B may be combined with compound II-C in the presence of an appropriate boronic ester (such as 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane) and a palladium catalyst to provide compound II-D. Compound II-E can be achieved according to methods such as those described in Example S6. Compound II-B may also be combined with compound II-E in the presence of an appropriate boronic ester (such as 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane) and a palladium catalyst. Subsequent deprotection under standard conditions provides compound II-D.

Scheme III.



[0114] Scheme III shows a route for preparing compounds of Formula (I) wherein Rings A and B are each a heteroarylene group such as thiazolylene, Ring C is a phenylene or heteroarylene group, Ar represents an aryl group, R is a C_{1-6} alkyl, and m, R^3, and R^1 are as defined herein. In some embodiments, coupling of compound III-A and compound III-B under standard conditions achieves compound II-B. Compound III-C may be combined with compound III-D in the presence of an appropriate boronic ester (such as 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane) and a palladium catalyst to provide compound III-E. Compound III-C may also be combined with compound II-

E in the presence of an appropriate boronic ester (such as 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane) and a palladium catalyst. Subsequent deprotection under standard conditions provides compound III-G.

[0115] It is understood that the synthetic processes disclosed herein may be modified to arrive at various compounds of the present disclosure by selection of appropriate reagents and starting materials. In some embodiments, the synthetic processes disclosed herein may be modified to arrive at compounds of Formula (I) having other substituents as those shown in the Schemes described herein by selection of appropriate reagents and starting materials.

[0116] All compounds of Formula (I) or any variation thereof as described herein which exist in free base or acid form can be converted to their pharmaceutically acceptable salts by treatment with the appropriate inorganic or organic base or acid by methods known to one skilled in the art. Salts of the compounds of the disclosure can be converted to their free base or acid form by standard techniques.

Pharmaceutical Compositions and Formulations

[0117] In another aspect, provided herein are pharmaceutical compositions of any of the compounds detailed herein. Thus, the present disclosure includes pharmaceutical compositions comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient. Pharmaceutical compositions according to the disclosure may take a form suitable for oral, buccal, parenteral, nasal, topical, or rectal administration, or a form suitable for administration by inhalation. Pharmaceutical compositions of the present disclosure comprise a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

[0118] A compound described herein can be used in the preparation of a composition, such as a pharmaceutical composition, by combining the compound as an active ingredient with a pharmaceutically acceptable excipient. Some examples of materials which can serve as pharmaceutically acceptable excipients include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; surfactants, such as polysorbate 80 (i.e., Tween 80); powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; pH buffered solutions; polyesters, polycarbonates and/or polyanhydrides; and other non-toxic compatible substances employed in pharmaceutical formulations. Pharmaceutical formulations may be prepared by known pharmaceutical methods. Suitable

formulations can be found in, for example, *Remington: The Science and Practice of Pharmacy*, Lippincott Williams & Wilkins, 21st ed. (2005), which is incorporated herein by reference.

[0119] Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

[0120] Examples of pharmaceutically-acceptable antioxidants include: water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol and the like; and metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid and the like.

[0121] Formulations of the present disclosure include those suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration. The amount of active ingredient that can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, this amount will range from about 1% to about 99% of active ingredient, or from about 5% to about 70%, or about 10% to about 30%.

[0122] In certain embodiments, a formulation of the present disclosure comprises an excipient selected from the group consisting of cyclodextrins, liposomes, micelle forming agents, e.g., bile acids and polymeric carriers, e.g., polyesters and polyanhydrides; and a compound of the present disclosure. In certain embodiments, an aforementioned formulation renders orally bioavailable a compound of the present disclosure.

[0123] Formulations of the disclosure suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules or as a solution or a suspension in an aqueous or non-aqueous liquid or as an oil-in-water or water-in-oil liquid emulsion or as an elixir or syrup or as pastilles (using an inert base, such as gelatin and glycerin or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present disclosure as an active ingredient. A compound of the present disclosure may also be administered as a bolus, electuary or paste.

[0124] In solid dosage forms of the disclosure for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the active ingredient is mixed with one or more pharmaceutically-

acceptable carriers, such as sodium citrate or dicalcium phosphate and/or any of the following: fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol and/or silicic acid; binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; humectants, such as glycerol; disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates and sodium carbonate; solution retarding agents, such as paraffin; absorption accelerators, such as quaternary ammonium compounds; wetting agents, such as, for example, cetyl alcohol, glycerol monostearate and non-ionic surfactants; absorbents, such as kaolin and bentonite clay; lubricants, such a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate and mixtures thereof; and coloring agents. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-shelled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

[0125] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made in a suitable machine in which a mixture of the powdered compound is moistened with an inert liquid diluent.

[0126] The tablets and other solid dosage forms of the pharmaceutical compositions of the present disclosure, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be formulated for rapid release, e.g., freeze-dried. They may be sterilized by, for example, filtration through a bacteria-retaining filter or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved in sterile water or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only or, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

[0127] Liquid dosage forms for oral administration of the compounds of the disclosure include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In

addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan and mixtures thereof.

[0128] Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

[0129] Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth and mixtures thereof.

[0130] Formulations of the pharmaceutical compositions of the disclosure for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more compounds of the disclosure with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

[0131] Dosage forms for the topical or transdermal administration of a compound of this disclosure include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically-acceptable carrier and with any preservatives, buffers or propellants which may be required.

[0132] The ointments, pastes, creams and gels may contain, in addition to an active compound of this disclosure, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide or mixtures thereof.

[0133] Powders and sprays can contain, in addition to a compound of this disclosure, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates, and polyamide powder or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

[0134] Pharmaceutical compositions of this disclosure suitable for parenteral administration comprise one or more compounds of the disclosure in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may

contain sugars, alcohols, antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

[0135] Examples of suitable aqueous and nonaqueous carriers, which may be employed in the pharmaceutical compositions of the disclosure include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol and the like) and suitable mixtures thereof, vegetable oils, such as olive oil and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

[0136] These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms upon the subject compounds may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenyl sorbic acid and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

[0137] In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

[0138] Injectable depot forms are made by forming microencapsule matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions, which are compatible with body tissue.

Methods of Use/Treatments

[0139] Compounds and compositions detailed herein, such as a pharmaceutical composition containing a compound of any formula provided herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient, may be used in methods of administration and treatment as provided herein. The compounds and compositions may also be used in *in vitro* methods, such as *in vitro* methods of administering a compound or composition to cells for screening purposes and/or for conducting quality control assays.

[0140] In one aspect, provided herein is a method of modulating bis-phosphoglycerate mutase (BPGM) comprising contacting either an effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or an effective amount of a pharmaceutical composition provided herein, with the BPGM. In certain embodiments, the compounds of the present disclosure are allosteric modulators of BPGM that affect both the synthase and phosphatase functions of the enzyme.

[0141] In another aspect, provided herein is a method of treating sickle cell disease in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound described here, or a pharmaceutically acceptable salt thereof, or a therapeutically effective amount of a pharmaceutical composition described herein. In some embodiments, the sickle cell disease is HbSS, also referred to as sickle cell anemia. In some embodiments, the sickle cell disease is HbSC. In some embodiments, the sickle cell disease is HbS beta thalassemia. In some embodiments, the sickle cell disease is HbSD, HbSE, or HbSO.

[0142] In some embodiments, the subject is a mammal. In some embodiments, the subject is a primate, dog, cat, rabbit, or rodent. In some embodiments, the subject is a primate. In some embodiments, the subject is a human. In some embodiments, the human is at least about or is about any of 18, 21, 30, 50, 60, 65, 70, 80, or 85 years old. In some embodiments, the human is a child. In some embodiments, the human is less than about or about any of 21, 18, 15, 10, 5, 4, 3, 2, or 1 years old.

Dosing and Method of Administration

[0143] The phrases "parenteral administration" and "administered parenterally" as used herein mean modes of administration other than enteral and topical administration, usually by injection and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticulare, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

[0144] The phrases "systemic administration," "administered systemically," "peripheral administration" and "administered peripherally" as used herein mean the administration of a compound, drug or other material other than directly into the central nervous system, such that it enters the patient's system and, thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

[0145] These compounds may be administered to humans and other animals for therapy by any suitable route of administration, including orally, nasally, as by, for example, a spray, rectally, intravaginally, parenterally, intracistemally and topically, as by powders, ointments or drops, including buccally and sublingually.

[0146] Regardless of the route of administration selected, the compounds of the present disclosure, or the pharmaceutical compositions of the present disclosure, are formulated into pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art.

[0147] Actual dosage levels of the active ingredients in the pharmaceutical compositions of this disclosure may be varied so as to obtain an amount of the active ingredient that is effective to achieve the desired therapeutic response for a particular patient, composition and mode of administration, without being toxic to the patient.

[0148] The selected dosage level will depend upon a variety of factors including the activity of the particular compound of the present disclosure employed or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion or metabolism of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated and like factors well known in the medical arts. A daily, weekly or monthly dosage (or other time interval) can be used.

[0149] A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the disclosure employed in the pharmaceutical composition at levels lower than that required to achieve the desired therapeutic effect and then gradually increasing the dosage until the desired effect is achieved.

[0150] In general, a suitable daily dose of a compound of the disclosure will be that amount of the compound that is the lowest dose effective to produce a therapeutic effect (e.g., inhibit necrosis). Such an effective dose will generally depend upon the factors described above. Generally doses of the compounds of this disclosure for a patient, when used for the indicated effects, will range from about 0.0001 to about 100 mg per kg of body weight per day. In some embodiments, the daily dosage will range from 0.001 to 50 mg of compound per kg of body weight, and in some embodiments, from 0.01 to 10 mg of compound per kg of body weight.

[0151] If desired, the effective daily dose of the active compound may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms.

[0152] In certain embodiments, the present disclosure relates to compounds for modulating BPGM, wherein the compounds are represented by Formula (I). In certain embodiments, the compounds of the present disclosure are allosteric modulators of BPGM that affect both the synthase and phosphatase functions of the enzyme. In any event, the compounds of the present disclosure, in some

embodiments,exert their effect on modulating BPGM at a concentration less than about 50 micromolar, or at a concentration less than about 10 micromolar or at a concentration less than 1 micromolar.

[0153] When the compounds of the present disclosure are administered as pharmaceuticals, to humans and animals, they can be given per se or as a pharmaceutical composition containing, for example, 0.1% to 99.5% (or, 0.5% to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

[0154] The compounds of the present application or the compositions thereof may be administered once, twice, three or four times daily, using any suitable mode described above. Also, administration or treatment with the compounds may be continued for a number of days; for example, commonly treatment would continue for at least 7 days, 14 days or 28 days, for one cycle of treatment. Treatment cycles are well known and are frequently alternated with resting periods of about 1 to 28 days, commonly about 7 days or about 14 days, between cycles. The treatment cycles, in certain embodiments, may also be continuous.

[0155] When administered orally, the total daily dosage for a human subject may be between 1 mg and 1,000 mg, between about 1,000-2,000 mg/day, between about 10-500 mg/day, between about 50-300 mg/day, between about 75-200 mg/day or between about 100-150 mg/day.

[0156] The daily dosage may also be described as a total amount of a compound described herein administered per dose or per day. Daily dosage of a compound may be between about 1 mg and 4,000 mg, between about 2,000 to 4,000 mg/day, between about 1 to 2,000 mg/day, between about 1 to 1,000 mg/day, between about 10 to 500 mg/day, between about 20 to 500 mg/day, between about 50 to 300 mg/day, between about 75 to 200 mg/day or between about 15 to 150 mg/day.

[0157] In certain embodiments, the method comprises administering to the subject an initial daily dose of about 1 to 800 mg of a compound described herein and increasing the dose by increments until clinical efficacy is achieved. Increments of about 5, 10, 25, 50 or 100 mg can be used to increase the dose. The dosage can be increased daily, every other day, twice per week or once per week.

[0158] In certain embodiments, a compound or pharmaceutical preparation is administered orally. In certain embodiments, the compound or pharmaceutical preparation is administered intravenously. Alternative routes of administration include sublingual, intramuscular and transdermal administrations.

[0159] The preparations of the present disclosure may be given orally, parenterally, topically or rectally. They are of course given in forms suitable for each administration route. For example, they are administered in tablets or capsule form, by injection, inhalation, eye lotion, ointment, suppository, etc. administration by injection, infusion or inhalation; topical by lotion or ointment; and rectal by suppositories. In certain embodiments, the administration is oral.

Kits/Articles of Manufacture

[0160] Also provided herein are kits that include a compound of the disclosure, or a pharmaceutically acceptable salt thereof, and suitable packaging. In certain embodiments, a kit further includes instructions for use. In one aspect, a kit includes a compound of the disclosure, or a pharmaceutically acceptable salt thereof, and a label and/or instructions for use of the compounds in the treatment of the indications, including the diseases or conditions, described herein.

[0161] Provided herein are also articles of manufacture that include a compound described herein, or a pharmaceutically acceptable salt thereof, in a suitable container. The container may be a vial, jar, ampoule, preloaded syringe and intravenous bag.

[0162] The kit can also contain instructions for using the compounds according to the disclosure. The kit can be compartmentalized to receive the containers in close confinement. As used herein, a kit such as a compartmentalized kit includes any kit in which compounds or agents are contained in separate containers. Illustrative examples of such containers include, but are not limited to, small glass containers, plastic containers or strips of plastic or paper. In some embodiments, the types of containers allow the skilled worker to efficiently transfer reagents from one compartment to another compartment such that the samples and reagents are not cross-contaminated and the agents or solutions of each container can be added in a quantitative fashion from one compartment to another. Such containers include, but are not limited to, a container that will accept a compound or combination of compounds and/or other agents of the disclosure. One or more compounds or agents can be provided as a powder (e.g. lyophilized powder) or precipitate. Such compound(s) can be resuspended prior to administration in a solution that may be provided as part of the kit or separately available. A kit can contain compounds or agents in other forms such as liquids, gels, solids, as described herein. Different compounds and/or agents may be provided in different forms in a single kit.

EXAMPLES

[0163] The examples and preparations provided below further illustrate and exemplify the compounds of the present disclosure and methods for testing such compounds. It is to be understood that the scope of the present disclosure is not limited in any way by the scope of the following examples.

[0164] The chemical reactions in the Examples described can be readily adapted to prepare a number of other compounds disclosed herein, and alternative methods for preparing the compounds of this disclosure are deemed to be within the scope of this disclosure. For example, the synthesis of non-exemplified compounds according to the present disclosure can be performed by modifications apparent to those skilled in the art, for example by appropriately protecting interfering groups, by utilizing other suitable reagents known in the art other than those described, or by making routine modification of reaction conditions, reagents, and starting materials. Alternatively, other reactions disclosed herein or

known in the art will be recognized as having applicability for preparing other compounds of the present disclosure.

[0165] The following abbreviations may be relevant for the application.

Abbreviations

ACN: acetonitrile

Bu: butyl

DCM: dichloromethane

DEAD: diethyl azodicarboxylate

DIAD: diisopropyl azodicarboxylate

DIEA: N,N-diisopropylethylamine

DMF: N,N-dimethylformamide

DMSO: dimethylsulfoxide

ES-MS: electrospray ionization mass spectrometry

EtOAc or EA: ethylacetate

EtOH: ethanol

HPLC: high performance liquid chromatography

LCMS: liquid chromatography-mass spectrometry

Me: methyl

MeOH: methanol

NBS: N-bromosuccinimide

NMR: nuclear magnetic resonance

OAc: acetate

$Pd(dppf)Cl_2.CH_2Cl_2$: [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II)

PE: petroleum ether

PPh_3: triphenylphosphine

sat.: saturated

SEM-Cl: 2-(trimethylsilyl)ethoxymethyl chloride

TBAF: tetra-n-butylammonium fluoride

TBSCl: tert-butyldimethylsilyl chloride

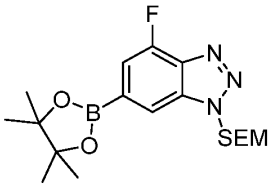
TFA: trifluoroacetic acid

THF: tetrahydrofuran

TLC: thin layer chromatography

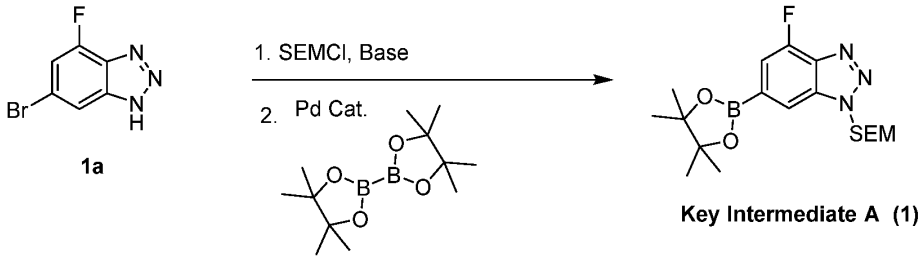
Synthetic Examples

[0166] Example S1. Preparation of 4-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d][1,2,3]triazole (1) (Key Intermediate A).

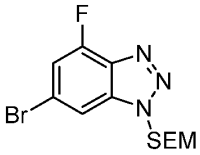


(1)

Scheme 1.



[0167] Step 1: Synthesis of 6-bromo-4-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d][1,2,3]triazole (1a).

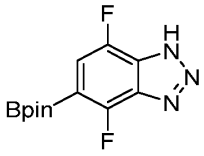


(1a)

To a solution of 5-bromo-7-fluoro-1H-benzotriazole (3 g, 12.50 mmol, 1 *eq*) in THF (100 mL) was added NaH (749.93 mg, 18.75 mmol, 60% purity, 1.5 *eq*). The mixture was stirred at 0 °C for 15 min. Then to the mixture was added SEM-Cl (3.13 g, 18.75 mmol, 3.32 mL, 1.5 *eq*). The mixture was stirred at 25 °C for 45 min. Water (40 mL) was added to the mixture. The mixture was extracted with ethyl acetate (40 mL x 2). The combined organic phase was washed with brine (40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuuo. The residue was purified with flash silica gel chromatography (ISCO®; 20 SepaFlash® Silica Flash Column, Eluent of 0~10% Petroleum/Ethyl acetate ether gradient @ 30 mL/min) to give 2-[(6-bromo-4-fluoro-benzotriazol-1-yl)methoxy]ethyl-trimethyl-silane **1a** (1.4 g, 3.64 mmol, 58.2% yield, 90% purity) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.70 (d, J = 1.2 Hz, 1H), 7.25 (dd, J = 9.2, 1.2 Hz, 1H), 5.96 (s, 2H), 3.56-3.61 (m, 2H), 0.89-0.95 (m, 2H), -0.04 (s, 9H).

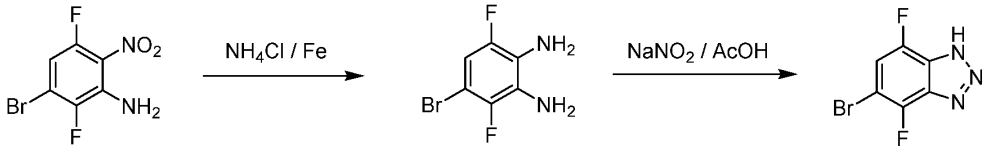
[0168] Step 2: Synthesis of 4-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d][1,2,3]triazole (1). A mixture of 2-[(6-bromo-4-fluoro-benzotriazol-1-yl)methoxy]ethyl-trimethyl-silane **1a** (600.00 mg, 1.56 mmol, 1 *eq*), potassium acetate (382.63 mg, 3.90 mmol, 2.5 *eq*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (514.82 mg, 2.03 mmol, 1.3 *eq*) and cyclopentyl(diphenyl)phosphane;dichloromethane;dichloropalladium; iron (127.35 mg, 155.95 µmol, 0.1 *eq*) in dioxane (8 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 12 h under N_2 atmosphere. Water (20 mL) was added to the mixture. The mixture was extracted with ethyl acetate (40 mL x 2). The combined organic phase was washed with brine (40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified with flash silica gel chromatography (ISCO®; 20g SepaFlash® Silica Flash Column, Eluent of 0~30% Petroleum/Ethyl acetate ether gradient @ 30 mL/min) to give 2-[[4-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzotriazol-1-yl]methoxy]ethyl-trimethyl-silane **1** (800 mg, 1.42 mmol, 91.3% yield, 70% purity) as a solid. ^{1}HNMR (400 MHz, $CDCl_3$) δ ppm 7.96 (s, 1H), 7.46 (d, J = 10.2 Hz, 1H), 6.01 (s, 2H), 3.58-3.64 (m, 2H), 1.39 (s, 12H), 0.89-0.95 (m, 2H), -0.05 (s, 9H).

[0169] Example S2. Preparation of 4,7-difluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzotriazole (2) (Key Intermediate B).

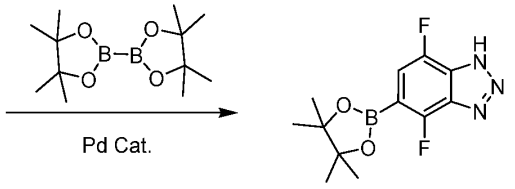


(2)

Scheme 2.

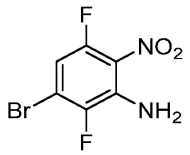


2a **2b** **2c**



Key Intermediate B (2)

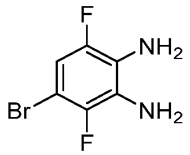
[0170] Step 1: Synthesis of 3-bromo-2,5-difluoro-6-nitro-aniline (2a).



(2a)

To a solution of 1-bromo-2,5-difluoro-4-nitro-benzene (5 g, 21.01 mmol, 1 *eq*) in DMSO (100 mL) was added amino(trimethyl)ammonium iodide (5.09 g, 25.21 mmol, 1.2 *eq*), then *t*-BuOK (9.43 g, 84.04 mmol, 4 *eq*) was added in one portion at 15 °C. After addition, the mixture was stirred at 15 °C for 15 min. TLC (PE/EtOAc = 10/1) showed the reaction was completed. The reaction mixture was quenched with 10% HCl (30 mL) to make pH = 4-5 at 10 °C, then the mixture was poured into water (400 mL) and extracted with EtOAc (300 mL x 3). The combined organic layers were washed with water (300 mL x 3), brine (300 mL x 3) and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified with flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~3.4% Ethyl acetate/Petroleum ether gradient @ 60 mL/min) to give 3-bromo-2,5-difluoro-6-nitro-aniline **2a** (1.8 g, 6.40 mmol, 15.2% yield, 90% purity) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.21 (s, 2H), 7.00 (dd, J = 5.6, 11.2 Hz, 1H).

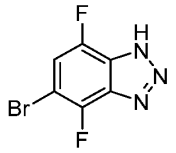
[0171] Step 2: Synthesis of 4-bromo-3,6-difluoro-benzene-1,2-diamine (2b).



(2b)

To a solution of 3-bromo-2,5-difluoro-6-nitro-aniline **2a** (2.6 g, 9.25 mmol, 1 *eq*) in EtOH (25 mL), THF (25 mL) and H_2O (15 mL) was added NH_4Cl (4.95 g, 92.49 mmol, 10 *eq*) and Fe power (5.17 g, 92.49 mmol, 10 *eq*). The reaction mixture was stirred at 55 °C for 2 h. TLC (PE/EtOAc = 10/1) showed the reaction was completed. The reaction mixture was filtered, filtrate was dried over Na_2SO_4, filtered and concentrated to give crude 4-bromo-3,6-difluoro-benzene-1,2-diamine **2b** (2 g, 8.07 mmol, 87.3% yield, 90% purity) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.64 (dd, J = 6.0, 10.0 Hz, 1H), 5.05 (br.s, 2H), 4.89 (br.s, 2H).

[0172] Step 3: Synthesis of 6-bromo-4,7-difluoro-1*H*-benzotriazole (2c)

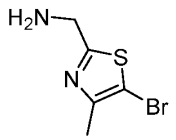


(2c)

To a solution of 4-bromo-3,6-difluoro-benzene-1,2-diamine **2b** (2 g, 8.97 mmol, 1 *eq*) in HOAc (15 mL) and H_2O (15 mL) was added HCl (12 M, 1.12 mL, 1.5 *eq*) and a solution of $NaNO_2$ (1.55 g, 22.42 mmol, 2.5 *eq*) in H_2O (15 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. TLC (PE/EtOAc = 1/1) showed the reaction was completed. The reaction mixture was poured into water (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with *sat.* $NaHCO_3$ (30 mL x 3) and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified with flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give 6-bromo-4,7-difluoro-1*H*-benzotriazole **2c** (1.6 g, 6.15 mmol, 68.6% yield, 90% purity) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.28 (dd, J = 4.4, 8.4 Hz, 1H).

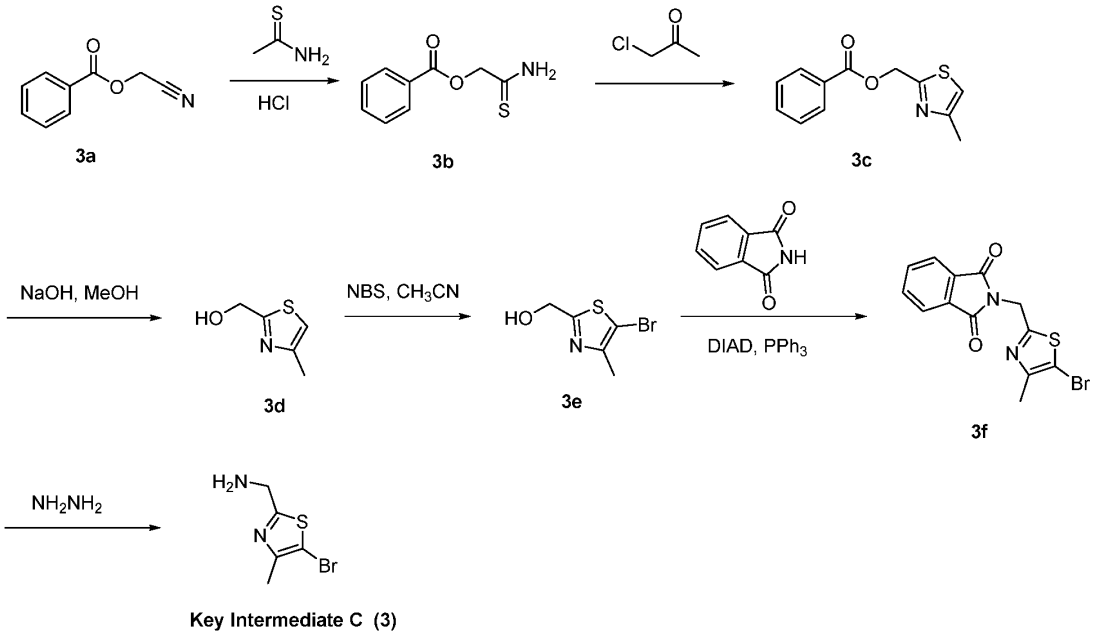
[0173] Step 4: Synthesis of 4,7-difluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzotriazole (2). A mixture of 6-bromo-4,7-difluoro-1*H*-benzotriazole **2c** (1.5 g, 5.77 mmol, 1 *eq*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (8.79 g, 34.62 mmol, 6 *eq*), Pd(dppf)Cl_2.CH_2Cl_2 (471.14 mg, 576.92 umol, 0.1 *eq*) and KOAc (4.53 g, 46.15 mmol, 8 *eq*) in DMSO (70 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 12 h. The reaction mixture was poured into water (200 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with water (100 mL x 3), brine (80 mL x 3) and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified with flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~28% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give 4,7-difluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzotriazole **2** (1.4 g, 3.74 mmol, 64.8% yield, 75% purity) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.37 (d, J = 9.6 Hz, 1H), 1.38 (s, 12H).

[0174] Example S3. Preparation of (5-bromo-4-methyl-thiazol-2-yl)methanamine (3) (Key Intermediate C).

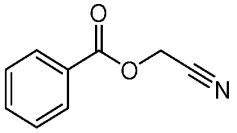


(3)

Scheme 3.



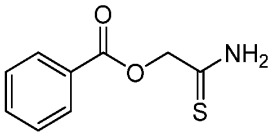
[0175] Step 1: Synthesis of cyanomethyl benzoate (3a).



(3a)

To a suspension of benzoic acid (500 g, 4.09 mol, 625.00 mL, 1 *eq*) in DMF (1500 mL), K_2CO_3 (700.00 g, 5.06 mol, 1.24 *eq*) was added and the mixture was stirred until the evolution of gas has ceased. The reaction mixture was cooled to 0°C and a solution of 2-bromoacetonitrile (491.10 g, 4.09 mol, 272.83 mL, 1 *eq*) in DMF (500 mL) was added drop-wise. The reaction mixture was stirred overnight (12 hr) at room temperature (25°C). TLC (Petroleum ether/Ethyl acetate=3/1) indicated the material was consumed completely and one new spot formed. The reaction mixture was filtered and diluted with H_2O (3000 mL) and extracted with EA (2000 mL × 2). The combined organic layers were washed with brine (2000 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure, the residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 5/1) to give cyanomethyl benzoate **3a** (650 g, 4.03 mol, 98.51% yield) as an oil. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.11 - 8.03 (m, 2H), 7.67 - 7.60 (m, 1H), 7.53 - 7.45 (m, 2H), 4.97 (s, 2H).

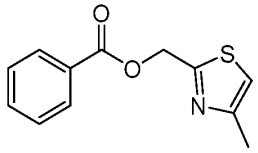
[0176] Step 2: Synthesis of (2-amino-2-thioxo-ethyl) benzoate (3b).



(3b)

Cyanomethyl benzoate **3a** (170 g, 1.05 mol, 1 *eq*) and thioacetamide (118.88 g, 1.58 mol, 1.5 *eq*) were dissolved in DMF (800 mL). HCl/dioxane (4 M, 1.02 L, 3.87 *eq*) was added and the mixture was heated at 100°C for 2 h. TLC (Petroleum ether/Ethyl acetate=1/1) indicated the material remained, and one major new spot with larger polarity was detected. The reaction mixture was reduced pressure to give a residue and then diluted with H_2O (1.2 L) and extracted with ethyl acetate (1.2 L × 2). The combined organic layers were washed with brine (1.2 L × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure and the crude product was triturated with Petroleum ether/Ethyl acetate=3/1 (300 mL) at 25°C for 30 min to give (2-amino-2-thioxo-ethyl) benzoate **3b** (130 g, crude) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.95 (br s, 1H), 9.37 (br s, 1H), 8.13 - 8.04 (m, 2H), 7.72 - 7.64 (m, 1H), 7.60 - 7.49 (m, 2H), 4.97 (s, 2H).

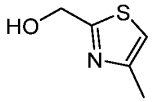
[0177] Step 3: Synthesis of (4-methylthiazol-2-yl)methyl benzoate (3c).



(3c)

To a solution of (2-amino-2-thioxo-ethyl) benzoate **3b** (900 g, 4.61 mol, 1 *eq*) in EtOH (9000 mL) was added 1-chloropropan-2-one (639.77 g, 6.91 mol, 1.5 *eq*). The mixture was stirred at 90°C for 12 hr. LCMS showed the material was consumed completely and one main peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The reaction mixture was diluted with H_2O (1000 mL) and extracted with Ethyl acetate (1000 mL × 2). The combined organic layers were washed with brine (1000 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give (4-methylthiazol-2-yl)methyl benzoate **3c** (1000 g, crude) as an oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.03 - 7.97 (m, 2H), 7.72 - 7.66 (m, 1H), 7.59 - 7.53 (m, 2H), 7.34 (d, *J* = 1.0 Hz, 1H), 5.58 (s, 2H), 2.37 (d, *J* = 0.9 Hz, 3H).

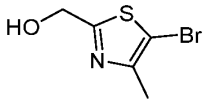
[0178] Step 4: Synthesis of (4-methylthiazol-2-yl)methanol (3d).



(3d)

To a solution of (4-methylthiazol-2-yl)methyl benzoate **3c** (250 g, 1.07 mol, 1 *eq*) in MeOH (1000 mL) was added NaOH (2 M, 1.25 L, 2.33 *eq*). The mixture was stirred at 25°C for 2 hr. TLC (Petroleum ether/Ethyl acetate=0/1) indicated the material was consumed completely and one new spot formed. The reaction mixture was diluted with H_2O (300 mL) and extracted with EA (300 mL × 2). The combined organic layers were washed with brine (300 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give (4-methylthiazol-2-yl)methanol **3d** (340 g, crude) as an oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.13 (d, *J* = 0.7 Hz, 1H), 5.96 (t, *J* = 5.9 Hz, 1H), 4.67 (d, *J* = 5.9 Hz, 2H), 2.32 (s, 3H).

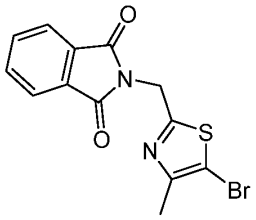
[0179] Step 5: Synthesis of (5-bromo-4-methyl-thiazol-2-yl)methanol (3e).



(3e)

To a solution of (4-methylthiazol-2-yl)methanol **3d** (100 g, 774.11 mmol, 1 *eq*) in MeCN (1000 mL) was added NBS (165.34 g, 928.94 mmol, 1.2 *eq*) at 0°C. The mixture was stirred at 25°C for 0.5 h. LCMS showed the material was consumed completely and one main peak with desired mass was detected. The reaction mixture was diluted with H_2O (500 mL) and extracted with EA (500 mL × 2). The combined organic layers were washed with brine (500 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue and purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 5/1) to give (5-bromo-4-methyl-thiazol-2-yl)methanol **3e** (106 g, 509.43 mmol, 65.81% yield) as a solid. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 4.83 (s, 2H), 3.40 - 3.12 (m, 1H), 2.36 (s, 3H).

[0180] Step 6: Synthesis of 2-[(5-bromo-4-methyl-thiazol-2-yl)methyl]isoindoline-1,3-dione (3f).

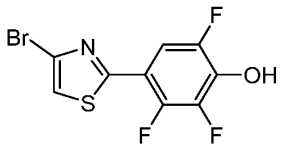


(3f)

To a solution of (5-bromo-4-methyl-thiazol-2-yl)methanol **3e** (3 g, 14.42 mmol, 1 eq), isoindoline-1,3-dione (2.76 g, 18.74 mmol, 1.3 eq) and triphenylphosphine (4.92 g, 18.74 mmol, 1.3 eq) in THF (40 mL). The mixture was stirred at 0°C for 0.5h. Then DIAD (3.79 g, 18.74 mmol, 3.64 mL, 1.3 eq) was added. The mixture was stirred at 25°C for 1.5 h. After completion, the reaction mixture was poured into ammonium chloride saturated aqueous solution (50 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~35% Ethyl acetate/Petroleum ether gradient @ 20 mL/min). The cut fraction was concentrated under reduced pressure to give 2-[(5-bromo-4-methyl-thiazol-2-yl)methyl]isoindoline-1,3-dione **3f** (7.5 g, 10.45 mmol, 72.51% yield, 47% purity) as a solid.

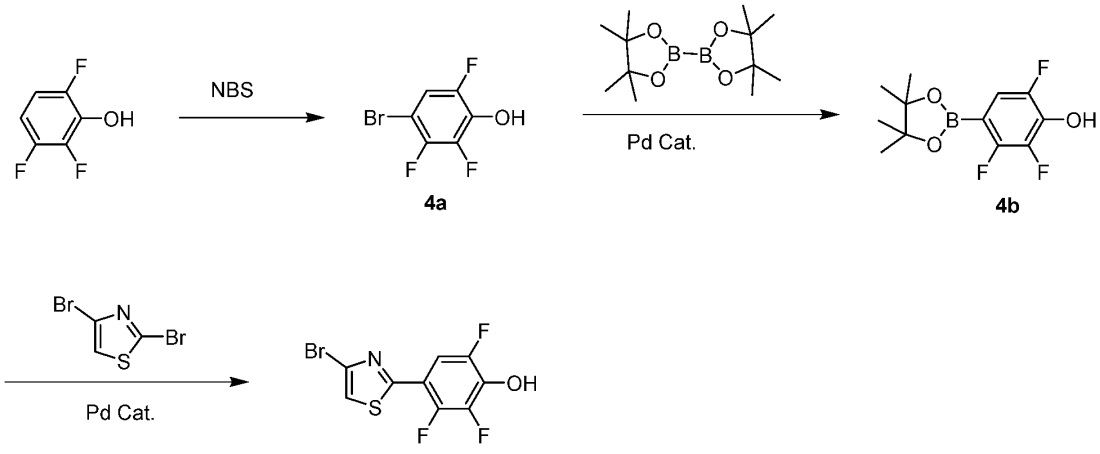
[0181] Step 7: Synthesis of (5-bromo-4-methyl-thiazol-2-yl)methanamine (3). To a solution of 2-[(5-bromo-4-methyl-thiazol-2-yl)methyl]isoindoline-1,3-dione **3f** (7.5 g, 10.45 mmol, 47% purity, 1 eq) in MeOH (150 mL) was added $NH_2NH_2.H_2O$ (7.85 g, 156.81 mmol, 7.62 mL, 15 eq). The mixture was stirred at 25°C for 16 h. After completion, the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The reaction mixture was poured into 1N HCl (30 mL) to pH=3. Next, EA (100 mL) was added to the mixture. Then aqueous phase was added to the 2N NaOH (50 mL) and extracted with ethyl acetate (100 mL x 3). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give (5-bromo-4-methyl-thiazol-2-yl)methanamine **3** (2.5 g, crude) as a solid. ^1H NMR (400MHz, DMSO-d_6) δ = 3.90 (s, 2H), 2.33 (s, 2H), 2.26 (s, 3H).

[0182] Example S4. Preparation of 4-(4-bromothiazol-2-yl)-2,3,6-trifluoro-phenol (4) (Key Intermediate D).



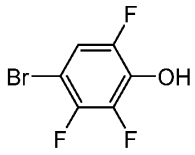
(4)

Scheme 4.



Key Intermediate D (4)

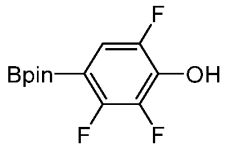
[0183] Step 1: Synthesis of 4-bromo-2,3,6-trifluoro-phenol (4a).



(4a)

A mixture of 2,3,6-trifluorophenol (20 g, 135.06 mmol, 1 *eq*), NBS (27.64 g, 155.32 mmol, 1.15 *eq*) in $CHCl_3$ (500 mL) was stirred at 0 °C for 2 h under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~15% Ethyl acetate/Petroleum ether gradient @ 80mL/min) to give 4-bromo-2,3,6-trifluoro-phenol **4a** (30 g, 118.95 mmol, 88.1% yield, 90% purity) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.16 (s, 1H), 7.67-7.42 (m, 1H).

[0184] Step 2: Synthesis of 2,3,6-trifluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (4b).



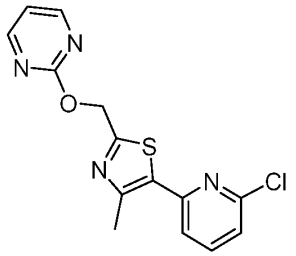
(4b)

A mixture of 4-bromo-2,3,6-trifluoro-phenol **4a** (10 g, 39.65 mmol, 1 *eq*), $Pd(dppf)Cl_2$ (1.45 g, 1.98 mmol, 0.05 *eq*), KOAc (9.73 g, 99.13 mmol, 2.5 *eq*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-

dioxaborolan-2-yl)-1,3,2-dioxaborolane (20.14 g, 79.30 mmol, 2 *eq*) in dioxane (250 mL) was degassed and purged with N_2 for 3 times, then the mixture was stirred at 80 °C for 12 h. The mixture was concentrated and then water (200 mL) was added then extracted with EtOAc (200 mL x 3). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified with flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient @ 60 mL/min) to give 2,3,6-trifluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol **4b** (4 g, 13.14 mmol, 33.1% yield, 90% purity) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.23 (s, 1H), 7.05-6.96 (m, 1H), 1.24 (s, 12H).

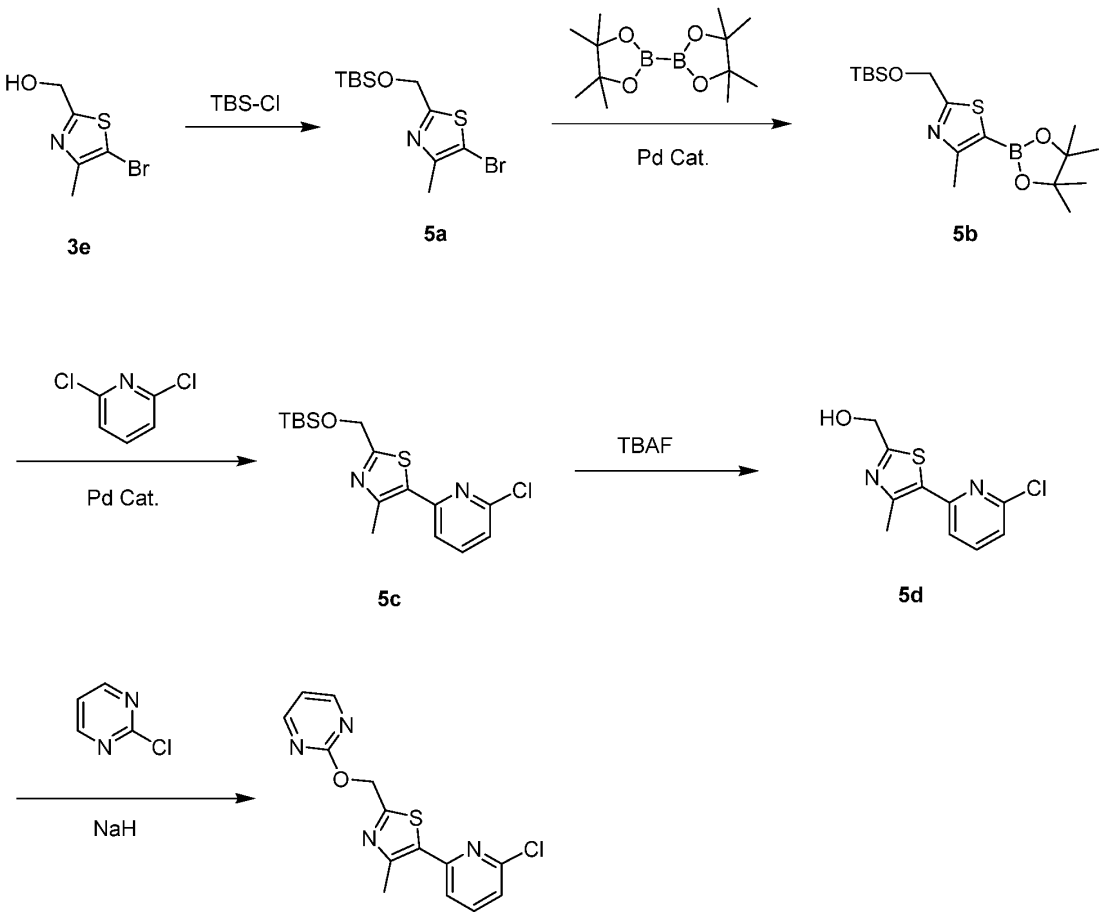
[0185] Step 3: Synthesis of 4-(4-bromothiazol-2-yl)-2,3,6-trifluoro-phenol (4). A mixture of 2,3,6-trifluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol **4b** (0.5 g, 1.64 mmol, 1 *eq*), Pd(dppf)Cl_2 (120.15 mg, 164.21 µmol, 0.1 *eq*), $K_3PO_4.3H_2O$ (1.31 g, 4.93 mmol, 3 *eq*), 2,4-dibromothiazole (1.20 g, 4.93 mmol, 3 *eq*) in dioxane (8 mL) and H_2O (2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 60 °C for 0.5 h under microwave (2 Bar). TLC (PE/EtOAc = 5/1) indicated the reaction was completed. The mixture was concentrated and water (200 mL) was added. The mixture was extracted with EtOAc (200 mL x 3). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified with flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 60 mL/min) to give 4-(4-bromothiazol-2-yl)-2,3,6-trifluoro-phenol **4** (0.28 g, 812.67 µmol, 49.5% yield, 90% purity) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.72 (br s, 1H), 8.05 (s, 1H), 7.74-7.71 (m, 1H).

[0186] Example S5. Preparation of 5-(6-chloro-2-pyridyl)-4-methyl-2-(pyrimidin-2-yloxymethyl)thiazole (5) (Key Intermediate E).

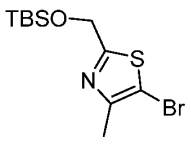


(5)

Scheme 5.



[0187] Step 1: Synthesis of 5-bromo-2-(((tert-butyldimethylsilyl)oxy)methyl)-4-methylthiazole (5a).

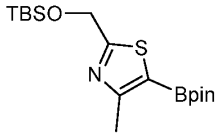


(5a)

To a solution of (5-bromo-4-methyl-thiazol-2-yl)methanol **3e** (40 g, 173.01 mmol, 1 *eq*) in anhydrous DCM (150 mL) was added TBSCl (33.90 g, 224.92 mmol, 27.56 mL, 1.3 *eq*) and imidazole (17.67 g, 259.52 mmol, 1.5 *eq*) at 0 °C. The mixture was warmed to 25 °C and stirred for 12 h. The reaction mixture was concentrated under reduced pressure to remove DCM. The residue was diluted with H_2O

(100 mL) and extracted with EtOAc (150 mL x 3). The combined organic layers were washed with brine (100 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~3% Ethyl acetate/Petroleum ether gradient @ 60 mL/min) to give (5-bromo-4-methyl-thiazol-2-yl)methoxy-tert-butyl-dimethyl-silane **5a** (57 g, 159.15 mmol, 92.0% yield, 90% purity) as an oil. ^{1}H NMR (400MHz, $CDCl_3$) δ ppm 4.85 (s, 2H), 2.36 (s, 3H), 0.95 (s, 9H), 0.13 (s, 6H).

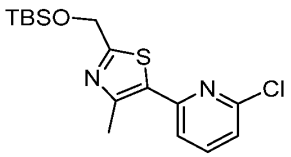
[0188] Step 2: Synthesis of 2-(((tert-butyldimethylsilyl)oxy)methyl)-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazole (5b).



(5b)

To a solution of (5-bromo-4-methyl-thiazol-2-yl)methoxy-*tert*-butyl-dimethyl-silane **5a** (10 g, 27.92 mmol, 1 *eq*) in anhydrous THF (200 mL) was added *n*-BuLi (2.5 M, 16.75 mL, 1.5 *eq*) dropwise at -78 °C under N_2. The reaction mixture was stirred at -78 °C for 0.5 h. 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (8.93 g, 69.80 mmol, 10.13 mL, 2.5 *eq*) was added to the mixture in dropwise at -78 °C for 0.5 h. After addition, the reaction was warmed to 25 °C and stirred for another 12 h. The reaction was quenched with saturated NH_4Cl (100 mL) at 0 °C and extracted with EtOAc (200 mL x 3) and washed with brine (500 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to give crude residue. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient @ 60 mL/min) to give 2-(((tert-butyldimethylsilyl)oxy)methyl)-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazole **5b** (6 g, 14.62 mmol, 52.4% yield, 90% purity) as an oil. ^{1}H NMR (400MHz, $CDCl_3$) *δ* ppm 4.95 (s, 2H), 2.60 (s, 3H), 1.34 (s, 12H), 0.96 (s, 9H), 0.13 (s, 6H).

[0189] Step 3: Synthesis of 2-(((tert-butyldimethylsilyl)oxy)methyl)-5-(6-chloropyridin-2-yl)-4-methylthiazole (5c).

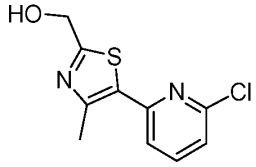


(5c)

To a solution of 2,6-dichloropyridine (2.34 g, 15.84 mmol, 1.3 *eq*) in dioxane (120 mL), H_2O (12 mL) was added 2-(((tert-butyldimethylsilyl)oxy)methyl)-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-

2-yl)thiazole **5b** (5 g, 12.18 mmol, 1 *eq*), Cs_2CO_3 (11.91 g, 36.55 mmol, 3 *eq*) and $Pd(dppf)Cl_2$ (534.81 mg, 730.91 μmol, 0.06 *eq*). The mixture was stirred at 90 °C for 2 h under N_2 atmosphere. The reaction was diluted with water (100 mL) and extracted with EtOAc (80 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethylacetate/Petroleum ethergradient @ 35mL/min) to give 2-(((tert-butyldimethylsilyl)oxy)methyl)-5-(6-chloropyridin-2-yl)-4-methylthiazole **5c** (1.9 g, 4.82 mmol, 39.5% yield, 90% purity) as an oil. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.68 (t, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.21 (d, *J* = 7.6 Hz, 1H), 4.94 (s, 2H), 2.67 (s, 3H), 0.97 (s, 9H), 0.16 (s, 6H).

[0190] Step 4: Synthesis of [5-(6-chloro-2-pyridyl)-4-methyl-thiazol-2-yl]methanol (5d).



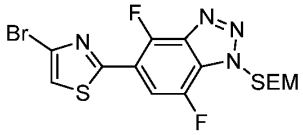
(5d)

To a solution of 2-(((tert-butyldimethylsilyl)oxy)methyl)-5-(6-chloropyridin-2-yl)-4-methylthiazole **5c** (1.9 g, 4.82 mmol, 1 *eq*) in THF (15 mL) was added TBAF (1 M, 5.78 mL, 1.2 *eq*). The mixture was stirred at 25 °C for 1 h under N_2 atmosphere. TLC (EtOAc) indicated the starting material was consumed. The reaction mixture was concentrated under reduced pressure to give residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 100% Ethyl acetate gradient @ 30 mL/min) to give [5-(6-chloro-2-pyridyl)-4-methyl-thiazol-2-yl]methanol **5d** (1 g, 3.74 mmol, 77.6% yield, 90% purity) as a solid. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.70 (t, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 4.93 (d, *J* = 6.0 Hz, 2H), 2.69 (s, 3H).

[0191] Step 5: Synthesis of 5-(6-chloro-2-pyridyl)-4-methyl-2-(pyrimidin-2-yloxymethyl)thiazole (5). To a solution of [5-(6-chloro-2-pyridyl)-4-methyl-thiazol-2-yl]methanol **5d** (1 g, 3.74 mmol, 1 *eq*) in anhydrous DMF (10 mL) was added NaH (164.50 mg, 4.11 mmol, 60% purity, 1.1 *eq*). The mixture was stirred at 0 °C for 15 min. Then 2-chloropyrimidine (1.28 g, 11.22 mmol, 3 *eq*) was added to the mixture at 0 °C. After addition, the mixture was stirred at 25 °C for 45 min. TLC (Petroleum ether/EtOAc = 1:1) indicated one major new spot formed. Water (40 mL) was added and extracted with ethyl acetate (40mL x 2). The combined organic phase was washed with brine (40 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~70% EtOAc/PE ethergradient @30 mL/min) to give 5-(6-chloro-2-pyridyl)-4-methyl-2-(pyrimidin-2-

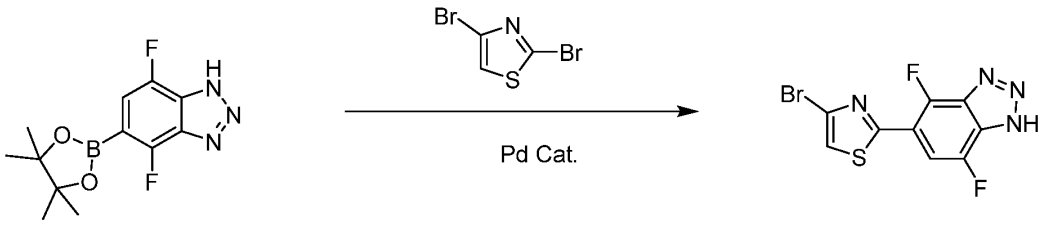
yloxymethyl)thiazole **5** (700 mg, 1.98 mmol, 52.9% yield, 90% purity) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.58 (d, *J* = 4.8 Hz, 2H), 7.68 (t, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.02 (t, *J* = 4.8 Hz, 1H), 5.71 (s, 2H), 2.71 (s, 3H).

[0192] Example S6. Preparation of 2-[[5-(4-bromothiazol-2-yl)-4,7-difluoro-benzotriazol-2-yl]methoxy]ethyl-trimethyl-silane (6) (Key Intermediate F).

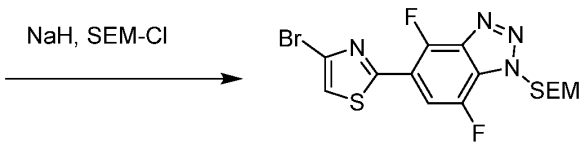


(6)

Scheme 6.

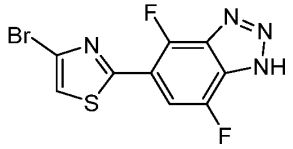


Key Intermediate B (2)



Key Intermediate F (6)

[0193] Step 1: Synthesis of 4-bromo-2-(4,7-difluoro-1H-benzotriazol-5-yl)thiazole (6a).



(6a)

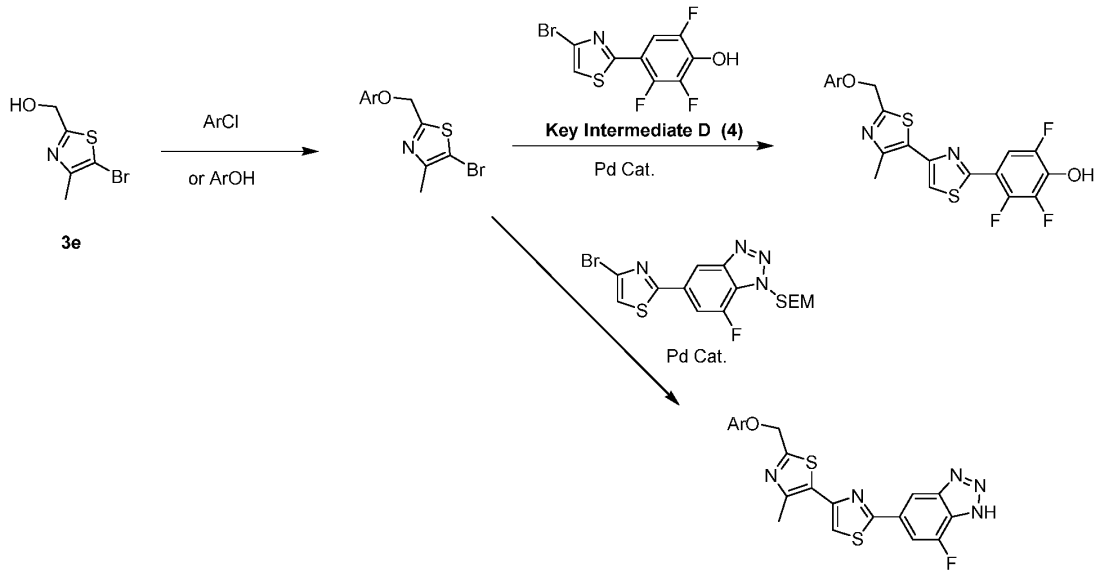
A mixture of 4,7-difluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzotriazole **Key Intermediate B (2)** (8 g, 28.46 mmol, 1 *eq*), 2,4-dibromothiazole (13.83 g, 56.93 mmol, 2 *eq*), Na_2CO_3 (9.05 g, 85.39 mmol, 3 *eq*) and $Pd(dppf)Cl_2.CH_2Cl_2$ (2.32 g, 2.85 mmol, 0.1 *eq*) in dioxane (100 mL) and H_2O (25 mL) was degassed and charged with N_2 three times. The reaction mixture was stirred at 80°C for

12 h under N_2. LCMS showed 22% of desired was observed. Ice-water (300 mL) was added, acidified by 1N HCl (~180 mL) to pH=5, extracted with EtOAc (500 mL x 2), washed with brine (300 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude. Then purified by reversed-phase HPLC (0.1% FA condition) to give 4-bromo-2-(4,7-difluoro-1H-benzotriazol-5-yl)thiazole **6a** (1.3 g, 4.10 mmol, 14.40% yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d6) δ = 8.13 (s, 1H), 7.95 - 7.90 (m, 1H).

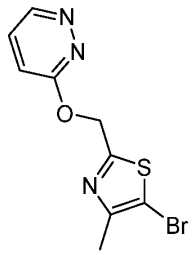
[0194] Step 2: Synthesis of 2-[[5-(4-bromothiazol-2-yl)-4,7-difluoro-benzotriazol-2-yl]methoxy]ethyl-trimethyl-silane (6). To a suspension of NaH (416.22 mg, 10.41 mmol, 60% purity, 3 *eq*) in THF (7 mL) was added a solution of 4-bromo-2-(4,7-difluoro-1H-benzotriazol-5-yl)thiazole **6a** (1.1 g, 3.47 mmol, 1 *eq*) in THF (7 mL) at 0°C under N_2 atmosphere. The mixture was stirred at 0°C for 30 min, then SEM-Cl (751.82 mg, 4.51 mmol, 798.11 uL, 1.3 *eq*) was added. The resulting mixture was stirred at 0 °C under N_2 atmosphere for 30 min. TLC showed material was consumed and some new spots formed. The reaction mixture was quenched with *sat.* NH_4Cl (20 mL) solution and extracted with ethyl acetate (20 mL x 2), the organic layer was dried over Na_2SO_4, filtered, filtrate was concentrated under reduced pressure. The residue was purified with flash silica gel chromatography (Eluent of 0~10% Ethyl acetate/Petroleum ether) to give 2-[[5-(4-bromothiazol-2-yl)-4,7-difluoro-benzotriazol-2-yl]methoxy]ethyl-trimethyl-silane **6** (550 mg, 1.23 mmol, 35.44% yield) as a solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.06 (dd, *J*=4.6, 10.6 Hz, 1H), 7.44 (s, 1H), 6.03 (s, 2H), 3.84 - 3.77 (m, 2H), 1.03 - 0.97 (m, 2H), 0.00 (s, 9H).

[0195] Example S7. Preparation of 5-[2-(7-fluoro-1*H*-benzotriazol-5-yl)thiazol-4-yl]-4-methyl-2-(pyridazin-3-yloxymethyl)thiazole (7).

General Scheme for Compounds 7, 10 and 11.



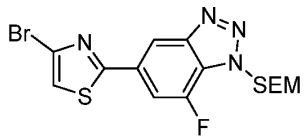
[0196] Step 1: Synthesis of 5-bromo-4-methyl-2-(pyridazin-3-yloxymethyl)thiazole (7a).



(7a)

To a mixture of (5-bromo-4-methyl-thiazol-2-yl)methanol **3e** (0.6 g, 2.60 mmol, 1 *eq*) in THF (15 mL) was added NaH (311.39 mg, 7.79 mmol, 60% purity, 3 *eq*) and purged with N_2 for 3 times, and then the mixture was stirred at 20 °C for 0.5 h. 3-Chloropyridazine (356.68 mg, 3.11 mmol, 1.2 *eq*) was added to the reaction mixture, the mixture was stirred at 20 °C for 12 h. The reaction mixture was quenched with addition of water (50 mL) at 0 °C. The mixture was extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified with flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~70% Ethylacetate/Petroleum ether gradient @ 40 mL/min) to give 5-bromo-4-methyl-2-(pyridazin-3-yloxymethyl)thiazole **7a** (110 mg, 345.97 µmol, 13.3% yield, 90% purity) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.97 (d, J = 4.4 Hz, 1H), 7.71 (dd, J = 4.4, 9.0 Hz, 1H), 7.36 (dd, J = 1.4, 8.8 Hz, 1H), 5.74 (s, 2H), 2.34 (s, 3H).

[0197] Step 2: Synthesis of 2-[[5-(4-bromothiazol-2-yl)-7-fluoro-benzotriazol-1-yl]methoxy]ethyl-trimethyl-silane (7b).

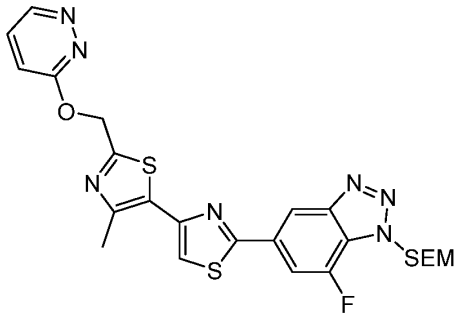


(7b)

A mixture of 2-[[7-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzotriazol-1-yl]methoxy]ethyl-trimethyl-silane **Key Intermediate A (1)** (0.6 g, 1.22 mmol, 1 *eq*), Pd(dppf)Cl_2 (89.29 mg, 122.03 µmol, 0.1 *eq*), $K_3PO_4{\cdot}3H_2O$ (974.96 mg, 3.66 mmol, 3 *eq*), 2,4-dibromothiazole (741.11 mg, 3.05 mmol, 2.5 *eq*) in dioxane (8 mL) and H_2O (2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 60 °C for 0.5 h under microwave (1bar). The mixture was concentrated and then water (100 mL) was added. The mixture was extracted with EtOAc (80 mL x 3). The combined organic layers were washed with brine (80 mL), dried over Na_2SO_4, filtered and concentrated. The residue

was purified with flash silica gel chromatography (ISCO®; 24 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethylacetate/Petroleum ether gradient @ 40 mL/min) to give 2-[[5-(4-bromothiazol-2-yl)-7-fluoro-benzotriazol-1-yl]methoxy]ethyl-trimethyl-silane **7b** (0.51 g, 1.07 mmol, 87.6% yield, 90% purity) as a solid. ^{1}HNMR (400 MHz, DMSO-d_6) δ ppm 8.55 (s, 1H), 8.02 (s, 2H), 6.10 (s, 2H), 3.62 (t, J = 8.0 Hz, 2H), 0.85 (t, J = 8.0 Hz, 2H), 0.09 (s, 9H).

[0198] Step 3: Synthesis of 2-[[7-fluoro-5-[4-[4-methyl-2-(pyridazin-3-yloxymethyl)thiazol-5-yl]thiazol-2-yl]benzotriazol-1-yl]methoxy]ethyl-trimethyl-silane (7c).



(7c)

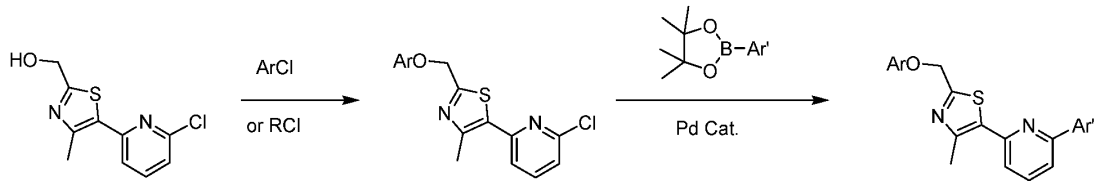
A mixture of bis(1-adamantyl)-butyl-phosphane (22.55 mg, 62.88 µmol, 0.2 *eq*) and diacetoxypalladium (14.12 mg, 62.88 µmol, 0.2 *eq*) in toluene (3 mL) was stirred at 20 °C for 0.5 h under N_2 atmosphere. The mixture was added to a mixture of 2-[[5-(4-bromothiazol-2-yl)-7-fluoro-benzotriazol-1-yl]methoxy]ethyl-trimethyl-silane **7b** (150 mg, 314.41 µmol, 1 *eq*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (319.36 mg, 1.26 mmol, 4 *eq*), CsF (143.27 mg, 943.22 µmol, 34.78 µL, 3 *eq*), 5-bromo-4-methyl-2-(pyridazin-3-yloxymethyl)thiazole **7a** (149.94 mg, 471.61 µmol, 1.5 *eq*) in MeOH (6 mL) was stirred at 50 °C for 0.5 h, the mixture was stirred at 80 °C for 12 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified with prep-HPLC (column: Boston Prime C18 150*30mm*5um; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 75%-95%,10min) to give 2-[[7-fluoro-5-[4-[4-methyl-2-(pyridazin-3-yloxymethyl)thiazol-5-yl]thiazol-2-yl]benzotriazol-1-yl]methoxy]ethyl-trimethyl-silane **7c** (50 mg, 80.98 µmol, 25.8% yield, 90% purity) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.09 (dd, J = 1.2, 4.4 Hz, 1H), 8.68 (d, J = 1.0 Hz, 1H), 8.28-8.12 (m, 2H), 7.83 (dd, J = 4.4, 8.8 Hz, 1H), 7.51 (dd, J = 1.2, 8.8 Hz, 1H), 6.22 (s, 2H), 5.92 (s, 2H), 3.74 (t, J = 8.0 Hz, 2H), 2.78 (s, 3H), 0.96 (t, J = 8.0 Hz, 2H), 0.00 (s, 9H).

[0199] Step 3: Synthesis of 5-[2-(7-fluoro-1*H*-benzotriazol-5-yl)thiazol-4-yl]-4-methyl-2-(pyridazin-3-yloxymethyl)thiazole (7). A mixture of 2-[[7-fluoro-5-[4-[4-methyl-2-(pyridazin-3-yloxymethyl)thiazol-5-yl]thiazol-2-yl]benzotriazol-1-yl]methoxy]ethyl-trimethyl-silane **7c** (50 mg, 80.98

μmol, 1 *eq*), TBAF (1 M in THF, 1.07 mL, 13.23 *eq*) in THF (2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 60 °C for 12 h. The mixture was concentrated and then water (10 mL) was added. The mixture was extracted with DCM (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified with prep-HPLC (column: Boston Prime C18 150*30mm*5um; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 25%-45%,10min) to give 5-[2-(7-fluoro-1*H*-benzotriazol-5-yl)thiazol-4-yl]-4-methyl-2-(pyridazin-3-yloxymethyl)thiazole **7** (31.4 mg, 72.37 umol, 89.4% yield, 98.06% purity) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.99 (dd, J = 1.4, 4.4 Hz, 1H), 8.29 (s, 1H), 8.04 (s, 1H), 7.80 (d, J = 10.8 Hz, 1H), 7.72 (dd, J = 4.8, 8.8 Hz, 1H), 7.41 (dd, J = 1.4, 8.8 Hz, 1H), 5.81 (s, 2H), 2.67 (s, 3H); HPLC (98.06% purity); ES-MS m/z 448.0 $[M+23]^+$.

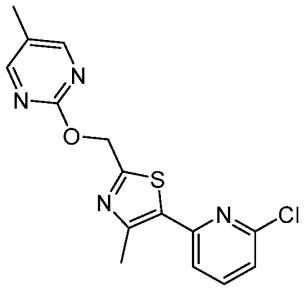
[0200] Example S8. Preparation of 5-[6-(4,7-difluoro-3H-benzotriazol-5-yl)-2-pyridyl]-4-methyl-2-[(5-methyl -pyrimidin-2-yl)oxymethyl]thiazole (8).

General Scheme for Compounds 8, 9, 12, 14, and 15.



5d

[0201] Step 1: Synthesis of 5-(6-chloro-2-pyridyl)-4-methyl-2-[(5-methylpyrimidin-2-yl)oxymethyl]thiazole (8a).



(8a)

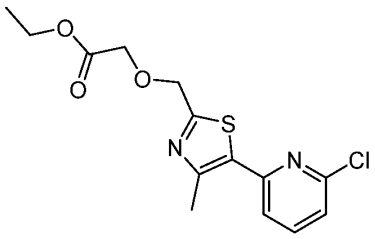
To a solution of [5-(6-chloro-2-pyridyl)-4-methyl-thiazol-2-yl]methanol **5d** (1 g, 4.15 mmol, 1 *eq*) in DMF (10 mL) was added NaH (332.32 mg, 8.31 mmol, 60% purity, 2 *eq*) at 0°C and stirred for 0.5h, and 2-chloro-5-methyl-pyrimidine (1.34 g, 10.39 mmol, 2.5 *eq*) was added. The mixture was stirred at 20°C for 2h. LCMS showed desired MS was detected. The reaction mixture was poured into ammonium chloride saturated aqueous solution (50 mL) and extracted with ethyl acetate (50 mL*3). The combined

organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography (SiO_2, DCM/MeOH=0/1 to 10/1) to give 5-(6-chloro-2-pyridyl)-4-methyl-2-[(5-methylpyrimidin-2-yl)oxymethyl]thiazole **8a** (0.8 g, 2.40 mmol, 57.86% yield) as a solid. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.31 (s, 2H), 7.60 (t, J = 7.8 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.13 (d, J = 7.9 Hz, 1H), 5.60 (s, 2H), 2.63 (s, 3H), 2.19 (s, 3H).

[0202] Step 2: Synthesis of 5-[6-(4,7-difluoro-3H-benzotriazol-5-yl)-2-pyridyl]-4-methyl-2-[(5-methyl -pyrimidin-2-yl)oxymethyl]thiazole (8). A mixture of 5-(6-chloro-2-pyridyl)-4-methyl-2-[(5-methylpyrimidin-2-yl)oxymethyl]thiazole **8a** (0.5 g, 1.50 mmol, 1 *eq*), 4,7-difluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) -1H-benzotriazole (**2**, **Key Intermediate B**, 760.08 mg, 2.70 mmol, 1.8 *eq*), Pd(dppf)Cl_2 (109.93 mg, 150.24 umol, 0.1 *eq*) and Cs_2CO_3 (1.22 g, 3.76 mmol, 2.5 *eq*) in dioxane (6 mL) and H_2O (2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100°C for 12 hr under N_2 atmosphere. LCMS showed desired MS was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~15% DCM/MeOH ethergradient @ 70 mL/min). The cut fraction was concentrated under reduced pressure to give the crude product. The crude product was purified by triturated with MeOH (10 mL). Then filter cake was collected and concentrated under reduced pressure to give product. The crude product was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~15% DCM/EA ether gradient @ 50 mL/min). The cut fraction was concentrated under reduced pressure to give 5-[6-(4,7-difluoro-3H-benzotriazol-5-yl)-2-pyridyl]-4-methyl-2-[(5-methylpyrimidin-2-yl)oxymethyl]thiazole **8** (250 mg, 553.77 umol, 36.86% yield, 98.20% purity) as a solid. ^{1}H NMR (400 MHz, DMSO-d6) δ = 8.51 (s, 2H), 8.12 - 8.04 (m, 1H), 7.92 (dd, J = 1.5, 7.8 Hz, 1H), 7.86 - 7.75 (m, 2H), 5.64 (s, 2H), 2.71 (s, 3H), 2.21 (s, 3H); HPLC (98.20% purity); ES-MS m/z 452.2 $[M+H]^+$.

[0203] Example S9. Preparation of 1-[[5-[6-(4,7-difluoro-3H-benzotriazol-5-yl)-2-pyridyl]-4-methyl-thiazol-2-yl]methoxy]-2-methyl-propan-2-ol (9).

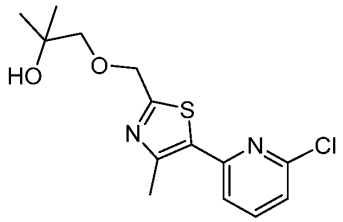
[0204] Step 1: Synthesis of ethyl 2-[[5-(6-chloro-2-pyridyl)-4-methyl-thiazol-2-yl]methoxy]acetate (9a).



(9a)

A mixture of [5-(6-chloro-2-pyridyl)-4-methyl-thiazol-2-yl]methanol (from **Example S5**, intermediate **5d**, 1 g, 4.15 mmol, 1 *eq*) in DMF (6 mL) cooled to 0 °C was added NaH (332.35 mg, 8.31 mmol, 60% purity, 2 *eq*) in portions under N_2 atmosphere. The mixture was stirred at 0°C for 15 min under N_2 atmosphere. Then a solution ethyl 2-bromoacetate (901.92 mg, 5.40 mmol, 597.30 uL, 1.3 *eq*) was added dropwise to the mixture. The whole mixture was stirred at 0°C for 1 h under N_2 atmosphere. Then the whole mixture was stirred at 25°C for 1 h under N_2 atmosphere. LCMS showed material was consumed completely and one main peak with desired MS was detected. TLC (PE:EA=1:1) indicated material was consumed completely and one new spot formed. The reaction mixture was quenched by addition NH_4Cl solution (15 mL) at 0°C, and then extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue and purified by flash silica gel chromatography (Eluent of 0~35% Ethyl acetate/Petroleum ether gradient) to give ethyl 2-[[5-(6-chloro-2-pyridyl)-4-methyl-thiazol-2-yl]methoxy]acetate **9a** (600 mg, 1.84 mmol, 44.19% yield) as an oil. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.70 (t, *J* = 7.8 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.24 (d, *J* = 7.5 Hz, 1H), 4.92 (s, 2H), 4.30 - 4.20 (m, 4H), 2.71 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H).

[0205] Step 2: Synthesis of 1-[[5-(6-chloro-2-pyridyl)-4-methyl-thiazol-2-yl]methoxy]-2-methyl-propan-2-ol (9b).



(9b)

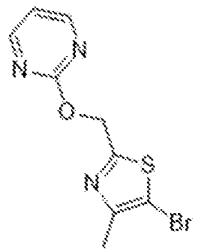
To a solution of ethyl 2-[[5-(6-chloro-2-pyridyl)-4-methyl-thiazol-2-yl]methoxy]acetate **9a** (600 mg, 1.84 mmol, 1 *eq*) in THF (10 mL) at 0°C was added MeMgBr (3 M, 1.84 mL, 3 *eq*) dropwise. The mixture was stirred at 25°C for 3 h. TLC (PE:EA=0:1) indicated material was consumed completely and one new main spot formed. LCMS showed material was consumed completely and one main peak with desired MS was detected. The reaction mixture was quenched by addition NH_4Cl saturated solution (5 mL) at 0°C, and then diluted with water (15 mL) and extracted with ethyl acetate (20 mL X 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. Then purified by flash silica gel chromatography (Eluent of 10~40% Ethyl acetate/Petroleum ether gradient) to give 1-[[5-(6-chloro-2-pyridyl)-4-methyl-thiazol-2-yl]methoxy]-2-methyl-propan-2-ol **9b** (350 mg, 1.12 mmol, 60.94% yield) as an oil. ^{1}H NMR (400 MHz,

CHLOROFORM-d) δ = 7.72 (t, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.25 (s, 1H), 4.91 (s, 2H), 3.50 (s, 2H), 2.79 - 2.67 (m, 3H), 1.27 (s, 6H).

[0206] Step 3: Synthesis of 1-[[5-[6-(4,7-difluoro-3H-benzotriazol-5-yl)-2-pyridyl]-4-methyl-thiazol-2-yl]methoxy]-2-methyl-propan-2-ol (9). A mixture of 1-[[5-(6-chloro-2-pyridyl)-4-methyl-thiazol-2-yl]methoxy]-2 -methyl-propan-2-ol **9b** (87 mg, 278.12 umol, 1 eq), 4,7-difluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzotriazole (**2**, **Key Intermediate B**, 156.34 mg, 556.24 umol, 2 eq), Cs_2CO_3 (271.85 mg, 834.36 umol, 3 eq) and $Pd(dppf)Cl_2.CH_2Cl_2$ (113.56 mg, 139.06 umol, 0.5 eq) in dioxane (1 mL)/H_2O (0.2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 105°C for 12 h under N_2 atmosphere. LCMS showed material was consumed completely and desired compound was detected. The reaction mixture was filtered and concentrated under reduced pressure to give a residue and purified by prep-HPLC (basic condition: column: Waters Xbridge C18 150*50mm* 10um; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 5%-35%,11min). Then re-purified by prep-TLC (SiO_2, Ethyl acetate : MeOH = 4:1) to give 1-[[5-[6-(4,7-difluoro-3H-benzotriazol-5-yl)-2-pyridyl]-4-methyl-thiazol-2-yl]methoxy]-2-methyl-propan-2-ol **9** (35 mg, 77.79 umol, 6.99% yield, 95.9% purity) as a solid. ^1H NMR (400 MHz, DMSO-d6) δ = 8.10 - 8.03 (m, 1H), 7.91 (dd, J = 1.4, 7.9 Hz, 1H), 7.81 - 7.74 (m, 2H), 4.80 (s, 2H), 4.47 (s, 1H), 3.36 (br s, 2H), 2.69 (s, 3H), 1.13 (s, 6H); HPLC (95.91% purity); ES-MS m/z 432.4 $[M+H]^+$.

[0207] Example S10. Preparation of 2,3,6-trifluoro-4-[4-[4-methyl-2-(pyrimidin-2-yloxymethyl)thiazol-5-yl]thiazol-2-yl]phenol (10).

[0208] Step 1: Synthesis of 5-bromo-4-methyl-2-(pyrimidin-2-yloxymethyl)thiazole (10a).



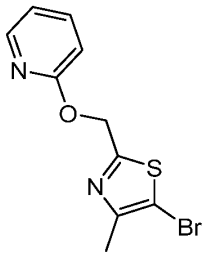
[0209] To a mixture of (5-bromo-4-methyl-thiazol-2-yl)methanol **3e** (500 mg, 2.40 mmol, 1 eq) in THF (12.5 mL) was added NaH (144.00 mg, 3.60 mmol, 60% purity, 1.5 eq) at 0°C and purged with N_2 for 3 times, and then the mixture was stirred at 15°C for 0.5 h. 2-chloropyrimidine (329.86 mg, 2.88 mmol, 1.2 eq) was added to the reaction mixture, the mixture was stirred at 15°C for 12 h. TLC (PE/EtOAc=2:1) showed a new spot was formed, and the desired MS was observed on LCMS. The reaction mixture was poured into ice-water (30 mL), extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by clumn chromatography (SiO_2, PE/EtOAc=4:1) to give 5-bromo-4-methyl-2-(pyrimidin-2-

yloxymethyl)thiazole **10a** (534 mg, 1.87 mmol, 77.76% yield) as a solid. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.58 (d, J = 4.6 Hz, 2H), 7.03 (t, J = 4.8 Hz, 1H), 5.63 (s, 2H), 2.41 (s, 3H).

[0210] Step 2: Synthesis of 2,3,6-trifluoro-4-[4-[4-methyl-2-(pyrimidin-2-yloxymethyl)thiazol-5-yl]thiazol-2-yl]phenol (10). A mixture of bis(1-adamantyl)-butyl-phosphane (62.44 mg, 174.14 mol, 0.2 *eq*) and $Pd(OAc)_2$ (19.55 mg, 87.07 µmol, 0.1 *eq*) in anhydrous toluene (30 mL) was stirred at 20 °C for 0.5 h under N_2 atmosphere. The above solution was added to a mixture of 4-(4-bromothiazol-2-yl)-2,3,6-trifluoro-phenol (**4**, **Key Intermediate D**, 300 mg, 870.71 µmol, 1 *eq*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (884.43 mg, 3.48 mmol, 4 *eq*), CsF (396.78 mg, 2.61 mmol, 96.31 µL, 3 *eq*), 5-bromo-4-methyl-2-(pyrimidin-2-yloxymethyl)thiazole **10a** (332.20 mg, 1.04 mmol, 1.2 *eq*) in anhydrous MeOH (100 mL) and then the mixture was stirred at 80 °C for 12 h under N_2 atmosphere. The reaction mixture was concentrated and then water (200 mL) was added. The mixture was extracted with DCM (200 mL x 3). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified with prep-HPLC (column: Boston Prime C18 150*30mm*5um;mobile phase: [water(0.2%FA)-ACN]; B%: 46%-69%,10min) to give 2,3,6-trifluoro-4-[4-[4-methyl-2-(pyrimidin-2-yloxymethyl)thiazol-5-yl]thiazol-2-yl]phenol **10** (49 mg, 110.03 µmol, 12.6% yield, 98% purity) of this batch as a solid. ^{1}H NMR (400MHz, DMSO-d_6) δ ppm 8.70 (d, J = 4.8 Hz, 2H), 8.03 (s, 1H), 7.75-7.71 (m, 1H), 7.25 (t, J = 4.8 Hz, 1H), 5.66 (s, 2H), 2.63 (s, 3H); HPLC (100.00% purity); ES-MS m/z 437.1 $[M+H]^+$.

[0211] Example S11. Preparation of 2,3,6-trifluoro-4-[4-[4-methyl-2-(2-pyridyloxymethyl)thiazol-5-yl]thiazol-2-yl]phenol (11).

[0212] Step 1: Synthesis of 5-bromo-4-methyl-2-(2-pyridyloxymethyl)thiazole (11a).



(11a)

To a solution of (5-bromo-4-methyl-thiazol-2-yl)methanol **3e** (0.4 g, 1.73 mmol, 1 eq) and pyridin-2-ol (329.07 mg, 3.46 mmol, 2 eq) in THF (4 mL) were added DEAD (602.64 mg, 3.46 mmol, 629.06 mL, 2 eq) and PPh_3 (907.60 mg, 3.46 mmol, 2 eq) under N_2. The reaction mixture was stirred at 20 °C for 1 h under N_2. The reaction mixture was concentrated under reduced pressure. The residue was purified with flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~35%

Ethylacetate/Petroleum ether gradient @ 35 mL/min) to give 5-bromo-4-methyl-2-(2-pyridyloxymethyl)thiazole **11a** (130 mg, 410.30 mmol, 23.7% yield, 90% purity) as a solid. ^{1}HNMR (400 MHz, $CDCl_3$) δ ppm 8.22-8.14 (m, 1H), 7.65-7.57 (m, 1H), 6.96-6.91 (m, 1H), 6.83 (d, J = 8.4 Hz, 1H), 5.57 (s, 2H), 2.40 (s, 3H).

[0213] Step 2: Synthesis of 2,3,6-trifluoro-4-[4-[4-methyl-2-(2-pyridyloxymethyl)thiazol-5-yl]thiazol-2-yl]phenol (11). A mixture of bis(1-adamantyl)-butyl-phosphane (31.22 mg, 87.07 mol, 0.2 *eq*) and diacetoxypalladium (19.55 mg, 87.07 umol, 0.2 eq) in toluene (6 mL) was stirred at 20 °C for 0.5 h under N_2 atmosphere, the mixture was added to a mixture of 5-bromo-4-methyl-2-(2-pyridyloxymethyl)thiazole **11a** (169.88 mg, 565.96 mol, 1.3 *eq*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (442.21 mg, 1.74 mmol, 4 *eq*), CsF (198.39 mg, 1.31 mmol, 48.15 µL, 3 *eq*), 4-(4-bromothiazol-2-yl)-2,3,6-trifluoro-phenol (**4**, **Key Intermediate D**, 150 mg, 435.36 mol, 1 *eq*) in MeOH (4 mL), the mixture was stirred at 80 °C for 1 h under microwave (2 bar). The mixture was concentrated and then water (50 mL) was added. The mixture was extracted with DCM (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified with prep-HPLC (column: YMC-Actus Triart C18 150*30mm*7um; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 14%-54%,11 min) to give the crude product. The crude product was purified with prep-HPLC (column: Phenomenex Gemini-NX 150*30mm*5um;mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 12%-52%, 10min) to give 2,3,6-trifluoro-4-[4-[4-methyl-2-(2-pyridyloxymethyl)thiazol-5-yl]thiazol-2-yl]phenol **11** (27.6 mg, 63.01 umol, 14.5% yield, 99.41% purity) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.67 (br s, 1H), 8.23 (dd, J = 1.6, 4.8 Hz, 1H), 8.01 (s, 1H), 7.83-7.67 (m, 2H), 7.07 (dd, J = 5.6, 6.8 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 5.62 (s, 2H), 2.63 (s, 3H); HPLC (Purity: 99.41%); ES-MS m/z 341.0 $[M+H]^+$.

[0214] Example S12. Preparation of 3-fluoro-2-hydroxy-5-[6-[4-methyl-2-(pyrimidin-2-yloxymethyl)thiazol-5-yl]-2-pyridyl]benzonitrile (12).

[0215] Step 1: Synthesis of 3-fluoro-2-hydroxy-benzonitrile (12a).

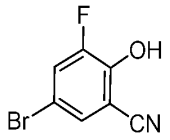


(12a)

To a solution of 2,3-difluorobenzonitrile (500 mg, 3.59 mmol, 400.00 µL, 1 *eq*) in DMF (15 mL) was added 2-methylsulfonylethanol (446.29 mg, 3.59 mmol, 1 *eq*) and NaH (287.53 mg, 7.19 mmol, 60% purity, 2 *eq*) in small portions at 25 °C. The reaction mixture was stirred at 25 °C for 0.5 h. The reaction

mixture was poured into water (30 mL) and washed with ethyl acetate (30 mL x 3), the aqueous phase was adjusted with pH = 2 with 1 N HCl and extracted with ethyl acetate (30 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, filtrate was concentrated under reduced pressure to give 3-fluoro-2-hydroxy-benzonitrile **12a** (350 mg, 2.30 mmol, 63.9% yield, 90% purity) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.45 (br s, 1H), 7.54-7.44 (m, 1H), 7.47-7.42 (m, 1H), 6.94 (dt, J = 4.8, 8.0 Hz, 1H).

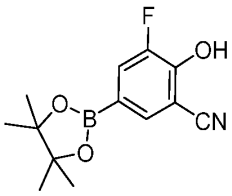
[0216] Step 2: Synthesis of 5-bromo-3-fluoro-2-hydroxy-benzonitrile (12b).



(12b)

To a solution of 3-fluoro-2-hydroxy-benzonitrile **12a** (350 mg, 2.30 mmol, 1 *eq*) in CH_3CN (5 mL) was added NBS (449.78 mg, 2.53 mmol, 1.1 *eq*) in one portion at 20 °C. The reaction mixture was stirred at 20 °C for 1 h. The reaction mixture was poured into *sat*. Na_2CO_3 (20 mL) and washed with ethyl acetate (20 mL x 3). Then the aqueous phase was adjusted to pH = 2 with 1 N HCl and extracted with ethyl acetate (20 mL x 3), the combined organic layers were dried over Na_2SO_4, filtered, filtrate was concentrated to give 5-bromo-3-fluoro-2-hydroxy-benzonitrile **12b** (300 mg, 1.19 mmol, 52.0% yield, 86% purity) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.87 (br. s, 1H), 7.88-7.85 (m, 1H), 7.77 (d, J = 1.6 Hz, 1H).

[0217] Step 3: Synthesis of 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (12c).



(12c)

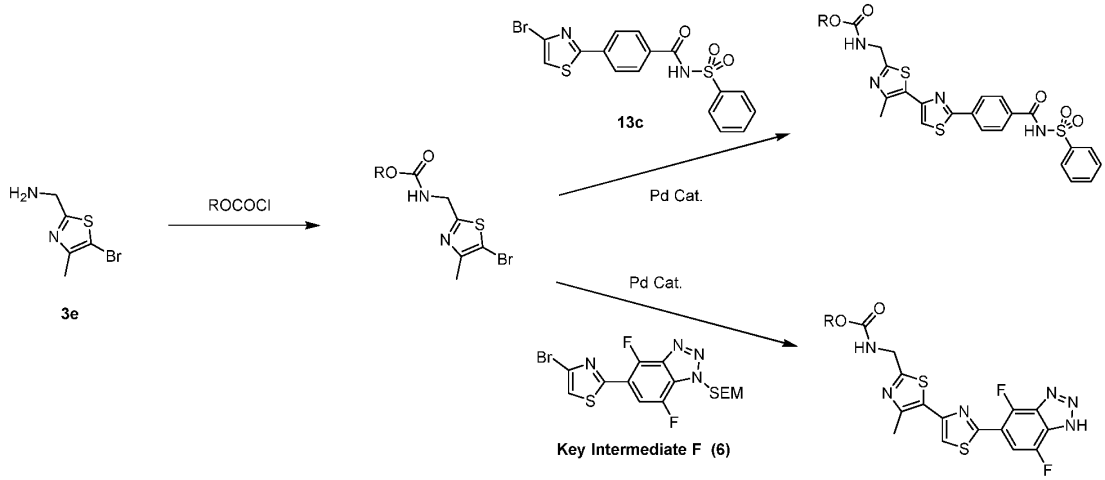
A mixture of 5-bromo-3-fluoro-2-hydroxy-benzonitrile **12b** (250 mg, 995.34 µmol, 1 *eq*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (631.88 mg, 2.49 mmol, 2.5 *eq*), KOAc (293.05 mg, 2.99 mmol, 3 *eq*) and $Pd(dppf)Cl_2.CH_2Cl_2$ (81.28 mg, 99.53 µmol, 0.1 *eq*) in 1,4-dioxane (10 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 85 °C for 12 h under N_2 atmosphere. TLC (petroleum ether/ethyl acetate = 1/1) showed the reaction was completed. The reaction mixture was concentrated under reduced pressure to give 3-fluoro-2-hydroxy-5-

(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile **12c** (300 mg, crude) as a gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.75 (s, 1H), 7.64 (d, J = 10.4 Hz, 1H), 7.43-7.38 (m, 1H), 1.33 (s, 12H).

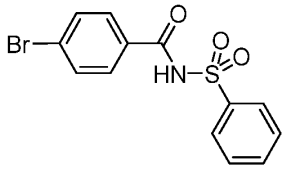
[0218] Step 4: Synthesis of 3-fluoro-2-hydroxy-5-[6-[4-methyl-2-(pyrimidin-2-yloxymethyl)thiazol-5-yl]-2-pyridyl]benzonitrile (12). A mixture of 5-(6-chloro-2-pyridyl)-4-methyl-2-(pyrimidin-2-yloxymethyl)thiazole (**5**, **Key Intermediate E**, 250 mg, 705.81 µmol, 1 *eq*), 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile **12c** (278.52 mg, 1.06 mmol, 1.5 *eq*), Cs_2CO_3 (459.94 mg, 1.41 mmol, 2 *eq*) and $Pd(dppf)Cl_2.CH_2Cl_2$ (57.64 mg, 70.58 µmol, 0.1 *eq*) in 1,4-dioxane (9 mL) and H_2O (3 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 85 °C for 12 h under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure. The residue was purified with reversed-phase HPLC (H_2O-ACN condition) to give crude product, which was purified with prep-HPLC (column: Boston Prime C18 150*30mm*5µm; mobile phase: [water (0.05%NH_3H_2O+10mM NH_4HCO_3)-ACN]; B%: 27%-50%,7min) to give 3-fluoro-2-hydroxy-5-[6-[4-methyl-2-(pyrimidin-2-yloxymethyl)thiazol-5-yl]-2-pyridyl]benzonitrile **12** (71.8 mg, 166.89 µmol, 23.6% yield, 97.49% purity) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.69 (d, J = 4.8 Hz, 2H), 7.79 (d, J = 2.4 Hz, 1H), 7.78-7.75 (m, 1H), 7.76 (d, J = 7.6 Hz, 1H), 7.75-7.70 (m, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.23 (t, J = 4.8 Hz, 2H), 5.64 (s, 2H), 2.66 (s, 3H); HPLC (Purity: 97.49%); ES-MS m/z 420.2 $[M+H]^+$.

[0219] Example S13. Preparation of methyl((4'-methyl-2-(4-((phenylsulfonyl)carbamoyl)phenyl)-[4,5'-bithiazol]-2'-yl)methyl)carbamate (13).

General Scheme for Compounds 13 and 16.



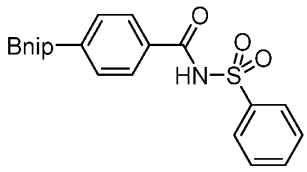
[0220] Step 1: Synthesis of 4-bromo-*N*-(phenylsulfonyl)benzamide (13a).



(13a)

[0221] To a solution of 4-bromobenzoyl chloride (3 g, 13.67 mmol, 1 *eq*) and benzenesulfonamide (2.36 g, 15.04 mmol, 1.1 *eq*) in DCM (30 mL) was added DIEA (5.30 g, 41.01 mmol, 7.14 mL, 3 *eq*). The mixture was stirred at 25 °C for 2 h. TLC (PE/EtOAc = 1/1) indicated starting material was consumed completely, and one major new spot with larger polarity was formed. The mixture was added H_2O (10 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with H_2O (100 mL x 3) and brine (100 mL x 2), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give *N*-(benzenesulfonyl)-4-bromo-benzamide **13a** (4.5 g, 11.91 μmol, 87.1% yield, 90% purity) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.86-7.80 (dd, J = 8, 12 Hz, 4H), 7.53 (d, J = 8.4 Hz, 2H), 7.40-7.47 (d, J = 5.6 Hz, 3H).

[0222] Step 2: Synthesis of *N*-(phenylsulfonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (13b).

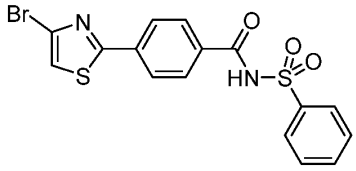


(13b)

[0223] A mixture of *N*-(benzenesulfonyl)-4-bromo-benzamide **13a** (5.2 g, 13.76 mmol, 1 *eq*), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (6.99 g, 27.51 mmol, 2 *eq*), Pd(dppf)Cl_2 (1.01 g, 1.38 mmol, 0.1 *eq*), KOAc (2.70 g, 27.51 mmol, 2 *eq*) in dioxane (100 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 12 h under N_2 atmosphere. TLC (PE/EtOAc = 1/1) indicated starting material was consumed completely, and one major new spot with lower polarity was formed. The mixture was concentrated and then water (100 mL) was added. The mixture was extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give *N*-(benzenesulfonyl)-4-(4,4,5,5-tetramethyl-1,3,2-

dioxaborolan-2-yl)benzamide **13b** (5.9 g, 13.71 mmol, 99.7% yield, 90% purity) as a solid. ^{1}H NMR (400MHz, $CDCl_3$) δ ppm 8.17 (d, J = 8 Hz, 2H), 7.89-7.83 (m, 2H), 7.80-7.74 (m, 2H), 7.66 (s, 1H), 7.59-7.53 (m, 2H), 1.34 (s, 12H).

[0224] Step 3: Synthesis of 4-(4-bromothiazol-2-yl)-*N*-(phenylsulfonyl)benzamide (13c).



(13c)

A mixture of *N*-(benzenesulfonyl)-4-bromo-benzamide **13b** (500 mg, 1.32 µmol, 1 *eq*), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (671.81 mg, 2.65 µmol, 2 *eq*), Pd(dppf)Cl_2 (96.79 mg, 132.28 µmol, 0.1 *eq*), KOAc (259.64 mg, 2.65 µmol, 2 *eq*) in dioxane (10 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 12 h under N_2 atmosphere. TLC (PE/EtOAc = 1/1) indicated starting material was remained, and one major new spot with lower polarity was formed. The mixture was concentrated and then water (10 mL) was added. The mixture was extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 25 mL/min) to give *N*-(benzenesulfonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide **13c** (510 mg, 1.19 µmol, 89.6% yield, 90% purity) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.05-7.92 (m, 5H), 7.88-7.47 (m, 5H).

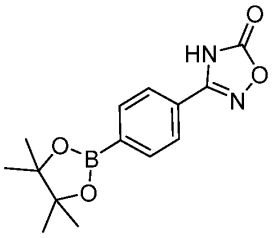
[0225] Step 4: Synthesis of methyl((4'-methyl-2-(4-((phenylsulfonyl)carbamoyl)phenyl)-[4,5'-bithiazol]-2'-yl)methyl)carbamate (13). A solution of bis(1-adamantyl)-butylphosphane (45.74 mg, 127.57 µmol, 0.2 *eq*) and diacetoxypalladium (28.64 mg, 127.57 µmol, 0.2 *eq*) in toluene (17.5 mL) was stirred at 20 °C for 0.5 h under N_2. The mixture was added to a solution of N-(benzenesulfonyl)-4-(4-bromothiazol-2-yl)benzamide **13c** (300 mg, 637.84 µmol, 1 *eq*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (647.89 mg, 2.55 mmol, 4 *eq*), methyl N-[(5-bromo-4-methyl-thiazol-2-yl)methyl]carbamate **16a** (263.06 mg, 892.98 µmol, 1.4 *eq*) and CsF (290.67 mg, 1.91 mmol, 70.55 µL, 3 *eq*) in MeOH (30 mL) at 50 °C under N_2. The mixture was stirred at 80 °C for 12 h. The mixture was concentrated and then DMSO (4 mL) was added. The mixture was filtered and the filtrate was purified by prep-HPLC (column: YMC-Triart Prep C18 150*40mm*7um;mobile phase: [water(0.225%FA)-ACN];B%: 45%-75%,8min) to give methyl N-[[5-[2-[4-(benzenesulfonylcarbamoyl)phenyl]thiazol-4-yl]-4-methyl-thiazol-2-yl]methyl]carbamate **13** (31.7 mg, 59.04 µmol, 9.3% yield, 98.45% purity) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.07 (d, J = 6.8

Hz, 3H), 8.05-7.97 (m, 5H), 7.76-7.69 (m, 1H), 7.69-7.61 (m, 2H), 4.42 (d, *J* = 4.0 Hz, 2H), 3.60 (s, 3H), 2.60 (s, 3H); HPLC (98.45% purity); ES-MS m/z 529.1 $[M+H]^+$.

[0226] Example S14. Preparation of 5-(6-(1H-benzo[d][1,2,3]triazol-6-yl)pyridin-2-yl)-4-methyl-2-((pyrimidin-2-yloxy)methyl)thiazole (14). To a 2.0 mL microwave tube was added 5-(6-chloropyridin-2-yl)-4-methyl-2-((pyrimidin-2-yloxy)methyl)thiazole (**5**, **Key Intermediate E**, 80 mg, 250.96 µmol), 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d][1,2,3]triazole (67.66 mg, 276.05 µmol), potassium carbonate (34.68 mg, 250.96 µmol), water (0.5 ml) and dioxane (1.5 ml). $PdCl_2$(dppf) (18.36 mg, 25.10 µmol) was finally added and the vial sealed and heated to 80 °C with stirring. After a total of 26 hr., the mixture was allowed to cool to room temp and then diluted with water and extracted with EtAc. The extracts were then washed once with water followed by brine solution, dried (Na2SO4), filtered and concentrated in vacuo. The crude product was chromatographed (ISCO, dry loading, 4g silica column, gradient = 60% EtAc/heptane to 100% EtAc, 18 min run time). The fractions containing product were then concentrated *in vacuo* to give 5-(6-(1H-benzo[d][1,2,3]triazol-6-yl)pyridin-2-yl)-4-methyl-2-((pyrimidin-2-yloxy)methyl)thiazole **14** (10 mg, 24.91 µmol, 9.9 % yield) as a solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 15.88 (s, 1H), 8.70 (d, J = 4.7 Hz, 3H), 8.41 - 7.94 (m, 4H), 7.73 (d, J = 7.7 Hz, 1H), 7.24 (t, J = 4.8 Hz, 1H), 5.68 (s, 2H), 2.73 (s, 3H). ES-MS m/z 402.4 $[M+H]^+$.

[0227] Example S15. Preparation of 3-(4-(6-(4-methyl-2-((pyrimidin-2-yloxy)methyl)thiazol-5-yl)pyridin-2-yl)phenyl)-1,2,4-oxadiazol-5(4H)-one (15).

[0228] Step 1: Synthesis of 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1,2,4-oxadiazol-5(4H)-one (15a).



(15a)

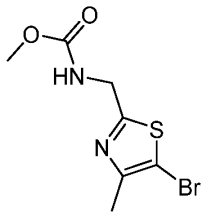
In a 5 mL microwave vial were placed bis(pinacolato)diboron (702.33 mg, 2.74 mmol), 3-(4-bromophenyl)-1,2,4-oxadiazol-5(4H)-one (330 mg, 1.37 mmol), potassium acetate (537.44 mg, 5.48 mmol) and DMSO (5 mL). After the mixture was purged with nitrogen for 5 min, $PdCl_2$(dppf) (75.13 mg, 102.68 µmol) was added at 20 °C. After 20 h at 80 °C, the mixture was poured into water (30 mL), stirred for 30 min, filtered, and dried to give 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-

1,2,4-oxadiazol-5(4H)-one **15a** (540 mg, 1.87 mmol, 136.9 % yield), which was used in the next step without further purification. ES-MS m/z 289.2 $[M+H]^+$.

[0229] Step 2: Synthesis of 3-(4-(6-(4-methyl-2-((pyrimidin-2-yloxy)methyl)thiazol-5-yl)pyridin-2-yl)phenyl)-1,2,4-oxadiazol-5(4H)-one (15). In a 5 mL microwave vial were placed 5-(6-chloropyridin-2-yl)-4-methyl-2-((pyrimidin-2-yloxy)methyl)thiazole (**5**, **Key Intermediate E**, 30 mg, 94.11 µmol), 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1,2,4-oxadiazol-5(4H)-one **15a** (54.23 mg, 188.22 µmol), cesium carbonate (76.66 mg, 235.27 µmol), water (0.6 ml), and 1,4-dioxane (3 ml). After the mixture was bubbled with nitrogen gas for 5 min, PalladiumTetrakis (10.88 mg, 9.41 µmol) was added at 20 °C. After 15 h at 90 °C, the mixture was diluted with EtOAc (20 mL) and water (10 mL), and acidified with 10% citric acid. The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated in a rotavap to give a residue, which was purified by HPLC to afford 3-(4-(6-(4-methyl-2-((pyrimidin-2-yloxy)methyl)thiazol-5-yl)pyridin-2-yl)phenyl)-1,2,4-oxadiazol-5(4H)-one **15** (9.2 mg, 20.70 µmol, 22.0 % yield) as a solid after lyophilization. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.72 (d, J = 4.8 Hz, 2H), 8.32 (d, J = 8.2 Hz, 2H), 8.06 (d, J = 5.8 Hz, 2H), 7.98 (d, J = 8.2 Hz, 2H), 7.77 (dd, J = 5.8, 2.8 Hz, 1H), 7.26 (t, J = 4.8 Hz, 1H), 5.70 (s, 2H), 2.74 (s, 3H), 2.56 (s, 1H). ES-MS m/z 445.3 $[M+H]^+$.

[0230] Example S16. Preparation of methyl N-[[5-[2-(4,7-difluoro-1H-benzotriazol-5-yl)thiazol-4-yl]-4-methyl-thiazol-2-yl]methyl]carbamate (16).

[0231] Step 1: Synthesis of methyl N-[(5-bromo-4-methyl-thiazol-2-yl)methyl]carbamate (16a).

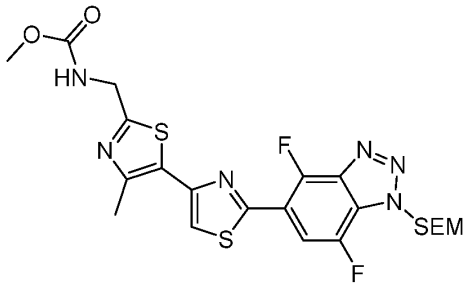


(16a)

To a solution of (5-bromo-4-methyl-thiazol-2-yl)methanamine (**3**, **Key Intermediate C**, 1 g, 4.83 mmol, 1 eq) in DCM (20 mL) was added TEA (2.44 g, 24.14 mmol, 3.36 mL, 5 eq) and methyl chloroformate (1.37 g, 14.49 mmol, 1.12 mL, 3 eq) at 0°C. The mixture was stirred at 25°C for 2 hr. LCMS showed the desired mass was detected. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was poured into ammonium chloride saturated aqueous solution (50 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~70% Ethylacetate/Petroleum ethergradient @ 20 mL/min). The cut fraction was concentrated under reduced

pressure to give methyl N-[(5-bromo-4-methyl-thiazol-2-yl)methyl]carbamate **16a** (440 mg, 1.66 mmol, 34.37% yield) was obtained as a solid. ^{1}H NMR (400MHz, CHLOROFORM-d) 7.26 (s, 1H), 5.46 - 5.22 (m, 1H), 4.55 (br d, J=6.0 Hz, 2H), 3.72 (s, 3H), 2.36 (s, 3H).

[0232] Step 2: Synthesis of methyl N-[[5-[2-[4,7-difluoro-1-(2-trimethylsilylethoxymethyl)benzotriazol-5-yl]thiazol-4-yl]-4-methyl-thiazol-2-yl]methyl]carbamate (16b).



(16b)

A mixture of $Pd(OAc)_2$ (19.07 mg, 84.94 umol, 0.1 eq) and bis(1-adamantyl)-butyl-phosphane (60.91 mg, 169.88 umol, 0.2 eq) in Tol. (8 mL) was stirred at 20°C for 0.5 h under N_2. The above mixture was added to a mixture of 2-[[5-(4-bromothiazol-2-yl)-4,7-difluoro-benzotriazol-1-yl]methoxy]ethyl-trimethyl-silane (**6**, **Key Intermediate F**, 380 mg, 849.40 umol, 1 eq), methyl N-[(5-bromo-4-methyl-thiazol-2-yl)methyl]carbamate **16a** (270.24 mg, 1.02 mmol, 1.2 eq), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (862.79 mg, 3.40 mmol, 4 eq) and CsF (387.07 mg, 2.55 mmol, 93.95 uL, 3 eq) in MeOH (32 mL). The mixture was taken up into a microwave tube. The sealed tube was heated at 80°C for 1 h under microwave under N_2. TLC indicated one new spot formed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified with flash silica gel chromatography (ISCO®; 20 g SepaFlash ® Silica Flash Column, Eluent of 0~100% PE/EA gradient @ 75mL /min) to give methyl N-[[5-[2-[4,7-difluoro-1-(2-trimethylsilylethoxymethyl)benzotriazol-5-yl]thiazol-4-yl]-4-methyl-thiazol-2-yl]methyl]carbamate **16b** (110 mg, 199.03 umol, 23.43% yield) as a solid.

[0233] Step 3: Synthesis of methyl N-[[5-[2-(4,7-difluoro-1H-benzotriazol-5-yl)thiazol-4-yl]-4-methyl- thiazol-2-yl]methyl]carbamate (16). To a solution of methyl N-[[5-[2-[4,7-difluoro-1-(2-trimethylsilylethoxymethyl)benzotriazol-5-yl]thiazol-4-yl]-4-methyl-thiazol-2-yl]methyl]carbamate **16b** (100 mg, 180.93 umol, 1 eq) in DCM (5 mL) was added TFA (3.08 g, 27.01 mmol, 2.00 mL, 149.29 eq) at 0°C, and the mixture was stirred at 20°C for 2h. LCMS showed desired MS was detected. The reaction mixture was concentrated under reduced pressure to give a residue and purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%:

10%-40%,11.5min), and was further purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um;mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 10%-40%,11.5min) to give methyl N-[[5-[2-(4,7-difluoro-1H-benzotriazol-5-yl)thiazol-4-yl]-4-methyl-thiazol-2-yl]methyl]carbamate **16** (26 mg, 61.55 umol, 34.02% yield, 99.67% purity) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.16 - 8.04 (m, 2H), 7.92 (dd, *J* = 4.4, 10.5 Hz, 1H), 4.44 (d, *J* = 6.1 Hz, 2H), 3.62 (s, 3H), 2.62 (s, 3H), HPLC (99.67% purity); ES-MS m/z 423.0 $[M+H]^+$.

[0234] **Example S17.** Compounds **17-212** were prepared in accordance with the procedures described in Examples S7-S16 using suitable reagents and modifications as would be known by a person of skill in the art.

[0235] Compounds described herein may be prepared according to the methods and examples as described herein and were characterized using standard techniques known in the art, such as ^{1}H NMR and mass spectra.

Biological Examples

[0236] **Example B1. BPGM Synthase Assay.**

[0237] ***Materials***

[0238] The following materials were used in this assay: deionized water; Bisphosphoglycerate mutase (BPGM; Standard Buffer: 50 mM Tris, 0.01% Tween 20, pH 7.4); BPGM Reaction Buffer (50 mM Tris, 0.01% Tween 20, 3.23 mM KH_2PO_4, pH 7.4); dithiothreitol (DTT; Stock solution: 100 mM in Standard Buffer); 384-Well Black Assay Plate (Corning, P/N 3575); DMSO; BPGM Stock Solution (500 nM in BPGM Standard Buffer); Glyceraldehyde 3-phosphate dehydrogenase (GAPDH; Stock Solution: 40 U/mL in 20 mM Tris-HCL Buffer with 20% Glycerol, 1mM EDTA, 1 mM DTT); Glyceraldehyde 3-phosphate (GAP; Stock Solution: 20 mM in BPGM Standard Buffer); 3-PG Stock Solution (500 μM in BPGM Standard Buffer); Nicotinamide adenine dinucleotide (NAD; Stock Solution: 50 mM in BPGM Standard Buffer); Koningic Acid (1 mM Stock in DMSO); Resazurin Stock Solution (10 mM in DMSO); Diaphorase Stock Solution (40 U/mL in BPGM Standard Buffer); DTT Reaction Buffer (1 mM DTT in BPGM Reaction Buffer); Enzyme Solution (5 nM BPGM, 0.4 U/mL GAPDH in DTT Reaction Buffer); GAPDH Solution (0.4 U/mL GAPDH in DTT Reaction Buffer); Substrate Solution (2 mM NAD, 20 μM 3PG, 800 μM GAP in DTT Reaction Buffer); and Resazurin Solution (5 U/mL Diaphorase, 500 μM Resazurin in BPGM Standard Buffer).

[0239] ***Procedures***

[0240] To the assay plate was added Enzyme Solution (20 uL) to columns 2-22 and 24 of the assay plate. To columns 1 and 23 was added GAPDH Solution (20 uL). A separate compound plate was prepared at the desired concentrations and all wells were normalized with 5% DMSO. The compound plate was incubated for 30 minutes at RT. Next, the substrate solution (20 μL) was dispensed to all

reaction wells and the plate was incubated for 60 minutes at RT. Koningic acid (1 μL) was added and the plate was incubated for 10 minutes at RT. During this time period, the NADH fluorescence was read at ex: 360 / em: 460. Next, Resazurin Solution (10 μL) was added to all reaction wells and the plate was incubated for 30 minutes at RT. The resorufin fluorescence was then read at ex:544/em:590.

[0241] The results of the BPGM synthase assay for select exemplary compounds are shown in Table 3.

Table 3. hBPGM Synthase IC_{50} Values for Exemplary Compounds.

Compound No.	hBPGM Synthase IC_{50} (nM)
7	92
8	21
9	19
10	159
11	511
12	256
13	169
14	1010
15	138
16	50

[0242] **Example B2. BPGM Phosphatase Assay.**

[0243] ***Materials***

[0244] The following materials were used in this assay: Tris buffer (50 mM Tris, 0.01% Tween 20, pH 7.4); cyclohexylammonium salt of 2,3-BPG (stock solution of 500 mM in ultapure distilled water; human Bisphosphoglycerate mutase (hBPGM; stock solution of 110 μM in Standard Buffer); 3-Phosphoglyceric acid (3-PG; stock solution of 100 mM in ultrapure distilled water); 384-Well Polystyrene Plates (Fisherbrand™, Catalog No.: 12-566-625); BIOMOL GREEN REAGENT (Enzo life sciences, BML-AK111-0250); and 1 mM DMSO stock of exemplary compounds.

[0245] ***Procedures***

[0246] A 3-PG enzyme mix solution (final enzyme concentration 62.5 nM, 3-PG concentration at 50 μM, 14.5 uL) was added to onto a 384-well clear plate. Solutions of the test compounds were then added to the plate and the DMSO content was normalized across the plate. The plate was incubated at RT for 15 min. Next, the substrate 2,3-BPG (5 μL) was added to all the wells, and the plate was sealed and incubated for 24 hr at RT. After incubation, BIOMOL green dye (40 μL) was added to all the wells, the plate was shaken to mix, and the plate was incubated at RT for 20-30 min. Absorbance measurements were recorded at 620 nm.

[0247] ***Results***

[0248] The results of the BPGM phosphatase assay for select exemplary compounds are shown in Table 4.

Table 4. hBPGM Phosphatase EC_{50} Values for Exemplary Compounds.

Compound No.	hBPGM Phosphatase EC_{50} (nM)
7	55
8	40
10	310
11	190
13	55
14	570
15	170

[0249] **Example B3. Human Cell-Based Assay.**

[0250] ***Materials***

[0251] The following materials were used in this assay: DMSO; Hemox buffer (30 mM TES, 135 mM NaCl, 5mM KCl, pH 7.4); Inosine (100 mM in hemox buffer); Glucose (1 M in water); human red blood cells; LC/MS Optima grade methanol; LC/MS Optima grade water; and Incubation buffer (30 mM TES, 135 mM NaCl, 5mM KCl, 50 mM inosine, 20 mM glucose pH 7.4).

[0252] ***Procedures***

[0253] Test compounds were loaded onto a 96-well plate (final concentration of DMSO was 1%). 10 mL whole blood was resuspended with an equivalent amount of 2X incubation buffer to make 25% hct & 50% plasma solution. The final solution contains 10 mM glucose and 25 mM inosine. The blood suspension (100 uL) was added to the wells of the plate. The plate was covered with an adhesive foil cover and plastic lid, and incubated at 37 °C for 24 h. The samples were extracted through an SPE column and the metabolites (2,3-BPG, ATP) were analyzed by LC/MS.

[0254] ***Results***

[0255] The results of the cell-based assay for a select exemplary compound is shown in Table 5.

Table 5. hRBC EC_{50} Values for Exemplary Compounds.

Compound No.	hRBC EC_{50} (μM)
16	22.5

[0256] Additional results from the hBPGM synthase and hBPGM phosphate assays as described herein are shown in Table 6.

Table 6. Additional Assay Results

Compound No.	huBPGM:phosphatase Enzyme EC50 (M)	huBPGM:synthase Enzyme IC50 (M)
7	5.50E-08	9.20E-08
8	4.00E-08	1.70E-08
9		1.90E-08
10	3.10E-07	1.30E-07
11	1.90E-07	5.10E-07
12		2.60E-07
13	3.20E-08	1.70E-07
15	1.70E-07	1.40E-07
24		2.50E-07
25		4.40E-06
26		1.10E-07
27		1.50E-06
28		1.60E-06
29		5.70E-06
30		2.00E-07
31		3.50E-08
32		7.60E-08
33		2.50E-07
34		2.50E-07
35		6.00E-07
36		1.30E-06
37		1.30E-05
38		3.60E-08
39		4.10E-08
40		4.40E-08
41		7.50E-08
42		4.10E-06
43		1.40E-08
44		2.50E-08
45		4.80E-08

Compound No.	huBPGM:phosphatase Enzyme EC50 (M)	huBPGM:synthase Enzyme IC50 (M)
46		1.30E-07
47		2.50E-08
48		3.10E-08
49		4.70E-08
50		7.40E-08
51		2.80E-07
52		3.90E-07
53		8.90E-07
54		9.10E-08
55		2.20E-07
56		2.60E-07
57		2.90E-07
58		1.90E-06
59		2.00E-08
60		5.50E-08
61		2.20E-07
62		3.50E-07
63		1.40E-06
64		4.30E-08
65		2.80E-07
66		1.60E-08
67		5.00E-08
68		2.00E-07
69		7.90E-08
70		2.00E-07
71		3.00E-07
72		5.10E-07
73		>2.5E-05
74		2.90E-07
75		4.40E-07
76		1.10E-06

Compound No.	huBPGM:phosphatase Enzyme EC50 (M)	huBPGM:synthase Enzyme IC50 (M)
77		1.30E-06
78		1.50E-06
79		2.40E-06
80		2.80E-06
81		3.00E-06
82		3.60E-06
83		>2.5E-05
84		>2.5E-05
85		2.10E-08
86		1.40E-07
87		3.80E-07
88		2.40E-08
89		2.80E-07
90		3.40E-07
91		6.40E-07
92		2.30E-06
93		9.00E-06
94		>2.5E-05
95	2.50E-08	2.50E-08
96	1.00E-06	1.60E-06
97	6.90E-06	1.80E-06
98	3.80E-07	2.20E-06
99	7.80E-06	4.70E-06
100	5.70E-08	3.10E-07
101	3.90E-08	4.50E-07
102	4.50E-08	6.20E-07
103	>2.5E-05	9.30E-07
104	>2.5E-05	2.30E-06
105		2.20E-07
106		3.30E-07
107		3.20E-06

Compound No.	huBPGM:phosphatase Enzyme EC50 (M)	huBPGM:synthase Enzyme IC50 (M)
108		1.40E-05
109		1.60E-07
110		1.60E-07
111		5.70E-07
112		6.50E-07
113		5.30E-07
114		1.20E-06
115		4.40E-06
116		6.50E-06
117		>2.5E-05
118		2.80E-08
119		2.90E-06
120		1.50E-06
121		3.30E-06
122		3.30E-08
123		1.60E-06
124		6.30E-06
125	2.70E-06	2.30E-08
126	>2.5E-05	2.10E-08
127	3.80E-07	4.30E-07
128		6.70E-06
129	4.00E-08	8.00E-09
130	1.00E-05	1.50E-08
131	5.70E-07	5.10E-07
132		8.10E-06
133		4.40E-06
134		>2.5E-05
135	2.40E-07	1.60E-07
136	7.00E-08	2.00E-07
137	2.00E-07	2.30E-07
138	>2.5E-05	9.60E-07

Compound No.	huBPGM:phosphatase Enzyme EC50 (M)	huBPGM:synthase Enzyme IC50 (M)
139	>2.5E-05	>2.5E-05
140	3.00E-08	
141	5.70E-08	5.40E-08
142	4.00E-08	2.60E-07
144	4.00E-08	3.30E-07
145	3.00E-08	2.50E-07
146		1.30E-05
147	4.90E-07	5.50E-07
148	2.50E-07	1.20E-06
149		4.50E-06
150		>9.9E-05
151	2.00E-05	1.50E-06
152	3.00E-08	4.00E-08
153	6.00E-08	8.10E-08
154	4.90E-08	1.10E-07
155	4.00E-08	4.40E-08
156	1.50E-07	2.00E-07
157	2.40E-07	1.70E-07
158	5.30E-07	2.40E-07
159	1.80E-06	2.90E-07
160	5.20E-07	4.60E-07
161		>2.5E-05
162		>2.5E-05
163	2.60E-07	1.70E-07
164	5.50E-07	6.80E-07
165	1.10E-07	9.20E-08
166	1.70E-07	1.10E-07
167	7.50E-08	1.30E-07
168	1.30E-07	2.20E-07
169	3.30E-07	5.60E-07
170	8.80E-07	1.10E-06

Compound No.	huBPGM:phosphatase Enzyme EC50 (M)	huBPGM:synthase Enzyme IC50 (M)
171	1.90E-06	8.10E-07
172	2.40E-07	2.80E-07
173	>2.5E-05	1.50E-06
174		5.00E-06
175	3.00E-08	7.90E-08
176	2.00E-08	3.40E-06
177	2.50E-07	4.40E-07
178	1.70E-06	1.70E-06
179		
180		>2.5E-05
181	7.90E-07	3.00E-07
182		1.90E-06
183		>2.5E-05
184		2.50E-07
185		8.90E-07
186	3.50E-07	2.40E-07
187	4.80E-07	3.00E-07
188	1.40E-07	8.40E-08
189	3.10E-07	9.80E-07
190	3.30E-06	4.20E-06
191	1.60E-06	1.10E-06
192	4.90E-07	1.00E-06
193		2.30E-05
194	3.70E-07	8.20E-07
196	4.90E-06	1.60E-06
197	4.00E-07	3.10E-06
198		5.20E-06
199		6.50E-06
200		1.20E-05
201	1.80E-07	4.10E-07
202		>2.5E-05

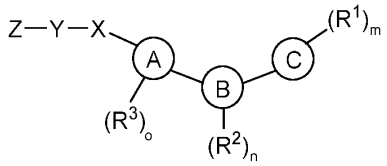
Compound No.	huBPGM:phosphatase Enzyme EC50 (M)	huBPGM:synthase Enzyme IC50 (M)
203	3.60E-06	6.10E-06
204		>2.5E-05
205	4.40E-07	3.40E-07
206	1.20E-06	1.40E-06
207	8.20E-06	6.50E-06
208	1.60E-05	3.10E-06
209		3.30E-06
210		7.50E-06
211		7.40E-07
212		2.60E-06
213	6.00E-08	1.60E-07
214	9.60E-08	1.80E-07
215		>2.5E-05
216		5.40E-06
217		1.20E-07
218		4.10E-07
219		5.80E-08
220		2.70E-08
221		1.70E-07
222		>2.5E-05
223		8.40E-07
224		3.00E-08
225		2.10E-07
226		8.20E-08
227		2.10E-08
228		>2.5E-05
229		>2.5E-05
230		>2.5E-05
231		8.70E-08
232		2.20E-06
233		3.90E-06

Compound No.	huBPGM:phosphatase Enzyme EC50 (M)	huBPGM:synthase Enzyme IC50 (M)
234		1.30E-06
235		1.30E-07
236		1.10E-07
237		2.20E-08
238		4.90E-08
239	4.80E-07	3.00E-07

[0257] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, the descriptions and examples should not be construed as limiting the scope of the invention. The disclosures of all patent and scientific literature cited herein are expressly incorporated herein in their entirety by reference.

CLAIMS

1. A compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is a 5-membered heteroarylene containing 1-3 heteroatoms selected from N and S;

Ring B is phenylene or a 5- to 6-membered heteroarylene containing 1-3 heteroatoms selected from N and S;

Ring C is a fused bicyclic 9- to 10-membered heteroaryl or heterocyclyl containing 1-4 heteroatoms selected from N and O, a 5- to 6-membered heteroaryl containing 1-4 nitrogen atoms, or phenyl substituted by one R^4;

each R^1 is independently -OH, halo, oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -CN, $-N(H)C(O)R^6$, $-N(H)SO_2R^6$, $-N(H)SO_2(C_6H_5)$, $-SO_2NR^6R^7$, or $-C(O)N(H)SO_2R^6$;

each R^2 is independently C_1-C_6 alkyl, C_1-C_6 haloalkyl, or halo;

each R^3 is independently C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_3-C_6 cycloalkyl;

R^4 is -OH, $-OP(O)(OH)_2$, $-NO_2$, $-C(O)N(H)SO_2R^5$, 5- to 6-membered heteroaryl or heterocyclyl, or -C(O)N(H)-(5- to 6-membered heteroaryl or heterocyclyl),
wherein the heteroaryl and heterocyclyl contain 1-4 heteroatoms selected from N, O, and S, and wherein the heterocyclyl is optionally substituted by 1-2 oxo groups;

m is 0-4;

n is 0-2;

o is 0-2;

R^5 is phenyl or C_1-C_6 alkyl;

X is $-CR^6R^7-$ or a bond;

Y is -O-, -N(H)-, or a bond;

each R^6 and R^7 is independently H or C_1-C_6 alkyl;

Z is Z^1 or Z^2;

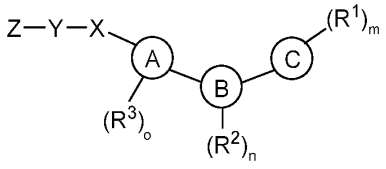
Z^1 is H, C_1-C_6 alkyl, $-C(O)(C_1$-C_6 alkyl), $-CO_2(C_1$-C_6 alkyl), $-C(O)NR^6R^7$, $-C(O)NR^6(C_1$-C_6 alkylene)NR^6R^7, $-CR^6R^7C(O)NR^6R^7$, $-CR^6R^7NR^6R^7$,

-C(O)(C_1-C_6 alkylene)NR^6R^7, -NR^6C(O)(C_1-C_6 alkyl), -NR^6R^7, -(C_1-C_6 alkyl)-CO_2H, -(C_1-C_6 alkyl)-OH, or -C(NR^6R^7)=N-CN, wherein C_1-C_6 alkylene is optionally substituted by 1-6 halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl;

Z^2 is 5- to 6-membered heteroaryl, -C(O)(5- to 6-membered heteroaryl), -CH_2C(O)(5- to 6-membered heteroaryl), 4- to 6-membered heterocyclyl, -C(O)(4- to 6-membered heterocyclyl), or -CH_2C(O)(4- to 6-membered heterocyclyl), wherein the heteroaryl and heterocyclyl contain 1-3 heteroatoms selected from N and O, and wherein the heteroaryl and heterocyclyl are optionally substituted by 1-3 R^8;

each R^8 is independently halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -NR^6R^7, -OH, oxo, -CO_2H, -O(C_1-C_6 alkyl), -CH_2-O(C_1-C_6 alkyl), or -(C_1-C_6 alkyl)-OH.

2. The compound of claim 1, wherein the compound is of Formula (I-a):



(I-a)

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is thiazolylene;

Ring B is phenylene or a 5- to 6-membered heteroarylene containing 1-3 heteroatoms selected from N and S;

Ring C is a fused bicyclic 9- to 10-membered heteroaryl or heterocyclyl containing 1-4 heteroatoms selected from N and O, a 5- to 6-membered heteroaryl containing 1-4 nitrogen atoms, or phenyl substituted by one R^4;

each R^1 is independently -OH, halo, oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -CN, -N(H)C(O)R^6, -N(H)SO_2R^6, -$SO_2NR^6R^7$, or -C(O)N(H)SO_2R^6;

each R^2 is independently C_1-C_6 alkyl, C_1-C_6 haloalkyl, or halo;

each R^3 is independently C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_3-C_6 cycloalkyl;

R^4 is -OH, -OP(O)$(OH)_2$, -NO_2, -C(O)N(H)SO_2R^5, 5- to 6-membered heteroaryl or heterocyclyl, or -C(O)N(H)-(5- to 6-membered heteroaryl or heterocyclyl), wherein the heteroaryl and heterocyclyl contain 1-4 heteroatoms selected from N, O, and S, and wherein the heterocyclyl is optionally substituted by 1-2 oxo groups;

m is 0-4;

n is 0-2;

o is 0-2;

R^5 is phenyl or C_1-C_6 alkyl;

X is $-CR^6R^7-$;

Y is -O-, -N(H)-, or a bond;

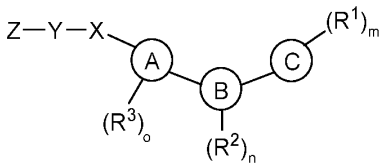
each R^6 and R^7 is independently H or C_1-C_6 alkyl;

Z is Z^2;

Z^2 is 5- to 6-membered heteroaryl, -C(O)(5- to 6-membered heteroaryl), $-CH_2C(O)$(5- to 6-membered heteroaryl), 4- to 6-membered heterocyclyl, -C(O)(4- to 6-membered heterocyclyl), or $-CH_2C(O)$(4- to 6-membered heterocyclyl), wherein the heteroaryl and heterocyclyl contain 1-3 heteroatoms selected from N and O, and wherein the heteroaryl and heterocyclyl are optionally substituted by 1-3 R^8; and

each R^8 is independently halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-NR^6R^7$, -OH, oxo, $-CO_2H$, $-O(C_1$-C_6 alkyl), $-CH_2-O(C_1$-C_6 alkyl), or $-(C_1$-C_6 alkyl)-OH.

3. The compound of claim 1, wherein the compound is of Formula (I-a1):



(I-a1)

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is thiazolylene;

Ring B is a 5- to 6-membered heteroarylene containing 1-3 heteroatoms selected from N and S;

Ring C is a fused bicyclic 9- to 10-membered heteroaryl or phenyl substituted by one R^4;

each R^1 is independently -OH, halo, oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -CN, $-N(H)C(O)R^6$, $-N(H)SO_2R^6$, $-SO_2NR^6R^7$, or $-C(O)N(H)SO_2R^6$;

each R^2 is independently C_1-C_6 alkyl, C_1-C_6 haloalkyl, or halo;

each R^3 is independently C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_3-C_6 cycloalkyl;

R^4 is -OH, $-OP(O)(OH)_2$, $-NO_2$, $-C(O)N(H)SO_2R^5$, 5- to 6-membered heteroaryl or heterocyclyl, or -C(O)N(H)-(5- to 6-membered heteroaryl or heterocyclyl), wherein the heteroaryl and heterocyclyl contain 1-4 heteroatoms selected from N, O, and S, and wherein the heterocyclyl is optionally substituted by 1-2 oxo groups;

m is 0-4;

n is 0-2;

o is 0-2;

R^5 is phenyl or C_1-C_6 alkyl;

X is $-CR^6R^7-$;

Y is -O-, -N(H)-, or a bond;

each R^6 and R^7 is independently H or C_1-C_6 alkyl;

Z is Z^2;

Z^2 is 5- to 6-membered heteroaryl, -C(O)(5- to 6-membered heteroaryl), $-CH_2C(O)$(5- to 6-membered heteroaryl), 4- to 6-membered heterocyclyl, -C(O)(4- to 6-membered heterocyclyl), or $-CH_2C(O)$(4- to 6-membered heterocyclyl), wherein the heteroaryl and heterocyclyl contain 1-3 heteroatoms selected from N and O, and wherein the heteroaryl and heterocyclyl are optionally substituted by 1-3 R^8; and

each R^8 is independently halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-NR^6R^7$, -OH, oxo, $-CO_2H$, $-O(C_1$-C_6 alkyl), $-CH_2-O(C_1$-C_6 alkyl), or $-(C_1$-C_6 alkyl)-OH.

4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Ring A is thiazolylene.

5. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein each R^3 is independently C_1-C_3 alkyl or C_3-C_6 cycloalkyl.

6. The compound of claim 4, or a pharmaceutically acceptable salt thereof, wherein each R^3 is independently $-CH_3$ or cyclopropyl.

7. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein o is 0 or 1.

8. The compound of any one of claims 1-2 or 4-7, or a pharmaceutically acceptable salt thereof, wherein Ring B is phenylene, pyridinylene, thiazolylene, pyrazolylene, pyrimidinylene, or thienylene.

9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein each R^2 is independently C_1-C_3 alkyl or halo.

10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein n is 0 or 1.

11. The compound of any one of claims 1-2 and 4-11, or a pharmaceutically acceptable salt thereof, wherein:

Ring C is a fused bicyclic 9-membered heteroaryl or heterocyclyl containing 1-4 heteroatoms selected from N and O, a 5- to 6-membered heteroaryl containing 1-4 nitrogen atoms, or phenyl substituted by one R^4.

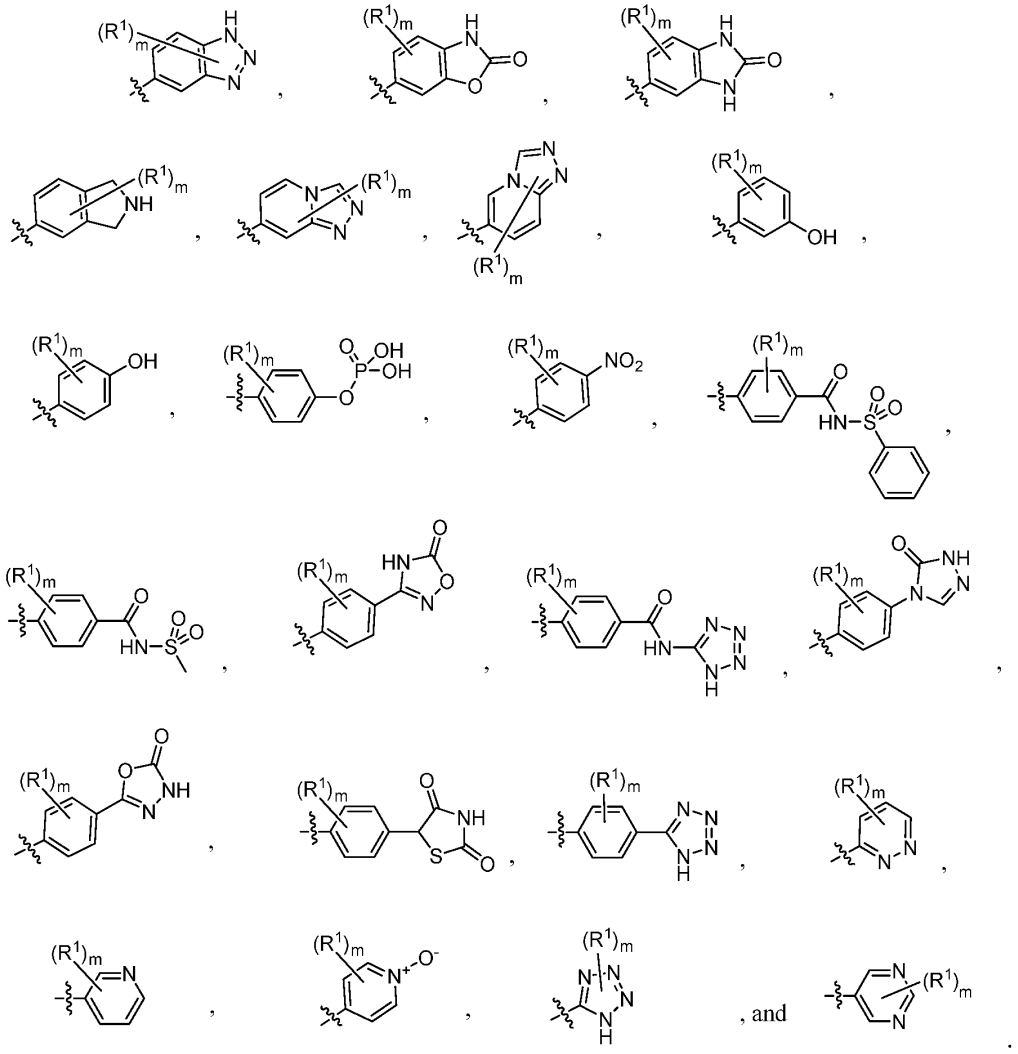
12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt thereof, wherein:

R^4 is -OH, $-OP(O)(OH)_2$, $-NO_2$, $-C(O)N(H)SO_2R^5$, 5- to 6-membered heteroaryl or heterocyclyl, or -C(O)N(H)-(5- to 6-membered heteroaryl or heterocyclyl),
wherein the heteroaryl and heterocyclyl contain 1-4 heteroatoms selected from N, O, and S, and wherein the heterocyclyl is optionally substituted by 1-2 oxo groups; and

R^5 is phenyl or C_1-C_3 alkyl.

13. The compound of any one of claims 1-2 and 4-12, or a pharmaceutically acceptable salt thereof, wherein:

Ring C-$(R^1)_m$ is selected from:



14. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, wherein:

each R^1 is independently -OH, halo, oxo, C_1-C_3 alkyl, C_1-C_3 haloalkyl, -CN, -N(H)C(O)R^6, -N(H)SO_2R^6, -$SO_2NR^6R^7$, or -C(O)N(H)SO_2R^6; and

each R^6 and R^7 is independently H or C_1-C_3 alkyl.

15. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, wherein:

each R^1 is independently -OH, F, oxo, $-CH_3$, -CN, -N(H)C(O)CH_3, -N(H)$SO_2(C_6H_5)$, -N(H)SO_2CH_3, -SO_2NH_2, or -C(O)N(H)SO_2CH_3.

16. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt thereof, wherein m is 0-3.

17. The compound of any one of claims 1 and 4-16, or a pharmaceutically acceptable salt thereof, wherein X is $-CR^6R^7-$.

18. The compound of any one of claims 1-3 and 17, or a pharmaceutically acceptable salt thereof, wherein R^6 and R^7 are each H.

19. The compound of any one of claims 1 and 4-16, or a pharmaceutically acceptable salt thereof, wherein X is a bond.

20. The compound of any one of claims 1-19, or a pharmaceutically acceptable salt thereof, wherein Y is -O-.

21. The compound of any one of claims 1-19, or a pharmaceutically acceptable salt thereof, wherein Y is -N(H)- or a bond.

22. The compound of any one of claims 1 and 4-21, or a pharmaceutically acceptable salt thereof, wherein Z is Z^1.

23. The compound of claim 22, or a pharmaceutically acceptable salt thereof, wherein:

Z^1 is H, C_1-C_3 alkyl, $-C(O)(C_1$-C_3 alkyl), $-CO_2(C_1$-C_3 alkyl), $-C(O)NR^6R^7$, $-C(O)NR^6(C_1$-C_3 alkylene)NR^6R^7, $-CR^6R^7C(O)NR^6R^7$, $-CR^6R^7NR^6R^7$, $-C(O)(C_1$-C_3 alkylene)NR^6R^7, $-NR^6C(O)(C_1$-C_3 alkyl), $-NR^6R^7$, $-(C_1$-C_3 alkyl)$-CO_2H$, $-(C_1$-C_3 alkyl)-OH, or $-C(NR^6R^7)$=N-CN, wherein C_1-C_3 alkylene is optionally substituted by 1-2 halo, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; and

each R^6 and R^7 is independently H or C_1-C_3 alkyl.

24. The compound of claim 22, or a pharmaceutically acceptable salt thereof, wherein:

Z^1 is H, $-CO_2CH_3$, $-CO_2C(CH_3)_3$, $-C(O)CH_3$, $-C(O)C(CH_3)_3$, $-C(N(CH_3)_2)$=N-CN, $-C(O)N(CH_3)_2$, $-CH_3$, $-CH_2CH_3$, $-CH_2C(CH_3)_3$, $-CH_2CO_2H$, $-CH_2C(CH_3)_2OH$,

$-C(O)N(CH_3)CH_2CH_2N(CH_3)_2$, $-CH_2C(O)N(CH_3)_2$, $-CH(CH_3)C(O)N(CH_3)_2$, $-N(CH_3)_2$, $-N(CH_3)C(O)CH_3$, or $-C(O)CH(CH_3)CH_2N(CH_3)_2$.

25. The compound of any one of claims 1-21, or a pharmaceutically acceptable salt thereof, wherein Z is Z^2.

26. The compound of claim 24, or a pharmaceutically acceptable salt thereof, wherein:

Z^2 is 5- to 6-membered heteroaryl, -C(O)(5- to 6-membered heteroaryl), $-CH_2C(O)$(5- to 6-membered heteroaryl), 4- to 6-membered heterocyclyl, -C(O)(4- to 6-membered heterocyclyl), or $-CH_2C(O)$(4- to 6-membered heterocyclyl), wherein the heteroaryl and heterocyclyl contain 1-2 heteroatoms selected from N and O, and wherein the heteroaryl and heterocyclyl are optionally substituted by 1-3 R^8.

27. The compound of claim 25, or a pharmaceutically acceptable salt thereof, wherein:

Z^2 is pyrimidinyl, pyridazinyl, pyrrolidinyl, piperidinyl, pyridazinyl, -C(O)(tetrahydropyranyl), -C(O)(pyrrolidinyl), -C(O)(pyridazinyl), -C(O)(piperidinyl), -C(O)(azetidinyl), -C(O)(pyrazolyl), -C(O)(piperazinyl), $-CH_2C(O)$(pyrrolidinyl), $-CH_2C(O)$(piperidinyl), or $-CH_2C(O)$(piperazinyl), wherein the heteroaryl and heterocyclyl are optionally substituted by 1-3 R^8.

28. The compound of any one of claims 1-21 and 25-27, or a pharmaceutically acceptable salt thereof, wherein:

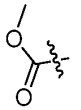
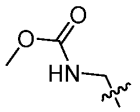
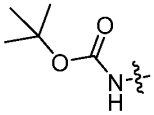
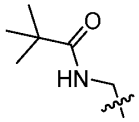
each R^8 is independently halo, C_1-C_3 alkyl, C_1-C_3 haloalkyl, $-NR^6R^7$, -OH, oxo, $-CO_2H$, $-O(C_1$-C_3 alkyl), $-CH_2$-$O(C_1$-C_3 alkyl), or $-(C_1$-C_3 alkyl)-OH; and

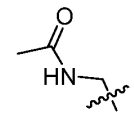
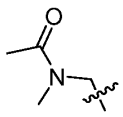
each R^6 and R^7 is independently H or C_1-C_3 alkyl.

29. The compound of claim 28, or a pharmaceutically acceptable salt thereof, wherein:

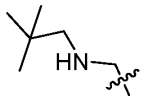
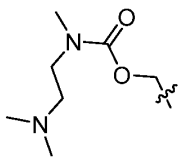
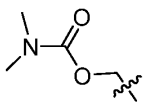
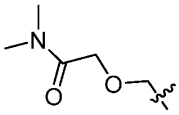
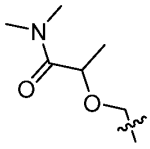
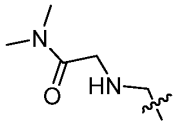
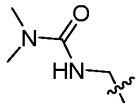
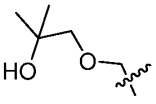
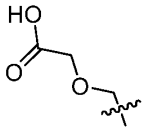
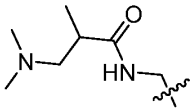
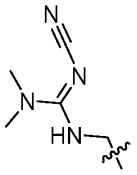
each R^8 is independently $-CH_3$, $-CH_2CH_3$, $-NH_2$, -OH, oxo, $-N(CH_3)_2$, $-OCH_3$, $-CH_2OCH_3$, $-CF_3$, $-CH_2CH_2OH$, $-CO_2H$, or Cl.

30. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Z-Y-X- is:


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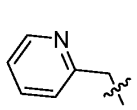
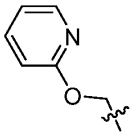
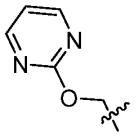
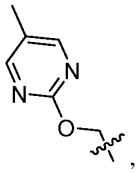
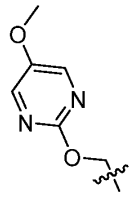
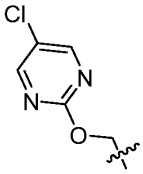
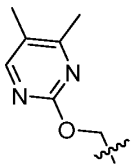
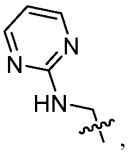
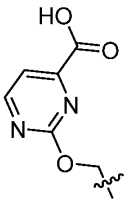
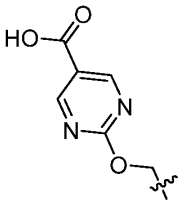
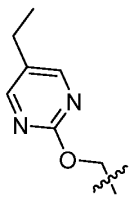
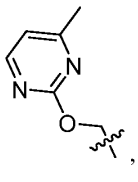

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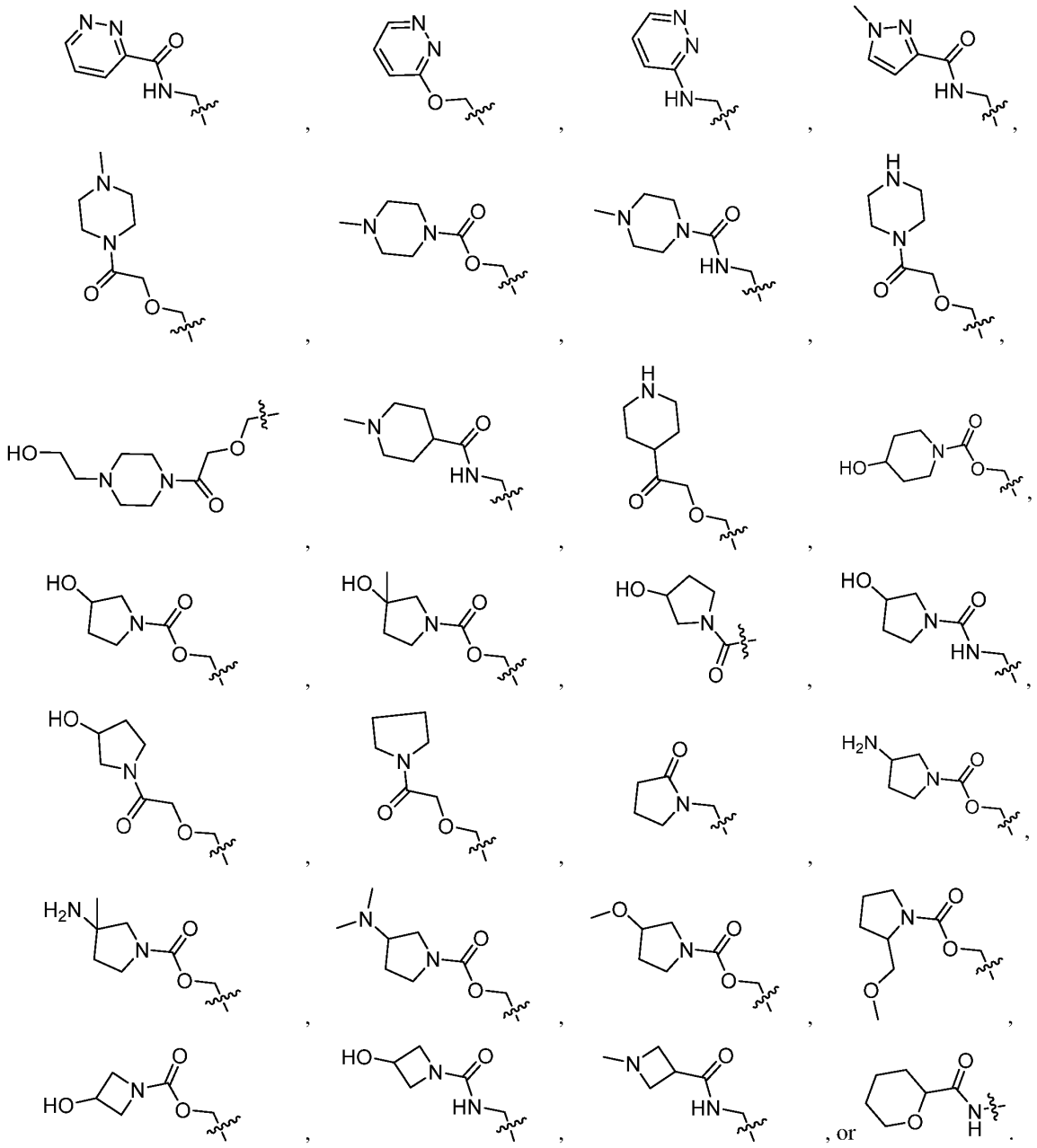
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-CH_3 ,

-CH_2OH , -OCH_2CH_3 , or -CH_2OCH_3.

31. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Z-Y-X- is:


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32. A compound selected from the compounds in Table 1, or a pharmaceutically acceptable salt thereof.

33. A compound selected from the compounds in Table 2, or a pharmaceutically acceptable salt thereof.

34. A pharmaceutical composition comprising the compound of any one of claims 1-33, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

35. A method of modulating bis-phosphoglycerate mutase (BPGM) comprising contacting an effective amount of the compound of any one of claims 1-33, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 34, with the BPGM.

36. A method of treating sickle cell disease in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the compound of any one of claims 1-33, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 34.