

HETEROCYCLIC COMPOUNDS AS BET INHIBITORS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 62/870,020, filed July 2, 2019, and U.S. Provisional Application No. 63/017,547, filed April 29, 2020, each of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to novel bromodomain and extraterminal domain (BET) inhibitors and to therapeutic methods of treating conditions and diseases using these novel BET inhibitors.

BACKGROUND OF THE INVENTION

[0003] Epigenetic dysregulation has a crucial role in driving aberrant gene expressions leading to various types of cancers. Many components involved in epigenetic regulation have been attractive targets for therapeutic interventions. Among them, the bromodomain and extra-terminal (BET) family of proteins attracted much attention in recent years. The BET family proteins include BRD2, BRD3, BRD4, and the testis-specific BRDT. Via their bromodomains (BRDs), they bind with a high affinity to acetylation motifs, including acetylated histones in chromatin, thereby regulating gene transcription. The genes regulated by BET family proteins include many important oncogenes responsible for cell survival and cell cycle progression.

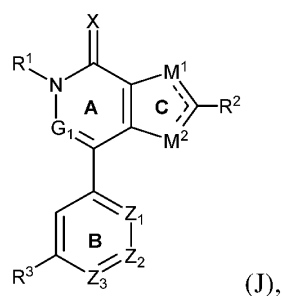
[0004] BET proteins are emerging targets in cancer, directly regulating the expression of oncogenes in hematological and solid tumors. BRD4, in addition to occupying gene promoters, has a strong preference for enhancers and super-enhancers in key driver genes such as c-MYC (Loven et al, Cell 2013; 153(2):320-34). BET family proteins have also been implicated in mediating acute inflammatory responses through the canonical NF-KB pathway (Huang et al., Mol. Cell. Biol. 29: 1375-1387 (2009)) resulting in the upregulation of genes associated with the production of cytokines (Nicodeme et al., Nature 468: 1119-1123, (2010)). In addition, bromodomain function has been implicated in kidney disease (Zhang, et al., J. Biol. Chem. 287: 28840-28851 (2012)). BRD2 function has also been linked to a predisposition for dyslipidemia or improper regulation of adipogenesis, elevated inflammatory profiles and increased susceptibility to autoimmune diseases (Denis, Discovery Medicine 10: 489-499 (2010)). The human immunodeficiency virus utilizes BRD4 to initiate transcription of viral RNA from stably integrated viral DNA (Jang et al., Mol.

Cell, 19: 523-534 (2005)). BET bromodomain inhibitors have also been shown to reactivate HIV transcription in models of latent T cell infection and latent monocyte infection (Banerjee, et al., J. Leukocyte Biol. doi:10.1189/jlb.0312165). BRDT has an important role in spermatogenesis (Matzuk, et al., Cell 150: 673-684 (2012)).

[0005] Due to this potential as an epigenetic target, a number of small molecule compounds that inhibit the function of BET family proteins have been developed, and many of them have demonstrated promising anti-cancer activities with both solid and hematologic malignancies in preclinical studies. This has led to several early-phase clinical trials. Included among these are RO6870810 (formerly TEN-010), ZEN003694, BMS-986158, CPI-0610, I-BET762, OTX015, FT-1101, INCB054329, PLX51107, GS-5829, and ABBV-075. While these efforts are promising, there is need for better selectivity and improved durability of BET inhibitors that provide enhanced efficacy while reducing toxicity related to off-target effects. The present invention relates to novel BET inhibitors.

SUMMARY OF THE INVENTION

[0006] In one aspect, provided is a compound of Formula (J):



or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein --- , X, G₁, R¹, R², R³, M¹, M², Z₁, Z₂, and Z₃ are defined herein.

[0007] In some embodiments, the compounds provided herein are BET inhibitors that selectively target and covalently bind the protein of interest. In some embodiments, the BET inhibitors comprise a compound of the Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0008] In some embodiments, provided herein is a pharmaceutical composition comprising a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, in combination with at least one pharmaceutically acceptable carrier, diluent, or excipient.

[0009] In some embodiments, use of a compound having the structure of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, for the manufacture of a medicament is provided.

[0010] In some embodiments, provided herein is a method of treating a disease mediated by inhibition of the BET family of proteins in an individual. In some embodiments, such method comprises administering to the subject an effective amount of a compound having the structure of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition comprising the same, at a frequency and for duration sufficient to provide a beneficial effect to the subject.

[0011] In some embodiments, provided herein are methods for treating or preventing disorders that are ameliorated by inhibition of BET. In some embodiments, such methods comprise of administering to the subject a therapeutically effective amount of a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, alone, or in combination with a pharmaceutically acceptable carrier.

[0012] In another aspect, the methods are directed to methods of treating or preventing an inflammatory disease or cancer or AIDS. In some embodiments, such methods comprise of administering to the subject a therapeutically effective amount of a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a tautomer or isomer thereof,

or a pharmaceutically acceptable salt of any of the foregoing, alone, or in combination with a pharmaceutically acceptable carrier.

[0013] In another aspect, provided herein is the use of a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, alone or in combination with a second active pharmaceutical agent, in the manufacture of a medicament for treating or preventing conditions and disorders disclosed herein, with or without a pharmaceutically acceptable carrier.

[0014] In another aspect, a method of synthesis is provided for a compound having the structure of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, as detailed herein.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0015] “Alkyl” refers to and includes saturated linear and branched univalent hydrocarbon structures and combination thereof, having the number of carbon atoms designated (*i.e.*, C₁-C₁₀ means one to ten carbons). Particular alkyl groups are those having 1 to 20 carbon atoms (a “C₁-C₂₀ alkyl”). More particular alkyl groups are those having 1 to 8 carbon atoms (a “C₁-C₈ alkyl”), 3 to 8 carbon atoms (a “C₃-C₈ alkyl”), 1 to 6 carbon atoms (a “C₁-C₆ alkyl”), 1 to 5 carbon atoms (a “C₁-C₅ alkyl”), or 1 to 4 carbon atoms (a “C₁-C₄ alkyl”). Examples of alkyl include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like.

[0016] “Alkenyl” as used herein refers to an unsaturated linear or branched univalent hydrocarbon chain or combination thereof, having at least one site of olefinic unsaturation (*i.e.*, having at least one moiety of the formula C=C) and having the number of carbon atoms designated (*i.e.*, C₂-C₁₀ means two to ten carbon atoms). The alkenyl group may be in “cis” or “trans” configurations, or alternatively in “E” or “Z” configurations. Particular alkenyl groups are those having 2 to 20 carbon atoms (a “C₂-C₂₀ alkenyl”), having 2 to 8 carbon atoms (a “C₂-C₈ alkenyl”), having 2 to 6 carbon atoms (a “C₂-C₆ alkenyl”), or having 2 to 4 carbon atoms (a “C₂-C₄ alkenyl”).

Examples of alkenyl include, but are not limited to, groups such as ethenyl (or vinyl), prop-1-enyl, prop-2-enyl (or allyl), 2-methylprop-1-enyl, but-1-enyl, but-2-enyl, but-3-enyl, buta-1,3-dienyl, 2-methylbuta-1,3-dienyl, homologs and isomers thereof, and the like.

[0017] “Alkylene” as used herein refers to the same residues as alkyl but having bivalency. Particular alkylene groups are those having 1 to 6 carbon atoms (a “C₁-C₆ alkylene”), 1 to 5 carbon atoms (a “C₁-C₅ alkylene”), 1 to 4 carbon atoms (a “C₁-C₄ alkylene”) or 1 to 3 carbon atoms (a “C₁-C₃ alkylene”). Examples of alkylene include, but are not limited to, groups such as methylene (-CH₂-), ethylene (-CH₂CH₂-), propylene (-CH₂CH₂CH₂-), butylene (-CH₂CH₂CH₂CH₂-), and the like.

[0018] “Alkynyl” as used herein refers to an unsaturated linear or branched univalent hydrocarbon chain or combination thereof, having at least one site of acetylenic unsaturation (*i.e.*, having at least one moiety of the formula C≡C) and having the number of carbon atoms designated (*i.e.*, C₂-C₁₀ means two to ten carbon atoms). Particular alkynyl groups are those having 2 to 20 carbon atoms (a “C₂-C₂₀ alkynyl”), having 2 to 8 carbon atoms (a “C₂-C₈ alkynyl”), having 2 to 6 carbon atoms (a “C₂-C₆ alkynyl”), or having 2 to 4 carbon atoms (a “C₂-C₄ alkynyl”). Examples of alkynyl include, but are not limited to, groups such as ethynyl (or acetylenyl), prop-1-ynyl, prop-2-ynyl (or propargyl), but-1-ynyl, but-2-ynyl, but-3-ynyl, homologs and isomers thereof, and the like.

[0019] “Aryl” refers to and includes polyunsaturated aromatic hydrocarbon groups. Aryl may contain additional fused rings (*e.g.*, from 1 to 3 rings), including additionally fused aryl, heteroaryl, cycloalkyl, and/or heterocyclyl rings. In one variation, the aryl group contains from 6 to 14 annular carbon atoms. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, biphenyl, and the like.

[0020] “Carbonyl” refers to the group C=O.

[0021] “Cycloalkyl” refers to and includes cyclic univalent hydrocarbon structures, which may be fully saturated, mono- or polyunsaturated, but which are non-aromatic, having the number of carbon atoms designated (*e.g.*, C₁-C₁₀ means one to ten carbons). Cycloalkyl can consist of one ring, such as cyclohexyl, or multiple rings, such as adamantly, but excludes aryl groups. A cycloalkyl comprising more than one ring may be fused, spiro or bridged, or combinations thereof. A preferred cycloalkyl is a cyclic hydrocarbon having from 3 to 13 annular carbon atoms. A more preferred cycloalkyl is a cyclic hydrocarbon having from 3 to 8 annular carbon atoms (a “C₃-C₈”).

cycloalkyl"). Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, norbornyl, and the like.

[0022] "Halo" or "halogen" refers to elements of the Group 17 series having atomic number 9 to 85. Preferred halo groups include fluoro, chloro, bromo and iodo. Where a residue is substituted by more than one halogen, it may be referred to by using a prefix corresponding to the number of halogen moieties attached, e.g., dihaloaryl, dihaloalkyl, trihaloaryl etc. refer to aryl and alkyl substituted by two ("di") or three ("tri") halo groups, which may be but are not necessarily the same halo; thus 4-chloro-3-fluorophenyl is within the scope of dihaloaryl. An alkyl group in which each hydrogen is replaced with a halo group is referred to as a "perhaloalkyl." A preferred perhaloalkyl group is trifluoroalkyl (-CF₃). Similarly, "perhaloalkoxy" refers to an alkoxy group in which a halogen takes the place of each H in the hydrocarbon making up the alkyl moiety of the alkoxy group. An example of a perhaloalkoxy group is trifluoromethoxy (-OCF₃).

[0023] "Heteroaryl" refers to and includes unsaturated aromatic cyclic groups having from 1 to 10 annular carbon atoms and at least one annular heteroatom, including but not limited to heteroatoms such as nitrogen, oxygen and sulfur, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule at an annular carbon or at an annular heteroatom. Heteroaryl may contain additional fused rings (e.g., from 1 to 3 rings), including additionally fused aryl, heteroaryl, cycloalkyl, and/or heterocyclyl rings. Examples of heteroaryl groups include, but are not limited to, pyridyl, pyrimidyl, pyridazinyl, thiophenyl, furanyl, thiazolyl, pyrrolyl, pyrazolyl, oxazolyl, isooxazolyl, imidazolyl, quinolyl, isoquinolyl, benzimidazolyl, benzpyrazolyl, benzotriazolyl, indole, benzothiazyl, benzoxazolyl, benzisoxazolyl, imidazopyridinyl and the like.

[0024] "Heterocycle" or "heterocyclyl" refers to a saturated or an unsaturated non-aromatic group having from 1 to 10 annular carbon atoms and from 1 to 4 annular heteroatoms, such as nitrogen, sulfur or oxygen, and the like, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heterocyclyl group may have a single ring or multiple condensed rings, but excludes heteroaryl groups. A heterocycle comprising more than one ring may be fused, spiro or bridged, or any combination thereof. In fused ring systems, one or more of the fused rings can be aryl or heteroaryl. Examples of heterocyclyl groups include, but are not limited to, tetrahydropyranyl, dihydropyranyl, piperidinyl, piperazinyl,

pyrrolidinyl, thiazolinyl, thiazolidinyl, tetrahydrofuranyl, dihydrooxazolyl, dihydroisoxazolyl, dioxolanyl, morpholinyl, dioxanyl, tetrahydrothiophenyl, and the like.

[0025] “Oxo” refers to the moiety =O.

[0026] “Optionally substituted” unless otherwise specified means that a group may be unsubstituted or substituted by one or more (e.g., 1, 2, 3, 4 or 5) of the substituents listed for that group in which the substituents may be the same or different. In one embodiment, an optionally substituted group has one substituent. In another embodiment, an optionally substituted group has two substituents. In another embodiment, an optionally substituted group has three substituents. In another embodiment, an optionally substituted group has four substituents. In some embodiments, an optionally substituted group has 1 to 2, 2 to 5, 3 to 5, 2 to 3, 2 to 4, 3 to 4, 1 to 3, 1 to 4 or 1 to 5 substituents.

[0027] Term “BET” refers to bromodomain and extraterminal domain family.

[0028] As used herein “BRD” refers to one or more bromodomain extraterminal domain family proteins (BRD2, BRD3, BRD4, and BRDT).

[0029] “Disease” specifically includes any unhealthy condition of an animal or part thereof. “Optional” or “optionally” means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not.

[0030] “Pharmaceutically acceptable” means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

[0031] “Pharmaceutically acceptable salts” means salts which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, o-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid p-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, p- toluenesulfonic

acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary-butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like.

[0032] In addition, pharmaceutically acceptable salts may be formed when an acidic proton present is capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine and the like.

[0033] “Therapeutically effective amount” means that amount which, when administered to an animal for treating a disease, is sufficient to affect such treatment for the disease.

[0034] “Treatment” or “treating” is an approach for obtaining beneficial or desired results including clinical results. For purposes of this disclosure, beneficial or desired results include, but are not limited to, one or more of the following: decreasing one or more symptoms resulting from the disease or disorder, diminishing the extent of the disease or disorder, stabilizing the disease or disorder (*e.g.*, preventing or delaying the worsening of the disease or disorder), delaying the occurrence or recurrence of the disease or disorder, delaying or slowing the progression of the disease or disorder, ameliorating the disease or disorder state, providing a remission (whether partial or total) of the disease or disorder, decreasing the dose of one or more other medications required to treat the disease or disorder, enhancing the effect of another medication used to treat the disease or disorder, delaying the progression of the disease or disorder, increasing the quality of life, and/or prolonging survival of a patient. Also encompassed by “treatment” is a reduction of pathological consequence of the disease or disorder. The methods of the disclosure contemplate any one or more of these aspects of treatment.

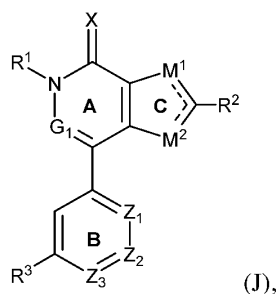
[0035] Compounds that have identical molecular formulae but differ in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space are termed “isomers.” Isomers that differ in the nature or sequence of bonding of their atoms are termed “constitutional isomers.” Isomers that differ only in the arrangement of their atoms in space are termed “stereoisomers.” Stereoisomers that are not mirror images of one another are termed “diastereomers” and stereoisomers that are mirror images are termed “enantiomers” or sometimes “optical isomers.” Stereoisomers that are superimposable upon their mirror images are termed

“achiral” and those not superimposable are termed “chiral.” A carbon atom bonded to four different groups is termed a “chiral center” or alternatively an “asymmetric carbon.”

[0036] When a compound has a chiral center, a pair of enantiomers of opposite chirality is possible. An enantiomer can be characterized by the absolute configuration of its chiral center and described by the R- and S-sequencing rules of Cahn and Prelog (i.e., as (R)- and (S)-isomers) or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+)- and (-)-isomers, respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is termed a "racemic mixture" or "racemate" and may be described as the (RS)- or (±)-mixture thereof. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. Conventions for stereochemical nomenclature, methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (see discussion in Chapter 4 of "Advanced Organic Chemistry", 3rd edition March, Jerry, John Wiley and Sons, New York, 1985).

Compounds

[0037] In some embodiments, provided is a compound of Formula (J):



or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

each $\equiv$ is independently a single bond or double bond;

X is O or S;

R¹ is hydrogen, C₁-C₃ alkyl, -(C₁-C₃ alkylene)OH, C₁-C₃ haloalkyl, or C₃-C₄ cycloalkyl;

G₁ is CR^a or N, wherein:

R^a is hydrogen, halogen, or C₁-C₄ alkyl;

Z_1 is C-W₁-R^c; wherein:

each W₁ is independently -O- or -NR^{w1}-, wherein:

R^{w1} is hydrogen, C₃-C₆ cycloalkyl, or C₁-C₄ alkyl optionally substituted by oxo, -OH, or halogen, and

R^c is independently C₃-C₆ cycloalkyl, 4- to 6- membered heterocyclyl, C₆-C₁₄ aryl, or 5- or 6-membered heteroaryl, each of which is independently optionally substituted by R^{c1}, wherein each R^{c1} is independently halogen, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, 3- to 6-membered heterocyclyl, cyano, oxo, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₁-C₄ haloalkyl, -OR¹⁰, -NR¹⁰R¹¹, -C(O)NR¹⁰R¹¹, -NR¹⁰C(O)R¹¹, -S(O)₂R¹⁰, -NR¹⁰S(O)₂R¹¹, or -S(O)₂NR¹⁰R¹¹;

Z_2 is C-W₂-R^d or N, wherein:

W₂ is -O-, -NR^{w2}-, or a bond, wherein:

R^{w2} is hydrogen, C₃-C₆ cycloalkyl, or C₁-C₄ alkyl optionally substituted by oxo, -OH, or halogen, and

R^d is independently hydrogen, halogen, cyano, 3- to 6-membered heterocyclyl, or C₁-C₄ alkyl;

Z_3 is C-R^e or N, wherein:

R^e is independently hydrogen, halogen, cyano, 3- to 6-membered heterocyclyl, or C₁-C₄ alkyl;

M^1 is S or CR^{1a};

M^2 is S or CR^{2a}, provided that

(1) when M^1 is S, then the $\equiv$ adjacent to M^1 is a single bond and the $\equiv$ adjacent to M^2 is a double bond,

(2) when M^2 is S, then the $\equiv$ adjacent to M^2 is a single bond and the $\equiv$ adjacent to M^1 is a double bond, and

(3) either M^1 or M^2 is S;

R^{1a} and R^{2a} are each independently hydrogen, halogen, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, 3- to 6-

membered heterocyclyl, 5- to 10-membered heteroaryl, cyano, oxo, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, -OR¹⁰, -NR¹⁰R¹¹, -C(O)OR¹⁰, -C(O)NR¹⁰R¹¹, -NR¹⁰C(O)R¹¹, -S(O)₂R¹⁰, -NR¹⁰S(O)₂R¹¹ or -S(O)₂NR¹⁰R¹¹, each of which is independently optionally substituted by R¹²;

R² is hydrogen, halogen, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, 3- to 6-membered heterocyclyl, -(C₁-C₃ alkylene)3- to 6-membered heterocyclyl, 5- to 10-membered heteroaryl, cyano, oxo, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, -OR¹⁰, -NR¹⁰R¹¹, -C(O)OR¹⁰, -C(O)NR¹⁰R¹¹, -NR¹⁰C(O)R¹¹, -S(O)₂R¹⁰, -NR¹⁰S(O)₂R¹¹, or -S(O)₂NR¹⁰R¹¹, each of which is independently optionally substituted by R¹²;

R³ is -(CH₂)_mNR¹³S(O)₂R¹⁴ wherein m is 0, 1, 2 or 3; C₃-C₆ cycloalkyl optionally substituted by halogen, oxo, -CN, or -OH; C₁-C₄ alkyl substituted by halogen, oxo, -CN, or -OH; or C₂-C₆ alkenyl;

R¹⁰ and R¹¹ are each independently hydrogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ alkenyl, C₃-C₆ cycloalkyl, C₆-C₁₄ aryl, 3- to 6-membered heterocyclyl, -(C₁-C₃ alkylene)C₃-C₆ cycloalkyl, -(C₁-C₃ alkylene) 3- to 6-membered heterocyclyl, -(C₁-C₃ alkylene) C₆-C₁₄ aryl, -NR¹⁵R¹⁶, or -C(O)R¹², wherein each of R¹⁰ and R¹¹ is independently optionally substituted by halogen, oxo, -CN, -CF₃, -OH, -NR¹³R¹⁴, -C(O)NR¹³R¹⁴, or C₁-C₄ alkyl optionally substituted by halogen, oxo, -CN, -CF₃, or -OH,

or R¹⁰ and R¹¹ are taken together with the atom or atoms to which they are attached to form a 3- to 6-membered heterocyclyl ring optionally substituted by halogen, oxo, -CN, -CF₃, -OH, or C₁-C₄ alkyl optionally substituted by halogen, oxo, -CN, or -OH;

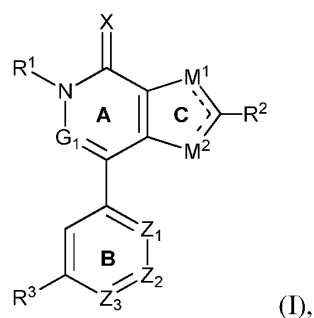
each R¹² is independently halogen, cyano, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, -OR¹⁵, -NR¹⁵R¹⁶, -C(O)NR¹⁵R¹⁶, -NR¹⁵C(O)R¹⁶, -S(O)₂R¹⁵, -NR¹⁵S(O)₂R¹⁶, -S(O)₂NR¹⁵R¹⁶, C₃-C₆ cycloalkyl, 3- to 6-membered heterocyclyl, or C₁-C₄ alkyl, each of which is independently optionally substituted by halogen, oxo, -CF₃, -CN, -OH, -NR¹³R¹⁴, or -NR¹³C(O)R¹⁴;

R¹³ and R¹⁴ are independently hydrogen, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, or 3- to 6-membered heterocyclyl, each of which is independently optionally substituted by halogen, oxo, -CN, or -OH,

or R¹³ and R¹⁴ are taken together with the atom or atoms to which they are attached to form a 3- to 6-membered heterocyclyl ring optionally substituted by halogen, oxo, -CN, -OH, or C₁-C₄ alkyl optionally substituted by halogen, oxo, -CN, or -OH; and

each R^{15} and R^{16} are independently hydrogen, C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, or 3- to 6-membered heterocyclyl, each of which is independently optionally substituted by halogen, oxo, -CN, or -OH, or R^{15} and R^{16} are taken together with the atoms to which they are attached to form a 3- to 6-membered heterocyclyl ring optionally substituted by halogen, oxo, -CN, -OH, or C_1 - C_4 alkyl optionally substituted by halogen, oxo, -CN, or -OH.

[0038] In some embodiments, provided is a compound of Formula (I):



or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

each $\equiv$ is independently a single bond or double bond;

X is O or S;

R^1 is hydrogen, C_1 - C_3 alkyl, $-(C_1$ - C_3 alkylene)OH, C_1 - C_3 haloalkyl, or C_3 - C_4 cycloalkyl;

G_1 is CR^a or N, wherein:

R^a is hydrogen, halogen, or C_1 - C_4 alkyl;

Z_1 is $C-W_1-R^c$; wherein:

each W_1 is independently -O- or $-NR^{w1}-$, wherein:

R^{w1} is hydrogen, C_3 - C_6 cycloalkyl, or C_1 - C_4 alkyl optionally substituted by oxo, -OH, or halogen, and

R^c is independently 4- to 6- membered heterocyclyl, C_6 - C_{14} aryl, or 5- or 6-membered heteroaryl, each of which is independently optionally substituted by R^{c1} , wherein each R^{c1} is independently halogen, C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, 3- to 6-membered heterocyclyl, cyano, oxo, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy, C_1 - C_4 haloalkyl, $-OR^{10}$, $-NR^{10}R^{11}$, $-C(O)NR^{10}R^{11}$, $-NR^{10}C(O)R^{11}$,

$-\text{S}(\text{O})_2\text{R}^{10}$, $-\text{NR}^{10}\text{S}(\text{O})_2\text{R}^{11}$, or $-\text{S}(\text{O})_2\text{NR}^{10}\text{R}^{11}$;

Z_2 is $\text{C}-\text{W}_2-\text{R}^d$ or N , wherein:

W_2 is $-\text{O}-$, $-\text{NR}^{\text{w}2}-$, or a bond, wherein:

$\text{R}^{\text{w}2}$ is hydrogen, C_3-C_6 cycloalkyl, or C_1-C_4 alkyl optionally substituted by oxo, $-\text{OH}$, or halogen, and

R^d is independently hydrogen, halogen, cyano, 3- to 6-membered heterocyclyl, or C_1-C_4 alkyl;

Z_3 is $\text{C}-\text{R}^e$ or N , wherein:

R^e is independently hydrogen, halogen, cyano, 3- to 6-membered heterocyclyl, or C_1-C_4 alkyl;

M^1 is S or CR^{1a} ;

M^2 is S or CR^{2a} , provided that

(1) when M^1 is S , then the ===== adjacent to M^1 is a single bond and the ===== adjacent to M^2 is a double bond,

(2) when M^2 is S , then the ===== adjacent to M^2 is a single bond and the ===== adjacent to M^1 is a double bond, and

(3) at least one of M^1 and M^2 is not S ;

R^{1a} and R^{2a} are each independently hydrogen, halogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, 3- to 6-membered heterocyclyl, 5- to 10-membered heteroaryl, cyano, oxo, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, $-\text{OR}^{10}$, $-\text{NR}^{10}\text{R}^{11}$, $-\text{C}(\text{O})\text{OR}^{10}$, $-\text{C}(\text{O})\text{NR}^{10}\text{R}^{11}$, $-\text{NR}^{10}\text{C}(\text{O})\text{R}^{11}$, $-\text{S}(\text{O})_2\text{R}^{10}$, $-\text{NR}^{10}\text{S}(\text{O})_2\text{R}^{11}$ or $-\text{S}(\text{O})_2\text{NR}^{10}\text{R}^{11}$, each of which is independently optionally substituted by R^{12} ;

R^2 is halogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, 3- to 6-membered heterocyclyl, $-(\text{C}_1-\text{C}_3 \text{ alkylene})_3$ - to 6-membered heterocyclyl, 5- to 10-membered heteroaryl, cyano, oxo, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, $-\text{OR}^{10}$, $-\text{NR}^{10}\text{R}^{11}$, $-\text{C}(\text{O})\text{OR}^{10}$, $-\text{C}(\text{O})\text{NR}^{10}\text{R}^{11}$, $-\text{NR}^{10}\text{C}(\text{O})\text{R}^{11}$, $-\text{S}(\text{O})_2\text{R}^{10}$, $-\text{NR}^{10}\text{S}(\text{O})_2\text{R}^{11}$, or $-\text{S}(\text{O})_2\text{NR}^{10}\text{R}^{11}$, each of which is independently optionally substituted by R^{12} ;

R^3 is $-(\text{CH}_2)_m\text{NR}^{13}\text{S}(\text{O})_2\text{R}^{14}$, C_3-C_6 cycloalkyl, or C_1-C_4 alkyl substituted by halogen, oxo, $-\text{CN}$, or $-\text{OH}$, wherein m is 0, 1, 2 or 3;

R^{10} and R^{11} are each independently hydrogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ alkenyl, C₃-C₆ cycloalkyl, 3- to 6-membered heterocyclyl, -(C₁-C₃ alkylene)C₃-C₆ cycloalkyl, -(C₁-C₃ alkylene) 3- to 6-membered heterocyclyl, -NR¹⁵R¹⁶, or -C(O)R¹², wherein each of R^{10} and R^{11} is independently optionally substituted by halogen, oxo, -CN, -CF₃, -OH, -NR¹³R¹⁴, -C(O)NR¹³R¹⁴, or C₁-C₄ alkyl optionally substituted by halogen, oxo, -CN, -CF₃, or -OH,

or R^{10} and R^{11} are taken together with the atom or atoms to which they are attached to form a 3- to 6-membered heterocyclyl ring optionally substituted by halogen, oxo, -CN, -CF₃, -OH, or C₁-C₄ alkyl optionally substituted by halogen, oxo, -CN, or -OH;

each R^{12} is independently halogen, cyano, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, -OR¹⁵, -NR¹⁵R¹⁶, -C(O)NR¹⁵R¹⁶, -NR¹⁵C(O)R¹⁶, -S(O)₂R¹⁵, -NR¹⁵S(O)₂R¹⁶, -S(O)₂NR¹⁵R¹⁶, C₃-C₆ cycloalkyl, 3- to 6-membered heterocyclyl, or C₁-C₄ alkyl, each of which is independently optionally substituted by halogen, oxo, -CF₃, -CN, -OH, -NR¹³R¹⁴, or -NR¹³C(O)R¹⁴,

R^{13} and R^{14} are independently hydrogen, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, or 3- to 6-membered heterocyclyl, each of which is independently optionally substituted by halogen, oxo, -CN, or -OH,

or R^{13} and R^{14} are taken together with the atom or atoms to which they are attached to form a 3- to 6-membered heterocyclyl ring optionally substituted by halogen, oxo, -CN, -OH, or C₁-C₄ alkyl optionally substituted by halogen, oxo, -CN, or -OH; and

each R^{15} and R^{16} are independently hydrogen, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, or 3- to 6-membered heterocyclyl, each of which is independently optionally substituted by halogen, oxo, -CN, or -OH,

or R^{15} and R^{16} are taken together with the atoms to which they are attached to form a 3- to 6-membered heterocyclyl ring optionally substituted by halogen, oxo, -CN, -OH, or C₁-C₄ alkyl optionally substituted by halogen, oxo, -CN, or -OH.

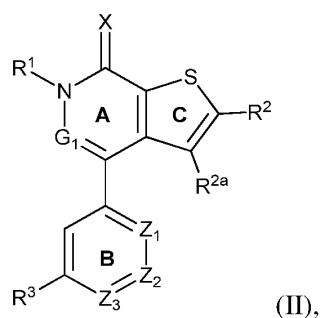
[0039] In some embodiments of compound of Formula (I), M^1 is S. In some embodiments, M^1 is CR^{1a}. In some embodiments, R^{1a} is hydrogen, halogen, or C₁-C₄ alkyl optionally substituted by R¹². In some embodiments, R^{1a} is hydrogen. In some embodiments, R^{1a} is halogen such as fluoro or chloro. In some embodiments, R^{1a} is C₁-C₄ alkyl such as methyl or ethyl. In some embodiments, M^1 is CR^{1a} and R^{1a} is hydrogen.

[0040] In some embodiments of compound of Formula (I), M^2 is S. In some embodiments, M^2 is CR^{2a}. In some embodiments, R^{2a} is hydrogen, halogen, or C₁-C₄ alkyl optionally substituted by R¹². In some embodiments, R^{2a} is hydrogen. In some embodiments, R^{2a} is halogen such as fluoro or

chloro. In some embodiments, R^{2a} is C_1 - C_4 alkyl such as methyl or ethyl. In some embodiments, M^2 is CR^{2a} and R^{2a} is hydrogen.

[0041] In some embodiments of a compound of Formula (I), M^1 is S and M^2 is CR^{2a} . In some embodiments, M^1 is S and M^2 is CR^{2a} , wherein R^{2a} is hydrogen. In some embodiments, M^1 is CR^{1a} and M^2 is S. In some embodiments, M^1 is CR^{1a} , wherein R^{1a} is hydrogen, and M^2 is S.

[0042] In some embodiments, provided is a compound of Formula (II),



or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X, G_1 , R^1 , R^2 , R^3 , R^{2a} , Z_1 , Z_2 , and Z_3 are defined herein for Formula (I).

[0043] In some embodiments, provided is a compound of any one of Formula (IIa-1) to (IIa-8):

(IIa-1)	(IIa-2)	(IIa-3)

(IIa-4)	(IIa-5)	(IIa-6)
(IIa-7)	(IIa-8)	

or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X, G₁, R¹, R², R³, R^{2a}, R^{c1}, R¹⁰, R¹¹, R¹², Z₁ and W₁ are defined herein for Formula (I), and n is 0, 1, 2, 3, 4, or 5;

p is 0, 1, 2, 3, or 4;

X₁ is N or C;

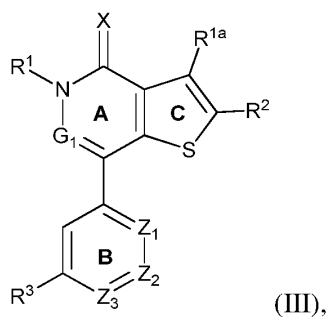
X₂, X₃, X₄ and X₅ are each independently C, CH, CR¹², S, O, N, NH, NR¹²;

provided that:

1. not more than one of X₂, X₃, X₄ and X₅ is S or O,
2. not more than three of X₁, X₂, X₃, X₄ and X₅ are N; and
3. at least one of X₂, X₃, X₄ and X₅ is CR¹² or NR¹².

In some embodiments, a compound of Formula (I) is of Formula (IIa-1). In some embodiments, a compound of Formula (I) is of Formula (IIa-2). In some embodiments, a compound of Formula (I) is of Formula (IIa-3). In some embodiments, a compound of Formula (I) is of Formula (IIa-4). In some embodiments, a compound of Formula (I) is of Formula (IIa-5). In some embodiments, a compound of Formula (I) is of Formula (IIa-6). In some embodiments, a compound of Formula (I) is of Formula (IIa-7). In some embodiments, a compound of Formula (I) is of Formula (IIa-8).

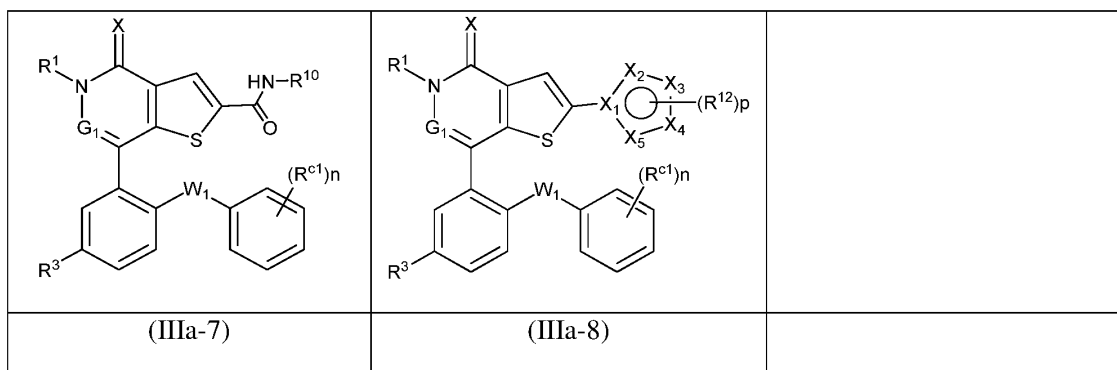
[0044] In some embodiments, provided is a compound of Formula (III),



or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X, G₁, R¹, R², R³, R^{1a}, Z₁, Z₂, and Z₃ are defined herein for Formula (I).

[0045] In some embodiments, provided is a compound of any one of Formula (IIIa-1) to (IIIa-8):

(IIIa-1)	(IIIa-2)	(IIIa-3)
(IIIa-4)	(IIIa-5)	(IIIa-6)



or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X, G₁, R¹, R², R³, R^{2a}, R^{c1}, R¹⁰, R¹¹, R¹², Z₁ and W₁ are defined herein Formula (I), and

n is 0, 1, 2, 3, 4, or 5;

p is 0, 1, 2, 3, or 4;

X₁ is N or C;

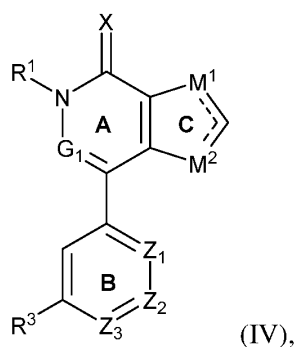
X₂, X₃, X₄ and X₅ are each independently C, CH, CR¹², S, O, N, NH, or NR¹²;

provided that

1. not more than one of X₂, X₃, X₄ and X₅ is S or O;
2. not more than three of X₁, X₂, X₃, X₄ and X₅ are N; and
3. at least one of X₂, X₃, X₄ and X₅ is CR¹² or NR¹².

In some embodiments, a compound of Formula (I) is of Formula (IIIa-1). In some embodiments, a compound of Formula (I) is of Formula (IIIa-2). In some embodiments, a compound of Formula (I) is of Formula (IIIa-3). In some embodiments, a compound of Formula (I) is of Formula (IIIa-4). In some embodiments, a compound of Formula (I) is of Formula (IIIa-5). In some embodiments, a compound of Formula (I) is of Formula (IIIa-6). In some embodiments, a compound of Formula (I) is of Formula (IIIa-7). In some embodiments, a compound of Formula (I) is of Formula (IIIa-8).

[0046] In some embodiments, provided is a compound of Formula (IV):



or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

each $\equiv$ is independently a single bond or double bond;

X is O or S;

R¹ is hydrogen, C₁-C₃ alkyl, -(C₁-C₃ alkylene)OH, C₁-C₃ haloalkyl, or C₃-C₄ cycloalkyl;

G_1 is CR^a or N , wherein:

R^a is hydrogen, halogen, C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

Z_1 is C- W_1 - R^c , wherein:

each W_1 is independently -O- or -NR^{w1}-, wherein:

R^{w1} is hydrogen, C₃-C₆ cycloalkyl, or C₁-C₄ alkyl optionally substituted by oxo, -OH, or halogen, and

R^c is independently C₃-C₆ cycloalkyl, 4- to 6- membered heterocyclyl, C₆-C₁₄ aryl, or 5- or 6-membered heteroaryl, each of which is independently optionally substituted by R^{c1}, wherein each R^{c1} is independently halogen, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, 3- to 6-membered heterocyclyl, cyano, oxo, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₁-C₄ haloalkyl, -OR¹⁰, -NR¹⁰R¹¹, -C(O)NR¹⁰R¹¹, -NR¹⁰C(O)R¹¹, -S(O)₂R¹⁰, -NR¹⁰S(O)₂R¹¹, or -S(O)₂NR¹⁰R¹¹;

Z_2 is C-W₂-R^d or N, wherein:

W₂ is -O-, -NR^{w2}-, or a bond, wherein:

R^{w2} is hydrogen, C₃-C₆ cycloalkyl, or C₁-C₄ alkyl optionally substituted by oxo, -OH, or halogen, and

R^d is independently hydrogen, halogen, cyano, 3- to 6-membered heterocyclyl, or C_1 - C_4 alkyl;

Z_3 is $C-R^e$ or N, wherein:

R^e is independently hydrogen, halogen, cyano, 3- to 6-membered heterocyclyl, or C_1 - C_4 alkyl;

M^1 is S or CR^{1a} ;

M^2 is S or CR^{2a} , provided that

(1) when M^1 is S, then the $====$ adjacent to M^1 is a single bond and the $====$ adjacent to M^2 is a double bond,

(2) when M^2 is S, then the $====$ adjacent to M^2 is a single bond and the $====$ adjacent to M^1 is a double bond, and

(3) at least one of M^1 and M^2 is S;

R^{1a} and R^{2a} are each independently hydrogen, halogen, C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, 3- to 6-membered heterocyclyl, 5- to 10-membered heteroaryl, cyano, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy, $-OR^{10}$, $-NR^{10}R^{11}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-NR^{10}C(O)R^{11}$, $-S(O)_2R^{10}$, $-NR^{10}S(O)_2R^{11}$ or $-S(O)_2NR^{10}R^{11}$, each of which is independently optionally substituted by R^{12} ;

R^3 is $-(CH_2)_mNR^{13}S(O)_2R^{14}$, wherein m is 0, 1, 2 or 3; C_3 - C_6 cycloalkyl optionally substituted by halogen, oxo, -CN, or -OH; or C_1 - C_4 alkyl substituted by halogen, oxo, -CN, or -OH;

R^{10} and R^{11} are each independently hydrogen, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_4 alkenyl, C_3 - C_6 cycloalkyl, 3- to 6-membered heterocyclyl, $-(C_1-C_3 \text{ alkylene}) C_3$ - C_6 cycloalkyl, $-(C_1-C_3 \text{ alkylene})$ 3- to 6-membered heterocyclyl, $-NR^{15}R^{16}$, or $-C(O)R^{12}$, wherein each of R^{10} and R^{11} is independently optionally substituted by halogen, oxo, -CN, $-CF_3$, -OH, $-NR^{13}R^{14}$, $-C(O)NR^{13}R^{14}$, or C_1 - C_4 alkyl optionally substituted by halogen, oxo, -CN, $-CF_3$, or -OH,

or R^{10} and R^{11} are taken together with the atom or atoms to which they are attached to form a 3- to 6-membered heterocyclyl ring optionally substituted by halogen, oxo, -CN, $-CF_3$, -OH, or C_1 - C_4 alkyl optionally substituted by halogen, oxo, -CN, or -OH;

each R^{12} is independently halogen, cyano, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy, $-OR^{15}$, $-NR^{15}R^{16}$, $-C(O)NR^{15}R^{16}$, $-NR^{15}C(O)R^{16}$, $-S(O)_2R^{15}$, $-NR^{15}S(O)_2R^{16}$, $-S(O)_2NR^{15}R^{16}$, C_3 - C_6

cycloalkyl, 3- to 6-membered heterocyclyl, or C₁-C₄ alkyl, each of which is independently optionally substituted by halogen, oxo, -CF₃, -CN, -OH, -NR¹³R¹⁴, or -NR¹³C(O)R¹⁴;

R¹³ and R¹⁴ are independently hydrogen, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, or 3- to 6-membered heterocyclyl, each of which is independently optionally substituted by halogen, oxo, -CN, or -OH,

or R¹³ and R¹⁴ are taken together with the atom or atoms to which they are attached to form a 3- to 6-membered heterocyclyl ring optionally substituted by halogen, oxo, -CN, -OH, or C₁-C₄ alkyl optionally substituted by halogen, oxo, -CN, or -OH; and

each R¹⁵ and R¹⁶ are independently hydrogen, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, or 3- to 6-membered heterocyclyl, each of which is independently optionally substituted by halogen, oxo, -CN, or -OH,

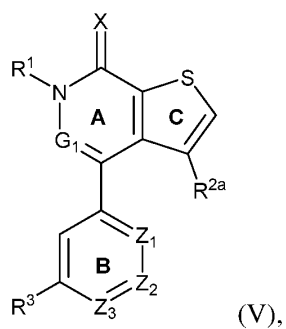
or R¹⁵ and R¹⁶ are taken together with the atoms to which they are attached to form a 3- to 6-membered heterocyclyl ring optionally substituted by halogen, oxo, -CN, -OH, or C₁-C₄ alkyl optionally substituted by halogen, oxo, -CN, or -OH.

[0047] In some embodiments of compound of Formula (IV), or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, M¹ is S. In some embodiments, M¹ is CR^{1a}. In some embodiments, R^{1a} is hydrogen, halogen, or C₁-C₄ alkyl optionally substituted by R¹². In some embodiments, R^{1a} is hydrogen. In some embodiments, R^{1a} is halogen such as fluoro or chloro. In some embodiments, R^{1a} is C₁-C₄ alkyl such as methyl or ethyl. In some embodiments, M¹ is CR^{1a} and R^{1a} is hydrogen.

[0048] In some embodiments of compound of Formula (IV), or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, M² is S. In some embodiments, M² is CR^{2a}. In some embodiments, R^{2a} is hydrogen, halogen, or C₁-C₄ alkyl optionally substituted by R¹². In some embodiments, R^{2a} is hydrogen. In some embodiments, R^{2a} is halogen such as fluoro or chloro. In some embodiments, R^{2a} is C₁-C₄ alkyl such as methyl or ethyl. In some embodiments, M² is CR^{2a} and R^{2a} is hydrogen.

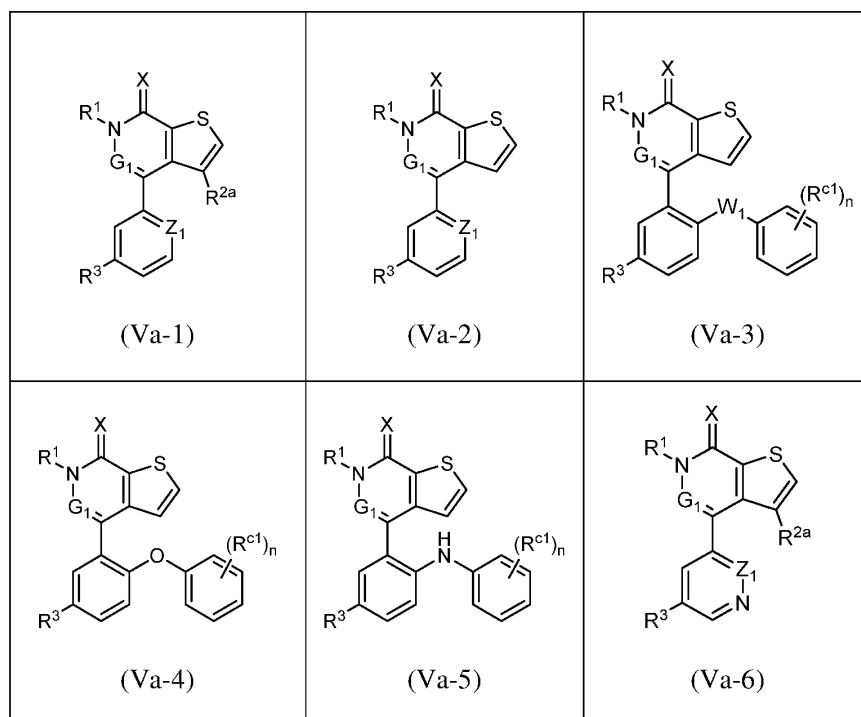
[0049] In some embodiments of a compound of Formula (IV), or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, M¹ is S and M² is CR^{2a}. In some embodiments, M¹ is S and M² is CR^{2a}, wherein R^{2a} is hydrogen. In some embodiments, M¹ is CR^{1a} and M² is S. In some embodiments, M¹ is CR^{1a}, wherein R^{1a} is hydrogen, and M² is S.

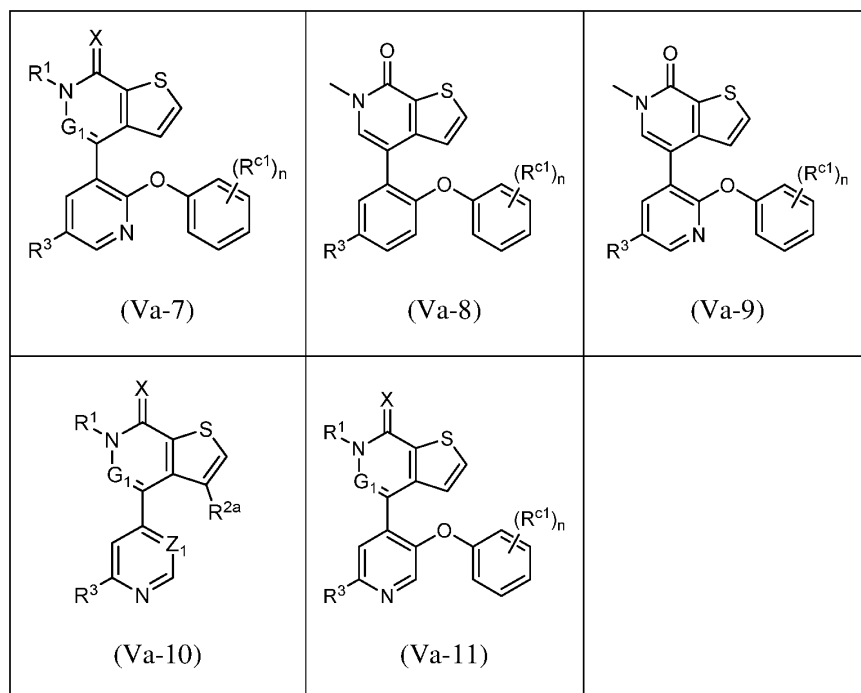
[0050] In some embodiments, provided is a compound of Formula (V),



or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X, G₁, R¹, R³, R^{2a}, Z₁, Z₂, and Z₃ are as detailed herein for Formula (IV).

[0051] In some embodiments, provided is a compound of any one of Formula (Va-1) to (Va-11):

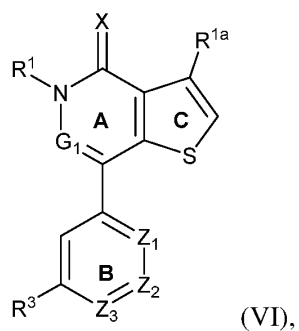




or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X, G₁, R¹, R³, R^{2a}, R^{c1}, Z₁ and W₁ are as detailed herein for Formula (IV), and

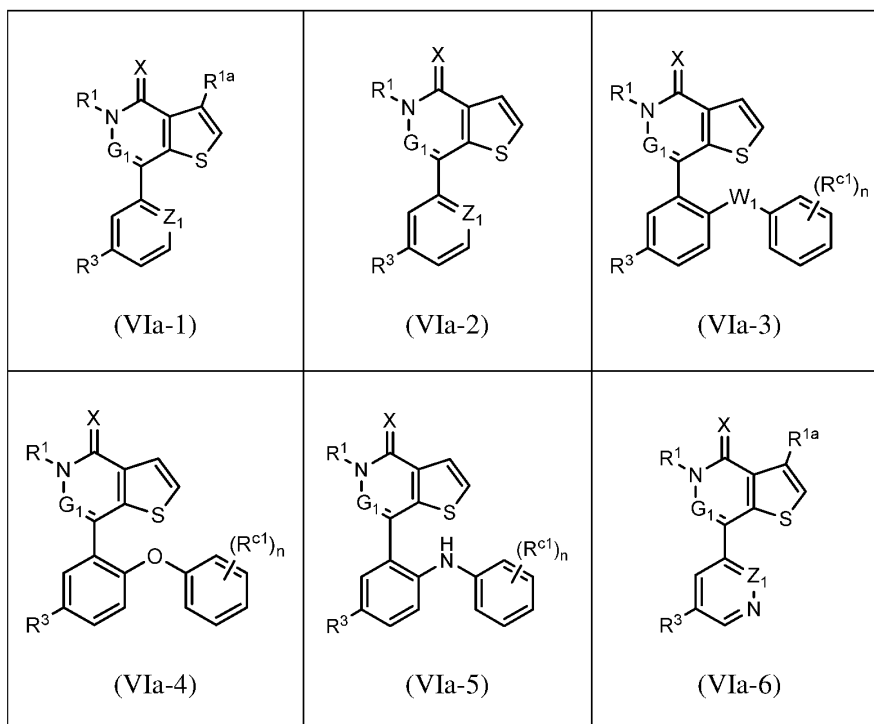
n is 0, 1, 2, 3, 4, or 5. In some embodiments, a compound of Formula (IV) is of Formula (Va-1). In some embodiments, a compound of Formula (IV) is of Formula (Va-2). In some embodiments, a compound of Formula (IV) is of Formula (Va-3). In some embodiments, a compound of Formula (IV) is of Formula (Va-4). In some embodiments, a compound of Formula (IV) is of Formula (Va-5). In some embodiments, a compound of Formula (IV) is of Formula (Va-6). In some embodiments, a compound of Formula (IV) is of Formula (Va-7). In some embodiments, a compound of Formula (IV) is of Formula (Va-8). In some embodiments, a compound of Formula (IV) is of Formula (Va-9). In some embodiments, a compound of Formula (IV) is of Formula (Va-10). In some embodiments, a compound of Formula (IV) is of Formula (Va-11).

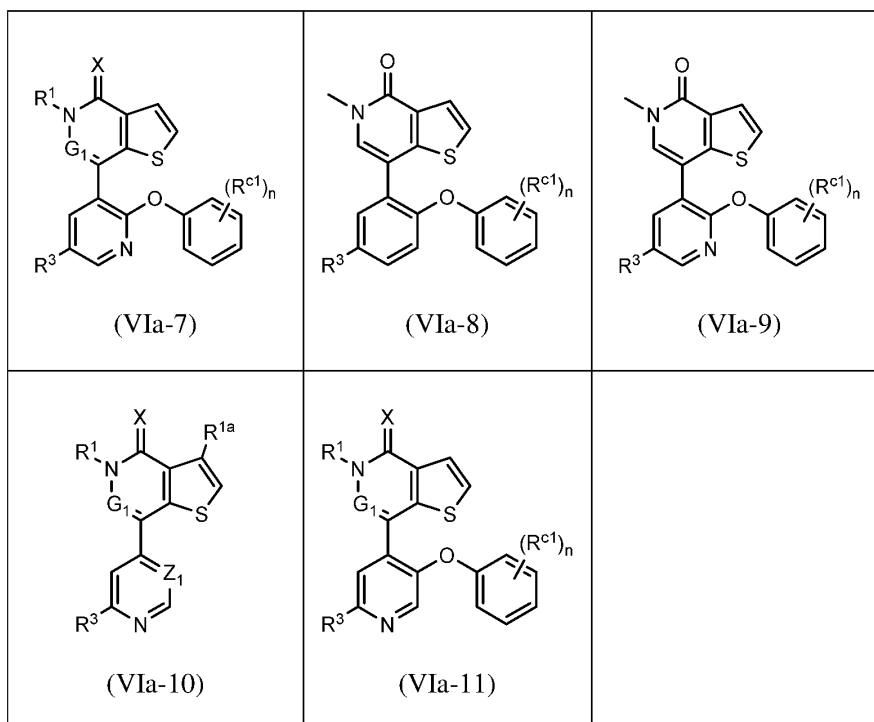
[0052] In some embodiments, provided is a compound of Formula (VI),



or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X, G₁, R¹, R³, R^{1a}, Z₁, Z₂, and Z₃ are as detailed herein for Formula (IV).

[0053] In some embodiments, provided is a compound of any one of Formula (VIa-1) to (VIa-11):





or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X, G₁, R¹, R³, R^{1a}, R^{c1}, Z₁ and W₁ are as detailed herein for Formula (IV), and

n is 0, 1, 2, 3, 4, or 5.

In some embodiments, a compound of Formula (IV) is of Formula (VIa-1). In some embodiments, a compound of Formula (IV) is of Formula (VIa-2). In some embodiments, a compound of Formula (IV) is of Formula (VIa-3). In some embodiments, a compound of Formula (IV) is of Formula (VIa-4). In some embodiments, a compound of Formula (IV) is of Formula (VIa-5). In some embodiments, a compound of Formula (IV) is of Formula (VIa-6). In some embodiments, a compound of Formula (IV) is of Formula (VIa-7). In some embodiments, a compound of Formula (IV) is of Formula (VIa-8). In some embodiments, a compound of Formula (IV) is of Formula (VIa-9). In some embodiments, a compound of Formula (IV) is of Formula (VIa-10). In some embodiments, a compound of Formula (IV) is of Formula (VIa-11).

[0054] Specific values described herein are values for a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt or pharmaceutically acceptable tautomer thereof. It is to be understood that two or more values

may combined. It is to be understood that any variable for a compound of Formula (J) or any related formulae may be combined with any other variable the same as if each and every combination of variables were specifically and individually listed. Thus, it is to be understood that any variable for a compound of Formula (I) or any related formulae may be combined with any other variable for a compound of Formula (I) or any related formulae the same as if each and every combination of variables were specifically and individually listed. Any embodiment provided for Formula (I) is equally applicable to other formulae where applicable, such as Formula (J), the same as if each and every embodiment were specifically and individually listed.

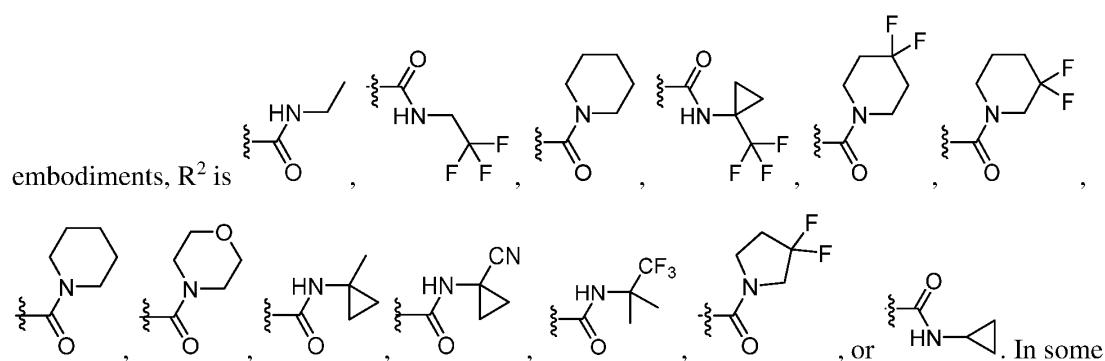
[0055] In some embodiments of a compound of Formula (I), X is O. In some embodiments of a compound of Formula (I), X is S. In some embodiments of a compound of Formula (J) or any related formulae where applicable, X is as provided herein to the same extent as is described for Formula (I).

[0056] In some embodiments of a compound of Formula (I), R¹ is hydrogen, C₁-C₃ alkyl, -(C₁-C₃ alkylene)OH, C₁-C₃ haloalkyl or C₃-C₄ cycloalkyl. In some embodiments of a compound of Formula (I), R¹ is hydrogen. In some embodiments of a compound of Formula (I), R¹ is C₁-C₃ alkyl, such as methyl, ethyl, n-propyl, or isopropyl. In some embodiments of a compound of Formula (I), R¹ is methyl. In some embodiments of a compound of Formula (I), R¹ is C₃-C₄ cycloalkyl, such as cyclopropyl or cyclobutyl. In some embodiments of a compound of Formula (I), R¹ is cyclopropyl. In some embodiments of a compound of Formula (I), R¹ is -(C₁-C₃ alkylene)OH, such as methanol, ethanol, 1-propanol, or 2-propanol. In some embodiments of a compound of Formula (J) or any related formulae where applicable, R¹ is as provided herein to the same extent as is described for Formula (I).

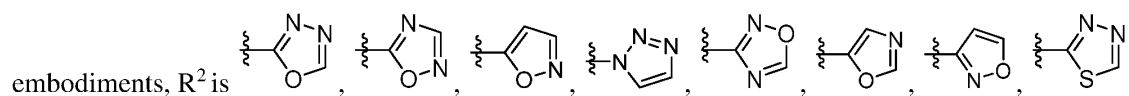
[0057] In some embodiments of a compound of Formula (I), G₁ is N. In some embodiments of a compound of Formula (I), G₁ is CR^a. In some embodiments of a compound of Formula (I), R^a is hydrogen. In some embodiments, R^a is C₁-C₄ alkyl such methyl or ethyl. In some embodiments, G₁ is CR^a and R^a is hydrogen. In some embodiments of a compound of Formula (J) or any related formulae where applicable, G₁ is as provided herein to the same extent as is described for Formula (I).

[0058] In some embodiments of a compound of Formula (J) or any related formulae where applicable, R² is as provided herein to the same extent as is described for Formula (I). In some embodiments of a compound of Formula (I), R² is -OR¹⁰ such as -OCH₃ or -OCF₃. In some

embodiments of a compound of Formula (I), R^2 is cyano. In some embodiments of a compound of Formula (I), R^2 is halogen such as fluoro or chloro. In some embodiments of a compound of Formula (I), R^2 is C_1 - C_4 alkyl such as methyl or ethyl. In some embodiments of a compound of Formula (I), R^2 is C_1 - C_4 haloalkyl such as $-CF_3$. In some embodiments of a compound of Formula (I), R^2 is ethyl. In some embodiments, R^2 is methyl. In some embodiments of a compound of Formula (I), R^2 is $-OCF_3$. In some embodiments, R^2 is $-OCH_3$. In some embodiments, R^2 is $-C(O)NR^{10}R^{11}$, 5- to 10-membered heteroaryl, $-(C_1-C_3 \text{ alkylene})_3$ - to 6-membered heterocyclyl, or C_1 - C_4 alkyl, each of which is independently optionally substituted by R^{12} . In some embodiments, R^2 is $-C(O)NR^{10}R^{11}$ which is optionally substituted by R^{12} . In some embodiments, when R^2 is $-C(O)NR^{10}R^{11}$ which is optionally substituted by R^{12} , then R^3 is C_3 - C_6 cycloalkyl or C_1 - C_4 alkyl substituted by halogen, oxo, $-CN$, or $-OH$. In some embodiments, R^2 is $-C(O)NR^{10}R^{11}$ which is optionally substituted by R^{12} , wherein R^{10} and R^{11} are each independently hydrogen, C_1 - C_4 alkyl, or C_3 - C_6 cycloalkyl, or R^{10} and R^{11} are taken together with the atom or atoms to which they are attached to form a 3- to 6-membered heterocyclyl ring optionally substituted by halogen. In some

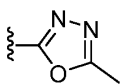
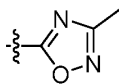
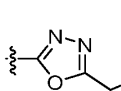
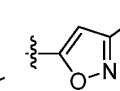
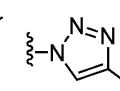
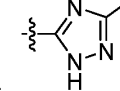
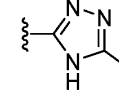
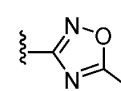
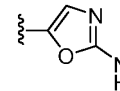
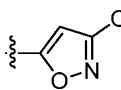
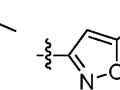
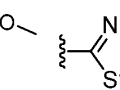
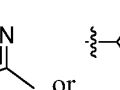


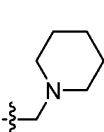
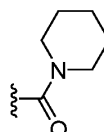
embodiments, R^2 is 5- to 10-membered heteroaryl optionally substituted by R^{12} . In some embodiments, R^2 is 5- to 10-membered heteroaryl which is unsubstituted. In some embodiments, R^2 is a 5- or 6- membered heteroaryl optionally substituted by R^{12} . In some embodiments, R^2 is a 5- or 6- membered heteroaryl which is unsubstituted. In some embodiments, R^2 is a 6-membered heteroaryl optionally substituted by R^{12} . In some embodiments, R^2 is a 6-membered heteroaryl which is unsubstituted. In some embodiments, R^2 is a 5-membered heteroaryl optionally substituted by R^{12} . In some embodiments, R^2 is a 5-membered heteroaryl which is unsubstituted. In some

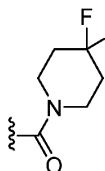
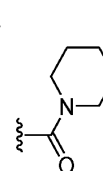
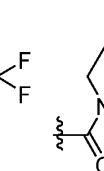
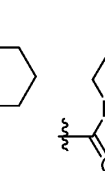
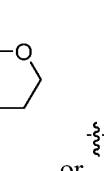


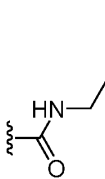
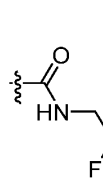
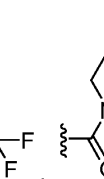
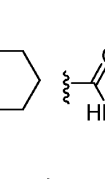
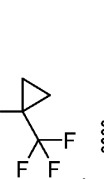
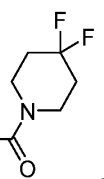
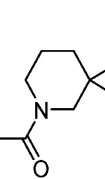
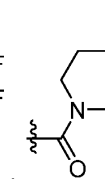
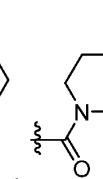
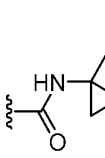
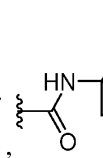
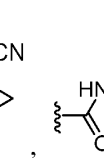
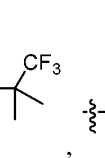
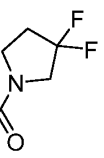
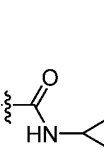
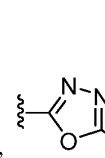
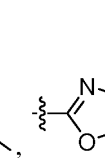
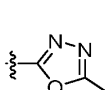
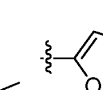
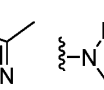
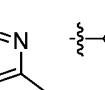
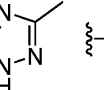
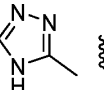
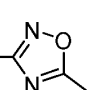
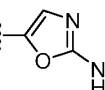
, or , each of which is independently optionally substituted by R¹². In some embodiments,

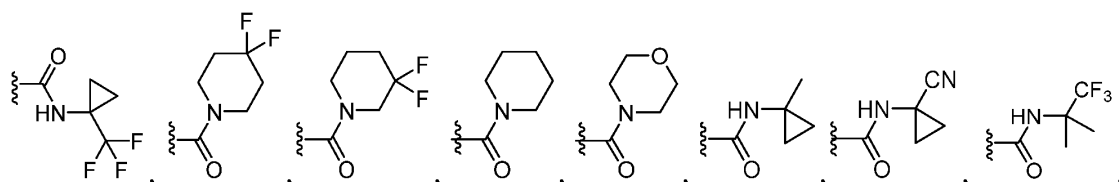
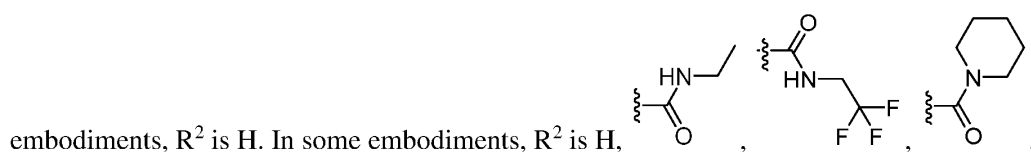
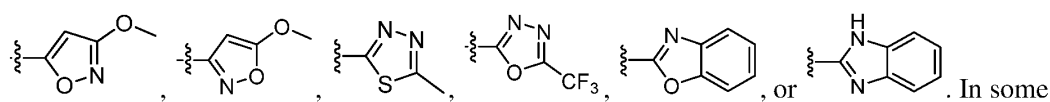
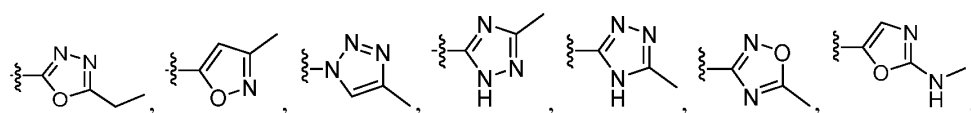
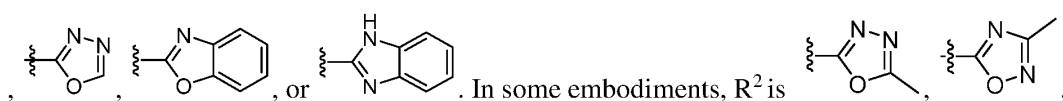
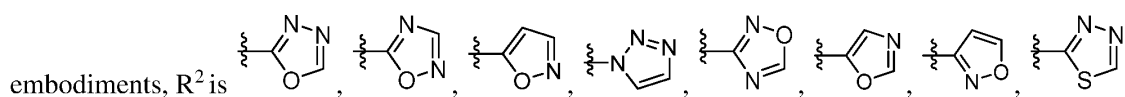
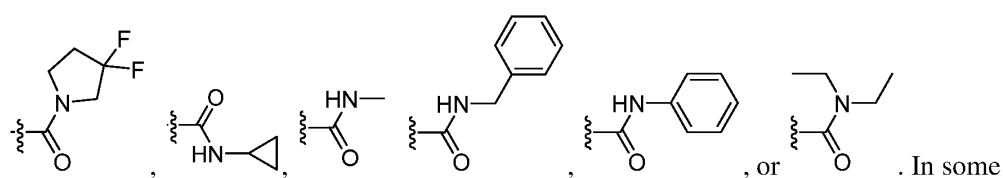
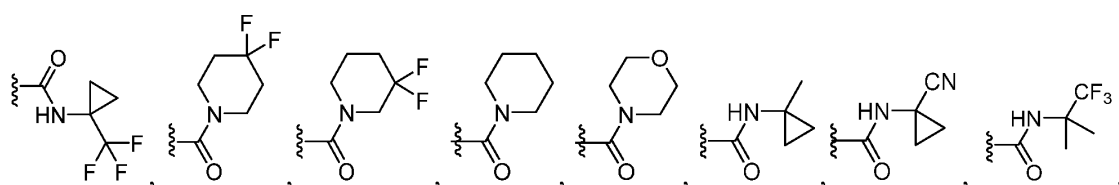
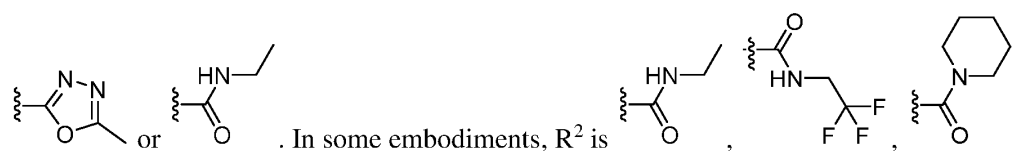
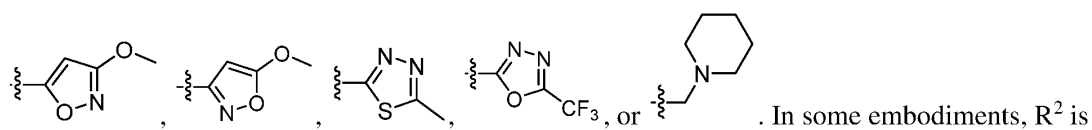
R² is , , , , , , , , or , each of which is optionally substituted by R¹², wherein each R¹² is independently C₁-C₄ haloalkyl,

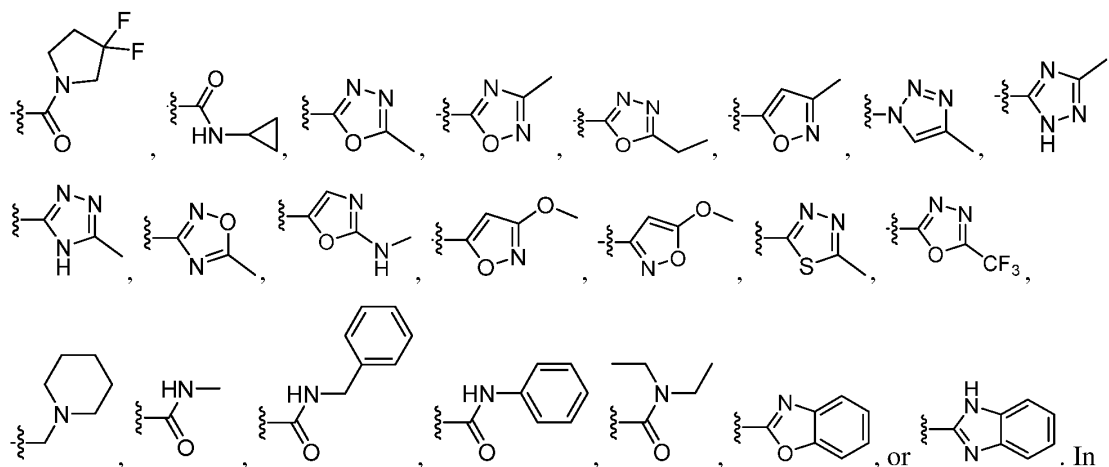
C₁-C₄ alkoxy, -NR¹⁵R¹⁶, or C₁-C₄ alkyl. In some embodiments, R² is , , , , , , , , , , , , or . In some embodiments, R² is C₁-C₄ alkyl optionally substituted by R¹². In some embodiments, R² is -(C₁-C₃ alkylene)3- to 6-membered heterocyclyl optionally substituted by R¹². In some embodiments, R² is -(C₁-C₃ alkylene)3- to 6-

membered heterocyclyl which is unsubstituted. In some embodiments, R² is , ,

, , , , or . In some embodiments, R² is

, , , , , , , , , , , , , , , , , , , , , , , , 

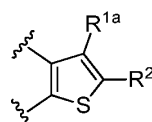
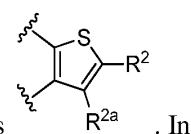




some embodiments of a compound of Formula (J) or any related formulae where applicable, **C** ring is as provided herein to the same extent as is described for Formula (I).

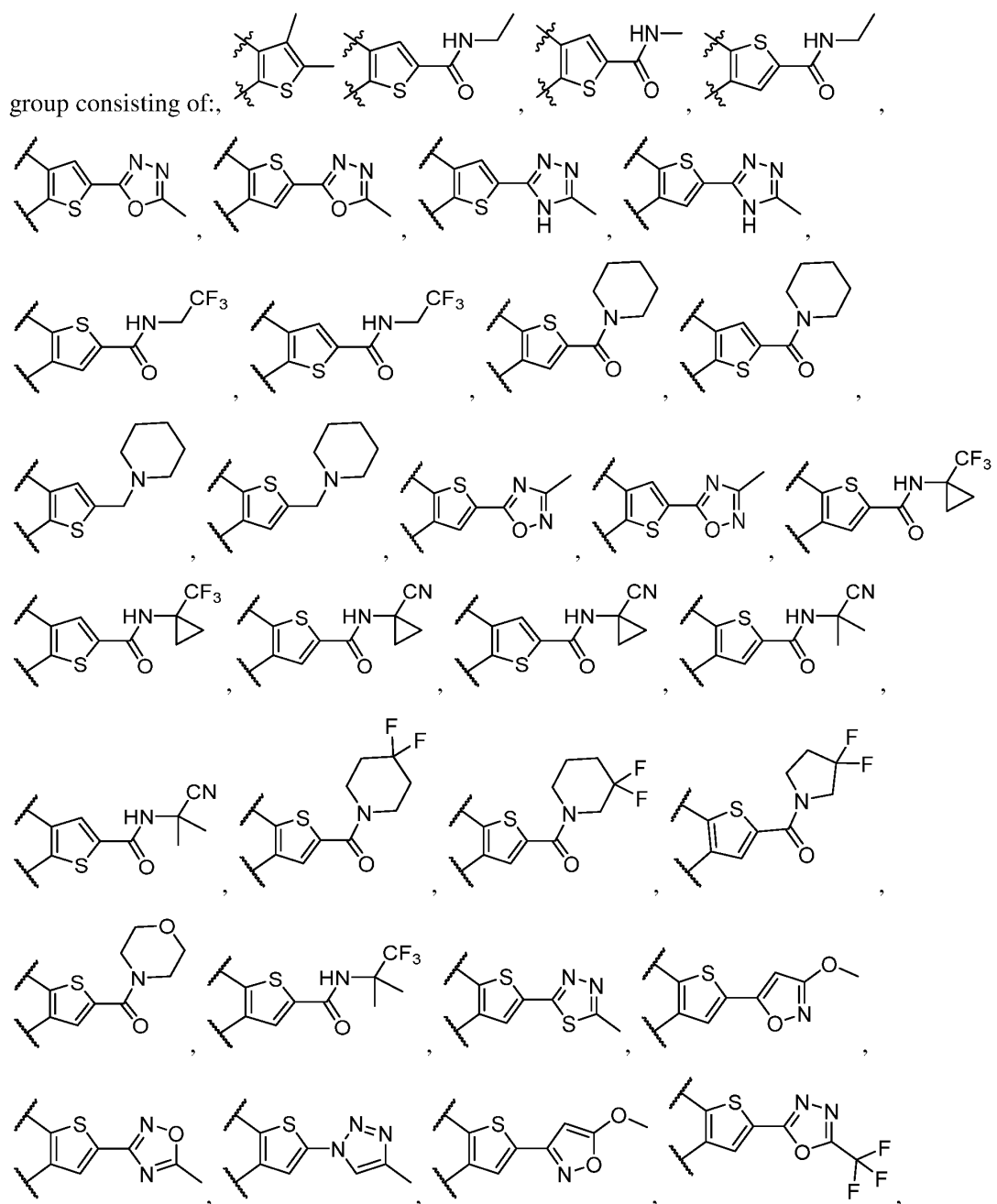
[0059] In some embodiments of a compound of Formula (I), **C** ring is thiophenyl substituted by R^2 , wherein R^2 is halogen, C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, 3- to 6-membered heterocyclyl, C_6 - C_{14} aryl, 5- to 10-membered heteroaryl, cyano, oxo, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy, $-OR^{10}$, $-NR^{10}R^{11}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-NR^{10}C(O)R^{11}$, $-S(O)_2R^{10}$, $-NR^{10}S(O)_2R^{11}$ or $-S(O)_2NR^{10}R^{11}$, each of which is independently optionally substituted by R^{12} . In some embodiments, R^2 is $-C(O)NR^{10}R^{11}$, 5- to 10-membered heteroaryl, or C_1 - C_4 alkyl, each of which is independently optionally substituted by R^{12} . In some embodiments, R^2 is $-C(O)NR^{10}R^{11}$, 5- to 10-membered heteroaryl optionally substituted by $-NR^{15}R^{16}$, OR^{15} , or C_1 - C_4 alkyl optionally substituted by halogen, or C_1 - C_4 alkyl optionally substituted by $-NR^{13}R^{14}$.

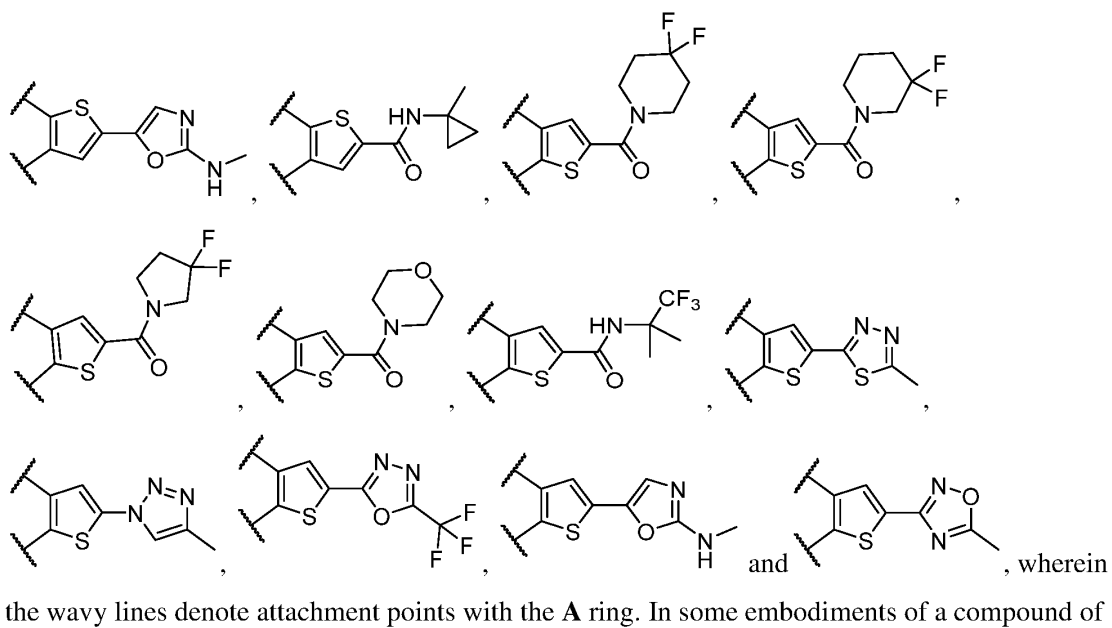
[0060] In some embodiments of a compound of Formula (I), the **C** ring is



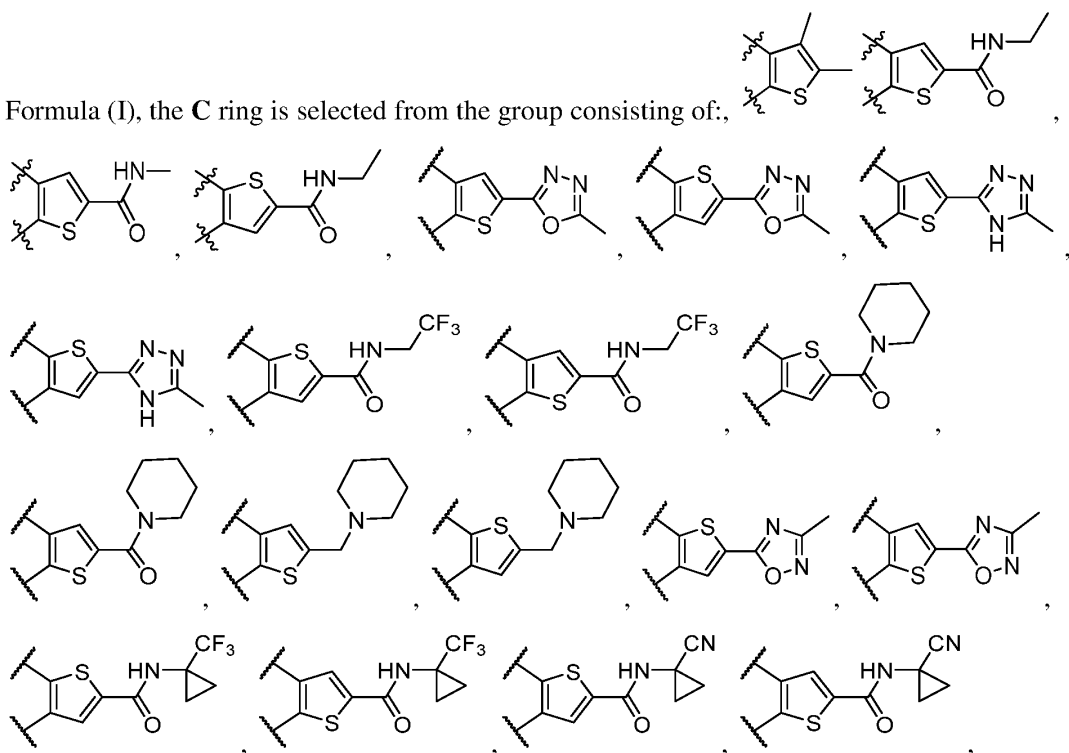
some embodiments of a compound of Formula (I), the **C** ring is , wherein the wavy lines denote attachment points with the **A** ring.

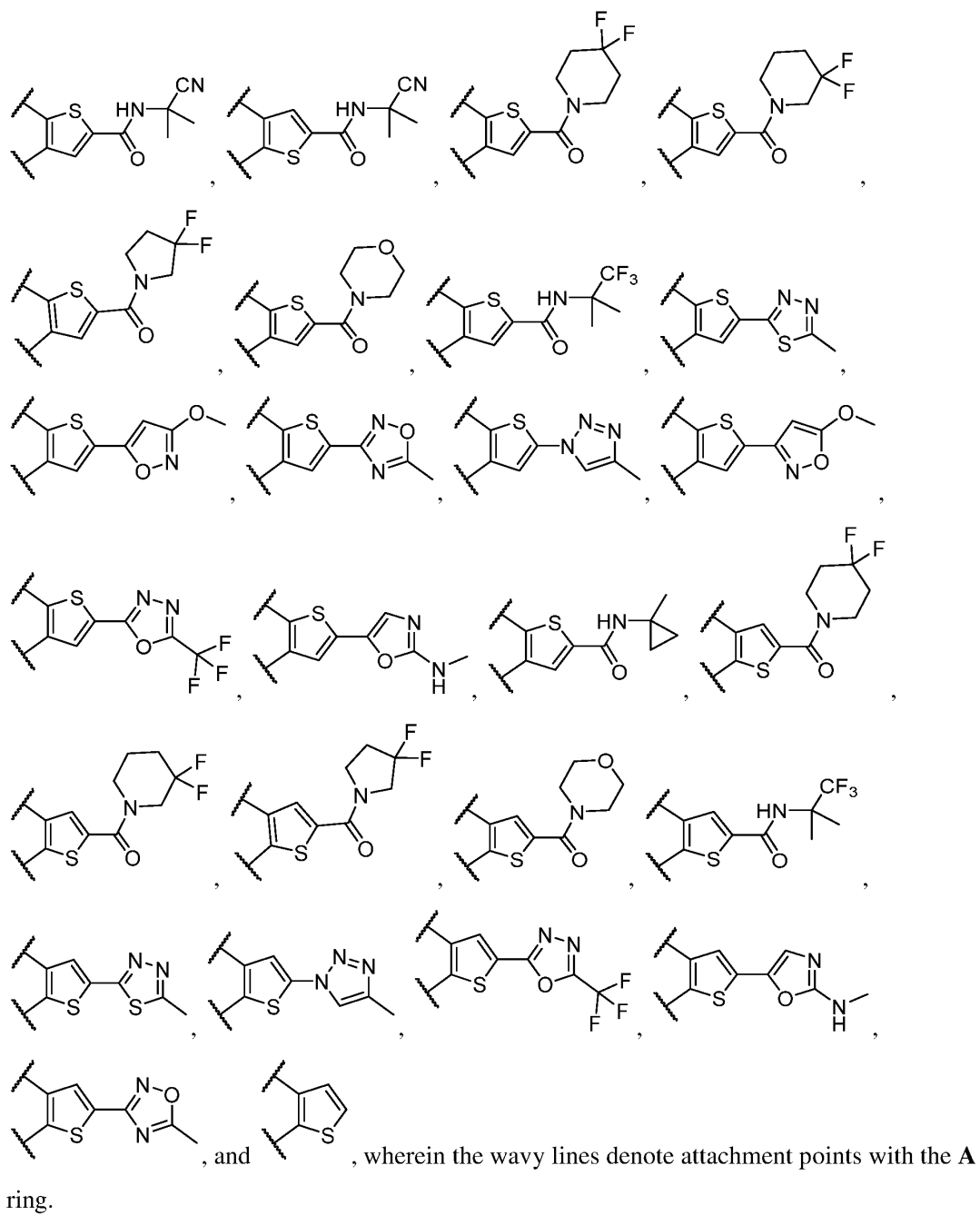
[0061] In some embodiments of a compound of Formula (I), the C ring is selected from the

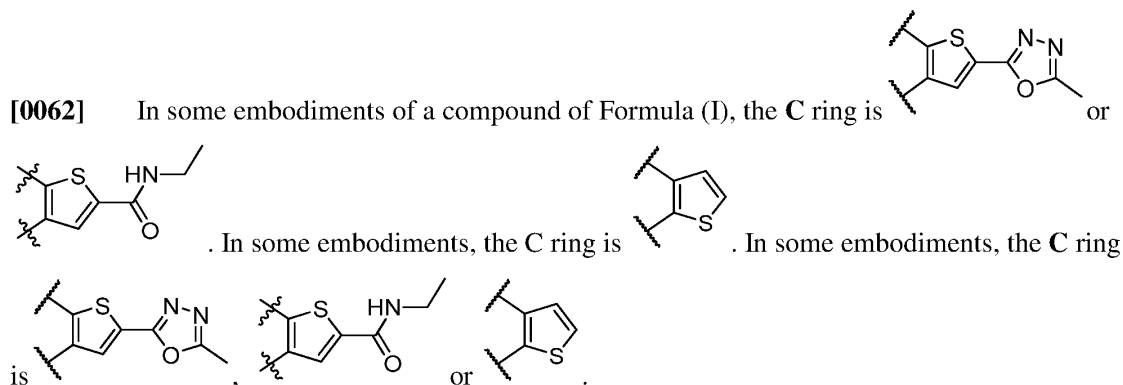




Formula (I), the **C** ring is selected from the group consisting of:





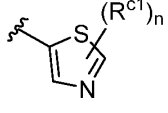
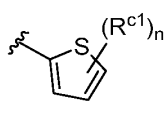
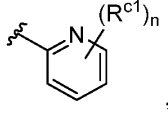
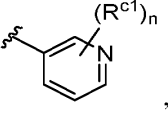
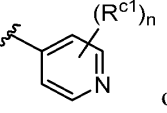


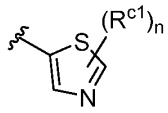
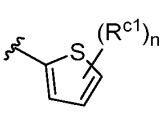
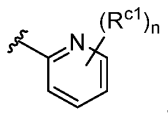
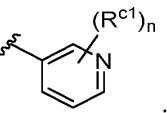
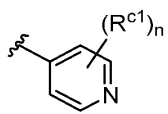
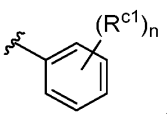
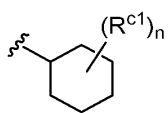
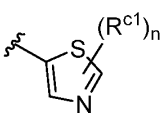
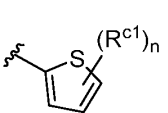
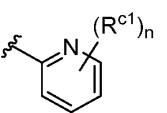
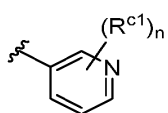
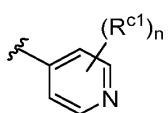
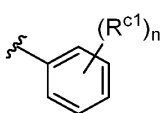
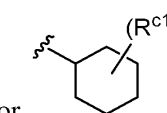
[0063] In some embodiments of a compound of Formula (I), W_1 is O and Z_1 is C-O- R^c . In some embodiments of a compound of Formula (I), W_1 is - NR^{w1} - and Z_1 is C- NR^{w1} - R^c . In some embodiments of a compound of Formula (I), R^{w1} is hydrogen, C₃-C₆ cycloalkyl or C₁-C₄ alkyl optionally substituted by oxo, OH or halogen. In some embodiments of a compound of Formula (I), R^{w1} is hydrogen. In some embodiments of a compound of Formula (I), R^{w1} is C₃-C₆ cycloalkyl. In some embodiments of a compound of Formula (I), R^{w1} is C₁-C₄ alkyl optionally substituted by oxo, OH or halogen. In some embodiments of a compound of Formula (I), R^{w1} is methyl. In some embodiments of a compound of Formula (I), W_1 is -NH- and Z_1 is C-NH- R^c . In some embodiments of a compound of Formula (J) or any related formulae where applicable, W_1 and Z_1 are as provided herein to the same extent as is described for Formula (I).

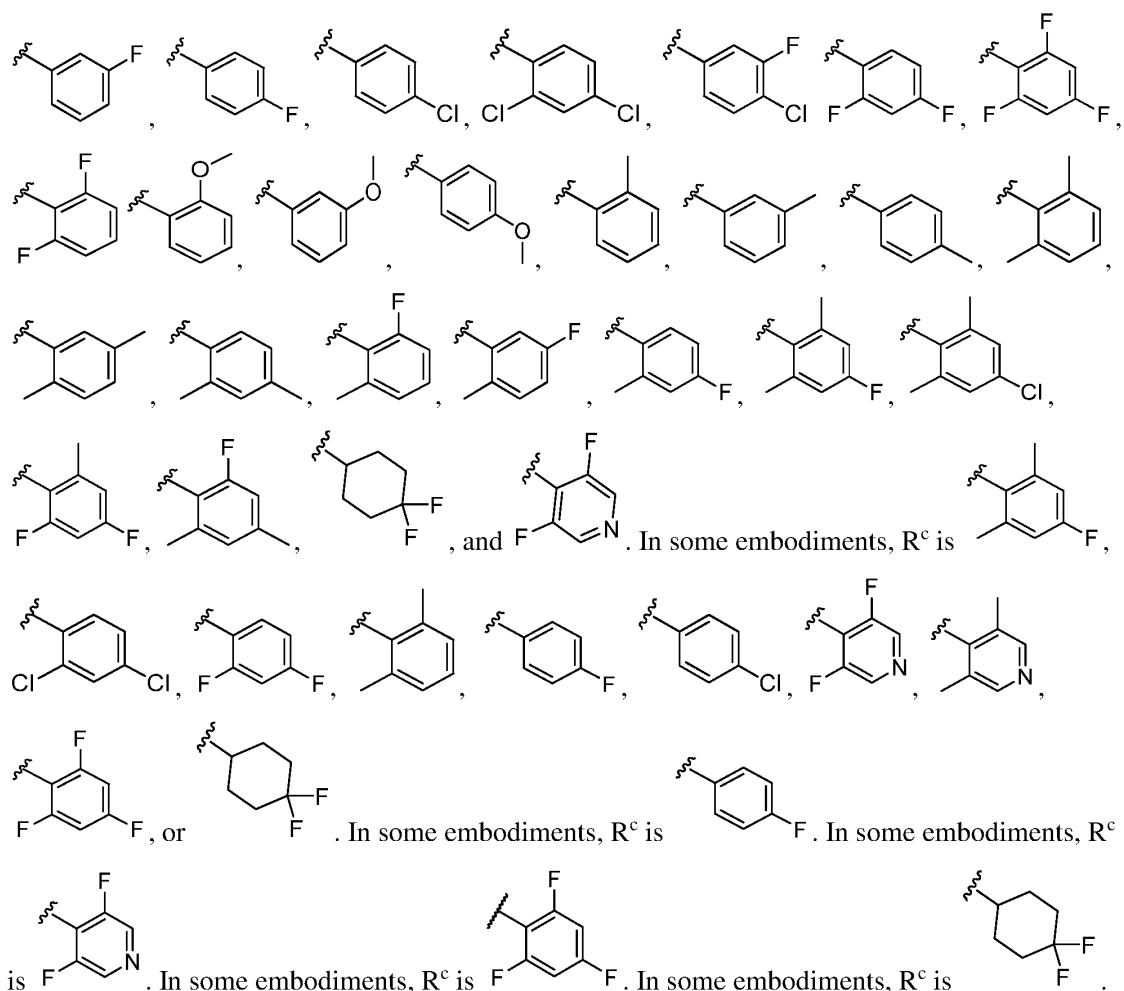
[0064] In some embodiments of a compound of Formula (I), R^c is C₆-C₁₄ aryl or 5- or 6-membered heteroaryl, wherein the C₆-C₁₄ aryl and 5- or 6-membered heteroaryl of R^c are independently optionally substituted by R^{c1} . In some embodiments, each R^{c1} is independently halogen or C₁-C₄ alkyl. In some embodiments of a compound of Formula (I), R^c is C₆-C₁₄ aryl optionally substituted by R^{c1} . In some embodiments of a compound of Formula (I), R^c is C₆-C₁₄ aryl which is unsubstituted. In some embodiments of a compound of Formula (I), R^c is phenyl optionally substituted by R^{c1} . In some embodiments, R^c is phenyl which is unsubstituted. In some embodiments, R^c is phenyl optionally substituted by R^{c1} , wherein each R^{c1} is independently halogen or C₁-C₄ alkyl. In some embodiments, R^c is phenyl optionally substituted by R^{c1} , wherein each R^{c1} is independently methyl or fluoro. In some embodiments of a compound of Formula (I), R^c is 5- or 6-membered heteroaryl optionally substituted by R^{c1} . In some embodiments, R^c is 5- or 6-membered heteroaryl which is unsubstituted, such as pyridinyl, pyrazinyl, pyridazinyl, primidinyl, triazinyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, oxazolyl, thiazolyl,

thiazolyl, or furanyl, each of which is unsubstituted. In some embodiments, R^c is 5- or 6-membered heteroaryl optionally substituted by R^{c1} , such as pyridinyl, pyrazinyl, pyridazinyl, primidinyl, triazinyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, oxazolyl, thiazolyl, thiazolyl, or furanyl, each of which is independently optionally substituted by R^{c1} . In some embodiments of a compound of Formula (J) or any related formulae where applicable, R^c is as provided herein to the same extent as is described for Formula (I).

[0065] In some embodiments, R^c is C_3 - C_6 cycloalkyl optionally substituted by R^{c1} , wherein each R^{c1} is independently halogen or C_1 - C_4 alkyl. In some embodiments, each R^{c1} is halogen. In some embodiments, R^c is C_6 - C_{14} aryl, 5- to 6-membered heteroaryl, or C_3 - C_6 cycloalkyl, wherein each R^c is optionally substituted by R^{c1} .

[0066] In some embodiments of a compound of Formula (I), R^c is , , , , or , wherein the wavy lines denote attachment points and n is 0, 1, 2, 3, 4, or 5. In some embodiments, R^c is

. In some embodiments, R^c is . In some embodiments, R^c is . In some embodiments, R^c is . In some embodiments, R^c is . In some embodiments, R^c is . In some embodiments, R^c is . In some embodiments, R^c is , , , , , , or . In some embodiments, each R^{c1} is independently halogen or C_1 - C_4 alkyl.



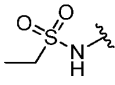
[0068] In some embodiments of a compound of Formula (I), Z₂ is N. In some embodiments of a compound of Formula (I), Z₂ is C-W₂-R^d. In some embodiments of a compound of Formula (I), W₂ is -O-. In some embodiments of a compound of Formula (I), W₂ is a bond. In some embodiments of a compound of Formula (I), W₂ is -NR^{w2}-. In some embodiments of a compound of Formula (I), R^{w2} is hydrogen or C₁-C₄ alkyl optionally substituted by oxo, OH or halogen. In some embodiments of a compound of Formula (I), W₂ is -NR^{w2}- and R^{w2} is hydrogen. In some embodiments, R^{w2} is C₁-C₄ alkyl optionally substituted by oxo, OH or halogen. In some embodiments of a compound of Formula (I), R^{w2} is methyl. In some embodiments of a compound of Formula (I), R^{w2} is C₃-C₆ cycloalkyl. In some embodiments of a compound of Formula (I), W₂ is -NR^{w2}- and R^{w2} is -CH₃-. In some embodiments of a compound of Formula (I), W₂ is -NR^{w2}- and

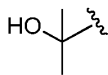
R^{w2} is hydrogen. In some embodiments of a compound of Formula (J) or any related formulae where applicable, Z_2 is provided herein to the same extent as is described for Formula (I).

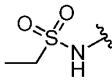
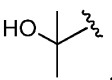
[0069] In some embodiments of a compound of Formula (I), R^d is hydrogen. In some embodiments of a compound of Formula (I), R^d is C_1 - C_4 alkyl, such as methyl, ethyl, n-propyl, or isopropyl. In some embodiments, R^d is methyl. In some embodiments, Z_2 is $C-W_2-R^d$, wherein W^2 is a bond and R^d is hydrogen.

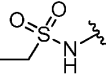
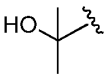
[0070] In some embodiments of a compound of Formula (I), Z_3 is N. In some embodiments of a compound of Formula (I), Z_3 is $C-R^e$. In some embodiments of a compound of Formula (I), R^e is hydrogen. In some embodiments of a compound of Formula (I), R^e is halogen, such as fluoro, chloro, bromo, or iodo. In some embodiments of a compound of Formula (I), R^e is cyano. In some embodiments, R^e is 3- to 6-membered heterocyclyl, such as tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl. In some embodiments, R^e is C_1 - C_4 alkyl such as methyl, ethyl, n-propyl, or isopropyl. In some embodiments, Z_3 is $C-R^e$ and R^e is hydrogen. In some embodiments of a compound of Formula (J) or any related formulae where applicable, Z_3 is provided herein to the same extent as is described for Formula (I).

[0071] In some embodiments of a compound of Formula (I), R^3 is $-(CH_2)_mNR^{13}S(O)_2R^{14}$ or C_1 - C_4 alkyl substituted by halogen, oxo, -CN or -OH. In some embodiments, R^3 is $-(CH_2)_mNR^{13}S(O)_2R^{14}$. In some embodiments of a compound of Formula (I), m is 0. In some embodiments of a compound of Formula (I), m is 1. In some embodiments of a compound of Formula (I), m is 2. In some embodiments of a compound of Formula (I), m is 3. In some embodiments, R^3 is $-(CH_2)_mNR^{13}S(O)_2R^{14}$, wherein m is 0. In some embodiments, R^3 is $-(CH_2)_mNR^{13}S(O)_2R^{14}$, wherein m is 0 and R^{13} and R^{14} are each independently hydrogen or C_1 - C_4 alkyl. In some embodiments, R^3 is $-(CH_2)_mNR^{13}S(O)_2R^{14}$, wherein m is 0, R^{13} is hydrogen, and R^{14}

is C_1 - C_4 alkyl such as methyl, ethyl, n-propyl, or isopropyl. In some embodiments, R^3 is . In some embodiments of a compound of Formula (I), R^3 is C_1 - C_4 alkyl optionally substituted by halogen, oxo, -CN or -OH. In some embodiments of a compound of Formula (I), R^3 is C_1 - C_4 alkyl

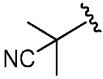
substituted by -OH. In some embodiments of a compound of Formula (I), R^3 is . In some

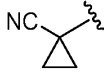
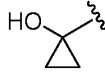
embodiments of a compound of Formula (I), R^3 is  or . In some embodiments,

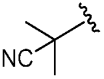
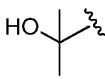
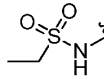
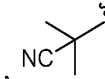
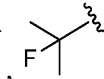
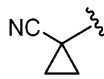
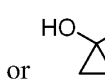
R^3 is . In some embodiments, R^3 is , wherein the wavy lines denote attachment points. In some embodiments of a compound of Formula (J) or any related formulae where applicable, R^3 is provided herein to the same extent as is described for Formula (I).

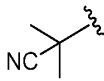
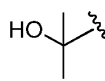
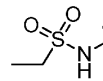
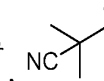
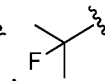
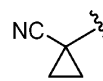
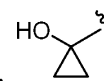
[0072] In some embodiments of a compound of Formula (J) or any related formulae where

applicable such as compound of Formula (I), R^3 is . In some embodiments, R^3 is C₃-C₆ cycloalkyl optionally substituted by halogen, oxo, -CN, or -OH. In some embodiments, R^3 is C₃-C₆ cycloalkyl optionally substituted by -CN or -OH. In some embodiments, R^3 is unsubstituted C₃-C₆

cycloalkyl. In some embodiments, R^3 is . In some embodiments, R^3 is . In some

embodiments, R^3 is . In some embodiments, R^3 is . In some embodiments, R^3 is

, , , , , , or . In some

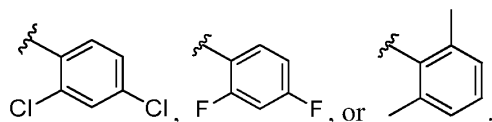
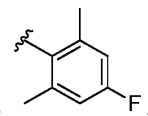
embodiments, R^3 is , , , , , , , or

, wherein the wave lines denote attachments points.

[0073] In some embodiments of a compound of Formula (J) or any related formulae where applicable such as a compound of Formula (I), the compound has one or more of the following features:

- (I) X is O;
- (II) R^1 is C₁-C₃ alkyl, such as methyl;
- (III) G_1 is CR^a, wherein R^a is hydrogen;
- (IV) Z₂ is CH;
- (V) Z₃ is CH;
- (VI) R^2 is

(VIII) Z₁ is C-O-R^c, wherein R^c is phenyl optionally substituted by R^{c1}, such as



In some embodiments, (I) applies. In some embodiments, (II) applies. In some embodiments, (III) applies. In some embodiments, (IV) applies. In some embodiments, (V) applies. In some embodiments, (VI) applies. In some embodiments, (VII) applies. In some embodiments, (VIII) applies. In some embodiments, (1) applies. In some embodiments, (2) applies. In some embodiments, (3) applies. In some embodiments, (4) applies. In some embodiments, (5) applies. In some embodiments, (I), (II), (III), (IV), (V), (VI), (VII), and (VIII) apply. In some embodiments, (I), (II), (III), (IV), (V), and (1) apply. In some embodiments, (I), (II), (III), (IV), (V), and (4) apply. In some embodiments, (I), (II), (III), (IV), (V), and (5) apply. In some embodiments, (I), (II), (III), (IV), (V), and (VIII) apply. In some embodiments, (I), (II), (III), (IV), (V), and (2) apply. In some embodiments, (I), (II), (III), (IV), (V), and (3) apply. In some embodiments, (I), (II), (III), (IV), (V), (1), (VII), and (VIII) apply. In some embodiments, (I), (II), (III), (IV), (V), (2), (VII), and (VIII) apply. In some embodiments, (I), (II), (III), (IV), (V), (3), (VII), and (VIII) apply. In some embodiments, (I), (II), (III), (IV), (V), (VI), (4), and (VIII) apply. In some embodiments, (I), (II), (III), (IV), (V), (VI), (5), and (VIII) apply. In some embodiments, (VIII) and (4) apply. In some embodiments, (VIII) and (5) apply. In some embodiments, (1) and (VIII) apply. In some embodiments, (2) and (VIII) apply. In some embodiments, (3) and (VIII) apply. In some embodiments, (1) and (4) apply. In some embodiments, (1) and (5) apply. In some embodiments, (2) and (4) apply. In some embodiments, (2) and (5) apply. In some embodiments, (3) and (4) apply. In some embodiments, (3) and (5) apply.

[0074] In some embodiments of a compound of Formula (J) or any related formulae where applicable such as a compound of Formula (I), the compound has one or more of the following features:

(I-1) X is O;

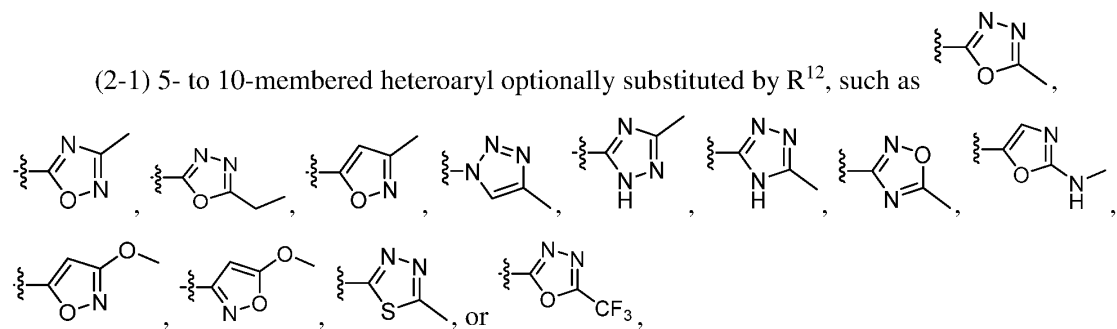
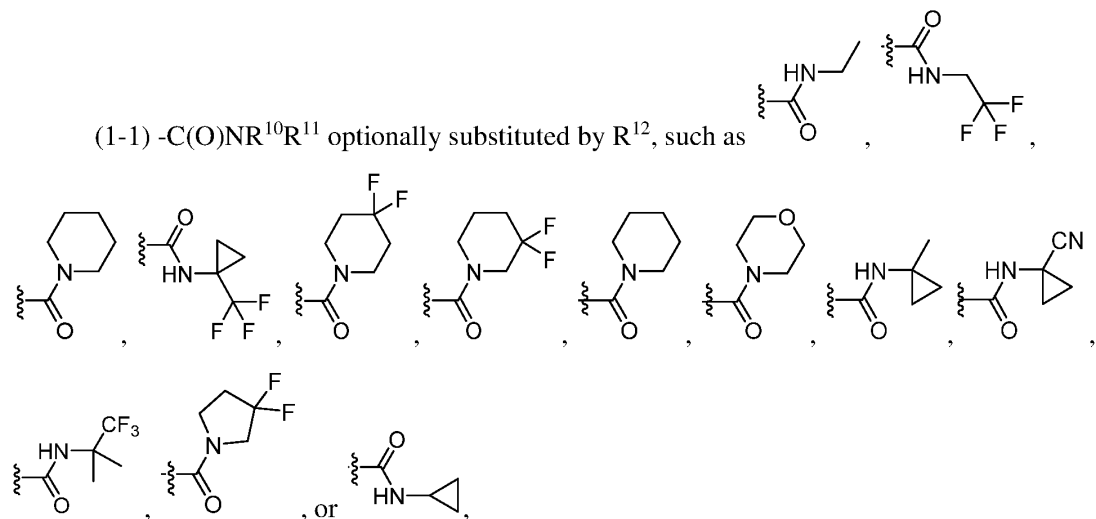
(II-1) R¹ is C₁-C₃ alkyl, such as methyl;

(III-1) G₁ is CR^a, wherein R^a is hydrogen;

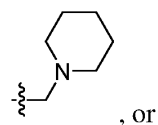
(IV-1) Z_2 is CH;

(V-1) Z_3 is CH;

(VI-1) R^2 is

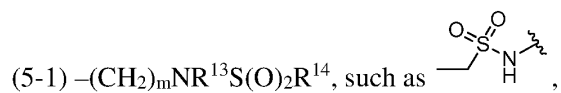


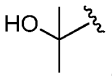
(3-1) $-(C_1-C_3 \text{ alkylene})$ 3- to 6-membered heterocyclyl optionally substituted by R^{12} , such as



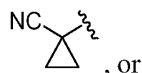
(4-1) hydrogen;

(VII) R^3 is

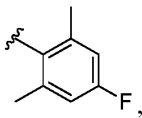


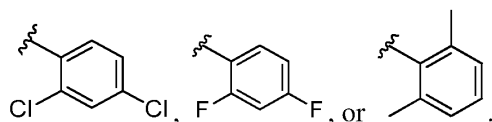
(6-1) C₁-C₄ alkyl substituted by -OH, such as ,

(7-1) C₃-C₆ cycloalkyl optionally substituted by halogen, oxo, -CN, or -OH, such as



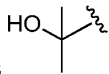
(8-1) C₂-C₆ alkenyl; and

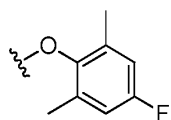
(VIII-1) Z₁ is C-O-R^c, wherein R^c is phenyl optionally substituted by R^{cl}, such as ,



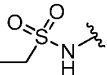
[0075] In some embodiments, (I-1) applies. In some embodiments, (II-1) applies. In some embodiments, (III-1) applies. In some embodiments, (IV-1) applies. In some embodiments, (V-1) applies. In some embodiments, (VI-1) applies. In some embodiments, (VII-1) applies. In some embodiments, (VIII-1) applies. In some embodiments, (1-1) applies. In some embodiments, (2-1) applies. In some embodiments, (3-1) applies. In some embodiments, (4-1) applies. In some embodiments, (5-1) applies. In some embodiments, (6-1) applies. In some embodiments, (7-1) applies. In some embodiments, (8-1) applies. In some embodiments, (I-1), (II-1), (III-1), (IV-1), (V-1), (VI-1), (VII-1), and (VIII-1) apply. In some embodiments, (I-1), (II-1), (III-1), (IV-1), (V-1), (VII-1) and (VIII-1) apply. In some embodiments, (I-1), (II-1), (III-1), (IV-1), (V-1), and (VIII-1) apply. In some embodiments, (I-1), (II-1), (III-1), (IV-1), (V-1), and (1-1) apply. In some embodiments, (I-1), (II-1), (III-1), (IV-1), (V-1), and (5-1) apply. In some embodiments, (I-1), (II-1), (III-1), (IV-1), (V-1), and (6-1) apply. In some embodiments, (I-1), (II-1), (III-1), (IV-1), (V-1), and (VIII-1) apply. In some embodiments, (I-1), (II-1), (III-1), (IV-1), (V-1), and (2-1) apply. In some embodiments, (I-1), (II-1), (III-1), (IV-1), (V-1), and (3-1) apply. In some embodiments, (I-1), (II-1), (III-1), (IV-1), (V-1), (1-1), (VII-1), and (VIII-1) apply. In some embodiments, (I-1), (II-1), (III-1), (IV-1), (V-1), (2-1), (VII-1), and (VIII-1) apply. In some embodiments, (I-1), (II-1), (III-1), (IV-1), (V-1), (3-1), (VII-1), and (VIII-1) apply. In some embodiments, (I-1), (II-1), (III-1), (IV-1), (V-1), (VI-1), (5-1), and (VIII-1) apply. In some embodiments, (I-1), (II-1), (III-1), (IV-1), (V-1),

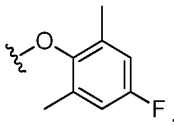
(VI-1), (6-1), and (VIII-1) apply. In some embodiments, (VIII-1) and (5-1) apply. In some embodiments, (VIII-1) and (6-1) apply. In some embodiments, (1-1) and (VIII-1) apply. In some embodiments, (2-1) and (VIII-1) apply. In some embodiments, (3-1) and (VIII-1) apply. In some embodiments, (1-1) and (5-1) apply. In some embodiments, (1-1) and (6-1) apply. In some embodiments, (2-1) and (5-1) apply. In some embodiments, (2-1) and (6-1) apply. In some embodiments, (3-1) and (5-1) apply. In some embodiments, (3-1) and (6-1) apply. In some embodiments, (I-1), (II-1), (III-1), (IV-1), (V-1), and (7-1) apply. In some embodiments, (I-1), (II-1), (III-1), (IV-1), (V-1), and (6-1) apply. In some embodiments, (I-1), (II-1), (III-1), (IV-1), (V-1), (1-1), and (VIII-1) apply. In some embodiments, (I-1), (II-1), (III-1), (IV-1), (V-1), (7-1), and (VIII-1) apply. In some embodiments, (I-1), (II-1), (III-1), (IV-1), (V-1), (6-1), and (VIII-1) apply. In some embodiments, (1-1) and (VIII-1) apply. In some embodiments, (7-1) and (VIII-1) apply. In some embodiments, (6-1) and (VIII-1) apply. In some embodiments, (I-1), (VII-1), and (8-1) apply. It is to be understood that any variable for a compound of Formula (J) or any related formulae where applicable such as a compound of formula (I) may be combined with any other variable for a compound of Formula (J) or any related formulae where applicable such as a compound of Formula (I) the same as if each and every combination of variables were specifically and individually listed. For example, it is understood that each description of R^3 may be combined with each description of other variation on **B** ring (Z_1, Z_2, Z_3) the same as if each and every combination were specifically and individually listed. It is similarly understood that each description of R^3 may be combined with each description of every variation on **A** ring (X, R^1, G_1) and/or each description of every variation on **C** ring the same as if each and every combination were specifically and individually listed. It is also understood that each description of every variation on **B** ring (R^3, Z_1, Z_2, Z_3) may be combined with each description of every variation on **A** ring (X, R^1, G_1) the same as if each and every combination were specifically and individually listed. It is similarly understood that each description of every variation on **B** ring (R^3, Z_1, Z_2, Z_3) may be combined with each description of every variation on **C** ring (M^1, M^2, R^2) the same as if each and every combination were specifically and individually listed. For example, in one aspect, it is understood that each description of every variation on **B** ring may be combined in one aspect with a variation of **A** ring in which X is O; G_1 is CH; and R^1 is methyl. In one such variation, **B** ring is as defined in any variation herein, **A** ring is with the variables such as X is O; G_1 is hydrogen; R^1 is methyl; and **C** ring is substituted thiophenyl. As another example, in another aspect, provided is a compound, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the

foregoing, wherein R^3 is ; Z_2 and Z_3 are CH; and Z_1 is C- W_1 - R^c , wherein - W_1 - R^c is



. As another example, provided is a compound, or a tautomer or isomer thereof, or a

pharmaceutically acceptable salt of any of the foregoing, wherein R^3 is ; Z_2 and Z_3 are

CH; and Z_1 is C- W_1 - R^c , wherein - W_1 - R^c is .

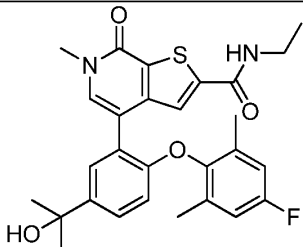
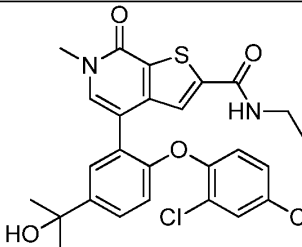
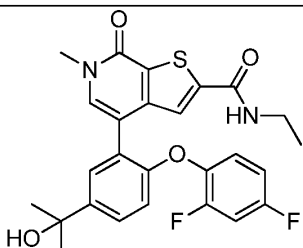
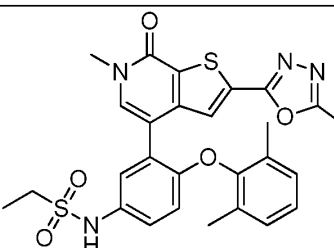
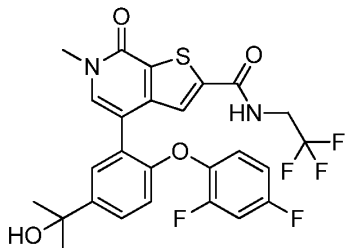
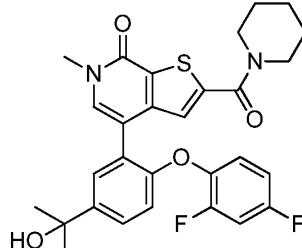
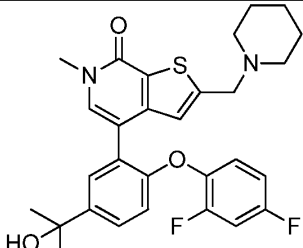
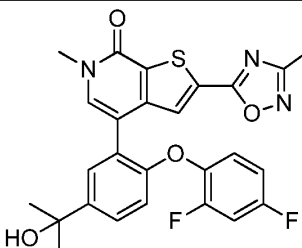
[0076] Also provided are salts of compounds referred to herein, such as pharmaceutically acceptable salts. The invention also includes any or all of the stereochemical forms, including any enantiomeric or diastereomeric forms, and any tautomers or other forms of the compounds described.

[0077] A compound as detailed herein may in one aspect be in a purified form and compositions comprising a compound in purified forms are detailed herein. Compositions comprising a compound as detailed herein or a salt thereof are provided, such as compositions of substantially pure compounds. In some embodiments, a composition containing a compound as detailed herein or a salt thereof is in substantially pure form. Unless otherwise stated, “substantially pure” intends a composition that contains no more than 35 % impurity, wherein the impurity denotes a compound other than the compound comprising the majority of the composition or a salt thereof. In some embodiments, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains no more than 25%, 20%, 15%, 10%, or 5% impurity. In some embodiments, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains or no more than 3%, 2%, 1% or 0.5% impurity.

[0078] Representative compounds are listed in Tables 1 and 2. It is understood that individual enantiomers and diastereomers are included in the tables below by Compound No. and their corresponding structures can be readily determined therefrom.

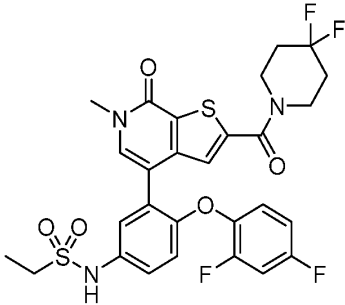
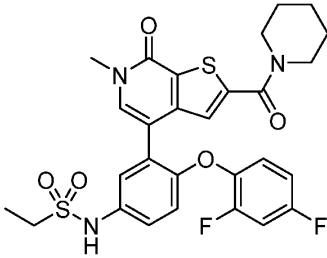
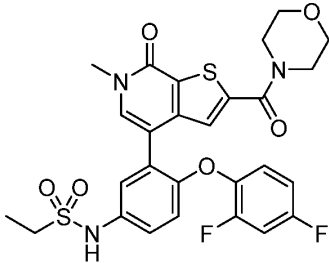
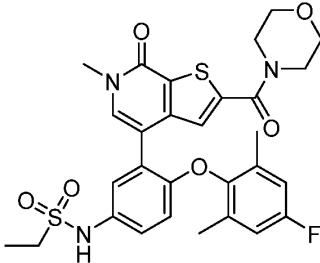
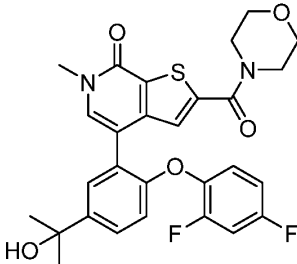
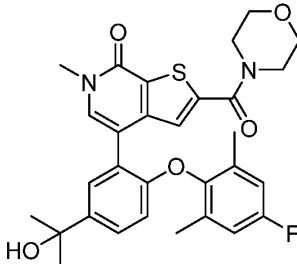
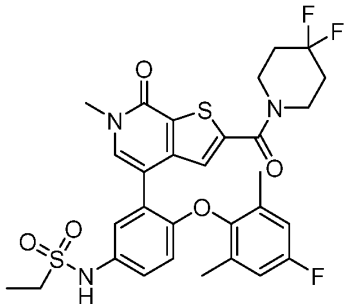
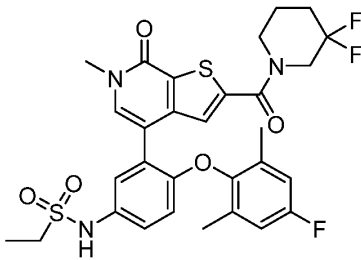
Table 1

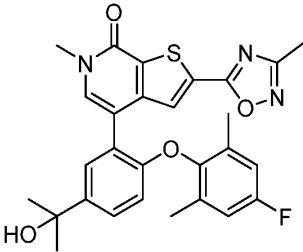
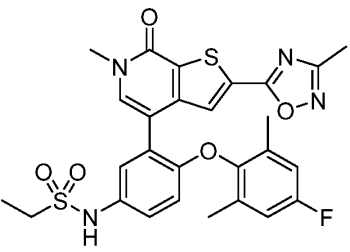
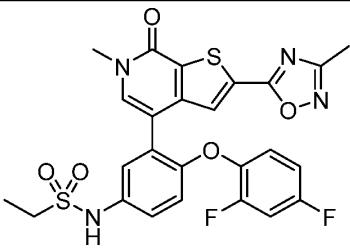
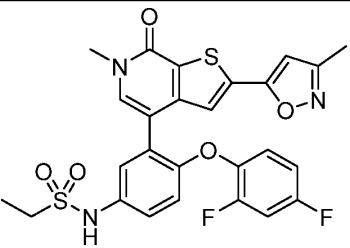
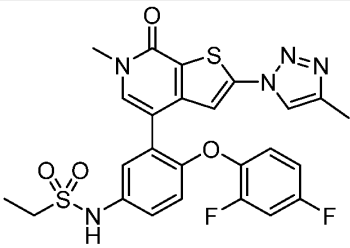
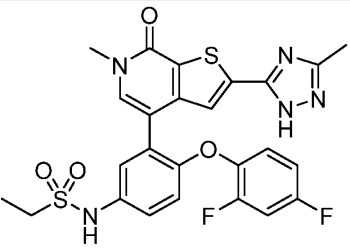
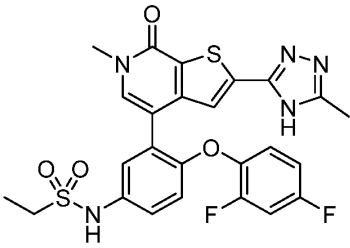
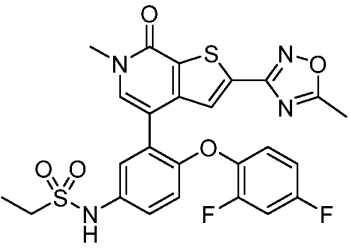
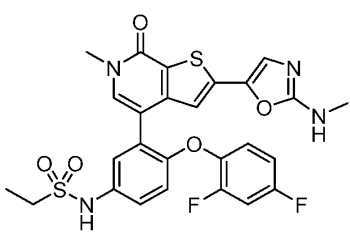
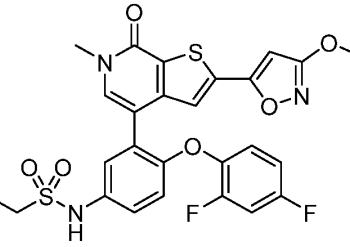
Representative Compounds

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7		8	

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11		12	
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Com. No.	Structure	Com. No.	Structure
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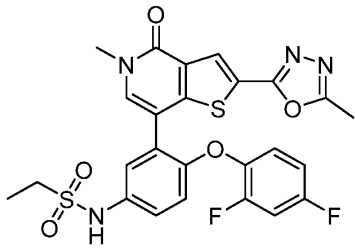
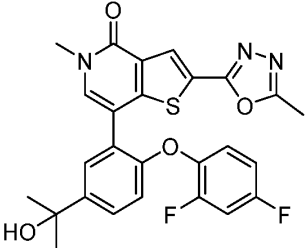
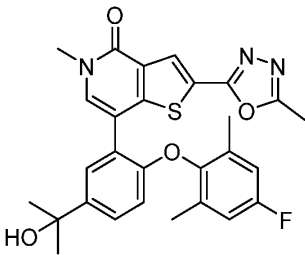
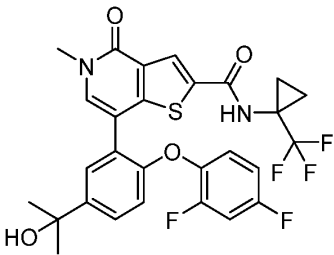
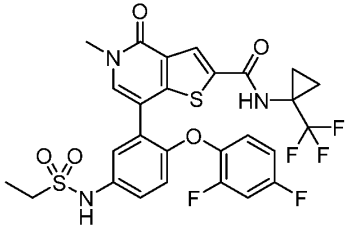
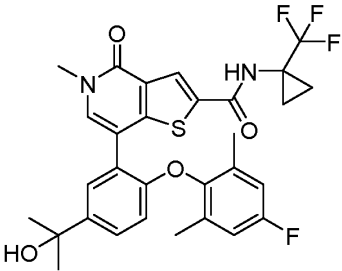
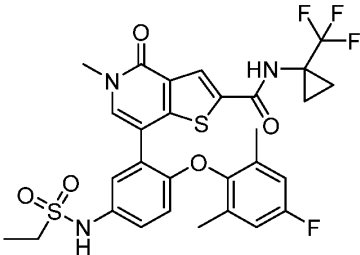
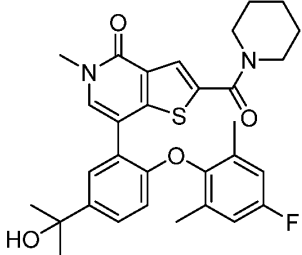
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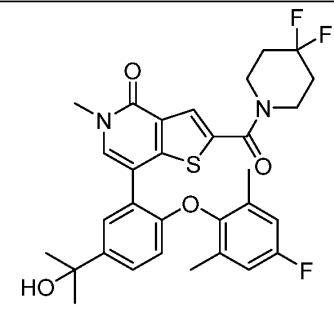
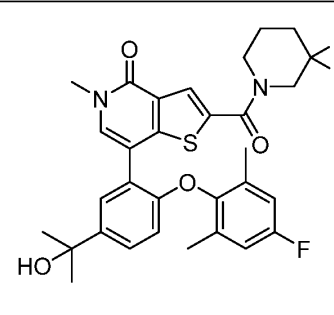
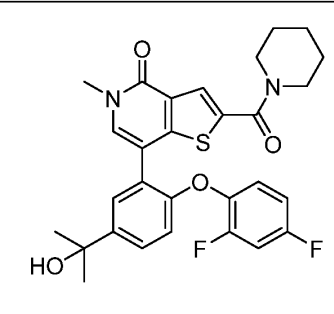
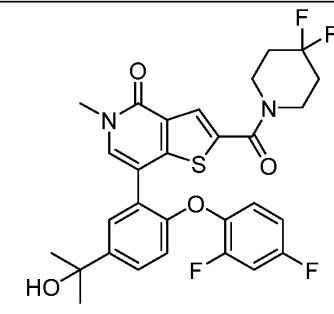
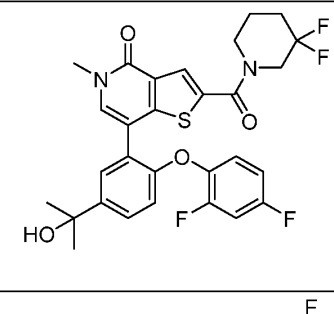
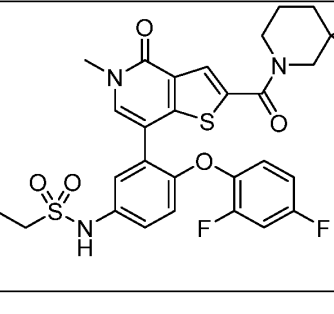
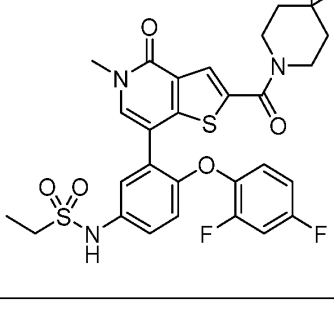
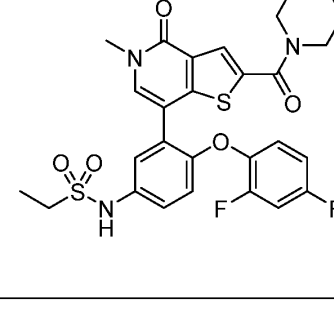
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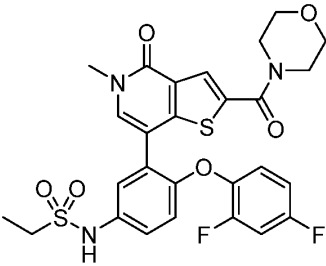
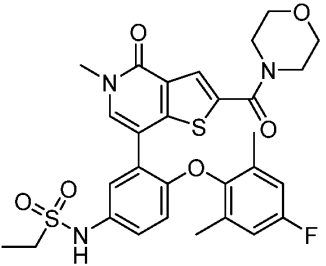
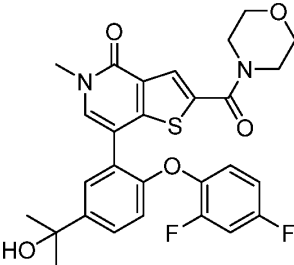
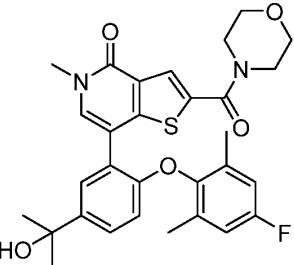
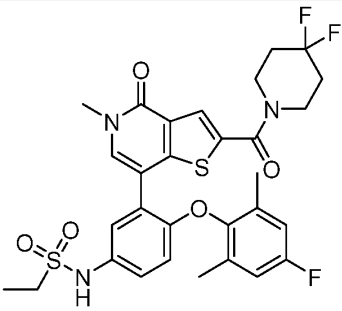
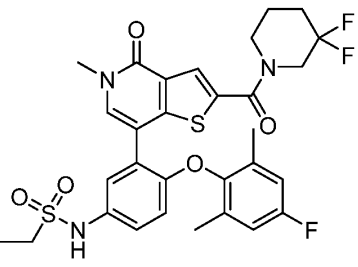
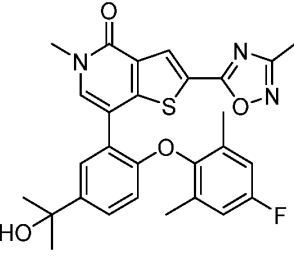
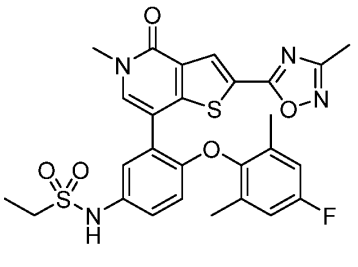
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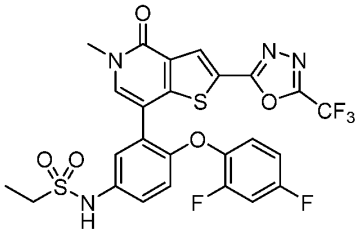
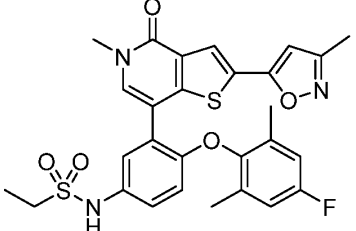
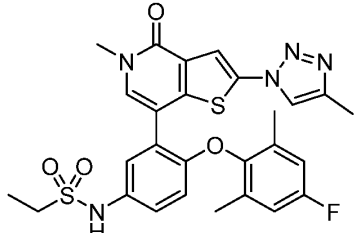
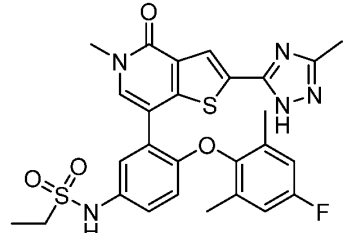
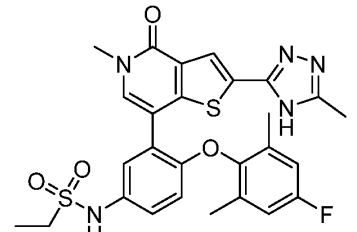
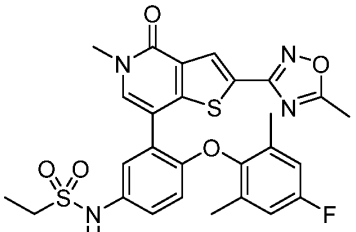
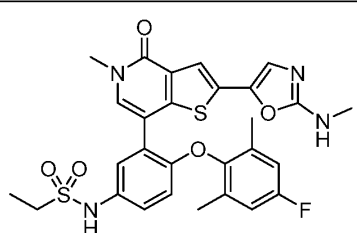
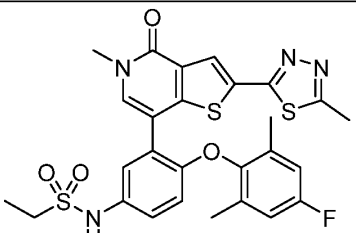
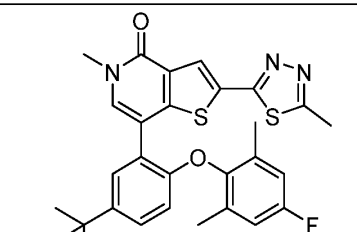
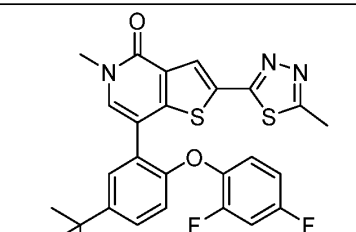
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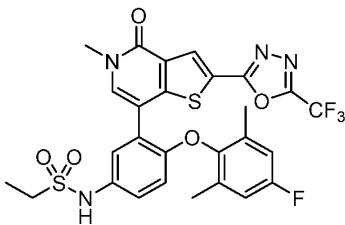
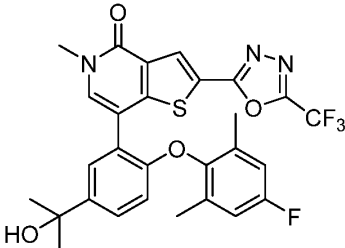
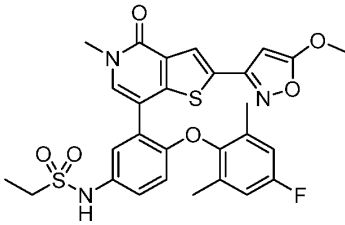
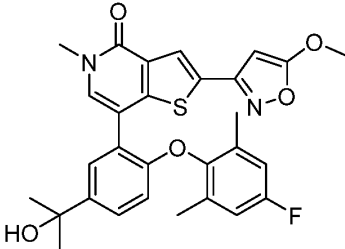
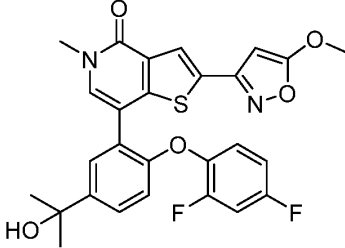
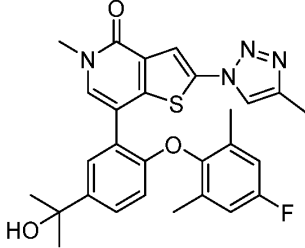
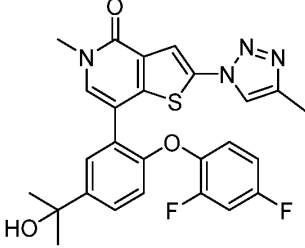
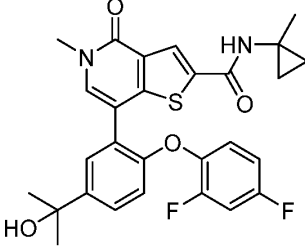
Com. No.	Structure	Com. No.	Structure
79		80	
81		82	
83		84	
85		86	

Com. No.	Structure	Com. No.	Structure
87		88	
89		90	
91		92	
93		94	

Com. No.	Structure	Com. No.	Structure
95		96	
97		98	
99		100	
101		102	

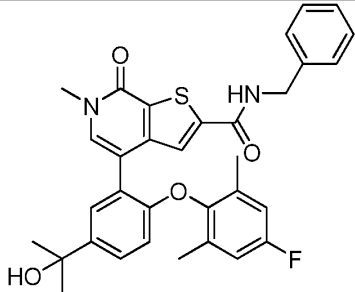
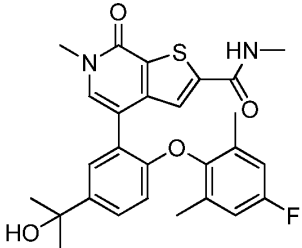
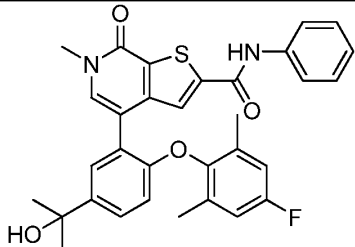
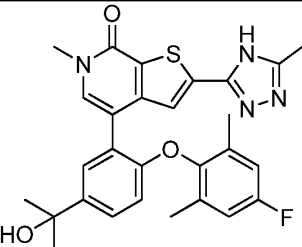
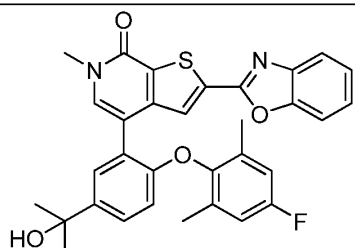
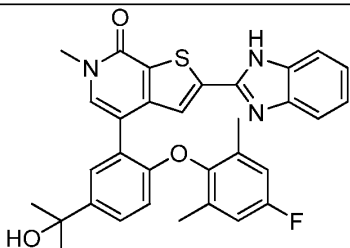
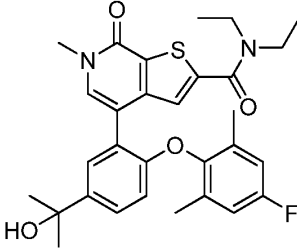
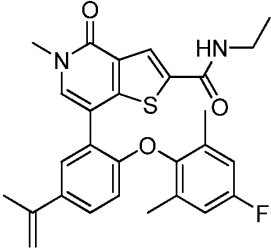
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105		106	
107		108	
109		110	
111		112	

Com. No.	Structure	Com. No.	Structure
113		114	
115		116	
117		118	
119		120	
121		122	

Com. No.	Structure	Com. No.	Structure
123		124	
125		126	
127		128	
129		130	

Com. No.	Structure	Com. No.	Structure
131		132	
133		134	
135		136	
137		138	
139		140	

Com. No.	Structure	Com. No.	Structure
141		142	
143		144	
145		146	
147		148	

Com. No.	Structure	Com. No.	Structure
149		150	
151		152	
153		154	
155		156	

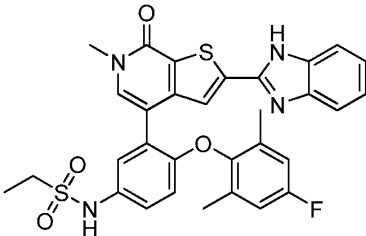
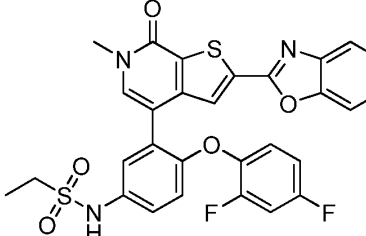
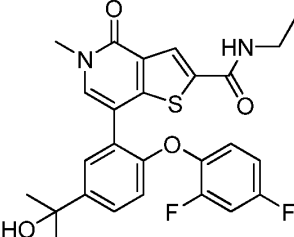
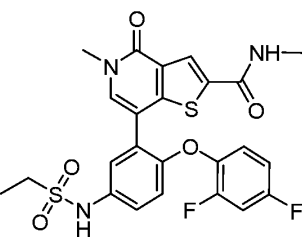
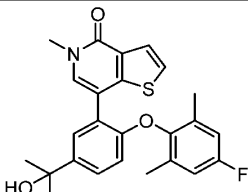
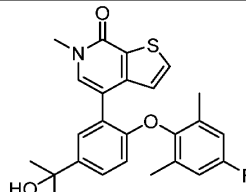
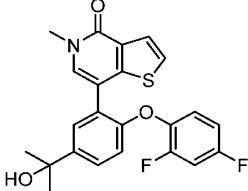
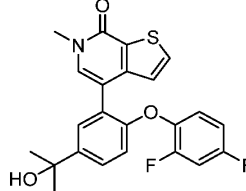
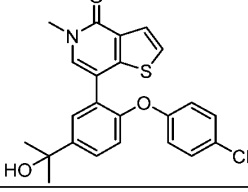
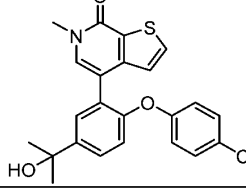
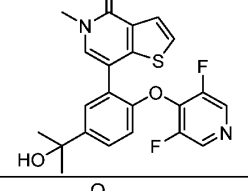
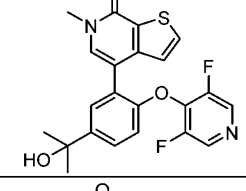
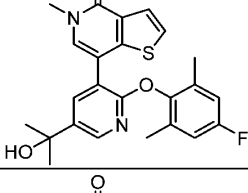
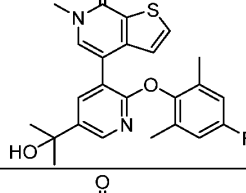
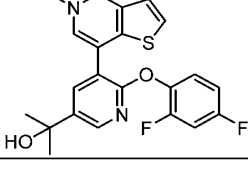
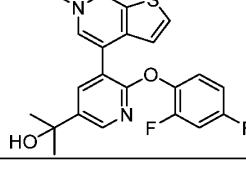
Com. No.	Structure	Com. No.	Structure
157		158	
159		160	

Table 2
Representative Compounds

CompoundNo.	Structure	Compound No.	Structure
2.1		2.2	
2.3		2.4	
2.5		2.6	
2.7		2.8	
2.9		2.10	
2.11		2.12	

CompoundNo.	Structure	Compound No.	Structure
2.13		2.14	
2.15		2.16	
2.17		2.18	
2.19		2.20	
2.21		2.22	
2.23		2.24	
2.25		2.26	

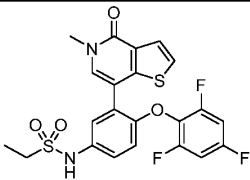
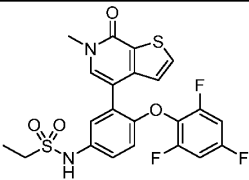
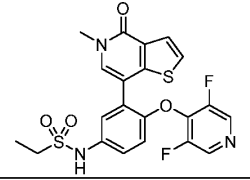
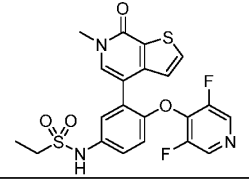
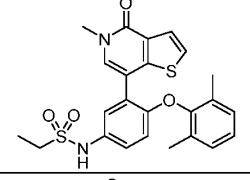
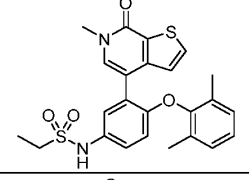
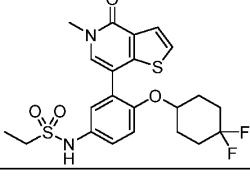
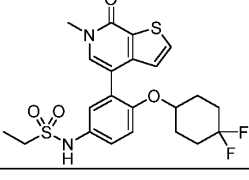
CompoundNo.	Structure	Compound No.	Structure
2.27		2.28	
2.29		2.30	
2.31		2.32	
2.33		2.34	
2.35		2.36	
2.37		2.38	
2.39		2.40	

CompoundNo.	Structure	Compound No.	Structure
2.41		2.42	
2.43		2.44	
2.45		2.46	
2.47		2.48	
2.49		2.50	
2.51		2.52	
2.53		2.54	

CompoundNo.	Structure	Compound No.	Structure
2.55		2.56	
2.57		2.58	
2.59		2.60	
2.61		2.62	
2.63		2.64	
2.65		2.66	
2.67		2.68	

CompoundNo.	Structure	Compound No.	Structure
2.69		2.70	
2.71		2.72	
2.73		2.74	
2.75		2.76	
2.77		2.78	
2.79		2.80	
2.81		2.82	

CompoundNo.	Structure	Compound No.	Structure
2.83		2.84	
2.85		2.86	
2.87		2.88	
2.89		2.90	
2.91		2.92	
2.93		2.94	
2.95		2.96	

CompoundNo.	Structure	Compound No.	Structure
2.97		2.98	
2.99		2.100	
2.101		2.102	
2.103		2.104	

[0079] In some embodiments, provided herein are compounds described in Table 1, including or a pharmaceutically acceptable salt, hydrate, solvate, isotope, individual isomer, or mixtures of isomers thereof, and uses thereof. In some embodiments, provided herein are compounds 1-147, including or a pharmaceutically acceptable salt, hydrate, solvate, isotope, individual isomer, or mixtures of isomers thereof, and uses thereof. In some embodiments, provided herein are compounds 2.1-2.104, including or a pharmaceutically acceptable salt, hydrate, solvate, isotope, individual isomer, or mixtures of isomers thereof, and uses thereof.

[0080] The embodiments and variations described herein are suitable for compounds of any formulae detailed herein, where applicable.

[0081] Representative examples of compounds detailed herein, including intermediates and final compounds according to the present disclosure are depicted herein. It is understood that in one aspect, any of the compounds may be used in the methods detailed herein, including, where applicable, intermediate compounds that may be isolated and administered to an individual.

[0082] The compounds depicted herein may be present as salts even if salts are not depicted and it is understood that the present disclosure embraces all salts and solvates of the compounds depicted here, as well as the non-salt and non-solvate form of the compound, as is well understood by the skilled artisan. In some embodiments, the salts of the compounds provided herein are pharmaceutically acceptable salts. Where one or more tertiary amine moiety is present in the compound, the N-oxides are also provided and described.

[0083] Where tautomeric forms may be present for any of the compounds described herein, each and every tautomeric form is intended even though only one or some of the tautomeric forms may be explicitly depicted. The tautomeric forms specifically depicted may or may not be the predominant forms in solution or when used according to the methods described herein.

[0084] The present disclosure also includes any or all of the stereochemical forms, including any enantiomeric or diastereomeric forms of the compounds described. The structure or name is intended to embrace all possible stereoisomers of a compound depicted, and each unique stereoisomer has a compound number bearing a suffix "a", "b", *etc.* All forms of the compounds are also embraced by the invention, such as crystalline or non-crystalline forms of the compounds. Compositions comprising a compound of the invention are also intended, such as a composition of substantially pure compound, including a specific stereochemical form thereof, or a composition comprising mixtures of compounds of the invention in any ratio, including two or more stereochemical forms, such as in a racemic or non-racemic mixture.

[0085] The invention also intends isotopically-labeled and/or isotopically-enriched forms of compounds described herein. The compounds herein may contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. In some embodiments, the compound is isotopically-labeled, such as an isotopically-labeled compound of the Formula (I) or variations thereof described herein, where a fraction of one or more atoms are replaced by an isotope of the same element. Exemplary isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, chlorine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}O , ^{17}O , ^{35}S , ^{18}F , ^{36}Cl . Certain isotope labeled compounds (e.g. ^3H and ^{14}C) are useful in compound or substrate tissue distribution study. Incorporation of heavier isotopes such as deuterium (^2H) can afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life, or reduced dosage requirements and, hence may be preferred in some instances.

[0086] Isotopically-labeled compounds of the present invention can generally be prepared by standard methods and techniques known to those skilled in the art or by procedures similar to those described in the accompanying Examples substituting appropriate isotopically-labeled reagents in place of the corresponding non-labeled reagent.

[0087] The invention also includes any or all metabolites of any of the compounds described. The metabolites may include any chemical species generated by a biotransformation of any of the compounds described, such as intermediates and products of metabolism of the compound, such as would be generated *in vivo* following administration to a human.

[0088] Articles of manufacture comprising a compound described herein, or a salt or solvate thereof, in a suitable container are provided. The container may be a vial, jar, ampoule, preloaded syringe, *i.v.* bag, and the like.

[0089] Preferably, the compounds detailed herein are orally bioavailable. However, the compounds may also be formulated for parenteral (*e.g.*, intravenous) administration.

[0090] One or several compounds described herein can be used in the preparation of a medicament by combining the compound or compounds as an active ingredient with a pharmacologically acceptable carrier, which are known in the art. Depending on the therapeutic form of the medication, the carrier may be in various forms. In one variation, the manufacture of a medicament is for use in any of the methods disclosed herein, *e.g.*, for the treatment of cancer.

General synthetic methods

[0091] The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter (such as the schemes provided in the Examples below). In the following process descriptions, the symbols when used in the formulae depicted are to be understood to represent those groups described above in relation to the formulae herein.

[0092] Where it is desired to obtain a particular enantiomer of a compound, this may be accomplished from a corresponding mixture of enantiomers using any suitable conventional procedure for separating or resolving enantiomers. Thus, for example, diastereomeric derivatives may be produced by reaction of a mixture of enantiomers, *e.g.*, a racemate, and an appropriate chiral compound. The diastereomers may then be separated by any convenient means, for example by crystallization and the desired enantiomer recovered. In another resolution process, a racemate

may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described.

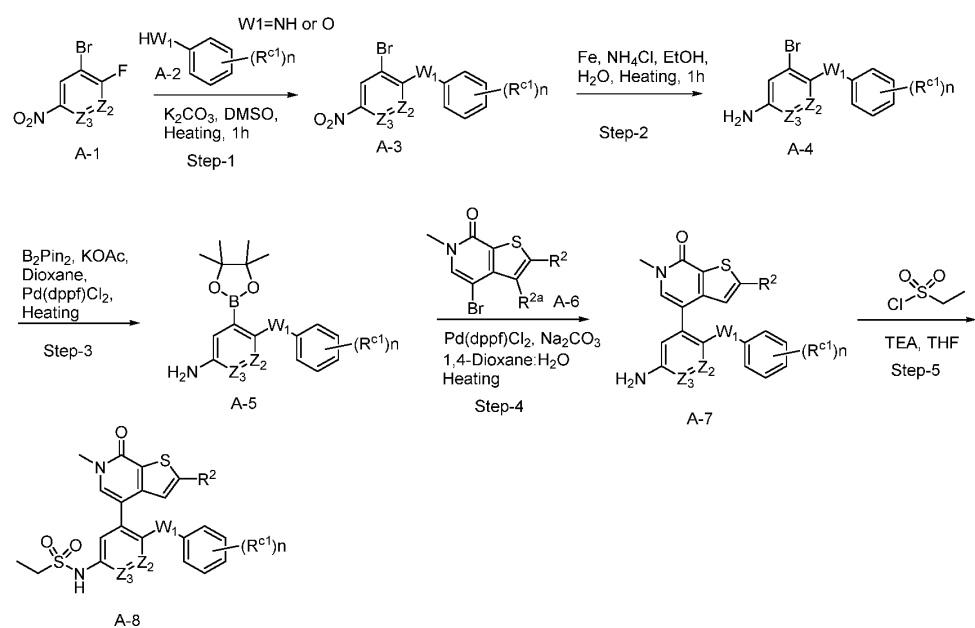
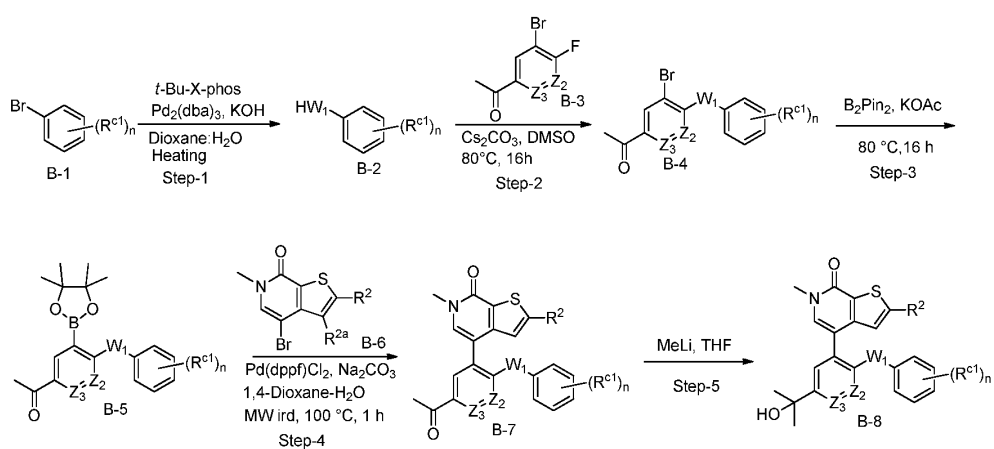
[0093] Chromatography, recrystallization and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular isomer of a compound or to otherwise purify a product of a reaction.

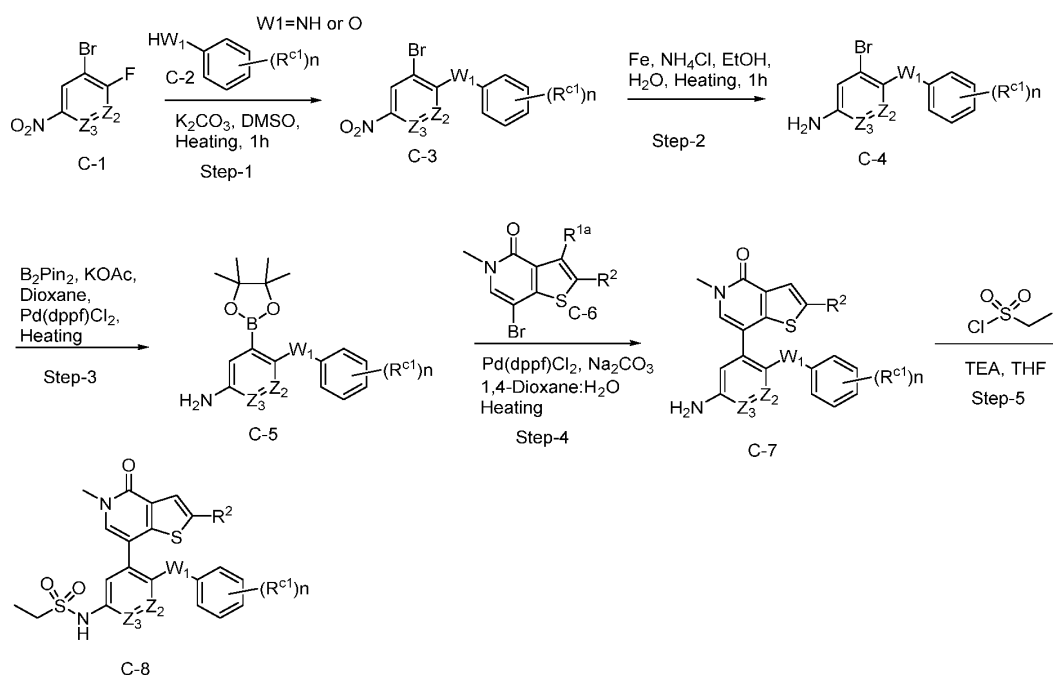
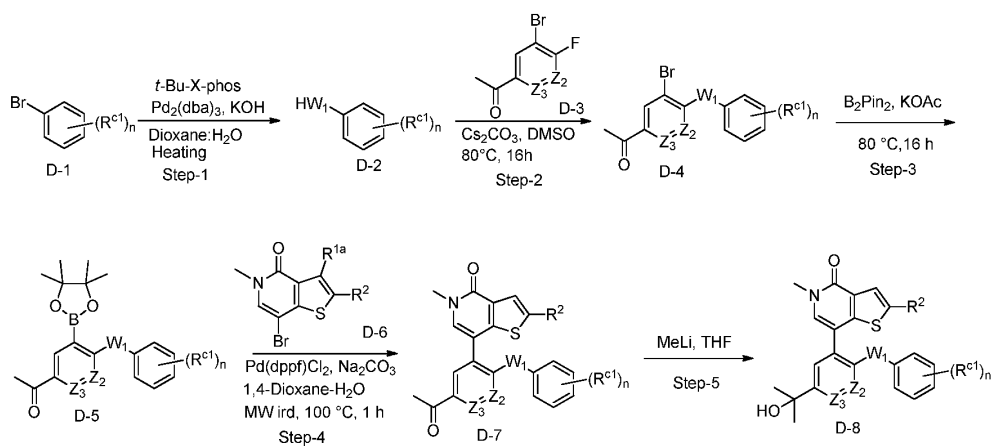
[0094] Solvates and/or polymorphs of a compound provided herein or a pharmaceutically acceptable salt thereof are also contemplated. Solvates contain either stoichiometric or nonstoichiometric amounts of a solvent, and are often formed during the process of crystallization. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol.

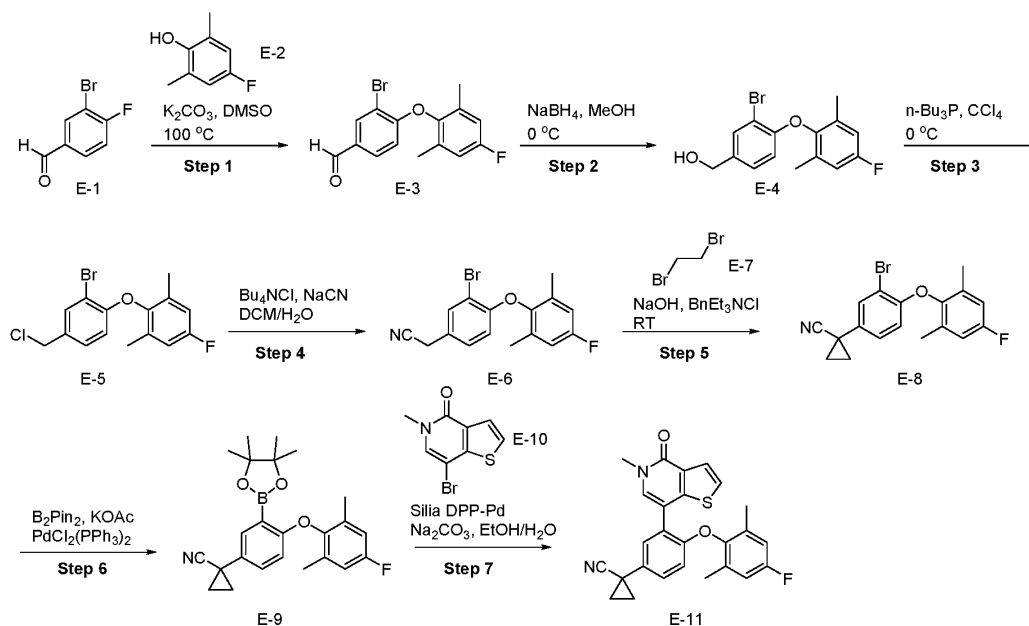
[0095] Polymorphs include the different crystal packing arrangements of the same elemental composition of a compound. Polymorphs usually have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shape, optical and electrical properties, stability, and/or solubility. Various factors such as the recrystallization solvent, rate of crystallization, and storage temperature may cause a single crystal form to dominate.

[0096] Abbreviations used in the descriptions of the schemes and the specific examples have the following meanings: EtOH for ethyl alcohol, B₂Pin₂ for Bis(pinacolato)diboron, KOAc for potassium acetate, DMSO for dimethyl sulfoxide, Pd(dppf)Cl₂ for [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II); EtOAc for ethyl acetate; Et₃N for triethylamine; DCM for dichloromethane, DIPEA for N,N-Diisopropylethylamine, THF for tetrahydrofuran, T₃P for Propylphosphonic Anhydride, DMAP for 4-Dimethylaminopyridine and HPLC for high performance liquid chromatography.

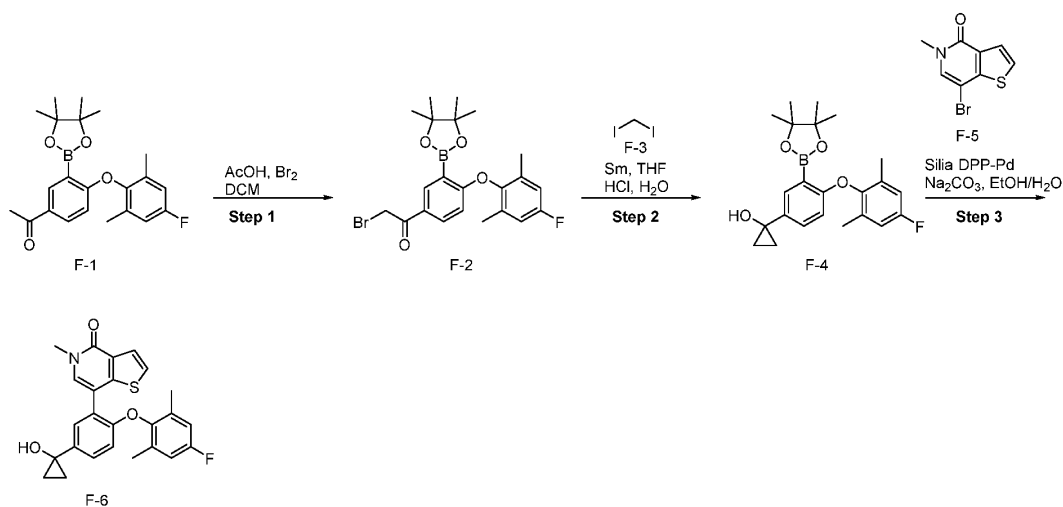
[0097] The compounds described herein, including compounds of general Formula (I), (II), (IIa-1) to (IIa-7), (III) or (IIIa-1) to (IIIa-7), and specific examples, may be prepared, for example, through the reaction routes depicted in the Scheme. The variables R¹, R², R⁴, R^{c1}, G₁, G₂, Z₂, Z₃, W₁ and m used in the scheme have the meanings as set forth in the summary and detailed description sections unless otherwise noted.

Scheme 1:**Scheme 2:**

Scheme 3:**Scheme 4:****Scheme 5:**



Scheme 6:



[0098] It is understood that General Synthetic Schemes 1 to Schemes 4 and present synthetic routes involving steps clearly familiar to those skilled in the art, wherein the substituents described in compounds of the Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8) herein can be varied with a choice of appropriate starting materials and reagents utilized in the steps presented.

[0099] It is understood that General Synthetic Schemes 1 to 6 and present synthetic routes involving steps clearly familiar to those skilled in the art, wherein the substituents described in

compounds of the Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11) herein can be varied with a choice of appropriate starting materials and reagents utilized in the steps presented.

[0100] Optimum reaction conditions and reaction times for each individual step may vary depending on the particular reactants employed and substituents present in the reactants used. Unless otherwise specified, solvents, temperatures and other reaction conditions may be readily selected by one of ordinary skill in the art. Specific procedures are provided in the Synthetic Examples section. Reactions may be further processed in the conventional manner, e.g. by eliminating the solvent from the residue and further purified according to methodologies generally known in the art such as, but not limited to, crystallization, distillation, extraction, trituration and chromatography.

[0101] Unless otherwise described, the starting materials and reagents are either commercially available or may be prepared by one skilled in the art from commercially available materials using methods described in the chemical literature.

[0102] Routine experimentations, including appropriate manipulation of the reaction conditions, reagents and sequence of the synthetic route, protection of any chemical functionality that may not be compatible with the reaction conditions, and deprotection at a suitable point in the reaction sequence of the method are included in the scope of the invention. Suitable protecting groups and the methods for protecting and deprotecting different substituents using such suitable protecting groups are well known to those skilled in the art; examples of which may be found in T. Greene and P. Wuts, *Protecting Groups in Chemical Synthesis* (3rd ed.), John Wiley & Sons, NY (1999), which is incorporated herein by reference in its entirety. Synthesis of the compounds of the invention may be accomplished by methods analogous to those described in the synthetic schemes described hereinabove and in specific examples.

[0103] Starting materials, if not commercially available, may be prepared by procedures selected from standard organic chemical techniques, techniques that are analogous to the synthesis of known, structurally similar compounds, or techniques that are analogous to the above described schemes or the procedures described in the synthetic examples section.

[0104] When an optically active form of a compound of the invention is required, it may be obtained by carrying out one of the procedures described herein using an optically active starting material (prepared, for example, by asymmetric induction of a suitable reaction step), or by resolution of a mixture of the stereoisomers of the compound or intermediates using a standard procedure (such as chromatographic separation, recrystallization or enzymatic resolution).

[0105] Similarly, when a pure geometric isomer of a compound of the invention is required, it may be obtained by carrying out one of the above procedures using a pure geometric isomer as a starting material, or by resolution of a mixture of the geometric isomers of the compound or intermediates using a standard procedure such as chromatographic separation.

Pharmaceutical Compositions and Formulations

[0106] Pharmaceutical compositions of any of the compounds detailed herein are embraced by this disclosure. Thus, the present disclosure includes pharmaceutical compositions comprising a compound as detailed herein or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient. In one aspect, the pharmaceutically acceptable salt is an acid addition salt, such as a salt formed with an inorganic or organic acid.

[0107] Pharmaceutical compositions may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration or a form suitable for administration by inhalation.

[0108] A compound as detailed herein may in one aspect be in a purified form and compositions comprising a compound in purified forms are detailed herein. Compositions comprising a compound as detailed herein or a salt thereof are provided, such as compositions of substantially pure compounds. In some embodiments, a composition containing a compound as detailed herein or a salt thereof is in substantially pure form.

[0109] In one variation, the compounds herein are synthetic compounds prepared for administration to an individual. In another variation, compositions are provided containing a compound in substantially pure form. In another variation, the present disclosure embraces pharmaceutical compositions comprising a compound detailed herein and a pharmaceutically acceptable carrier. In another variation, methods of administering a compound are provided. The purified forms, pharmaceutical compositions and methods of administering the compounds are suitable for any compound or form thereof detailed herein.

[0110] A compound detailed herein or salt thereof may be formulated for any available delivery route, including an oral, mucosal (*e.g.*, nasal, sublingual, vaginal, buccal or rectal), parenteral (*e.g.*, intramuscular, subcutaneous or intravenous), topical or transdermal delivery form. A compound or salt thereof may be formulated with suitable carriers to provide delivery forms that include, but are not limited to, tablets, caplets, capsules (such as hard gelatin capsules or soft elastic gelatin capsules), cachets, troches, lozenges, gums, dispersions, suppositories, ointments, cataplasms (poultices), pastes, powders, dressings, creams, solutions, patches, aerosols (*e.g.*, nasal spray or inhalers), gels, suspensions (*e.g.*, aqueous or non-aqueous liquid suspensions, oil-in-water emulsions or water-in-oil liquid emulsions), solutions and elixirs.

[0111] One or several compounds described herein or a salt thereof can be used in the preparation of a formulation, such as a pharmaceutical formulation, by combining the compound or compounds, or a salt thereof, as an active ingredient with a pharmaceutically acceptable carrier, such as those mentioned above. Depending on the therapeutic form of the system (*e.g.*, transdermal patch vs. oral tablet), the carrier may be in various forms. In addition, pharmaceutical formulations may contain preservatives, solubilizers, stabilizers, re-wetting agents, emulgators, sweeteners, dyes, adjusters, and salts for the adjustment of osmotic pressure, buffers, coating agents or antioxidants. Formulations comprising the compound may also contain other substances which have valuable therapeutic properties. Pharmaceutical formulations may be prepared by known pharmaceutical methods. Suitable formulations can be found, *e.g.*, in *Remington's Pharmaceutical Sciences*, Mack Publishing Company, Philadelphia, PA, 20th ed. (2000), which is incorporated herein by reference

[0112] Compounds as described herein may be administered to individuals in a form of generally accepted oral compositions, such as tablets, coated tablets, and gel capsules in a hard or in soft shell, emulsions or suspensions. Examples of carriers, which may be used for the preparation of such compositions, are lactose, corn starch or its derivatives, talc, stearate or its salts, *etc.*

[0113] Acceptable carriers for gel capsules with soft shell are, for instance, plant oils, wax, fats, semisolid and liquid poly-ols, and so on. In addition, pharmaceutical formulations may contain preservatives, solubilizers, stabilizers, re-wetting agents, emulgators, sweeteners, dyes, adjusters, and salts for the adjustment of osmotic pressure, buffers, coating agents or antioxidants.

[0114] Any of the compounds described herein can be formulated in a tablet in any dosage form described, for example, a compound as described herein or a pharmaceutically acceptable salt thereof can be formulated as a 10 mg tablet.

[0115] Compositions comprising a compound provided herein are also described. In one variation, the composition comprises a compound or salt thereof and a pharmaceutically acceptable carrier or excipient. In another variation, a composition of substantially pure compound is provided.

Methods of Use

[0116] Compounds and compositions detailed herein, such as a pharmaceutical composition containing a compound of any formula provided herein or a salt thereof and a pharmaceutically acceptable carrier or excipient, may be used in methods of administration and treatment as provided herein. The compounds and compositions may also be used in *in vitro* methods, such as *in vitro* methods of administering a compound or composition to cells for screening purposes and/or for conducting quality control assays.

[0117] In another embodiment, there are provided methods of making a composition of a compound described herein including formulating a compound of the invention with a pharmaceutically acceptable carrier or diluent. In some embodiments, the pharmaceutically acceptable carrier or diluent is suitable for oral administration. In some such embodiments, the methods can further include the step of formulating the composition into a tablet or capsule. In other embodiments, the pharmaceutically acceptable carrier or diluent is suitable for parenteral administration. In some such embodiments, the methods further include the step of lyophilizing the composition to form a lyophilized preparation. In an embodiment, use of a compound having the structure of Formula (I), (II), (IIa-1) to (IIa-7), (III) or (IIIa-1) to (IIIa-7), or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope, or salt thereof, for the manufacture of a medicament is provided.

[0118] In another embodiment, there are provided methods of making a composition of a compound described herein including formulating a compound of the invention with a pharmaceutically acceptable carrier or diluent. In some embodiments, the pharmaceutically acceptable carrier or diluent is suitable for oral administration. In some such embodiments, the methods can further include the step of formulating the composition into a tablet or capsule. In

other embodiments, the pharmaceutically acceptable carrier or diluent is suitable for parenteral administration. In some such embodiments, the methods further include the step of lyophilizing the composition to form a lyophilized preparation. In an embodiment, use of a compound having the structure of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope, or salt thereof, for the manufacture of a medicament is provided.

[0119] Provided herein is a method of treating a disease in an individual comprising administering an effective amount of a compound of Formula (I) or any embodiment, variation or aspect thereof (collectively, a compound of Formula (I) or the present compounds or the compounds detailed or described herein) or a pharmaceutically acceptable salt thereof, to the individual. In some embodiments, provided herein is a method of treating a disease mediated by inhibition of the BET family of proteins in an individual comprising administering an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the individual. In an embodiment, the present invention provides for methods for treating or preventing disorders that are ameliorated by inhibition of BET.

[0120] Provided herein is a method of treating a disease in an individual comprising administering an effective amount of a compound of Formula (J) or any embodiment, variation or aspect thereof (collectively, a compound of Formula (J) or the present compounds or the compounds detailed or described herein) or a pharmaceutically acceptable salt thereof, to the individual. In some embodiments, provided herein is a method of treating a disease mediated by inhibition of the BET family of proteins in an individual comprising administering an effective amount of a compound of Formula (J), or a pharmaceutically acceptable salt thereof, to the individual. In an embodiment, the present invention provides for methods for treating or preventing disorders that are ameliorated by inhibition of BET.

[0121] The present compounds or salts thereof are believed to be effective for treating a variety of diseases and disorders. For example, in some embodiments, the present compositions may be used to treat an inflammatory disease, a proliferative disease, such as cancer, or AIDS.

[0122] In another aspect, the present invention relates to methods of treating cancer in a subject comprising administering a therapeutically effective amount of a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-

8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof, to a subject in need thereof. In some embodiments, the present invention relates to methods of treating cancer in a subject comprising administering a therapeutically effective amount of a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8) or a pharmaceutically acceptable salt thereof, to a subject in need thereof. In certain embodiments, the cancer is selected from the group consisting of: acoustic neuroma, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia (monocytic, myeloblastic, adenocarcinoma, angiosarcoma, astrocytoma, myelomonocytic and promyelocytic), acute T-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, brain cancer, breast cancer, bronchogenic carcinoma, cervical cancer, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic (granulocytic) leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, dysproliferative changes (dysplasias and metaplasias), embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fibrosarcoma, follicular lymphoma, germ cell testicular cancer, glioma, glioblastoma, gliosarcoma, heavy chain disease, hemangioblastoma, hepatoma, hepatocellular cancer, hormone sensitive and insensitive prostate cancer, enzalutamide (XTANDI) and abiraterone resistant prostate cancer in the pre- and post- chemo stages, leiomyosarcoma, leukemia, liposarcoma, lung cancer, lymphagioendotheliosarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma (Hodgkin's and non-Hodgkin's), malignancies and hyperproliferative disorders of the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus, lymphoid malignancies of T-cell or B-cell origin, leukemia, lymphoma, medullary carcinoma, medulloblastoma, melanoma, meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, NUT midline carcinoma (NMC), non-small cell lung cancer, oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, pinealoma, polycythemia vera, prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small cell lung carcinoma, solid tumors (carcinomas and sarcomas), small cell lung cancer, stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, thyroid cancer, Waldenström's macroglobulinemia, testicular tumors, uterine cancer and Wilms' tumor. In certain embodiments, the methods further comprise administering a therapeutically effective

amount of at least one additional therapeutic agent. In certain embodiments, the additional therapeutic agent is an anti-cancer agent. In particular embodiments, the additional therapeutic agents are selected from the group consisting of cytarabine, bortezomib, and 5-azacitidine.

[0123] In some embodiments, the cancer is a solid tumor. In some embodiments the cancer is any of adult and pediatric oncology, myxoid and round cell carcinoma, locally advanced tumors, metastatic cancer, human soft tissue sarcomas, including Ewing's sarcoma, cancer metastases, including lymphatic metastases, squamous cell carcinoma, particularly of the head and neck, esophageal squamous cell carcinoma, oral carcinoma, blood cell malignancies, including multiple myeloma, leukemias, including acute lymphocytic leukemia, acute nonlymphocytic leukemia, chronic lymphocytic leukemia, chronic myelocytic leukemia, and hairy cell leukemia, effusion lymphomas (body cavity based lymphomas), thymic lymphoma lung cancer, including small cell carcinoma, cutaneous T cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cancer of the adrenal cortex, ACTH-producing tumors, non-small cell cancers, breast cancer, including small cell carcinoma and ductal carcinoma, gastrointestinal cancers, including stomach cancer, colon cancer, colorectal cancer, polyps associated with colorectal neoplasia, pancreatic cancer, liver cancer, urological cancers, including bladder cancer, including primary superficial bladder tumors, invasive transitional cell carcinoma of the bladder, and muscle-invasive bladder cancer, prostate cancer, malignancies of the female genital tract, including ovarian carcinoma, primary peritoneal epithelial neoplasms, cervical carcinoma, uterine endometrial cancers, vaginal cancer, cancer of the vulva, uterine cancer and solid tumors in the ovarian follicle, malignancies of the male genital tract, including testicular cancer and penile cancer, kidney cancer, including renal cell carcinoma, brain cancer, including intrinsic brain tumors, neuroblastoma, astrocytic brain tumors, gliomas, metastatic tumor cell invasion in the central nervous system, bone cancers, including osteomas and osteosarcomas, skin cancers, including melanoma, tumor progression of human skin keratinocytes, squamous cell cancer, thyroid cancer, retinoblastoma, neuroblastoma, peritoneal effusion, malignant pleural effusion, mesothelioma, Wilms's tumors, gall bladder cancer, trophoblastic neoplasms, hemangiopericytoma, and Kaposi's sarcoma.

[0124] In some embodiments, the cancer in the individual has one or more mutations or amplification or overexpression of the genes encoding BET proteins. In some embodiments, the cancer in the individual has mutation or amplification or overexpression of BRD4. In some embodiments, the cancer in the individual has mutation or amplification or overexpression of c-

MYC. In some embodiments, the cancer in the individual has mutation or amplification or overexpression of *MYCN*. In some embodiments, the cancer in the individual is characterized by Androgen Receptor (AR) expression.

[0125] In some embodiments, there is provided a method of treating a cancer in an individual, comprising (a) selecting the individual for treatment based on (i) the mutation or amplification or overexpression of BRD4 or other BET family members, or (ii) presence of mutation or amplification or overexpression of c-MYC in the cancer, and administering an effective amount of the compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8) or a pharmaceutically acceptable salt thereof, to the individual. In some embodiments, the cancer is sequenced to detect the one or more mutations or amplifications. In some embodiments, the gene is sequenced from the biopsied cancer. In some embodiments, the gene is sequenced by sequencing circulating-tumor DNA (ctDNA) from the individual. In some embodiments, there is provided a method of treating a cancer in an individual, comprising (a) selecting the individual for treatment based on (i) the mutation or amplification or overexpression of BRD4 or other BET family members, or (ii) presence of mutation or amplification or overexpression of c-MYC in the cancer, and administering an effective amount of the compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof, to the individual. In some embodiments, the cancer is sequenced to detect the one or more mutations or amplifications. In some embodiments, the gene is sequenced from the biopsied cancer. In some embodiments, the gene is sequenced by sequencing circulating-tumor DNA (ctDNA) from the individual.

[0126] In another aspect, the present invention relates to methods of treating a disease or condition in a subject comprising administering a therapeutically effective amount of a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof, to a subject in need thereof, wherein said disease or condition is selected from the group consisting of: Addison's disease, acute gout, ankylosing spondylitis, asthma, atherosclerosis, Behcet's disease, bullous skin diseases, chronic obstructive pulmonary disease (COPD), Crohn's disease, dermatitis, eczema, giant cell arteritis, glomerulonephritis, hepatitis, hypophysitis, inflammatory bowel disease, Kawasaki disease, lupus nephritis, multiple sclerosis, myocarditis, myositis, nephritis, organ transplant rejection, osteoarthritis, pancreatitis, pericarditis, Polyarteritis

nodosa, pneumonitis, primary biliary cirrhosis, psoriasis, psoriatic arthritis, rheumatoid arthritis, scleritis, sclerosing cholangitis, sepsis, systemic lupus erythematosus, Takayasu's Arteritis, toxic shock, thyroiditis, type I diabetes, ulcerative colitis, uveitis, vitiligo, vasculitis, and Wegener's granulomatosis. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent. In another aspect, the present invention relates to methods of treating a disease or condition in a subject comprising administering a therapeutically effective amount of a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof, to a subject in need thereof, wherein said disease or condition is selected from the group consisting of: Addison's disease, acute gout, ankylosing spondylitis, asthma, atherosclerosis, Behcet's disease, bullous skin diseases, chronic obstructive pulmonary disease (COPD), Crohn's disease, dermatitis, eczema, giant cell arteritis, glomerulonephritis, hepatitis, hypophysitis, inflammatory bowel disease, Kawasaki disease, lupus nephritis, multiple sclerosis, myocarditis, myositis, nephritis, organ transplant rejection, osteoarthritis, pancreatitis, pericarditis, Polyarteritis nodosa, pneumonitis, primary biliary cirrhosis, psoriasis, psoriatic arthritis, rheumatoid arthritis, scleritis, sclerosing cholangitis, sepsis, systemic lupus erythematosus, Takayasu's Arteritis, toxic shock, thyroiditis, type I diabetes, ulcerative colitis, uveitis, vitiligo, vasculitis, and Wegener's granulomatosis. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent. In another aspect, the present invention relates to methods of treating a chronic kidney disease or condition in a subject comprising administering a therapeutically effective amount of a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8)) or a pharmaceutically acceptable salt thereof, to a subject in need thereof, wherein said disease or condition is selected from the group consisting of: diabetic nephropathy, hypertensive nephropathy, HIV-associated nephropathy, glomerulonephritis, lupus nephritis, IgA nephropathy, focal segmental glomerulosclerosis, membranous glomerulonephritis, minimal change disease, polycystic kidney disease and tubular interstitial nephritis. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent. In certain embodiments, the methods

further comprise administering a therapeutically effective amount of at least one additional therapeutic agent. In another aspect, the present invention relates to methods of treating a chronic kidney disease or condition in a subject comprising administering a therapeutically effective amount of a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof, to a subject in need thereof, wherein said disease or condition is selected from the group consisting of: diabetic nephropathy, hypertensive nephropathy, HIV-associated nephropathy, glomerulonephritis, lupus nephritis, IgA nephropathy, focal segmental glomerulosclerosis, membranous glomerulonephritis, minimal change disease, polycystic kidney disease and tubular interstitial nephritis. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent.

[0127] In another aspect, the present invention relates to methods of treating an acute kidney injury or disease or condition in a subject comprising administering a therapeutically effective amount of a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof, to a subject in need thereof, wherein said acute kidney injury or disease or condition is selected from the group consisting of: ischemia-reperfusion induced, cardiac and major surgery induced, percutaneous coronary intervention induced, radio-contrast agent induced, sepsis induced, pneumonia induced, and drug toxicity induced. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent. In another aspect, the present invention relates to methods of treating an acute kidney injury or disease or condition in a subject comprising administering a therapeutically effective amount of a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof, to a subject in need thereof, wherein said acute kidney injury or disease or condition is selected from the group consisting of: ischemia-reperfusion induced, cardiac and major surgery induced, percutaneous coronary intervention induced, radio-contrast agent induced, sepsis induced, pneumonia induced, and drug toxicity induced. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at

least one additional therapeutic agent. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent.

[0128] In another aspect, the present invention relates to methods of treating AIDS in a subject comprising administering a therapeutically effective amount of a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof, to a subject in need thereof. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent. In another aspect, the present invention relates to methods of treating AIDS in a subject comprising administering a therapeutically effective amount of a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof, to a subject in need thereof. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent.

[0129] In another aspect, the present invention relates to methods of treating obesity, dyslipidemia, hypercholesterolemia, Alzheimer's disease, metabolic syndrome, hepatic steatosis, type II diabetes, insulin resistance, diabetic retinopathy or diabetic neuropathy in a subject comprising administering a therapeutically effective amount of a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof, to a subject in need thereof. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent. In another aspect, the present invention relates to methods of treating obesity, dyslipidemia, hypercholesterolemia, Alzheimer's disease, metabolic syndrome, hepatic steatosis, type II diabetes, insulin resistance, diabetic retinopathy or diabetic neuropathy in a subject comprising administering a therapeutically effective amount of a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof, to a subject in need thereof. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent.

[0130] In another aspect, the present invention relates to methods of preventing conception by inhibiting spermatogenesis in a subject comprising administering a therapeutically effective amount of a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8), or a

pharmaceutically acceptable salt thereof, to a subject in need thereof. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent. In another aspect, the present invention relates to methods of preventing conception by inhibiting spermatogenesis in a subject comprising administering a therapeutically effective amount of a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof, to a subject in need thereof. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent.

Combination Therapy

[0131] As provided herein, the presently disclosed compounds or a salt thereof may be combined with an additional therapeutic agent. In some embodiments, a method of treating a disease in an individual is provided, the method comprising administering an effective amount of a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8), or any embodiment, variation or aspect thereof (collectively, a compound of formula Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8)), or the present compounds or the compounds detailed or described herein) or a pharmaceutically acceptable salt thereof, and an additional therapeutic agent to the individual. In some embodiments, the disease is a proliferative disease such as cancer. In another aspect, the present invention relates to methods of preventing conception by inhibiting spermatogenesis in a subject comprising administering a therapeutically effective amount of a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof, to a subject in need thereof. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent.

[0132] In some embodiments, the additional therapeutic agent is a cancer immunotherapy agent. In some embodiments, the additional therapeutic agent is an immunostimulatory agent. In some embodiments, the additional therapeutic agent targets a checkpoint protein (for example an immune checkpoint inhibitor). In some embodiments, the additional therapeutic agent is effective to stimulate, enhance or improve an immune response against a tumor.

[0133] In some embodiments, a method of treating a disease in an individual is provided, the method comprising administering an effective amount of Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8), or any embodiment, variation or aspect thereof (collectively, a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8)), or the present compounds or the compounds detailed or described herein) or a pharmaceutically acceptable salt thereof, in combination with radiation therapy. In some embodiments, a method of treating a disease in an individual is provided, the method comprising administering an effective amount of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or any embodiment, variation or aspect thereof (collectively, a compound of (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), (VIa-1) to (VIa-11)), or the present compounds or the compounds detailed or described herein) or a pharmaceutically acceptable salt thereof, in combination with radiation therapy.

[0134] In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8), or any embodiment, variation or aspect thereof (collectively, Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of a chemotherapeutic agent. In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the chemotherapeutic agent. In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the chemotherapeutic agent. In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), (VIa-1) to (VIa-11), or any embodiment, variation or aspect thereof (collectively, Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), (VIa-1) to (VIa-11)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of a chemotherapeutic agent. In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the

chemotherapeutic agent. In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the chemotherapeutic agent.

[0135] Examples of chemotherapeutic agents that can be used in combination with Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof include a DNA alkylating agent (such as cyclophosphamide, mechlorethamine, chlorambucil, melphalan, dacarbazine, or nitrosoureas), a topoisomerase inhibitor (such as a Topoisomerase I inhibitor (e.g., irinotecan or topotecan) or a Topoisomerase II inhibitor (e.g., etoposide or teniposide), an anthracycline (such as daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone, or valrubicin), a histone deacetylase inhibitor (such as vorinostat or romidepsin), another bromodomain inhibitor, other epigenetic inhibitors, a taxane (such as paclitaxel or docetaxel), a kinase inhibitor (such as bortezomib, erlotinib, gefitinib, imatinib, vemurafenib, vismodegib, ibrutinib), a mTOR inhibitor, a DNA Damage Repair (DDR) pathway inhibitor, such as a PARP inhibitor, ATM inhibitor, ATR inhibitor, a Wee1 inhibitor, a proteasome inhibitor (such as bortezomib), an anti-angiogenic inhibitor, endocrine therapy, anti-estrogen therapy, anti-androgen therapy, glucocorticoid receptor inhibitor, a nucleotide analog or precursor analog (such as azacitidine, azathioprine, capecitabine, cytarabine, doxifluridine, 5-fluorouracil, gemcitabine, hydroxyurea, mercaptopurine, methotrexate, or tioguanine), or a platinum-based chemotherapeutic agent (such as cisplatin, carboplatin, or oxaliplatin), pemetrexed, or a combination thereof. Examples of chemotherapeutic agents that can be used in combination with Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof include a DNA alkylating agent (such as cyclophosphamide, mechlorethamine, chlorambucil, melphalan, dacarbazine, or nitrosoureas), a topoisomerase inhibitor (such as a Topoisomerase I inhibitor (e.g., irinotecan or topotecan) or a Topoisomerase II inhibitor (e.g., etoposide or teniposide), an anthracycline (such as daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone, or valrubicin), a histone deacetylase inhibitor (such as vorinostat or romidepsin), another bromodomain inhibitor, other epigenetic inhibitors, a taxane (such as paclitaxel or docetaxel), a kinase inhibitor (such as bortezomib, erlotinib, gefitinib, imatinib, vemurafenib, vismodegib, ibrutinib), a mTOR inhibitor, a DNA Damage Repair (DDR) pathway inhibitor, such as a PARP inhibitor, ATM inhibitor, ATR inhibitor, a Wee1 inhibitor, a

proteasome inhibitor (such as bortezomib), an anti-angiogenic inhibitor, endocrine therapy, anti-estrogen therapy, anti-androgen therapy, glucocorticoid receptor inhibitor, a nucleotide analog or precursor analog (such as azacitidine, azathioprine, capecitabine, cytarabine, doxifluridine, 5-fluorouracil, gemcitabine, hydroxyurea, mercaptopurine, methotrexate, or tioguanine), or a platinum-based chemotherapeutic agent (such as cisplatin, carboplatin, or oxaliplatin), pemetrexed, or a combination thereof.

[0136] In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8), or any embodiment, variation or aspect thereof (collectively, Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of a DNA damaging agent. In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the DNA damaging agent. In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the DNA damaging agent. In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), (VIa-1) to (VIa-11), or any embodiment, variation or aspect thereof (collectively, Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), (VIa-1) to (VIa-11)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of a DNA damaging agent. In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the DNA damaging agent. In some embodiments, Formula ((I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the DNA damaging agent.

[0137] In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (I), (II), (IIa-1) to (IIa-8),

(III) or (IIIa-1) to (IIIa-8), or any embodiment, variation or aspect thereof (collectively, Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of a DNA alkylating agent (such as cyclophosphamide, mechlorethamine, chlorambucil, melphalan, dacarbazine, or nitrosoureas). In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the DNA alkylating agent. In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the DNA alkylating agent. In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), (VIa-1) to (VIa-11), or any embodiment, variation or aspect thereof (collectively, Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), (VIa-1) to (VIa-11)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of a DNA alkylating agent (such as cyclophosphamide, mechlorethamine, chlorambucil, melphalan, dacarbazine, or nitrosoureas). In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the DNA alkylating agent. In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the DNA alkylating agent.

[0138] In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8), or any embodiment, variation or aspect thereof (collectively, Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of a topoisomerase inhibitor (such as a Topoisomerase I inhibitor (e.g., irinotecan or topotecan) or a Topoisomerase II inhibitor (e.g., etoposide or teniposide)). In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-

administered with the topoisomerase inhibitor. In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the topoisomerase inhibitor. In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or any embodiment, variation or aspect thereof (collectively, Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), (VIa-1) to (VIa-11)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of a topoisomerase inhibitor (such as a Topoisomerase I inhibitor (e.g., irinotecan or topotecan) or a Topoisomerase II inhibitor (e.g., etoposide or teniposide)). In some embodiments, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the topoisomerase inhibitor. In some embodiments, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the topoisomerase inhibitor.

[0139] In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8), or any embodiment, variation or aspect thereof (collectively, Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of an anthracycline (such as daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone, or valrubicin). In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the anthracycline. In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the anthracycline. In some embodiments, a method of treating a disease in an individual is provided, the method

comprising (a) administering an effective amount of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or any embodiment, variation or aspect thereof (collectively, Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), (VIa-1) to (VIa-11)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of an anthracycline (such as daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone, or valrubicin). In some embodiments, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the anthracycline. In some embodiments, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the anthracycline.

[0140] In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8), or any embodiment, variation or aspect thereof (collectively, Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of a histone deacetylase inhibitor (such as vorinostat or romidepsin). In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the histone deacetylase inhibitor. In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the histone deacetylase inhibitor. In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or any embodiment, variation or aspect thereof (collectively, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11)) or

a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of a histone deacetylase inhibitor (such as vorinostat or romidepsin). In some embodiments, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the histone deacetylase inhibitor. In some embodiments, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the histone deacetylase inhibitor.

[0141] In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8), or any embodiment, variation or aspect thereof (collectively, Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of a taxane (such as paclitaxel or docetaxel). In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) or (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the taxane. In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the taxane. In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (J) or any related formulae where applicable, such as Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or any embodiment, variation or aspect thereof (collectively, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of a taxane (such as paclitaxel or docetaxel). In some embodiments, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the taxane. In some embodiments, Formula (J) or any related

formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the taxane.

[0142] In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or any embodiment, variation or aspect thereof (collectively, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of a nucleotide analog or precursor analog (such as azacitidine, azathioprine, capecitabine, cytarabine, doxifluridine, 5-fluorouracil, gemcitabine, hydroxyurea, mercaptopurine, methotrexate, or tioguanine). In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the nucleotide analog or precursor analog. In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the nucleotide analog or precursor analog. In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or any embodiment, variation or aspect thereof (collectively, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of a nucleotide analog or precursor analog (such as azacitidine, azathioprine, capecitabine, cytarabine, doxifluridine, 5-fluorouracil, gemcitabine, hydroxyurea, mercaptopurine, methotrexate, or tioguanine). In some embodiments, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the nucleotide analog or precursor analog. In some embodiments, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered

1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the nucleotide analog or precursor analog.

[0143] In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or any embodiment, variation or aspect thereof (collectively, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of a platinum-based chemotherapeutic agent (such as cisplatin, carboplatin, or oxaliplatin). In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the platinum-based chemotherapeutic agent. In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the platinum-based chemotherapeutic agent. In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or any embodiment, variation or aspect thereof (collectively, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of a platinum-based chemotherapeutic agent (such as cisplatin, carboplatin, or oxaliplatin). In some embodiments, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the platinum-based chemotherapeutic agent. In some embodiments, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the platinum-based chemotherapeutic agent.

[0144] In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or any embodiment, variation or aspect thereof (collectively, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of pemetrexed. In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the pemetrexed. In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the pemetrexed. In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or any embodiment, variation or aspect thereof (collectively, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of pemetrexed. In some embodiments, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the pemetrexed. In some embodiments, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the pemetrexed.

[0145] In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or any embodiment, variation or aspect thereof (collectively, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of a kinase inhibitor (such as bortezomib, erlotinib, gefitinib, imatinib, vemurafenib, vismodegib, or ibrutinib). In some embodiments, Formula I or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-

administered with the kinase inhibitor. In some embodiments, Formula I or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the kinase inhibitor. In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or any embodiment, variation or aspect thereof (collectively, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of a kinase inhibitor (such as bortezomib, erlotinib, gefitinib, imatinib, vemurafenib, vismodegib, or ibrutinib). In some embodiments, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11) or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the kinase inhibitor. In some embodiments, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11) or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the kinase inhibitor.

[0146] In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or any embodiment, variation or aspect thereof (collectively, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of a mTOR inhibitor (such as everolimus). In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the mTOR inhibitor. In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or any embodiment, variation or aspect thereof (collectively, Formula (J) or any related formulae where applicable, such as Formula (I),

(II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of a mTOR inhibitor (such as everolimus). In some embodiments, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the mTOR inhibitor.

[0147] In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or any embodiment, variation or aspect thereof (collectively, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of a PI3K or Akt inhibitor. In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the PI3K or Akt inhibitor. In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the PI3K or Akt inhibitor. In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or any embodiment, variation or aspect thereof (collectively, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of a PI3K or Akt inhibitor. In some embodiments, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the PI3K or Akt inhibitor. In some embodiments, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the PI3K or Akt inhibitor.

[0148] In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or any embodiment, variation or aspect thereof (collectively, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8),) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of a Bruton's tyrosine kinase (BTK) inhibitor. In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the BTK inhibitor. In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the BTK inhibitor. In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or any embodiment, variation or aspect thereof (collectively, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of a Bruton's tyrosine kinase (BTK) inhibitor. In some embodiments, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the BTK inhibitor. In some embodiments, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the BTK inhibitor.

[0149] In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8)), or any embodiment, variation or aspect thereof (collectively, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of a Cyclin-dependent kinase (CDK) inhibitor, such as inhibitor of CDK1, CDK2, CDK4, CDK5, CDK6, CDK7, or CDK9, or any combination thereof. In

some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the CDK inhibitor. In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the CDK inhibitor. In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or any embodiment, variation or aspect thereof (collectively, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of a Cyclin-dependent kinase (CDK) inhibitor, such as inhibitor of CDK1, CDK2, CDK4, CDK5, CDK6, CDK7, or CDK9, or any combination thereof. In some embodiments, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the CDK inhibitor. In some embodiments, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the CDK inhibitor.

[0150] In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or any embodiment, variation or aspect thereof (collectively, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of a DNA damage repair (DDR) pathway inhibitor. In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the DDR pathway inhibitor. In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or

more hours, or 48 or more hours) prior to or after the DDR pathway inhibitor. Examples of inhibitors of the DDR pathway include poly(ADP-ribose) polymerase (PARP) inhibitors (such as olaparib, rucaparib, niraparib, or talazoparib), ataxia telangiectasia mutated (ATM) protein inhibitors, ataxia telangiectasia and Rad3-related (ATR) protein inhibitors, checkpoint kinase 1 (Chk1) inhibitors, or combinations thereof. In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or any embodiment, variation or aspect thereof (collectively, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of a DNA damage repair (DDR) pathway inhibitor. In some embodiments, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the DDR pathway inhibitor. In some embodiments, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the DDR pathway inhibitor. Examples of inhibitors of the DDR pathway include poly(ADP-ribose) polymerase (PARP) inhibitors (such as olaparib, rucaparib, niraparib, or talazoparib), ataxia telangiectasia mutated (ATM) protein inhibitors, ataxia telangiectasia and Rad3-related (ATR) protein inhibitors, checkpoint kinase 1 (Chk1) inhibitors, or combinations thereof.

[0151] In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or any embodiment, variation or aspect thereof (collectively, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8),) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of a PARP inhibitor (such as olaparib, rucaparib, niraparib, or talazoparib). In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the PARP inhibitor. In some embodiments, Formula (I), (II),

(IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the PARP inhibitor. In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or any embodiment, variation or aspect thereof (collectively, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of a PARP inhibitor (such as olaparib, rucaparib, niraparib, or talazoparib). In some embodiments, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the PARP inhibitor. In some embodiments, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the PARP inhibitor.

[0152] In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or any embodiment, variation or aspect thereof (collectively, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of an ATM protein inhibitor. In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the ATM protein inhibitor. In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the ATM protein inhibitor. In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-

1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or any embodiment, variation or aspect thereof (collectively, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of an ATM protein inhibitor. In some embodiments, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the ATM protein inhibitor. In some embodiments, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the ATM protein inhibitor.

[0153] In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8)), or any embodiment, variation or aspect thereof (collectively, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of an ATR protein inhibitor. In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the ATR protein inhibitor. In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the ATR protein inhibitor. In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or any embodiment, variation or aspect thereof (collectively, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of an ATR protein inhibitor. In some embodiments, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8),

(IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the ATR protein inhibitor. In some embodiments, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the ATR protein inhibitor.

[0154] In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or any embodiment, variation or aspect thereof (collectively, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of a Chk1 inhibitor. In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the Chk1 inhibitor. In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the Chk1 inhibitor. In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or any embodiment, variation or aspect thereof (collectively, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of a Chk1 inhibitor. In some embodiments, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the Chk1 inhibitor. In some embodiments, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the Chk1 inhibitor.

[0155] In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or any embodiment, variation or aspect thereof (collectively, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of a Wee1 inhibitor. In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the Wee1 inhibitor. In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the Wee1 inhibitor. In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or any embodiment, variation or aspect thereof (collectively, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of a Wee1 inhibitor. In some embodiments, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the Wee1 inhibitor. In some embodiments, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the Wee1 inhibitor.

[0156] In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or any embodiment, variation or aspect thereof (collectively, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of an endocrine therapy agent. In some embodiments, the endocrine therapy is antiestrogen therapy. In some embodiments, the endocrine therapy is a

selective estrogen receptor degrader (SERD, such as fulvestrant). In some embodiments, the endocrine therapy is an aromatase inhibitor (such as letrozole). In some embodiments, the endocrine therapy is an anti-androgen therapy (such as enzalutamide or apalutamide). In some embodiments, the endocrine therapy is a CYP17 inhibitor (such as abiraterone). In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the endocrine therapy agent. In some embodiments, Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the endocrine therapy agent. In some embodiments, a method of treating a disease in an individual is provided, the method comprising (a) administering an effective amount of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or any embodiment, variation or aspect thereof (collectively, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11)) or a pharmaceutically acceptable salt thereof, and (b) administering an effective amount of an endocrine therapy agent. In some embodiments, the endocrine therapy is antiestrogen therapy. In some embodiments, the endocrine therapy is a selective estrogen receptor degrader (SERD, such as fulvestrant). In some embodiments, the endocrine therapy is an aromatase inhibitor (such as letrozole). In some embodiments, the endocrine therapy is an anti-androgen therapy (such as enzalutamide or apalutamide). In some embodiments, the endocrine therapy is a CYP17 inhibitor (such as abiraterone). In some embodiments, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered prior to, after, or simultaneously co-administered with the endocrine therapy agent. In some embodiments, Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a pharmaceutically acceptable salt thereof is administered 1 or more hours (such as 2 or more hours, 4 or more hours, 8 or more hours, 12 or more hours, 24 or more hours, or 48 or more hours) prior to or after the endocrine therapy agent.

[0157] In another aspect, provided herein is a combination therapy in which a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a salt thereof is coadministered (which may be separately or simultaneously) with one or more additional agents that are effective in stimulating immune responses to thereby further enhance, stimulate or upregulate immune responses in a subject. For example, provided is a method for stimulating an immune response in a subject comprising administering to the subject a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a salt thereof and one or more immunostimulatory antibodies, such as an anti-PD-1 antibody, an anti-PD-L1 antibody and/or an anti-CTLA-4 antibody, such that an immune response is stimulated in the subject, for example to inhibit tumor growth. In one embodiment, the subject is administered a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a salt thereof and an anti-PD-1 antibody. In another embodiment, the subject is administered a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a salt thereof and an anti-PD-L1 antibody. In yet another embodiment, the subject is administered a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a salt thereof and an anti-CTLA-4 antibody. In another embodiment, the immunostimulatory antibody (e.g., anti-PD-1, anti-PD-L1 and/or anti-CTLA-4 antibody) is a human antibody. Alternatively, the immunostimulatory antibody can be, for example, a chimeric or humanized antibody (e.g., prepared from a mouse anti-PD-1, anti-PD-L1 and/or anti-CTLA-4 antibody). In another aspect, provided herein is a combination therapy in which a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a salt thereof is coadministered (which may be separately or simultaneously) with one or more additional agents that are effective in stimulating immune responses to thereby further enhance, stimulate or upregulate immune responses in a subject. For example, provided is a method for stimulating an immune response in a subject comprising administering to the subject a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a salt thereof and one or more immunostimulatory antibodies, such as an anti-PD-1 antibody, an anti-PD-L1 antibody and/or an anti-CTLA-4 antibody, such that an immune response is stimulated in the subject, for example to inhibit tumor growth. In one embodiment, the subject is administered a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a salt thereof and an

anti-PD-1 antibody. In another embodiment, the subject is administered a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a salt thereof and an anti-PD-L1 antibody. In yet another embodiment, the subject is administered a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a salt thereof and an anti-CTLA-4 antibody. In another embodiment, the immunostimulatory antibody (e.g., anti-PD-1, anti-PD-L1 and/or anti-CTLA-4 antibody) is a human antibody. Alternatively, the immunostimulatory antibody can be, for example, a chimeric or humanized antibody (e.g., prepared from a mouse anti-PD-1, anti-PD-L1 and/or anti-CTLA-4 antibody).

[0158] In one embodiment, the present disclosure provides a method for treating a proliferative disease (e.g., cancer), comprising administering a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a salt thereof and an anti-PD-1 antibody or to a subject. In further embodiments, a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a salt thereof is administered at a subtherapeutic dose, the anti-PD-1 antibody is administered at a subtherapeutic dose, or both are administered at a subtherapeutic dose. In another embodiment, the present disclosure provides a method for altering an adverse event associated with treatment of a hyperproliferative disease with an immunostimulatory agent, comprising administering a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a salt thereof and a subtherapeutic dose of anti-PD-1 antibody to a subject. In certain embodiments, the subject is human. In certain embodiments, the anti-PD-1 antibody is a human sequence monoclonal antibody. In one embodiment, the present disclosure provides a method for treating a proliferative disease (e.g., cancer), comprising administering a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a salt thereof and an anti-PD-1 antibody or to a subject. In further embodiments, a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a salt thereof is administered at a subtherapeutic dose, the anti-PD-1 antibody is administered at a subtherapeutic dose, or both are administered at a subtherapeutic dose. In another embodiment, the present disclosure provides a method for altering an adverse event associated with treatment of a hyperproliferative disease with an immunostimulatory agent, comprising administering a compound of Formula (J) or any related formulae where applicable,

such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a salt thereof and a subtherapeutic dose of anti-PD-1 antibody to a subject. In certain embodiments, the subject is human. In certain embodiments, the anti-PD-1 antibody is a human sequence monoclonal antibody.

[0159] In one embodiment, the present invention provides a method for treating a hyperproliferative disease (e.g., cancer), comprising administering a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a salt thereof and an anti-PD-L1 antibody to a subject. In further embodiments, a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a salt thereof is administered at a subtherapeutic dose, the anti-PD-L1 antibody is administered at a subtherapeutic dose, or both are administered at a subtherapeutic dose. In another embodiment, the present invention provides a method for altering an adverse event associated with treatment of a hyperproliferative disease with an immunostimulatory agent, comprising administering a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a salt thereof and a subtherapeutic dose of anti-PD-L1 antibody to a subject. In certain embodiments, the subject is human. In certain embodiments, the anti-PD-L1 antibody is a human sequence monoclonal antibody. In one embodiment, the present invention provides a method for treating a hyperproliferative disease (e.g., cancer), comprising administering a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a salt thereof and an anti-PD-L1 antibody to a subject. In further embodiments, a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a salt thereof is administered at a subtherapeutic dose, the anti-PD-L1 antibody is administered at a subtherapeutic dose, or both are administered at a subtherapeutic dose. In another embodiment, the present invention provides a method for altering an adverse event associated with treatment of a hyperproliferative disease with an immunostimulatory agent, comprising administering a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a salt thereof and a subtherapeutic dose of anti-PD-L1 antibody to a subject. In certain embodiments, the subject is human. In certain embodiments, the anti-PD-L1 antibody is a human sequence monoclonal antibody.

[0160] In certain embodiments, the combination of therapeutic agents discussed herein can be administered concurrently as a single composition in a pharmaceutically acceptable carrier, or concurrently as separate compositions each in a pharmaceutically acceptable carrier. In another embodiment, the combination of therapeutic agents can be administered sequentially. For example, an anti-CTLA-4 antibody and a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a salt thereof can be administered sequentially, such as anti-CTLA-4 antibody being administered first and a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a salt thereof second, or a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a salt thereof being administered first and anti-CTLA-4 antibody second. Additionally or alternatively, an anti-PD-1 antibody and a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a salt thereof can be administered sequentially, such as anti-PD-1 antibody being administered first and a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a salt thereof second, or a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a salt thereof being administered first and anti-PD-1 antibody second. Additionally or alternatively, an anti-PD-L1 antibody and a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a salt thereof can be administered sequentially, such as anti-PD-L1 antibody being administered first and a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a salt thereof second, or a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a salt thereof being administered first and anti-PD-L1 antibody second. In certain embodiments, the combination of therapeutic agents discussed herein can be administered concurrently as a single composition in a pharmaceutically acceptable carrier, or concurrently as separate compositions each in a pharmaceutically acceptable carrier. In another embodiment, the combination of therapeutic agents can be administered sequentially. For example, an anti-CTLA-4 antibody and a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a salt thereof can be administered sequentially, such as anti-CTLA-4 antibody being administered first and a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a salt thereof second, or a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a salt thereof being administered first and anti-CTLA-4 antibody second. Additionally or alternatively, an anti-

PD-1 antibody and a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a salt thereof can be administered sequentially, such as anti-PD-1 antibody being administered first and a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a salt thereof second, or a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a salt thereof being administered first and anti-PD-1 antibody second. Additionally or alternatively, an anti-PD-L1 antibody and a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a salt thereof can be administered sequentially, such as anti-PD-L1 antibody being administered first and a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a salt thereof second, or a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a salt thereof being administered first and anti-PD-L1 antibody second.

[0161] Furthermore, if more than one dose of the combination therapy is administered sequentially, the order of the sequential administration can be reversed or kept in the same order at each time point of administration, sequential administrations can be combined with concurrent administrations, or any combination thereof.

[0162] Optionally, the combination of a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a salt thereof can be further combined with an immunogenic agent, such as cancerous cells, purified tumor antigens (including recombinant proteins, peptides, and carbohydrate molecules), cells, and cells transfected with genes encoding immune stimulating cytokines. Optionally, the combination of a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a salt thereof can be further combined with an immunogenic agent, such as cancerous cells, purified tumor antigens (including recombinant

proteins, peptides, and carbohydrate molecules), cells, and cells transfected with genes encoding immune stimulating cytokines.

[0163] A compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a salt thereof can also be further combined with standard cancer treatments. For example, a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a salt thereof can be effectively combined with chemotherapeutic regimens. In these instances, it is possible to reduce the dose of other chemotherapeutic reagent administered with the combination of the instant disclosure. Other combination therapies with a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a salt thereof include radiation, surgery, or hormone deprivation. Angiogenesis inhibitors can also be combined with a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a salt thereof. Inhibition of angiogenesis leads to tumor cell death, which can be a source of tumor antigen fed into host antigen presentation pathways. A compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a salt thereof can also be further combined with standard cancer treatments. For example, a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a salt thereof can be effectively combined with chemotherapeutic regimens. In these instances, it is possible to reduce the dose of other chemotherapeutic reagent administered with the combination of the instant disclosure. Other combination therapies with a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a salt thereof include radiation, surgery, or hormone deprivation. Angiogenesis inhibitors can also be combined with a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a salt thereof. Inhibition of angiogenesis leads to tumor cell death, which can be a source of tumor antigen fed into host antigen presentation pathways.

[0164] In another example, a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a salt thereof can be used in conjunction with anti-neoplastic antibodies. By way of example and not wishing to be bound by theory, treatment with an anti-cancer antibody or an anti-cancer antibody conjugated to a toxin can lead to cancer cell death (e.g., tumor cells) which would

potentiate an immune response mediated by CTLA-4, PD-1, PD-L1 or a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a salt thereof. In an exemplary embodiment, a treatment of a hyperproliferative disease (e.g., a cancer tumor) can include an anti-cancer antibody in combination with a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a salt thereof and anti-CTLA-4 and/or anti-PD-1 and/or anti-PD-L1 antibodies, concurrently or sequentially or any combination thereof, which can potentiate anti-tumor immune responses by the host. Other antibodies that can be used to activate host immune responsiveness can be further used in combination with a compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a salt thereof. In another example, a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a salt thereof can be used in conjunction with anti-neoplastic antibodies. By way of example and not wishing to be bound by theory, treatment with an anti-cancer antibody or an anti-cancer antibody conjugated to a toxin can lead to cancer cell death (e.g., tumor cells) which would potentiate an immune response mediated by CTLA-4, PD-1, PD-L1 or a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a salt thereof. In an exemplary embodiment, a treatment of a hyperproliferative disease (e.g., a cancer tumor) can include an anti-cancer antibody in combination with a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a salt thereof and anti-CTLA-4 and/or anti-PD-1 and/or anti-PD-L1 antibodies, concurrently or sequentially or any combination thereof, which can potentiate anti-tumor immune responses by the host. Other antibodies that can be used to activate host immune responsiveness can be further used in combination with a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a salt thereof.

[0165] In yet further embodiments, the compound of Formula (I), (II), (IIa-1) to (IIa-8), (III) and (IIIa-1) to (IIIa-8), or a salt thereof is administered in combination with another BET inhibitor. In yet further embodiments, the compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a salt thereof is administered in combination with another BET inhibitor.

Dosing and Method of Administration

[0166] The dose of a compound administered to an individual (such as a human) may vary with the particular compound or salt thereof, the method of administration, and the particular disease, such as type and stage of cancer, being treated. In some embodiments, the amount of the compound or salt thereof is a therapeutically effective amount.

[0167] The effective amount of the compound may in one aspect be a dose of between about 0.01 and about 100 mg/kg. Effective amounts or doses of the compounds of the invention may be ascertained by routine methods, such as modeling, dose escalation, or clinical trials, taking into account routine factors, e.g., the mode or route of administration or drug delivery, the pharmacokinetics of the agent, the severity and course of the disease to be treated, the subject's health status, condition, and weight. An exemplary dose is in the range of about from about 0.7 mg to 7 g daily, or about 7 mg to 350 mg daily, or about 350 mg to 1.75 g daily, or about 1.75 to 7 g daily.

[0168] Any of the methods provided herein may in one aspect comprise administering to an individual a pharmaceutical composition that contains an effective amount of a compound provided herein or a salt thereof and a pharmaceutically acceptable excipient.

[0169] A compound or composition of the invention may be administered to an individual in accordance with an effective dosing regimen for a desired period of time or duration, such as at least about one month, at least about 2 months, at least about 3 months, at least about 6 months, or at least about 12 months or longer, which in some variations may be for the duration of the individual's life. In one variation, the compound is administered on a daily or intermittent schedule. The compound can be administered to an individual continuously (for example, at least once daily) over a period of time. The dosing frequency can also be less than once daily, e.g., about a once weekly dosing. The dosing frequency can be more than once daily, e.g., twice or three times daily. The dosing frequency can also be intermittent, including a 'drug holiday' (e.g., once daily dosing for 7 days followed by no doses for 7 days, repeated for any 14 day time period, such as about 2 months, about 4 months, about 6 months or more). Any of the dosing frequencies can employ any of the compounds described herein together with any of the dosages described herein.

[0170] The compounds provided herein or a salt thereof may be administered to an individual via various routes, including, e.g., intravenous, intramuscular, subcutaneous, oral and transdermal.

A compound provided herein can be administered frequently at low doses, known as “metronomic therapy,” or as part of a maintenance therapy using compound alone or in combination with one or more additional drugs. Metronomic therapy or maintenance therapy can comprise administration of a compound provided herein in cycles. Metronomic therapy or maintenance therapy can comprise intra-tumoral administration of a compound provided herein.

[0171] In one aspect, the invention provides a method of treating cancer in an individual by parenterally administering to the individual (e.g., a human) an effective amount of a compound or salt thereof. In some embodiments, the route of administration is intravenous, intra-arterial, intramuscular, or subcutaneous. In some embodiments, the route of administration is oral. In still other embodiments, the route of administration is transdermal.

[0172] The invention also provides compositions (including pharmaceutical compositions) as described herein for the use in treating, preventing, and/or delaying the onset and/or development of cancer and other methods described herein. In certain embodiments, the composition comprises a pharmaceutical formulation which is present in a unit dosage form.

[0173] Also provided are articles of manufacture comprising a compound of the disclosure or a salt thereof, composition, and unit dosages described herein in suitable packaging for use in the methods described herein. Suitable packaging is known in the art and includes, for example, vials, vessels, ampules, bottles, jars, flexible packaging and the like. An article of manufacture may further be sterilized and/or sealed kits.

[0174] The present disclosure further provides kits for carrying out the methods of the invention, which comprises one or more compounds described herein or a composition comprising a compound described herein. The kits may employ any of the compounds disclosed herein. In one variation, the kit employs a compound described herein or a pharmaceutically acceptable salt thereof. The kits may be used for any one or more of the uses described herein, and, accordingly, may contain instructions for the treatment of cancer.

[0175] Kits generally comprise suitable packaging. The kits may comprise one or more containers comprising any compound described herein. Each component (if there is more than one component) can be packaged in separate containers or some components can be combined in one container where cross-reactivity and shelf life permit.

[0176] The kits may be in unit dosage forms, bulk packages (*e.g.*, multi-dose packages) or subunit doses. For example, kits may be provided that contain sufficient dosages of a compound as disclosed herein and/or a second pharmaceutically active compound useful for a disease detailed herein (*e.g.*, hypertension) to provide effective treatment of an individual for an extended period, such as any of a week, 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks, 3 months, 4 months, 5 months, 7 months, 8 months, 9 months, or more. Kits may also include multiple unit doses of the compounds and instructions for use and be packaged in quantities sufficient for storage and use in pharmacies (*e.g.*, hospital pharmacies and compounding pharmacies).

[0177] The kits may optionally include a set of instructions, generally written instructions, although electronic storage media (*e.g.*, magnetic diskette or optical disk) containing instructions are also acceptable, relating to the use of component(s) of the methods of the present invention. The instructions included with the kit generally include information as to the components and their administration to an individual.

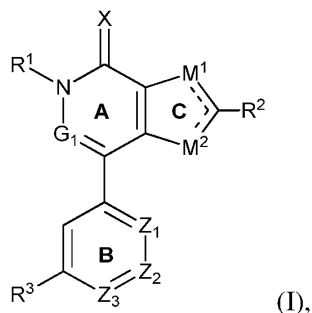
[0178] The invention can be further understood by reference to the following examples, which are provided by way of illustration and are not meant to be limiting.

General Information

[0179] ^1H NMR spectra and ^{13}C NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer. Spectra are referenced to residual chloroform (δ 7.26, ^1H), DMSO (δ 2.54, ^1H) or methanol (δ 3.34, ^1H) unless otherwise noted. Chemical shifts are reported in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sext (sextet), m (multiplet) and br (broad). Coupling constants, *J*, are reported in Hertz. Analytical HPLC was performed on an Agilent 1200 HPLC with an Agilent G1365D diode array detector using an Agilent Eclipse XDB-C18 (4.6 $\times$ 150 mm, 5 μm) column. Analytical LCMS was performed on an Agilent 6410 triple quadrupole LCMS. Commercially available reagents and solvents were used as received unless otherwise indicated.

Selected embodiments

Embodiment 1. A compound of Formula (I):



or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

each $\equiv$ is independently a single bond or double bond;

X is O or S;

R¹ is hydrogen, C₁-C₃ alkyl, -(C₁-C₃ alkylene)OH, C₁-C₃ haloalkyl, or C₃-C₄ cycloalkyl;

G₁ is CR^a or N, wherein:

R^a is hydrogen, halogen, or C₁-C₄ alkyl;

Z₁ is C-W₁-R^c; wherein:

each W₁ is independently -O- or -NR^{w1}-, wherein:

R^{w1} is hydrogen, C₃-C₆ cycloalkyl, or C₁-C₄ alkyl optionally substituted by oxo, -OH, or halogen, and

R^c is independently 4- to 6- membered heterocyclyl, C₆-C₁₄ aryl, or 5- or 6-membered heteroaryl, each of which is independently optionally substituted by R^{c1}, wherein each R^{c1} is independently halogen, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, 3- to 6-membered heterocyclyl, cyano, oxo, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₁-C₄ haloalkyl, -OR¹⁰, -NR¹⁰R¹¹, -C(O)NR¹⁰R¹¹, -NR¹⁰C(O)R¹¹, -S(O)₂R¹⁰, -NR¹⁰S(O)₂R¹¹, or -S(O)₂NR¹⁰R¹¹;

Z₂ is C-W₂-R^d or N, wherein:

W₂ is -O-, -NR^{w2}-, or a bond, wherein:

R^{w2} is hydrogen, C₃-C₆ cycloalkyl, or C₁-C₄ alkyl optionally substituted by oxo, -OH, or halogen, and

R^d is independently hydrogen, halogen, cyano, 3- to 6-membered heterocyclyl, or C₁-C₄ alkyl;

Z_3 is C-R^e or N, wherein:

R^e is independently hydrogen, halogen, cyano, 3- to 6-membered heterocyclyl, or C₁-C₄ alkyl;

M¹ is S or CR^{1a};

M² is S or CR^{2a}, provided that

- (1) when M¹ is S, then the --- adjacent to M¹ is a single bond and the = adjacent to M² is a double bond,
- (2) when M² is S, then the --- adjacent to M² is a single bond and the = adjacent to M¹ is a double bond, and
- (3) at least one of M¹ and M² is not S;

R^{1a} and R^{2a} are each independently hydrogen, halogen, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, 3- to 6-membered heterocyclyl, 5- to 10-membered heteroaryl, cyano, oxo, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, -OR¹⁰, -NR¹⁰R¹¹, -C(O)OR¹⁰, -C(O)NR¹⁰R¹¹, -NR¹⁰C(O)R¹¹, -S(O)₂R¹⁰, -NR¹⁰S(O)₂R¹¹ or -S(O)₂NR¹⁰R¹¹, each of which is independently optionally substituted by R¹²;

R² is halogen, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, 3- to 6-membered heterocyclyl, -(C₁-C₃ alkylene)3- to 6-membered heterocyclyl, 5- to 10-membered heteroaryl, cyano, oxo, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, -OR¹⁰, -NR¹⁰R¹¹, -C(O)OR¹⁰, -C(O)NR¹⁰R¹¹, -NR¹⁰C(O)R¹¹, -S(O)₂R¹⁰, -NR¹⁰S(O)₂R¹¹, or -S(O)₂NR¹⁰R¹¹, each of which is independently optionally substituted by R¹²;

R³ is -(CH₂)_mNR¹³S(O)₂R¹⁴, C₃-C₆ cycloalkyl, or C₁-C₄ alkyl substituted by halogen, oxo, -CN, or -OH, wherein m is 0, 1, 2 or 3;

R¹⁰ and R¹¹ are each independently hydrogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ alkenyl, C₃-C₆ cycloalkyl, 3- to 6-membered heterocyclyl, -(C₁-C₃ alkylene)C₃-C₆ cycloalkyl, -(C₁-C₃ alkylene) 3- to 6-membered heterocyclyl, -NR¹⁵R¹⁶, or -C(O)R¹², wherein each of R¹⁰ and R¹¹ is independently optionally substituted by halogen, oxo, -CN, -CF₃, -OH, -NR¹³R¹⁴, -C(O)NR¹³R¹⁴, or C₁-C₄ alkyl optionally substituted by halogen, oxo, -CN, -CF₃, or -OH,

or R¹⁰ and R¹¹ are taken together with the atom or atoms to which they are attached to form a 3- to 6-membered heterocyclyl ring optionally substituted by halogen, oxo, -CN, -CF₃, -OH, or C₁-C₄ alkyl optionally substituted by halogen, oxo, -CN, or -OH;

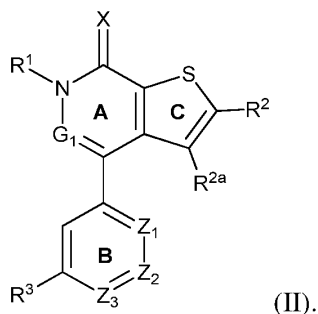
each R¹² is independently halogen, cyano, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, -OR¹⁵,

$-\text{NR}^{15}\text{R}^{16}$, $-\text{C}(\text{O})\text{NR}^{15}\text{R}^{16}$, $-\text{NR}^{15}\text{C}(\text{O})\text{R}^{16}$, $-\text{S}(\text{O})_2\text{R}^{15}$, $-\text{NR}^{15}\text{S}(\text{O})_2\text{R}^{16}$, $-\text{S}(\text{O})_2\text{NR}^{15}\text{R}^{16}$, $\text{C}_3\text{-C}_6$ cycloalkyl, 3- to 6-membered heterocyclyl, or $\text{C}_1\text{-C}_4$ alkyl, each of which is independently optionally substituted by halogen, oxo, $-\text{CF}_3$, $-\text{CN}$, $-\text{OH}$, $-\text{NR}^{13}\text{R}^{14}$, or $-\text{NR}^{13}\text{C}(\text{O})\text{R}^{14}$,

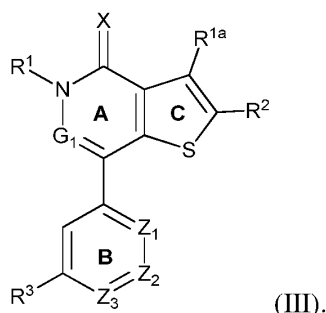
R^{13} and R^{14} are independently hydrogen, $\text{C}_1\text{-C}_4$ alkyl $\text{C}_3\text{-C}_6$ cycloalkyl, or 3- to 6-membered heterocyclyl, each of which is independently optionally substituted by halogen, oxo, $-\text{CN}$, or $-\text{OH}$, or R^{13} and R^{14} are taken together with the atom or atoms to which they are attached to form a 3- to 6-membered heterocyclyl ring optionally substituted by halogen, oxo, $-\text{CN}$, $-\text{OH}$, or $\text{C}_1\text{-C}_4$ alkyl optionally substituted by halogen, oxo, $-\text{CN}$, or $-\text{OH}$; and

each R^{15} and R^{16} are independently hydrogen, $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_3\text{-C}_6$ cycloalkyl, or 3- to 6-membered heterocyclyl, each of which is independently optionally substituted by halogen, oxo, $-\text{CN}$, or $-\text{OH}$, or R^{15} and R^{16} are taken together with the atoms to which they are attached to form a 3- to 6-membered heterocyclyl ring optionally substituted by halogen, oxo, $-\text{CN}$, $-\text{OH}$, or $\text{C}_1\text{-C}_4$ alkyl optionally substituted by halogen, oxo, $-\text{CN}$, or $-\text{OH}$.

Embodiment 2. The compound of embodiment 1, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is of Formula (II),



Embodiment 3. The compound of embodiment 1, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is of Formula (III),



Embodiment 4. The compound of any one of embodiments 1-3, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X is O.

Embodiment 5. The compound of any one of embodiments 1-4, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein G₁ is CH.

Embodiment 6. The compound of any one of embodiments 1-5, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Z¹ is C-W₁-R^c and R^c is C₆-C₁₄ aryl optionally substituted by R^{c1}.

Embodiment 7. The compound of embodiment 6, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^c is phenyl optionally substituted by halogen or C₁-C₄ alkyl.

Embodiment 8. The compound of any one of embodiments 1-7, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Z₂ is CH.

Embodiment 9. The compound of any one of embodiments 1-8, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Z₃ is CH.

Embodiment 10. The compound of any one of embodiments 1-9, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R¹ is C₁-C₃ alkyl.

Embodiment 11. The compound of any one of embodiments 1-10, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R² is -C(O)NR¹⁰R¹¹, 5- to 10-membered heteroaryl, -(C₁-C₃ alkylene)₃- to 6-membered heterocyclyl, or C₁-C₄ alkyl, each of which is independently optionally substituted by R¹².

Embodiment 12. The compound of embodiment 11, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R² is -C(O)NR¹⁰R¹¹ which is

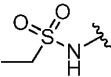
optionally substituted by R^{12} , wherein R^{10} and R^{11} are each independently hydrogen, C_1 - C_4 alkyl, or C_3 - C_6 cycloalkyl, or R^{10} and R^{11} are taken together with the atom or atoms to which they are attached to form a 3- to 6-membered heterocyclyl ring optionally substituted by halogen.

Embodiment 13. The compound of embodiment 11, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is 5- to 10-membered heteroaryl optionally substituted by R^{12} .

Embodiment 14. The compound of any one of embodiments 1-13, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^3 is - $(CH_2)_mNR^{13}S(O)_2R^{14}$ or C_1 - C_4 alkyl substituted by halogen, oxo, -CN, or -OH.

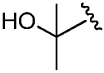
Embodiment 15. The compound of any one of embodiments 1-14, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^3 is - $(CH_2)_mNR^{13}S(O)_2R^{14}$.

Embodiment 16. The compound of any one of embodiments 1-15, or a tautomer or isomer

thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^3 is .

Embodiment 17. The compound of any one of embodiments 1-14, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^3 is C_1 - C_4 alkyl substituted by -OH.

Embodiment 18. The compound of embodiment 17, or a tautomer or isomer thereof, or a

pharmaceutically acceptable salt of any of the foregoing, wherein R^3 is .

Embodiment 19. The compound of any one of embodiments 1 and 3-18, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^{1a} is hydrogen.

Embodiment 20. The compound of any one of embodiments 1, 2, and 4-18, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^{2a} is hydrogen.

Embodiment 21. The compound of embodiment 1, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of the compounds in Table 1.

Embodiment 22. A pharmaceutical composition comprising the compound of any one of embodiments 1-21, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and a pharmaceutically acceptable carrier.

Embodiment 23. A method of treating disease mediated by bromodomain and extraterminal domain (BET) in an individual in need thereof comprising administering to the individual a therapeutically effective amount of the compound of any one of embodiments 1-21, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

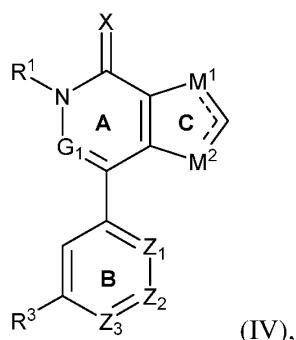
Embodiment 24. A method of treating cancer in an individual in need thereof comprising administering to the individual a therapeutically effective amount of the compound of any one of embodiments 1-21, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

Embodiment 25. A method of inhibiting bromodomain and extraterminal domain (BET) in a cell, comprising administering the compound of any one of embodiments 1-21, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, to the cells.

Embodiment 26. Use of the compound of any one of embodiments 1-21, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, in the manufacture of a medicament for treatment of a disease mediated by bromodomain and extraterminal domain (BET).

Embodiment 27. A kit comprising the compound of any one of embodiments 1-21, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

Embodiment 2.1. A compound of Formula (IV):



or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

each --- is independently a single bond or double bond;

X is O or S;

R¹ is hydrogen, C₁-C₃ alkyl, -(C₁-C₃ alkylene)OH, C₁-C₃ haloalkyl, or C₃-C₄ cycloalkyl;

G₁ is CR^a or N, wherein:

R^a is hydrogen, halogen, C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

Z₁ is C-W₁-R^c, wherein:

each W₁ is independently -O- or -NR^{w1}-, wherein:

R^{w1} is hydrogen, C₃-C₆ cycloalkyl, or C₁-C₄ alkyl optionally substituted by oxo, -OH, or halogen, and

R^c is independently C₃-C₆ cycloalkyl, 4- to 6- membered heterocyclyl, C₆-C₁₄ aryl, or 5- or 6-membered heteroaryl, each of which is independently optionally substituted by R^{c1}, wherein each R^{c1} is independently halogen, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, 3- to 6-membered heterocyclyl, cyano, oxo, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₁-C₄ haloalkyl, -OR¹⁰, -NR¹⁰R¹¹, -C(O)NR¹⁰R¹¹, -NR¹⁰C(O)R¹¹, -S(O)₂R¹⁰, -NR¹⁰S(O)₂R¹¹, or -S(O)₂NR¹⁰R¹¹;

Z₂ is C-W₂-R^d or N, wherein:

W₂ is -O-, -NR^{w2}-, or a bond, wherein:

R^{w2} is hydrogen, C₃-C₆ cycloalkyl, or C₁-C₄ alkyl optionally substituted by oxo, -OH, or halogen, and

R^d is independently hydrogen, halogen, cyano, 3- to 6-membered heterocyclyl, or C₁-C₄ alkyl;

Z₃ is C-R^e or N, wherein:

R^e is independently hydrogen, halogen, cyano, 3- to 6-membered heterocyclyl, or C₁-C₄ alkyl;

M¹ is S or CR^{1a};

M² is S or CR^{2a}, provided that

(1) when M^1 is S, then the $\equiv$ adjacent to M^1 is a single bond and the $\equiv$ adjacent to M^2 is a double bond,

(2) when M^2 is S, then the $\equiv$ adjacent to M^2 is a single bond and the $\equiv$ adjacent to M^1 is a double bond, and

(3) at least one of M^1 and M^2 is S;

R^{1a} and R^{2a} are each independently hydrogen, halogen, C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, 3- to 6-membered heterocyclyl, 5- to 10-membered heteroaryl, cyano, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy, $-OR^{10}$, $-NR^{10}R^{11}$, $-C(O)OR^{10}$, $-C(O)NR^{10}R^{11}$, $-NR^{10}C(O)R^{11}$, $-S(O)_2R^{10}$, $-NR^{10}S(O)_2R^{11}$ or $-S(O)_2NR^{10}R^{11}$, each of which is independently optionally substituted by R^{12} ;

R^3 is $-(CH_2)_mNR^{13}S(O)_2R^{14}$, wherein m is 0, 1, 2 or 3; C_3 - C_6 cycloalkyl optionally substituted by halogen, oxo, -CN, or -OH; or C_1 - C_4 alkyl substituted by halogen, oxo, -CN, or -OH;

R^{10} and R^{11} are each independently hydrogen, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_4 alkenyl, C_3 - C_6 cycloalkyl, 3- to 6-membered heterocyclyl, $-(C_1-C_3 \text{ alkylene}) C_3$ - C_6 cycloalkyl, $-(C_1-C_3 \text{ alkylene})$ 3- to 6-membered heterocyclyl, $-NR^{15}R^{16}$, or $-C(O)R^{12}$, wherein each of R^{10} and R^{11} is independently optionally substituted by halogen, oxo, -CN, $-CF_3$, -OH, $-NR^{13}R^{14}$, $-C(O)NR^{13}R^{14}$, or C_1 - C_4 alkyl optionally substituted by halogen, oxo, -CN, $-CF_3$, or -OH,

or R^{10} and R^{11} are taken together with the atom or atoms to which they are attached to form a 3- to 6-membered heterocyclyl ring optionally substituted by halogen, oxo, -CN, $-CF_3$, -OH, or C_1 - C_4 alkyl optionally substituted by halogen, oxo, -CN, or -OH;

each R^{12} is independently halogen, cyano, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy, $-OR^{15}$, $-NR^{15}R^{16}$, $-C(O)NR^{15}R^{16}$, $-NR^{15}C(O)R^{16}$, $-S(O)_2R^{15}$, $-NR^{15}S(O)_2R^{16}$, $-S(O)_2NR^{15}R^{16}$, C_3 - C_6 cycloalkyl, 3- to 6-membered heterocyclyl, or C_1 - C_4 alkyl, each of which is independently optionally substituted by halogen, oxo, $-CF_3$, -CN, -OH, $-NR^{13}R^{14}$, or $-NR^{13}C(O)R^{14}$;

R^{13} and R^{14} are independently hydrogen, C_1 - C_4 alkyl C_3 - C_6 cycloalkyl, or 3- to 6-membered heterocyclyl, each of which is independently optionally substituted by halogen, oxo, -CN, or -OH,

or R^{13} and R^{14} are taken together with the atom or atoms to which they are attached to form a 3- to 6-membered heterocyclyl ring optionally substituted by halogen, oxo, -CN, -OH, or C_1 - C_4 alkyl optionally substituted by halogen, oxo, -CN, or -OH; and

each R^{15} and R^{16} are independently hydrogen, C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, or 3- to 6-membered

heterocyclyl, each of which is independently optionally substituted by halogen, oxo, -CN, or -OH,

or R^{15} and R^{16} are taken together with the atoms to which they are attached to form a 3- to 6-membered heterocyclyl ring optionally substituted by halogen, oxo, -CN, -OH, or C_1 - C_4 alkyl optionally substituted by halogen, oxo, -CN, or -OH.

Embodiment 2.2. The compound of embodiment 2.1, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein M^1 is S.

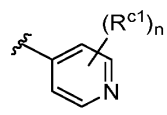
Embodiment 2.3. The compound of embodiment 2.1, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein M^2 is S.

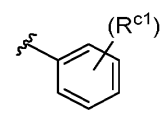
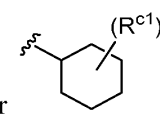
Embodiment 2.4. The compound of any one of embodiments 2.1-2.3, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X is O.

Embodiment 2.5. The compound of any one of embodiments 2.1-2.4, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Z_1 is $C-O-R^c$.

Embodiment 2.6. The compound of embodiment 2.5, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^c is phenyl, pyridinyl, or cyclohexyl, each of which is independently optionally substituted by R^{c1} .

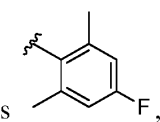
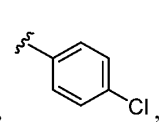
Embodiment 2.7. The compound of embodiment 2.5 or 2.6, or a tautomer or isomer thereof, or

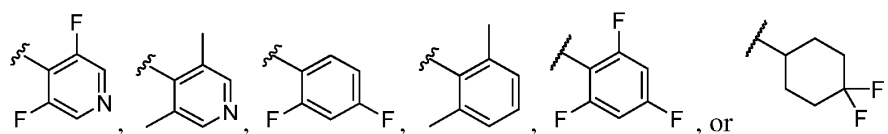
a pharmaceutically acceptable salt of any of the foregoing, wherein R^c is ,

, or , wherein n is 0, 1, 2, 3, or 4.

Embodiment 2.8. The compound of embodiment 2.6 or 2.7, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein each R^{c1} is independently halogen or C_1 - C_4 alkyl.

Embodiment 2.9. The compound of embodiment 2.8, or a tautomer or isomer thereof, or a

pharmaceutically acceptable salt of any of the foregoing, wherein R^c is , ,



Embodiment 2.10. The compound of any one of embodiments 2.1-2.9, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Z_2 is CH.

Embodiment 2.11. The compound of any one of embodiments 2.1-2.9, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Z_2 is N.

Embodiment 2.12. The compound of any one of embodiments 2.1-2.11, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Z_3 is CH.

Embodiment 2.13. The compound of any one of embodiment 2.1-2.12, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is C_1 - C_3 alkyl.

Embodiment 2.14. The compound of embodiment 2.13, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is methyl.

Embodiment 2.15. The compound of any one of embodiment 2.1-2.14, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein G_1 is CR^a , wherein R^a is hydrogen.

Embodiment 2.16. The compound of any one of embodiment 2.1-2.15, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein G_1 is N.

Embodiment 2.17. The compound of embodiment 2.1, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is selected from the compounds in Table 1.

Embodiment 2.18. A pharmaceutical composition comprising the compound of any one of embodiments 2.1-2.17, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and a pharmaceutically acceptable carrier.

Embodiment 2.19. A method of treating disease mediated by bromodomain and extraterminal domain (BET) in an individual in need thereof comprising administering to the individual a therapeutically effective amount of the compound of any one of embodiments 2.1-2.17, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

Embodiment 2.20. A method of treating cancer in an individual in need thereof comprising

administering to the individual a therapeutically effective amount of the compound of any one of embodiments 2.1-2.17, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

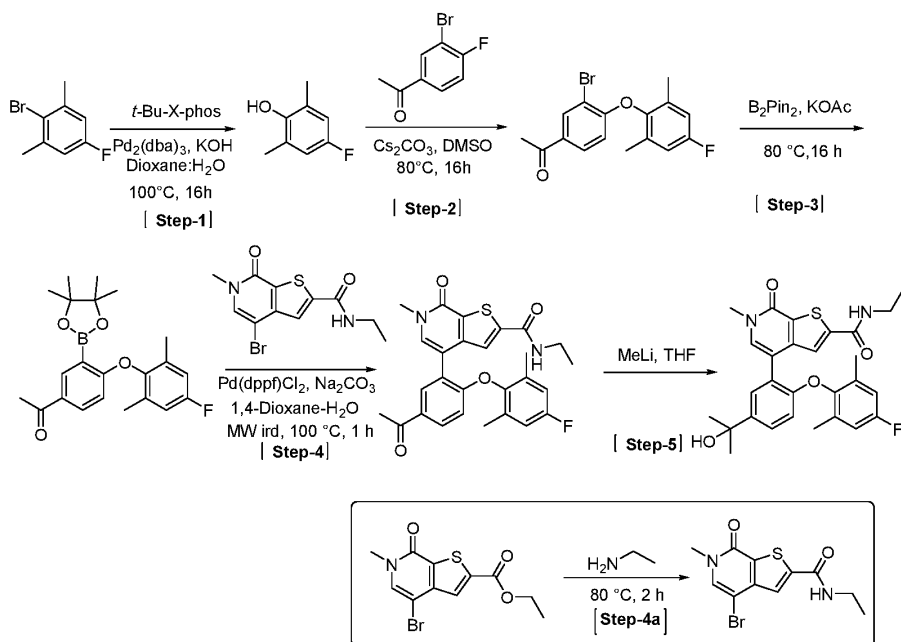
Embodiment 2.21. A method of inhibiting bromodomain and extraterminal domain (BET) in a cell, comprising administering the compound of any one of embodiments 2.1-2.17, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, to the cells.

Embodiment 2.22. Use of the compound of any one of embodiments 2.1-2.17, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, in the manufacture of a medicament for treatment of a disease mediated by bromodomain and extraterminal domain (BET).

Embodiment 2.23. A kit comprising the compound of any one of embodiment 2.1-2.17, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

Synthetic Examples

Example S-1: Synthesis of N-ethyl-4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (General Procedure 1) (Compound 1)



[0180] Step 1. Synthesis of 4-fluoro-2,6-dimethylphenol: Step 1: Synthesis of 4-fluoro-2,6-dimethylphenol: A solution of 2-bromo-5-fluoro-1,3-dimethylbenzene (5.0 g, 24.7 mmol, 1eq) in 1,4-Dioxane : water (25 mL : 25 mL) was added KOH (4.15 g, 74.2 mmol, 3eq) and the mixture was degassed under nitrogen for 15 min. In another set-up, t-Bu-X-phos (839 mg, 7.98 mmol 0.08eq) and Pd₂(dba)₃ (452 mg, 0.49 mmol, 0.08eq) in 1,4-dioxane: water (10 mL : 10 mL) was degassed under nitrogen for 15 min. The contents of the first degassed mixture was transferred into the degassed solution of the second and the mixture was heated at 100 °C and monitored by TLC and LC-MS. The reaction was complete after 16 h and the mixture was acidified with 6N-HCl (pH ~2-3) and extracted with EtOAc (700 mL). The organic layer was washed with water (300 mL) , brine (200 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to obtain a crude residue which was purified by CombiFlash chromatography to afford 4-fluoro-2,6-dimethylphenol (2.2 g, 64 %) as a viscous brown solid. LCMS: 141 [M+1]⁺

[0181] Step 2. Synthesis of 1-(3-bromo-4-(4-fluoro-2,6-dimethylphenoxy)phenyl)ethanone: To a solution of 4-fluoro-2,6-dimethylphenol (0.50 g, 3.57 mmol) in DMSO (20 mL) was added Cs₂CO₃ (8.9 g, 27.2 mmol) at RT and the mixture was stirred for 15 min. 1-(3-bromo-4-fluorophenyl)ethanone (0.93 g, 4.28 mmol, 1.2 eq) was then added to the mixture and the resultant mixture was heated 80 °C for 16 h. The reaction was complete after 16 h and the mixture was diluted with water (200 mL) and extracted with EtOAc (200 mL × 2). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to obtain a crude which was purified by CombiFlash Chromatography to afford 1-(3-bromo-4-(4-fluoro-2,6-dimethyl phenoxy) phenyl)ethanone (0.30 g, 25 %) as an off-white solid. LCMS: 337 [M+H]⁺, 339 [M+H+2]⁺

[0182] Step 3. Synthesis of 1-(4-(4-fluoro-2,6-dimethylphenoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone: To a solution of 1-(3-bromo-4-(4-fluoro-2,6-dimethylphenoxy)phenyl)ethanone (0.55 g , 1.63 mmol, 1 eq) in dioxane (5 mL), was added B₂Pin₂ (0.50 g , 1.96 mmol), KOAc (0.48 g, 4.89 mmol), and Pd(dppf)Cl₂ (0.12 g, 0.16 mmol). The reaction mixture was degassed and purged with N₂. Then the mixture was stirred at overnight at 80 °C. TLC analysis indicated the reaction was complete. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give 1-(4-(4-fluoro-2,6-dimethylphenoxy)-3-(4,4,5,5-tetra methyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone as black viscous liquid (0.35 g, 56%). ¹H NMR (400 MHz, CDCl₃): δ 8.35 (d, *J* = 2.4 Hz, 1 H),

7.86 (s, 1H), 6.81 (d, $J=8.8$ Hz, 2H), 6.35 (d, $J=8.8$ Hz, 1H), 2.57 (s, 3H), 1.37 (s, 6H), 1.25 (d, $J=7.3$ Hz, 12H)

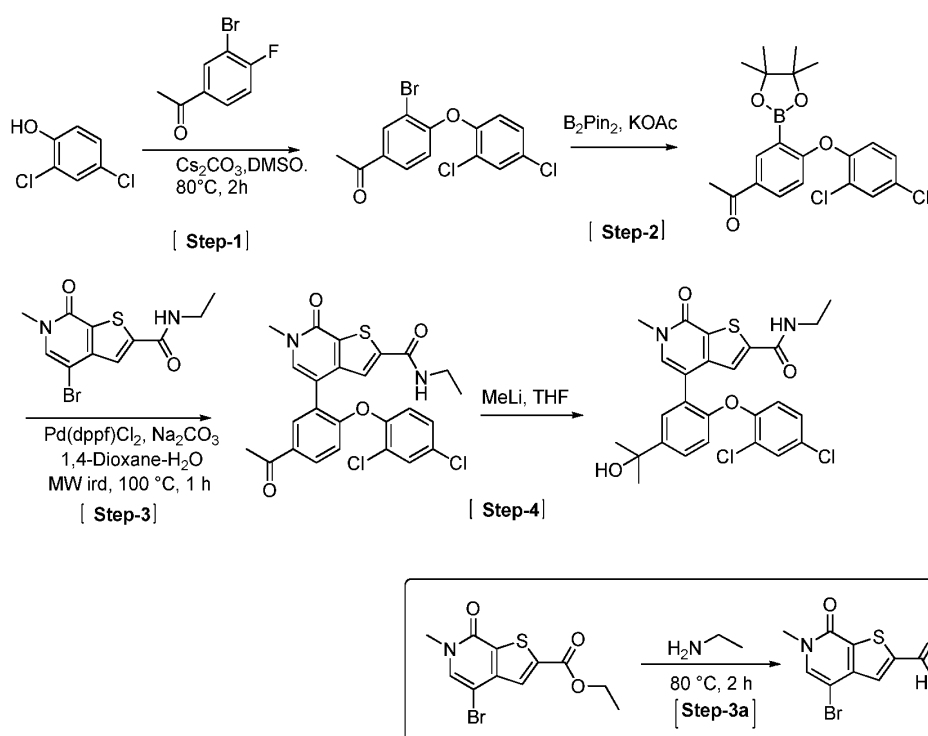
[0183] Step 4a. Synthesis of 4-bromo-*N*-ethyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-*c*]pyridine-2-carboxamide: To ethyl 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-*c*]pyridine-2-carboxylate (1.5 g, 4.3 mmol, 1eq), was added ethyl amine (17 mL; 70 % solution in H₂O) and the mixture was heated at 80 °C and monitored by TLC. The reaction was complete after 2h and to it was added ice-cold water (50 mL) to obtain a precipitate which was filtered over Büchner funnel; dried under vacuum to afford 4-bromo-*N*-ethyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-*c*]pyridine-2-carboxamide (1.23 g, 95%) as a white solid. LCMS: 315 [M+H]⁺, 317 [M+H+2]⁺

[0184] Step 4. Synthesis of 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-*N*-ethyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-*c*]pyridine-2-carboxamide: To a stirred solution of 4-bromo-*N*-ethyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-*c*]pyridine-2-carboxamide (0.27 g, 0.86 mmol, 1 eq) in 1,4-dioxane (1 mL) was added 1-(4-(4-fluoro-2,6-dimethylphenoxy)-3-(4,4,5,5-tetra methyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone (0.49 g, 1.28 mmol, 1.5 eq) and Na₂CO₃ (0.27 g, 2.57 mmol, 3 eq) dissolved in water (0.3 mL) followed by addition of Pd(dppf)Cl₂ (63 mg, 0.085 mmol, 0.1 eq) at RT. The reaction mixture was heated by microwave irradiation at 100 °C and monitored by TLC. The reaction was complete after 45 min and the mixture was diluted with water (200 mL) and extracted with EtOAc (300 mL). The organic layer was washed with water (100 mL), brine (150 mL) dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford a crude material which was purified by CombiFlash chromatography-to afford 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-*N*-ethyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-*c*]pyridine-2-carboxamide (0.16 g, 38 %) as brown viscous liquid. LCMS: 493 [M+H]⁺

Step 5. Synthesis of *N*-ethyl-4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-*c*]pyridine-2-carboxamide: To a stirred solution of 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-*N*-ethyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-*c*]pyridine-2-carboxamide (0.050 g, 0.10 mmol) in anhydrous THF (3 mL) was added methyl lithium (0.2 mL, 0.33 mmol, 6 eq) at 0 °C dropwise and the mixture was stirred at same temperature for 10 min. The reaction was complete after 10 min and the mixture was quenched with saturated NH₄Cl solution (10 mL) slowly. The aqueous layer was then extracted with EtOAc (100 mL × 2). The combined organic layers were washed with water (50 mL), brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to obtain

a crude which was purified by reversed phase HPLC to afford *N*-ethyl-4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-*c*]pyridine-2-carboxamide (3.5 mg, 7%) as an off white solid. LCMS: 509 [M+1]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.86 (t, *J* = 5.6 Hz, 1H), 7.85 (s, 1H), 7.69 (s, 1H), 7.51 (d, *J* = 2.4 Hz, 1H), 7.40 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.97 (d, *J* = 9.0 Hz, 2H), 6.35 (d, *J* = 8.6 Hz, 1H), 5.02 (s, 1H), 3.63 (s, 3H), 3.24 (q, *J* = 7.2 Hz, 2H), 2.00 (s, 6H), 1.45 (s, 6H), 1.09 (t, *J* = 7.2 Hz, 3H).

*Example S-2: Synthesis of 4-(2-(2,4-dichlorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-N-ethyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-*c*]pyridine-2-carboxamide (Compound 2)*



[0185] Step 1. Synthesis of 1-(3-bromo-4-(2,4-dichlorophenoxy)phenyl)ethanone: 1-(3-bromo-4-(2,4-dichlorophenoxy)phenyl)ethanone (1.56 g, 71%, white solid) was prepared following General Procedure 1, Step 2 using 2,4-dichlorophenol (1 g, 6.1 mmol, 1eq). LCMS: 359 [M+H]⁺, 361 [M+H+2]⁺

[0186] Step 2: Synthesis of 1-(4-(2,4-dichlorophenoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone: 1-(4-(2,4-dichlorophenoxy)-3-(4,4,5,5-tetramethyl-1,3,2-

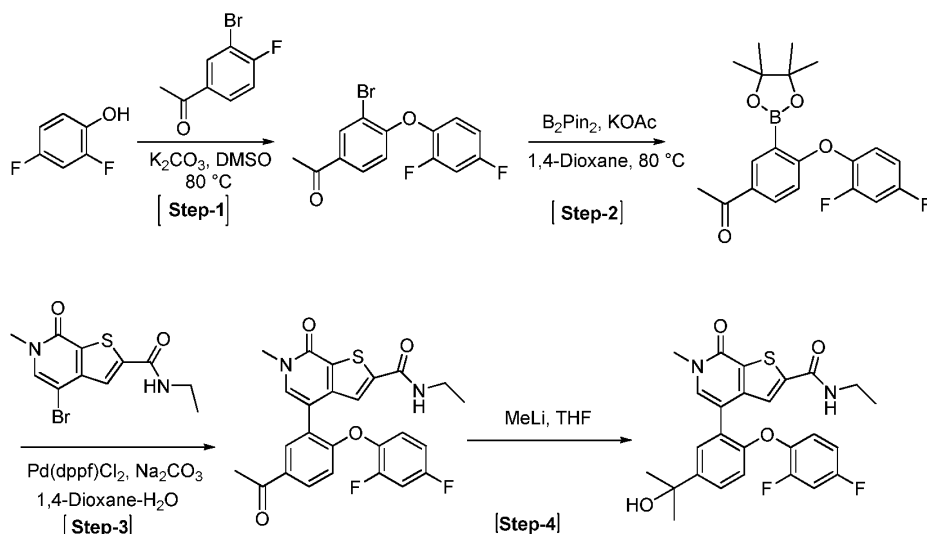
dioxaborolan-2-yl)phenyl)ethanone (0.19 g, 17%, white solid) was prepared following General Procedure 1, Step 3 using 1-(3-bromo-4-(2,4-dichlorophenoxy)phenyl)ethanone (1 g, 2.77 mmol, 1eq). LCMS: 407 [M+H]⁺

[0187] Step 3a. Synthesis of 4-Bromo-N-ethyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide: 4-Bromo-N-ethyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (1.23 g, 95%, white solid) was prepared following General Procedure 1, Step 4a using ethyl 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate (1.5 g, 4.3 mmol, 1eq). LCMS: 315 [M+H]⁺, 317[M+H+2]⁺

[0188] Step 3: Synthesis of 4-(5-acetyl-2-(2,4-dichlorophenoxy)phenyl)-N-ethyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide: 4-(5-acetyl-2-(2,4-dichlorophenoxy)phenyl)-N-ethyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (0.10 g, 61 %, black viscous liquid) was prepared following General Procedure 1, Step 4 using 1-(4-(2,4-dichlorophenoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone (0.1 g, 0.31 mmol, 1.0eq). LCMS: 515 [M+H]⁺

[0189] Step 4: Synthesis of 4-(2-(2,4-dichlorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-N-ethyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide: 4-(2-(2,4-dichlorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-N-ethyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (0.012 mg, 11.5%, off-white solid)) was prepared following General Procedure 1, Step 5 using 4-(5-acetyl-2-(2,4-dichlorophenoxy)phenyl)-N-ethyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (1.0g, 0.19 mmol, 1.0 eq). LCMS: 531 [M+H]⁺, ¹H NMR (400 MHz, MeOH-*d*₄): δ 7.68 (s, 1H), 7.65-7.57 (m, 2H), 7.50 (s, 1H), 7.33 (d, *J* = 2.6 Hz, 1H), 7.13-7.06 (m, 2H), 6.74 (d, *J* = 8.8 Hz, 1H), 3.65 (s, 3H), 3.40-3.35 (m, 2H), 1.59 (s, 6H), 1.20 (t, *J* = 7.3 Hz, 3H).

Example S-3: Synthesis of 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-N-ethyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (Compound 3)



[0190] Step 1: Synthesis of 1-(3-bromo-4-(2,4-difluorophenoxy)phenyl)ethan-1-one: 1-(3-bromo-4-(2,4-difluorophenoxy)phenyl)ethan-1-one (1.0 g, 40 %, white solid) was prepared following General Procedure 1, Step 2 using 2,4-difluorophenol (0.98 g, 8.46 mmol, 1.1 eq). LCMS: 327[M+H]⁺, 329 [M+H+2]⁺

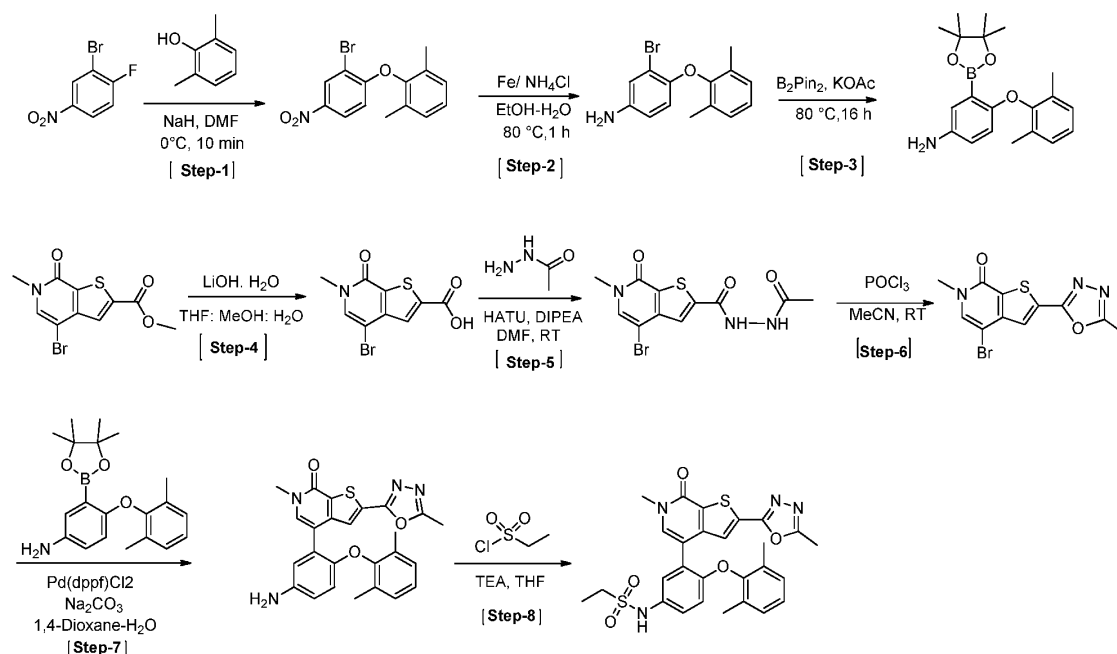
[0191] Step 2: Synthesis of 1-(4-(2,4-difluorophenoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone: 1-(4-(2,4-difluorophenoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone (1.0 g, 87%, white solid) was prepared following General Procedure 1, Step 3 using 1-(3-bromo-4-(2,4-difluorophenoxy)phenyl)ethan-1-one (1.0 g, 3.06 mmol, 1.0 eq). LCMS: 375 [M+H]⁺

[0192] Step 3: Synthesis of 4-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-N-ethyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide: 4-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-N-ethyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (0.2 g, 65%, white solid) was prepared following General Procedure 1, Step 4 using 1-(4-(2,4-difluorophenoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone (0.28 g, 0.76 mmol, 1.2 eq). LCMS: 483 [M+H]⁺

[0193] Step 4: Synthesis of 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-N-ethyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide: 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-N-ethyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-

c]pyridine-2-carboxamide (0.006 g, 7%, off-white solid) was prepared following General Procedure 1, Step 5 using 4-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-N-ethyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (0.08 g, 0.16 mmol, 1 eq). LCMS: 499 [M+1]⁺, ¹H NMR (400 MHz, MeOH-*d*₄): δ 7.69 (s, 1H), 7.58 (d, *J* = 2.4 Hz, 1H), 7.54 (d, *J* = 9.2 Hz, 2H), 7.04-6.91 (m, 3H), 6.88-6.78 (m, 1H), 3.68 (s, 3H), 3.38 (q, *J* = 7.2 Hz, 2H), 1.58 (s, 6H).

Example S-4: Synthesis of N-(4-(2-(6-dimethylphenoxy)-3-(6-methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)-7-oxo-6,7-dihydrothieno[2,3-c]pyridin-4-yl)phenyl)ethanesulfonamide (General Procedure 2) (Compound 4)



[0194] Step 1: Synthesis of 2-(2-bromo-4-nitrophenoxy)-1,3-dimethylbenzene: To a stirred solution of 2,6-dimethylphenol (2.0 g, 16.03 mmol, 1.0 eq) in DMF (10 mL) was added NaH (0.721 g, 18.00 mmol, 1.1 eq) at 0 °C followed by an addition of 2-bromo-1-fluoro-4-nitrobenzene (3.49 g, 18.0 mmol, 1.1 eq) and monitored by TLC and LC-MS. The reaction was complete after 10 min and to the mixture was added ice-cold water (50 mL) to obtain a precipitate which was filtered over Büchner funnel; dried under vacuum to afford 2-(2-bromo-4-nitrophenoxy)-1,3-dimethylbenzene (4.5 g, 68%) as a yellow solid. LCMS: 322 [M+H]⁺, 324 [M+H+2]⁺

[0195] Step 2: Synthesis of 3-bromo-4-(2,6-dimethylphenoxy)aniline: To a solution of 2-(2-bromo-4-nitrophenoxy)-1,3-dimethylbenzene (4.0 g, 12.42 mmol, 1.0eq) in ethanol (20 mL), a solution of NH_4Cl (6.6 g, 124.16 mmol) in water (22 mL) was added followed by addition of iron powder (5.5 g, 99.3 mmol). The reaction mixture was stirred at 90 °C for 1 h. TLC analysis indicated the reaction was complete. The reaction mixture was filtered through a pad of Celite. The filtrate was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give 3-bromo-4-(2,6-dimethylphenoxy)aniline (3.5 g, 97 %) as a black viscous liquid. LCMS: 292 $[\text{M}+\text{H}]^+$, 294 $[\text{M}+\text{H}+2]^+$

[0196] Step 3: Synthesis of 4-(2,6-dimethylphenoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline: 4-(2,6-dimethylphenoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.700 g, 66 %, black viscous liquid) was prepared following General Procedure 1, Step 3 using 3-bromo-4-(2,6-dimethylphenoxy)aniline (1.0g, 45.6 mmol, 1.0 eq) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (0.16 g, 0.228 mmol, 0.05 eq). ^1H NMR: (400 MHz, CDCl_3) δ 6.97 - 7.11 (m, 3H), 6.58 (d, J = 3.95 Hz, 1H), 6.14 (d, J = 8.77 Hz, 1H), 2.05 - 2.18 (m, 6H), 1.23 - 1.28 (m, 12H).

[0197] Step 4: Synthesis of 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid: To a stirred solution of methyl 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate (0.50 g, 1.66 mmol, 1eq) in THF : MeOH : H_2O (6 : 3 : 1) (10 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (0.7 g, 16.6 mmol, 10 eq) and the mixture was stirred at RT for 1 h. The reaction was complete after 1 h and the mixture was concentrated under reduced pressure. The residue obtained was then diluted with ice-cold water (20 mL) and acidified using 2N-HCl (pH~2) to obtain a precipitate which was filtered over Büchner funnel to afford 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (430 mg, 90%) as an off-white solid. LCMS: 288 $[\text{M}+1]^+$, 290 $[\text{M}+\text{H}+2]^+$

[0198] Step 5: Synthesis of N'-acetyl-4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carbohydrazide: To a stirred solution of 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (0.43 g, 1.49 mmol) in DMF (7 mL) were successively added HATU (1.10 g, 3.0 mmol, 2.0 eq) and DIPEA (1.6 mL, 8.84 mmol, 6 eq) at 0 °C and the mixture was stirred at same temperature 10 min. Acetohydrazide (0.33 g, 4.47 mmol, 3.0 eq) was then added to the mixture and the resultant mixture was stirred at RT for 1 h. The reaction was complete after 1h, the mixture was diluted with water (20 mL) and extracted with

EtOAc (30 mL × 2). The combined organic layers were washed with water (25 mL), brine (25 mL) dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to obtain a crude which was purified by CombiFlash Chromatography to afford N'-acetyl-4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carbohydrazide (350 mg, 68%) as a yellow solid. LCMS: 344 [M+1]⁺, 346 [M+H+2]⁺

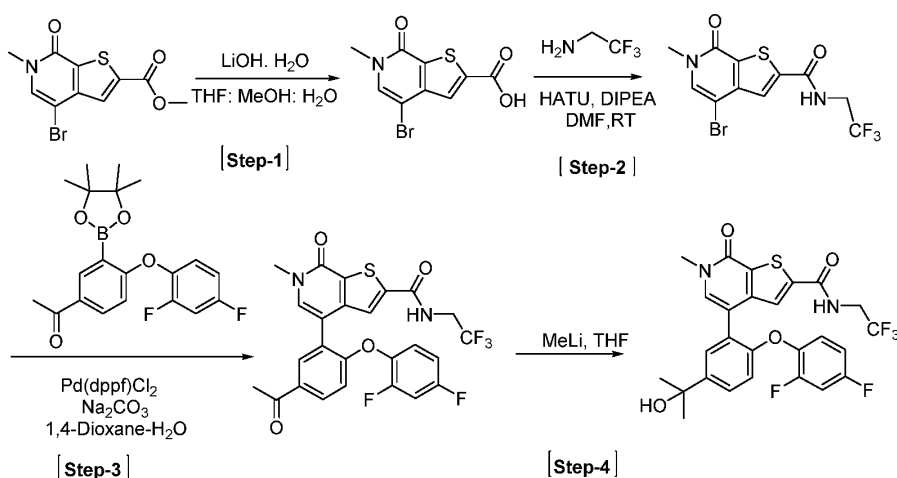
[0199] Step 6: Synthesis of 4-bromo-6-methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)thieno[2,3-c]pyridin-7(6H)-one: To a stirred solution of N'-acetyl-4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carbohydrazide (0.2 g, 0.58 mmol) in acetonitrile (10 mL) was added POCl₃ (0.35 g, 2.38 mmol, 5.0 eq) at 0 °C and the mixture was heated at 50 °C for 1 h. The reaction was complete after 1 h and the mixture was quenched slowly with saturated NaHCO₃ solution at ice-cold condition and then extracted with EtOAc (100 mL × 3). The combined organic layers were washed with water (100 mL), brine (100 mL) dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to obtain a crude which was purified by CombiFlash Chromatography to afford 4-bromo-6-methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)thieno[2,3-c]pyridin-7(6H)-one (110 mg, 58 %) as a yellow sticky solid. LCMS: 326 [M+1]⁺, 328 [M+H+2]⁺

[0200] Step 7: Synthesis of 4-(5-amino-2-(2,6-dimethylphenoxy)phenyl)-6-methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)thieno[2,3-c]pyridin-7(6H)-one: 4-(5-amino-2-(2,6-dimethylphenoxy)phenyl)-6-methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)thieno[2,3-c]pyridin-7(6H)-one (0.085 g, 56 %, off-white solid) was prepared following General Procedure 1, Step 3 using 4-bromo-6-methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)thieno[2,3-c]pyridin-7(6H)-one (0.11 g, 0.33 mmol, 1 eq). LCMS: 459 [M+1]

[0201] Step 8: Synthesis of N-(4-(2,6-dimethylphenoxy)-3-(6-methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)-7-oxo-6,7-dihydrothieno[2,3-c]pyridin-4-yl)phenyl)ethanesulfonamide: To a stirred solution of 4-(5-amino-2-(2,6-dimethylphenoxy)phenyl)-6-methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)thieno[2,3-c]pyridin-7(6H)-one (0.085 g, 0.185 mmol) in THF (8 mL) was added triethylamine (0.056 g, 0.55 mmol, 3 eq) followed by the addition of ethanesulfonyl chloride (0.095 g, 0.74 mmol, 4.0 eq) at 0 °C and the resultant mixture was stirred at RT for 16 h. The reaction was complete after 16 h and to the mixture was added water (30 mL) and extracted with EtOAc (30 mL × 2). The combined organic layers was washed with saturated NaHCO₃ solution (30 mL), brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to obtain a crude which was purified by reversed-phase HPLC to afford N-(4-(2,6-dimethylphenoxy)-3-(6-

methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)-7-oxo-6,7-dihydrothieno[2,3-c]pyridin-4-yl)phenyl)ethanesulfonamide (4.2 mg, 4.1 %) as an off-white solid. LCMS: 551 [M+1]⁺, ¹H NMR (400 MHz, MeOH-*d*₄): δ 7.88 (s, 1H), 7.74 (s, 1H), 7.38 (d, *J* = 2.7 Hz, 1H), 7.18 (dd, *J* = 8.8, 2.7 Hz, 1H), 7.12-6.99 (m, 3H), 6.45 (d, *J* = 8.8 Hz, 1H), 3.77 (s, 3H), 3.21-3.15 (m, 2H), 2.62 (s, 3H), 2.07 (s, 6H), 1.34 (t, *J* = 7.4 Hz, 3H).

Example S-5: Synthesis of 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-N-(2,2,2-trifluoroethyl)-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (Compound 5)



[0202] Step 1: Synthesis of 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid: 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (0.43 g, 90%, off-white solid) was prepared following General Procedure 2, Step 4 using Methyl-4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate (0.50 g, 1.66 mmol, 1eq). LCMS: 288 [M+1]⁺, 290 [M+H+2]⁺

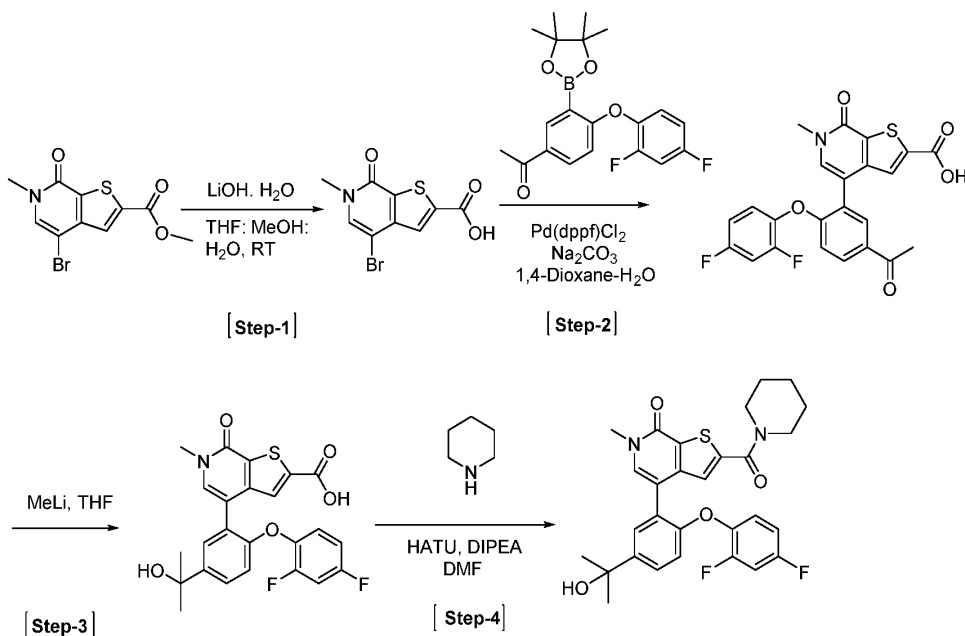
[0203] Step 2: Synthesis of 4-bromo-6-methyl-7-oxo-N-(2,2,2-trifluoroethyl)-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide: 4-bromo-6-methyl-7-oxo-N-(2,2,2-trifluoroethyl)-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (0.2 g, 78%, off-white solid) was prepared following General Procedure 2, Step 5 using 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (0.2 g, 0.69 mmol, 1eq) and 2,2,2-trifluoroethanamine (0.04 g, 0.26 mmol, 2.0 eq). LCMS: 369 [M+1]⁺, 371 [M+H+2]⁺

[0204] Step 3: Synthesis of 4-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-6-methyl-7-oxo-N-(2,2,2-trifluoroethyl)-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide: 4-(5-acetyl-2-(2,4-difluoro

phenoxy)phenyl)-6-methyl-7-oxo-N-(2,2,2-trifluoroethyl)-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (70 mg, 24 %, white solid) was prepared following General Procedure 1, Step 4 using 4-bromo-6-methyl-7-oxo-N-(2,2,2-trifluoroethyl)-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (0.2 g, 0.54 mmol, 1.0 eq). LCMS: 537 [M+1]⁺

[0205] Step 4: Synthesis of 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-N-(2,2,2-trifluoroethyl)-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide: 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-N-(2,2,2-trifluoroethyl)-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (0.006 g, 12.5 %, off-white solid) was prepared following General Procedure 1, Step 5 using 4-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-6-methyl-7-oxo-N-(2,2,2-trifluoroethyl)-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (0.095 g, 0.18 mmol, 1.0 eq). LCMS: 553 [M+1]⁺, ¹H NMR (400 MHz, MeOD-*d*₄): δ 7.79 (s, 1H), 7.62-7.50 (m, 3H), 7.03-6.90 (m, 3H), 6.82 (ddd, *J* = 12.8, 6.9, 2.3 Hz, 1H), 4.05 (q, *J* = 9.3 Hz, 2H), 3.69 (s, 3H), 1.58 (s, 6H).

Example S-6: Synthesis of 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-2-(piperidine-1-carbonyl)thieno[2,3-c]pyridin-7(6H)-one (Compound 6)



[0206] Step 1: Synthesis of 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid: To a stirred solution of methyl 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate (1.0 g, 3.3 mmol) in THF : MeOH : H₂O [6 : 3 : 1; (10 mL)] was LiOH.H₂O (1.39 mg, 33.3 mmol, 10 eq) and the mixture was stirred at RT for 1 h. The reaction was complete after 1h and the mixture was concentrated under reduced pressure. The residue obtained was diluted with water (30 mL) and acidified using 1N-HCl (pH ~2) to obtain a precipitate solid which was filtered over Büchner funnel to afford 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (380 mg, 39%) as an off-white solid. LCMS: 287 [M+1]⁺, 290 [M+H+2]⁺

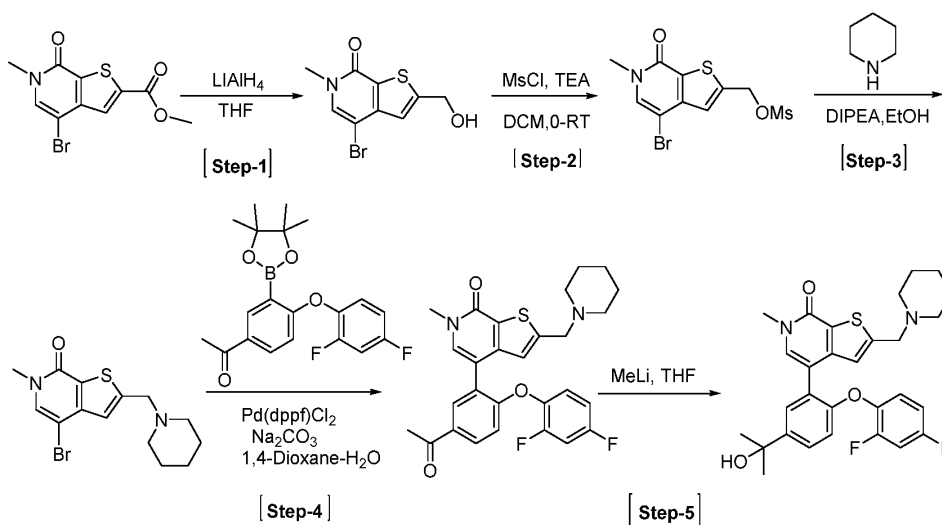
[0207] Step 2: Synthesis of 4-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid: 4-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (0.1 g, 79%, white solid) was prepared following General Procedure 1, Step 4 using 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (0.08 g, 0.28 mmol, 1 eq). LCMS: 456 [M+1]⁺

[0208] Step 3: Synthesis of 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid: 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (0.10 g, 97%, off-white solid) was prepared following General Procedure 1, Step 5 using 4-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (0.10 g, 0.22 mmol, 1 eq). LCMS: 472 [M+1]⁺

[0209] Step 4: Synthesis of 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-2-(piperidine-1-carbonyl)thieno[2,3-c]pyridin-7(6H)-one: To a stirred solution of 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (0.1 g, 0.22 mmol, 1eq) in DMF (4 mL) were successively added HATU (0.13 g, 0.33 mmol, 1.5 eq) and DIPEA (0.153 mL, 0.88 mmol, 4 eq) at 0 °C and the mixture was stirred at same temperature for 10 min. Piperidine (37 mg, 0.44 mmol, 2.0 eq) was then added to the mixture and the resultant mixture was stirred at RT for 2 h. The reaction was complete after 2 h and the mixture was diluted with water (100 mL) and extracted with EtOAc (100 mL × 2). The combined organic layers were washed with water (100 mL), brine (150 mL) dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford a crude which was purified by reversed phase HPLC to afford 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-

2-yl)phenyl)-6-methyl-2-(piperidine-1-carbonyl)thieno [2,3-c]pyridin-7(6H)-one (0.004 g, 4%) as an off-white solid. LCMS: 539 [M+1]⁺, ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.69 (s, 1H), 7.54 (d, *J* = 2.3 Hz, 1H), 7.49 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.38 (ddd, *J* = 11.3, 8.7, 3.0 Hz, 1H), 7.20 (s, 1H), 7.11 (td, *J* = 9.3, 5.6 Hz, 1H), 7.02 (t, *J* = 8.6 Hz, 1H), 6.85 (d, *J* = 8.5 Hz, 1H), 5.08 (s, 1H), 3.60 (s, 3H), 3.52 (m, 4H), 2.08 (m, 4H), 1.60 (m, 2H), 1.46 (s, 6H).

Example S-7: Synthesis of 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-2-(piperidin-1-ylmethyl)thieno[2,3-c]pyridin-7(6H)-one (Compound 7)



[0210] Step 1: Synthesis of 4-bromo-2-(hydroxymethyl)-6-methylthieno[2,3-c]pyridin-7(6H)-one: To LiAlH₄ (113 mg, 2.9 mmol, 1.8 eq) in THF (10 mL) was added methyl 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate (500 mg, 1.60 mmol in THF) at -10 °C slowly and the mixture was stirred at same temperature for 10 min. The reaction was complete after 10 min and the mixture was slowly quenched with saturated sodium sulphate solution (30 mL). The crude mixture was filtered through celite bed washing with EtOAc (500 mL). The organic layer was then washed with water (200 mL), brine (150 mL) dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford a crude material which was purified by CombiFlash Chromatography to afford 4-bromo-2-(hydroxymethyl)-6-methylthieno [2,3-c]pyridin-7(6H)-one (305 mg, 67%) as a sticky solid. LCMS: 274 [M+1]⁺, 276 [M+H+2]⁺

[0211] Step 2: Synthesis of (4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridin-2-yl)methyl methanesulfonate: To a stirred solution of 4-bromo-2-(hydroxymethyl)-6-methylthieno[2,3-c]pyridin-7(6H)-one (300 mg, 1.1 mmol, 1 eq) in DCM (10 mL) were successively added triethylamine (0.75 mL, 5.5 mmol, 5 eq) and methane sulphonyl chloride (0.18 mL, 2.2 mmol, 3 eq) at 0 °C slowly and the mixture was stirred at RT for 1 h. The reaction was complete after 1 h and to the mixture was added ice-cold water (100 mL) and extracted with DCM (100 mL × 2). The combined organic layers was washed with water (100 mL × 2), brine (150 mL) dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford (4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridin-2-yl)methyl methanesulfonate (300 mg, 77%) as a brown sticky liquid which was taken to next step without further purification. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.02 (s, 1H), 7.49 (s, 1H), 5.61 (s, 2H), 3.50-3.56 (m, 3 H).

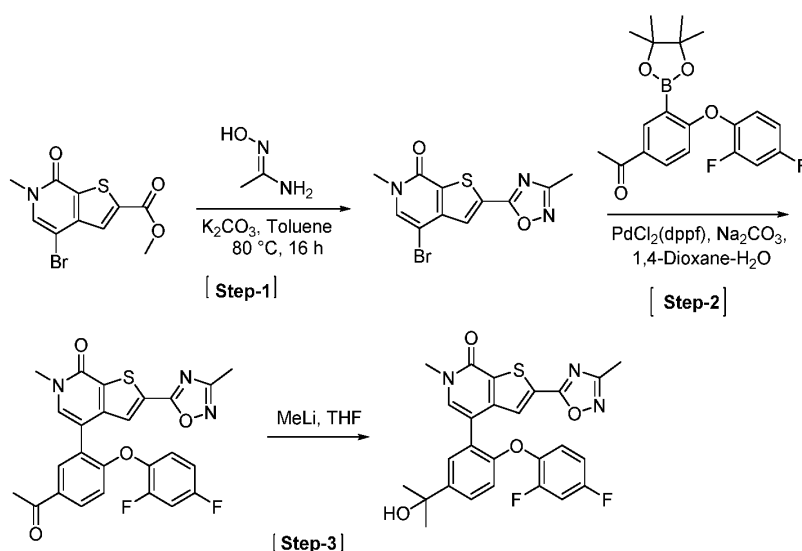
[0212] Step 3: Synthesis of 4-bromo-6-methyl-2-(piperidin-1-ylmethyl)thieno[2,3-c]pyridin-7(6H)-one: To a stirred solution of piperidine (0.114 mg, 1.7 mmol, 2 eq) in ethanol (8 mL) was added DIPEA (0.5 mL, 3.4 mmol, 4 eq) and the mixture was stirred at RT for 15 min. (4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridin-2-yl)methyl methanesulfonate (300 mg, 0.85 mmol) dissolved in EtOH (2 mL) was then added to the mixture and the mixture was heated at 100 °C for 1 h. The reaction was complete after 1 h and the mixture was concentrated under reduced pressure to obtain a crude which was purified by CombiFlash Chromatograph to afford 4-bromo-6-methyl-2-(piperidin-1-ylmethyl)thieno[2,3-c]pyridin-7(6H)-one (120 mg, 41%) as an off-white solid. LCMS: 341 [M+1]⁺, 343 [M+H+2]⁺

[0213] Step 4: Synthesis of 4-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-6-methyl-2-(piperidin-1-ylmethyl)thieno[2,3-c]pyridin-7(6H)-one: 4-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-6-methyl-2-(piperidin-1-ylmethyl)thieno[2,3-c]pyridin-7(6H)-one (140 mg, 78%, off-white solid) was prepared following General Procedure 1, Step 4 using 4-bromo-6-methyl-2-(piperidin-1-ylmethyl)thieno[2,3-c]pyridin-7(6H)-one (120 mg, 0.35 mmol, 1 eq). LCMS: 509 [M+1]⁺

[0214] Step 5: Synthesis of 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-2-(piperidin-1-ylmethyl)thieno[2,3-c]pyridin-7(6H)-one: 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-2-(piperidin-1-ylmethyl) thieno [2,3-c]pyridin-7(6H)-one (28 mg, 40%, off-white solid) was prepared following General Procedure 1, Step 5 using 4-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-6-methyl-2-(piperidin-1-ylmethyl) thieno [2,3-c]pyridin-7(6H)-one (0.070 g, 0.13 mmol, 1 eq). LCMS: 525 [M+1]⁺, ¹H NMR (400 MHz, MeOH-*d*₄): δ 7.56

(d, $J = 2.4$ Hz, 1H), 7.52 (dd, $J = 8.5, 2.4$ Hz, 1H), 7.48 (s, 1H), 7.04-6.88 (m, 4H), 6.87-6.77 (m, 1H), 3.75 (s, 2H), 3.68 (s, 3H), 2.46 (s, 4H), 1.93 (d, $J = 2.5$ Hz, 2H), 1.58 (d, $J = 6.2$ Hz, 10H).

Example S-8: Synthesis of 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-2-(3-methyl-1,2,4-oxadiazol-5-yl)thieno[2,3-c]pyridin-7(6H)-one (Compound 8)



[0215] Step 1: Synthesis of 4-bromo-6-methyl-2-(3-methyl-1,2,4-oxadiazol-5-yl)thieno[2,3-c]pyridin-7(6H)-one: To a stirred solution of methyl 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate (0.4 g, 1.32 mmol) in toluene (6 mL) were successively added K_2CO_3 (0.27 g, 1.99 mmol, 3 eq) and (E)-N'-hydroxyacetimidamide (0.15 g, 1.99 mmol, 1.5 eq) at RT and the mixture was heated at 120 °C for 16 h. The reaction was complete after 16 h and to the mixture was added water (20 mL). The aqueous layer was then extracted with EtOAc (30 mL $\times$ 2). The combined organic layers were washed with water (10 mL), brine (15 mL) dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to

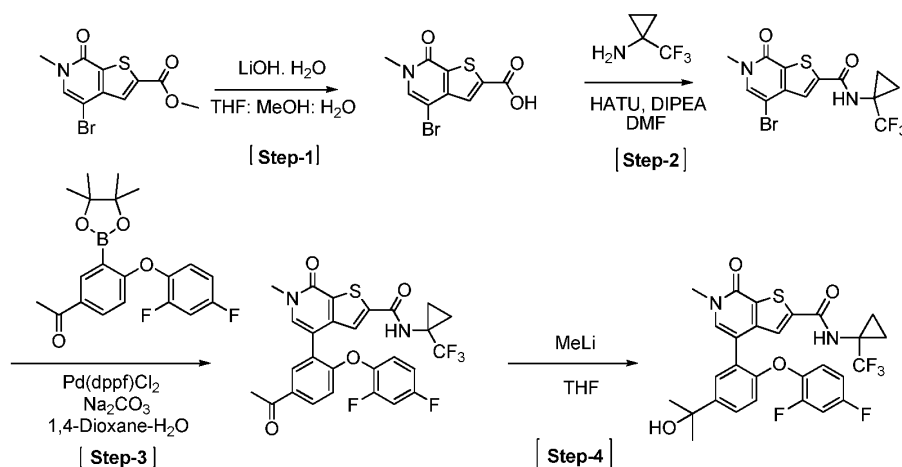
obtain a crude which was purified by CombiFlash Chromatograph to afford 4-bromo-6-methyl-2-(3-methyl-1,2,4-oxadiazol-5-yl)thieno[2,3-c]pyridin-7(6H)-one (0.4 g, 92%) an off-white solid.

LCMS: 326 [M+1]⁺, 328 [M+H+2]⁺

[0216] Step 2: Synthesis of 4-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-6-methyl-2-(3-methyl-1,2,4-oxadiazol-5-yl)thieno[2,3-c]pyridin-7(6H)-one: 4-(5-acetyl-2-(2,4-difluorophenoxy) phenyl)-6-methyl-2-(3-methyl-1,2,4-oxadiazol-5-yl)thieno[2,3-c]pyridin-7(6H)-one (0.15 g, 33%, off-white solid) was prepared following General Procedure 1, Step 4 using 4-bromo-6-methyl-2-(3-methyl-1,2,4-oxadiazol-5-yl)thieno[2,3-c]pyridin-7(6H)-one (0.3 g, 0.92 mmol, 1eq). LCMS: 494 [M+1]⁺

[0217] Step 3: Synthesis of 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-2-(3-methyl-1,2,4-oxadiazol-5-yl)thieno[2,3-c]pyridin-7(6H)-one: 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-2-(3-methyl-1,2,4-oxadiazol-5-yl)thieno[2,3-c]pyridin-7(6H)-one (2 mg, 2.7%, off-white solid) was prepared following General Procedure 1, Step 5 using 4-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-6-methyl-2-(3-methyl-1,2,4-oxadiazol-5-yl)thieno[2,3-c]pyridin-7(6H)-one (0.070 g, 0.14 mmol, 1eq). LCMS: 510 [M+1]⁺, ¹H NMR (400 MHz, MeOH-*d*₄): δ 7.89 (s, 1H), 7.65-7.59 (m, 2H), 7.56 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.07-6.96 (m, 2H), 6.92 (d, *J* = 8.5 Hz, 1H), 6.85 (t, *J* = 8.7 Hz, 1H), 3.72 (s, 3H), 2.44 (s, 3H), 1.59 (s, 6H).

Example S-9: Synthesis of 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-N-(1-(trifluoromethyl)cyclopropyl)-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (Compound 14)



[0218] Step 1: Synthesis of 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid: 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (430 mg, 90%, off-white solid) was prepared following General Procedure 2, Step 4 using methyl 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate (0.50 g, 1.66 mmol, 1eq). LCMS: 288 [M+1]⁺, 290 [M+H+2]⁺

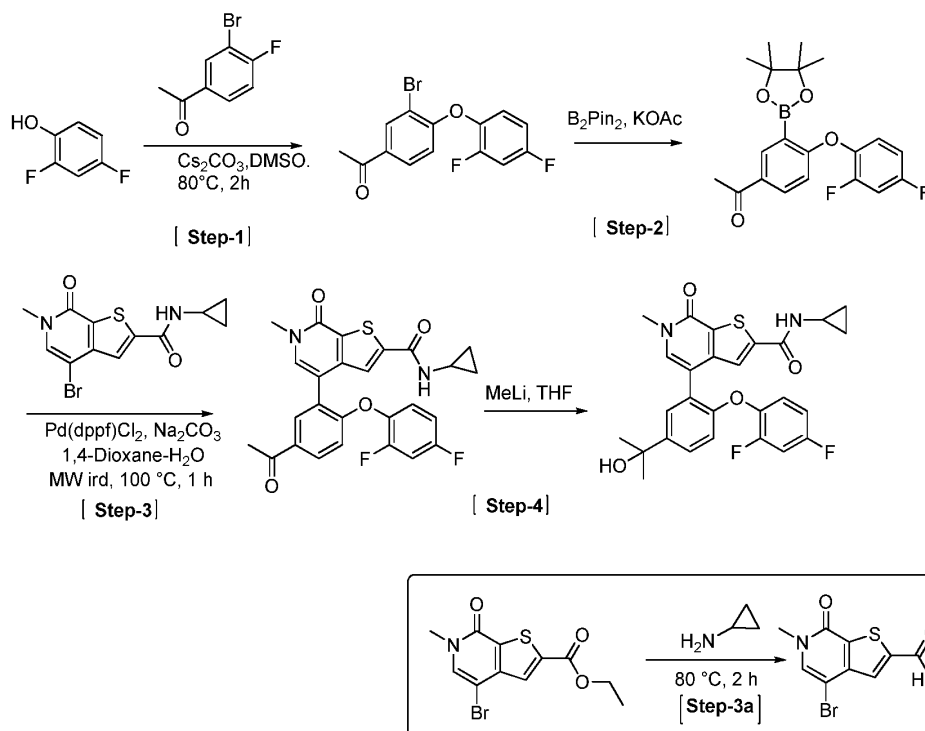
[0219] Step 2: Synthesis of 4-bromo-6-methyl-7-oxo-N-(1-(trifluoromethyl)cyclopropyl)-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide: 4-bromo-6-methyl-7-oxo-N-(1-(trifluoromethyl)cyclopropyl)-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (0.14 g, 59%, off-white solid) was prepared following General Procedure 2, Step 5 using 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (0.18 g, 0.63 mmol, 1eq) and 1-(trifluoromethyl)cyclopropanamine (0.30 g, 1.8 mmol, 3.0 eq). LCMS: 395 [M+1]⁺, 397 [M+H+2]⁺

[0220] Step 3: Synthesis of 4-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-6-methyl-7-oxo-N-(1-(trifluoromethyl)cyclopropyl)-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide: 4-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-6-methyl-7-oxo-N-(1-(trifluoromethyl)cyclopropyl)-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (0.16 g, 80%, off-white solid) was prepared following General Procedure 1, Step 4 using 4-bromo-6-methyl-7-oxo-N-(1-(trifluoromethyl)cyclopropyl)-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (0.14 g, 0.36 mmol, 1 eq) and 1-(4-(2,4-difluorophenoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone (0.19 g, 0.55 mmol, 1.5 eq). LCMS: 563 [M+1]⁺

[0221] Step 4: Synthesis of 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-N-(1-(trifluoromethyl)cyclopropyl)-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide: 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-N-(1-(trifluoromethyl)cyclopropyl)-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (5 mg, 6%, off-white solid) was prepared following General Procedure 20, Step 5 using 4-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-6-methyl-7-oxo-N-(1-(trifluoromethyl)cyclopropyl)-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (0.080 g, 0.14 mmol, 1eq). LCMS: 579 [M+1]⁺, ¹H NMR (400 MHz, MeOH-*d*₄): δ 7.77 (s, 1H), 7.61-7.50 (m, 3H), 6.97 (dt, *J* = 15.5, 9.4 Hz, 3H), 6.83 (t, *J* = 8.2 Hz, 1H), 3.68 (s, 3H), 1.57 (s, 6H), 1.43-1.31 (m, 2H), 1.18 (s, 2H).

Example S-10: Synthesis of N-cyclopropyl-4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-

yl)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (**Compound 145**)



[0222] Step 1: Synthesis of 1-(3-bromo-4-(2,4-difluorophenoxy)phenyl)ethanone: 1-(3-bromo-4-(2,4-difluorophenoxy)phenyl)ethanone (1.0 g, 40 %, white solid) was prepared following General Procedure 1, Step 2 using 1-(3-bromo-4-fluorophenyl)ethanone (0.98 g, 8.46 mmol, 1.1 eq). LCMS: 327[M+H]⁺, 329 [M+H+2]⁺

[0223] Step 2: Synthesis of 1-(4-(2,4-difluorophenoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone: 1-(4-(2,4-difluorophenoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone (1.0 g, 87 %, white solid) was prepared following General Procedure 1, Step 3 using 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-N-ethyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (1.0 g, 3.06 mmol, 1.0 eq). LCMS: 375[M+H]⁺

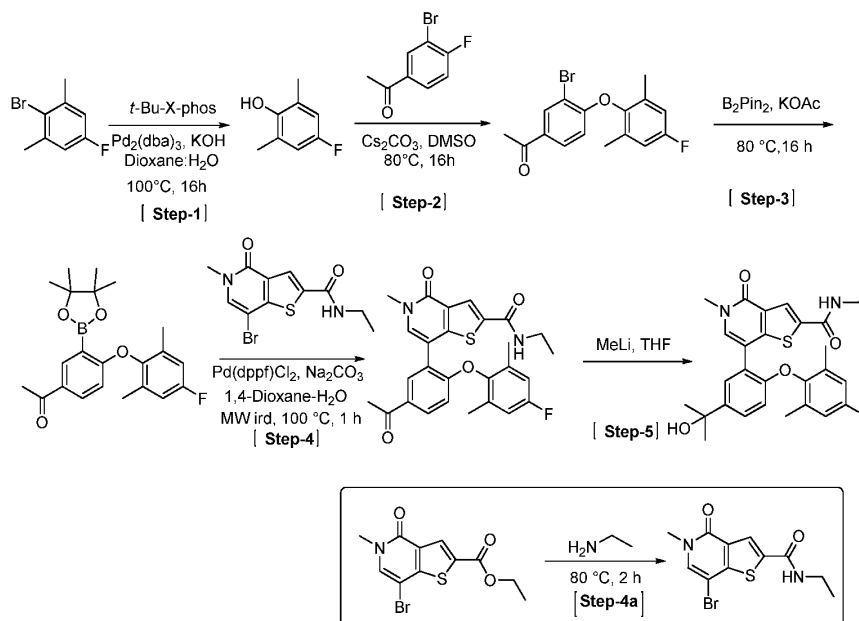
[0224] Step 3a: Synthesis of 4-bromo-N-cyclopropyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide: 4-bromo-N-cyclopropyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (0.20 g, 93 %, white solid) was prepared following

General Procedure 1, Step 4a using ethyl 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate (0.2 g, 0.664 mmol, 1eq). LCMS: 327 [M+H]⁺, 329 [M+H+2]⁺

[0225] Step 3: Synthesis of 4-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-N-cyclopropyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide: 4-(5-acetyl-2-(2,4-difluorophenoxy) phenyl)-N-cyclopropyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide e (0.07 g, 41%, brown solid) was prepared following General Procedure 1, Step 4 using 1-(4-(2,4-difluorophenoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone (0.13 g, 0.97 mmol, 1.2 eq). LCMS: 495 [M+H]⁺

[0226] Step 4: Synthesis N-cyclopropyl-4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide: N-cyclopropyl-4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (0.009 g, 12 %, off-white solid) was prepared following General Procedure 1, Step 5 using 4-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-N-cyclopropyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (0.070 g, 0.141 mmol, 1.0 eq). LCMS: 511[M+H]⁺, ¹H NMR (400 MHz, MeOH-*d*₄): δ 7.68 (s, 1H), 7.60-7.49 (m, 3H), 7.04-6.90 (m, 3H), 6.83 (t, *J* = 8.5 Hz, 1H), 3.68 (s, 3H), 2.83 (tt, *J* = 7.4, 3.8 Hz, 1H), 1.57 (s, 6H), 0.79 (td, *J* = 7.1, 5.0 Hz, 2H), 0.62 (p, *J* = 4.7 Hz, 2H).

Example S-11: Synthesis of N-ethyl-7-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide (Compound 146)



[0227] **Step 1: Synthesis of 4-fluoro-2,6-dimethylphenol:** 4-fluoro-2,6-dimethylphenol (2.2 g, 64 %) was prepared following General Procedure 1, Step 1 using 2-bromo-5-fluoro-1,3-dimethylbenzene (5.0 g, 24.7 mmol 1 eq). LCMS: 141 [M+1]⁺

[0228] **Step 2: Synthesis of 1-(3-bromo-4-(4-fluoro-2,6-dimethylphenoxy)phenyl)ethanone:** 1-(3-bromo-4-(4-fluoro-2,6-dimethylphenoxy)phenyl)ethanone (0.30 g, 25 %, off-white solid) was prepared following General Procedure 1, Step 2 using 1-(3-bromo-4-fluorophenyl)ethanone (0.93 g, 4.28 mmol, 1.2 eq). LCMS: 337 [M+H]⁺, 339 [M+H+2]⁺

[0229] **Step 3: Synthesis of 1-(4-(4-fluoro-2,6-dimethylphenoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone:** 1-(4-(4-fluoro-2,6-dimethylphenoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone (0.35 g, 56 %, black viscous liquid) was prepared following General Procedure 1, Step 3 using 1-(3-bromo-4-(4-fluoro-2,6-dimethylphenoxy)phenyl)ethanone (0.55 g, 1.63 mmol, 1 eq).

¹H NMR (400 MHz, CDCl₃): δ 8.35 (d, *J* = 2.4 Hz, 1 H), 7.86 (s, 1H), 6.81 (d, *J* = 8.8 Hz, 2H), 6.35 (d, *J* = 8.8 Hz, 1H), 2.57 (s, 3H), 1.37 (s, 6H), 1.25 (d, *J* = 7.3 Hz, 12H).

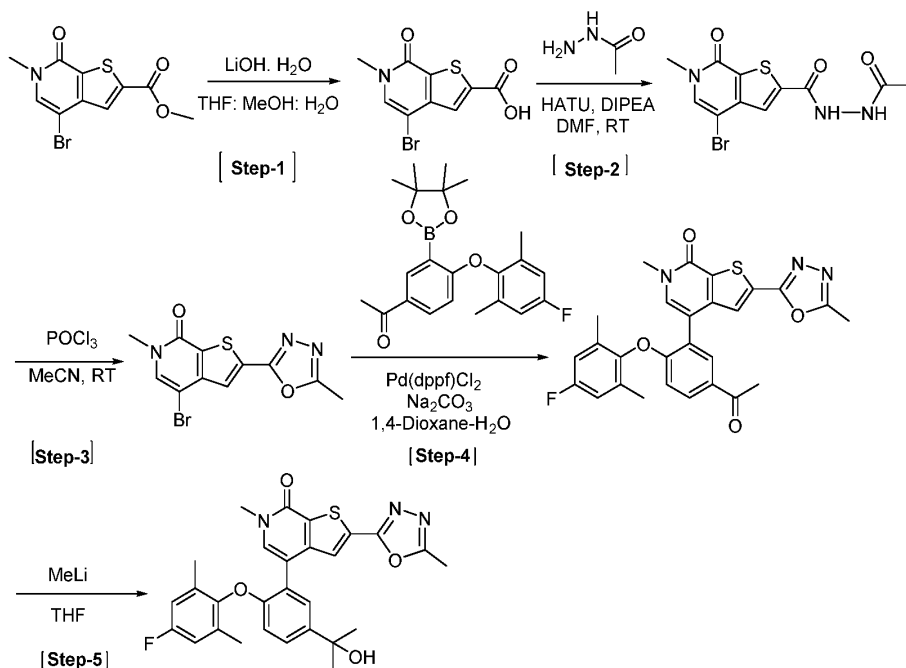
[0230] **Step 4a: Synthesis of 7-bromo-N-ethyl-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide:** 7-bromo-N-ethyl-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-

carboxamide (1.23 g, 95%, white solid) was prepared following General Procedure 1, Step 4a using ethyl 7-bromo-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxylate (1.5 g, 4.3 mmol, 1eq). LCMS: 315 [M+H]⁺, 317 [M+H+2]⁺

[0231] Step 4: Synthesis of 7-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-N-ethyl-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide: 7-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-N-ethyl-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide (0.13 g, 52 %, brown solid) was prepared following General Procedure 1, Step 4 using 1-(4-(4-fluoro-2,6-dimethylphenoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone (0.25 g, 0.66 mmol, 1.3 eq) and 7-bromo-N-ethyl-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide (0.16 g, 0.80 mmol, 1 eq). LCMS: 493 [M+H]⁺

[0232] Step 5: Synthesis of N-ethyl-7-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide: N-ethyl-7-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide (35 mg, 25 %, off-white solid) was prepared following General Procedure 1, Step 5 using 7-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-N-ethyl-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide (0.13 g, 0.263 mmol, 1.0 eq). LCMS: 509 [M+1]⁺, ¹H NMR (400 MHz, MeOH-*d*₄): δ 8.14 (s, 1H), 7.67 (s, 1H), 7.62 (d, *J* = 2.5 Hz, 1H), 7.43 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.85 (d, *J* = 8.9 Hz, 2H), 6.42 (d, *J* = 8.7 Hz, 1H), 3.72 (s, 3H), 3.45-3.32 (m, 2H), 2.07 (s, 6H), 1.55 (s, 6H), 1.23 (t, *J* = 7.2 Hz, 3H).

Example S-12: Synthesis of 4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)thieno[2,3-c]pyridin-7(6H)-one (Compound 13)



[0233] Step 1: Synthesis of 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid: 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (0.43 g, 90 %, off-white solid) was prepared following General Procedure 2, Step 4 using methyl 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate (0.50 g, 1.66 mmol, 1eq). LCMS: 288 [M+1]⁺, 290 [M+H+2]⁺

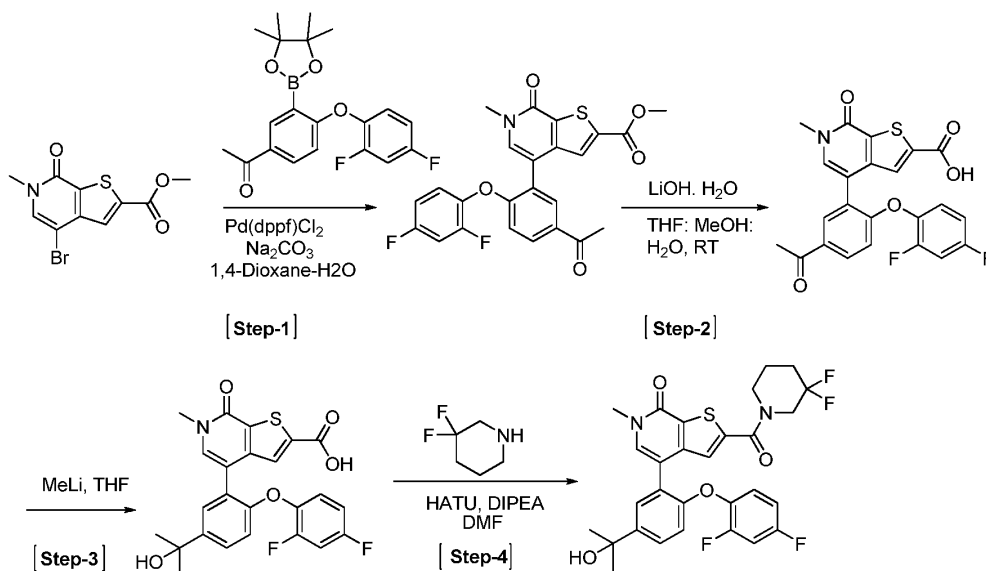
[0234] Step 2: Synthesis of N'-acetyl-4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carbohydrazide: N'-acetyl-4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carbohydrazide (350 mg, 68 %, yellow solid) was prepared following General Procedure 2, Step 5 using 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (0.43 g, 1.49 mmol, 1eq). LCMS: 344 [M+1]⁺, 346 [M+H+2]⁺

[0235] Step 3: Synthesis of 4-bromo-6-methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)thieno[2,3-c]pyridin-7(6H)-one: 4-bromo-6-methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)thieno[2,3-c]pyridin-7(6H)-one (110 mg, 58 %, yellow solid) was prepared following General Procedure 2, Step 6 using N'-acetyl-4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carbohydrazide (0.20 g, 0.58 mmol, 1eq). LCMS: 326 [M+1]⁺, 328 [M+H+2]⁺

[0236] Step 4: Synthesis of 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-6-methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)thieno[2,3-c]pyridin-7(6H)-one: 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-6-methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)thieno[2,3-c]pyridin-7(6H)-one (0.1 g, 32 %, off-white solid) was prepared following General Procedure 2, Step 7 using 4-bromo-6-methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)thieno[2,3-c]pyridin-7(6H)-one (0.2 g, 0.306 mmol, 1 eq) and 1-(4-(4-fluoro-2,6-dimethylphenoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone (0.306 g, 0.797 mmol, 1.3 eq). LCMS: 504 [M+1]⁺

[0237] Step 5: Synthesis of 4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)thieno[2,3-c]pyridin-7(6H)-one: 4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)thieno[2,3-c]pyridin-7(6H)-one (13 mg, 25 %, off-white solid) was prepared following General Procedure 1, Step 5 using 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-6-methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)thieno[2,3-c]pyridin-7(6H)-one (0.05 g, 0.099 mmol, 1 eq). LCMS: 520 [M+1]⁺, ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.82 (s, 1H), 7.66 (s, 1H), 7.53 (d, *J* = 2.4 Hz, 1H), 7.41 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.99 (d, *J* = 9.1 Hz, 2H), 6.37 (d, *J* = 8.6 Hz, 1H), 5.04 (s, 1H), 3.67 (s, 3H), 2.57 (s, 3H), 2.02 (s, 6H), 1.45 (s, 6H)

Example S-13: Synthesis of 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-2-(3,3-difluoro piperidine-1-carbonyl)-6-methylthieno[2,3-c]pyridin-7(6H)-one (Compound 23)



[0238] Step 1: Synthesis of methyl 4-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate: Methyl 4-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate (0.85 mg, 65 %, white solid) was prepared following General Procedure 1, Step 4 using methyl 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate (0.9 g, 3.3 mmol, 1 eq). LCMS: 470 [M+1]⁺

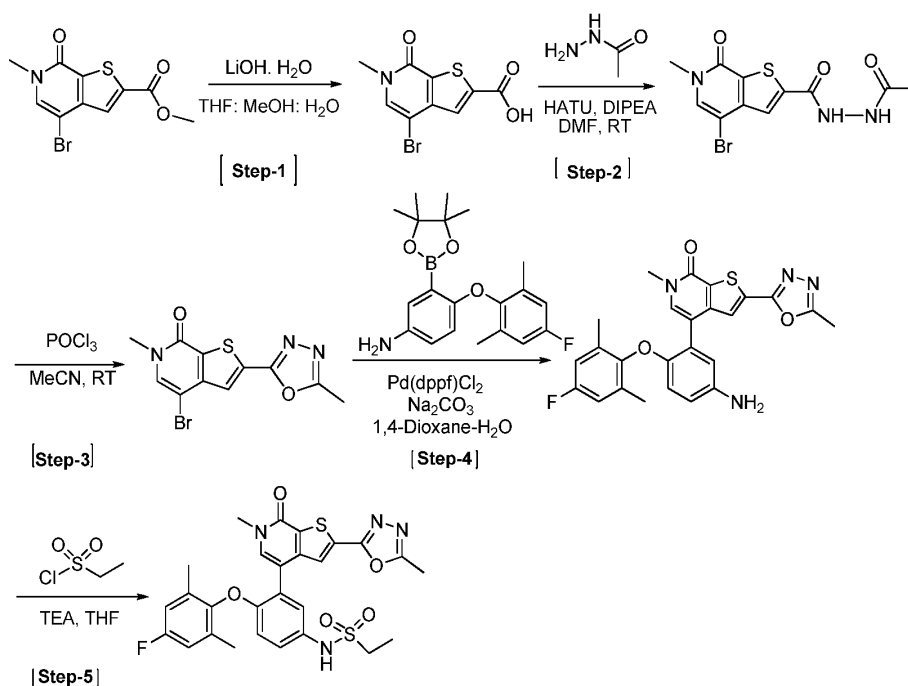
[0239] Step 2: Synthesis of 4-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid: 4-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (450 mg, 92 %, off-white solid) was prepared following General Procedure 2, Step 4 using 4-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate (0.50 g, 1.06 mmol, 1eq). LCMS: 456 [M+1]⁺

[0240] Step 3: Synthesis of 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid: 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (200 mg, 72 %, off-white solid) was prepared following General Procedure 1, Step 5 using 4-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (0.20 g, 0.44 mmol, 1eq). LCMS: 472 [M+1]⁺

[0241] Step 4: Synthesis of 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-2-(3,3-difluoro piperidine-1-carbonyl)-6-methylthieno[2,3-c]pyridin-7(6H)-one: 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-2-(3,3-difluoro piperidine-1-carbonyl)-6-methylthieno[2,3-c]pyridin-7(6H)-one (0.018 g, 10 %, off-white solid) was prepared following General Procedure 2, Step 5 using 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (0.15 g, 0.33 mmol, 1 eq) and 3,3-difluoropiperidine (0.150 g, 0.95 mmol, 3.0 eq). LCMS: 575 [M+1]⁺, ¹HNMR (400 MHz, DMSO-*d*₆): δ 7.70 (s, 1H), 7.54 (d, *J* = 2.4 Hz, 1H), 7.50 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.35 (ddd, *J* = 11.4, 8.7, 3.0 Hz, 1H), 7.27 (s, 1H), 7.09 (td, *J* = 9.1, 5.4 Hz, 1H), 7.04-6.95 (m, 1H), 6.86 (d, *J* = 8.5 Hz, 1H), 5.09 (s, 1H), 3.91 (t, *J* = 11.8 Hz, 2H), 3.60 (s, 5H), 2.10 (ddt, *J* = 14.5, 10.4, 6.3 Hz, 2H), 1.67 (s, 2H), 1.46 (s, 6H).

Example S-14: Synthesis of N-(4-(4-fluoro-2,6-dimethylphenoxy)-3-(6-methyl-2-(5-methyl-1,3,4-

oxadiazol-2-yl)-7-oxo-6,7-dihydrothieno[2,3-c]pyridin-4-yl)phenyl)ethanesulfonamide (**Compound 10**)



[0242] Step 1: Synthesis of 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid: 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (0.43 mg, 90 %, off-white solid) was prepared following General Procedure 2, Step 4 using methyl 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate (0.5 g, 1.66 mmol, 1 eq). LCMS: 288 [M+1]⁺, 290 [M+H+2]⁺

[0243] Step 2: Synthesis of N'-acetyl-4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carbohydrazide: N'-acetyl-4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carbohydrazide (450 mg, 87 %, yellow solid) was prepared following General Procedure 2, Step 5 using 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (0.43 g, 1.5 mmol, 1eq). LCMS: 344 [M+1]⁺, 346 [M+H+2]⁺

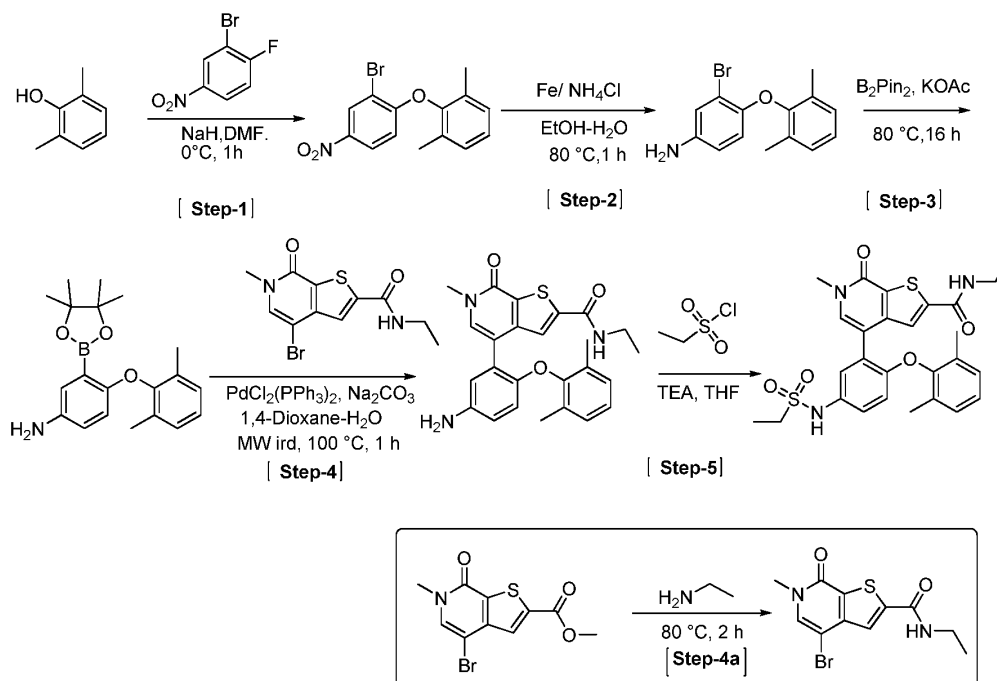
[0244] Step 3: Synthesis of 4-bromo-6-methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)thieno[2,3-c]pyridin-7(6H)-one: 4-bromo-6-methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)thieno[2,3-c]pyridin-7(6H)-one (240 mg, 50 %, yellow solid) was prepared following General Procedure 2, Step 6 using

N'-acetyl-4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carbohydrazide (0.45 g, 1.35 mmol, 1 eq). LCMS: 326 [M+1]⁺, 328 [M+H+2]⁺

[0245] Step 4: Synthesis of 4-(5-amino-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-6-methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)thieno[2,3-c]pyridin-7(6H)-one: 4-(5-amino-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-6-methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)thieno[2,3-c]pyridin-7(6H)-one (0.018 g, 10 %, off-white solid) was prepared following General Procedure 2, Step 7 using 4-bromo-6-methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)thieno[2,3-c]pyridin-7(6H)-one (0.24 g, 0.73 mmol, 1 eq). LCMS: 477 [M+1]⁺

[0246] Step 5: Synthesis of N-(4-(4-fluoro-2,6-dimethylphenoxy)-3-(6-methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)-7-oxo-6,7-dihydrothieno[2,3-c]pyridin-4-yl)phenyl)ethanesulfonamide: N-(4-(4-fluoro-2,6-dimethylphenoxy)-3-(6-methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)-7-oxo-6,7-dihydrothieno[2,3-c]pyridin-4-yl)phenyl)ethanesulfonamide (0.018 g, 16 %, off-white solid) was prepared following General Procedure 2, Step 8 using 4-(5-amino-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-6-methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)thieno[2,3-c]pyridin-7(6H)-one (0.11 g, 0.23 mmol, 1 eq). LCMS: 569 [M+1]⁺, ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.85 (s, 1H), 7.71 (s, 1H), 7.26 (d, *J* = 2.6 Hz, 1H), 7.14 (d, *J* = 8.8 Hz, 1H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.40 (d, *J* = 8.8 Hz, 1H), 3.66 (s, 3H), 3.06 (d, *J* = 7.5 Hz, 2H), 2.57 (s, 3H), 2.02 (s, 6H), 1.21 (t, *J* = 7.5 Hz, 3H).

Example S-15: Synthesis of 4-(2-(2,6-dimethylphenoxy)-5-(ethylsulfonamido)phenyl)-N-ethyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (Compound 147)



[0247] Step 1: Synthesis of 2-(2-bromo-4-nitrophenoxy)-1,3-dimethylbenzene: 2-(2-bromo-4-nitrophenoxy)-1,3-dimethylbenzene (4.5 g, 68%, yellow solid) was prepared following General Procedure 2, Step 1 using 2,6-dimethylphenol (2.0 g, 16.03 mmol, 1.0 eq). LCMS: 322 [M+H]⁺, 324 [M+H+2]⁺

[0248] Step 2: Synthesis of 3-bromo-4-(2,6-dimethylphenoxy)aniline: 3-bromo-4-(2,6-dimethylphenoxy)aniline (3.5 g, 97 %, black viscous liquid) was prepared following General Procedure 2, Step 2 using 2-(2-bromo-4-nitrophenoxy)-1,3-dimethylbenzene (4.0 g, 12.46 mmol, 1.0eq). LCMS: 292 [M+H]⁺, 294 [M+H+2]⁺

[0249] Step 3: Synthesis of 4-(2,6-dimethylphenoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline: 4-(2,6-dimethylphenoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.700 g, 66 %, black viscous liquid) was prepared following General Procedure 2, Step 3 using 3-bromo-4-(2,6-dimethylphenoxy)aniline (1.0 g, 45.6 mmol, 1.0 eq). ¹H NMR: (400 MHz, CDCl₃) δ 6.97-7.11 (m, 3H), 6.58 (d, *J* = 3.95 Hz, 1H), 6.14 (d, *J* = 8.77 Hz, 1H), 2.05-2.18 (m, 6H), 1.23-1.28 (m, 12H).

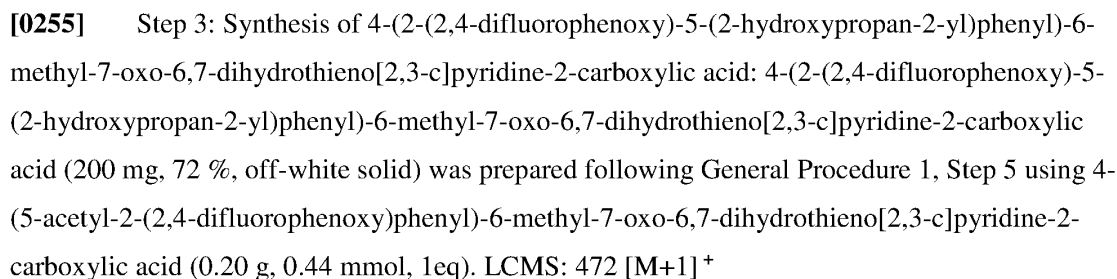
[0250] Step 4a: Synthesis of 7-bromo-*N*-ethyl-5-methyl-4-oxo-4,5-dihydrothieno[3,2-*c*]pyridine-2-carboxamide: 7-bromo-*N*-ethyl-5-methyl-4-oxo-4,5-dihydrothieno[3,2-*c*]pyridine-2-

carbox amide (100 mg, 67%, brown solid)) was prepared following General Procedure 1, Step 4a using ethyl 7-bromo-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxylate (1.0g, 45.6 mmol, 1.0 eq). LCMS: 315 [M+H]⁺, 317 [M+H+2]⁺

[0251] Step 4: Synthesis of 7-(5-amino-2-(2,6-dimethylphenoxy)phenyl)-N-ethyl-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide : 7-(5-amino-2-(2,6-dimethylphenoxy)phenyl)-N-ethyl-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide (0.23 g, 30 %, brown viscous liquid) was prepared following General Procedure 2, Step 7 using 4-(2,6-dimethylphenoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.807 g, 2.37 mmol, 1.5 eq) and 7-bromo-N-ethyl-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide (0.50 g, 1.58 mmol, 1eq). LCMS: 448[M+H]⁺

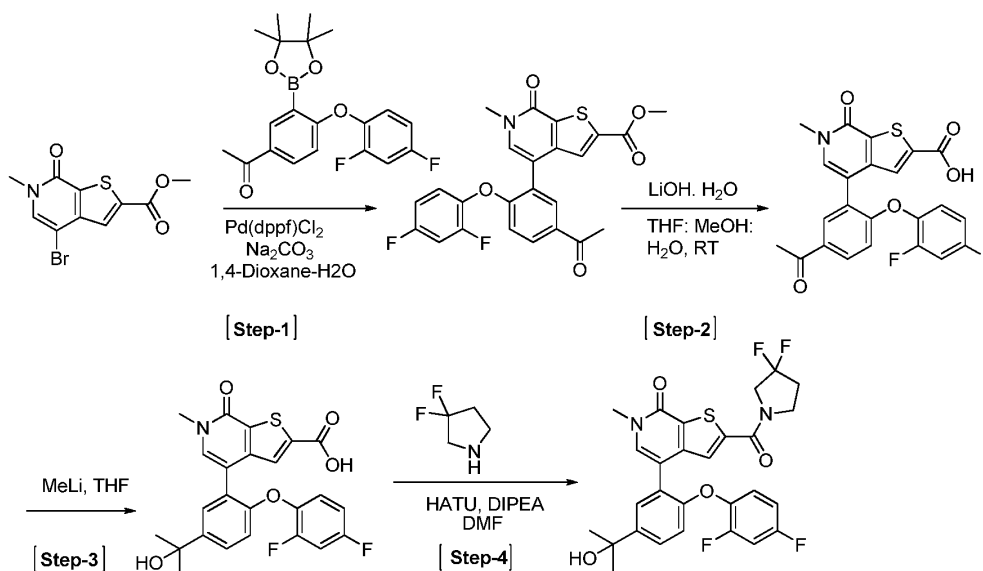
[0252] Step 5: Synthesis of 4-(2-(2,6-dimethylphenoxy)-5-(ethylsulfonamido)phenyl)-N-ethyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide: 4-(2-(2,6-dimethylphenoxy)-5-(ethylsulfonamido)phenyl)-N-ethyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (30 mg, 16.5 %) was prepared following General Procedure 2, Step-8 using 7-(5-amino-2-(2,6-dimethylphenoxy)phenyl)-N-ethyl-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide (0.15 g, 0.335 mmol, 1.0 eq). LCMS: 540 [M+H]⁺, ¹H NMR: (400 MHz, MeOH-*d*₄) δ 7.81 (s, 1H), 7.68 (s, 1H), 7.35 (d, *J* = 2.6 Hz, 1H), 7.17 (d, *J* = 8.8 Hz, 1H), 7.12-6.98 (m, 3H), 6.43 (d, *J* = 8.8 Hz, 1H), 3.75 (s, 3H), 3.40-3.20 (m, 2H), 3.09 (d, *J* = 7.5 Hz, 2H), 2.05 (s, 6H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.20 (t, *J* = 7.2 Hz, 3H).

Example S-16: Synthesis of 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-2-(4,4-difluoropiperidine-1-carbonyl)-6-methylthieno[2,3-c]pyridin-7(6H)-one (Compound 22)



[0256] Step 4: Synthesis of 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-2-(4,4-difluoropiperidine-1-carbonyl)-6-methylthieno[2,3-c]pyridin-7(6H)-one: 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-2-(4,4-difluoropiperidine-1-carbonyl)-6-methylthieno[2,3-c]pyridin-7(6H)-one (0.018 g, 10 %, off-white solid) was prepared following General Procedure 2, Step 5 using 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (0.09 g, 0.19 mmol, 1 eq) and 4,4-difluoropiperidine (0.90 g, 0.57 mmol, 3.0 eq). LCMS: 575 [M+1]⁺, ¹H NMR (400 MHz, MeOH-*d*₄): δ 7.64-7.49 (m, 3H), 7.36 (s, 1H), 7.02 (br. s., 1H), 6.99-6.88 (m, 2H), 6.86-6.8 (m, 1H), 3.8 (br. s., 4H), 3.69 (s, 3H), 2.04 (br. s., 4H), 1.58 (s, 6H).

*Example S-17: Synthesis of 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-2-(3,3-difluoropyrrolidine-1-carbonyl)-6-methylthieno[2,3-*c*]pyridin-7(6*H*)-one (Compound 76)*



[0257] Step 1: Synthesis of methyl 4-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate: Methyl 4-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate (0.85 mg, 65 %, white solid) was prepared following General Procedure 1, Step 4 using methyl 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate (0.9 g, 3.3mmol, 1 eq). LCMS: 470 [M+1]⁺

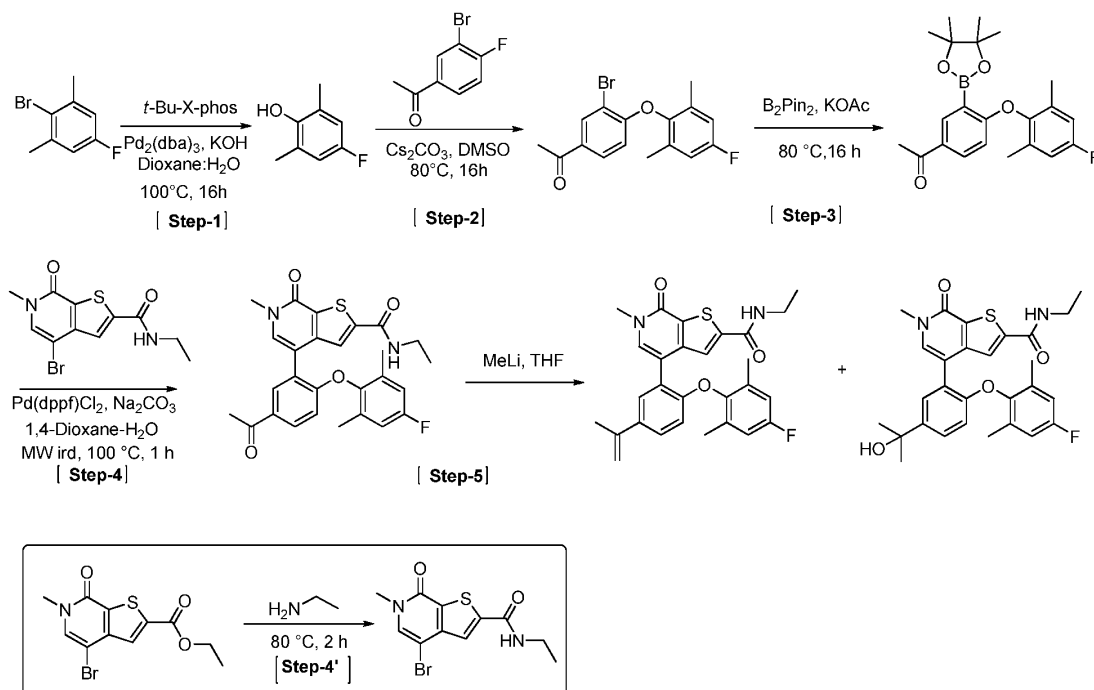
[0258] Step 2: Synthesis of 4-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid: 4-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (450 mg, 92 %, off-white solid)

was prepared following General Procedure 2, Step 4 using 4-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate (0.50 g, 1.06 mmol, 1eq). LCMS: 456 [M+1]⁺

[0259] Step 3: Synthesis of 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid: 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (200 mg, 72 %, off-white solid) was prepared following General Procedure 1, Step 5 using 4-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (0.20 g, 0.44 mmol, 1eq). LCMS: 472 [M+1]⁺

[0260] Step 4: Synthesis of 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-2-(3,3-difluoropyrrolidine-1-carbonyl)-6-methylthieno[2,3-c]pyridin-7(6H)-one: 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-2-(3,3-difluoropyrrolidine-1-carbonyl)-6-methylthieno[2,3-c]pyridin-7(6H)-one (0.006 g, 2.2 %, off-white solid) was prepared following General Procedure 2, Step 5 using 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (0.15 g, 0.3 mmol, 1 eq) and 3,3-difluoropyrrolidine (0.15 g, 0.95 mmol, 3.0 eq). LCMS: 561 [M+1]⁺, ¹HNMR (400 MHz, MeOH-*d*₄): δ 7.61 (s, 1H), 7.60-7.48 (m, 3H), 7.05-6.91 (m, 3H), 6.85 (d, *J* = 6.6 Hz, 1H), 4.17 (br. s., 1H), 4.01 (br. s., 2H), 3.86 (br. s., 1H), 3.70 (s, 3H), 2.49 (br. s., 2H), 1.58 (s, 6H).

Example S-18: Synthesis of N-ethyl-4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(prop-1-en-2-yl)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (**Compound 148**)



[0261] Step 1: Synthesis of 4-fluoro-2,6-dimethylphenol: 4-fluoro-2,6-dimethylphenol (2.2 g, 64%) was prepared following General Procedure 1, Step 1 using 2-bromo-5-fluoro-1,3-dimethylbenzene (5.0 g, 24.7 mmol, 1eq). LCMS: 141 $[\text{M}+1]^+$

[0262] Step 2: Synthesis of 1-(3-bromo-4-(4-fluoro-2,6-dimethylphenoxy)phenyl)ethanone: 1-(3-bromo-4-(4-fluoro-2,6-dimethylphenoxy)phenyl)ethanone (0.30 g, 25%) was prepared following General Procedure 1, Step 2 using 4-fluoro-2,6-dimethylphenol (0.50 g, 3.57 mmol) and 1-(3-bromo-4-fluorophenyl)ethanone (0.93 g, 4.28 mmol, 1.2 eq). LCMS: 337 $[\text{M}+\text{H}]^+$, 339 $[\text{M}+\text{H}+2]^+$

[0263] Step 3: Synthesis of 1-(4-(4-fluoro-2,6-dimethylphenoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone: 1-(4-(4-fluoro-2,6-dimethylphenoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone (0.35 g, 56%) was prepared following General Procedure 1, Step 3 using 1-(3-bromo-4-(4-fluoro-2,6-dimethylphenoxy)phenyl)ethanone (0.55 g, 1.63 mmol, 1 eq). ^1H NMR (400 MHz, CDCl_3): δ 8.35 (d, $J = 2.4$ Hz, 1 H), 7.86 (s, 1H), 6.81 (d, $J = 8.8$ Hz, 2H), 6.35 (d, $J = 8.8$ Hz, 1H), 2.57 (s, 3H), 1.37 (s, 6H), 1.25 (d, $J = 7.3$ Hz, 12H)

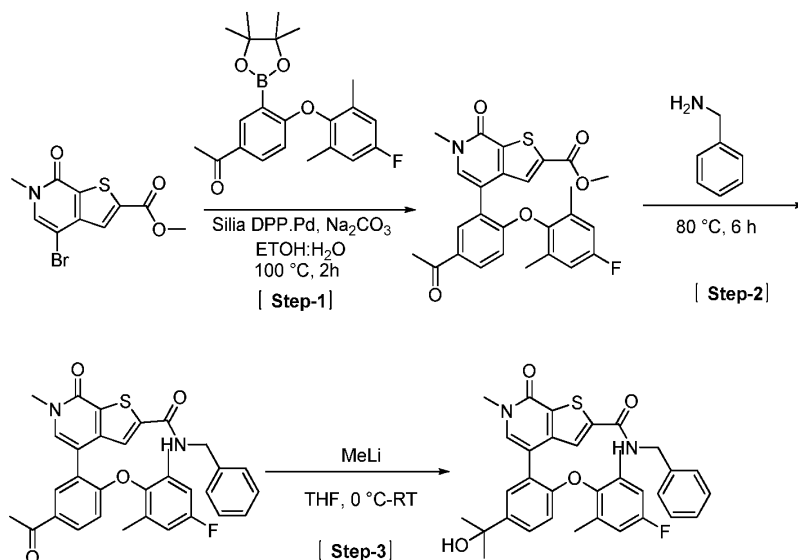
[0264] Step 4a: Synthesis of 4-bromo-*N*-ethyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-*c*]pyridine-2-carboxamide: 4-bromo-*N*-ethyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-*c*]pyridine-2-carboxamide (1.23 g, 95%, white solid) was prepared following General Procedure 1, Step 4a using ethyl 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-*c*]pyridine-2-carboxylate (1.5 g, 4.3 mmol, 1 eq). LCMS: 315 [M+H]⁺, 317 [M+H+2]⁺

[0265] Step 4: Synthesis of 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-*N*-ethyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-*c*]pyridine-2-carboxamide: 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-*N*-ethyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-*c*]pyridine-2-carboxamide (0.16 g, 38%, off white solid) was prepared following General Procedure 1, Step 4 using 1-(4-(4-fluoro-2,6-dimethylphenoxy)-3-(4,4,5,5-tetra methyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone (0.46 g, 1.2 mmol, 1.5 eq) and 4-Bromo-*N*-ethyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-*c*]pyridine-2-carboxamide (0.27 g, 0.80 mmol, 1 eq). LCMS: 493 [M+H]⁺

[0266] Step 5: Synthesis of *N*-ethyl-4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(prop-1-en-2-yl)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-*c*]pyridine-2-carboxamide: To a stirred solution of 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-*N*-ethyl-6-methyl-7-oxo-6,7-dihydrothieno [2,3-*c*]pyridine-2-carboxamide (0.60 g, 1.21 mmol) in anhydrous THF (10 mL) was added MeLi (3.0 mL, 4.86 mmol, 4 eq) at 0 °C dropwise and the mixture was stirred at same temperature for 10 min. The reaction was complete after 10 min and the mixture was quenched with saturated NH₄Cl solution (10 mL) slowly. The aqueous layer was then extracted with EtOAc (100 mL × 2). The combined organic layers were washed with water (50 mL), brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to obtain a crude which was purified by CombiFlash Chromatography to afford *N*-ethyl-4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-*c*]pyridine-2-carboxamide as a major product and *N*-ethyl-4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(prop-1-en-2-yl)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-*c*]pyridine-2-carboxamide as a minor product (46 mg, 7%). LCMS: 491 [M+1]⁺; ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.82 (s, 1H), 7.86 (s, 1H), 7.77 (s, 1H), 7.58 (d, *J* = 2.2 Hz, 1H), 7.48 (dd, *J* = 2.4, 8.6 Hz, 1H), 6.99 (d, *J* = 9.2 Hz, 2H), 6.55 (s, 1H), 6.40 (d, *J* = 8.8 Hz, 1H), 3.62 (s, 3H), 3.29-3.19 (m, 2H), 2.11 (s, 3H), 2.00 (br. s., 6H), 1.08 (t, *J* = 7.2 Hz, 3H)

*Example S-19: Synthesis of N-benzyl-4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-*c*]pyridine-2-carboxamide (General Procedure*

3) (Compound 149)



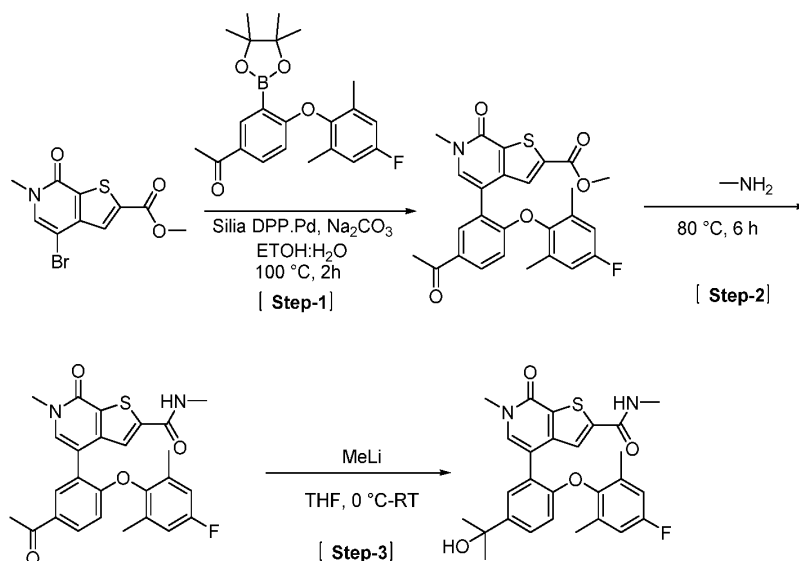
[0267] Step 1: Synthesis of methyl 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate: To a stirred solution of methyl 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate (5 g, 16.55 mmol, 1 eq) in ethanol (90 mL) were added 1-(4-(4-fluoro-2,6-dimethylphenoxy)-3-(4,4,5,5-tetra methyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone (7.62 g, 19.86 mmol, 1.2 eq) and Na₂CO₃ (3.50 g, 33.11 mmol, 2 eq) dissolved in water (10 mL). Silia DPP-Pd (0.30 mmol/g loading; 1.65 g, 0.496 mmol, 0.03 eq) was then added to the mixture and the resultant mixture was then heated at 100 °C for 2 h. The reaction was complete after 2 h and the mixture was filtered through the celite bed, washed with 5% MeOH in DCM (200 mL). The filtrate obtained was concentrated under reduced pressure to obtain a crude residue. The residue obtained (7.0 g) was stirred in MeOH (50 mL) for 30 min, filtered over Büchner funnel concentrated under reduced pressure to obtain a solid compound. Then solid obtained (6.0 g) was further stirred in diethyl ether (50 mL) for 30 min, filtered over Büchner funnel; dried under vacuum to afford title compound (5.0 g, 63%). LCMS: 480 [M+1]+

[0268] Step 2: Synthesis of 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-N-benzyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide: To methyl 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate (0.1 g, 0.208 mmol) was added benzylamine (2 mL) and the mixture was heated at 80 °C. The reaction was complete after 6 h and the mixture was concentrated under reduced pressure to obtain a crude

residue which was purified by CombiFlash Chromatography-to afford the title compound (0.1 g, 86%). LCMS: 555 [M+1]⁺

[0269] Step 3: Synthesis of N-benzyl-4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide: N-benzyl-4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (0.016 g, 15.6%) was prepared following General Procedure 1, Step 5 using 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-N-benzyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (0.10 g, 0.18 mmol). LCMS: 571 [M+]⁺; ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.42 (s, 1H), 7.91 (s, 1H), 7.69 (s, 1H), 7.50 (d, *J* = 2.2 Hz, 1H), 7.43-7.21 (m, 6H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.34 (d, *J* = 8.3 Hz, 1H), 5.00 (s, 1H), 4.43 (d, *J* = 5.3 Hz, 2H), 3.63 (s, 3H), 1.96 (br. s., 6H), 1.44 (s, 6H).

Example S-20: Synthesis of 4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-N,6-dimethyl-7-oxo-6,7-dihydrothienof[2,3-c]pyridine-2-carboxamide (Compound 150)



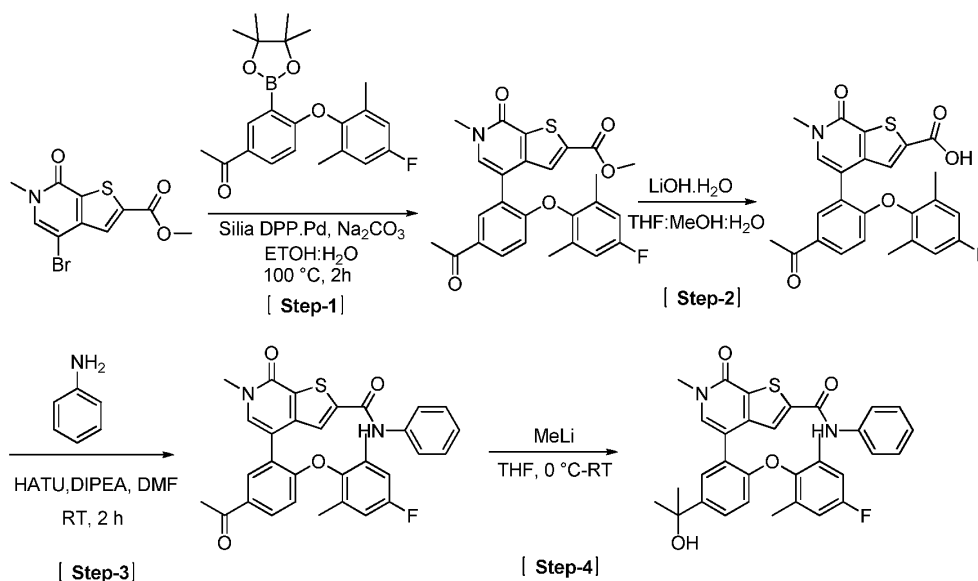
[0270] Step 1: Synthesis of methyl 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate: Methyl 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate (5.0 g, 63 %) was prepared following General Procedure 3, Step 1 using methyl 4-bromo-6-methyl-7-oxo-

6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate (5 g, 16.55 mmol, 1 eq) and 1-(4-(4-fluoro-2,6-dimethylphenoxy)-3-(4,4,5,5-tetra methyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone (7.62 g, 19.86 mmol, 1.2 eq). LCMS: 480 [M+1]⁺

[0271] Step 2: Synthesis of 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-N,6-dimethyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide: 4-(5-acetyl-2-(4-fluoro-2,6-dimethyl phenoxy)phenyl)-N,6-dimethyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (0.14 g, 73%) was prepared following General Procedure 3, Step 2 using methyl 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate (0.2 g, 0.42 mmol, 1 eq). LCMS: 479 [M+1]⁺

[0272] Step 3: Synthesis of 4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-N,6-dimethyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide: 4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-N,6-dimethyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (0.009 g, 9%) was prepared following General Procedure 1, Step 5 using 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-N,6-dimethyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (0.10 g, 0.209 mmol). LCMS: 495 [M+1]⁺; ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.81 (d, *J* = 4.4 Hz, 1H), 7.78 (s, 1H), 7.69 (s, 1H), 7.50 (d, *J* = 2.2 Hz, 1H), 7.40 (dd, *J* = 2.2, 8.8 Hz, 1H), 6.97 (d, *J* = 9.2 Hz, 2H), 6.35 (d, *J* = 8.3 Hz, 1H), 5.01 (s, 1H), 3.63 (s, 3H), 2.74 (d, *J* = 4.8 Hz, 3H), 1.99 (s, 6H), 1.45 (s, 6H).

Example S-21: Synthesis of 4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-N-phenyl-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (Compound 151)



[0273] Step 1: Synthesis of methyl 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate: Methyl 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate (5.0 g, 63%) was prepared following General Procedure 3, Step 1 using methyl 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate (5 g, 16.55 mmol, 1 eq) and 1-(4-(4-fluoro-2,6-dimethylphenoxy)-3-(4,4,5,5-tetra methyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone (7.62 g, 19.86 mmol, 1.2 eq). LCMS: 480 [M+1]⁺

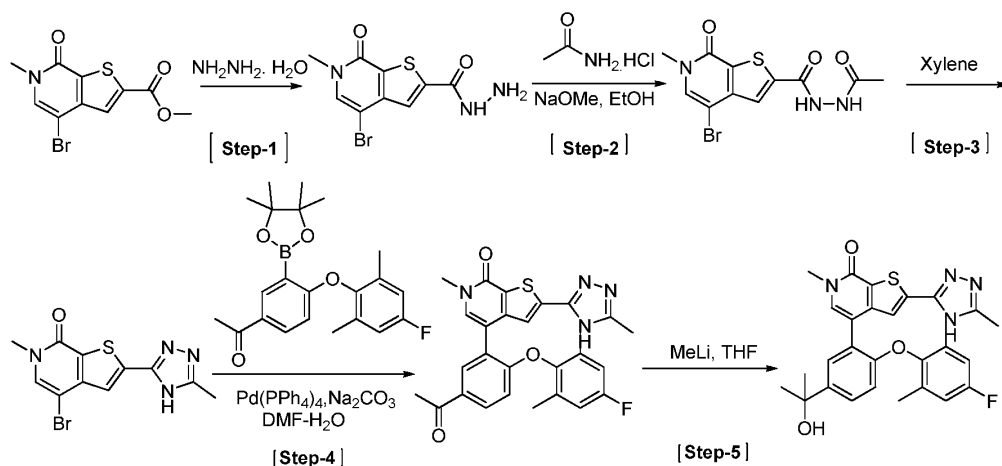
[0274] Step 2: Synthesis of 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid: 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (0.35 g, 86%) was prepared following General Procedure 2, Step 4 using methyl 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate (0.30 g, 0.626 mmol). LCMS: 466 [M+1]⁺

[0275] Step 3: Synthesis of 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-6-methyl-7-oxo-N-phenyl-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide: To a stirred solution of 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (0.1 g, 0.215 mmol) in DMF (5 mL) was added HATU (0.16 g, 0.43 mmol, 2.0 eq) at 0 °C and the mixture was stirred for 10 min. DIPEA (0.19 mL, 1.07 mmol, 4 eq)

and aniline (0.3 g, 0.332 mmol, 1.5 eq) were then added to the mixture and the resultant mixture was stirred at RT for 16 h. The reaction was complete after 16 h and to the mixture was added water (200 mL) and extracted with EtOAc (300 mL). The organic layer was washed with water (100 mL), brine (150 mL) dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford a crude residue which was purified by CombiFlash Chromatography to afford the title compound (0.1 g, 86%). LCMS: 541 [M+1]⁺

[0276] Step 4: Synthesis of 4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-N-phenyl-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide : 4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-N-phenyl-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (0.007 g, 14%) was prepared following General Procedure 1, Step 5 using 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-6-methyl-7-oxo-N-phenyl-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (0.050 g, 0.090 mmol). LCMS:557 [M+1]⁺; ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.59 (s, 1H), 8.20 (s, 1H), 7.77-7.66 (m, 2H), 7.56 (d, *J* = 2.2 Hz, 1H), 7.45-7.39 (m, 1 H), 7.38-7.32 (m, 1 H), 7.13 (s, 1H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.38 (d, *J* = 8.3 Hz, 1H), 5.03 (s, 1H), 3.66 (s, 3H), 2.02 (br. s., 6H), 1.47 (s, 6H).

Example S-22: Synthesis of 4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-2-(5-methyl-4H-1,2,4-triazol-3-yl)thieno[2,3-c]pyridin-7(6H)-one (General Procedure 4) (Compound 152)



[0277] Step 1: Synthesis of 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carbohydrazide: To a stirred solution of methyl 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno [2,3-

c]pyridine-2-carboxylate (0.50 g, 1.66 mmol) in MeOH (10 mL) was added hydrazine hydrate (5.3 mL, 16.61 mmol, 10 eq) and the mixture was refluxed at 80 °C for 3 h. The reaction was complete after 3 h; water (100 mL) was added to it to obtain a precipitate which was filtered over Büchner funnel, washed with EtOAc (100 mL) to afford the title compound (400 mg, 80%). LCMS: 302 [M+H]⁺, 304 [M+H+2]⁺

[0278] Step 2: Synthesis of N'-acetyl-4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carbohydrazide: To a stirred solution of acetamide hydrochloride (0.22 g, 2.31 mmol) in ethanol (5 mL) was added sodium methoxide (0.125 g, 2.13 mmol, 2.0 eq) and the mixture was heated at 70 °C for 3 h. After 3 h, the mixture was filtered by over Büchner funnel. To the filtrate obtained was added 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carbohydrazide (0.35 mg, 1.115 mmol) and the mixture was further heated at 70 °C for 16 h. The reaction was complete after 16 h and the mixture was poured in water (50 mL) to obtain a precipitate which was filtered over a Büchner funnel to afford the title compound (300 mg, 75%). LCMS: 343 [M]⁺, 344 [M+2H]⁺, 346 [M+H+2]⁺

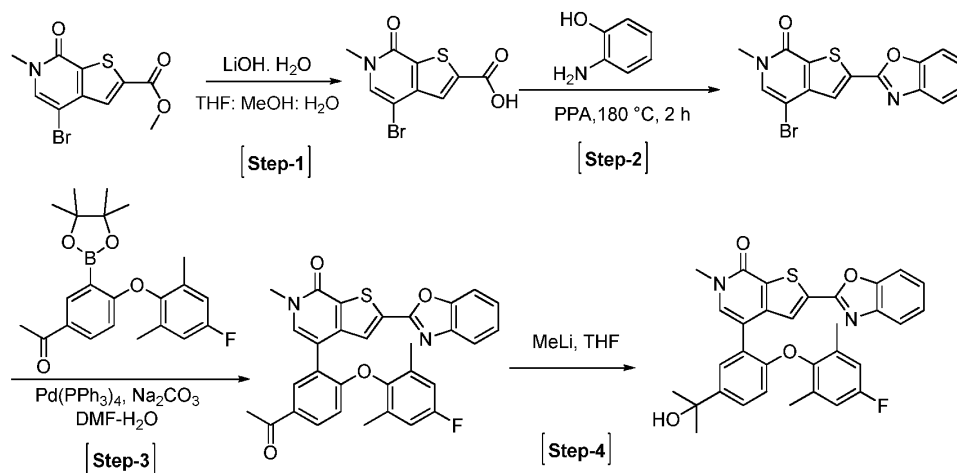
[0279] Step 3: Synthesis of 4-bromo-6-methyl-2-(5-methyl-4H-1,2,4-triazol-3-yl)thieno[2,3-c]pyridin-7(6H)-one: N'-acetyl-4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carbohydrazide (0.30 g, 0.87 mmol) in a mixture of xylene (5 mL) and EtOH (2 mL) was heated at 120 °C for 48 h. Upon completion, the mixture was filtrated through a Büchner funnel and filtrate was collected, concentrated under reduced pressure to obtain a crude which was purified by CombiFlash Chromatography to afford the title compound (100 mg, 35%). LCMS: 325 [M+H]⁺, 327 [M+H+2]⁺

[0280] Step 4: Synthesis of 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-6-methyl-2-(5-methyl-4H-1,2,4-triazol-3-yl)thieno[2,3-c]pyridin-7(6H)-one: To a stirred solution of 4-bromo-6-methyl-2-(5-methyl-4H-1,2,4-triazol-3-yl)thieno[2,3-c]pyridin-7(6H)-one (0.1 g, 0.307 mmol, 1 eq) in DMF (3 mL) were added 1-(4-(4-fluoro-2,6-dimethylphenoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone (0.15 g, 0.04 mmol, 1.3 eq) and Na₂CO₃ (0.08 g, 0.77 mmol, 2.5 eq) dissolved in water (0.5 mL) and the mixture was degassed under nitrogen for 40 min. Pd(PPh₃)₄ (0.017 g, 0.01 mmol, 0.03 eq) was then added to the mixture and the mixture was further degassed under nitrogen for 20 min. The resultant mixture was then heated at 120 °C for 16 h. Upon completion, the mixture was diluted with water (50 mL) and extracted with EtOAc (100 mL × 2). The combined organic layers were washed with water (50 mL), brine (40 mL), dried over

anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to obtain a crude residue which was purified by CombiFlash Chromatography to afford the title compound (0.075 g, 50 %). LCMS: 503 $[\text{M}+1]^+$

[0281] Step 5: Synthesis of 4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-2-(5-methyl-4H-1,2,4-triazol-3-yl)thieno[2,3-c]pyridin-7(6H)-one: 4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-2-(5-methyl-4H-1,2,4-triazol-3-yl)thieno[2,3-c]pyridin-7(6H)-one (0.009 g, 17.6 %) was prepared following General Procedure 1, Step 5 using 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-6-methyl-2-(5-methyl-4H-1,2,4-triazol-3-yl)thieno[2,3-c]pyridin-7(6H)-one (0.050 g, 0.099 mmol). LCMS: 519 $[\text{M}+1]^+$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 13.93 (br. s., 1H), 7.71 (br. s., 1H), 7.51 (br. s., 2H), 7.39 (br. s., 1H), 6.97 (d, $J = 8.8$ Hz, 2H), 6.33 (br. s., 1H), 5.02 (br. s., 1H), 3.64 (br. s., 3H), 2.39 (br. s., 3H), 2.01 (br. s., 6H), 1.45 (br. s., 6H)

Example S-23: Synthesis of 2-(benzo[d]oxazol-2-yl)-4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methylthieno[2,3-c]pyridin-7(6H)-one (General Procedure 5) (Compound 153)



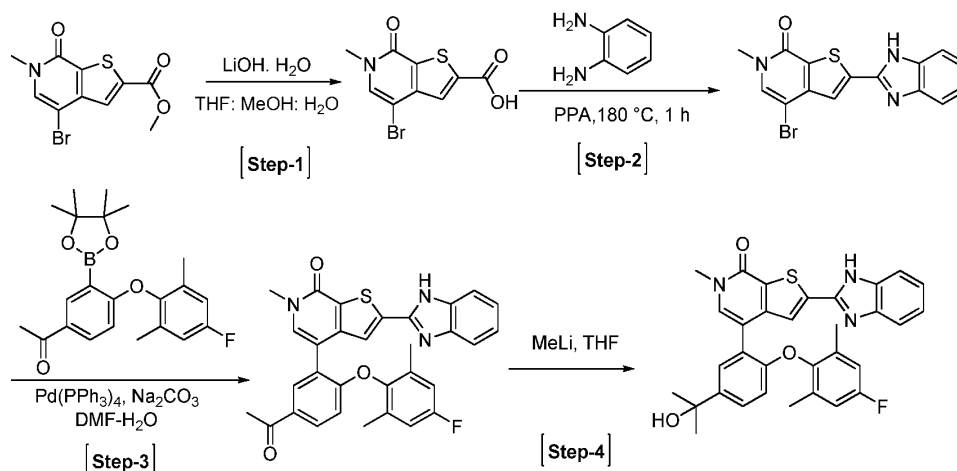
[0282] Step 1: Synthesis of 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid: 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (4 g, 84%) was prepared following General Procedure 2, Step 4 using methyl 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate (5.0 g, 16.6 mmol). LCMS: 288 $[\text{M}+\text{H}]^+$, 290 $[\text{M}+\text{H}+2]^+$

[0283] Step 2: Synthesis of 2-(benzo[d]oxazol-2-yl)-4-bromo-6-methylthieno[2,3-c]pyridin-7(6H)-one: To a stirred solution of 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (1.0 g, 3.47 mmol) in polyphosphoric acid (10 mL) was added 2-aminophenol (0.45 g, 4.10 mmol, 1.2 eq) and the mixture was heated at 180 °C. The reaction was complete after 2 h and the mixture was quenched with 2N-NaOH (200 mL) to obtain a precipitate which was filtered over Büchner funnel to afford the title compound (0.5 g, 41%). LCMS: 361 [M+H]⁺, 363 [M+H+2]⁺

[0284] Step 3: Synthesis of 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-2-(benzo[d]oxazol-2-yl)-6-methylthieno[2,3-c]pyridin-7(6H)-one: 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-2-(benzo[d]oxazol-2-yl)-6-methylthieno[2,3-c]pyridin-7(6H)-one (0.15 g, 20%) was prepared following General Procedure 4, Step 4 using 2-(benzo[d]oxazol-2-yl)-4-bromo-6-methylthieno[2,3-c]pyridin-7(6H)-one (0.5 g, 1.392 mmol, 1 eq). LCMS: 539 [M+1]⁺

[0285] Step 4: Synthesis of 2-(benzo[d]oxazol-2-yl)-4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methylthieno[2,3-c]pyridin-7(6H)-one: 2-(benzo[d]oxazol-2-yl)-4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methylthieno[2,3-c]pyridin-7(6H)-one (0.022 g, 21%) was prepared following General Procedure 1, Step 5 using 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-2-(benzo[d]oxazol-2-yl)-6-methylthieno[2,3-c]pyridin-7(6H)-one (0.10 g, 0.185 mmol). LCMS: 555 [M+1]⁺; ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.84 (d, *J* = 8.3 Hz, 3H), 7.78 (d, *J* = 7.5 Hz, 1H), 7.56 (d, *J* = 2.2 Hz, 1H), 7.52-7.37 (m, 3H), 6.98 (d, *J* = 9.2 Hz, 2H), 6.40 (d, *J* = 8.8 Hz, 1H), 5.06 (s, 1H), 3.68 (s, 3H), 2.05 (s, 6H), 1.46 (s, 6H).

Example S-24: Synthesis of 2-(1H-benzo[d]imidazol-2-yl)-4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methylthieno[2,3-c]pyridin-7(6H)-one (General Procedure 6) (Compound 154)



[0286] Step 1: Synthesis of 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid: 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (4 g, 84%) was prepared following General Procedure 2, Step 4 using methyl 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate (5.0 g, 16.6 mmol). LCMS: 288 [M+H]⁺, 290 [M+H+2]⁺

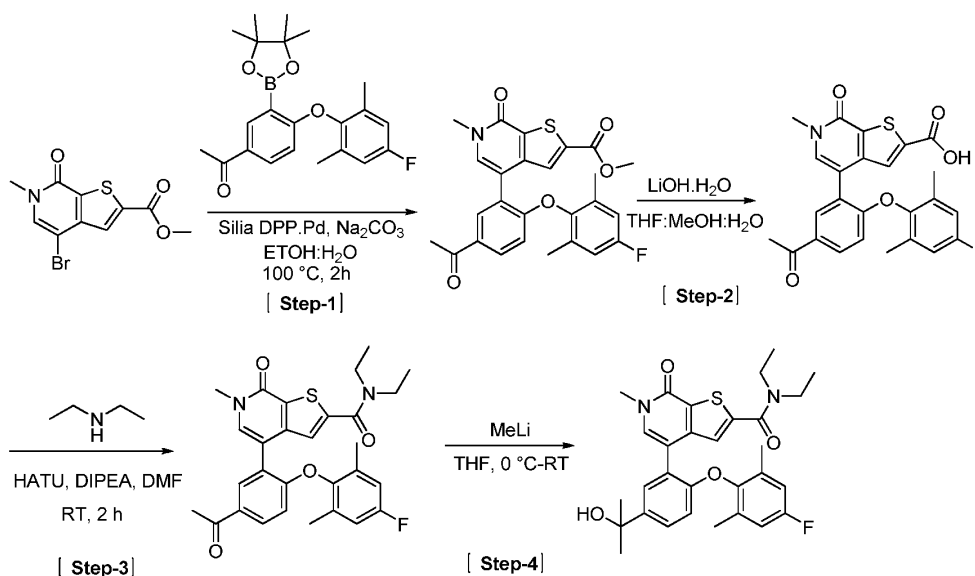
[0287] Step 2: Synthesis of 2-(1H-benzo[d]imidazol-2-yl)-4-bromo-6-methylthieno[2,3-c]pyridin-7(6H)-one: To a stirred solution of 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (1.0 g, 3.47 mmol) in polyphosphoric acid (10 mL) was added benzene-1,2-diamine (449 mg, 4.10 mmol, 1.2 eq) and the mixture was heated at 180 °C. The reaction was complete after 1 h and the mixture was quenched with 2N-NaOH (200 mL) to obtain a precipitate which was filtered over Büchner funnel to afford the title compound (0.5 g, 41%). LCMS: 360 [M+H]⁺, 362 [M+H+2]⁺

[0288] Step 3: Synthesis of 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-2-(1H-benzo[d]imidazol-2-yl)-6-methylthieno[2,3-c]pyridin-7(6H)-one: 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-2-(1H-benzo[d]imidazol-2-yl)-6-methylthieno[2,3-c]pyridin-7(6H)-one (0.2 g, 26%) was prepared following General Procedure 4, Step 4 using 2-(1H-benzo[d]imidazol-2-yl)-4-bromo-6-methylthieno[2,3-c]pyridin-7(6H)-one (0.5 g, 1.39 mmol, 1 eq). LCMS: 538 [M+1]⁺

[0289] Step 4: Synthesis of 2-(1H-benzo[d]imidazol-2-yl)-4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methylthieno[2,3-c]pyridin-7(6H)-one: 2-

(1H-benzo[d]imidazol-2-yl)-4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methylthieno[2,3-c]pyridin-7(6H)-one (0.007 g, 7%) was prepared following General Procedure 1, Step 5 using 4-(5-amino-2-(2,6-dimethylphenoxy)phenyl)-6-methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)thieno[2,3-c]pyridin-7(6H)-one (0.20 g, 0.186 mmol, 1eq). LCMS: 554 [M+1]⁺; ¹H NMR (400 MHz, MeOH-*d*₄): δ 7.84 (s, 1H), 7.69-7.61 (m, 2H), 7.55-7.50 (m, 1H), 7.43 (dd, *J* = 2.4, 8.6 Hz, 1H), 7.29 (d, *J* = 3.5 Hz, 3H), 6.81 (d, *J* = 8.8 Hz, 2H), 6.46 (d, *J* = 8.3 Hz, 1H), 3.77 (s, 3H), 2.05 (s, 6H), 1.58 (s, 6H).

Example S-25: Synthesis of N,N-diethyl-4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (Compound 155)



[0290] Step1: Synthesis of methyl 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate: Methyl 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate (5.0 g, 63 %) was prepared following General Procedure 3, Step 1 using methyl 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate (5 g, 16.55 mmol, 1 eq) and 1-(4-(4-fluoro-2,6-dimethylphenoxy)-3-(4,4,5,5-tetra methyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone (7.62 g, 19.86 mmol, 1.2 eq). LCMS: 480 [M+1]⁺

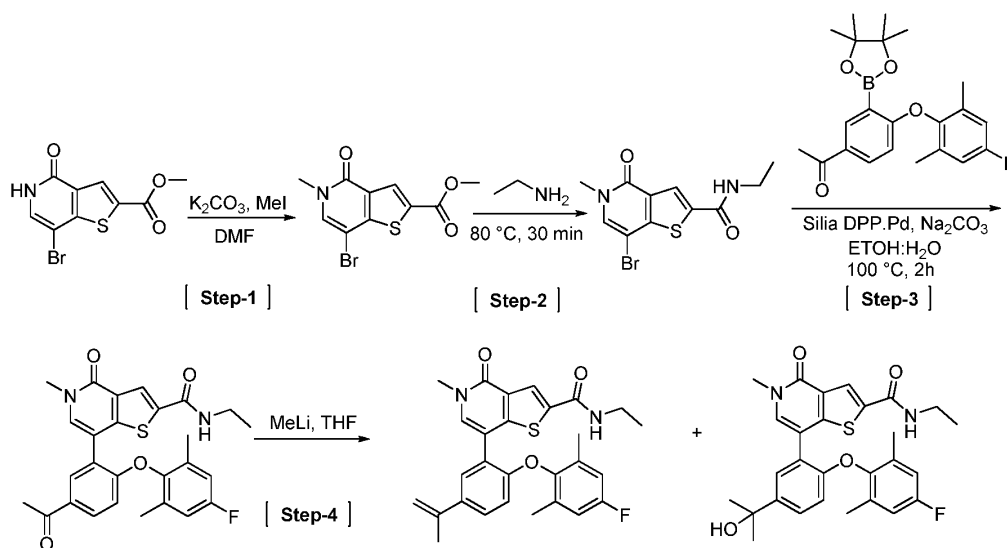
[0291] Step 2: Synthesis of 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid: 4-(5-acetyl-2-(4-fluoro-2,6-

dimethylphenoxy)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (0.35 g, 86%) was prepared following General Procedure 2, Step 4 using methyl 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate (0.30 g, 0.626 mmol). LCMS: 466 [M+1]⁺

[0292] Step 3: Synthesis of 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-N,N-diethyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide: To a stirred solution of 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (100 mg, 0.215 mmol) in DMF (4 mL) was added HATU (163 mg, 0.43 mmol, 2.0 eq) at 0 °C and the mixture was stirred for 10 min. DIPEA (0.11 mL mg, 0.645 mmol, 3 eq) and diethylamine (31 mg, 0.430 mmol, 2.0 eq) were then added to the mixture and the resultant mixture was stirred at RT for 16 h. The reaction was complete after 16 h and to the mixture was added water (200 mL) and extracted with EtOAc (300 mL). The organic layer was washed with water (100 mL), brine (150 mL) dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford a crude residue which was purified by CombiFlash Chromatography to afford the title compound (100 mg, 90%). LCMS: 521 [M+1]⁺

[0293] Step 4: Synthesis of N,N-diethyl-4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxy propan-2-yl)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide: N,N-diethyl-4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxy propan-2-yl)phenyl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (3 mg, 5.8%) was prepared following General Procedure 1, Step 5 using 4-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy) phenyl)-N,N-diethyl-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxamide (0.050 g, 0.096 mmol). LCMS: 537 [M+1]⁺; ¹H NMR (400 MHz, MeOH-*d*₄): δ 7.65 (s, 1H), 7.56 (d, *J* = 2.6 Hz, 1H), 7.40 (dd, *J* = 2.6, 8.8 Hz, 1H), 7.33 (s, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.42 (d, *J* = 8.3 Hz, 1H), 3.76 (s, 3H), 3.52 (d, *J* = 7.5 Hz, 4H), 2.07-1.95 (m, 6H), 1.60-1.50 (m, 6H), 1.20 (br. s., 6H).

Example S-26: Synthesis of N-ethyl-7-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(prop-1-en-2-yl)phenyl)-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide (General Procedure 7) (Compound 156)



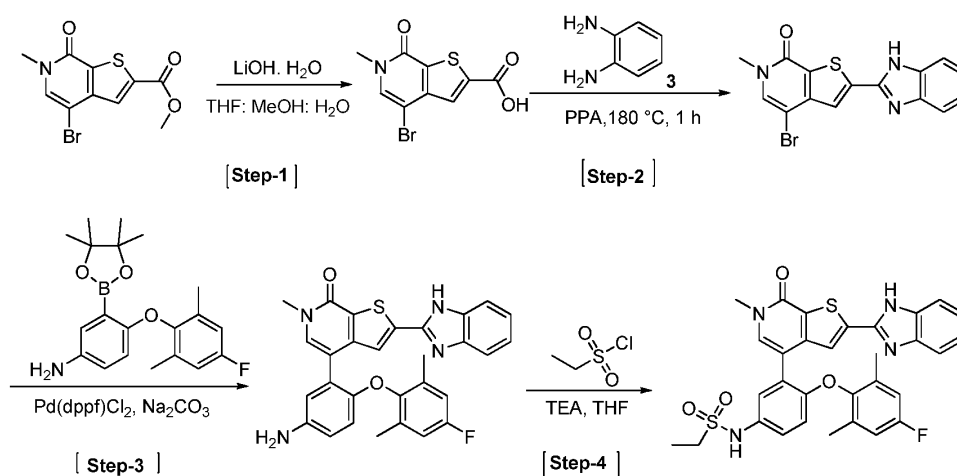
[0294] Step 1: Synthesis of Methyl 7-bromo-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxylate: To a stirred solution of methyl 7-bromo-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxylate (6.7 g, 23.3 mmol) in DMF (60 mL) was added K_2CO_3 (4.83 g, 35 mmol, 1.5 eq) at 0 °C slowly over a period of 15 min and the mixture was stirred at same temperature for 30 min. MeI (4.43 mL, 70.3 mmol) was then slowly added to the mixture at 0 °C and the resultant mixture was stirred at RT for 30 min. The reaction was monitored on TLC. Upon completion, the mixture was slowly quenched with ice-cold water (500 mL) and extracted with EtOAc (500 mL $\times$ 3). The combined organic layers were washed with water (500 mL), brine (150 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to obtain a crude which was triturated with diethyl ether (20 mL) to afford the title compound (5.2 g, 74 %). LC-MS: 301 $[M]^+$, 303 $[M+2H]^+$; ^1H NMR: (400 MHz, $DMSO-d_6$) δ 8.18 (s, 1H), 8.14 (s, 1H), 3.88 (s, 3H), 3.52 (s, 4H)

[0295] Step 2: Synthesis of 7-bromo-N-ethyl-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide : 7-bromo-N-ethyl-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide (5.2 g, 96%) was prepared following General Procedure 1, Step 4a using methyl 7-bromo-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxylate (5.2 g, 17.27 mmol, 1 eq). LC-MS: 314 $[M]^+$, 316 $[M+2H]^+$; ^1H NMR: (400 MHz, $DMSO-d_6$) δ 8.81 (s, 1H), 8.35 (s, 1H), 8.07 (s, 1H), 3.33 (s, 3H), 3.27 (dd, J = 5.5, 7.2 Hz, 2H), 1.13 (t, J = 7.2 Hz, 3H)

[0296] Step 3: Synthesis of 7-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-N-ethyl-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide: 7-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-N-ethyl-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide (2.0 g, 48%) was prepared following General Procedure 3, Step 1 using 7-bromo-N-ethyl-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide (2.63 g, 8.34 mmol, 1 eq). LCMS: 493 [M+H]⁺

[0297] Step 4: Synthesis of N-ethyl-7-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(prop-1-en-2-yl)phenyl)-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide: To a stirred solution of 7-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-N-ethyl-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide (1.0 g, 2.03 mmol) in anhydrous THF (40 mL) was added methyl lithium (5.0 mL, 8.13 mmol, 4 eq) at 0 °C dropwise and the mixture was stirred at same temperature for 10 min. The reaction was complete after 10 min and the mixture was quenched with saturated NH₄Cl solution (50 mL) slowly. The aqueous layer was then extracted with EtOAc (300 mL × 2). The combined organic layers were washed with water (100 mL), brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to obtain a crude which was purified by CombiFlash Chromatography to afford N-ethyl-7-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-5-methyl-4-oxo-4,5-dihydro thieno[3,2-c]pyridine-2-carboxamide as a major product and N-ethyl-7-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(prop-1-en-2-yl)phenyl)-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide (0.0065 g, 0.65%). LCMS: 491 [M+1]⁺; ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.76 (s, 1H), 8.30 (s, 1H), 7.83 (s, 1H), 7.62 (d, *J* = 2.2 Hz, 1H), 7.47 (d, *J* = 6.1 Hz, 1H), 7.02 (d, *J* = 9.2 Hz, 2H), 6.38 (d, *J* = 8.8 Hz, 1H), 5.41 (s, 1H), 5.06 (s, 1H), 3.60 (s, 3H), 3.29-3.19 (m, 2H), 2.10 (s, 3H), 2.03 (s, 6H), 1.11 (t, *J* = 7.2 Hz, 3H)

Example S-27: Synthesis of N-(3-(2-(1H-benzof[d]imidazol-2-yl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridin-4-yl)-4-(4-fluoro-2,6-dimethylphenoxy)phenyl)ethanesulfonamide (Compound 157)



[0298] Step 1: Synthesis of 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid: 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (4 g, 84%) was prepared following General Procedure 2, Step 4 using methyl 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate (5.0 g, 16.6 mmol). LCMS: 288 [M+H]⁺, 290 [M+H+2]⁺

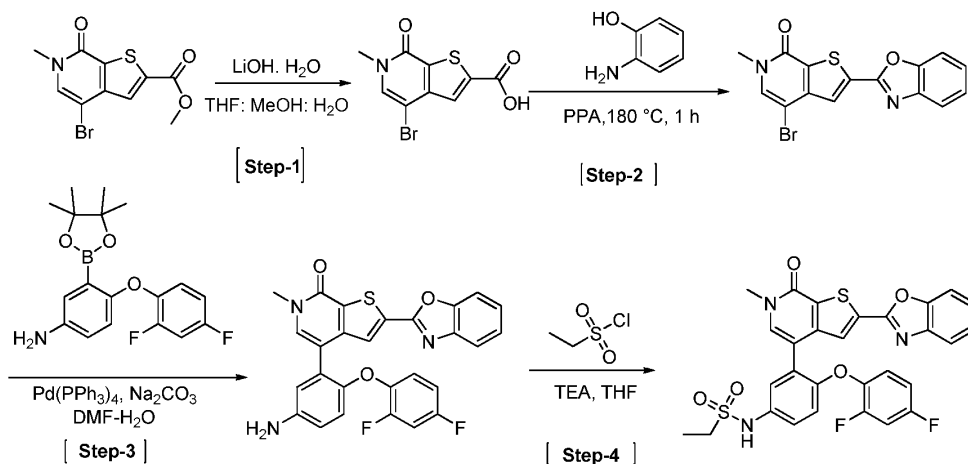
[0299] Step 2: Synthesis of 2-(1H-benzo[d]imidazol-2-yl)-4-bromo-6-methylthieno[2,3-c]pyridin-7(6H)-one: 2-(1H-benzo[d]imidazol-2-yl)-4-bromo-6-methylthieno[2,3-c]pyridin-7(6H)-one (0.9 g, 72%) was prepared following General Procedure 6, Step 2 using 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (1.0 g, 3.47 mmol). LCMS: 360 [M+H]⁺, 362 [M+H+2]⁺

[0300] Step 3: Synthesis of 4-(5-amino-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-2-(1H-benzo[d]imidazol-2-yl)-6-methylthieno[2,3-c]pyridin-7(6H)-one: 4-(5-amino-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-2-(1H-benzo[d]imidazol-2-yl)-6-methylthieno[2,3-c]pyridin-7(6H)-one (120 mg, 24%, off-white solid) was prepared following General Procedure 2, Step 7 using 2-(1H-benzo[d]imidazol-2-yl)-4-bromo-6-methylthieno[2,3-c]pyridin-7(6H)-one (340 mg, 0.947 mmol, 1 eq). LCMS: 511 [M+1]⁺

[0301] Step 4: Synthesis of N-(3-(2-(1H-benzo[d]imidazol-2-yl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridin-4-yl)-4-(4-fluoro-2,6-dimethylphenoxy)phenyl)ethane sulfonamide: N-(3-(2-(1H-benzo[d]imidazol-2-yl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridin-4-yl)-4-(4-fluoro-2,6-dimethylphenoxy)phenyl) ethanesulfonamide (0.016 g, 27 %) was prepared following

General Procedure 2, Step 8 using 4-(5-amino-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-2-(1H-benzo[d]imidazol-2-yl)-6-methylthieno[2,3-c]pyridin-7(6H)-one (0.05 g, 0.098 mmol). LCMS: 603 [M+1]⁺; ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.75 (s, 1H), 7.90 (s, 1H), 7.78 (s, 1H), 7.60 (br. s., 2H), 7.30 (d, *J* = 2.6 Hz, 1H), 7.27-7.16 (m, 3H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.46 (d, *J* = 8.8 Hz, 1H), 3.64 (s, 3H), 3.17-3.03 (m, 2H), 2.00 (s, 6H), 1.23 (t, *J* = 7.2 Hz, 3H)

Example S-28: N-(3-(2-(benzo[d]oxazol-2-yl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridin-4-yl)-4-(2,4-difluorophenoxy)phenyl)ethanesulfonamide (**Compound 158**)



[0302] Step 1: Synthesis of 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid: 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (4 g, 84%) was prepared following General Procedure 2, Step 4 using methyl 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate (5.0 g, 16.6 mmol). LCMS: 288 [M+H]⁺, 290 [M+H+2]⁺

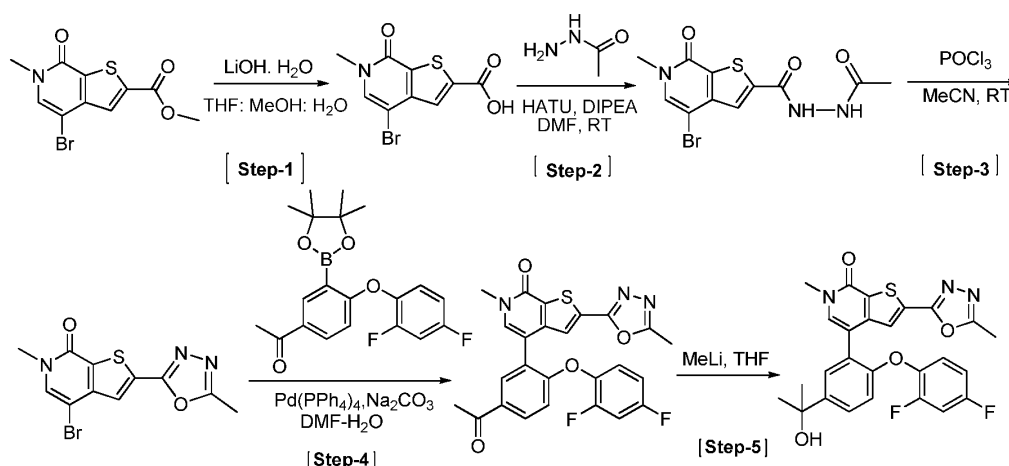
[0303] Step 2: Synthesis of 2-(benzo[d]oxazol-2-yl)-4-bromo-6-methylthieno[2,3-c]pyridin-7(6H)-one: 2-(benzo[d]oxazol-2-yl)-4-bromo-6-methylthieno[2,3-c]pyridin-7(6H)-one (0.5 g, 41%) was prepared following General Procedure 5, Step 2 using 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (1.0 g, 3.47 mmol). LCMS: 361 [M+H]⁺, 363 [M+H+2]⁺

[0304] Step 3: Synthesis of 4-(5-amino-2-(2,4-difluorophenoxy)phenyl)-2-(benzo[d]oxazol-2-yl)-6-methylthieno[2,3-c]pyridin-7(6H)-one: 4-(5-amino-2-(2,4-difluorophenoxy)phenyl)-2-(benzo[d]oxazol-2-yl)-6-methylthieno[2,3-c]pyridin-7(6H)-one (0.105 g, 75%) was prepared

following General Procedure 2, Step 7 using 2-(benzo[d]oxazol-2-yl)-4-bromo-6-methylthieno[2,3-c]pyridin-7(6H)-one (0.1 g, 0.278 mmol, 1 eq). LCMS: 502 [M+1]⁺

[0305] Step 4: Synthesis of N-(3-(2-(benzo[d]oxazol-2-yl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridin-4-yl)-4-(2,4-difluorophenoxy)phenyl)ethanesulfonamide: N-(3-(2-(benzo[d]oxazol-2-yl)-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridin-4-yl)-4-(2,4-difluorophenoxy)phenyl)ethanesulfonamide (16 mg, 27 %) was prepared following General Procedure 2, Step 8 using 4-(5-amino-2-(2,4-difluorophenoxy)phenyl)-2-(benzo[d]oxazol-2-yl)-6-methylthieno[2,3-c]pyridin-7(6H)-one (0.09 g, 0.17 mmol, 1eq). LCMS: 594 [M+1]⁺; ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.90 (s, 1H), 7.81 (s, 3H), 7.85 (s, 1H), 7.56-7.41 (m, 2H), 7.40-7.24 (m, 3H), 7.13 (d, *J* = 5.7 Hz, 1H), 7.03 (d, *J* = 8.3 Hz, 2H), 3.61 (s, 3H), 3.16 (d, *J* = 7.5 Hz, 2H), 1.25 (t, *J* = 7.0 Hz, 3H)

Example S-29: Synthesis of 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)thieno[2,3-c]pyridin-7(6H)-one (Compound 12)



[0306] Step 1: Synthesis of 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid: 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (0.5 g, 52%) was prepared following General Procedure 2, Step 4 using methyl 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylate (1.0 g, 3.3 mmol, 1eq). LCMS: 288 [M+H]⁺, 290 [M+H+2]⁺

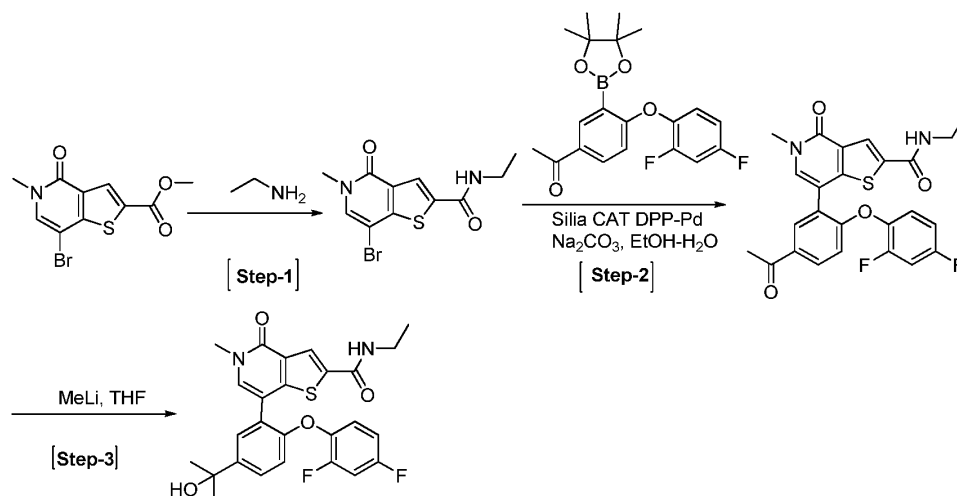
[0307] Step 2: Synthesis of N'-acetyl-4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carbohydrazide: N'-acetyl-4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carbohydrazide (0.35 g, 68%) was prepared following General Procedure 2, Step 5 using 4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carboxylic acid (0.43 g, 1.49 mmol, 1eq). LCMS: 344 [M+1]⁺, 346 [M+H+2]⁺

[0308] Step 3: Synthesis of 4-bromo-6-methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)thieno[2,3-c]pyridin-7(6H)-one: 4-bromo-6-methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)thieno[2,3-c]pyridin-7(6H)-one (0.11 g, 58%) was prepared following General Procedure 2, Step 6 using N'-acetyl-4-bromo-6-methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-2-carbohydrazide (0.35 g, 1.023 mmol, 1eq). LCMS: 326 [M+H]⁺, 328 [M+H+2]⁺

[0309] Step 4: Synthesis of 4-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-6-methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)thieno[2,3-c]pyridin-7(6H)-one: 4-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-6-methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)thieno[2,3-c]pyridin-7(6H)-one (0.20 g, 66 %) was prepared following General Procedure 4, Step 4 using 4-bromo-6-methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)thieno[2,3-c]pyridin-7(6H)-one (0.20 g, 0.615 mmol, 1 eq). LCMS: 494 [M+1]⁺

Step 5: Synthesis of 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)thieno[2,3-c]pyridin-7(6H)-one: 4-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)thieno [2,3-c]pyridin-7(6H)-one (0.023 g, 12 %) was prepared following General Procedure 1, Step 5 using 4-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-6-methyl-2-(5-methyl-1,3,4-oxadiazol-2-yl)thieno[2,3-c]pyridin-7(6H)-one (0.175 g, 0.354 mmol, 1eq). LCMS: 510 [M+1]⁺; ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.77 (br. s., 1H), 7.63 (br. s., 1H), 7.58-7.48 (m, 2H), 7.37 (br. s., 1H), 7.12 (br. s., 1H), 7.03 (br. s., 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 5.11 (br. s., 1H), 3.62 (br. s., 3H), 2.58 (br. s., 3H), 1.47 (br. s., 6H)

Example S-30: Synthesis of 7-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-N-ethyl-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide (Compound 159)



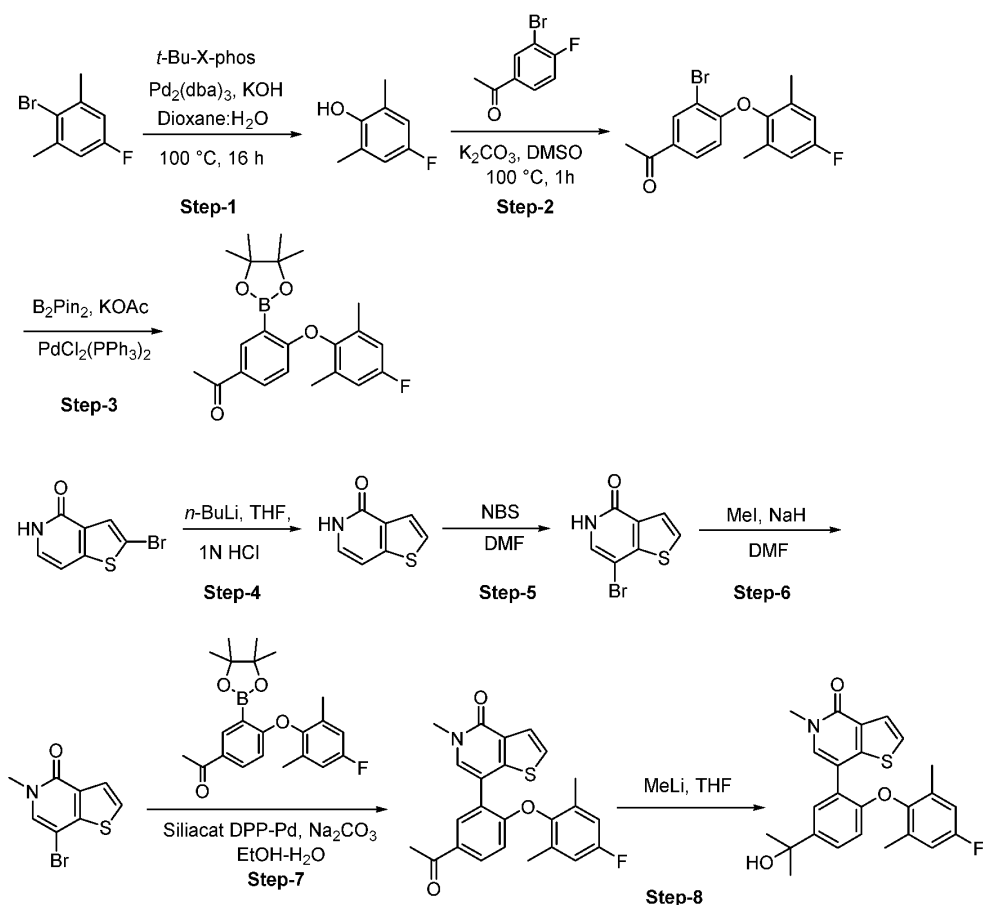
[0310] Step 1: Synthesis of 7-bromo-N-ethyl-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide: 7-bromo-N-ethyl-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide (0.28 g, 90%) was prepared following General Procedure 1, Step 4a using methyl 7-bromo-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxylate (0.3 g, 1 mmol). LCMS: 315 [M+H]⁺, 317 [M+H+2]⁺

[0311] Step 2. Synthesis of 7-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-N-ethyl-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide: 7-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-N-ethyl-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide (0.1 g, 23.4 %) was prepared following General Procedure 3, Step 1 using 7-bromo-N-ethyl-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide (0.28 g, 0.9 mmol, 1 eq) and 1-(4-(2,4-difluorophenoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone (0.43 g, 1.15 mmol, 1.3 eq) LCMS: 483 [M+H]⁺

[0312] Step 3: Synthesis of 7-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-N-ethyl-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide: 7-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-N-ethyl-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide (0.013 g, 13%) was prepared following General Procedure 1, Step 5 using 7-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-N-ethyl-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide (0.1 g, 0.2 mmol, 1eq) LCMS: 499 [M+H]⁺; ¹H NMR (400 MHz, MeOH-*d*₄): δ 8.09 (s, 1H), 7.66 (d, J = 2.6 Hz, 1H), 7.62 (s, 1H), 7.56 (dd, J =

2.4, 8.6 Hz, 1H), 7.09-6.96 (m, 2H), 6.92 (d, J = 8.3 Hz, 1H), 6.84 (br. s., 1H), 3.67 (s, 3H), 3.39 (q, J = 7.0 Hz, 2H), 1.57 (s, 6H), 1.22 (t, J = 7.2 Hz, 3H).

Example S-31: Synthesis of 7-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-5-methylthieno[3,2-c]pyridin-4(5H)-one (Compound 2.1)



[0313] Step 1: Synthesis of 4-fluoro-2,6-dimethylphenol. A solution of 2-bromo-5-fluoro-1,3-dimethylbenzene (5.0 g, 24.7 mmol, 1 eq) in 1,4-dioxane: water (50 mL, 1:1) was added KOH (4.15 g, 74.2 mmol, 3 eq) and the mixture was degassed under nitrogen for 15 min. In another set-up, *t*-Bu-X-phos (839 mg, 7.98 mmol 0.08 eq) and $\text{Pd}_2(\text{dba})_3$ (452 mg, 0.49 mmol, 0.08 eq) in 1,4-dioxane:water (20 mL, 1:1) was degassed under nitrogen for 15 min. The contents of the first degassed mixture were transferred into the degassed solution of the second and the mixture was heated at 100 °C and monitored by TLC and LCMS. The reaction was complete after 16 h and the mixture was acidified with 6N-HCl (pH ~2-3) and extracted with EtOAc (700 mL). The organic

layer was washed with water (300 mL), brine (200 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to obtain a crude residue which was purified by CombiFlash chromatography to afford the title compound. LCMS: 141 [M+H]⁺.

[0314] Step 2: Synthesis of 1-(3-bromo-4-(4-fluoro-2,6 dimethylphenoxy)phenyl)-ethanone. To a solution of 4-fluoro-2,6-dimethylphenol (0.50 g, 3.57 mmol) in DMSO (20 mL) was added K₂CO₃ (0.98 g, 7.15 mmol, 2 eq) at RT and the mixture was stirred for 15 min. 1-(3-bromo-4-fluorophenyl)ethanone (0.93 g, 4.28 mmol, 1.2 eq) was then added to the mixture and the resultant mixture was heated 80 °C for 2 h. The reaction was complete after 2 h and to the mixture was added water (200 mL) to obtain a precipitate which was filtered over Büchner funnel; dried under vacuum to afford the title compound. LCMS: 337 [M+H]⁺, 339 [M+H+2]⁺.

[0315] Step 3: Synthesis of 1-(4-(4-fluoro-2,6-dimethylphenoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone. To a solution of 1-(3-bromo-4-(4-fluoro-2,6-dimethylphenoxy)phenyl)ethanone (0.55 g, 1.63 mmol, 1 eq) in 1,4-dioxane (5 mL), was added B₂Pin₂ (0.50 g, 1.96 mmol, 1.2 eq), KOAc (0.48 g, 4.89 mmol, 3 eq), and Pd(dppf)Cl₂ (0.12 g, 0.16 mmol, 0.1 eq). The reaction mixture was degassed and purged with N₂. Then the mixture was stirred at overnight at 80 °C. TLC analysis indicated the reaction was complete. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to afford the title compound.

[0316] Step 4: Synthesis of thieno[3,2-c]pyridin-4(5H)-one. To a solution of 2-bromothieno[3,2-c]pyridin-4(5H)-one (3.0 g, 13.04 mmol) in THF (100 mL) was added *n*-BuLi (1.6 M in *n*-hexane; 31.4 mL, 52.16 mmol, 4 eq) at -78 °C and the mixture was stirred at same temperature for 2 h. After 2 h, the reaction mixture was slowly quenched with 1N-HCl (3 mL) at 0 °C and extracted with EtOAc (500 mL). The organic layer was washed with water (100 mL), brine (150 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound. LCMS: 152 [M+H]⁺.

[0317] Step 5: Synthesis of 7-bromothieno[3,2-c]pyridin-4(5H)-one: To a stirred solution of thieno[3,2-c]pyridin-4(5H)-one (1.8 g, 11.92 mmol) in DMF (30 mL) was added NBS (2.33 g, 13.11 mmol, 1.2 eq) at 0 °C and the mixture was stirred at RT for 16 h. The reaction was complete after 16 h and to the mixture was added ice-cold water (200 mL) to obtain a precipitate which was filtered over Büchner funnel to afford the title compound. LCMS: 230 [M+H]⁺, 232 [M+H+2]⁺.

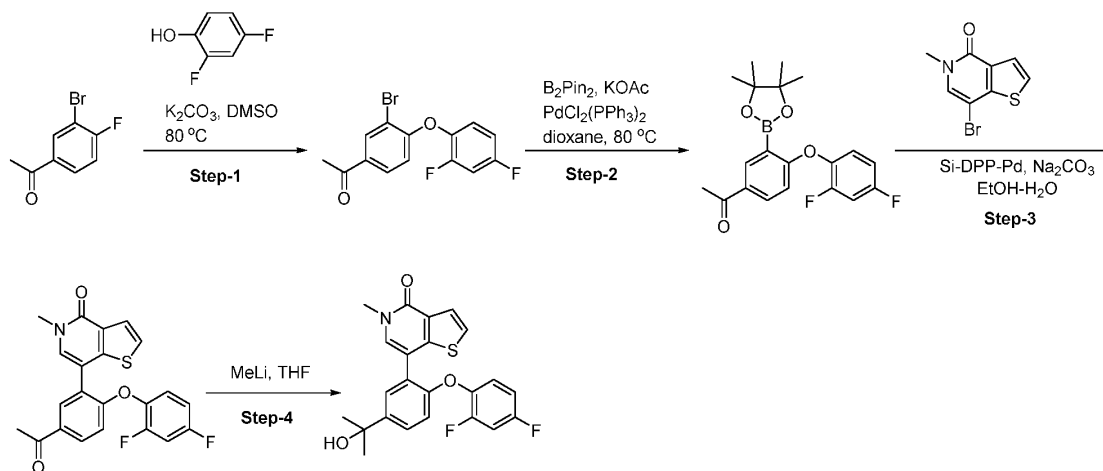
[0318] Step 6: Synthesis of 7-bromo-5-methylthieno[3,2-c]pyridin-4(5H)-one. To a solution of 7-bromothieno[3,2-c]pyridin-4(5H)-one (2.2 g, 9.96 mmol) in DMF (20 mL) was added NaH (60 % suspension in mineral oil, 1.19 g, 29.88 mmol, 3 eq) slowly at 0 °C over a period of 20 min and the mixture was stirred at same temperature for 30 min. MeI (1.85 mL, 29.88 mmol, 3 eq) was then added to the mixture slowly 0 °C and the resultant mixture was stirred at RT for 30 min. The reaction was monitored on TLC. Upon completion, the mixture was slowly quenched with ice-cold water (200 mL) and the precipitated solid was filtered over Büchner funnel to afford the title compound. LCMS: 244 [M+H]⁺, 246 [M+H+2]⁺.

[0319] Step 7: Synthesis of 7-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-5-methylthieno [3,2-c]pyridin-4(5H)-one. To a stirred solution of 7-bromo-N-ethyl-5-methyl-4-oxo-4,5-dihydrofuro[3,2-c]pyridine-2-carboxamide 7-bromo-5-methylthieno[3,2-c]pyridin-4(5H)-one (0.30 g, 1.23 mmol, 1 eq) in ethanol (18 mL) were added 1-(4-(4-fluoro-2,6-dimethyl phenoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone (0.57 g, 1.47 mmol, 1.2 eq) and Na₂CO₃ (0.26 g, 2.45 mmol, 2 eq) dissolved in water (2 mL). Siliacat DPP-Pd (0.30 mmol/g loading; 0.2 g, 0.06 mmol, 0.05 eq) was then added to the mixture and the resultant mixture was then heated at 85 °C for 2 h. The reaction was complete after 2 h and the mixture was filtered through the celite bed, washed with 5% MeOH in DCM (50 mL). The filtrate obtained was concentrated under reduced pressure to obtain a crude residue. The residue obtained was stirred in MeOH (10 mL) for 20 min, filtered over Büchner funnel, dried under vacuum to obtain a solid compound. Then solid obtained was further triturated with diethyl ether (5 mL ×2), dried to afford title compound. LCMS: 422 [M+H]⁺.

[0320] Step 8: Synthesis of 7-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-5-methylthieno[3,2-c]pyridin-4(5H)-one. To a stirred solution of 7-(5-acetyl-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-5-methylthieno[3,2-c]pyridin-4(5H)-one (0.10 g, 0.23 mmol) in anhydrous THF (8 mL) was added methyl lithium (1.6 M in Et₂O; 0.9 mL, 1.42 mmol, 6 eq) at 0 °C dropwise and the mixture was stirred at same temperature for 10 min. The progress of the reaction was monitored by TLC. After 10 min and the mixture was quenched with saturated NH₄Cl solution (10 mL) slowly. The aqueous layer was then extracted with EtOAc (60 mL × 2). The combined organic layers were washed with water (50 mL), brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to obtain a crude which was purified by reversed phase HPLC to afford the title compound. LCMS: 438 [M+1]⁺; ¹H NMR (400 MHz,

DMSO-*d*₆): δ 7.67 (s, 1H), 7.63 (d, J = 5.3 Hz, 1H), 7.58-7.51 (m, 2H), 7.38 (dd, J = 2.4, 8.6 Hz, 1H), 6.99 (d, J = 9.2 Hz, 2H), 6.32 (d, J = 8.8 Hz, 1H), 5.00 (br s, 1H), 3.60 (s, 3H), 2.03 (s, 6H), 1.43 (s, 6H).

Example S-32: Synthesis of 7-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-5-methylthieno[3,2-*c*]pyridin-4(5H)-one (**Compound 2.3**)



[0321] Step 1: Synthesis 1-(3-bromo-4-(2,4-difluorophenoxy)phenyl)ethanone: To a stirred solution of 2,4-difluorophenol (1 g, 7.9 mmol, 1 eq) in DMSO (20 mL) was added K₂CO₃ (3.2 g, 23 mmol, 3 eq) at RT followed by the addition of 1-(3-bromo-4-fluorophenyl) ethanone (0.98 g, 8.5 mmol, 1.1 eq) and the mixture was heated at 80 °C for 2 h. The reaction was complete after 2 h and to the mixture was added ice-cold water (100 mL) to obtain a precipitate which was filtered over Büchner funnel; dried under vacuum to afford the title compound. LCMS: 327 [M+H]⁺, 329 [M+H+2]⁺.

[0322] Step 2: Synthesis of 1-(4-(2,4-difluorophenoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone: To a solution of 1-(3-bromo-4-(2,4-difluorophenoxy)phenyl)ethanone (1.0 g, 3.06 mmol, 1 eq) in 1, 4-dioxane (20 mL) was added B₂Pin₂ (1.16 g, 4.6 mmol, 1.5 eq), KOAc (0.9 g, 9.3 mmol, 3 eq) and the mixture was degassed under N₂ for 20 min. PdCl₂(PPh₃)₂ (0.22 g, 0.3 mmol, 0.1 eq) was then added to the mixture and the resultant mixture was heated at 80 °C for 16 h. The reaction was monitored by TLC. Upon completion, the mixture was filtered through a pad of Celite and concentrated under reduced pressure. The residue obtained was diluted with water (200 mL) and extracted with EtOAc (250 mL × 2). The combined organic layers were washed with water (200 mL), brine (100 mL), dried over anhydrous Na₂SO₄, filtered

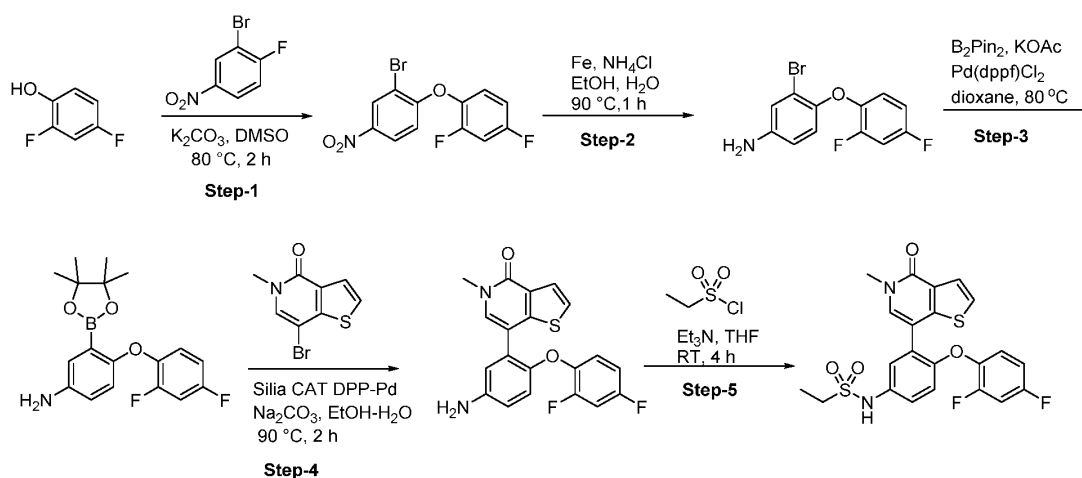
and concentrated under reduced pressure to obtain a crude residue which was purified by CombiFlash chromatography to afford the title compound. LCMS: 375 [M+H]⁺.

[0323] Step 3: Synthesis of 7-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-5-methylthieno[3,2-c]pyridin-4(5H)-one:

The title compound was prepared following Example S-1, step 7 using 7-bromo-5-methylthieno[3,2-c]pyridin-4(5H)-one (0.30 g, 1.23 mmol, 1 eq) and 1-(4-(2,4-difluorophenoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone (0.55 g, 1.47 mmol, 1.2 eq). LCMS: 412 [M+H]⁺.

[0324] Step 4: Synthesis of 7-(2-(2,4-difluorophenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-5-methylthieno[3,2-c]pyridin-4(5H)-one: The title compound was prepared following Example S-1, step 8 using 7-(5-acetyl-2-(2,4-difluorophenoxy)phenyl)-5-methylthieno[3,2-c]pyridin-4(5H)-one (0.14 g, 0.29 mmol, 1 eq). LCMS: 428 [M+1]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.67 (d, *J* = 2.6 Hz, 1H), 7.60 (d, *J* = 5.7 Hz, 1H), 7.57-7.47 (m, 3H), 7.00 (dd, *J* = 2.9, 8.6 Hz, 2H), 6.92 (d, *J* = 8.3 Hz, 1H), 6.83 (br s, 1H), 3.68 (s, 3H), 1.57 (s, 6H).

Example S-33: Synthesis of N-(4-(2,4-difluorophenoxy)-3-(5-methyl-4-oxo-4,5-dihydrothieno [3,2-c]pyridin-7-yl)phenyl)ethanesulfonamide (Compound 2.91)



[0325] Step 1: Synthesis of 2-bromo-1-(2,4-difluorophenoxy)-4-nitrobenzene: To a stirred solution of 2,4-difluorophenol (3.0 g, 23 mmol, 1 eq) in DMSO (20 mL) was added K₂CO₃ (3.0 g, 46 mmol, 2 eq) at RT followed by the addition of 2-bromo-1-fluoro-4-nitrobenzene (5.6 g, 25.3 mmol, 1.1 eq) and the mixture was heated at 100 °C for 1 h. The reaction was complete after 2 h and to the mixture was added ice-cold water (100 mL) to obtain a precipitate which was filtered

over Büchner funnel and dried under vacuum to afford the title compound. LCMS: 330 [M+H]⁺, 332 [M+H+2]⁺

[0326] Step 2: Synthesis of 3-bromo-4-(2,4-difluorophenoxy)aniline: To a solution of 2-bromo-1-(2,4-difluorophenoxy)-4-nitrobenzene (6 g, 18.2 mmol, 1 eq) in ethanol (50 mL), a solution of NH₄Cl (7.8 g, 145.4 mmol, 8 eq) in water (50 mL) was added followed by addition of iron powder (5.1 g, 91 mmol, 5 eq). The resultant mixture was heated at 90 °C for 1 h. The reaction was monitored by TLC. Upon completion, the mixture was filtered through a pad of Celite and concentrated under reduced pressure. The residue obtained was diluted with water (200 mL) and extracted with EtOAc (300 mL × 2). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to obtain a crude residue which was purified by CombiFlash chromatography to afford the title compound. LCMS: 340 [M+H]⁺, 342 [M+H+2]⁺

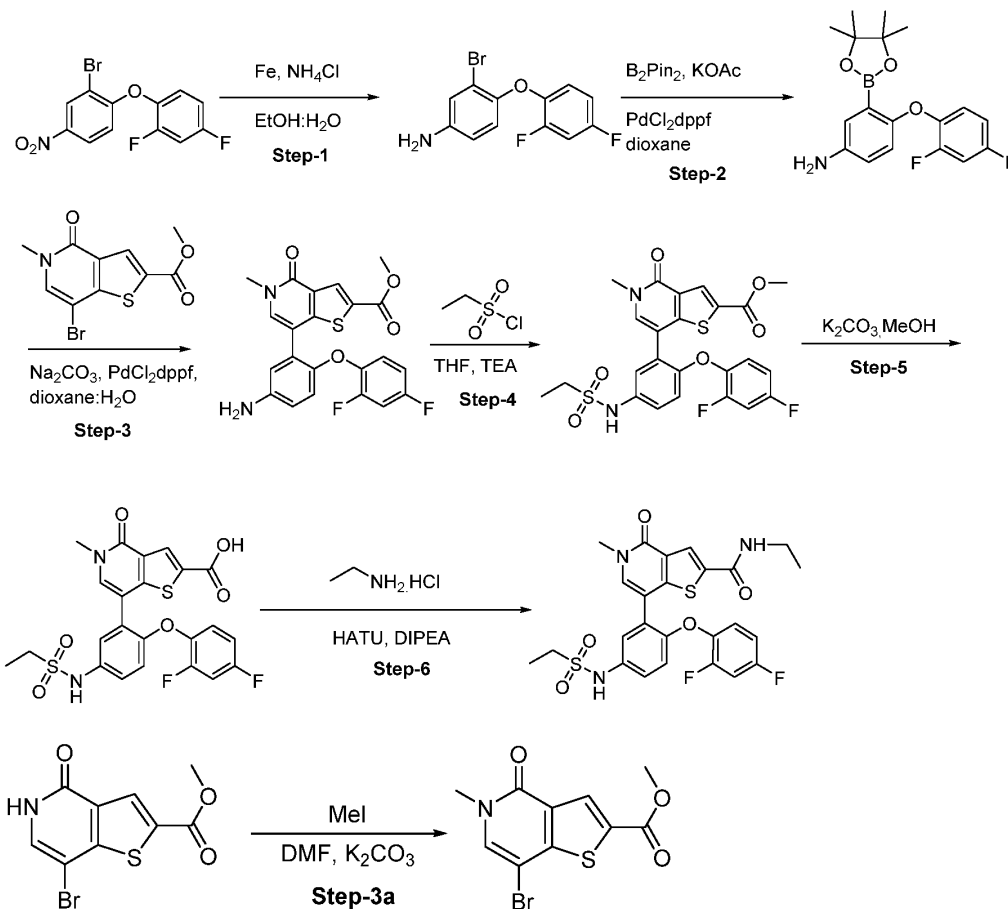
[0327] Step 3: Synthesis of 4-(2,4-difluorophenoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline: To a solution of 3-bromo-4-(2,4-difluorophenoxy)aniline (4.0 g, 13.4 mmol, 1 eq) in 1, 4-dioxane (40 mL) was added B₂Pin₂ (5.1 g, 20.1 mmol, 1.5 eq), KOAc (8.5 g, 33.6 mmol, 2.5 eq) and the mixture was degassed under N₂ for 20 min. Pd(dppf)Cl₂·DCM (1.1 g, 1.34 mmol, 0.1 eq) was then added to the mixture and the resultant mixture was heated at 80 °C for 16 h. The reaction was monitored by TLC. Upon completion, the mixture was filtered through a pad of Celite and concentrated under reduced pressure. The residue obtained was diluted with water (200 mL) and extracted with EtOAc (250 mL × 2). The combined organic layers were washed with water (200 mL), brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to obtain a crude residue which was purified by CombiFlash chromatography to afford the title compound. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.31 (m, 1H), 6.94 (d, *J* = 2.8 Hz, 1H), 6.87 (m, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.71 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.50 (m, 1H), 5.09 (br s, 2H), 1.06 (s, 12H).

[0328] Step 4: Synthesis of 7-(5-amino-2-(2,4-difluorophenoxy)phenyl)-5-methylthieno[3,2-c]pyridin-4(5H)-one: To a stirred solution of 7-bromo-5-methylthieno[3,2-c]pyridin-4(5H)-one (0.15 g, 0.61 mmol, 1 eq) in ethanol (9 mL) were added 4-(2,4-difluorophenoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.32 g, 0.9 mmol, 1.5 eq) and Na₂CO₃ (0.13 g, 1.2 mmol, 2 eq) dissolved in water (1 mL). Silia DPP-Pd (0.30 mmol/g loading; 0.6 g, 0.018 mmol, 0.03 eq) was then added to the mixture and the resultant mixture was

heated at 90 °C for 2 h. The reaction was complete after 2 h and the mixture was filtered through the celite bed, washed with 5% MeOH in DCM (50 mL) and concentrated to obtain a crude residue which was purified by CombiFlash chromatography to afford the title compound. LCMS: 385 [M+H]⁺

[0329] Step 5: Synthesis of N-(4-(2,4-difluorophenoxy)-3-(5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridin-7-yl)phenyl)ethanesulfonamide: To a stirred solution of 7-(5-amino-2-(2,4-difluorophenoxy) phenyl)-5-methylthieno[3,2-c]pyridin-4(5H)-one (0.15 g, 0.4 mmol, 1.0 eq) in THF (15 mL) was added triethylamine (0.15 g, 1.17 mmol, 3 eq) followed by the addition of ethanesulfonyl chloride (0.13 g, 1 mmol, 2.5 eq) at 0 °C and the resultant mixture was stirred at RT for 4 h. The reaction was complete after 4 h and to the mixture was added water (20 mL) and extracted with EtOAc (30 mL × 2). The combined organic layers was washed with saturated NaHCO₃ solution (30 mL), brine (25 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to obtain a crude which was purified by prep HPLC to afford the title compound. LCMS: 477 [M+H]⁺; ¹H NMR (400 MHz, MeOH-*d*₄): δ 7.60 (d, *J* = 5.3 Hz, 1H), 7.56 (s, 1H), 7.52 (d, *J* = 5.7 Hz, 1H), 7.45 (d, *J* = 2.6 Hz, 1H), 7.32 (dd, *J* = 2.4, 8.6 Hz, 1H), 7.05-6.93 (m, 3H), 6.82 (br s, 1H), 3.67 (s, 3H), 3.14 (q, *J* = 7.5 Hz, 2H), 1.35 (t, *J* = 7.5 Hz, 3H).

Example S-34: Synthesis of 7-(2-(2,4-difluorophenoxy)-5-(ethylsulfonamido)phenyl)-N-ethyl-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide (Compound 160)



[0330] Step 1: Preparation of 3-bromo-4-(2,4-difluorophenoxy)aniline: To a stirred solution of 2-bromo-1-(2,4-difluorophenoxy)-4-nitrobenzene (9 g, 27.24 mmol, 1 eq) in ethanol (60 mL), a solution of NH_4Cl (11.7 g, 217.92 mmol, 8 eq) in water (60 mL) was added followed by addition of iron powder (7.56 g, 136.2 mmol, 5 eq). The resultant mixture was heated at 100 °C for 2 h. The progress of the reaction was monitored by TLC & LCMS. After completion, the mixture was filtered through a pad of celite and concentrated under reduced pressure. The residue obtained was diluted with water (200 mL) and extracted with EtOAc (300 mL $\times$ 2). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to obtain a crude residue which was purified by CombiFlash Chromatography to afford the title compound (6.8 g, 84%). LCMS: 300 $[\text{M}+\text{H}]^+$, 302 $[\text{M}+\text{H}+2]^+$

[0331] Step 2: Preparation of 4-(2,4-difluorophenoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline: To a stirred solution of 3-bromo-4-(2,4-difluorophenoxy)aniline (4.5 g,

15 mmol, 1 eq) in dioxane (100 mL) were added B2Pin2 (5.7 g, 22.5 mmol, 1.5 eq), KOAc (3.7 g, 37.5 mmol, 2.5 eq) and the mixture was degassed under N₂ for 20 min. Pd(dppf)Cl₂.DCM (1.1 g, 1.35 mmol, 0.09 eq) was then added to the mixture and the resultant mixture was heated at 80 °C for 16 h. The progress of the reaction was monitored by TLC & LCMS. After completion, the mixture was diluted with EtOAc (250 mL), filtered through a pad of celite and concentrated under reduced pressure to obtain a crude residue which was purified by CombiFlash Chromatography to afford the title compound (3 g, 57%). LCMS: 348 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.31 (m, 1H), 6.94 (d, *J* = 2.8 Hz, 1H), 6.87 (m, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.71 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.50 (m, 1H), 5.09 (br s, 2H), 1.06 (s, 12H).

[0332] Step 3a: Preparation of methyl 7-bromo-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxylate: To a stirred solution of methyl 7-bromo-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxylate (3 g, 10.4 mmol, 1 eq) in DMF (30 mL) was added potassium carbonate (2.1 g, 15.6 mmol) at RT and the mixture was stirred for 10 min. Methyl iodide (4.43g, 31.23 mmol) was then added at 0 °C and the resultant mixture was stirred at RT for 1 h. The progress of the reaction was monitored by TLC & LCMS. After completion, the mixture was diluted with ethyl acetate (300 mL) and washed with water (200 mL × 2), brine (50 mL × 2), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to obtain a crude which was triturated with *n*-pentane (100 mL × 2) to afford the title compound (2.5 g, 79%). LCMS: 302 [M+H]⁺, 304 [M+H+2]⁺

[0333] Step 3: Preparation of methyl 7-(5-amino-2-(2,4-difluorophenoxy)phenyl)-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxylate: To a stirred solution of methyl 7-bromo-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxylate (0.7 g, 2.3 mmol, 1eq) in dioxane (100 mL) were added 4-(2,4-difluorophenoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.61 g, 4.63 mmol, 2 eq), sodium carbonate (0.37 g, 3.46 mmol, 1.5 eq) dissolved in water (3 mL) and the mixture was degassed under nitrogen for 20 min. PdCl₂(dppf) (0.084 g, 0.11 mmol, 0.5 eq) was then added to the mixture and the mixture was further degassed for 10 min. The resultant mixture was heated at 80 °C for 4 h. The progress of the reaction was monitored by TLC and LCMS. After completion, the mixture was diluted with DCM (250 mL). The organic layer was washed with water (100 mL), brine (100 mL) dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to obtain a crude which was purified by CombiFlash Chromatography to afford the title compound (0.6 g, 58%). LCMS: 443 [M+H]⁺

[0334] Step 4: Preparation of methyl 7-(2-(2,4-difluorophenoxy)-5-(ethylsulfonamido)-phenyl)-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxylate: To a stirred solution of methyl 7-(5-amino-2-(2,4-difluorophenoxy)phenyl)-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxylate (0.5 g, 1.12 mmol, 1 eq) in THF (15 mL) was added Et₃N (0.34 g, 3.36 mmol, 3 eq) at 0 °C and the mixture was stirred for 5 min. Ethanesulfonyl chloride (0.5 g, 3.95 mmol, 3.5eq) was then added to the mixture at 0 °C and the resultant mixture was stirred at RT for 2.5 h. The progress of the reaction was monitored by TLC & LCMS. After completion, the mixture was concentrated under reduced pressure and the residue obtained was diluted with DCM (100 mL) and washed with water (30 mL × 2). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound (0.7 g, crude) which was used in the next step without further purification. LCMS: 535 [M+H]⁺

[0335] Step 5 : Preparation of 7-(2-(2,4-difluorophenoxy)-5-(ethylsulfonamido)phenyl)-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxylic acid: To a stirred solution of methyl 7-(2-(2,4-difluorophenoxy)-5-(ethylsulfonamido)phenyl)-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxylate (0.8 g, 0.66 mmol, 1eq) in methanol (20 mL) was added potassium carbonate (0.92 g, 6.68 mmol, 10 eq) and the mixture was stirred at RT for 16 h. The progress of the reaction was monitored by TLC and LCMS. After completion, the mixture was filtered and the filtrate was evaporated to dryness. This residue obtained was dissolved in water (20 mL) and washed with diethyl ether (20 mL). The aqueous layer was then acidified with using 1N-HCl (pH ~ 2) at 0 °C and extracted with 5% MeOH:DCM (200 mL × 2). The combined organic layers washed with water (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound (0.4 g, 51 %) which was used in the next step without further purification. LCMS: 521 [M+H]⁺

[0336] Step 6: Preparation of 7-(2-(2,4-difluorophenoxy)-5-(ethylsulfonamido)phenyl)-N-ethyl-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide: To a stirred solution of 7-(2-(2,4-difluorophenoxy)-5-(ethylsulfonamido)phenyl)-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxylic acid (0.15 g, 0.28 mmol, 1 eq) in DMF (3 mL) was added HATU (0.16 g, 0.42 mmol, 1.5 eq) at 0 °C and the mixture was stirred at same temperature for 20 min. DIPEA (0.44 g, 3.42 mmol, 6 eq) and ethylamine hydrochloride (182 mg, 1.4 mmol, 5 eq) were then added to the mixture and the resultant mixture was stirred at RT for 3 h. The progress of the reaction was monitored by TLC & LCMS. After completion, the mixture was diluted with water (50 mL) and

extracted with 5% MeOH/DCM (50 mL $\times$ 2). The combined organic layers were washed with water (50 mL $\times$ 2), and brine (20 mL $\times$ 2), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to obtain a crude which was purified by prep HPLC to afford the title compound (0.02 g, 13%) LCMS: 548 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆): δ 8.74 (br. s., 1H), 8.22 (s, 1H), 7.70 (s, 1H), 7.31 (br. s., 1H), 7.21 (d, J = 2.2 Hz, 1H), 7.09 (d, J = 2.6 Hz, 1H), 6.95 (d, J = 6.6 Hz, 2H), 6.89 (d, J = 8.8 Hz, 1H), 3.52 (s, 3H), 3.28-3.20 (m, 2H), 2.95 (d, J = 7.5 Hz, 2H), 1.22-1.13 (m, 3 H), 1.13-1.05 (m, 3H). It is understood that compounds from Tables-1 and 2 are synthesized using the General Synthetic Schemes 1 to 6 or using the experimental procedures as described in the examples S1-S34 and the steps involved in the synthetic routes are clearly familiar to those skilled in the art, wherein the substituents described in compounds of the Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), herein can be varied with a choice of appropriate starting materials and reagents utilized in the steps presented.

Biological Examples

Example B-1

Bromodomain and Extraterminal Domain (BET) Binding Assay

[0337] The bromodomain binding assays were performed by Reaction Biology Corp., Malvern, Pennsylvania, USA (www.reactionbiology.com). The BET binding assays were conducted in 384 well microplates in assay buffer (50 mM HEPES-HCl, pH 7.5, 100 mM NaCl, 1 mg/ml BSA, 0.05% CHAPS, and 0.5% DMSO) with compounds added as DMSO stocks at a single concentration or with 10-point dose response titrations. BET protein or assay buffer were delivered to the appropriate wells of the microplate. Test compound was then delivered by acoustic technology via a Labcyte Echo550 liquid handler. The microplate was centrifuged for 5 min and pre-incubated for 30 min at RT with gentle shaking. The ligand (histone H4 peptide (1- 21) K5/8/12/16Ac-biotin) was delivered and the microplate was again centrifuged for 5 min and allowed to incubate for 30 min at RT with gentle shaking. Donor beads were then added in the absence of light and the microplate was centrifuged and gently shaken. After 5 min, acceptor beads were added in the absence of light and the microplate was centrifuged and gently shaken in the dark for 60 min. The microplate was read using a Perkin Elmer EnSpire Alpha plate reader (λ Ex/ λ Em = 680/520-620 nm). Percent inhibition was calculated relative to positive and negative controls on

a per plate basis. For titration experiments, IC₅₀ values were determined by fitting the percent inhibition versus compound concentration.

Final Protein and Ligand Concentrations

Target	Protein Conc. (nM)	Ligand Conc. (nM)
BRD2-1	40	40
BRD2-2	120	60
BRD3-1	30	40
BRD3-2	75	75
BRD4-1	20	20
BRD4-2	130	70
BRDT-1	60	40

[0338] Compounds described herein were assayed and found to bind to bromodomain and extraterminal domain proteins. BRD4-1 and BRD4-2 IC₅₀ for compounds of the invention are shown in Table 3. ND means “not determined.”

Table 3. BRD4-1 and BRD4-2 IC₅₀ (μM)

Synthesis Example No.	Compound No.	BRD4-1 IC ₅₀ (μM)	BRD4-2 IC ₅₀ (μM)
S-1	1	10.1	0.002
S-2	2	ND	0.001
S-3	3	2.050	< 0.002
S-4	4	0.197	0.006
S-5	5	0.744	0.018

Synthesis Example No.	Compound No.	BRD4-1 IC ₅₀ (μM)	BRD4-2 IC ₅₀ (μM)
S-6	6	1.485	0.032
S-7	7	ND	0.497
S-8	8	0.094	0.074
S-9	14	1.170	0.047
S-10	145	0.601	0.007
S-11	146	2.922	0.002
S-12	13	4.942	0.009
S-13	23	1.120	0.018
S-14	10	0.111	0.0034
S-15	147	0.299	0.0018
S-16	22	0.638	0.0110
S-17	76	0.265	0.0170
S-18	148	>10	0.1027
S-19	149	>10	0.1027
S-20	150	3.595	0.0012
S-21	151	9.380	0.0032
S-22	152	1.492	0.0090
S-23	153	>10	0.5260
S-24	154	>10	0.2836
S-25	155	>10	4.066

Synthesis Example No.	Compound No.	BRD4-1 IC ₅₀ (μM)	BRD4-2 IC ₅₀ (μM)
S-26	156	>10	0.7400
S-27	157	>10	0.1452
S-28	158	0.103	0.1962
S-29	12	0.017	0.0125
S-30	159	0.018	0.0017
S-31	2.1	2.495	0.0198
S-32	2.3	0.118	0.0285
S-33	2.91	0.015	0.0073

ND: not determined

Example B-2

Cell Viability Assays

[0339] The effects of test compounds were studied in a cell viability assay in the MV-4-11 human acute myeloid leukemia cell line. The cells were harvested during the logarithmic growth period and counted. Cells were seeded at a count of 15000 cells per well/100 μl. After seeding, cells were incubated at 37°C, 5% CO₂ for 1 hr. Cells were treated with test compounds at 8 concentrations within a desired concentration range (e.g. 5 nM – 10 μM) for generation of dose response curves by preparing serial dilutions of the test compound in DMSO which were further diluted with culture medium and then added to each well. The plate was further incubated for another 72 hrs in a humidified incubator at 37°C and 5% CO₂. The assay was terminated by addition of Cell Titer-Glo reagent (Promega, Madison, WI) at 1/4 the volume of total medium per well. Contents were mixed, the plate was incubated for 10 min at room temperature and luminescence was measured. Cell viability data were plotted using GraphPad Prism (GraphPad Software, Inc., San Diego, CA). In addition, a nonlinear regression model with a sigmoidal dose

response and variable slope within GraphPad Prism was used to calculate the IC₅₀ value of individual test compounds. IC₅₀ values are given in Table 4.

Table 4. Cell Viability IC₅₀s for compounds in MV4-11 cells

Synthesis Example No.	Compound No.	IC ₅₀ (μM)
S-1	1	0.131
S-2	2	0.111
S-3	3	0.074
S-4	4	0.115
S-5	5	0.597
S-6	6	1.792
S-7	7	2.476
S-8	8	0.379
S-9	14	0.768
S-10	145	0.245
S-11	146	0.084
S-12	13	0.540
S-13	23	0.768
S-14	10	0.126
S-15	147	0.047
S-16	22	1.412
S-17	76	0.879
S-18	148	1.283

S-19	149	1.501
S-20	150	0.193
S-21	151	0.282
S-22	152	0.536
S-23	153	3.830
S-24	154	2.890
S-27	157	0.550
S-28	158	0.560
S-29	12	0.074
S-31	2.1	0.470
S-32	2.3	0.163

[0340] The effects of test compounds were also studied in the IEC-6 rat intestinal epithelial cell line to assess potential toxicity to non-cancerous cells. The cells were harvested during the logarithmic growth period and counted. In Protocol A, cells were seeded at a count of 3000 cells per well/100 μ l in a 96-well plate. After seeding, cells were incubated at 37°C, 5% CO₂ for 24 hr. Cells were treated with test compounds at 8 concentrations within a desired concentration range (e.g. 5 nM – 10 μ M) for generation of dose response curves by preparing serial dilutions of the test compound in DMSO which were further diluted with culture medium and then added to each well. The plate was further incubated for another 96 hrs in humidified incubator at 37°C and 5% CO₂. The assay was terminated by addition of resazurin (#R7017, Sigma). The plate was incubated for 4 hr at 37°C, 5% CO₂ and fluorescence was measured using excitation and emission wavelengths of 535 and 590 nm, respectively. Cell viability data were plotted using GraphPad Prism (GraphPad Software, Inc., San Diego, CA). In addition, a nonlinear regression model with a sigmoidal dose response and variable slope within GraphPad Prism was used to calculate the IC₅₀ value of individual test compounds. Protocol B was the same as Protocol A except that cells were seeded at

a count of 4000 cells per well/100 μ l in a 96-well plate, and the incubation with test compound was for 48 hrs instead of 96 hrs. IC₅₀ values are given in Table 5.

Table 5. Cell Viability IC₅₀s for compounds in IEC-6 cells

Synthesis No.	Compound No.	Protocol A IC ₅₀ (μ M)	Protocol B IC ₅₀ (μ M)
S-1	1	0.266	4.91
S-2	2	0.061	ND
S-3	3	0.089	ND
S-4	4	0.048	0.283
S-8	8	0.156	0.521
S-10	145	ND	0.691
S-11	146	ND	0.729
S-12	13	ND	2.500
S-13	23	ND	1.62
S-14	10	ND	0.780
S-15	147	ND	1.770

ND: not determined

[0341] Other compounds of the invention are also assayed for effect on cell viability. In addition, a panel of BET-sensitive and insensitive cell lines is profiled for effect on cell viability using test compounds. Cells are cultured in the presence of inhibitors at various concentrations for up to 72 hr. For cell viability assays as previously described (Guo Y, et al. 2012. J Hematol Oncol 5:72; Chen Y, et al. 2016. Oncogene 35:2971-8), 0.08 mg/ml XTT (2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)- 2H-tetrazolium-5-carboxanilide) and 8 μ M phenazine methyl sulfate (PMS) are added to the cells at the end of the test compound or vehicle treatment duration, and absorbance at 450 nm is measured after 3 hr incubation at 37 °C. Assays are performed in triplicates. IC₅₀ values

are estimated using a non-linear mixed effect model fitting a sigmoid curve to the experimental dose response data (Vis DJ, et al. 2016. Pharmacogenomics 17(7):691-700).

Example B-3

Histologic Analysis

[0342] The inhibitory effects of test compounds on the growth of cells are demonstrated by Wright- Giemsa staining of cells fixed to glass slides after incubation of the test compound or vehicle with the cells for a certain duration (e.g., 48 h). Morphologic changes of treated cells associated with cell cycle arrest, such as condensed nuclei and shrinking or swollen cell membranes are noted.

Example B-4

In Vivo Efficacy Study

[0343] A study to evaluate test compound pharmacodynamics in MV-4-11 systemic leukemia model in NOD SCID mice is conducted. Female NOD SCID mice are inoculated with MV-4-11 cells systemically. Four weeks after cell inoculation, each animal is administered a single IV dose of test compound or vehicle. The dosing volume is 10 mL/kg (0.200 mL/20 g mouse), with volume adjusted according to body weight. Four hours after dosing, animals are sacrificed. Bone marrow and spleen (weight and size are recorded) are dissected, crushed in PBS and made into single cell suspensions for analysis by flow cytometry for the assessment of leukemic engraftment. Western blot analyses of bone marrow and spleen cell extracts with antibody against the housekeeping protein c-Myc are carried out for animals with successful leukemic engraftment.

Example B-5

Mouse Xenograft Model

[0344] To examine the in vivo antitumor activity of test compound (as a single agent and in combination with other agents such as enzalutamide) in a castration resistant prostate cancer mouse model, tumor growth experiments are performed in a VCaP cell line mouse xenograft model. Cells are implanted subcutaneously into the flanks of 4-week old male immunodeficient mice (such as nude or SCID mice) and allowed to grow. Tumors are measured using a caliper and tumor volumes calculated using the formula: Tumor volume = $(a \times b^2)/2$ where 'b' is the smallest diameter and 'a' is the largest diameter. Once the established tumors reach approximately 200 mm³, the tumor-

bearing mice are surgically castrated. The mice are stratified into treatment groups once the tumors grow back to the pre-castration size. The treatment groups are, for example: vehicle control, enzalutamide alone, test compound alone, and enzalutamide + test compound at 10 mice per group. The exact treatment groups, drug dose, and dosing schedule are determined according to the specific needs of the study. Tumor growth is monitored, and volume recorded at regular intervals. When the individual tumor of each mouse reaches an approximate end-point (tumor volume $>1,500 \text{ mm}^3$), the mouse is sacrificed. The tumor growth inhibition (TGI) is calculated by comparing the control group's tumor measurements with the other study groups once the predetermined endpoint is reached in the control group.

[0345] The disclosures of all publications, patents, patent applications and published patent applications referred to herein by an identifying citation are hereby incorporated herein by reference in their entirety.

[0346] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is apparent to those skilled in the art that certain minor changes and modifications will be practiced in light of the above teaching. Therefore, the description and examples should not be construed as limiting the scope of the invention. All references disclosed herein are hereby incorporated herein by reference.