

FUSED BICYCLIC HETEROCYCLIC OR HETEROARYL AMIDE COMPOUNDS

[0001] In various embodiments, the present disclosure generally relates to novel compounds, compositions comprising the same, methods of preparing and methods of using the same, e.g., for inhibiting Polθ enzyme activity and/or for treating or preventing a disease or disorder described herein.

BACKGROUND

[0002] DNA polymerase theta (Polθ) is encoded by the *POLQ* gene and mediates one of the three major double strand break (DSB) repair pathways: theta-mediated end joining (TMEJ). DNA repair deficient cancers often become dependent on backup DNA repair pathways. When non-homologous end joining (NHEJ) and/or homologous recombination (HR) in a cancer cell are not functioning properly, Polθ is usually overexpressed and TMEJ is activated to provide a backup pathway for DSB repairs for the cancer cell's survival (*see e.g.*, Barszczewska-Pietraszek, G. *et al. Int. J. Mol. Sci.* 24:319 (2023)). TMEJ pathway activation is also observed in NHEJ-proficient cells.

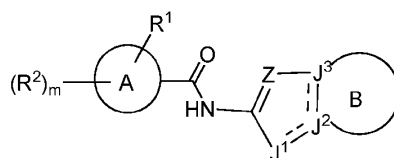
[0003] Polθ is a promising target for anticancer drug development, especially in cancers with DNA repair deficiency. Polθ knockout in non-cancerous cells had minimal effect. However, Polθ overexpression has been identified in various human cancers, such as breast cancer, lung cancer, ovarian cancer, etc. It has also been reported that Polθ overexpression is associated with poor clinical outcomes in breast or liver cancer patients with HR deficiency. Inhibition of Polθ was shown to kill cancer cells both *in vitro* and *in vivo*. In addition, inhibition of Polθ was shown to activate the cGAS-STING pathway and can be used in combination with an immune checkpoint inhibitor for treating BRCA-deficient cancer. *See e.g.*, Patterson-Fortin, J. *et al. Nature Communications* 14:1390 (2023). Additionally, inhibition of Polθ can enhance the effect of a poly (ADP-ribose) polymerase (PARP) inhibitor and can overcome PARP inhibitor resistance.

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BRIEF SUMMARY

[0004] In various embodiments, the present disclosure is based in part on the discovery of certain novel bicyclic heterocyclic or heteroaryl amide compounds that can be Polθ inhibitors and can be used for inhibiting Polθ enzyme activity in a cell (e.g., a cancer cell) and/or for treating or preventing a disease or disorder associated with Polθ, such as cancer, as described herein.

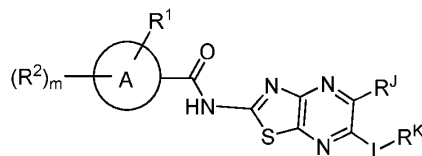
[0005] In some embodiments, the present disclosure provides a compound of Formula A, or a pharmaceutically acceptable salt thereof:



Formula A,

wherein the variables are defined herein. In some embodiments, the compound of Formula A can be characterized as having a structure according to a subformula selected from Formula I, I-1, I-1a, I-1b, I-1c, I-1d, I-1e, I-1f, I-1g, II, II-1, III, III-1, A1, A2, A3, A1a, A1b, A1c, A2a, A2b, A2c, A2b-1, A2b-2, A2b-3, A2b-4, A2b-5, or A2b-6, as defined herein.

[0006] In some embodiments, the present disclosure provides a compound of Formula K, or a pharmaceutically acceptable salt thereof:



Formula K

wherein the variables are defined herein. In some embodiments, the compound of Formula K can be characterized as having a structure according to a subformula selected from Formula K-1, K-2, K-3, K-4, K-5, K-6, K-7a, K-7b, K-8a, K-8b, K-9a, K-9b, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, K-1b-4, K-3a, K-3b, K-5a, or K-5b, as defined herein.

[0007] In some embodiments, the present disclosure also provides a compound selected from Table 1 herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the present disclosure also provides a compound selected from Examples 1-266 herein, or a pharmaceutically acceptable salt thereof.

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[0008] Some embodiments of the present disclosure are directed to a pharmaceutical composition comprising one or more compounds of the present disclosure (e.g., a compound of Formula A (e.g., Formula I, I-1, I-1a, I-1b, I-1c, I-1d, I-1e, I-1f, I-1g, II, II-1, III, III-1, A1, A2, A3, A1a, A1b, A1c, A2a, A2b, A2c, A2b-1, A2b-2, A2b-3, A2b-4, A2b-5, or A2b-6), Formula K (e.g., Formula K-1, K-2, K-3, K-4, K-5, K-6, K-7a, K-7b, K-8a, K-8b, K-9a, K-9b, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, K-1b-4, K-3a, K-3b, K-5a, or K-5b), any of Examples 1-266, any of the compounds listed in Table 1 herein, or a pharmaceutically acceptable salt thereof) and optionally a pharmaceutically acceptable excipient. The pharmaceutical composition described herein can be formulated for different routes of administration, such as for oral administration or parenteral injection.

[0009] Certain embodiments of the present disclosure are directed to a method of treating a disease or disorder associated with Polθ, such as a cancer herein. In some embodiments, the method comprises administering to a subject in need thereof a therapeutically effective amount of a compound of the present disclosure (e.g., a compound of Formula A (e.g., Formula I, I-1, I-1a, I-1b, I-1c, I-1d, I-1e, I-1f, I-1g, II, II-1, III, III-1, A1, A2, A3, A1a, A1b, A1c, A2a, A2b, A2c, A2b-1, A2b-2, A2b-3, A2b-4, A2b-5, or A2b-6), Formula K (e.g., Formula K-1, K-2, K-3, K-4, K-5, K-6, K-7a, K-7b, K-8a, K-8b, K-9a, K-9b, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, K-1b-4, K-3a, K-3b, K-5a, or K-5b), any of Examples 1-266, any of the compounds listed in Table 1 herein, or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition herein.

[0010] Certain embodiments of the present disclosure are directed to a method of treating a cancer. In some embodiments, the cancer is a homologous recombination (HR) deficient cancer. In some embodiments, the cancer is characterized by a reduction or absence of BRCA gene expression, the absence of the BRCA gene, and/or reduced function of BRCA protein. In some embodiments, the cancer is resistant to poly(ADP-ribose) polymerase (PARP) inhibitor therapy. In some embodiments, the method comprises administering to a subject in need thereof a therapeutically effective amount of a compound of the present disclosure (e.g., a compound of Formula A (e.g., Formula I, I-1, I-1a, I-1b, I-1c, I-1d, I-1e, I-1f, I-1g, II, II-1, III, III-1, A1, A2, A3, A1a, A1b, A1c, A2a, A2b, A2c, A2b-1, A2b-2, A2b-3, A2b-4, A2b-5, or A2b-6), Formula K (e.g., Formula K-1, K-2, K-3, K-4, K-5, K-6, K-7a, K-7b, K-8a, K-8b, K-9a, K-9b, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, K-1b-4, K-3a, K-3b, K-5a, or K-5b), any of Examples 1-266, any of the compounds listed in Table

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l herein, or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition herein.

[0011] The administering in the methods herein is not limited to any particular route of administration. For example, in some embodiments, the administering can be orally, nasally, transdermally, pulmonary, inhalationally, buccally, sublingually, intraperitoneally, subcutaneously, intramuscularly, intravenously, rectally, intrapleurally, intrathecally, or parenterally. In some embodiments, the administering is orally. In some embodiments, the administering is a parenteral injection, such as an intravenous injection.

[0012] Compounds of the present disclosure can be used as a monotherapy or in a combination therapy. In some embodiments according to the methods described herein, one or more compounds of the present disclosure can be administered as the only active ingredient(s). In some embodiments, the method herein further comprises administering to the subject an additional therapeutic agent, such as additional anticancer agents described herein, for example, a PARP inhibitor, a signal transduction inhibitor, a chemotherapeutic agent, and/or an immune checkpoint inhibitor.

[0013] It is to be understood that both the foregoing summary and the following detailed description are exemplary and explanatory only, and are not restrictive of the invention herein.

DETAILED DESCRIPTION

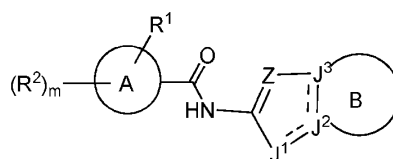
[0014] In various embodiments, provided herein are novel compounds, pharmaceutical compositions, methods of preparation and methods of use. The compounds of the present disclosure are generally Polθ inhibitors, which are also useful for treating various diseases or disorders, such as those described herein, e.g., cancer.

Compounds

Formula A

[0015] In some embodiments, the present disclosure provides a compound of Formula A, or a pharmaceutically acceptable salt thereof:

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Formula A,

wherein:

J¹ is S, O, N, CR^{10A} or NR^{10B};

J² is C or N;

J³ is C or N;

Z is N or CR^{10A}, preferably, Z is N;

provided that the 5-membered ring containing Z, J¹, J², and J³ is a heteroaryl ring having 1-3 ring heteroatoms;

Ring A is a phenyl ring or 5-10-membered heteroaryl ring having 1 to 4 ring heteroatoms independently selected from N, O, and S;

Ring B is an optionally substituted 5-7 membered carbocyclic or heterocyclic ring, or an optionally substituted phenyl ring, or an optionally substituted 5 or 6-membered heteroaryl ring having 1-3 ring heteroatoms each independently N, S, or O; preferably, Ring B is an optionally substituted 6-membered heteroaryl ring having 1 or 2 ring nitrogen atoms;

R¹ is an optionally substituted phenyl, optionally substituted naphthyl, an optionally substituted 3-10 membered carbocyclic, or an optionally substituted 5-10 membered heterocyclic or heteroaryl, preferably, R¹ is ortho to the amide group (-C(O)-NH-) shown in Formula A;

the subscript **m** is an integer of 0-4, as valency permits;

R² at each occurrence is independently deuterium, halogen, OH, NH₂, CN, SF₅, COOH, CONH₂, SO₂NH₂, R²⁰, OR²⁰, SR²⁰, N(R²⁰)(R²¹), SO₂R²⁰, SO₂N(R²⁰)(R²¹), N(R²¹)SO₂R²⁰, COR²⁰, CON(R²⁰)(R²¹), or N(R²¹)COR²⁰, wherein R²⁰ at each occurrence is independently an optionally substituted C₁₋₆ alkyl, an optionally substituted C₂₋₆ alkenyl, an optionally substituted C₂₋₆ alkynyl, an optionally substituted C₁₋₆ heteroalkyl, or an optionally substituted 3-10 membered ring structure; and R²¹ at each occurrence is independently hydrogen, an optionally substituted C₁₋₆ alkyl, an optionally substituted C₃₋₆ alkenyl, an optionally substituted C₃₋₆ alkynyl, an optionally substituted C₁₋₆ heteroalkyl, or an optionally substituted 3-10 membered ring structure; or as applicable, R²⁰ and R²¹

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together with the intervening atom (e.g., the nitrogen atom) or atoms are joined to form an optionally substituted 4-8 membered heterocyclic ring;

or two instances of R² are joined to form an optionally substituted 4-7 membered ring;

wherein:

R^{10A} at each occurrence is independently hydrogen, deuterium, halogen, CN, or a C₁₋₃ alkyl optionally substituted with deuterium or F; and

R^{10B} is hydrogen or a C₁₋₃ alkyl optionally substituted with deuterium or F. As used herein, a variable attached to a nitrogen or oxygen atom or a sulfur atom in a non-oxidized form, should preferably not connect with the nitrogen or oxygen atom or the sulfur atom through a carbon atom of a carbon carbon double bond of an alkenyl or a carbon carbon triple bond of an alkynyl, and thus such variable preferably does not include a C₂ alkenyl or C₂ alkynyl.

[0016] In some embodiments, the compound of Formula A (including any of the applicable sub-formulae as described herein) can comprise one or more asymmetric centers and/or axial chirality, and thus can exist in various stereoisomeric forms, *e.g.*, enantiomers and/or diastereomers. In some embodiments, the compound of Formula A can exist in the form of an individual enantiomer and/or diastereomer, as applicable, or a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomers. In some embodiments, when applicable, the compound of Formula A (including any of the applicable sub-formulae as described herein) can exist as an individual enantiomer substantially free of the other enantiomer, such as having an enantiomeric excess ("ee") of greater than 60%, preferably, greater than 80% ee, greater than 90% ee, greater than 95% ee, greater than 98% ee, or greater than 99% ee. In some embodiments, when applicable, the compound of Formula A (including any of the applicable sub-formulae as described herein) can also exist as a mixture of stereoisomers in any ratio, such as a racemic mixture.

[0017] In some embodiments, the compound of Formula A (including any of the applicable sub-formulae as described herein) can exist as an isotopically labeled compound, particularly, a deuterated analog, wherein one or more of the hydrogen atoms of the compound of Formula A is/are substituted with a deuterium atom with an abundance above its natural abundance, *e.g.*, a CD₃ analog when the compound has a CH₃ group. Without wishing to be bound by theories, it is believed that in certain situations, substitution with

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deuterium can lead to a deuterated analog with a better pharmacokinetic profile. Deuterated analogs can be generally prepared by using commercially available deuterating reagents.

[0018] It should be apparent to those skilled in the art that in certain cases, the compound of Formula A may exist as a mixture of tautomers. The present disclosure is not limited to any specific tautomer. Rather, the present disclosure encompasses any and all of such tautomers whether or not explicitly drawn or referred to.

[0019] In Formula A (including any applicable subformulae), the 5-membered ring containing Z, J¹, J², and J³ is a heteroaryl ring having 1-3, such as 2 ring heteroatoms. Typically, Z in the 5-membered ring is N. In some embodiments, Z is N, and the 5-membered ring has one additional ring heteroatom, such as an additional ring oxygen, sulfur, or nitrogen. In some embodiments, J¹ is CR^{10A} (e.g., CH). In some embodiments, Z is N and J¹ is CR^{10A} (e.g., CH). In some preferred embodiments, the 5-membered ring is a thiazole ring, wherein Z is N, J¹ is S, and J² and J³ are C. In some embodiments, the 5-membered ring can be an oxazole, imidazole, or pyrazole ring. For example, in some embodiments, Z is N, J¹ is CR^{10A} (e.g., CH), and J² is C and J³ is N. In some embodiments, Z is N, J¹ is CR^{10A} (e.g., CH), and J³ is C and J² is N. Typically, in embodiments wherein J¹ is CR^{10A}, R^{10A} is hydrogen, halogen, or methyl optionally substituted with deuterium or F, preferably, R^{10A} is hydrogen. In some embodiments, Z can be CR^{10A}, wherein R^{10A} is defined herein.

[0020] In Formula A (including any applicable subformulae), Ring B is typically an optionally substituted phenyl ring, or an optionally substituted 5 or 6-membered heteroaryl ring having 1-3 ring heteroatoms each independently N, S, or O. For example, Ring B can be a benzene, pyridine, pyridone (e.g., pyridin-2-one), pyrazine, pyridazine, or pyrimidine ring, each of which is optionally substituted. To be clear, as used herein, a pyridone is considered a 6-membered heteroaryl ring. When substituted, the phenyl or 5 or 6-membered heteroaryl ring can preferably be substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, NH₂, SF₅, CN, or -Y¹-Y², wherein Y¹ is null, O, S, NH, NY³, C(O), SO₂, C(O)NH, C(O)NY³, P(O)Y³, SO₂NH, or SO₂NY³, and each of Y² and Y³ at each occurrence is independently an optionally substituted C₁₋₆ alkyl, an optionally substituted C₂₋₆ alkenyl, an optionally substituted C₂₋₆ alkynyl, an optionally substituted C₁₋₆ heteroalkyl, an optionally substituted 3-10 membered carbocyclic or heterocyclic ring, an optionally substituted phenyl, or an optionally substituted 5 or 6-membered heteroaryl. Preferably, in the definition of variables or substituents herein, or the combination of

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substituents and/or variables herein, a carbon atom of a carbon-carbon double bond of an alkenyl or carbon-carbon triple bond of an alkynyl group is not directly bonded with an oxygen or nitrogen atom. To be clear, unless otherwise specified or contrary from context, as used herein, a bivalent structure herein, such as a $-Y^1-$ as defined herein, can connect to the remainder of the molecule in either direction. For example, when $-Y^1-$ is stated to be $C(O)NY^3$, then the moiety $-Y^1-Y^2$ can be $-C(O)N(Y^3)-Y^2$ or $-N(Y^3)C(O)-Y^2$. Other similar expressions should be understood similarly.

[0021] In some preferred embodiments, the optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} heteroalkyl, 3-10 membered carbocyclic or heterocyclic ring, phenyl, or 5 or 6-membered heteroaryl, referred to in the definition of Y^2 and Y^3 herein, can be independently unsubstituted or substituted with one or more (e.g., 1-3) substituents each independently selected from deuterium, halogen, OH, NH_2 , SF_5 , CN, or $-Y^{1A}-Y^{2A}$, wherein Y^{1A} is null, O, S, NH, NY^{3A} , $C(O)$, SO_2 , $C(O)NH$, $C(O)NY^{3A}$, $P(O)Y^{3A}$, SO_2NH , or SO_2NY^{3A} , and each of Y^{2A} and Y^{3A} at each occurrence is independently (i) C_{1-6} alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, C_{1-4} alkoxy, or a 3-6 membered ring, (ii) C_{2-6} alkenyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, C_{1-4} alkoxy, or a 3-6 membered ring, (iii) C_{2-6} alkynyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, C_{1-4} alkoxy, or a 3-6 membered ring, (iv) C_{1-6} heteroalkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, C_{1-4} alkoxy, or a 3-6 membered ring, (v) a 3-8 membered carbocyclic or heterocyclic optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, oxo, OH, CN, C_{1-4} alkyl, C_{1-4} alkoxy, or a 3-6 membered ring; or (vi) a phenyl or 5 or 6-membered heteroaryl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, OH, CN, C_{1-4} alkyl, C_{1-4} alkoxy, or a 3-6 membered ring (preferably carbocyclic or heterocyclic ring); wherein each of the 3-6 membered ring referred to in (i)-(vi) can be independently selected from 3-6 membered carbocyclic or heterocyclic ring, phenyl, or a 5, or 6-membered heteroaryl, and wherein each of the C_{1-4} alkyl, C_{1-4} alkoxy, or 3-6 membered ring referred to in (i)-(vi) is independently unsubstituted or substituted with one or more (e.g., 1-3) substituents independently selected from deuterium, halogen (e.g., F), CN, OH, oxo (as applicable), C_{1-4} alkyl (e.g., methyl) optionally substituted with deuterium or F, C_{1-4}

heteroalkyl (e.g., methoxy) optionally substituted with deuterium or F, or 3-4 membered carbocyclic or heterocyclic ring (e.g., cyclopropyl, cyclobutyl, azetidiny, oxetanyl, etc.) optionally substituted with deuterium, F, OH, and/or methyl.

[0022] In some preferred embodiments, the optionally substituted C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ heteroalkyl, 3-10 membered carbocyclic or heterocyclic ring, phenyl, or 5 or 6-membered heteroaryl, referred to in the definition of Y² and Y³ herein, can be independently unsubstituted or substituted with one or more (e.g., 1-3) substituents each independently selected from deuterium, halogen, OH, CN, C₁₋₄ alkyl optionally substituted with deuterium or F, C₁₋₄ heteroalkyl optionally substituted with deuterium or F, or a 3-6 membered ring (e.g., 3-6 membered carbocyclic or heterocyclic ring, phenyl, or 5, or 6-membered heteroaryl) optionally substituted with oxo, deuterium, halogen, OH, CN, C₁₋₄ alkyl optionally substituted with deuterium or F, or C₁₋₄ heteroalkyl optionally substituted with deuterium or F.

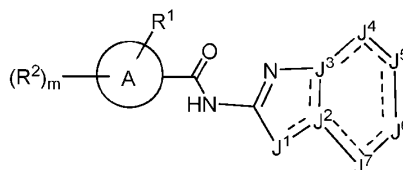
[0023] In some preferred embodiments, each occurrence of the C₁₋₆ heteroalkyl as referred to in the definition of Y², Y³, Y^{2A}, or Y^{3A}, is independently a C₁₋₆ alkoxy, NH(C₁₋₆ alkyl), N(C₁₋₄ alkyl)(C₁₋₄ alkyl), -(C₁₋₅ alkylene)-O-(C₁₋₅ alkyl), -(C₁₋₅ alkylene)-NH(C₁₋₅ alkyl), -(C₁₋₄ alkylene)-N(C₁₋₄ alkyl)(C₁₋₄ alkyl), -(C₁₋₅ alkylene)-S-(C₁₋₅ alkyl), -(C₁₋₅ alkylene)-SO₂-(C₁₋₅ alkyl), SO₂(C₁₋₆ alkyl), P(O)(C₁₋₄ alkyl)(C₁₋₄ alkyl), SO₂NH(C₁₋₆ alkyl), SO₂N(C₁₋₄ alkyl)(C₁₋₄ alkyl), -(C₁₋₅ alkylene)-SO₂NH-(C₁₋₅ alkyl), or -(C₁₋₄ alkylene)-SO₂N(C₁₋₄ alkyl)(C₁₋₄ alkyl), provided that the total number of carbons are no greater than 6, not counting any optional substituents. It should be noted that for "N(C₁₋₄ alkyl)(C₁₋₄ alkyl)", the two C₁₋₄ alkyl can be the same or different, for example, both N(CH₃)₂ and N(CH₃)(C₂H₅) are within the definition of N(C₁₋₄ alkyl)(C₁₋₄ alkyl) herein. Unless otherwise specified or contrary from context, other similar expressions herein of a variable containing two or more groups of the same type (e.g., two alkyl groups) which are also designated as having the same range of carbon atoms should be understood similarly, i.e., the two or more groups are independently selected and can be the same or different.

[0024] In some preferred embodiments, each occurrence of the C₁₋₄ heteroalkyl as referred to in the definition of Y², Y³, Y^{2A}, or Y^{3A}, is independently a C₁₋₄ alkoxy, NH(C₁₋₄ alkyl), N(C₁₋₃ alkyl)(C₁₋₃ alkyl), -(C₁₋₃ alkylene)-O-(C₁₋₃ alkyl), -(C₁₋₃ alkylene)-NH(C₁₋₃ alkyl), -(C₁₋₂ alkylene)-N(C₁₋₂ alkyl)(C₁₋₂ alkyl), -(C₁₋₃ alkylene)-S-(C₁₋₃ alkyl), -(C₁₋₃ alkylene)-SO₂-(C₁₋₃ alkyl), SO₂(C₁₋₄ alkyl), P(O)(C₁₋₃ alkyl)(C₁₋₃ alkyl), SO₂NH(C₁₋₄ alkyl),

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SO₂N(C₁₋₃ alkyl)(C₁₋₃ alkyl), -(C₁₋₃ alkylene)-SO₂NH-(C₁₋₃ alkyl), or -(C₁₋₂ alkylene)-SO₂N(C₁₋₂ alkyl)(C₁₋₂ alkyl), provided that the total number of carbons are no greater than 4, not counting any optional substituents.

[0025] In some preferred embodiments, the compound of Formula A (including any applicable subformulae) can be characterized as having a structure according to Formula I:



Formula I

wherein:

J⁴ is CR¹¹ or N;

J⁵ is CR¹² or N;

J⁶ is CR^{13A} or N, and **J⁷** is CR¹⁴ or N; or

J⁶ is NR^{13B} and **J⁷** is C(O);

provided that the bicyclic ring containing J¹, J², J³, J⁴, J⁵, J⁶, and J⁷ is a heteroaryl ring having 1-4 ring heteroatoms in addition to the ring nitrogen atom shown in Formula I;

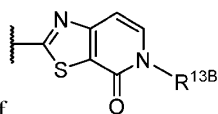
R¹¹, **R¹²**, **R^{13A}**, and **R¹⁴** are each independently hydrogen, deuterium, halogen, OH, NH₂, SF₅, CN, or -Y¹-Y², wherein Y¹ is null, O, S, NH, NY³, C(O), SO₂, C(O)NH, C(O)NY³, P(O)Y³, SO₂NH, or SO₂NY³, and Y² and Y³ are each independently an optionally substituted C₁₋₆ alkyl, an optionally substituted C₂₋₆ alkenyl, an optionally substituted C₂₋₆ alkynyl, an optionally substituted C₁₋₆ heteroalkyl, an optionally substituted 3-10 membered carbocyclic or heterocyclic ring, an optionally substituted phenyl, or an optionally substituted 5 or 6-membered heteroaryl; and

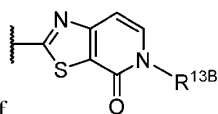
R^{13B} is hydrogen, an optionally substituted C₁₋₆ alkyl, an optionally substituted C₃₋₆ alkenyl, an optionally substituted C₃₋₆ alkynyl, an optionally substituted C₁₋₆ heteroalkyl, an optionally substituted 3-10 membered carbocyclic or heterocyclic ring, an optionally substituted phenyl, or an optionally substituted 5 or 6-membered heteroaryl,

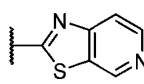
wherein J¹, J², J³, Ring A, R¹, m, and R² are defined herein.

[0026] To be clear, a bicyclic ring having J⁶ as NR^{13B} and J⁷ as C(O) is considered a heteroaryl ring if the bicyclic ring is aromatic when J⁶-J⁷ is replaced with C=N. For example,

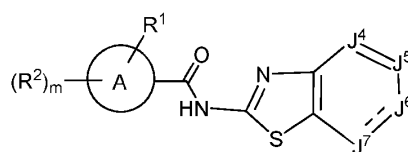
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the bicyclic ring of  is considered a heteroaryl ring herein, as when the C(O)-NR^{13B} portion of the ring (i.e., a J⁶-J⁷) is replaced with C=N, the resulting ring has a

structure of , which is aromatic.

[0027] In some preferred embodiments, J¹ in Formula I is S, and J² and J³ are C, and the compound can have a structure according to Formula I-1:



Formula I-1,

wherein the variables are defined herein. The bond between J⁶ and J⁷ can be a single bond when J⁶ is NR^{13B} and J⁷ is C(O). In other embodiments, wherein J⁶ is CR^{13A} or N, and J⁷ is CR¹⁴ or N, the bond between J⁶ and J⁷ is a double bond.

[0028] In some embodiments, in Formula I or I-1, J⁴ is N.

[0029] In some embodiments, in Formula I or I-1, J⁵ is N.

[0030] In some embodiments, in Formula I or I-1, J⁷ is N.

[0031] In some embodiments, in Formula I or I-1, J⁴ is N, J⁵ is CR¹², and J⁷ is CR¹⁴.

[0032] In some embodiments, in Formula I or I-1, J⁵ is N, J⁴ is CR¹¹, and J⁷ is CR¹⁴.

[0033] In some embodiments, in Formula I or I-1, J⁷ is N, J⁴ is CR¹¹, and J⁵ is CR¹².

[0034] In some embodiments, in Formula I or I-1, J⁴ and J⁷ are both N, and J⁵ is CR¹².

[0035] In some embodiments, in Formula I or I-1, J⁴ and J⁵ are both N, and J⁷ is CR¹⁴.

[0036] In some embodiments, in Formula I or I-1, J⁴ is CR¹¹, and J⁵ and J⁷ are both N.

[0037] Typically, in embodiments where J⁴ is CR¹¹, R¹¹ is hydrogen. In some embodiments, R¹¹ can be deuterium, halogen, OH, NH₂, SF₅, CN, or -Y¹-Y², as defined herein. For example, in some embodiments, R¹¹ can be halogen, such as F or Cl, CN, an optionally substituted C₁₋₆ alkyl, or an optionally substituted C₁₋₆ heteroalkyl. In some embodiments, R¹¹ can be halogen, CN, a C₁₋₄ alkyl optionally substituted with deuterium or F, or a C₁₋₄ heteroalkyl (e.g., a C₁₋₄ alkoxy) optionally substituted with deuterium or F.

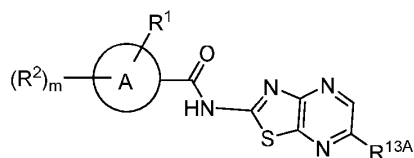
[0038] Typically, in embodiments where J⁵ is CR¹², R¹² is hydrogen. In some embodiments, R¹² can be deuterium, halogen, OH, NH₂, SF₅, CN, or -Y¹-Y², as defined

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herein. For example, in some embodiments, R^{12} can be halogen, such as F or Cl, CN, an optionally substituted C_{1-6} alkyl, or an optionally substituted C_{1-6} heteroalkyl. In some embodiments, R^{12} can be halogen, CN, a C_{1-4} alkyl optionally substituted with deuterium or F, or a C_{1-4} heteroalkyl (e.g., a C_{1-4} alkoxy) optionally substituted with deuterium or F.

[0039] Typically, in embodiments where J^7 is CR^{14} , R^{14} is hydrogen. In some embodiments, R^{14} can be deuterium, halogen, OH, NH_2 , SF_5 , CN, or $-Y^1-Y^2$, as defined herein. For example, in some embodiments, R^{14} can be halogen, such as F or Cl, CN, an optionally substituted C_{1-6} alkyl, or an optionally substituted C_{1-6} heteroalkyl. In some embodiments, R^{14} can be halogen, CN, a C_{1-4} alkyl optionally substituted with deuterium or F, or a C_{1-4} heteroalkyl (e.g., a C_{1-4} alkoxy) optionally substituted with deuterium or F.

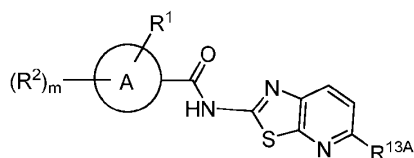
[0040] Typically, in Formula I or I-1, J^6 is CR^{13A} , wherein R^{13A} is defined herein. For example, in some embodiments, the compound of Formula I or I-1 can be characterized as having a structure according to Formula I-1a:



Formula I-1a,

wherein R^{13A} , Ring A, R^1 , m , and R^2 are defined herein.

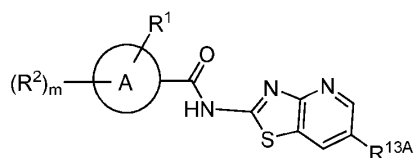
[0041] In some embodiments, the compound of Formula I or I-1 can be characterized as having a structure according to Formula I-1b:



Formula I-1b,

wherein R^{13A} , Ring A, R^1 , m , and R^2 are defined herein.

[0042] In some embodiments, the compound of Formula I or I-1 can be characterized as having a structure according to Formula I-1c:

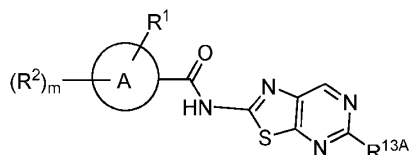


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Formula I-1c,

wherein R^{13A} , Ring A, R^1 , m, and R^2 are defined herein.

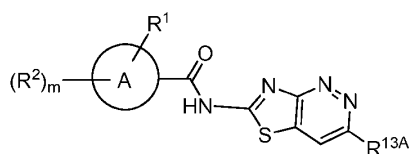
[0043] In some embodiments, the compound of Formula I or I-1 can be characterized as having a structure according to Formula I-1d:



Formula I-1d,

wherein R^{13A} , Ring A, R^1 , m, and R^2 are defined herein.

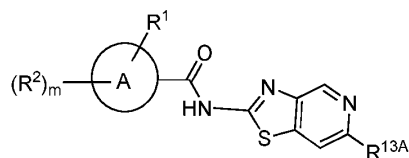
[0044] In some embodiments, the compound of Formula I or I-1 can be characterized as having a structure according to Formula I-1e:



Formula I-1e,

wherein R^{13A} , Ring A, R^1 , m, and R^2 are defined herein.

[0045] In some embodiments, the compound of Formula I or I-1 can be characterized as having a structure according to Formula I-1f:



Formula I-1f,

wherein R^{13A} , Ring A, R^1 , m, and R^2 are defined herein.

[0046] In some embodiments according to Formula I or I-1 (e.g., Formula I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f), J^6 is CR^{13A} , and R^{13A} is hydrogen.

[0047] In some embodiments according to Formula I or I-1 (e.g., Formula I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f), J^6 is CR^{13A} , and R^{13A} is halogen, such as F, Cl, or Br.

[0048] In some embodiments according to Formula I or I-1 (e.g., Formula I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f), J^6 is CR^{13A} , and R^{13A} is CN.

[0049] In some embodiments according to Formula I or I-1 (e.g., Formula I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f), J^6 is CR^{13A} , and R^{13A} is $-Y^1-Y^2$ as defined herein. For example, in some embodiments, R^{13A} is $-Y^1-Y^2$, wherein Y^1 is null, in other words, R^{13A} is Y^2 as defined herein. In some embodiments, R^{13A} is Y^2 , wherein Y^2 is an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, or an optionally substituted C_{2-6} alkynyl. In some embodiments, R^{13A} is Y^2 , wherein Y^2 is an optionally substituted C_{1-6} heteroalkyl.

[0050] In some embodiments according to Formula I or I-1 (e.g., Formula I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f), J^6 is CR^{13A} , and R^{13A} is $-Y^1-Y^2$, wherein Y^1 is O, NH, or NY^3 , wherein Y^2 and Y^3 are defined herein.

[0051] In some preferred embodiments, R^{13A} is Y^2 , wherein Y^2 is an optionally substituted 3-10 membered carbocyclic or heterocyclic ring. Suitable 3-10 membered carbocyclic or heterocyclic rings are not particularly limited and include those described herein, which can be monocyclic or have a fused, spiro, or bridged bicyclic structure. In some embodiments, the 3-10 membered carbocyclic ring can have two rings in which one of the rings is phenyl and the other ring is fused to the phenyl ring. In some embodiments, the 3-10 membered heterocyclic ring can have 1-4 ring heteroatoms each independently N, O, or S, wherein the S atom is optionally oxidized such as existing as $S=O$, SO_2 , etc. In some embodiments, the 3-10 membered heterocyclic ring can have two rings in which one of the rings is phenyl or 5, or 6-membered heteroaryl, and the other ring is fused to the phenyl or heteroaryl ring.

[0052] In some embodiments, Y^2 can be a C_{3-7} cycloalkyl, which is optionally substituted with one or more substituents herein, e.g., one or more substituents independently selected from halogen (e.g., F), OH, C_{1-4} alkyl optionally substituted with deuterium or F, or C_{1-4} heteroalkyl optionally substituted with deuterium or F. In some embodiments, Y^2 can be an unsubstituted C_{3-6} cycloalkyl, such as cyclopropyl.

[0053] In some embodiments, Y^2 can be a 4-10 membered heterocyclic ring, such as a 4-8 membered heterocyclic ring (e.g., tetrahydropyran, piperidine, etc.) having 1-3 ring heteroatoms each independently N, O, or S, wherein the S atom is optionally oxidized (e.g., as SO_2), which is optionally substituted with one or more substituents herein, e.g., one or more substituents independently selected from halogen (e.g., F), OH, C_{1-4} alkyl optionally substituted with deuterium or F, or C_{1-4} heteroalkyl optionally substituted with deuterium or

F. In some embodiments, Y^2 can be a tetrahydropyran or piperidine, which is optionally substituted with a C_{1-4} alkyl optionally substituted with deuterium or F.

[0054] In some preferred embodiments, R^{13A} is Y^2 , wherein Y^2 is an optionally substituted phenyl. In some preferred embodiments, R^{13A} is Y^2 , wherein Y^2 is an optionally substituted 5-membered heteroaryl having 1-4 ring heteroatoms each independently N, O, or S, such as an optionally substituted pyrazolyl. In some preferred embodiments, R^{13A} is Y^2 , wherein Y^2 is an optionally substituted 6-membered heteroaryl having 1 or 2 ring nitrogens, such as an optionally substituted pyridyl, pyrimidinyl, pyridazinyl, or pyrazinyl.

[0055] In some embodiments according to Formula I or I-1 (e.g., Formula I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f), J^6 is CR^{13A} , and R^{13A} can be hydrogen, halogen (e.g., Cl, Br, etc.), CN, an optionally substituted C_{1-4} alkyl, an optionally substituted C_{2-4} alkenyl, an optionally substituted C_{2-4} alkynyl, an optionally substituted C_{1-4} heteroalkyl, SF_5 , an optionally substituted C_{3-7} cycloalkyl, or an optionally substituted 4-10 membered heterocyclic ring having 1-3 ring heteroatoms each independently N, O, or S. In some preferred embodiments, when substituted, the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} heteroalkyl, C_{3-7} cycloalkyl, or 4-10 membered heterocyclic ring, is substituted with one or more (e.g., 1-3) substituents each independently selected from deuterium, halogen (e.g., F), OH, SF_5 , CN, oxo, $CONR^{30}R^{31}$, $N(R^{30})C(O)R^{31}$, $SO_2NR^{30}R^{31}$, $N(R^{30})SO_2R^{31}$, SR^{31} , OR^{31} , SO_2R^{31} , C_{1-4} alkyl optionally substituted with deuterium or F, or a 3-4 membered carbocyclic or heterocyclic ring (e.g., cyclopropyl, cyclobutyl, azetidyl, oxetanyl, etc.) optionally substituted with deuterium, F, OH, and/or methyl, wherein each of R^{30} and R^{31} at each occurrence is independently hydrogen, C_{1-4} alkyl optionally substituted with deuterium or F, or a 3-6 membered carbocyclic or heterocyclic ring (e.g., cyclopropyl, cyclobutyl, azetidyl, oxetanyl, etc.) optionally substituted with deuterium, F, OH, and/or methyl; or as applicable, R^{30} and R^{31} together with the intervening atom or atoms are joined to form an optionally substituted 4-8 membered heterocyclic ring (e.g., optionally substituted with deuterium, F, OH, and/or methyl). For example, in some embodiments, R^{13A} can be hydrogen, halogen (e.g., Cl or Br), CN, C_{1-4} alkyl optionally substituted with deuterium or F (e.g., CF_2H or CF_3), cyclopropyl, C_{1-4} alkoxy optionally substituted with deuterium or F (e.g., OCF_2H or OCF_3), or a 4-10 membered heterocyclic ring having 1-3 ring heteroatoms each independently N, O, or S, which is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, C_{1-4} alkyl optionally substituted with deuterium or F

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(e.g., CF₂H or CF₃), or C₁₋₄ alkoxy optionally substituted with deuterium or F (e.g., OCF₂H or OCF₃). In some embodiments, R^{13A} can be a 4-10 membered heterocycloalkyl ring having 1-3 ring heteroatoms each independently N, O, or S, such as a monocyclic 4-8 membered heterocycloalkyl, e.g., a tetrahydropyran or piperidinyl ring, which is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, C₁₋₄ alkyl optionally substituted with deuterium or F (e.g., CF₂H or CF₃), and C₁₋₄ alkoxy optionally substituted with deuterium or F (e.g., OCF₂H or OCF₃).

[0056] In some preferred embodiments according to Formula I or I-1 (e.g., Formula I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f), J⁶ is CR^{13A}, and R^{13A} is an optionally substituted phenyl. In some embodiments, the phenyl is unsubstituted or substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen (e.g., F, Cl, Br, etc.), CN, OH, NH₂, SF₅, G¹, or -X¹-X²-G¹,

wherein X¹ is null, C₁₋₄ alkylene or C₁₋₄ heteroalkylene, and

X² is O, S, NH, NG¹, C(O), SO₂, C(O)NH, C(O)NG¹, SO₂NH, or SO₂NG¹, and wherein G¹ at each occurrence is independently an optionally substituted C₁₋₄ alkyl, an optionally substituted C₂₋₄ alkenyl, an optionally substituted C₂₋₄ alkynyl, an optionally substituted C₁₋₄ heteroalkyl, an optionally substituted C₃₋₆ cycloalkyl, an optionally substituted 4-7 membered heterocyclic ring having 1 or 2 ring heteroatoms each independently N, O, or S, or an optionally substituted 5 or 6-membered heteroaryl having 1-3 ring heteroatoms each independently N, O, or S. Preferably, when substituted, the C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ heteroalkyl, C₃₋₆ cycloalkyl, 4-7 membered heterocyclic ring, or 5 or 6-membered heteroaryl is substituted with one or more (e.g., 1-3) substituents each independently selected from deuterium, halogen (e.g., F), OH, CN, oxo, C₁₋₄ alkyl optionally substituted with deuterium or F, C₁₋₄ alkoxy optionally substituted with deuterium or F, or a 3-4 membered carbocyclic or heterocyclic ring (e.g., cyclopropyl, cyclobutyl, azetidiny, oxetanyl, etc.) optionally substituted with deuterium, F, OH, and/or methyl. In some embodiments, the phenyl is unsubstituted or substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen (e.g., F, Cl, Br, etc.), CN, OH, NH₂, SF₅, G¹, or -X¹-X²-G¹, wherein X¹ is null, CH₂, or CH₂CH₂, wherein X² and G¹ are defined herein. In some embodiments, the phenyl is unsubstituted or substituted with one or more (e.g., 1-3) substituents each independently deuterium,

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halogen (e.g., F, Cl, Br, etc.), CN, OH, NH₂, SF₅, SCF₃, G¹, NHG¹, NG¹G¹, OG¹, or SO₂G¹, wherein G¹ is defined herein.

[0057] In some preferred embodiments according to Formula I or I-1 (e.g., Formula I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f), J⁶ is CR^{13A}, and R^{13A} is an optionally substituted 5 or 6 membered heteroaryl, e.g., pyrazolyl, pyridinyl, pyrimidinyl, pyridazinyl, or pyrazinyl. In some embodiments, the 5 or 6 membered heteroaryl is unsubstituted or substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen (e.g., F, Cl, Br, etc.), CN, OH, NH₂, SF₅, G¹, or -X¹-X²-G¹,

wherein X¹ is null, C₁₋₄ alkylene or C₁₋₄ heteroalkylene, and

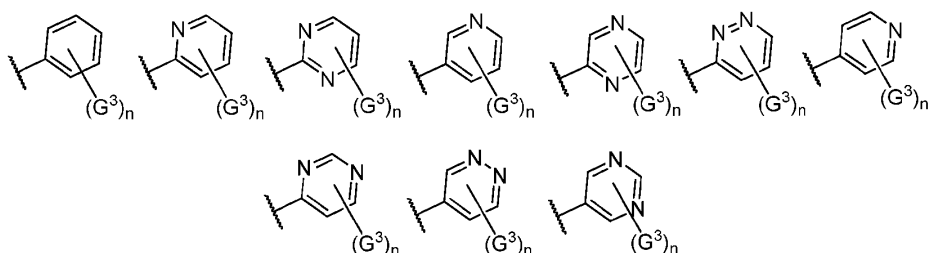
X² is O, S, NH, NG¹, C(O), SO₂, C(O)NH, C(O)NG¹, SO₂NH, or SO₂NG¹, and

wherein G¹ at each occurrence is independently an optionally substituted C₁₋₄ alkyl, an optionally substituted C₂₋₄ alkenyl, an optionally substituted C₂₋₄ alkynyl, an optionally substituted C₁₋₄ heteroalkyl, an optionally substituted C₃₋₆ cycloalkyl, an optionally substituted 4-7 membered heterocyclic ring having 1 or 2 ring heteroatoms each independently N, O, or S, or an optionally substituted 5 or 6-membered heteroaryl having 1-3 ring heteroatoms each independently N, O, or S. Preferably, when substituted, the C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ heteroalkyl, C₃₋₆ cycloalkyl, 4-7 membered heterocyclic ring, or 5 or 6-membered heteroaryl is substituted with one or more (e.g., 1-3) substituents each independently selected from deuterium, halogen (e.g., F), OH, CN, oxo, C₁₋₄ alkyl optionally substituted with deuterium or F, C₁₋₄ alkoxyl optionally substituted with deuterium or F, or a 3-4 membered carbocyclic or heterocyclic ring (e.g., cyclopropyl, cyclobutyl, azetidyl, oxetanyl, etc.) optionally substituted with deuterium, F, OH, and/or methyl. In some embodiments, the 5 or 6 membered heteroaryl is unsubstituted or substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen (e.g., F, Cl, Br, etc.), CN, OH, NH₂, SF₅, G¹, or -X¹-X²-G¹, wherein X¹ is null, CH₂, or CH₂CH₂, wherein X² and G¹ are defined herein. In some embodiments, the 5 or 6 membered heteroaryl is unsubstituted or substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen (e.g., F, Cl, Br, etc.), CN, OH, NH₂, SF₅, SCF₃, G¹, NHG¹, NG¹G¹, OG¹, or SO₂G¹, wherein G¹ is defined herein.

[0058] In some preferred embodiments according to Formula I or I-1 (e.g., Formula I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f), J⁶ is CR^{13A}, and R^{13A} is an optionally substituted phenyl,

pyrazolyl, pyridinyl, pyrimidinyl, pyridazinyl, or pyrazinyl. In some embodiments, the phenyl, pyrazolyl, pyridinyl, pyrimidinyl, pyridazinyl, or pyrazinyl is unsubstituted or substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen (e.g., F, Cl, Br, etc.), CN, OH, NH₂, SF₅, SCF₃, G², NHG², NG²G², OG², or SO₂G², wherein G² at each occurrence is independently an optionally substituted C₁₋₄ alkyl, an optionally substituted C₃₋₆ cycloalkyl, or an optionally substituted 4-7 membered heterocyclic ring having 1 or 2 ring heteroatoms each independently N, O, or S. Preferably, when substituted, the C₁₋₄ alkyl, C₃₋₆ cycloalkyl, or 4-7 membered heterocyclic ring, is substituted with one or more (e.g., 1-3) substituents each independently selected from deuterium, halogen (e.g., F), OH, CN, oxo, C₁₋₄ alkyl optionally substituted with deuterium or F, C₁₋₄ alkoxy optionally substituted with deuterium or F, or a 3-4 membered carbocyclic or heterocyclic ring (e.g., cyclopropyl, cyclobutyl, azetidyl, oxetanyl, etc.) optionally substituted with deuterium, F, OH, and/or methyl.

[0059] In some more specific embodiments according to Formula I or I-1 (e.g., Formula I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f), J⁶ is CR^{13A}, and R^{13A} is selected from the following:



wherein

n is an integer of 0-3, and

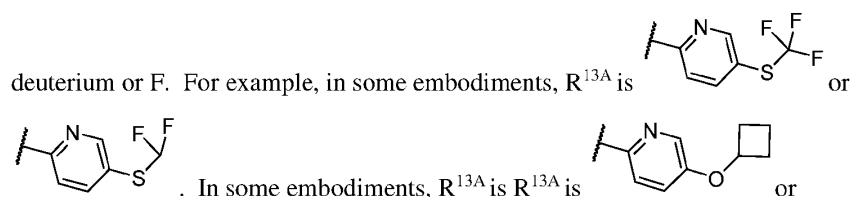
(i) G³ at each occurrence is independently deuterium, halogen (e.g., F or Cl), CN, C₁₋₄ alkyl, O-(C₁₋₄ alkyl), SO₂-(C₁₋₄ alkyl), OH, NH₂, NH(C₁₋₄ alkyl), N(C₁₋₄ alkyl)(C₁₋₄ alkyl), 3-4 membered carbocyclic or heterocyclic ring, O-(3-4 membered carbocyclic or heterocyclic ring), (C₁₋₄ alkylene)-(3-4 membered carbocyclic or heterocyclic ring) or O-(C₁₋₄ alkylene)-(3-4 membered carbocyclic or heterocyclic ring),

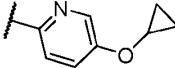
wherein each of the aforementioned C₁₋₄ alkyl is independently optionally substituted with 1-7 deuterium or F, and wherein the C₁₋₄ alkylene or 3-4 membered carbocyclic or heterocyclic ring is optionally substituted with one or more (e.g., 1-3) substituents independently deuterium, F, OH, or methyl; or (ii) one instance of G³ is S-(C₁₋₄ alkyl),

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wherein the C₁₋₄ alkyl is optionally substituted with 1-7 deuterium or F, e.g., one G³ is SCF₂ or SCF₃, and any remaining G³ is as defined in (i). In some embodiments, the 3-4 membered carbocyclic or heterocyclic ring is cyclopropyl or cyclobutyl. In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, one instance of G³ is C₁₋₄ alkyl optionally substituted with 1-7 deuterium or F or C₁₋₄ alkoxy optionally substituted with 1-7 deuterium or F, such as OCH₃, OCF₂H, OCF₃, CF₃, CH₃, CF₂H, or CH₂CF₃, and any other instance(s) of G³, if present, is defined above. For example, in some embodiments, when n is 2, the remaining instance of G³ can be a halogen.

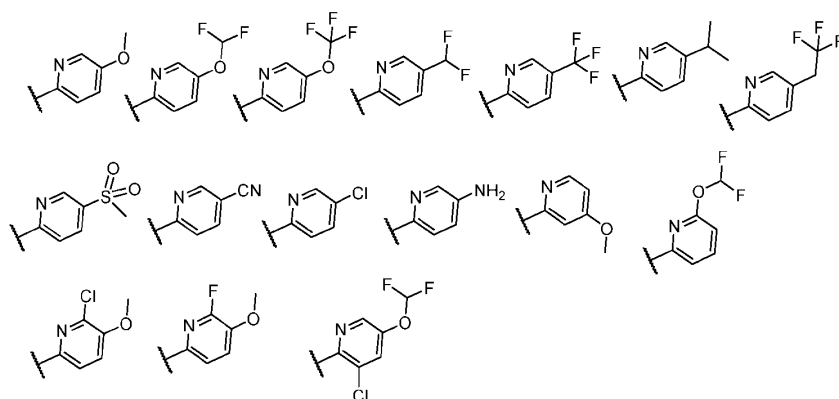
[0060] In some more specific embodiments according to Formula I or I-1 (e.g., Formula I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f), J⁶ is CR^{13A}, and R^{13A} is a pyridinyl (e.g., 2-pyridinyl, 3-pyridinyl, or 4-pyridinyl) substituted with (i) 1 or 2 substituents independently selected from deuterium, halogen (e.g., F or Cl), CN, C₁₋₄ alkyl, O-(C₁₋₄ alkyl), SO₂-(C₁₋₄ alkyl), OH, NH₂, NH(C₁₋₄ alkyl), or N(C₁₋₄ alkyl)(C₁₋₄ alkyl), or (ii) one substituent is S-(C₁₋₄ alkyl), SF₅, cyclopropoxy, or cyclobutoxy, and any remaining substituent(s) is as defined in (i); wherein each of the aforementioned C₁₋₄ alkyl is independently optionally substituted with 1-7



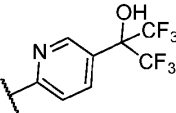
 . Preferably, the pyridinyl is substituted with one substituent selected from OCH₃, OCF₂H, OCF₃, CF₃, CH₃, CF₂H, or CH₂CF₃, and optionally a further substituent selected from F or Cl.

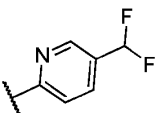
[0061] In some preferred embodiments according to Formula I or I-1 (e.g., Formula I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f), J⁶ is CR^{13A}, and R^{13A} is a 2-pyridinyl substituted with one substituent selected from OCH₃, OCF₂H, OCF₃, SO₂CH₃, NH₂, CN, Cl, isopropyl, CF₃, CH₃, CF₂H, or CH₂CF₃, and optionally a further substituent selected from F or Cl, for example, selected from the following:

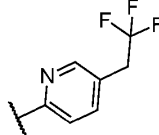
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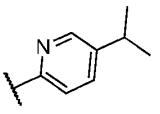


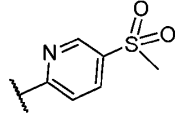
[0062] In some preferred embodiments according to Formula I or I-1 (e.g., Formula I-1a,

I-1b, I-1c, I-1d, I-1e, or I-1f), J^6 is CR^{13A} , and R^{13A} is . In some preferred embodiments according to Formula I or I-1 (e.g., Formula I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f),

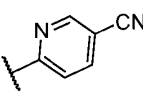
J^6 is CR^{13A} , and R^{13A} is . In some preferred embodiments according to Formula I or I-1 (e.g., Formula I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f), J^6 is CR^{13A} , and R^{13A} is In some preferred embodiments according to Formula I or I-1 (e.g., Formula I-1a, I-1b, I-1c, I-

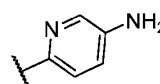
1d, I-1e, or I-1f), J^6 is CR^{13A} , and R^{13A} is . In some preferred embodiments according to Formula I or I-1 (e.g., Formula I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f), J^6 is CR^{13A} ,

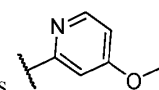
and R^{13A} is . In some preferred embodiments according to Formula I or I-1

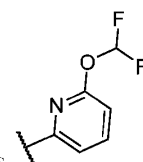
(e.g., Formula I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f), J^6 is CR^{13A} , and R^{13A} is . In some preferred embodiments according to Formula I or I-1 (e.g., Formula I-1a, I-1b, I-1c,

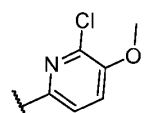
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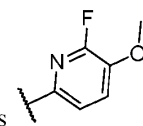
I-1d, I-1e, or I-1f), J⁶ is CR^{13A}, and R^{13A} is . In some preferred embodiments according to Formula I or I-1 (e.g., Formula I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f), J⁶ is CR^{13A},

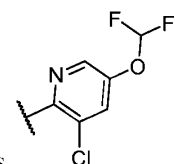
and R^{13A} is . In some preferred embodiments according to Formula I or I-1

(e.g., Formula I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f), J⁶ is CR^{13A}, and R^{13A} is . In some preferred embodiments according to Formula I or I-1 (e.g., Formula I-1a, I-1b, I-1c, I-

1d, I-1e, or I-1f), J⁶ is CR^{13A}, and R^{13A} is . In some preferred embodiments according to Formula I or I-1 (e.g., Formula I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f), J⁶ is CR^{13A},

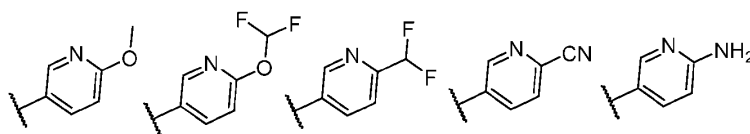
and R^{13A} is . In some preferred embodiments according to Formula I or I-1

(e.g., Formula I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f), J⁶ is CR^{13A}, and R^{13A} is . In some preferred embodiments according to Formula I or I-1 (e.g., Formula I-1a, I-1b, I-1c, I-

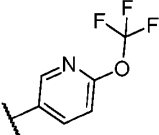
1d, I-1e, or I-1f), J⁶ is CR^{13A}, and R^{13A} is .

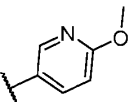
[0063] In some preferred embodiments according to Formula I or I-1 (e.g., Formula I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f), J⁶ is CR^{13A}, and R^{13A} is a 3-pyridinyl substituted with one substituent selected from OCH₃, OCF₂H, OCF₃, SO₂CH₃, NH₂, CN, Cl, isopropyl, CF₃, CH₃, CF₂H, or CH₂CF₃, and optionally a further substituent selected from F or Cl, for example, selected from the following:

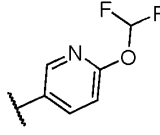
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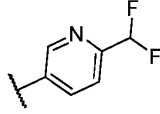


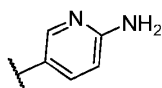
In some preferred embodiments according to Formula I or I-1 (e.g., Formula I-1a, I-1b, I-1c, I-

1d, I-1e, or I-1f), J^6 is CR^{13A} , and R^{13A} is . In some preferred embodiments according to Formula I or I-1 (e.g., Formula I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f), J^6 is CR^{13A} , and

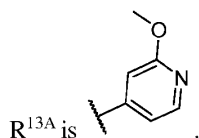
R^{13A} is . In some preferred embodiments according to Formula I or I-1 (e.g.,

Formula I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f), J^6 is CR^{13A} , and R^{13A} is . In some preferred embodiments according to Formula I or I-1 (e.g., Formula I-1a, I-1b, I-1c, I-1d, I-1e, or

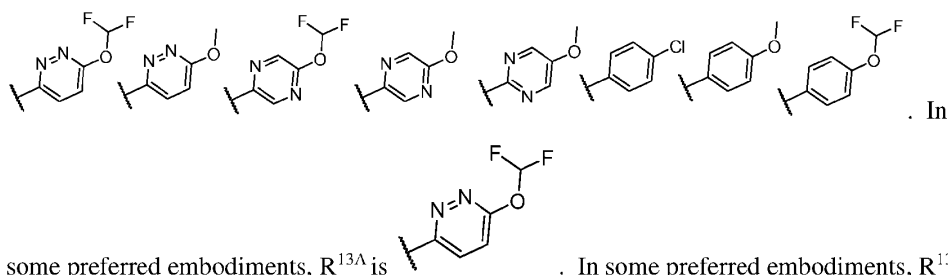
I-1f), J^6 is CR^{13A} , and R^{13A} is . In some preferred embodiments according to Formula I or I-1 (e.g., Formula I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f), J^6 is CR^{13A} , and R^{13A} is



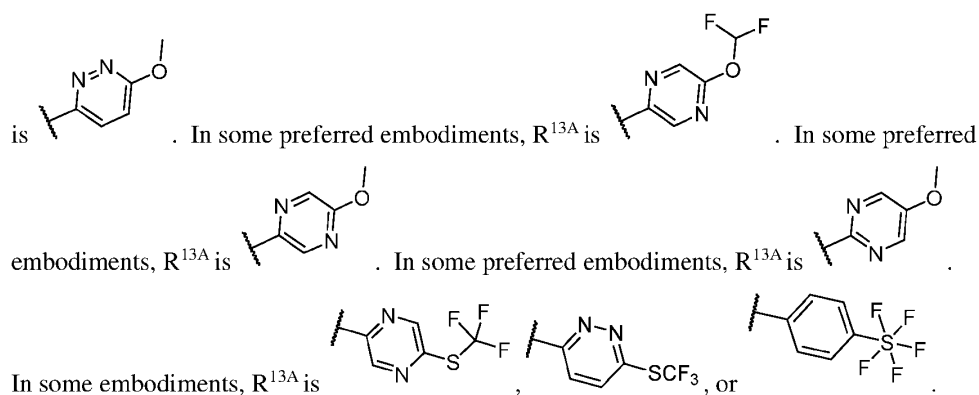
[0064] In some preferred embodiments according to Formula I or I-1 (e.g., Formula I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f), J^6 is CR^{13A} , and R^{13A} is a 4-pyridinyl substituted with one substituent selected from OCH_3 , OCF_2H , OCF_3 , SO_2CH_3 , NH_2 , CN , Cl , isopropyl, CF_3 , CH_3 , CF_2H , or CH_2CF_3 , and optionally a further substituent selected from F or Cl , for example,



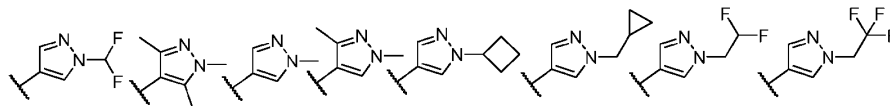
[0065] In some more specific embodiments according to Formula I or I-1 (e.g., Formula I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f), J^6 is CR^{13A} , and R^{13A} is a phenyl, pyrimidinyl, pyridazinyl, or pyrazinyl, which is substituted with (i) 1 or 2 substituents independently selected from deuterium, halogen (e.g., F or Cl), CN, C_{1-4} alkyl, O-(C_{1-4} alkyl), SO_2 -(C_{1-4} alkyl), OH, NH_2 , $NH(C_{1-4}$ alkyl), or $N(C_{1-4}$ alkyl)(C_{1-4} alkyl), or (ii) one substituent is S-(C_{1-4} alkyl), SF_5 , cyclopropoxy, or cyclobutoxy, and any remaining substituent(s) is as defined in (i); wherein each of the aforementioned C_{1-4} alkyl is independently optionally substituted with 1-7 deuterium or F. In some more specific embodiments according to Formula I or I-1 (e.g., Formula I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f), J^6 is CR^{13A} , and R^{13A} is a pyrimidinyl which is substituted with 1 or 2 substituents independently selected from deuterium, halogen (e.g., F or Cl), CN, C_{1-4} alkyl, O-(C_{1-4} alkyl), SO_2 -(C_{1-4} alkyl), OH, NH_2 , $NH(C_{1-4}$ alkyl), or $N(C_{1-4}$ alkyl)(C_{1-4} alkyl), wherein each of the aforementioned C_{1-4} alkyl is independently optionally substituted with 1-7 deuterium or F. In some more specific embodiments according to Formula I or I-1 (e.g., Formula I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f), J^6 is CR^{13A} , and R^{13A} is a pyridazinyl, which is substituted with 1 or 2 substituents independently selected from deuterium, halogen (e.g., F or Cl), CN, C_{1-4} alkyl, O-(C_{1-4} alkyl), SO_2 -(C_{1-4} alkyl), OH, NH_2 , $NH(C_{1-4}$ alkyl), or $N(C_{1-4}$ alkyl)(C_{1-4} alkyl), wherein each of the aforementioned C_{1-4} alkyl is independently optionally substituted with 1-7 deuterium or F. In some more specific embodiments according to Formula I or I-1 (e.g., Formula I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f), J^6 is CR^{13A} , and R^{13A} is a pyrazinyl which is substituted with 1 or 2 substituents independently selected from deuterium, halogen (e.g., F or Cl), CN, C_{1-4} alkyl, O-(C_{1-4} alkyl), SO_2 -(C_{1-4} alkyl), OH, NH_2 , $NH(C_{1-4}$ alkyl), or $N(C_{1-4}$ alkyl)(C_{1-4} alkyl), wherein each of the aforementioned C_{1-4} alkyl is independently optionally substituted with 1-7 deuterium or F. In some preferred embodiments, R^{13A} is selected from the following:



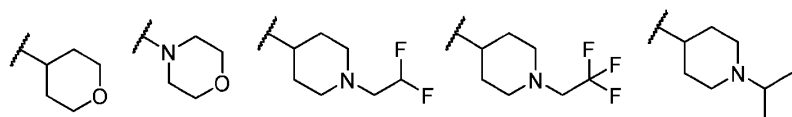
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[0066] In some more specific embodiments according to Formula I or I-1 (e.g., Formula I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f), J⁶ is CR^{13A}, and R^{13A} is a pyrazolyl, optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen (e.g., F, Cl, Br, etc.), C₁₋₄ alkyl, 3-4 membered carbocyclic or heterocyclic ring, or (C₁₋₄ alkylene)-(3-4 membered carbocyclic or heterocyclic ring), wherein the C₁₋₄ alkyl, C₁₋₄ alkylene, or 3-4 membered carbocyclic or heterocyclic ring is optionally substituted with one or more (e.g., 1-3) substituents independently deuterium, F, OH, or methyl. In some preferred embodiments, R^{13A} is selected from the following:



[0067] In some more specific embodiments according to Formula I or I-1 (e.g., Formula I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f), J⁶ is CR^{13A}, and R^{13A} is a 5-7 membered heterocyclic ring, such as a tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl, etc., which is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen (e.g., F), oxo, C₁₋₄ alkyl, 3-4 membered carbocyclic or heterocyclic ring, or (C₁₋₄ alkylene)-(3-4 membered carbocyclic or heterocyclic ring), wherein the C₁₋₄ alkyl, C₁₋₄ alkylene, or 3-4 membered carbocyclic or heterocyclic ring is optionally substituted with one or more (e.g., 1-3) substituents independently deuterium, F, OH, or methyl. In some preferred embodiments, R^{13A} is selected from the following:

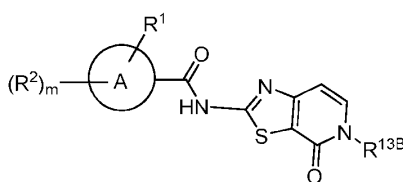


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[0068] In some embodiments according to Formula I or I-1 (e.g., Formula I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f), J^6 is CR^{13A} , and R^{13A} can be $L-R^K$ as defined herein in connection with Formula K or its subformulae. In some embodiments according to Formula I or I-1 (e.g., Formula I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f), J^6 is CR^{13A} , and R^{13A} can also be any of the respective groups of the compounds shown in Table 1 or Examples 1-266 herein.

[0069] In some embodiments, in Formula I or I-1, J^6 is NR^{13B} and J^7 is $C(O)$.

[0070] For example, in some embodiments, the compound of Formula I or I-1 can be characterized as having a structure according to Formula I-1g:



Formula I-1g,

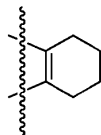
wherein the variables are defined herein.

[0071] In some embodiments, in Formula I or I-1, J^6 is NR^{13B} , and R^{13B} is an optionally substituted C_{1-6} alkyl, an optionally substituted C_{3-6} alkenyl, an optionally substituted C_{3-6} alkynyl, an optionally substituted C_{1-6} heteroalkyl, an optionally substituted 3-10 membered carbocyclic or heterocyclic ring, an optionally substituted phenyl, or an optionally substituted 5 or 6-membered heteroaryl, preferably, when substituted, the C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, C_{1-6} heteroalkyl, 3-10 membered carbocyclic or heterocyclic ring, phenyl, or 5 or 6-membered heteroaryl is substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, NH_2 , SF_5 , CN, or $-Y^1-Y^2$, wherein Y^1 is null, O, S, NH, NY^3 , $C(O)$, SO_2 , $C(O)NH$, $C(O)NY^3$, $P(O)Y^3$, SO_2NH , or SO_2NY^3 , and each of Y^2 and Y^3 at each occurrence is independently an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl, an optionally substituted C_{1-6} heteroalkyl, an optionally substituted 3-10 membered carbocyclic or heterocyclic ring, an optionally substituted phenyl, or an optionally substituted 5 or 6-membered heteroaryl.

[0072] In some embodiments, the compound of Formula I can also have a bicyclic heteroaryl in which one of the fused rings is a pyrazole or imidazole ring. For example, in some embodiments, J^1 in Formula I can be CH, and one of J^2 and J^3 is C and the other of J^2 and J^3 is N.

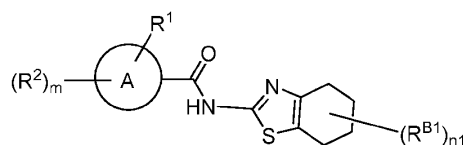
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[0073] In some embodiments according to Formula A (including any applicable subformulae), Ring B can also be an optionally substituted 5-7 membered carbocyclic or heterocyclic ring. For example, in some embodiments, Ring B can be a 5-7 membered



carbocyclic ring, such as a cyclohexylene ring, , which is optionally substituted.

[0074] For example, in some embodiments, the compound of Formula A has a structure according to Formula II:



Formula II,

wherein:

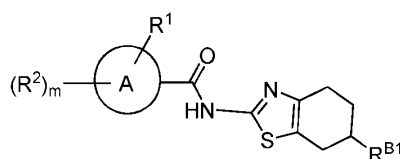
n_1 is 0, 1, 2, 3, or 4,

R^{B1} at each occurrence is independently deuterium, halogen, OH, CN, NH_2 , an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl, an optionally substituted C_{1-6} heteroalkyl, an optionally substituted 3-10 membered carbocyclic or heterocyclic ring, an optionally substituted phenyl, or an optionally substituted 5 or 6-membered heteroaryl, preferably, when substituted, the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} heteroalkyl, 3-10 membered carbocyclic or heterocyclic ring, phenyl, or 5 or 6-membered heteroaryl is substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, NH_2 , SF_5 , CN, or $-Y^1-Y^2$, wherein Y^1 is null, O, S, NH, NY^3 , C(O), SO_2 , C(O)NH, C(O) NY^3 , P(O) Y^3 , SO_2NH , or SO_2NY^3 , and each of Y^2 and Y^3 at each occurrence is independently an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl, an optionally substituted C_{1-6} heteroalkyl, an optionally substituted 3-10 membered carbocyclic or heterocyclic ring, an optionally substituted phenyl, or an optionally substituted 5 or 6-membered heteroaryl; and the other variables are defined herein.

[0075] In some embodiments, n_1 in Formula II is 0.

[0076] In some embodiments, n_1 in Formula II is 1, and the compound has a structure according to Formula II-1:

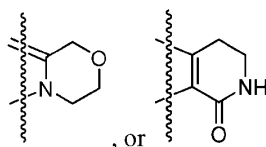
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Formula II-1,

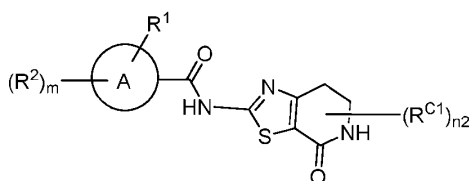
wherein the variables are defined herein. In some embodiments, R^{B1} is an optionally substituted phenyl or 5 or 6-membered heteroaryl. In some embodiments, R^{B1} is an optionally substituted phenyl, such as phenyl or 4-chlorophenyl. When substituted, the phenyl or 5 or 6-membered heteroaryl ring can preferably be substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, NH_2 , SF_5 , CN, or Y^1 - Y^2 , wherein Y^1 is null, O, S, NH, NY^3 , $C(O)$, SO_2 , $C(O)NH$, $C(O)NY^3$, $P(O)Y^3$, SO_2NH , or SO_2NY^3 , and each of Y^2 and Y^3 at each occurrence is independently an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl, an optionally substituted C_{1-6} heteroalkyl, an optionally substituted 3-10 membered carbocyclic or heterocyclic ring, an optionally substituted phenyl, or an optionally substituted 5 or 6-membered heteroaryl.

[0077] In some embodiments, Ring B can be a 5-7 membered heterocyclic ring having 1



or 2 ring heteroatoms, such as , or , which is optionally substituted.

[0078] For example, in some embodiments, the compound of Formula A has a structure according to Formula III:



Formula III,

wherein:

n_2 is 0, 1, 2, 3, or 4,

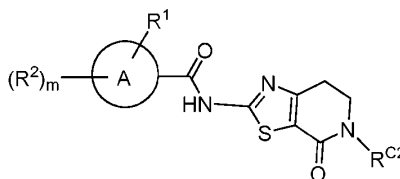
R^{C1} at each occurrence is independently deuterium, halogen, OH, CN, NH_2 , an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6}

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alkynyl, an optionally substituted C₁₋₆ heteroalkyl, an optionally substituted 3-10 membered carbocyclic or heterocyclic ring, an optionally substituted phenyl, or an optionally substituted 5 or 6-membered heteroaryl, preferably, when substituted, the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ heteroalkyl, 3-10 membered carbocyclic or heterocyclic ring, phenyl, or 5 or 6-membered heteroaryl is substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, NH₂, SF₅, CN, or -Y¹-Y², wherein Y¹ is null, O, S, NH, NY³, C(O), SO₂, C(O)NH, C(O)NY³, P(O)Y³, SO₂NH, or SO₂NY³, and each of Y² and Y³ at each occurrence is independently an optionally substituted C₁₋₆ alkyl, an optionally substituted C₂₋₆ alkenyl, an optionally substituted C₂₋₆ alkynyl, an optionally substituted C₁₋₆ heteroalkyl, an optionally substituted 3-10 membered carbocyclic or heterocyclic ring, an optionally substituted phenyl, or an optionally substituted 5 or 6-membered heteroaryl; and the other variables are defined herein.

[0079] In some embodiments according to Formula III, n₂ is 0.

[0080] In some embodiments according to Formula III, and the compound has a structure according to Formula III-1:



Formula III-1,

wherein R^{C2} is an optionally substituted C₁₋₆ alkyl, an optionally substituted C₃₋₆ alkenyl, an optionally substituted C₃₋₆ alkynyl, an optionally substituted C₁₋₆ heteroalkyl, an optionally substituted 3-10 membered carbocyclic or heterocyclic ring, an optionally substituted phenyl, or an optionally substituted 5 or 6-membered heteroaryl, and the other variables are defined herein. In some embodiments, R^{C2} is an optionally substituted phenyl or 5 or 6-membered heteroaryl. When substituted, the phenyl or 5 or 6-membered heteroaryl ring can preferably be substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, NH₂, SF₅, CN, or -Y¹-Y², wherein Y¹ is null, O, S, NH, NY³, C(O), SO₂, C(O)NH, C(O)NY³, P(O)Y³, SO₂NH, or SO₂NY³, and Y² and Y³ are each independently an optionally substituted C₁₋₆ alkyl, an optionally substituted C₂₋₆ alkenyl, an optionally substituted C₂₋₆ alkynyl, an optionally substituted C₁₋₆ heteroalkyl, an optionally substituted

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3-10 membered carbocyclic or heterocyclic ring, an optionally substituted phenyl, or an optionally substituted 5 or 6-membered heteroaryl.

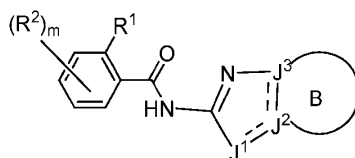
[0081] Ring A in Formula A (e.g., Formula I, II, or III, or any of the subformulae) is typically a phenyl ring or a 5 or 6-membered heteroaryl ring having 1 to 3 ring heteroatoms independently selected from N, O, and S, such as pyridine ring. In some embodiments, Ring A in Formula A can also be a fused bicyclic heteroaryl having 1 to 4 ring heteroatoms independently selected from N, O, and S.

[0082] In some embodiments, Ring A in Formula A (e.g., Formula I, II, or III, or any of the subformulae) is a phenyl, pyridinyl, pyrimidinyl, or imidazo[1,2-a]pyridinyl ring.

[0083] In some preferred embodiments, Ring A in Formula A (e.g., Formula I, II, or III, or any of the subformulae) is a phenyl ring.

[0084] In some preferred embodiments, Ring A in Formula A (e.g., Formula I, II, or III, or any of the subformulae) is a pyridinyl ring.

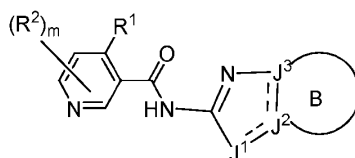
[0085] For example, in some embodiments, the compound of Formula A can have a structure according to Formula A1:



Formula A1

wherein the variables are defined herein.

[0086] In some embodiments, the compound of Formula A can have a structure according to Formula A2:

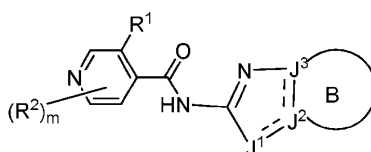


Formula A2

wherein the variables are defined herein.

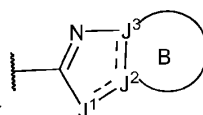
[0087] In some embodiments, the compound of Formula A can have a structure according to Formula A3:

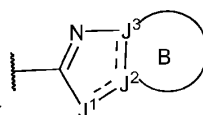
- 30 -



Formula A3

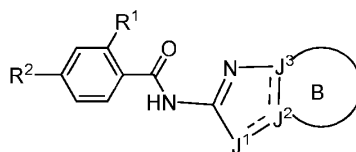
wherein the variables are defined herein.



[0088] In some embodiments, the moiety of  in Formula A1, A2, or A3, or any of the subformulae described herein, has the respective definition of any of those described herein for Formula I (e.g., I-1, I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f), Formula II (e.g., II-1), or Formula III (e.g., III-1).

[0089] In some embodiments, the subscript "m" in Formula A (e.g., any of the applicable subformulae) is 0 or 1, typically 1. Typically, when m is 1, R² is meta to R¹.

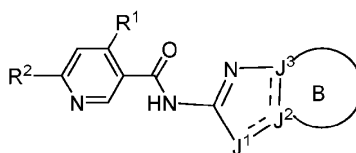
[0090] For example, in some embodiments, the compound of Formula A1 can have a structure according to Formula A1a:



Formula A1a

wherein the variables are defined herein.

[0091] In some embodiments, the compound of Formula A2 can have a structure according to Formula A2a:



Formula A2a

wherein the variables are defined herein.

[0092] Typically, in embodiments according to Formula A (e.g., any of the applicable subformulae), R² at each occurrence is independently deuterium, halogen, CN, OH, (C₁₋₄ alkylene)-CN, G^A, or X^a-X^b-G^A,

wherein:

X^a at each occurrence is independently null, C₁₋₄ alkylene, or C₁₋₄ heteroalkylene;

X^b at each occurrence is independently null, O, NH, N(G^B), C(O), C(O)O, C(O)NH, C(O)N(G^B), NHC(O), N(G^B)C(O), SO₂, SO₂NH, or SO₂N(G^B); and

G^A at each occurrence is independently:

- (i) C₁₋₆ alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, C₁₋₄ alkoxy, or a 3-6 membered ring;
 - (ii) C₁₋₆ heteroalkyl optionally substituted with one or more (e.g., 1-3) substituents independently deuterium, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, or a 3-6 membered ring;
 - (iii) a 3-7 membered carbocyclic or heterocyclic ring, which is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, oxo, OH, CN, C₁₋₄ alkyl, C₁₋₄ alkoxy, or a 3-6 membered ring;
- or
- (iv) a 5 or 6-membered heteroaryl, which is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, CN, C₁₋₄ alkyl, C₁₋₄ alkoxy, or a 3-6 membered ring (preferably carbocyclic or heterocyclic ring),

wherein the C₁₋₄ alkyl or C₁₋₄ alkoxy in each of (i)-(iv) is independently optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, C₁₋₄ alkoxy, or a 3-4 membered carbocyclic or heterocyclic ring, and

wherein each of the 3-6 membered ring in each of (i)-(iv) is independently optionally substituted with one or more (e.g., 1-3) substituents each independently oxo, deuterium, halogen, OH, CN, C₁₋₄ alkyl optionally substituted with deuterium or F, or C₁₋₄ alkoxy optionally substituted with deuterium or F;

G^B at each occurrence is independently C₁₋₆ alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, C₁₋₄ alkoxy optionally substituted with deuterium or F, or a 3-6 membered ring (preferably carbocyclic or heterocyclic ring) optionally substituted with oxo, deuterium, halogen, OH, CN, C₁₋₄ alkyl optionally substituted with deuterium or F, or C₁₋₄ alkoxy optionally substituted with deuterium or F, or

when applicable, G^A and G^B are joined to form a 4-7 membered heterocyclic ring, which is optionally substituted with one or more (e.g., 1-3) substituents each independently halogen, oxo, OH, C_{1-4} alkyl optionally substituted with F, or C_{1-4} alkoxy optionally substituted with F.

[0093] In some preferred embodiments, in Formula A (e.g., any of the applicable subformulae), one instance of R^2 is a C_{1-4} alkyl optionally substituted with deuterium, F, and/or OH, e.g., methyl, difluoromethyl, or hydroxymethyl, and if present, any remaining instance(s) of R^2 is as defined herein, preferably, selected from halogen, OH, CN, C_{1-4} alkyl optionally substituted with deuterium or F, or C_{1-4} alkoxy optionally substituted with deuterium or F.

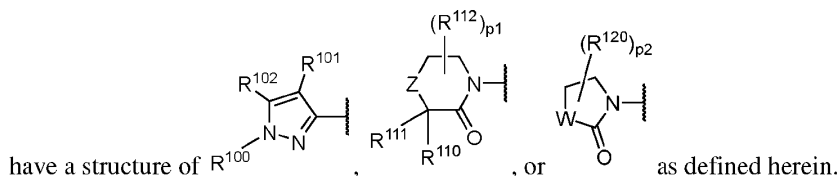
[0094] In some embodiments, in Formula A (e.g., any of the applicable subformulae), one instance of R^2 is a 5 or 6-membered heteroaryl, which is optionally substituted with 1-3 substituents each independently halogen, OH, CN, C_{1-4} alkyl, C_{1-4} alkoxy, or a 3-5 membered carbocyclic or heterocyclic ring, wherein the C_{1-4} alkyl or C_{1-4} alkoxy is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen (e.g., F), OH, C_{1-4} alkoxy, or a 3-5 membered carbocyclic or heterocyclic ring, wherein each of the 3-5 membered carbocyclic or heterocyclic ring, when present, is independently optionally substituted with deuterium, F, OH, and/or methyl, and if present, any remaining instance(s) of R^2 is as defined herein, preferably, selected from halogen, OH, CN, C_{1-4} alkyl optionally substituted with deuterium or F, or C_{1-4} alkoxy optionally substituted with deuterium or F.

[0095] In some embodiments, in Formula A (e.g., any of the applicable subformulae), one instance of R^2 is $-(C_{1-4} \text{ alkylene})-C(O)NHG^A$, $-(C_{1-4} \text{ alkylene})-C(O)N(G^A)(G^B)$ or $-(C_{1-4} \text{ alkylene})-CN$, wherein G^A and G^B are defined herein. In some embodiments, G^A and G^B are each independently a C_{1-4} alkyl optionally substituted with deuterium, F and/or OH, and if present, any remaining instance(s) of R^2 is as defined herein, preferably, selected from halogen, OH, CN, C_{1-4} alkyl optionally substituted with deuterium or F, or C_{1-4} alkoxy optionally substituted with deuterium or F. For example, in some embodiments, m is 1, and R^2 can be $CH_2C(O)NHCH_3$ or $CH_2C(O)N(CH_3)_2$.

[0096] In some embodiments, in Formula A (e.g., any of the applicable subformulae), R^2 can also have any of the R^2 definitions as defined in connection with Formula K and its subformulae. For example, in any of the embodiments described herein, m is 1, and R^2 in Formula A (e.g., any of the applicable subformulae), can have a structure according to M-1 to

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M-13 as defined herein below in connection with Formula K and its subformulae. In some embodiments, m is 1, and R^2 in Formula A (e.g., any of the applicable subformulae), can



[0097] In Formula A (e.g., any of the applicable subformulae), R^1 is typically an optionally substituted phenyl or an optionally substituted 5-10 membered heteroaryl. For example, in some embodiments, R^1 is an optionally substituted phenyl. In some embodiments, R^1 is an optionally substituted pyridinyl. In some embodiments, R^1 is an optionally substituted pyrimidinyl, benzopyrazolyl, benzimidazolyl, imidazolyl, pyridazyl, imidazo[1,2-a]pyrimidinyl, oxazolo[4,5-b]pyridinyl, oxazolo[5,4-b]pyridinyl, thiazolo[4,5-b]pyridinyl, benzo[d]thiazole, indazolyl, [1,2,4]triazolo[1,5-a]pyrimidinyl, [1,2,4]triazolo[1,5-b]pyridazinyl, or tetrazolo[1,5-a]pyridinyl. When substituted, the optionally substituted phenyl or an optionally substituted 5-10 membered heteroaryl, e.g., optionally substituted phenyl or pyridinyl, is preferably substituted with one or more (e.g., 1-3) substituents independently selected from: deuterium, halogen, CN, OH, NH₂, COOH, CONH₂, (C₁₋₄ alkylene)-CN, G^C, or X^c-X^d-G^C,

wherein:

X^c at each occurrence is independently null, C₁₋₄ alkylene, or C₁₋₄ heteroalkylene;

X^d at each occurrence is independently null, O, NH, N(G^D), C(O), C(O)O, C(O)NH, C(O)N(G^D), NHC(O), N(G^D)C(O), P(O)(G^D), SO₂, SO₂NH, or SO₂N(G^D); and

G^C at each occurrence is independently:

- (i) C₁₋₆ alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, C₁₋₄ alkoxy, or a 3-6 membered ring;
 - (ii) C₁₋₆ heteroalkyl optionally substituted with one or more (e.g., 1-3) substituents independently deuterium, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, or a 3-6 membered ring;
 - (iii) a 3-7 membered carbocyclic or heterocyclic ring, which is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, oxo, OH, CN, C₁₋₄ alkyl, C₁₋₄ alkoxy, or a 3-6 membered ring;
- or

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(iv) a 5 or 6-membered heteroaryl, which is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, CN, C₁₋₄ alkyl, C₁₋₄ alkoxy, or a 3-6 membered ring (preferably carbocyclic or heterocyclic ring),

wherein the C₁₋₄ alkyl or C₁₋₄ alkoxy in each of (i)-(iv) is independently optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, C₁₋₄ alkoxy, or a 3-4 membered carbocyclic or heterocyclic ring, and

wherein each of the 3-6 membered ring in each of (i)-(iv) is independently optionally substituted with oxo, deuterium, halogen, OH, CN, C₁₋₄ alkyl optionally substituted with deuterium or F, or C₁₋₄ alkoxy optionally substituted with deuterium or F;

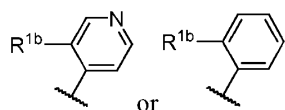
G^D at each occurrence is independently C₁₋₆ alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, C₁₋₄ alkoxy optionally substituted with deuterium or F, or a 3-6 membered ring optionally substituted with oxo, deuterium, halogen, OH, CN, C₁₋₄ alkyl optionally substituted with deuterium or F, or C₁₋₄ alkoxy optionally substituted with deuterium or F, or

when applicable, G^C and G^D together with the heteroatom they are both attached to are joined to form a 4-7 membered heterocyclic ring, which is optionally substituted with one or more (e.g., 1-3) substituents each independently halogen, oxo, OH, C₁₋₄ alkyl optionally substituted with deuterium or F, or C₁₋₄ alkoxy optionally substituted with deuterium or F. In some embodiments, the one or more substituents for the optionally substituted phenyl or optionally substituted 5-10 membered heteroaryl are each independently selected from: deuterium, halogen, CN, OH, NH₂, COOH, CONH₂, (C₁₋₄ alkylene)-CN, G^C, or X^c-X^d-G^C, wherein X^c is null, and X^d and G^C are defined herein. In some embodiments, the one or more substituents for the optionally substituted phenyl or optionally substituted 5-10 membered heteroaryl are each independently selected from: halogen, C₁₋₆ alkyl optionally substituted with deuterium, F, CN, and/or OH, C₁₋₆ alkoxy optionally substituted with deuterium, F, CN, and/or OH, C₃₋₆ cycloalkyl optionally substituted with deuterium, F, CN, methyl, and/or OH, NH₂, NH(C₁₋₄ alkyl), or N(C₁₋₄ alkyl)(C₁₋₄ alkyl). In some embodiments, the one or more substituents for the optionally substituted phenyl or optionally substituted 5-10 membered heteroaryl can include one

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substituent of SCF_3 , with the remaining substituent(s) as defined herein. In some embodiments, the one or more substituents for the optionally substituted phenyl or optionally substituted 5-10 membered heteroaryl are each independently selected from: halogen, C_{1-4} alkyl optionally substituted with deuterium, F and/or OH, C_{1-4} alkoxy optionally substituted with deuterium or F, C_{3-4} cycloalkyl optionally substituted with deuterium, F, CN, methyl, and/or OH, NH_2 , $\text{NH}(\text{C}_{1-3} \text{ alkyl})$, or $\text{N}(\text{C}_{1-3} \text{ alkyl})(\text{C}_{1-3} \text{ alkyl})$. In some more specific embodiments, the one or more substituents for the optionally substituted phenyl or optionally substituted 5-10 membered heteroaryl are each independently selected from: methyl, ethyl, fluoro, chloro, bromo, trifluoromethyl, difluoromethyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, cyclopropyl, $-\text{NH}_2$, hydroxymethyl, and 1-hydroxy ethyl, preferably, the substituents are independently selected from methyl, fluoro, chloro, trifluoromethyl, difluoromethyl, methoxy, ethoxy, difluoromethoxy, and cyclopropyl.

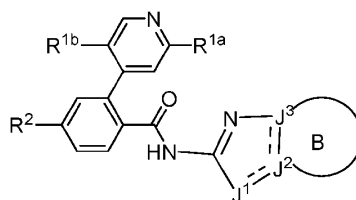
[0098] In some embodiments, in Formula A (e.g., any of the applicable subformulae), R^1 can be a phenyl or pyridinyl substituted with one substituent. In such embodiments, the one substituent is preferably ortho to ring A. For example, in some embodiments, R^1 can be



, wherein R^{1b} can be halogen, C_{1-6} alkyl optionally substituted with deuterium, F, CN, and/or OH, C_{1-6} alkoxy optionally substituted with deuterium, F, CN, and/or OH, C_{3-6} cycloalkyl optionally substituted with deuterium, F, CN, methyl, and/or OH, NH_2 , $\text{NH}(\text{C}_{1-4} \text{ alkyl})$, or $\text{N}(\text{C}_{1-4} \text{ alkyl})(\text{C}_{1-4} \text{ alkyl})$.

[0099] In some embodiments, in Formula A (e.g., any of the applicable subformulae), R^1 can be a phenyl or pyridinyl substituted with two substituents. Typically, the two substituents are para to each other, with one of the substituents ortho to ring A.

[0100] For example, in some embodiments, the compound of Formula A can have a structure according to Formula A1b:

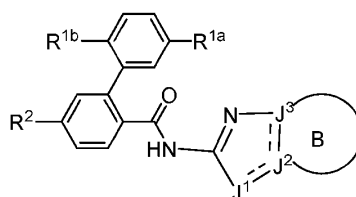


Formula A1b,

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wherein R^{1a} and R^{1b} are each independently halogen, C_{1-6} alkyl optionally substituted with deuterium, F, CN, and/or OH, C_{1-6} alkoxy optionally substituted with deuterium, F, CN, and/or OH, C_{3-6} cycloalkyl optionally substituted with deuterium, F, CN, methyl, and/or OH, NH_2 , $NH(C_{1-4} \text{ alkyl})$, or $N(C_{1-4} \text{ alkyl})(C_{1-4} \text{ alkyl})$, and the other variables are defined herein.

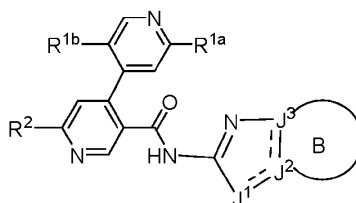
[0101] In some embodiments, the compound of Formula A can have a structure according to Formula A1c:



Formula A1c,

wherein R^{1a} and R^{1b} are each independently halogen, C_{1-6} alkyl optionally substituted with deuterium, F, CN, and/or OH, C_{1-6} alkoxy optionally substituted with deuterium, F, CN, and/or OH, C_{3-6} cycloalkyl optionally substituted with deuterium, F, CN, methyl, and/or OH, NH_2 , $NH(C_{1-4} \text{ alkyl})$, or $N(C_{1-4} \text{ alkyl})(C_{1-4} \text{ alkyl})$, and the other variables are defined herein.

[0102] In some embodiments, the compound of Formula A can have a structure according to Formula A2b:

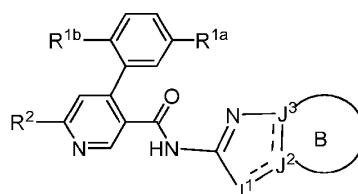


Formula A2b,

wherein R^{1a} and R^{1b} are each independently halogen, C_{1-6} alkyl optionally substituted with deuterium, F, CN, and/or OH, C_{1-6} alkoxy optionally substituted with deuterium, F, CN, and/or OH, C_{3-6} cycloalkyl optionally substituted with deuterium, F, CN, methyl, and/or OH, NH_2 , $NH(C_{1-4} \text{ alkyl})$, or $N(C_{1-4} \text{ alkyl})(C_{1-4} \text{ alkyl})$, and the other variables are defined herein.

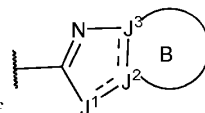
[0103] In some embodiments, the compound of Formula A can have a structure according to Formula A2c:

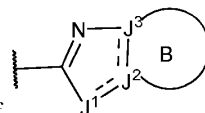
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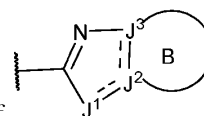


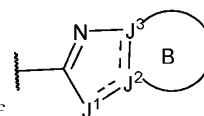
Formula A2c,

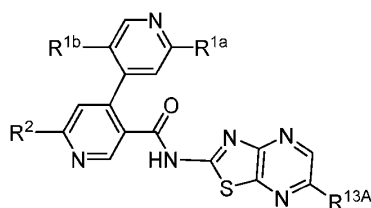
wherein R^{1a} and R^{1b} are each independently halogen, C_{1-6} alkyl optionally substituted with deuterium, F, CN, and/or OH, C_{1-6} alkoxy optionally substituted with deuterium, F, CN, and/or OH, C_{3-6} cycloalkyl optionally substituted with deuterium, F, CN, methyl, and/or OH, NH_2 , $NH(C_{1-4} \text{ alkyl})$, or $N(C_{1-4} \text{ alkyl})(C_{1-4} \text{ alkyl})$, and the other variables are defined herein.



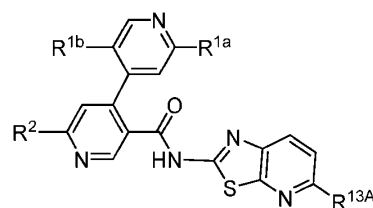
[0104] In some embodiments, the moiety of  in Formula A1a, A1b, A1c, A2a, A2b, or A2c, has the respective definition of any of those described herein for Formula I (e.g., I-1, I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f), Formula II (e.g., II-1), or Formula III (e.g., III-1), preferably, any of those described herein for Formula I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f.



[0105] To illustrate, in some embodiments, the moiety of  in Formula A2b can have the respective definition of any of those described herein for Formula I-1a, I-1b, I-1c, I-1d, I-1e, or I-1f, and in such embodiments, the compound of Formula A2b can have a structure according to any of the following Formula A2b-1, A2b-2, A2b-3, A2b-4, A2b-5, or A2b-6:

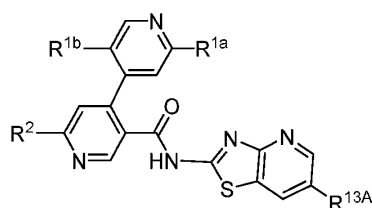


Formula A2b-1

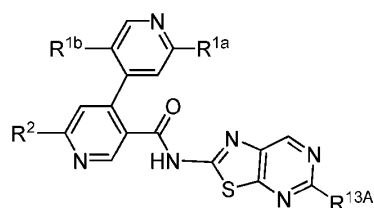


Formula A2b-2

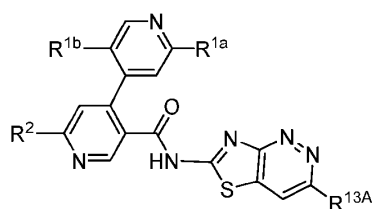
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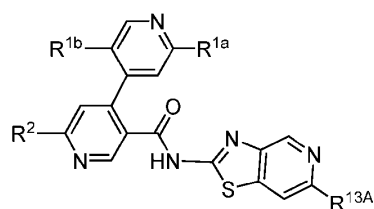
Formula A2b-3



Formula A2b-4



Formula A2b-5



Formula A2b-6

wherein R^{1a} , R^{1b} , R^2 , and R^{13A} are defined herein.

[0106] In some preferred embodiments, in Formula A1b, A1c, A2b, A2b-1, A2b-2, A2b-3, A2b-4, A2b-5, A2b-6, or A2c, R^{1a} and R^{1b} are each independently selected from methyl, ethyl, fluoro, chloro, bromo, trifluoromethyl, difluoromethyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, cyclopropyl, $-NH_2$, hydroxymethyl, and 1-hydroxy ethyl, more preferably, R^{1a} and R^{1b} are each independently selected from methyl, fluoro, chloro, trifluoromethyl, difluoromethyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, and cyclopropyl.

[0107] In some preferred embodiments, in Formula A1b, A1c, A2b, A2b-1, A2b-2, A2b-3, A2b-4, A2b-5, A2b-6, or A2c, R^{1b} is C_{1-2} alkoxy optionally substituted with 1-3 deuterium or F, preferably, R^{1b} is methoxy, ethoxy, or difluoromethoxy.

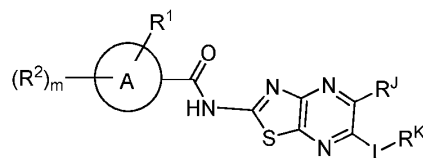
[0108] In some preferred embodiments, in Formula A1b, A1c, A2b, A2b-1, A2b-2, A2b-3, A2b-4, A2b-5, A2b-6, or A2c, R^{1a} is halogen, C_{1-3} alkyl optionally substituted with 1-3 deuterium or F, or cyclopropyl, preferably, R^{1a} is methyl, fluoro, chloro, trifluoromethyl, difluoromethyl, or cyclopropyl.

[0109] In some preferred embodiments, in Formula A1b, A1c, A2b, A2b-1, A2b-2, A2b-3, A2b-4, A2b-5, A2b-6, or A2c, R^{1b} is C_{1-2} alkoxy optionally substituted with 1-3 deuterium or F, preferably, R^{1b} is methoxy, ethoxy, or difluoromethoxy; and R^{1a} is halogen, C_{1-3} alkyl optionally substituted with 1-3 deuterium or F, or cyclopropyl, preferably, R^{1a} is methyl, fluoro, chloro, trifluoromethyl, difluoromethyl, or cyclopropyl.

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Formula K

[0110] In some embodiments, the present disclosure provides a compound of Formula K, or a pharmaceutically acceptable salt thereof:



Formula K

wherein:

Ring A is a phenyl ring or 5-10-membered heteroaryl ring having 1 to 4 ring heteroatoms independently selected from N, O, and S;

R^1 is an optionally substituted phenyl, optionally substituted naphthyl, an optionally substituted 3-10 membered carbocyclic, or an optionally substituted 5-10 membered heterocyclic or heteroaryl, preferably, R^1 is ortho to the amide group (-C(O)-NH-) shown in Formula K;

the subscript m is an integer of 0-4, as valency permits;

R^2 at each occurrence is independently deuterium, halogen, OH, NH_2 , CN, SF_5 , COOH, $CONH_2$, SO_2NH_2 , R^{20} , OR^{20} , SR^{20} , $N(R^{20})(R^{21})$, SO_2R^{20} , $S(=O)(=NR^{21})R^{20}$, $SO_2N(R^{20})(R^{21})$, $N(R^{21})SO_2R^{20}$, COR^{20} , $COOR^{20}$, $OC(O)R^{20}$, $CON(R^{20})(R^{21})$, or $N(R^{21})COR^{20}$, wherein R^{20} at each occurrence is independently an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl, an optionally substituted C_{1-6} heteroalkyl, or an optionally substituted 3-10 membered ring structure; and R^{21} at each occurrence is independently hydrogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{3-6} alkenyl, an optionally substituted C_{3-6} alkynyl, an optionally substituted C_{1-6} heteroalkyl, or an optionally substituted 3-10 membered ring structure; or as applicable, R^{20} and R^{21} together with the intervening atom (e.g., the nitrogen atom) or atoms are joined to form an optionally substituted 4-8 membered heterocyclic ring;

or two instances of R^2 are joined to form an optionally substituted 4-7 membered ring;

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R^J is hydrogen, halogen, optionally substituted C₁₋₆ alkyl, an optionally substituted C₂₋₆ alkenyl, an optionally substituted C₂₋₆ alkynyl, an optionally substituted C₁₋₆ heteroalkyl, or an optionally substituted 3-10 membered ring structure;

L is C₁₋₄ alkylene, C₂₋₄ alkenylene, C₂₋₄ alkynylene, or C₁₋₄ heteroalkylene, each of which is optionally substituted with deuterium and/or F, and

R^K is hydrogen, deuterium, an optionally substituted C₁₋₆ alkyl, an optionally substituted C₁₋₆ heteroalkyl, or an optionally substituted 3-10 membered ring structure.

[0111] In some embodiments, the compound of Formula K (including any of the applicable sub-formulae as described herein) can comprise one or more asymmetric centers and/or axial chirality, and thus can exist in various stereoisomeric forms, *e.g.*, enantiomers and/or diastereomers. In some embodiments, the compound of Formula K can exist in the form of an individual enantiomer and/or diastereomer, as applicable, or a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomers. In some embodiments, when applicable, the compound of Formula K (including any of the applicable sub-formulae as described herein) can exist as an individual enantiomer substantially free of the other enantiomer, such as having an enantiomeric excess ("ee") of greater than 60%, preferably, greater than 80% ee, greater than 90% ee, greater than 95% ee, greater than 98% ee, or greater than 99% ee. In some embodiments, when applicable, the compound of Formula K (including any of the applicable sub-formulae as described herein) can also exist as a mixture of stereoisomers in any ratio, such as a racemic mixture.

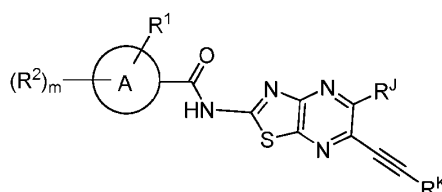
[0112] In some embodiments, the compound of Formula K (including any of the applicable sub-formulae as described herein) can exist as an isotopically labeled compound, particularly, a deuterated analog, wherein one or more of the hydrogen atoms of the compound of Formula K is/are substituted with a deuterium atom with an abundance above its natural abundance, *e.g.*, a CD₃ analog when the compound has a CH₃ group. Without wishing to be bound by theories, it is believed that in certain situations, substitution with deuterium can lead to a deuterated analog with a better pharmacokinetic profile. Deuterated analogs can be generally prepared by using commercially available deuterating/deuterated reagents.

[0113] It should be apparent to those skilled in the art that in certain cases, the compound of Formula K may exist as a mixture of tautomers. The present disclosure is not limited to

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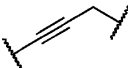
any specific tautomer. Rather, the present disclosure encompasses any and all of such tautomers whether or not explicitly drawn or referred to.

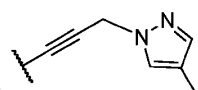
[0114] In some preferred embodiments, L in Formula K is C₂₋₄ alkynylene, which is optionally substituted with deuterium and/or F. For example, in some preferred embodiments, the compound of Formula K can be characterized as having a structure according to Formula K-1:



Formula K-1.

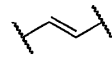
[0115] In some embodiments, L can also be a C₃₋₄ alkynylene, optionally substituted with

deuterium and/or F, such as , typically, in such embodiments, the CH₂ end is

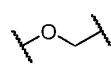
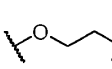
bonded with R^K. For example, in some embodiments, L-R^K can be .

[0116] In some embodiments, L in Formula K is C₁₋₄ alkylene, which is optionally substituted with deuterium and/or F. The C₁₋₄ alkylene can be linear or branched. For example, in some embodiments, L can be linear C₁₋₄ alkylene, such as CH₂CH₂, CH₂CH₂CH₂, or CH₂CH₂CH₂CH₂.

[0117] In some embodiments, L in Formula K is C₂₋₄ alkenylene, which is optionally substituted with deuterium and/or F. For example, in some embodiments, L can be a C₂

alkenylene, e.g., .

[0118] In some embodiments, L in Formula K is C₁₋₄ heteroalkylene, which is optionally substituted with deuterium and/or F. For example, in some embodiments, L can be

, or , wherein the oxygen atom can be bonded with R^K or to the thiazolopyrazine ring.

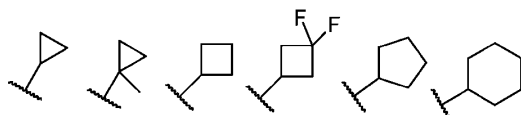
[0119] In some preferred embodiments, R^K in Formula K (e.g., any of the subformulae described herein, as applicable) can be an optionally substituted C₃₋₈ cycloalkyl. Typically, the C₃₋₈ cycloalkyl is a monocyclic ring. However, in some embodiments, the C₃₋₈ cycloalkyl

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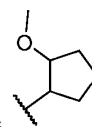
can also be a bicyclic ring structure, such as a fused, bridged, or spiro bicyclic ring structure. When substituted, the C₃₋₈ cycloalkyl is preferably substituted with one or more (e.g., 1, 2, or 3) substituents independently selected from deuterium, halogen, OH, CN, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ heteroalkyl, or a 3-10 membered ring, wherein each of the C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ heteroalkyl, or 3-10 membered ring is independently optionally substituted with one or more substituents independently selected from deuterium, halogen, CN, OH, oxo, C₁₋₄ alkyl optionally substituted with deuterium and/or F, C₁₋₄ heteroalkyl optionally substituted with deuterium and/or F, and 3-6 membered ring (e.g., carbocyclic, heterocyclic, heteroaryl, or phenyl ring), wherein the 3-6 membered ring at each occurrence is independently optionally substituted with one or more substituents independently selected from deuterium, halogen, CN, OH, oxo, C₁₋₄ alkyl optionally substituted with deuterium and/or F, and C₁₋₄ heteroalkyl optionally substituted with deuterium and/or F.

[0120] In some embodiments, R^K in Formula K (e.g., any of the subformulae described herein, as applicable) can be cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, each of which is optionally substituted with one or more, e.g., 1-5 or 1-3, substituents independently selected from deuterium, F, OH, CN, C₁₋₄ alkyl optionally substituted with F, C₁₋₄ heteroalkyl optionally substituted with F, or 3-6 membered ring optionally substituted with one or more substituents independently selected from deuterium, halogen, CN, OH, oxo, C₁₋₄ alkyl optionally substituted with F, and C₁₋₄ heteroalkyl optionally substituted with F.

[0121] For example, in some more specific embodiments, R^K in Formula K (e.g., any of the subformulae described herein, as applicable) can be selected from:

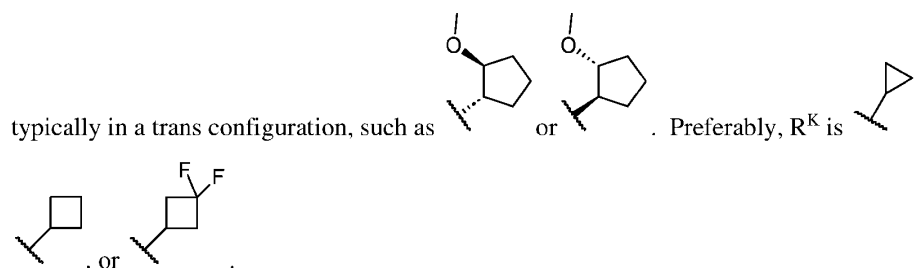


. In some embodiments, R^K in Formula K

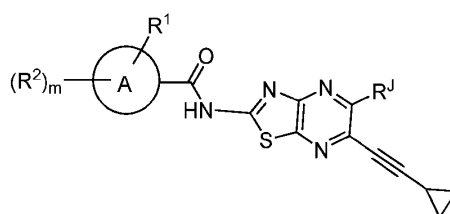


(e.g., any of the subformulae described herein, as applicable) can be , which is

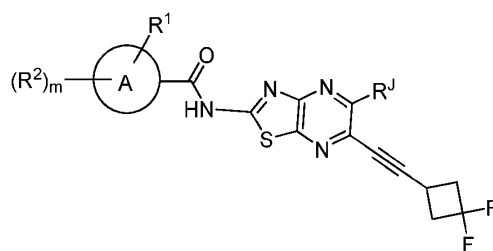
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[0122] For example, in some preferred embodiments, the compound of Formula K-1 can have a structure according to Formula K-1a-1 or K-1a-2:



Formula K-1a-1



Formula K-1a-2

wherein the variables are defined and preferred herein. In some embodiments, R^K in Formula K (e.g., any of the subformulae described herein, as applicable) can be an optionally substituted 4-8 membered heterocyclyl. Typically, the 4-8 membered heterocyclyl has 1-3 ring heteroatoms each independently O, S, or N, wherein the sulfur atom, if present, is optionally oxidized. The 4-8 membered heterocyclyl is typically a monocyclic ring. In some embodiments, the 4-8 membered heterocyclyl can also be a fused, bridged, or spiro bicyclic ring structure. When substituted, the 4-8 membered heterocyclyl is preferably substituted with one or more (e.g., 1, 2, or 3) substituents independently selected from deuterium, halogen, OH, oxo, CN, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ heteroalkyl, or a 3-10 membered ring, wherein each of the C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ heteroalkyl, or 3-10 membered ring is independently

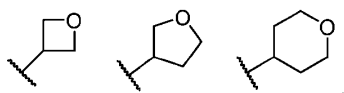
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optionally substituted with one or more substituents independently selected from deuterium, halogen, CN, OH, oxo, C₁₋₄ alkyl optionally substituted with deuterium and/or F, C₁₋₄ heteroalkyl optionally substituted with deuterium and/or F, and 3-6 membered ring (e.g., carbocyclic, heterocyclic, heteroaryl, or phenyl ring), wherein the 3-6 membered ring at each occurrence is independently optionally substituted with one or more substituents independently selected from deuterium, halogen, CN, OH, oxo, C₁₋₄ alkyl optionally substituted with deuterium and/or F, and C₁₋₄ heteroalkyl optionally substituted with deuterium and/or F.

[0123] In some embodiments, R^K in Formula K (e.g., any of the subformulae described herein, as applicable) is 4-6 membered heterocyclyl having one or two ring heteroatoms, each independently O, S, or N, wherein the sulfur atom, if present, is optionally oxidized, wherein the 4-6 membered heterocyclyl is optionally substituted with one or more (e.g., 1-3) substituents independently selected from deuterium, F, oxo, OH, CN, C₁₋₄ alkyl optionally substituted with deuterium and/or F, C₁₋₄ heteroalkyl optionally substituted with deuterium and/or F, 3-6 membered ring, (C₁₋₄ alkylene)-(3-6 membered ring), or (C₁₋₄ heteroalkylene)-(3-6 membered ring), wherein the C₁₋₄ alkylene or C₁₋₄ heteroalkylene is optionally substituted with deuterium and/or F, and wherein each of the 3-6 membered ring is optionally substituted with one or more substituents independently selected from deuterium, halogen, CN, OH, oxo, C₁₋₄ alkyl optionally substituted with F, and C₁₋₄ heteroalkyl optionally substituted with F.

[0124] For example, in some embodiments, R^K in Formula K (e.g., any of the subformulae described herein, as applicable) can be a monocyclic 4-6 membered heterocyclyl having one ring heteroatom, which is O, and the 4-6 membered heterocyclyl is unsubstituted or substituted with 1-3 substituents each independently deuterium, F, OH, C₁₋₄ alkyl optionally substituted with deuterium and/or F, or C₁₋₄ heteroalkyl optionally substituted with deuterium and/or F.

[0125] For example, in some embodiments, R^K in Formula K (e.g., any of the subformulae described herein, as applicable) can be selected from:



[0126] In some embodiments, R^K in Formula K (e.g., any of the subformulae described herein, as applicable) can be an optionally substituted 5 or 6-membered heteroaryl.

Typically, a 5-membered hetaryl has 1-3 ring heteroatoms each independently O, S, or N; and a 6-membered heteroaryl has 1 or 2 ring nitrogen atoms. When substituted, the 5 or 6-membered heteroaryl is preferably substituted with one or more (e.g., 1, 2, or 3) substituents independently selected from deuterium, halogen, OH, CN, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ heteroalkyl, or a 3-10 membered ring, wherein each of the C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ heteroalkyl, or 3-10 membered ring is independently optionally substituted with one or more substituents independently selected from deuterium, halogen, CN, OH, oxo, C₁₋₄ alkyl optionally substituted with deuterium and/or F, C₁₋₄ heteroalkyl optionally substituted with deuterium and/or F, and 3-6 membered ring (e.g., carbocyclic, heterocyclic, heteroaryl, or phenyl ring), wherein the 3-6 membered ring at each occurrence is independently optionally substituted with one or more substituents independently selected from deuterium, halogen, CN, OH, oxo, C₁₋₄ alkyl optionally substituted with deuterium and/or F, and C₁₋₄ heteroalkyl optionally substituted with deuterium and/or F.

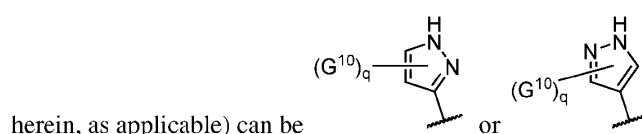
[0127] In some embodiments, R^K in Formula K (e.g., any of the subformulae described herein, as applicable) can be a 5-membered heteroaryl having 1-4 ring heteroatoms, each independently O, S, or N, wherein the 5-membered heteroaryl is optionally substituted with 1-3 substituents independently selected from F, Cl, OH, CN, C₁₋₄ alkyl optionally substituted with deuterium and/or F, C₁₋₄ heteroalkyl optionally substituted with deuterium and/or F, 3-6 membered ring, (C₁₋₄ alkylene)-(3-6 membered ring), or (C₁₋₄ heteroalkylene)-(3-6 membered ring), wherein the C₁₋₄ alkylene or C₁₋₄ heteroalkylene is optionally substituted with deuterium and/or F, and wherein each of the 3-6 membered ring is optionally substituted with one or more substituents independently selected from deuterium, halogen, CN, OH, oxo, C₁₋₄ alkyl optionally substituted with F, and C₁₋₄ heteroalkyl optionally substituted with F. The 3-6 membered ring at each occurrence can be independently a 3-6 membered carbocyclic, 4-6 membered heterocyclic, 5 or 6-membered heteroaryl, or phenyl ring.

[0128] In some embodiments, R^K in Formula K (e.g., any of the subformulae described herein, as applicable) can be a 5-membered heteroaryl selected from pyrazolyl, isoxazolyl, oxadiazolyl, or thiadiazolyl, which is optionally substituted, as valency permits, with 1-3 substituents independently selected from F, Cl, OH, CN, C₁₋₄ alkyl optionally substituted with deuterium and/or F, C₁₋₄ heteroalkyl optionally substituted with deuterium and/or F, 3-6 membered ring, (C₁₋₂ alkylene)-(3-6 membered ring), or (C₁₋₂ heteroalkylene)-(3-6 membered ring), wherein the C₁₋₂ alkylene or C₁₋₂ heteroalkylene is optionally substituted with deuterium

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and/or F, and wherein, preferably, the 3-6 membered ring at each occurrence is independently selected from (a) C₃₋₆ cycloalkyl optionally substituted with methyl and/or F; or (b) 4-6 membered heterocyclyl having 1 or 2 ring heteroatoms independently selected from O, S, and N, wherein the sulfur atom, if present, is optionally oxidized, and wherein the 4-6 membered heterocyclyl is optionally substituted with 1-3 substituents independently selected from deuterium, F, OH, oxo, CN, C₁₋₄ alkyl optionally substituted with F, or C₁₋₄ heteroalkyl optionally substituted with F.

[0129] In some embodiments, R^K in Formula K (e.g., any of the subformulae described



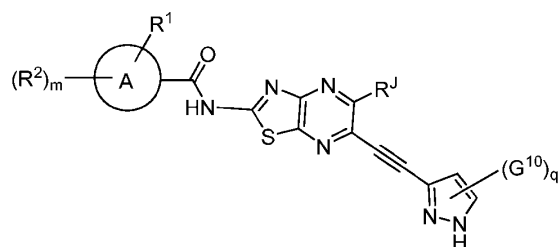
wherein:

q is 0, 1, 2, or 3; and

G¹⁰ at each occurrence is independently F, Cl, CN, C₁₋₄ alkyl optionally substituted with deuterium and/or F, C₁₋₄ heteroalkyl optionally substituted with deuterium and/or F, 3-6 membered ring, (C₁₋₂ alkylene)-(3-6 membered ring), or (C₁₋₂ heteroalkylene)-(3-6 membered ring), wherein the C₁₋₂ alkylene or C₁₋₂ heteroalkylene is optionally substituted with deuterium and/or F, and wherein, preferably, the 3-6 membered ring at each occurrence is independently selected from (a) C₃₋₆ cycloalkyl optionally substituted with methyl and/or F; or (b) 4-6 membered heterocyclyl having 1 or 2 ring heteroatoms independently selected from O, S, and N, wherein the sulfur atom, if present, is optionally oxidized, and wherein the 4-6 membered heterocyclyl is optionally substituted with 1-3 substituents independently selected from deuterium, F, OH, oxo, CN, C₁₋₄ alkyl optionally substituted with F, or C₁₋₄ heteroalkyl optionally substituted with F. In some embodiments, q is 0. In some embodiments, q is 1. In some embodiments, q is 2.

[0130] For example, in some embodiments, the compound of Formula K-1 can have a structure according to Formula K-1b:

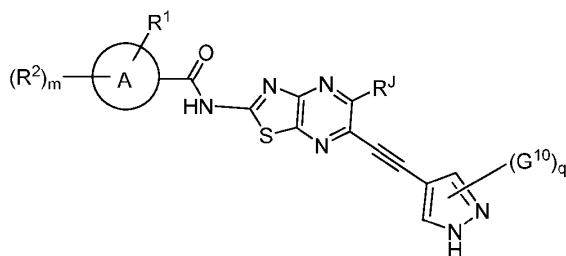
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Formula K-1b

wherein the variables are defined and preferred herein.

[0131] In some embodiments, the compound of Formula K-1 can have a structure according to Formula K-1c:

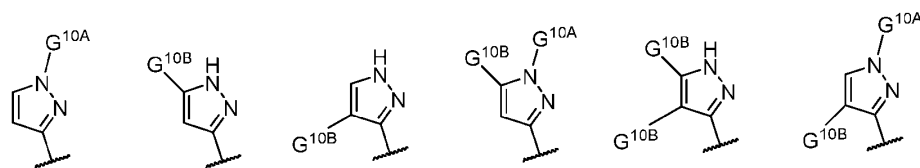


Formula K-1c

wherein the variables are defined and preferred herein.

[0132] It should be understood that in Formula K-1b or K-1c, or similar structures or partial structures herein, the G^{10} group(s), when present, can be attached to any of the available positions of the pyrazole ring, including ring nitrogen atom.

[0133] In some embodiments, R^K in Formula K (e.g., any of the subformulae described herein, as applicable) can be selected from:



wherein:

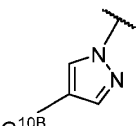
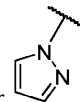
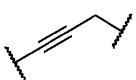
G^{10A} at each occurrence is independently C_{1-4} alkyl optionally substituted with deuterium and/or F, 3-6 membered ring, or $(C_{1-2}$ alkylene)-(3-6 membered ring), wherein the C_{1-2} alkylene or C_{1-2} heteroalkylene is optionally substituted with deuterium and/or F, and wherein, preferably, the 3-6 membered ring at each occurrence is independently selected

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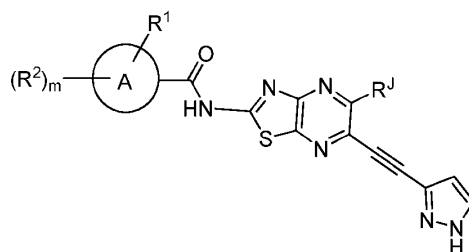
from (a) C₃₋₆ cycloalkyl optionally substituted with methyl and/or F; or (b) 4-6 membered heterocyclyl having 1 or 2 ring heteroatoms independently selected from O, S, and N, wherein the sulfur atom, if present, is optionally oxidized, and wherein the 4-6 membered heterocyclyl is optionally substituted with 1-3 substituents independently selected from deuterium, F, OH, oxo, CN, C₁₋₄ alkyl optionally substituted with F, or C₁₋₄ heteroalkyl optionally substituted with F; and

G^{10B} at each occurrence is independently F, Cl, CN, or G^{10A}.

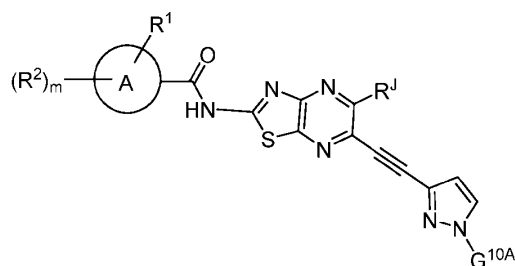
[0134] In some embodiments, R^K in Formula K (e.g., any of the subformulae described

herein, as applicable) can be  or , when L is , wherein G^{10B} is defined herein.

[0135] For example, in some embodiments, the compound of Formula K-1 can have a structure according to Formula K-1b-1, K-1b-2, K-1b-3, or K-1b-4:

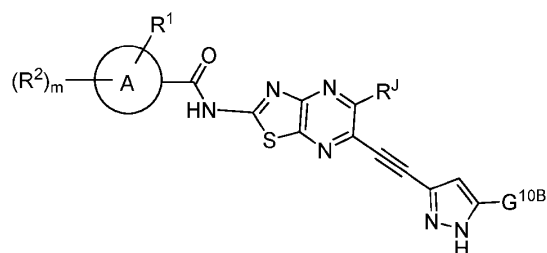


Formula K-1b-1

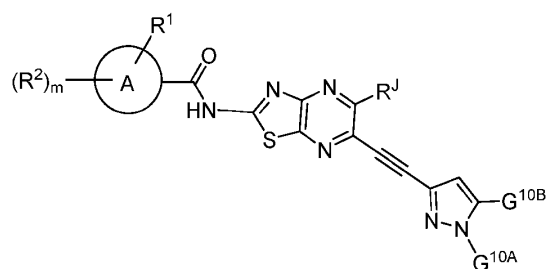


Formula K-1b-2

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Formula K-1b-3



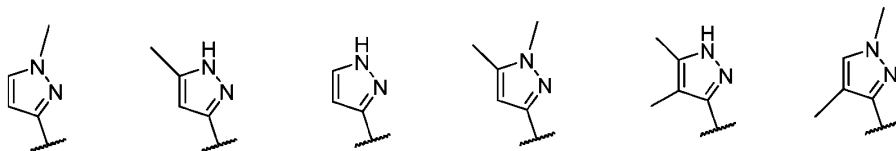
Formula K-1b-4

wherein the variables are defined and preferred herein.

[0136] In some embodiments, G^{10A} at each occurrence is independently C_{1-4} alkyl (e.g., methyl) optionally substituted with deuterium and/or F, cyclopropyl, cyclobutyl, $(C_{1-2}$ alkylene)-(cyclopropyl) or $(C_{1-2}$ alkylene)-(cyclobutyl). For example, in some embodiments, in Formula K-1b-2 or K-1b-4, G^{10A} is C_{1-4} alkyl optionally substituted with deuterium and/or F, such as methyl.

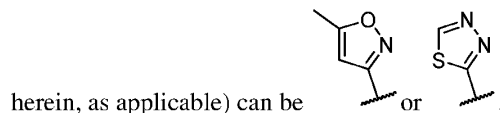
[0137] In some embodiments, G^{10B} at each occurrence is independently F, Cl, C_{1-4} alkyl (e.g., methyl) optionally substituted with deuterium and/or F, cyclopropyl, cyclobutyl, $(C_{1-2}$ alkylene)-(cyclopropyl) or $(C_{1-2}$ alkylene)-(cyclobutyl). For example, in some embodiments, in Formula K-1b-3 or K-1b-4, G^{10B} is C_{1-4} alkyl optionally substituted with deuterium and/or F, such as methyl.

[0138] In some embodiments, R^K in Formula K (e.g., any of the subformulae described herein, as applicable) can be selected from:

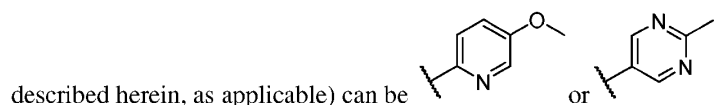


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[0139] In some embodiments, R^K in Formula K (e.g., any of the subformulae described



[0140] In some embodiments, R^K in Formula K (e.g., any of the subformulae described herein, as applicable) can be a 6-membered heteroaryl having 1 or 2 ring nitrogen atoms, e.g., pyridyl, pyrimidyl, etc., wherein the 6-membered heteroaryl is optionally substituted with 1-3 substituents independently selected from F, Cl, OH, CN, C_{1-4} alkyl optionally substituted with deuterium and/or F, C_{1-4} heteroalkyl optionally substituted with deuterium and/or F, 3-6 membered ring, (C_{1-4} alkylene)-(3-6 membered ring), or (C_{1-4} heteroalkylene)-(3-6 membered ring), wherein the C_{1-4} alkylene or C_{1-4} heteroalkylene is optionally substituted with deuterium and/or F, and wherein each of the 3-6 membered ring is optionally substituted with one or more substituents independently selected from deuterium, halogen, CN, OH, oxo, C_{1-4} alkyl optionally substituted with F, and C_{1-4} heteroalkyl optionally substituted with F. For example, in some specific embodiments, R^K in Formula K (e.g., any of the subformulae

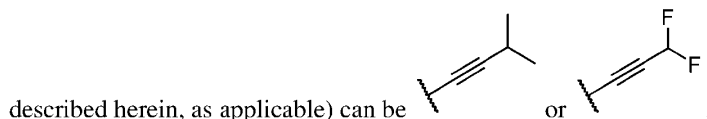


[0141] In some embodiments, R^K in Formula K (e.g., any of the subformulae described herein, as applicable) can also be hydrogen.

[0142] In some embodiments, R^K in Formula K (e.g., any of the subformulae described herein, as applicable) can also be an optionally substituted C_{1-6} alkyl. When substituted, the C_{1-6} alkyl can be preferably substituted with one or more (e.g., 1, 2, or 3) substituents independently selected from deuterium, halogen, OH, CN, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} heteroalkyl, or a 3-10 membered ring, wherein each of the C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} heteroalkyl, or 3-10 membered ring is independently optionally substituted with one or more substituents independently selected from deuterium, halogen, CN, OH, oxo, C_{1-4} alkyl optionally substituted with deuterium and/or F, C_{1-4} heteroalkyl optionally substituted with deuterium and/or F, and 3-6 membered ring (e.g., carbocyclic, heterocyclic, heteroaryl, or phenyl ring), wherein the 3-6 membered ring at each occurrence is independently optionally substituted with one or more substituents independently selected from deuterium, halogen, CN, OH, oxo, C_{1-4} alkyl optionally substituted with deuterium and/or F, and C_{1-4} heteroalkyl optionally substituted with deuterium and/or F.

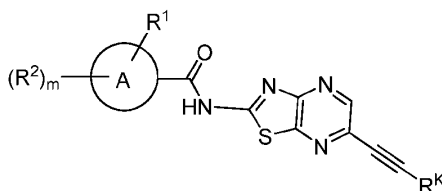
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[0143] In some embodiments, R^K in Formula K (e.g., any of the subformulae described herein, as applicable) can also be a C_{1-4} alkyl optionally substituted with deuterium and/or F. For example, in some embodiments, $L-R^K$ in Formula K (e.g., any of the subformulae



[0144] Typically, R^J in Formula K (e.g., any of the subformulae described herein, as applicable, such as Formula K-1, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, or K-1b-4) is hydrogen.

[0145] For example, in some embodiments, the compound of Formula K can be characterized as having a structure according to Formula K-2:

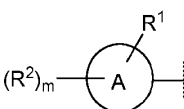


Formula K-2,

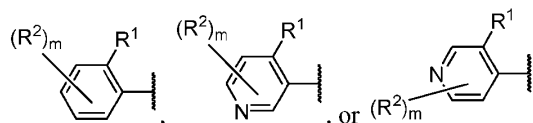
wherein the variables are defined and preferred herein.

[0146] In some embodiments, ring A in Formula K (e.g., any of the subformulae described herein, as applicable, such as Formula K-1, K-2, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, or K-1b-4) can be a phenyl ring. In some embodiments, ring A in Formula K (e.g., any of the subformulae described herein, as applicable, such as Formula K-1, K-2, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, or K-1b-4) can be a 5 or 6-membered heteroaryl ring having 1 to 3 ring heteroatoms independently selected from N, O, and S. In some embodiments, ring A can be a pyridinyl, pyrimidinyl, or imidazo[1,2-a]pyridinyl ring.

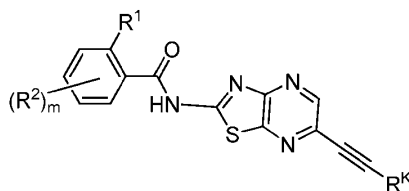
[0147] In some preferred embodiments, ring A in Formula K (e.g., any of the subformulae described herein, as applicable, such as Formula K-1, K-2, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, or K-1b-4) is a phenyl ring or a pyridyl ring. For

example, in some embodiments, the moiety of  in Formula K is selected from:

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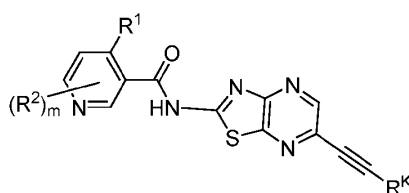
[0148] In some embodiments, the compound of Formula K can be characterized as having a structure of Formula K-3:



Formula K-3,

wherein the variables are defined and preferred herein.

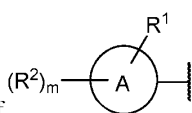
[0149] In some embodiments, the compound of Formula K can be characterized as having a structure of Formula K-5:

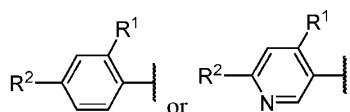


Formula K-5,

wherein the variables are defined and preferred herein.

[0150] The integer m in Formula K is typically 1 or 2. When m is 1, R^2 is typically meta

to R^1 . For example, in some embodiments, the moiety of  in Formula K is



[0151] In some embodiments, m can also be 0.

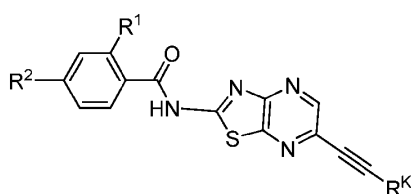
[0152] In some embodiments, m can also be 2 or 3, where two instances of R^2 are joined to form an optionally substituted 4-7 membered ring and the remaining R^2 , if present, is as defined herein. In some embodiments, the 4-7 membered ring can be a 5-membered heterocyclic ring having one or two ring heteroatoms each independently O, N, or S, which is

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optionally substituted, e.g., with one or more substituents each independently selected from deuterium, F, or methyl. For example, in some embodiments, the moiety of



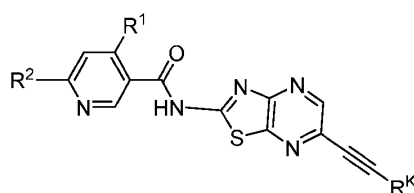
[0153] In some embodiments, the compound of Formula K can be characterized as having a structure of Formula K-4:



Formula K-4,

wherein the variables are defined and preferred herein.

[0154] In some embodiments, the compound of Formula K can be characterized as having a structure of Formula K-6:



Formula K-6,

wherein the variables are defined and preferred herein.

[0155] In some embodiments, in Formula K (e.g., any of the subformulae described herein, as applicable, such as Formula K-1, K-2, K-3, K-4, K-5, K-6, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, or K-1b-4), R² at each occurrence is independently deuterium, halogen, CN, OH, (C₁₋₄ alkylene)-CN, G^A, or X^a-X^b-G^A,

wherein:

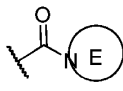
X^a at each occurrence is independently null, C₁₋₄ alkylene, or C₁₋₄ heteroalkylene;

X^b at each occurrence is independently null, , O, NH, N(G^B), C(O), C(O)O, C(O)NH, C(O)N(G^B), NHC(O), N(G^B)C(O), SO₂, S(=O)(=NH), S(=O)(=NG^B), SO₂NH, or SO₂N(G^B); and

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G^A at each occurrence is independently:

- (i) C₁₋₆ alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, C₁₋₄ alkoxy, C(O)-NH(C₁₋₄ alkyl), C(O)-N(C₁₋₄ alkyl)(C₁₋₄ alkyl), or a 3-6 membered ring;
- (ii) C₁₋₆ heteroalkyl optionally substituted with one or more (e.g., 1-3) substituents independently deuterium, halogen, oxo, C₁₋₄ alkyl, C₁₋₄ alkoxy, or a 3-6 membered ring;
- (iii) a 3-8 membered carbocyclic or heterocyclic ring, which is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, oxo, OH, CN, C₁₋₄ alkyl, C₁₋₄ alkoxy, C(O)NH₂, C(O)-NH(C₁₋

4 alkyl), C(O)-N(C₁₋₄ alkyl)(C₁₋₄ alkyl), , wherein the nitrogen containing Ring E is a 4-8 membered heterocyclic ring, or a 3-6 membered ring;

or

- (iv) a 5 or 6-membered heteroaryl, which is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, CN, C₁₋₄ alkyl, C₁₋₄ alkoxy, or a 3-6 membered ring (preferably carbocyclic or heterocyclic ring),

wherein each of the C₁₋₄ alkyl or C₁₋₄ alkoxy in each of (i)-(iv) is independently optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, C₁₋₄ alkoxy, or a 3-4 membered carbocyclic or heterocyclic ring, and

wherein each of the 3-6 membered ring in each of (i)-(iv) or Ring E is independently optionally substituted with one or more (e.g., 1-3) substituents each independently oxo, deuterium, halogen, OH, CN, C₁₋₄ alkyl optionally substituted with deuterium or F, or C₁₋₄ alkoxy optionally substituted with deuterium or F;

G^B at each occurrence is independently C₁₋₆ alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, C₁₋₄ alkoxy optionally substituted with deuterium or F, or a 3-6 membered ring optionally substituted with oxo, deuterium, halogen, OH, CN, C₁₋₄ alkyl optionally substituted with deuterium or F, or C₁₋₄ alkoxy optionally substituted with deuterium or F, or

when applicable, G^A and G^B are joined to form a 4-8 membered heterocyclic ring, which is optionally substituted with one or more (e.g., 1-3) substituents each independently halogen, oxo, OH, C_{1-4} alkyl optionally substituted with F, or C_{1-4} alkoxy optionally substituted with F.

[0156] In some embodiments, in Formula K (e.g., any of the subformulae described herein, as applicable, such as Formula K-1, K-2, K-3, K-4, K-5, K-6, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, or K-1b-4), R^2 at each occurrence is independently G^A , wherein G^A is defined herein. In some embodiments, one instance of R^2 can be $(C_{1-4}$ alkylene)- G^A or $\text{---}\equiv\text{---}G^A$, wherein G^A is defined herein; and any remaining R^2 can be independently any of those defined herein, such as F or Cl.

[0157] In some embodiments, in Formula K (e.g., any of the subformulae described herein, as applicable, such as Formula K-1, K-2, K-3, K-4, K-5, K-6, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, or K-1b-4), R^2 at each occurrence is independently a C_{1-4} alkyl optionally substituted with deuterium, F, and/or OH, e.g., methyl, difluoromethyl, or hydroxymethyl.

[0158] In some embodiments, in Formula K (e.g., any of the subformulae described herein, as applicable, such as Formula K-1, K-2, K-3, K-4, K-5, K-6, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, or K-1b-4), R^2 at each occurrence is independently a 5 or 6-membered heteroaryl, which is optionally substituted with 1-3 substituents each independently halogen, OH, CN, C_{1-4} alkyl, C_{1-4} alkoxy, or a 3-5 membered carbocyclic or heterocyclic ring, wherein the C_{1-4} alkyl or C_{1-4} alkoxy is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen (e.g., F), OH, C_{1-4} alkoxy, or a 3-5 membered carbocyclic or heterocyclic ring, wherein each of the 3-5 membered carbocyclic or heterocyclic ring, when present, is independently optionally substituted with deuterium, F, OH, and/or methyl.

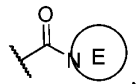
[0159] In some embodiments, in Formula K (e.g., any of the subformulae described herein, as applicable, such as Formula K-1, K-2, K-3, K-4, K-5, K-6, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, or K-1b-4), R^2 at each occurrence is independently $-(C_{1-4}$ alkylene)- $C(O)NHG^A$, $-(C_{1-4}$ alkylene)- $C(O)N(G^A)(G^B)$ or $-(C_{1-4}$ alkylene)-CN, wherein G^A and G^B are defined herein. For example, in some embodiments, G^A and G^B are each independently a C_{1-4} alkyl optionally substituted with deuterium, F and/or OH. In some embodiments, G^A and G^B , together with the nitrogen atom they are both attached to, are

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joined to form a 4-8 membered heterocyclic ring, which is optionally substituted as described herein.

[0160] In some specific embodiments, in Formula K (e.g., any of the subformulae described herein, as applicable, such as Formula K-1, K-2, K-3, K-4, K-5, K-6, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, or K-1b-4), m is 1, and R^2 is CN, halogen, SCF_3 , C_{1-3} alkyl optionally substituted with 1-3 substituents each independently CN, OH, F, or C_{1-3} alkoxy optionally substituted with F. For example, in some embodiments, R^2 is CN, CH_2 -CN, CH_2 - OCF_3 , methyl, difluoromethyl, SCF_3 , or Cl.

[0161] In some embodiments, in Formula K (e.g., any of the subformulae described herein, as applicable, such as Formula K-1, K-2, K-3, K-4, K-5, K-6, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, or K-1b-4), m is 1, and R^2 is $-(C_{1-4} \text{ alkylene})-G^{A1}$, wherein

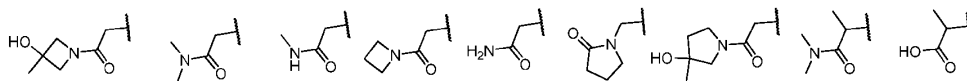
G^{A1} is $C(O)NH_2$, $C(O)OH$, $C(O)NH(C_{1-4} \text{ alkyl})$, $C(O)N(C_{1-4} \text{ alkyl})(C_{1-4} \text{ alkyl})$, ,

or , wherein the nitrogen containing Ring E is a 4-8 membered heterocyclic ring, wherein each of the C_{1-4} alkyl in $C(O)NH(C_{1-4} \text{ alkyl})$ or $C(O)N(C_{1-4} \text{ alkyl})(C_{1-4} \text{ alkyl})$ is independently optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, C_{1-4} alkoxy, or a 3-4 membered carbocyclic or heterocyclic ring, wherein the 3-4 membered carbocyclic or heterocyclic ring is unsubstituted or substituted with 1 or 2 substituents each independently F, OH, methyl, or methoxy; and wherein each of the Ring E is independently optionally substituted with one or more (e.g., 1-3) substituents each independently oxo, deuterium, halogen, OH, CN, C_{1-4} alkyl optionally substituted with deuterium or F, or C_{1-4} alkoxy optionally substituted with deuterium or F.

In some embodiments, the C_{1-4} alkylene is a straight chain alkylene, for example, R^2 can be $-CH_2-G^{A1}$. In some embodiments, the C_{1-4} alkylene can be a branched alkylene, for example, R^2 can be $-CH(CH_3)-G^{A1}$ or $-CH(CH_2CH_3)-G^{A1}$.

[0162] For example, in some embodiments, in Formula K (e.g., any of the subformulae described herein, as applicable, such as Formula K-1, K-2, K-3, K-4, K-5, K-6, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, or K-1b-4), m is 1, and R^2 is selected from the following:

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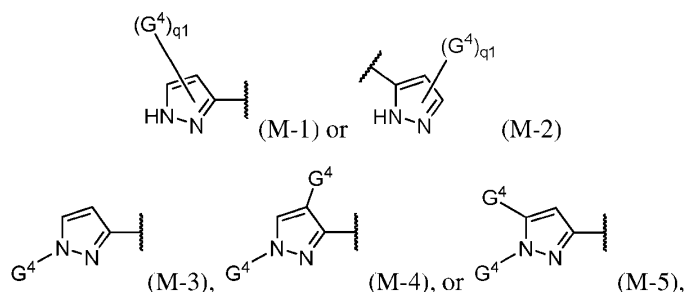
- [0163]** In some embodiments, in Formula K (e.g., any of the subformulae described herein, as applicable, such as Formula K-1, K-2, K-3, K-4, K-5, K-6, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, or K-1b-4), m is 1, and R^2 is a 5-membered heteroaryl having 2-4 ring heteroatoms, such as pyrazolyl, imidazolyl, oxadiazolyl, triazolyl, or thiadiazolyl, etc., which is optionally substituted. When substituted, the 5-membered heteroaryl is preferably substituted with 1 or 2 substituents, as valency permits, each independently deuterium, halogen, OH, CN, C_{1-4} alkyl, C_{1-4} heteroalkyl (such as C_{1-4} alkoxy), a 3-6 membered carbocyclic or heterocyclic ring, (C_{1-4} alkylene)-(3-6 membered carbocyclic or heterocyclic ring); or (C_{1-4} heteroalkylene)-(3-6 membered carbocyclic or heterocyclic ring); wherein the C_{1-4} alkyl, C_{1-4} alkylene, C_{1-4} heteroalkyl, or C_{1-4} heteroalkylene is optionally substituted with one or more (e.g., 1-3) substituents each independently oxo, deuterium, halogen (e.g., F) or OH; and wherein each of the 3-6 membered carbocyclic or heterocyclic ring is optionally substituted with one or more (e.g., 1-3) substituents each independently oxo, deuterium, halogen, OH, CN, C_{1-4} alkyl optionally substituted with deuterium or F, or C_{1-4} alkoxy optionally substituted with deuterium or F.

- [0164]** In some preferred embodiments, in Formula K (e.g., any of the subformulae described herein, as applicable, such as Formula K-1, K-2, K-3, K-4, K-5, K-6, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, or K-1b-4), m is 1, and R^2 is pyrazolyl, which is optionally substituted with one or two substituents, with one substituent being (i) a C_{1-4} alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; (ii) a 3-4 membered carbocyclic or heterocyclic ring; or (iii) (C_{1-4} alkylene)-(3-4 membered carbocyclic or heterocyclic ring); wherein the 3-4 membered carbocyclic or heterocyclic ring in (ii) or (iii) is unsubstituted or substituted with 1 or 2 substituents each independently F, OH, methyl, or methoxy; and the other substituent, if present, is halogen, CN, or C_{1-4} alkyl optionally substituted 1-3 substituents each independently deuterium, F, or OH.

- [0165]** In some embodiments, in Formula K (e.g., any of the subformulae described herein, as applicable, such as Formula K-1, K-2, K-3, K-4, K-5, K-6, K-1a-1, K-1a-2, K-1b,

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K-1c, K-1b-1, K-1b-2, K-1b-3, or K-1b-4), m is 1, and R² can have a structure according to M-1 to M-5:



wherein:

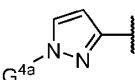
$q1$ is 0, 1, 2, or 3, preferably, 1 or 2; and

G^4 at each occurrence is independently halogen; CN; OH; a C₁₋₄ alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; a C₁₋₄ heteroalkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, oxo, F, or OH; a 3-6 membered carbocyclic or heterocyclic ring; (C₁₋₄ alkylene)-(3-6 membered carbocyclic or heterocyclic ring); or (C₁₋₄ heteroalkylene)-(3-6 membered carbocyclic or heterocyclic ring); wherein each of the 3-6 membered carbocyclic or heterocyclic ring is optionally substituted with one or more (e.g., 1 or 2) substituents each independently F, OH, or C₁₋₄ alkyl optionally substituted with F, provided that when G^4 is attached to a ring nitrogen, then G^4 is not halogen, CN, or OH, and G^4 does not bond to the ring nitrogen through a heteroatom. In some embodiments, $q1$ is 0. In some embodiments, $q1$ is 1, and G^4 is C₁₋₄ alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; a 3-6 membered carbocyclic or heterocyclic ring; or (C₁₋₄ alkylene)-(3-6 membered carbocyclic or heterocyclic ring); wherein each of the 3-6 membered carbocyclic or heterocyclic ring is optionally substituted with one or more (e.g., 1 or 2) substituents each independently F, OH, or C₁₋₄ alkyl optionally substituted with F. In some embodiments, $q1$ is 2, one G^4 is C₁₋₄ alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; a 3-6 membered carbocyclic or heterocyclic ring; or (C₁₋₄ alkylene)-(3-6 membered carbocyclic or heterocyclic ring); wherein each of the 3-6 membered carbocyclic or heterocyclic ring is optionally substituted with one or more (e.g., 1 or 2) substituents each independently F, OH, or C₁₋₄ alkyl optionally

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substituted with F; and the other G^4 is F, Cl, CN, or C_{1-4} alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH.

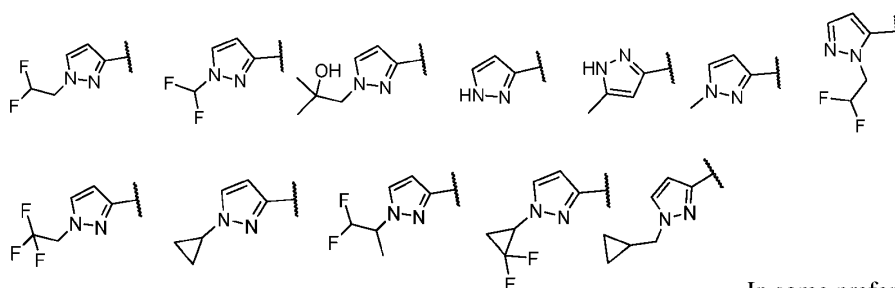
[0166] In some preferred embodiments, in Formula K (e.g., any of the subformulae described herein, as applicable, such as Formula K-1, K-2, K-3, K-4, K-5, K-6, K-1a-1, K-1a-

2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, or K-1b-4), m is 1, and R^2 can be G^{4a}  (M-6),

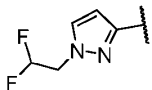
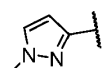
wherein:

G^{4a} is a C_{1-4} alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; a 3-4 membered carbocyclic or heterocyclic ring; or (C_{1-4} alkylene)-(3-4 membered carbocyclic or heterocyclic ring); wherein each of the 3-4 membered carbocyclic or heterocyclic ring is optionally substituted with one or more (e.g., 1 or 2) substituents each independently F, OH, methyl, or methoxy. In some embodiments, the 3-4 membered carbocyclic or heterocyclic ring is a cyclopropyl or cyclobutyl ring.

[0167] For example, in some embodiments, R^2 is selected from the following:



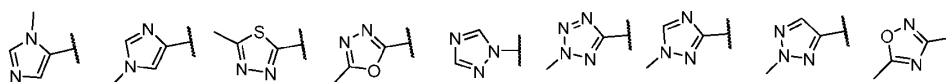
. In some preferred

embodiments, R^2 is  or .

[0168] In some embodiments, in Formula K (e.g., any of the subformulae described herein, as applicable, such as Formula K-1, K-2, K-3, K-4, K-5, K-6, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, or K-1b-4), m is 1, and R^2 is imidazolyl, 1,3,4-oxadiazolyl, triazolyl, tetrazolyl, 1,3,4-thiadiazolyl, or 1,2,4-oxadiazolyl, which is optionally substituted, e.g., with one or more suitable substituents described herein, such as with one or more G^4 groups as defined herein. In some embodiments, when substituted, the aforementioned

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heteroaryl is preferably substituted with one or two substituents, as valency permits, with one substituent being (i) a C₁₋₄ alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; (ii) a 3-4 membered carbocyclic or heterocyclic ring; or (iii) (C₁₋₄ alkylene)-(3-4 membered carbocyclic or heterocyclic ring); wherein the 3-4 membered carbocyclic or heterocyclic ring in (ii) or (iii) is unsubstituted or substituted with 1 or 2 substituents each independently F, OH, methyl, or methoxy; and the other substituent, if present, is halogen, CN, or C₁₋₄ alkyl optionally substituted 1-3 substituents each independently deuterium, F, or OH. For example, in some embodiments, R² is selected from the following:



[0169] In some embodiments, in Formula K (e.g., any of the subformulae described herein, as applicable, such as Formula K-1, K-2, K-3, K-4, K-5, K-6, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, or K-1b-4), m is 1, and R² is a 5-membered or 6-membered heterocyclic ring having 1-3 ring heteroatoms each independently N, O, or S, wherein the 5-membered or 6-membered heterocyclic ring contains one or two ring carbon atoms in the form of C(=O), or the 5-membered or 6-membered heterocyclic ring contains a ring sulfur atom in the form of SO₂, wherein the 5-membered or 6-membered heterocyclic ring is optionally substituted. When substituted, the 5-membered or 6-membered heterocyclic ring is preferably substituted with one or more (e.g., 1, 2, or 3) substituents: (i) each independently deuterium, halogen, OH, CN, C₁₋₄ alkyl, C(O)-C₁₋₄ alkyl, C₁₋₄ heteroalkyl (such as C₁₋₄ alkoxy), 3-6 membered carbocyclic or heterocyclic ring, (C₁₋₄ alkylene)-(3-6 membered carbocyclic or heterocyclic ring), or (C₁₋₄ heteroalkylene)-(3-6 membered carbocyclic or heterocyclic ring); or (ii) two optional substituents, together with the ring atom(s) they are attached to, are joined to form a 3-6 membered carbocyclic or heterocyclic ring, and any remaining substituent(s) is as defined in (i);

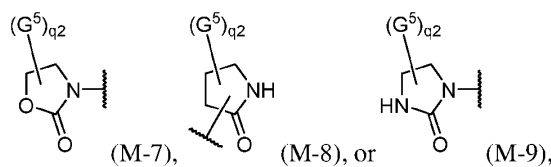
wherein the C₁₋₄ alkyl, C₁₋₄ alkylene, C₁₋₄ heteroalkyl, or C₁₋₄ heteroalkylene is optionally substituted with one or more (e.g., 1-3) substituents each independently oxo, deuterium, halogen (e.g., F) or OH; and

each of the 3-6 membered carbocyclic or heterocyclic ring is optionally substituted with one or more (e.g., 1-3) substituents each independently oxo, deuterium, halogen, OH, CN,

C₁₋₄ alkyl optionally substituted with deuterium or F, or C₁₋₄ alkoxy optionally substituted with deuterium or F.

[0170] In some embodiments, in Formula K (e.g., any of the subformulae described herein, as applicable, such as Formula K-1, K-2, K-3, K-4, K-5, K-6, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, or K-1b-4), m is 1, and R² is a 5-membered heterocyclic ring having 1-3 ring heteroatoms each independently N, O, or S, wherein the 5-membered heterocyclic ring contains one or two ring carbon atoms in the form of C(=O), or the 5-membered heterocyclic ring contains a ring sulfur atom in the form of SO₂, wherein the 5-membered heterocyclic ring is optionally substituted with 1-3 (e.g., 1 or 2) substituents each independently (i) halogen, OH, or CN; (ii) a C₁₋₄ alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; (iii) C(O)-C₁₋₄ alkyl, wherein the C₁₋₄ alkyl is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; (iv) a 3-4 membered carbocyclic or heterocyclic ring; or (v) (C₁₋₄ alkylene)-(3-4 membered carbocyclic or heterocyclic ring); wherein the 3-4 membered carbocyclic or heterocyclic ring in (iv) or (v) is unsubstituted or substituted with 1 or 2 substituents each independently F, OH, methyl, or methoxy. More preferably, the 5-membered heterocyclic ring having 1 or 2 ring heteroatoms each independently N or O, wherein the 5-membered heterocyclic ring contains one or two ring carbon atoms in the form of C(=O), and the 5-membered heterocyclic ring is optionally substituted with one or two substituents each independently halogen or C₁₋₄ alkyl optionally substituted 1-3 substituents each independently deuterium, F, or OH.

[0171] In some preferred embodiments, the 5-membered heterocyclic ring is a ring selected from pyrrolidinone, imidazolidinone, oxazolidinone, or hydantoin ring. For example, in some embodiments, in Formula K (e.g., any of the subformulae described herein, as applicable, such as Formula K-1, K-2, K-3, K-4, K-5, K-6, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, or K-1b-4), m is 1, and R² has a structure according to M-7 to M-9:



wherein:

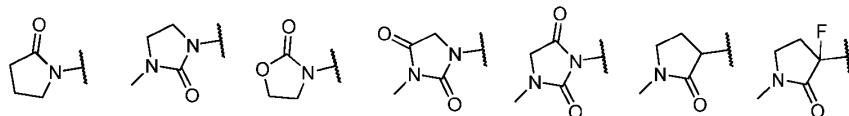
q₂ is 0-4, preferably, 0, 1, or 2; and

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(i) G^5 at each occurrence is independently halogen; CN; OH; a C_{1-4} alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; C(O)- C_{1-4} alkyl, wherein the C_{1-4} alkyl is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; a C_{1-4} heteroalkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, oxo, F, or OH; a 3-6 membered carbocyclic or heterocyclic ring; (C_{1-4} alkylene)-(3-6 membered carbocyclic or heterocyclic ring); or (C_{1-4} heteroalkylene)-(3-6 membered carbocyclic or heterocyclic ring); or

(ii) two G^5 , together with the ring atom(s) they are attached to, are joined to form a 3-6 membered carbocyclic or heterocyclic ring, and any remaining G^5 is defined in (i) above; wherein each of the 3-6 membered carbocyclic or heterocyclic ring in (i) or (ii) is optionally substituted with one or more (e.g., 1 or 2) substituents each independently F, OH, or C_{1-4} alkyl optionally substituted with F, provided that when G^5 is attached to a ring nitrogen, then G^5 is not halogen, CN, or OH, and G^5 does not bond to the ring nitrogen through a heteroatom. In some embodiments, q_2 is 0. In some embodiments, q_2 is 1, and G^5 is halogen (e.g., F), OH, CN, C_{1-4} alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; a 3-6 membered carbocyclic or heterocyclic ring; or (C_{1-4} alkylene)-(3-6 membered carbocyclic or heterocyclic ring); wherein each of the 3-6 membered carbocyclic or heterocyclic ring is optionally substituted with one or more (e.g., 1 or 2) substituents each independently F, OH, or C_{1-4} alkyl optionally substituted with F. In some embodiments, q_2 is 1, and G^5 is C_{1-4} alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH. In some embodiments, q_2 is 2, one G^5 is C_{1-4} alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; a 3-6 membered carbocyclic or heterocyclic ring; or (C_{1-4} alkylene)-(3-6 membered carbocyclic or heterocyclic ring); wherein each of the 3-6 membered carbocyclic or heterocyclic ring is optionally substituted with one or more (e.g., 1 or 2) substituents each independently F, OH, or C_{1-4} alkyl optionally substituted with F; and the other G^5 is F, OH, CN, or C_{1-4} alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH. In some specific embodiments, G^5 at each occurrence is independently F or C_{1-4} alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH.

[0172] In some specific embodiments, R^2 is selected from the following:



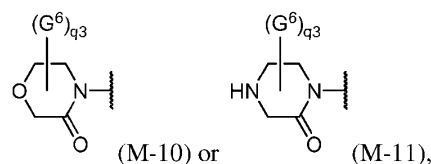
[0173] In some embodiments, in Formula K (e.g., any of the subformulae described herein, as applicable, such as Formula K-1, K-2, K-3, K-4, K-5, K-6, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, or K-1b-4), m is 1, and R^2 is a 6-membered heterocyclic ring having 1 or 2 ring heteroatoms each independently N or O, wherein the 6-membered heterocyclic ring contains one or two ring carbon atoms in the form of $C(=O)$, wherein the 6-membered heterocyclic ring is optionally substituted with 1-3 (e.g., 1 or 2) substituents each independently (i) a C_{1-4} alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; (ii) $C(O)-C_{1-4}$ alkyl, wherein the C_{1-4} alkyl is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; (iii) a 3-4 membered carbocyclic or heterocyclic ring; or (iv) $(C_{1-4} \text{ alkylene})-(3-4 \text{ membered carbocyclic or heterocyclic ring})$; wherein the 3-4 membered carbocyclic or heterocyclic ring in (iii) or (iv) is unsubstituted or substituted with 1 or 2 substituents each independently F, OH, methyl, or methoxy. In some preferred embodiments, the 6-membered heterocyclic ring is optionally substituted with one or two substituents each independently (i) C_{1-4} alkyl optionally substituted 1-3 F, (ii) $C(O)-C_{1-4}$ alkyl; or (iii) cyclopropyl optionally substituted with F.

[0174] In some embodiments, in Formula K (e.g., any of the subformulae described herein, as applicable, such as Formula K-1, K-2, K-3, K-4, K-5, K-6, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, or K-1b-4), m is 1, and R^2 is a 6-membered heterocyclic ring having 1 or 2 ring heteroatoms each independently N or O, wherein the 6-membered heterocyclic ring contains one ring carbon atom in the form of $C(=O)$, wherein two gem substituents of the 6-membered heterocyclic ring are joined to form a 3-4 membered spiro carbocyclic or heterocyclic ring, preferably, spiro cyclopropyl ring, which is unsubstituted or substituted with 1 or 2 substituents each independently F, OH, methyl, or methoxy, and the 6-membered heterocyclic ring optionally has one or more further substituents (e.g., 1 or 2) each independently (i) a C_{1-4} alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; (ii) $C(O)-C_{1-4}$ alkyl, wherein the C_{1-4} alkyl is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium,

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F, or OH; (iii) a 3-4 membered carbocyclic or heterocyclic ring; or (iv) (C₁₋₄ alkylene)-(3-4 membered carbocyclic or heterocyclic ring); wherein the 3-4 membered carbocyclic or heterocyclic ring in (iii) or (iv) is unsubstituted or substituted with 1 or 2 substituents each independently F, OH, methyl, or methoxy. In some preferred embodiments, the two gem substituents of the 6-membered heterocyclic ring are joined to form a spiro cyclopropyl ring, which is unsubstituted or substituted with 1 or 2 substituents each independently F or methyl.

[0175] In some preferred embodiments, the 6-membered heterocyclic ring is a morpholinone or piperazinone ring. For example, in some embodiments, in Formula K (e.g., any of the subformulae described herein, as applicable, such as Formula K-1, K-2, K-3, K-4, K-5, K-6, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, or K-1b-4), m is 1, and R² is M-10 or M-11:



wherein:

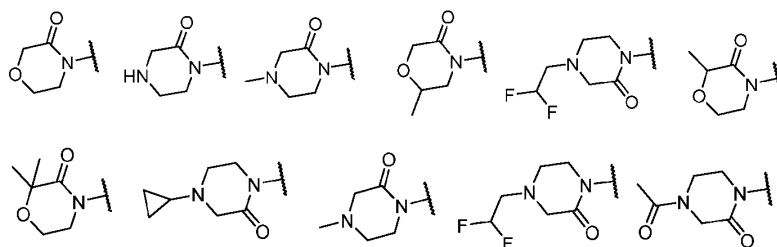
q₃ is 0-5, preferably, 0, 1, 2, or 3; and

(i) G⁶ at each occurrence is independently a C₁₋₄ alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; a C(O)-C₁₋₄ alkyl, wherein the C₁₋₄ alkyl is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; a C₁₋₄ heteroalkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, oxo, F, or OH; a 3-6 membered carbocyclic or heterocyclic ring; (C₁₋₄ alkylene)-(3-6 membered carbocyclic or heterocyclic ring); or (C₁₋₄ heteroalkylene)-(3-6 membered carbocyclic or heterocyclic ring); or

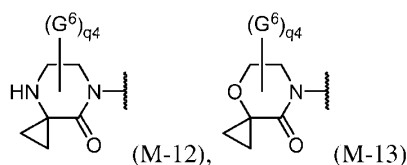
(ii) two G⁶, together with the ring atom(s) they are attached to, are joined to form a 3-6 membered carbocyclic or heterocyclic ring, and any remaining G⁶ is defined in (i) above; wherein each of the 3-6 membered carbocyclic or heterocyclic ring in (i) or (ii) is optionally substituted with one or more (e.g., 1 or 2) substituents each independently F, OH, or C₁₋₄ alkyl optionally substituted with F, provided that when G⁶ is attached to a ring nitrogen, then G⁶ does not bond to the ring nitrogen through a heteroatom. In some embodiments, G⁶ at each occurrence is independently (i) a C₁₋₄ alkyl optionally

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substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; (ii) C(O)-C₁₋₄ alkyl, wherein the C₁₋₄ alkyl is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; (iii) a 3-4 membered carbocyclic or heterocyclic ring; or (iv) (C₁₋₄ alkylene)-(3-4 membered carbocyclic or heterocyclic ring); wherein the 3-4 membered carbocyclic or heterocyclic ring in (iii) or (iv) is unsubstituted or substituted with 1 or 2 substituents each independently F, OH, methyl, or methoxy. In some embodiments, q₃ is 0. In some embodiments, q₃ is 1. In some embodiments, q₃ is 2 or 3, wherein each G⁶ is independently C₁₋₄ alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH. For example, in some specific embodiments, R² is selected from the following:

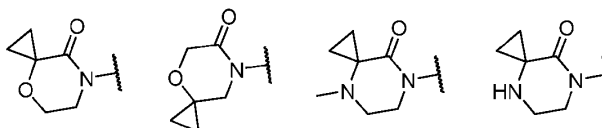


[0176] In some embodiments, in M-10 or M-11, two G⁶ are bonded to the same ring carbon atom, and the two G⁶, together with the carbon atom they are both attached to, are joined to form a cyclopropyl ring, and if present, any remaining G⁶ is defined herein. For example, in some preferred embodiments, R² can be M-12 or M-13:



wherein:

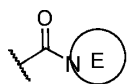
q₄ is 0, 1, or 2, preferably, 0 or 1, and G⁶ is defined herein; preferably, G⁶ at each occurrence is independently C₁₋₄ alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH, for example, methyl. For example, in some



embodiments, R² is selected from

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[0177] In some embodiments, in Formula K (e.g., any of the subformulae described herein, as applicable, such as Formula K-1, K-2, K-3, K-4, K-5, K-6, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, or K-1b-4), m is 1, and R^2 is G^{A2} or $\text{---}\equiv\text{---}G^{A2}$, wherein G^{A2} is a 3-6 membered carbocyclic or heterocyclic ring, which is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, oxo, OH, CN, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)-NH(C_{1-4} \text{ alkyl})$, $C(O)-N(C_{1-4} \text{ alkyl})(C_{1-4} \text{ alkyl})$, or



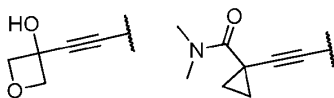
, wherein the nitrogen containing Ring E is a 4-8 membered heterocyclic ring; wherein each of the C_{1-4} alkyl (i.e., including the C_{1-4} alkyl in $C(O)-NH(C_{1-4} \text{ alkyl})$ or $C(O)-N(C_{1-4} \text{ alkyl})(C_{1-4} \text{ alkyl})$) or C_{1-4} alkoxy is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, C_{1-4} alkoxy, or a 3-4 membered carbocyclic or heterocyclic ring, wherein the 3-4 membered carbocyclic or heterocyclic ring is unsubstituted or substituted with 1 or 2 substituents each independently F, OH, methyl, or methoxy; and wherein Ring E is independently optionally substituted with one or more (e.g., 1-3) substituents each independently oxo, deuterium, halogen, OH, CN, C_{1-4} alkyl optionally substituted with deuterium or F, or C_{1-4} alkoxy optionally substituted with deuterium or F.

[0178] In some embodiments, in Formula K (e.g., any of the subformulae described herein, as applicable, such as Formula K-1, K-2, K-3, K-4, K-5, K-6, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, or K-1b-4), m is 1, and R^2 is G^{A2} , wherein G^{A2} is defined



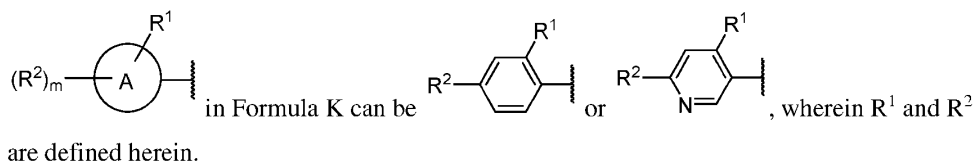
herein, for example, R^2 is .

[0179] In some embodiments, in Formula K (e.g., any of the subformulae described herein, as applicable, such as Formula K-1, K-2, K-3, K-4, K-5, K-6, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, or K-1b-4), m is 1, and R^2 is $\text{---}\equiv\text{---}G^{A2}$, wherein G^{A2} is defined herein, for example, R^2 is selected from the following:



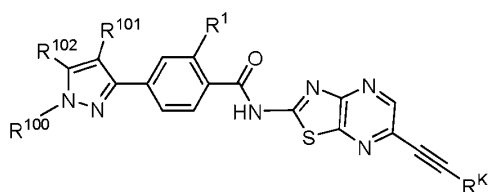
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[0180] In any of the embodiments described herein, when m is 1, the moiety of

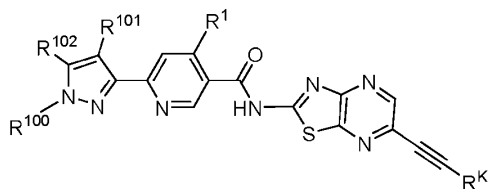


[0181] In some embodiments, in Formula K (e.g., any of the subformulae described herein, as applicable, such as Formula K-1, K-2, K-3, K-4, K-5, K-6, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, or K-1b-4), m can also be 2. In such embodiments, one instance of R² can be any of those described herein, e.g., any of M-1 to M-13, or any of those defined in embodiments when m is specified as 1, and the other instance of R² is typically a small group, such as F, Cl, methyl optionally substituted with F, etc. In some embodiments, when m is 2, one instance of R² can be F or Cl, and the other instance of R² is defined herein.

[0182] In some preferred embodiments, the compound of Formula K can be characterized as having a structure according to Formula K-7a or K-7b:



Formula K-7a,



Formula K-7b,

wherein:

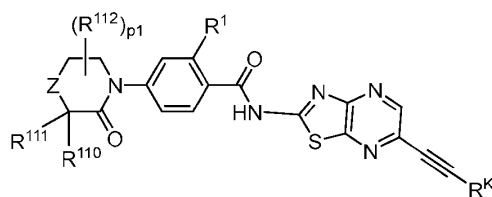
R¹⁰⁰ is selected from

(i) hydrogen; (ii) a C₁₋₄ alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; (iii) a 3-4 membered carbocyclic or heterocyclic ring; or (iv) (C₁₋₄ alkylene)-(3-4 membered carbocyclic or heterocyclic ring); wherein the 3-4 membered carbocyclic or heterocyclic ring in (iii) or (iv) is unsubstituted or substituted with 1 or 2 substituents each independently F, OH, methyl, or methoxy;

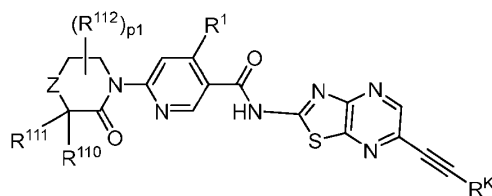
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R^{101} and R^{102} are each independently halogen, CN, or (i)-(iv) as defined for R^{100} , and wherein R^1 and R^K are defined and preferred herein.

- [0183] In some embodiments, in Formula K-7a or K-7b, R^{101} is hydrogen.
- [0184] In some embodiments, in Formula K-7a or K-7b, R^{102} is hydrogen.
- [0185] In some embodiments, in Formula K-7a or K-7b, both R^{101} and R^{102} are hydrogen.
- [0186] In some embodiments, in Formula K-7a or K-7b, R^{100} is C_{1-4} alkyl optionally substituted with deuterium or F, for example, R^{100} is methyl, CD_3 , ethyl, fluorine-substituted methyl (e.g., difluoromethyl or trifluoromethyl), or fluorine-substituted ethyl, such as 2,2-difluoroethyl, 2,2,2-trifluoroethyl, etc.
- [0187] In some embodiments, in Formula K-7a or K-7b, R^{100} is cyclopropyl optionally substituted with 1 or 2 substituents, each independently F or methyl.
- [0188] In some preferred embodiments, the compound of Formula K can be characterized as having a structure according to Formula K-8a or K-8b:



Formula K-8a,



Formula K-8b,

wherein:

Z is O, NH, or NR^{113} ,

p_1 is 0, 1, or 2;

R^{110} and R^{111} are each independently hydrogen or C_{1-4} alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; or R^{110} and R^{111} , together with the carbon atom they are both attached to, are joined to form a 3-4 membered ring, preferably, a cyclopropyl ring, which is optionally substituted with 1 or 2 substituents each independently F, OH, methyl, or methoxy;

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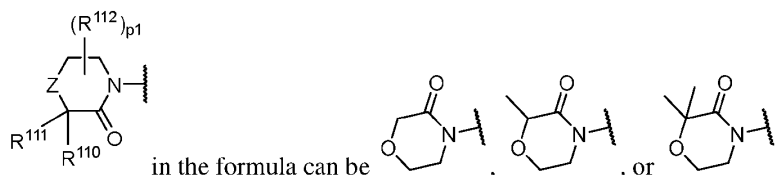
R^{112} at each occurrence is independently a C_{1-4} alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; or when applicable, two R^{112} , together with the carbon atom they are both attached to, are joined to form $C(=O)$, or a 3-4 membered ring, preferably, a cyclopropyl ring, which is optionally substituted with 1 or 2 substituents each independently F, OH, methyl, or methoxy; and R^{113} is (i) a C_{1-4} alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; (ii) a 3-4 membered carbocyclic or heterocyclic ring; or (iii) (C_{1-4} alkylene)-(3-4 membered carbocyclic or heterocyclic ring); wherein the 3-4 membered carbocyclic or heterocyclic ring in (ii) or (iii) is unsubstituted or substituted with 1 or 2 substituents each independently F, OH, methyl, or methoxy, and wherein R^1 and R^K are defined and preferred herein.

[0189] In some embodiments, in Formula K-8a or K-8b, Z is O.

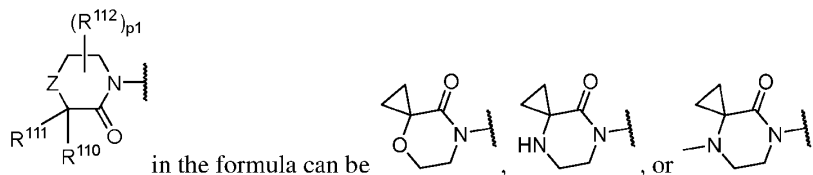
[0190] In some embodiments, in Formula K-8a or K-8b, Z is NH.

[0191] In some embodiments, in Formula K-8a or K-8b, Z is NR^{113} . In some embodiments, R^{113} is C_{1-4} alkyl optionally substituted with deuterium or F, for example, methyl, CD_3 , ethyl, fluorine-substituted methyl (e.g., difluoromethyl or trifluoromethyl), or fluorine-substituted ethyl, such as 2,2-difluoroethyl, 2,2,2-trifluoroethyl etc.

[0192] In some embodiments, in Formula K-8a or K-8b, R^{110} and R^{111} are each independently hydrogen or methyl. For example, in some embodiments, the moiety of



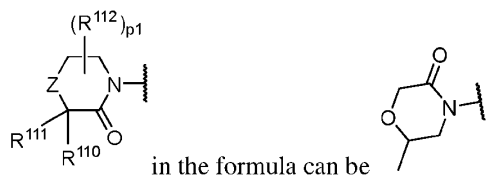
[0193] In some embodiments, in Formula K-8a or K-8b, R^{110} and R^{111} , together with the carbon atom they are both attached to, are joined to form a cyclopropyl ring. For example, in some embodiments, the moiety of



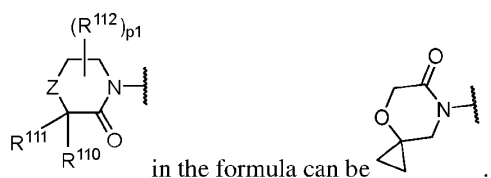
[0194] Typically, in Formula K-8a or K-8b, p_1 is 0.

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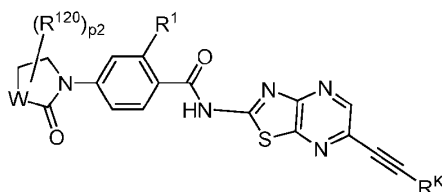
[0195] In some embodiments, in Formula K-8a or K-8b, p_1 is 1 or 2, and R^{112} at each occurrence is methyl. For example, in some embodiments, the moiety of



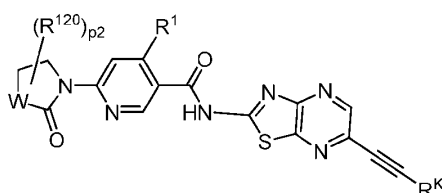
[0196] In some embodiments, in Formula K-8a or K-8b, p_1 is 2, and two R^{112} are attached to the same ring carbon, and the two R^{112} , together with to the ring carbon they are both attached to, are joined to form a cyclopropyl ring. For example, in some embodiments, the moiety of



[0197] In some preferred embodiments, the compound of Formula K can be characterized as having a structure according to Formula K-9a or K-9b:



Formula K-9a,



Formula K-9b,

wherein:

W is O, NH, $C(R^{121})(R^{122})$, or NR^{123} ,

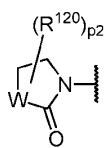
p_2 is 0, 1, or 2;

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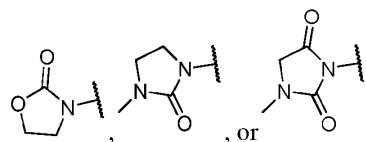
R^{120} at each occurrence is independently a C_{1-4} alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; or when applicable, two R^{120} , together with the carbon atom they are both attached to, are joined to form $C(=O)$ or a 3-4 membered spiro or fused ring, which is optionally substituted with 1 or 2 substituents each independently F, OH, methyl, or methoxy; R^{121} and R^{122} are each independently hydrogen or C_{1-4} alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; or R^{121} and R^{122} , together with the carbon atom they are both attached to, are joined to form a 3-4 membered ring, preferably, a cyclopropyl ring, which is optionally substituted with 1 or 2 substituents each independently F, OH, methyl, or methoxy; and R^{123} is (i) a C_{1-4} alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; (ii) a 3-4 membered carbocyclic or heterocyclic ring; or (iii) $(C_{1-4} \text{ alkylene})-(3-4 \text{ membered carbocyclic or heterocyclic ring})$; wherein the 3-4 membered carbocyclic or heterocyclic ring in (ii) or (iii) is unsubstituted or substituted with 1 or 2 substituents each independently F, OH, methyl, or methoxy, and wherein R^1 and R^K are defined and preferred herein.

- [0198] In some embodiments, in Formula K-9a or K-9b, W is O.
- [0199] In some embodiments, in Formula K-9a or K-9b, W is NH.
- [0200] In some embodiments, in Formula K-9a or K-9b, W is NR^{123} . In some embodiments, R^{123} is C_{1-4} alkyl optionally substituted with deuterium or F, for example, methyl, CD_3 , ethyl, fluorine-substituted methyl (e.g., difluoromethyl or trifluoromethyl), or fluorine-substituted ethyl, such as 2,2-difluoroethyl, 2,2,2-trifluoroethyl, etc.
- [0201] In some embodiments, in Formula K-9a or K-9b, W is $C(R^{121})(R^{122})$. In some embodiments, R^{121} and R^{122} are each independently hydrogen or methyl, for example, both R^{121} and R^{122} are hydrogen.
- [0202] In Formula K-9a or K-9b, p2 is typically 0.
- [0203] In some embodiments, in Formula K-9a or K-9b, p2 is 1 or 2, and R^{120} at each occurrence is methyl.
- [0204] In some embodiments, in Formula K-9a or K-9b, p2 is 2, and two gem R^{120} , and the same ring carbon they are both attached to, together represent $C(=O)$.
- [0205] In some embodiments, the moiety of

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in Formula K-9a or K-9b is selected from



[0206] R^1 in Formula K (e.g., any of the subformulae described herein, as applicable, such as Formula K-1, K-2, K-3, K-4, K-5, K-6, K-7a, K-7b, K-8a, K-8b, K-9a, K-9b, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, or K-1b-4) is typically an optionally substituted phenyl or heteroaryl. For example, in some embodiments, R^1 is a phenyl, pyridinyl, pyrimidinyl, benzopyrazolyl, benzimidazolyl, imidazolyl, pyridazyl, imidazo[1,2-a]pyrimidinyl, oxazolo[4,5-b]pyridinyl, oxazolo[5,4-b]pyridinyl, thiazolo[4,5-b]pyridinyl, benzo[d]thiazole, indazolyl, [1,2,4]triazolo[1,5-a]pyrimidinyl, [1,2,4]triazolo[1,5-b]pyridazinyl, or tetrazolo[1,5-a]pyridinyl, each of which is optionally substituted.

[0207] In some embodiments, in Formula K (e.g., any of the subformulae described herein, as applicable, such as Formula K-1, K-2, K-3, K-4, K-5, K-6, K-7a, K-7b, K-8a, K-8b, K-9a, K-9b, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, or K-1b-4), R^1 is a phenyl or pyridinyl, each of which is optionally substituted with 1-3 substituents independently selected from: deuterium, halogen, CN, OH, NH_2 , COOH, CONH $_2$, (C_{1-4} alkylene)-CN, G^C , or $X^c-X^d-G^C$,

wherein:

X^c at each occurrence is independently null, C_{1-4} alkylene, or C_{1-4} heteroalkylene;

X^d at each occurrence is independently null, O, NH, N(G^D), C(O), C(O)O, C(O)NH, C(O)N(G^D), NHC(O), N(G^D)C(O), P(O)(G^D), SO $_2$, SO $_2$ NH, or SO $_2$ N(G^D); and

G^C at each occurrence is independently:

- (i) C_{1-6} alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, C_{1-4} alkoxy, or a 3-6 membered ring;
 - (ii) C_{1-6} heteroalkyl optionally substituted with one or more (e.g., 1-3) substituents independently deuterium, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, or a 3-6 membered ring;
 - (iii) a 3-7 membered carbocyclic or heterocyclic ring, which is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, oxo, OH, CN, C_{1-4} alkyl, C_{1-4} alkoxy, or a 3-6 membered ring;
- or
- (iv) a 5 or 6-membered heteroaryl, which is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, CN, C_{1-4}

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alkyl, C₁₋₄ alkoxy, or a 3-6 membered ring (preferably carbocyclic or heterocyclic ring),

wherein the C₁₋₄ alkyl or C₁₋₄ alkoxy in each of (i)-(iv) is independently optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, C₁₋₄ alkoxy, or a 3-4 membered carbocyclic or heterocyclic ring, and

wherein each of the 3-6 membered ring in each of (i)-(iv) is independently optionally substituted with oxo, deuterium, halogen, OH, CN, C₁₋₄ alkyl optionally substituted with deuterium or F, or C₁₋₄ alkoxy optionally substituted with deuterium or F;

G^D at each occurrence is independently C₁₋₆ alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, C₁₋₄ alkoxy optionally substituted with deuterium or F, or a 3-6 membered ring optionally substituted with oxo, deuterium, halogen, OH, CN, C₁₋₄ alkyl optionally substituted with deuterium or F, or C₁₋₄ alkoxy optionally substituted with deuterium or F, or

when applicable, G^C and G^D together with the heteroatom they are both attached to are joined to form a 4-7 membered heterocyclic ring, which is optionally substituted with one or more (e.g., 1-3) substituents each independently halogen, oxo, OH, C₁₋₄ alkyl optionally substituted with deuterium or F, or C₁₋₄ alkoxy optionally substituted with deuterium or F.

[0208] In some embodiments, in Formula K (e.g., any of the subformulae described herein, as applicable, such as Formula K-1, K-2, K-3, K-4, K-5, K-6, K-7a, K-7b, K-8a, K-8b, K-9a, K-9b, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, or K-1b-4), R¹ can be a phenyl or pyridinyl, each of which is optionally substituted with one or more (e.g., 1-3) substituents independently selected from halogen, C₁₋₆ alkyl optionally substituted with deuterium, F, CN, and/or OH, C₁₋₆ alkoxy optionally substituted with deuterium, F, CN, and/or OH, C₃₋₆ cycloalkyl optionally substituted with deuterium, F, CN, methyl, and/or OH, SCF₃, NH₂, NH(C₁₋₄ alkyl), or N(C₁₋₄ alkyl)(C₁₋₄ alkyl).

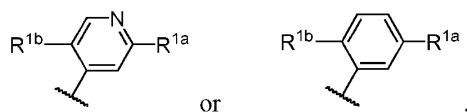
[0209] In some embodiments, in Formula K (e.g., any of the subformulae described herein, as applicable, such as Formula K-1, K-2, K-3, K-4, K-5, K-6, K-7a, K-7b, K-8a, K-8b, K-9a, K-9b, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, or K-1b-4), R¹ can be a phenyl or pyridinyl, each of which is optionally substituted with one or more (e.g., 1-3)

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substituents independently selected from halogen, C₁₋₄ alkyl optionally substituted with deuterium, F and/or OH, C₁₋₄ alkoxy optionally substituted with deuterium or F, C₃₋₄ cycloalkyl optionally substituted with deuterium, F, CN, methyl, and/or OH, NH₂, NH(C₁₋₃ alkyl), or N(C₁₋₃ alkyl)(C₁₋₃ alkyl).

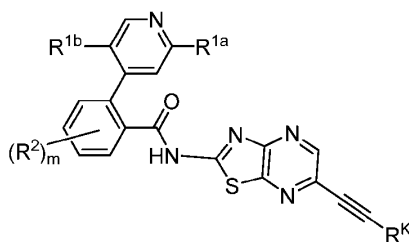
[0210] In some embodiments, in Formula K (e.g., any of the subformulae described herein, as applicable, such as Formula K-1, K-2, K-3, K-4, K-5, K-6, K-7a, K-7b, K-8a, K-8b, K-9a, K-9b, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, or K-1b-4), R¹ can be a phenyl or pyridinyl, each of which is optionally substituted with 1-3 substituents independently selected from methyl, ethyl, fluoro, chloro, bromo, trifluoromethyl, difluoromethyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, cyclopropyl, -NH₂, hydroxymethyl, and 1-hydroxyethyl, preferably, the substituents are independently selected from methyl, fluoro, chloro, trifluoromethyl, difluoromethyl, methoxy, ethoxy, difluoromethoxy, and cyclopropyl.

[0211] In some embodiments, in Formula K (e.g., any of the subformulae described herein, as applicable, such as Formula K-1, K-2, K-3, K-4, K-5, K-6, K-7a, K-7b, K-8a, K-8b, K-9a, K-9b, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, or K-1b-4), R¹ can be



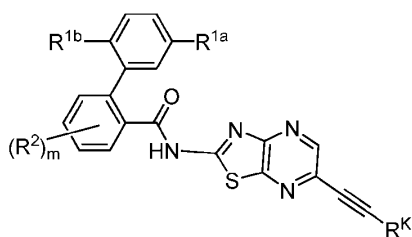
wherein R^{1a} and R^{1b} are each independently halogen, C₁₋₆ alkyl optionally substituted with deuterium, F, CN, and/or OH, C₁₋₆ alkoxy optionally substituted with deuterium, F, CN, and/or OH, C₃₋₆ cycloalkyl optionally substituted with deuterium, F, CN, methyl, and/or OH, SCF₃, NH₂, NH(C₁₋₄ alkyl), or N(C₁₋₄ alkyl)(C₁₋₄ alkyl).

[0212] For example, in some embodiments, the compound of Formula K can be characterized as having a structure according to Formula K-3a or K-3b:



Formula K-3a

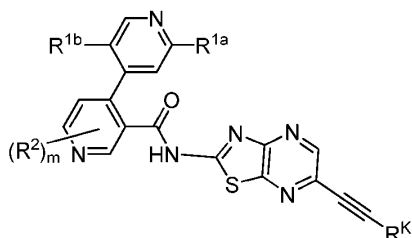
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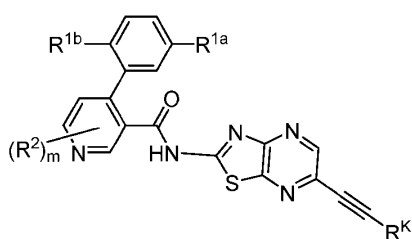
Formula K-3b,

wherein the variables are defined and preferred herein.

[0213] In some embodiments, the compound of Formula K can be characterized as having a structure according to Formula K-5a or K-5b:



Formula K-5a



Formula K-5b,

wherein the variables are defined and preferred herein.

[0214] In some embodiments, in any of the applicable formulae or a partial structure, e.g., in Formula K-3a, K-3b, K-5a, or K-5b, R^{1a} and R^{1b} can each independently be selected from methyl, ethyl, fluoro, chloro, bromo, trifluoromethyl, difluoromethyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, cyclopropyl, -NH₂, hydroxymethyl, and 1-hydroxyethyl.

[0215] In some embodiments, in any of the applicable formulae or a partial structure, e.g., in Formula K-3a, K-3b, K-5a, or K-5b, R^{1b} can be C₁₋₄ alkoxy optionally substituted with 1-3 deuterium or F, for example, methoxy, ethoxy, or difluoromethoxy.

[0216] In some embodiments, in any of the applicable formulae or a partial structure, e.g., in Formula K-3a, K-3b, K-5a, or K-5b, R^{1a} can be (i) halogen (e.g., F or Cl); (ii) C₁₋₄ alkyl

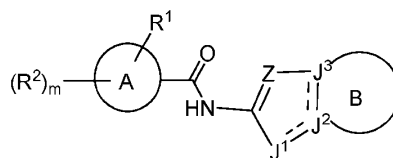
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optionally substituted with 1-3 deuterium or F, e.g., methyl, trifluoromethyl, difluoromethyl, etc.; or (iii) cyclopropyl or cyclobutyl, optionally substituted with methyl and/or F.

[0217] Ring A, R^1 , R^2 , and m in Formula K (e.g., any of the subformulae described herein, as applicable, such as Formula K-1, K-2, K-3, K-4, K-5, K-6, K-7a, K-7b, K-8a, K-8b, K-9a, K-9b, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, K-1b-4, K-3a, K-3b, K-5a, or K-5b) can also have any of the definition described herein in connection with Formula A or its subformulae.

[0218] In some embodiments, the present disclosure provides compounds according to any of the following enumerated embodiments A1-A44:

Embodiment A1. A compound of Formula A, or a pharmaceutically acceptable salt thereof:



Formula A

wherein:

J^1 is S, O, N, CR^{10A} or NR^{10B} ;

J^2 is C or N;

J^3 is C or N;

Z is N or CR^{10A} , preferably, Z is N;

provided that the 5-membered ring containing Z, J^1 , J^2 , and J^3 is a heteroaryl ring having 1-3 ring heteroatoms;

Ring A is a phenyl ring or 5-10-membered heteroaryl ring having 1 to 4 ring heteroatoms independently selected from N, O, and S;

Ring B is an optionally substituted 5-7 membered carbocyclic or heterocyclic ring, or an optionally substituted phenyl ring, or an optionally substituted 5 or 6-membered heteroaryl ring having 1-3 ring heteroatoms each independently N, S, or O; preferably,

Ring B is an optionally substituted 6-membered heteroaryl ring having 1 or 2 ring nitrogen atoms;

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R¹ is an optionally substituted phenyl, optionally substituted naphthyl, an optionally substituted 3-10 membered carbocyclic, or an optionally substituted 5-10 membered heterocyclic or heteroaryl, preferably, R¹ is ortho to the amide group (-C(O)-NH-) shown in Formula A;

the subscript m is an integer of 0-4, as valency permits;

R² at each occurrence is independently deuterium, halogen, OH, NH₂, CN, SF₅, COOH, CONH₂, SO₂NH₂, R²⁰, OR²⁰, SR²⁰, N(R²⁰)(R²¹), SO₂R²⁰, SO₂N(R²⁰)(R²¹), N(R²¹)SO₂R²⁰, COR²⁰, COOR²⁰, OC(O)R²⁰, CON(R²⁰)(R²¹), or N(R²¹)COR²⁰, wherein R²⁰ at each occurrence is independently an optionally substituted C₁₋₆ alkyl, an optionally substituted C₂₋₆ alkenyl, an optionally substituted C₂₋₆ alkynyl, an optionally substituted C₁₋₆ heteroalkyl, or an optionally substituted 3-10 membered ring structure; and R²¹ at each occurrence is independently hydrogen, an optionally substituted C₁₋₆ alkyl, an optionally substituted C₃₋₆ alkenyl, an optionally substituted C₃₋₆ alkynyl, an optionally substituted C₁₋₆ heteroalkyl, or an optionally substituted 3-10 membered ring structure; or as applicable, R²⁰ and R²¹ together with the intervening atom (e.g., the nitrogen atom) or atoms are joined to form an optionally substituted 4-8 membered heterocyclic ring; wherein:

R^{10A} at each occurrence is independently hydrogen, deuterium, halogen, CN, or a C₁₋₃ alkyl optionally substituted with deuterium or F; and

R^{10B} is hydrogen or a C₁₋₃ alkyl optionally substituted with deuterium or F.

Embodiment A2. The compound of Embodiment A1, or a pharmaceutically acceptable salt thereof, wherein J¹ is S, J² and J³ are C, preferably, Z is N, J¹ is S, J² and J³ are C.

Embodiment A3. The compound of Embodiment A1, or a pharmaceutically acceptable salt thereof, wherein (i) Z is N; (ii) J¹ is CH; or (iii) Z is N and J¹ is CH.

Embodiment A4. The compound of Embodiment A1 or 3, or a pharmaceutically acceptable salt thereof, wherein J² is C and J³ is N.

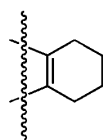
Embodiment A5. The compound of Embodiment A1 or 3, or a pharmaceutically acceptable salt thereof, wherein J³ is C and J² is N.

Embodiment A6. The compound of any of Embodiments A1-5, or a pharmaceutically acceptable salt thereof, wherein Ring B is a benzene, pyridine,

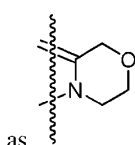
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pyridone (e.g., pyridin-2-one), pyrazine, pyridazine, or pyrimidine ring, each of which is optionally substituted.

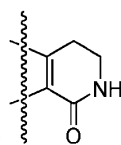
Embodiment A7. The compound of any of Embodiments A1-5, or a pharmaceutically acceptable salt thereof, wherein Ring B is a cyclohexene ring,



, or a 5-7 membered heterocyclic ring having 1 or 2 ring heteroatoms, such

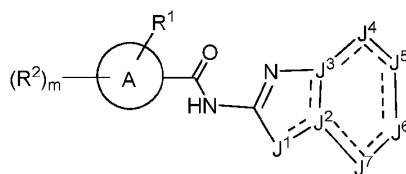


, or



, each of which is optionally substituted.

Embodiment A8. The compound of any of Embodiments A1-5, or a pharmaceutically acceptable salt thereof, characterized as having a structure according to Formula I:



Formula I

wherein:

J⁴ is CR¹¹ or N;

J⁵ is CR¹² or N;

J⁶ is CR^{13A} or N, and J⁷ is CR¹⁴ or N; or

J⁶ is NR^{13B} and J⁷ is C(O);

provided that the bicyclic ring containing J¹, J², J³, J⁴, J⁵, J⁶, and J⁷ is a heteroaryl ring

having 1-4 ring heteroatoms in addition to the ring nitrogen atom shown in Formula I;

R¹¹, R¹², R^{13A}, and R¹⁴ are each independently hydrogen, deuterium, halogen, OH, NH₂,

SF₅, CN, or -Y¹-Y², wherein Y¹ is null, O, S, NH, NY³, C(O), SO₂, C(O)NH, C(O)NY³,

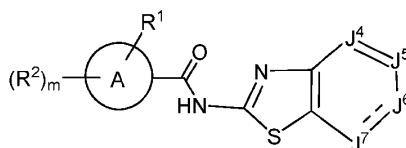
P(O)Y³, SO₂NH, or SO₂NY³, and each of Y² and Y³ at each occurrence is independently

an optionally substituted C₁₋₆ alkyl, an optionally substituted C₂₋₆ alkenyl, an optionally

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substituted C₂₋₆ alkynyl, an optionally substituted C₁₋₆ heteroalkyl, an optionally substituted 3-10 membered carbocyclic or heterocyclic ring, an optionally substituted phenyl, or an optionally substituted 5 or 6-membered heteroaryl; and R^{13B} is hydrogen, an optionally substituted C₁₋₆ alkyl, an optionally substituted C₃₋₆ alkenyl, an optionally substituted C₃₋₆ alkynyl, an optionally substituted C₁₋₆ heteroalkyl, an optionally substituted 3-10 membered carbocyclic or heterocyclic ring, an optionally substituted phenyl, or an optionally substituted 5 or 6-membered heteroaryl.

Embodiment A9. The compound of Embodiment A8, or a pharmaceutically acceptable salt thereof, characterized as having a structure according to Formula I-1:



Formula I-1.

Embodiment A10. The compound of Embodiment A8 or 9, or a pharmaceutically acceptable salt thereof, wherein J⁷ is N.

Embodiment A11. The compound of Embodiment A8 or 9, or a pharmaceutically acceptable salt thereof, wherein J⁴ is N.

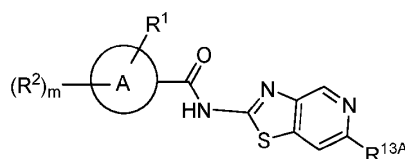
Embodiment A12. The compound of Embodiment A8 or 9, or a pharmaceutically acceptable salt thereof, wherein J⁵ is N.

Embodiment A13. The compound of Embodiment A8 or 9, or a pharmaceutically acceptable salt thereof, wherein (i) J⁴ is N, J⁵ is CR¹², and J⁷ is CR¹⁴; (ii) J⁵ is N, J⁴ is CR¹¹, and J⁷ is CR¹⁴; or (iii) J⁷ is N, J⁴ is CR¹¹, and J⁵ is CR¹².

Embodiment A14. The compound of Embodiment A8 or 9, or a pharmaceutically acceptable salt thereof, wherein (i) J⁴ and J⁷ are both N, and J⁵ is CR¹², preferably CH; (ii) J⁴ and J⁵ are both N, and J⁷ is CR¹⁴, preferably CH; or (iii) J⁴ is CR¹¹, preferably CH, and J⁵ and J⁷ are both N.

Embodiment A15. The compound of any of Embodiments A8-14, or a pharmaceutically acceptable salt thereof, wherein as applicable, (i) when J⁵ is CR¹², R¹² is H; (ii) when J⁴ is CR¹¹, R¹¹ is H; and/or (iii) when J⁷ is CR¹⁴, R¹⁴ is H.

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Formula I-1f.

Embodiment A18. The compound of any of Embodiments A8-17, or a pharmaceutically acceptable salt thereof, wherein R^{13A} , when present, is hydrogen, halogen (e.g., Cl, Br, etc.), CN, an optionally substituted C_{1-4} alkyl, an optionally substituted C_{2-4} alkenyl, an optionally substituted C_{2-4} alkynyl, an optionally substituted C_{1-4} heteroalkyl, SF_5 , an optionally substituted C_{3-7} cycloalkyl, or an optionally substituted 4-10 membered heterocyclic ring having 1-3 ring heteroatoms each independently N, O, or S, preferably, when substituted, the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} heteroalkyl, C_{3-7} cycloalkyl, or 4-10 membered heterocyclic ring, is substituted with one or more (e.g., 1-3) substituents each independently selected from deuterium, halogen (e.g., F), OH, SF_5 , CN, oxo, $CONR^{30}R^{31}$, $N(R^{30})C(O)R^{31}$, $SO_2NR^{30}R^{31}$, $N(R^{30})SO_2R^{31}$, SR^{31} , OR^{31} , SO_2R^{31} , C_{1-4} alkyl optionally substituted with deuterium or F, or a 3-4 membered carbocyclic or heterocyclic ring (e.g., cyclopropyl, cyclobutyl, azetidiny, oxetanyl, etc.) optionally substituted with deuterium, F, OH, and/or methyl, wherein each of R^{30} and R^{31} at each occurrence is independently hydrogen, C_{1-4} alkyl optionally substituted with deuterium or F, or a 3-6 membered carbocyclic or heterocyclic ring (e.g., cyclopropyl, cyclobutyl, azetidiny, oxetanyl, etc.) optionally substituted with deuterium, F, OH, and/or methyl; or as applicable, R^{30} and R^{31} together with the intervening atom or atoms are joined to form an optionally substituted 4-8 membered heterocyclic ring (e.g., optionally substituted with deuterium, F, OH, and/or methyl); for example, R^{13A} is hydrogen, halogen (e.g., Cl or Br), CN, C_{1-4} alkyl optionally substituted with deuterium or F (e.g., CF_2H or CF_3), cyclopropyl, C_{1-4} alkoxy optionally substituted with deuterium or F (e.g., OCF_2H or OCF_3), or a 4-10 membered heterocyclic ring having 1-3 ring heteroatoms each independently N, O, or S, which is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, C_{1-4} alkyl optionally substituted with deuterium or F (e.g., CF_2H or CF_3), or C_{1-4} alkoxy optionally substituted with deuterium or F (e.g., OCF_2H or OCF_3).

Embodiment A19. The compound of any of Embodiments A8-17, or a pharmaceutically acceptable salt thereof, wherein R^{13A} , when present, is an optionally substituted phenyl or optionally substituted 5 or 6-membered heteroaryl, preferably, when substituted, the phenyl or 5 or 6-membered heteroaryl is substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen (e.g., F, Cl, Br, etc.), CN, OH, NH_2 , SF_5 , G^1 , or $-X^1-X^2-G^1$,

wherein X^1 is null, C_{1-4} alkylene or C_{1-4} heteroalkylene, and

X^2 is O, S, NH, NG^1 , C(O), SO_2 , C(O)NH, C(O)NG¹, SO_2NH , or SO_2NG^1 ,

wherein G^1 at each occurrence is independently an optionally substituted C_{1-4} alkyl, an optionally substituted C_{2-4} alkenyl, an optionally substituted C_{2-4} alkynyl, an optionally substituted C_{1-4} heteroalkyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted 4-7 membered heterocyclic ring having 1 or 2 ring heteroatoms each independently N, O, or S, or an optionally substituted 5 or 6-membered heteroaryl having 1-3 ring heteroatoms each independently N, O, or S,

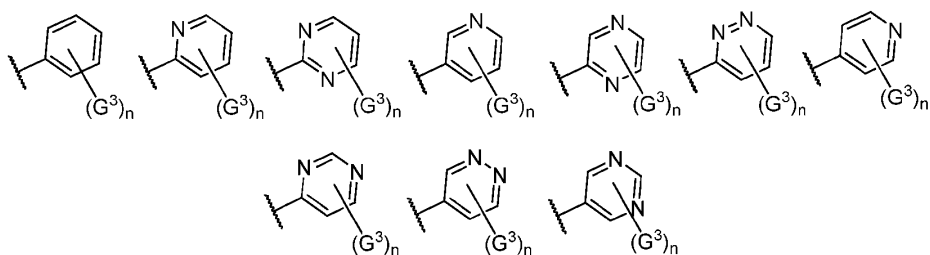
preferably, when substituted, the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} heteroalkyl, C_{3-6} cycloalkyl, 4-7 membered heterocyclic ring, or 5 or 6-membered heteroaryl is substituted with one or more (e.g., 1-3) substituents each independently selected from deuterium, halogen (e.g., F), OH, CN, oxo, C_{1-4} alkyl optionally substituted with deuterium or F, C_{1-4} alkoxy optionally substituted with deuterium or F, or a 3-4 membered carbocyclic or heterocyclic ring (e.g., cyclopropyl, cyclobutyl, azetidyl, oxetanyl, etc.) optionally substituted with deuterium, F, OH, and/or methyl.

Embodiment A20. The compound of any of Embodiments A8-17, or a pharmaceutically acceptable salt thereof, wherein R^{13A} , when present, is an optionally substituted phenyl, pyrazolyl, pyridinyl, pyrimidinyl, pyridazinyl, or pyrazinyl, preferably, when substituted, the phenyl, pyrazolyl, pyridinyl, pyrimidinyl, pyridazinyl, or pyrazinyl is substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen (e.g., F, Cl, Br, etc.), CN, OH, SF_5 , SCF_3 , NH_2 , G^2 , NHG^2 , NG^2G^2 , OG^2 , or SO_2G^2 , wherein G^2 at each occurrence is independently an optionally substituted C_{1-4} alkyl, an optionally substituted C_{3-6} cycloalkyl, or an optionally substituted 4-7 membered heterocyclic ring having 1 or 2 ring heteroatoms each independently N, O, or S, preferably, when substituted, the C_{1-4} alkyl, C_{3-6} cycloalkyl, or 4-7 membered heterocyclic ring, is substituted with one or more (e.g.,

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1-3) substituents each independently selected from deuterium, halogen (e.g., F), OH, CN, oxo, C₁₋₄ alkyl optionally substituted with deuterium or F, C₁₋₄ alkoxy optionally substituted with deuterium or F, or a 3-4 membered carbocyclic or heterocyclic ring (e.g., cyclopropyl, cyclobutyl, azetidiny, oxetanyl, etc.) optionally substituted with deuterium, F, OH, and/or methyl.

Embodiment A21. The compound of any of Embodiments A8-17, or a pharmaceutically acceptable salt thereof, wherein R^{13A}, when present, is selected from the following:



wherein

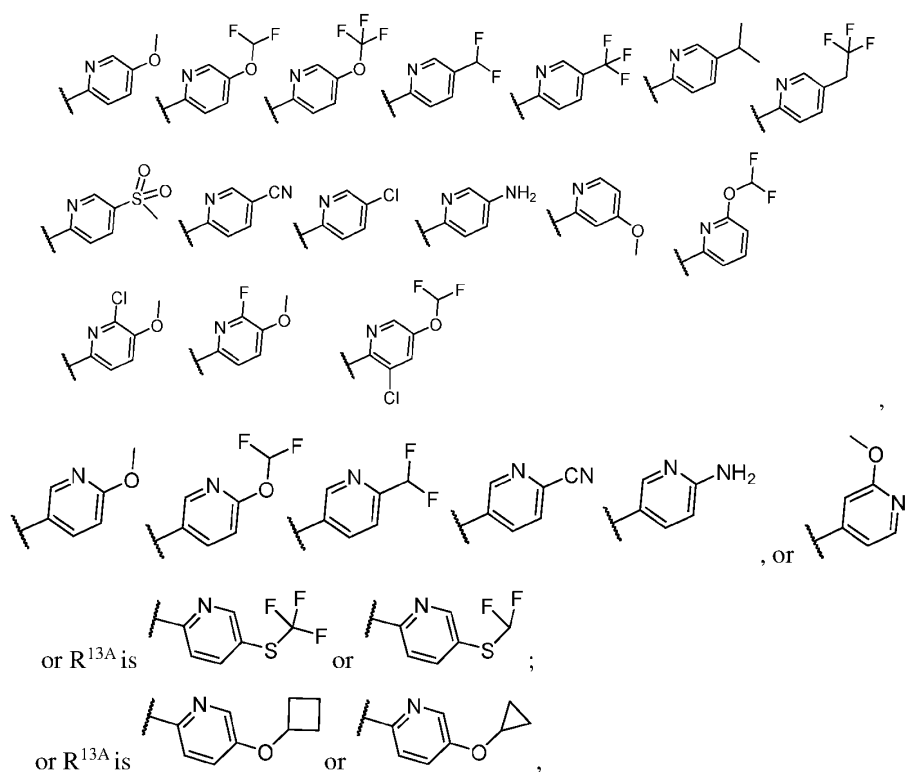
n is an integer of 0-3,

(i) G³ at each occurrence is independently deuterium, halogen (e.g., F or Cl), CN, C₁₋₄ alkyl, O-(C₁₋₄ alkyl), SO₂-(C₁₋₄ alkyl), OH, NH₂, NH(C₁₋₄ alkyl), N(C₁₋₄ alkyl)(C₁₋₄ alkyl), 3-4 membered carbocyclic or heterocyclic ring, O-(3-4 membered carbocyclic or heterocyclic ring), (C₁₋₄ alkylene)-(3-4 membered carbocyclic or heterocyclic ring) or O-(C₁₋₄ alkylene)-(3-4 membered carbocyclic or heterocyclic ring), wherein each of the aforementioned C₁₋₄ alkyl is independently optionally substituted with 1-7 deuterium or F, and wherein the C₁₋₄ alkylene or 3-4 membered carbocyclic or heterocyclic ring is optionally substituted with one or more (e.g., 1-3) substituents independently deuterium, F, OH, or methyl, preferably, one instance of G³ is C₁₋₄ alkyl optionally substituted with 1-7 deuterium or F or C₁₋₄ alkoxy optionally substituted with 1-7 deuterium or F, such as OCH₃, OCF₂H, OCF₃, CF₃, CH₃, CF₂H, or CH₂CF₃; or (ii) one instance of G³ is S-(C₁₋₄ alkyl), wherein the C₁₋₄ alkyl is optionally substituted with 1-7 deuterium or F, e.g., one G³ is SCF₂ or SCF₃; and any remaining G³ is as defined in (i).

Embodiment A22. The compound of any of Embodiments A8-17, or a pharmaceutically acceptable salt thereof, wherein R^{13A}, when present, is a pyridinyl (e.g., 2-pyridinyl or 3-pyridinyl) substituted with (i) 1 or 2 substituents independently

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selected from deuterium, halogen (e.g., F or Cl), CN, C₁₋₄ alkyl, O-(C₁₋₄ alkyl), SO₂-(C₁₋₄ alkyl), OH, NH₂, NH(C₁₋₄ alkyl), or N(C₁₋₄ alkyl)(C₁₋₄ alkyl), or (ii) one substituent selected from S-(C₁₋₄ alkyl), SF₅, cyclopropoxy, or cyclobutoxy, and any remaining substituent(s) as defined in (i); wherein each of the aforementioned C₁₋₄ alkyl is independently optionally substituted with 1-7 deuterium or F, for example, R^{13A} can be selected from the following:

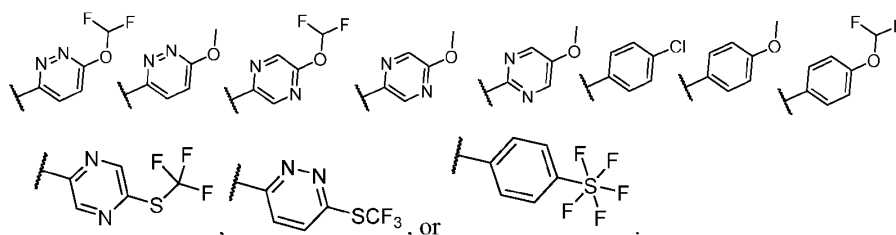


preferably, the pyridinyl is substituted with one substituent selected from OCH₃, OCF₂H, OCF₃, SO₂CH₃, NH₂, CN, Cl, isopropyl, CF₃, CH₃, CF₂H, or CH₂CF₃, and optionally a further substituent selected from F or Cl.

Embodiment A23. The compound of any of Embodiments A8-17, or a pharmaceutically acceptable salt thereof, wherein R^{13A}, when present, is a phenyl, pyrimidinyl, pyridazinyl, or pyrazinyl, which is substituted with (i) 1 or 2 substituents independently selected from deuterium, halogen (e.g., F or Cl), CN, C₁₋₄ alkyl, O-(C₁₋₄ alkyl), SO₂-(C₁₋₄ alkyl), OH, NH₂, NH(C₁₋₄ alkyl), or N(C₁₋₄ alkyl)(C₁₋₄ alkyl), or (ii) one substituent selected from S-(C₁₋₄ alkyl), SF₅, cyclopropoxy, or cyclobutoxy, and

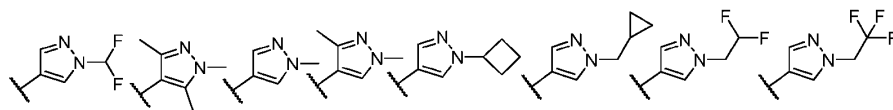
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any remaining substituent(s) as defined in (i); wherein each of the aforementioned C₁₋₄ alkyl is independently optionally substituted with 1-7 deuterium or F, for example, R^{13A} can be selected from the following:



Embodiment A24. The compound of any of Embodiments A8-17, or a pharmaceutically acceptable salt thereof, wherein R^{13A}, when present, is a pyrazolyl, optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen (e.g., F, Cl, Br, etc.), C₁₋₄ alkyl, 3-4 membered carbocyclic or heterocyclic ring, or (C₁₋₄ alkylene)-(3-4 membered carbocyclic or heterocyclic ring), wherein the C₁₋₄ alkyl, C₁₋₄ alkylene, or 3-4 membered carbocyclic or heterocyclic ring is optionally substituted with one or more (e.g., 1-3) substituents independently deuterium, F, OH, or methyl,

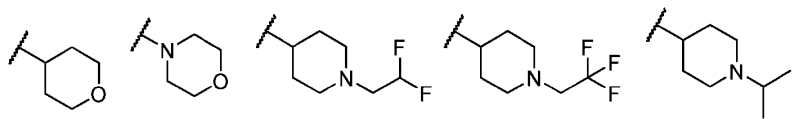
for example, R^{13A} can be selected from the following:



Embodiment A25. The compound of any of Embodiments A8-17, or a pharmaceutically acceptable salt thereof, wherein R^{13A}, when present, is a 5-7 membered heterocyclic ring, such as a tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl, etc., which is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen (e.g., F), oxo, C₁₋₄ alkyl, 3-4 membered carbocyclic or heterocyclic ring, or (C₁₋₄ alkylene)-(3-4 membered carbocyclic or heterocyclic ring), wherein the C₁₋₄ alkyl, C₁₋₄ alkylene, or 3-4 membered carbocyclic or heterocyclic ring is optionally substituted with one or more (e.g., 1-3) substituents independently deuterium, F, OH, or methyl,

for example, R^{13A} can be selected from the following:

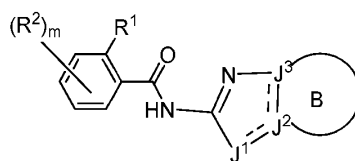
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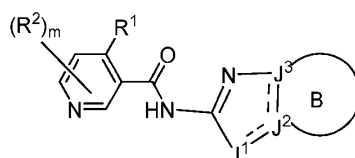
Embodiment A26. The compound of any of Embodiments A1-25, or a pharmaceutically acceptable salt thereof, wherein ring A is a phenyl ring or a 5 or 6-membered heteroaryl having 1 to 3 ring heteroatoms independently selected from N, O, and S, such as pyridine ring.

Embodiment A27. The compound of any of Embodiments A1-25, or a pharmaceutically acceptable salt thereof, wherein ring A is a phenyl, pyridinyl, pyrimidinyl, or imidazo[1,2-a]pyridinyl ring, preferably, a phenyl or pyridinyl ring.

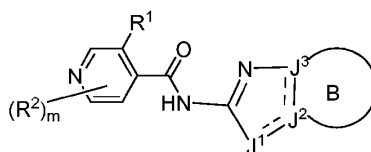
Embodiment A28. The compound of any of Embodiments A1-25, or a pharmaceutically acceptable salt thereof, characterized as having a structure according to Formula A1, A2, or A3:



Formula A1



Formula A2



Formula A3.

Embodiment A29. The compound of any of Embodiments A1-28, or a pharmaceutically acceptable salt thereof, wherein m is 0, 1, or 2, and R² at each

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occurrence is independently deuterium, halogen, CN, OH, (C₁₋₄ alkylene)-CN, G^A, or X^a-X^b-G^A,

wherein:

X^a at each occurrence is independently null, C₁₋₄ alkylene, or C₁₋₄ heteroalkylene;

X^b at each occurrence is independently null, O, NH, N(G^B), C(O), C(O)O, C(O)NH, C(O)N(G^B), NHC(O), N(G^B)C(O), SO₂, SO₂NH, or SO₂N(G^B); and

G^A at each occurrence is independently:

- (i) C₁₋₆ alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, C₁₋₄ alkoxy, or a 3-6 membered ring;
 - (ii) C₁₋₆ heteroalkyl optionally substituted with one or more (e.g., 1-3) substituents independently deuterium, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, or a 3-6 membered ring;
 - (iii) a 3-7 membered carbocyclic or heterocyclic ring, which is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, oxo, OH, CN, C₁₋₄ alkyl, C₁₋₄ alkoxy, or a 3-6 membered ring;
- or
- (iv) a 5 or 6-membered heteroaryl, which is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, CN, C₁₋₄ alkyl, C₁₋₄ alkoxy, or a 3-6 membered ring (preferably carbocyclic or heterocyclic ring),

wherein the C₁₋₄ alkyl or C₁₋₄ alkoxy in each of (i)-(iv) is independently optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, C₁₋₄ alkoxy, or a 3-4 membered carbocyclic or heterocyclic ring, and

wherein each of the 3-6 membered ring in each of (i)-(iv) is independently optionally substituted with one or more (e.g., 1-3) substituents each independently oxo, deuterium, halogen, OH, CN, C₁₋₄ alkyl optionally substituted with deuterium or F, or C₁₋₄ alkoxy optionally substituted with deuterium or F;

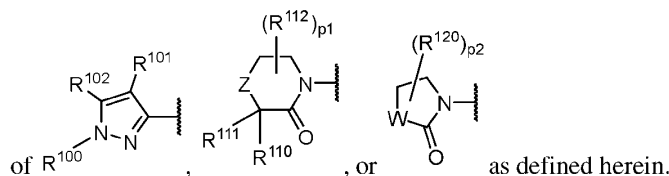
G^B at each occurrence is independently C₁₋₆ alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, C₁₋₄ alkoxy optionally substituted with deuterium or F, or a 3-6 membered ring optionally substituted with oxo, deuterium, halogen, OH, CN, C₁₋₄ alkyl optionally substituted with deuterium or F, or C₁₋₄ alkoxy optionally substituted with deuterium or F, or

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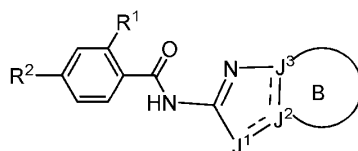
when applicable, G^A and G^B are joined to form a 4-7 membered heterocyclic ring, which is optionally substituted with one or more (e.g., 1-3) substituents each independently halogen, oxo, OH, C_{1-4} alkyl optionally substituted with F, or C_{1-4} alkoxy optionally substituted with F.

Embodiment A30. The compound of Embodiment A29, or a pharmaceutically acceptable salt thereof, wherein m is 0.

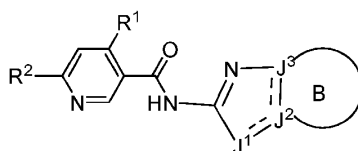
Embodiment A31. The compound of Embodiment A1 or 29, or a pharmaceutically acceptable salt thereof, wherein m is 1, e.g., R^2 has a structure according to M-1 to M-13 as defined herein in connection with Formula K and its subformulae, or a structure



Embodiment A32. The compound of Embodiment A31, or a pharmaceutically acceptable salt thereof, wherein the compound is characterized as having a structure according to Formula A1a or A2a:



Formula A1a



Formula A2a.

Embodiment A33. The compound of Embodiment A31 or 32, or a pharmaceutically acceptable salt thereof, wherein R^2 is a C_{1-4} alkyl optionally substituted with deuterium, F, and/or OH, e.g., methyl, difluoromethyl, or hydroxymethyl.

Embodiment A34. The compound of Embodiment A31 or 32, or a pharmaceutically acceptable salt thereof, wherein R^2 is a 5 or 6-membered heteroaryl, which is

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optionally substituted with 1-3 substituents each independently halogen, OH, CN, C₁₋₄ alkyl, C₁₋₄ alkoxy, or a 3-5 membered carbocyclic or heterocyclic ring, wherein the C₁₋₄ alkyl or C₁₋₄ alkoxy is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen (e.g., F), OH, C₁₋₄ alkoxy, or a 3-5 membered carbocyclic or heterocyclic ring, wherein each of the 3-5 membered carbocyclic or heterocyclic ring, when present, is independently optionally substituted with deuterium, F, OH, and/or methyl.

Embodiment A35. The compound of Embodiment A31 or 32, or a pharmaceutically acceptable salt thereof, wherein R² is -(C₁₋₄ alkylene)-C(O)NHG^A, -(C₁₋₄ alkylene)-C(O)N(G^A)(G^B) or -(C₁₋₄ alkylene)-CN, preferably, G^A and G^B are each independently a C₁₋₄ alkyl optionally substituted with deuterium, F and/or OH.

Embodiment A36. The compound of any of Embodiments A1-35, or a pharmaceutically acceptable salt thereof, wherein R¹ is a phenyl, pyridinyl, pyrimidinyl, benzopyrazolyl, benzimidazolyl, imidazolyl, pyridazyl, imidazo[1,2-a]pyrimidinyl, oxazolo[4,5-b]pyridinyl, oxazolo[5,4-b]pyridinyl, thiazolo[4,5-b]pyridinyl, benzo[d]thiazole, indazolyl, [1,2,4]triazolo[1,5-a]pyrimidinyl, [1,2,4]triazolo[1,5-b]pyridazinyl, or tetrazolo[1,5-a]pyridinyl, each of which is optionally substituted.

Embodiment A37. The compound of any of Embodiments A1-35, or a pharmaceutically acceptable salt thereof, wherein R¹ is a phenyl or pyridinyl, each of which is optionally substituted with 1-3 substituents independently selected from: deuterium, halogen, CN, OH, NH₂, COOH, CONH₂, (C₁₋₄ alkylene)-CN, G^C, or X^c-X^d-G^C,

wherein:

X^c at each occurrence is independently null, C₁₋₄ alkylene, or C₁₋₄ heteroalkylene;

X^d at each occurrence is independently null, O, NH, N(G^D), C(O), C(O)O, C(O)NH,

C(O)N(G^D), NHC(O), N(G^D)C(O), P(O)(G^D), SO₂, SO₂NH, or SO₂N(G^D); and

G^C at each occurrence is independently:

- (i) C₁₋₆ alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, C₁₋₄ alkoxy, or a 3-6 membered ring;
- (ii) C₁₋₆ heteroalkyl optionally substituted with one or more (e.g., 1-3) substituents independently deuterium, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, or a 3-6 membered ring;

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(iii) a 3-7 membered carbocyclic or heterocyclic ring, which is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, oxo, OH, CN, C₁₋₄ alkyl, C₁₋₄ alkoxy, or a 3-6 membered ring; or

(iv) a 5 or 6-membered heteroaryl, which is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, CN, C₁₋₄ alkyl, C₁₋₄ alkoxy, or a 3-6 membered ring (preferably carbocyclic or heterocyclic ring),

wherein the C₁₋₄ alkyl or C₁₋₄ alkoxy in each of (i)-(iv) is independently optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, C₁₋₄ alkoxy, or a 3-4 membered carbocyclic or heterocyclic ring, and

wherein each of the 3-6 membered ring in each of (i)-(iv) is independently optionally substituted with oxo, deuterium, halogen, OH, CN, C₁₋₄ alkyl optionally substituted with deuterium or F, or C₁₋₄ alkoxy optionally substituted with deuterium or F;

G^D at each occurrence is independently C₁₋₆ alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, C₁₋₄ alkoxy optionally substituted with deuterium or F, or a 3-6 membered ring optionally substituted with oxo, deuterium, halogen, OH, CN, C₁₋₄ alkyl optionally substituted with deuterium or F, or C₁₋₄ alkoxy optionally substituted with deuterium or F, or

when applicable, G^C and G^D together with the heteroatom they are both attached to are joined to form a 4-7 membered heterocyclic ring, which is optionally substituted with one or more (e.g., 1-3) substituents each independently halogen, oxo, OH, C₁₋₄ alkyl optionally substituted with deuterium or F, or C₁₋₄ alkoxy optionally substituted with deuterium or F.

Embodiment A38. The compound of any of Embodiments A1-35, or a pharmaceutically acceptable salt thereof, wherein R¹ is a phenyl or pyridinyl, each of which is optionally substituted with one or more (e.g., 1-3) substituents independently selected from halogen, C₁₋₆ alkyl optionally substituted with deuterium, F, CN, and/or OH, C₁₋₆ alkoxy optionally substituted with deuterium, F, CN, and/or OH, C₃₋₆

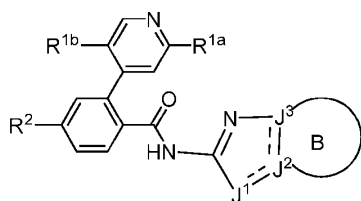
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cycloalkyl optionally substituted with deuterium, F, CN, methyl, and/or OH, NH₂, NH(C₁₋₄ alkyl), or N(C₁₋₄ alkyl)(C₁₋₄ alkyl).

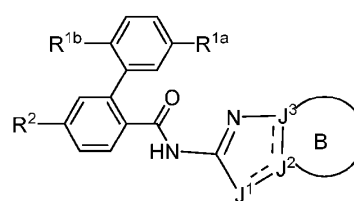
Embodiment A39. The compound of any of Embodiments A1-35, or a pharmaceutically acceptable salt thereof, wherein R¹ is a phenyl or pyridinyl, each of which is optionally substituted with one or more (e.g., 1-3) substituents independently selected from halogen, C₁₋₄ alkyl optionally substituted with deuterium, F and/or OH, C₁₋₄ alkoxy optionally substituted with deuterium or F, C₃₋₄ cycloalkyl optionally substituted with deuterium, F, CN, methyl, and/or OH, NH₂, NH(C₁₋₃ alkyl), or N(C₁₋₃ alkyl)(C₁₋₃ alkyl).

Embodiment A40. The compound of any of Embodiments A1-35, or a pharmaceutically acceptable salt thereof, wherein R¹ is a phenyl or pyridinyl, each of which is optionally substituted with 1-3 substituents independently selected from methyl, ethyl, fluoro, chloro, bromo, trifluoromethyl, difluoromethyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, cyclopropyl, -NH₂, hydroxymethyl, and 1-hydroxy ethyl, preferably, the substituents are independently selected from methyl, fluoro, chloro, trifluoromethyl, difluoromethyl, methoxy, ethoxy, difluoromethoxy, and cyclopropyl.

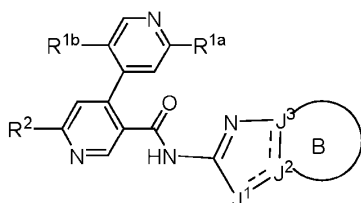
Embodiment A41. The compound of any of Embodiments A1-35, or a pharmaceutically acceptable salt thereof, characterized as having a structure according to Formula A1b, A1c, A2b or A2c:



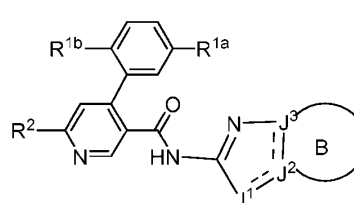
Formula A1b



Formula A1c



Formula A2b



Formula A2c,

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wherein R^{1a} and R^{1b} are each independently halogen, C_{1-6} alkyl optionally substituted with deuterium, F, CN, and/or OH, C_{1-6} alkoxy optionally substituted with deuterium, F, CN, and/or OH, C_{3-6} cycloalkyl optionally substituted with deuterium, F, CN, methyl, and/or OH, NH_2 , $NH(C_{1-4}$ alkyl), or $N(C_{1-4}$ alkyl)(C_{1-4} alkyl).

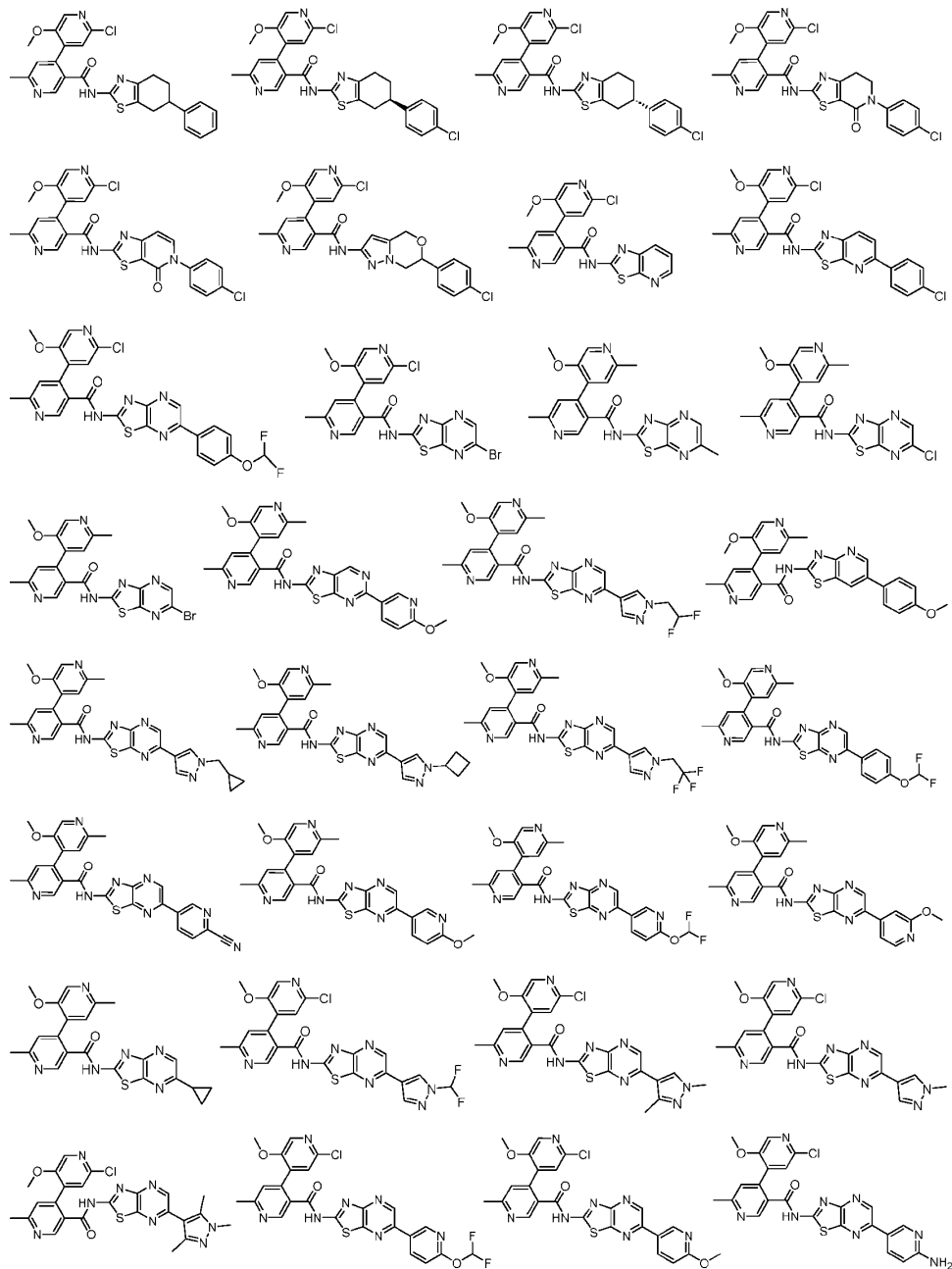
Embodiment A42. The compound of Embodiment A41, or a pharmaceutically acceptable salt thereof, wherein R^{1a} and R^{1b} are each independently selected from methyl, ethyl, fluoro, chloro, bromo, trifluoromethyl, difluoromethyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, cyclopropyl, $-NH_2$, hydroxymethyl, and 1-hydroxy ethyl, more preferably, R^{1a} and R^{1b} are each independently selected from methyl, fluoro, chloro, trifluoromethyl, difluoromethyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, and cyclopropyl.

Embodiment A43. The compound of Embodiment A41, or a pharmaceutically acceptable salt thereof, wherein R^{1b} is C_{1-2} alkoxy optionally substituted with 1-3 deuterium or F, preferably, R^{1b} is methoxy, ethoxy, or difluoromethoxy.

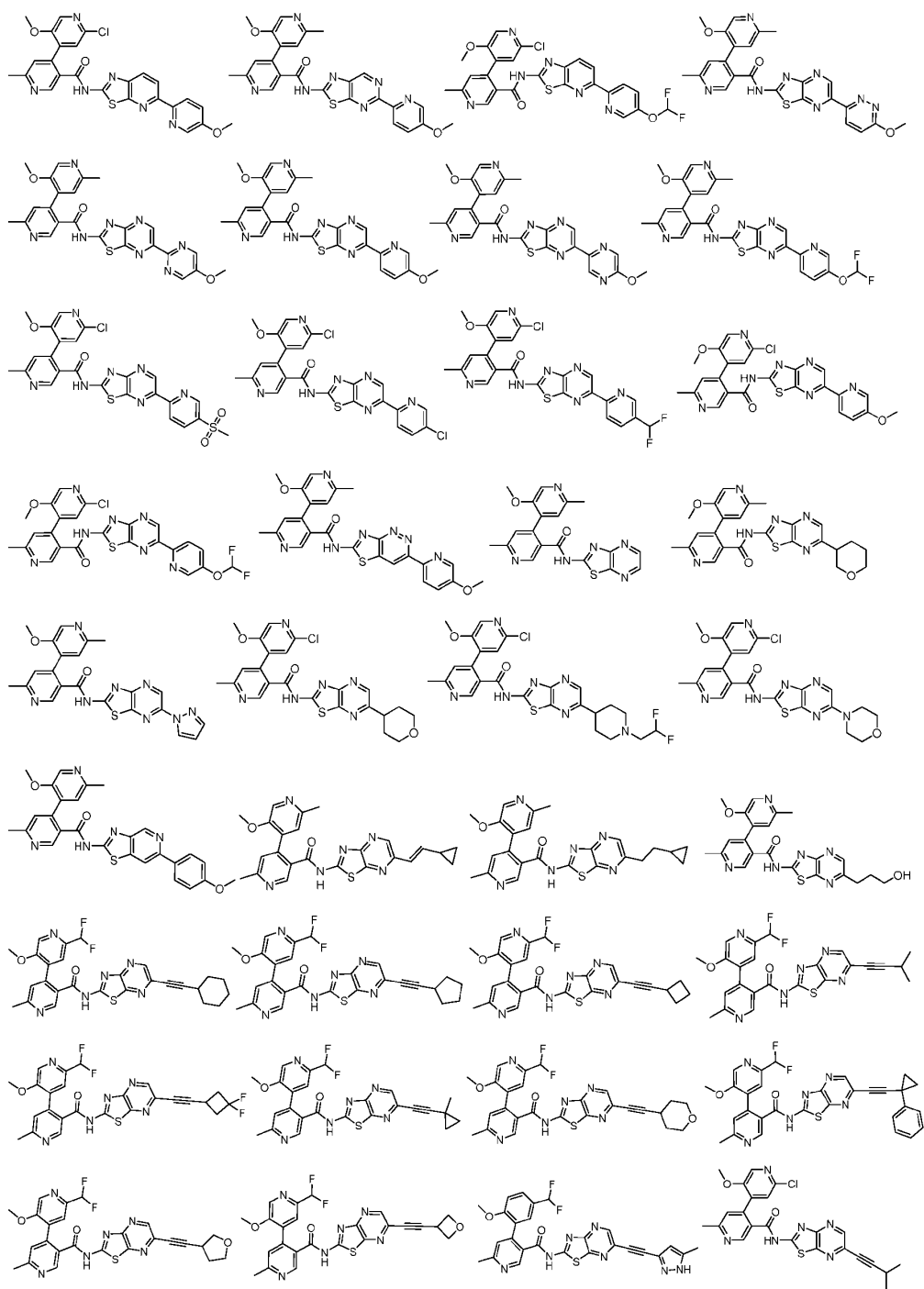
Embodiment A44. The compound of any of Embodiments A41-43, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is halogen, C_{1-3} alkyl optionally substituted with 1-3 deuterium or F, or cyclopropyl, preferably, R^{1a} is methyl, fluoro, chloro, trifluoromethyl, difluoromethyl, or cyclopropyl.

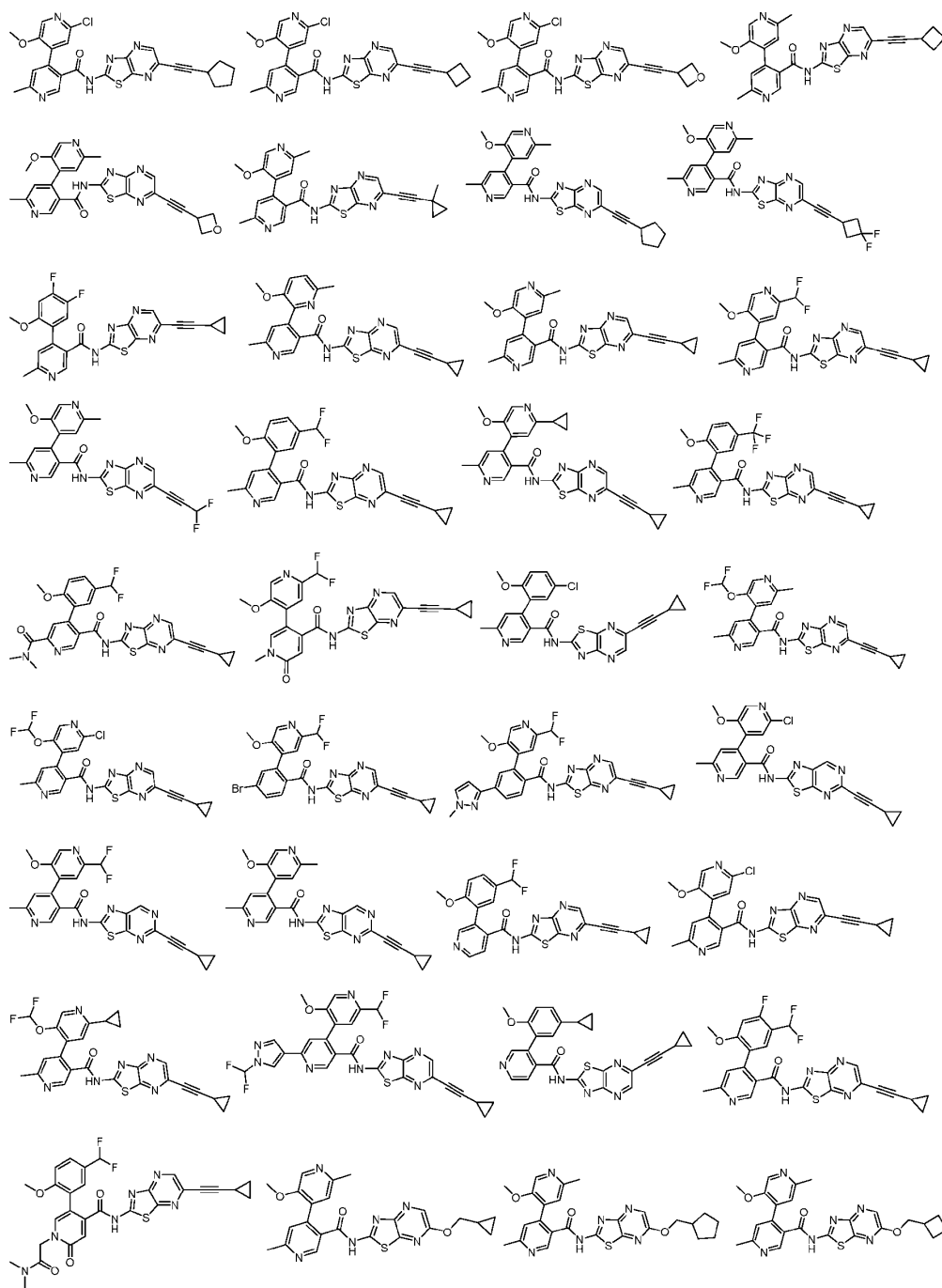
[0219] In some embodiments, the present disclosure also provides a compound selected from Table 1 below, a deuterated analog thereof, a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:

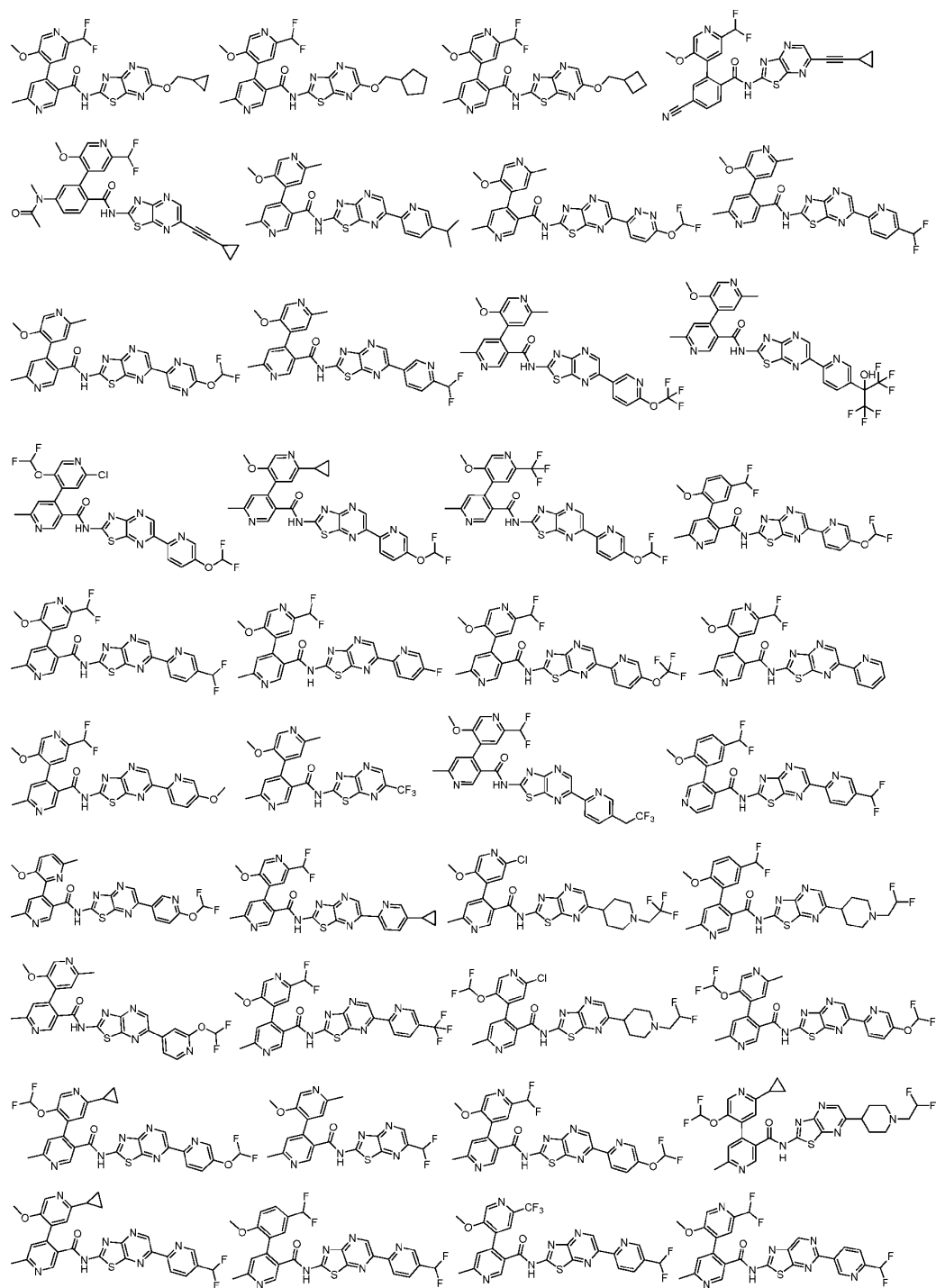
Table 1. List of Compounds

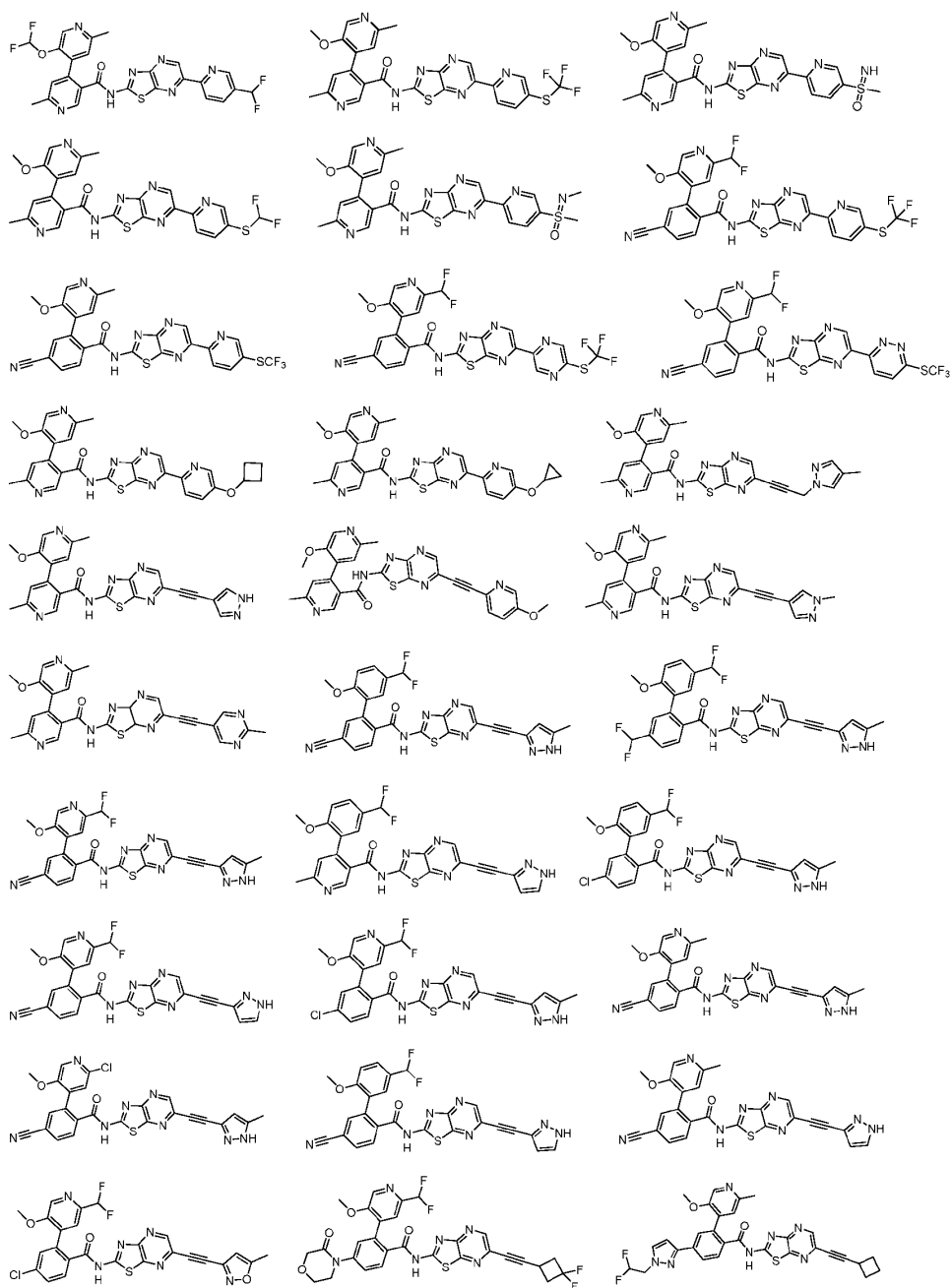


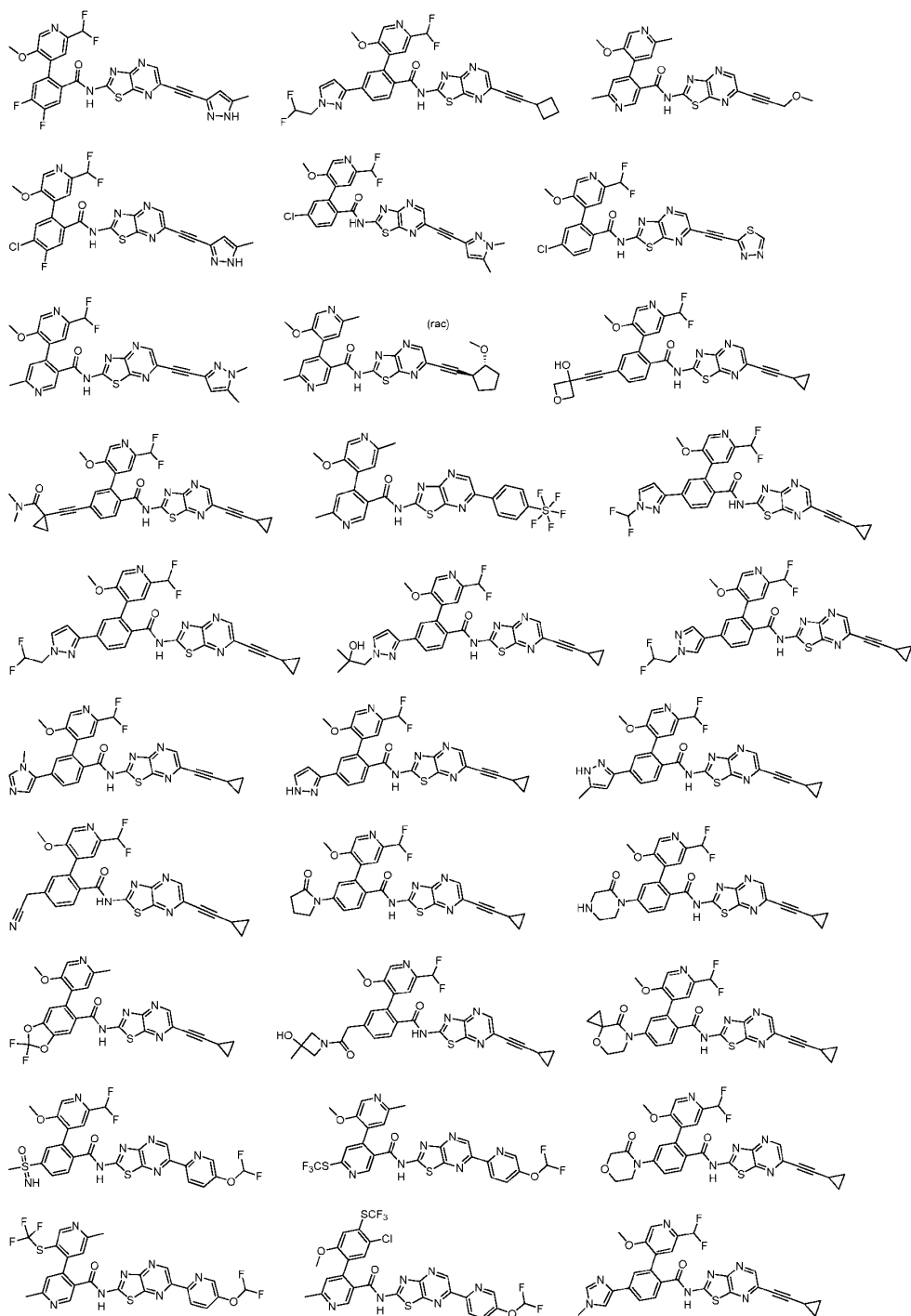
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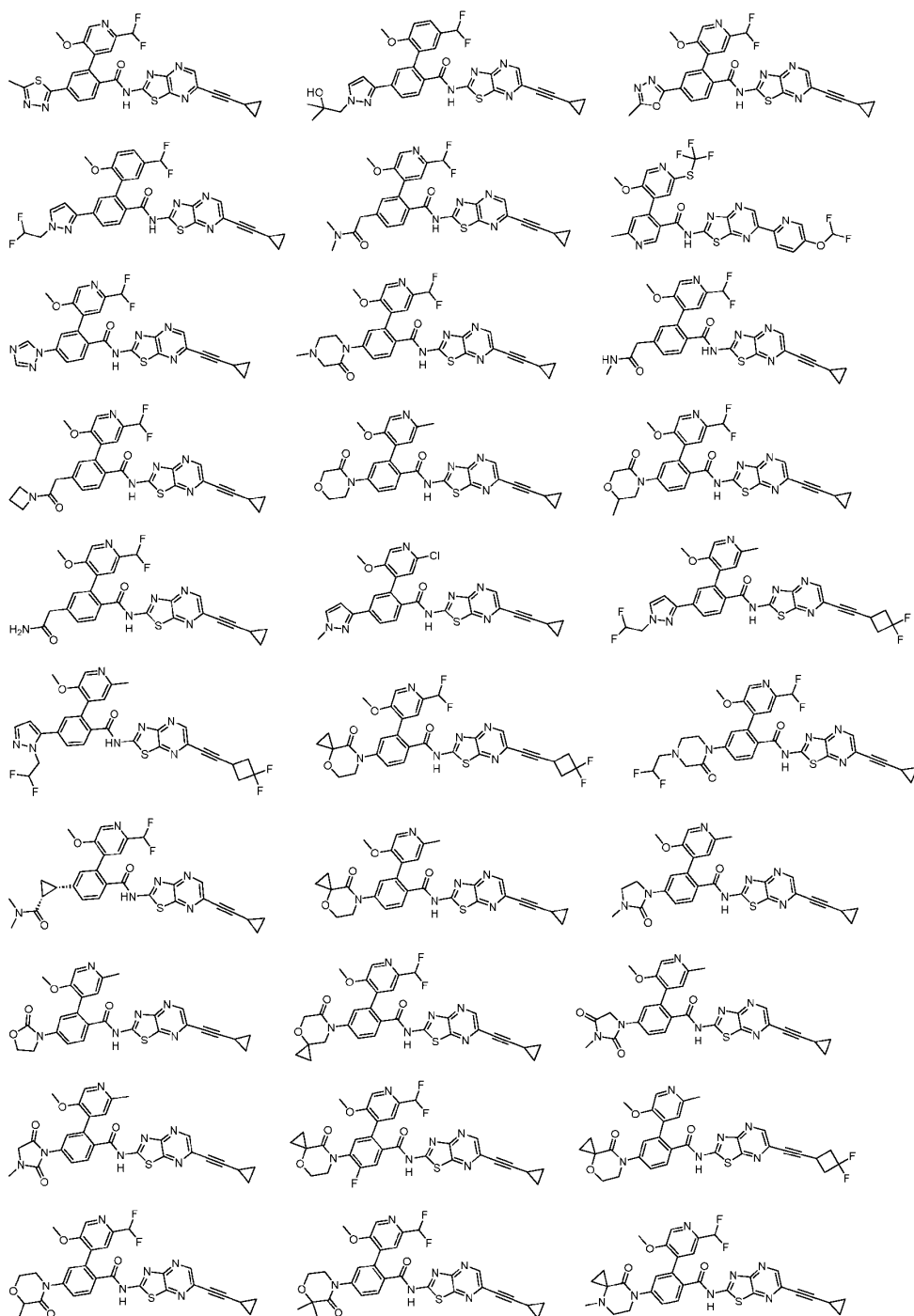


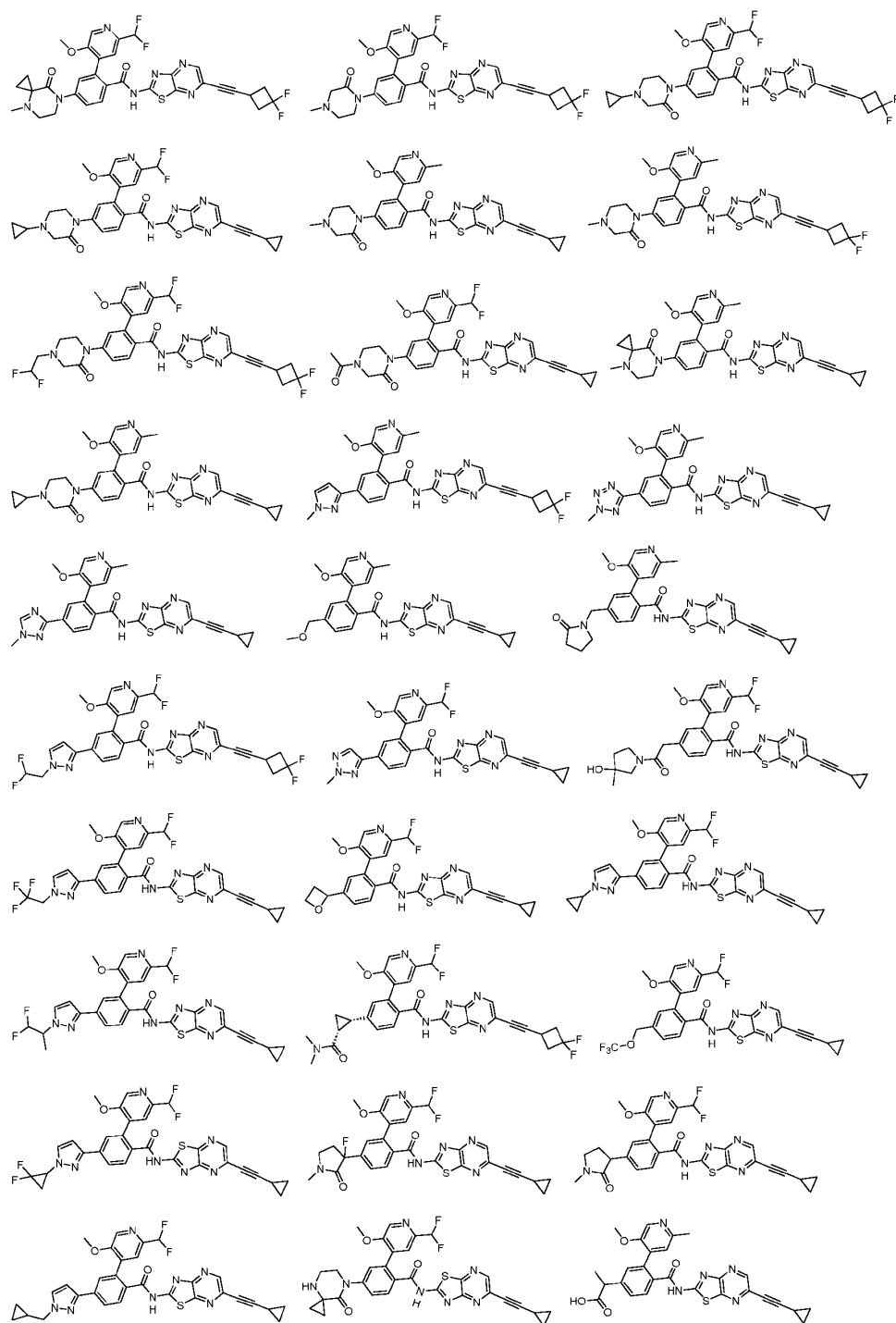




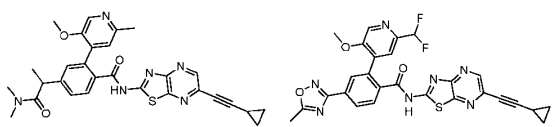








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[0220] In some embodiments, to the extent applicable, the genus of compounds described herein also excludes any specifically known single compounds prior to this disclosure. In some embodiments, to the extent applicable, any sub-genus or species of compounds prior to this disclosure that are entirely within a genus of compounds described herein can also be excluded from such genus herein.

Method of Synthesis

[0221] The compounds of the present disclosure can be readily synthesized by those skilled in the art in view of the present disclosure. Exemplified syntheses are also shown in the Examples section.

[0222] As will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. Suitable protecting groups for various functional groups as well as suitable conditions for protecting and deprotecting particular functional groups are well known in the art. For example, numerous protecting groups are described in "Protective Groups in Organic Synthesis", 4th ed. P. G. M. Wuts; T. W. Greene, John Wiley, 2007, and references cited therein. The reagents for the reactions described herein are generally known compounds or can be prepared by known procedures or obvious modifications thereof. For example, many of the reagents are available from commercial suppliers such as Sigma-Aldrich (Milwaukee, Wisconsin, USA). Others may be prepared by procedures, or obvious modifications thereof, described in standard reference texts such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-15 (John Wiley and Sons, 1991), Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplemental (Elsevier Science Publishers, 1989), Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March's Advanced Organic Chemistry, (Wiley, 7th Edition), and Larock's Comprehensive Organic Transformations (Wiley-VCH, 1999), and any of available updates as of this filing.

Pharmaceutical Compositions

[0223] Certain embodiments are directed to a pharmaceutical composition comprising one or more compounds of the present disclosure.

[0224] The pharmaceutical composition can optionally contain a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition comprises a compound of the present disclosure (e.g., a compound of Formula A (e.g., Formula I, I-1, I-1a, I-1b, I-1c, I-1d, I-1e, I-1f, I-1g, II, II-1, III, III-1, A1, A2, A3, A1a, A1b, A1c, A2a, A2b, A2c, A2b-1, A2b-2, A2b-3, A2b-4, A2b-5, or A2b-6), Formula K (e.g., Formula K-1, K-2, K-3, K-4, K-5, K-6, K-7a, K-7b, K-8a, K-8b, K-9a, K-9b, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, K-1b-4, K-3a, K-3b, K-5a, or K-5b), any of Examples 1-266, any of the compounds listed in Table 1 herein, or a pharmaceutically acceptable salt thereof) and a pharmaceutically acceptable excipient. Pharmaceutically acceptable excipients are known in the art. Non-limiting suitable excipients include, for example, encapsulating materials or additives such as antioxidants, binders, buffers, carriers, coating agents, coloring agents, diluents, disintegrating agents, emulsifiers, extenders, fillers, flavoring agents, humectants, lubricants, perfumes, preservatives, propellants, releasing agents, sterilizing agents, sweeteners, solubilizers, wetting agents and mixtures thereof. See also Remington's The Science and Practice of Pharmacy, 21st Edition, A. R. Gennaro (Lippincott, Williams & Wilkins, Baltimore, Md., 2005; incorporated herein by reference), which discloses various excipients used in formulating pharmaceutical compositions and known techniques for the preparation thereof.

[0225] The pharmaceutical composition can include any one or more of the compounds of the present disclosure. For example, in some embodiments, the pharmaceutical composition comprises a compound of Formula A or a pharmaceutically acceptable salt thereof, e.g., in a therapeutically effective amount. In any of the embodiments described herein, the pharmaceutical composition can comprise a therapeutically effective amount (e.g., for treating a cancer herein) of a compound selected from any of Examples 1-266, or any of the specific compounds disclosed in Table 1 herein, or a pharmaceutically acceptable salt thereof. In some preferred embodiments, the pharmaceutical composition can comprise a compound selected from the compounds according to Examples 1-266 that have an IC₅₀ value less than 100 nM, more preferably, less than 50 nM, as measured according to Biological Example 1.

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[0226] The pharmaceutical composition herein can be formulated for delivery via any of the known routes of delivery, which include but not limited to administering orally, nasally, transdermally, pulmonary, inhalationally, buccally, sublingually, intraperitoneally, subcutaneously, intramuscularly, intravenously, rectally, intrapleurally, intrathecally or parenterally.

[0227] In some embodiments, the pharmaceutical composition can be formulated for oral administration. The oral formulations can be presented in discrete units, such as capsules, pills, cachets, lozenges, or tablets, each containing a predetermined amount of the active compound; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. Excipients for the preparation of compositions for oral administration are known in the art. Non-limiting suitable excipients include, for example, agar, alginic acid, aluminum hydroxide, benzyl alcohol, benzyl benzoate, 1,3-butylene glycol, carbomers, castor oil, cellulose, cellulose acetate, cocoa butter, corn starch, corn oil, cottonseed oil, cross-povidone, diglycerides, ethanol, ethyl cellulose, ethyl laureate, ethyl oleate, fatty acid esters, gelatin, germ oil, glucose, glycerol, groundnut oil, hydroxypropylmethyl cellulose, isopropanol, isotonic saline, lactose, magnesium hydroxide, magnesium stearate, malt, mannitol, monoglycerides, olive oil, peanut oil, potassium phosphate salts, potato starch, povidone, propylene glycol, Ringer's solution, safflower oil, sesame oil, sodium carboxymethyl cellulose, sodium phosphate salts, sodium lauryl sulfate, sodium sorbitol, soybean oil, stearic acids, stearyl fumarate, sucrose, surfactants, talc, tragacanth, tetrahydrofurfuryl alcohol, triglycerides, water, and mixtures thereof.

[0228] In some embodiments, the pharmaceutical composition is formulated for parenteral administration (such as intravenous injection or infusion, subcutaneous or intramuscular injection). The parenteral formulations can be, for example, an aqueous solution, a suspension, or an emulsion. Excipients for the preparation of parenteral formulations are known in the art. Non-limiting suitable excipients include, for example, 1,3-butanediol, castor oil, corn oil, cottonseed oil, dextrose, germ oil, groundnut oil, liposomes, oleic acid, olive oil, peanut oil, Ringer's solution, safflower oil, sesame oil, soybean oil, U.S.P. or isotonic sodium chloride solution, water and mixtures thereof.

[0229] Compounds of the present disclosure can be used alone, in combination with each other, or in combination with one or more additional therapeutic agents, e.g., in combination

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with an additional anticancer therapeutic agent, such as a PARP inhibitor, a signal transduction inhibitor, a chemotherapeutic agent, and/or an immune checkpoint inhibitor.

[0230] When used in combination with one or more additional therapeutic agents, compounds of the present disclosure or pharmaceutical compositions herein can be administered to the subject either concurrently or sequentially in any order with such additional therapeutic agents. In some embodiments, the pharmaceutical composition can comprise one or more compounds of the present disclosure and the one or more additional therapeutic agents in a single composition. In some embodiments, the pharmaceutical composition comprising one or more compounds of the present disclosure can be included in a kit which also comprises a separate pharmaceutical composition comprising the one or more additional therapeutic agents.

[0231] The pharmaceutical composition can include various amounts of the compounds of the present disclosure, depending on various factors such as the intended use and potency and selectivity of the compounds. In some embodiments, the pharmaceutical composition comprises a therapeutically effective amount of a compound of the present disclosure. In some embodiments, the pharmaceutical composition comprises a therapeutically effective amount of the compound of the present disclosure and a pharmaceutically acceptable excipient. As used herein, a therapeutically effective amount of a compound of the present disclosure is an amount effective to treat a disease or disorder as described herein, such as a cancer herein, which can depend on the recipient of the treatment, the disorder, condition or disease being treated and the severity thereof, the composition containing the compound, the time of administration, the route of administration, the duration of treatment, the compound potency, its rate of clearance and whether or not another drug is co-administered.

Method of Treatment/Use

[0232] Compounds of the present disclosure have various utilities. For example, compounds of the present disclosure can be used as therapeutic active substances for the treatment and/or prophylaxis of a disease or disorder associated with Polθ, such as overexpression of Polθ. Accordingly, some embodiments of the present disclosure are also directed to methods of using one or more compounds of the present disclosure or pharmaceutical compositions herein for treating or preventing a disease or disorder associated with Polθ in a subject in need thereof, such as for treating cancer in a subject in need thereof.

[0233] In some embodiments, the present disclosure provides a method of inhibiting Polθ enzyme activity, e.g., DNA repair activity mediated by Polθ, in a cell, the method comprising contacting the cell with an effective amount of the compound of present disclosure (e.g., a compound of Formula A (e.g., Formula I, I-1, I-1a, I-1b, I-1c, I-1d, I-1e, I-1f, I-1g, II, II-1, III, III-1, A1, A2, A3, A1a, A1b, A1c, A2a, A2b, A2c, A2b-1, A2b-2, A2b-3, A2b-4, A2b-5, or A2b-6), Formula K (e.g., Formula K-1, K-2, K-3, K-4, K-5, K-6, K-7a, K-7b, K-8a, K-8b, K-9a, K-9b, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, K-1b-4, K-3a, K-3b, K-5a, or K-5b), any of Examples 1-266, any of the compounds listed in Table 1 herein, or a pharmaceutically acceptable salt thereof). In some embodiment, contacting the cell occurs *in vitro*. In some embodiment, contacting the cell occurs *in vivo*. In some embodiments, the cell is a cancer cell. In some embodiments, the cell is an HR deficient cell. In some embodiments, the cancer cell has overexpression of Polθ. The cancer cell can be a cell of any of the cancer described herein.

[0234] In some embodiments, the present disclosure provides a method of inhibiting cell proliferation, *in vitro* or *in vivo*, the method comprising contacting the cell with an effective amount of the compound of present disclosure (e.g., a compound of Formula A (e.g., Formula I, I-1, I-1a, I-1b, I-1c, I-1d, I-1e, I-1f, I-1g, II, II-1, III, III-1, A1, A2, A3, A1a, A1b, A1c, A2a, A2b, A2c, A2b-1, A2b-2, A2b-3, A2b-4, A2b-5, or A2b-6), Formula K (e.g., Formula K-1, K-2, K-3, K-4, K-5, K-6, K-7a, K-7b, K-8a, K-8b, K-9a, K-9b, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, K-1b-4, K-3a, K-3b, K-5a, or K-5b), any of Examples 1-266, any of the compounds listed in Table 1 herein, or a pharmaceutically acceptable salt thereof). In some embodiments, the cell is a cancer cell. In some embodiments, the cell is an HR deficient cell. In some embodiments, the cancer cell has overexpression of Polθ. The cancer cell can be a cell of any of the cancer described herein.

[0235] In some embodiments, the present disclosure provides a method of treating a disease or disorder associated with Polθ in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the compound of present disclosure (e.g., a compound of Formula A (e.g., Formula I, I-1, I-1a, I-1b, I-1c, I-1d, I-1e, I-1f, I-1g, II, II-1, III, III-1, A1, A2, A3, A1a, A1b, A1c, A2a, A2b, A2c, A2b-1, A2b-2, A2b-3, A2b-4, A2b-5, or A2b-6), Formula K (e.g., Formula K-1, K-2, K-3, K-4, K-5, K-6, K-7a, K-7b, K-8a, K-8b, K-9a, K-9b, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, K-1b-4, K-3a, K-3b, K-5a, or K-5b), any of Examples 1-266, any of the compounds listed in Table

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l herein, or a pharmaceutically acceptable salt thereof), or a pharmaceutical composition as defined herein. In some embodiments, the disease or disorder associated with Polθ is a cancer described herein. In some embodiments, the disease or disorder associated with Polθ is characterized by an overexpression of Polθ. In some embodiments, the cancer is a homologous recombination (HR) deficient cancer. In some embodiments, the cancer is characterized by a reduction or absence of BRCA gene expression, the absence of the BRCA gene, or reduced function of BRCA protein. In some embodiments, the cancer is resistant to poly(ADP-ribose) polymerase (PARP) inhibitor therapy. In some embodiments, the cancer is selected from lymphoma, rhabdoid tumor, multiple myeloma, uterine cancer, gastric cancer, peripheral nervous system cancer, rhabdomyosarcoma, bone cancer, colorectal cancer, mesothelioma, breast cancer, ovarian cancer, lung cancer, fibroblast cancer, central nervous system cancer, urinary tract cancer, upper aerodigestive cancer, leukemia, kidney cancer, skin cancer, esophageal cancer, and pancreatic cancer.

[0236] In some embodiments, the present disclosure provides a method of treating a homologous recombination (HR) deficient cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the compound of present disclosure (e.g., a compound of Formula A (e.g., Formula I, I-1, I-1a, I-1b, I-1c, I-1d, I-1e, I-1f, I-1g, II, II-1, III, III-1, A1, A2, A3, A1a, A1b, A1c, A2a, A2b, A2c, A2b-1, A2b-2, A2b-3, A2b-4, A2b-5, or A2b-6), Formula K (e.g., Formula K-1, K-2, K-3, K-4, K-5, K-6, K-7a, K-7b, K-8a, K-8b, K-9a, K-9b, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, K-1b-4, K-3a, K-3b, K-5a, or K-5b), any of Examples 1-266, any of the compounds listed in Table 1 herein, or a pharmaceutically acceptable salt thereof), or a pharmaceutical composition as defined herein. In some embodiments, the HR-deficient cancer is breast cancer. Breast cancer includes, but is not limited to, lobular carcinoma in situ (LCIS), a ductal carcinoma in situ (DCIS), an invasive ductal carcinoma (IDC), inflammatory breast cancer, Paget disease of the nipple, Phyllodes tumor, Angiosarcoma, adenoid cystic carcinoma, low-grade adenosquamous carcinoma, medullary carcinoma, mucinous carcinoma, papillary carcinoma, tubular carcinoma, metaplastic carcinoma, micropapillary carcinoma, mixed carcinoma, or another breast cancer, including but not limited to triple negative, HER positive, estrogen receptor positive, progesterone receptor positive, HER and estrogen receptor positive, HER and progesterone receptor positive, estrogen and progesterone receptor positive, and HER and estrogen and progesterone receptor positive. In

some embodiments, the HR-deficient cancer is ovarian cancer. Ovarian cancer includes, but is not limited to, epithelial ovarian carcinomas (EOC), maturing teratomas, dysgerminomas, endodermal sinus tumors, granulosa-theca tumors, Sertoli-Leydig cell tumors, and primary peritoneal carcinoma.

[0237] In some embodiments, the present disclosure provides a method of treating a cancer in a subject in need thereof, wherein the cancer is characterized by a reduction or absence of BRCA gene expression, the absence of the BRCA gene, and/or reduced function of BRCA protein, the method comprising administering to the subject a therapeutically effective amount of the compound of present disclosure (e.g., a compound of Formula A (e.g., Formula I, I-1, I-1a, I-1b, I-1c, I-1d, I-1e, I-1f, I-1g, II, II-1, III, III-1, A1, A2, A3, A1a, A1b, A1c, A2a, A2b, A2c, A2b-1, A2b-2, A2b-3, A2b-4, A2b-5, or A2b-6), Formula K (e.g., Formula K-1, K-2, K-3, K-4, K-5, K-6, K-7a, K-7b, K-8a, K-8b, K-9a, K-9b, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, K-1b-4, K-3a, K-3b, K-5a, or K-5b), any of Examples 1-266, any of the compounds listed in Table 1 herein, or a pharmaceutically acceptable salt thereof), or a pharmaceutical composition as defined herein.

[0238] In some embodiments, the present disclosure provides a method of treating a cancer in a subject in need thereof, wherein the cancer is resistant to poly(ADP-ribose) polymerase (PARP) inhibitor therapy, the method comprising administering to the subject a therapeutically effective amount of the compound of present disclosure (e.g., a compound of Formula A (e.g., Formula I, I-1, I-1a, I-1b, I-1c, I-1d, I-1e, I-1f, I-1g, II, II-1, III, III-1, A1, A2, A3, A1a, A1b, A1c, A2a, A2b, A2c, A2b-1, A2b-2, A2b-3, A2b-4, A2b-5, or A2b-6), Formula K (e.g., Formula K-1, K-2, K-3, K-4, K-5, K-6, K-7a, K-7b, K-8a, K-8b, K-9a, K-9b, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, K-1b-4, K-3a, K-3b, K-5a, or K-5b), any of Examples 1-266, any of the compounds listed in Table 1 herein, or a pharmaceutically acceptable salt thereof), or a pharmaceutical composition as defined herein. In some embodiments, the cancer resistant to PARP inhibitor therapy is selected from breast cancer, ovarian cancer, lung cancer, bladder cancer, liver cancer, head and neck cancer, pancreatic cancer, gastrointestinal cancer, and colorectal cancer. As used herein and unless otherwise specified, the phrase “cancer resistant to PARP inhibitor therapy” means that the cancer is not responding to a PARP inhibitor or that the cancer is not responding sufficiently to the PARP inhibitor or that the cancer has progressed on or after treatment with the PARP inhibitor. For example, in some cases, the subject having the cancer may at one time be

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responsive to the PARP inhibitor but has become no longer responsive to such treatment or is no longer responding sufficiently to such treatment.

[0239] The compound of the present disclosure can be used alone, in combination with a different Polθ inhibitor, or in combination with other active agents or other prophylactic or therapeutic modalities. In some embodiments, the compound of the present disclosure can be used in a combination therapy, such as in combination with one or more active therapeutic agents (e.g., chemotherapeutic agents) or other prophylactic or therapeutic modalities (e.g., radiation). In such combination therapy, the various active agents frequently have different, complementary mechanisms of action. Such combination therapy may be especially advantageous by allowing a dose reduction of one or more of the agents, thereby reducing or eliminating the adverse effects associated with one or more of the agents.

[0240] In some embodiments, the compound of the present disclosure is administered in combination with at least one additional therapeutic agent, such as a PARP inhibitor, a signal transduction inhibitor, a chemotherapeutic agent, and/or an immune checkpoint inhibitor.

[0241] In some embodiments, the additional therapeutic agent is a signal transduction inhibitor (STI) or chemotherapeutic agent. As used herein, the term “signal transduction inhibitor” refers to an agent that selectively inhibits one or more steps in a signaling pathway. In some embodiments, chemotherapeutic agents include anti-hormonal agents that act to regulate or inhibit hormonal action on tumors such as anti-estrogens. In certain embodiments, combination therapy comprises administration of a hormone or related hormonal agent. Agents involved in immunomodulation can also be used in combination with one or more compounds of the present disclosure.

[0242] In some embodiments, the compound of the present disclosure is administered in combination with one or more poly ADP ribose polymerase (PARP) inhibitors. For example, in some embodiments, the method herein is for treating a cancer in a subject who is not responsive to a PARP inhibitor therapy or has developed resistance to the PARP inhibitor, the method can comprise administering to the subject one or more compounds of the present disclosure in combination with a PARP inhibitor. Without wishing to be bound by theories, it is believed that in such embodiments, the administration of Polθ sensitizes or resensitizes the cancer to PARP inhibitor treatment. Suitable PARP inhibitors include any of those known in the art, such as those approved for marketing by the U.S. Food and Drug Administration or a non-US counterpart agency. In some embodiments, the method

comprises administering to the subject a PARP inhibitor selected from niraparib, rucaparib, olaparib, talazoparib, veliparib, and fluzoparib.

[0243] In some embodiments, the compound of the present disclosure is administered in combination with an immune checkpoint inhibitor. The tremendous number of genetic and epigenetic alterations that are characteristic of all cancers provides a diverse set of antigens that the immune system can use to distinguish tumor cells from their normal counterparts. In the case of T cells, the ultimate amplitude (e.g., levels of cytokine production or proliferation) and quality (e.g., the type of immune response generated, such as the pattern of cytokine production) of the response, which is initiated through antigen recognition by the T-cell receptor (TCR), is regulated by a balance between co-stimulatory and inhibitory signals (immune checkpoints). Under normal physiological conditions, immune checkpoints are crucial for the prevention of autoimmunity (i.e., the maintenance of self-tolerance) and for the protection of tissues from damage when the immune system is responding to pathogenic infection. The expression of immune checkpoint proteins can be dysregulated by tumors as an important immune resistance mechanism. Examples of immune checkpoint inhibitors include but are not limited to those targeting CTLA-4, PD-1, PD-L1, BTLA, TIM3, LAG3, OX40, 4 IBB, VISTA, CD96, TGFp, CD73, CD39, A2AR, A2BR, IDO1, TDO2, Arginase, B7-H3, and/or B7-H4. For example, in some embodiments, the method comprises administering to the subject an anti-PD-1 antibody, such as pembrolizumab or nivolumab, and/or an anti-PD-L1 antibody, such as avelumab or atezolizumab. In some embodiments, the method comprises administering to the subject an anti-CTLA-4 antibody, such as ipilimumab. Cell-based modulators of anti-cancer immunity are also contemplated. Agents that may be combined with a Polθ inhibitor also include those described in WO2020243459A1, WO2022118210A1, WO2022259204A1, and WO2023067515A1.

[0244] As understood herein, the term "combination" refers to simultaneous, separate or sequential administration. In one aspect of the invention "combination" refers to simultaneous administration. In another aspect of the invention "combination" refers to separate administration. In a further aspect of the invention "combination" refers to sequential administration. Where the administration is sequential or separate, the delay in administering the second component should not be such as to lose the beneficial effect of the combination.

[0245] Dosing regimen including doses for the methods described herein can vary and be adjusted, which can depend on the recipient of the treatment, the disorder, condition or

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disease being treated and the severity thereof, the composition containing the compound, the time of administration, the route of administration, the duration of treatment, the compound potency, its rate of clearance and whether or not another drug is co-administered.

Definitions

- [0246] It is meant to be understood that proper valences are maintained for all moieties and combinations thereof.
- [0247] It is also meant to be understood that a specific embodiment of a variable moiety herein can be the same or different as another specific embodiment having the same identifier.
- [0248] Suitable groups for the variables in compounds of Formula A, Formula K, or a subformula thereof, as applicable, are independently selected. Non-limiting useful groups for the variables in compounds of Formula A, Formula K, or a subformula thereof, as applicable, include any of the respective groups, individually or in any combination, as shown in the Examples or in the specific compounds described in Table 1 herein. In addition, it is to be understood that the definition of a variable in Formula A or Formula K can have the same definition for the variable defined in a subformula of Formula A or Formula K, respectively. Similarly, unless otherwise specified or contrary from context, the definition of a subformula of Formula A or Formula K can have the same definition for the variable defined in connection with Formula A or Formula K or another subformula of Formula A or Formula K, respectively.
- [0249] The described embodiments of the present disclosure can be combined. Such combination is contemplated and within the scope of the present disclosure. For example, it is contemplated that the definition(s) of any one or more of Z, J¹, J², J³, R¹, R², Ring A, Ring B, and m of Formula A can be combined with the definition of any one or more of the other(s) of Z, J¹, J², J³, R¹, R², Ring A, Ring B, and m, as applicable, and the resulted compounds from the combination are contemplated and within the scope of the present disclosure.
- [0250] The symbol, , when displayed perpendicular to (or otherwise crossing) a bond, indicates the point at which the displayed moiety is attached to the remainder of the molecule. It should be noted that for a divalent structure (or multivalent structure), the immediately connected group or groups or appropriate variable(s) shown in a formula may be shown in the divalent structure (or multivalent structure) beyond the symbol, , to indicate direction of attachment. When the immediately connected group(s) or variable is not shown for either

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of the two attaching points of a divalent structure, it should mean that either direction of attachment to the remainder of the molecule is allowed, unless otherwise specified or obviously contrary from context.

[0251] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987. The disclosure is not intended to be limited in any manner by the exemplary listing of substituents described herein.

[0252] Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various stereoisomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high performance liquid chromatography (HPLC), chiral supercritical fluid chromatography (SFC), and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). The disclosure additionally encompasses compounds described herein as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers including racemic mixtures. When a stereochemistry is specifically drawn, unless otherwise contradictory from context, it should be understood that with respect to that particular chiral center or axial chirality, the compound can exist

predominantly as the as-drawn stereoisomer, such as with less than 20%, less than 10%, less than 5%, less than 1%, by weight, by HPLC or SFC area, or both, or with a non-detectable amount of the other stereoisomer(s), for example, the compound can have an enantiomeric excess of greater than 60%, greater than 80%, greater than 90%, greater than 95%, greater than 98%, or greater than 99%. The presence and/or amounts of stereoisomers can be determined by those skilled in the art in view of the present disclosure, including through the use of a chiral HPLC or chiral SFC. As understood by those skilled in the art, when a "*" is shown in the chemical structures herein, unless otherwise contradictory from context, it is to designate that the corresponding chiral center is enantiomerically pure or enriched in either of the configurations or is enantiomerically pure or enriched in the as-drawn configuration, such as with less than 20%, less than 10%, less than 5%, less than 1%, by weight, by HPLC or SFC area, or both, or with a non-detectable amount of the other stereoisomer(s). Also, when no stereochemistry is specifically drawn, and no "*" is used in the chemical structures, unless otherwise contradictory from context, it should be understood that such structures include the corresponding compound in any stereoisomeric forms, including individual isomers substantially free of other isomers and mixtures of various isomers including racemic mixtures.

[0253] When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example "C₁₋₆" is intended to encompass, C₁, C₂, C₃, C₄, C₅, C₆, C₁₋₆, C₁₋₅, C₁₋₄, C₁₋₃, C₁₋₂, C₂₋₆, C₂₋₅, C₂₋₄, C₂₋₃, C₃₋₆, C₃₋₅, C₃₋₄, C₄₋₆, C₄₋₅, and C₅₋₆.

[0254] As used herein, the term "compound(s) of the present disclosure" refers to any of the compounds described herein according to Formula A (e.g., Formula I, I-1, I-1a, I-1b, I-1c, I-1d, I-1e, I-1f, I-1g, II, II-1, III, III-1, A1, A2, A3, A1a, A1b, A1c, A2a, A2b, A2c, A2b-1, A2b-2, A2b-3, A2b-4, A2b-5, or A2b-6), Formula K (e.g., Formula K-1, K-2, K-3, K-4, K-5, K-6, K-7a, K-7b, K-8a, K-8b, K-9a, K-9b, K-1a-1, K-1a-2, K-1b, K-1c, K-1b-1, K-1b-2, K-1b-3, K-1b-4, K-3a, K-3b, K-5a, or K-5b), any of Examples 1-266, or any of the specific compounds disclosed in Table 1 herein, isotopically labeled compound(s) thereof (such as a deuterated analog wherein one or more of the hydrogen atoms is/are substituted with a deuterium atom with an abundance above its natural abundance, e.g., a CD₃ analog when the compound has a CH₃ group), possible regioisomers, possible geometric isomers, possible stereoisomers thereof (including diastereoisomers, enantiomers, and racemic mixtures), tautomers thereof, conformational isomers thereof, pharmaceutically acceptable esters

thereof, and/or possible pharmaceutically acceptable salts thereof (e.g., acid addition salt such as HCl salt or base addition salt such as Na salt). Hydrates and solvates of the compounds of the present disclosure are considered compositions of the present disclosure, wherein the compound(s) is in association with water or solvent, respectively.

[0255] Compounds of the present disclosure can exist in isotope-labeled or -enriched form containing one or more atoms having an atomic mass or mass number different from the atomic mass or mass number most abundantly found in nature. Isotopes can be radioactive or non-radioactive isotopes. Isotopes of atoms such as hydrogen, carbon, phosphorous, sulfur, fluorine, chlorine, and iodine include, but are not limited to ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{32}P , ^{35}S , ^{18}F , ^{36}Cl , and ^{125}I . Compounds that contain other isotopes of these and/or other atoms are within the scope of this invention.

[0256] As used herein, the phrase "administration" of a compound, "administering" a compound, or other variants thereof means providing the compound or a prodrug of the compound to the individual in need of treatment.

[0257] As used herein, the term "alkyl" as used by itself or as part of another group refers to a straight- or branched-chain aliphatic saturated hydrocarbon. In some embodiments, the alkyl can include one to twelve carbon atoms (i.e., C_{1-12} alkyl) or the number of carbon atoms designated. In one embodiment, the alkyl group is a straight chain C_{1-10} alkyl group. In another embodiment, the alkyl group is a branched chain C_{3-10} alkyl group. In another embodiment, the alkyl group is a straight chain C_{1-6} alkyl group. In another embodiment, the alkyl group is a branched chain C_{3-6} alkyl group. In another embodiment, the alkyl group is a straight chain C_{1-4} alkyl group. For example, a C_{1-4} alkyl group includes methyl, ethyl, propyl (n-propyl), isopropyl, butyl (n-butyl), sec-butyl, tert-butyl, and iso-butyl. As used herein, the term "alkylene" as used by itself or as part of another group refers to a divalent radical derived from an alkyl group. For example, non-limiting straight chain alkylene groups include $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$, $-\text{CH}_2-\text{CH}_2-$, and the like.

[0258] As used herein, the term "alkenyl" as used by itself or as part of another group refers to a straight- or branched-chain aliphatic hydrocarbon containing one or more, for example, one, two or three carbon-to-carbon double bonds. In one embodiment, the alkenyl group is a C_{2-6} alkenyl group. In another embodiment, the alkenyl group is a C_{2-4} alkenyl group. Non-limiting exemplary alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, sec-butenyl, pentenyl, and hexenyl.

- [0259] As used herein, the term "alkynyl" as used by itself or as part of another group refers to a straight- or branched-chain aliphatic hydrocarbon containing one or more, for example, one to three carbon-to-carbon triple bonds. In one embodiment, the alkynyl has one carbon-carbon triple bond. In one embodiment, the alkynyl group is a C₂₋₆ alkynyl group. In another embodiment, the alkynyl group is a C₂₋₄ alkynyl group. Non-limiting exemplary alkynyl groups include ethynyl, propynyl, butynyl, 2-butynyl, pentynyl, and hexynyl groups.
- [0260] As used herein, the term "alkoxy" as used by itself or as part of another group refers to a radical of the formula OR^{a1}, wherein R^{a1} is an alkyl.
- [0261] As used herein, the term "cycloalkoxy" as used by itself or as part of another group refers to a radical of the formula OR^{a1}, wherein R^{a1} is a cycloalkyl.
- [0262] As used herein, the term "haloalkyl" as used by itself or as part of another group refers to an alkyl substituted with one or more fluorine, chlorine, bromine and/or iodine atoms. In preferred embodiments, the haloalkyl is an alkyl group substituted with one, two, or three fluorine atoms. In one embodiment, the haloalkyl group is a C₁₋₁₀ haloalkyl group. In one embodiment, the haloalkyl group is a C₁₋₆ haloalkyl group. In one embodiment, the haloalkyl group is a C₁₋₄ haloalkyl group.
- [0263] As used herein, the term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched-chain alkyl group, e.g., having from 2 to 14 carbons, such as 2 to 10 carbons in the chain, in which one or more of the carbons has been replaced by a heteroatom selected from S, O, P and N, and wherein the nitrogen, phosphine, and sulfur atoms can optionally be oxidized and the nitrogen heteroatom can optionally be quaternized. The heteroatom(s) S, O, P and N may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. When the heteroalkyl is said to be substituted, the substituent(s) can replace one or more hydrogen atoms attached to the carbon atom(s) and/or the heteroatom(s) of the heteroalkyl. In some embodiments, the heteroalkyl is a C₁₋₄ heteroalkyl, which refers to the heteroalkyl defined herein having 1-4 carbon atoms. Examples of C₁₋₄ heteroalkyl include, but are not limited to, C₄ heteroalkyl such as -CH₂-CH₂-N(CH₃)-CH₃, C₃ heteroalkyl such as -CH₂-CH₂-O-CH₃, -CH₂-CH₂-NH-CH₃, -CH₂-S-CH₂-CH₃, -CH₂-CH₂-S(O)-CH₃, -CH₂-CH₂-S(O)₂-CH₃, C₂ heteroalkyl such as -CH₂-CH₂-OH, -CH₂-CH₂-NH₂, -CH₂-NH(CH₃), -O-CH₂-CH₃ and C₁ heteroalkyl such as, -CH₂-OH, -CH₂-NH₂, -O-CH₃. Preferably, the C₁₋₄ heteroalkyl (or C₁₋₄ heteroalkylene) herein contains 1 or 2 heteroatoms,

such as one oxygen, one nitrogen, two oxygens, two nitrogens, or one oxygen and one nitrogen. Similarly, the term "heteroalkylene" by itself or as part of another substituent means a divalent radical derived from heteroalkyl, as exemplified, but not limited by, -CH₂-CH₂-O-CH₂-CH₂- and -O-CH₂-CH₂-NH-CH₂-. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (*e.g.*, alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. Where "heteroalkyl" is recited, followed by recitations of specific heteroalkyl groups, such as -NR'R" or the like, it will be understood that the terms heteroalkyl and -NR'R" are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term "heteroalkyl" should not be interpreted herein as excluding specific heteroalkyl groups, such as -NR'R" or the like.

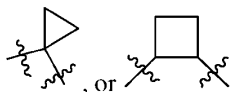
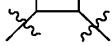
[0264] In some preferred embodiments, unless otherwise specified or contrary from context, a C₁₋₆ heteroalkyl herein can be a C₁₋₆ alkoxy, NH(C₁₋₆ alkyl), N(C₁₋₄ alkyl)(C₁₋₄ alkyl), -(C₁₋₅ alkylene)-O-(C₁₋₅ alkyl), -(C₁₋₅ alkylene)-NH(C₁₋₅ alkyl), -(C₁₋₄ alkylene)-N(C₁₋₄ alkyl)(C₁₋₄ alkyl), -(C₁₋₅ alkylene)-S-(C₁₋₅ alkyl), -(C₁₋₅ alkylene)-SO₂-(C₁₋₅ alkyl), SO₂(C₁₋₆ alkyl), P(O)(C₁₋₄ alkyl)(C₁₋₄ alkyl), SO₂NH(C₁₋₆ alkyl), SO₂N(C₁₋₄ alkyl)(C₁₋₄ alkyl), -(C₁₋₅ alkylene)-SO₂NH-(C₁₋₅ alkyl), or -(C₁₋₄ alkylene)-SO₂N(C₁₋₄ alkyl)(C₁₋₄ alkyl), provided that the total number of carbons are no greater than 6, not counting any optional substituents.

[0265] In some preferred embodiments, unless otherwise specified or contrary from context, a C₁₋₄ heteroalkyl herein can be a C₁₋₄ alkoxy, NH(C₁₋₄ alkyl), N(C₁₋₃ alkyl)(C₁₋₃ alkyl), -(C₁₋₃ alkylene)-O-(C₁₋₃ alkyl), -(C₁₋₃ alkylene)-NH(C₁₋₃ alkyl), -(C₁₋₂ alkylene)-N(C₁₋₂ alkyl)(C₁₋₂ alkyl), -(C₁₋₃ alkylene)-S-(C₁₋₃ alkyl), -(C₁₋₃ alkylene)-SO₂-(C₁₋₃ alkyl), SO₂(C₁₋₄ alkyl), P(O)(C₁₋₃ alkyl)(C₁₋₃ alkyl), SO₂NH(C₁₋₄ alkyl), SO₂N(C₁₋₃ alkyl)(C₁₋₃ alkyl), -(C₁₋₃ alkylene)-SO₂NH-(C₁₋₃ alkyl), or -(C₁₋₂ alkylene)-SO₂N(C₁₋₂ alkyl)(C₁₋₂ alkyl), provided that the total number of carbons are no greater than 4, not counting any optional substituents.

[0266] "Carbocyclyl" or "carbocyclic" as used by itself or as part of another group refers to a radical of a non-aromatic cyclic hydrocarbon group having at least 3 carbon atoms, *e.g.*, from 3 to 10 ring carbon atoms ("C₃₋₁₀ carbocyclyl"), and zero heteroatoms in the non-aromatic ring system. The carbocyclyl group can be either monocyclic ("monocyclic carbocyclyl") or contain a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic carbocyclyl") and can be saturated or can be partially unsaturated. Non-limiting

exemplary carbocyclyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, norbornyl, decalin, adamantyl, cyclopentenyl, and cyclohexenyl. As used herein, the term "carbocyclylene" as used by itself or as part of another group refers to a divalent radical derived from the carbocyclyl group defined herein.

[0267] In some embodiments, "carbocyclyl" is fully saturated, which is also referred to as cycloalkyl. In some embodiments, the cycloalkyl can have from 3 to 10 ring carbon atoms ("C₃₋₁₀ cycloalkyl"). In preferred embodiments, the cycloalkyl is a monocyclic ring. As used herein, the term "cycloalkylene" as used by itself or as part of another group refers to a

divalent radical derived from a cycloalkyl group, for example, , or , etc.

[0268] Unless otherwise defined or contrary from context, a heteroatom herein refers to an atom selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon.

[0269] "Heterocyclyl" or "heterocyclic" as used by itself or as part of another group refers to a radical of a 3-membered or larger, such as 3- to 14-membered, non-aromatic ring system having ring carbon atoms and at least one ring heteroatom, such as 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon. In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic ("monocyclic heterocyclyl") or a fused, bridged, or spiro ring system, such as a bicyclic system ("bicyclic heterocyclyl"), and can be saturated or can be partially unsaturated. When all ring carbon atoms in a heterocyclyl as defined herein are saturated carbons, then the heterocyclyl may also be referred to as a heterocycloalkyl. Heterocyclyl bicyclic ring systems can include one or more heteroatoms in one or both rings, and the point of attachment can be on any ring. As used herein, the term "heterocyclylene" as used by itself or as part of another group refers to a divalent radical derived from the heterocyclyl group defined herein. The heterocyclyl or heterocyclylene can be optionally linked to the rest of the molecule through a carbon or nitrogen atom.

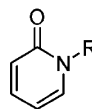
[0270] Exemplary 3-membered heterocyclyl groups containing one heteroatom include, without limitation, aziridinyl, oxiranyl, thiiranyl. Exemplary 4-membered heterocyclyl groups containing one heteroatom include, without limitation, azetidiny, oxetanyl and thietanyl. Exemplary 5-membered heterocyclyl groups containing one heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl,

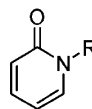
pyrrolidinyl, dihydropyrrolyl, and pyrrolyl-2,5-dione. Exemplary 5-membered heterocyclyl groups containing two heteroatoms include, without limitation, dioxolanyl, oxasulfuranyl, disulfuranyl, and oxazolidin-2-one. Exemplary 5-membered heterocyclyl groups containing three heteroatoms include, without limitation, triazolanyl, oxadiazolanyl, and thiadiazolanyl. Exemplary 6-membered heterocyclyl groups containing one heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6-membered heterocyclyl groups containing two heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, and dioxanyl. Exemplary 6-membered heterocyclyl groups containing two heteroatoms include, without limitation, triazinanyl. Exemplary 7-membered heterocyclyl groups containing one heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8-membered heterocyclyl groups containing one heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Exemplary 5-membered heterocyclyl groups fused to a C₆ aryl ring (also referred to herein as an example of a 5,6-bicyclic heterocyclic ring) include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothieryl, benzoxazolinonyl, and the like. Exemplary 6-membered heterocyclyl groups fused to an aryl ring (also referred to herein as an example of a 6,6-bicyclic heterocyclic ring) include, without limitation, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and the like.

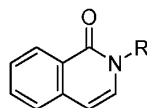
[0271] “Aryl” as used by itself or as part of another group refers to a radical of a monocyclic or polycyclic (*e.g.*, bicyclic or tricyclic) 4n+2 aromatic ring system (*e.g.*, having 6, 10, or 14 pi electrons shared in a cyclic array) having 6–14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system (“C_{6–14} aryl”). In some embodiments, an aryl group has six ring carbon atoms (“C₆ aryl”; *e.g.*, phenyl). In some embodiments, an aryl group has ten ring carbon atoms (“C₁₀ aryl”; *e.g.*, naphthyl such as 1-naphthyl and 2-naphthyl). In some embodiments, an aryl group has fourteen ring carbon atoms (“C₁₄ aryl”; *e.g.*, anthracyl). As used herein, the term “arylene” as used by itself or as part of another group refers to a divalent radical derived from the aryl group defined herein.

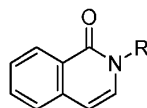
[0272] “Aralkyl” as used by itself or as part of another group refers to an alkyl substituted with one or more aryl groups, preferably, substituted with one aryl group. Examples of aralkyl include benzyl, phenethyl, etc. When an aralkyl is said to be optionally substituted, either the alkyl portion or the aryl portion of the aralkyl can be optionally substituted.

[0273] “Heteroaryl” as used by itself or as part of another group refers to a radical of a 5–14 membered monocyclic, bicyclic, or tricyclic $4n+2$ aromatic ring system (*e.g.*, having 6 or 10 pi electrons shared in a cyclic array) having ring carbon atoms and at least one, preferably, 1–4, ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur (“5–14 membered heteroaryl”). As



used herein, for clarity, a pyridone (*e.g.*, a pyridin-2-one, , wherein R can be hydrogen or a nitrogen atom substituent), pyrimidinone, or the like, such as a pyridone fused



to an aryl or heteroaryl (*e.g.*, , wherein R can be hydrogen or a nitrogen atom substituent), is considered a heteroaryl ring herein. In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl bicyclic ring systems can include one or more heteroatoms in one or both rings. In bicyclic heteroaryl groups wherein one ring does not contain a heteroatom (*e.g.*, indolyl, quinoliny, and the like), the point of attachment can be on either ring, *i.e.*, either the ring bearing a heteroatom (*e.g.*, 2-indolyl) or the ring that does not contain a heteroatom (*e.g.*, 5-indolyl). As used herein, the term “heteroarylene” as used by itself or as part of another group refers to a divalent radical derived from the heteroaryl group defined herein.

[0274] Exemplary 5-membered heteroaryl groups containing one heteroatom include, without limitation, pyrrolyl, furanyl, and thiophenyl. Exemplary 5-membered heteroaryl groups containing two heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5-membered heteroaryl groups containing three heteroatoms include, without limitation, triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5-membered heteroaryl groups containing four heteroatoms include, without limitation, tetrazolyl. Exemplary 6-membered heteroaryl groups containing one heteroatom include, without limitation, pyridinyl. Exemplary 6-membered heteroaryl groups containing two heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6-membered heteroaryl groups containing three or four heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7-membered heteroaryl groups containing one heteroatom include, without limitation, azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6-bicyclic heteroaryl groups include, without limitation, indolyl,

isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indoliziny, and puriny. Exemplary 6,6-bicyclic heteroaryl groups include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl.

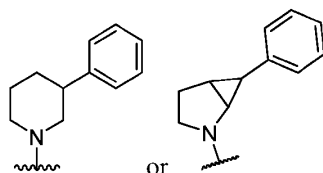
[0275] "Heteroaralkyl" as used by itself or as part of another group refers to an alkyl substituted with one or more heteroaryl groups, preferably, substituted with one heteroaryl group. When a heteroaralkyl is said to be optionally substituted, either the alkyl portion or the heteroaryl portion of the heteroaralkyl can be optionally substituted.

[0276] As used herein, unless specified or otherwise contrary, a "ring structure", "cyclic structure", or simply "ring", with a designated number of ring members, such as a "3-10 membered ring structure", a "3-12 membered ring structure", or a "5- or 6-membered ring", should be understood as encompassing any ring structure (e.g., carbocyclic, heterocyclic, aryl, heteroaryl, etc.) having the designated number of ring members, which can be (1) monocyclic or polycyclic (as chemically feasible), such as a monocyclic ring or a bicyclic or tricyclic ring (including fused, spiro, and bridged bicyclic or tricyclic ring, and those ring systems where two monocyclic rings are connected through a single or double bond); (2) aromatic, partially unsaturated, or fully saturated; and in the case of a polycyclic structure, each ring can be independently aromatic, partially unsaturated, or fully saturated; and (3) containing no heteroatom (i.e., all ring members are carbon atoms) or 1-4 heteroatoms; or in the case of a polycyclic structure, each ring can independently have no ring heteroatom or 1-4 ring heteroatoms (e.g., O, N, S, etc.). When a ring is said to contain a ring sulfur or nitrogen atom, the sulfur or nitrogen atom can be optionally oxidized. One or more ring carbon atoms in a ring structure can be present as C(=O). A fully saturated ring refers to a ring in which none of the ring carbon atom(s) and any present ring heteroatom(s) (e.g., nitrogen) forms a double bond or triple bond with any other atom. The ring structure can be optionally substituted with one or more substituents described herein. The substituents of a ring structure herein can also have a cyclic structure, and in some cases, two substituents of a ring structure may be said to be joined to form a cyclic structure.

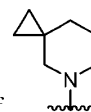
[0277] As commonly understood in the art, for clarity, when a structure can be characterized in multiple ways, as long as one such characterization falls within the scope of the definition of a variable herein, it can be said that the structure is a suitable definition for

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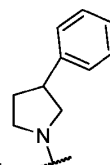
the variable. For example, when a monovalent variable is defined as an optionally substituted 6-membered ring, the variable encompasses, among other structures, (a) the structure of



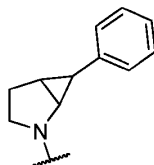
or , which can be viewed as a 6-membered monocyclic or



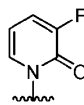
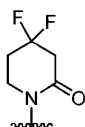
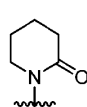
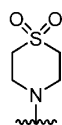
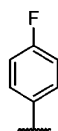
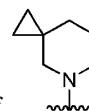
bicyclic ring substituted with a phenyl group; and (b) the structure of , which can be viewed as a 6-membered ring, wherein two substituents are joined to form a cyclopropyl ring (unless the optional substituents for the 6-membered ring are specified and do not include this



as an option); but the variable would not encompass because the attaching ring is not a 6-membered ring under any characterization of the structure. To further explain, when the variable is instead defined as an optionally substituted monocyclic 6-membered ring, then



the variable does not encompass , but encompasses the structure of (unless the optional substituents for the 6-membered ring are specified and do not include this as an option). And if the variable is defined as a 6-membered ring optionally substituted with halogen, then the variable can encompass structures such as,



as each of which can be viewed as a 6-membered ring that is unsubstituted or substituted with 1 or two fluorine atoms.

[0278] As commonly understood in the art, alkylene, alkenylene, alkynylene, heteroalkylene, carbocyclylene, heterocyclylene, arylene, and heteroarylene refer to the

corresponding divalent radicals of alkyl, alkenyl, alkynyl, heteroalkyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl groups, respectively.

[0279] An “optionally substituted” group, such as an optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl groups, refers to the respective group that is unsubstituted or substituted. In general, the term “substituted”, whether preceded by the term “optionally” or not, means that at least one hydrogen present on a group (*e.g.*, a carbon or nitrogen atom) is replaced with a permissible substituent, *e.g.*, a substituent which upon substitution results in a stable compound, *e.g.*, a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a “substituted” group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent can be the same or different at each position. Typically, when substituted, the optionally substituted groups herein can be substituted with 1-5 substituents. Substituents can be a carbon atom substituent, a nitrogen atom substituent, an oxygen atom substituent or a sulfur atom substituent, as applicable, each of which can be optionally isotopically labeled, such as deuterated. Two of the optional substituents can join to form a ring structure, such as an optionally substituted cycloalkyl, heterocyclyl, aryl, or heteroaryl ring. Substitution can occur on any available carbon, oxygen, or nitrogen atom, and can form a spirocycle. Typically, substitution herein does not result in an O-O, O-N, S-S, S-N (except SO₂-N bond), heteroatom-halogen, or -C(O)-S bond or three or more consecutive heteroatoms, with the exception of O-SO₂-O, O-SO₂-N, and N-SO₂-N, except that some of such bonds or connections may be allowed if in a stable aromatic system.

[0280] In a broad aspect, the permissible substituents herein include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this disclosure, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. Substituents can include any substituents described herein, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl, or an acyl),

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a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxy, a cycloalkoxy, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a heterocyclyl, an aralkyl, an aryl, or a heteroaryl, each of which can be substituted, if appropriate.

[0281] Exemplary substituents include, but not limited to, alkyl, alkenyl, alkynyl, aryl, heteroaryl, -alkylene-aryl, -arylene-alkyl, -alkylene-heteroaryl, -alkenylene-heteroaryl, -alkynylene-heteroaryl, —OH, hydroxyalkyl, haloalkyl, —O-alkyl, —O-haloalkyl, -alkylene-O-alkyl, —O-aryl, —O-alkylene-aryl, —O-heteroaryl, —O-alkylene-heteroaryl, —O-cycloalkyl, —O-heterocycloalkyl, acyl, —C(O)-alkyl, —C(O)-haloalkyl, —C(O)-aryl, —C(O)-alkylene-aryl, —C(O)-heteroaryl, —C(O)-alkylene-heteroaryl, —C(O)-cycloalkyl, —C(O)-heterocycloalkyl, halo, —NO₂, —CN, —SF₅, —C(O)OH, —C(O)O-alkyl, —C(O)O-aryl, —C(O)O—alkylene-aryl, —S(O)-alkyl, —S(O)₂-alkyl, —S(O)-haloalkyl, —S(O)₂-haloalkyl, —S(O)-aryl, —S(O)₂-aryl, —S(O)-heteroaryl, —S(O)₂-heteroaryl, —S-alkyl, —S-aryl, —S-heteroaryl, —S-alkylene-aryl, —S-alkylene-heteroaryl, —S(O)₂-alkylene-aryl, —S(O)₂-alkylene-heteroaryl, —S-cycloalkyl, —S-heterocycloalkyl, —S(O)-cycloalkyl, —S(O)-heterocycloalkyl, —S(O)₂-cycloalkyl, —S(O)₂-heterocycloalkyl, —S(O)(=NH)-alkyl, —S(O)(=NH)-haloalkyl, —S(O)(=NH)-aryl, —S(O)(=NH)-alkylene-aryl, —S(O)(=NH)-heteroaryl, —S(O)(=NH)-alkylene-heteroaryl, —S(O)(=NH)-cycloalkyl, —S(O)(=NH)-heterocycloalkyl, —S(O)(=Nalkyl)-alkyl, —S(O)(=Nalkyl)-haloalkyl, —S(O)(=Nalkyl)-aryl, —S(O)(=Nalkyl)-alkylene-aryl, —S(O)(=Nalkyl)-heteroaryl, —S(O)(=Nalkyl)-alkylene-heteroaryl, —S(O)(=Nalkyl)-cycloalkyl, —S(O)(=Nalkyl)-heterocycloalkyl, cycloalkyl, heterocycloalkyl, —O—C(O)-alkyl, —O—C(O)-aryl, —O—C(O)-cycloalkyl, —C(=N—CN)—NH₂, —C(=NH)—NH₂, —C(=NH)—NH(alkyl), —N(Y₁)(Y₂), -alkylene-N(Y₁)(Y₂), —C(O)N(Y₁)(Y₂) and —S(O)₂N(Y₁)(Y₂), wherein Y₁ and Y₂ can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, haloalkyl, aryl, -alkylene-aryl, heteroaryl, -alkylene-heteroaryl, cycloalkyl, heterocycloalkyl, and Y₁ and Y₂ with the nitrogen they linked can form a heterocyclic ring.

[0282] Some examples of suitable substituents include, but not limited to, (C₁-C₈)alkyl groups, (C₂-C₈)alkenyl groups, (C₂-C₈)alkynyl groups, (C₃-C₁₀)cycloalkyl groups, halogen

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(F, Cl, Br or I), halogenated (C₁-C₈)alkyl groups (for example but not limited to —CF₃), —O—(C₁-C₈)alkyl groups, —OH, —S—(C₁-C₈)alkyl groups, —SH, —NH(C₁-C₈)alkyl groups, —N((C₁-C₈)alkyl)₂ groups, —NH₂, —C(O)NH₂, —C(O)NH(C₁-C₈)alkyl groups, —C(O)N((C₁-C₈)alkyl)₂, —NHC(O)H, —NHC(O)(C₁-C₈)alkyl groups, —NHC(O)(C₃-C₈)cycloalkyl groups, —N((C₁-C₈)alkyl)C(O)H, —N((C₁-C₈)alkyl)C(O)(C₁-C₈)alkyl groups, —NHC(O)NH₂, —NHC(O)NH(C₁-C₈)alkyl groups, —N((C₁-C₈)alkyl)C(O)NH₂ groups, —NHC(O)N((C₁-C₈)alkyl)₂ groups, —N((C₁-C₈)alkyl)C(O)N((C₁-C₈)alkyl)₂ groups, —N((C₁-C₈)alkyl)C(O)NH((C₁-C₈)alkyl), —C(O)H, —C(O)(C₁-C₈)alkyl groups, —CN, —NO₂, —S(O)(C₁-C₈)alkyl groups, —S(O)₂(C₁-C₈)alkyl groups, —S(O)₂N((C₁-C₈)alkyl)₂ groups, —S(O)₂NH(C₁-C₈)alkyl groups, —S(O)₂NH(C₃-C₈)cycloalkyl groups, —S(O)₂NH₂ groups, —NHS(O)₂(C₁-C₈)alkyl groups, —N((C₁-C₈)alkyl)S(O)₂(C₁-C₈)alkyl groups, —(C₁-C₈)alkyl-O—(C₁-C₈)alkyl groups, —O—(C₁-C₈)alkyl-O—(C₁-C₈)alkyl groups, —C(O)OH, —C(O)O(C₁-C₈)alkyl groups, NHOH, NHO(C₁-C₈)alkyl groups, —O-halogenated (C₁-C₈)alkyl groups (for example but not limited to —OCF₃), —S(O)₂-halogenated (C₁-C₈)alkyl groups (for example but not limited to —S(O)₂CF₃), —S-halogenated (C₁-C₈)alkyl groups (for example but not limited to —SCF₃), —(C₁-C₆) heterocycle (for example but not limited to pyrrolidine, tetrahydrofuran, pyran or morpholine), —(C₁-C₆) heteroaryl (for example but not limited to tetrazole, imidazole, furan, pyrazine or pyrazole), -phenyl, —NHC(O)O—(C₁-C₆)alkyl groups, —N((C₁-C₆)alkyl)C(O)O—(C₁-C₆)alkyl groups, —C(=NH)—(C₁-C₆)alkyl groups, —C(=NOH)—(C₁-C₆)alkyl groups, or —C(=N—O—(C₁-C₆)alkyl)-(C₁-C₆)alkyl groups.

[0283] Exemplary carbon atom substituents include, but are not limited to, deuterium, halogen, —CN, —NO₂, —N₃, hydroxyl, alkoxy, cycloalkoxy, aryloxy, amino, monoalkyl amino, dialkyl amino, amide, sulfonamide, thiol, acyl, carboxylic acid, ester, sulfone, sulfoxide, alkyl, haloalkyl, alkenyl, alkynyl, C₃₋₁₀ carbocyclyl, C₆₋₁₀ aryl, 3–10 membered heterocyclyl, 5–10 membered heteroaryl, etc. For example, exemplary carbon atom substituents can include F, Cl, —CN, —SO₂H, —SO₃H, —OH, —OC₁₋₆ alkyl, —NH₂, —N(C₁₋₆ alkyl)₂, —NH(C₁₋₆ alkyl), —SH, —SC₁₋₆ alkyl, —C(=O)(C₁₋₆ alkyl), —CO₂H, —CO₂(C₁₋₆ alkyl), —OC(=O)(C₁₋₆ alkyl), —OCO₂(C₁₋₆ alkyl), —C(=O)NH₂, —C(=O)N(C₁₋₆ alkyl)₂, —OC(=O)NH(C₁₋₆ alkyl), —NHC(=O)(C₁₋₆ alkyl), —N(C₁₋₆ alkyl)C(=O)(C₁₋₆ alkyl), —NHCO₂(C₁₋₆ alkyl), —NHC(=O)N(C₁₋₆ alkyl)₂, —NHC(=O)NH(C₁₋₆ alkyl), —NHC(=O)NH₂, —NHSO₂(C₁₋₆ alkyl), —SO₂N(C₁₋₆ alkyl)₂, —SO₂NH(C₁₋₆ alkyl), —SO₂NH₂, —SO₂C₁₋₆ alkyl, —SO₂OC₁₋₆ alkyl, —

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OSO₂C₁₋₆ alkyl, -SOC₁₋₆ alkyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocyclyl, C₆₋₁₀ aryl, 3-10 membered heterocyclyl, 5-10 membered heteroaryl; or two geminal substituents can be joined to form =O.

[0284] Nitrogen atoms can be substituted or unsubstituted as valency permits, and include primary, secondary, tertiary, and quaternary nitrogen atoms. Exemplary nitrogen atom substituents include, but are not limited to, acyl groups, esters, sulfone, sulfoxide, C₁₋₁₀ alkyl, C₁₋₁₀ haloalkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ carbocyclyl, 3-14 membered heterocyclyl, C₆₋₁₄ aryl, and 5-14 membered heteroaryl, or two substituent groups attached to a nitrogen atom are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl can be further substituted as defined herein. In certain embodiments, the substituent present on a nitrogen atom is a nitrogen protecting group (also referred to as an amino protecting group). Nitrogen protecting groups are well known in the art and include those described in detail in *Protective Groups in Organic Synthesis*, 4th ed. P. G. M. Wuts; T. W. Greene, John Wiley, 2007, incorporated by reference herein. Exemplary nitrogen protecting groups include, but not limited to, those forming carbamates, such as Carbobenzyloxy (Cbz) group, p-Methoxybenzyl carbonyl (Moz or MeOZ) group, tert-Butyloxycarbonyl (BOC) group, Troc, 9-Fluorenylmethyloxycarbonyl (Fmoc) group, etc., those forming an amide, such as acetyl, benzoyl, etc., those forming a benzylic amine, such as benzyl, p-methoxybenzyl, 3,4-dimethoxybenzyl, etc., those forming a sulfonamide, such as tosyl, Nosyl, etc., and others such as p-methoxyphenyl.

[0285] Exemplary oxygen atom substituents include, but are not limited to, acyl groups, esters, sulfonates, C₁₋₁₀ alkyl, C₁₋₁₀ haloalkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ carbocyclyl, 3-14 membered heterocyclyl, C₆₋₁₄ aryl, and 5-14 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl can be further substituted as defined herein. In certain embodiments, the oxygen atom substituent present on an oxygen atom is an oxygen protecting group (also referred to as a hydroxyl protecting group). Oxygen protecting groups are well known in the art and include those described in detail in *Protective Groups in Organic Synthesis*, 4th ed. P. G. M. Wuts; T. W. Greene, John Wiley, 2007, incorporated herein by reference. Exemplary oxygen protecting groups include, but are not limited to, those forming alkyl ethers or substituted alkyl ethers, such as methyl, allyl, benzyl, substituted benzylys such as 4-methoxybenzyl, methoxymethyl (MOM), benzyloxymethyl

(BOM), 2-methoxyethoxymethyl (MEM), etc., those forming silyl ethers, such as trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), t-butyldimethylsilyl (TBDMS), etc., those forming acetals or ketals, such as tetrahydropyranyl (THP), those forming esters such as formate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, etc., those forming carbonates or sulfonates such as methanesulfonate (mesylate), benzyisulfonate, and tosylate (Ts), etc.

[0286] Unless expressly stated to the contrary, combinations of substituents and/or variables are allowable only if such combinations are chemically allowed and result in a stable compound. A “stable” compound is a compound that can be prepared and isolated and whose structure and properties remain or can be caused to remain essentially unchanged for a period of time sufficient to allow use of the compound for the purposes described herein (e.g., therapeutic administration to a subject).

[0287] Unless otherwise specified or contrary from context, the optionally substituted groups as referred to herein can be (A) unsubstituted; (B) substituted with one or more substituents each independently deuterium, halogen, CN, or Q^1 - Q^2 - Q^3 - Q^4 , wherein Q^1 , Q^2 , and Q^3 are each independently null, O, NQ^4 , C(O), S, SO, SO_2 , S(O)(=NQ⁴), C₁₋₄ alkylene optionally substituted with deuterium, F, and/or OH, or P(O)Q⁴, wherein Q⁴ at each occurrence is independently hydrogen, C₁₋₆ alkyl optionally substituted with one or more Q¹⁰, C₂₋₆ alkenyl optionally substituted with one or more Q¹⁰, C₂₋₆ alkynyl optionally substituted with one or more Q¹⁰, C₁₋₆ heteroalkyl optionally substituted with one or more Q¹⁰, or 3-14 membered ring optionally substituted with one or more Q¹⁰, wherein Q¹⁰ at each occurrence is independently deuterium, halogen, oxo (as applicable), CN, or Q²⁰-Q²¹-Q²²-Q²³, wherein Q²⁰, Q²¹, and Q²² are each independently null, O, NQ^{23} , C(O), S, SO, SO_2 , S(O)(=NQ²³), C₁₋₄ alkylene optionally substituted with deuterium, F, and/or OH, or P(O)Q²³, wherein Q²³ at each occurrence is independently hydrogen, C₁₋₆ alkyl optionally substituted with one or more Q³⁰, C₂₋₆ alkenyl optionally substituted with one or more Q³⁰, C₂₋₆ alkynyl optionally substituted with one or more Q³⁰, C₁₋₆ heteroalkyl optionally substituted with one or more Q³⁰, or 3-8 membered ring optionally substituted with one or more Q³⁰, wherein Q³⁰ at each occurrence is independently deuterium, halogen, oxo (as applicable), CN, OH, NH₂, C₁₋₄ alkyl optionally substituted with one or more Q³¹, C₁₋₄ heteroalkyl optionally substituted with one or more Q³¹, or 3-5 membered ring optionally substituted with one or more Q³¹, wherein Q³¹ at each occurrence is independently deuterium, F, OH, C₁₋₄ alkyl optionally substituted

with deuterium and/or F, or C₁₋₄ heteroalkyl optionally substituted with deuterium and/or F; or (C) two or more substituents of the respective optionally substituted group, and/or one of the substituents of the respective optionally substituted group and another variable herein, are joined to form a ring (e.g., a spiro ring, a fused ring, or a bridged ring), which is optionally substituted with one or more substituents as defined in (B), and any remaining substituents of the respective optionally substituted group are as defined in (B). In some preferred embodiments, the optionally substituted groups as defined in connection with a formula herein can be unsubstituted or substituted with one or more substituents as defined in (B). The combination of Q¹, Q², and Q³ is not particularly limited, which can preferably be (a) a linker of O, NQ⁴, C(O), S, SO, SO₂, or P(O)Q⁴, when two of Q¹, Q², and Q³ are null, or (b) a linker of amide (C(O)NQ⁴), ester (C(O)O), sulfonamide (SO₂NQ⁴), etc., when one of Q¹, Q², and Q³ is null, or (c) a linker of carbamate (OC(O)NQ⁴), urea (NQ⁴C(O)NQ⁴), sulfamoylamino (NQ⁴SO₂NQ⁴), etc., when none of Q¹, Q², and Q³ is null. The combination of Q²⁰, Q²¹, and Q²² should be understood similarly.

[0288] Unless otherwise specified or contrary from context, when a group herein is defined as being optionally substituted with one or more substituents selected from a defined list or simply a defined list of substituents, the group is typically unsubstituted or substituted with 1, 2, 3, or 4 substituents as defined, although in some embodiments, the group can also be substituted with more than 4 substituents. For example, an alkyl group optionally substituted with one or more substituents independently selected from deuterium, F, and OH can be typically unsubstituted or substituted with 1-4 substituents each independently deuterium, F, or OH. Similarly, an alkyl group optionally substituted with deuterium and/or F is typically unsubstituted or substituted with 1-4 substituents each independently deuterium or F.

[0289] Unless otherwise specified or contrary from context, a 3-x membered ring herein, wherein x is an integer of 6 or greater, e.g., 3-14 membered, 3-8 membered ring, etc., can be (i) 3-x membered carbocyclic ring, (ii) 4-x membered heterocyclic ring having 1-3 ring heteroatoms each independently O, S, and N, wherein the sulfur atom, if present, is optionally oxidized; (iii) phenyl ring, or phenyl or naphthyl ring when x is 10 or greater; (iv) a 5 or 6-membered heteroaryl ring having 1-4 ring heteroatoms each independently O, S, and N, or a 5 or 6-membered heteroaryl ring or bicyclic heteroaryl ring having 1-4 ring heteroatoms each independently O, S, and N, when x is 9 or greater.

[0290] Unless otherwise specified or contrary from context, a 3-6 membered ring herein can be a (i) 3-6 membered carbocyclic ring, e.g., cyclopropyl, cyclobutyl, etc., (ii) 4-6 membered heterocyclic ring having 1-2 ring heteroatoms each independently O, S, and N, wherein the sulfur atom, if present, is optionally oxidized, e.g., oxetane, azetidine, etc.; (iii) a 5-membered heteroaryl ring having 1-4 ring heteroatoms each independently O, S, and N; (iv) a 6-membered heteroaryl ring having 1 or 2 ring nitrogen atoms; or (v) a phenyl ring.

[0291] Unless otherwise specified or contrary from context, a 3-5 membered ring herein can be a (i) 3-5 membered carbocyclic ring, e.g., cyclopropyl, cyclobutyl, etc., (ii) 4-5 membered heterocyclic ring having 1-2 ring heteroatoms each independently O, S, and N, wherein the sulfur atom, if present, is optionally oxidized, e.g., oxetane, azetidine, etc.; or (iii) a 5-membered heteroaryl ring having 1-4 ring heteroatoms each independently O, S, and N.

[0292] In some embodiments, the “optionally substituted” alkyl, alkylene, heteroalkyl, heteroalkylene, alkenyl, alkynyl, carbocyclic, carbocyclylene, cycloalkyl, cycloalkylene, alkoxy, cycloalkoxy, heterocyclyl, or heterocyclylene herein can each be independently unsubstituted or substituted with 1, 2, 3, or 4 substituents independently selected from deuterium, F, Cl, -OH, CN, protected hydroxyl, oxo (as applicable), NH₂, protected amino, NH(C₁₋₄ alkyl) or a protected derivative thereof, N(C₁₋₄ alkyl)(C₁₋₄ alkyl), C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkoxy, phenyl, 5 or 6 membered heteroaryl containing 1, 2, or 3 ring heteroatoms independently selected from O, S, and N, 3-7 membered heterocyclyl containing 1 or 2 ring heteroatoms independently selected from O, S, and N, wherein each of the alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkoxy, phenyl, heteroaryl, and heterocyclyl, is optionally substituted with 1, 2, or 3 substituents independently selected from deuterium, F, -OH, oxo (as applicable), C₁₋₄ alkyl, fluoro-substituted C₁₋₄ alkyl (e.g., CF₃), C₁₋₄ alkoxy and fluoro-substituted C₁₋₄ alkoxy. In some embodiments, the “optionally substituted” aryl, arylene, heteroaryl or heteroarylene group herein can each be independently unsubstituted or substituted with 1, 2, 3, or 4 substituents independently selected from deuterium, F, Cl, -OH, -CN, NH₂, protected amino, NH(C₁₋₄ alkyl) or a protected derivative thereof, N(C₁₋₄ alkyl)(C₁₋₄ alkyl), -S(=O)(C₁₋₄ alkyl), -SO₂(C₁₋₄ alkyl), C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkoxy, phenyl, 5 or 6 membered heteroaryl containing 1, 2 or 3 ring heteroatoms independently selected from O, S, and N, 3-7 membered heterocyclyl containing 1 or 2 ring heteroatoms independently selected from O, S, and N, wherein each of the alkyl, alkenyl, alkynyl, alkoxy,

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cycloalkyl, cycloalkoxy, phenyl, heteroaryl, and heterocyclyl, is optionally substituted with 1, 2, or 3 substituents independently selected from deuterium, F, -OH, oxo (as applicable), C₁₋₄ alkyl, fluoro-substituted C₁₋₄ alkyl, C₁₋₄ alkoxy and fluoro-substituted C₁₋₄ alkoxy.

[0293] "Halo" or "halogen" refers to fluorine (fluoro, -F), chlorine (chloro, -Cl), bromine (bromo, -Br), or iodine (iodo, -I).

[0294] The term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art.

[0295] The term "tautomers" or "tautomeric" refers to two or more interconvertible compounds resulting from tautomerization. The exact ratio of the tautomers depends on several factors, including for example temperature, solvent, and pH. Tautomerizations are known to those skilled in the art. Exemplary tautomerizations include keto-to-enol, amide-to-imide, lactam-to-lactim, enamine-to-imine, and enamine-to-(a different enamine) tautomerizations.

[0296] The term "subject" (alternatively referred to herein as "patient") as used herein, refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

[0297] The term "inhibiting", "reducing," or any variation of these terms in relation of Polθ, includes any measurable decrease or complete inhibition to achieve a desired result. For example, there may be a decrease of about, at most about, or at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or more, or any range derivable therein, reduction of Polθ activity compared to its normal activity.

[0298] The term "homologous recombination" refers to the cellular process of genetic recombination in which nucleotide sequences are exchanged between two similar or identical DNA.

[0299] The term "homologous recombination (HR) deficient cancer", or any variation thereof, refers to a cancer that is characterized by a reduction or absence of a functional HR repair pathway. HR deficiency may arise from absence of one or more HR-associated genes or presence of one or more mutations in one or more HR-associated genes. Examples of HR-

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associated genes include BRCA1, BRCA2, RAD54, RAD51B, CtIP (Choline Transporter-Like Protein), PALB2 (Partner and Localizer of BRCA2), XRCC2 (X-ray repair complementing defective repair in Chinese hamster cells 2), RECQL4 (RecQ Protein-Like 4), BLM (Bloom syndrome, RecQ helicase-like), WRN (Werner syndrome, one or more HR-associated genes) Nbs 1 (Nbs1), and genes encoding Fanconi anemia (FA) proteins or FA-like genes e.g., FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANJ (BRIP1), FANCL, FANCM, FANCN (PALB2), FANCP (SLX4), FANCS (BRCA1), RAD51C, and XPF.

[0300] The term "Polθ overexpression", or any variation thereof, refers to the increased expression or activity of Polθ in a diseased cell, e.g., cancerous cell, relative to expression or activity of Polθ in a normal cell (e.g., non-diseased cell of the same kind). The amount of Polθ can be at least 2-fold, at least 3-fold, at least 4-fold, at least 5-fold, at least 10-fold, or more relative to the Polθ expression in a normal cell. Examples of cancers having overexpression of Polθ include, but are not limited to, breast, ovarian, cervical, lung, colorectal, gastric, bladder and prostate cancers.

[0301] As used herein, the terms "treat," "treating," "treatment," and the like refer to eliminating, reducing, or ameliorating a disease or condition, and/or symptoms associated therewith. Although not precluded, treating a disease or condition does not require that the disease, condition, or symptoms associated therewith be completely eliminated. As used herein, the terms "treat," "treating," "treatment," and the like may include "prophylactic treatment," which refers to reducing the probability of redeveloping a disease or condition, or of a recurrence of a previously-controlled disease or condition, in a subject who does not have, but is at risk of or is susceptible to, redeveloping a disease or condition or a recurrence of the disease or condition. The term "treat" and synonyms contemplate administering a therapeutically effective amount of a compound described herein to a subject in need of such treatment.

[0302] The term "effective amount" refers to that amount of a compound or combination of compounds as described herein that is sufficient to effect the intended application including, but not limited to, prophylaxis or treatment of diseases. A therapeutically effective amount may vary depending upon the intended application (*in vitro* or *in vivo*), or the subject and disease condition being treated (e.g., the weight, age and gender of the subject), the severity of the disease condition, the manner of administration, etc. which can readily be

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determined by one of ordinary skill in the art. The term also applies to a dose that will induce a particular response in target cells and/or tissues. The specific dose will vary depending on the particular compounds chosen, the dosing regimen to be followed, whether the compound is administered in combination with other compounds, timing of administration, the tissue to which it is administered, and the physical delivery system in which the compound is carried.

[0303] As used herein, the singular form “a”, “an”, and “the”, includes plural references unless it is expressly stated or is unambiguously clear from the context that such is not intended.

[0304] The term “and/or” as used in a phrase such as “A and/or B” herein is intended to include both A and B; A or B; A (alone); and B (alone). Likewise, the term “and/or” as used in a phrase such as “A, B, and/or C” is intended to encompass each of the following embodiments: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

[0305] Headings and subheadings are used for convenience and/or formal compliance only, do not limit the subject technology, and are not referred to in connection with the interpretation of the description of the subject technology. Features described under one heading or one subheading of the subject disclosure may be combined, in various embodiments, with features described under other headings or subheadings. Further it is not necessarily the case that all features under a single heading or a single subheading are used together in embodiments.

Examples

[0306] Abbreviations

4Å MS	4Å molecular sieves
BINAP	(S)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
B ₂ Pin ₂	bis(pinacolato)diboron
tBuXPhos	2-di-tert-butylphosphino-2',4',6'-triisopropylbiphenyl
cataCXium	bis(adamant-1-yl)(butyl)phosphine
cataCXium A Pd G3	methanesulfonato(diadamantyl-n-butylphosphino)-2'-amino-1,1'-biphenyl-2-yl)palladium(II) Gen. 3
CbzCl	benzyloxycarbonyl chloride
CMPI	2-chloro-1-methylpyridinium iodide

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DAST	diethylaminosulfur trifluoride
DCM	dichloromethane
DIAD	diisopropyl azodicarboxylate
DIPEA	N,N-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
Dtbbpy	dibutyl [2,2'-bipyridine]-4,4'-dicarboxylate
EDCI	<i>N</i> -(3-dimethylaminopropyl)- <i>N'</i> -ethylcarbodiimide hydrochloride
FA	formic acid
HATU	hexafluorophosphate azabenzotriazole tetramethyl uronium
HPLC	high-pressure liquid chromatography
HOBT	1-hydroxybenzotriazole
Ir(ppy) ₃	tris(2-phenylpyridine)iridium(III)
hrs	hours
LCMS	liquid chromatography-mass spectrometry
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
NBS	N-bromosuccinimide
NiBr ₂ (dtbbpy)	[4,4'-bis(tert-butyl)-2,2'-bipyridine]nickel dibromide
Ni(DME)Cl ₂	Nickel(II) chloride ethylene glycol dimethyl ether complex
NMI	N-methylimidazole
NMP	1-methyl-2-pyrrolidinone
Pd ₂ (dba) ₃	tris(dibenzylideneacetone)dipalladium
Pd(dppf)Cl ₂	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
PE	petroleum ether
Selectfluor	1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
SFC	super critical fluid
TBAI	tetrabutylammonium iodide
TCFH	N,N,N',N'-tetramethylchloroformamidinium hexafluorophosphate
TEA	triethylamine

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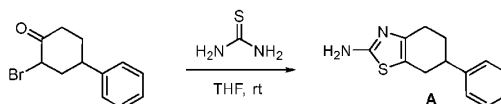
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
Xantphos Pd G3	methanesulfonato[(4,5-bis(diphenylphosphino)-9,9-dimethylxanthene)-2-(2'-amino-1,1'-biphenyl)]palladium(II) Gen. 3
XPhos	dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine
XPhos Pd G2	chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II)

[0307] The various starting materials, intermediates, and compounds of embodiments herein can be isolated and purified where appropriate using conventional techniques such as precipitation, filtration, crystallization, evaporation, distillation, and chromatography. Characterization of these compounds can be performed using conventional methods such as by melting point, mass spectrum, nuclear magnetic resonance, and various other spectroscopic analyses. The abbreviations used in the Examples section should be understood as having their ordinary meanings in the art unless specifically indicated otherwise or obviously contrary from context. The examples are illustrative only and do not limit the claimed invention in any way.

[0308] Exemplary embodiments of steps for performing the synthesis of products described herein are described in greater detail infra.

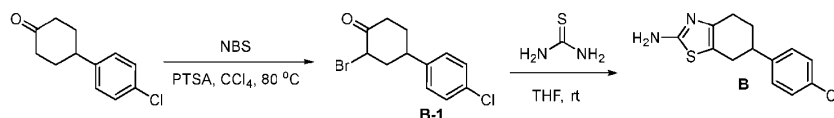
Intermediate A

6-phenyl-4,5,6,7-tetrahydrobenzo[d]thiazol-2-amine



[0309] To a solution of 2-bromo-4-phenyl-cyclohexanone (1.3 g, 5.14 mmol) in THF (15 mL) was added thiourea (390.9 mg, 5.14 mmol). The mixture was stirred at room temperature for 24 hrs. LCMS showed the reaction was complete. The reaction mixture was concentrated under reduced pressure. The residue was treated with water and extracted with EtOAc. The combined organic layers were washed with saturate brine, dried over anhydrous Na₂SO₄, filtered and concentrated to afford the crude Intermediate A (1.3 g), which was used without further purification. LCMS (ESI, m/z): [M+H]⁺ = 231.1.

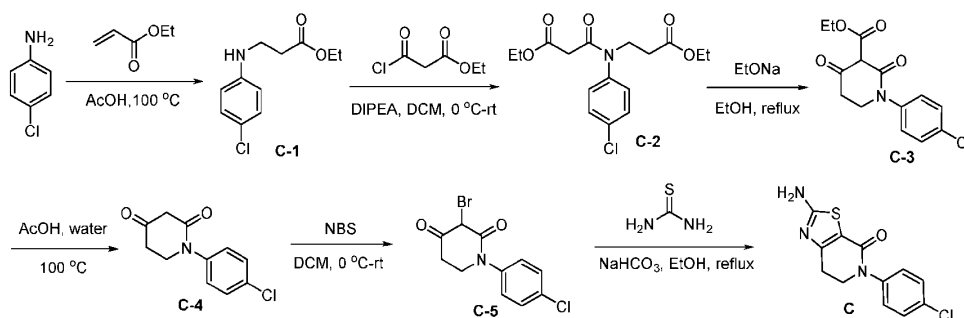
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Intermediate B6-(4-chlorophenyl)-4,5,6,7-tetrahydro-1,3-benzothiazol-2-amineStep 1: 2-bromo-4-(4-chlorophenyl) cyclohexanone (**B-1**)

[0310] A mixture of 4-(4-chlorophenyl) cyclohexanone (340 mg, 1.63 mmol), NBS (290 mg, 1.63 mmol) and *p*-toluenesulfonic acid (28.1 mg, 0.163 mmol) in CCl₄ (5 mL) was stirred at 80 °C for 4 hrs. After completion, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with 1-5% EtOAc in PE) to afford 2-bromo-4-(4-chlorophenyl) cyclohexanone (210 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.43-7.30 (m, 4H), 4.63-4.57 (m, 1H), 3.43-3.33 (m, 1H), 3.22-3.12 (m, 1H), 2.68-2.58 (m, 1H), 2.34-2.18 (m, 2H), 2.09-1.93 (m, 2H).

Step 2: 6-(4-chlorophenyl)-4,5,6,7-tetrahydro-1,3-benzothiazol-2-amine (**B**)

[0311] A solution of 2-bromo-4-(4-chlorophenyl) cyclohexanone (210 mg, 0.73 mmol) and thiourea (133 mg, 1.75 mmol) in THF (10 mL) was stirred at room temperature for 2 hrs under N₂ atmosphere. LCMS showed the reaction was complete. The reaction mixture was treated with water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum to afford Intermediate **B** (180 mg). LCMS (ESI, *m/z*): [M+H]⁺ = 265.0.

Intermediate C2-amino-5-(4-chlorophenyl)-6,7-dihydrothiazolo[5,4-c]pyridin-4(5H)-oneStep 1: ethyl 3-((4-chlorophenyl)amino)propanoate (**C-1**)

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[0312] To a solution of 4-chloroaniline (13.8 g, 0.108 mol) in acetic acid (8 mL) was added ethyl acrylate (13.0 g, 0.130 mol). The mixture was stirred at 100 °C for 16 hrs. LCMS showed the reaction was complete. The reaction mixture was cooled to room temperature and poured into saturated aqueous sodium bicarbonate solution. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (eluting with 5% EtOAc in PE) to afford ethyl 3-((4-chlorophenyl)amino)propanoate (13 g). LCMS (ESI, m/z): [M+H]⁺ = 228.1.

Step 2: ethyl 3-((4-chlorophenyl)(3-ethoxy-3-oxopropyl)amino)-3-oxopropanoate (C-2)

[0313] To a solution of ethyl 3-((4-chlorophenyl)amino)propanoate (13.0 g, 0.057 mol) in DCM (40 mL) was added DIPEA (14.7 g, 0.114 mol). After cooling to 0 °C, ethyl 3-chloro-3-oxopropanoate (10.2 g, 0.068 mol) was added under N₂. The mixture was stirred at room temperature for 18 hrs. LCMS showed the reaction was complete. The reaction mixture was poured into ice cold water and extracted with dichloromethane. The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (eluting with 25% EtOAc in PE) to afford ethyl 3-((4-chlorophenyl)(3-ethoxy-3-oxopropyl)amino)-3-oxopropanoate (10.0 g). LCMS (ESI, m/z): [M+H]⁺ = 342.2.

Step 3: ethyl 1-(4-chlorophenyl)-2,4-dioxopiperidine-3-carboxylate (C-3)

[0314] To a mixture of ethyl 3-((4-chlorophenyl)(3-ethoxy-3-oxopropyl)amino)-3-oxopropanoate (10.0 g, 0.029 mol) in ethanol (20 mL) was added sodium ethoxide (21% in ethanol, 19.1 g, 0.059 mol). The resulting mixture was stirred at reflux for 16 hrs under N₂. LCMS showed the reaction was complete. The reaction mixture was concentrated under vacuum. The residue was dispersed in chloroform, acidified to pH = 3.0 with 1 N aqueous HCl and extracted with chloroform. The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum to afford the crude product which was used without purification. LCMS (ESI, m/z): [M+H]⁺ = 296.1.

Step 4: 1-(4-chlorophenyl)piperidine-2,4-dione (C-4)

[0315] To a round-bottom flask was added ethyl 1-(4-chlorophenyl)-2,4-dioxopiperidine-3-carboxylate (6.5 g, 0.022 mol), acetic acid (50 mL) and water (10 mL). The mixture was stirred at 100 °C for 4 hrs. LCMS showed the reaction was complete. The mixture was concentrated under reduced pressure. The residue was dispersed with water and extracted

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with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum to afford the crude product which was used without purification.

LCMS (ESI, m/z): [M+H]⁺ = 224.0.

Step 5: 3-bromo-1-(4-chlorophenyl)piperidine-2,4-dione (C-5)

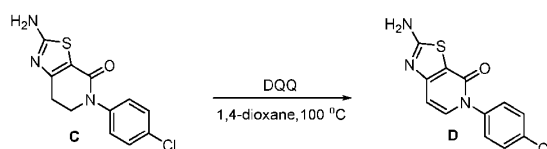
[0316] To a solution of 1-(4-chlorophenyl)piperidine-2,4-dione (1.0 g, 4.47 mmol) in CH₂Cl₂ (25 mL) was added NBS (0.952 g, 5.34 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 18 hrs. LCMS showed the reaction was complete. The reaction mixture was treated with water and extracted with DCM. The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The crude product was used without further purification. LCMS (ESI, m/z): [M+H]⁺ = 301.7.

Step 6: 2-amino-5-(4-chlorophenyl)-6,7-dihydrothiazolo[5,4-c]pyridin-4(5H)-one (C)

[0317] To the mixture of 3-bromo-1-(4-chlorophenyl)piperidine-2,4-dione (1.045 g, 3.45 mmol), sodium bicarbonate (320 mg, 3.81 mmol) in ethanol (20 mL) was added thiourea (291 mg, 3.82 mmol). The mixture was stirred at reflux for 2.5 hrs. LCMS showed the reaction was complete. The reaction mixture was concentrated under vacuum. The residue was dispersed with water and extracted with EtOAc. The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by prep-HPLC (0.05% NH₄HCO₃) to afford Intermediate C (0.45 g). LCMS (ESI, m/z): [M+H]⁺ = 280.1.

Intermediate D

2-amino-5-(4-chlorophenyl)thiazolo[5,4-c]pyridin-4(5H)-one



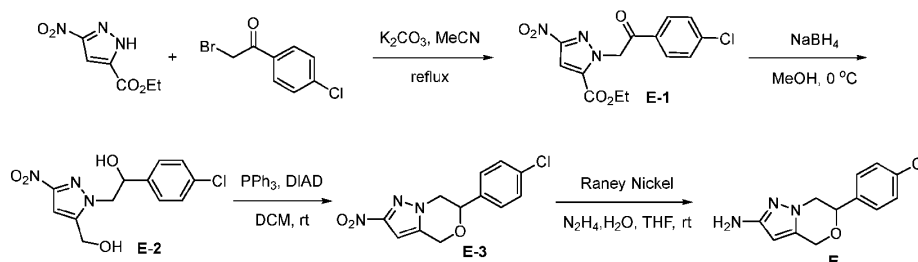
[0318] To a solution of Intermediate C (220 mg, 0.79 mmol) in 1,4-dioxane was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (536 mg, 2.36 mmol) at room temperature. The mixture was stirred at 100 °C for 6 hrs. LCMS showed the reaction was complete. The reaction mixture was treated with saturated aqueous sodium bicarbonate solution and extracted with EtOAc. The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by

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flash column chromatography on silica gel (eluting with 5% EtOAc in PE) to afford Intermediate **D** (65.0 mg). LCMS (ESI, m/z): $[M+H]^+ = 278.1$.

Intermediate E

6-(4-chlorophenyl)-6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-2-amine



Step 1: ethyl 1-(2-(4-chlorophenyl)-2-oxoethyl)-3-nitro-1H-pyrazole-5-carboxylate (**E-1**)

[0319] To a solution of ethyl 3-nitro-1H-pyrazole-5-carboxylate (1.00 g, 5.40 mmol) in MeCN (60 mL) was added 2-bromo-1-(4-chlorophenyl)ethanone (1.39 g, 5.95 mmol) and K_2CO_3 (1.49 g, 10.8 mmol). The mixture was stirred at reflux for 5 hrs. LCMS showed the reaction was complete. The reaction mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with 5% aqueous citric acid, dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with 30% EtOAc in PE) to afford ethyl 2-[2-(4-chlorophenyl)-2-oxo-ethyl]-5-nitro-pyrazole-3-carboxylate (1.59 g). LCMS (ESI, m/z): $[M+H]^+ = 336.0$.

Step 2: 1-(4-chlorophenyl)-2-(5-(hydroxymethyl)-3-nitro-1H-pyrazol-1-yl)ethan-1-ol (**E-2**)

[0320] To a solution of ethyl 2-[2-(4-chlorophenyl)-2-oxo-ethyl]-5-nitro-pyrazole-3-carboxylate (1.59 g, 4.71 mmol) in MeOH (59.5 mL) was added sodium borohydride (0.53 g, 14.1 mmol) at 0 °C. The mixture was stirred at 0 °C for 4 hrs. LCMS showed the reaction was complete. The reaction mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with 5% aqueous citric acid, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with 20-60% EtOAc in PE) to afford 1-(4-chlorophenyl)-2-[5-(hydroxymethyl)-3-nitro-pyrazol-1-yl]ethanol (861.0 mg). LCMS (ESI, m/z): $[M+H]^+ = 296.2$.

Step 3: 6-(4-chlorophenyl)-2-nitro-6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazine (**E-3**)

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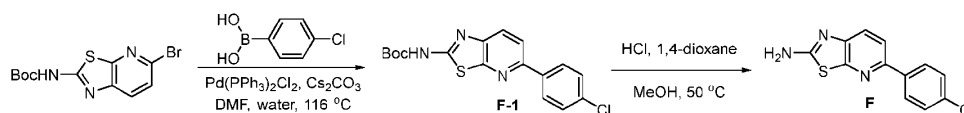
[0321] To a degassed solution of 1-(4-chlorophenyl)-2-[5-(hydroxymethyl)-3-nitro-pyrazol-1-yl]ethanol (340.0 mg, 1.14 mmol) in DCM (4 mL) was added PPh_3 (898.7 mg, 3.43 mmol) and DIAD (692.8 mg, 3.43 mmol) under N_2 . The mixture was stirred at room temperature for 3 hrs. After completion, the mixture was treated with water and extracted with DCM. The combined organic layers were washed with saturated brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with 25% EtOAc in PE) to afford 6-(4-chlorophenyl)-2-nitro-6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazine (184.0 mg). LCMS (ESI, m/z): $[\text{M}+\text{H}]^+ = 280.1$.

Step 4: 6-(4-chlorophenyl)-6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-2-amine (E)

[0322] To a solution of 6-(4-chlorophenyl)-2-nitro-6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazine (180.0 mg, 0.64 mmol) in THF (3 mL) was added Raney nickel (37.8 mg) at room temperature under N_2 . Hydrazine (85% in water, 379 mg, 6.44 mmol) was added dropwise at 0°C . The mixture was stirred at room temperature for 3 hrs. LCMS showed the reaction was complete. The mixture was filtered and concentrated under reduced pressure. The residue was purified by reverse phase column chromatography (0.05% NH_4HCO_3) to afford Intermediate **E** (125.0 mg). LCMS (ESI, m/z): $[\text{M}+\text{H}]^+ = 250.2$.

Intermediate F

5-(4-chlorophenyl)thiazolo[5,4-b]pyridin-2-amine



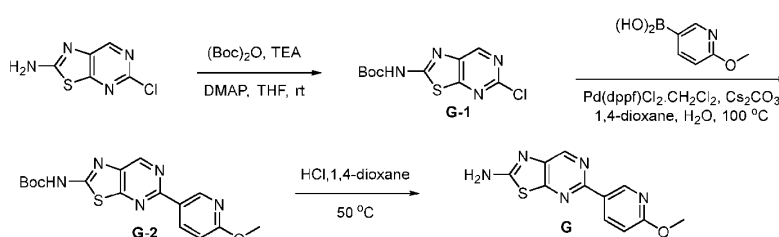
Step 1: *tert*-butyl (5-(4-chlorophenyl)thiazolo[5,4-b]pyridin-2-yl)carbamate (F-1)

[0323] A mixture of *tert*-butyl (5-bromothiazolo[5,4-b]pyridin-2-yl)carbamate (700 mg, 2.12 mmol), (4-chlorophenyl)boronic acid (497 mg, 3.18 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (298 mg, 0.424 mmol) and Cs_2CO_3 (1.45 g, 4.45 mmol) in DMF (36 mL) and water (9 mL) was degassed and stirred at 116°C for 4 hrs under N_2 atmosphere. LCMS showed the reaction was complete. The reaction mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with saturated brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (eluting with 10-50% EtOAc in PE) to afford *tert*-butyl (5-(4-chlorophenyl)thiazolo[5,4-b]pyridin-2-yl)carbamate (450 mg). LCMS (ESI, m/z): $[\text{M}+\text{H}]^+ = 362.1$.

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Step 2: 5-(4-chlorophenyl)thiazolo[5,4-b]pyridin-2-amine (F)

[0324] A solution of *tert*-butyl 5-(4-chlorophenyl) thiazolo[5,4-b] pyridine-2-yl) carbamate (450 mg, 1.24 mmol) and HCl (4 M in 1,4-dioxane, 10 mL) in MeOH (10 mL) was stirred at 50 °C for 1 hr. LCMS showed the reaction was complete. The reaction mixture was concentrated under vacuum to afford crude Intermediate **F** (400 mg). LCMS (ESI, m/z): [M+H]⁺ = 261.9.

Intermediate G5-(6-methoxy-3-pyridyl)thiazolo[5,4-d]pyrimidin-2-amineStep 1: *tert*-butyl 5-(5-chlorothiazolo[5,4-d]pyrimidin-2-yl)carbamate (G-1)

[0325] To a solution of 5-chlorothiazolo[5,4-d]pyrimidin-2-amine (500 mg, 2.68 mmol), DMAP (33 mg, 0.27 mmol) and TEA (542 mg, 5.36 mmol) in THF (10 mL) was added Boc₂O (1.75 g, 8.02 mmol). The mixture was stirred at room temperature for 8 hrs. LCMS showed the reaction was complete. The mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with 30% EtOAc in PE) to afford *tert*-butyl 5-(5-chlorothiazolo[5,4-d]pyrimidin-2-yl)carbamate (500 mg). LCMS (ESI, m/z): [M+H]⁺ = 287.1.

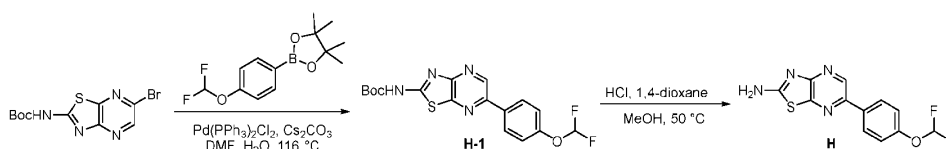
Step 2: *tert*-butyl 5-(6-methoxypyridin-3-yl)thiazolo[5,4-d]pyrimidin-2-yl)carbamate (G-2)

[0326] A mixture of *tert*-butyl 5-(5-chlorothiazolo[5,4-d]pyrimidin-2-yl)carbamate (220 mg, 0.767 mmol), (6-methoxy-3-pyridyl)boronic acid (141 mg, 0.921 mmol) in 1,4-dioxane (8 mL) and H₂O (2 mL) was added Pd(dppf)Cl₂·CH₂Cl₂ complex (125 mg, 0.154 mmol) and Cs₂CO₃ (750 mg, 2.30 mmol) under N₂. The mixture was degassed and stirred at 100 °C for 12 hrs under N₂ atmosphere. LCMS showed the reaction was complete. The mixture was treated with water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (eluting with 20-50% EtOAc in PE) to afford *tert*-butyl 5-(6-methoxypyridin-3-yl)thiazolo[5,4-d]pyrimidin-2-yl)carbamate (270 mg). LCMS (ESI, m/z): [M+H]⁺ = 360.3.

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Step 3: 5-(6-methoxy-3-pyridyl)thiazolo[5,4-d]pyrimidin-2-amine (G)

[0327] A solution of *tert*-butyl N-[5-(6-methoxy-3-pyridyl)thiazolo[5,4-d]pyrimidin-2-yl]carbamate (260 mg, 0.723 mmol) in HCl (4 M in 1,4-dioxane, 5 mL) was stirred at 50 °C for 12 hrs. LCMS showed the reaction was complete. The mixture was concentrated under vacuum to afford crude Intermediate **G**, which was used without further purification. LCMS (ESI, m/z): [M+H]⁺ = 260.1.

Intermediate H6-[4-(difluoromethoxy)phenyl]thiazolo[4,5-b]pyrazin-2-amineStep 1: *tert*-butyl N-[6-[4-(difluoromethoxy)phenyl]thiazolo[4,5-b]pyrazin-2-yl]carbamate (H-1)

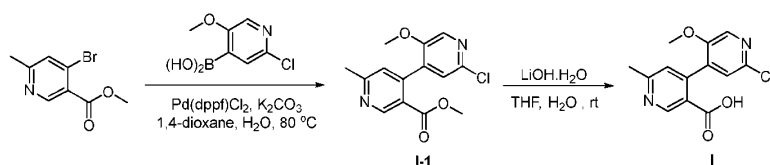
[0328] A solution of *tert*-butyl N-(6-bromothiazolo[4,5-b]pyrazin-2-yl)carbamate (500 mg, 1.51 mmol), 2-[4-(difluoromethoxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (530 mg, 1.96 mmol), Pd(PPh₃)₂Cl₂ (212 mg, 0.30 mmol) and Cs₂CO₃ (984 mg, 3.02 mmol) in DMF (8 mL) and water (2 mL) was degassed and stirred at 116 °C for 4 hrs under N₂ atmosphere. LCMS showed the reaction was complete. The reaction mixture was treated with water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (eluting with 30% EtOAc in PE) to afford *tert*-butyl N-[6-[4-(difluoromethoxy)phenyl]thiazolo[4,5-b]pyrazin-2-yl]carbamate (550 mg). LCMS (ESI, m/z): [M+H]⁺ = 394.9.

Step 2: 6-[4-(difluoromethoxy)phenyl]thiazolo[4,5-b]pyrazin-2-amine (H)

[0329] To a mixture of *tert*-butyl N-[6-[4-(difluoromethoxy)phenyl]thiazolo[4,5-b]pyrazin-2-yl]carbamate (400 mg, 1.01 mmol) in MeOH (4 mL) was added HCl (4.0 M in 1,4-dioxane, 4 mL). The mixture was stirred at 50 °C for 2 hrs. LCMS showed the reaction was complete. The mixture was treated with saturated aqueous NaHCO₃ solution and extracted with DCM. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude Intermediate **H** was used without further purification. LCMS (ESI, m/z): [M+H]⁺ = 295.2.

Intermediate I2'-chloro-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxylic acid

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Step 1: methyl 2'-chloro-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxylate (I-1)

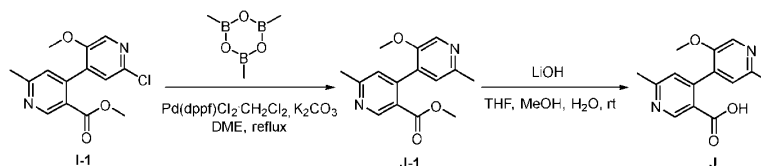
[0330] To a solution of methyl 4-bromo-6-methylnicotinate (10 g, 43.5 mmol) and (2-chloro-5-methoxypyridin-4-yl)boronic acid (8.96 g, 47.8 mmol) in 1,4-dioxane (100 mL) and H₂O (25 mL) was added K₂CO₃ (18.0 g, 130.2 mmol) and Pd(dppf)Cl₂·CH₂Cl₂ complex (3.18 g, 4.3 mmol) under N₂. The mixture was degassed and stirred at 80 °C under N₂ atmosphere for 2 hrs. LCMS showed the reaction was complete. The reaction mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (eluting with 10-50% EtOAc in PE) to afford methyl 2'-chloro-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxylate (10.1 g). LCMS (ESI, m/z): [M+H]⁺ = 293.3.

Step 2: 2'-chloro-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxylic acid (I)

[0331] To a solution of methyl 2'-chloro-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxylate (10.1 g, 34.5 mmol) in THF (50 mL) and H₂O (50 mL) was added LiOH·H₂O (5.79 g, 138.0 mmol). The mixture was stirred at room temperature for 2 hrs. LCMS showed the reaction was complete. The reaction mixture was concentrated in vacuo to remove most THF. The resulting mixture was acidified with aqueous HCl solution (2 N) to pH = 4-5. The mixture was extracted with 10% MeOH in DCM. The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (eluting with 10% MeOH in DCM) to afford Intermediate I (8.7 g). LCMS (ESI, m/z): [M+H]⁺ = 278.9. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.05 (br s, 1H), 8.89 (s, 1H), 8.21 (s, 1H), 7.44 (s, 1H), 7.30 (s, 1H), 3.78 (s, 3H), 2.56 (s, 3H).

Intermediate J

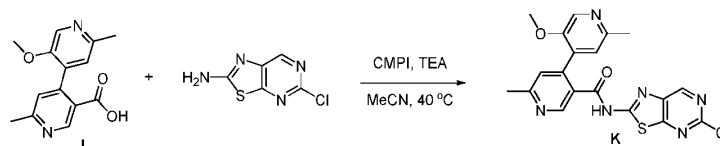
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5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxylic acidStep 1: methyl 5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxylate (J-1)

[0332] To a solution of methyl 2'-chloro-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxylate (8.0 g, 27.3 mmol) in DME (100 mL) was added 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (3.5 M in THF, 25 mL, 87.5 mmol), Pd(dppf)Cl₂·CH₂Cl₂ complex (3.96 g, 5.41 mmol) and K₂CO₃ (11.3 g, 81.8 mmol) under N₂. The mixture was degassed and stirred at reflux for 16 hrs. LCMS showed the reaction was complete. The reaction mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (eluting with 10-50% EtOAc in PE) to afford methyl 5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxylate (6.0 g). LCMS (ESI, m/z): [M+H]⁺ = 273.2.

Step 2: 5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxylic acid (J)

[0333] To a solution of methyl 5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxylate (6.0 g, 22.0 mmol) in THF (30 mL), methanol (10 mL) and water (10 mL) was added LiOH (1.05 g, 43.8 mmol). The mixture was stirred at room temperature for 3 hrs. LCMS showed the reaction was complete. The reaction mixture was concentrated under vacuum to remove most of the solvent. The remaining aqueous phase was acidified with aqueous HCl solution (2 N) to pH = 4-5. The mixture was purified with prep-HPLC (0.05% FA) to afford Intermediate J (3.0 g). LCMS (ESI, m/z): [M+H]⁺ = 259.1; ¹H NMR (400 MHz, CD₃OD) δ 8.88 (s, 1H), 8.12 (s, 1H), 7.28 (s, 1H), 7.23 (s, 1H), 3.84 (s, 3H), 2.63 (s, 3H), 2.54 (s, 3H).

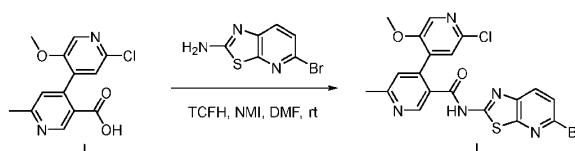
Intermediate KN-(5-chlorothiazolo[5,4-d]pyrimidin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide

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[0334] To a solution of Intermediate **J** (1.00 g, 3.87 mmol) in MeCN (10 mL) was added 5-chlorothiazolo[5,4-d]pyrimidin-2-amine (0.86 g, 4.61 mmol), CMPI (1.98 g, 7.75 mmol) and Et₃N (1.96 g, 19.4 mmol). The mixture was stirred at 40 °C for 3 hrs under N₂. LCMS showed the reaction was complete. The mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with saturate brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was triturated with EtOAc and PE (2/1) and filtered to afford Intermediate **K** (0.98 g). LCMS (ESI, m/z): [M+H]⁺ = 427.2.

Intermediate L

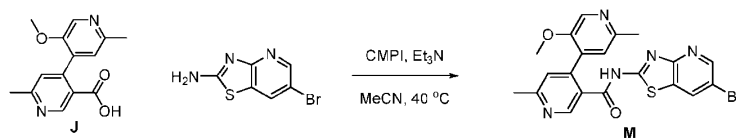
N-(5-bromothiazolo[5,4-b]pyridin-2-yl)-2'-chloro-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide



[0335] To a stirred solution of Intermediate **I** (1.00 g, 3.59 mmol) and 5-bromothiazolo[5,4-b]pyridin-2-amine (2.48 g, 10.8 mmol) in DMF (40 mL) was added TCFH (3.02 g, 10.8 mmol) and NMI (1.77 g, 21.6 mmol) at room temperature. The mixture was stirred at room temperature for 16 hrs under N₂. LCMS showed the reaction was complete. The reaction mixture was treated with water and extracted with DCM. The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (eluting with 50-80% EA in PE) to afford Intermediate **L** (860 mg). LCMS (ESI, m/z): [M+H]⁺ = 490.0.

Intermediate M

N-(6-bromothiazolo[4,5-b]pyridin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide



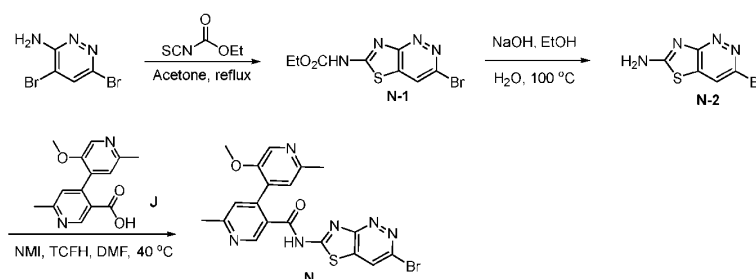
[0336] To a solution of Intermediate **J** (1 g, 3.87 mmol) in MeCN (10 mL) was added 6-bromothiazolo[4,5-b]pyridin-2-amine (1.66 g, 7.21 mmol), CMPI (1.98 g, 7.75 mmol) and

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Et₃N (1.96 g, 19.4 mmol). The mixture was stirred at 40 °C under N₂ for 2 hrs. LCMS showed the reaction was complete. The mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (eluting with 5% MeOH in DCM) to afford Intermediate **M** (600 mg). LCMS (ESI, m/z): [M+H]⁺ = 470.1.

Intermediate N

N-(3-bromothiazolo[4,5-*c*]pyridazin-6-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide



Step 1: ethyl (3-bromothiazolo[4,5-*c*]pyridazin-6-yl)carbamate (**N-1**)

[0337] To a solution of 4,6-dibromopyridazin-3-amine (2 g, 7.91 mmol) in acetone (20 mL) was added O-ethyl carbonisothiocyanatide (9.10 g, 69.4 mmol). The mixture was stirred under N₂ at reflux for 16 hrs. LCMS showed the reaction was complete. The mixture was treated with water and extracted with MeOH/DCM (1/3). The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum to afford the crude product which was used without further purification. LCMS (ESI, m/z): [M+H]⁺ = 303.0.

Step 2: 3-bromothiazolo[4,5-*c*]pyridazin-6-amine (**N-2**)

[0338] To a solution of the crude ethyl *N*-(3-bromothiazolo[4,5-*c*]pyridazin-6-yl)carbamate from step 1 in MeOH (20 mL) was added aqueous NaOH solution (2 N, 20 mL, 40 mmol). The mixture was stirred at 100 °C for 4 hrs. LCMS showed the reaction was complete. The reaction mixture was neutralized by aqueous HCl solution (1 N). The precipitate was collected, washed with water, and dried under vacuum to afford 3-bromothiazolo[4,5-*c*]pyridazin-6-amine (600 mg). LCMS (ESI, m/z): [M+H]⁺ = 231.0.

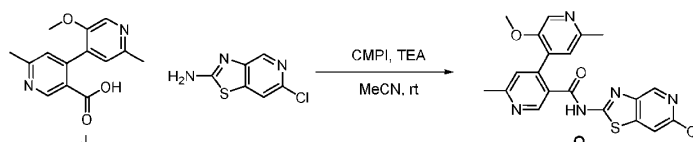
Step 3: *N*-(3-bromothiazolo[4,5-*c*]pyridazin-6-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide (**N**)

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[0339] To a solution of 3-bromothiazolo[4,5-c]pyridazin-6-amine (280 mg, 1.21 mmol), Intermediate **J** (344 mg, 1.33 mmol) and NMI (497 mg, 6.05 mmol) in DMF (10 mL) was added TCFH (680 mg, 2.42 mmol). The mixture was stirred at 40 °C for 24 hrs. LCMS showed the reaction was complete. The mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (eluting with 5% MeOH in DCM) to afford Intermediate **N** (60 mg). LCMS (ESI, m/z): [M+H]⁺ = 471.1.

Intermediate O

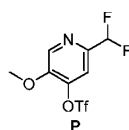
N-(6-chlorothiazolo[4,5-c]pyridin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide



[0340] To a mixture of 6-chlorothiazolo[4,5-c]pyridin-2-amine (600 mg, 3.23 mmol) and Intermediate **J** (557 mg, 2.16 mmol) in MeCN (15 mL) was added CMPI (550 mg, 2.15 mmol) and TEA (218 mg, 2.15 mmol). After stirring under N₂ at room temperature for 16 hrs, LCMS showed the reaction was complete. The mixture was treated with water and extracted with DCM. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (eluting with 5% MeOH in DCM) to give Intermediate **O** (590 mg). LCMS (ESI, m/z): [M+H]⁺ = 426.2.

Intermediate P

2-(difluoromethyl)-5-methoxypyridin-4-yl trifluoromethanesulfonate

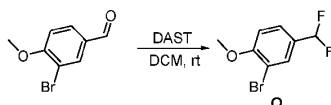


[0341] Intermediate **P** was synthesized following a literature reported procedure (WO202350007).

Intermediate Q

2-bromo-4-(difluoromethyl)-1-methoxybenzene

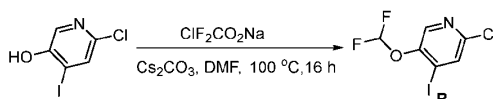
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- [0342] To a stirred solution of 3-bromo-4-methoxy-benzaldehyde (4.3 g, 20.5 mmol) in DCM (10 mL) was added DAST (5.61 g, 4.60 mL, 34.8 mmol) at 0 °C. After stirring at room temperature for 16 hrs, the reaction mixture was quenched with saturated aqueous NaHCO₃ solution and extracted with DCM. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (20:1), to afford Intermediate **Q** (2.69 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.70 (s, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.57 (t, *J* = 56.8 Hz, 1H), 3.93 (s, 3H).

Intermediate R

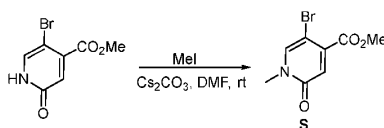
2-chloro-5-(difluoromethoxy)-4-iodopyridine



- [0343] A mixture of 6-chloro-4-iodo-pyridin-3-ol (15 g, 58.7 mmol), sodium chlorodifluoroacetate (17.9 g, 117.4 mmol) and Cs₂CO₃ (38.3 g, 117.4 mmol) in DMF (200 mL) was stirred at 100 °C for 16 hrs. After completion, the reaction mixture was treated with saturated brine and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with PE/EtOAc (10:1), to afford Intermediate **R** (12 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.31 (s, 1H), 8.24 (s, 1H), 7.40 (t, *J* = 72.6 Hz, 1H).

Intermediate S

methyl 5-bromo-1-methyl-2-oxo-1,2-dihydropyridine-4-carboxylate



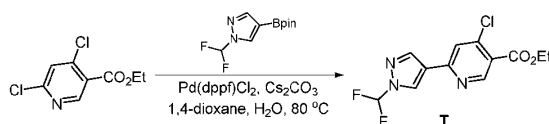
- [0344] To a stirred solution of methyl 5-bromo-2-oxo-1,2-dihydropyridine-4-carboxylate (2 g, 8.62 mmol) and Cs₂CO₃ (8.44 g, 25.9 mmol) in DMF (30 mL) at 0 °C was added methyl iodide (1.84 g, 13.0 mmol) under N₂ atmosphere. After stirring for 2 hrs at room temperature, the reaction mixture was treated with water and extracted with EtOAc. The combined organic

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layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated under vacuum to afford Intermediate **S** (1.5 g). LCMS (ESI, m/z): $[\text{M}+\text{H}]^+ = 246.0$.

Intermediate T

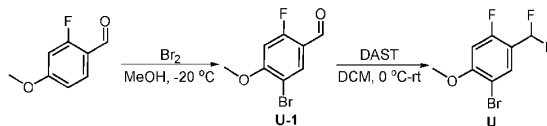
ethyl 4-chloro-6-(1-(difluoromethyl)-1H-pyrazol-4-yl)nicotinate



[0345] A mixture of ethyl 4,6-dichloronicotinate (700 mg, 3.18 mmol), 1-(difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (698 mg, 2.86 mmol), Pd(dppf)Cl_2 (234 mg, 0.32 mmol), and Cs_2CO_3 (2.07 g, 6.36 mmol) in 1,4-dioxane (10 mL) and H_2O (2.5 mL) was degassed and stirred at 80 °C for 2 hrs under N_2 atmosphere. After completion, the reaction mixture was treated with H_2O and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel, eluting with PE/EtOAc (10:1), to afford Intermediate **T** (400 mg). LCMS (ESI, m/z): $[\text{M}+\text{H}]^+ = 301.9$.

Intermediate U

1-bromo-5-(difluoromethyl)-4-fluoro-2-methoxybenzene



Step 1: 5-bromo-2-fluoro-4-methoxybenzaldehyde (U-1)

[0346] To a stirred solution of Br_2 (10.37 g, 64.8 mmol) in MeOH (50 mL) was added 2-fluoro-4-methoxybenzaldehyde (5 g, 32.4 mmol) in MeOH (10 mL) dropwise at -20 °C. After stirring at -20 °C, the reaction mixture was quenched with saturated aqueous sodium hydrogen sulfite solution and water. The precipitates were collected by filtration, washed with water, and dried under reduce pressure to give 5-bromo-2-fluoro-4-methoxybenzaldehyde (**U-1**, 6 g). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.02 (s, 1H), 7.97 (d, $J = 7.6$ Hz, 1H), 7.25 (d, $J = 12.4$ Hz, 1H), 3.98 (s, 3H).

Step 2: 1-bromo-5-(difluoromethyl)-4-fluoro-2-methoxybenzene (U)

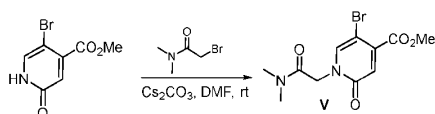
[0347] To a stirred solution of 5-bromo-2-fluoro-4-methoxybenzaldehyde (5.9 g, 25.3 mmol) in DCM (6 mL) at 0 °C was added DAST (8.16 g, 50.6 mmol) under N_2 atmosphere. After stirring for 2 hrs at room temperature, the reaction mixture was quenched with MeOH

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followed by water and extracted with DCM. The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (20:1), to afford Intermediate U (3.12 g). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.82 (d, $J = 7.6$ Hz, 1H), 7.25 (d, $J = 12.4$ Hz, 1H), 7.10 (t, $J = 54.0$ Hz, 1H), 3.92 (s, 3H).

Intermediate V

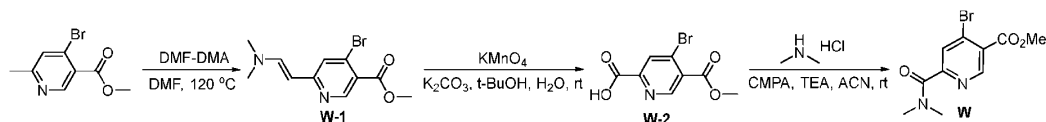
methyl 5-bromo-1-(2-(dimethylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridine-4-carboxylate



[0348] To a stirred solution of methyl 5-bromo-2-oxo-1,2-dihydropyridine-4-carboxylate (2 g, 8.62 mmol) in DMF (20 mL) was added Cs_2CO_3 (8.43 g, 25.9 mmol) and 2-bromo-*N,N*-dimethylacetamide (2.15 g, 13.0 mmol) under N_2 atmosphere. After stirring for 2 hrs at room temperature, the reaction mixture was treated with water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated under vacuum to afford Intermediate **V** (800 mg). LCMS (ESI, m/z): $[\text{M}+\text{H}]^+ = 316.9$.

Intermediate W

methyl 4-bromo-6-(dimethylcarbamoyl)nicotinate



Step 1: methyl (*E*)-4-bromo-6-(2-(dimethylamino)vinyl)nicotinate (**W-1**)

[0349] A solution of methyl 4-bromo-6-methylnicotinate (2.3 g, 10 mmol) and *N,N*-Dimethylformamide dimethyl acetal (3.57 g, 30 mmol) in DMF (10 mL) was stirred at 120 °C for 18 hrs under N_2 atmosphere. LCMS showed the reaction was complete. After cooling to room temperature, the reaction mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (10:1), to afford methyl (*E*)-4-bromo-6-(2-(dimethylamino)vinyl)nicotinate (**W-1**, 1.1 g). LCMS (ESI, m/z): $[\text{M}+\text{H}]^+ = 284.9$.

Step 2: 4-bromo-5-(methoxycarbonyl)picolinic acid (**W-2**)

[0350] To a solution of methyl (*E*)-4-bromo-6-(2-(dimethylamino)vinyl)nicotinate (**W-1**, 1 g, 3.51 mmol) and K_2CO_3 (969 mg, 7.01 mmol) in *t*-BuOH (17 mL) and water (17 mL) was

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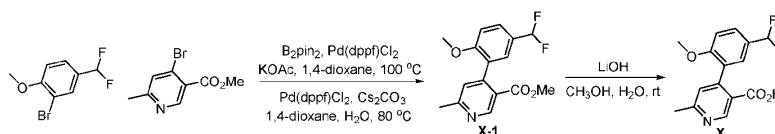
added KMnO_4 (1.66 g, 10.5 mmol) portion-wise. After stirring for 1 hr at room temperature, the reaction mixture was filtered. The filtrate was purified by reverse-phase column chromatography (0.1% FA) to afford 4-bromo-5-(methoxycarbonyl)picolinic acid (**W-2**, 550 mg). LCMS (ESI, m/z): $[\text{M}+\text{H}]^+ = 260.0$.

Step 3: methyl 4-bromo-6-(dimethylcarbamoyl)nicotinate (**W**)

[0351] To a stirred solution of 4-bromo-5-(methoxycarbonyl)picolinic acid (**W-2**, 600 mg, 2.31 mmol) and dimethylamine hydrochloride (282 mg, 3.46 mmol) in MeCN (30 mL) was added CMPI (884 mg, 3.46 mmol) and TEA (934 mg, 1.29 mL, 9.23 mmol) under N_2 . After stirring at rt for 1 hr, the reaction mixture was treated with water and extracted with DCM. The combined organic layers were washed with saturated brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (10:1 to 1:1), to afford Intermediate **W** (135 mg). LCMS (ESI, m/z): $[\text{M}+\text{H}]^+ = 286.9$.

Intermediate X

4-(5-(difluoromethyl)-2-methoxyphenyl)-6-methylnicotinic acid



Step 1: methyl 4-(5-(difluoromethyl)-2-methoxyphenyl)-6-methylnicotinate (**X-1**)

[0352] A mixture of 2-bromo-4-(difluoromethyl)-1-methoxybenzene (2.68 g, 11.3 mmol), B_2pin_2 (4.32 g, 17.0 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (827 mg, 1.13 mmol) and KOAc (3.33 g, 33.9 mmol) in 1,4-dioxane (100 mL) was degassed and stirred at 100 °C for 3 hrs under N_2 atmosphere. After cooling to room temperature, methyl 4-bromo-6-methylnicotinate (2.17 g, 9.43 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (690 mg, 0.943 mmol), Cs_2CO_3 (6.16 g, 18.9 mmol) and water (25 mL) were added to the mixture. The resulting mixture was degassed and stirred at 80 °C for another 2 hrs under N_2 atmosphere. LCMS showed the reaction was complete. The reaction mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with saturated brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (10:1 to 2:1), to afford methyl 4-(5-(difluoromethyl)-2-methoxyphenyl)-6-methylnicotinate (**X-1**, 2 g). LCMS (ESI, m/z): $[\text{M}+\text{H}]^+ = 308.2$.

Step 2: 4-(5-(difluoromethyl)-2-methoxyphenyl)-6-methylnicotinic acid (**X**)

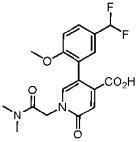
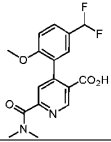
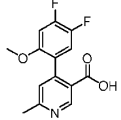
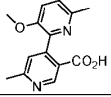
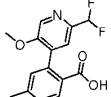
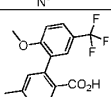
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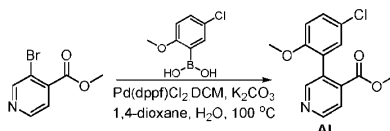
[0353] To a stirred solution of methyl 4-(5-(difluoromethyl)-2-methoxyphenyl)-6-methylnicotinate (1.8 g, 5.86 mmol) in MeOH (10 mL) and was added LiOH·H₂O (1.23 g, 29.3 mmol) in water (20 mL). After stirring at room temperature for 3 hrs, the reaction mixture was concentrated under vacuum to remove most MeOH and water. The residue was acidified to pH = 5-6 with aqueous HCl solution (1 N). The mixture was purified by reversed-phase column chromatography (0.1% FA) to afford Intermediate **X** (1.3 g). LCMS (ESI, m/z): [M+H]⁺ = 294.1.

[0354] The intermediates in the table below were synthesized using conditions analogous to that used to synthesize Intermediates **X**, by converting appropriate aromatic halide or triflate to the corresponding boronic reagents, Suzuki coupling and hydrolysis.

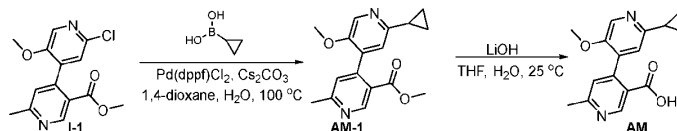
Intermediate Number	Structure	Name	LCMS (ESI, m/z): [M+H] ⁺
Y		4-(5-chloro-2-methoxyphenyl)-6-methylnicotinic acid	278.1
Z		3-(5-(difluoromethyl)-2-methoxyphenyl)isonicotinic acid	280.1
AA		2'-chloro-5'-(difluoromethoxy)-6-methyl-[4,4'-bipyridine]-3-carboxylic acid	315.1
AB		2'-(difluoromethyl)-5'-methoxy-1-methyl-6-oxo-1,6-dihydro-[3,4'-bipyridine]-4-carboxylic acid	311.0
AC		4-bromo-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoic acid	358.2
AD		2'-(difluoromethyl)-6-(1-(difluoromethyl)-1H-pyrazol-4-yl)-5'-methoxy-[4,4'-bipyridine]-3-carboxylic acid	397.2
AE		4-(5-(difluoromethyl)-4-fluoro-2-methoxyphenyl)-6-methylnicotinic acid	312.0

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AF		5-(5-(difluoromethyl)-2-methoxyphenyl)-1-(2-(dimethylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridine-4-carboxylic acid	381.3
AG		4-(5-(difluoromethyl)-2-methoxyphenyl)-6-(dimethylcarbamoyl)nicotinic acid	351.2
AH		4-(4,5-difluoro-2-methoxyphenyl)-6-methylnicotinic acid	280.1
AI		3-methoxy-6,6'-dimethyl-[2,4'-bipyridine]-3'-carboxylic acid	259.2
AJ		2'-(difluoromethyl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxylic acid	294.1
AK		4-(2-methoxy-5-(trifluoromethyl)phenyl)-6-methylnicotinic acid	312.2

Intermediate ALmethyl 3-(5-chloro-2-methoxyphenyl)isonicotinate

[0355] To a solution of (5-chloro-2-methoxyphenyl)boronic acid (3 g, 16.1 mmol) and methyl 3-bromoisonicotinate (3.47 g, 16.1 mmol) in 1,4-dioxane (50 mL) and water (15 mL) was added Pd(dppf)Cl₂.DCM (1.29 g, 1.58 mmol) and K₂CO₃ (5.55 g, 40.2 mmol) under N₂. The mixture was degassed and stirred at 100 °C for 4 hrs under N₂ atmosphere. LCMS showed the reaction was complete. The reaction mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (1:1), to afford Intermediate **AL** (2.5 g). LCMS (ESI, m/z): [M+H]⁺ = 278.3.

Intermediate AM**Step 1: methyl 2'-cyclopropyl-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxylate (AM-1)**

[0356] To a solution of methyl 2'-chloro-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxylate (**I-1**, 2.2 g, 7.52 mmol) in 1,4-dioxane (40 mL), water (10 mL) was added cyclopropylboronic acid (6.46 g, 75.2 mmol), Cs₂CO₃ (7.35 g, 22.6 mmol) and Pd(dppf)Cl₂ (1.10 g, 1.50 mmol) under N₂. The mixture was degassed and stirred at 90 °C for 6 hrs under N₂ atmosphere. After completion, the reaction mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluting with EtOAc, to afford methyl 2'-cyclopropyl-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxylate (**AM-1**, 2 g) as a brown oil. LCMS (ESI, m/z): [M+H]⁺ = 299.2.

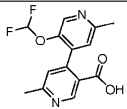
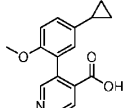
Step 2: 2'-cyclopropyl-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxylic acid (AM)

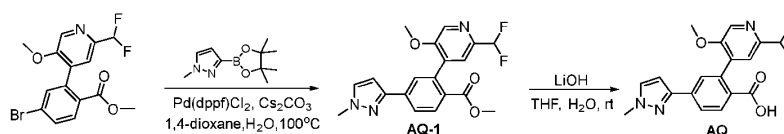
[0357] To a solution of methyl 2'-cyclopropyl-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxylate (**AM-1**, 2 g, 6.70 mmol) in THF (30 mL) and water (15 mL) was added LiOH.H₂O (1.41 g, 33.6 mmol). After stirring at room temperature for 16 hrs, the reaction mixture was concentrated under vacuum to remove most THF and water. The residue was acidified to pH = 5-6 with aqueous HCl solution (1 N). The mixture was purified by reversed-phase column chromatography (0.1% FA) to afford Intermediate **AL** (1.6 g). LCMS (ESI, m/z): [M+H]⁺ = 285.2.

[0358] The intermediates in the table below were synthesized using conditions analogous to that used to synthesize Intermediate **AL** by reacting the synthesized hetero-biaryl chloride with commercially available boronic acid derivatives, via Suzuki coupling, then hydrolysis.

Intermediate Number	Structure	Name	LCMS (ESI, m/z): [M+H] ⁺
AN		2'-cyclopropyl-5'-(difluoromethoxy)-6-methyl-[4,4'-bipyridine]-3-carboxylic acid	321.2

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AO		5'-(difluoromethoxy)-2',6-dimethyl-[4,4'-bipyridine]-3-carboxylic acid	295.2
AP		3-(5-cyclopropyl-2-methoxyphenyl)isonicotinic acid	270.1

Intermediate AQ2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(1-methyl-1H-pyrazol-3-yl)benzoic acidStep 1: methyl 2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(1-methyl-1H-pyrazol-3-yl)benzoate (AQ-1)

[0359] To a solution of methyl 4-bromo-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoate (precursor of Intermediate **AD**) (100 mg, 0.27 mmol) in 1,4-dioxane (3 mL) and water (1 mL) was added 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (84 mg, 0.40 mmol), Pd(dppf)Cl₂·CH₂Cl₂ (24 mg, 0.029 mmol) and Cs₂CO₃ (263 mg, 0.80 mmol) under N₂. The mixture was degassed and stirred at 100 °C for 3 hrs under N₂ atmosphere. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified with silica gel column chromatography, eluting with PE/EtOAc (5:1) to afford methyl 2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(1-methyl-1H-pyrazol-3-yl)benzoate (**AQ-1**, 80 mg). LCMS (ESI, m/z): [M+H]⁺ = 374.3.

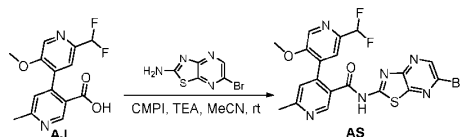
Step 2: 2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(1-methyl-1H-pyrazol-3-yl)benzoic acid (AQ)

[0360] To a solution of methyl 2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(1-methyl-1H-pyrazol-3-yl)benzoate (**AQ-1**, 80 mg, 0.21 mmol) in THF (2 mL) and H₂O (2 mL) was added LiOH·H₂O (13.5 mg, 0.32 mmol). After stirring at room temperature for 12 hrs, the reaction mixture was concentrated to remove most THF. The mixture was acidified with aqueous HCl solution (1 N) to pH = 6. The resulting precipitates were collected by filtration, washed by water, and dried under vacuum to afford Intermediate **AQ** (70 mg). LCMS (ESI, m/z): [M+H]⁺ = 360.2.

Intermediate AS

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N-(6-bromothiazolo[4,5-*b*]pyrazin-2-yl)-2'-(difluoromethyl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide



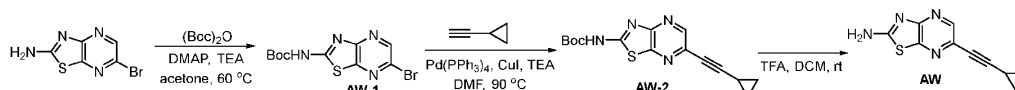
[0361] To a solution of Intermediate **AJ** (180 mg, 0.61 mmol) in MeCN (2.0 mL) was added 6-bromothiazolo[4,5-*b*]pyrazin-2-amine (141 mg, 0.61 mmol), Et₃N (257 mg, 2.54 mmol) and CMPI (258 mg, 1.01 mmol) under N₂. After stirring at room temperature for 4 hrs, the reaction mixture was concentrated to dryness under vacuum. The residue was purified by prep-HPLC (0.05% NH₄HCO₃) to afford Intermediate **AS** (150 mg). LCMS (ESI, *m/z*): [M+H]⁺ = 507.2.

[0362] The Intermediates in the table below were synthesized using conditions analogous to that used to synthesize Intermediates **AS** from the corresponding acids, via amide coupling reaction.

Intermediate Number	Structure	Name	LCMS (ESI, <i>m/z</i>) [M+H] ⁺
AT		<i>N</i> -(6-bromothiazolo[4,5- <i>b</i>]pyrazin-2-yl)-4-(5-(difluoromethyl)-2-methoxyphenyl)-6-methylnicotinamide	505.9
AU		<i>N</i> -(6-bromothiazolo[4,5- <i>b</i>]pyrazin-2-yl)-4-(4,5-difluoro-2-methoxyphenyl)-6-methylnicotinamide	492.0
AV		<i>N</i> -(6-bromothiazolo[4,5- <i>b</i>]pyrazin-2-yl)-3-methoxy-6,6'-dimethyl-[2,4'-bipyridine]-3'-carboxamide	471.1

Intermediate AW

6-(cyclopropylethynyl)thiazolo[4,5-*b*]pyrazin-2-amine



Step 1: *tert*-butyl (6-bromothiazolo[4,5-*b*]pyrazin-2-yl)carbamate (**AW-1**)

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[0363] A mixture of 6-bromothiazolo[4,5-b]pyrazin-2-amine (5 g, 21.6 mmol), (Boc)₂O (7.09 g, 32.5 mmol), DMAP (794 mg, 6.5 mmol) and TEA (4.38 g, 43.3 mmol) in acetone (150 mL) was stirred at 60 °C for 4 hrs. After completion, the reaction mixture was treated with water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (8:1 to 1:1), to afford *tert*-butyl (6-bromothiazolo[4,5-b]pyrazin-2-yl)carbamate (**AW-1**, 4 g). LCMS (ESI, m/z): [M+H]⁺ = 331.0.

Step 2: *tert*-butyl (6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)carbamate (**AW-2**)

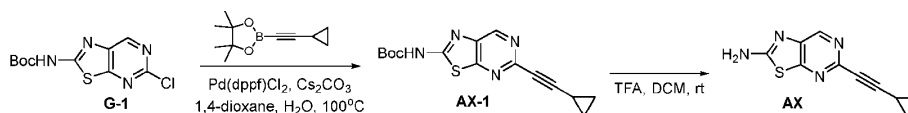
[0364] To a stirred mixture of *tert*-butyl (6-bromothiazolo[4,5-b]pyrazin-2-yl)carbamate (**AW-1**, 4 g, 12.1 mmol), ethynylcyclopropane (2.40 g, 36.3 mmol) and TEA (3.67 g, 36.3 mmol) in DMF (40 mL) was added CuI (230 mg, 1.21 mmol) and Pd(PPh₃)₄ (1.40 g, 1.21 mmol) under N₂. The mixture was degassed and stirred at 90 °C for 2 hrs under N₂ atmosphere. The mixture was treated with water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (3:1), to afford *tert*-butyl (6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)carbamate (**AW-2**, 3 g). LCMS (ESI, m/z): [M+H]⁺ = 317.2.

Step 3: 6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-amine (**AW**)

[0365] To a stirred solution of *tert*-butyl (6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)carbamate (**AW-2**, 3 g, 9.48 mmol) in DCM (25 ml) was added TFA (12.5 ml). After stirring at room temperature for 2 hrs, the reaction mixture was concentrated to dryness under vacuum. The residue was purified by trituration with the mixture of aqueous ammonia and methanol to afford Intermediate **AV** (1.8 g). LCMS (ESI, m/z): [M+H]⁺ = 217.2.

Intermediate AX

5-(cyclopropylethynyl)thiazolo[5,4-d]pyrimidin-2-amine



Step 1: *tert*-butyl (5-(cyclopropylethynyl)thiazolo[5,4-d]pyrimidin-2-yl)carbamate (**AX-1**)

[0366] To a solution of *tert*-butyl (5-chlorothiazolo[5,4-d]pyrimidin-2-yl)carbamate (**G-1**, 200 mg, 0.70 mmol) in 1,4-dioxane (3 mL) was added 2-(cyclopropylethynyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (201 mg, 1.05 mmol), Pd(dppf)Cl₂ (51 mg, 0.07 mmol) and

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Cs_2CO_3 (683 mg, 2.09 mmol) under N_2 . The mixture was degassed and stirred at 100 °C for 12 hrs under N_2 atmosphere. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (0.05% NH_4HCO_3) to afford *tert*-butyl 5-(cyclopropylethynyl)thiazolo[5,4-d]pyrimidin-2-yl)carbamate (**AX-1**, 50 mg).

LCMS (ESI, m/z): $[\text{M}+\text{H}]^+ = 317.2$.

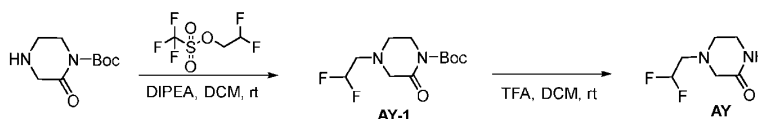
Step 2: 5-(cyclopropylethynyl)thiazolo[5,4-d]pyrimidin-2-amine (**AX**)

[0367] To a solution of *tert*-butyl 5-(cyclopropylethynyl)thiazolo[5,4-d]pyrimidin-2-yl)carbamate (**AX-1**, 50 mg, 0.174 mmol) in THF (2 mL) was added TFA (1 mL). After stirring at room temperature for 2 hrs, the reaction mixture was concentrated to dryness under vacuum to afford Intermediate **AX** which was used for the next step without purification.

LCMS (ESI, m/z): $[\text{M}+\text{H}]^+ = 217.1$.

Intermediate **AY**

4-(2,2-Difluoroethyl)piperazin-2-one



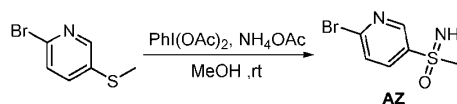
Step 1: *tert*-butyl 4-(2,2-difluoroethyl)-2-oxopiperazine-1-carboxylate (**AY-1**)

[0368] 2,2-Difluoroethyl trifluoromethanesulfonate (962 mg, 4.50 mmol) and DIPEA (581 mg, 4.50 mmol) were added to a solution of *tert*-butyl 2-oxopiperazine-1-carboxylate (900 mg, 4.50 mmol) in DCM (5 mL) under N_2 . After stirring for 2 hrs at rt, the mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography, eluting with EtOAc/PE (6:4), to afford *tert*-butyl 4-(2,2-difluoroethyl)-2-oxopiperazine-1-carboxylate (**AY-1**, 560.0 mg). LCMS (ESI, m/z): $[\text{M}+\text{H}]^+ = 265.2$.

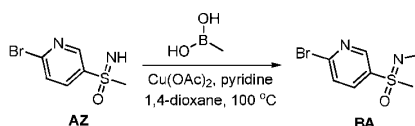
Step 2: 4-(2,2-difluoroethyl)piperazin-2-one (**AY**)

[0369] TFA (6 mL) was added to a solution of *tert*-butyl 4-(2,2-difluoroethyl)-2-oxo-piperazine-1-carboxylate (**AY-1**, 560 mg, 2.12 mmol) in DCM (2 mL) at rt. After stirring for 2 hrs, the mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated under vacuum. The residue was purified by prep-HPLC (0.1% FA) to afford Intermediate **AY** (287 mg). LCMS (ESI, m/z): $[\text{M}+\text{H}]^+ = 165.1$.

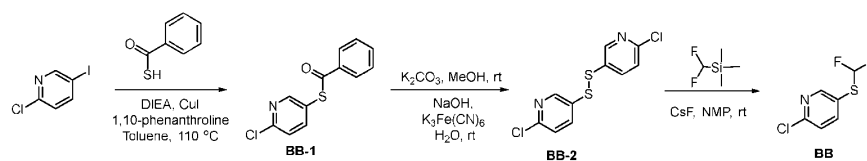
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Intermediate (AZ)(6-Bromopyridin-3-yl)(imino)(methyl)- λ^6 -sulfanone

[0370] Ammonium acetate (378 mg, 4.90 mmol) and (diacetoxyiodo)benzene (1.58 g, 4.91 mmol) were added to a solution of 2-bromo-5-(methylthio)pyridine (500 mg, 2.45 mmol) in MeOH (2 mL) at rt. After stirring for 2 hrs, the mixture was filtered and concentrated in vacuo. The residue was purified by reverse phase column chromatography (0.05% FA) to afford Intermediate **AZ** (300 mg). LCMS (ESI, m/z): $[M+H]^+ = 235.0$.

Intermediate BA(6-Bromopyridin-3-yl)(methyl)(methylimino)- λ^6 -sulfanone

[0371] Cupric acetate monohydrate (17.0 mg, 0.085 mmol), pyridine (33.6 mg, 0.425 mmol) and methylboronic acid (127 mg, 2.13 mmol) were added to a solution of (6-bromopyridin-3-yl)(imino)(methyl)- λ^6 -sulfanone (**AZ**, 100 mg, 0.425 mmol) in 1,4-dioxane (2 mL) at rt under O₂ atmosphere. After stirring for 1 hr at 100 °C, the mixture was filtered and concentrated in vacuo. The residue was purified by reverse phase column chromatography (0.05% FA) to afford Intermediate **BA** (30 mg). LCMS (ESI, m/z): $[M+H]^+ = 248.9$.

Intermediate BB2-Chloro-5-((difluoromethyl)thio)pyridineStep 1: S-(6-chloropyridin-3-yl) benzothioate (**BB-1**)

[0372] Benzothioic S-acid (16.0 g, 0.116 mol), DIPEA (28.6 g, 0.221 mol), 1,10-phenanthroline (3.78 g, 20.9 mmol) and CuI (20.0 g, 10.5 mmol) were added to a solution of 2-chloro-5-iodo-pyridine (20.0 g, 0.084 mol) in toluene (150 mL) under N₂. The resulting

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mixture was degassed, stirred at 110 °C for 4 hrs, treated with water and extracted with EtOAc. The combined organic layers were dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography, eluting with EtOAc/PE (1:6), to afford *S*-(6-chloropyridin-3-yl) benzothioate (**BB-1**, 19 g). LCMS (ESI, *m/z*): [M+H]⁺ = 250.1.

Step 2: 1,2-bis(6-chloropyridin-3-yl)disulfane (**BB-2**)

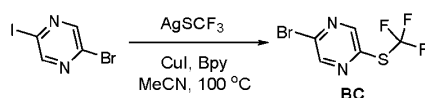
[0373] K₂CO₃ (21.0 g, 0.152 mol) was added to a solution of *S*-(6-chloropyridin-3-yl) benzothioate (**BB-1**, 19.0 g, 0.076 mol) in MeOH (300 mL) at rt. After stirring for 2 hrs, the mixture was concentrated under vacuum. The residue was treated with 1 N aqueous NaOH (70 mL) and K₃Fe(CN)₆ (75.2 g, 0.228 mol). After stirring for 2 hrs, the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography, eluting with EtOAc/PE (1:2), to afford 1,2-bis(6-chloropyridin-3-yl)disulfane (**BB-2**, 8.0 g). LCMS (ESI, *m/z*): [M+H]⁺ = 290.2

Step 3: 2-chloro-5-((difluoromethyl)thio)pyridine (**BB**)

[0374] (Difluoromethyl)trimethylsilane (1.37 g, 11.1 mmol) and CsF (3.36 g, 22.1 mmol) were added to a solution of 1,2-bis(6-chloropyridin-3-yl)disulfane (**BB-2**, 800 mg, 2.77 mmol) in NMP (5 mL) under N₂. After stirring for 2 hrs, the mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography, eluting with EtOAc/PE (1:1), to afford Intermediate **BB** (100 mg). LCMS (ESI, *m/z*): [M+H]⁺ = 196.1.

Intermediate BC

2-Bromo-5-((trifluoromethyl)thio)pyrazine



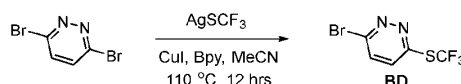
[0375] A mixture of 2-bromo-5-iodopyrazine (500 mg, 1.76 mmol), AgSCF₃ (440 mg, 2.11 mmol), CuI (335 mg, 1.76 mmol) and 2,2'-bipyridine (276 mg, 1.76 mmol) in MeCN (10 mL) was degassed and backfilled with N₂. After stirring at 100 °C for 2 hrs, the mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by flash

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column chromatography on silica gel, eluting EtOAc/PE (1:30), to afford Intermediate **BC** (300 mg). ^1H NMR (400 MHz, CDCl_3) δ ppm 8.72 (s, 1H), 8.56 (s, 1H).

Intermediate BD

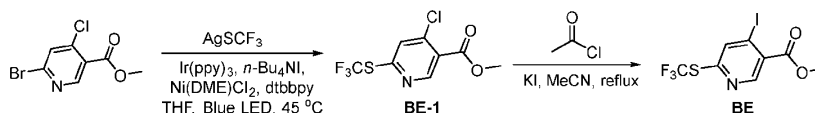
3-Bromo-6-((trifluoromethyl)thio)pyridazine



[0376] Following conditions analogous to synthesis of **BC**, Intermediate **BD** was synthesized from 3,6-dibromopyridazine. ^1H NMR (400 MHz, CDCl_3) δ ppm 7.70 (d, $J = 9.2$ Hz, 1H), 7.57 (d, $J = 9.2$ Hz, 1H).

Intermediate BE

Methyl 4-iodo-6-((trifluoromethyl)thio)nicotinate



Step 1: methyl 4-chloro-6-((trifluoromethyl)thio)nicotinate (**BE-1**)

[0377] A mixture of methyl 6-bromo-4-chloronicotinate (500 mg, 2.00 mmol), AgSCF_3 (630 mg, 3.00 mmol), Ir(ppy)_3 (26.2 mg, 0.04 mmol), $n\text{-Bu}_4\text{NI}$ (1.11 g, 3.00 mmol), Ni(DME)Cl_2 (17.6 mg, 0.08 mmol) and dtbbpy (21.5 mg, 0.08 mmol) in THF (10 mL) was degassed and backfilled with N_2 . After stirring at $45\text{ }^\circ\text{C}$ under irradiation (18 W blue LEDs) for 3 hrs, the mixture was treated with EtOAc, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc/PE (1:4), to afford methyl 4-chloro-6-((trifluoromethyl)thio)nicotinate (**BE-1**, 400 mg). LCMS (ESI, m/z): $[\text{M}+\text{H}]^+ = 272.0$.

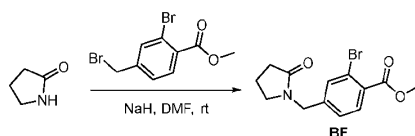
Step 2: methyl 4-iodo-6-((trifluoromethyl)thio)nicotinate (**BE**)

[0378] Acetyl chloride (86.4 mg, 1.10 mmol) was added to a mixture of methyl 4-chloro-6-((trifluoromethyl)thio)nicotinate (**BE-1**, 200 mg, 0.736 mmol) and KI (1.22 g, 7.36 mmol) in MeCN (5.0 mL) at $0\text{ }^\circ\text{C}$ under N_2 . After stirring at reflux for 16 hrs, the mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to afford Intermediate **BE** (180 mg). LCMS (ESI, m/z): $[\text{M}+\text{H}]^+ = 364.0$.

Intermediate BF

Methyl 2-bromo-4-((2-oxopyrrolidin-1-yl)methyl)benzoate

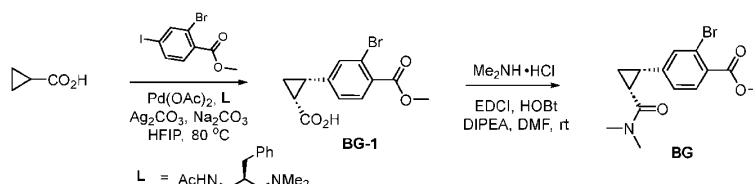
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[0379] NaH (60% dispersion in mineral oil, 38.2 mg, 0.954 mmol) and methyl 2-bromo-4-(bromomethyl)benzoate (146 mg, 0.477 mmol) were sequentially added to a solution of pyrrolidin-2-one (40.6 mg, 0.477 mmol) in DMF (4 mL) under N₂. After stirring for 1 hr at rt, the mixture was quenched with water and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography, eluting with EtOAc/PE (3:7), to afford Intermediate **BF** (98.0 mg). LCMS (ESI, m/z): [M+H]⁺ = 311.8.

Intermediate BG

Methyl 2-bromo-4-((1*S*,2*R*)-2-(dimethylcarbamoyl)cyclopropyl)benzoate



Step 1: (1*R*,2*S*)-2-(3-bromo-4-(methoxycarbonyl)phenyl)cyclopropane-1-carboxylic acid (**BG-1**)

[0380] A mixture of cyclopropanecarboxylic acid (274 mg, 3.18 mmol), methyl 2-bromo-4-iodobenzoate (2.17 g, 6.37 mmol), Pd(OAc)₂ (72.0 mg, 0.318 mmol), (*R*)-*N*-(2-benzyl-3-(dimethylamino)propyl)acetamide (149 mg, 0.637 mmol), Ag₂CO₃ (1.32 mg, 4.77 mmol) and Na₂CO₃ (506 mg, 4.77 mmol) in 1,1,1,3,3,3-hexafluoroisopropanol (5 mL) was stirred at 80 °C for 5 hrs while open to air. The resulting mixture was filtered to remove solid residue. The filtrate was treated with water, acidified to pH 5 with 1 N HCl solution and extracted with EtOAc. The combined organic layers were dried (Na₂SO₄), filtered, and concentrated in vacuo to afford (1*R*,2*S*)-2-(3-bromo-4-(methoxycarbonyl)phenyl)cyclopropane-1-carboxylic acid (**BG-1**, 200 mg). LCMS (ESI, m/z): [M-H]⁻ = 297.1.

Step 2: methyl 2-bromo-4-((1*S*,2*R*)-2-(dimethylcarbamoyl)cyclopropyl)benzoate (**BG**)

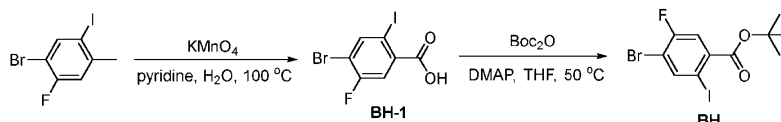
[0381] EDCI (385 mg, 2.01 mmol) and HOBt (272 mg, 2.01 mmol) were added to a stirred solution of (1*R*,2*S*)-2-(3-bromo-4-(methoxycarbonyl)phenyl)cyclopropane-1-carboxylic acid (**BG-1**, 200 mg, 0.669 mmol), DIPEA (1.3 g, 10 mmol) and dimethylamine hydrochloride (164 mg, 2.01 mmol) in DMF (5 mL) under N₂. After stirring at rt for 3 hrs, the mixture was treated with water and extracted with EtOAc. The organic layers were

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washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel, eluting with MeOH/DCM (1:30), to afford Intermediate **BG** (150 mg). LCMS (ESI, m/z): $[\text{M}+\text{H}]^+ = 326.1$.

Intermediate BH

tert-Butyl 4-bromo-5-fluoro-2-iodobenzoate



Step 1: 4-bromo-5-fluoro-2-iodobenzoic acid (**BH-1**)

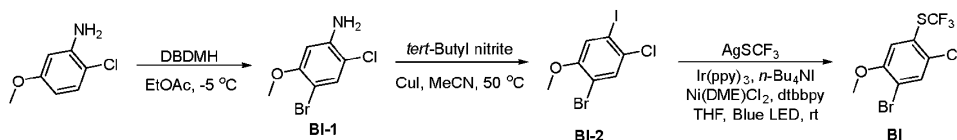
[0382] KMnO_4 (10.0 g, 63.3 mmol) was added to a solution of 1-bromo-2-fluoro-5-iodo-4-methylbenzene (2.0 g, 6.39 mmol) in pyridine (5 mL) and water (24 mL). After stirring at 100 °C for 16 hrs, the mixture was filtered, and the filter cake rinsed with EtOAc and water. The filtrate was acidified to pH 3 with 1 N HCl and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo to afford 4-bromo-5-fluoro-2-iodobenzoic acid (**BH-1**, 1.0 g). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 13.66 (s, 1H), 8.31 (d, $J = 6.8$ Hz, 1H), 7.70 (d, $J = 9.2$ Hz, 1H).

Step 2: *tert*-butyl 4-bromo-5-fluoro-2-iodobenzoate (**BH**)

[0383] DMAP (283 mg, 2.32 mmol) and Boc_2O (5.06 g, 23.2 mmol) were added to a solution of 4-bromo-5-fluoro-2-iodobenzoic acid (**BH-1**, 4.0 g, 11.6 mmol) in THF (50 mL). After stirring at 50 °C for 16 hrs, the mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography, eluting with EtOAc/PE (1:20), to afford Intermediate **BH** (3.4 g). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.30 (d, $J = 6.8$ Hz, 1H), 7.65 (d, $J = 9.2$ Hz, 1H), 1.56 (s, 9H).

Intermediate BI

(4-Bromo-2-chloro-5-methoxyphenyl) (trifluoromethyl)sulfane



Step 1: 4-bromo-2-chloro-5-methoxyaniline (**BI-1**)

[0384] 1,3-Dibromo-5,5-dimethylhydantoin (907 mg, 3.17 mmol) was added to a stirred solution of 2-chloro-5-methoxyaniline (1.0 g, 6.35 mmol) in EtOAc (15 mL) at -5 °C.

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After stirring for 1 hr, the mixture was treated with water and extracted with EtOAc. The combined organic layers were dried (Na₂SO₄), filtered, and concentrated in vacuo to afford 4-bromo-2-chloro-5-methoxyaniline (**BI-1**, 1.4 g). LCMS (ESI, m/z): [M+H]⁺ = 236.0.

Step 2: 1-bromo-5-chloro-4-iodo-2-methoxybenzene (**BI-2**)

[0385] 4-Bromo-2-chloro-5-methoxy-aniline (**BI-1**, 1.30 g, 5.50 mmol) was added to a stirred mixture of CuI (1.26 g, 6.62 mmol) and *tert*-butyl nitrite (850 mg, 8.24 mmol) in MeCN (26 mL) at 0 °C under N₂. After stirring at 50 °C for 15 hrs, the mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc/PE (0 to 1/20), to afford 1-bromo-5-chloro-4-iodo-2-methoxybenzene (**BI-2**, 800 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.80 (s, 1H), 7.56 (s, 1H), 3.86 (s, 3H).

Step 3: (4-bromo-2-chloro-5-methoxyphenyl) (trifluoromethyl)sulfane (**BI**)

[0386] Following conditions analogous to synthesis of **BE-1**, Intermediate **BI-2** was converted to **BI**. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.05 (s, 1H), 7.54 (s, 1H), 3.92 (s, 3H).

Intermediate BJ

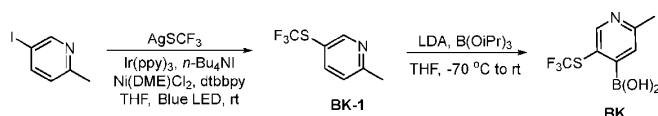
4-Bromo-2-(difluoromethyl)-5-methoxypyridine



[0387] Following conditions analogous to synthesis of **Q**, 4-bromo-5-methoxypicolinaldehyde was converted to **BJ**. LCMS (ESI, m/z): [M+H]⁺ = 237.9.

Intermediate BK

(2-Methyl-5-((trifluoromethyl)thio)pyridin-4-yl)boronic acid



Step 1: 2-methyl-5-((trifluoromethyl)thio)pyridine (**BK-1**)

[0388] Following conditions analogous to synthesis of **BE-1**, 5-iodo-2-methylpyridine was converted to Intermediate **BK-1**. LCMS (ESI, m/z): [M+H]⁺ = 193.9.

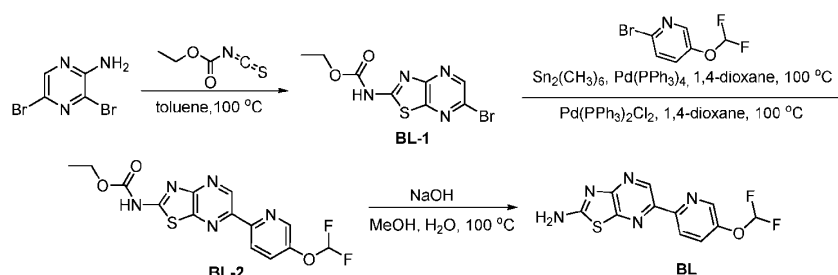
Step 2: (2-methyl-5-((trifluoromethyl)thio)pyridin-4-yl)boronic acid (**BK**)

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[0389] A 2 M THF solution of LDA (3.73 mL, 7.46 mmol) was added dropwise to a solution of 2-methyl-5-((trifluoromethyl)thio)pyridine (**BK-1**, 720 mg, 3.73 mmol) in THF (18 mL) at -70 °C under N₂. After stirring at -70 °C for 1 hr, triisopropyl borate (1.40 g, 7.45 mmol) was added. The mixture was allowed to warm to rt, stirred for 16 hrs, quenched with aqueous NH₄Cl, and concentrated in vacuo. The residue was purified by reverse phase column chromatography (0.1% FA) to afford Intermediate **BK** (85 mg). LCMS (ESI, m/z): [M+H]⁺ = 237.9.

Intermediate BL

6-(5-(Difluoromethoxy)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-amine



Step 1: ethyl (6-bromothiazolo[4,5-b]pyrazin-2-yl) carbamate (**BL-1**)

[0390] A mixture of 3,5-dibromopyrazin-2-amine (50 g, 198 mmol) and O-ethyl carbonisothio cyanatide (51.8 g, 395 mmol) in toluene (500 mL) was stirred under N₂ at 100 °C for 48 hrs. After cooling to rt, the precipitates were collected by filtration and washed with EtOAc. The solid product was further purified by trituration with MeOH/H₂O (2:1) to afford ethyl N-(6-bromothiazolo[4,5-b]pyrazin-2-yl) carbamate (**BL-1**, 49 g). LCMS (ESI, m/z): [M-H]⁻ = 300.9.

Step 2: ethyl 6-(5-(difluoromethoxy)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl carbamate (**BL-2**)

[0391] Following conditions analogous to synthesis of Example 34, Intermediate **BL-1** was converted to the corresponding tin reagent and coupled with 2-bromo-5-(difluoromethoxy)pyridine to provide Intermediate **BL-2**. LCMS (ESI, m/z): [M+H]⁺ = 368.2.

Step 3: 6-(5-(difluoromethoxy)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-amine (**BL**)

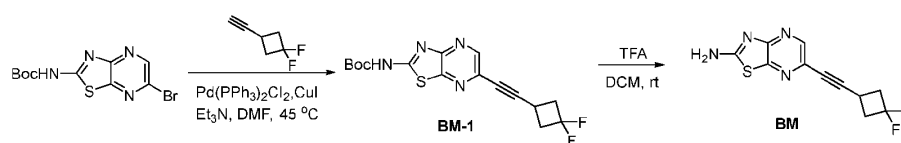
[0392] A solution of NaOH (1.45 g, 36.3 mmol) in water (20 mL) was added to a mixture of ethyl 6-(5-(difluoromethoxy)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl carbamate (**BL-2**, 2.20 g, 5.99 mmol) in MeOH (20 mL) under N₂. After stirring at 100 °C for 5 hrs, the mixture was concentrated in vacuo to remove most MeOH. The aqueous residue was acidified to pH 4

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with 1 N HCl until precipitates were formed. The precipitates were collected by filtration and washed with DCM to afford Intermediate **BL** (1.2 g). LCMS (ESI, m/z): $[M+H]^+ = 295.9$.

Intermediate **BM**

6-((3,3-Difluorocyclobutyl)ethynyl)thiazolo[4,5-b]pyrazin-2-amine



Step 1: *tert*-butyl (6-((3,3-difluorocyclobutyl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)carbamate (**BM-1**)

[0393] CuI (115 mg, 0.604 mmol), 3-ethynyl-1,1-difluorocyclobutane (701 mg, 6.034 mmol) and bis(triphenylphosphine)palladium(II) chloride (212 mg, 0.030 mmol) were added to a solution of *tert*-butyl (6-bromothiazolo[4,5-b]pyrazin-2-yl)carbamate (1 g, 3.02 mmol) in Et₃N (2.5 mL) and DMF (25 mL) under N₂. The mixture was degassed and backfilled with N₂. After stirring at 45 °C for 2 hrs, the mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by reverse phase column chromatography (0.05% FA) to afford *tert*-butyl (6-((3,3-difluorocyclobutyl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)carbamate (**BM-1**, 750 mg). LCMS (ESI, m/z): $[M+H]^+ = 367.2$.

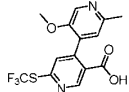
Step 2: 6-((3,3-difluorocyclobutyl)ethynyl)thiazolo[4,5-b]pyrazin-2-amine (**BM**)

[0394] TFA (6 mL) was added to a solution of *tert*-butyl (6-((3,3-difluorocyclobutyl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)carbamate (**BM-1**, 750 mg, 2.05 mmol) in DCM (3 mL) at rt. After stirring for 2 hrs, the mixture was concentrated in vacuo. The residue was purified by reverse phase column chromatography (0.05% FA) to afford Intermediate **BM** (400 mg). LCMS (ESI, m/z): $[M+H]^+ = 267.1$.

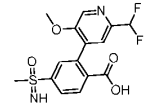
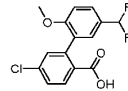
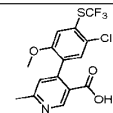
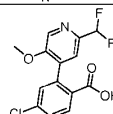
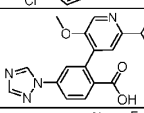
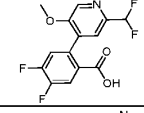
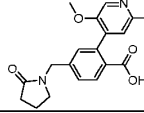
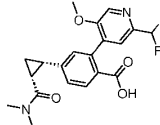
[0395] Following conditions analogous to synthesis of **I**, Intermediates **BN-BP** in the table below were synthesized in two steps from **BK**, **BE** or commercially available reagents.

Intermediate Number	Structure	Name	LCMS (ESI, m/z): $[M+H]^+$
BN		2',6-dimethyl-5'-((trifluoromethyl)thio)-[4,4'-bipyridine]-3-carboxylic acid	328.9
BO		2-(2-chloro-5-methoxypyridin-4-yl)-4-cyanobenzoic acid	289.0

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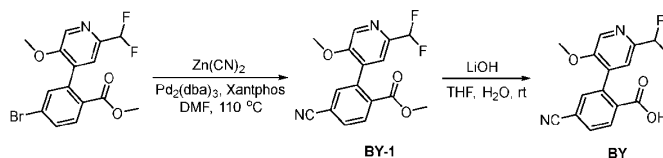
BP		5'-methoxy-2'-methyl-6-((trifluoromethyl)thio)-[4,4'-bipyridine]-3-carboxylic acid	345.0
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[0396] Following conditions analogous to synthesis of **X**, Intermediates **BQ-BX** in the table below were synthesized in two steps from **P**, **Q**, **BF**, **BG**, **BI** or commercially available reagents.

Intermediate Number	Structure	Name	LCMS (ESI, m/z): [M+H] ⁺
BQ		2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(S-methylsulfonimidoyl)benzoic acid	357.2
BR		5-chloro-5'-(difluoromethyl)-2'-methoxy-[1,1'-biphenyl]-2-carboxylic acid	313.2
BS		4-(5-chloro-2-methoxy-4-((trifluoromethyl)thio)phenyl)-6-methylnicotinic acid	378.1
BT		4-chloro-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoic acid	314.6
BU		2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(1H-1,2,4-triazol-1-yl)benzoic acid	347.2
BV		2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4,5-difluorobenzoic acid	316.1
BW		2-(5-methoxy-2-methylpyridin-4-yl)-4-((2-oxopyrrolidin-1-yl)methyl)benzoic acid	341.0
BX		2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-((1S,2R)-2-(dimethylcarbamoyl)cyclopropyl)benzoic acid	391.2

Intermediate BY

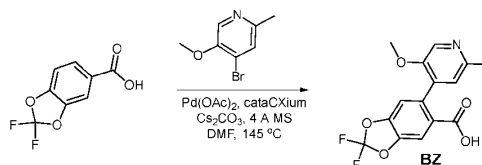
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4-Cyano-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoic acidStep 1: methyl 4-cyano-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoate (BY-1)

[0397] A mixture of methyl 4-bromo-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoate (precursor of **AC**, 400 mg, 1.07 mmol), $\text{Zn}(\text{CN})_2$ (189 g, 1.61 mmol), $\text{Pd}_2(\text{dba})_3$ (196 mg, 0.214 mmol) and Xantphos (311 mg, 0.537 mmol) in DMF (30mL) was degassed and backfilled with N_2 . After stirring at 110 °C for 2 hrs, the mixture was treated with water and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc/PE (1:4), to afford methyl 4-cyano-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoate (**BY-1**, 350 mg). LCMS (ESI, m/z): $[\text{M}+\text{H}]^+ = 319.0$.

Step 2: 4-cyano-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoic acid (BY)

[0398] $\text{LiOH} \cdot \text{H}_2\text{O}$ (224 mg, 5.34 mmol) was added to a stirred solution of methyl 4-cyano-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoate (**BY-1**, 340 mg, 1.07 mmol) in THF (5 mL) and H_2O (5 mL). After stirring for 12 hrs, the mixture was treated with water and washed with EtOAc. The aqueous phase was acidified to pH 5-6 with 1 N HCl and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo to afford Intermediate **BY** (310 mg). LCMS (ESI, m/z): $[\text{M}+\text{H}]^+ = 305.2$.

Intermediate BZ2,2-Difluoro-6-(5-methoxy-2-methylpyridin-4-yl)benzo[d][1,3]dioxole-5-carboxylic acid

[0399] A mixture of 2,2-difluorobenzo[d][1,3]dioxole-5-carboxylic acid (303 mg, 1.5 mmol), 4-bromo-5-methoxy-2-methylpyridine (202 mg, 1.0 mmol), 4 Å MS (450 mg), $\text{Pd}(\text{OAc})_2$ (34.0 mg, 0.15 mmol), Cs_2CO_3 (1.01 g, 3.0 mmol) and cataCXium (108 mg, 0.30 mmol) in DMF (5 mL) was degassed and backfilled with N_2 . After stirring at 145 °C for 24

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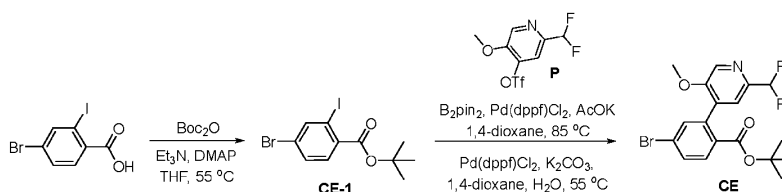
hrs, the mixture was filtered to remove the solid residue. The filtrate was acidified to pH 5-6 with 1 N HCl and concentrated in vacuo. The residue was purified by reverse phase column chromatography (0.1% FA) to afford Intermediate **BZ** (100 mg). LCMS (ESI, m/z): [M+H]⁺ = 324.2.

[0400] Following conditions analogous to synthesis of **BZ**, Intermediates **CA-CD** in the table below were synthesized from **Q**, **BJ** or commercially available reagents.

Intermediate Number	Structure	Name	LCMS (ESI, m/z): [M+H] ⁺
CA		5-cyano-5'-(difluoromethyl)-2'-methoxy-[1,1'-biphenyl]-2-carboxylic acid	[M-H] ⁻ = 302.0
CB		4-cyano-2-(5-methoxy-2-methylpyridin-4-yl)benzoic acid	[M-H] ⁻ = 267.1
CC		5,5'-bis(difluoromethyl)-2'-methoxy-[1,1'-biphenyl]-2-carboxylic acid	[M-H] ⁻ = 327.0
CD		4-chloro-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-5-fluorobenzoic acid	331.9

Intermediate CE

tert-Butyl 4-bromo-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoate



Step 1: *tert*-butyl 4-bromo-2-iodobenzoate (**CE-1**)

[0401] DMAP (1.49 g, 12.2 mmol) and di-*tert*-butyl dicarbonate (26.7 g, 122 mmol) were added to a solution of 4-bromo-2-iodobenzoic acid (20 g, 61.2 mmol) in THF (300 mL) under N₂. After stirring at 55 °C for 18 hrs, the mixture was treated with water, extracted with EtOAc, filtered, and concentrated in vacuo to afford *tert*-butyl 4-bromo-2-iodobenzoate (**CE-1**, 20 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.16 (*J* = 2.4 Hz, 1H), 7.67 (dd, *J* = 8.0 Hz, 2.4 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 1.54 (s, 9H).

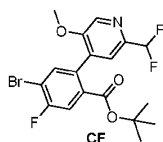
Step 2: *tert*-butyl 4-bromo-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoate (**CE**)

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[0402] Bis(pinacolato)diboron (9.09 g, 35.8 mmol), KOAc (9.58 g, 97.7 mmol) and Pd(dppf)Cl₂ (2.38 g, 3.26 mmol) were added to a solution of 2-(difluoromethyl)-5-methoxypyridin-4-yl trifluoromethanesulfonate (**P**, 10 g, 32.6 mmol) in 1,4-dioxane (50 mL) under N₂. The mixture was degassed and backfilled with N₂. After stirring at 85 °C for 2 hrs, the mixture was cooled to rt. *tert*-Butyl 4-bromo-2-iodobenzoate (**CE-1**, 9 g, 23.5 mmol), Pd(dppf)Cl₂ (1.35 g, 1.84 mmol), K₂CO₃ (9.74 g, 70.5 mmol), water (10 mL) and 1,4-dioxane (20 mL) were added. The resulting mixture was degassed and backfilled with N₂. After stirring at 55 °C for 16 hrs, the mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography, eluting with EtOAc/PE (3:7), to afford Intermediate **CE** (7.8 g). LCMS (ESI, m/z): [M+H]⁺ = 414.2

Intermediate CF

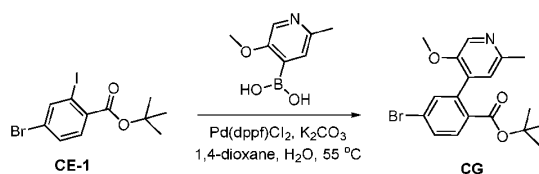
tert-Butyl 4-bromo-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-5-fluorobenzoate



[0403] Following conditions analogous to synthesis of **CE**, Intermediate **CF** was synthesized from the corresponding commercially available acid. LCMS (ESI, m/z): [M+H]⁺ = 432.2.

Intermediate CG

tert-Butyl 4-bromo-2-(5-methoxy-2-methylpyridin-4-yl)benzoate



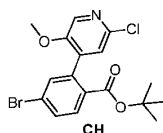
[0404] *tert*-Butyl 4-bromo-2-iodobenzoate (**CE-1**, 11.5 g, 29.9 mmol), K₂CO₃ (12.4 g, 89.8 mmol) and Pd(dppf)Cl₂ (2.19 g, 3.00 mmol) were added to a stirred solution of (5-methoxy-2-methyl-4-pyridyl)boronic acid (5 g, 29.9 mmol) in 1,4-dioxane (40 mL) and water (10 mL) under N₂. The mixture was degassed and backfilled with N₂. After stirring at 55 °C for 18 hrs, the mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated in vacuo.

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The residue was purified by silica gel column chromatography, eluting with EtOAc/PE (3:7), to afford Intermediate **CG** (5.5 g). LCMS (ESI, m/z): $[M+H]^+ = 378.2$.

Intermediate CH

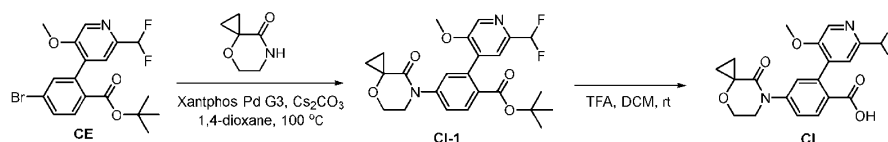
tert-Butyl 4-bromo-2-(2-chloro-5-methoxypyridin-4-yl)benzoate



[0405] Following conditions analogous to synthesis of **CG**, Intermediate **CH** was synthesized from the corresponding commercially available boronic acid. LCMS (ESI, m/z): $[M+H]^+ = 400.1$

Intermediate CI

2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(8-oxo-4-oxa-7-azaspiro[2.5]octan-7-yl)benzoic acid



Step 1: *tert*-butyl 2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(8-oxo-4-oxa-7-azaspiro[2.5]octan-7-yl)benzoate (**CI-1**)

[0406] 4-Oxa-7-azaspiro[2.5]octan-8-one (307 mg, 2.42 mmol), Cs_2CO_3 (2.36 g, 7.24 mmol) and Xantphos Pd G3 (345 mg, 0.363 mmol) were added to a solution of *tert*-butyl 4-bromo-2-[2-(difluoromethyl)-5-methoxy-4-pyridyl]benzoate (**CE**, 150 mg, 0.363 mmol) in 1,4-dioxane (5 mL) under N_2 . The mixture was degassed and backfilled with N_2 . After stirring at 100 °C for 2 hrs, the mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography, eluting with MeOH/DCM (1:20), to afford *tert*-butyl 2-[2-(difluoromethyl)-5-methoxy-4-pyridyl]-4-(8-oxo-4-oxa-7-azaspiro[2.5]octan-7-yl)benzoate (**CI-1**, 100 mg). LCMS (ESI, m/z): $[M+H]^+ = 461.2$.

Step 2: 2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(8-oxo-4-oxa-7-azaspiro[2.5]octan-7-yl)benzoic acid (**CI**)

[0407] TFA (0.3 mL) was added to a solution of *tert*-butyl 2-[2-(difluoromethyl)-5-methoxy-4-pyridyl]-4-(8-oxo-4-oxa-7-azaspiro[2.5]octan-7-yl)benzoate (**CI-1**, 100 mg, 0.217

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mmol) in DCM (2 mL) at rt. After stirring for 2 hrs, the mixture was concentrated in vacuo.

The residue was purified by reverse phase column chromatography (0.05% FA) to afford the

Intermediate **CI** (80.0 mg). LCMS (ESI, m/z): [M+H]⁺ = 405.3.

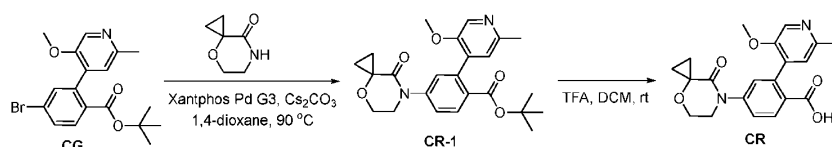
[0408] Following conditions analogous to synthesis of **CI**, Intermediates **CJ-CQ** in the table below were synthesized from **CE** or **CF**.

Intermediate Number	Structure	Name	LCMS (ESI, m/z): [M+H] ⁺
CJ		2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(4-methyl-2-oxopiperazin-1-yl)benzoic acid	392.3
CK		2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(2-methyl-5-oxomorpholino)benzoic acid	393.2
CL		2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(6-oxo-4-oxa-7-azaspiro[2.5]octan-7-yl)benzoic acid	405.2
CM		2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(3-oxomorpholino)benzoic acid	379.3
CN		2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-5-fluoro-4-(8-oxo-4-oxa-7-azaspiro[2.5]octan-7-yl)benzoic acid	423.1
CO		2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(2-methyl-3-oxomorpholino)benzoic acid	393.2
CP		2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(2,2-dimethyl-3-oxomorpholino)benzoic acid	407.3
CQ		4-(4-(2,2-difluoroethyl)-2-oxopiperazin-1-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoic acid	442.2

Intermediate CR

2-(5-Methoxy-2-methylpyridin-4-yl)-4-(8-oxo-4-oxa-7-azaspiro[2.5]octan-7-yl)benzoic acid

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Step 1: *tert*-butyl 2-(5-methoxy-2-methylpyridin-4-yl)-4-(8-oxo-4-oxa-7-azaspiro[2.5]octan-7-yl)benzoate (**CR-1**)

[0409] A mixture of *tert*-butyl 4-bromo-2-(5-methoxy-2-methylpyridin-4-yl)benzoate (**CG**, 300 mg, 0.793 mmol), 4-oxa-7-azaspiro[2.5]octan-8-one (202 mg, 1.59 mmol), XantPhos Pd G3 (75.3 mg, 0.0793 mmol) and Cs₂CO₃ (518 mg, 1.59 mmol) in 1,4-dioxane (5 mL) was degassed and backfilled with N₂. After stirring at 90 °C for 2 hrs, the mixture was treated with H₂O and extracted with EtOAc. The combined organic layers were dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc/PE (1:1 to 1:0), to afford *tert*-butyl 2-(5-methoxy-2-methylpyridin-4-yl)-4-(8-oxo-4-oxa-7-azaspiro[2.5]octan-7-yl)benzoate (**CR-1**, 210 mg). LCMS (ESI, m/z): [M+H]⁺ = 425.3.

Step 2: 2-(5-methoxy-2-methylpyridin-4-yl)-4-(8-oxo-4-oxa-7-azaspiro[2.5]octan-7-yl)benzoic acid (**CR**)

[0410] TFA (2 mL) was added to a solution of *tert*-butyl 2-(5-methoxy-2-methylpyridin-4-yl)-4-(8-oxo-4-oxa-7-azaspiro[2.5]octan-7-yl)benzoate (**CR-1**, 200 mg, 0.47 mmol) in DCM (2 mL) at rt. After stirring for 3 hrs, the mixture was concentrated in vacuo. The residue was purified by reverse phase column chromatography (0.1% FA) to afford Intermediate **CR** (120 mg). LCMS (ESI, m/z): [M+H]⁺ = 369.2.

[0411] Following conditions analogous to synthesis of **CR**, Intermediates **CS-CX** in the table below were synthesized from **CG**.

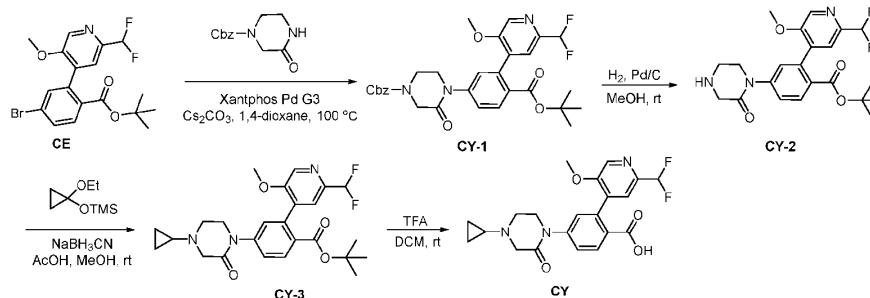
Intermediate Number	Structure	Name	LCMS (ESI, m/z): [M+H] ⁺
CS		2-(5-methoxy-2-methylpyridin-4-yl)-4-(3-oxomorpholino)benzoic acid	343.3
CT		2-(5-methoxy-2-methylpyridin-4-yl)-4-(3-methyl-2-oxoimidazolidin-1-yl)benzoic acid	342.2
CU		2-(5-methoxy-2-methylpyridin-4-yl)-4-(2-oxooxazolidin-3-yl)benzoic acid	329.0

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CV		2-(5-methoxy-2-methylpyridin-4-yl)-4-(3-methyl-2,4-dioxoimidazolidin-1-yl)benzoic acid	356.2
CW		2-(5-methoxy-2-methylpyridin-4-yl)-4-(3-methyl-2,5-dioxoimidazolidin-1-yl)benzoic acid	356.2
CX		2-(5-methoxy-2-methylpyridin-4-yl)-4-(4-methyl-2-oxopiperazin-1-yl)benzoic acid	356.2

Intermediate CY

4-(4-Cyclopropyl-2-oxopiperazin-1-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoic acid



Step 1: benzyl 4-(4-(*tert*-butoxycarbonyl)-3-(2-(difluoromethyl)-5-methoxypyridin-4-yl)phenyl)-3-oxopiperazine-1-carboxylate (**CY-1**)

[0412] Following conditions analogous to synthesis of **CI-1**, Intermediate **CE** was converted to **CY-1**. LCMS (ESI, *m/z*): [*M*+*H*]⁺ = 568.3.

Step 2: *tert*-butyl 2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(2-oxopiperazin-1-yl)benzoate (**CY-2**)

[0413] Pd/C (10% palladium on carbon, wetted with ca.55% water for safety, 245 mg) was added to a mixture of benzyl 4-(4-(*tert*-butoxycarbonyl)-3-(2-(difluoromethyl)-5-methoxypyridin-4-yl)phenyl)-3-oxopiperazine-1-carboxylate (**CY-1**, 1.30 g, 2.29 mmol) in MeOH (7 mL) under N₂. The mixture was purged with H₂ and stirred under H₂ (1 atm) for 6 hrs. After removal of the catalyst by filtration, the filtrate was concentrated in vacuo to give *tert*-butyl 2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(2-oxopiperazin-1-yl)benzoate (**CY-2**, 800 mg). LCMS (ESI, *m/z*): [*M*+*H*]⁺ = 434.0.

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Step 3: *tert*-butyl 4-(4-cyclopropyl-2-oxopiperazin-1-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoate (CY-3)

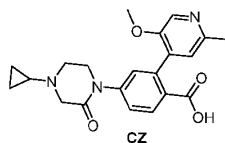
[0414] AcOH (691 mg, 11.5 mmol) and NaBH₃CN (363 mg, 5.77 mmol) were added to a mixture of *tert*-butyl 2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(2-oxopiperazin-1-yl)benzoate (CY-2, 498 mg, 1.15 mmol) and (1-ethoxycyclopropoxy)trimethyl silane (1.20 g, 6.90 mmol) in MeOH (10 mL) under N₂. After stirring for 16 hrs, the mixture was treated with water and extracted with EtOAc. The combined organic layers were dried (Na₂SO₄), filtered, and concentrated in vacuo to give *tert*-butyl 4-(4-cyclopropyl-2-oxopiperazin-1-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl) benzoate (CY-3, 410 mg). LCMS (ESI, m/z): [M+H]⁺ = 474.1.

Step 4: 4-(4-cyclopropyl-2-oxopiperazin-1-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoic acid (CY)

[0415] Following conditions analogous to Step 2 of Intermediate CR, Intermediate CY-3 was converted to CY. LCMS (ESI, m/z): [M+H]⁺ = 418.0.

Intermediate CZ

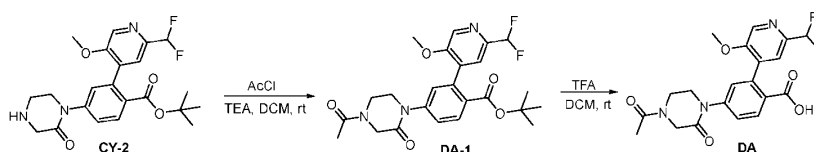
4-(4-Cyclopropyl-2-oxopiperazin-1-yl)-2-(5-methoxy-2-methylpyridin-4-yl)benzoic acid



[0416] Following conditions analogous to synthesis of CY, Intermediate CG was converted to CZ. LCMS (ESI, m/z): [M+H]⁺ = 382.3.

Intermediate DA

4-(4-Acetyl-2-oxopiperazin-1-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoic acid



Step 1: *tert*-butyl 4-(4-acetyl-2-oxopiperazin-1-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoate (DA-1)

[0417] Acetyl chloride (40.7 mg, 0.519 mmol) was added to a mixture of *tert*-butyl 2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(2-oxopiperazin-1-yl)benzoate (CY-2, 150 mg, 0.346 mmol) and TEA (70.0 mg, 0.692 mmol) in DCM (6 mL) at 0 °C under N₂. After

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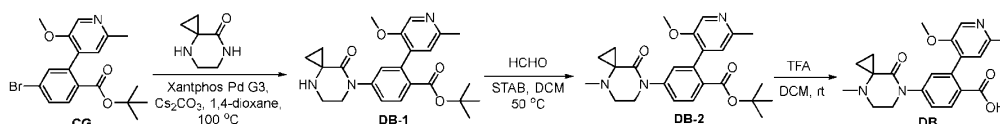
stirring at rt for 1 hr, the mixture was treated with water and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo to afford *tert*-butyl 4-(4-acetyl-2-oxopiperazin-1-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoate (**DA-1**, 120 mg). LCMS (ESI, m/z): $[\text{M}+\text{H}]^+ = 476.3$.

Step 2: 4-(4-Acetyl-2-oxopiperazin-1-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoic acid (**DA**)

[0418] Following conditions analogous to Step 2 of Intermediate **CR**, Intermediate **DA-1** was converted to **DA**. LCMS (ESI, m/z): $[\text{M}+\text{H}]^+ = 420.2$.

Intermediate DB

2-(5-Methoxy-2-methylpyridin-4-yl)-4-(4-methyl-8-oxo-4,7-diazaspiro[2.5]octan-7-yl)benzoic acid



Step 1: *tert*-butyl 2-(5-methoxy-2-methylpyridin-4-yl)-4-(8-oxo-4,7-diazaspiro[2.5]octan-7-yl)benzoate (**DB-1**)

[0419] Following conditions analogous to synthesis of **CR-1**, Intermediate **CG** was reacted with 4,7-diazaspiro[2.5]octan-8-one to give **DB-1**. LCMS (ESI, m/z): $[\text{M}+\text{H}]^+ = 424.3$.

Step 2: *tert*-butyl 2-(5-methoxy-2-methylpyridin-4-yl)-4-(4-methyl-8-oxo-4,7-diazaspiro[2.5]octan-7-yl)benzoate (**DB-2**)

[0420] Sodium triacetoxyborohydride (50.0 mg, 0.236 mmol) was added to a solution of *tert*-butyl 2-(5-methoxy-2-methyl-4-pyridyl)-4-(8-oxo-4,7-diazaspiro[2.5]octan-7-yl)benzoate (**DB-1**, 50.0 mg, 0.118 mmol) and formaldehyde (1 mL) in DCM (1 mL) under N_2 . After stirring at 50 °C for 2 hrs, the mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography, eluting with EtOAc/PE (1:1), to afford *tert*-butyl 2-(5-methoxy-2-methyl-4-pyridyl)-4-(4-methyl-8-oxo-4,7-diazaspiro[2.5]octan-7-yl)benzoate (**DB-2**, 27 mg). LCMS (ESI, m/z): $[\text{M}+\text{H}]^+ = 438.4$.

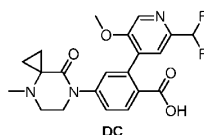
Step 3: 2-(5-methoxy-2-methylpyridin-4-yl)-4-(4-methyl-8-oxo-4,7-diazaspiro[2.5]octan-7-yl)benzoic acid (**DB**)

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[0421] Following conditions analogous to Step 2 of Intermediate **CR**, Intermediate **DB-2** was converted to **DB**. LCMS (ESI, m/z): $[M+H]^+ = 382.4$.

Intermediate DC

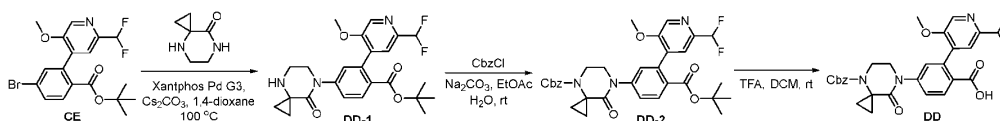
2-(2-(Di fluoromethyl)-5-methoxypyridin-4-yl)-4-(4-methyl-8-oxo-4,7-diazaspiro[2.5]octan-7-yl)benzoic acid



[0422] Following conditions analogous to synthesis of **DB**, Intermediate **CE** was converted to **DC**. LCMS (ESI, m/z): $[M+H]^+ = 418.3$.

Intermediate DD

4-(4-((Benzyloxy)carbonyl)-8-oxo-4,7-diazaspiro[2.5]octan-7-yl)-2-(2-(di fluoromethyl)-5-methoxypyridin-4-yl)benzoic acid



Step 1: tert-butyl 2-(2-(di fluoromethyl)-5-methoxypyridin-4-yl)-4-(8-oxo-4,7-diazaspiro[2.5]octan-7-yl)benzoate (DD-1)

[0423] Following conditions analogous to synthesis of **CI-1**, Intermediate **CE** was reacted with 4,7-diazaspiro[2.5]octan-8-one to give **DD-1**. LCMS (ESI, m/z): $[M+H]^+ = 460.3$

Step 2: benzyl 7-(4-(tert-butoxycarbonyl)-3-(2-(di fluoromethyl)-5-methoxypyridin-4-yl)phenyl)-8-oxo-4,7-diazaspiro[2.5]octane-4-carboxylate (DD-2)

[0424] CbzCl (150 mg, 0.881 mmol) was added to a stirred mixture of *tert*-butyl 2-(2-(di fluoromethyl)-5-methoxypyridin-4-yl)-4-(8-oxo-4,7-diazaspiro[2.5]octan-7-yl)benzoate (**DD-1**, 270 mg, 0.587 mmol) and Na_2CO_3 (187 mg, 1.76 mmol) in EtOAc (4 mL) and water (4 mL) under N_2 . After stirring for 3 hrs, the mixture was treated with water and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo to afford benzyl 7-(4-(tert-butoxycarbonyl)-3-(2-(di fluoromethyl)-5-methoxypyridin-4-yl)phenyl)-8-oxo-4,7-diazaspiro[2.5]octane-4-carboxylate (**DD-2**, 340 mg). LCMS (ESI, m/z): $[M+H]^+ = 594.3$

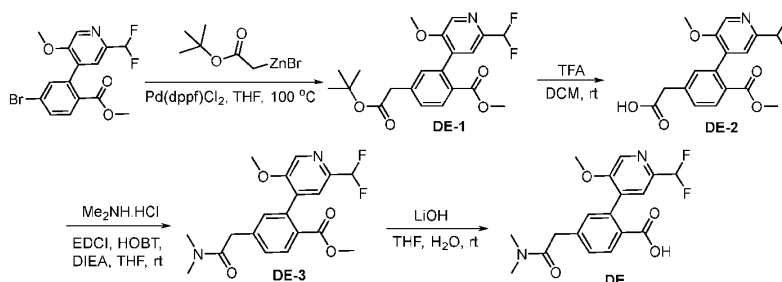
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Step 3: 4-(4-((benzyloxy)carbonyl)-8-oxo-4,7-diazaspiro[2.5]octan-7-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoic acid (**DD**)

[0425] Following conditions analogous to Step 2 of Intermediate **CR**, Intermediate **DD-2** was converted to **DD**. LCMS (ESI, m/z): [M+H]⁺ = 538.2.

Intermediate DE

2-(2-(Difluoromethyl)-5-methoxypyridin-4-yl)-4-(2-(dimethylamino)-2-oxoethyl)benzoic acid



Step 1: methyl 4-(2-(*tert*-butoxy)-2-oxoethyl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoate (**DE-1**)

[0426] Methyl 4-bromo-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoate (precursor of **AC**, 748 mg, 2.02 mmol) and Pd(dppf)Cl₂ (147 mg, 0.202 mmol) were added to a solution of (2-(*tert*-butoxy)-2-oxoethyl)zinc(II) bromide (0.5 M in THF, 20 mL, 10 mmol) in THF (10 mL) under N₂. The mixture was degassed and backfilled with N₂. After stirring at 80 °C for 12 hrs, the mixture was treated with water and extracted with EtOAc. The combined organic layers were dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by prep-HPLC (0.05% NH₄CO₃) to afford methyl 4-(2-(*tert*-butoxy)-2-oxoethyl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoate (**DE-1**, 145 mg). LCMS (ESI, m/z): [M+H]⁺ = 408.3.

Steps 2: 2-(3-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(methoxycarbonyl)phenyl)acetic acid (**DE-2**)

[0427] Following conditions analogous to Step 2 of Intermediate **CR**, Intermediate **DE-1** was converted to **DE-2**. LCMS (ESI, m/z): [M+H]⁺ = 352.2.

Steps 3: methyl 2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(2-(dimethylamino)-2-oxoethyl)benzoate (**DE-3**)

[0428] Following conditions analogous to Step 2 of Intermediate **BG**, Intermediate **DE-2** was converted to **DE-3**. LCMS (ESI, m/z): [M+H]⁺ = 379.4.

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Steps 4: 2-(2-(Difluoromethyl)-5-methoxypyridin-4-yl)-4-(2-(dimethylamino)-2-oxoethyl)benzoic acid (**DE**)

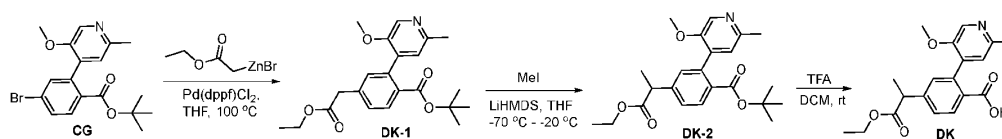
[0429] Following conditions analogous to Step 2 of Intermediate **BY**, Intermediate **DE-1** was converted to **DE**. LCMS (ESI, m/z): [M+H]⁺ = 365.3.

[0430] Following conditions analogous to Steps 3 and 4 of **DE**, Intermediates **DF-DJ** in the table below were synthesized from **DE-2**.

Intermediate Number	Structure	Name	LCMS (ESI, m/z): [M+H] ⁺
DF		2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(2-(3-hydroxy-3-methylazetidin-1-yl)-2-oxoethyl)benzoic acid	407.1
DG		2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(2-(methylamino)-2-oxoethyl)benzoic acid	351.2
DH		4-(2-(azetidin-1-yl)-2-oxoethyl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoic acid	377.0
DI		4-(2-amino-2-oxoethyl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoic acid	366.9
DJ		2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(2-(3-hydroxy-3-methylpyrrolidin-1-yl)-2-oxoethyl)benzoic acid	421.1

Intermediate DK

4-(1-Ethoxy-1-oxopropan-2-yl)-2-(5-methoxy-2-methylpyridin-4-yl)benzoic acid



Step 1: *tert*-butyl 4-(2-ethoxy-2-oxoethyl)-2-(5-methoxy-2-methylpyridin-4-yl)benzoate (**DK-1**)

[0431] Following conditions analogous to synthesis of **DE-1**, Intermediate **CG** was converted to **DK-1**. LCMS (ESI, m/z): [M+H]⁺ = 386.3.

Step 2: *tert*-butyl 4-(1-ethoxy-1-oxopropan-2-yl)-2-(5-methoxy-2-methylpyridin-4-yl)benzoate (**DK-2**)

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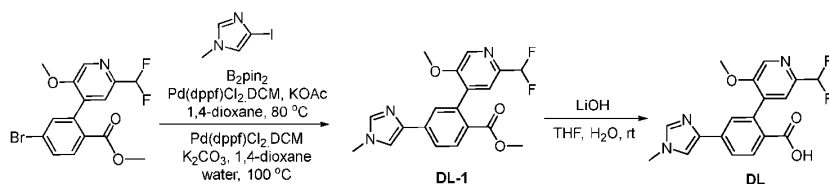
[0432] A 1 M THF solution of LiHMDS (0.89 mL, 0.89 mmol) was added dropwise to a stirred solution of *tert*-butyl 4-(2-ethoxy-2-oxoethyl)-2-(5-methoxy-2-methylpyridin-4-yl)benzoate (**DK-1**, 320 mg, 0.830 mmol) in THF (10 mL) at -70 °C under N₂. After stirring for 30 min, MeI (138 mg, 0.972 mmol) was added. After another 30 min at -20 °C, the mixture was quenched with NH₄Cl solution and extracted with EtOAc. The combined organic layers were dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel, eluting with MeOH/DCM (1:1), to afford *tert*-butyl 4-(1-ethoxy-1-oxopropan-2-yl)-2-(5-methoxy-2-methylpyridin-4-yl)benzoate (**DK-2**, 200 mg). LCMS (ESI, m/z): [M+H]⁺ = 400.3.

Step 3: 4-(1-ethoxy-1-oxopropan-2-yl)-2-(5-methoxy-2-methylpyridin-4-yl)benzoic acid (**DK**)

[0433] Following conditions analogous to Step 2 of **CR**, Intermediate **DK-2** was converted to **DK**. LCMS (ESI, m/z): [M+H]⁺ = 344.0.

Intermediate DL

2-(2-(Difluoromethyl)-5-methoxypyridin-4-yl)-4-(1-methyl-1*H*-imidazol-4-yl)benzoic acid



Step 1: methyl 2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(1-methyl-1*H*-imidazol-4-yl)benzoate (**DL-1**)

[0434] Bis(pinacolato)diboron (34.1 mg, 0.135 mmol), KOAc (26.4 mg, 0.269 mmol) and Pd(dppf)Cl₂ DCM (21.9 mg, 0.027 mmol) were added to a solution of methyl 4-bromo-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoate (precursor of **AC**, 50.0 mg, 0.135 mmol) in 1,4-dioxane (4 mL) under N₂. The mixture was degassed and refilled with N₂. After stirring at 85 °C for 2 hrs, the mixture was cooled to rt. 4-iodo-1-methyl-1*H*-imidazole (99.2 mg, 0.477 mmol), Pd(dppf)Cl₂ DCM (39 mg, 0.048 mmol), K₂CO₃ (132 mg, 0.954 mmol), 1,4-dioxane (2 mL) and water (2 mL) were added under N₂. After stirring at 100 °C for another 2 hrs, the mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography, eluting with EtOAc/PE (1:1), to afford methyl 2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(1-methyl-1*H*-imidazol-4-yl)benzoate (**DL-1**, 60 mg). LCMS (ESI, m/z): [M+H]⁺ = 374.1

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Step 2: 2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(1-methyl-1H-imidazol-4-yl)benzoic acid (**DL**)

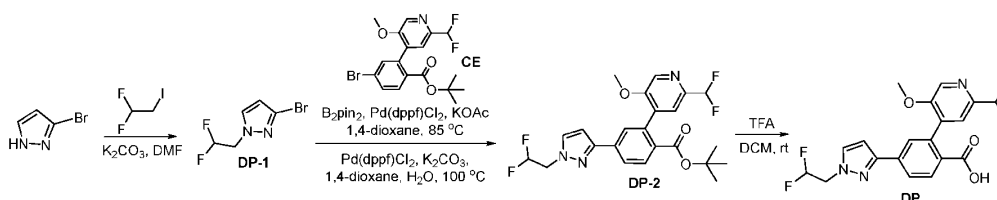
[0435] Following conditions analogous to Step 2 of **BY**, Intermediate **DL-1** was converted to **DL**. LCMS (ESI, m/z): [M+H]⁺ = 360.1.

[0436] Following conditions analogous to synthesis of **DL**, Intermediates **DM-DO** in the table below were synthesized from **AC-1**.

Intermediate Number	Structure	Name	LCMS (ESI, m/z): [M+H] ⁺
DM		2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(5-methyl-1,3,4-thiadiazol-2-yl)benzoic acid	378.2
DN		2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(5-methyl-1,3,4-oxadiazol-2-yl)benzoic acid	362.2
DO		4-(1-cyclopropyl-1H-pyrazol-3-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoic acid	386.2

Intermediate DP

4-(1-(2,2-Difluoroethyl)-1H-pyrazol-3-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoic acid



Step 1: 3-bromo-1-(2,2-difluoroethyl)-1H-pyrazole (**DP-1**)

[0437] 1,1-Difluoro-2-iodoethane (9.79 g, 51.0 mmol) and K₂CO₃ (14.1 g, 102 mmol) were added to a solution of 3-bromo-1H-pyrazole (5.0 g, 34.0 mmol) in DMF (20 mL) under N₂. After stirring at rt for 16 hrs, the mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated in vacuo to afford 3-bromo-1-(2,2-difluoroethyl)-1H-pyrazole (**DP-1**, 4.0 g). LCMS (ESI, m/z): [M+H]⁺ = 211.2.

Step 2: *tert*-butyl 4-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoate (**DP-2**)

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[0438] Bis(pinacolato)diboron (1.23 g, 4.84 mmol) and Pd(dppf)Cl₂ (0.353 g, 0.483 mmol) were added to a solution of *tert*-butyl 4-bromo-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoate (**CE**, 2.0 g, 4.83 mmol) in 1,4-dioxane (20 mL) under N₂. The mixture was degassed, stirred at 85 °C for 2 hrs and cooled to rt. K₂CO₃ (1.80 g, 13.0 mmol), 3-bromo-1-(2,2-difluoroethyl)-1H-pyrazole (**DP-1**, 1.10 g, 5.20 mmol), Pd(dppf)Cl₂ (0.317 g, 0.434 mmol), 1,4-dioxane (20 mL) and water (10 mL) were added under N₂. After stirring at 100 °C for another 2 hrs, the mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography, eluting with EtOAc/PE (1:3), to afford *tert*-butyl 4-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoate (**DP-2**, 1.1 g). LCMS (ESI, m/z): [M+H]⁺ = 466.1

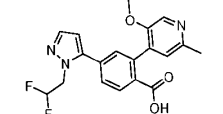
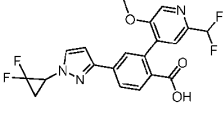
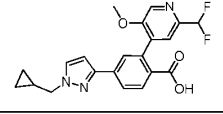
Step 3: 4-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoic acid (**DP**)

[0439] TFA (1 mL) was added to a solution of *tert*-butyl 4-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoate (**DP-2**, 1.10 g, 2.36 mmol) in DCM (6 mL). After stirring for 2 hrs, the mixture was concentrated in vacuo. The residue was purified by reverse phase column chromatography (0.1% FA) to afford Intermediate **DP** (450 mg). LCMS (ESI, m/z): [M+H]⁺ = 410.2.

[0440] Following conditions analogous to synthesis of **DL**, Intermediates **DQ-DW** in the table below were synthesized from **CE** or **CG**.

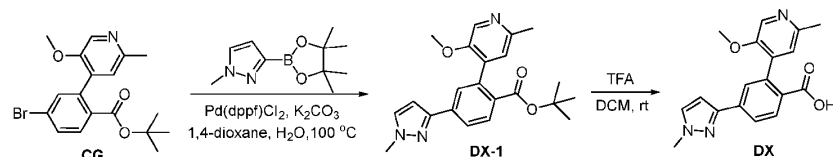
Intermediate Number	Structure	Name	LCMS (ESI, m/z): [M+H] ⁺
DQ		4-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)-2-(5-methoxy-2-methylpyridin-4-yl)benzoic acid	374.2
DR		2-(5-methoxy-2-methylpyridin-4-yl)-4-(2-methyl-2H-tetrazol-5-yl)benzoic acid	326.1
DS		2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(2-methyl-2H-1,2,3-triazol-4-yl)benzoic acid	361.2
DT		2-(5-methoxy-2-methylpyridin-4-yl)-4-(1-methyl-1H-1,2,4-triazol-3-yl)benzoic acid	325.0

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DU		4-(1-(2,2-difluoroethyl)-1H-pyrazol-5-yl)-2-(5-methoxy-2-methylpyridin-4-yl)benzoic acid	374.3
DV		4-(1-(2,2-difluorocyclopropyl)-1H-pyrazol-3-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoic acid	422.2
DW		4-(1-(cyclopropylmethyl)-1H-pyrazol-3-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoic acid	400.3

Intermediate DX

2-(5-Methoxy-2-methylpyridin-4-yl)-4-(1-methyl-1H-pyrazol-3-yl)benzoic acid



Step 1: *tert*-butyl 2-(5-methoxy-2-methylpyridin-4-yl)-4-(1-methyl-1H-pyrazol-3-yl)benzoate (**DX-1**)

[0441] 1-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (198 mg, 0.952 mmol), K₂CO₃ (219 mg, 1.59 mmol) and Pd(dppf)Cl₂ (58.0 mg, 0.079 mmol) were added to a solution of *tert*-butyl 4-bromo-2-(5-methoxy-2-methyl-4-pyridyl)benzoate (**CG**, 300 mg, 0.793 mmol) in 1,4-dioxane (5 mL) and water (1 mL) under N₂. The mixture was degassed and backfilled with N₂. After stirring at 100 °C for 2 hrs, the mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered, concentrated in vacuo. The residue was purified by silica gel column chromatography, eluting with EtOAc/PE (1:4), to afford *tert*-butyl 2-(5-methoxy-2-methyl-4-pyridyl)-4-(1-methylpyrazol-3-yl)benzoate (**DX-1**, 250 mg). LCMS (ESI, m/z): [M+H]⁺ = 380.3.

Step 2: 2-(5-methoxy-2-methylpyridin-4-yl)-4-(1-methyl-1H-pyrazol-3-yl)benzoic acid (**DX**)

[0442] TFA (0.8 mL) was added to a solution of *tert*-butyl 2-(5-methoxy-2-methyl-4-pyridyl)-4-(1-methylpyrazol-3-yl)benzoate (**DX-1**, 250 mg, 0.66 mmol) in DCM (3 mL) at rt. After stirring for 2 hrs, the mixture was concentrated in vacuo. The residue was purified by

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reverse phase column chromatography (0.05% FA) to afford Intermediate **DX** (180 mg).

LCMS (ESI, m/z): [M+H]⁺ = 324.2.

[0443] Following conditions analogous to synthesis of **DX**, Intermediates **DY-DZ** in the table below were synthesized from **CG**, **CE** or **CH**.

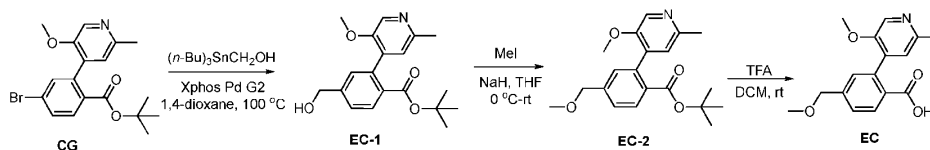
Intermediate Number	Structure	Name	LCMS (ESI, m/z): [M+H] ⁺
DY		2-(2-chloro-5-methoxypyridin-4-yl)-4-(1-methyl-1H-pyrazol-3-yl)benzoic acid	344.2
DZ		2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-3-yl)benzoic acid	428.3

[0444] Following conditions analogous to synthesis of **AQ**, Intermediates **EA-EB** in the table below were synthesized.

Intermediate Number	Structure	Name	LCMS (ESI, m/z): [M+H] ⁺
EA		2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(1-(1,1-difluoropropan-2-yl)-1H-pyrazol-3-yl)benzoic acid	424.0
EB		5'-(difluoromethyl)-5-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-3-yl)-2'-methoxy-[1,1'-biphenyl]-2-carboxylic acid	417.3

Intermediate EC

2-(5-Methoxy-2-methylpyridin-4-yl)-4-(methoxymethyl)benzoic acid



Step 1: *tert*-butyl 4-(hydroxymethyl)-2-(5-methoxy-2-methylpyridin-4-yl)benzoate (**EC-1**)

[0445] A mixture of *tert*-butyl 4-bromo-2-(5-methoxy-2-methylpyridin-4-yl)benzoate (**CG**, 500 mg, 1.32 mmol), (*n*-Bu)₃SnCH₂OH (511 mg, 1.59 mmol) and Xphos Pd G2 (104 mg, 0.132 mmol) in 1,4-dioxane (10 mL) was degassed and backfilled with N₂. After stirring at 100 °C for 5 hrs, the mixture was treated with water and extracted with EtOAc. The

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combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc/PE (3:7), to afford *tert*-butyl 4-(hydroxymethyl)-2-(5-methoxy-2-methylpyridin-4-yl)benzoate (**EC-1**, 280 mg). LCMS (ESI, m/z): $[\text{M}+\text{H}]^+ = 330.1$.

Step 2: *tert*-butyl 2-(5-methoxy-2-methylpyridin-4-yl)-4-(methoxymethyl)benzoate (**EC-2**)

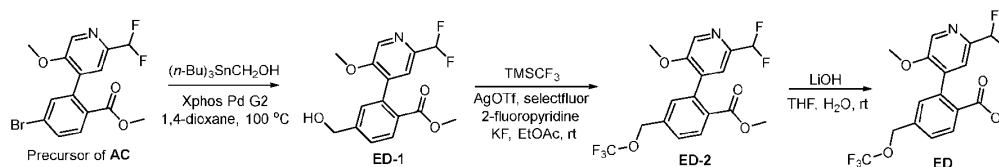
[0446] NaH (60% dispersion in mineral oil, 63 mg, 1.58 mmol) was added to a solution of *tert*-butyl 4-(hydroxymethyl)-2-(5-methoxy-2-methylpyridin-4-yl)benzoate (**EC-1**, 260 mg, 0.789 mmol) in THF (10 mL) at 0 °C under N_2 atmosphere. After stirring for 30 mins, MeI (224 mg, 1.58 mmol) was added. The mixture was stirred at rt for 5 hrs, quenched with water and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc/PE (1:4), to afford *tert*-butyl 2-(5-methoxy-2-methylpyridin-4-yl)-4-(methoxymethyl)benzoate (**EC-2**, 180 mg). LCMS (ESI, m/z): $[\text{M}+\text{H}]^+ = 344.1$.

Step 3: 2-(5-methoxy-2-methylpyridin-4-yl)-4-(methoxymethyl)benzoic acid (**EC**)

[0447] TFA (2.5 mL) was added to a solution of 2-(5-methoxy-2-methylpyridin-4-yl)-4-(methoxymethyl)benzoate (**EC-2**, 180 mg, 0.524 mmol) in DCM (5 mL). After stirring for 2 hrs, the mixture was concentrated in vacuo. The residue was purified by reverse phase column chromatography (0.1% FA) to afford Intermediate **EC** (110 mg). LCMS (ESI, m/z): $[\text{M}+\text{H}]^+ = 288.0$.

Intermediate ED

2-(2-(Difluoromethyl)-5-methoxypyridin-4-yl)-4-((trifluoromethoxy)methyl)benzoic acid



Step 1: methyl 2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(hydroxymethyl)benzoate (**ED-1**)

[0448] Following conditions analogous to synthesis of **EC-1**, Intermediates **ED-1** was synthesized from precursor of **AC**. LCMS (ESI, m/z): $[\text{M}+\text{H}]^+ = 324.1$.

Step 2: methyl 2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-((trifluoromethoxy)methyl)benzoate (**ED-2**)

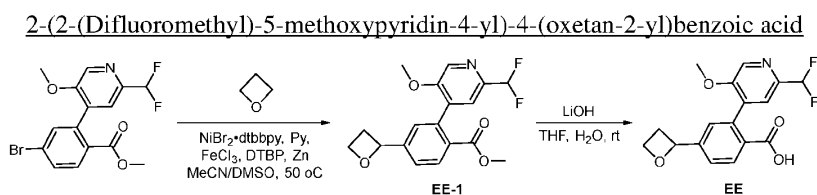
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[0449] A mixture of methyl 2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(hydroxymethyl) benzoate (**ED-1**, 200 mg, 0.619 mmol), AgOTf (478 mg, 1.86 mmol), Selectfluor (219 mg, 0.619 mmol), KF (144 mg, 2.47 mmol), 2-fluoropyridine (181 mg, 1.86 mmol) and TMSCF₃ (264 mg, 0.275 mL, 1.86 mmol) in EtOAc (3 mL) was stirred at rt under N₂ for 36 hrs. After completion, the mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel, eluting with MeOH/ DCM (1:30), to afford methyl 2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-((trifluoromethoxy)methyl)benzoate (**ED-2**, 80 mg). LCMS (ESI, m/z): [M+H]⁺ = 392.0.

Step 3: 2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-((trifluoromethoxy)methyl)benzoic acid (**ED**)

[0450] Following conditions analogous to Step 2 of **BY**, Intermediate **ED-2** was converted to **ED**. LCMS (ESI, m/z): [M+H]⁺ = 378.1.

Intermediate EE



Step 1: methyl 2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(oxetan-2-yl)benzoate (**EE-1**)

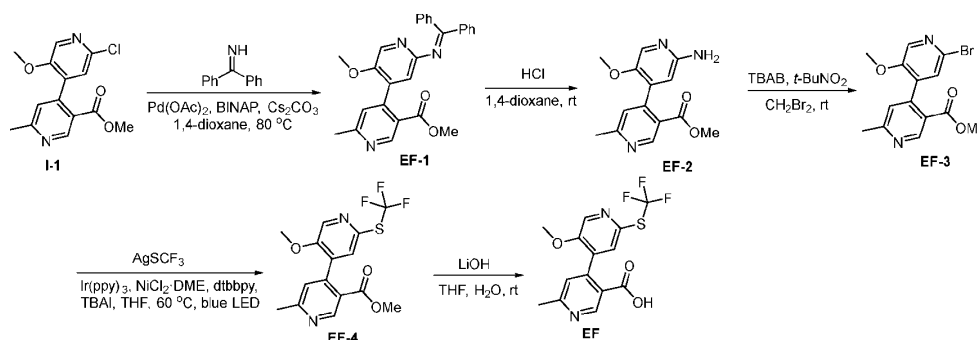
[0451] A mixture of methyl 4-bromo-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoate (precursor of **AC**, 279 mg, 0.75 mmol), oxetane (871 mg, 15.0 mmol), NiBr₂(dtbbpy) (22.5 mg, 0.045 mmol), pyridine (8.90 mg, 0.112 mmol), FeCl₃ (12.2 mg, 0.075 mmol), di-tert-butyl peroxide (439 mg, 3.0 mmol), zinc powder (98 mg, 1.5 mmol) in MeCN (2.25mL) and DMSO (0.75 mL) was degassed and backfilled with N₂. After stirring at 50 °C for 16 hrs, the mixture was filtered, treated with water, and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc/PE (1:20 to 1:2), to afford methyl 2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(oxetan-2-yl)benzoate (**EE-1**, 94 mg). LCMS (ESI, m/z): [M+H]⁺ = 350.2.

Step 2: 2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(oxetan-2-yl)benzoic acid (**EE**)

[0452] Following conditions analogous to Step 2 of **BY**, Intermediate **EE-1** was converted to **EE**. LCMS (ESI, m/z): $[M+H]^+ = 336.0$

Intermediate EF

5'-Methoxy-6-methyl-2'-((trifluoromethyl)thio)-[4,4'-bipyridine]-3-carboxylic acid



Step 1: methyl 2'-((diphenylmethylene)amino)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxylate (**EF-1**)

[0453] A mixture of methyl 2'-chloro-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxylate (**I-1**, 1.0 g, 3.42 mmol), diphenylmethanimine (928 mg, 5.12 mmol), BINAP (423 mg, 0.68 mmol), Pd(OAc)₂ (77 mg, 0.34 mmol) and Cs₂CO₃ (3.36 g, 10.3 mmol) in 1,4-dioxane (10 mL) was degassed and backfilled with N₂. After stirring at 80 °C for 24 hrs, the mixture was treated with water and extracted with DCM. The combined organic layers were dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc/PE (1:10 to 1:4), to afford methyl 2'-((diphenylmethylene)amino)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxylate (**EF-1**, 900 mg). LCMS (ESI, m/z): $[M+H]^+ = 438.1$.

Step 2: methyl 2'-amino-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxylate (**EF-2**)

[0454] A 4 M 1,4-dioxane solution of HCl (2.5 mL) was added to a stirred solution of methyl 2'-((diphenylmethylene)amino)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxylate (**EF-1**, 900 mg, 2.06 mmol) in THF (8 mL). After stirring at rt for 2 hrs, the mixture was basified to pH 8 with saturated NaHCO₃. The mixture was concentrated in vacuo to remove most of the solvent. The residue was purified by reverse phase flash chromatography (0.1% FA) to afford methyl 2'-amino-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxylate (**EF-2**, 500 mg). LCMS (ESI, m/z): $[M+H]^+ = 274.0$.

Step 3: methyl 2'-bromo-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxylate (**EF-3**)

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[0455] *tert*-Butyl nitrite (1.51 g, 14.6 mmol) was added dropwise to a mixture of methyl 2'-amino-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxylate (**EF-2**, 400 mg, 1.46 mmol) and tetrabutylammonium bromide (1.88 g, 5.84 mmol) in CH₂Br₂ (8 mL) at 0 °C under N₂. After stirring at rt for 4 hrs, the mixture was treated with water and extracted with EtOAc. The combined organic layers were dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc/PE (1:5), to afford methyl 2'-bromo-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxylate (**EF-3**, 280 mg). LCMS (ESI, m/z): [M+H]⁺ = 337.2.

Step 4: methyl 5'-methoxy-6-methyl-2'-((trifluoromethyl)thio)-[4,4'-bipyridine]-3-carboxylate (**EF-4**)

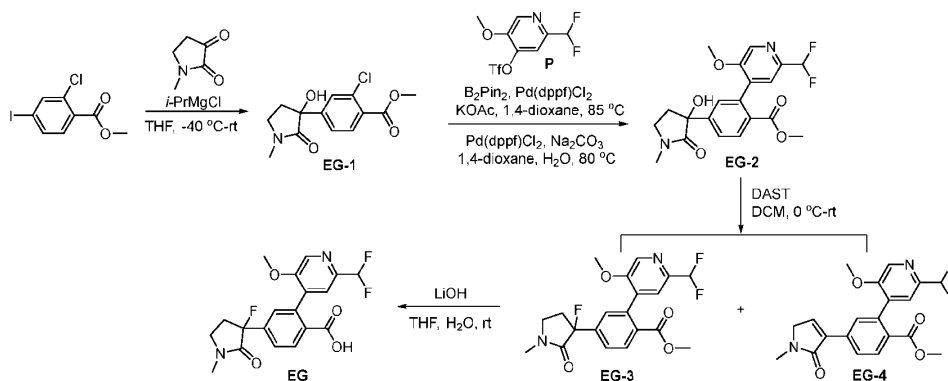
[0456] Following conditions analogous to synthesis of **BE-1**, Intermediate **EF-3** was converted to **EF-4**. LCMS (ESI, m/z): [M+H]⁺ = 359.2.

Step 5: 5'-methoxy-6-methyl-2'-((trifluoromethyl)thio)-[4,4'-bipyridine]-3-carboxylic acid (**EF**)

[0457] Following conditions analogous to Step 2 of **BY**, Intermediate **EF-4** was converted to **EF**. LCMS (ESI, m/z): [M+H]⁺ = 345.2.

Intermediate EG

2-(2-(Difluoromethyl)-5-methoxypyridin-4-yl)-4-(3-fluoro-1-methyl-2-oxopyrrolidin-3-yl)benzoic acid



Step 1: methyl 2-chloro-4-(3-hydroxy-1-methyl-2-oxopyrrolidin-3-yl)benzoate (**EG-1**)

[0458] A 2 M THF solution of *i*-PrMgCl (1.18 mL, 2.36 mmol) was added to a stirred solution of methyl 2-chloro-4-iodobenzoate (700 mg, 2.36 mmol) in THF (10 mL) at -40 °C under N₂. After stirring at -40 °C for 1 hr, 1-methylpyrrolidine-2,3-dione (400 mg, 3.54 mmol) was added. After stirring at rt for 1 hr, the mixture was treated with water and extracted with EtOAc. The combined organic layers were dried (Na₂SO₄), filtered, and

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concentrated in vacuo. The residue was purified by flash column chromatography on silica gel, eluting with MeOH/DCM (1:30), to afford methyl 2-chloro-4-(3-hydroxy-1-methyl-2-oxopyrrolidin-3-yl)benzoate (**EG-1**, 300 mg). LCMS (ESI, m/z): $[M+H]^+ = 283.9$.

Step 2: methyl 2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(3-hydroxy-1-methyl-2-oxopyrrolidin-3-yl)benzoate (**EG-2**)

[0459] Following conditions analogous to synthesis of **X-1**, Intermediate **EG-2** was synthesized from **EG-1** and *in situ* generated boronate of **P**. LCMS (ESI, m/z): $[M+H]^+ = 407.2$.

Step 3: methyl 2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(3-fluoro-1-methyl-2-oxopyrrolidin-3-yl)benzoate (**EG-3**) and methyl 2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(1-methyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)benzoate (**EG-4**)

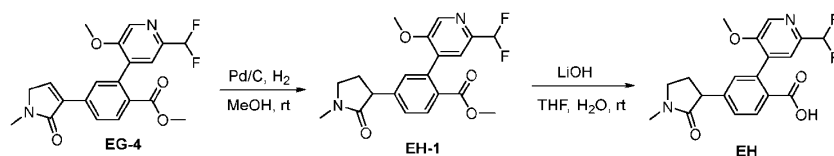
[0460] DAST (109 mg, 0.68 mmol) was added to a stirred solution of methyl 2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(3-hydroxy-1-methyl-2-oxopyrrolidin-3-yl)benzoate (**EG-2**, 230 mg, 0.566 mmol) in DCM (3 mL) at 0 °C under N₂. After stirring at rt for 2 hrs, the mixture was treated with MeOH and water, and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel, eluting with MeOH/DCM (1:30), to afford methyl 2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(3-fluoro-1-methyl-2-oxopyrrolidin-3-yl)benzoate (**EG-3**) and methyl 2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(1-methyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)benzoate (**EG-4**). LCMS (ESI, m/z): **EG-3** $[M+H]^+ = 409.0$, **EG-4** $[M+H]^+ = 389.0$.

Step 4: 2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(3-fluoro-1-methyl-2-oxopyrrolidin-3-yl)benzoic acid (**EG**)

[0461] Following conditions analogous to Step 2 of **BY**, Intermediate **EG-4** was converted to **EG**. LCMS (ESI, m/z): $[M+H]^+ = 394.9$.

Intermediate EH

2-(2-(Difluoromethyl)-5-methoxypyridin-4-yl)-4-(1-methyl-2-oxopyrrolidin-3-yl)benzoic acid



Step 1: methyl 2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(1-methyl-2-oxopyrrolidin-3-yl)benzoate (**EH-1**)

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[0462] 10% Pd/C (80 mg, wetted with ca.55% water for safety) was added to a solution of methyl 2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(1-methyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)benzoate (**EG-4**, 180 mg, 0.463 mmol) in MeOH (3 mL) under N₂. The mixture was purged with H₂, stirred under H₂ atmosphere (1 atm) at rt for 16 hrs, and filtered. The filtrate was concentrated in vacuo to give Intermediate **EH-1**. LCMS (ESI, m/z): [M+H]⁺ = 391.2.

Step 2: 2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(1-methyl-2-oxopyrrolidin-3-yl)benzoic acid (**EH**)

[0463] Following conditions analogous to Step 2 of **BY**, Intermediate **EH-1** was converted to **EH**. LCMS (ESI, m/z): [M+H]⁺ = 377.0.

[0464] Intermediates **EI-ET** in the table below were synthesized using conditions analogous to synthesis of Intermediate **AS** from the corresponding acids.

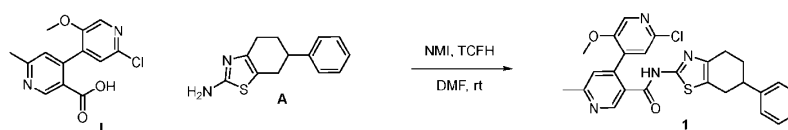
Intermediate Number	Structure	Name	LCMS (ESI, m/z): [M+H] ⁺
EI		<i>N</i> -(6-bromothiazolo[4,5-b]pyrazin-2-yl)-5'-cyano-5'-(difluoromethyl)-2'-methoxy-[1,1'-biphenyl]-2-carboxamide	[M-H] ⁻ = 514.0
EJ		<i>N</i> -(6-bromothiazolo[4,5-b]pyrazin-2-yl)-4-cyano-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzamide	516.8
EK		<i>N</i> -(6-bromothiazolo[4,5-b]pyrazin-2-yl)-5,5'-bis(difluoromethyl)-2'-methoxy-[1,1'-biphenyl]-2-carboxamide	[M-H] ⁻ = 539.0
EL		<i>N</i> -(6-bromothiazolo[4,5-b]pyrazin-2-yl)-5-chloro-5'-(difluoromethyl)-2'-methoxy-[1,1'-biphenyl]-2-carboxamide	525.3
EM		<i>N</i> -(6-bromothiazolo[4,5-b]pyrazin-2-yl)-4-chloro-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzamide	525.9
EN		<i>N</i> -(6-bromothiazolo[4,5-b]pyrazin-2-yl)-2-(2-chloro-5-methoxypyridin-4-yl)-4-cyanobenzamide	501.1

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EO		<i>N</i> -(6-bromothiazolo[4,5-b]pyrazin-2-yl)-4-chloro-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-5-fluorobenzamide	543.9
EP		<i>N</i> -(6-bromothiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(3-oxomorpholino)benzamide	591.2
EQ		<i>N</i> -(6-bromothiazolo[4,5-b]pyrazin-2-yl)-4-(1-(2,2-difluoroethyl)-1 <i>H</i> -pyrazol-3-yl)-2-(5-methoxy-2-methylpyridin-4-yl)benzamide	586.3
ER		<i>N</i> -(6-bromothiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4,5-difluorobenzamide	528.0
ES		<i>N</i> -(6-bromothiazolo[4,5-b]pyrazin-2-yl)-4-cyano-2-(5-methoxy-2-methylpyridin-4-yl)benzamide	481.2
ET		<i>N</i> -(6-bromothiazolo[4,5-b]pyrazin-2-yl)-4-(1-(2,2-difluoroethyl)-1 <i>H</i> -pyrazol-3-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzamide	622.1

Example 1

2'-chloro-5'-methoxy-6-methyl-N-(6-phenyl-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)-[4,4'-bipyridine]-3-carboxamide



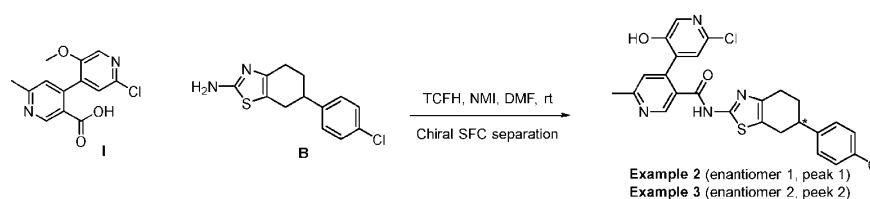
[0465] To a solution of Intermediate **I** (100.0 mg, 0.36 mmol) in DMF (2 mL) was added TCFH (151.5 mg, 0.54 mmol) and NMI (147.8 mg, 1.80 mmol), followed by Intermediate **A** (92.0 mg, 0.40 mmol). The resulting mixture was stirred at room temperature for 2 hrs. LCMS showed the reaction was complete. The reaction mixture was directly purified by

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prep-HPLC (0.05% NH_4HCO_3) to afford Example 1. LCMS (ESI, m/z): $[\text{M}+\text{H}]^+ = 491.5$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.49 (br s, 1H), 8.78 (s, 1H), 8.17 (s, 1H), 7.51 (s, 1H), 7.41 (s, 1H), 7.35-7.30 (m, 4H), 7.24-7.20 (m, 1H), 3.62 (s, 3H), 3.05-2.99 (m, 1H), 2.95-2.90 (m, 1H), 2.81-2.69 (m, 3H), 2.58 (s, 3H), 2.07-1.97 (m, 2H).

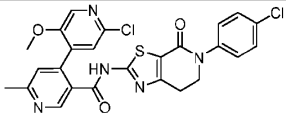
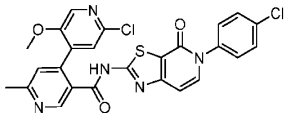
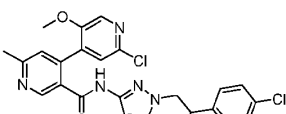
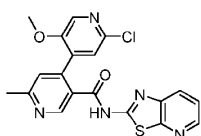
Examples 2 and 3

(S)-2'-chloro-N-(6-(4-chlorophenyl)-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide and (R)-2'-chloro-N-(6-(4-chlorophenyl)-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide

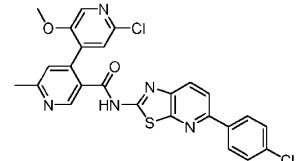
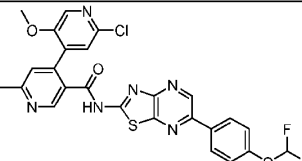
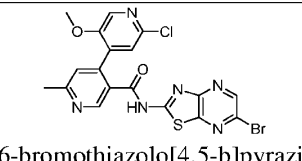


[0466] Following conditions analogous to synthesis of Example 1, Intermediate **I** (170 mg, 0.642 mmol), Intermediate **B** (268 mg, 0.962 mmol) were coupled to afford 2'-chloro-N-(6-(4-chlorophenyl)-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide (100 mg). The racemate was purified by SFC with the following conditions (OJ column, 0.05% DEA) to afford two separate enantiomers (S)-2'-chloro-N-(6-(4-chlorophenyl)-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide and (R)-2'-chloro-N-(6-(4-chlorophenyl)-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide. Example 2 (peak 1): LCMS (ESI, m/z): $[\text{M}+\text{H}]^+ = 525.2$; Retention time on UPCC (YMC Triart C18) 11.6 min; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.47 (br s, 1H), 8.78 (s, 1H), 8.17 (s, 1H), 7.51 (s, 1H), 7.40 (s, 1H), 7.38-7.34 (m, 4H), 3.62 (s, 3H), 3.09-3.01 (m, 1H), 2.95-2.87 (m, 1H), 2.77-2.66 (m, 3H), 2.58 (s, 3H), 2.05-1.95 (m, 2H). Example 3 (peak 2): LCMS (ESI, m/z): $[\text{M}+\text{H}]^+ = 525.2$, Retention time on UPCC (YMC Triart C18) 8.8 min; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.41 (br s, 1H), 8.78 (s, 1H), 8.17 (s, 1H), 7.51 (s, 1H), 7.40 (s, 1H), 7.38-7.34 (m, 4H), 3.62 (s, 3H), 3.09-3.01 (m, 1H), 2.95-2.87 (m, 1H), 2.77-2.66 (m, 3H), 2.58 (s, 3H), 2.05-1.95 (m, 2H).

[0467] Examples 4-10 were synthesized using conditions analogous to that used to synthesize Example 1, by reacting acid Intermediate **I** with appropriate aminothiazoles from intermediate list or commercial sources.

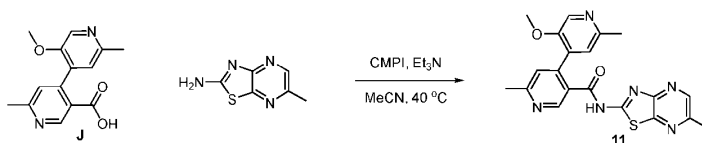
Example Number	Structure	NMR	LCMS (ESI, m/z): [M+H] ⁺
4	 2'-chloro-N-(5-(4-chlorophenyl)-4-oxo-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 8.86 (s, 1H), 8.17 (s, 1H), 7.52 (s, 1H), 7.48-7.33 (m, 5H), 4.04 (t, <i>J</i> = 6.8 Hz, 2H), 3.61 (s, 3H), 3.08 (t, <i>J</i> = 6.8 Hz, 2H), 2.59 (s, 3H).	540.1
5	 2'-chloro-N-(5-(4-chlorophenyl)-4-oxo-4,5-dihydrothiazolo[5,4-c]pyridin-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 13.31 (br s, 1H), 8.87 (s, 1H), 8.17 (s, 1H), 7.70 (d, <i>J</i> = 7.2 Hz, 1H), 7.60 (d, <i>J</i> = 9.6 Hz, 2H), 7.58 (s, 1H), 7.51 (d, <i>J</i> = 9.6 Hz, 2H), 7.45 (m, 1H), 6.84 (d, <i>J</i> = 7.2 Hz, 1H), 3.59 (s, 3H), 2.62 (s, 3H)	538.0
6	 2'-chloro-N-(6-(4-chlorophenyl)-6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.98 (br s, 1H), 8.76 (s, 1H), 8.23 (s, 1H), 7.62-7.51 (m, 5H), 7.42 (s, 1H), 6.41 (s, 1H), 5.16-5.11 (m, 2H), 4.95 (d, <i>J</i> = 14.8 Hz, 1H), 4.39 (dd, <i>J</i> = 12.4 Hz, 3.6 Hz, 1H), 3.97 (t, <i>J</i> = 11.6 Hz, 1H), 3.74 (s, 3H), 2.63 (s, 3H)	510.4
7	 2'-chloro-5'-methoxy-6-methyl-N-(thiazolo[5,4-b]pyridin-2-yl)-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 13.08 (br s, 1H), 8.88 (s, 1H), 8.47 (d, <i>J</i> = 4.8 Hz, 1H), 8.17 (s, 1H), 8.11 (d, <i>J</i> = 7.2, 1H), 7.57 (s, 1H), 7.49 (dd, <i>J</i> = 7.2 Hz, 4.8 Hz, 1H), 7.45 (s, 1H), 3.62 (s, 3H), 2.61 (s, 3H)	412.2

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8	 2'-chloro-N-(5-(4-chlorophenyl)thiazolo[5,4-b]pyridin-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.89 (s, 1H), 8.18–8.04 (m, 5H), 7.59–7.52 (m, 3H), 7.44 (s, 1H), 3.63 (s, 3H), 2.60 (s, 3H)	522.1
9	 4-(2-chloro-5-methoxy-4-pyridyl)-N-[6-(4-(difluoromethoxy)phenyl)thiazolo[4,5-b]pyrazin-2-yl]-6-methyl-pyridine-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.48 (br s, 1H), 9.16 (s, 1H), 8.94 (s, 1H), 8.22 (d, <i>J</i> = 8.4 Hz, 2H), 8.17 (s, 1H), 7.56 (s, 1H), 7.43 (s, 1H), 7.35 (t, <i>J</i> = 73.8 Hz, 1H), 7.33 (d, <i>J</i> = 8.4 Hz, 2H), 3.64 (s, 3H), 2.60 (s, 3H)	555.2
10	 N-(6-bromothiazolo[4,5-b]pyrazin-2-yl)-2'-chloro-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.59 (br s, 1H), 8.89 (s, 1H), 8.80 (s, 1H), 8.18 (s, 1H), 7.61 (s, 1H), 7.49 (s, 1H), 3.62 (s, 3H), 2.61 (s, 3H)	491.0

Example 11

5'-methoxy-2',6-dimethyl-N-(6-methylthiazolo[4,5-b]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide

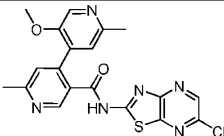
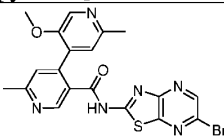
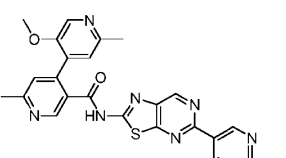


[0468] To a stirred solution of Intermediate **J** (100 mg, 0.387 mmol) in MeCN (3 mL) was added 6-methylthiazolo[4,5-b]pyrazin-2-amine (96.5 mg, 0.581 mmol), CMPI (197.8 mg, 0.774 mmol) and TEA (195.9 mg, 1.94 mmol). The mixture was stirred at 40 °C for 2 hrs under N₂. LCMS showed the reaction was complete. The mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (0.1% FA) to afford Example **11**.

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LCMS (ESI, m/z): [M+H]⁺ = 407.2; ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.29 (br s, 1H), 8.84 (s, 1H), 8.50 (s, 1H), 8.18 (s, 1H), 7.39 (s, 1H), 7.29 (s, 1H), 3.57 (s, 3H), 2.60 (s, 3H), 2.59 (s, 3H), 2.49 (s, 3H).

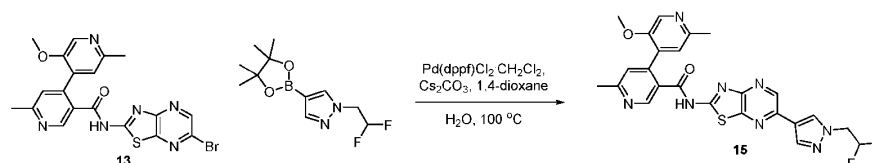
[0469] Examples **12-14** were synthesized using conditions analogous to that used to synthesize Example **11**, by reacting acid Intermediate **J** with appropriate aminothiazoles from intermediate list or commercial sources.

Example Number	Structure	NMR	LCMS (ESI, m/z): [M+H] ⁺
12	 <i>N</i> -(6-chlorothiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.54 (br s, 1H), 8.84 (s, 1H), 8.73 (s, 1H), 8.19 (s, 1H), 7.42 (s, 1H), 7.31 (s, 1H), 3.58 (s, 3H), 2.61 (s, 3H), 2.51 (s, 3H)	427.1
13	 <i>N</i> -(6-bromothiazolo[4,5-b]pyrazin-2-yl)-4-(5-methoxy-2-methyl-4-pyridyl)-6-methyl-pyridine-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.55 (s, 1H), 8.87 (s, 1H), 8.71 (s, 1H), 8.18 (s, 1H), 7.37 (s, 1H), 7.28 (s, 1H), 3.57 (s, 3H), 2.60 (s, 3H), 2.48 (s, 3H)	473.1
14	 5'-methoxy- <i>N</i> -(5-(6-methoxypyridin-3-yl)thiazolo[5,4-d]pyrimidin-2-yl)-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.15 (d, <i>J</i> = 2.4 Hz, 1H), 9.09 (s, 1H), 8.89 (s, 1H), 8.61 (dd, <i>J</i> = 8.8 Hz, 2.4 Hz, 1H), 8.18 (s, 1H), 7.33 (s, 1H), 7.25 (s, 1H), 6.95 (d, <i>J</i> = 8.8 Hz, 1H), 3.94 (s, 3H), 3.59 (s, 3H), 2.59 (s, 3H), 2.48 (s, 3H)	500.3

Example 15

N-(6-(1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide

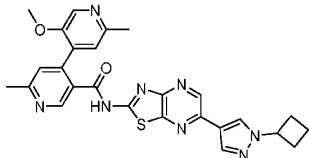
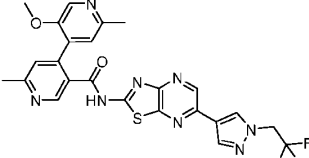
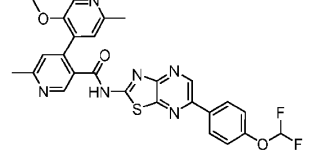
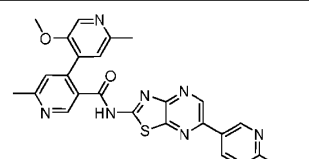
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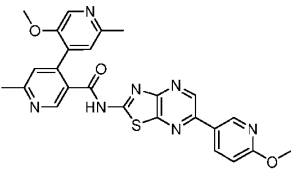
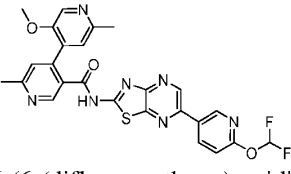
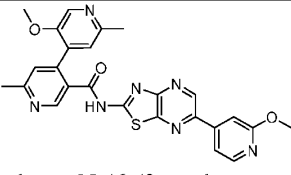
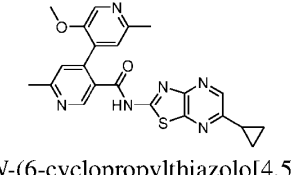
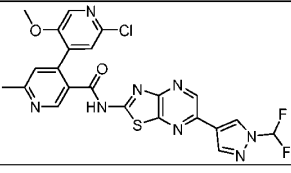


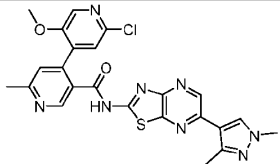
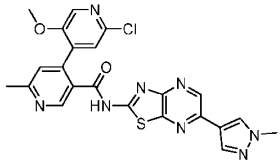
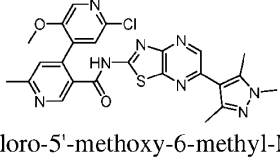
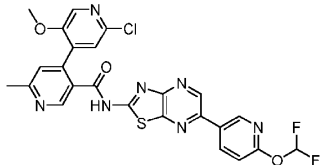
[0470] To a solution of Example **13** (100 mg, 0.212 mmol) in 1,4-dioxane (3 mL) and water (1 mL) was added 1-(2,2-difluoroethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (65.7 mg, 0.255 mmol), Pd(dppf)Cl₂·DCM complex (17 mg, 0.021 mmol) and Cs₂CO₃ (207 mg, 0.637 mmol) under N₂. The mixture was degassed and stirred for 5 hrs at 100 °C under N₂ atmosphere. LCMS showed the reaction was complete. The mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (0.05% FA) to afford Example **15**. LCMS (ESI, m/z): [M+H]⁺ = 523.3; ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.35 (br s, 1H), 9.01 (s, 1H), 8.83 (s, 1H), 8.55 (s, 1H), 8.26 (s, 1H), 8.19 (s, 1H), 7.41 (s, 1H), 7.31 (s, 1H), 6.57-6.30(m, 1H), 4.78-4.65 (m, 2H), 3.59 (s, 3H), 2.61 (s, 3H), 2.53 (s, 3H).

[0471] Examples **16-32** were synthesized using conditions analogous to that used to synthesize Example **15**, by reacting Intermediates **M**, Example **10** or Example **13** with appropriate boronic acids or boronic acid esters from commercial sources.

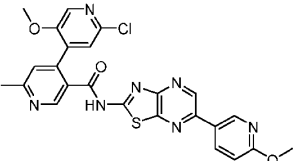
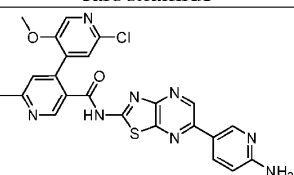
Example Number	Structure	NMR	LCMS (ESI, m/z): [M+H] ⁺
16	5'-methoxy-N-(6-(4-methoxyphenyl)thiazolo[4,5-b]pyridin-2-yl)-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.18 (br s, 1H), 8.83 (s, 1H), 8.82 (m, 1H), 8.66 (s, 1H), 8.18 (s, 1H), 7.71 (d, <i>J</i> = 8.8 Hz, 2H), 7.40 (s, 1H), 7.31 (s, 1H), 7.08 (d, <i>J</i> = 8.8 Hz, 2H), 3.82 (s, 3H), 3.57 (s, 3H), 2.61 (s, 3H), 2.52 (s, 3H)	498.3
17		¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.32 (br s, 1H), 8.99 (s, 1H), 8.83 (s, 1H), 8.52 (s, 1H), 8.19 (s, 1H), 8.16 (s, 1H), 7.41 (s, 1H), 7.32 (s, 1H), 4.04 (d, <i>J</i> = 7.2 Hz, 2H), 3.59 (s, 3H),	513.3

	<i>N</i> -[6-[1-(cyclopropylmethyl)pyrazol-4-yl]thiazolo[4,5- <i>b</i>]pyrazin-2-yl]-4-(5-methoxy-2-methyl-4-pyridyl)-6-methyl-pyridine-3-carboxamide	2.61 (s, 3H), 2.51 (s, 3H), 1.35-1.24 (m, 1H), 0.59-0.53 (m, 2H), 0.44-0.39 (m, 2H)	
18	 <i>N</i> -(6-(1-cyclobutyl-1H-pyrazol-4-yl)thiazolo[4,5- <i>b</i>]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.33 (br s, 1H), 8.97 (s, 1H), 8.83 (s, 1H), 8.59 (s, 1H), 8.19 (s, 1H), 8.17 (s, 1H), 7.40 (s, 1H), 7.31 (s, 1H), 4.94-4.86 (m, 1H), 3.59 (s, 3H), 2.61 (s, 3H), 2.51 (s, 3H), 2.45-2.39 (m, 4H), 1.86-1.77 (m, 2H).	513.3
19	 5'-methoxy-2',6-dimethyl- <i>N</i> -(6-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)thiazolo[4,5- <i>b</i>]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.37 (br s, 1H), 9.03 (s, 1H), 8.84 (s, 1H), 8.60 (s, 1H), 8.32 (s, 1H), 8.19 (s, 1H), 7.41 (s, 1H), 7.31 (s, 1H), 5.29-5.18 (m, 2H), 3.59 (s, 3H), 2.61 (s, 3H), 2.49 (s, 3H).	541.3
20	 <i>N</i> -(6-(4-(difluoromethoxy)phenyl)thiazolo[4,5- <i>b</i>]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.40 (br s, 1H), 9.19 (s, 1H), 8.87 (s, 1H), 8.22 (d, <i>J</i> = 8.8 Hz, 2H), 8.19 (s, 1H), 7.38 (s, 1H), 7.35 (t, <i>J</i> = 74.0 Hz, 1H), 7.33 (d, <i>J</i> = 8.8 Hz, 2H), 7.29 (s, 1H), 3.60 (s, 3H), 2.60 (s, 3H), 2.49 (s, 3H).	535.3
21	 <i>N</i> -(6-(6-cyanopyridin-3-yl)thiazolo[4,5- <i>b</i>]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.68 (br s, 1H), 9.53 (d, <i>J</i> = 2.4 Hz, 1H), 9.44 (s, 1H), 8.94 (s, 1H), 8.78 (dd, <i>J</i> = 8.4 Hz, 2.4 Hz, 1H), 8.34 (s, 1H), 8.23 (d, <i>J</i> = 8.4 Hz, 1H), 7.63 (s, 1H), 7.48 (s, 1H), 3.65 (s, 3H), 2.64 (s, 3H), 2.60 (s, 3H).	495.2

22	 5'-methoxy-N-(6-(6-methoxypyridin-3-yl)thiazolo[4,5-b]pyrazin-2-yl)-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.42 (br s, 1H), 9.22 (s, 1H), 8.97 (d, <i>J</i> = 2.4 Hz, 1H), 8.85 (s, 1H), 8.45 (dd, <i>J</i> = 8.4 Hz, 2.4 Hz, 1H), 8.19 (s, 1H), 7.41 (s, 1H), 7.31 (s, 1H), 6.99 (d, <i>J</i> = 8.4 Hz, 1H), 3.94 (s, 3H), 3.59 (s, 3H), 2.61 (s, 3H), 2.48 (s, 3H).	500.3
23	 <i>N</i>-(6-(6-(difluoromethoxy)pyridin-3-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.49 (br s, 1H), 9.27 (s, 1H), 9.04 (d, <i>J</i> = 2.0 Hz, 1H), 8.87 (s, 1H), 8.64 (dd, <i>J</i> = 8.4 Hz, 2.0 Hz, 1H), 8.19 (s, 1H), 7.98 (t, <i>J</i> = 72.4 Hz, 1H), 7.40 (s, 1H), 7.31 (s, 1H), 7.26 (d, <i>J</i> = 8.4 Hz, 1H), 3.59 (s, 3H), 2.61 (s, 3H), 2.51 (s, 3H).	536.3
24	 5'-methoxy-N-(6-(2-methoxypyridin-4-yl)thiazolo[4,5-b]pyrazin-2-yl)-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.54 (br s, 1H), 9.27 (s, 1H), 8.90 (s, 1H), 8.31 (d, <i>J</i> = 5.4 Hz, 1H), 8.19 (s, 1H), 7.73 (d, <i>J</i> = 5.4 Hz, 1H), 7.54 (s, 1H), 7.37 (s, 1H), 7.29 (s, 1H), 3.92 (s, 3H), 3.59 (s, 3H), 2.60 (s, 3H), 2.49 (s, 3H).	500.2
25	 <i>N</i>-(6-cyclopropylthiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.92 (s, 1H), 8.39 (s, 1H), 8.15 (s, 1H), 7.25 (s, 1H), 7.20 (s, 1H), 3.57 (s, 3H), 2.56 (s, 3H), 2.46 (s, 3H), 2.26-2.17 (m, 1H), 1.05-0.90 (m, 4H).	433.3
26	 <i>N</i>-(6-(6-chloro-3-methoxypyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.45 (br s, 1H), 9.02-8.90 (m, 3H), 8.46 (s, 1H), 8.16 (s, 1H), 7.89 (t, <i>J</i> = 59.2 Hz, 1H),	529.3

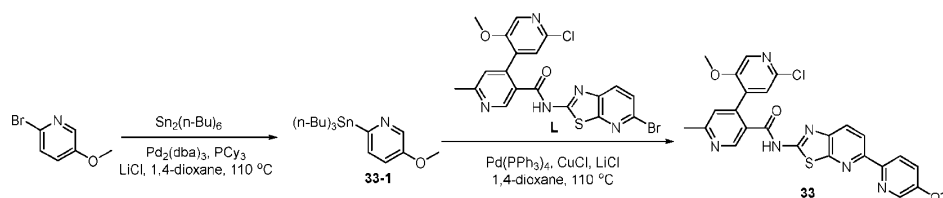
	2'-chloro-N-(6-(1-(difluoromethyl)-1H-pyrazol-4-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	7.52 (s, 1H), 7.38 (s, 1H) 3.64 (s, 3H), 2.59 (s, 3H)	
27	 2'-chloro-N-(6-(1,3-dimethyl-1H-pyrazol-4-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.35 (br s, 1H), 8.88 (s, 1H), 8.85 (s, 1H), 8.37 (s, 1H), 8.18 (s, 1H), 7.61 (s, 1H), 7.49 (s, 1H), 3.83 (s, 3H), 3.64 (s, 3H), 2.62 (s, 3H), 2.47 (s, 3H).	507.2
28	 2'-chloro-5'-methoxy-6-methyl-N-(6-(1-methyl-1H-pyrazol-4-yl)thiazolo[4,5-b]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.33 (br s, 1H), 8.93 (s, 1H), 8.90 (s, 1H), 8.44 (s, 1H), 8.17 (s, 1H), 8.12 (s, 1H), 7.58 (s, 1H), 7.45 (s, 1H), 3.91 (s, 3H), 3.64 (s, 3H), 2.61 (s, 3H).	493.2
29	 2'-chloro-5'-methoxy-6-methyl-N-(6-(1,3,5-trimethyl-1H-pyrazol-4-yl)thiazolo[4,5-b]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.38 (br s, 1H), 8.92 (s, 1H), 8.60 (s, 1H), 8.17 (s, 1H), 7.57 (s, 1H), 7.44 (s, 1H), 3.74 (s, 3H), 3.64 (s, 3H), 2.60 (s, 3H), 2.41 (s, 3H), 2.30 (s, 3H).	521.3
30	 2'-chloro-N-(6-(6-(difluoromethoxy)pyridin-3-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.52 (br s, 1H), 9.25 (s, 1H), 9.03 (d, <i>J</i> = 2.4 Hz, 1H), 8.93 (s, 1H), 8.64 (dd, <i>J</i> = 8.8 Hz, 2.4 Hz, 1H), 8.17 (s, 1H), 7.80 (t, <i>J</i> = 72.8 Hz, 1H), 7.58 (s, 1H), 7.45 (s, 1H), 7.27 (d, <i>J</i> = 8.4 Hz, 1H), 3.64 (s, 3H), 2.61 (s, 3H).	556.2

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31	 2'-chloro-N-(6-(6-(difluoromethoxy)pyridin-3-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.47 (br s, 1H), 9.20 (s, 1H), 8.96 (d, <i>J</i> = 2.4 Hz, 1H), 8.93 (s, 1H), 8.44 (dd, <i>J</i> = 8.4 Hz, 2.4 Hz, 1H), 8.17 (s, 1H), 7.58 (s, 1H), 7.46 (s, 1H), 6.99 (d, <i>J</i> = 8.8 Hz, 1H), 3.94 (s, 3H), 3.64 (s, 3H), 2.61 (s, 3H).	520.2
32	 N-(6-(6-aminopyridin-3-yl)thiazolo[4,5-b]pyrazin-2-yl)-2'-chloro-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.36 (s, 1H), 9.06 (s, 1H), 8.91 (s, 1H), 8.73 (d, <i>J</i> = 2.4 Hz, 1H), 8.17 (s, 1H), 8.15-8.11 (m, 1H), 7.57 (s, 1H), 7.45 (s, 1H), 6.57 (d, <i>J</i> = 8.8 Hz, 1H), 6.41 (s, 2H), 3.64 (s, 3H), 2.61 (s, 3H).	505.3

Example 33

2'-chloro-5'-methoxy-N-(5-(5-methoxypyridin-2-yl)thiazolo[5,4-b]pyridin-2-yl)-6-methyl-[4,4'-bipyridine]-3-carboxamide

**Step 1: 5-methoxy-2-(tributylstannyl)pyridine (33-1)**

[0472] A mixture of 2-bromo-5-methoxypyridine (500 mg, 2.66 mmol), Sn₂(n-Bu)₆ (4.63 g, 7.98 mmol), Pd₂(dba)₃ (244 mg, 0.266 mmol), tricyclohexylphosphine (149 mg, 0.531 mmol) and LiCl (564 mg, 13.3 mmol) in 1,4-dioxane (30 mL) was degassed and stirred at 110 ° C under N₂ for 4 hrs. LCMS showed the reaction was complete. The mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with petroleum ether) to afford 5-methoxy-2-(tributylstannyl)pyridine (550 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.45 (d, *J* = 2.8 Hz,

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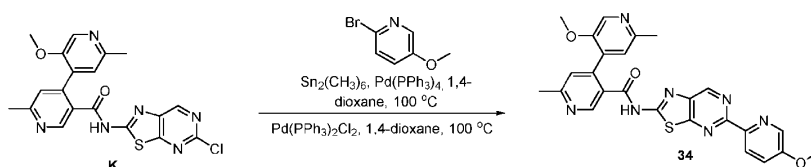
1H), 7.36 (d, $J = 8.0$ Hz, 1H), 7.23 (dd, $J = 8.0$ Hz, 2.8 Hz, 1H), 3.79 (s, 3H), 1.58-1.42 (m, 6H), 1.32-1.23 (m, 6H), 1.10-0.98 (m, 6H), 0.83 (t, $J = 7.2$, 9H).

Step 2: 2'-chloro-5'-methoxy-N-(5-(5-methoxypyridin-2-yl)thiazolo[5,4-b]pyridin-2-yl)-6-methyl-[4,4'-bipyridine]-3-carboxamide (33-2)

[0473] A mixture of Intermediate **L** (100 mg, 0.204 mmol), 5-methoxy-2-(tributylstannyl)pyridine (121.7 mg, 0.306 mmol), CuCl (40.4 mg, 0.408 mmol), LiCl (43.2 mg, 1.02 mmol) and Pd(PPh₃)₄ (47.1 mg, 0.041 mmol) in 1,4-dioxane (5 mL) was degassed and stirred at 110 °C under N₂ for 16 hrs. LCMS showed the reaction was complete. The mixture was filtered through a celite pad. The filtrate was concentrated under reduced pressure and purified by prep-HPLC (0.1% NH₄OH) to afford Example **33**. LCMS (ESI, m/z): $[M+H]^+ = 519.3$; ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.13 (br s, 1H), 8.87 (s, 1H), 8.44-8.37 (m, 3H), 8.21 (d, $J = 8.4$ Hz, 1H), 8.18 (s, 1H), 7.60 (s, 1H), 7.55 (dd, $J = 8.4$ Hz, 3.2 Hz, 1H), 7.48 (s, 1H), 3.91 (s, 3H), 3.63 (s, 3H), 2.61 (s, 3H).

Example 34

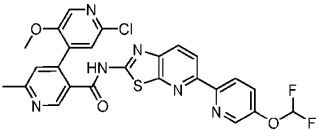
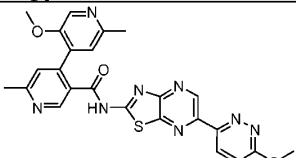
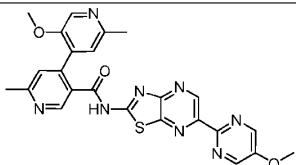
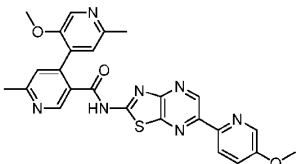
5'-methoxy-N-(5-(5-methoxypyridin-2-yl)thiazolo[5,4-d]pyrimidin-2-yl)-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide

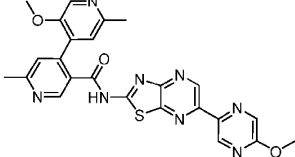
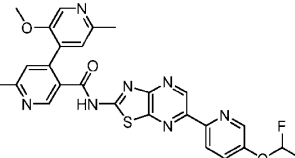
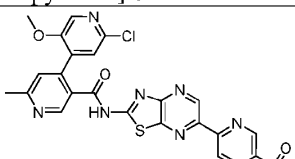
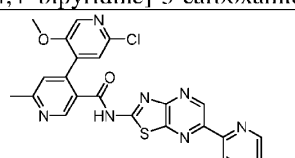


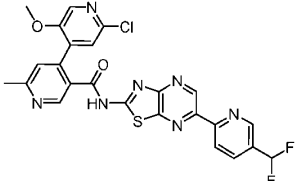
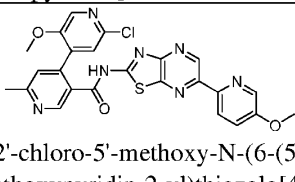
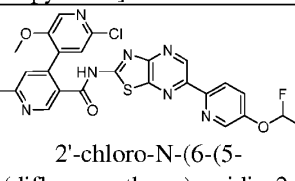
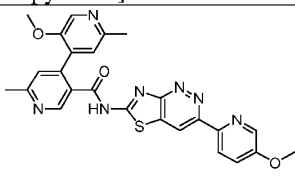
[0474] To a solution of 2-bromo-5-methoxypyridine (110 mg, 0.59 mmol) in 1,4-dioxane (4 mL) was added hexamethylditin (231 mg, 0.71 mmol) and Pd(PPh₃)₄ (67 mg, 0.058 mmol) under N₂. The mixture was degassed, then stirred at 100 °C under N₂ for 2 hrs. After cooling to room temperature, Intermediate **K** (124 mg, 0.29 mmol) and Pd(PPh₃)₂Cl₂ (41 mg, 0.058 mmol) were added. The mixture was degassed and stirred at 100 °C under N₂ for 2 hrs. LCMS showed the reaction was complete. After concentration in vacuo, the residue was purified by prep-HPLC (0.05% NH₄HCO₃) to afford Example **34**. LCMS (ESI, m/z): $[M+H]^+ = 500.3$; ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.34 (br s, 1H), 9.22 (s, 1H), 8.85 (s, 1H), 8.46-8.41 (m, 2H), 8.19 (s, 1H), 7.55 (dd, $J = 8.4$ Hz, 3.2 Hz, 1H), 7.40 (s, 1H), 7.30 (s, 1H), 3.92 (s, 3H), 3.59 (s, 3H), 2.61 (s, 3H), 2.51 (s, 3H).

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[0475] Examples **35-46** were synthesized using conditions analogous to that used to synthesize Examples **33** and **34**, by converting appropriate commercially available heteroaryl halide to the corresponding tin reagents and subsequent Stille coupling.

Example Number	Structure	NMR	LCMS (ESI, m/z): [M+H] ⁺
35	 2'-chloro-N-(5-(5-(difluoromethoxy)pyridin-2-yl)thiazolo[5,4-b]pyridin-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.14 (br s, 1H), 8.89 (s, 1H), 8.59 (d, <i>J</i> = 2.8 Hz, 1H), 8.49-8.45 (m, 2H), 8.22 (d, <i>J</i> = 8.5 Hz, 1H), 8.17 (s, 1H), 7.83-7.80 (dd, <i>J</i> = 8.5 Hz, 2.8 Hz, 1H), 7.58 (s, 1H), 7.46 (s, 1H), 7.41 (t, <i>J</i> = 72 Hz, 1H), 3.63 (s, 3H), 2.61 (s, 3H).	555.2
36	 5'-methoxy-N-(6-(6-methoxypyridazin-3-yl)thiazolo[4,5-b]pyrazin-2-yl)-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.55 (br s, 1H), 9.58 (s, 1H), 8.88 (s, 1H), 8.44 (d, <i>J</i> = 9.2 Hz, 1H), 8.20 (s, 1H), 7.43-7.38 (m, 2H), 7.32 (s, 1H), 4.13 (s, 3H), 3.59 (s, 3H), 2.61 (s, 3H), 2.49 (s, 3H)	501.3
37	 5'-methoxy-N-(6-(5-methoxypyrimidin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.54 (br s, 1H), 9.44 (s, 1H), 8.89 (s, 1H), 8.74 (s, 2H), 8.19 (s, 1H), 7.37 (s, 1H), 7.29 (s, 1H), 4.01 (s, 3H), 3.60 (s, 3H), 2.60 (s, 3H), 2.49 (s, 3H).	501.3
38	 5'-methoxy-N-(6-(5-methoxypyrimidin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.48 (br s, 1H), 9.46 (s, 1H), 8.85 (s, 1H), 8.45 (d, <i>J</i> = 3.2 Hz, 1H), 8.33 (d, <i>J</i> = 8.8 Hz, 1H), 8.20 (s, 1H), 7.58 (dd, <i>J</i> = 8.8 Hz, 3.2 Hz, 1H), 7.42 (s, 1H), 7.33 (s, 1H),	500.3

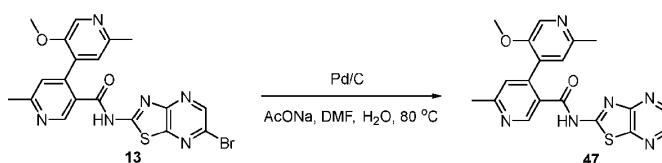
	5'-methoxy-N-(6-(5-methoxypyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	3.92 (s, 3H), 3.60 (s, 3H), 2.61 (s, 3H), 2.49 (s, 3H).	
39	 5'-methoxy-N-(6-(5-methoxypyrazin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.50 (br s, 1H), 9.26 (s, 1H), 9.06 (s, 1H), 8.95 (s, 1H), 8.44 (s, 1H), 8.18 (s, 1H), 7.31 (s, 1H), 7.24 (s, 1H), 4.00 (s, 3H), 3.59 (s, 3H), 2.58 (s, 3H), 2.48 (s, 3H).	501.2
40	 N-(6-(5-(difluoromethoxy)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.53 (br s, 1H), 9.47 (s, 1H), 8.89 (s, 1H), 8.63 (s, 1H), 8.43 (s, 1H), 8.19 (s, 1H), 7.85 (s, 1H), 7.61-7.23 (m, 3H), 3.59 (s, 3H), 2.60 (s, 3H), 2.50 (s, 3H).	534.2
41	 2'-chloro-5'-methoxy-6-methyl-N-(6-(5-(methylsulfonyl)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.53 (br s, 1H), 9.47 (s, 1H), 8.89 (s, 1H), 8.63 (s, 1H), 8.43 (s, 1H), 8.19 (s, 1H), 7.85 (s, 1H), 7.61-7.23 (m, 3H), 3.59 (s, 3H), 2.60 (s, 3H), 2.50 (s, 3H).	568.2
42	 2'-chloro-N-(6-(5-chloropyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.61 (br s, 1H), 9.50 (s, 1H), 8.91 (s, 1H), 8.78 (d, <i>J</i> = 2.8 Hz, 1H), 8.39 (d, <i>J</i> = 8.4 Hz, 1H), 8.18 (s, 1H), 8.10 (dd, <i>J</i> = 8.4 Hz, 2.8 Hz, 1H), 7.61 (s, 1H), 7.48 (s, 1H), 3.64 (s, 3H), 2.62 (s, 3H).	524.2

43	 2'-chloro-N-(6-(5-(difluoromethyl)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.63 (br s, 1H), 9.60 (s, 1H), 8.95 (s, 1H), 8.91 (s, 1H), 8.53 (d, <i>J</i> = 8.4 Hz, 1H), 8.21 (d, <i>J</i> = 8.4 Hz, 1H), 8.19 (s, 1H), 7.63 (s, 1H), 7.50 (s, 1H), 7.26 (t, <i>J</i> = 55.2 Hz, 1H), 3.65 (s, 3H), 2.62 (s, 3H).	540.3
44	 2'-chloro-5'-methoxy-N-(6-(5-methoxypyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-6-methyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.46 (br s, 1H), 9.41 (s, 1H), 8.93 (s, 1H), 8.45-8.27 (m, 2H), 8.17 (s, 1H), 7.57 (s, 2H), 7.43 (s, 1H), 3.91 (s, 3H), 3.64 (s, 3H), 2.60 (s, 3H).	520.1
45	 2'-chloro-N-(6-(5-(difluoromethoxy)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.57 (br s, 1H), 9.46 (s, 1H), 8.92 (s, 1H), 8.63 (d, <i>J</i> = 2.8 Hz, 1H), 8.42 (d, <i>J</i> = 8.8 Hz, 1H), 8.17 (s, 1H), 7.85 (dd, <i>J</i> = 8.8 Hz, 2.8 Hz, 1H), 7.61 (s, 1H), 7.45 (s, 1H), 7.42 (t, <i>J</i> = 73.2 Hz, 1H), 3.64 (s, 3H), 2.61 (s, 3H).	556.1
46	 5'-methoxy-N-(3-(5-methoxypyridin-2-yl)thiazolo[4,5-c]pyridazin-6-yl)-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.52 (br s, 1H), 8.93 (br s, 2H), 8.55 (d, <i>J</i> = 8.4 Hz, 1H), 8.43 (d, <i>J</i> = 3.2 Hz, 1H), 8.18 (s, 1H), 7.61 (dd, <i>J</i> = 8.4 Hz, 3.2 Hz, 1H), 7.34 (s, 1H), 7.25 (s, 1H), 3.92 (s, 3H), 3.59 (s, 3H), 2.59 (s, 3H), 2.48 (s, 3H).	500.2

Example 47

5'-methoxy-2',6-dimethyl-N-(thiazolo[4,5-b]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide

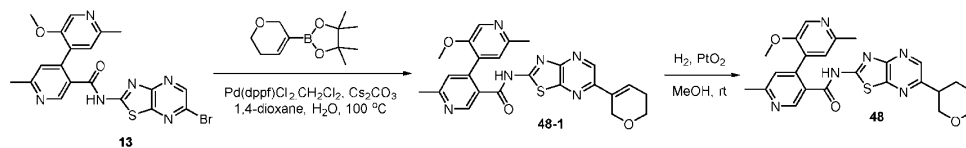
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[0476] To a stirred solution of Example **13** (70.0 mg, 0.149 mmol) in DMF (2 ml) and water (0.5 mL) was added NaOAc (40.3 mg, 0.492 mmol) and Pd/C (containing 55% water, 17.3 mg). The reaction mixture was stirred at 80 °C for 14 hrs. LCMS showed the reaction was complete. The mixture was filtered and the filtrate concentrated under vacuum. The residue was purified by prep-HPLC (0.05% FA) to afford Example **47**. LCMS (ESI, m/z): $[M+H]^+ = 393.2$; ^1H NMR (400 MHz, DMSO- d_6) δ 13.42 (br s, 1H), 8.84 (s, 1H), 8.63 (d, $J = 2.4$ Hz, 1H), 8.49 (d, $J = 2.4$ Hz, 1H), 8.18 (s, 1H), 7.40 (s, 1H), 7.31 (s, 1H), 3.58 (s, 3H), 2.60 (s, 3H), 2.49 (s, 3H).

Example 48

5'-methoxy-2',6-dimethyl-N-(6-(tetrahydro-2H-pyran-3-yl)thiazolo[4,5-b]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide



Step 1: N-(6-(5,6-dihydro-2H-pyran-3-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide (48-1)

[0477] To a solution of Example **13** (100 mg, 0.212 mmol) in 1,4-dioxane (3 mL) and water (0.5 mL) was added 2-(5,6-dihydro-2H-pyran-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (44.6 mg, 0.212 mmol), Pd(dppf)Cl₂·CH₂Cl₂ complex (17 mg, 0.021 mmol) and Cs₂CO₃ (207 mg, 0.635 mmol) under N₂. The mixture was degassed and stirred at 100 °C under N₂ for 3 hrs. LCMS showed the reaction was complete. The mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (0.1% FA) to give N-(6-(5,6-dihydro-2H-pyran-3-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide (22 mg). LCMS (ESI, m/z): $[M+H]^+ = 475.2$.

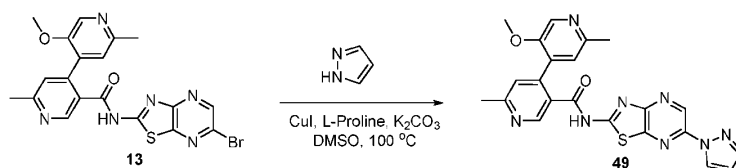
Step 2: 5'-methoxy-2',6-dimethyl-N-(6-(tetrahydro-2H-pyran-3-yl)thiazolo[4,5-b]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide (48)

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[0478] To a solution of N-(6-(5,6-dihydro-2H-pyran-3-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide (22 mg, 0.046 mmol) in MeOH (3 mL) was added PtO₂ (2.3 mg, 0.010 mmol) under N₂. The mixture was purged with H₂, then stirred under H₂ atmosphere (1 atm) at room temperature for 16 hrs. LCMS showed the reaction was complete. The mixture was filtered. The filtrate was concentrated under vacuum and purified by prep-HPLC (0.1% NH₄HCO₃) to afford Example **48**. LCMS (ESI, m/z): [M+H]⁺ = 477.3; ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.34 (br s, 1H), 8.86 (s, 1H), 8.53 (s, 1H), 8.17 (s, 1H), 7.36 (s, 1H), 7.27 (s, 1H), 3.98 (dd, *J* = 8.8 Hz, 3.2 Hz, 1H), 3.88 (d, *J* = 7.2 Hz, 1H), 3.57 (s, 3H), 3.52 (t, *J* = 10.8 Hz, 1H), 3.41 (m, 1H), 3.11 (m, 1H), 2.59 (s, 3H), 2.48 (s, 3H), 2.01 (m, 1H), 1.90 (m, 1H), 1.68 (m, 2H).

Example 49

N-(6-(1H-pyrazol-1-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide

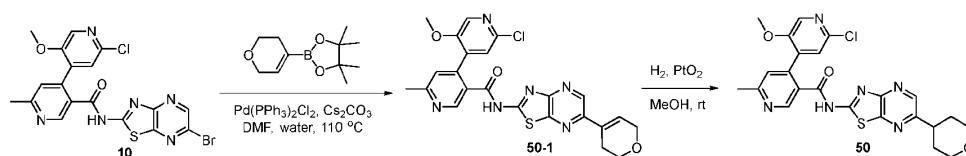


[0479] To a solution of Example **13** (100 mg, 0.212 mmol) in DMSO (4 mL) was added 1H-pyrazole (43 mg, 0.632 mmol), CuI (8.1 mg, 0.043 mmol), L-proline (4.9 mg, 0.043 mmol) and K₂CO₃ (58.6 mg, 0.424 mmol) under N₂. The mixture was degassed and stirred at 100 °C under N₂ for 18 hrs. LCMS showed the reaction was complete. The mixture was directly purified by prep-HPLC (0.05% FA) to afford Example **49**. LCMS (ESI, m/z): [M+H]⁺ = 459.3; ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.54 (br s, 1H), 9.21 (s, 1H), 8.89 (s, 1H), 8.68 (d, *J* = 2.8 Hz, 1H), 8.28 (s, 1H), 7.93 (d, *J* = 2.0 Hz, 1H), 7.51 (s, 1H), 7.45 (s, 1H), 6.66 (dd, *J* = 2.8 Hz, 2.0 Hz, 1H), 3.63 (s, 3H), 2.63 (s, 3H), 2.56 (s, 3H).

Example 50

2'-chloro-5'-methoxy-N-(6-(5-methoxypyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-6-methyl-[4,4'-bipyridine]-3-carboxamide

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Step 1: 2'-chloro-N-(6-(3,6-dihydro-2H-pyran-4-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide (50-1)

[0480] A mixture of Example **10** (150 mg, 0.305 mmol), 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (96.1 mg, 0.458 mmol), Pd(PPh₃)₂Cl₂ (42.8 mg, 0.061 mmol) and Cs₂CO₃ (248 mg, 0.763 mmol) in DMF (8 mL) and water (2 mL) was degassed and stirred at 110 °C under N₂ for 4 hrs. LCMS showed the reaction was complete. The mixture was concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (eluting with 1-5% MeOH in DCM) to afford 2'-chloro-N-(6-(3,6-dihydro-2H-pyran-4-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide (110 mg). LCMS (ESI, m/z): [M+H]⁺ = 495.1.

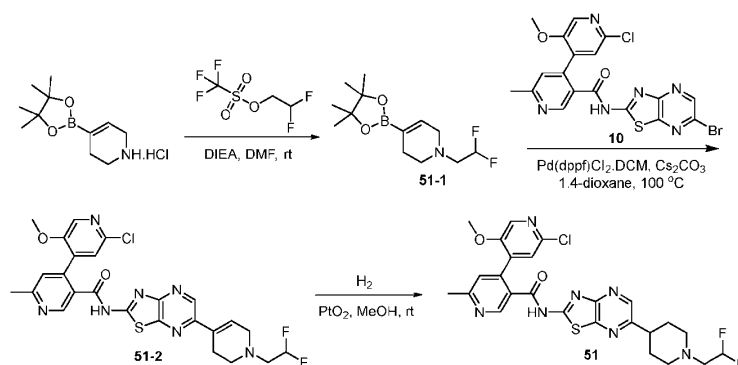
Step 2: 2'-chloro-5'-methoxy-6-methyl-N-(6-(tetrahydro-2H-pyran-4-yl)thiazolo[4,5-b]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide (50)

[0481] To a mixture of 2'-chloro-N-(6-(3,6-dihydro-2H-pyran-4-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide (70.0 mg, 0.141 mmol) in MeOH (20 mL) was added PtO₂ (64.2 mg, 0.283 mmol) under N₂. The mixture was purged with H₂ and stirred at room temperature for 16 hrs under H₂ (1 atm). LCMS showed the reaction was complete. The mixture was filtered through a celite pad. The filtrate was concentrated under reduced pressure. The residue was purified by prep-HPLC (0.1% FA) to afford Example **50**. LCMS (ESI, m/z): [M+H]⁺ = 497.3; ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.36 (br s, 1H), 8.89 (s, 1H), 8.58 (s, 1H), 8.16 (s, 1H), 7.58 (s, 1H), 7.46 (s, 1H), 4.01-3.95 (m, 2H), 3.62 (s, 3H), 3.51-3.44 (m, 2H), 3.18-3.10 (m, 1H), 2.61 (s, 3H), 1.87-1.79 (m, 4H).

Example 51

2'-chloro-N-(6-(1-(2,2-difluoroethyl)piperidin-4-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide

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Step 1: 1-(2,2-difluoroethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine (**51-1**)

[0482] To a solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine hydrochloride (1.5 g, 6.11 mmol) in DMF (6 mL) was added 2,2-difluoroethyl trifluoromethanesulfonate (2.2 g, 10.3 mmol) and DIPEA (1.85 g, 14.2 mmol). The mixture was stirred at room temperature for 2 hrs. After completion, the reaction mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with saturated brine, dried over anhydrous Na_2SO_4 , filtered and concentrated to afford 1-(2,2-difluoroethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine (1.0 g). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 6.36-6.32 (m, 1H), 6.11 (tt, $J = 55.6$ Hz, 4.4 Hz, 1H), 3.10 (m, 2H), 2.76 (td, $J = 15.6$ Hz, 4.4 Hz, 2H), 2.57 (t, $J = 5.6$ Hz, 2H), 2.12-2.07 (m, 2H), 1.19 (s, 12H).

Step 2: 2'-chloro-N-(6-(1-(2,2-difluoroethyl)-1,2,3,6-tetrahydropyridin-4-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide (**51-2**)

[0483] To a solution of Example **10** (100 mg, 0.203 mmol) in 1,4-dioxane (4 mL) was added 1-(2,2-difluoroethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine (66.7 mg, 0.244 mmol), $\text{Pd(dppf)Cl}_2\cdot\text{DCM}$ complex (16.2 mg, 0.020 mmol) and Cs_2CO_3 (199 mg, 0.61 mmol) under N_2 . The mixture was degassed and stirred at 100 °C under N_2 for 2 hrs. LCMS showed the reaction was complete. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (0.05% FA) to afford 2'-chloro-N-(6-(1-(2,2-difluoroethyl)-1,2,3,6-tetrahydropyridin-4-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide (50 mg). LCMS (ESI, m/z): $[\text{M}+\text{H}]^+ = 558.2$.

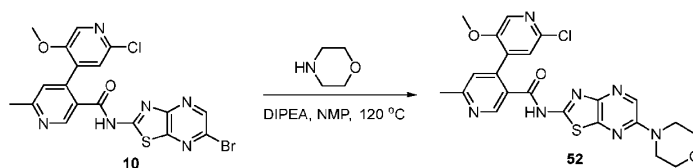
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Step 3: 2'-chloro-N-(6-(1-(2,2-difluoroethyl)piperidin-4-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide (**51**)

[0484] To a solution of 2'-chloro-N-(6-(1-(2,2-difluoroethyl)-1,2,3,6-tetrahydropyridin-4-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide (50 mg, 0.90 mmol) in methanol (2 mL) was added PtO_2 (5 mg, 0.02 mmol) under N_2 . The mixture was purged with H_2 and stirred at room temperature under H_2 (1 atm) for 2 hrs. LCMS showed the reaction was complete. The mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (0.05% FA) to afford Example **51**. LCMS (ESI, m/z): $[\text{M}+\text{H}]^+ = 560.3$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 13.32 (br s, 1H), 8.90 (s, 1H), 8.55 (s, 1H), 8.16 (s, 1H), 7.57 (s, 1H), 7.44 (s, 1H), 6.16 (tt, $J = 56.0$ Hz, 4.0 Hz, 1H), 3.62 (s, 3H), 3.03 (m, 2H), 2.89-2.72 (m, 3H), 2.60 (s, 3H), 2.35-2.27 (m, 2H), 1.88-1.77 (m, 4H).

Example 52

2'-chloro-5'-methoxy-6-methyl-N-(6-morpholinothiazolo[4,5-b]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide

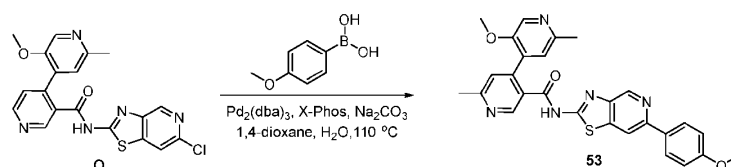


[0485] To a solution of Example **10** (70.0 mg, 0.14 mmol) in NMP (2 mL) was added morpholine (124 mg, 1.42 mmol) and DIPEA (185 mg, 1.43 mmol). The mixture was stirred at 120 °C for 16 hrs under N_2 . LCMS showed the reaction was complete. The reaction mixture was purified by prep-HPLC (0.05% NH_4HCO_3) to afford Example **52**. LCMS (ESI, m/z): $[\text{M}+\text{H}]^+ = 498.2$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 13.00 (br s, 1H), 8.87 (s, 1H), 8.31 (s, 1H), 8.16 (s, 1H), 7.55 (s, 1H), 7.42 (s, 1H), 3.77-3.70 (m, 4H), 3.62 (s, 3H), 3.57-3.51 (m, 4H), 2.59 (s, 3H).

Example 53

5'-methoxy-N-(6-(4-methoxyphenyl)thiazolo[4,5-c]pyridin-2-yl)-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide

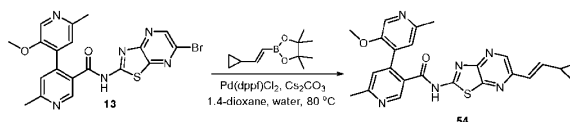
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[0486] A mixture of Intermediate **O** (200 mg, 0.470 mmol), (4-methoxyphenyl)boronic acid (286 mg, 1.88 mmol), X-Phos (45 mg, 0.094 mmol), Pd₂(dba)₃ (43 mg, 0.047 mmol) and Na₂CO₃ (149 mg, 1.41 mmol) in 1,4-dioxane (7.5 mL) and water (2.5 mL) was degassed. The mixture was stirred at 110 °C under N₂ for 1 hr. LCMS showed the reaction was complete. The mixture was treated with water and extracted with DCM/MeOH (10:1). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by prep-HPLC (0.1% FA) to give Example **53**. LCMS (ESI, m/z): [M+H]⁺ = 498.3; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.99 (s, 1H), 8.85 (s, 1H), 8.49 (s, 1H), 8.18 (s, 1H), 8.07 (d, *J* = 8.8 Hz, 2H), 7.36 (s, 1H), 7.27 (s, 1H), 7.05 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H), 3.57 (s, 3H), 2.59 (s, 3H), 2.48 (s, 3H).

Example 54

(*E*)-*N*-(6-(2-cyclopropylvinyl)thiazolo[4,5-*b*]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide

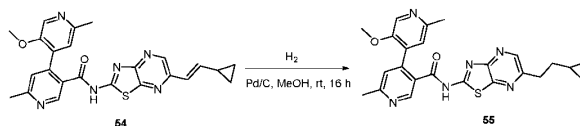


[0487] A mixture of Example **13** (150 mg, 0.318 mmol), (*E*)-2-(2-cyclopropylvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (92.6 mg, 0.477 mmol), Pd(dppf)Cl₂ (23.3 mg, 0.032 mmol) and Cs₂CO₃ (207 mg, 0.636 mmol) in 1,4-dioxane (8 mL) and water (2 mL) was degassed and stirred at 80 °C for 2 hrs under N₂ atmosphere. LCMS showed the reaction was complete. The reaction mixture was concentrated under vacuum. The residue was purified by reversed-phase column chromatography (0.1% FA) to afford Example **54** (110 mg). LCMS (ESI, m/z): [M+H]⁺ = 459.3; ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.32 (brs, 1H), 8.82 (s, 1H), 8.57 (s, 1H), 8.18 (s, 1H), 7.40 (s, 1H), 7.31 (s, 1H), 6.72 (d, *J* = 15.6 Hz, 1H), 6.43 (dd, *J* = 15.6 Hz, 9.6 Hz, 1H), 3.58 (s, 3H), 2.60 (s, 3H), 2.49 (s, 3H), 1.71-1.68 (m, 1H), 0.92-0.82 (m, 2H), 0.70-0.62 (m, 2H).

Example 55

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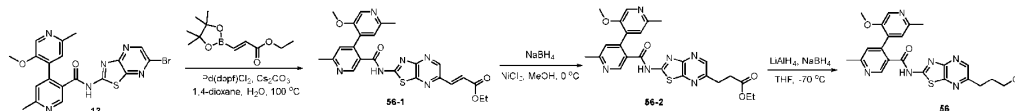
N-(6-(2-cyclopropylethyl)thiazolo[4,5-*b*]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide



[0488] A mixture of Example **54** (90 mg, 0.196 mmol) in MeOH (10 mL) was added Pd/C (10% palladium on carbon, wetted with ca.55% water for safety, 90 mg) under N₂ atmosphere. The mixture was purged with H₂, then stirred under H₂ atmosphere (1 atm) at room temperature for 16 hrs. LCMS showed the reaction was complete. The reaction mixture was filtered through a Celite pad. The filtrate was concentrated under vacuum. The residue was purified by prep-HPLC (0.1% FA) to afford Example **55**. LCMS (ESI, *m/z*): [M+H]⁺ = 461.4; ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.29 (brs, 1H), 8.83 (s, 1H), 8.53 (s, 1H), 8.18 (s, 1H), 7.39 (s, 1H), 7.30 (s, 1H), 3.57 (s, 3H), 2.95 (t, *J* = 7.6 Hz, 2H), 2.60 (s, 3H), 2.49 (s, 3H), 1.63 (m, 2H), 0.73 (m, 1H), 0.41-0.36 (m, 2H), 0.06-0.01 (m, 2H).

Example 56

N-(6-(3-hydroxypropyl)thiazolo[4,5-*b*]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide



Step 1: ethyl (E)-3-(2-(5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamido)thiazolo[4,5-*b*]pyrazin-6-yl)acrylate (**56-1**)

[0489] To a solution of Example **13** (203 mg, 0.43 mmol) in 1,4-dioxane (5 mL) and water (1 mL) was added ethyl (*E*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acrylate (117.6 mg, 0.52 mmol), Pd(dppf)Cl₂·CH₂Cl₂ (32.4 mg, 0.04 mmol) and Cs₂CO₃ (277 mg, 0.85 mmol) under N₂. The mixture was degassed and stirred at 100 °C for 3 hrs under N₂ atmosphere. LCMS showed the reaction was complete. The reaction mixture was concentrated under reduced pressure. The residue was purified with flash column chromatography, eluting with PE/EtOAc (1:1) to give ethyl (E)-3-(2-(5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamido)thiazolo[4,5-*b*]pyrazin-6-yl)acrylate (**56-1**, 150 mg). LCMS (ESI, *m/z*): [M+H]⁺ = 491.3.

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Step 2: ethyl 3-(2-(5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamido)thiazolo[4,5-b]pyrazin-6-yl)propanoate (**56-2**)

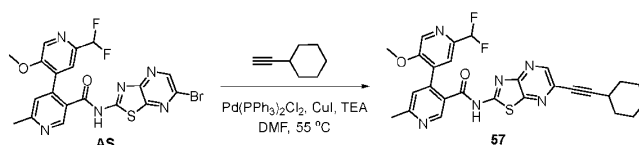
[0490] To a solution of ethyl (E)-3-(2-(5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamido)thiazolo[4,5-b]pyrazin-6-yl)acrylate (**56-1**, 150 mg, 0.306 mmol) and NiCl₂ (4 mg, 0.031 mmol) in MeOH (5 mL) was added NaBH₄ (11 mg, 0.306 mmol) at 0 °C. After stirring at room temperature for 2 hrs, the filtrate was concentrated under vacuum. The residue was purified by prep-HPLC (0.1% FA) to afford ethyl 3-(2-(5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamido)thiazolo[4,5-b]pyrazin-6-yl)propanoate (**56-2**, 90 mg). LCMS (ESI, m/z): [M+H]⁺ = 493.2.

Step 3: *N*-(6-(3-hydroxypropyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide (**56**)

[0491] To a solution of ethyl 3-(2-(5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamido)thiazolo[4,5-b]pyrazin-6-yl)propanoate (**56-2**, 90 mg, 0.182 mmol) in dry THF (5 mL) was added LiAlH₄ (7 mg, 0.182 mmol) and NaBH₄ (11 mg, 0.306 mmol) under N₂ at -70 °C. After stirring at -70 °C for 1 hr, the reaction mixture was quenched with water and concentrated to dryness under vacuum. The residue was purified by prep-HPLC (0.05% NH₄HCO₃) to afford Example **56**. LCMS (ESI, m/z): [M+H]⁺ = 451.3; ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.31 (brs, 1H), 8.83 (s, 1H), 8.54 (s, 1H), 8.20 (s, 1H), 7.42 (s, 1H), 7.34 (s, 1H), 4.50 (brs, 1H), 3.58 (s, 3H), 3.46 (t, *J* = 6.4 Hz, 2H), 2.92 (t, *J* = 6.4 Hz, 2H), 2.61 (s, 3H), 2.49 (s, 3H), 1.89 (m, 2H).

Example 57

N-(6-(cyclohexylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2'-(difluoromethyl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide

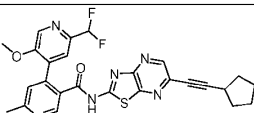
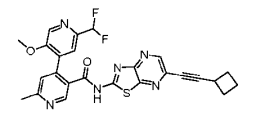
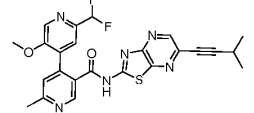
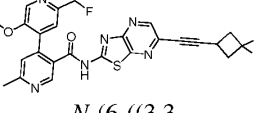


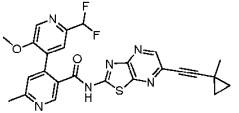
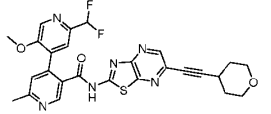
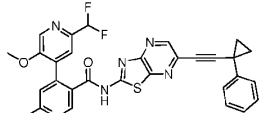
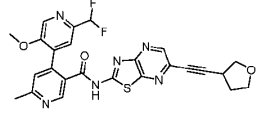
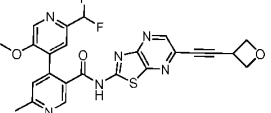
[0492] To a solution of Intermediate **AS** (80.0 mg, 0.16 mmol) in DMF (2 mL) was added ethynylcyclohexane (85.3 mg, 0.79 mmol), CuI (3.8 mg, 0.020 mmol), Et₃N (81 mg, 0.80 mmol) and Pd(PPh₃)₂Cl₂ (14.1 mg, 0.020 mmol) under N₂. The mixture was degassed and stirred at 55 °C for 16 hrs under N₂ atmosphere. LCMS showed the reaction was complete. The reaction mixture was purified by prep-HPLC (0.1% FA) to afford Example **57**. LCMS (ESI, m/z): [M+H]⁺ = 535.4; ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.56 (brs, 1H), 8.93

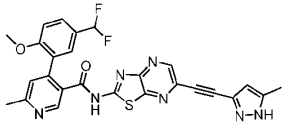
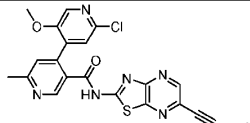
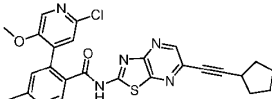
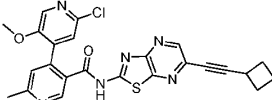
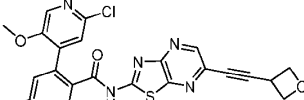
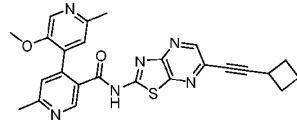
- 210 -

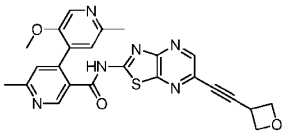
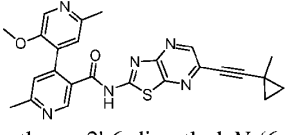
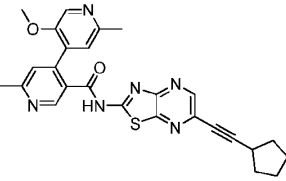
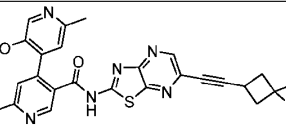
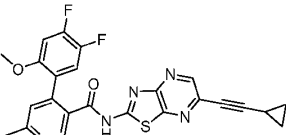
(s, 1H), 8.58 (s, 1H), 8.46 (s, 1H), 7.71 (s, 1H), 7.43 (s, 1H), 6.99 (t, $J = 55.2$ Hz, 1H), 3.70 (s, 3H), 2.73 (m, 1H), 2.61 (s, 3H), 1.88-1.85 (m, 2H), 1.72-1.68 (m, 2H), 1.52-1.48 (m, 3H), 1.38-1.34 (m, 3H).

[0493] The Examples in the table below were synthesized using conditions analogous to that used to synthesize Example **57** from the corresponding bromide and commercially available alkyne, via Sonogashira coupling reaction.

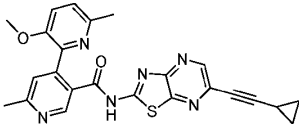
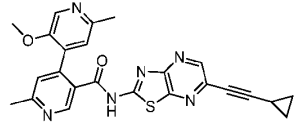
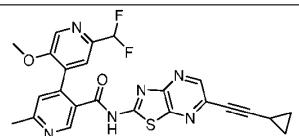
Example Number	Structure	NMR	LCMS (ESI, m/z): $[M+H]^+$
58	 <i>N</i>-(6-(cyclopentylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2'-(difluoromethyl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	^1H NMR (400 MHz, DMSO- d_6) δ 13.56 (s, 1H), 8.91 (s, 1H), 8.61 (s, 1H), 8.47 (s, 1H), 7.73 (s, 1H), 7.45 (s, 1H), 6.99 (t, $J = 55.2$ Hz, 1H), 3.70 (s, 3H), 2.97 (m, 1H), 2.62 (s, 3H), 2.08-1.96 (m, 2H), 1.77-1.55 (m, 6H).	521.2
59	 <i>N</i>-(6-(cyclobutylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2'-(difluoromethyl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	^1H NMR (400 MHz, DMSO- d_6) : δ 13.54 (brs, 1H), 8.92 (s, 1H), 8.61 (s, 1H), 8.46 (s, 1H), 7.72 (s, 1H), 7.44 (s, 1H), 6.99 (t, $J = 55.2$ Hz, 1H), 3.70 (s, 3H), 3.38 (m, 1H), 2.61 (s, 3H), 2.38-2.31 (m, 2H), 2.24-2.15 (m, 2H), 2.03-1.88 (m, 2H).	507.3
60	 2'-(difluoromethyl)-5'-methoxy-6-methyl-<i>N</i>-(6-(3-methylbut-1-yn-1-yl)thiazolo[4,5-b]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide	^1H NMR (400 MHz, DMSO- d_6): δ 13.56 (brs, 1H), 8.89 (s, 1H), 8.65 (s, 1H), 8.47 (s, 1H), 7.75 (s, 1H), 7.48 (s, 1H), 7.00 (t, $J = 55.2$ Hz, 1H), 3.70 (s, 3H), 2.95-2.86 (m, 1H), 2.62 (s, 3H), 1.27 (s, $J = 6.8$ Hz, 6H).	495.3
61	 <i>N</i>-(6-((3,3-difluorocyclobutyl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2'-(difluoromethyl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	^1H NMR (400 MHz, DMSO- d_6) δ 13.60 (s, 1H), 8.92 (s, 1H), 8.66 (s, 1H), 8.46 (s, 1H), 7.72 (s, 1H), 7.45 (s, 1H), 6.99 (t, $J = 55.2$ Hz, 1H), 3.70 (s, 3H), 3.39-	543.3

	methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	3.30 (m, 1H), 3.12 -3.05 (m, 2H), 2.86-2.74 (m, 2H), 2.61 (s, 3H).	
62	 2'-(difluoromethyl)-5'-methoxy-6-methyl-N-(6-((1-methylcyclopropyl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 13.56 (brs, 1H), 8.92 (s, 1H), 8.57 (s, 1H), 8.46 (s, 1H), 7.71 (s, 1H), 7.43 (s, 1H), 6.99 (t, <i>J</i> = 55.2 Hz, 1H), 3.70 (s, 3H), 2.61 (s, 3H), 1.36 (s, 3H), 1.06-1.01 (m, 2H), 0.85-0.80 (m, 2H).	507.3
63	 2'-(difluoromethyl)-5'-methoxy-6-methyl-N-(6-((tetrahydro-2H-pyran-4-yl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.58 (brs, 1H), 8.91 (s, 1H), 8.66 (s, 1H), 8.47 (s, 1H), 7.74 (s, 1H), 7.47 (s, 1H), 7.00 (t, <i>J</i> = 54.8 Hz, 1H), 3.85-3.80 (m, 2H), 3.70 (s, 3H), 3.47 (m, 2H), 3.01 (m, 1H), 2.62 (s, 3H), 1.92-1.85 (m, 2H), 1.70-1.61 (m, 2H).	537.3
64	 2'-(difluoromethyl)-5'-methoxy-6-methyl-N-(6-((1-phenylcyclopropyl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.57 (brs, 1H), 9.02 (s, 1H), 8.52 (s, 1H), 8.44 (s, 1H), 7.62 (s, 1H), 7.44-7.22 (m, 6H), 6.97 (t, <i>J</i> = 55.2 Hz, 1H), 3.70 (s, 3H), 2.58 (s, 3H), 1.61-1.57 (m, 2H), 1.47-1.43 (m, 2H).	569.3
65	 2'-(difluoromethyl)-5'-methoxy-6-methyl-N-(6-((tetrahydrofuran-3-yl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.52 (s, 1H), 8.40 (s, 1H), 7.58 (s, 1H), 7.40 (s, 1H), 7.06-6.79 (m, 2H), 3.94 (t, <i>J</i> = 7.6 Hz, 1H), 3.84-3.55 (m, 7H), 2.55-2.50 (m, 1H), 2.46 (s, 3H), 2.24 (m, 1H), 1.94 (m, 1H).	523.3
66	 2'-(difluoromethyl)-5'-methoxy-6-methyl-N-(6-(oxetan-3-ylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 13.60 (brs, 1H), 8.90 (s, 1H), 8.72 (s, 1H), 8.47 (s, 1H), 7.74 (s, 1H), 7.48 (s, 1H), 7.00 (t, <i>J</i> = 55.2 Hz, 1H), 4.85 (dd, <i>J</i> = 8.4 Hz, 5.2 Hz, 2H), 4.67 (dd, <i>J</i> = 8.4 Hz, 5.2 Hz, 2H), 4.25 (m, 1H), 3.71 (s, 3H), 2.62 (s, 3H).	509.3

67	 4-(5-(difluoromethyl)-2-methoxyphenyl)-6-methyl-N-(6-((5-methyl-1H-pyrazol-3-yl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)nicotinamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.49 (brs, 1H), 13.04 (brs, 1H), 8.81 (s, 1H), 8.77 (s, 1H), 7.64-7.60 (m, 2H), 7.38 (s, 1H), 7.12 (d, <i>J</i> = 8.4 Hz, 1H), 7.05 (t, <i>J</i> = 56.0 Hz, 1H), 6.39 (s, 1H), 3.57 (s, 3H), 2.60 (s, 3H), 2.26 (s, 3H).	532.3
68	 2'-chloro-5'-methoxy-6-methyl-N-(6-(3-methylbut-1-yn-1-yl)thiazolo[4,5-b]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.55 (brs, 1H), 8.91 (s, 1H), 8.60 (s, 1H), 8.17 (s, 1H), 7.57 (s, 1H), 7.44 (s, 1H), 3.63 (s, 3H), 2.91 (m, 1H), 2.60 (s, 3H), 1.26 (d, <i>J</i> = 6.8 Hz, 6H).	479.3
69	 2'-chloro-N-(6-(cyclopentylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.53 (brs, 1H), 8.96 (s, 1H), 8.51 (s, 1H), 8.16 (s, 1H), 7.51 (s, 1H), 7.37 (s, 1H), 3.63 (s, 3H), 2.95 (m, 1H), 2.59 (s, 3H), 2.04-1.98 (m, 2H), 1.75-1.56 (m, 6H).	505.1
70	 2'-chloro-N-(6-(cyclobutylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.54 (brs, 1H), 8.93 (s, 1H), 8.58 (s, 1H), 8.17 (s, 1H), 7.55 (s, 1H), 7.42 (s, 1H), 3.63 (s, 3H), 3.38 (m, 1H), 2.60 (s, 3H), 2.37-2.30 (m, 2H), 2.22-2.17 (m, 2H), 2.02-1.91 (m, 2H).	491.3
71	 2'-chloro-5'-methoxy-6-methyl-N-(6-(oxetan-3-ylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.58 (brs, 1H), 8.91 (s, 1H), 8.69 (s, 1H), 8.17 (s, 1H), 7.58 (s, 1H), 7.45 (s, 1H), 4.87-4.82 (m, 2H), 4.69-4.64 (m, 2H), 4.25 (m, 1H), 3.63 (s, 3H), 2.61 (s, 3H).	493.2
72	 2'-chloro-N-(6-(cyclobutylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.52 (brs, 1H), 8.84 (s, 1H), 8.67 (s, 1H), 8.21 (s, 1H), 7.42	471.3

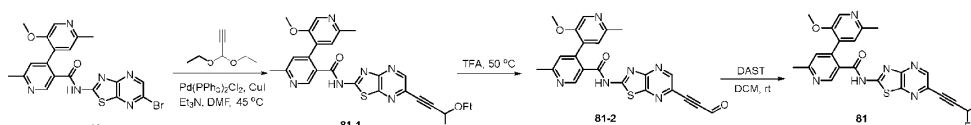
	<i>N</i> -(6-(cyclobutylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	(s, 1H), 7.36 (s, 1H), 3.59 (s, 3H), 3.41-3.37 (m, 1H), 2.61 (s, 3H), 2.50 (s, 3H), 2.38-2.31 (m, 2H), 2.24-2.15 (m, 2H), 2.03-1.89 (m, 2H).	
73	 5'-methoxy-2',6-dimethyl- <i>N</i> -(6-(oxetan-3-ylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.59 (brs, 1H), 8.87 (s, 1H), 8.74 (s, 1H), 8.27 (s, 1H), 7.47 (s, 1H), 7.44 (s, 1H), 4.85 (m, 2H), 4.67 (m, 2H), 4.26 (m, 1H), 3.61 (s, 3H), 2.62 (s, 3H), 2.50 (s, 3H).	473.3
74	 5'-methoxy-2',6-dimethyl- <i>N</i> -(6-((1-methylcyclopropyl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 13.50 (brs, 1H), 8.95 (s, 1H), 8.40 (s, 1H), 8.16 (s, 1H), 7.24 (s, 1H), 7.18 (s, 1H), 3.58 (s, 3H), 2.56 (s, 3H), 2.46 (s, 3H), 1.35 (s, 3H), 1.01 (m, 2H), 0.80 (m, 2H).	471.3
75	 <i>N</i> -(6-(cyclopentylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 13.50 (brs, 1H), 8.87 (s, 1H), 8.58 (s, 1H), 8.18 (s, 1H), 7.36 (s, 1H), 7.27 (s, 1H), 3.58 (s, 3H), 2.96 (m, 1H), 2.59 (s, 3H), 2.48 (s, 3H), 2.05-1.96 (m, 2H), 1.76-1.57 (m, 6H).	485.2
76	 <i>N</i> -(6-((3,3-difluorocyclobutyl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 13.53 (brs, 1H), 8.87 (s, 1H), 8.63 (s, 1H), 8.18 (s, 1H), 7.36 (s, 1H), 7.27 (s, 1H), 3.58 (s, 3H), 3.37 (m, 1H), 3.15-3.03 (m, 1H), 2.86-2.73 (m, 1H), 2.59 (s, 3H), 2.48 (s, 3H).	507.3
77		¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 13.39 (brs, 1H), 8.78 (s, 1H), 8.62 (s, 1H), 7.57 (t, <i>J</i> = 10.0 Hz, 1H), 7.37 (s, 1H), 7.17 (dd, <i>J</i> = 12.8 Hz, 6.8 Hz, 1H), 3.50 (s,	478.3

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	<i>N</i> -(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(4,5-difluoro-2-methoxyphenyl)-6-methylnicotinamide	3H), 2.59 (s, 3H), 1.66 (m, 1H), 1.01-0.96 (m, 2H), 0.86-0.82 (m, 2H).	
78	 <i>N</i> -(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-3-methoxy-6,6'-dimethyl-[2,4'-bipyridine]-3'-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.47 (brs, 1H), 8.78 (s, 1H), 8.61 (s, 1H), 7.55 (s, 1H), 7.41 (d, <i>J</i> = 8.4 Hz, 1H), 7.27 (d, <i>J</i> = 8.4 Hz, 1H), 3.60 (s, 3H), 2.60 (s, 3H), 2.37 (s, 3H), 1.66 (m, 1H), 1.00-0.95 (m, 2H), 0.86-0.82 (m, 2H).	457.3
79	 <i>N</i> -(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.40 (brs, 1H), 8.89 (s, 1H), 8.59 (s, 1H), 8.23 (s, 1H), 7.38 (s, 1H), 7.30 (s, 1H), 3.58 (s, 3H), 2.59 (s, 3H), 2.48 (s, 3H), 1.68-1.62 (m, 1H), 0.99-0.95 (m, 2H), 0.86-0.81 (m, 2H).	457.3
80	 <i>N</i> -(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2'-(difluoromethyl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.55 (brs, 1H), 8.90 (s, 1H), 8.61 (s, 1H), 8.46 (s, 1H), 7.73 (s, 1H), 7.46 (s, 1H), 7.00 (t, <i>J</i> = 55.2 Hz, 1H), 3.70 (s, 3H), 2.62 (s, 3H), 1.65 (m, 1H), 1.01-0.95 (m, 2H), 0.86-0.82 (m, 2H).	493.2

Example 81

N-(6-(3,3-difluoroprop-1-yn-1-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide



Step 1: *N*-(6-(3,3-diethoxyprop-1-yn-1-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide (**81-1**)

[0494] To a solution of Example **13** (2.0 g, 4.24 mmol) in DMF (10 mL) was added 3,3-diethoxyprop-1-yne (1.63 g, 12.6 mmol), Pd(PPh₃)₂Cl₂ (0.30 g, 0.43 mmol), CuI (81 mg, 0.43 mmol) and Et₃N (2.15 g, 21.3 mmol) under N₂. The mixture was degassed and stirred at

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45 °C for 2 hrs under N₂ atmosphere. LCMS showed the reaction was complete. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (0.05% NH₄HCO₃) to afford *N*-(6-(3,3-diethoxyprop-1-yn-1-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide (**81-1**, 1.50 g). LCMS (ESI, m/z): [M+H]⁺ = 519.2.

Step 2: 5'-methoxy-2',6-dimethyl-N-(6-(3-oxoprop-1-yn-1-yl)thiazolo[4,5-b]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide (**81-2**)

[0495] A solution of *N*-(6-(3,3-diethoxyprop-1-yn-1-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide (**81-1**, 1.50 g, 2.90 mmol) in TFA (10 mL) was stirred at 50 °C for 2 hrs. LCMS showed the reaction was complete. The reaction mixture was concentrated under vacuum. The residue was purified by prep-HPLC (0.1% FA) to afford 5'-methoxy-2',6-dimethyl-N-(6-(3-oxoprop-1-yn-1-yl)thiazolo[4,5-b]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide (**81-2**, 490 mg). LCMS (ESI, m/z): [M+H]⁺ = 445.2.

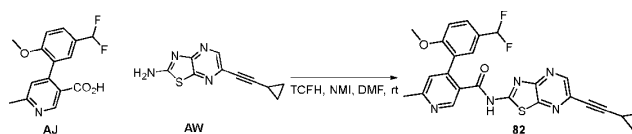
Step 3: N-(6-(3,3-difluoroprop-1-yn-1-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide (**81**)

[0496] To a solution of 5'-methoxy-2',6-dimethyl-N-(6-(3-oxoprop-1-yn-1-yl)thiazolo[4,5-b]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide (**81-2**, 490 mg, 1.10 mmol) in DCM (6 mL) was added DAST (355 mg, 2.20 mmol) dropwise at 0 °C under N₂. After stirring at rt for 2 hrs under N₂ atmosphere, the reaction mixture was quenched by saturated aqueous NaHCO₃ solution and extracted with DCM. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with DCM/MeOH (20:1-10:1), to afford the impure product, which was further purified by prep-HPLC (0.1% FA) to afford Example **81**. LCMS (ESI, m/z): [M+H]⁺ = 467.3; ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.07 (s, 1H), 8.49 (s, 1H), 8.16 (s, 1H), 8.14 (s, 1H), 7.13 (s, 1H), 7.10 (s, 1H), 7.02 (t, *J* = 54.0 Hz, 1 H), 3.58 (s, 3H), 2.54 (s, 3H), 2.45 (s, 3H).

Example 82

N-(6-(cyclopropylethynyl) thiazolo[4,5-b] pyrazin-2-yl)-4-(5-(difluoromethyl)-2-methoxyphenyl)-6-methylnicotinamide

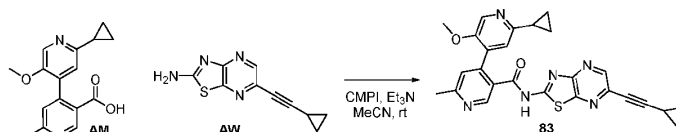
- 216 -



[0497] To a stirred solution of Intermediate **AJ** (100 mg, 0.341 mmol) and Intermediate **AW** (111 mg, 0.513 mmol) in DMF (4 mL) was added TCFH (143 mg, 0.510 mmol) and NMI (83.7 mg, 1.02 mmol) under N₂. After stirring at room temperature for 16 hrs, the reaction mixture was treated with water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by prep-HPLC (0.1% FA) to provide Example **82**. LCMS (ESI, m/z): [M+H]⁺ = 492.3; ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.43 (brs, 1H), 8.78 (s, 1H), 8.63 (s, 1H), 7.63 (m, 2H), 7.39 (s, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 7.05 (t, *J* = 56.0 Hz, 1H), 3.55 (s, 3H), 2.60 (s, 3H), 1.66 (m, 1H), 1.00-0.95 (m, 2H), 0.87-0.82 (m, 2H).

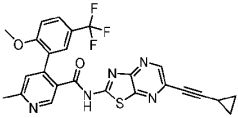
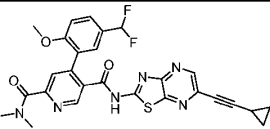
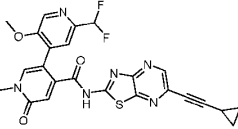
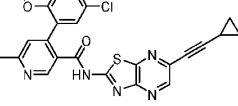
Example 83

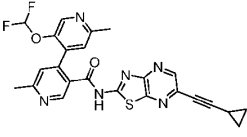
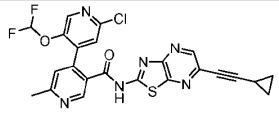
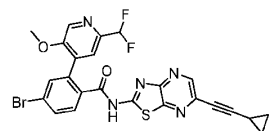
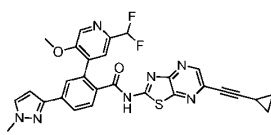
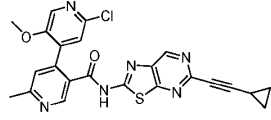
2'-cyclopropyl-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide

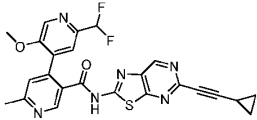
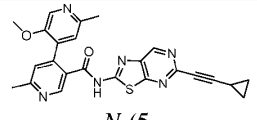
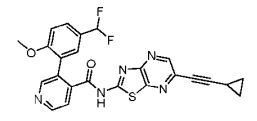
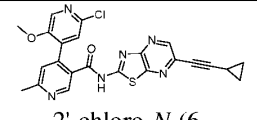
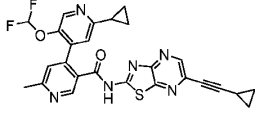


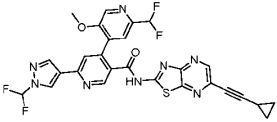
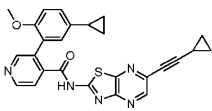
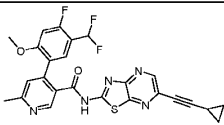
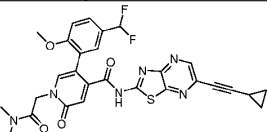
[0498] To a solution of Intermediate **AM** (51.2 mg, 0.18 mmol) in MeCN (5 mL) was added Intermediate **AW** (45.4 mg, 0.21 mmol), Et₃N (53.6 mg, 0.53 mmol) and CMPI (89.4 mg, 0.35 mmol). After stirring at room temperature for 16 hrs, the reaction mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by prep-HPLC (0.1% NH₄OH) to afford Example **83**. LCMS (ESI, m/z): [M+H]⁺ = 483.2; ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.48 (brs, 1H), 8.86 (s, 1H), 8.58 (s, 1H), 8.15 (s, 1H), 7.40 (s, 1H), 7.31 (s, 1H), 3.56 (s, 3H), 2.60 (s, 3H), 2.14 (m, 1H), 1.65 (m, 1H), 0.99-0.88 (m, 6H), 0.86-0.81 (m, 2H).

[0499] The Examples in the table below were synthesized using conditions analogous to that used to synthesize Example **83** from the corresponding acids and amines, via amide coupling reactions.

Example Number	Structure	NMR	LCMS (ESI, m/z): [M+H] ⁺
84	 <i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(2-methoxy-5-(trifluoromethyl)phenyl)-6-methylnicotinamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.44 (brs, 1 H), 8.82 (s, 1H), 8.60 (s, 1H), 7.78 (dd, <i>J</i> = 8.8 Hz, 2.4 Hz, 1H), 7.73 (d, <i>J</i> = 2.4 Hz, 1H), 7.42 (s, 1H), 7.18 (d, <i>J</i> = 8.8 Hz, 1H), 3.59 (s, 3H), 2.60 (s, 3H), 1.66 (m, 1H), 1.00-0.95 (m, 2H), 0.86-0.82 (m, 2H).	510.3
85	 <i>N</i>⁵-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(5-(difluoromethyl)-2-methoxyphenyl)-<i>N</i>²,<i>N</i>²-dimethylpyridine-2,5-dicarboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.56 (br s, 1H), 8.93 (s, 1H), 8.61 (s, 1H), 7.66-7.61 (m, 3H), 7.15 (d, <i>J</i> = 8.4 Hz, 1H), 7.05 (t, <i>J</i> = 56.0 Hz, 1H), 3.58 (s, 3H), 3.05 (s, 3H), 3.02 (s, 3H), 1.67 (m, 1H), 1.02-0.94 (m, 2H), 0.89-0.81 (m, 2H).	TCFH 549.3
86	 <i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2'-(difluoromethyl)-5'-methoxy-1-methyl-6-oxo-1,6-dihydro-[3,4'-bipyridine]-4-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.61 (brs, 1H), 8.64 (s, 1H), 8.33 (s, 1H), 8.04 (s, 1H), 7.71 (s, 1H), 6.95 (t, <i>J</i> = 55.2 Hz, 1H), 6.85 (s, 1H), 3.63 (s, 3H), 3.54 (s, 3H), 1.65 (m, 1H), 0.99-0.95 (m, 2H), 0.86-0.83 (m, 2H).	509.3
87	 4-(5-chloro-2-methoxyphenyl)-<i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-6-methylnicotinamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.37 (brs, 1H), 8.80 (s, 1H), 8.57 (s, 1H), 7.47-7.40 (m, 2H), 7.36 (s, 1H), 7.00 (d, <i>J</i> = 9.2 Hz, 1H), 3.50 (s, 3H), 2.58 (s, 3H), 1.65 (m, 1H), 1.00-0.94 (m, 2H), 0.85-0.81 (m, 2H).	476.2

88	 <i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-(difluoromethoxy)-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.63 (brs, 1H), 8.97 (s, 1H), 8.63 (s, 1H), 8.34 (s, 1H), 7.43 (s, 2H), 7.05 (t, <i>J</i> = 72.8 Hz, 1H), 2.62 (s, 3H), 2.54 (s, 3H), 1.66 (m, 1H), 1.00-0.95 (m, 2H), 0.86-0.83 (m, 2H).	493.3
89	 2'-chloro-<i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-(difluoromethoxy)-6-methyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.68 (brs, 1H), 9.03 (s, 1H), 8.64 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.50 (s, 1H), 7.16 (t, <i>J</i> = 72.4 Hz, 1H), 2.63 (s, 3H), 1.66 (m, 1H), 1.00-0.95 (m, 2H), 0.87-0.83 (m, 2H).	513.2
90	 4-bromo-<i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.46 (brs, 1H), 8.43 (s, 1H), 8.40 (s, 1H), 7.93 (d, <i>J</i> = 8.4 Hz, 1H), 7.77 (d, <i>J</i> = 8.4 Hz, 1H), 7.60 (s, 1H), 7.59 (s, 1H), 6.95 (t, <i>J</i> = 54.8 Hz, 1H), 3.69 (s, 3H), 1.62 (m, 1H), 0.97-0.92 (m, 2H), 0.83-0.79 (m, 2H).	557.2
91	 <i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(1-methyl-1H-pyrazol-3-yl)benzamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 13.40 (brs, 1H), 8.61 (s, 1H), 8.42 (s, 1H), 8.01 (dd, <i>J</i> = 8.0 Hz, 1.6 Hz, 1H), 7.91 (d, <i>J</i> = 8.0 Hz, 1H), 7.86 (s, 1H), 7.80 (d, <i>J</i> = 2.0 Hz, 1H), 7.71 (s, 1H), 7.00 (t, <i>J</i> = 55.2 Hz, 1H), 6.92 (d, <i>J</i> = 2.0 Hz, 1H), 3.92 (s, 3H), 3.70 (s, 3H), 1.66 (m, 1H), 1.01-0.96 (m, 2H), 0.86-0.82 (m, 2H).	558.3
92	 2'-chloro-<i>N</i>-(5-(cyclopropylethynyl)thiazolo[5,4-b]pyrazin-2-yl)-5-(difluoromethoxy)-6-methyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 13.40 (brs, 1H), 8.98 (s, 1H), 8.91 (s, 1H), 8.16 (s, 1H), 7.53 (s, 1H), 7.40 (s, 1H), 3.61 (s, 3H), 2.59 (s, 3H), 1.62 (m, 1H).	477.0

	d]pyrimidin-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	1H), 0.98-0.95 (m, 2H), 0.84-0.82 (m, 2H).	
93	 <i>N</i>-(5-(cyclopropylethynyl)thiazolo[5,4-d]pyrimidin-2-yl)-2'-(difluoromethyl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.48 (s, 1H), 8.94 (m, 2H), 8.44 (s, 1H), 7.66 (s, 1H), 7.38 (s, 1H), 6.98 (t, <i>J</i> = 55.2 Hz, 1H), 3.69 (s, 3H), 2.59 (s, 3H), 1.61 (m, 1H), 0.98-0.93 (m, 2H), 0.85-0.80 (m, 2H).	493.3
94	 <i>N</i>-(5-(cyclopropylethynyl)thiazolo[5,4-d]pyrimidin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 13.35 (brs, 1H), 8.98 (s, 1H), 8.86 (s, 1H), 8.17 (s, 1H), 7.34 (s, 1H), 7.25 (s, 1H), 3.56 (s, 3H), 2.58 (s, 3H), 2.48 (s, 3H), 1.62 (m, 1H), 0.98-0.94 (m, 2H), 0.85-0.82 (m, 2H).	457.3
95	 <i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-3-(5-(difluoromethyl)-2-methoxyphenyl)isonicotinamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.56 (brs, 1H), 8.79 (d, <i>J</i> = 5.2 Hz, 1H), 8.67 (s, 1H), 8.62 (s, 1H), 7.75 (d, <i>J</i> = 5.2 Hz, 1H), 7.63-7.58 (m, 2H), 7.12 (d, <i>J</i> = 9.2 Hz, 1H), 7.04 (t, <i>J</i> = 56.0 Hz, 1H), 3.56 (s, 3H), 1.65 (m, 1H), 1.00-0.95 (m, 2H), 0.86-0.82 (m, 2H).	478.3
96	 2'-chloro-<i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.53 (brs, 1H), 8.88 (s, 1H), 8.64 (s, 1H), 8.18 (s, 1H), 7.60 (s, 1H), 7.48 (s, 1H), 3.62 (s, 3H), 2.61 (s, 3H), 1.66 (m, 1H), 1.01-0.96 (m, 2H), 0.86-0.83 (m, 2H).	477.3
97	 2'-cyclopropyl-<i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-3-(5-(difluoromethyl)-2-methoxyphenyl)isonicotinamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.63 (brs, 1H), 8.98 (s, 1H), 8.62 (s, 1H), 8.28 (s, 1H), 7.46 (s, 1H), 7.45 (s, 1H), 7.01 (t, <i>J</i> = 73.0 Hz, 1H), 2.62 (s, 3H),	519.3

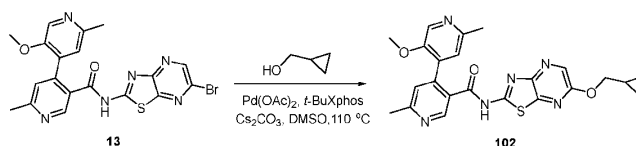
	b]pyrazin-2-yl)-5'-(difluoromethoxy)-6-methyl-[4,4'-bipyridine]-3-carboxamide	2.21 (m, 1H), 1.66 (m, 1H), 1.04-0.93 (m, 6H), 0.87-0.82 (m, 2H).	
98	 <i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2'-(difluoromethyl)-6-(1-(difluoromethyl)-1H-pyrazol-4-yl)-5'-methoxy-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.61 (brs, 1H), 9.07 (s, 1H), 9.03 (s, 1H), 8.59 (s, 1H), 8.53 (s, 1H), 8.49 (s, 1H), 8.01 (s, 1H), 7.90 (t, <i>J</i> = 58.8 Hz, 1H), 7.82 (s, 1H), 7.02 (t, <i>J</i> = 55.2 Hz, 1H), 3.72 (s, 3H), 1.65 (m, 1H), 1.00-0.95 (m, 2H), 0.86-0.82 (m, 2H).	595.3
99	 3-(5-(cyclopropyl-2-methoxyphenyl)-<i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)isonicotinamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.45 (brs, 1H), 8.73 (d, <i>J</i> = 5.2 Hz, 1H), 8.65 (s, 1H), 8.61 (s, 1H), 7.69 (d, <i>J</i> = 5.2 Hz, 1H), 7.12-7.06 (m, 2H), 6.86 (d, <i>J</i> = 8.4 Hz, 1H), 3.47 (s, 3H), 1.93 (m, 1H), 1.66 (m, 1H), 1.00-0.96 (m, 2H), 0.94-0.88 (m, 2H), 0.88-0.82 (m, 2H), 0.68-0.64 (m, 2H).	468.2
100	 <i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(5-(difluoromethyl)-4-fluoro-2-methoxyphenyl)-6-methylnicotinamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.42 (brs, 1H), 8.79 (s, 1H), 8.62 (s, 1H), 7.66 (d, <i>J</i> = 8.0 Hz, 1H), 7.39 (s, 1H), 7.20 (t, <i>J</i> = 54.4 Hz, 1H), 7.11 (d, <i>J</i> = 12.8 Hz, 1H), 3.57 (s, 3H), 2.60 (s, 3H), 1.66 (m, 1H), 1.00-0.95 (m, 2H), 0.86-0.82 (m, 2H).	510.3
101	 <i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5-(5-(difluoromethyl)-2-methoxyphenyl)-1-(2-(dimethylamino)-2-oxoethyl)-2-methoxyphenyl)-6-methylnicotinamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.54 (brs, 1H), 8.58 (s, 1H), 7.70 (s, 1H), 7.51 (d, <i>J</i> = 8.4 Hz, 1H), 7.45 (s, 1H), 7.02 (d, <i>J</i> = 8.4 Hz, 1H), 7.02 (t, <i>J</i> = 56.0 Hz, 1H), 6.79 (s, 1H), 4.91 (s, 2H), 3.51 (s, 3H), 3.07 (s, 3H), 2.87 (s, 3H), 1.64 (m, 1H),	579.4

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	oxo-1,2-dihydropyridine-4-carboxamide	0.99-0.94 (m, 2H), 0.85-0.81 (m, 2H).	
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Example 102

N-(6-(cyclopropylmethoxy)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide

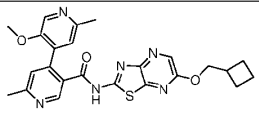
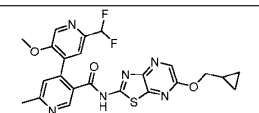
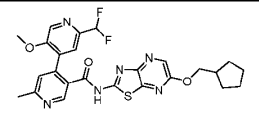
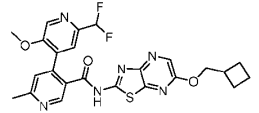


[0500] To a solution of Example **13** (90 mg, 0.19 mmol), cyclopropylmethanol (1.0 mL), Cs₂CO₃ (124 mg, 0.38 mmol) in DMSO (1.0 mL) was added Pd(OAc)₂ (4.3 mg, 0.019 mmol) and *t*-BuXphos (8.1 mg, 0.019 mmol) under N₂. The mixture was degassed and stirred at 110 °C for 3 hrs under N₂ atmosphere. After completion, the reaction mixture was treated with water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by prep-HPLC (0.1% FA) to afford Example **102**. LCMS (ESI, *m/z*): [M+H]⁺ = 463.3; ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.16 (s, 1H), 8.81 (s, 1H), 8.28 (s, 1H), 8.18 (s, 1H), 7.39 (s, 1H), 7.29 (s, 1H), 4.19 (d, *J* = 7.2 Hz, 2H), 3.57 (s, 3H), 2.60 (s, 3H), 2.49 (s, 3H), 1.28 (m, 1H), 0.61-0.56 (m, 2H), 0.40-0.36 (m, 2H).

[0501] The Examples in the table below were synthesized using conditions analogous to that used to synthesize Example **102** from the corresponding bromides and alcohols, via C-O coupling reactions.

Example Number	Structure	NMR	LCMS (ESI, <i>m/z</i>): [M+H] ⁺
103	<i>N</i>-(6-(cyclopentylmethoxy)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.16 (brs, 1H), 8.83 (s, 1H), 8.22 (s, 1H), 8.18 (s, 1H), 7.35 (s, 1H), 7.27 (s, 1H), 4.21 (d, <i>J</i> = 7.2 Hz, 2H), 3.57 (s, 3H), 2.59 (s, 3H), 2.48 (s, 3H), 2.36 (m, 1H), 1.82-1.74 (m, 2H), 1.64-1.52 (m, 4H), 1.40-1.33 (m, 2H).	491.3

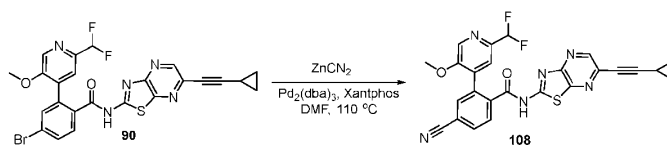
- 222 -

104	 <i>N</i>-(6-(cyclobutylmethoxy)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.16 (brs, 1H), 8.81 (s, 1H), 8.26 (s, 1H), 8.18 (s, 1H), 7.39 (s, 1H), 7.30 (s, 1H), 4.33 (d, <i>J</i> = 6.8 Hz, 2H), 3.57 (s, 3H), 2.77 (m, 1H), 2.60 (s, 3H), 2.49 (s, 3H), 2.12-2.05 (m, 2H), 1.94-1.83 (m, 4H).	477.3
105	 <i>N</i>-(6-(cyclopropylmethoxy)thiazolo[4,5-b]pyrazin-2-yl)-2'-(difluoromethyl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.22 (brs, 1H), 8.86 (s, 1H), 8.46 (s, 1H), 8.30 (s, 1H), 7.74 (s, 1H), 7.47 (s, 1H), 7.00 (t, <i>J</i> = 54.8 Hz, 1H), 4.19 (d, <i>J</i> = 7.2 Hz, 2H), 3.70 (s, 3H), 2.62 (s, 3H), 1.28 (m, 1H), 0.61-0.56 (m, 2H), 0.40-0.36 (m, 2H).	499.3
106	 <i>N</i>-(6-(cyclopentylmethoxy)thiazolo[4,5-b]pyrazin-2-yl)-2'-(difluoromethyl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.22 (brs, 1H), 8.86 (s, 1H), 8.46 (s, 1H), 8.28 (s, 1H), 7.74 (s, 1H), 7.47 (s, 1H), 7.00 (t, <i>J</i> = 55.0 Hz, 1H), 4.23 (d, <i>J</i> = 7.2 Hz, 2H), 3.70 (s, 3H), 2.62 (s, 3H), 2.36 (m, 1H), 1.83-1.74 (m, 2H), 1.65-1.52 (m, 4H), 1.40-1.33 (m, 2H).	527.3
107	 <i>N</i>-(6-(cyclobutylmethoxy)thiazolo[4,5-b]pyrazin-2-yl)-2'-(difluoromethyl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.17 (brs, 1H), 8.89 (s, 1H), 8.46 (s, 1H), 8.23 (s, 1H), 7.71 (s, 1H), 7.43 (s, 1H), 6.99 (t, <i>J</i> = 55.0 Hz, 1H), 4.32 (d, <i>J</i> = 6.8 Hz, 2H), 3.70 (s, 3H), 2.86 (m, 1H), 2.61 (s, 3H), 2.12-2.05 (m, 2H), 1.94-1.81 (m, 4H).	513.1

Example 108

4-cyano-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzamide

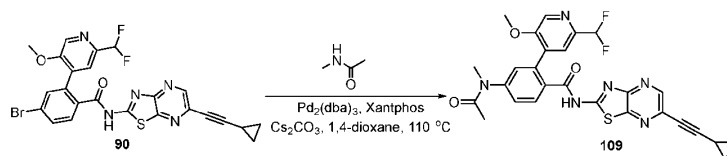
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[0502] To a solution of Example **90** (50 mg, 0.090 mmol) in DMF (1 mL) was added $\text{Zn}(\text{CN})_2$ (11.6 mg, 0.10 mmol), Xantphos (10.4 mg, 0.018 mmol) and $\text{Pd}_2(\text{dba})_3$ (8.2 mg, 0.0090 mmol) under N_2 . The mixture was degassed and stirred at 110 °C for 1 hr under N_2 atmosphere. After completion, the reaction mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with saturated brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated under vacuum. The residue was purified by prep-HPLC (0.1% FA) to afford Example **108**. LCMS (ESI, m/z): $[\text{M}+\text{H}]^+ = 503.2$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 13.63 (brs, 1H), 8.64 (s, 1H), 8.44 (s, 1H), 8.15 (d, $J = 8.0$ Hz, 1H), 8.09 (s, 1H), 8.02 (d, $J = 8.0$ Hz, 1H), 7.79 (s, 1H), 6.98 (t, $J = 55.2$ Hz, 1H), 3.69 (s, 3H), 1.66 (m, 1H), 1.00-0.96 (m, 2H), 0.87-0.83 (m, 2H).

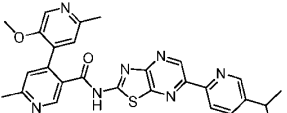
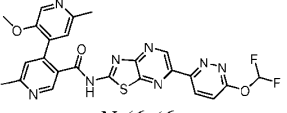
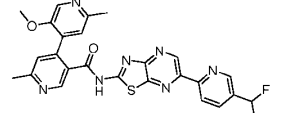
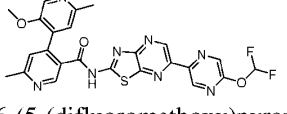
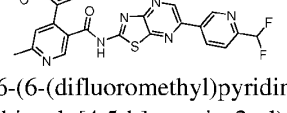
Example 109

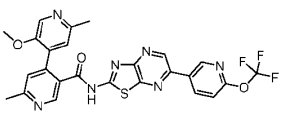
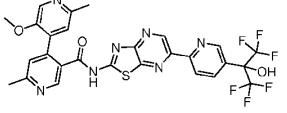
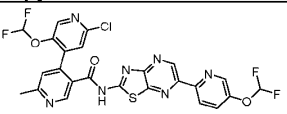
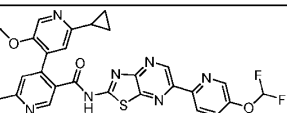
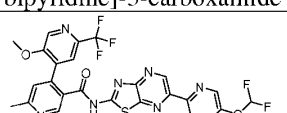
N-(6-(cyclopropylethynyl)thiazolo[4,5-*b*]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(*N*-methylacetamido)benzamide

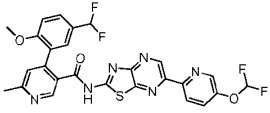
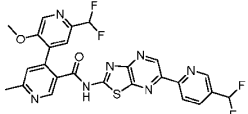
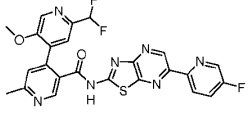
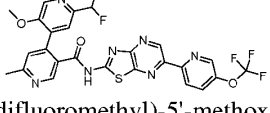
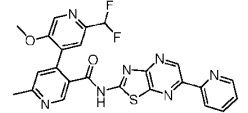


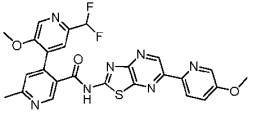
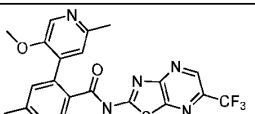
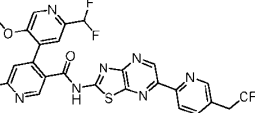
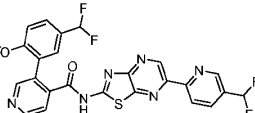
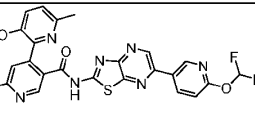
[0503] To a solution of Example **90** (70 mg, 0.13 mmol) in 1,4-dioxane (2 mL) was added *N*-methylacetamide (10.1 mg, 0.14 mmol), Cs_2CO_3 (82 mg, 0.25 mmol), $\text{Pd}_2(\text{dba})_3$ (58 mg, 0.06 mmol) and Xantphos (7.3 mg, 0.013 mmol) under N_2 . The mixture was degassed and stirred at 110 °C for 2 hrs. LCMS showed the reaction was complete. The reaction mixture was treated with water and extracted with EtOAc. The combined organic phase was washed with saturated brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated under vacuum. The residue was purified by prep-HPLC (0.05% NH_4HCO_3) to afford Example **109**. LCMS (ESI, m/z): $[\text{M}+\text{H}]^+ = 549.3$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 13.36 (s, 1H), 8.52 (s, 1H), 8.40 (s, 1H), 7.95 (d, $J = 8.4$ Hz, 1H), 7.68 (s, 1H), 7.56 (d, $J = 8.4$ Hz, 1H), 7.46 (s, 1H), 6.96 (t, $J = 55.2$ Hz, 1H), 3.68 (s, 3H), 3.26 (s, 3H), 1.97 (s, 3H), 1.63 (m, 1H), 0.99-0.93 (m, 2H), 0.85-0.80 (m, 2H).

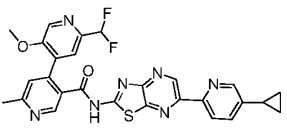
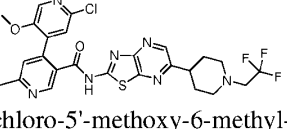
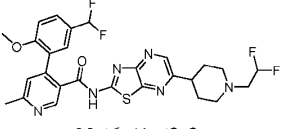
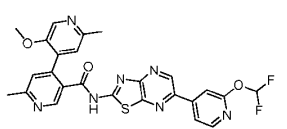
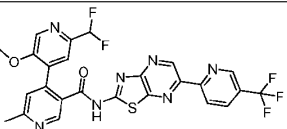
[0504] The examples in the table below were synthesized via either Suzuki or Stille coupling reaction, under the conditions described for previous examples.

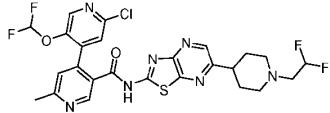
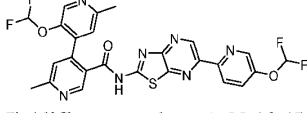
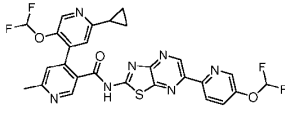
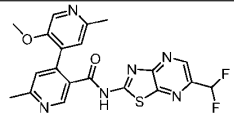
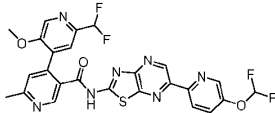
Example Number	Structure	NMR	LCMS (ESI, m/z): [M+H] ⁺
110	 <i>N</i>-(6-(5-isopropylpyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 13.51 (brs, 1H), 9.45 (s, 1H), 8.90 (s, 1H), 8.63 (s, 1H), 8.28 (d, <i>J</i> = 8.4 Hz, 1H), 8.19 (s, 1H), 7.86 (d, <i>J</i> = 8.4 Hz, 1H), 7.36 (s, 1H), 7.28 (s, 1H), 3.60 (s, 3H), 3.03 (m, 1H), 2.60 (s, 3H), 2.50 (s, 3H), 1.28 (d, <i>J</i> = 6.8 Hz, 6H).	512.3
111	 <i>N</i>-(6-(6-(difluoromethoxy)pyridazin-3-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.61 (brs, 1H), 9.50 (s, 1H), 8.94 (s, 1H), 8.62 (d, <i>J</i> = 9.2 Hz, 1H), 8.18 (s, 1H), 7.99 (t, <i>J</i> = 71.6 Hz, 2H), 7.67 (d, <i>J</i> = 9.2 Hz, 1H), 7.31 (s, 1H), 7.25 (s, 1H), 3.59 (s, 3H), 2.59 (s, 3H), 2.48 (s, 3H).	537.4
112	 <i>N</i>-(6-(5-(difluoromethyl)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.56 (brs, 1H), 9.51 (s, 1H), 8.91 (m, 2H), 8.49 (d, <i>J</i> = 8.4 Hz, 1H), 8.19 (m, 2H), 7.36 (s, 1H), 7.28 (s, 1H), 7.24 (t, <i>J</i> = 55.2 Hz, 1H), 3.60 (s, 3H), 2.60 (s, 3H), 2.49 (s, 3H).	520.2
113	 <i>N</i>-(6-(5-(difluoromethoxy)pyrazin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.58 (brs, 1H), 9.36 (s, 1H), 9.17 (d, <i>J</i> = 1.2 Hz, 1H), 8.89 (s, 1H), 8.71 (d, <i>J</i> = 1.2 Hz, 1H), 8.19 (s, 1H), 7.79 (t, <i>J</i> = 71.6 Hz, 1H), 7.38 (s, 1H), 7.30 (s, 1H), 3.60 (s, 3H), 2.60 (s, 3H), 2.49 (s, 3H).	537.1
114	 <i>N</i>-(6-(6-(difluoromethyl)pyridin-3-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.48 (s, 1H), 9.43 (d, <i>J</i> = 2.4 Hz, 1H), 9.33 (s, 1H), 8.88 (s, 1H), 8.71 (dd, <i>J</i> = 8.2 Hz, 2.4 Hz, 1H), 8.19 (s, 1H), 7.86 (d, <i>J</i> = 8.2 Hz,	520.3

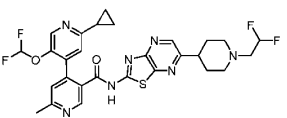
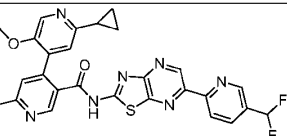
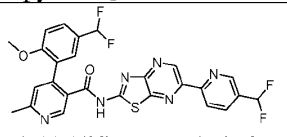
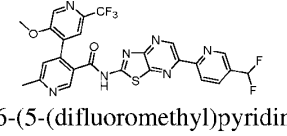
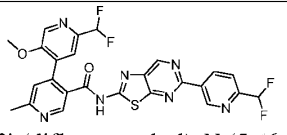
	methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	1H), 7.39 (s, 1H), 7.30 (s, 1H), 7.05 (t, $J = 54.8$ Hz, 1H), 3.59 (s, 3H), 2.60 (s, 3H), 2.49 (s, 3H).	
115	 5'-methoxy-2',6-dimethyl-N-(6-(6-(trifluoromethoxy)pyridin-3-yl)thiazolo[4,5-b]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide	^1H NMR (400 MHz, DMSO- d_6) δ 13.45 (brs, 1H), 9.26 (s, 1H), 9.11 (d, $J = 2.4$ Hz, 1H), 8.88 (s, 1H), 8.71 (dd, $J = 8.8$ Hz, 2.4 Hz, 1H), 8.18 (s, 1H), 7.45 (d, $J = 8.8$ Hz, 1H), 7.38 (s, 1H), 7.29 (s, 1H), 3.59 (s, 3H), 2.60 (s, 3H), 2.49 (s, 3H).	554.4
116	 N-(6-(5-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	^1H NMR (400 MHz, DMSO- d_6): δ 13.49 (brs, 1H), 9.43 (s, 1H), 9.18 (s, 1H), 8.96 (s, 1H), 8.95 (s, 1H), 8.48 (d, $J = 8.4$ Hz, 1H), 8.24 (d, $J = 8.4$ Hz, 1H), 8.18 (s, 1H), 7.29 (s, 1H), 7.24 (s, 1H), 3.61 (s, 3H), 2.59 (s, 3H), 2.49 (s, 3H).	636.3
117	 2'-chloro-5'-(difluoromethoxy)-N-(6-(5-(difluoromethoxy)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-6-methyl-[4,4'-bipyridine]-3-carboxamide	^1H NMR (400 MHz, DMSO- d_6) δ 13.74 (brs, 1H), 9.50 (s, 1H), 9.05 (s, 1H), 8.64 (d, $J = 2.8$ Hz, 1H), 8.43 (d, $J = 8.8$ Hz, 1H), 8.36 (s, 1H), 7.86 (dd, $J = 8.8$ Hz, 2.8 Hz, 1H), 7.80 (s, 1H), 7.52 (s, 1H), 7.43 (t, $J = 73.2$ Hz, 1H), 7.18 (t, $J = 72.4$ Hz, 1H), 2.64 (s, 3H).	592.2
118	 2'-cyclopropyl-N-(6-(5-(difluoromethoxy)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	^1H NMR (400 MHz, DMSO- d_6) δ 9.34 (s, 1H), 8.95 (s, 1H), 8.60 (s, 1H), 8.39 (d, $J = 8.4$ Hz, 1H), 8.14 (s, 1H), 7.82 (d, $J = 8.4$ Hz, 1H), 7.40 (t, $J = 73.2$ Hz, 1H), 7.31 (s, 1H), 7.25 (s, 1H), 3.58 (s, 3H), 2.58 (s, 3H), 2.12 (m, 1H), 1.28-1.18 (m, 2H), 0.95-0.85 (m, 2H).	562.4
119	 N-(6-(5-(difluoromethoxy)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-2'-	^1H NMR (400 MHz, DMSO- d_6) δ 13.60 (br s, 1H), 9.49 (s, 1H), 8.92 (s, 1H), 8.64 (d, $J = 2.8$ Hz, 1H), 8.55 (s, 1H), 8.42 (d, $J = 8.8$ Hz, 1H), 7.98 (s, 1H), 7.85 (dd, $J = 8.8$ Hz, 2.8 Hz, 1H), 7.53 (s, 1H), 7.43	590.3

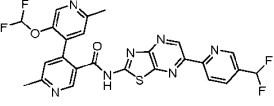
	(trifluoromethyl)-[4,4'-bipyridine]-3-carboxamide	(t, $J = 73.2$ Hz, 1H), 3.75 (s, 3H), 2.62 (s, 3H).	
120	 <i>N</i> -(6-(5-(difluoromethoxy)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-4-(5-(difluoromethyl)-2-methoxyphenyl)-6-methylnicotinamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.49 (brs, 1H), 9.50 (s, 1H), 8.81 (s, 1H), 8.64 (d, $J = 2.8$ Hz, 1H), 8.44 (d, $J = 8.8$ Hz, 1H), 7.86 (dd, $J = 8.8$ Hz, 2.8 Hz, 1H), 7.65-7.63 (m, 2H), 7.43 (t, $J = 73.2$ Hz, 1H), 7.40 (s, 1H), 7.13 (d, $J = 9.2$ Hz, 1H), 7.07 (t, $J = 56.0$ Hz, 1H), 3.57 (s, 3H), 2.61 (s, 3H).	571.1
121	 2'-(difluoromethyl)- <i>N</i> -(6-(5-(difluoromethyl)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 13.65 (brs, 1H), 9.59 (s, 1H), 8.94 (s, 1H), 8.91 (s, 1H), 8.51 (d, $J = 8.4$ Hz, 1H), 8.48 (s, 1H), 8.21 (d, $J = 8.4$ Hz, 1H), 7.77 (s, 1H), 7.50 (s, 1H), 7.25 (t, $J = 55.2$ Hz, 1H), 7.01 (t, $J = 55.2$ Hz, 1H), 3.72 (s, 3H), 2.63 (s, 3H).	556.3
122	 2'-(difluoromethyl)- <i>N</i> -(6-(5-fluoropyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.61 (brs, 1H), 9.46 (s, 1H), 8.93 (s, 1H), 8.74 (d, $J = 2.8$ Hz, 1H), 8.47 (s, 1H), 8.43 (m, 1H), 7.92 (m, 1H), 7.75 (s, 1H), 7.47 (s, 1H), 7.01 (t, $J = 55.2$ Hz, 1H), 3.72 (s, 3H), 2.63 (s, 3H).	524.3
123	 2'-(difluoromethyl)-5'-methoxy-6-methyl- <i>N</i> -(6-(5-(trifluoromethoxy)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) : δ 13.61 (brs, 1H), 9.48 (s, 1H), 8.95 (s, 1H), 8.82 (d, $J = 2.4$ Hz, 1H), 8.49 (d, $J = 8.4$ Hz, 1H), 8.47 (s, 1H), 8.07 (d, $J = 8.4$ Hz, 1H), 7.73 (s, 1H), 7.45 (s, 1H), 7.00 (t, $J = 55.2$ Hz, 1H), 3.72 (s, 3H), 2.62 (s, 3H).	590.3
124	 2'-(difluoromethyl)-5'-methoxy-6-methyl- <i>N</i> -(6-(pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.59 (brs, 1H), 9.54 (s, 1H), 8.93 (s, 1H), 8.74 (dd, $J = 4.8$ Hz, 2.0 Hz, 1H), 8.47 (s, 1H), 8.37 (d, $J = 8.0$ Hz, 1H), 8.00 (td, $J = 8.0$ Hz, 2.0 Hz, 1H), 7.75 (s, 1H), 7.53-7.46 (	506.2

	yl)thiazolo[4,5-b]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide	m, 2H), 7.01 (t, $J = 55.2$ Hz, 1H), 3.72 (s, 3H), 2.63 (s, 3H).	
125	 2'-(difluoromethyl)-5'-methoxy-<i>N</i>-(6-(5-methoxypyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-6-methyl-[4,4'-bipyridine]-3-carboxamide	^1H NMR (400 MHz, DMSO- d_6) δ 13.52 (brs, 1H), 9.45 (s, 1H), 8.91 (s, 1H), 8.47 (s, 1H), 8.45 (d, $J = 2.8$ Hz, 1H), 8.33 (d, $J = 8.8$ Hz, 1H), 7.75 (s, 1H), 7.58 (dd, $J = 8.8$ Hz, 2.8 Hz, 1H), 7.48 (s, 1H), 7.01 (t, $J = 55.2$ Hz, 1H), 3.92 (s, 3H), 3.72 (s, 3H), 2.63 (s, 3H).	536.2
126	 5'-methoxy-2',6-dimethyl-<i>N</i>-(6-(trifluoromethyl)thiazolo[4,5-b]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide	^1H NMR (400 MHz, DMSO- d_6) δ 13.78 (brs, 1H), 9.10 (s, 1H), 8.87 (s, 1H), 8.19 (s, 1H), 7.42 (s, 1H), 7.32 (s, 1H), 3.58 (s, 3H), 2.61 (s, 3H), 2.49 (s, 3H).	461.2
127	 2'-(difluoromethyl)-5'-methoxy-6-methyl-<i>N</i>-(6-(5-(2,2,2-trifluoroethyl)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide	^1H NMR (400 MHz, DMSO- d_6) δ 13.60 (brs, 1H), 9.55 (s, 1H), 8.91 (s, 1H), 8.73 (s, 1H), 8.48 (s, 1H), 8.40 (d, $J = 8.0$ Hz, 1H), 8.01 (d, $J = 8.0$ Hz, 1H), 7.76 (s, 1H), 7.49 (s, 1H), 7.01 (t, $J = 55.2$ Hz, 1H), 3.85 (q, $J = 11.6$ Hz, 2H), 3.72 (s, 3H), 2.63 (s, 3H).	588.3
128	 3-(5-(difluoromethyl)-2-methoxyphenyl)-<i>N</i>-(6-(5-(difluoromethyl)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)isonicotinamide	^1H NMR (400 MHz, DMSO- d_6) δ 13.65 (brs, 1H), 9.59 (s, 1H), 8.94 (s, 1H), 8.82 (d, $J = 5.2$ Hz, 1H), 8.71 (s, 1H), 8.51 (d, $J = 8.0$ Hz, 1H), 8.21 (d, $J = 8.0$ Hz, 1H), 7.78 (d, $J = 5.2$ Hz, 1H), 7.66-7.62 (m, 2H), 7.25 (t, $J = 55.2$ Hz, 1H), 7.13 (d, $J = 8.4$ Hz, 1H), 7.05 (t, $J = 56.0$ Hz, 1H), 3.58 (s, 3H).	541.3
129	 <i>N</i>-(6-(6-(difluoromethoxy)pyridin-3-yl)thiazolo[4,5-b]pyrazin-2-yl)-3-methoxy-6,6'-dimethyl-[2,4'-bipyridine]-3'-carboxamide	^1H NMR (400 MHz, DMSO- d_6) δ 13.45 (brs, 1H), 9.28 (s, 1H), 9.04 (d, $J = 2.4$ Hz, 1H), 8.80 (s, 1H), 8.65 (dd, $J = 8.4$ Hz, 2.4 Hz, 1H), 7.80 (t, $J = 72.6$ Hz, 1H), 7.57 (s, 1H), 7.42 (d, $J = 8.8$ Hz, 1H),	536.3

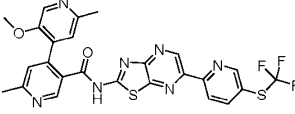
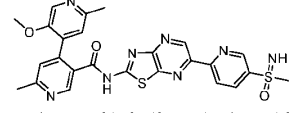
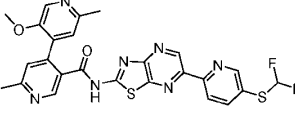
		7.29-7.26 (m, 2H), 3.62 (s, 3H), 2.61 (s, 3H), 2.38 (s, 3H).	
130	 <i>N</i>-(6-(5-cyclopropylpyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-2'-(difluoromethyl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.56 (brs, 1H), 9.50 (s, 1H), 8.92 (s, 1H), 8.56 (d, <i>J</i> = 2.0 Hz, 1H), 8.47 (s, 1H), 8.24 (d, <i>J</i> = 8.4 Hz, 1H), 7.75 (s, 1H), 7.61 (dd, <i>J</i> = 8.4 Hz, 2.0 Hz, 1H), 7.48 (s, 1H), 7.01 (t, <i>J</i> = 55.2 Hz, 1H), 3.72 (s, 3H), 2.63 (s, 3H), 2.04 (m, 1H), 1.11-1.05 (m, 2H), 0.86-0.81 (m, 2H).	546.2
131	 2'-chloro-5'-methoxy-6-methyl-<i>N</i>-(6-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)thiazolo[4,5-b]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.17 (brs, 1H), 8.94 (s, 1H), 8.51 (s, 1H), 8.16 (s, 1H), 7.55 (s, 1H), 7.41 (s, 1H), 3.63 (s, 3H), 3.22 (q, <i>J</i> = 10.0 Hz, 2H), 3.05 (m, 2H), 2.85 (s, 1H), 2.60 (s, 3H), 2.52 (m, 2H), 1.85 (m, 4H).	578.4
132	 <i>N</i>-(6-(1-(2,2-difluoroethyl)piperidin-4-yl)thiazolo[4,5-b]pyrazin-2-yl)-4-(5-(difluoromethyl)-2-methoxyphenyl)-6-methylnicotinamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.23 (br s, 1H), 8.80 (s, 1H), 8.52 (s, 1H), 7.62-7.58 (m, 2H), 7.34 (s, 1H), 7.10 (d, <i>J</i> = 8.4 Hz, 1H), 7.04 (t, <i>J</i> = 56.0 Hz, 1H), 6.15 (m, 1H), 3.55 (s, 3H), 3.02 (m, 2H), 2.84-2.72 (m, 3H), 2.59 (s, 3H), 2.33-2.27 (m, 2H), 1.85-1.76 (m, 4H).	575.4
133	 <i>N</i>-(6-(2-(difluoromethoxy)pyridin-4-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.57 (brs, 1H), 9.37 (s, 1H), 8.89 (s, 1H), 8.42 (d, <i>J</i> = 5.2 Hz, 1H), 8.19 (s, 1H), 8.04 (d, <i>J</i> = 5.2 Hz, 1H), 7.83 (s, 1H), 7.78 (t, <i>J</i> = 72.8 Hz, 1H), 7.39 (s, 1H), 7.30 (s, 1H), 3.59 (s, 3H), 2.61 (s, 3H), 2.49 (s, 3H).	536.4
134	 2'-(difluoromethyl)-5'-methoxy-6-methyl-<i>N</i>-(6-(5-(difluoromethyl)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.68 (brs, 1H), 9.54 (s, 1H), 9.11 (s, 1H), 8.96 (s, 1H), 8.55 (d, <i>J</i> = 8.4 Hz, 1H), 8.47 (s, 1H), 8.38 (d, <i>J</i> = 8.4 Hz, 1H), 7.72 (s, 1H), 7.44	574.3

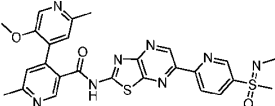
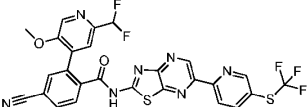
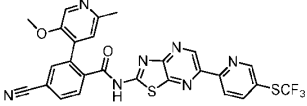
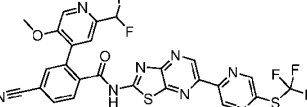
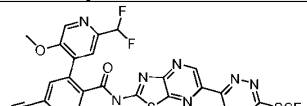
	(trifluoromethyl)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide	(s, 1H), 7.00 (t, $J = 55.2$ Hz, 1H), 3.72 (s, 3H), 2.62 (s, 3H).	
135	 2'-chloro-N-(6-(1-(2,2-difluoroethyl)piperidin-4-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-(difluoromethoxy)-6-methyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.50 (brs, 1H), 9.05 (s, 1H), 8.55 (s, 1H), 8.33 (s, 1H), 7.75 (s, 1H), 7.46 (s, 1H), 7.16 (t, $J = 72.4$ Hz, 1H), 6.16 (m, 1H), 3.04 (d, $J = 28.0$ Hz, 2H), 2.90-2.70 (m, 3H), 2.62 (s, 3H), 2.36-2.26 (m, 2H), 1.88-1.77 (m, 4H).	596.3
136	 5'-(difluoromethoxy)-N-(6-(5-(difluoromethoxy)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.68 (brs, 1H), 9.48 (s, 1H), 9.00 (s, 1H), 8.63 (d, $J = 2.8$ Hz, 1H), 8.42 (d, $J = 8.8$ Hz, 1H), 8.34 (s, 1H), 7.85 (dd, $J = 8.8$ Hz, 2.8 Hz, 1H), 7.44 (m, 2H), 7.42 (t, $J = 73.2$ Hz, 1H), 7.07 (t, $J = 72.8$ Hz, 1H), 2.63 (s, 3H), 2.55 (s, 3H).	572.3
137	 2'-cyclopropyl-5'-(difluoromethoxy)-N-(6-(5-(difluoromethoxy)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-6-methyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.67 (brs, 1H), 9.48 (s, 1H), 8.99 (s, 1H), 8.63 (d, $J = 2.8$ Hz, 1H), 8.42 (d, $J = 8.8$ Hz, 1H), 8.28 (s, 1H), 7.85 (dd, $J = 8.8$ Hz, 2.8 Hz, 1H), 7.48 (s, 1H), 7.47 (s, 1H), 7.42 (t, $J = 73.2$ Hz, 1H), 7.02 (t, $J = 72.8$ Hz, 1H), 2.63 (s, 3H), 2.22 (m, 1H), 1.02-0.96 (m, 4H).	598.3
138	 N-(6-(difluoromethyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.65 (brs, 1H), 8.91 (s, 1H), 8.82 (s, 1H), 8.18 (s, 1H), 7.35 (s, 1H), 7.27 (s, 1H), 7.18 (t, $J = 54.4$ Hz, 1H), 3.58 (s, 3H), 2.59 (s, 3H), 2.48 (s, 3H).	443.2
139	 N-(6-(5-(difluoromethoxy)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-2'-(difluoromethyl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.61 (brs, 1H), 9.49 (s, 1H), 8.92 (s, 1H), 8.65 (d, $J = 2.8$ Hz, 1H), 8.47 (s, 1H), 8.44 (d, $J = 8.8$ Hz, 1H), 7.86 (dd, $J = 8.8$ Hz, 2.8 Hz, 1H), 7.76 (s, 1H), 7.48 (s, 1H), 7.43 (t, $J = 73.2$ Hz, 1H), 7.01 (t, J	572.2

	methyl-[4,4'-bipyridine]-3-carboxamide	= 55.2 Hz, 1H), 3.72 (s, 3H), 2.63 (s, 3H).	
140	 2'-cyclopropyl-N-(6-(1-(2,2-difluoroethyl)piperidin-4-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-(difluoromethoxy)-6-methyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.44 (brs, 1H), 8.98 (s, 1H), 8.58 (s, 1H), 8.27 (s, 1H), 7.46 (m, 2H), 7.02 (t, <i>J</i> = 72.8 Hz, 1H), 6.16 (t, <i>J</i> = 56.0 Hz, 4.4 Hz, 1H), 3.03 (m, 2H), 2.87 (m, 1H), 2.77 (m, 2H), 2.63 (s, 3H), 2.32 (m, 2H), 2.21 (m, 1H), 1.89-1.77 (m, 4H), 1.04-0.92 (m, 4H).	602.4
141	 2'-cyclopropyl-N-(6-(5-(difluoromethyl)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 13.59 (brs, 1H), 9.59 (s, 1H), 8.95 (s, 1H), 8.86 (s, 1H), 8.52 (d, <i>J</i> = 8.0 Hz, 1H), 8.21 (d, <i>J</i> = 8.0 Hz, 1H), 8.17 (s, 1H), 7.47 (s, 1H), 7.38 (s, 1H), 7.25 (t, <i>J</i> = 55.2 Hz, 1H), 3.59 (s, 3H), 2.62 (s, 3H), 2.17 (m, 1H), 0.98-0.91 (m, 4H).	546.4
142	 4-(5-(difluoromethyl)-2-methoxyphenyl)-N-(6-(5-(difluoromethyl)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-6-methylnicotinamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.48 (brs, 1H), 9.46 (s, 1H), 8.92-8.86 (m, 2H), 8.47 (d, <i>J</i> = 8.4 Hz, 1H), 8.16 (d, <i>J</i> = 8.4 Hz, 1H), 7.64-7.55 (s, 2H), 7.37-6.89 (m, 4H), 3.57 (s, 3H), 2.59 (s, 3H).	555.3
143	 N-(6-(5-(difluoromethyl)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-2'-(trifluoromethyl)-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.08 (brs, 1H), 9.39 (s, 1H), 9.06 (s, 1H), 8.88 (s, 1H), 8.53 (s, 1H), 8.45 (d, <i>J</i> = 8.4 Hz, 1H), 8.15 (d, <i>J</i> = 8.4 Hz, 1H), 7.85 (s, 1H), 7.36 (s, 1H), 7.22 (t, <i>J</i> = 55.6 Hz, 1H), 3.75 (s, 3H), 2.59 (s, 3H).	574.3
144	 2'-(difluoromethyl)-N-(5-(6-(difluoromethyl)pyridin-3-yl)thiazolo[5,4-d]pyrimidin-2-yl)-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.48 (brs, 1H), 9.63 (s, 1H), 9.31 (s, 1H), 8.91-8.88 (m, 2H), 8.47 (s, 1H), 7.88 (d, <i>J</i> = 8.4 Hz, 1H), 7.75 (s, 1H), 7.48 (s, 1H), 7.07 (t, <i>J</i> =	556.2

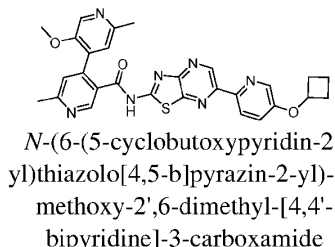
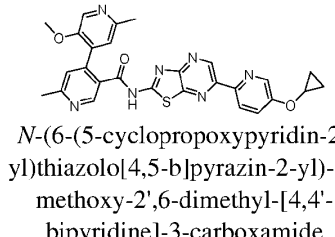
	5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	55.2 Hz, 1H), 7.01 (t, J = 55.2 Hz, 1H), 3.71 (s, 3H), 2.63 (s, 3H).	
145	 5'-(difluoromethoxy)- <i>N</i> -(6-(5-(difluoromethyl)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.73 (brs, 1H), 9.59 (s, 1H), 9.00 (s, 1H), 8.94 (s, 1H), 8.51 (d, J = 8.0 Hz, 1H), 8.34 (s, 1H), 8.21 (d, J = 8.0 Hz, 1H), 7.46 (m, 2H), 7.25 (t, J = 55.2 Hz, 1H), 7.08 (t, J = 73.0 Hz, 1H), 2.64 (s, 3H), 2.56 (s, 3H).	556.3

[0505] Following conditions analogous to synthesis of Example 34, Examples 146-153 in the table below were synthesized by Stille coupling of Example 13 or Intermediate EJ with the corresponding monocyclic heteroaryl tin reagents, which were generated from the halides in situ. For synthesis of Examples 154 and 155, CuCl and LiCl (0.1 eq. each) were also added to accelerate the reaction.

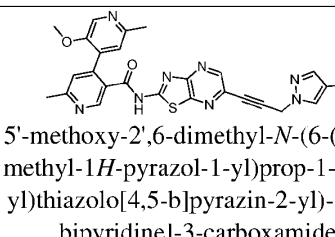
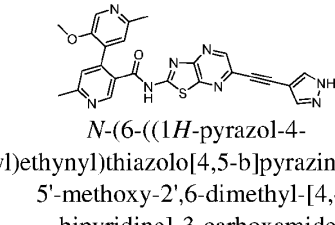
Example Number	Structure	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm	LCMS (ESI, m/z): [M+H] ⁺
146	 5'-methoxy-2',6-dimethyl- <i>N</i> -(6-(5-((trifluoromethyl)thio)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide	13.61 (br s, 1H), 9.47 (s, 1H), 9.02-8.85 (m, 2H), 8.47 (d, J = 8.4 Hz, 1H), 8.32 (d, J = 8.4 Hz, 1H), 8.18 (s, 1H), 7.33 (s, 1H), 7.26 (s, 1H), 3.60 (s, 3H), 2.59 (s, 3H), 2.49 (s, 3H).	570.3
147	 5'-methoxy-2',6-dimethyl- <i>N</i> -(6-(5-(<i>S</i> -methylsulfonimidoyl)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide	13.62 (br s, 1H), 9.61 (s, 1H), 9.18 (d, J = 2.4 Hz, 1H), 8.86 (s, 1H), 8.57 (d, J = 8.4 Hz, 1H), 8.46 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 8.20 (s, 1H), 7.43 (s, 1H), 7.33 (s, 1H), 4.61 (s, 1H), 3.60 (s, 3H), 3.22 (s, 3H), 2.62 (s, 3H), 2.51 (s, 3H).	547.2
148	 <i>N</i> -(6-(5-((difluoromethyl)thio)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	13.59 (br s, 1H), 9.44 (s, 1H), 8.94 (s, 1H), 8.83 (d, J = 2.4 Hz, 1H), 8.42 (d, J = 8.0 Hz, 1H), 8.20 - 8.15 (m, 2H), 7.60 (t, J = 55.2 Hz, 1H), 7.32 (s, 1H), 7.25 (s, 1H), 3.60 (s, 3H), 2.59 (s, 3H), 2.49 (s, 3H).	552.2

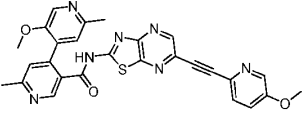
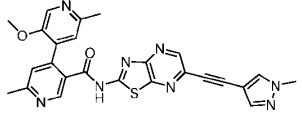
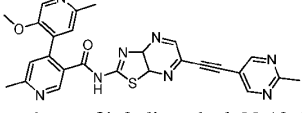
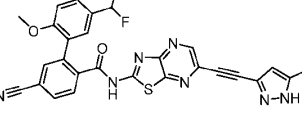
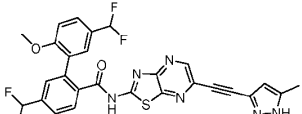
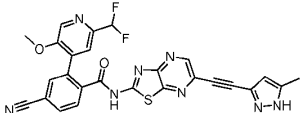
	methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide		
149	 <i>N</i>-(6-(5-(<i>N,S</i>-dimethylsulfonimidoyl)pyridin-2-yl)thiazolo[4,5-<i>b</i>]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	13.63 (br s, 1H), 9.60 (s, 1H), 9.08 (s, 1H), 8.87 (s, 1H), 8.58 (d, <i>J</i> = 8.4 Hz, 1H), 8.37 (d, <i>J</i> = 8.4 Hz, 1H), 8.20 (s, 1H), 7.41 (s, 1H), 7.31 (s, 1H), 3.60 (s, 3H), 3.28 (s, 3H), 2.61 (s, 3H), 2.54 (s, 3H), 2.49 (s, 3H).	561.4
150	 4-cyano-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-<i>N</i>-(6-(5-((trifluoromethyl)thio)pyridin-2-yl)thiazolo[4,5-<i>b</i>]pyrazin-2-yl)benzamide	13.74 (br s, 1H), 9.56 (s, 1H), 8.98 (d, <i>J</i> = 2.4 Hz, 1H), 8.50 (d, <i>J</i> = 8.0 Hz, 1H), 8.45 (s, 1H), 8.36 (dd, <i>J</i> = 8.0 Hz, 2.2 Hz, 1H), 8.14 (dd, <i>J</i> = 8.0 Hz, 2.4 Hz, 1H), 8.09 (d, <i>J</i> = 1.6 Hz, 1H), 8.05 (d, <i>J</i> = 8.0 Hz, 1H), 7.80 (s, 1H), 6.98 (t, <i>J</i> = 55.2 Hz, 1H), 3.71 (s, 3H).	616.3
151	 4-cyano-2-(5-methoxy-2-methylpyridin-4-yl)-<i>N</i>-(6-(5-((trifluoromethyl)thio)pyridin-2-yl)thiazolo[4,5-<i>b</i>]pyrazin-2-yl)benzamide	9.41 (s, 1H), 8.94 (d, <i>J</i> = 2.4 Hz, 1H), 8.46 (d, <i>J</i> = 8.4 Hz, 1H), 8.31 (dd, <i>J</i> = 8.4 Hz, 2.4 Hz, 1H), 8.15 (s, 1H), 8.08 (d, <i>J</i> = 8.0 Hz, 1H), 8.01 (d, <i>J</i> = 8.0 Hz, 1H), 7.87 (s, 1H), 7.26 (s, 1H), 3.58 (s, 3H), 2.47 (s, 3H).	580.3
152	 4-cyano-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-<i>N</i>-(6-(5-((trifluoromethyl)thio)pyrazin-2-yl)thiazolo[4,5-<i>b</i>]pyrazin-2-yl)benzamide	13.79 (br s, 1H), 9.58 (s, 1H), 9.50 (s, 1H), 9.09 (s, 1H), 8.45 (s, 1H), 8.15 (d, <i>J</i> = 8.0 Hz, 1H), 8.10 (s, 1H), 8.06 (d, <i>J</i> = 8.0 Hz, 1H), 7.81 (s, 1H), 6.99 (t, <i>J</i> = 55.2 Hz, 1H), 3.71 (s, 3H).	617.0
153	 4-cyano-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-<i>N</i>-(6-(6-((trifluoromethyl)thio)pyridazin-3-yl)thiazolo[4,5-<i>b</i>]pyrazin-2-yl)benzamide	9.49 (s, 1H), 8.56 (d, <i>J</i> = 8.8 Hz, 1H), 8.40 (s, 1H), 8.18-8.15 (m, 2H), 8.01 (d, <i>J</i> = 8.0 Hz, 1H), 7.88 (s, 1H), 7.65 (s, 1H), 6.95 (t, <i>J</i> = 54.8 Hz, 1H), 3.69 (s, 3H).	617.3

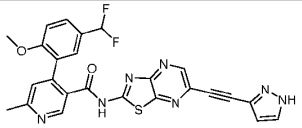
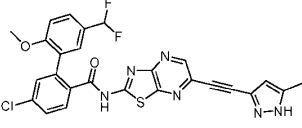
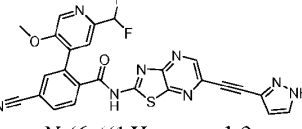
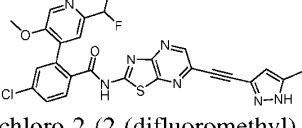
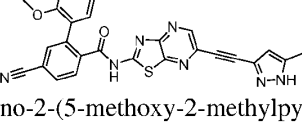
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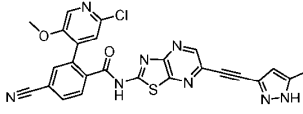
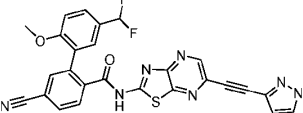
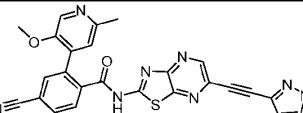
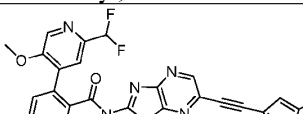
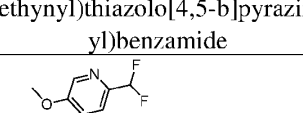
	yl)thiazolo[4,5-b]pyrazin-2-yl)benzamide		
154	 <i>N</i> -(6-(5-cyclobutoxy)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	13.25 (br s, 1H), 9.31 (s, 1H), 8.93 (s, 1H), 8.33 (d, <i>J</i> = 3.2 Hz, 1H), 8.26 (d, <i>J</i> = 8.8 Hz, 1H), 8.18 (s, 1H), 7.44 (dd, <i>J</i> = 8.4 Hz, 3.2 Hz, 1H), 7.30 (s, 1H), 7.24 (s, 1H), 4.86 (m, 1H), 3.60 (s, 3H), 2.58 (s, 3H), 2.52-2.42 (m, 5H), 2.15-2.05 (m, 2H), 1.88-1.79 (m, 1H), 1.74-1.63 (m, 1H).	540.3
155	 <i>N</i> -(6-(5-cyclopropoxy)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	13.31 (br s, 1H), 9.36 (s, 1H), 8.91 (s, 1H), 8.49 (d, <i>J</i> = 3.2 Hz, 1H), 8.31 (d, <i>J</i> = 8.8 Hz, 1H), 8.18 (s, 1H), 7.68 (dd, <i>J</i> = 8.8 Hz, 3.2 Hz, 1H), 7.34 (s, 1H), 7.26 (s, 1H), 4.05 (m, 1H), 3.60 (s, 3H), 2.59 (s, 3H), 2.49 (s, 3H), 0.89-0.84 (m, 2H), 0.78-0.73 (m, 2H).	526.3

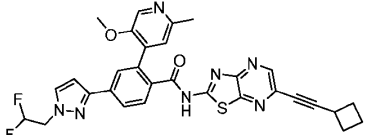
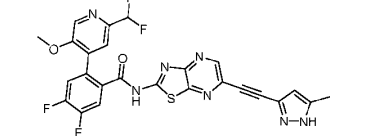
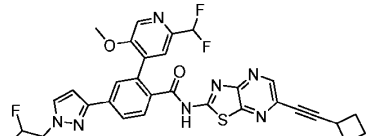
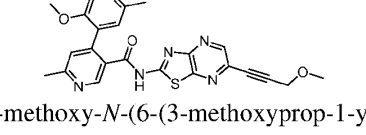
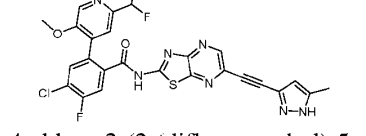
[0506] Following conditions for the synthesis of Example **57**, Examples **156-178** in the table below were prepared by Sonogashira reaction between the corresponding tetracyclic bromide intermediates (**13**, **EI**, **EJ**, **EK**, **EL**, **EM**, **EN**, **EO**, **EP**, **EQ**, **ER**, and **ET**) and commercially available acetylenes.

Example Number	Structure	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm	LCMS (ESI, <i>m/z</i>): [M+H] ⁺
156	 5'-methoxy-2',6-dimethyl- <i>N</i> -(6-(3-(4-methyl-1 <i>H</i> -pyrazol-1-yl)prop-1-yn-1-yl)thiazolo[4,5-b]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide	13.25 (br s, 1H), 9.06 (s, 1H), 8.27 (s, 1H), 8.13 (s, 1H), 7.63 (s, 1H), 7.29 (s, 1H), 7.09 (s, 1H), 7.08 (s, 1H), 5.24 (s, 2H), 3.57 (s, 3H), 2.53 (s, 3H), 2.44 (s, 3H), 2.02 (s, 3H).	511.4
157	 <i>N</i> -(6-((1 <i>H</i> -pyrazol-4-yl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	13.54 (br s, 1H), 13.34 (br s, 1H), 8.86 (s, 1H), 8.71 (s, 1H), 8.27 (s, 1H), 8.19 (s, 1H), 7.85 (s, 1H), 7.38 (s, 1H), 7.29 (s, 1H), 3.59 (s, 3H), 2.60 (s, 3H), 2.49 (s, 3H).	483.2

158	 5'-methoxy-<i>N</i>-(6-((5-methoxypyridin-2-yl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	13.59 (br s, 1H), 8.87 (s, 1H), 8.83 (s, 1H), 8.38 (d, <i>J</i> = 2.8 Hz, 1H), 8.19 (s, 1H), 7.74 (d, <i>J</i> = 8.4 Hz, 1H), 7.49 (dd, <i>J</i> = 8.4 Hz, 2.8 Hz, 1H), 7.38 (s, 1H), 7.30 (s, 1H), 3.90 (s, 3H), 3.59 (s, 3H), 2.60 (s, 3H), 2.49 (s, 3H).	524.3
159	 5'-methoxy-2',6-dimethyl-<i>N</i>-(6-((1-methyl-1<i>H</i>-pyrazol-4-yl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide	13.53 (br s, 1H), 8.86 (s, 1H), 8.75 (s, 1H), 8.20 (s, 2H), 7.80 (s, 1H), 7.40 (s, 1H), 7.31 (s, 1H), 3.89 (s, 3H), 3.59 (s, 3H), 2.60 (s, 3H), 2.50 (s, 3H).	497.3
160	 5'-methoxy-2',6-dimethyl-<i>N</i>-(6-((2-methylpyrimidin-5-yl)ethynyl)-3a,7a-dihydrothiazolo[4,5-b]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide	13.63 (br s, 1H), 9.00 (s, 2H), 8.87 (s, 2H), 8.20 (s, 1H), 7.40 (s, 1H), 7.30 (s, 1H), 3.59 (s, 3H), 2.69 (s, 3H), 2.60 (s, 3H), 2.49 (s, 3H).	509.3
161	 5-cyano-5'-(difluoromethyl)-2'-methoxy-<i>N</i>-(6-((5-methyl-1<i>H</i>-pyrazol-3-yl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-[1,1'-biphenyl]-2-carboxamide	13.55 (br s, 1H), 13.06 (br s, 1H), 8.77 (s, 1H), 8.04 (d, <i>J</i> = 8.0 Hz, 1H), 8.02-7.92 (m, 2H), 7.65-7.55 (m, 2H), 7.11 (d, <i>J</i> = 8.4 Hz, 1H), 7.03 (t, <i>J</i> = 56.0 Hz, 1H), 6.39 (s, 1H), 3.57 (s, 3H), 2.26 (s, 3H).	542.1
162	 5,5'-bis(difluoromethyl)-2'-methoxy-<i>N</i>-(6-((5-methyl-1<i>H</i>-pyrazol-3-yl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-[1,1'-biphenyl]-2-carboxamide	12.95 (br s, 1H), 8.49 (s, 1H), 8.06 (d, <i>J</i> = 8.0 Hz, 1H), 7.66 (d, <i>J</i> = 8.4 Hz, 1H), 7.54 (d, <i>J</i> = 8.4 Hz, 1H), 7.46 (s, 1H), 7.44 (s, 1H), 7.12 (t, <i>J</i> = 56.0 Hz, 1H), 7.07 (d, <i>J</i> = 8.4 Hz, 1H), 7.01 (t, <i>J</i> = 56.0 Hz, 1H), 6.35 (s, 1H), 3.55 (s, 3H), 2.25 (s, 3H)	567.4
163	 5-cyano-5'-(difluoromethyl)-2'-methoxy-<i>N</i>-(6-((5-methyl-1<i>H</i>-pyrazol-3-yl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-[1,1'-biphenyl]-2-carboxamide	13.02 (br s, 1H), 8.69 (s, 1H), 8.43 (s, 1H), 8.08 (s, 2H), 8.00 (s, 1H), 7.73 (s, 1H), 6.96 (t, <i>J</i>	543.3

	4-cyano-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)- <i>N</i> -(6-((5-methyl-1 <i>H</i> -pyrazol-3-yl)ethynyl)thiazolo[4,5- <i>b</i>]pyrazin-2-yl)benzamide	= 55.2 Hz, 1H), 6.38 (s, 1H), 3.69 (s, 3H), 2.25 (s, 3H)	
164	 <i>N</i> -(6-((1 <i>H</i> -pyrazol-3-yl)ethynyl)thiazolo[4,5- <i>b</i>]pyrazin-2-yl)-4-(5-(difluoromethyl)-2-methoxyphenyl)-6-methylnicotinamide	13.51 (br s, 1H), 13.37 (br s, 1H), 8.85-8.78 (m, 2H), 7.90 (s, 1H), 7.65-7.58 (m, 2H), 7.39 (s, 1H), 7.13 (d, <i>J</i> = 8.0 Hz, 1H), 7.06 (t, <i>J</i> = 56.0 Hz, 1H), 6.67 (s, 1H), 3.57 (s, 3H), 2.61 (s, 3H).	518.4
165	 5-chloro-5'-(difluoromethyl)-2'-methoxy- <i>N</i> -(6-((5-methyl-1 <i>H</i> -pyrazol-3-yl)ethynyl)thiazolo[4,5- <i>b</i>]pyrazin-2-yl)-[1,1'-biphenyl]-2-carboxamide	13.42 (br s, 1H), 13.05 (s, 1H), 8.78 (s, 1H), 7.82 (d, <i>J</i> = 8.4 Hz, 1H), 7.64 (dd, <i>J</i> = 8.4 Hz, 2.0 Hz, 1H), 7.62-7.55 (m, 2 H), 7.52 (d, <i>J</i> = 2.0 Hz, 1H), 7.09 (d, <i>J</i> = 8.4 Hz, 1H), 7.03 (t, <i>J</i> = 56.4 Hz, 1H), 6.38 (s, 1H), 3.57 (s, 3H), 2.27 (s, 3H).	551.3
166	 <i>N</i> -(6-((1 <i>H</i> -pyrazol-3-yl)ethynyl)thiazolo[4,5- <i>b</i>]pyrazin-2-yl)-4-cyano-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzamide	13.70 (br s, 1H), 13.34 (s, 1H), 8.71 (s, 1H), 8.43 (s, 1H), 8.08 (s, 2H), 8.00 (s, 1H), 7.87 (s, 1H), 7.73 (s, 1H), 6.96 (t, <i>J</i> = 54.8 Hz, 1H), 6.66 (s, 1H), 3.69 (s, 3H).	529.3
167	 4-chloro-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)- <i>N</i> -(6-((5-methyl-1 <i>H</i> -pyrazol-3-yl)ethynyl)thiazolo[4,5- <i>b</i>]pyrazin-2-yl)benzamide	13.55 (br s, 1H), 13.02 (s, 1H), 8.72 (s, 1H), 8.42 (s, 1H), 7.94 (s, 1H), 7.75-7.50 (m, 3H), 6.97 (t, <i>J</i> = 55.2 Hz, 1H), 6.37 (s, 1H), 3.70 (s, 3H), 2.26 (s, 3H).	552.3
168	 4-cyano-2-(5-methoxy-2-methylpyridin-4-yl)- <i>N</i> -(6-((5-methyl-1 <i>H</i> -pyrazol-3-yl)ethynyl)thiazolo[4,5- <i>b</i>]pyrazin-2-yl)benzamide	13.61 (br s, 1H), 13.02 (br s, 1H), 8.71 (s, 1H), 8.17 (d, <i>J</i> = 12.8 Hz, 1H), 8.09-7.98 (m, 2H), 7.93 (s, 1H), 7.30 (s, 1H), 6.38 (s, 1H), 3.58 (s, 3H), 2.47 (s, 3H), 2.26 (s, 3H).	507.3

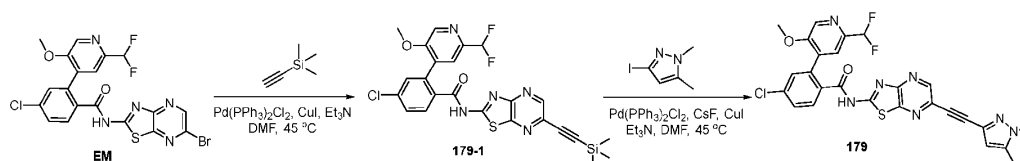
169	 2-(2-chloro-5-methoxypyridin-4-yl)-4-cyano-<i>N</i>-(6-((5-methyl-1<i>H</i>-pyrazol-3-yl)ethynyl)thiazolo[4,5-<i>b</i>]pyrazin-2-yl)benzamide	13.71 (br s, 1H), 13.05 (br s, 1H), 8.77 (s, 1H), 8.18-8.02 (m, 4H), 7.63 (s, 1H), 6.39 (s, 1H), 3.63 (s, 3H), 2.28 (s, 3H).	[M-H] ⁻ = 525.1
170	 <i>N</i>-(6-((1<i>H</i>-pyrazol-3-yl)ethynyl)thiazolo[4,5-<i>b</i>]pyrazin-2-yl)-5-cyano-5'-(difluoromethyl)-2'-methoxy-[1,1'-biphenyl]-2-carboxamide	13.63 (br s, 1H), 13.27 (br s, 1H), 8.51 (s, 1H), 8.06 (d, <i>J</i> = 8.0 Hz, 1H), 7.91 (d, <i>J</i> = 8.0 Hz, 1H), 7.86 (s, 1H), 7.76 (s, 1H), 7.55 (d, <i>J</i> = 8.4 Hz, 1H), 7.48 (s, 1H), 7.08 (d, <i>J</i> = 8.4 Hz, 1H), 6.99 (t, <i>J</i> = 56.0 Hz, 1H), 6.62 (s, 1H), 3.55 (s, 3H).	528.0
171	 <i>N</i>-(6-((1<i>H</i>-pyrazol-3-yl)ethynyl)thiazolo[4,5-<i>b</i>]pyrazin-2-yl)-4-cyano-2-(5-methoxy-2-methylpyridin-4-yl)benzamide	13.68 (br s, 1H), 13.34 (br s, 1H), 8.67 (s, 1H), 8.15 (s, 1H), 8.07-7.98 (m, 2H), 7.95-7.75 (m, 2H), 7.27 (s, 1H), 6.65 (s, 1H), 3.58 (s, 3H), 2.47 (s, 3H).	493.2
172	 4-chloro-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-<i>N</i>-(6-((5-methylisoxazol-3-yl)ethynyl)thiazolo[4,5-<i>b</i>]pyrazin-2-yl)benzamide	13.64 (br s, 1H), 8.90 (s, 1H), 8.43 (s, 1H), 7.92 (d, <i>J</i> = 8.4 Hz, 1H), 7.75-7.70 (m, 2H), 7.63 (s, 1H), 6.98 (t, <i>J</i> = 55.2 Hz, 1H), 6.67 (s, 1H), 3.70 (s, 3H), 2.49 (s, 3H).	553.3
173	 <i>N</i>-(6-((3,3-difluorocyclobutyl)ethynyl)thiazolo[4,5-<i>b</i>]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(3-oxomorpholino)benzamide	13.47 (s, 1H), 8.67 (s, 1H), 8.41 (s, 1H), 7.92 (d, <i>J</i> = 8.4 Hz, 1H), 7.72-7.65 (m, 2H), 7.60 (s, 1H), 6.99 (t, <i>J</i> = 55.2 Hz, 1H), 4.26 (s, 2H), 4.01 (t, <i>J</i> = 5.2 Hz, 2H), 3.88 (t, <i>J</i> = 5.2 Hz, 2H), 3.69 (s, 3H), 3.38 (m, 1H), 3.15-3.03 (m, 2H), 2.86-2.74 (m, 2H).	627.3

174	 <i>N</i>-(6-(cyclobutylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(1-(2,2-difluoroethyl)-1<i>H</i>-pyrazol-3-yl)-2-(5-methoxypyridin-4-yl)benzamide	13.36 (br s, 1H), 8.64 (s, 1H), 8.15 (s, 1H), 8.00 (d, <i>J</i> = 8.0 Hz, 1H), 7.92-7.84 (m, 3H), 7.30 (s, 1H), 7.00 (s, 1H), 6.44 (tt, <i>J</i> = 54.8 Hz, 3.6 Hz, 1H), 4.72 (td, <i>J</i> = 15.2 Hz, 4.0 Hz, 2H), 3.58 (s, 3H), 2.51 (s, 3H), 2.39-2.30 (m, 1H), 2.24-2.12 (m, 3H), 2.04-1.85 (m, 3H).	586.2
175	 2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4,5-difluoro-<i>N</i>-(6-((5-methyl-1<i>H</i>-pyrazol-3-yl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)benzamide	13.04 (br s, 1H), 8.72 (s, 1H), 8.43 (s, 1H), 8.05 (dd, <i>J</i> = 10.8 Hz, 8.0 Hz, 1H), 7.67 (m, 2H), 6.96 (t, <i>J</i> = 55.2 Hz, 1H), 6.39 (s, 1H), 3.71 (s, 3H), 2.26 (s, 3H).	[<i>M</i> -H] ⁻ = 552.1
176	 <i>N</i>-(6-(cyclobutylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(1-(2,2-difluoroethyl)-1<i>H</i>-pyrazol-3-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzamide	13.44 (br s, 1H), 8.57 (s, 1H), 8.42 (s, 1H), 8.05-7.94 (m, 2H), 7.91 (d, <i>J</i> = 2.4 Hz, 1H), 7.85 (s, 1H), 7.68 (s, 1H), 7.01 (d, <i>J</i> = 2.4 Hz, 1H), 7.00 (t, <i>J</i> = 55.2 Hz, 1H), 6.44 (td, <i>J</i> = 55.2 Hz, 4.0 Hz, 1H), 4.72 (td, <i>J</i> = 15.2 Hz, 3.6 Hz, 2H), 3.70 (s, 3H), 3.39 (m, 1H), 2.37-2.30 (m, 2H), 2.25-2.14 (m, 2H), 2.03-1.86 (m, 2H).	622.2
177	 5'-methoxy-<i>N</i>-(6-(3-methoxyprop-1-yn-1-yl)thiazolo[4,5-b]pyrazin-2-yl)-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	13.56 (br s, 1H), 8.87 (s, 1H), 8.69 (s, 1H), 8.18 (s, 1H), 7.37 (s, 1H), 7.28 (s, 1H), 4.42 (s, 2H), 3.58 (s, 3H), 3.37 (s, 3H), 2.59 (s, 3H), 2.48 (s, 3H).	461.3
178	 4-chloro-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-5-fluoro-<i>N</i>-(6-((5-methyl-1<i>H</i>-pyrazol-3-yl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)benzamide	13.01 (br s, 1H), 8.68 (s, 1H), 8.42 (s, 1H), 8.00 (d, <i>J</i> = 9.6 Hz, 1H), 7.74 (d, <i>J</i> = 7.2 Hz, 1H), 7.67 (s, 1H), 6.95 (t, <i>J</i> = 54.8 Hz, 1H), 6.38 (s, 1H), 3.70 (s, 3H), 2.25 (s, 3H).	570.1

	yl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)benzamide		
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Example 179

4-Chloro-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-N-(6-((1,5-dimethyl-1H-pyrazol-3-yl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)benzamide



Step 1: 4-chloro-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-N-(6-((trimethylsilyl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)benzamide (**179-1**)

[0507] Following conditions analogous to synthesis of Example **57**, compound **179-1** was synthesized from **EM**. LCMS (ESI, m/z): [M+H]⁺ = 544.3

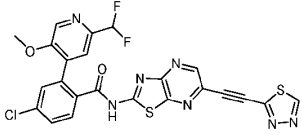
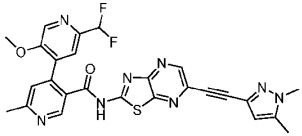
Step 2: 4-chloro-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-N-(6-((1,5-dimethyl-1H-pyrazol-3-yl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)benzamide (**179**)

[0508] 3-Iodo-1,5-dimethyl-pyrazole (29 mg, 0.13 mmol), triethylamine (65.8 mg, 0.65 mmol), CuI (5.0 mg, 0.026 mmol), cesium fluoride (26 mg, 0.17 mmol) and Pd(PPh₃)₂Cl₂ (9.5 mg, 0.015 mmol) were added to a solution of 4-chloro-2-[2-(difluoromethyl)-5-methoxy-4-pyridyl]-N-[6-(2-trimethylsilylethynyl)thiazolo[4,5-b]pyrazin-2-yl]benzamide (**179-1**, 70 mg, 0.13 mmol) in DMF (0.5 mL) under N₂. The mixture was degassed and backfilled with N₂. After stirring at 45 °C for 1 hr, the mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by prep-HPLC (0.1% FA) to afford Example **179**. LCMS (ESI, m/z): [M+H]⁺ = 566.4; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 13.50 (br s, 1H), 8.54 (s, 1H), 8.40 (s, 1H), 8.04 (br s, 1H), 7.68-7.55 (m, 2H), 7.45 (s, 1H), 6.95 (t, *J* = 55.2 Hz, 1H), 6.38 (s, 1H), 3.77 (s, 3H), 3.70 (s, 3H), 2.27 (s, 3H).

[0509] Following conditions analogous to synthesis Example **179**, Examples **180** and **181** in the table below were synthesized from Intermediate **EM** and Example **13**.

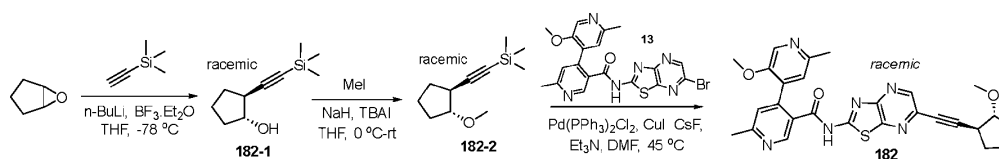
Example Number	Structure	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm	LCMS (ESI, m/z): [M+H] ⁺
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180	 <i>N</i>-(6-((1,3,4-thiadiazol-2-yl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-chloro-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzamide	13.68 (br s, 1H), 9.78 (s, 1H), 8.79 (s, 1H), 8.41 (s, 1H), 8.04 (s, 1H), 7.70-7.52 (m, 2H), 7.48 (s, 1H), 6.95 (t, <i>J</i> = 55.2 Hz, 1H), 3.70 (s, 3H).	[M-H] ⁺ = 554.0
181	 2'-(difluoromethyl)-<i>N</i>-(6-((1,5-dimethyl-1H-pyrazol-3-yl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	13.62 (br s, 1H), 8.92 (s, 1H), 8.77 (s, 1H), 8.47 (s, 1H), 7.73 (s, 1H), 7.46 (s, 1H), 7.00 (t, <i>J</i> = 55.2 Hz, 1H), 6.43 (s, 1H), 3.78 (s, 3H), 3.71 (s, 3H), 2.62 (s, 3H), 2.28 (s, 3H).	547.2

Example 182

rac-5'-Methoxy-*N*-(6-(((1*R*,2*S*)-2-methoxycyclopentyl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide

**Step 1: *rac*-(1*R*,2*S*)-2-((trimethylsilyl)ethynyl)cyclopentan-1-ol (182-1)**

[0510] A 2.5 M hexane solution of *n*-BuLi (164 mL, 0.410 mol) and BF₃·Et₂O (38.8 g, 0.273 mol) were added to a solution of ethynyltrimethylsilane (40.3 g, 0.410 mol) in anhydrous THF (300 mL) under N₂ at -78 °C. After stirring at -78 °C for 40 mins, 6-oxabicyclo[3.1.0]hexane (23.0 g, 0.273 mol) was added dropwise. After stirring for another 3 hrs at -78 °C, the mixture was quenched with saturated aqueous NH₄Cl and extracted with DCM. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography, eluting with EtOAc/PE (1:1), to afford *rac*-(1*R*,2*S*)-2-((trimethylsilyl)ethynyl)cyclopentan-1-ol (**182-1**, 14 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 4.89 (s, 1H), 3.97 (q, *J* = 5.2 Hz, 1H), 2.49-2.44 (m, 1H), 2.04-1.92 (m, 1H), 1.80 (dd, *J* = 12.8 Hz, 8.4 Hz, 1H), 1.69-1.57 (m, 2H), 1.54-1.39 (m, 2H), 0.11 (s, 9H).

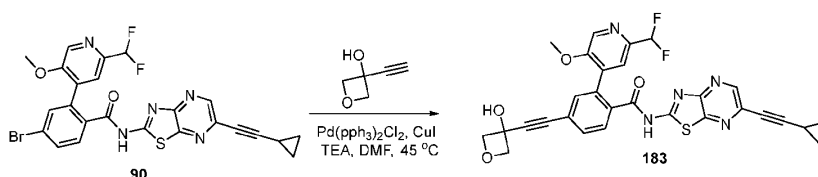
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Step 2: *rac*-(((1*R*,2*S*)-2-methoxycyclopentyl)ethynyl)trimethylsilane (**182-2**)

[0511] Sodium hydride (60% dispersion in mineral oil, 527 mg, 13.2 mmol) was added to a solution of *rac*-(1*R*,2*S*)-2-((trimethylsilyl)ethynyl)cyclopentan-1-ol (**182-1**, 2.00 g, 11.0 mmol) in THF (10 mL) under N₂ at 0 °C. After stirring for 10 mins, iodomethane (310.0 mg, 21.9 mol) and TBAI (6.08 g, 16.5 mol) were added. After stirring at rt for 3 hrs, the mixture was quenched with saturated ammonium chloride and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography, eluting with EtOAc/PE (1:6), to afford Intermediate **182-2** (800 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.69 (m, 1H), 3.24 (s, 3H), 2.65 (dd, *J* = 12.8 Hz, 8.4 Hz, 1H), 1.97-1.77 (m, 2H), 1.64-1.51 (m, 4H), 0.11 (s, 9H).

Step 3: *rac*-5'-Methoxy-N-(6-(((1*R*,2*S*)-2-methoxycyclopentyl)ethynyl)thiazolo[4,5-*b*]pyrazin-2-yl)-2'-6-dimethyl-[4,4'-bipyridine]-3-carboxamide (**182**)

[0512] Following conditions analogous to synthesis of Example **179**, Example **182** was synthesized from Example **13** and Intermediate **182-2**. LCMS (ESI, *m/z*): [M+H]⁺ = 515.3; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 13.51 (s, 1H), 8.86 (s, 1H), 8.61 (s, 1H), 8.19 (s, 1H), 7.37 (s, 1H), 7.28 (s, 1H), 3.88 (m, 1H), 3.58 (s, 3H), 3.31 (s, 3H), 2.97 (m, 1H), 2.60 (s, 3H), 2.48 (s, 3H), 2.08 (m, 1H), 1.94 (m, 1H), 1.75-1.60 (m, 4H).

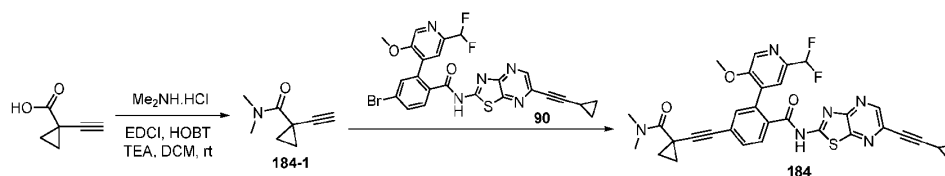
Example 183*N*-(6-(Cyclopropylethynyl)thiazolo[4,5-*b*]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-((3-hydroxyoxetan-3-yl)ethynyl)benzamide

[0513] Following conditions analogous to synthesis of Example **57**, Example **183** was synthesized from Example **90**. LCMS (ESI, *m/z*): [M+H]⁺ = 574.1; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 13.45 (br s, 1H), 8.70 (br s, 1H), 8.41 (s, 1H), 7.85-7.45 (m, 3H), 6.95 (t, *J* = 55.2 Hz, 1H), 6.70 (s, 1H), 4.80 (d, *J* = 6.4 Hz, 2H), 4.62 (d, *J* = 6.4 Hz, 2H), 3.70 (s, 3H), 1.63 (m, 1H), 0.98-0.92 (m, 2H), 0.84-0.78 (m, 2H).

Example 184

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N-(6-(Cyclopropylethynyl)thiazolo[4,5-*b*]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-((1-(dimethylcarbamoyl) cyclopropyl)ethynyl)benzamide



Step 1: 1-Ethynyl-*N,N*-dimethylcyclopropane-1-carboxamide (**184-1**)

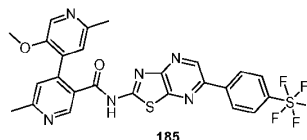
[0514] HOBT (246 mg, 1.82 mmol), TEA (460 mg, 4.55 mmol) and EDCI (349 mg, 1.82 mmol) were added to a stirred mixture of 1-ethynylcyclopropanecarboxylic acid (100 mg, 0.908 mmol), dimethylamine hydrochloride (223 mg, 2.73 mmol) in DCM (2 mL) under N₂. After stirring for 4 hrs, the mixture was treated with water and extracted with DCM. The combined organic layers were dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc/PE (1:8), to afford Intermediate **184-1** (80 mg). ¹H NMR (400 MHz, CDCl₃) δ ppm 3.29 (s, 3H), 2.94 (s, 3H), 2.06 (s, 1H), 1.36-1.33 (m, 2H), 1.20-1.17 (m, 2H).

Step 2: *N*-(6-(cyclopropylethynyl)thiazolo[4,5-*b*]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-((1-(dimethylcarbamoyl) cyclopropyl)ethynyl)benzamide (**184**)

[0515] Following conditions analogous to synthesis of Example **57**, Example **184** was synthesized from Intermediate **184-1** and Example **90**. LCMS (ESI, *m/z*): [M+H]⁺ = 613.5; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 13.39 (br s, 1H), 8.45 (s, 1H), 8.38 (s, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.60-7.58 (m, 2H), 7.41 (s, 1H), 6.95 (t, *J* = 55.2 Hz, 1H), 3.67 (s, 3H), 3.31 (s, 3H), 2.86 (s, 3H), 1.62 (m, 1H), 1.39-1.34 (m, 2H), 1.32-1.27 (m, 2H), 0.97-0.91 (m, 2H), 0.85-0.78 (m, 2H).

Example 185

5'-Methoxy-2',6'-dimethyl-*N*-(6-(4-(pentafluoro-λ⁶-sulfaneyl)phenyl)thiazolo[4,5-*b*]pyrazin-2-yl)-[4,4'-bipyridine]-3-carboxamide



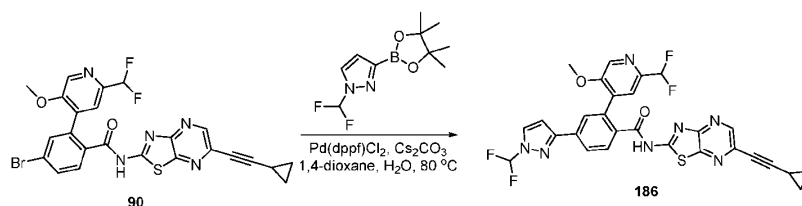
[0516] Following conditions analogous to synthesis of Example **15**, Example **185** was synthesized by Suzuki coupling of Example **13** with (4-(pentafluorosulfanyl)phenyl)boronic acid. LCMS (ESI, *m/z*): [M+H]⁺ = 595.4; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.25 (s,

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1H), 8.89 (s, 1H), 8.37 (d, $J = 8.4$ Hz, 2H), 8.18 (s, 1H), 8.05 (d, $J = 8.8$ Hz, 2H), 7.36 (s, 1H), 7.28 (s, 1H), 3.59 (s, 3H), 2.60 (s, 3H), 2.49 (s, 3H).

Example 186

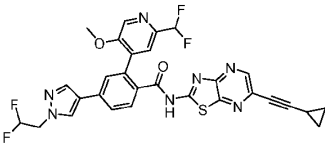
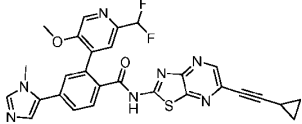
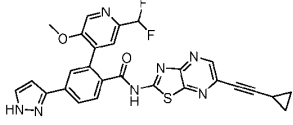
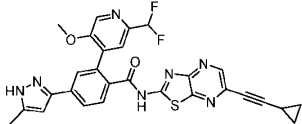
N-(6-(Cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzamide



[0517] Following conditions analogous to synthesis of intermediate **AQ-1**, Example **186** was synthesized from Example **90**. LCMS (ESI, m/z): $[M+H]^+ = 594.4$; 1H NMR (400 MHz, DMSO- d_6) δ ppm 13.46 (br s, 1H), 8.58 (s, 1H), 8.43 (s, 1H), 8.37 (d, $J = 2.8$ Hz, 1H), 8.12 (dd, $J = 8.0$ Hz, 1.6 Hz, 1H), 7.99 (d, $J = 8.0$ Hz, 1H), 7.95 (d, $J = 1.6$ Hz, 1H), 7.90 (t, $J = 59.2$ Hz, 1H), 7.74 (s, 1H), 7.26 (d, $J = 2.8$ Hz, 1H), 7.00 (t, $J = 55.2$ Hz, 1H), 3.70 (s, 3H), 1.65 (m, 1H), 1.00-0.94 (m, 2H), 0.86-0.81 (m, 2H).

[0518] Following conditions analogous to synthesis of Example **186**, Examples **187-192** in the table below were synthesized from Example **90**.

Example Number	Structure	1H NMR (400 MHz, DMSO- d_6) δ ppm	LCMS (ESI, m/z): $[M+H]^+$
187	<i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(1-(2,2-difluoroethyl)-1<i>H</i>-pyrazol-3-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzamide	13.42 (br s, 1H), 8.61 (s, 1H), 8.43 (s, 1H), 8.04 (dd, $J = 8.0$ Hz, 1.8 Hz, 1H), 7.94-7.88 (m, 3H), 7.72 (s, 1H), 7.02 (d, $J = 2.4$ Hz, 1H), 7.00 (tt, $J = 54.8$ Hz, 4.0 Hz, 1H), 6.58-6.29 (m, 1H), 4.76-4.68 (m, 2H), 3.70 (s, 3H), 1.66 (m, 1H), 1.00-0.95 (m, 2H), 0.86-0.82 (m, 2H).	608.4
188		13.07 (br s, 1H), 8.44 (s, 1H), 8.40 (s, 1H), 8.03 (d, $J = 8.0$ Hz, 1H), 7.96 (d, $J = 8.0$ Hz, 1H), 7.79-7.71 (m, 2H), 7.61 (s, 1H), 6.98 (t, $J = 55.2$ Hz,	616.4

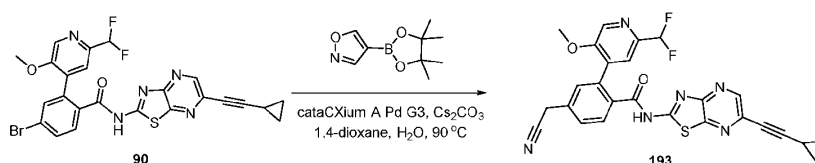
	<i>N</i> -(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(1-(2-hydroxy-2-methylpropyl)-1 <i>H</i> -pyrazol-3-yl)benzamide	1H), 6.88 (d, <i>J</i> = 2.0 Hz, 1H), 4.75 (s, 1H), 4.09 (s, 2H), 3.69 (s, 3H), 1.63 (m, 1H), 1.10 (s, 6H), 0.98-0.92 (m, 2H), 0.84-0.78(m, 2H).	
189	 <i>N</i> -(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(1-(2,2-difluoroethyl)-1 <i>H</i> -pyrazol-4-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzamide	13.33 (br s, 1H), 8.55 (s, 1H), 8.46 (s, 1H), 8.41(s, 1H), 8.18 (s, 1H), 7.92 (d, <i>J</i> = 8.0 Hz, 1H), 7.83 (d, <i>J</i> = 8.0 Hz, 1H), 7.72-7.65 (m, 2H), 6.99 (d, <i>J</i> = 55.2 Hz, 1H), 6.42 (tt, <i>J</i> = 54.8 Hz, 4.0 Hz, 1H), 4.66 (td, <i>J</i> = 15.2 Hz, 4.0 Hz, 2H), 3.69 (s, 3H), 1.65 (m, 1H), 0.99-0.94 (m, 2H), 0.85-0.80 (m, 2H).	608.4
190	 <i>N</i> -(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(1-methyl-1 <i>H</i> -imidazol-5-yl)benzamide	13.45 (br s, 1H), 8.57 (s, 1H), 8.42 (s, 1H), 7.97 (d, <i>J</i> = 8.2 Hz, 1H), 7.80-7.68 (m, 3H), 7.59 (s, 1H), 7.29 (s, 1H), 6.96 (t, <i>J</i> = 55.2 Hz, 1H), 3.79 (s, 3H), 3.70 (s, 3H), 1.64 (m, 1H), 1.00-0.93 (m, 2H), 0.88-0.80 (m, 2H).	558.2
191	 <i>N</i> -(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(1 <i>H</i> -pyrazol-3-yl)benzamide	13.10 (br s, 1H), 8.55 (s, 1H), 8.41 (s, 1H), 8.02 (d, <i>J</i> = 8.0 Hz, 1H), 7.95 (d, <i>J</i> = 8.0 Hz, 1H), 7.87 (s, 1H), 7.80 (s, 1H) 7.69 (s, 1H), 6.99 (t, <i>J</i> = 55.2 Hz, 1H), 6.93 (d, <i>J</i> = 2.4 Hz, 1H), 3.70 (s, 3H), 1.64 (m, 1H), 0.99-0.92 (m, 2H), 0.88-0.80 (m, 2H).	544.3
192	 <i>N</i> -(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(1 <i>H</i> -pyrazol-3-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzamide	12.86 (br s, 2H), 8.48 (s, 1H), 8.40 (s, 1H), 7.97 (<i>J</i> = 8.0 Hz, 1H), 7.92 (<i>J</i> = 8.0 Hz, 1H), 7.76 (s, 1H), 7.64 (s, 1H), 6.98 (t, <i>J</i> = 55.2 Hz, 1H), 6.63 (s, 1H), 3.69 (s, 3H),	558.4

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	b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxy-pyridin-4-yl)-4-(5-methyl-1 <i>H</i> -pyrazol-3-yl)benzamide	2.27 (s, 3H), 1.63 (m, 1H), 1.00-0.92 (m, 2H), 0.86-0.78(m, 2H).	
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Example 193

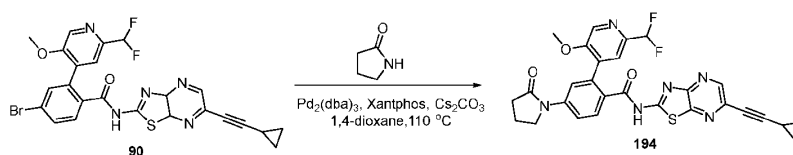
4-(Cyanomethyl)-*N*-(6-(cyclopropylethynyl)thiazolo[4,5-*b*]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzamide



[0519] A mixture of 4-bromo-*N*-(6-(cyclopropylethynyl)thiazolo[4,5-*b*]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzamide (Example **90**, 40 mg, 0.0719 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole (42.1 mg, 0.216 mmol), Cs₂CO₃ (46.9 mg, 0.144 mmol), cataCXium A Pd G3 (5.2 mg, 0.0072 mmol), 1,4-dioxane (1.6 mL) and water (0.4 mL) was degassed and backfilled with N₂. After stirring at 90 °C for 16 hrs, the mixture was treated with water and extracted with EtOAc. The combined organic layers were dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by prep-HPLC (0.1% FA) to afford Example **193**. LCMS (ESI, *m/z*): [M+H]⁺ = 517.3; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 13.42 (br s, 1H), 8.50 (s, 1H), 8.40 (s, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.61 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.42 (s, 1H), 6.97 (t, *J* = 55.2 Hz, 1H), 4.19 (s, 2H), 3.67 (s, 3H), 1.64 (m, 1H), 0.99-0.93 (m, 2H), 0.85-0.79 (m, 2H).

Example 194

N-(6-(Cyclopropylethynyl)thiazolo[4,5-*b*]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(2-oxopyrrolidin-1-yl)benzamide



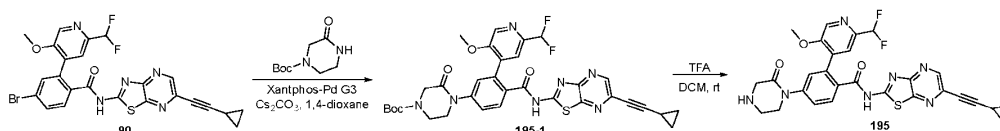
[0520] Following conditions analogous to synthesis of Example **109**, Example **194** was synthesized from Example **90**. LCMS (ESI, *m/z*): [M+H]⁺ = 561.4; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 13.35 (br s, 1H), 8.58 (s, 1H), 8.41 (s, 1H), 7.95-7.80 (m, 2H), 7.77 (s, 1H),

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7.63 (s, 1H), 6.98 (t, $J = 55.2$ Hz, 1H), 3.94 (t, $J = 7.2$ Hz, 2H), 3.69 (s, 3H), 2.56 (t, $J = 8.0$ Hz, 2H), 2.15-2.05(m, 2H), 1.65 (m, 1H), 1.01-0.92 (m, 2H), 0.89-0.80 (m, 2H).

Example 195

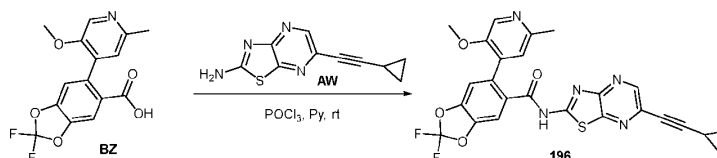
N-(6-(Cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(2-oxopiperazin-1-yl)benzamide



[0521] Following conditions analogous to steps 1 and 3 of Intermediate **DD**, Example **195** was synthesized from **90**. LCMS (ESI, m/z): $[M+H]^+ = 576.4$; ^1H NMR (400 MHz, DMSO- d_6) δ ppm 13.25 (br s, 1H), 8.55 (s, 1H), 8.40 (s, 1H), 7.92 (d, $J = 8.4$ Hz, 1H), 7.62 (s, 1H), 7.59 (dd, $J = 8.4$ Hz, 2.0 Hz, 1H), 7.48 (d, $J = 2.0$ Hz, 1H), 6.98 (t, $J = 55.2$ Hz, 1H), 3.75 (t, $J = 5.6$ Hz, 2H), 3.68 (s, 3H), 3.48 (s, 2H), 3.10 (t, $J = 5.6$ Hz, 2H), 1.65 (m, 1H), 0.99-0.94 (m, 2H), 0.87-0.80 (m, 2H).

Example 196

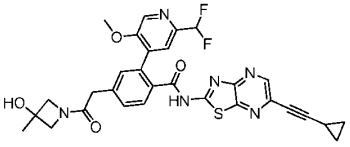
N-(6-(Cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2,2-difluoro-6-(5-methoxy-2-methylpyridin-4-yl)benzo[d][1,3]dioxole-5-carboxamide



[0522] POCl₃ (143 mg, 0.930 mmol) was added to a solution of 2,2-difluoro-6-(5-methoxy-2-methylpyridin-4-yl)benzo[d][1,3]dioxole-5-carboxylic acid (**BZ**, 50.0 mg, 0.155 mmol), 6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-amine (**AW**, 40.2 mg, 0.186 mmol) in pyridine (2 mL) at 0 °C under N₂. After stirring at rt for 16 hrs, the mixture was treated with water and extracted with EtOAc. The combined organic layers were dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by prep-HPLC (0.1% FA) to afford Example **195**. LCMS (ESI, m/z): $[M+H]^+ = 522.3$; ^1H NMR (400 MHz, DMSO- d_6) δ ppm 8.21 (s, 1H), 8.10 (s, 1H), 7.95 (s, 1H), 7.27 (s, 1H), 7.04 (s, 1H), 3.58 (s, 3H), 2.41 (s, 3H), 1.58 (m, 1H), 0.95-0.87 (m, 2H), 0.81-0.74 (m, 2H).

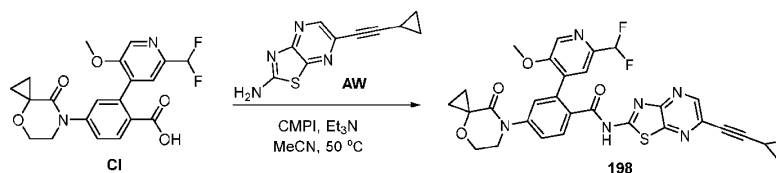
[0523] Following conditions analogous to synthesis of Example **196**, Example **197** was synthesized from Intermediates **DF** and **AW**.

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Example Number	Structure	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm	LCMS (ESI, <i>m/z</i>): [M+H] ⁺
197	 <i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-<i>b</i>]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(2-(3-hydroxy-3-methylazetidin-1-yl)-2-oxoethyl)benzamide	13.35 (br s, 1H), 8.57 (s, 1H), 8.39 (s, 1H), 7.82 (d, <i>J</i> = 8.0 Hz, 1H), 7.60 (s, 1H), 7.47 (d, <i>J</i> = 8.0 Hz, 1H), 7.35 (s, 1H), 6.98 (t, <i>J</i> = 55.2 Hz, 1H), 5.66 (s, 1H), 4.10-4.02 (m, 2H), 3.75-3.65 (m, 5H), 3.60 (s, 2H), 1.65 (m, 1H), 1.38 (s, 3H), 0.99-0.92 (m, 2H), 0.88-0.81 (m, 2H).	605.2

Example 198

N-(6-(Cyclopropylethynyl)thiazolo[4,5-*b*]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(8-oxo-4-oxa-7-azaspiro[2.5]octan-7-yl)benzamide

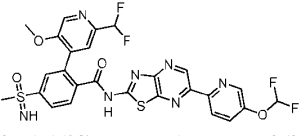
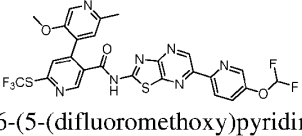
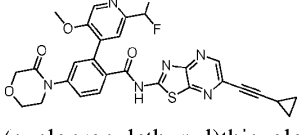
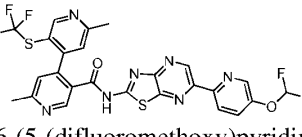


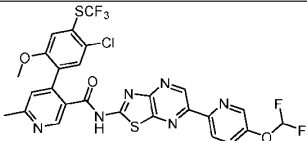
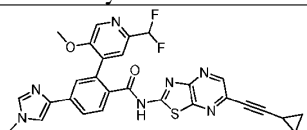
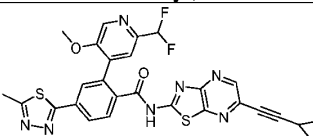
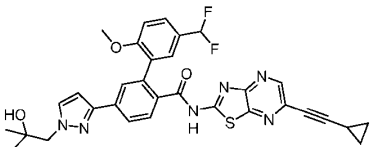
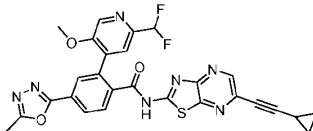
[0524] 6-(2-Cyclopropylethynyl)thiazolo[4,5-*b*]pyrazin-2-amine (AW, 42.8 mg, 0.198 mmol), Et₃N (40.1 mg, 0.396 mmol) and CMPI (75.9 mg, 0.297 mmol) were added to a solution of 2-[2-(difluoromethyl)-5-methoxy-4-pyridyl]-4-(8-oxo-4-oxa-7-azaspiro[2.5]octan-7-yl)benzoic acid (CI, 80.0 mg, 0.198 mmol) in ACN (10 mL) under N₂. After stirring at 50 °C for 18 hrs, the mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by prep-HPLC (0.1% NH₄HCO₃) to afford Example 198. LCMS (ESI, *m/z*): [M+H]⁺ = 603.2; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 13.43 (brs, 1H), 8.62 (s, 1H), 8.41 (s, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.72-7.65 (m, 2H), 7.61 (s, 1H), 6.99 (t, *J* = 55.2 Hz, 1H), 4.12-4.01 (m, 4H), 3.68 (s, 3H), 1.66 (m, 1H), 1.29-1.24 (m, 2H), 1.09-1.04 (m, 2H), 0.99-0.95 (m, 2H), 0.86-0.81 (m, 2H).

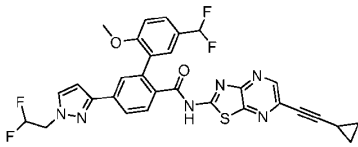
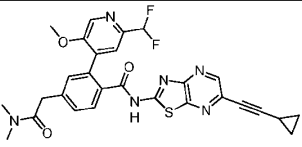
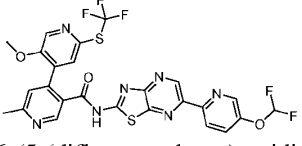
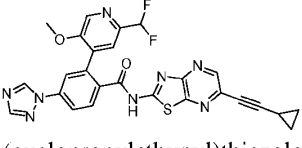
[0525] Following conditions analogous to synthesis of Example 198, Example 199-223 were synthesized from the corresponding acids (BN, BP, BQ, BS, BU, BX, CI, CJ, CM,

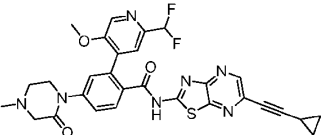
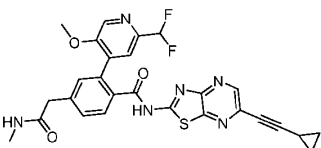
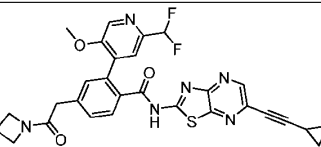
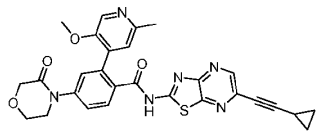
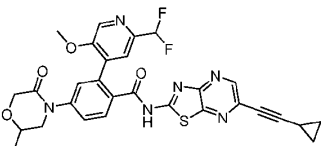
- 247 -

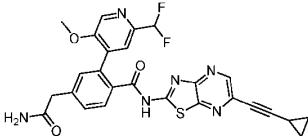
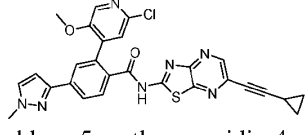
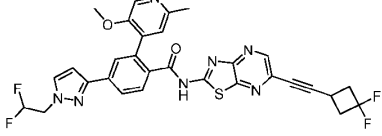
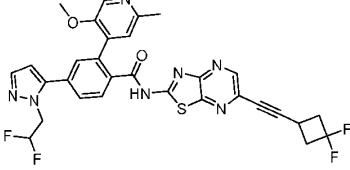
CO, CQ, CS, DE, DG, DH, DI, DL, DL, DN, DP, DQ, DU, EB and EF) and amines (AW, BL and BM).

Example Number	Structure	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm	LCMS (ESI, <i>m/z</i>): [M+H] ⁺
199	 <i>N</i>-(6-(5-(difluoromethoxy)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(<i>S</i>-methylsulfonimidoyl)benzamide	13.67 (br s, 1H), 9.47 (s, 1H), 8.64 (d, <i>J</i> = 2.4 Hz, 1H), 8.44 (s, 1H), 8.42 (s, 1H), 8.14 (d, <i>J</i> = 8.0 Hz, 1H), 8.11 (d, <i>J</i> = 8.0 Hz, 1H), 7.99 (s, 1H), 7.85 (dd, <i>J</i> = 8.0 Hz, 2.4 Hz, 1H), 7.80 (s, 1H), 7.43 (t, <i>J</i> = 73.2 Hz, 1H), 7.01 (t, <i>J</i> = 55.2 Hz, 1H), 4.50 (s, 1H), 3.70 (s, 3H), 3.21 (s, 3H).	634.2
200	 <i>N</i>-(6-(5-(difluoromethoxy)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-2'-methyl-6-((trifluoromethyl)thio)-[4,4'-bipyridine]-3-carboxamide	13.70 (br s, 1H), 9.52 (s, 1H), 9.03 (s, 1H), 8.65 (d, <i>J</i> = 2.8 Hz, 1H), 8.44 (d, <i>J</i> = 8.8 Hz, 1H), 8.24 (s, 1H), 7.81-7.82 (m, 2H), 7.44 (t, <i>J</i> = 73.2 Hz, 1H), 7.39 (s, 1H), 3.62 (s, 3H), 2.50 (s, 3H).	622.2
201	 <i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(3-oxomorpholino)benzamide	13.42 (br s, 1H), 8.57 (s, 1H), 8.41 (s, 1H), 7.94 (d, <i>J</i> = 8.4 Hz, 1H), 7.73-7.61 (m, 2H), 7.58 (s, 1H), 6.99 (d, <i>J</i> = 55.2 Hz, 1H), 4.26 (s, 2H), 4.02 (m, 2H), 3.88 (m, 2H), 3.69 (s, 3H), 1.65 (m, 1H), 1.00-0.95 (m, 2H), 0.86-0.80 (m, 2H).	577.4
202	 <i>N</i>-(6-(5-(difluoromethoxy)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-2',6-dimethyl-5'-((trifluoromethyl)thio)-[4,4'-bipyridine]-3-carboxamide	13.78 (br s, 1H), 9.50 (s, 1H), 9.13 (s, 1H), 8.81 (s, 1H), 8.64 (d, <i>J</i> = 2.8 Hz, 1H), 8.41 (d, <i>J</i> = 8.8 Hz, 1H), 7.86 (dd, <i>J</i> = 8.8 Hz, 2.8 Hz, 1H), 7.50 (s, 1H), 7.43 (t, <i>J</i> = 73.2 Hz, 1H), 7.40 (s, 1H), 2.64 (s, 3H), 2.61 (s, 3H).	606.0

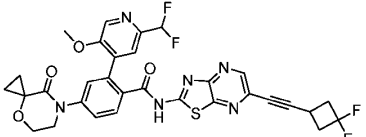
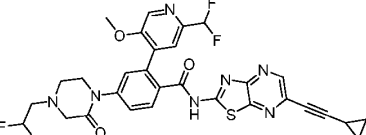
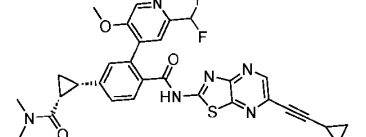
203	 4-(5-chloro-2-methoxy-4-((trifluoromethyl)thio)phenyl)-N-(6-(5-(difluoromethoxy)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-6-methylnicotinamide	13.53 (br s, 1H), 9.48 (s, 1H), 8.87 (s, 1H), 8.64 (d, $J = 2.8$ Hz, 1H), 8.43 (d, $J = 8.8$ Hz, 1H), 7.86 (dd, $J = 8.8$ Hz, 2.8 Hz, 1H), 7.80 (s, 1H), 7.47 (s, 1H), 7.45 (s, 1H), 7.43 (t, $J = 73.2$ Hz, 1H), 3.59 (s, 3H), 2.61 (s, 3H).	655.3
204	 <i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(1-methyl-1H-imidazol-4-yl)benzamide	13.34 (br s, 1H), 8.58 (s, 1H), 8.41 (s, 1H), 7.94 (d, $J = 8.0$ Hz, 1H), 7.92-7.80 (m, 2H), 7.79 (s, 1H), 7.71 (s, 1H), 7.66 (s, 1H), 7.00 (t, $J = 55.2$ Hz, 1H), 3.71 (s, 3H), 3.69 (s, 3H), 1.64 (m, 1H), 0.99-0.94 (m, 2H), 0.86-0.81 (m, 2H).	558.2
205	 <i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(5-methyl-1,3,4-thiadiazol-2-yl)benzamide	13.58 (br s, 1H), 8.62 (s, 1H), 8.44 (s, 1H), 8.18 (dd, $J = 8.0$ Hz, 2.0 Hz, 1H), 8.05-8.01 (m, 2H), 7.80 (s, 1H), 7.00 (t, $J = 55.2$ Hz, 1H), 3.70 (s, 3H), 2.84 (s, 3H), 1.66 (m, 1H), 1.00-0.96 (m, 2H), 0.87-0.82 (m, 2H).	576.3
206	 <i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-(difluoromethyl)-5-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-3-yl)-2'-methoxy-[1,1'-biphenyl]-2-carboxamide	13.25 (br s, 1H), 8.61 (s, 1H), 7.94 (d, $J = 8.0$ Hz, 1H), 7.84-7.78 (m, 2H), 7.77 (d, $J = 2.4$ Hz, 1H), 7.61-7.54 (m, 2H), 7.10 (d, $J = 8.0$ Hz, 1H), 7.07 (t, $J = 55.2$ Hz, 1H), 6.90 (d, $J = 2.4$ Hz, 1H), 4.72 (s, 1H), 4.10 (s, 2H), 3.56 (s, 3H), 1.66 (m, 1H), 1.10 (s, 6H), 0.99-0.95 (m, 2H), 0.87-0.82 (m, 2H).	615.4
207	 <i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(1-methyl-1H-imidazol-4-yl)benzamide	13.60 (br s, 1H), 8.62 (s, 1H), 8.45 (s, 1H), 8.20 (d, $J = 8.0$ Hz, 1H), 8.08 (d, $J = 8.0$ Hz, 1H), 8.02 (s, 1H), 7.77 (s, 1H), 7.00 (t, $J = 55.2$ Hz, 1H), 3.71 (s, 3H), 2.63 (s, 3H),	560.4

	5-methoxypyridin-4-yl)-4-(5-methyl-1,3,4-oxadiazol-2-yl)benzamide	1.66 (m, 1H), 1.01-0.93 (m, 2H), 0.87-0.81 (m, 2H).	
208	 <i>N</i> -(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5-(1-(2,2-difluoroethyl)-1 <i>H</i> -pyrazol-3-yl)-5'-(difluoromethyl)-2'-methoxy-[1,1'-biphenyl]-2-carboxamide	13.28 (br s, 1H), 8.59 (s, 1H), 7.96 (d, <i>J</i> = 8.4 Hz, 1H), 7.90 (d, <i>J</i> = 2.4 Hz, 1H), 7.87-7.80 (m, 2H), 7.60-7.55 (m, 2H), 7.09 (d, <i>J</i> = 8.4 Hz, 1H), 7.06 (t, <i>J</i> = 56.4 Hz, 1H), 6.98 (d, <i>J</i> = 2.4 Hz, 1H), 6.43 (tt, <i>J</i> = 55.2 Hz, 3.6 Hz, 1H), 4.71 (td, <i>J</i> = 14.8 Hz, 3.6 Hz, 2H), 3.56 (s, 3H), 1.65 (m, 1H), 1.01-0.95 (m, 2H), 0.86-0.82 (m, 2H).	607.4
209	 <i>N</i> -(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(2-(dimethylamino)-2-oxoethyl)benzamide	13.37 (br s, 1H), 8.55 (s, 1H), 8.39 (s, 1H), 7.83 (d, <i>J</i> = 8.0 Hz, 1H), 7.59 (s, 1H), 7.43 (d, <i>J</i> = 8.0 Hz, 1H), 7.32 (s, 1H), 6.98 (t, <i>J</i> = 55.2 Hz, 1H), 3.85 (s, 2H), 3.67 (s, 3H), 3.06 (s, 3H), 2.85 (s, 3H), 1.64 (m, 1H), 0.99-0.94 (m, 2H), 0.86-0.81 (m, 2H).	563.4
210	 <i>N</i> -(6-(5-(difluoromethoxy)pyridin-2-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-2'-((trifluoromethyl)thio)-[4,4'-bipyridine]-3-carboxamide	13.63 (br s, 1H), 9.46 (s, 1H), 8.95 (s, 1H), 8.63 (d, <i>J</i> = 2.8 Hz, 1H), 8.51 (s, 1H), 8.42 (d, <i>J</i> = 8.8 Hz, 1H), 7.89-7.80 (m, 2H), 7.43 (t, <i>J</i> = 73.2 Hz, 1H), 3.73 (s, 3H), 2.62 (s, 3H).	622.0
211	 <i>N</i> -(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(1 <i>H</i> -1,2,4-triazol-1-yl)benzamide	13.54 (br s, 1H), 9.52 (s, 1H), 8.62 (s, 1H), 8.46 (s, 1H), 8.34 (s, 1H), 8.13 (dd, <i>J</i> = 8.4 Hz, 2.0 Hz, 1H), 8.08 (d, <i>J</i> = 8.4 Hz, 1H), 8.04 (d, <i>J</i> = 2.0 Hz, 1H), 7.81 (s, 1H), 7.01 (d, <i>J</i> = 55.2 Hz, 1H), 3.71 (s, 3H), 1.66 (m, 1H), 1.01-0.96 (m, 2H), 0.88-0.82 (m, 2H).	[M-H] ⁻ = 543.1

212	 <i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(4-methyl-2-oxopiperazin-1-yl)benzamide	13.42 (br s, 1H), 8.60 (s, 1H), 8.41 (s, 1H), 7.91 (d, $J = 8.4$ Hz, 1H), 7.66 (s, 1H), 7.63 (d, $J = 8.4$ Hz, 1H), 7.53 (s, 1H), 6.99 (t, $J = 55.2$ Hz, 1H), 3.81 (t, $J = 5.2$ Hz, 2H), 3.69 (s, 3H), 3.17 (s, 2H), 2.77 (t, $J = 5.2$ Hz, 2H), 2.31 (s, 3H), 1.66 (m, 1H), 1.01-0.95 (m, 2H), 0.87-0.82 (m, 2H).	590.2
213	 <i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(2-(methylamino)-2-oxoethyl)benzamide	13.29 (br s, 1H), 8.57 (s, 1H), 8.39 (s, 1H), 8.05 (q, $J = 4.8$ Hz, 1H), 7.82 (d, $J = 8.0$ Hz, 1H), 7.62 (s, 1H), 7.47 (d, $J = 8.0$ Hz, 1H), 7.36 (s, 1H), 6.99 (t, $J = 55.2$ Hz, 1H), 3.67 (s, 3H), 3.55 (s, 2H), 2.59 (d, $J = 4.8$ Hz, 3H), 1.64 (m, 1H), 1.00-0.94 (m, 2H), 0.86-0.80 (m, 2H).	549.3
214	 4-(2-(azetidin-1-yl)-2-oxoethyl)-<i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzamide	8.51 (s, 1H), 8.38 (s, 1H), 7.85 (br, 1H), 7.58 (s, 1H), 7.45 (br, 1H), 7.31 (s, 1H), 6.98 (t, $J = 55.2$ Hz, 1H), 4.22 (m, 2H), 3.86 (m, 2H), 3.67 (s, 3H), 3.55 (s, 2H), 2.20 (m, 2H), 1.63 (m, 1H), 0.96 (m, 2H), 0.82 (m, 2H).	575.4
215	 <i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(5-methoxy-2-methylpyridin-4-yl)-4-(3-oxomorpholino)benzamide	13.34 (br s, 1H), 8.54 (s, 1H), 8.12 (s, 1H), 7.88 (d, $J = 8.4$ Hz, 1H), 7.62 (d, $J = 8.4$ Hz, 1H), 7.49 (s, 1H), 7.21 (s, 1H), 4.24 (s, 2H), 4.04-3.97 (m, 2H), 3.88-3.82 (m, 2H), 3.56 (s, 3H), 2.47 (s, 3H), 1.64 (m, 1H), 0.99-0.93 (m, 2H), 0.85-0.81 (m, 2H).	541.1
216	 <i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(3-oxomorpholino)benzamide	13.42 (br s, 1H), 8.57 (s, 1H), 8.40 (s, 1H), 7.93 (d, $J = 8.4$ Hz, 1H), 7.68-7.62 (m, 2H), 7.56 (s, 1H), 6.98 (t, $J = 55.2$ Hz, 1H), 4.27 (d, $J = 2.8$ Hz, 2H), 4.10 (m, 1H), 3.77-3.72 (m, 2H), 3.68 (s, 3H), 1.65	591.2

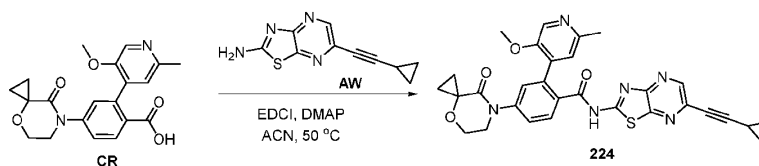
	5-methoxypyridin-4-yl)-4-(2-methyl-5-oxomorpholino)benzamide	(m, 1H), 1.24 (d, $J = 6.4$ Hz, 3H), 0.99-0.95 (m, 2H), 0.87-0.80 (m, 2H).	
217	 4-(2-amino-2-oxoethyl)-<i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzamide	8.45 (s, 1H), 8.37 (s, 1H), 7.89 (d, $J = 8.0$ Hz, 1H), 7.56 (m, 2H), 7.44 (d, $J = 8.0$ Hz, 1H), 7.29 (s, 1H), 6.97 (t, $J = 55.2$ Hz, 1H), 6.94 (s, 1H), 3.66 (s, 3H), 3.51 (s, 2H), 1.61 (m, 1H), 0.98-0.91 (m, 2H), 0.85-0.78 (m, 2H).	535.3
218	 2-(2-chloro-5-methoxypyridin-4-yl)-<i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(1-methyl-1<i>H</i>-pyrazol-3-yl)benzamide	13.37 (br s, 1H), 8.58 (s, 1H), 8.12 (s, 1H), 8.01 (d, $J = 8.0$ Hz, 1H), 7.93 (d, $J = 8.0$ Hz, 1H), 7.84 (s, 1H), 7.81 (d, $J = 2.0$ Hz, 1H), 7.54 (s, 1H), 6.93 (d, $J = 2.0$ Hz, 1H), 3.93 (s, 3H), 3.63 (s, 3H), 1.66 (m, 1H), 1.00-0.95 (m, 2H), 0.87-0.82 (m, 2H).	542.3
219	 <i>N</i>-(6-((3,3-difluorocyclobutyl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(1-(2,2-difluoroethyl)-1<i>H</i>-pyrazol-3-yl)-2-(5-methoxy-2-methylpyridin-4-yl)benzamide	13.40 (br s, 1H), 8.65 (s, 1H), 8.14 (s, 1H), 7.99 (d, $J = 8.0$ Hz, 1H), 7.93-7.80 (m, 3H), 7.29 (s, 1H), 7.00 (s, 1H), 6.44 (tt, $J = 54.8$ Hz, 4.0 Hz, 1H), 4.71 (td, $J = 15.2$ Hz, 4.0 Hz, 2H), 3.58 (s, 3H), 3.37 (m, 1H), 3.15-3.03 (m, 2H), 2.87-2.73 (m, 2H), 2.50 (s, 3H).	622.2
220	 <i>N</i>-(6-((3,3-difluorocyclobutyl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(1-(2,2-difluoroethyl)-1<i>H</i>-pyrazol-5-yl)-2-(5-methoxy-2-methylpyridin-4-yl)benzamide	13.48 (br s, 1H), 8.66 (s, 1H), 8.15 (s, 1H), 7.96 (d, $J = 8.0$ Hz, 1H), 7.73-7.66 (m, 2H), 7.55 (s, 1H), 7.31 (s, 1H), 6.63 (s, 1H), 6.40 (tt, $J = 54.8$ Hz, 4.0 Hz, 1H), 4.66 (td, $J = 15.2$ Hz, 4.0 Hz, 2H), 3.59 (s, 3H), 3.37 (m, 1H), 3.16-3.04 (m, 2H), 2.87-2.74 (m, 2H), 2.47 (s, 3H).	622.3

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221	 <i>N</i>-(6-((3,3-difluorocyclobutyl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(8-oxo-4-oxa-7-azaspiro[2.5]octan-7-yl)benzamide	13.47 (br s, 1H), 8.64 (s, 1H), 8.41 (s, 1H), 7.93 (d, <i>J</i> = 8.4 Hz, 1H), 7.70-7.64 (m, 2H), 7.58 (s, 1H), 6.99 (t, <i>J</i> = 55.2 Hz, 1H), 4.11-4.00 (m, 4H), 3.69 (s, 3H), 3.37 (m, 1H), 3.15-3.03 (m, 2H), 2.86-2.74 (m, 2H), 1.30-1.24 (m, 2H), 1.09-1.03 (m, 2H).	653.2
222	 <i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(4-(2,2-difluoroethyl)-2-oxopiperazin-1-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzamide	13.42 (br s, 1H), 8.62 (s, 1H), 8.41 (s, 1H), 7.89 (d, <i>J</i> = 8.4 Hz, 1H), 7.68 (s, 1H), 7.65 (dd, <i>J</i> = 8.4 Hz, 2.0 Hz, 1H), 7.57 (d, <i>J</i> = 2.0 Hz, 1H), 6.99 (t, <i>J</i> = 55.2 Hz, 1H), 6.23 (tt, <i>J</i> = 55.2 Hz, 4.4 Hz, 1H), 3.82 (t, <i>J</i> = 5.2 Hz, 2H), 3.69 (s, 3H), 3.43 (s, 2H), 3.03-2.89 (m, 4H), 1.66 (m, 1H), 1.01-0.96 (m, 2H), 0.87-0.82 (m, 2H).	640.3
223	 <i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-((1<i>S</i>,2<i>R</i>)-2-(dimethylcarbamoyl)cyclopropyl)benzamide	13.30 (s, 1H), 8.59 (s, 1H), 8.38 (s, 1H), 7.72 (d, <i>J</i> = 8.0 Hz, 1H), 7.54 (s, 1H), 7.37 (d, <i>J</i> = 8.0 Hz, 1H), 7.20 (s, 1H), 6.98 (t, <i>J</i> = 55.2 Hz, 1H), 3.66 (s, 3H), 3.02 (s, 3H), 2.69 (s, 3H), 2.64 (m, 1H), 2.44 (m, 1H), 1.68-1.60 (m, 2H), 1.32 (m, 1H), 0.99-0.95 (m, 2H), 0.86-0.81 (m, 2H).	589.3

Example 224

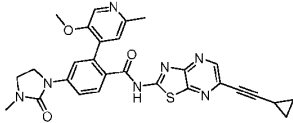
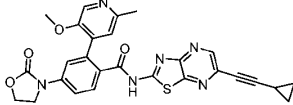
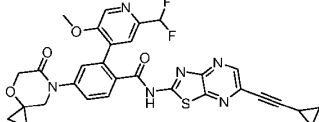
N-(6-(Cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(5-methoxy-2-methylpyridin-4-yl)-4-(8-oxo-4-oxa-7-azaspiro[2.5]octan-7-yl)benzamide



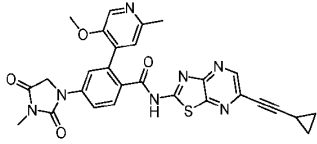
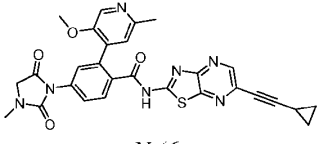
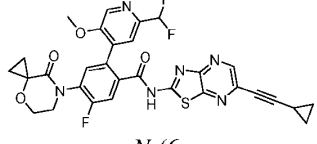
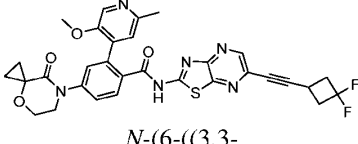
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[0526] EDCI (62.5 mg, 0.326 mmol) and DMAP (19.9 mg, 0.163 mmol) were added to a stirred mixture of 2-(5-methoxy-2-methylpyridin-4-yl)-4-(8-oxo-4-oxa-7-azaspiro[2.5]octan-7-yl)benzoic acid (**CR**, 60.0 mg, 0.163 mmol) and 6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-amine (**AW**, 52.8 mg, 0.244 mmol) in ACN (1.5 mL) under N₂. After stirring at 50 °C for 4 hrs, the mixture was treated with H₂O and extracted with EtOAc. The combined organic layers were dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by prep-HPLC (0.1% FA) to afford Example **224**. LCMS (ESI, m/z): [M+H]⁺ = 567.4; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 13.34 (br s, 1H), 8.61 (s, 1H), 8.13 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.64 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 7.54 (d, *J* = 2.4 Hz, 1H), 7.25 (s, 1H), 4.10-4.01 (m, 4H), 3.56 (s, 3H), 2.48 (s, 3H), 1.65 (m, 1H), 1.29-1.25 (m, 2H), 1.08-1.04 (m, 2H), 1.00-0.95 (m, 2H), 0.86-0.82 (m, 2H).

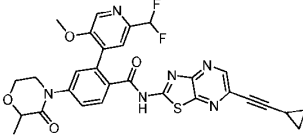
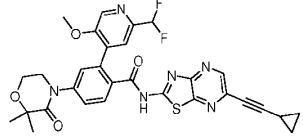
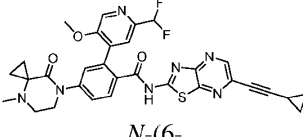
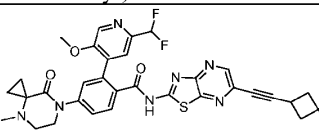
[0527] Following conditions analogous to synthesis of Example **224**, Example **225-244** were synthesized from the corresponding acids (**CJ**, **CN**, **CO**, **CP**, **CQ**, **CR**, **CT**, **CU**, **CV**, **CW**, **CX**, **CY**, **CZ**, **DA**, **DB** and **DC**) and amines (**AW**, **BL** and **BM**).

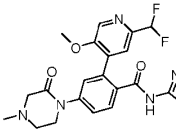
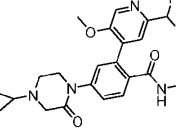
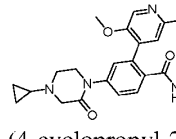
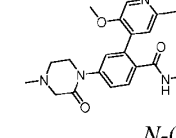
Example Number	Structure	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm	LCMS (ESI, m/z): [M+H] ⁺
225	 <i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(5-methoxy-2-methylpyridin-4-yl)-4-(3-methyl-2-oxoimidazolidin-1-yl)benzamide	8.52 (s, 1H), 8.20 (s, 1H), 7.84 (d, <i>J</i> = 8.4 Hz, 1H), 7.69-7.58 (m, 2H), 7.17 (s, 1H), 3.88 (m, 2H), 3.56 (s, 3H), 3.49 (m, 2H), 2.79 (s, 3H), 2.47 (s, 3H), 1.63 (m, 1H), 1.00-0.92 (m, 2H), 0.85-0.79 (m, 2H).	540.3
226	 <i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(5-methoxy-2-methylpyridin-4-yl)-4-(2-oxooxazolidin-3-yl)benzamide	13.16 (br s, 1H), 8.51 (s, 1H), 8.13 (s, 1H), 7.93 (d, <i>J</i> = 8.4 Hz, 1H), 7.72 (dd, <i>J</i> = 8.8 Hz, 2.4 Hz, 1H), 7.56 (d, <i>J</i> = 2.4 Hz, 1H), 7.18 (s, 1H), 4.49 (t, <i>J</i> = 8.0 Hz, 2H), 4.16 (t, <i>J</i> = 8.0 Hz, 2H), 3.57 (s, 3H), 2.47 (s, 3H), 1.64 (m, 1H), 0.99-0.93 (m, 2H), 0.85-0.79 (m, 2H).	527.3
227		13.44 (br s, 1H), 8.52 (s, 1H), 8.39 (s, 1H), 7.96 (d, <i>J</i> = 8.0 Hz, 1H), 7.67 (d, <i>J</i> = 8.0 Hz, 1H), 7.62 (s, 1H), 7.54 (s, 1H), 6.97	603.2

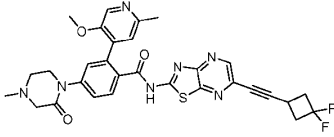
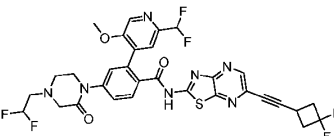
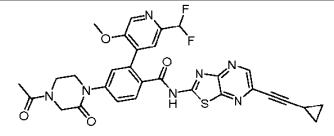
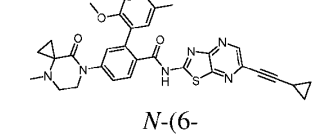
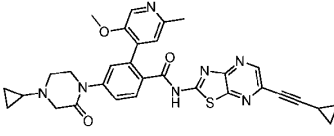
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	<i>N</i> -(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(6-oxo-4-oxa-7-azaspiro[2.5]octan-7-yl)benzamide	(t, $J = 55.2$ Hz, 1H), 4.26 (s, 2H), 3.90 (s, 2H), 3.68 (s, 3H), 1.63 (m, 1H), 0.99-0.94 (m, 4H), 0.85-0.79 (m, 4H).	
228	 <i>N</i> -(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(5-methoxy-2-methylpyridin-4-yl)-4-(3-methyl-2,4-dioxoimidazolidin-1-yl)benzamide	13.06 (br s, 1H), 8.47 (s, 1H), 8.13 (s, 1H), 7.95 (d, $J = 8.4$ Hz, 1H), 7.78 (dd, $J = 8.4$ Hz, 2.4 Hz, 1H), 7.61 (d, $J = 2.4$ Hz, 1H), 7.17 (s, 1H), 4.57 (s, 2H), 3.57 (s, 3H), 2.95 (s, 3H), 2.48 (s, 3H), 1.63 (m, 1H), 0.98-0.92 (m, 2H), 0.84-0.78 (m, 2H).	554.3
229	 <i>N</i> -(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(5-methoxy-2-methylpyridin-4-yl)-4-(3-methyl-2,5-dioxoimidazolidin-1-yl)benzamide	13.41 (br s, 1H), 8.58 (s, 1H), 8.15 (s, 1H), 7.94 (d, $J = 8.4$ Hz, 1H), 7.59 (d, $J = 8.4$ Hz, 1H), 7.47 (s, 1H), 7.18 (s, 1H), 4.15 (s, 2H), 3.58 (s, 3H), 2.96 (s, 3H), 2.48 (s, 3H), 1.66 (m, 1H), 1.00-0.95 (m, 2H), 0.87-0.82 (m, 2H).	554.4
230	 <i>N</i> -(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-5-fluoro-4-(8-oxo-4-oxa-7-azaspiro[2.5]octan-7-yl)benzamide	13.52 (br s, 1H), 8.59 (s, 1H), 8.40 (s, 1H), 7.87 (d, $J = 8.4$ Hz, 1H), 7.75-7.66 (m, 2H), 6.98 (t, $J = 55.2$ Hz, 1H), 4.11-4.05 (m, 2H), 4.00-3.93 (m, 2H), 3.67 (s, 3H), 1.65 (m, 1H), 1.27-1.21 (m, 2H), 1.11-1.05 (m, 2H), 1.01-0.93 (m, 2H), 0.88-0.80 (m, 2H).	621.3
231	 <i>N</i> -(6-((3,3-difluorocyclobutyl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(5-methoxy-2-methylpyridin-4-yl)-4-(8-oxo-4-oxa-7-azaspiro[2.5]octan-7-yl)benzamide	13.38 (br s, 1H), 8.63 (s, 1H), 8.13 (s, 1H), 7.87 (d, $J = 8.4$ Hz, 1H), 7.62 (d, $J = 8.4$ Hz, 1H), 7.51 (s, 1H), 7.23 (s, 1H), 4.10-3.98 (m, 4H), 3.56 (s, 3H), 3.37 (m, 1H), 3.15-3.03 (m, 2H), 2.86-2.73 (m, 2H), 2.48 (s, 3H),	617.3

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	oxa-7-azaspiro[2.5]octan-7-yl)benzamide	1.29-1.24 (m, 2H), 1.08-1.03 (m, 2H).	
232	 <i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(2-methyl-3-oxomorpholino)benzamide	13.43 (br s, 1H), 8.59 (s, 1H), 8.40 (s, 1H), 7.92 (d, <i>J</i> = 8.0 Hz, 1H), 7.68-7.60 (m, 2H), 7.56 (s, 1H), 6.99 (t, <i>J</i> = 55.2 Hz, 1H), 4.36 (q, <i>J</i> = 6.8 Hz, 1H), 4.11-3.94 (m, 3H), 3.75 (d, <i>J</i> = 11.2 Hz, 1H), 3.68 (s, 3H), 1.65 (m, 1H), 1.40 (d, <i>J</i> = 6.8 Hz, 3H), 1.00-0.94 (m, 2H), 0.87-0.81 (m, 2H).	591.2
233	 <i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(2,2-dimethyl-3-oxomorpholino)benzamide	13.44 (br s, 1H), 8.61 (s, 1H), 8.41 (s, 1H), 7.90 (d, <i>J</i> = 8.4 Hz, 1H), 7.68 (s, 1H), 7.64 (dd, <i>J</i> = 8.4 Hz, 2.0 Hz, 1H), 7.55 (d, <i>J</i> = 2.0 Hz, 1H), 6.99 (t, <i>J</i> = 55.2 Hz, 1H), 4.01-3.97 (m, 2H), 3.89-3.84 (m, 2H), 3.68 (s, 3H), 1.65 (m, 1H), 1.44 (s, 6H), 1.00-0.94 (m, 2H), 0.87-0.81 (m, 2H).	605.3
234	 <i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(4-methyl-8-oxo-4,7-diazaspiro[2.5]octan-7-yl)benzamide	13.25 (br s, 1H), 8.42-8.32 (m, 2H), 8.01 (d, <i>J</i> = 8.4 Hz, 1H), 7.58-7.51 (m, 2H), 7.39 (s, 1H), 6.96 (t, <i>J</i> = 55.2 Hz, 1H), 4.01 (t, <i>J</i> = 5.6 Hz, 2H), 3.66 (s, 3H), 3.24 (t, <i>J</i> = 5.6 Hz, 2H), 2.51 (s, 3H), 1.61 (m, 1H), 1.22-1.17 (m, 2H), 0.97-0.88 (m, 4H), 0.83-0.78 (m, 2H).	616.2
235	 <i>N</i>-(6-((3,3-difluorocyclobutyl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(4-methyl-8-oxo-4,7-diazaspiro[2.5]octan-7-yl)benzamide	13.47 (br s, 1H), 8.66 (s, 1H), 8.40 (s, 1H), 7.90 (d, <i>J</i> = 8.4 Hz, 1H), 7.68-7.61 (m, 2H), 7.54 (s, 1H), 6.99 (t, <i>J</i> = 55.2 Hz, 1H), 4.04 (t, <i>J</i> = 5.6 Hz, 2H), 3.68 (s, 3H), 3.37 (m, 1H), 3.25 (t, <i>J</i> = 5.6 Hz, 2H), 3.16-3.03 (m, 2H), 2.87-2.73 (m, 2H), 2.52 (s, 3H), 1.23-1.18 (m, 2H), 0.95-0.88 (m, 2H).	666.3

236	 <i>N</i>-(6-((3,3-difluorocyclobutyl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(4-methyl-2-oxopiperazin-1-yl)benzamide	13.45 (br s, 1H), 8.69 (s, 1H), 8.41 (s, 1H), 7.89 (d, <i>J</i> = 8.4 Hz, 1H), 7.67 (s, 1H), 7.64 (d, <i>J</i> = 8.4 Hz, 1H), 7.55 (s, 1H), 6.98 (t, <i>J</i> = 55.2 Hz, 1H), 3.80 (t, <i>J</i> = 5.6 Hz, 2H), 3.68 (s, 3H), 3.38 (m, 1H), 3.18 (s, 2H), 3.13-3.04 (m, 2H), 2.85-2.75 (m, 4H), 2.31 (s, 3H).	640.3
237	 4-(4-cyclopropyl-2-oxopiperazin-1-yl)-<i>N</i>-(6-((3,3-difluorocyclobutyl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzamide	13.42 (br s, 1H), 8.63 (s, 1H), 8.39 (s, 1H), 7.90 (d, <i>J</i> = 8.4 Hz, 1H), 7.64 (s, 1H), 7.59 (dd, <i>J</i> = 8.4 Hz, 2.4 Hz, 1H), 7.50 (s, 1H), 6.96 (t, <i>J</i> = 55.2 Hz, 1H), 3.75 (t, <i>J</i> = 5.2 Hz, 2H), 3.67 (s, 3H), 3.40-3.32 (m, 3H), 3.14-3.03 (m, 2H), 2.99-2.96 (m, 2H), 2.85-2.72 (m, 2H), 1.83 (m, 1H), 0.51-0.46 (m, 2H), 0.44-0.38 (m, 2H).	666.2
238	 4-(4-cyclopropyl-2-oxopiperazin-1-yl)-<i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzamide	13.33 (br s, 1H), 8.52 (s, 1H), 8.39 (s, 1H), 7.93 (d, <i>J</i> = 8.4 Hz, 1H), 7.62 (s, 1H), 7.57 (d, <i>J</i> = 8.4 Hz, 1H), 7.46 (s, 1H), 6.97 (t, <i>J</i> = 54.8 Hz, 1H), 3.75 (t, <i>J</i> = 5.6 Hz, 2H), 3.67 (s, 3H), 3.36 (s, 2H), 2.98 (t, <i>J</i> = 5.6 Hz, 2H), 1.83 (m, 1H), 1.64 (m, 1H), 0.99-0.92 (m, 2H), 0.86-0.80 (m, 2H), 0.52-0.46 (m, 2H), 0.44-0.39 (m, 2H).	616.4
239	 <i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(5-methoxy-2-methylpyridin-4-yl)-4-(4-methyl-2-oxopiperazin-1-yl)benzamide	13.35 (br s, 1H), 8.60 (s, 1H), 8.12 (s, 1H), 7.83 (d, <i>J</i> = 8.4 Hz, 1H), 7.58 (dd, <i>J</i> = 8.4 Hz, 2.0 Hz, 1H), 7.46 (d, <i>J</i> = 2.0 Hz, 1H), 7.24 (s, 1H), 3.78 (t, <i>J</i> = 5.6 Hz, 2H), 3.56 (s, 3H), 3.16 (s, 2H), 2.76 (t, <i>J</i> = 5.6 Hz, 2H), 2.47 (s, 3H), 2.30 (s, 3H), 1.65 (m, 1H), 1.00-0.95 (m, 2H), 0.86-0.81 (m, 2H).	554.3

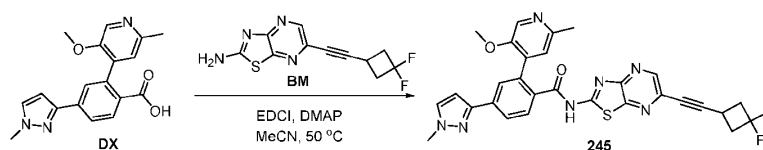
240	 <i>N</i>-(6-((3,3-difluorocyclobutyl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(5-methoxy-2-methylpyridin-4-yl)-4-(4-methyl-2-oxopiperazin-1-yl)benzamide	13.36 (br s, 1H), 8.68 (s, 1H), 8.13 (s, 1H), 7.83 (d, <i>J</i> = 8.0 Hz, 1H), 7.59 (dd, <i>J</i> = 8.4 Hz, 2.0 Hz, 1H), 7.48 (d, <i>J</i> = 2.0 Hz, 1H), 7.25 (s, 1H), 3.79 (t, <i>J</i> = 5.2 Hz, 2H), 3.56 (s, 3H), 3.37 (m, 1H), 3.17 (s, 2H), 3.13-3.04 (m, 2H), 2.84-2.74 (m, 4H), 2.48 (s, 3H), 2.31 (s, 3H).	604.3
241	 <i>N</i>-(6-((3,3-difluorocyclobutyl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(4-(2,2-difluoroethyl)-2-oxopiperazin-1-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzamide	13.46 (br s, 1H), 8.67 (s, 1H), 8.41 (s, 1H), 7.90 (d, <i>J</i> = 8.4 Hz, 1H), 7.67 (s, 1H), 7.64 (dd, <i>J</i> = 8.4 Hz, 2.0 Hz, 1H), 7.55 (d, <i>J</i> = 2.0 Hz, 1H), 6.98 (t, <i>J</i> = 55.2 Hz, 1H), 6.23 (tt, <i>J</i> = 55.2 Hz, 4.0 Hz, 1H), 3.81 (t, <i>J</i> = 5.2 Hz, 2H), 3.68 (s, 3H), 3.42 (s, 2H), 3.39-3.31 (m, 1H), 3.12-3.08 (m, 2H), 3.02-2.88 (m, 4H), 2.84-2.74 (m, 2H).	690.3
242	 4-(4-(acetyl-2-oxopiperazin-1-yl)-<i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzamide	13.43 (br s, 1H), 8.60 (s, 1H), 8.41 (s, 1H), 7.92 (d, <i>J</i> = 8.4 Hz, 1H), 7.67 (s, 1H), 7.63 (dd, <i>J</i> = 8.0 Hz, 2.2 Hz, 1H), 7.54 (d, 2.4 Hz, 1H), 6.99 (t, <i>J</i> = 55.2 Hz, 1H), 4.32 (s, 1H), 4.21 (s, 1H), 3.94 (m, 1H), 3.86 (m, 3H), 3.68 (s, 3H), 2.08 (d, <i>J</i> = 10.8 Hz, 3H), 1.66 (m, 1H), 1.00-0.95 (m, 2H), 0.86-0.82 (m, 2H).	618.3
243	 <i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(5-methoxy-2-methylpyridin-4-yl)-4-(4-methyl-8-oxo-4,7-diazaspiro[2.5]octan-7-yl)benzamide	13.45 (br s, 1H), 8.29 (s, 1H), 8.08 (s, 1H), 8.00 (d, <i>J</i> = 8.4 Hz, 1H), 7.46 (d, <i>J</i> = 8.4 Hz, 1H), 7.26 (s, 1H), 7.09 (s, 1H), 3.98 (t, <i>J</i> = 5.6 Hz, 2H), 3.55 (s, 3H), 2.31 (s, 3H), 3.23 (d, <i>J</i> = 5.6 Hz, 2H), 2.45 (s, 3H), 1.60 (m, 1H), 1.20-1.73 (m, 2H), 0.96-0.87 (m, 4H), 0.81-0.76 (m, 2H).	580.3
244	 <i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(5-methoxy-2-methylpyridin-4-yl)-4-(4-methyl-2-oxopiperazin-1-yl)benzamide	13.31 (br s, 1H), 8.59 (s, 1H), 8.12 (s, 1H), 7.83 (d, <i>J</i> = 8.4 Hz, 1H), 7.56 (dd, <i>J</i> = 8.4 Hz, 2.0 Hz, 1H), 7.45 (d, <i>J</i> = 2.0 Hz, 1H), 7.23 (s, 1H), 3.75 (t, <i>J</i> =	580.3

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	4-(4-cyclopropyl-2-oxopiperazin-1-yl)- <i>N</i> -(6-(cyclopropylethynyl)thiazolo[4,5- <i>b</i>]pyrazin-2-yl)-2-(5-methoxy-2-methylpyridin-4-yl)benzamide	5.6 Hz, 2H), 3.55 (s, 3H), 3.36 (s, 2H), 2.98 (t, <i>J</i> = 5.6 Hz, 2H), 2.47 (s, 3H), 1.85 (m, 1H), 1.65 (m, 1H), 1.00-0.94 (m, 2H), 0.86-0.81 (m, 2H), 0.51-0.46 (m, 2H), 0.44-0.39 (m, 2H).	
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Example 245

N-(6-((3,3-Difluorocyclobutyl)ethynyl)thiazolo[4,5-*b*]pyrazin-2-yl)-2-(5-methoxy-2-methylpyridin-4-yl)-4-(1-methyl-1*H*-pyrazol-3-yl)benzamide



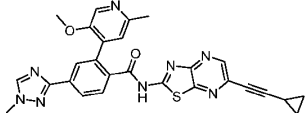
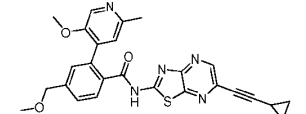
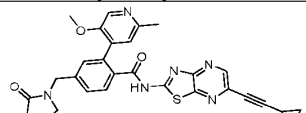
[0528] DMAP (30.2 mg, 0.247 mmol), EDCI (71.1 mg, 0.371 mmol) and 6-[2-(3,3-difluorocyclobutyl)ethynyl]thiazolo[4,5-*b*]pyrazin-2-amine (**BM**, 72.5 mg, 0.272 mmol) were added to a solution of 2-(5-methoxy-2-methyl-4-pyridyl)-4-(1-methylpyrazol-3-yl)benzoic acid (**DX**, 80.0 mg, 0.247 mmol) in ACN (4 mL) under N₂. After stirring at 50 °C for 2 hrs, the mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by reverse phase column chromatography (0.05% FA) to afford Example **245**.

LCMS (ESI, *m/z*): [M+H]⁺ = 572.2; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 13.37 (br s, 1H), 8.67 (s, 1H), 8.14 (s, 1H), 7.97 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 2.0 Hz, 1H), 7.80 (d, *J* = 2.0 Hz, 1H), 7.30 (s, 1H), 6.90 (d, *J* = 2.0 Hz, 1H), 3.92 (s, 3H), 3.57 (s, 3H), 3.37 (m, 1H), 3.16-3.02 (m, 2H), 2.88-2.74 (m, 2H), 2.49 (s, 3H).

[0529] Following conditions analogous to synthesis of Example **245**, Example **246-249** were synthesized from the corresponding acids (**BW**, **DR**, **DT**, and **EC**) and amine (**AW**).

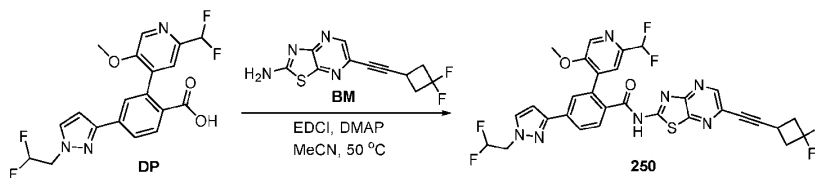
Example Number	Structure	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm	LCMS (ESI, <i>m/z</i>): [M+H] ⁺
246	 <i>N</i> -(6-(cyclopropylethynyl)thiazolo[4,5- <i>b</i>]pyrazin-2-yl)-2-(5-methoxy-2-	13.49 (br s, 1H), 8.55 (s, 1H), 8.21 (d, <i>J</i> = 8.0 Hz, 1H), 8.16 (s, 1H), 8.10-7.95 (m, 2H), 7.30 (s, 1H), 4.47 (s, 3H), 3.58 (s, 3H), 2.51 (s, 3H), 1.64 (m, 1H), 1.00-0.92 (m, 2H), 0.87-0.79 (m, 2H).	524.3

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	methyipyridin-4-yl)-4-(2-methyl-2H-tetrazol-5-yl)benzamide		
247	 <i>N</i> -(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(5-methoxy-2-methylpyridin-4-yl)-4-(1-methyl-1H-1,2,4-triazol-3-yl)benzamide	13.27 (br s, 1H), 8.60 (s, 1H), 8.51 (s, 1H), 8.16-8.09 (m, 2H), 7.98-7.92 (m, 2H), 7.25 (s, 1H), 3.96 (s, 3H), 3.57 (s, 3H), 2.49 (s, 3H), 1.67-1.61 (m, 1H), 0.99-0.93 (m, 2H), 0.85-0.80 (m, 2H).	523.2
248	 <i>N</i> -(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(5-methoxy-2-methylpyridin-4-yl)-4-(methoxymethyl)benzamide	8.50 (s, 1H), 8.16 (s, 1H), 7.78 (d, <i>J</i> = 8.0 Hz, 1H), 7.50 (d, <i>J</i> = 8.0 Hz, 1H), 7.34 (s, 1H), 7.11 (s, 1H), 4.56 (s, 2H), 3.77 (s, 3H), 3.46 (s, 3H), 2.55 (s, 3H), 1.54 (m, 1H), 0.98-0.91 (m, 4H).	486.3
249	 <i>N</i> -(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(5-methoxy-2-methylpyridin-4-yl)-4-((2-oxopyrrolidin-1-yl)methyl)benzamide	13.30 (br s, 1H), 8.50 (s, 1H), 8.11 (s, 1H), 7.84 (d, <i>J</i> = 8.0 Hz, 1H), 7.37 (d, <i>J</i> = 8.0 Hz, 1H), 7.24 (s, 1H), 7.18 (s, 1H), 4.47 (s, 2H), 3.55 (s, 3H), 3.32-3.25 (m, 2H), 2.46 (s, 3H), 2.35-2.28 (m, 2H), 2.00-1.91 (m, 2H), 1.64 (m, 1H), 0.99-0.92 (m, 2H), 0.86-0.79 (m, 2H).	539.3

Example 250

N-(6-((3,3-Difluorocyclobutyl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzamide

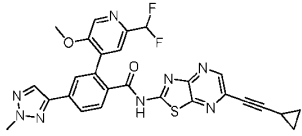
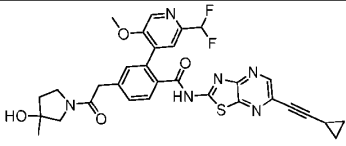


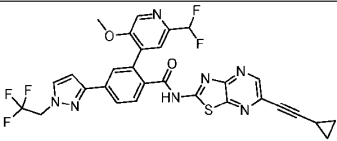
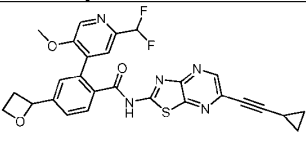
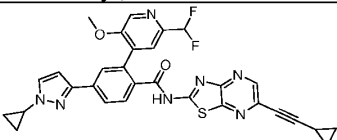
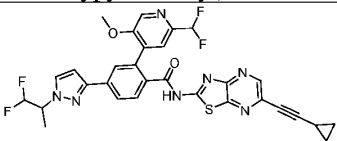
[0530] 6-((3,3-Difluorocyclobutyl)ethynyl)thiazolo[4,5-b]pyrazin-2-amine (**BM**, 65 mg, 0.244 mmol) and DMAP (29.8 mg, 0.244 mmol) were added to a solution of 4-(1-(2,2-difluoroethyl)-1H-pyrazol-3-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzoic acid

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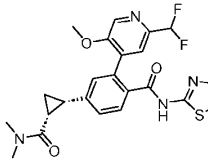
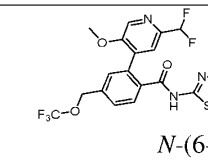
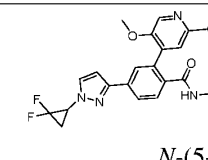
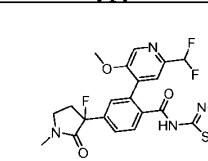
(**DP**, 100 mg, 0.244 mmol) and EDCI (281 mg, 1.47 mmol) in MeCN (2 mL) under N₂. After stirring at 50 °C for 4 hrs, the mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by prep-HPLC (0.1% FA) to afford Example **250**. LCMS (ESI, m/z): [M+H]⁺ = 658.2; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 13.48 (br s, 1H), 8.64 (s, 1H), 8.42 (s, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 2.4 Hz, 1H), 7.86 (s, 1H), 7.70 (s, 1H), 7.02 (d, *J* = 2.4 Hz, 1H), 7.00 (t, *J* = 55.2 Hz, 1H), 6.44 (tt, *J* = 55.2 Hz, 3.6 Hz, 1H), 4.72 (td, *J* = 15.2 Hz, 4.0 Hz, 2H), 3.70 (s, 3H), 3.37 (m, 1H), 3.14-3.03 (m, 2H), 2.86-2.75 (m, 2H).

[0531] Following conditions analogous to synthesis of Example **250**, Example **251-262** were synthesized from the corresponding acids (**BX**, **DJ**, **DO**, **DS**, **DV**, **DW**, **DZ**, **EA**, **ED**, **EE**, **EG** and **EH**) and amines (**AW** and **BM**).

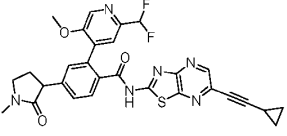
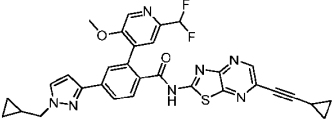
Example Number	Structure	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm	LCMS (ESI, m/z): [M+H] ⁺
251	 <i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(2-methyl-2H-1,2,3-triazol-4-yl)benzamide	13.41 (br s, 1H), 8.45-8.32 (m, 3H), 8.11 (d, <i>J</i> = 8.4 Hz, 1H), 8.00 (d, <i>J</i> = 8.4 Hz, 1H), 7.78 (s, 1H), 7.61 (s, 1H), 6.97 (t, <i>J</i> = 55.2 Hz, 1H), 4.22 (s, 3H), 3.69 (s, 3H), 1.62 (m, 1H), 0.97-0.90 (m, 2H), 0.84-0.76 (m, 2H).	559.2
252	 <i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(2-(3-hydroxy-3-methylpyrrolidin-1-yl)-2-oxoethyl)benzamide	13.33 (br s, 1H), 8.57 (s, 1H), 8.39 (s, 1H), 7.82 (d, <i>J</i> = 8.0 Hz, 1H), 7.60 (s, 1H), 7.46 (d, <i>J</i> = 8.0 Hz, 1H), 7.35 (s, 1H), 6.98 (t, <i>J</i> = 55.2 Hz, 1H), 4.81 (d, <i>J</i> = 41.0 Hz, 1H), 3.76 (d, <i>J</i> = 21.2 Hz, 2H), 3.67 (s, 3H), 3.48-3.05 (m, 4H), 1.90-1.61 (m, 3H), 1.29 (d, <i>J</i> = 8.4 Hz, 3H), 1.00-0.94 (m, 2H), 0.86-0.81 (m, 2H).	619.3

253	 <i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(1-(2,2,2-trifluoroethyl)-1<i>H</i>-pyrazol-3-yl)benzamide	13.43 (br s, 1H), 8.57 (s, 1H), 8.42 (s, 1H), 8.04 (d, <i>J</i> = 8.0 Hz, 1H), 7.98 (d, <i>J</i> = 8.0 Hz, 1H), 7.97 (s, 1H), 7.86 (s, 1H), 7.70 (s, 1H), 7.07 (d, <i>J</i> = 2.0 Hz, 1H), 7.00 (t, <i>J</i> = 55.2 Hz, 1H), 5.24 (m, 2H), 3.70 (s, 3H), 1.65 (m, 1H), 1.01-0.94 (m, 2H), 0.86-0.79 (m, 2H).	626.2
254	 <i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(oxetan-2-yl)benzamide	13.33 (br s, 1H), 8.50 (s, 1H), 8.39 (s, 1H), 7.97 (d, <i>J</i> = 8.0 Hz, 1H), 7.68-7.60 (m, 2H), 7.44 (s, 1H), 6.98 (t, <i>J</i> = 55.2 Hz, 1H), 5.86 (t, <i>J</i> = 7.4 Hz, 1H), 4.75-4.69 (m, 1H), 4.63-4.57 (m, 1H), 3.67 (s, 3H), 3.05 (m, 1H), 2.62 (m, 1H), 1.64 (m, 1H), 0.99-0.93 (m, 2H), 0.85-0.79 (m, 2H).	534.2
255	 4-(1-cyclopropyl-1<i>H</i>-pyrazol-3-yl)-<i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzamide	8.48 (s, 1H), 8.40 (s, 1H), 8.02-7.93 (m, 2H), 7.87 (d, <i>J</i> = 2.4 Hz, 1H), 7.77 (s, 1H), 7.64 (s, 1H), 6.99 (t, <i>J</i> = 54.8 Hz, 1H), 6.88 (d, <i>J</i> = 2.4 Hz, 1H), 3.79 (m, 1H), 3.69 (s, 3H), 1.63 (m, 1H), 1.13-1.09 (m, 2H), 1.03-0.92 (m, 4H), 0.85-0.80 (m, 2H)	584.3
256	 <i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(1-(1,1-difluoropropan-2-yl)-1<i>H</i>-pyrazol-3-yl)benzamide	12.94 (br s, 1H), 8.39 (s, 1H), 8.32 (s, 1H), 8.13 (s, 1H), 7.96-7.90 (m, 2H), 7.69 (s, 1H), 7.55 (s, 1H), 6.96 (t, <i>J</i> = 55.2 Hz, 1H), 6.94 (d, <i>J</i> = 2.4 Hz, 1H), 6.32 (td, <i>J</i> = 55.2 Hz, 4.0 Hz, 1H), 4.89 (m, 1H), 3.69 (s, 3H), 1.64-1.55 (m, 4H), 0.95-0.89 (m, 2H), 0.82-0.76 (m, 2H).	622.3

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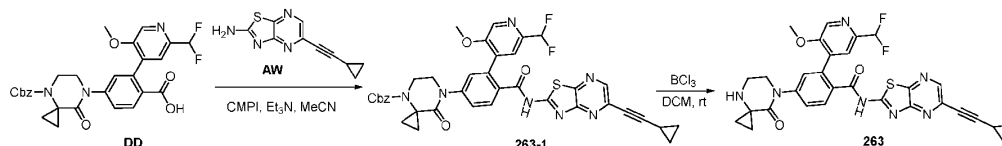
257	 <i>N</i>-(6-((3,3-difluorocyclobutyl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-((1<i>S</i>,2<i>R</i>)-2-(dimethylcarbamoyl)cyclopropyl)benzamide	13.37 (br s, 1H), 8.69 (s, 1H), 8.39 (s, 1H), 7.71 (d, <i>J</i> = 8.0 Hz, 1H), 7.56 (s, 1H), 7.39 (d, <i>J</i> = 8.0 Hz, 1H), 7.23 (s, 1H), 6.99 (t, <i>J</i> = 54.8 Hz, 1H), 3.67 (s, 3H), 3.37 (m, 1H), 3.15-3.06 (m, 2H), 3.02 (s, 3H), 2.86-2.76 (m, 2H), 2.70 (s, 3H), 2.67 (m, 1H), 2.44 (m, 1H), 1.63 (m, 1H), 1.33 (m, 1H).	639.3
258	 <i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-((trifluoromethoxy)methyl)benzamide	13.47 (br s, 1H), 8.64 (s, 1H), 8.42 (s, 1H), 7.91 (d, <i>J</i> = 8.0 Hz, 1H), 7.72-7.66 (m, 2H), 7.60 (s, 1H), 7.00 (t, <i>J</i> = 55.2 Hz, 1H), 5.34 (s, 2H), 3.68 (s, 3H), 1.65 (m, 1H), 1.01-0.94 (m, 2H), 0.88-0.81 (m, 2H).	576.3
259	 <i>N</i>-(5-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(1-(2,2-difluorocyclopropyl)-1<i>H</i>-pyrazol-3-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzamide	13.37 (br s, 1H), 8.53 (s, 1H), 8.42 (s, 1H), 8.05-7.94 (m, 3H), 7.83 (s, 1H), 7.59 (s, 1H), 7.03 (d, <i>J</i> = 2.8 Hz, 1H), 6.99 (d, <i>J</i> = 55.2 Hz, 1H), 4.64 (m, 1H), 3.70 (s, 3H), 2.55 (m, 1H), 2.37 (m, 1H), 1.64 (m, 1H), 0.99-0.93 (m, 2H), 0.86-0.80 (m, 2H).	620.2
260	 <i>N</i>-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(3-fluoro-2-methylpiperidin-1-yl)benzamide	13.47 (br s, 1H), 8.63 (s, 1H), 8.42 (s, 1H), 7.91 (d, <i>J</i> = 8.0 Hz, 1H), 7.70 (s, 1H), 7.67 (dd, <i>J</i> = 8.0 Hz, 2.0 Hz, 1H), 7.49 (d, <i>J</i> = 2.0 Hz, 1H), 7.00 (t, <i>J</i> = 55.2 Hz, 1H), 3.68 (s, 3H), 3.63-3.48 (m, 2H), 2.89 (s, 3H), 2.85-2.74 (m, 1H), 2.69-2.56 (m, 1H), 1.65 (m, 1H), 1.00-0.95 (m, 2H), 0.86-0.82 (m, 2H).	593.3

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	1-methyl-2-oxopyrrolidin-3-yl)benzamide		
261	 <i>N</i> -(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(1-methyl-2-oxopyrrolidin-3-yl)benzamide	13.34 (br s, 1H), 8.57 (s, 1H), 8.39 (s, 1H), 7.84 (d, <i>J</i> = 8.0 Hz, 1H), 7.64 (s, 1H), 7.47 (d, <i>J</i> = 8.0 Hz, 1H), 7.34 (s, 1H), 6.99 (t, <i>J</i> = 54.8 Hz, 1H), 3.82 (t, <i>J</i> = 9.2 Hz, 1H), 3.67 (s, 3H), 3.50-3.37 (m, 2H), 2.81 (s, 3H), 2.50 (s, 1H), 2.14 (m, 1H), 1.65 (m, 1H), 1.00-0.93 (m, 2H), 0.87-0.80 (m, 2H).	575.3
262	 <i>N</i> -(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(1-(cyclopropylmethyl)-1H-pyrazol-3-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzamide	13.30 (br s, 1H), 8.54 (s, 1H), 8.41 (s, 1H), 8.01 (d, <i>J</i> = 8.4 Hz, 1H), 7.95 (d, <i>J</i> = 8.4 Hz, 1H), 7.88 (d, <i>J</i> = 2.0 Hz, 1H), 7.82 (s, 1H), 7.68 (s, 1H), 7.00 (t, <i>J</i> = 55.2 Hz, 1H), 6.91 (d, <i>J</i> = 2.0 Hz, 1H), 4.04 (d, <i>J</i> = 7.2 Hz, 2H), 3.70 (s, 3H), 1.64 (m, 1H), 1.29 (m, 1H), 0.99-0.94 (m, 2H), 0.85-0.80 (m, 2H), 0.58-0.53 (m, 2H), 0.41-0.37 (m, 2H).	598.3

Example 263

N-(5-(Cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(8-oxo-4,7-diazaspiro[2.5]octan-7-yl)benzamide



Step 1: benzyl 7-(4-((5-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)carbamoyl)-3-(2-(difluoromethyl)-5-methoxypyridin-4-yl)phenyl)-8-oxo-4,7-diazaspiro[2.5]octane-4-carboxylate (263-1)

[0532] Following conditions analogous to synthesis of Example 198, Intermediate 263-1 was prepared from DD and AW. LCMS (ESI, *m/z*): [M+H]⁺ = 736.3

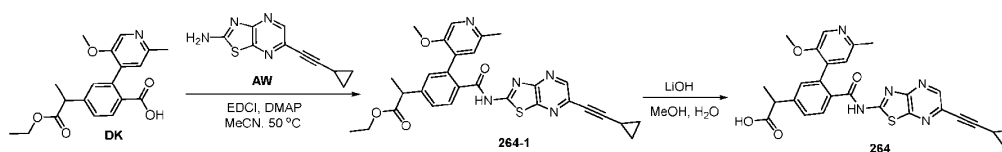
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Step 2: *N*-(5-(cyclopropylethynyl)thiazolo[4,5-*b*]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(8-oxo-4,7-diazaspiro[2.5]octan-7-yl)benzamide (**263**)

[0533] Boron trichloride (19.1 mg, 0.163 mmol) was added to a solution of benzyl 7-(4-((5-(cyclopropylethynyl)thiazolo[4,5-*b*]pyrazin-2-yl)carbamoyl)-3-(2-(difluoromethyl)-5-methoxypyridin-4-yl)phenyl)-8-oxo-4,7-diazaspiro[2.5]octane-4-carboxylate (**263-1**, 40 mg, 0.054 mmol) in DCM (3 mL) under N₂. After stirring at rt for 2 hrs, the mixture was concentrated in vacuo. The residue was purified by prep-HPLC (0.1% NH₃·H₂O) to afford Example **263**. LCMS (ESI, *m/z*): [M+H]⁺ = 602.3; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 13.45 (br s, 1H), 8.54 (s, 1H), 8.40 (s, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.62 (s, 1H), 7.58 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H), 7.46 (s, 1H), 6.98 (t, *J* = 55.2 Hz, 1H), 3.90 (t, *J* = 5.6 Hz, 2H), 3.69 (s, 3H), 3.12 (t, *J* = 5.6 Hz, 2H), 1.65 (m, 1H), 1.22-1.86 (m, 2H), 0.99-0.94 (m, 2H), 0.86-0.78 (m, 4H).

Example 264

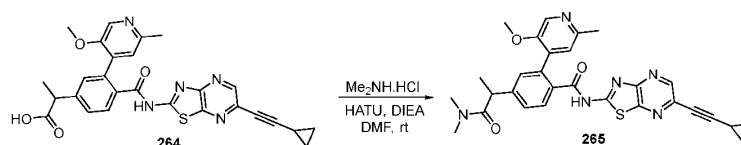
2-(4-((6-(Cyclopropylethynyl)thiazolo[4,5-*b*]pyrazin-2-yl)carbamoyl)-3-(5-methoxy-2-methylpyridin-4-yl)phenyl)propanoic acid



[0534] Following conditions analogous to synthesis of Example **245** and step 2 of Intermediate **BY**, Example **264** was synthesized from Intermediates **DK** and **AW**. LCMS (ESI, *m/z*): [M+H]⁺ = 514.3; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 13.28 (br s, 1H), 12.51 (br s, 1H), 8.61 (s, 1H), 8.12 (s, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.36 (s, 1H), 7.23 (s, 1H), 3.86 (q, *J* = 7.2 Hz, 1H), 3.55 (s, 3H), 2.48 (s, 3H), 1.65 (m, 1H), 1.44 (d, *J* = 6.8 Hz, 3H), 1.00-0.95 (m, 2H), 0.86-0.82 (m, 2H).

Example 265

N-(6-(Cyclopropylethynyl)thiazolo[4,5-*b*]pyrazin-2-yl)-4-(1-(dimethylamino)-1-oxopropan-2-yl)-2-(5-methoxy-2-methylpyridin-4-yl)benzamide

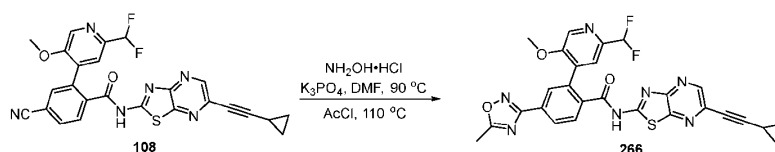


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[0535] HATU (81.0 mg, 0.213 mmol) was added to a stirred solution of 2-((6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)carbamoyl)-3-(5-methoxy-2-methylpyridin-4-yl)phenyl propanoic acid (**264**, 73.0 mg, 0.142 mmol), dimethylamine hydrochloride (34.5 mg, 0.423 mmol) and DIPEA (91.9 mg, 0.711 mmol) in DMF (7 mL) under N₂. After stirring for 1 hr, the mixture was treated with water and extracted with EtOAc. The combined organic layers were dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by reversed phase column chromatography (0.1% FA) to afford Example **265**. LCMS (ESI, m/z): [M+H]⁺ = 541.2; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 13.20 (br s, 1H), 8.58 (s, 1H), 8.12 (s, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.37 (s, 1H), 7.20 (s, 1H), 4.25 (q, *J* = 6.8 Hz, 1H), 3.55 (s, 3H), 2.97 (s, 3H), 2.84 (s, 3H), 2.48 (s, 3H), 1.65 (m, 1H), 1.35 (d, *J* = 6.8 Hz, 3H), 0.99-0.94 (m, 2H), 0.85-0.81 (m, 2H).

Example 266

N-(6-(Cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)-4-(5-methyl-1,2,4-oxadiazol-3-yl)benzamide



[0536] NH₂OH·HCl (12.4 mg, 0.179 mmol) and K₃PO₄ (47.5 mg, 0.224 mmol) were added to a solution of 4-cyano-*N*-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-(2-(difluoromethyl)-5-methoxypyridin-4-yl)benzamide (**108**, 75 mg, 0.149 mmol) in DMF (1 mL) under N₂. After stirring at 90 °C for 1 hr, AcCl (17.6 mg, 0.224 mmol) was added. The mixture was stirred at 110 °C for 1 hr, treated with water and extracted with EtOAc. The combined organic layers were dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by prep-HPLC (0.1% FA in) to afford Example **266**. LCMS (ESI, m/z): [M+H]⁺ = 560.3; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 13.58 (s, 1H), 8.61 (s, 1H), 8.44 (s, 1H), 8.22 (dd, *J* = 8.0 Hz, 2.4 Hz, 1H), 8.09-8.01 (m, 2H), 7.75 (s, 1H), 7.00 (t, *J* = 54.8 Hz, 1H), 3.70 (s, 3H), 2.71 (s, 3H), 1.64 (m, 1H), 1.00-0.94 (m, 2H), 0.87-0.81 (m, 2H).

Biological Example 1

Biochemical Enzymatic Assay

Protein expression

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[0537] For Polθ helicase domain (amino acids 2-894) expression the sequence was first synthesized via gene synthesis. This sequence was then cloned into the pFastBac bacmid for Sf9 cell expression. Sf9 cells were then plated and transfected with the target bacmid. After three days, baculovirus was harvested and used to transduce freshly plated Sf9 cells. After 60 hours, cell pellets were harvested, lysed and the protein purified using Ni-HP Superdex 200 columns. Purified protein was then subject to size exclusion chromatography - high-performance liquid chromatography to confirm protein identity and purity.

Polθ helicase ATP assay

[0538] A 4X stock of compound was prepared by serially dilution at a 1:3 dilution in assay buffer (Tris pH7.5 25 mM, NaCl 6 mM, MgCl₂ 1.5 mM, Glycerol 5% (V/V) Triton X-100 0.01%, DTT 1 mM and ddH₂O) containing 4% DMSO, with a top final working concentration of 4μM (1μM final concentration) and a ten-point dose-response curve (1% final DMSO concentration). 1μl of this stock was then transferred to a 384-well assay plate and centrifuged. A 4X POLθ (2-894) enzyme solution (6.25nM working concentration, 1.5625nM final concentration) was then prepared in assay buffer. 1μl of this solution was then added to the 384-well assay plate followed centrifugation and incubation at 23°C for 10 minutes. A 4X stock of cofactor (30bp single stranded DNA sequence, CCAGTGAATTGTTGCTCGGTACCTGCTAAC (SEQ ID NO: 1), 400nM working concentration, 100nM final concentration) and a 4X stock of ATP substrate (200μM working concentration, 50μM final concentration) were then prepared in assay buffer. 1μl of the cofactor solution was then added to the assay plate, centrifuged, and incubated at 23°C for 30 minutes. 1μl of the substrate solution was then added to the plate, centrifuged, and incubated for 120 minutes at 23°C. 4μl of ADP-Glo Reagent was then added to the plate, centrifuged, and incubated for 120 minutes at 23°C. Finally, 8ul of Kinase Detection Reagent was then added to the plate, centrifuged, and incubated for 30 minutes at 23°C. Luminescence was then measured on an Envision plate reader. Percent inhibition was calculated as: % Inhibition = 100% - (compound signal - min signal) / (max signal - min signal) * 100%, where minimum signal equals signal from wells with substate only and maximum signal equals signal from wells with enzyme + substate. IC₅₀s were calculated by fitting % Inhibition (Y) values and log of compound concentrations (X) to nonlinear regression (log[inhibitor]) vs. response - Variable slope (four parameters) with GraphPad 9.4.1 (Y=Bottom + (Top-Bottom)/(1+10^{-(LogIC₅₀-X) *hillslope) where X equals.}

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[0539] For biochemical activity, bracket is denoted as: A < 20 nM; 20 nM < B < 200 nM;
C > 200 nM

Example	Polθ helicase ATP assay IC ₅₀	Example	Polθ helicase ATP assay IC ₅₀
1	A	2	B
3	B	4	A
5	A	6	C
7	B	8	A
9	A	10	A
11	B	12	A
13	A	14	A
15	A	16	A
17	A	18	A
19	A	20	A
21	A	22	A
23	A	24	A
25	B	26	A
27	A	28	A
29	A	30	A
31	A	32	A
33	A	34	A
35	A	36	A
37	B	38	A
39	A	40	A
41	A	42	A
43	A	44	A
45	A	46	A
47	B	48	A
49	A	50	A
51	A	52	B
53	A	54	A
55	A	56	B
57	A	58	A
59	A	60	A
61	A	62	A
63	A	64	A
65	A	66	A
67	A	68	A
69	A	70	A
71	A	72	A
73	A	74	A
75	A	76	A
77	A	78	A
79	A	80	A
81	A	82	A
83	A	84	A

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85	A	86	A
87	A	88	A
89	A	90	A
91	A	92	A
93	A	94	A
95	A	96	A
97	A	98	A
99	A	100	A
101	A	102	A
103	A	104	A
105	A	106	A
107	A	108	A
109	A	110	A
111	A	112	A
113	A	114	A
115	A	116	A
117	A	118	A
119	A	120	A
121	A	122	A
123	A	124	A
125	A	126	A
127	A	128	A
129	A	130	A
131	A	132	A
133	A	134	A
135	A	136	A
137	A	138	B
139	A	140	A
141	A	142	A
143	A	144	A
145	A	146	A
147	B	148	A
149	B	150	A
151	A	152	A
153	A	154	A
155	A	156	A
157	A	158	A
159	A	160	A
161	A	162	A
163	A	164	A
165	A	166	A
167	A	168	A
169	A	170	A
171	A	172	A
173	A	174	A
175	A	176	A
177	A	178	A

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179	A	180	A
181	A	182	A
183	A	184	A
185	A	186	A
187	A	188	A
189	A	190	A
191	A	192	A
193	A	194	A
195	A	196	B
197	A	198	A
199	C	200	A
201	A	202	B
203	B	204	A
205	A	206	B
207	A	208	A
209	A	210	A
211	A	212	A
213	A	214	A
215	A	216	A
217	A	218	A
219	A	220	A
221	A	222	A
223	C	224	A
225	A	226	A
227	A	228	A
229	A	230	A
231	A	232	A
233	A	234	A
235	A	236	A
237	A	238	A
239	A	240	A
241	A	242	A
243	A	244	A
245	A	246	A
247	A	248	A
249	A	250	A
251	A	252	A
253	A	254	A
255	A	256	A
257	C	258	A
259	A	260	A
261	A	262	A
263	A	264	A
265	A	266	A

Biological Example 2

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Cellular Viability Assay

[0540] DLD-1 BRCA2^{-/-} cells were plated at a density of 100 cells per well, in 40μl of complete media, in a 384-well plate and incubated overnight at 37°C in a humidified, 5% CO₂, environment. 24 hours later, compounds were added starting at a top dose of 10μM for a 9-point dose response curve at a 1:3 dilution using an iDOT HT liquid handler and incubated for 7 days at 37°C in a 5% CO₂ humidified environment. After 7 days and at Day 0, plates were incubated at room temperature for 30 minutes followed by the addition of 30μl of CellTiter-Glo Reagent. Plates were then mixed for 10 minutes on an orbital shaker followed by incubation at room temperature for 20 minutes. Luminescence was then read using the Envision plate reader. Percent Growth Inhibition was then calculated using the following equation: Percent Growth Inhibition normalized=100-(compound signal-T0)/(max signal-T0)*100%, where Max Signal refers to the DMSO only treated cells and T0 refers to the Day0 viability measurement. Growth Inhibition 50 was then calculated using the following equation: $Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + 10^{((\text{LogIC}_{50} - X) * \text{hillslope}))}$.

[0541] For cell activity, bracket is denoted as: A < 100 nM; 100 nM < B < 1000 nM; C > 1000 nM.

Example	Cellular viability assay IC ₅₀	Example	Cellular viability assay IC ₅₀
1	A	4	B
5	A	8	A
9	A	10	A
12	C	13	C
14	A	15	B
17	B	18	A
19	A	20	B
21	A	22	A
23	A	24	A
26	A	27	A
28	A	29	B
30	A	31	A
32	A	33	A
34	A	35	A
36	A	37	A
38	A	39	A
40	A	41	A
42	A	43	A
44	A	45	A
46	B	47	B
48	B	49	A
50	A	51	A

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52	A	53	A
54	B	55	B
57	A	58	A
59	A	60	A
61	A	62	A
63	A	64	A
65	A	66	A
67	A	68	A
69	A	70	A
71	A	72	A
73	A	74	A
75	A	76	A
77	A	78	B
79	A	80	A
81	B	82	A
83	A	84	A
85	A	86	B
87	B	88	A
89	A	90	B
91	A	92	A
93	A	94	A
95	B	96	A
97	A	98	A
99	B	100	A
101	B	102	B
103	B	104	B
105	B	106	B
107	A	108	A
109	A	110	A
111	A	112	A
113	A	114	A
115	A	116	A
117	A	118	A
119	A	120	A
121	A	122	A
123	A	124	A
125	A	127	A
128	A	129	B
130	A	131	A
132	A	133	A
134	A	135	A
136	A	137	A
139	A	140	A
141	A	142	A
143	A	144	A
145	A	146	A
148	A	150	B

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151	B	152	B
153	B	154	A
155	A	157	C
158	A	159	B
160	A	161	A
162	B	163	B
164	A	165	A
166	B	167	A
168	B	169	B
170	B	171	C
172	A	173	A
174	A	175	C
176	A	177	B
178	B	179	A
180	B	181	A
182	A	183	A
184	A	185	A
186	A	187	A
188	A	189	A
190	B	191	B
192	A	193	A
194	A	195	A
197	A	198	A
200	B	201	A
204	A	205	A
207	B	208	A
209	A	210	B
211	A	212	A
213	A	214	A
215	A	216	A
217	B	218	A
219	A	220	A
221	A	222	A
224	A	225	A
226	B	227	A
228	B	229	A
230	A	231	A
232	A	233	A
234	A	235	A
236	A	237	A
238	A	239	A
240	A	241	A
242	A	243	A
244	A	245	A
246	B	247	A
248	B	249	B
250	A	251	A

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252	A	253	A
254	A	255	A
256	A	258	A
259	A	260	B
261	A	262	A
263	A	264	C
265	C	266	B

[0542] The Summary and Abstract sections may set forth one or more but not all exemplary embodiments of the present invention as contemplated by the inventor(s), and thus, are not intended to limit the present invention and the appended claims in any way.

[0543] The present invention has been described above with the aid of functional building blocks illustrating the implementation of specified functions and relationships thereof. The boundaries of these functional building blocks have been arbitrarily defined herein for the convenience of the description. Alternate boundaries can be defined so long as the specified functions and relationships thereof are appropriately performed.

[0544] With respect to aspects of the invention described as a genus, all individual species are individually considered separate aspects of the invention. If aspects of the invention are described as "comprising" a feature, embodiments also are contemplated "consisting of" or "consisting essentially of" the feature.

[0545] The foregoing description of the specific embodiments will so fully reveal the general nature of the invention that others can, by applying knowledge within the skill of the art, readily modify and/or adapt for various applications such specific embodiments, without undue experimentation, without departing from the general concept of the present invention. Therefore, such adaptations and modifications are intended to be within the meaning and range of equivalents of the disclosed embodiments, based on the teaching and guidance presented herein. It is to be understood that the phraseology or terminology herein is for the purpose of description and not of limitation, such that the terminology or phraseology of the present specification is to be interpreted by the skilled artisan in light of the teachings and guidance.

[0546] The breadth and scope of the present invention should not be limited by any of the above-described exemplary embodiments.

[0547] All of the various aspects, embodiments, and options described herein can be combined in any and all variations.

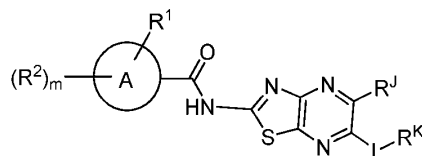
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[0548] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference. To the extent that any meaning or definition of a term in this document conflicts with any meaning or definition of the same term in a document incorporated by reference, the meaning or definition assigned to that term in this document shall govern.

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WHAT IS CLAIMED IS:

1. A compound of Formula K, or a pharmaceutically acceptable salt thereof:



Formula K

wherein:

Ring A is a phenyl ring or 5-10-membered heteroaryl ring having 1 to 4 ring heteroatoms independently selected from N, O, and S;

R^1 is an optionally substituted phenyl, optionally substituted naphthyl, an optionally substituted 3-10 membered carbocyclic, or an optionally substituted 5-10 membered heterocyclic or heteroaryl, preferably, R^1 is ortho to the amide group (-C(O)-NH-) shown in Formula K;

the subscript m is an integer of 0-4, as valency permits;

R^2 at each occurrence is independently deuterium, halogen, OH, NH_2 , CN, SF_5 , COOH, $CONH_2$, SO_2NH_2 , R^{20} , OR^{20} , SR^{20} , $N(R^{20})(R^{21})$, SO_2R^{20} , $S(=O)(=NR^{21})R^{20}$, $SO_2N(R^{20})(R^{21})$, $N(R^{21})SO_2R^{20}$, COR^{20} , $COOR^{20}$, $OC(O)R^{20}$, $CON(R^{20})(R^{21})$, or $N(R^{21})COR^{20}$, wherein R^{20} at each occurrence is independently an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl, an optionally substituted C_{1-6} heteroalkyl, or an optionally substituted 3-10 membered ring structure; and R^{21} at each occurrence is independently hydrogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{3-6} alkenyl, an optionally substituted C_{3-6} alkynyl, an optionally substituted C_{1-6} heteroalkyl, or an optionally substituted 3-10 membered ring structure; or as applicable, R^{20} and R^{21} together with the intervening atom (e.g., the nitrogen atom) or atoms are joined to form an optionally substituted 4-8 membered heterocyclic ring;

or two instances of R^2 are joined to form an optionally substituted 4-7 membered ring;

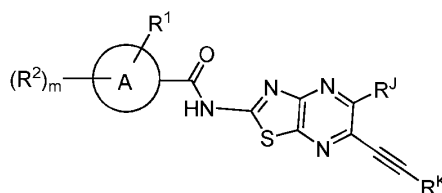
R^J is hydrogen, halogen, optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl, an optionally substituted C_{1-6} heteroalkyl, or an optionally substituted 3-10 membered ring structure;

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L is C₁₋₄ alkylene, C₂₋₄ alkenylene, C₂₋₄ alkynylene, or C₁₋₄ heteroalkylene, each of which is optionally substituted with deuterium and/or F, and

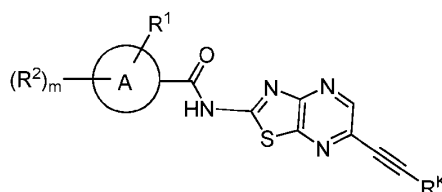
R^K is hydrogen, deuterium, an optionally substituted C₁₋₆ alkyl, an optionally substituted C₁₋₆ heteroalkyl, or an optionally substituted 3-10 membered ring structure.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, characterized as having a structure according to Formula K-1:



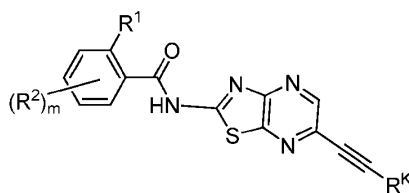
Formula K-1.

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, characterized as having a structure according to Formula K-2:



Formula K-2.

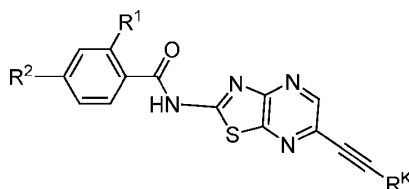
4. The compound of any of claims 1-3, or a pharmaceutically acceptable salt thereof, characterized as having a structure according to Formula K-3:



Formula K-3.

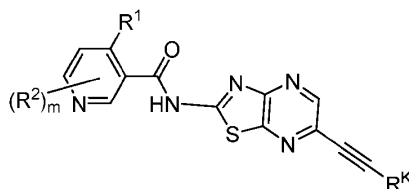
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5. The compound of any of claims 1-4, or a pharmaceutically acceptable salt thereof, characterized as having a structure according to Formula K-4:



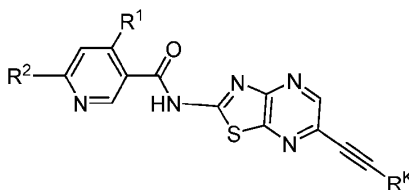
Formula K-4.

6. The compound of any of claims 1-3, or a pharmaceutically acceptable salt thereof, characterized as having a structure according to Formula K-5:



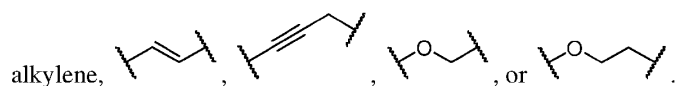
Formula K-5.

7. The compound of any of claims 1-3 or 6, or a pharmaceutically acceptable salt thereof, characterized as having a structure according to Formula K-6:



Formula K-6.

8. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein L is C₂₋₄

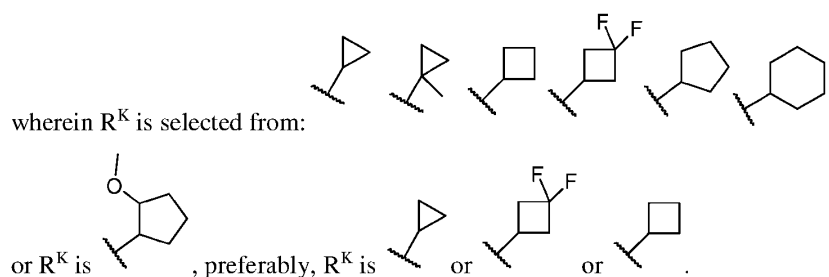


9. The compound of any of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein R^K is an optionally substituted C₃₋₈ cycloalkyl.

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10. The compound of any of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein R^K is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, each of which is optionally substituted with one or more, e.g., 1-5, substituents independently selected from deuterium, F, OH, CN, C_{1-4} alkyl optionally substituted with F, C_{1-4} heteroalkyl optionally substituted with F, or 3-6 membered ring optionally substituted with one or more substituents independently selected from deuterium, halogen, CN, OH, oxo, C_{1-4} alkyl optionally substituted with F, and C_{1-4} heteroalkyl optionally substituted with F.

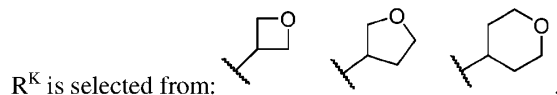
11. The compound of any of claims 1-9, or a pharmaceutically acceptable salt thereof,



12. The compound of any of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein R^K is an optionally substituted 4-8 membered heterocyclyl.
13. The compound of claim 12, or a pharmaceutically acceptable salt thereof, wherein R^K is 4-6 membered heterocyclyl having one or two ring heteroatoms, each independently O, S, or N, wherein the sulfur atom, if present, is optionally oxidized, wherein the 4-6 membered heterocyclyl is optionally substituted with one or more (e.g., 1-3) substituents independently selected from deuterium, F, oxo, OH, CN, C_{1-4} alkyl optionally substituted with deuterium and/or F, C_{1-4} heteroalkyl optionally substituted with deuterium and/or F, 3-6 membered ring, (C_{1-4} alkylene)-(3-6 membered ring), or (C_{1-4} heteroalkylene)-(3-6 membered ring), wherein the C_{1-4} alkylene or C_{1-4} heteroalkylene is optionally substituted with deuterium and/or F, and wherein each of the 3-6 membered ring is optionally substituted with one or more substituents independently selected from deuterium, halogen, CN, OH, oxo, C_{1-4} alkyl optionally substituted with F, and C_{1-4} heteroalkyl optionally substituted with F.

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14. The compound of claim 12 or 13, or a pharmaceutically acceptable salt thereof, wherein

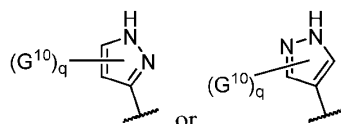


15. The compound of any of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein R^K is an optionally substituted 5 or 6-membered heteroaryl.
16. The compound of claim 15, or a pharmaceutically acceptable salt thereof, wherein R^K is a 5-membered heteroaryl having 1-4 ring heteroatoms, each independently O, S, or N, wherein the 5-membered heteroaryl is optionally substituted with 1-3 substituents independently selected from F, Cl, OH, CN, C₁₋₄ alkyl optionally substituted with deuterium and/or F, C₁₋₄ heteroalkyl optionally substituted with deuterium and/or F, 3-6 membered ring, (C₁₋₄ alkylene)-(3-6 membered ring), or (C₁₋₄ heteroalkylene)-(3-6 membered ring), wherein the C₁₋₄ alkylene or C₁₋₄ heteroalkylene is optionally substituted with deuterium and/or F, and wherein each of the 3-6 membered ring is optionally substituted with one or more substituents independently selected from deuterium, halogen, CN, OH, oxo, C₁₋₄ alkyl optionally substituted with F, and C₁₋₄ heteroalkyl optionally substituted with F.
17. The compound of claim 15 or 16, or a pharmaceutically acceptable salt thereof, wherein R^K is a 5-membered heteroaryl selected from pyrazolyl, isoxazolyl, oxadiazolyl, or thiadiazolyl, which is optionally substituted, as valency permits, with 1-3 substituents independently selected from F, Cl, OH, CN, C₁₋₄ alkyl optionally substituted with deuterium and/or F, C₁₋₄ heteroalkyl optionally substituted with deuterium and/or F, 3-6 membered ring, (C₁₋₂ alkylene)-(3-6 membered ring), or (C₁₋₂ heteroalkylene)-(3-6 membered ring), wherein the C₁₋₂ alkylene or C₁₋₂ heteroalkylene is optionally substituted with deuterium and/or F, and wherein, preferably, the 3-6 membered ring at each occurrence is independently selected from (a) C₃₋₆ cycloalkyl optionally substituted with methyl and/or F; or (b) 4-6 membered heterocyclyl having 1 or 2 ring heteroatoms independently selected from O, S, and N, wherein the sulfur atom, if present, is optionally oxidized, and wherein the 4-6 membered heterocyclyl is optionally substituted with 1-3

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substituents independently selected from deuterium, F, OH, oxo, CN, C₁₋₄ alkyl optionally substituted with F, or C₁₋₄ heteroalkyl optionally substituted with F.

18. The compound of any of claims 15-17, or a pharmaceutically acceptable salt thereof, wherein R^K is

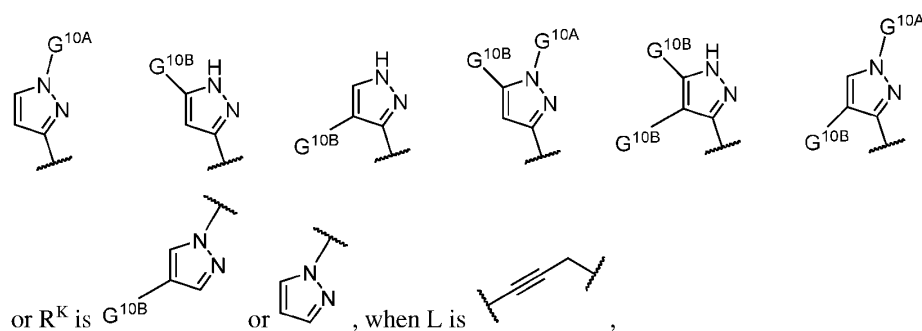


wherein:

q is 0, 1, 2, or 3; and

G¹⁰ at each occurrence is independently F, Cl, CN, C₁₋₄ alkyl optionally substituted with deuterium and/or F, C₁₋₄ heteroalkyl optionally substituted with deuterium and/or F, 3-6 membered ring, (C₁₋₂ alkylene)-(3-6 membered ring), or (C₁₋₂ heteroalkylene)-(3-6 membered ring), wherein the C₁₋₂ alkylene or C₁₋₂ heteroalkylene is optionally substituted with deuterium and/or F, and wherein, preferably, the 3-6 membered ring at each occurrence is independently selected from (a) C₃₋₆ cycloalkyl optionally substituted with methyl and/or F; or (b) 4-6 membered heterocyclyl having 1 or 2 ring heteroatoms independently selected from O, S, and N, wherein the sulfur atom, if present, is optionally oxidized, and wherein the 4-6 membered heterocyclyl is optionally substituted with 1-3 substituents independently selected from deuterium, F, OH, oxo, CN, C₁₋₄ alkyl optionally substituted with F, or C₁₋₄ heteroalkyl optionally substituted with F.

19. The compound of claim 1 or 18, or a pharmaceutically acceptable salt thereof, wherein R^K is selected from:



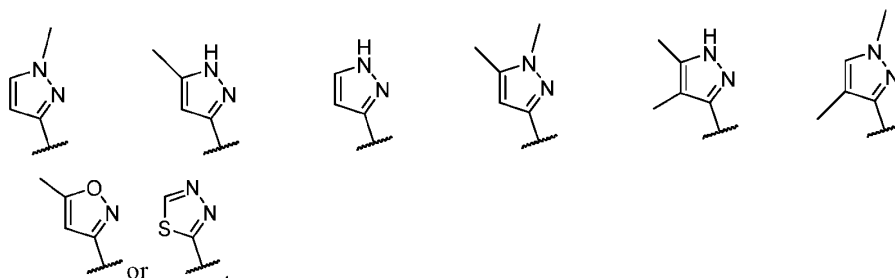
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wherein:

G^{10A} at each occurrence is independently C_{1-4} alkyl optionally substituted with deuterium and/or F, 3-6 membered ring, or $(C_{1-2}$ alkylene)-(3-6 membered ring), wherein the C_{1-2} alkylene or C_{1-2} heteroalkylene is optionally substituted with deuterium and/or F, and wherein, preferably, the 3-6 membered ring at each occurrence is independently selected from (a) C_{3-6} cycloalkyl optionally substituted with methyl and/or F; or (b) 4-6 membered heterocyclyl having 1 or 2 ring heteroatoms independently selected from O, S, and N, wherein the sulfur atom, if present, is optionally oxidized, and wherein the 4-6 membered heterocyclyl is optionally substituted with 1-3 substituents independently selected from deuterium, F, OH, oxo, CN, C_{1-4} alkyl optionally substituted with F, or C_{1-4} heteroalkyl optionally substituted with F; and

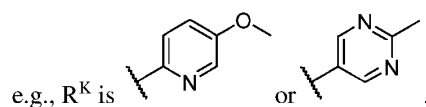
G^{10B} at each occurrence is independently F, Cl, CN, or G^{10A} .

20. The compound of claim 19, or a pharmaceutically acceptable salt thereof, wherein G^{10A} at each occurrence is independently C_{1-4} alkyl (e.g., methyl) optionally substituted with deuterium and/or F, cyclopropyl, cyclobutyl, $(C_{1-2}$ alkylene)-(cyclopropyl) or $(C_{1-2}$ alkylene)-(cyclobutyl).
21. The compound of claim 19 or 20, or a pharmaceutically acceptable salt thereof, wherein G^{10B} at each occurrence is independently F, Cl, C_{1-4} alkyl (e.g., methyl) optionally substituted with deuterium and/or F, cyclopropyl, cyclobutyl, $(C_{1-2}$ alkylene)-(cyclopropyl) or $(C_{1-2}$ alkylene)-(cyclobutyl).
22. The compound of claim 15 or 16, or a pharmaceutically acceptable salt thereof, wherein R^K is selected from:

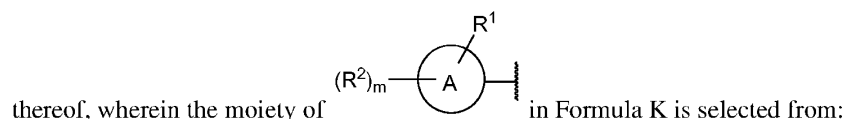


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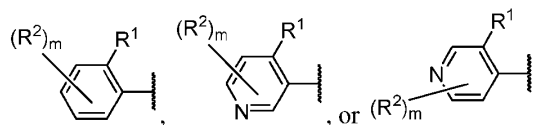
23. The compound of claim 15, or a pharmaceutically acceptable salt thereof, wherein R^K is a 6-membered heteroaryl having 1 or 2 ring nitrogen atoms, e.g., pyridyl, pyrimidyl, etc., wherein the 6-membered heteroaryl is optionally substituted with 1-3 substituents independently selected from F, Cl, OH, CN, C_{1-4} alkyl optionally substituted with deuterium and/or F, C_{1-4} heteroalkyl optionally substituted with deuterium and/or F, 3-6 membered ring, (C_{1-4} alkylene)-(3-6 membered ring), or (C_{1-4} heteroalkylene)-(3-6 membered ring), wherein the C_{1-4} alkylene or C_{1-4} heteroalkylene is optionally substituted with deuterium and/or F, and wherein each of the 3-6 membered ring is optionally substituted with one or more substituents independently selected from deuterium, halogen, CN, OH, oxo, C_{1-4} alkyl optionally substituted with F, and C_{1-4} heteroalkyl optionally substituted with F,



24. The compound of any of claims 1, 2, and 8-23, or a pharmaceutically acceptable salt thereof, wherein R^J is hydrogen.
25. The compound of any of claims 1-3 and 8-24, or a pharmaceutically acceptable salt thereof, wherein ring A is a phenyl ring or a 5 or 6-membered heteroaryl ring having 1 to 3 ring heteroatoms independently selected from N, O, and S, such as pyridine ring.
26. The compound of any of claims 1-3 and 8-24, or a pharmaceutically acceptable salt thereof, wherein ring A is a phenyl, pyridinyl, pyrimidinyl, or imidazo[1,2-a]pyridinyl ring, preferably, a phenyl or pyridinyl ring.
27. The compound of any of claims 1-3 and 8-24, or a pharmaceutically acceptable salt



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28. The compound of any of claims 1-27, or a pharmaceutically acceptable salt thereof, wherein m is 0, 1, or 2, and R^2 at each occurrence is independently deuterium, halogen, CN, OH, $(C_{1-4} \text{ alkylene})\text{-CN}$, G^A , or $X^a\text{-X}^b\text{-G}^A$,

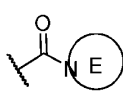
wherein:

X^a at each occurrence is independently null, C_{1-4} alkylene, or C_{1-4} heteroalkylene;

X^b at each occurrence is independently null, $\text{---}\equiv\text{---}$, O, NH, $N(G^B)$, $C(O)$, $C(O)O$, $C(O)NH$, $C(O)N(G^B)$, $NHC(O)$, $N(G^B)C(O)$, SO_2 , $S(=O)(=NH)$, $S(=O)(=NG^B)$, SO_2NH , or $SO_2N(G^B)$; and

G^A at each occurrence is independently:

- (i) C_{1-6} alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, C_{1-4} alkoxy, $C(O)\text{-NH}(C_{1-4} \text{ alkyl})$, $C(O)\text{-N}(C_{1-4} \text{ alkyl})(C_{1-4} \text{ alkyl})$, or a 3-6 membered ring;
- (ii) C_{1-6} heteroalkyl optionally substituted with one or more (e.g., 1-3) substituents independently deuterium, halogen, oxo, C_{1-4} alkyl, C_{1-4} alkoxy, or a 3-6 membered ring;
- (iii) a 3-8 membered carbocyclic or heterocyclic ring, which is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, oxo, OH, CN, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)\text{-NH}(C_{1-4} \text{ alkyl})$, $C(O)\text{-N}(C_{1-4} \text{ alkyl})(C_{1-4} \text{ alkyl})$,

, wherein the nitrogen containing Ring E is a 4-8 membered heterocyclic ring, or a 3-6 membered ring;

or

- (iv) a 5 or 6-membered heteroaryl, which is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, CN, C_{1-4} alkyl, C_{1-4} alkoxy, or a 3-6 membered ring (preferably carbocyclic or heterocyclic ring),

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wherein each of the C₁₋₄ alkyl or C₁₋₄ alkoxy in each of (i)-(iv) is independently optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, C₁₋₄ alkoxy, or a 3-4 membered carbocyclic or heterocyclic ring, and

wherein each of the 3-6 membered ring in each of (i)-(iv) or Ring E is independently optionally substituted with one or more (e.g., 1-3) substituents each independently oxo, deuterium, halogen, OH, CN, C₁₋₄ alkyl optionally substituted with deuterium or F, or C₁₋₄ alkoxy optionally substituted with deuterium or F;

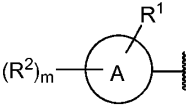
G^B at each occurrence is independently C₁₋₆ alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, C₁₋₄ alkoxy optionally substituted with deuterium or F, or a 3-6 membered ring optionally substituted with oxo, deuterium, halogen, OH, CN, C₁₋₄ alkyl optionally substituted with deuterium or F, or C₁₋₄ alkoxy optionally substituted with deuterium or F, or

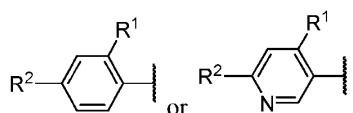
when applicable, G^A and G^B are joined to form a 4-8 membered heterocyclic ring, which is optionally substituted with one or more (e.g., 1-3) substituents each independently halogen, oxo, OH, C₁₋₄ alkyl optionally substituted with F, or C₁₋₄ alkoxy optionally substituted with F.

29. The compound of claim 28, or a pharmaceutically acceptable salt thereof, wherein m is 0.

30. The compound of claim 28, or a pharmaceutically acceptable salt thereof, wherein m is 1.

31. The compound of claim 30, or a pharmaceutically acceptable salt thereof, wherein the

moiety of  in Formula K is

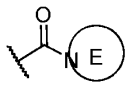
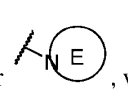


32. The compound of any of claims 1-27, 30 and 31, or a pharmaceutically acceptable salt thereof, wherein R² at each occurrence is independently (i) a C₁₋₄ alkyl optionally

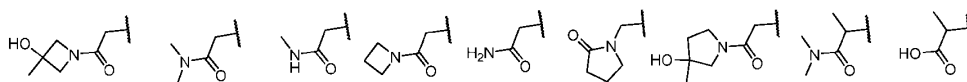
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substituted with deuterium, F, and/or OH, e.g., methyl, difluoromethyl, or hydroxymethyl; (ii) a 5 or 6-membered heteroaryl, which is optionally substituted with 1-3 substituents each independently halogen, OH, CN, C₁₋₄ alkyl, C₁₋₄ alkoxy, or a 3-5 membered carbocyclic or heterocyclic ring, wherein the C₁₋₄ alkyl or C₁₋₄ alkoxy is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen (e.g., F), OH, C₁₋₄ alkoxy, or a 3-5 membered carbocyclic or heterocyclic ring, wherein each of the 3-5 membered carbocyclic or heterocyclic ring, when present, is independently optionally substituted with deuterium, F, OH, and/or methyl; or (iii) -(C₁₋₄ alkylene)-C(O)NHG^A, -(C₁₋₄ alkylene)-C(O)N(G^A)(G^B) or -(C₁₋₄ alkylene)-CN, for example, G^A and G^B are each independently a C₁₋₄ alkyl optionally substituted with deuterium, F and/or OH, or G^A and G^B, together with the nitrogen atom they are both attached to, are joined to form a 4-8 membered heterocyclic ring, which is optionally substituted.

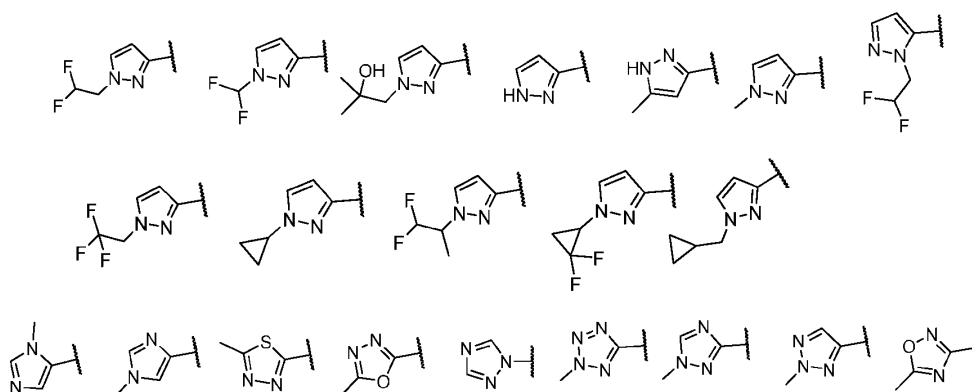
33. The compound of any of claims 1-27, or a pharmaceutically acceptable salt thereof, wherein m is 1, and R² is CN, halogen, SCF₃, C₁₋₃ alkyl optionally substituted with 1-3 substituents each independently CN, OH, F, or C₁₋₃ alkoxy optionally substituted with F, for example, R² is CN, CH₂-CN, CH₂-OCH₃, CH₂-OCF₃, methyl, difluoromethyl, SCF₃, or Cl.
34. The compound of any of claims 1-27, or a pharmaceutically acceptable salt thereof, wherein m is 1, and R² is -(C₁₋₄ alkylene)-G^{A1}, wherein G^{A1} is C(O)NH₂, C(O)OH,

C(O)NH(C₁₋₄ alkyl), C(O)N(C₁₋₄ alkyl)(C₁₋₄ alkyl), , or , wherein the nitrogen containing Ring E is a 4-8 membered heterocyclic ring, wherein each of the C₁₋₄ alkyl in C(O)NH(C₁₋₄ alkyl) or C(O)N(C₁₋₄ alkyl)(C₁₋₄ alkyl) is independently optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, C₁₋₄ alkoxy, or a 3-4 membered carbocyclic or heterocyclic ring, wherein the 3-4 membered carbocyclic or heterocyclic ring is unsubstituted or substituted with 1 or 2 substituents each independently F, OH, methyl, or methoxy; and

wherein each of the Ring E is independently optionally substituted with one or more (e.g., 1-3) substituents each independently oxo, deuterium, halogen, OH, CN, C₁₋₄ alkyl optionally substituted with deuterium or F, or C₁₋₄ alkoxy optionally substituted with deuterium or F; for example, R² is selected from the following:

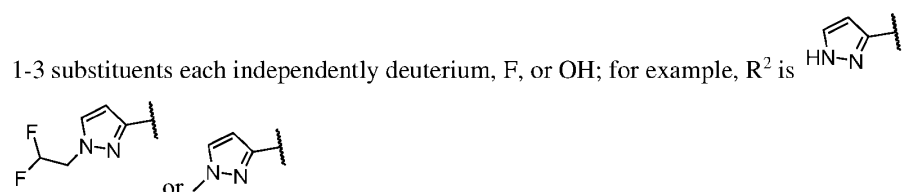


35. The compound of any of claims 1-27, or a pharmaceutically acceptable salt thereof, wherein m is 1, and R² is a 5-membered heteroaryl having 2-4 ring heteroatoms, such as pyrazolyl, imidazolyl, oxadiazolyl, triazolyl, or thiadiazolyl, etc., which is optionally substituted, for example, with 1 or 2 substituents, as valency permits, each independently deuterium, halogen, OH, CN, C₁₋₄ alkyl, C₁₋₄ heteroalkyl (such as C₁₋₄ alkoxy), a 3-6 membered carbocyclic or heterocyclic ring, (C₁₋₄ alkylene)-(3-6 membered carbocyclic or heterocyclic ring); or (C₁₋₄ heteroalkylene)-(3-6 membered carbocyclic or heterocyclic ring); wherein the C₁₋₄ alkyl, C₁₋₄ alkylene, C₁₋₄ heteroalkyl, or C₁₋₄ heteroalkylene is optionally substituted with one or more (e.g., 1-3) substituents each independently oxo, deuterium, halogen (e.g., F) or OH; and wherein each of the 3-6 membered carbocyclic or heterocyclic ring is optionally substituted with one or more (e.g., 1-3) substituents each independently oxo, deuterium, halogen, OH, CN, C₁₋₄ alkyl optionally substituted with deuterium or F, or C₁₋₄ alkoxy optionally substituted with deuterium or F, for example, R² is selected from the following:



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36. The compound of claim 35 or a pharmaceutically acceptable salt thereof, wherein m is 1, and R^2 is a pyrazolyl optionally substituted with one or two substituents, with one substituent being (i) a C_{1-4} alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; (ii) a 3-4 membered carbocyclic or heterocyclic ring; or (iii) $(C_{1-4}$ alkylene)-(3-4 membered carbocyclic or heterocyclic ring); wherein the 3-4 membered carbocyclic or heterocyclic ring in (ii) or (iii) is unsubstituted or substituted with 1 or 2 substituents each independently F, OH, methyl, or methoxy; and the other substituent, if present, is halogen, OH, CN, or C_{1-4} alkyl optionally substituted

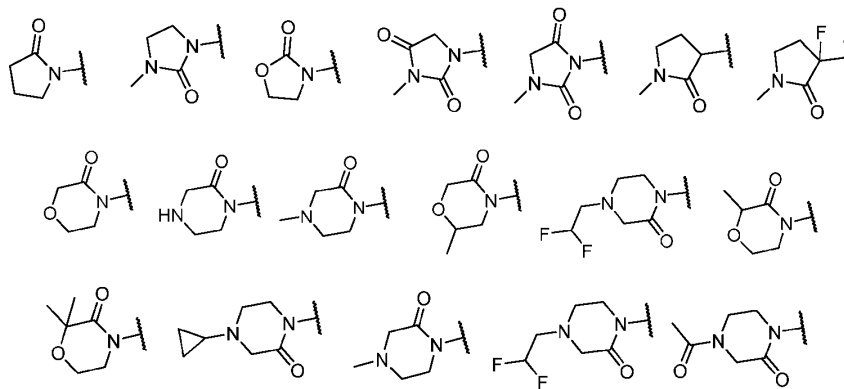


37. The compound of any of claims 1-27, or a pharmaceutically acceptable salt thereof, wherein m is 1, and R^2 is a 5-membered or 6-membered heterocyclic ring having 1 or 2 ring heteroatoms each independently N, O, or S, wherein the 5-membered or 6-membered heterocyclic ring contains one or two ring carbon atoms in the form of $C(=O)$, or the 5-membered or 6-membered heterocyclic ring contains a ring sulfur atom in the form of SO_2 , wherein the 5-membered or 6-membered heterocyclic ring is optionally substituted with one or more (e.g., 1, 2, or 3) substituents: (i) each independently deuterium, halogen, OH, CN, C_{1-4} alkyl, $C(O)-C_{1-4}$ alkyl, C_{1-4} heteroalkyl (such as C_{1-4} alkoxy), 3-6 membered carbocyclic or heterocyclic ring, $(C_{1-4}$ alkylene)-(3-6 membered carbocyclic or heterocyclic ring), or $(C_{1-4}$ heteroalkylene)-(3-6 membered carbocyclic or heterocyclic ring); or (ii) two optional substituents, together with the ring atom(s) they are attached to, are joined to form a 3-6 membered carbocyclic or heterocyclic ring, and any remaining substituent(s) is as defined in (i); wherein the C_{1-4} alkyl, C_{1-4} alkylene, C_{1-4} heteroalkyl, or C_{1-4} heteroalkylene is optionally substituted with one or more (e.g., 1-3) substituents each independently oxo, deuterium, halogen (e.g., F) or OH; and each of the 3-6 membered carbocyclic or heterocyclic ring is optionally substituted with one or more (e.g., 1-3) substituents each independently oxo, deuterium, halogen, OH, CN,

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C₁₋₄ alkyl optionally substituted with deuterium or F, or C₁₋₄ alkoxy optionally substituted with deuterium or F;

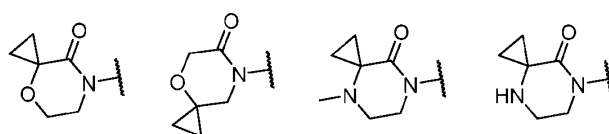
for example, R² is selected from the following:

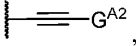
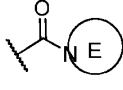


38. The compound of claim 37, or a pharmaceutically acceptable salt thereof, wherein R² is a 6-membered heterocyclic ring having 1 or 2 ring heteroatoms each independently N or O, wherein the 6-membered heterocyclic ring contains one ring carbon atom in the form of C(=O), wherein the 6-membered heterocyclic ring is optionally substituted with 1-3 (e.g., 1 or 2) substituents each independently (i) a C₁₋₄ alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; (ii) C(O)-C₁₋₄ alkyl, wherein the C₁₋₄ alkyl is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; (iii) a 3-4 membered carbocyclic or heterocyclic ring; or (iv) (C₁₋₄ alkylene)-(3-4 membered carbocyclic or heterocyclic ring); wherein the 3-4 membered carbocyclic or heterocyclic ring in (iii) or (iv) is unsubstituted or substituted with 1 or 2 substituents each independently F, OH, methyl, or methoxy.
39. The compound of claim 37, or a pharmaceutically acceptable salt thereof, wherein R² is a 6-membered heterocyclic ring having 1 or 2 ring heteroatoms each independently N or O, wherein the 6-membered heterocyclic ring contains one ring carbon atom in the form of C(=O), wherein two gem substituents of the 6-membered heterocyclic ring are joined to form a spiro cyclopropyl ring, which is unsubstituted or substituted with 1 or 2 substituents each independently F or methyl, wherein the 6-membered heterocyclic ring is optionally further substituted with one or more (e.g., 1 or 2) substituents each

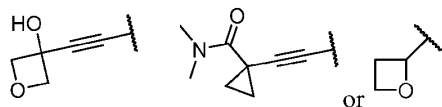
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independently (i) a C₁₋₄ alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; (ii) C(O)-C₁₋₄ alkyl, wherein the C₁₋₄ alkyl is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; (iii) a 3-4 membered carbocyclic or heterocyclic ring; or (iv) (C₁₋₄ alkylene)-(3-4 membered carbocyclic or heterocyclic ring); wherein the 3-4 membered carbocyclic or heterocyclic ring in (iii) or (iv) is unsubstituted or substituted with 1 or 2 substituents each independently F, OH, methyl, or methoxy, for example, R² is selected from the following:



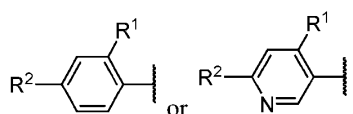
40. The compound of any of claims 1-27, or a pharmaceutically acceptable salt thereof, wherein m is 1, and R² is G^{A2} or , wherein G^{A2} is a 3-6 membered carbocyclic or heterocyclic ring, which is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, oxo, OH, CN, C₁₋₄ alkyl, C₁₋₄ alkoxy, C(O)NH₂, C(O)-NH(C₁₋₄ alkyl), C(O)-N(C₁₋₄ alkyl)(C₁₋₄ alkyl), or , wherein the nitrogen containing Ring E is a 4-8 membered heterocyclic ring; wherein each of the C₁₋₄ alkyl or C₁₋₄ alkoxy is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, C₁₋₄ alkoxy, or a 3-4 membered carbocyclic or heterocyclic ring, wherein the 3-4 membered carbocyclic or heterocyclic ring is unsubstituted or substituted with 1 or 2 substituents each independently F, OH, methyl, or methoxy; and wherein Ring E is independently optionally substituted with one or more (e.g., 1-3) substituents each independently oxo, deuterium, halogen, OH, CN, C₁₋₄ alkyl optionally substituted with deuterium or F, or C₁₋₄ alkoxy optionally substituted with deuterium or F.
41. The compound of claim 40, or a pharmaceutically acceptable salt thereof, wherein R² is selected from the following:

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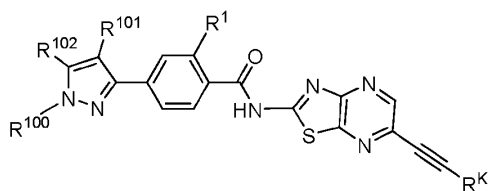
42. The compound of any of claims 33-41, or a pharmaceutically acceptable salt thereof,

wherein the moiety of $(R^2)_m$ —A in Formula K is

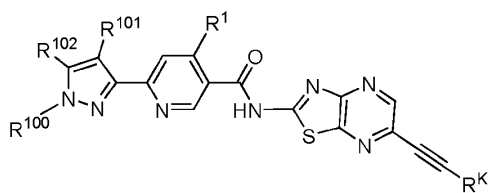


43. The compound of any of claims 1-27, or a pharmaceutically acceptable salt thereof, wherein m is 2, and one R^2 is as defined in any of claims 28 and 32-41, and the other R^2 is F or Cl.

44. The compound of any of claims 1-7 and 9-27, or a pharmaceutically acceptable salt thereof, characterized as having a structure according to Formula K-7a or K-7b:



Formula K-7a,



Formula K-7a,

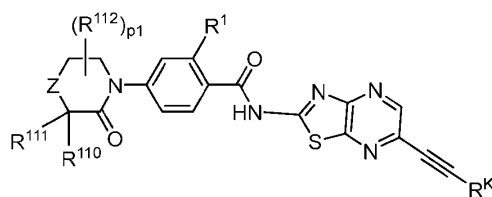
wherein:

R^{100} is selected from

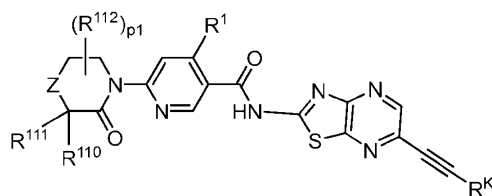
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(i) hydrogen; (ii) a C₁₋₄ alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; (iii) a 3-4 membered carbocyclic or heterocyclic ring; or (iv) (C₁₋₄ alkylene)-(3-4 membered carbocyclic or heterocyclic ring); wherein the 3-4 membered carbocyclic or heterocyclic ring in (iii) or (iv) is unsubstituted or substituted with 1 or 2 substituents each independently F, OH, methyl, or methoxy; R¹⁰¹ and R¹⁰² are each independently halogen, CN, or (i)-(iv) as defined for R¹⁰⁰.

45. The compound of claim 44, or a pharmaceutically acceptable salt thereof, wherein (i) R¹⁰¹ is hydrogen; (ii) R¹⁰² is hydrogen; or (iii) both R¹⁰¹ and R¹⁰² are hydrogen.
46. The compound of claim 44 or 45, or a pharmaceutically acceptable salt thereof, wherein R¹⁰⁰ is C₁₋₄ alkyl optionally substituted with deuterium or F, for example, R¹⁰⁰ is methyl, CD₃, ethyl, fluorine-substituted methyl (e.g., difluoromethyl or trifluoromethyl), or fluorine-substituted ethyl, such as 2,2-difluoroethyl, 2,2,2-trifluoroethyl, etc.
47. The compound of claim 44 or 45, or a pharmaceutically acceptable salt thereof, wherein R¹⁰⁰ is cyclopropyl optionally substituted with 1 or 2 substituents, each independently F or methyl.
48. The compound of any of claims 1-7 and 9-27, or a pharmaceutically acceptable salt thereof, characterized as having a structure according to Formula K-8a or K-8b:



Formula K-8a,



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Formula K-8b,

wherein:

Z is O, NH, or NR¹¹³,

p1 is 0, 1, or 2;

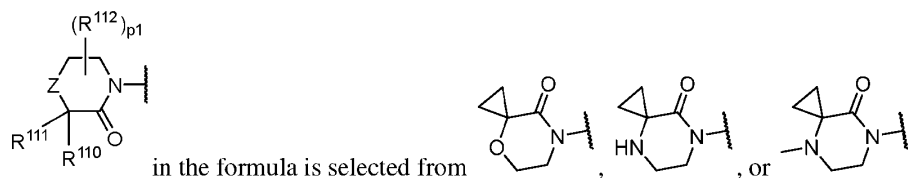
R¹¹⁰ and R¹¹¹ are each independently hydrogen or C₁₋₄ alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; or R¹¹⁰ and R¹¹¹, together with the carbon atom they are both attached to, are joined to form a 3-4 membered ring, preferably, a cyclopropyl ring, which is optionally substituted with 1 or 2 substituents each independently F, OH, methyl, or methoxy;

R¹¹² at each occurrence is independently a C₁₋₄ alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; or when applicable, two R¹¹², together with the carbon atom they are both attached to, are joined to form C(=O), or a 3-4 membered ring, preferably, a cyclopropyl ring, which is optionally substituted with 1 or 2 substituents each independently F, OH, methyl, or methoxy; and R¹¹³ is (i) a C₁₋₄ alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; (ii) a 3-4 membered carbocyclic or heterocyclic ring; or (iii) (C₁₋₄ alkylene)-(3-4 membered carbocyclic or heterocyclic ring); wherein the 3-4 membered carbocyclic or heterocyclic ring in (ii) or (iii) is unsubstituted or substituted with 1 or 2 substituents each independently F, OH, methyl, or methoxy.

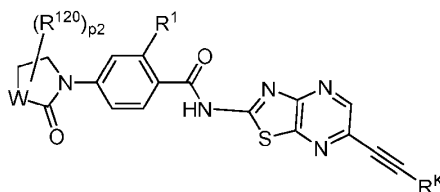
49. The compound of claim 48, or a pharmaceutically acceptable salt thereof, wherein Z is O.
50. The compound of claim 48, or a pharmaceutically acceptable salt thereof, wherein Z is NH or NR¹¹³.
51. The compound of claim 50, or a pharmaceutically acceptable salt thereof, wherein R¹¹³ is C₁₋₄ alkyl optionally substituted with deuterium or F, for example, methyl, CD₃, ethyl, fluorine-substituted methyl (e.g., difluoromethyl or trifluoromethyl), or fluorine-substituted ethyl, such as 2,2-difluoroethyl, 2,2,2-trifluoroethyl etc.
52. The compound of any of claims 48-51, or a pharmaceutically acceptable salt thereof, wherein R¹¹⁰ and R¹¹¹ are each independently hydrogen or methyl.

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53. The compound of any of claims 48-51, or a pharmaceutically acceptable salt thereof, wherein R^{110} and R^{111} , together with the carbon atom they are both attached to, are joined to form a cyclopropyl ring.
54. The compound of any of claims 48-53, or a pharmaceutically acceptable salt thereof, wherein p_1 is 0.
55. The compound of any of claims 48-53, or a pharmaceutically acceptable salt thereof, wherein p_1 is 1 or 2, and R^{112} at each occurrence is methyl.
56. The compound of any of claims 48-53, or a pharmaceutically acceptable salt thereof, wherein p_1 is 2, and two R^{112} are attached to the same ring carbon, and the two R^{112} , together with to the ring carbon they are both attached to, are joined to form a cyclopropyl ring.
57. The compound of claim 48, or a pharmaceutically acceptable salt thereof, wherein the moiety of

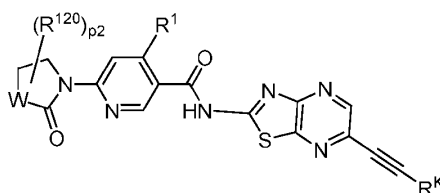


58. The compound of any of claims 1-7 and 9-27, or a pharmaceutically acceptable salt thereof, characterized as having a structure according to Formula K-9a or K-9b:



Formula K-9a,

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Formula K-9b,

wherein:

W is O, NH, C(R¹²¹)(R¹²²), or NR¹²³,

p₂ is 0, 1, or 2;

R¹²⁰ at each occurrence is independently a C₁₋₄ alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; or

when applicable, two R¹²⁰, together with the carbon atom they are both attached to, are joined to form C(=O) or a 3-4 membered spiro or fused ring, which is optionally substituted with 1 or 2 substituents each independently F, OH, methyl, or methoxy;

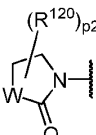
R¹²¹ and R¹²² are each independently hydrogen or C₁₋₄ alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; or

R¹²¹ and R¹²², together with the carbon atom they are both attached to, are joined to form a 3-4 membered ring, preferably, a cyclopropyl ring, which is optionally substituted with 1 or 2 substituents each independently F, OH, methyl, or methoxy; and

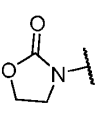
R¹²³ is (i) a C₁₋₄ alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, F, or OH; (ii) a 3-4 membered carbocyclic or heterocyclic ring; or (iii) (C₁₋₄ alkylene)-(3-4 membered carbocyclic or heterocyclic ring); wherein the 3-4 membered carbocyclic or heterocyclic ring in (ii) or (iii) is unsubstituted or substituted with 1 or 2 substituents each independently F, OH, methyl, or methoxy.

59. The compound of claim 58, or a pharmaceutically acceptable salt thereof, wherein W is O.
60. The compound of claim 58, or a pharmaceutically acceptable salt thereof, wherein W is NH or NR¹²³.

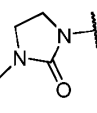
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61. The compound of claim 60, or a pharmaceutically acceptable salt thereof, wherein R^{123} is C_{1-4} alkyl optionally substituted with deuterium or F, for example, methyl, CD_3 , ethyl, fluorine-substituted methyl (e.g., difluoromethyl or trifluoromethyl), or fluorine-substituted ethyl, such as 2,2-difluoroethyl, 2,2,2-trifluoroethyl, etc.
62. The compound of of claim 58, or a pharmaceutically acceptable salt thereof, wherein W is $C(R^{121})(R^{122})$, wherein R^{121} and R^{122} are each independently hydrogen or methyl.
63. The compound of any of claims 58-62, or a pharmaceutically acceptable salt thereof, wherein p_2 is 0.
64. The compound of any of claims 58-62, or a pharmaceutically acceptable salt thereof, wherein p_2 is 1 or 2, and R^{120} at each occurrence is methyl.
65. The compound of any of claims 58-62, or a pharmaceutically acceptable salt thereof, wherein p_2 is 2, and two gem R^{120} , and the same ring carbon they are both attached to, together represent $C(=O)$.
66. The compound of claim 58, or a pharmaceutically acceptable salt thereof, wherein the moiety of
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in the formula is selected from

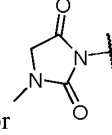


,



,

or



.

67. The compound of any of claims 1-66, or a pharmaceutically acceptable salt thereof, wherein R^1 is a phenyl, pyridinyl, pyrimidinyl, benzopyrazolyl, benzimidazolyl, imidazolyl, pyridazyl, imidazo[1,2-a]pyrimidinyl, oxazolo[4,5-b]pyridinyl, oxazolo[5,4-b]pyridinyl, thiazolo[4,5-b]pyridinyl, benzo[d]thiazole, indazolyl, [1,2,4]triazolo[1,5-a]pyrimidinyl, [1,2,4]triazolo[1,5-b]pyridazinyl, or tetrazolo[1,5-a]pyridinyl, each of which is optionally substituted.

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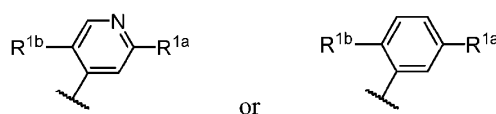
68. The compound of any of claims 1-66, or a pharmaceutically acceptable salt thereof, wherein R^1 is a phenyl or pyridinyl, each of which is optionally substituted with 1-3 substituents independently selected from: deuterium, halogen, CN, OH, NH_2 , COOH, $CONH_2$, $(C_{1-4} \text{ alkylene})-CN$, G^C , or $X^c-X^d-G^C$, wherein:
- X^c at each occurrence is independently null, C_{1-4} alkylene, or C_{1-4} heteroalkylene;
- X^d at each occurrence is independently null, O, NH, $N(G^D)$, $C(O)$, $C(O)O$, $C(O)NH$, $C(O)N(G^D)$, $NHC(O)$, $N(G^D)C(O)$, $P(O)(G^D)$, SO_2 , SO_2NH , or $SO_2N(G^D)$; and
- G^C at each occurrence is independently:
- (i) C_{1-6} alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, C_{1-4} alkoxy, or a 3-6 membered ring;
 - (ii) C_{1-6} heteroalkyl optionally substituted with one or more (e.g., 1-3) substituents independently deuterium, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, or a 3-6 membered ring;
 - (iii) a 3-7 membered carbocyclic or heterocyclic ring, which is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, oxo, OH, CN, C_{1-4} alkyl, C_{1-4} alkoxy, or a 3-6 membered ring;
- or
- (iv) a 5 or 6-membered heteroaryl, which is optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, CN, C_{1-4} alkyl, C_{1-4} alkoxy, or a 3-6 membered ring (preferably carbocyclic or heterocyclic ring),
- wherein the C_{1-4} alkyl or C_{1-4} alkoxy in each of (i)-(iv) is independently optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, C_{1-4} alkoxy, or a 3-4 membered carbocyclic or heterocyclic ring, and
- wherein each of the 3-6 membered ring in each of (i)-(iv) is independently optionally substituted with oxo, deuterium, halogen, OH, CN, C_{1-4} alkyl optionally substituted with deuterium or F, or C_{1-4} alkoxy optionally substituted with deuterium or F;
- G^D at each occurrence is independently C_{1-6} alkyl optionally substituted with one or more (e.g., 1-3) substituents each independently deuterium, halogen, OH, C_{1-4} alkoxy optionally substituted with deuterium or F, or a 3-6 membered ring optionally substituted with oxo,

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deuterium, halogen, OH, CN, C₁₋₄ alkyl optionally substituted with deuterium or F, or C₁₋₄ alkoxy optionally substituted with deuterium or F, or
when applicable, G^C and G^D together with the heteroatom they are both attached to are joined to form a 4-7 membered heterocyclic ring, which is optionally substituted with one or more (e.g., 1-3) substituents each independently halogen, oxo, OH, C₁₋₄ alkyl optionally substituted with deuterium or F, or C₁₋₄ alkoxy optionally substituted with deuterium or F.

69. The compound of any of claims 1-66, or a pharmaceutically acceptable salt thereof, wherein R¹ is a phenyl or pyridinyl, each of which is optionally substituted with one or more (e.g., 1-3) substituents independently selected from halogen, C₁₋₆ alkyl optionally substituted with deuterium, F, CN, and/or OH, C₁₋₆ alkoxy optionally substituted with deuterium, F, CN, and/or OH, C₃₋₆ cycloalkyl optionally substituted with deuterium, F, CN, methyl, and/or OH, NH₂, NH(C₁₋₄ alkyl), or N(C₁₋₄ alkyl)(C₁₋₄ alkyl).
70. The compound of any of claims 1-66, or a pharmaceutically acceptable salt thereof, wherein R¹ is a phenyl or pyridinyl, each of which is optionally substituted with one or more (e.g., 1-3) substituents independently selected from halogen, C₁₋₄ alkyl optionally substituted with deuterium, F and/or OH, C₁₋₄ alkoxy optionally substituted with deuterium or F, C₃₋₄ cycloalkyl optionally substituted with deuterium, F, CN, methyl, and/or OH, NH₂, NH(C₁₋₃ alkyl), or N(C₁₋₃ alkyl)(C₁₋₃ alkyl).
71. The compound of any of claims 1-66, or a pharmaceutically acceptable salt thereof, wherein R¹ is a phenyl or pyridinyl, each of which is optionally substituted with 1-3 substituents independently selected from methyl, ethyl, fluoro, chloro, bromo, trifluoromethyl, difluoromethyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, cyclopropyl, -NH₂, hydroxymethyl, and 1-hydroxy ethyl, preferably, the substituents are independently selected from methyl, fluoro, chloro, trifluoromethyl, difluoromethyl, methoxy, ethoxy, difluoromethoxy, and cyclopropyl.
72. The compound of any of claims 1-66, or a pharmaceutically acceptable salt thereof, wherein R¹ is

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wherein R^{1a} and R^{1b} are each independently halogen, C_{1-6} alkyl optionally substituted with deuterium, F, CN, and/or OH, C_{1-6} alkoxy optionally substituted with deuterium, F, CN, and/or OH, C_{3-6} cycloalkyl optionally substituted with deuterium, F, CN, methyl, and/or OH, NH_2 , $NH(C_{1-4} \text{ alkyl})$, or $N(C_{1-4} \text{ alkyl})(C_{1-4} \text{ alkyl})$.

73. The compound of claim 72, or a pharmaceutically acceptable salt thereof, wherein R^{1b} is C_{1-4} alkoxy optionally substituted with 1-3 deuterium or F, for example, methoxy, ethoxy, or difluoromethoxy.
74. The compound of claim 72 or 73, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is (i) halogen (e.g., F or Cl); (ii) C_{1-4} alkyl optionally substituted with 1-3 deuterium or F, e.g., methyl, trifluoromethyl, difluoromethyl, etc.; or (iii) cyclopropyl or cyclobutyl, optionally substituted with methyl and/or F.
75. A compound selected from Table 1, or Examples 1-266, or a pharmaceutically acceptable salt thereof.
76. A pharmaceutical composition comprising the compound of any of claims 1-75, or a pharmaceutically acceptable salt thereof and optionally a pharmaceutically acceptable excipient.
77. A method of treating a disease or disorder in a subject in need thereof, wherein the disease or disorder is characterized by overexpression of Polθ, the method comprising administering to the subject a therapeutically effective amount of the compound of any of claims 1-75, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 76.
78. The method of claim 77, wherein the disease or disorder is cancer.

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79. A method of treating a homologous recombination (HR) deficient cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the compound of any of claims 1-75, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 76.
80. A method for treating a cancer in a subject in need thereof, wherein the cancer is characterized by a reduction or absence of BRCA gene expression, the absence of the BRCA gene, and/or reduced function of BRCA protein, the method comprising administering to the subject a therapeutically effective amount of the compound of any of claims 1-75, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 76.
81. The method of any one of claims 78-80, wherein the cancer is selected from lymphoma, rhabdoid tumor, multiple myeloma, uterine cancer, gastric cancer, peripheral nervous system cancer, rhabdomyosarcoma, bone cancer, colorectal cancer, mesothelioma, breast cancer, ovarian cancer, lung cancer, fibroblast cancer, central nervous system cancer, urinary tract cancer, upper aerodigestive cancer, leukemia, kidney cancer, skin cancer, esophageal cancer, and pancreatic cancer.
82. The method of any one of claims 77-81, further comprising administering to the subject one or more additional therapeutic agents selected from a PARP inhibitor, a signal transduction inhibitor, a chemotherapeutic agent, and/or an immune checkpoint inhibitor.
83. A method for treating a cancer in a subject in need thereof, wherein the cancer is resistant to poly(ADP-ribose) polymerase (PARP) inhibitor therapy, the method comprising administering to the subject a therapeutically effective amount of the compound of any of claims 1-75, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 76.
84. The method of claim 83, wherein the cancer is breast cancer, ovarian cancer, lung cancer, bladder cancer, liver cancer, head and neck cancer, pancreatic cancer, gastrointestinal cancer, or colorectal cancer.

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85. The method of claim 83 or 84, further comprising administering to the subject a PARP inhibitor.