

INHIBITORS OF BRUTON'S TYROSINE KINASE AND METHODS OF THEIR USE**CROSS REFERENCE TO OTHER APPLICATIONS**

[0001] This application claims priority to U.S. Provisional Application No. 63/196,843
5 filed on June 4, 2021 titled "Inhibitors Of Bruton's Tyrosine Kinase And Methods Of Their Use"
which is incorporated herein by reference in its entirety.

TECHNICAL FIELD

[0002] The present disclosure is directed to the use of small molecule tyrosine kinase
10 inhibitors for the treatment of malignancies.

BACKGROUND

[0003] Malignancies, in particular diffuse large B-cell lymphoma (DLBCL), mantle
cell lymphoma (MCL), follicular lymphoma (FL), marginal zone lymphoma (MZL), chronic
15 lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), Waldenström
macroglobulinemia, and other conditions such as chronic graft versus host disease, continues to
afflict patients. Alternative, effective treatments of cancer are still needed.

[0004] Human Bruton's tyrosine kinase ("BTK") is a ~76 kDa protein belonging to the
Tec family of non-receptor tyrosine kinases. Tec kinases form the second largest family of
20 cytoplasmic tyrosine kinases in mammalian cells, which consists of four other members in
addition to BTK: the eponymous kinase TEC, ITK, TXK/RLK and BMX. Tec kinases are
evolutionarily conserved throughout vertebrates. They are related to, but structurally distinct
from, the larger Src and Syk kinase families. Tec family proteins are abundantly expressed in
hematopoietic tissues and play important roles in the growth and differentiation of blood and
25 endothelial cells in mammals.

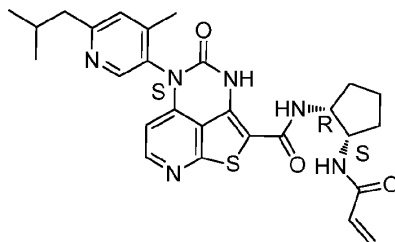
[0005] Based upon BTK expression from IHC studies described in the art, Btk
inhibition has the potential to modulate biology associated with B cells, macrophages, mast cells,
osteoclasts, and platelet microparticles. Corneth, O.B., et al. Curr. Top. Microbiol. Immunol.
BTK Signaling in B Cell Differentiation and Autoimmunity. 2015 Sept. 5.

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SUMMARY

[0006] Compositions comprising the compound of Formula (III) are described.
Methods of using the compound of Formula (III) are also within the scope of the disclosure.

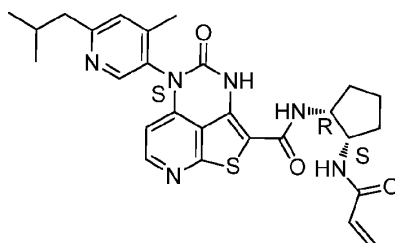
Also described are methods of treating a malignancy in an individual in need thereof, comprising administering a therapeutically effective amount of a compound of Formula (III):



(III)

5 or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof. In some aspects, the malignancy is selected from the group consisting of a diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), marginal zone lymphoma (MZL), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), and Waldenström macroglobulinemia, Chronic graft versus host disease.

10 **[0007]** Some aspects are directed to methods of treating chronic graft versus host disease in an individual in need thereof, comprising administering a therapeutically effective amount of a compound of Formula (III):



(III)

15 or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof.

[0008] In some aspects the therapeutically effective amount of the compound of Formula (III) is from about 140 mg to about 560 mg. In some aspects, the therapeutically effective amount of the compound of Formula (III) is administered once a day. In some aspects, the therapeutically effective amount of the compound of Formula (III) is administered twice daily. In some aspects, the therapeutically effective amount of the compound of Formula (III) is about 140 mg. In some aspects, the therapeutically effective amount of the compound of

Formula (III) is about 280 mg. In some aspects, the therapeutically effective amount of the compound of Formula (III) is about 560 mg.

[0009] In some aspects the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max, day1)}$ of about 59.992 ng/ml to about 2,377.2 ng/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max, day1)}$ of about 239.97 ng/ml to about 9,509 ng/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max, ss)}$ of about 66.855 ng/ml to about 2,395.4 ng/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max, ss)}$ of about 267.42 ng/ml to about 9,581.5 ng/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day 1)}$ of about 312.1 ng.hr/ml to about 11,517 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day 1)}$ of about 1,248.4 ng.hr/ml to about 46,068 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 312.27 ng.hr/ml to about 13,015 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 1,249.1 ng.hr/ml to about 52,061 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day1)}$ of about 30.9% occupancy to about 99.8% occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day1)}$ of about 87.1 % occupancy to about 100 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/ss)}$ of about 59.4% occupancy to about 99.9 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/ss)}$ of about 90.2 % occupancy to about 100 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day1)}$ of about 23.3 % occupancy to about 91.3 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day1)}$ of about 63.9 % occupancy to about 97.3 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/ss)}$ of about 50.2 % occupancy to about 95.4 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula

(III) is an amount that results in a $BTKO_{(trough/ss)}$ of about 75.5% occupancy to about 99.3 % occupancy.

[0010] In some aspects, the therapeutically effective amount of the compound of Formula (III) is administered once a day. In some aspects, the therapeutically effective amount of the compound of Formula (III) is administered twice a day. In some aspects, the therapeutically effective amount of the compound of Formula (III) is administered three times a day. In some aspects the compound of Formula (III) is administered orally.

[0011] In some aspects, the methods described herein further comprise administering 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)benzamide). In some aspects, the methods described herein further comprise administering cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab.

FIGURES

[0012] Figure 1 depicts a schematic overview of the design for NCT03607513 (MAD=multiple ascending dose; PBO=placebo; SAD=single ascending dose).

[0013] Figure 2 depicts a mechanistic PK/BTKO Model. Aa = Amount of compound of Formula (III) in the depot compartment of the PK model; Ka = absorption rate constant; Q = intercompartmental clearance between compartments 1 and 2; CL = apparent clearance; Syn = synthesis rate constant for free BTK; Kdegf = degradation rate constant of free BTK; Kon = association rate constant; Koff = dissociation rate constant; Kdegi = degradation rate of bound BTK; Kinact = covalent binding rate; BTK = free BTK; BTKb = bound BTK; BTKi = inactivated BTK.

[0014] Figure 3 depicts SAD fasted male cohorts plasma concentrations by time.

[0015] Figure 4 depicts the arithmetic mean of the compound of formula (III) plasma concentration-time profiles following a single dose of 100 mg of the compound of Formula (III) oral solution in healthy male subjects under fasted or fed conditions (high-fat breakfast) (log-linear) (Phase I Study-SAD part: Pharmacokinetic Analysis Set).

[0016] Figure 5 depicts mean (SD) compound of Formula (III) plasma concentration-time profiles following multiple doses of the compound of Formula (III) oral solution in healthy male and female subjects under fed conditions (standard breakfast).

[0017] Figure 6 depicts BTK occupancy and plasma concentrations by time following single doses of the compound of Formula (III) oral solution in fasted males.

[0018] Figure 7 depicts observed % BTK Occupancy at 24 hours post-dose.

[0019] Figure 8 depicts predicted %BTKO for multiple dosing based on PK/BTKO
5 Simulations Based on Oral Solution Data from SAD Cohorts 1-5.

[0020] Figure 9A-B depict Goodness-of-Fit Plots for the Population PK Model Using (A) First 5 SAD Cohorts Data (B) All SAD and MAD Data. $iWRES$ =absolute individual weighted residuals. Units: Observations or predictions=ng/mL; Time=hour.

[0021] Figure 10A-B depict Goodness-of-Fit Plots for the PD Model Using (A) Cohort
10 2-5 Data (B) All SAD and MAD Data. $iWRES$ =absolute individual weighted residuals. Units: Observations or predictions=ng/mL; Time=hour.

[0022] Figure 11. depicts Prediction-Corrected Visual Predictive Check for (A) Population PK (B) PD.

[0023] Figure 12 depicts exemplary covalent BTK inhibitors.

[0024] Figure 13 depicts concentration-dependent occupancy of Bruton's tyrosine
15 kinase by the compound of Formula (III) in Ramos human B cells (mean $\pm$ SD; n = 11).

[0025] Figure 14 depicts time-dependent occupancy of Bruton's tyrosine kinase in Ramos B cells by the compound of Formula (III).

[0026] Figure 15 depicts plasma concentration and receptor occupancy of Bruton's
20 tyrosine kinase by the compound of Formula (III) from two independent studies (A-B). Target-site occupancy was measured using enzyme-linked immunosorbent assay, and plasma concentration was measured using liquid chromatography-mass spectrometry. Data represent mean $\pm$ SEM (n = 4/group).

[0027] Figure 16 depicts the effect of the compound of Formula (III) on hind paw
25 inflammation in the rat effect of the compound of Formula (III) (0.3, 1, 2, 3, 10 mg/kg/day, PO, QD, for all 7 days (day 10-16) of dosing) on hind paw inflammation in rats. Data represent mean and error bars indicate standard error of the mean (SEM) (n=6 for the naïve group, n=8 for treatment groups).

[0028] Figure 17 depicts antiproliferative activity of the compound of Formula (III) in
30 ABC-DLBCL cell lines (8 days) (n = 4).

[0029] Figure 18 depicts circulating human IL-10 cytokine serum levels of mice treated with the compound of Formula (III). IL-10 cytokine levels are graphed as % normalized to vehicle control IL-10 levels $\pm$ SEM. Female NSG mice were implanted SC with OCI-LY10

cells on the right flank on Day 0. After tumors were established 39 days post implantation, mice were randomized into experimental groups and dosed orally with a single dose (n=5/dose level/time point). Serum samples were collected 2, 4, 8, 12, 16 and 24 hours after compound administration.

5 **[0030]** Figure 19 depicts BTK protein occupancy in OCI-LY10 ABC-DLBCL tumor lysates of NSG mice treated with the compound of Formula (III). Unoccupied BTK protein levels are graphed as % normalized to vehicle control BTK levels $\pm$ SEM. Female mice were implanted SC on the right flank on day 0. Tumors were established 39 days post implantation, randomized into experimental groups and dosed orally with a single dose (n=5/dose level/time point). Tumor samples were harvested 4, 12 and 24 hours after compound administration.

10 **[0031]** Figure 20 depicts the effect of the compound of Formula (III) on growth of established OCI-LY10 human ABC-DLBCL xenografts in mice PEG400/PVP-VA64, Polyethylene glycol 400/ N-vinylpyrrolidone and vinyl acetate 64; SEM, standard error of the mean. Group tumor volumes are graphed as the mean $\pm$ SEM. Bar below x-axis indicates the treatment period. Groups are plotted while at least 2/3 of the animals remained on the study. Mice were implanted SC on the right flank on Day 0. Tumors were established 33 days post implantation, mice were randomized into experimental groups and dosed orally twice or once daily for 3 weeks (n=10/group).

15 **[0032]** Figure 21 depicts a LY2298 tumor xenograft study with the compound of Formula (III) and venetoclax as single agents and in combination. Tumor Growth inhibition of the compound of Formula (III)-100 mpk QD, venetoclax-40 mpk QD, the compound of Formula (III)-100mpk+ venetoclax- 40mpk in LY2298 were 59.2%, -4.8% and 87.0% respectively.

20 **[0033]** Figure 22 depicts plasma concentration and inhibition of B-cell activation by the compound of Formula (III) at 2, 3, and 10 mg/kg achieved prolonged inhibition of B-cell activation compared with plasma concentration, with an inhibition ratio of 78% or greater at 8 hours. Data represent mean $\pm$ SEM (n = 3/group).

25 **[0034]** Figure 23 depicts kinase percent inhibition by the compound of Formula (III) grouped by kinase family.

30 **[0035]** Figure 24 depicts simulation of tolbutamide (500 mg on day 5) plasma concentrations upon coadministration with the compound of Formula (III) (10 mg once daily for 5 days).

[0036] Figure 25 depicts metabolism of the compound of Formula (III) by human rCYPs.

DETAILED DESCRIPTION

[0037] The disclosure may be more fully appreciated by reference to the following description, including the following glossary of terms and the concluding examples. It is to be appreciated that certain features of the disclosed compositions and methods which are, for clarity, described herein in the context of separate aspects, may also be provided in combination in a single aspect. Conversely, various features of the disclosed compositions and methods that are, for brevity, described in the context of a single aspect, may also be provided separately or in any subcombination. It will be understood by those within the art that, in general, terms used herein, and especially in the appended claims (for example, bodies of the appended claims) are generally intended as “open” terms (for example, the term “including” should be interpreted as “including but not limited to,” the term “having” should be interpreted as “having at least,” the term “includes” should be interpreted as “includes but is not limited to,” etc.). It will be further understood by those within the art that if a specific number of an introduced claim recitation is intended, such an intent will be explicitly recited in the claim, and in the absence of such recitation no such intent is present. For example, as an aid to understanding, the following appended claims may contain usage of the introductory phrases “at least one” and “one or more” to introduce claim recitations. However, the use of such phrases should not be construed to imply that the introduction of a claim recitation by the indefinite articles “a” or “an” limits any particular claim containing such introduced claim recitation to aspects containing only one such recitation, even when the same claim includes the introductory phrases “one or more” or “at least one” and indefinite articles such as “a” or “an” (for example, “a” and/or “an” should be interpreted to mean “at least one” or “one or more”); the same holds true for the use of definite articles used to introduce claim recitations. In addition, even if a specific number of an introduced claim recitation is explicitly recited, those skilled in the art will recognize that such recitation should be interpreted to mean at least the recited number (for example, the bare recitation of “two recitations,” without other modifiers, means at least two recitations, or two or more recitations). Furthermore, in those instances where a convention analogous to “at least one of A, B, and C, etc.” is used, in general such a construction is intended in the sense one having skill in the art would understand the convention (for example, “a system having at least one of A, B, and C” would include but not be limited to systems that have A alone, B alone, C alone, A and B together, A and C together, B and C together, and/or A, B, and C together, etc.). In those instances where a convention analogous to “at least one of A, B, or C, etc.” is used, in general

such a construction is intended in the sense one having skill in the art would understand the convention (for example, “a system having at least one of A, B, or C” would include but not be limited to systems that have A alone, B alone, C alone, A and B together, A and C together, B and C together, and/or A, B, and C together, etc.). It will be further understood by those within
5 the art that virtually any disjunctive word and/or phrase presenting two or more alternative terms, whether in the description, claims, or drawings, should be understood to contemplate the possibilities of including one of the terms, either of the terms, or both terms. For example, the phrase “A or B” will be understood to include the possibilities of “A” or “B” or “A and B.”

[0038] In addition, where features or aspects of the disclosure are described in terms of
10 Markush groups, those skilled in the art will recognize that the disclosure is also thereby described in terms of any individual member or subgroup of members of the Markush group.

[0039] As will be understood by one skilled in the art, for any and all purposes, such as in terms of providing a written description, all ranges disclosed herein also encompass any and all possible subranges and combinations of subranges thereof. Any listed range can be easily
15 recognized as sufficiently describing and enabling the same range being broken down into at least equal halves, thirds, quarters, fifths, tenths, etc. As a non-limiting example, each range discussed herein can be readily broken down into a lower third, middle third and upper third, etc. As will also be understood by one skilled in the art all language such as “up to,” “at least,” and the like include the number recited and refer to ranges which can be subsequently broken down
20 into subranges as discussed above. Finally, as will be understood by one skilled in the art, a range includes each individual member. Thus, for example, a group having 1-3 cells refers to groups having 1, 2, or 3 cells. Similarly, a group having 1-5 cells refers to groups having 1, 2, 3, 4, or 5 cells, and so forth.

[0040] Various of the above-disclosed and other features and functions, or alternatives
25 thereof, may be combined into many other different systems or applications. Various presently unforeseen or unanticipated alternatives, modifications, variations or improvements therein may be subsequently made by those skilled in the art, each of which is also intended to be encompassed by the disclosed aspect.

[0041] The term “about” as used herein when immediately preceding a numerical value
30 means a range of plus or minus 10% of that value, for example, “about 50” means 45 to 55, “about 25,000” means 22,500 to 27,500, etc., unless the context of the disclosure indicates otherwise, or is inconsistent with such an interpretation.

[0042] The term "alkyl," when used alone or as part of a substituent group, refers to a straight- or branched-chain alkyl group having from 1 to 12 carbon atoms ("C₁₋₁₂"), preferably 1 to 6 carbons atoms ("C₁₋₆"), in the chain. Examples of alkyl groups include methyl (Me, C₁alkyl) ethyl (Et, C₂alkyl), n-propyl (C₃alkyl), isopropyl (C₃alkyl), butyl (C₄alkyl), isobutyl (C₄alkyl),
5 sec-butyl (C₄alkyl), tert-butyl (C₄alkyl), pentyl (C₅alkyl), isopentyl (C₅alkyl), tert-pentyl (C₅alkyl), hexyl (C₆alkyl), isohexyl (C₆alkyl), and groups that in light of the ordinary skill in the art and the teachings provided herein would be considered equivalent to any one of the foregoing examples.

[0043] When a range of carbon atoms is used herein, for example, C₁₋₆, all ranges, as
10 well as individual numbers of carbon atoms are encompassed. For example, "C₁₋₃" includes C₁₋₃, C₁₋₂, C₂₋₃, C₁, C₂, and C₃.

[0044] The term "C₁₋₆alk" refers to an aliphatic linker having 1, 2, 3, 4, 5, or 6 carbon atoms and includes, for example, CH₂, CH(CH₃), CH(CH₃)-CH₂, and C(CH₃)₂. The term "-C₀alk-" refers to a bond. In some aspects, the C₁₋₆alk can be substituted with an oxo group or an
15 OH group.

[0045] The term "alkenyl," when used alone or as part of a substituent group, refers to straight and branched carbon chains having from 2 to 12 carbon atoms ("C₂₋₁₂"), preferably 2 to 6 carbon atoms ("C₂₋₆"), wherein the carbon chain contains at least one, preferably one to two, more preferably one double bond. For example, alkenyl moieties include, but are not limited to
20 allyl, 1-propen-3-yl, 1-buten-4-yl, propa-1,2-dien-3-yl, and the like.

[0046] The term "alkynyl," when used alone or as part of a substituent group, refers to straight and branched carbon chains having from 2 to 12 carbon atoms ("C₂₋₁₂"), preferably 2 to 6 carbon atoms ("C₂₋₆"), wherein the carbon chain contains at least one, preferably one to two, more preferably one triple bond. For example, alkynyl moieties include, but are not limited to
25 vinyl, 1-propyn-3-yl, 2-butyn-4-yl, and the like.

[0047] The term "aryl" refers to carbocyclic aromatic groups having from 6 to 10 carbon atoms ("C₆₋₁₀") such as phenyl, naphthyl, and the like.

[0048] The term "cycloalkyl" refers to monocyclic, non-aromatic hydrocarbon groups having from 3 to 10 carbon atoms ("C₃₋₁₀"), preferably from 3 to 6 carbon atoms ("C₃₋₆").
30 Examples of cycloalkyl groups include, for example, cyclopropyl (C₃), cyclobutyl (C₄), cyclopentyl (C₅), cyclohexyl (C₆), 1-methylcyclopropyl (C₄), 2-methylcyclopentyl (C₄), adamantanyl (C₁₀) and the like.

[0049] The term “heterocycloalkyl” refers to any five to ten membered monocyclic or bicyclic, saturated ring structure containing at least one heteroatom selected from the group consisting of O, N and S. The heterocycloalkyl group may be attached at any heteroatom or carbon atom of the ring such that the result is a stable structure. Examples of suitable heterocycloalkyl groups include, but are not limited to, azepanyl, aziridinyl, azetidiny, pyrrolidinyl, dioxolanyl, imidazolidinyl, pyrazolidinyl, piperazinyl, piperidinyl, dioxanyl, morpholinyl, dithianyl, thiomorpholinyl, oxazepanyl, oxiranyl, oxetanyl, quinuclidinyl, tetrahydrofuranly, tetrahydropyranyl, piperazinyl, hexahydro-5H-[1,4]dioxino[2,3-c]pyrrolyl, benzo[d][1,3]dioxolyl, and the like.

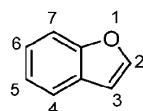
[0050] The term “heteroaryl” refers to a mono-or bicyclic aromatic ring structure including carbon atoms as well as up to four heteroatoms selected from nitrogen, oxygen, and sulfur. Heteroaryl rings can include a total of 5, 6, 9, or 10 ring atoms (“C₅₋₁₀”). Examples of heteroaryl groups include but are not limited to, pyrrolyl, furyl, thienyl, oxazolyl, imidazolyl, purazolyl, isoxazolyl, isothiazolyl, triazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranly, furazanyl, indoliziny, indolyl, isoindolinyl, indazolyl, benzofuryl, benzothienyl, benzimidazolyl, benzthiazolyl, purinyl, quinoliziny, quinolinyl, isoquinolinyl, isothiazolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxaliny, naphthyridinyl, pteridinyl, and the like.

[0051] The term “halogen” represents chlorine, fluorine, bromine, or iodine. The term “halo” represents chloro, fluoro, bromo, or iodo.

[0052] The term “haloalkyl” refers to an alkyl moiety wherein one or more of the hydrogen atoms has been replaced with one or more halogen atoms. One exemplary substituent is fluoro. Preferred haloalkyl groups of the disclosure include trihalogenated alkyl groups such as trifluoromethyl groups.

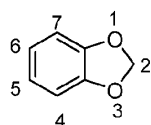
[0053] The term “oxo” refers to a =O moiety, wherein two hydrogens from the same carbon atom have been replaced with a carbonyl. For example, an oxo-substituted pyrrolidinyl moiety could be a pyrrolidin-2-one moiety or a pyrrolidin-3-one moiety.

[0054] The term “benzofuranyl” represents the following moiety:

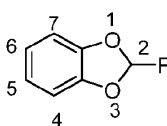
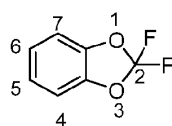


The benzofuranyl moiety can be attached through any one of the 2-, 3-, 4-, 5-, 6-, or 7-carbon atoms.

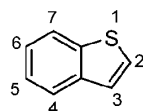
[0055] The term “benzo[d][1,3]dioxolyl” represents the following moiety:



The benzo[d][1,3]dioxolyl moiety can be attached through any one of the 2-, 4-, 5-, 6-, or 7- carbon atoms. In those aspects wherein the benzo[d][1,3]dioxolyl moiety is substituted with halogen,” the following moieties are preferred:



[0056] The term “benzothiophenyl” represents the following moiety:



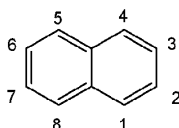
The benzothiophenyl moiety can be attached through any one of the 2-, 3-, 4-, 5-, 6-, or 7- carbon atoms.

[0057] The term “phenyl” represents the following moiety:



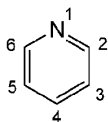
The phenyl moiety can be attached through any of the carbon atoms.

[0058] The term “naphthalenyl” (i.e., naphthyl) represents the following moiety:



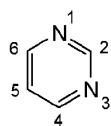
The naphthalenyl moiety can be attached through any one of the 1-, 2-, 3-, 4-, 5-, 6-, 7-, or 8-position carbon atoms.

[0059] The term “pyridyl” represents the following moiety:



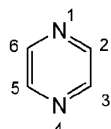
The pyridyl moiety can be attached through any one of the 2-, 3-, 4-, 5-, or 6-position carbon atoms.

[0060] The term “pyrimidinyl” represents the following moiety:



The pyrimidinyl moiety can be attached through any one of the 2-, 4-, 5-, or 6-position carbon atoms.

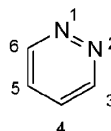
[0061] The term “pyrazinyl” represents the following moiety:



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The pyrazinyl moiety can be attached through any one of the 2-, 3-, 5-, or 6-position carbon atoms.

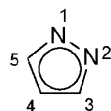
[0062] The term “pyridazinyl” represents the following moiety:



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The pyridazinyl moiety can be attached through any one of the 3-, 4-, 5-, or 6-position carbon atoms.

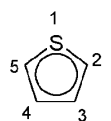
[0063] The term “pyrazolyl” represents the following moiety:



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The pyrazolyl moiety can be attached through any one of the 1-, 2-, 3-, 4-, or 5-position carbon atoms.

[0064] The term “thiophenyl” represents the following moiety:

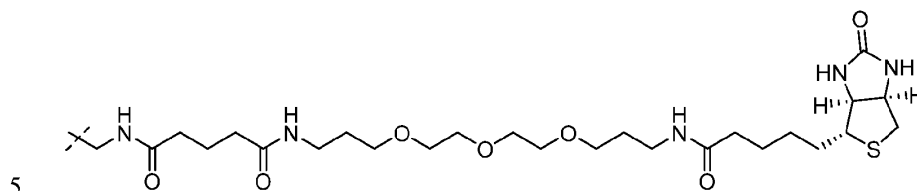


The thiophenyl moiety can be attached through any one of the 2-, 3-, 4-, or 5-position carbon atoms.

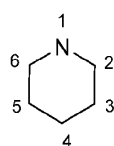
20

[0065] The term “linker-PEG-Biotin” refers to a moiety comprising –linker-PEG-CH₂-NH-biotinyl. Compounds of the disclosure that include a linker-PEG-Biotin moiety can be used according to any of the methods described herein. Alternatively, compounds of the disclosure that include a linker-PEG-Biotin moiety can be used as diagnostic probes

according to methods known in the art. Preferred linkers are known in the art, with the linker –CH₂-NHC(O)-(CH₂)₃-C(O)-NH-CH₂- being particularly preferred. Preferred PEG moieties include at least two or three repeating –CH₂-CH₂-O- moieties. A preferred linker-PEG-Biotin moiety is

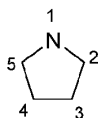


[0066] The term “piperidinyl” represents the following moiety:



When the piperidinyl moiety is a substituent, it can be attached through any one of the 1-, 2-, 3-, 4-, 5-, or 6-position atoms, as permitted.

10 **[0067]** The term “pyrrolidinyl” represents the following moiety:



When the piperidinyl moiety is a substituent, it can be attached through any one of the 1-, 2-, 3-, 4-, or 5- position atoms, as permitted.

15 **[0068]** The term “oxazepanyl” refers to a 7-membered heterocycloalkyl moiety having one ring nitrogen atom and one ring oxygen atom. Examples include 1,3-oxazepanyl and 1,4-oxazepanyl moieties



1,3-oxazepanyl



1,4-oxazepanyl

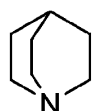
When the oxazepanyl moiety is a substituent, it can be attached through any ring carbon atom or through the nitrogen atom, as permitted

20 **[0069]** The term “aziridinyl” represents a 3-membered heterocycloalkyl moiety having one ring nitrogen. When the aziridinyl moiety is a substituent, it can be attached through any ring carbon atom or through the nitrogen atom, as permitted.

[0070] The term “azetidiny” represents a 4-membered heterocycloalkyl moiety having one ring nitrogen. When the azetidiny moiety is a substituent, it can be attached through any carbon atom or through the nitrogen atom, as permitted.

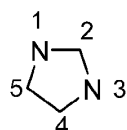
[0071] The term “azepanyl” represents a 7-membered heterocycloalkyl moiety having one ring nitrogen. When the azepanyl moiety is a substituent, it can be attached through any carbon atom or through the nitrogen atom, as permitted

[0072] The term “quinuclidiny” represents the following moiety:



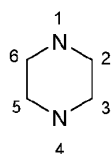
Within the disclosure, when the quinuclidiny moiety is a substituent, it can be attached to the compound of Formula (I) through any one of the ring carbon atoms.

[0073] The term “imidazolidiny” represents the following moiety:



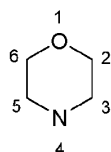
When the imidazolidiny moiety is a substituent, it can be attached through any one of the 1-, 2-, 3-, 4-, or 5-position atoms., as permitted

[0074] The term “piperaziny” represents the following moiety:



When the piperaziny moiety is a substituent, it can be attached through any one of the 1-, 2-, 3-, 4-, 5-, or 6-position atoms, as permitted

[0075] The term “morpholiny” represents the following moiety:



When the morpholiny moiety is a substituent, it can be attached through any one of the 2-, 3-, 4-, 5-, or 6-position atoms, as permitted.

[0076] The term “tetrahydropyranyl” represents a 6-membered heterocycloalkyl moiety having one ring oxygen. The tetrahydropyranyl moiety can be attached through any carbon atom on the ring.

[0077] The term “tetrahydrofuranyl” represents a 5-membered heterocycloalkyl moiety having one ring oxygen. The tetrahydrofuranyl moiety can be attached through any carbon atom on the ring.

[0078] As used herein, the term “compound(s) of Formula (I)” includes those compounds of “Formula (I),” as well as compounds of any of the Formula (I) subgenera.

[0079] “Pharmaceutically acceptable” means approved or approvable by a regulatory agency of the Federal or a state government or the corresponding agency in countries other than the United States, or that is listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, and more particularly, in humans.

[0080] “Pharmaceutically acceptable salt” refers to a salt of a compound of the disclosure that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. In particular, such salts are non-toxic may be inorganic or organic acid addition salts and base addition salts. Specifically, such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic 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; or (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine and the like. Salts further include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the compound contains a basic functionality, salts of non-toxic organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like.

[0081] “Pharmaceutically acceptable vehicle” refers to a diluent, adjuvant, excipient or carrier with which a compound of the disclosure is administered. A “pharmaceutically acceptable excipient” refers to a substance that is non-toxic, biologically tolerable, and otherwise biologically suitable for administration to a subject, such as an inert substance, added to a pharmacological composition or otherwise used as a vehicle, carrier, or diluent to facilitate administration of an agent and that is compatible therewith. Examples of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils, and polyethylene glycols.

[0082] “Subject” includes humans. The terms “human,” “patient,” and “subject” are used interchangeably herein.

[0083] “Treating” or “treatment” of any disease or disorder refers, in one aspect, to ameliorating the disease or disorder (i.e., arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another aspect “treating” or “treatment” refers to ameliorating at least one physical parameter, which may not be discernible by the subject. In yet another aspect, “treating” or “treatment” refers to modulating the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both. In yet another aspect, “treating” or “treatment” refers to delaying the onset of the disease or disorder.

[0084] The term “administer” or “administered” or “administering” refers to the administration of compound(s) of Formula (I) and their respective solvates or pharmaceutically acceptable salt forms thereof, or a pharmaceutical compositions thereof to a subject by any method known to those skilled in the art in view of the present disclosure, such as by intramuscular, subcutaneous, oral, intravenous, cutaneous, intramucosal (e.g., gut), intranasal or intraperitoneal route of administration. In particular embodiments, a pharmaceutical composition of the invention is administered to a subject orally.

[0085] The terms “therapeutically effective amount” or “therapeutically effective dose” are used interchangeably and means an amount or dose sufficient to generally bring about the desired therapeutic benefit in patients in need of such treatment for the designated disease, disorder, or condition.

[0086] As used herein, the term “condition” refers to any disease, syndrome, or disorder detected or diagnosed by a researcher, veterinarian, medical doctor, or other clinician, wherein said researcher, veterinarian, medical doctor, or other clinician determines that it

desirable to seek a biological or medicinal response in an animal tissue system, particularly a mammalian or human tissue system.

[0087] “Compounds of the present disclosure,” and equivalent expressions, are meant to embrace compounds of the Formula (I) as described herein, and in particular the compound of Formula (III), which expression includes the pharmaceutically acceptable salts, and the solvates, e.g., hydrates, and polymorphs thereof, where the context so permits. Similarly, reference to intermediates, whether or not they themselves are claimed, is meant to embrace their salts, and solvates, where the context so permits.

[0088] As used herein, the term “isotopic variant” refers to a compound that contains unnatural proportions of isotopes at one or more of the atoms that constitute such compound. For example, an “isotopic variant” of a compound can be radiolabeled, that is, contain one or more non-radioactive isotopes, such as for example, deuterium (^2H or D), carbon-13 (^{13}C), nitrogen-15 (^{15}N), or the like. It will be understood that, in a compound where such isotopic substitution is made, the following atoms, where present, may vary, so that for example, any hydrogen may be $^2\text{H}/\text{D}$, any carbon may be ^{13}C , or any nitrogen may be ^{15}N , and that the presence and placement of such atoms may be determined within the skill of the art. Likewise, the disclosure may include the preparation of isotopic variants with radioisotopes, in the instance for example, where the resulting compounds may be used for drug and/or substrate tissue distribution studies. Radiolabeled compounds of the disclosure can be used in diagnostic methods such as Single-photon emission computed tomography (SPECT). The radioactive isotopes tritium, *i.e.* ^3H , and carbon-14, *i.e.* ^{14}C , are particularly useful for their ease of incorporation and ready means of detection. Further, compounds may be prepared that are substituted with positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , and would be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

[0089] All isotopic variants of the compounds of the disclosure, radioactive or not, are intended to be encompassed within the scope of the disclosure.

[0090] It is also to be understood that compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed “isomers.” Isomers that differ in the arrangement of their atoms in space are termed “stereoisomers,” for example, diastereomers, enantiomers, and atropisomers.

[0091] Stereoisomers that are not mirror images of one another are termed “diastereomers” and those that are non-superimposable mirror images of each other are termed “enantiomers.” When a compound has an asymmetric center, for example, it is bonded to four

different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R-and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (*i.e.*, as (+) or (-)-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 called a “racemic mixture.”

[0092] “Atropisomers” refer to stereoisomers that arise because of hindered rotation around a single bond.

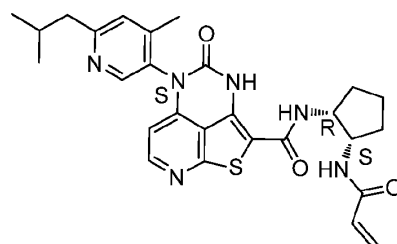
[0093] “Tautomers” refer to compounds that are interchangeable forms of a particular compound structure, and that vary in the displacement of hydrogen atoms and electrons. Thus, two structures may be in equilibrium through the movement of π electrons and an atom (usually H). For example, enols and ketones are tautomers because they are rapidly interconverted by treatment with either acid or base. Another example of tautomerism is the aci-and nitro-forms of phenyl nitromethane, that are likewise formed by treatment with acid or base.

[0094] Tautomeric forms may be relevant to the attainment of the optimal chemical reactivity and biological activity of a compound of interest.

[0095] The compounds of this disclosure may possess one or more asymmetric centers; such compounds can therefore be produced as individual (*R*)-or (*S*)-stereoisomers or as mixtures thereof.

[0096] 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. Within the present disclosure, any open valency appearing on a carbon, oxygen, or nitrogen atom in any structure described herein indicates the presence of a hydrogen atom. Where a chiral center exists in a structure, but no specific stereochemistry is shown for that center, both enantiomers, separately or as a mixture, are encompassed by that structure. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art.

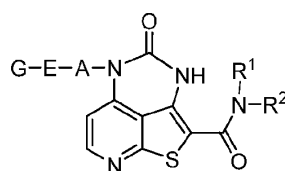
[0097] The present disclosure is directed to the use of a compound of Formula (III):



(III)

or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof. The compound of Formula (III) is also known as *N*-((1*R*,2*S*)-2-Acrylamidocyclopentyl)-5-(*S*)-(6-isobutyl-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide or compound of Formula (III).

[0098] The present disclosure is also directed to the use of compounds of Formula (I):



(I)

10 or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof;

wherein

R^1 is H or C_{1-6} alkyl;

R^2 is selected from the group consisting of: C_{0-6} alk-cycloalkyl optionally substituted with 1, 2, or

3 substituents each independently selected from the group consisting of: $NR^8-C(O)-C(R^3)=CR^4(R^5)$; NR^6R^7 ; OH; CN; oxo; $O-C_{1-6}$ alkyl; halogen; C_{1-6} alkyl; C_{1-6} haloalkyl; C_{1-6} alk-OH; C_{3-6} cycloalkyl; C_{1-6} alkaryl; SO_2C_{1-6} alkyl; SO_2C_{2-6} alkenyl; $NR^8-C(O)-C_{1-6}$ alk- NR^6R^7 ; $NR^8-C(O)-C_{1-6}$ alkyl; $NR^8-C(O)-O-C_{1-6}$ alkyl; $NR^8-C(O)-C_{3-6}$ cycloalkyl; $NR^8-C(O)H$; $NR^8-C(O)-C_{3-6}$ cycloalkyl; $NR^8-C(O)-C_{1-6}$ haloalkyl; $NR^8-C(O)-alkynyl$; $NR^8-C(O)-C_{6-10}aryl$; $NR^8-C(O)-heteroaryl$; $NR^8-C(O)-C_{1-6}alk-CN$; $NR^8-C(O)-C_{1-6}alk-OH$; $NR^8-C(O)-C_{1-6}alk-SO_2-C_{1-6}alkyl$; $NR^8-C(O)-O-C_{1-6}alkyl$; $NR^8-C(O)-C_{1-6}alk-NR^6R^7$; $NR^8-C(O)-C_{1-6}alk-O-C_{1-6}alkyl$, wherein the $C_{1-6}alk-$ is optionally substituted with a member selected from the group consisting of: OH, $OC_{1-6}alkyl$, and NR^6R^7 ; and $NR^8-C(O)-C_{0-6}alk-heterocycloalkyl$ wherein the $C_{0-6}alk$ is optionally substituted with oxo and the heterocycloalkyl is optionally substituted with $C_{1-6}alkyl$;

wherein R^6 and R^7 are each independently selected from the group consisting of:

H; C_{1-6} alkyl, C_{3-6} cycloalkyl, $C(O)H$, and CN;

R^3 is selected from the group consisting of: H, CN, halogen, C_{1-6} haloalkyl, and C_{1-6} alkyl;

5 R^4 and R^5 are each independently selected from the group consisting of: H; C_{0-6} alk-NR⁶R⁷; C_{1-6} alk-OH; C_{0-6} alk- C_{3-6} cycloalkyl optionally substituted with C_{1-6} alkyl; halogen; C_{1-6} alkyl; OC_{1-6} alkyl; NR⁶R⁷; C_{1-6} alk-O- C_{1-6} alkyl; C_{1-6} alk-NH- C_{0-6} alk-O- C_{1-6} alkyl; C_{0-6} alk-heterocycloalkyl optionally substituted with $C(O)C_{1-6}$ alkyl or C_{1-6} alkyl; C_{1-6} alk-NHSO₂- C_{1-6} alkyl; 10 C_{1-6} alk-SO₂- C_{1-6} alkyl; NHC(O)- C_{1-6} alkyl; and linker-PEG-Biotin;

R^8 is H or C_{1-6} alkyl;

A is selected from the group consisting of: a bond; pyridyl; phenyl; naphthalenyl; pyrimidinyl; pyrazinyl; pyridazinyl; benzo[d][1,3]dioxolyl optionally substituted with halogen; benzothiophenyl; and pyrazolyl; optionally substituted with 1, 2, or 3 substituents each

15 independently selected from the group consisting of: C_{1-6} alkyl; halogen; SF₅; OC_{1-6} alkyl; $C(O)-C_{1-6}$ alkyl; and C_{1-6} haloalkyl;

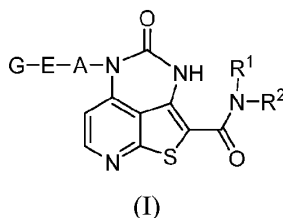
E is selected from the group consisting of: O, a bond, $C(O)-NH$, CH_2 , and CH_2-O ;

G is selected from the group consisting of: H; C_{3-6} cycloalkyl; phenyl; thiophenyl; C_{1-6} alkyl; pyrimidinyl; pyridyl; pyridazinyl; benzofuranyl; C_{1-6} haloalkyl; heterocycloalkyl that 20 contains an oxygen heteroatom; phenyl- CH_2-O -phenyl; C_{1-6} alk-O- C_{1-6} alkyl; NR⁶R⁷; SO₂ C_{1-6} alkyl; and OH; wherein the phenyl, pyridyl, pyridazinyl, benzofuranyl, or thiophenyl is optionally substituted with 1, 2, or 3 substituents each independently selected from the group consisting of: halogen; C_{1-6} alkyl, C_{1-6} haloalkyl, OC_{1-6} haloalkyl, C_{3-6} cycloalkyl, OC_{1-6} alkyl, CN, OH, C_{1-6} alk-O- C_{1-6} alkyl, $C(O)-NR^6R^7$, and $C(O)-C_{1-6}$ alkyl; and 25

stereoisomers and isotopic variants thereof; and

pharmaceutically acceptable salts thereof.

[0099] The present disclosure is also directed to the use of compounds of Formula (I):



or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof;

wherein

R¹ is H or C₁₋₆alkyl;

R¹ and R², together with the nitrogen atom to which they are attached, form an optionally

5 substituted ring that is a pyrrolidinyl ring or a piperidinyl ring;

wherein the pyrrolidinyl ring or piperidinyl ring formed from the joining of R¹ and R² are

optionally substituted with 1, 2, or 3 substituents each independently selected from the

group consisting of: NR⁸-C(O)-C(R³)=CR⁴(R⁵); NR⁶R⁷; OH; CN; oxo; O-C₁₋₆alkyl;

halogen; C₁₋₆alkyl; C₁₋₆haloalkyl; C₁₋₆alk-OH; C₃₋₆cycloalkyl; C₁₋₆alkaryl; SO₂C₁₋₆alkyl;

10 SO₂C₂₋₆alkenyl; -NR⁸-C(O)-C₁₋₆alk-NR⁶R⁷; NR⁸-C(O)-C₁₋₆alkyl; NR⁸-C(O)-O-C₁₋₆alkyl;

NR⁸-C(O)-C₃₋₆cycloalkyl; NR⁸-C(O)H; NR⁸-C(O)-C₁₋₆alkyl; NR⁸-C(O)-C₃₋

6cycloalkyl; NR⁸-C(O)-C₁₋₆haloalkyl; NR⁸-C(O)-alkynyl; NR⁸-C(O)-C₆₋₁₀aryl; NR⁸-C(O)-

heteroaryl; NR⁸-C(O)-C₁₋₆alk-CN; NR⁸-C(O)-C₁₋₆alk-OH; NR⁸-C(O)-C₁₋₆alk-SO₂-C₁₋

6alkyl; NR⁸-C(O)-O-C₁₋₆alkyl; NR⁸-C(O)-C₁₋₆alk-NR⁶R⁷; NR⁸-C(O)-C₁₋₆alk-O-C₁₋₆alkyl

15 wherein the C₁₋₆alk- is optionally substituted with OH, OC₁₋₆alkyl, or NR⁶R⁷; and

NR⁸-C(O)-C₀₋₆alk-heterocycloalkyl wherein the C₀₋₆alk is optionally substituted with oxo

and the heterocycloalkyl is optionally substituted with C₁₋₆alkyl;

wherein R⁶ and R⁷ are each independently selected from the group consisting of:

H, C₁₋₆alkyl, C₃₋₆cycloalkyl, C(O)H, and -CN;

20 R³ is selected from the group consisting of: H, CN, halogen, C₁₋₆haloalkyl, and C₁₋₆alkyl;

R⁴ and R⁵ are each independently selected from the group consisting of: H; C₀₋

6alk-NR⁶R⁷; C₁₋₆alk-OH; C₀₋₆alk-C₃₋₆cycloalkyl optionally substituted with

C₁₋₆alkyl; halogen; C₁₋₆alkyl; -OC₁₋₆alkyl; NR⁶R⁷; C₁₋₆alk-O-C₁₋₆alkyl;

25 C₁₋₆alk-NH-C₀₋₆alk-O-C₁₋₆alkyl; C₀₋₆alk-heterocycloalkyl optionally

substituted with C(O)C₁₋₆alkyl or C₁₋₆alkyl; C₁₋₆alk-NHSO₂-C₁₋₆alkyl;

C₁₋₆alk-SO₂-C₁₋₆alkyl; NHC(O)-C₁₋₆alkyl; or linker-PEG-Biotin;

R⁸ is H or C₁₋₆alkyl;

A is selected from the group consisting of: a bond; pyridyl; phenyl; naphthalenyl; pyrimidinyl;

30 pyrazinyl; pyridazinyl; benzo[d][1,3]dioxolyl optionally substituted with halogen;

benzothiophenyl; or pyrazolyl; optionally substituted with 1, 2, or 3 substituents

independently selected from the group consisting of C₁₋₆alkyl, halogen, SF₅, OC₁₋₆alkyl,

C(O)-C₁₋₆alkyl, and C₁₋₆haloalkyl;

E is selected from the group consisting of: O, a bond, C(O)-NH, CH₂, and CH₂-O;

G is selected from the group consisting of: H; C₃₋₆cycloalkyl; phenyl; thiophenyl; C₁₋₆alkyl;

pyrimidinyl; pyridyl; pyridazinyl; benzofuranyl; -C₁₋₆haloalkyl; heterocycloalkyl that

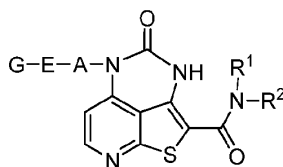
contains an oxygen heteroatom; phenyl-CH₂-O-phenyl; C₁₋₆alk-O-C₁₋₆alkyl; NR⁶R⁷;

5 SO₂C₁₋₆alkyl; or OH; wherein the phenyl, pyridyl, pyridazinyl, benzofuranyl, or thiophenyl is optionally substituted with 1, 2, or 3 substituents each independently selected from the group consisting of: halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, OC₁₋₆haloalkyl, C₃₋₆cycloalkyl, OC₁₋₆alkyl, CN, OH, C₁₋₆alk-O-C₁₋₆alkyl, C(O)-NR⁶R⁷, and C(O)-C₁₋₆alkyl; and

10 stereoisomers and isotopic variants thereof; and

pharmaceutically acceptable salts thereof.

[00100] The present disclosure is also directed to the use of compounds of Formula (I):



(I)

15 or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof;
wherein

R¹ is H;

R² is selected from the group consisting of: CH₂-cyclohexyl, wherein the cyclohexyl is optionally substituted with OH; 3-hydroxyadamantan-1-yl; and C₃₋₆cycloalkyl optionally substituted
20 with 1, 2, or 3 substituents each independently selected from the group consisting of: OH, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, OC₁₋₆alkyl, CN, NR⁶R⁷, NR⁸-C(O)H, NR⁸-C(O)-C₁₋₆alkyl, NR⁸-C(O)-C₁₋₆haloalkyl, NR⁸-C(O)-O-C₁₋₆alkyl, NR⁸-C(O)-C₁₋₆alk-OH, NR⁸-C(O)-C₁₋₆alk-NR⁶R⁷, and NR⁸-C(O)-C(R³)=CR⁴(R⁵); wherein

25 R³ is selected from the group consisting of: H, CN, halogen, C₁₋₆haloalkyl, and C₁₋₆alkyl;

R⁴ and R⁵ are each independently selected from the group consisting of: H; C₀₋₆alk-NR⁶R⁷; C₁₋₆alk-O-C₁₋₆alkyl; C₃₋₆cycloalkyl; heterocycloalkyl optionally substituted with C₁₋₆alkyl; and -linker-PEG-Biotin;

30 R⁶ and R⁷ are each independently selected from the group consisting of: H, C₁₋₆alkyl, C(O)H, and CN; and

R^8 is H;

or R^1 and R^2 , together with the nitrogen atom to which they are attached, form a pyrrolidinyl ring optionally substituted with NR^6R^7 , where R^6 and R^7 are each independently selected from the group consisting of H; C_{1-6} alkyl; $NR^8-C(O)-C_{1-6}$ alkyl; and $NR^8-C(O)-$

5 $C(R^3)=CR^4(R^5)$, wherein R^3 is H or CN, R^4 is H and R^5 is H or cyclopropyl;

A is selected from the group consisting of: pyridyl; phenyl; pyrimidinyl; pyrazinyl; pyridin-2(1H)-one; and pyridazinyl; wherein the A is optionally substituted with 1, 2, or 3 substituents each independently selected from the group consisting of: halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, and OC_{1-6} alkyl;

10 E is selected from the group consisting of: O, a bond, and CH_2 ;

G is selected from the group consisting of: H; halogen; C_{1-6} alkyl; C_{1-6} haloalkyl; $NH(C_{1-6}$ alkyl); C_{3-6} cycloalkyl; phenyl; pyrimidinyl; pyridyl; pyridazinyl; pyridin-2(1H)-one; heterocycloalkyl that contains an oxygen heteroatom; and phenyl- CH_2 -O-phenyl, wherein the -O-phenyl is substituted with CN; wherein the phenyl, pyridyl, pyridazinyl, and
15 pyridin-2(1H)-one is optionally substituted with 1, 2, or 3 substituents each independently selected from the group consisting of: halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, OC_{1-6} haloalkyl, and OC_{1-6} alkyl; and

stereoisomers or isotopic variant thereof; and
pharmaceutically acceptable salts thereof.

20 **[00101]** According to the disclosure, R^1 is H or C_{1-6} alkyl. In some aspects, R^1 is C_{1-6} alkyl, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, s-butyl, or t-butyl. In preferred aspects, R^1 is H.

[00102] According to the disclosure, R^2 is a C_{0-6} alk-cycloalkyl moiety that can be unsubstituted. In other aspects of the disclosure, R^2 is a C_{0-6} alk-cycloalkyl moiety substituted
25 with 1, 2, or 3 substituents, preferably 1 or 2 substituents, more preferably 1 substituent. In those aspects wherein R^2 is C_0 alk-cycloalkyl, the cycloalkyl is directly attached to the compound of Formula (I) through a bond. In those aspects wherein R^2 is a C_{1-6} alk-cycloalkyl moiety, the cycloalkyl moiety is attached to the compound of Formula (I) through an aliphatic linker having 1, 2, 3, 4, 5, or 6 carbon atoms, wherein the C_{1-6} alk includes, for example, $-CH_2-$, $-CH(CH_3)-$,
30 $CH(CH_3)-CH_2-$, and $-C(CH_3)_2-$. In preferred aspects, R^2 is C_{0-1} alk-cycloalkyl, for example C_0 alk-cycloalkyl (i.e., cycloalkyl) or C_1 alk-cycloalkyl (i.e., CH_2 -cycloalkyl).

[00103] In preferred aspects, the R² cycloalkyl moiety is a 3-, 4-, 5-, 6-, or 10-membered cycloalkyl, preferably a 5- or 6-membered cycloalkyl, with a 5-membered cycloalkyl being most preferred.

[00104] In some aspects of the disclosure, R² is C₀₋₆alk-cyclopropyl, preferably C₀ alk-cyclopropyl or C₁ alk-cyclopropyl, optionally substituted with 1, 2, or 3 substituents as recited herein. In more preferred aspects, R² is C₀₋₆alk-cyclopropyl, preferably C₀ alk-cyclopropyl or C₁ alk-cyclopropyl, substituted with 1 or 2 substituents as recited herein. The substituents can be attached through any position on the cyclopropyl ring.

[00105] In some aspects of the disclosure, R² is C₀₋₆alk-cyclobutyl, preferably C₀ alk-cyclobutyl or C₁ alk-cyclobutyl, optionally substituted with 1, 2, or 3 substituents as recited herein. In more preferred aspects, R² is C₀₋₆alk-cyclobutyl, preferably C₀ alk-cyclobutyl or C₁ alk-cyclobutyl, substituted with 1 or 2 substituents as recited herein. The substituents can be attached through any position on the cyclobutyl ring.

[00106] In preferred aspects of the disclosure, R² is C₀₋₆alk-cyclopentyl, preferably C₀ alk-cyclopentyl or C₁ alk-cyclopentyl, optionally substituted with 1, 2, or 3 substituents as recited herein. In more preferred aspects, R² is C₀₋₆alk-cyclopentyl, preferably C₀ alk-cyclopentyl or C₁ alk-cyclopentyl, substituted with 1 or 2 substituents as recited herein. The substituents can be attached through any position on the cyclopentyl ring.

[00107] In some aspects of the disclosure, R² is C₀₋₆alk-cyclohexyl, preferably C₀ alk-cyclohexyl or C₁ alk-cyclohexyl, optionally substituted with 1, 2, or 3 substituents as recited herein. In more preferred aspects, R² is C₀₋₆alk-cyclohexyl, preferably C₀ alk-cyclohexyl or C₁ alk-cyclohexyl, substituted with 1 or 2 substituents as recited herein. The substituents can be attached through any position on the cyclohexyl ring.

[00108] In some aspects of the disclosure, R² is C₀₋₆alk-adamantanyl, preferably C₀ alk-adamantanyl or C₁ alk-adamantanyl, optionally substituted with 1, 2, or 3 substituents as recited herein. In more preferred aspects, R² is C₀₋₆alk-adamantanyl, preferably C₀ alk-adamantanyl or C₁ alk-adamantanyl, substituted with 1 or 2 substituents as recited herein. The substituents can be attached through any position on the adamantanyl ring.

[00109] According to the disclosure, the R² cycloalkyl can be unsubstituted. In some aspects, the R² cycloalkyl is substituted with 1, 2, or 3 substituents. In preferred aspects, the R² cycloalkyl is substituted with 1 or 2 substituents, more preferably 1 substituent. In those aspects wherein the R² cycloalkyl is substituted, the substituents may be independently selected from the group consisting of NR⁸-C(O)-C(R³)=CR⁴(R⁵); NR⁶R⁷; OH; CN; oxo; O-C₁₋₆alkyl; halogen;

- C₁₋₆alkyl; C₁₋₆haloalkyl; C₁₋₆alk-OH; C₃₋₆cycloalkyl; C₁₋₆alkaryl; SO₂C₁₋₆alkyl;
 SO₂C₂₋₆alkenyl; NR⁸-C(O)-C₁₋₆alk-NR⁶R⁷; NR⁸-C(O)-C₁₋₆alkyl; NR⁸-C(O)-O-C₁₋₆alkyl;
 NR⁸-C(O)-C₃₋₆cycloalkyl; NR⁸-C(O)H; NR⁸-C(O)-C₃₋₆cycloalkyl;
 NR⁸-C(O)-C₁₋₆haloalkyl; NR⁸-C(O)-alkynyl; NR⁸-C(O)-C₆₋₁₀aryl; NR⁸-C(O)-heteroaryl;
 5 NR⁸-C(O)-C₁₋₆alk-CN; NR⁸-C(O)-C₁₋₆alk-OH; NR⁸-C(O)-C₁₋₆alk-SO₂-C₁₋₆alkyl;
 NR⁸-C(O)-C₁₋₆alk-NR⁶R⁷; NR⁸-C(O)-C₁₋₆alk-O-C₁₋₆alkyl wherein the C₁₋₆alk- is optionally
 substituted with OH, OC₁₋₆alkyl, or NR⁶R⁷; NR⁸-C(O)-C₀₋₆alk-heterocycloalkyl wherein the –
 alk- is optionally substituted with oxo and the heterocycloalkyl is optionally substituted with
 C₁₋₆alkyl; and wherein R³, R⁴, R⁵, R⁶, R⁷, and R⁸ are as defined herein.
- 10 **[00110]** In some aspects, the R² cycloalkyl is substituted with an oxo moiety, for
 example one oxo moiety. In those aspects wherein the R² cycloalkyl is substituted with an oxo
 moiety, the cycloalkyl ring may optionally be substituted with one or two additional substituents
 as defined herein for the R² substituents.
- [00111]** In some aspects, the R² cycloalkyl is substituted with a halogen, for example a
 15 fluorine or chlorine or bromine. In some aspects, the R² cycloalkyl is substituted with one or two
 halogens, preferably one halogen. In those aspects wherein the R² cycloalkyl is substituted with
 a halogen, the cycloalkyl ring may optionally be substituted with one or two additional
 substituents as defined herein for the R² substituents.
- [00112]** In some aspects, the R² cycloalkyl is substituted with CN. In some aspects, the
 20 R² cycloalkyl is substituted with one or two CN, preferably one CN. In those aspects wherein
 the R² cycloalkyl is substituted with CN, the cycloalkyl ring may optionally be substituted with
 one or two additional substituents as defined herein for the R² substituents.
- [00113]** In some aspects, the R² cycloalkyl is substituted with OH. In some aspects, the
 R² cycloalkyl is substituted with one or two OH, preferably one OH. In those aspects wherein
 25 the R² cycloalkyl is substituted with OH, the cycloalkyl ring may optionally be substituted with
 one or two additional substituents as defined herein for the R² substituents.
- [00114]** In some aspects, the R² cycloalkyl is substituted with NR⁶R⁷ wherein R⁶ and
 R⁷ are each independently H; C₁₋₆alkyl, C₃₋₆cycloalkyl; C(O)H; or CN. In preferred aspects, R⁶
 and R⁷ are each independently H or C₁₋₆alkyl. In those aspects wherein the R² cycloalkyl is
 30 substituted with NR⁶R⁷, the cycloalkyl ring may optionally be substituted with one or two
 additional substituents as defined herein for the R² substituents.
- [00115]** In some aspects, the R² cycloalkyl is substituted with C₁₋₆alkyl, for example,
 C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl. In some aspects, the R² cycloalkyl is

substituted with one or two C₁₋₆alkyl, preferably one C₁₋₆alkyl. In those aspects wherein the R² cycloalkyl is substituted with C₁₋₆alkyl, the cycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R² substituents.

[00116] In some aspects, the R² cycloalkyl is substituted with C₁₋₆alk-OH, for example, C₁₋₅alk-OH, C₁₋₄alk-OH, C₁₋₃alk-OH, C₁₋₂alk-OH, or C₁alk-OH, wherein the -OH moiety can be attached to any carbon of the C₁₋₆alk group, preferably the ω carbon. In some aspects, the R² cycloalkyl is substituted with one or two C₁₋₆alk-OH, preferably one C₁₋₆alk-OH. In those aspects wherein the R² cycloalkyl is substituted with C₁₋₆alk-OH, the cycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R² substituents.

[00117] In some aspects, the R² cycloalkyl is substituted with OC₁₋₆alkyl, for example, OC₁₋₅alkyl, OC₁₋₄alkyl, OC₁₋₃alkyl, OC₁₋₂alkyl, or OC₁alkyl. In some aspects, the R² cycloalkyl is substituted with one or two OC₁₋₆alkyl, preferably one OC₁₋₆alkyl. In those aspects wherein the R² cycloalkyl is substituted with OC₁₋₆alkyl, the cycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R² substituents.

[00118] In some aspects, the R² cycloalkyl is substituted with a C₃₋₆cycloalkyl moiety, for example, a cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl moiety. In some aspects, the R² cycloalkyl is substituted with one or two C₃₋₆cycloalkyl, preferably one C₃₋₆cycloalkyl. In those aspects wherein the R² cycloalkyl is substituted with C₃₋₆cycloalkyl, the cycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R² substituents.

[00119] In some aspects, the R² cycloalkyl is substituted with C₁₋₆alkaryl, for example, benzyl (i.e., CH₂-phenyl). In some aspects, the R² cycloalkyl is substituted with one or two C₁₋₆alkaryl, preferably one C₁₋₆alkaryl. In those aspects wherein the R² cycloalkyl is substituted with C₁₋₆alkaryl, the cycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R² substituents.

[00120] In some aspects, the R² cycloalkyl is substituted with SO₂C₁₋₆alkyl, for example, SO₂C₁₋₅alkyl, SO₂C₁₋₄alkyl, SO₂C₁₋₃alkyl, SO₂C₁₋₂alkyl, or SO₂C₁alkyl. In some aspects, the R² cycloalkyl is substituted with one or two SO₂C₁₋₆alkyl, preferably one SO₂C₁₋₆alkyl. In those aspects wherein the R² cycloalkyl is substituted with SO₂C₁₋₆alkyl, the cycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R² substituents.

[00121] In some aspects, the R^2 cycloalkyl is substituted with $SO_2C_{2-6}alkenyl$, for example, $-SO_2C_{2-5}alkenyl$, $SO_2C_{2-4}alkenyl$, $SO_2C_{2-3}alkenyl$, or $SO_2C_2alkenyl$. In some aspects, the R^2 cycloalkyl is substituted with one or two $SO_2C_{2-6}alkenyl$, preferably one $SO_2C_{2-6}alkenyl$. In those aspects wherein the R^2 cycloalkyl is substituted with $SO_2C_{2-6}alkenyl$, the cycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R^2 substituents.

[00122] In some aspects, the R^2 cycloalkyl is substituted with $NR^8-C(O)H$ wherein R^8 is H or $C_{1-6}alkyl$, for example, $C_{1-5}alkyl$, $C_{1-4}alkyl$, $C_{1-3}alkyl$, $C_{1-2}alkyl$, or C_1alkyl . In preferred aspects, R^8 is H. In some aspects, the R^2 cycloalkyl is substituted with one or two $NR^8-C(O)H$, preferably one $NR^8-C(O)H$. In those aspects wherein the R^2 cycloalkyl is substituted with $NR^8-C(O)H$, the cycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R^2 substituents.

[00123] In some aspects, the R^2 cycloalkyl is substituted with $NR^8-C(O)-C_{1-6}alkyl$, for example, $NR^8-C(O)-C_{1-5}alkyl$, $NR^8-C(O)-C_{1-4}alkyl$, $NR^8-C(O)-C_{1-3}alkyl$, $NR^8-C(O)-C_{1-2}alkyl$, or $NR^8-C(O)-C_1alkyl$, wherein R^8 is H or $C_{1-6}alkyl$, for example, $C_{1-5}alkyl$, $C_{1-4}alkyl$, $C_{1-3}alkyl$, $C_{1-2}alkyl$, or C_1alkyl . In preferred aspects, R^8 is H. In some aspects, the R^2 cycloalkyl is substituted with one or two $NR^8-C(O)-C_{1-6}alkyl$, preferably one $NR^8-C(O)-C_{1-6}alkyl$. In those aspects wherein the R^2 cycloalkyl is substituted with $NR^8-C(O)-C_{1-6}alkyl$, the cycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R^2 substituents.

[00124] In some aspects, the R^2 cycloalkyl is substituted with $NR^8-C(O)-C_{3-6}cycloalkyl$, for example, $NR^8-C(O)-cyclopropyl$, $NR^8-C(O)-cyclobutyl$, $NR^8-C(O)-cyclopentyl$, or $NR^8-C(O)-cyclohexyl$, wherein R^8 is H or $C_{1-6}alkyl$, for example, $C_{1-5}alkyl$, $C_{1-4}alkyl$, $C_{1-3}alkyl$, $C_{1-2}alkyl$, or C_1alkyl . In preferred aspects, R^8 is H. In some aspects, the R^2 cycloalkyl is substituted with one or two $NR^8-C(O)-C_{3-6}cycloalkyl$, preferably one $NR^8-C(O)-C_{3-6}cycloalkyl$. In those aspects wherein the R^2 cycloalkyl is substituted with $NR^8-C(O)-C_{3-6}cycloalkyl$, the cycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R^2 substituents.

[00125] In some aspects, the R^2 cycloalkyl is substituted with $C_{1-6}haloalkyl$, for example, $C_{1-5}haloalkyl$, $C_{1-4}haloalkyl$, $C_{1-3}haloalkyl$, $C_{1-2}haloalkyl$, or $C_1haloalkyl$, including CF_3 , CH_2CH_2F , and the like. In some aspects, the R^2 cycloalkyl is substituted with one or two $C_{1-6}haloalkyl$, preferably one $C_{1-6}haloalkyl$. In those aspects wherein the R^2 cycloalkyl is

substituted with C₁₋₆haloalkyl, the cycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R² substituents.

[00126] In some aspects, the R² cycloalkyl is substituted with NR⁸-C(O)-C₁₋₆haloalkyl, for example, NR⁸-C(O)-C₁₋₅haloalkyl, NR⁸-C(O)-C₁₋₄haloalkyl, NR⁸-C(O)-C₁₋₃haloalkyl, 5 NR⁸-C(O)-C₁₋₂haloalkyl, or NR⁸-C(O)-C₁haloalkyl, including NR⁸-C(O)-CF₃, NR⁸-C(O)-CH₂CH₂F, and the like, wherein R⁸ is H or C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl. In preferred aspects, R⁸ is H. In some aspects, the R² cycloalkyl is substituted with one or two NR⁸-C(O)-C₁₋₆haloalkyl, preferably one NR⁸-C(O)-C₁₋₆haloalkyl. In those aspects wherein the R² cycloalkyl is substituted with 10 NR⁸-C(O)-C₁₋₆haloalkyl, the cycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R² substituents.

[00127] In some aspects, the R² cycloalkyl is substituted with NR⁸-C(O)-C₂₋₆alkynyl, for example, NR⁸-C(O)-C₂₋₅alkynyl, NR⁸-C(O)-C₂₋₄alkynyl, NR⁸-C(O)-C₂₋₃alkynyl, or NR⁸-C(O)-C₂alkynyl, wherein R⁸ is H or C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, 15 C₁₋₂alkyl, or C₁alkyl. In preferred aspects, R⁸ is H. In some aspects, the R² cycloalkyl is substituted with one or two NR⁸-C(O)-C₂₋₆alkynyl, preferably one NR⁸-C(O)-C₂₋₆alkynyl. In those aspects wherein the R² cycloalkyl is substituted with NR⁸-C(O)-C₂₋₆alkynyl, the cycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R² substituents.

[00128] In some aspects, the R² cycloalkyl is substituted with NR⁸-C(O)-C₆₋₁₀aryl, for example, NR⁸-C(O)-phenyl or NR⁸-C(O)-naphthalenyl, wherein R⁸ is H or C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl. In preferred aspects, R⁸ is H. In some 20 aspects, the R² cycloalkyl is substituted with one or two NR⁸-C(O)-C₆₋₁₀aryl, preferably one NR⁸-C(O)-C₆₋₁₀aryl. In those aspects wherein the R² cycloalkyl is substituted with NR⁸-C(O)-C₆₋₁₀aryl, the cycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R² substituents. 25

[00129] In some aspects, the R² cycloalkyl is substituted with NR⁸-C(O)-heteroaryl, for example, NR⁸-C(O)-pyrrolyl, NR⁸-C(O)-thienyl, NR⁸-C(O)-oxazolyl, NR⁸-C(O)-pyrazolyl, NR⁸-C(O)-pyridyl, NR⁸-C(O)-pyrimidinyl, and the like, wherein R⁸ is H or C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl. In preferred aspects, R⁸ is H. In some aspects, 30 the R² cycloalkyl is substituted with one or two NR⁸-C(O)-heteroaryl, preferably one NR⁸-C(O)-heteroaryl. In those aspects wherein the R² cycloalkyl is substituted with NR⁸-C(O)-heteroaryl,

the cycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R² substituents.

[00130] In some aspects, the R² cycloalkyl is substituted with NR⁸-C(O)-C₁₋₆alk-CN, for example, NR⁸-C(O)-C₁₋₅alk-CN, NR⁸-C(O)-C₁₋₄alk-CN, NR⁸-C(O)-C₁₋₃alk-CN, NR⁸-C(O)-C₁₋₂alk-CN, or NR⁸-C(O)-C₁alk-CN, wherein R⁸ is H or C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl. In preferred aspects, R⁸ is H. In some aspects, the R² cycloalkyl is substituted with one or two NR⁸-C(O)-C₁₋₆alk-CN, preferably one NR⁸-C(O)-C₁₋₆alk-CN. In those aspects wherein the R² cycloalkyl is substituted with NR⁸-C(O)-C₁₋₆alk-CN, the cycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R² substituents.

[00131] In some aspects, the R² cycloalkyl is substituted with NR⁸-C(O)-C₁₋₆alk-OH, for example, NR⁸-C(O)-C₁₋₅alk-OH, NR⁸-C(O)-C₁₋₄alk-OH, NR⁸-C(O)-C₁₋₃alk-OH, NR⁸-C(O)-C₁₋₂alk-OH, or NR⁸-C(O)-C₁alk-OH, wherein R⁸ is H or C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl. In preferred aspects, R⁸ is H. In some aspects, the R² cycloalkyl is substituted with one or two NR⁸-C(O)-C₁₋₆alk-OH, preferably one NR⁸-C(O)-C₁₋₆alk-OH. In those aspects wherein the R² cycloalkyl is substituted with NR⁸-C(O)-C₁₋₆alk-OH, the cycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R² substituents.

[00132] In some aspects, the R² cycloalkyl is substituted with NR⁸-C(O)-C₁₋₆alk-SO₂-C₁₋₆alkyl, for example, NR⁸-C(O)-C₁₋₅alk-SO₂-C₁₋₅alkyl, NR⁸-C(O)-C₁₋₄alk-SO₂-C₁₋₄alkyl, NR⁸-C(O)-C₁₋₃alk-SO₂-C₁₋₃alkyl, NR⁸-C(O)-C₁₋₂alk-SO₂-C₁₋₂alkyl, or NR⁸-C(O)-C₁alk-SO₂-C₁alkyl, wherein R⁸ is H or C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl. In preferred aspects, R⁸ is H. In some aspects, the R² cycloalkyl is substituted with one or two NR⁸-C(O)-C₁₋₆alk-SO₂-C₁₋₆alkyl, preferably one NR⁸-C(O)-C₁₋₆alk-SO₂-C₁₋₆alkyl. In those aspects wherein the R² cycloalkyl is substituted with NR⁸-C(O)-C₁₋₆alk-SO₂-C₁₋₆alkyl, the cycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R² substituents.

[00133] In some aspects, the R² cycloalkyl is substituted with NR⁸-C(O)-O-C₁₋₆alkyl, for example, NR⁸-C(O)-O-C₁₋₅alkyl, NR⁸-C(O)-O-C₁₋₄alkyl, NR⁸-C(O)-O-C₁₋₃alkyl, NR⁸-C(O)-O-C₁₋₂alkyl, or NR⁸-C(O)-O-C₁alkyl, wherein R⁸ is H or C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl. In preferred aspects, R⁸ is H. In some aspects, the R² cycloalkyl is substituted with one or two NR⁸-C(O)-O-C₁₋₆alkyl, preferably one NR⁸-C(O)-O-C₁₋₆alkyl. In those aspects wherein the R² cycloalkyl is substituted with

NR⁸-C(O)-O-C₁₋₆alkyl, the cycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R² substituents.

[00134] In some aspects, the R² cycloalkyl is substituted with NR⁸-C(O)-C₁₋₆alk-NR⁶R⁷, for example, NR⁸-C(O)-C₁₋₅alk-NR⁶R⁷, NR⁸-C(O)-C₁₋₄alk-NR⁶R⁷, NR⁸-C(O)-C₁₋₃alk-NR⁶R⁷, NR⁸-C(O)-C₁₋₂alk-NR⁶R⁷, or NR⁸-C(O)-C₁alk-NR⁶R⁷, wherein R⁶ and R⁷ are each independently H; C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl; C₃₋₆cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; C(O)H, or CN. In preferred aspects, R⁶ and R⁷ are each independently H, C₁₋₆alkyl; or C₃₋₆cycloalkyl, with H and C₁₋₆alkyl being preferred, and H and C₁₋₂alkyl being more preferred.

In these aspects, R⁸ is H or C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl. In preferred aspects, R⁸ is H. In some aspects, the R² cycloalkyl is substituted with one or two NR⁸-C(O)-C₁₋₆alk-NR⁶R⁷, preferably one NR⁸-C(O)-C₁₋₆alk-NR⁶R⁷. In those aspects wherein the R² cycloalkyl is substituted with NR⁸-C(O)-C₁₋₆alk-NR⁶R⁷, the cycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R² substituents.

[00135] In some aspects, the R² cycloalkyl is substituted with NR⁸-C(O)-C₁₋₆alk-O-C₁₋₆alkyl, for example, NR⁸-C(O)-C₁₋₅alk-O-C₁₋₅alkyl, NR⁸-C(O)-C₁₋₄alk-O-C₁₋₄alkyl, NR⁸-C(O)-C₁₋₃alk-O-C₁₋₃alkyl, NR⁸-C(O)-C₁₋₂alk-O-C₁₋₂alkyl, or NR⁸-C(O)-C₁alk-O-C₁alkyl, wherein R⁸ is H or C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl. In preferred aspects, R⁸ is H. In certain aspects wherein the R² cycloalkyl is substituted with NR⁸-C(O)-C₁₋₆alk-O-C₁₋₆alkyl, the C₁₋₆alk- is optionally substituted with OH; OC₁₋₆alkyl, for example, OC₁₋₅alkyl, OC₁₋₄alkyl, OC₁₋₃alkyl, OC₁₋₂alkyl, or OC₁alkyl; or NR⁶R⁷, wherein R⁶ and R⁷ are each independently H; C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl; C₃₋₆cycloalkyl; C(O)H, or CN. In preferred aspects, R⁶ and R⁷ are each independently H, C₁₋₆alkyl; or C₃₋₆cycloalkyl, with H and C₁₋₆alkyl being preferred, and H and C₁₋₂alkyl being more preferred. In some aspects, the C₁₋₆alk- of the NR⁸-C(O)-C₁₋₆alk-O-C₁₋₆alkyl moiety is substituted with OH. In other aspects, the C₁₋₆alk- is substituted with OC₁₋₆alkyl, for example, OC₁₋₅alkyl, OC₁₋₄alkyl, OC₁₋₃alkyl, OC₁₋₂alkyl, or OC₁alkyl. In some aspects, the R² cycloalkyl is substituted with one or two NR⁸-C(O)-C₁₋₆alk-O-C₁₋₆alkyl, preferably one NR⁸-C(O)-C₁₋₆alk-O-C₁₋₆alkyl. In those aspects wherein the R² cycloalkyl is substituted with NR⁸-C(O)-C₁₋₆alk-O-C₁₋₆alkyl, the cycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R² substituents.

[00136] In some aspects, the R^2 cycloalkyl is substituted with $NR^8-C(O)-C_{0-6}alk-heterocycloalkyl$, for example, $NR^8-C(O)-C_{0-5}alk-heterocycloalkyl$, $NR^8-C(O)-C_{0-4}alk-heterocycloalkyl$, $NR^8-C(O)-C_{0-3}alk-heterocycloalkyl$, $NR^8-C(O)-C_{0-2}alk-heterocycloalkyl$, $NR^8-C(O)-C_{0-1}alk-heterocycloalkyl$,
 5 $NR^8-C(O)-C_1alk-heterocycloalkyl$, or $NR^8-C(O)-C_0alk-heterocycloalkyl$, wherein R^8 is H or $C_{1-6}alkyl$, for example, $C_{1-5}alkyl$, $C_{1-4}alkyl$, $C_{1-3}alkyl$, $C_{1-2}alkyl$, or C_1alkyl . In preferred aspects, R^8 is H. Preferred substituent heterocycloalkyl groups include tetrahydrofuranyl, piperidinyl, pyrrolidinyl, and the like. In certain aspects wherein the R^2 cycloalkyl is substituted with $NR^8-C(O)-C_{1-6}alk-heterocycloalkyl$ the $C_{1-6}alk-$ is optionally substituted with oxo. In certain aspects
 10 wherein the R^2 cycloalkyl is substituted with $NR^8-C(O)-C_{0-6}alk-heterocycloalkyl$, the substituent heterocycloalkyl moiety can be unsubstituted or substituted with $C_{1-6}alkyl$, for example, $C_{1-5}alkyl$, $C_{1-4}alkyl$, $C_{1-3}alkyl$, $C_{1-2}alkyl$, or C_1alkyl . In those aspects wherein the R^2 cycloalkyl is substituted with $C(O)-C_{0-6}alk-heterocycloalkyl$, the R^2 cycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R^2 substituents.

[00137] In some aspects, the R^2 cycloalkyl is substituted with $NR^8-C(O)-C(R^3)=CR^4(R^5)$, wherein R^3 , R^4 , and R^5 are as described herein and R^8 is H or $C_{1-6}alkyl$, for example, $C_{1-5}alkyl$, $C_{1-4}alkyl$, $C_{1-3}alkyl$, $C_{1-2}alkyl$, or C_1alkyl . In preferred aspects, R^8 is H. In these aspects, R^3 is H; CN; halogen; $C_{1-6}haloalkyl$; or $C_{1-6}alkyl$. In some aspects, R^3 is H. In other aspects, R^3 is CN. In still other aspects, R^3 is halogen, for example F or Cl. In yet other
 20 aspects, R^3 is $C_{1-6}haloalkyl$, for example, $C_{1-5}haloalkyl$, $C_{1-4}haloalkyl$, $C_{1-3}haloalkyl$, $C_{1-2}haloalkyl$, or $C_1haloalkyl$, including CF_3 , CH_2CH_2F , and the like. In further aspects, R^3 is $C_{1-6}alkyl$, for example, $C_{1-5}alkyl$, $C_{1-4}alkyl$, $C_{1-3}alkyl$, $C_{1-2}alkyl$, or C_1alkyl . In those aspects wherein the R^2 cycloalkyl is substituted with $NR^8-C(O)-C(R^3)=CR^4(R^5)$, the cycloalkyl ring may optionally be substituted with one or two additional substituents as defined herein for the R^2
 25 substituents.

[00138] In preferred aspects, the R^2 cycloalkyl is substituted with $NR^8-C(O)-C(R^3)=CR^4(R^5)$; $NR^8-C(O)-C_{1-6}alk-NR^6R^7$; $NR^8-C(O)-C_{1-6}alkyl$; or NR^6R^7 . In more preferred aspects, the R^2 cycloalkyl is substituted with $NR^8-C(O)-C(R^3)=CR^4(R^5)$. In other preferred aspects, the R^2 cycloalkyl is substituted with $NR^8-C(O)-C_{1-6}alk-NR^6R^7$; $NR^8-C(O)-C_{1-6}alkyl$; or
 30 NR^6R^7 ; wherein R^6 and R^7 are each independently H or $C_{1-6}alkyl$.

[00139] In some preferred aspects, R^2 is $CH_2-cyclohexyl$, wherein the cyclohexyl is optionally substituted with OH; 3-hydroxyadamantan-1-yl; or $C_{3-6}cycloalkyl$ optionally substituted with 1, 2, or 3 substituents each independently selected from the group consisting of:

OH, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, OC₁₋₆alkyl, CN, NR⁶R⁷, NR⁸-C(O)H, NR⁸-C(O)-C₁₋₆alkyl, NR⁸-C(O)-C₁₋₆haloalkyl, NR⁸-C(O)-O-C₁₋₆alkyl, NR⁸-C(O)-C₁₋₆alk-OH, NR⁸-C(O)-C₁₋₆alk-NR⁶R⁷, and NR⁸-C(O)-C(R³)=CR⁴(R⁵); wherein R³ is selected from the group consisting of: H, CN, halogen, C₁₋₆haloalkyl, and C₁₋₆alkyl; R⁴ and R⁵ are each independently selected from the group consisting of: H; C₀₋₆alk-NR⁶R⁷; C₁₋₆alk-O-C₁₋₆alkyl; C₃₋₆cycloalkyl; heterocycloalkyl optionally substituted with C₁₋₆alkyl; and -linker-PEG-Biotin; R⁶ and R⁷ are each independently selected from the group consisting of: H, C₁₋₆alkyl, C(O)H, and CN; and R⁸ is H. In some aspects, the R² is substituted with 1 or 2 substituents. In some aspects, the R² is substituted with at least one substituent, preferably 1 or 2 substituents, independently selected from the group consisting of OH, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, OC₁₋₆alkyl, and CN.

[00140] In some preferred aspects, R² is CH₂-cyclohexyl. In other preferred aspects, R² is CH₂-cyclohexyl wherein the cyclohexyl is substituted with OH.

[00141] In some preferred aspects, R² is 3-hydroxyadamantan-1-yl.

[00142] In other preferred aspects, R² is C₃₋₆cycloalkyl. In some other preferred aspects, R² is C₃₋₆cycloalkyl substituted with 1, 2, or 3 substituents. Those substituents can be independently selected from the group consisting of OH, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, OC₁₋₆alkyl, CN, NR⁶R⁷, NR⁸-C(O)H, NR⁸-C(O)-C₁₋₆alkyl, NR⁸-C(O)-C₁₋₆haloalkyl, NR⁸-C(O)-O-C₁₋₆alkyl, NR⁸-C(O)-C₁₋₆alk-OH, NR⁸-C(O)-C₁₋₆alk-NR⁶R⁷, and NR⁸-C(O)-C(R³)=CR⁴(R⁵).

[00143] In those aspects employing R⁴ and R⁵, that is, those aspects wherein the R² cycloalkyl is substituted with NR⁸-C(O)-C(R³)=CR⁴(R⁵), R⁴ and R⁵ are each independently H; halogen; C₀₋₆alk-NR⁶R⁷; C₁₋₆alkyl; OC₁₋₆alkyl; C₀₋₆alk-C₃₋₆cycloalkyl optionally substituted with C₁₋₆alkyl; C₀₋₆alk-heterocycloalkyl optionally substituted with -C(O)C₁₋₆alkyl or C₁₋₆alkyl; C₁₋₆alk-OH; C₁₋₆alk-O-C₁₋₆alkyl; C₁₋₆alk-NH-C₀₋₆alk-O-C₁₋₆alkyl; C₁₋₆alk-NHSO₂-C₁₋₆alkyl; -C₁₋₆alk-SO₂-C₁₋₆alkyl; -NHC(O)-C₁₋₆alkyl; or linker-PEG-Biotin.

[00144] Within the scope of this disclosure, the double bond present in -NR⁸-C(O)-C(R³)=CR⁴(R⁵) may be of the *Z* or *E* configuration.

[00145] In some aspects, neither R⁴ nor R⁵ is H.

[00146] In most preferred aspects, each of R⁴ and R⁵ is H.

[00147] In some aspects, one of R⁴ and R⁵ is H. In certain of these aspects, the other of R⁴ and R⁵ is halogen, for example F or Cl.

[00148] In some aspects, one of R⁴ and R⁵ is H. In certain of these aspects, the other of R⁴ and R⁵ is C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl.

[00149] In some aspects, one of R^4 and R^5 is H. In certain of these aspects, the other of R^4 and R^5 is $OC_{1-6}alkyl$, for example, $OC_{1-5}alkyl$, $OC_{1-4}alkyl$, $OC_{1-3}alkyl$, $OC_{1-2}alkyl$, or $OC_{1}alkyl$.

[00150] In some aspects, one of R^4 and R^5 is H. In certain of these aspects, the other of R^4 and R^5 is $C_{0-6}alk-C_{3-6}cycloalkyl$, for example, $C_{0-5}alk-C_{3-5}cycloalkyl$, $C_{0-4}alk-C_{3-4}cycloalkyl$, $C_{0-3}alk-C_{3-3}cycloalkyl$, $C_{0-2}alk-C_{3-6}cycloalkyl$, $C_{0-1}alk-C_{3-6}cycloalkyl$, $C_{0}alk-C_{3-6}cycloalkyl$ or $C_{1}alk-C_{3-6}cycloalkyl$. In these aspects, the cycloalkyl moiety can be unsubstituted or can be substituted with $C_{1-6}alkyl$, for example, $C_{1-5}alkyl$, $C_{1-4}alkyl$, $C_{1-3}alkyl$, $C_{1-2}alkyl$, or $C_{1}alkyl$. The substitution can be a spiro-substitution or a non-spiro-substitution.

[00151] In some aspects, one of R^4 and R^5 is H. In certain of these aspects, the other of R^4 and R^5 is $C_{0-6}alk-heterocycloalkyl$, for example, $C_{1-6}alk-heterocycloalkyl$, $C_{0-4}alk-heterocycloalkyl$, $C_{0-3}alk-heterocycloalkyl$, $C_{0-2}alk-heterocycloalkyl$, $C_{0-1}alk-heterocycloalkyl$, $C_{1}alk-heterocycloalkyl$, or $C_{0}alk-heterocycloalkyl$. In these aspects, the substituent heterocycloalkyl is preferably an oxygen-containing heterocycloalkyl, for example, tetrahydropyranyl, tetrahydrofuranyl, or oxetanyl. In other aspects, the heterocycloalkyl is a nitrogen-containing heterocycloalkyl, for example, pyrrolidinyl, aziridinyl, or piperidinyl. In certain of these aspects, the substituent heterocycloalkyl can be substituted with $C(O)C_{1-6}alkyl$, for example, $C(O)C_{1-5}alkyl$, $C(O)C_{1-4}alkyl$, $C(O)C_{1-3}alkyl$, $C(O)C_{1-2}alkyl$, or $C(O)C_{1}alkyl$. In other aspects, the substituent heterocycloalkyl can be substituted with $C_{1-6}alkyl$, for example, $C_{1-5}alkyl$, $C_{1-4}alkyl$, $C_{1-3}alkyl$, $C_{1-2}alkyl$, or $C_{1}alkyl$.

[00152] In some aspects, one of R^4 and R^5 is H. In certain of these aspects, the other of R^4 and R^5 is $C_{1-6}alk-OH$, for example, $C_{1-5}alk-OH$, $C_{1-4}alk-OH$, $C_{1-3}alk-OH$, $C_{1-2}alk-OH$, or $C_{1}alk-OH$. The OH moiety can be attached to any carbon of the $C_{1-6}alk$ group, preferably the ω carbon.

[00153] In some aspects, one of R^4 and R^5 is H. In certain of these aspects, the other of R^4 and R^5 is $C_{0-6}alk-NR^6R^7$, for example, $C_{0-5}alk-NR^6R^7$, $C_{0-4}alk-NR^6R^7$, $C_{0-3}alk-NR^6R^7$, $C_{0-2}alk-NR^6R^7$, $C_{0-1}alk-NR^6R^7$, $C_{1}alk-NR^6R^7$, or $C_{0}alk-NR^6R^7$, wherein R^6 and R^7 are each independently H; $C_{1-6}alkyl$, for example, $C_{1-5}alkyl$, $C_{1-4}alkyl$, $C_{1-3}alkyl$, $C_{1-2}alkyl$, or $C_{1}alkyl$; $C_{3-6}cycloalkyl$, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; $C(O)H$; or CN. In preferred aspects, R^6 and R^7 are each independently H; $C_{1-6}alkyl$; or $C_{3-6}cycloalkyl$, more preferably, R^6 and R^7 are each independently H or $C_{1-6}alkyl$.

[00154] In some aspects, one of R^4 and R^5 is H. In certain of these aspects, the other of R^4 and R^5 is $C_{1-6}alk-O-C_{1-6}alkyl$, for example, $C_{1-5}alk-O-C_{1-5}alkyl$, $C_{1-4}alk-O-C_{1-4}alkyl$, $C_{1-3}alk-O-C_{1-3}alkyl$, $C_{1-2}alk-O-C_{1-2}alkyl$, or $C_{1-1}alk-O-C_{1-1}alkyl$.

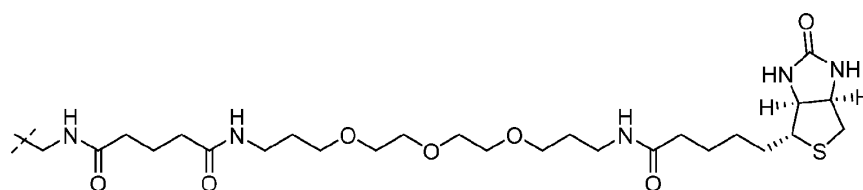
[00155] In some aspects, one of R^4 and R^5 is H. In certain of these aspects, the other of R^4 and R^5 is $C_{1-6}alk-NH-C_{0-6}alk-O-C_{1-6}alkyl$, for example, $C_{1-5}alk-NH-C_{0-6}alk-O-C_{1-5}alkyl$, $C_{1-4}alk-NH-C_{0-6}alk-O-C_{1-4}alkyl$, $C_{1-3}alk-NH-C_{0-6}alk-O-C_{1-3}alkyl$, $C_{1-2}alk-NH-C_{0-6}alk-O-C_{1-2}alkyl$, $C_{1-1}alk-NH-C_{0-6}alk-O-C_{1-1}alkyl$, $C_{1-5}alk-NH-C_{0-6}alk-O-C_{1-5}alkyl$, $C_{1-4}alk-NH-C_{1-5}alk-O-C_{1-4}alkyl$, $C_{1-3}alk-NH-C_{1-4}alk-O-C_{1-3}alkyl$, $C_{1-2}alk-NH-C_{1-3}alk-O-C_{1-2}alkyl$, $C_{1-1}alk-NH-C_{1-2}alk-O-C_{1-1}alkyl$, or $C_{1-6}alk-NH-C_{0-6}alk-O-C_{1-6}alkyl$.

[00156] In some aspects, one of R^4 and R^5 is H. In certain of these aspects, the other of R^4 and R^5 is $C_{1-6}alk-NHSO_2-C_{1-6}alkyl$, for example, $C_{1-5}alk-NHSO_2-C_{1-5}alkyl$, $C_{1-4}alk-NHSO_2-C_{1-4}alkyl$, $C_{1-3}alk-NHSO_2-C_{1-3}alkyl$, $C_{1-2}alk-NHSO_2-C_{1-2}alkyl$, or $C_{1-1}alk-NHSO_2-C_{1-1}alkyl$.

[00157] In some aspects, one of R^4 and R^5 is H. In certain of these aspects, the other of R^4 and R^5 is $C_{1-6}alk-SO_2-C_{1-6}alkyl$, for example, $C_{1-5}alk-SO_2-C_{1-5}alkyl$, $C_{1-4}alk-SO_2-C_{1-4}alkyl$, $C_{1-3}alk-SO_2-C_{1-3}alkyl$, $C_{1-2}alk-SO_2-C_{1-2}alkyl$, or $C_{1-1}alk-SO_2-C_{1-1}alkyl$.

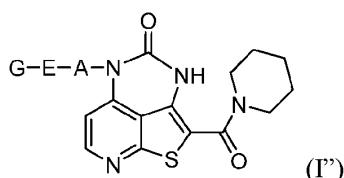
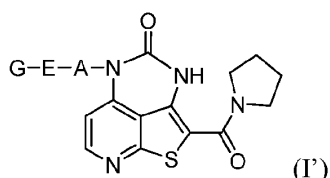
[00158] In some aspects, one of R^4 and R^5 is H. In certain of these aspects, the other of R^4 and R^5 is $NHC(O)-C_{1-6}alkyl$, for example, $NHC(O)-C_{1-5}alkyl$, $NHC(O)-C_{1-4}alkyl$, $NHC(O)-C_{1-3}alkyl$, $NHC(O)-C_{1-2}alkyl$, or $NHC(O)-C_{1-1}alkyl$.

[00159] In some aspects, one of R^4 and R^5 is H. In certain of these aspects, the other of R^4 and R^5 is linker-PEG-Biotin, preferably



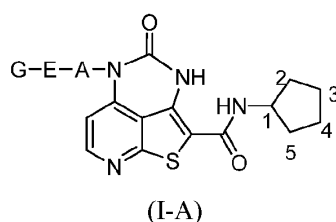
[00160] In preferred aspects, one of R^4 and R^5 is H and the other of R^4 and R^5 is $C_{1-6}alkyl$ (e.g., methyl, t-butyl); cycloalkyl (e.g., cyclopropyl); $C_{1-6}alk-NR^6R^7$ (e.g., CH_2-NH_2 , CH_2-NHCH_3 , $CH_2-N(CH_3)_2$, $C(CH_3)_2-NH_2$, $C(CH_3)_2-NHCH_3$, $C(CH_3)_2-N(CH_3)_2$; $C_{1-6}alk-O-C_{1-6}alkyl$ (e.g., $C(CH_3)_2-OCH_3$, $C(CH_3)_2-OCH_2CH_3$); $C_{0-6}alk$ -heterocycloalkyl substituted with $C_{1-6}alkyl$ (e.g., $C(CH_3)$ -oxetanyl).

[00161] In some aspects, or R^1 and R^2 , together with the nitrogen atom to which they are attached, form an optionally substituted ring that is a pyrrolidinyl ring or a piperidinyl ring, for example, compounds of Formula (I)' or Formula (I''):



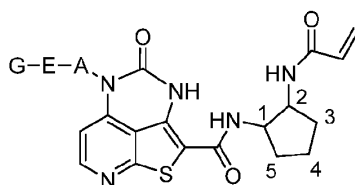
- 5 In these aspects, ring formed by the joining of R^1 and R^2 can be unsubstituted. In some aspects, the ring formed by the joining of R^1 and R^2 is substituted with 1, 2, or 3 substituents. In preferred aspects, the ring formed by the joining of R^1 and R^2 is substituted with 1 or 2 substituents, more preferably 1 substituent. In those aspects wherein the ring formed by the joining of R^1 and R^2 is substituted, the substituents may be independently selected from the
- 10 group consisting of $NR^8-C(O)-C(R^3)=CR^4(R^5)$; NR^6R^7 ; OH; CN; oxo; O- C_{1-6} alkyl; halogen; C_{1-6} alkyl; C_{1-6} haloalkyl; C_{1-6} alk-OH; C_{3-6} cycloalkyl; C_{1-6} alkaryl; SO_2C_{1-6} alkyl; SO_2C_{2-6} alkenyl; $NR^8-C(O)-C_{1-6}$ alk- NR^6R^7 ; $NR^8-C(O)-C_{1-6}$ alkyl; $NR^8-C(O)-O-C_{1-6}$ alkyl; $NR^8-C(O)-C_{3-6}$ cycloalkyl; $NR^8-C(O)H$; $NR^8-C(O)-C_{3-6}$ cycloalkyl; $NR^8-C(O)-C_{1-6}$ haloalkyl; $NR^8-C(O)$ -alkynyl; $NR^8-C(O)-C_{6-10}$ aryl; $NR^8-C(O)$ -heteroaryl;
- 15 $NR^8-C(O)-C_{1-6}$ alk-CN; $NR^8-C(O)-C_{1-6}$ alk-OH; $NR^8-C(O)-C_{1-6}$ alk- SO_2-C_{1-6} alkyl; $NR^8-C(O)-C_{1-6}$ alk- NR^6R^7 ; $NR^8-C(O)-C_{1-6}$ alk-O- C_{1-6} alkyl wherein the C_{1-6} alk- is optionally substituted with -OH, OC_{1-6} alkyl, or NR^6R^7 ; $NR^8-C(O)-C_{0-6}$ alk-heterocycloalkyl wherein the C_{0-6} alk- is optionally substituted with oxo and the heterocycloalkyl is optionally substituted with C_{1-6} alkyl; and wherein R^3 , R^4 , R^5 , R^6 , R^7 , and R^8 are as defined herein.

- 20 [00162] A preferred subgenus of Formula (I) is a compound of Formula (IA):



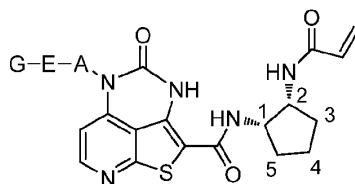
wherein the cyclopentyl ring is substituted at the 2 position with any of the R^2 substituents defined herein.

- 25 [00163] Other preferred subgenera of Formula (I) are:



(I-B-1)

and



(I-B-2)

5 [00164] Within the scope of the disclosure, A can be a bond. Also within the scope of the disclosure, A can be pyridyl; phenyl; naphthalenyl; pyrimidinyl; pyrazinyl; pyridazinyl; benzo[d][1,3]dioxolyl optionally substituted with halogen; benzothiophenyl; or pyrazolyl. Also within the disclosure, A can be pyridyl; phenyl; pyrimidinyl; pyrazinyl; pyridine-2(1H)-one, or
 10 pyridazinyl. Also according to the disclosure, any of the A moieties (excluding a bond) can be unsubstituted or substituted with 1, 2, or 3 substituents, preferably 1 or 2 substituents, more preferably 1 substituent, independently selected from the group consisting of C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl; halogen, for example F or Cl; SF₅; OC₁₋₆alkyl, for example, OC₁₋₅alkyl, OC₁₋₄alkyl, OC₁₋₃alkyl, OC₁₋₂alkyl, or OC₁alkyl;
 15 C(O)-C₁₋₆alkyl, for example, C(O)-C₁₋₅alkyl, C(O)-C₁₋₄alkyl, C(O)-C₁₋₃alkyl, C(O)-C₁₋₂alkyl, or C(O)-C₁alkyl; and C₁₋₆haloalkyl, for example, C₁₋₅haloalkyl, C₁₋₄haloalkyl, C₁₋₃haloalkyl, C₁₋₂haloalkyl, or C₁haloalkyl, including CF₃, CH₂CH₂F, and the like. Preferably, the A moieties can be substituted with 1, 2, or 3 substituents, preferably 1 or 2 substituents, independently selected from the group consisting of halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, and OC₁₋₆alkyl.
 20

[00165] In some aspects, A is pyridyl. The pyridyl can be attached to any of the compounds of Formula (I) (or its subgenera) through any ring carbon atom, but preferably it attached through the 2- or 3-position carbon. Preferably, the pyridyl is substituted with one or two substituents, preferably one substituent. The pyridyl substituent can be attached to any ring
 25 carbon atom of the pyridyl ring. In those aspects wherein the pyridyl is attached to the compound of Formula (I) through the 3-position carbon, the substituent is preferably attached to

the pyridyl at the 2- or 4-position. The pyridyl can be substituted at any available ring carbon atom with C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl. The pyridyl can be substituted at any available ring carbon atom with halogen, for example F or Cl. The pyridyl can be substituted at any available ring carbon atom with SF₅. The pyridyl can be substituted at any available ring carbon atom with OC₁₋₆alkyl, for example, OC₁₋₅alkyl, OC₁₋₄alkyl, OC₁₋₃alkyl, OC₁₋₂alkyl, or OC₁alkyl. The pyridyl can be substituted at any available ring carbon atom with C(O)-C₁₋₆alkyl, for example, C(O)-C₁₋₅alkyl, C(O)-C₁₋₄alkyl, C(O)-C₁₋₃alkyl, C(O)-C₁₋₂alkyl, or C(O)-C₁alkyl. The pyridyl can be substituted at any available ring carbon atom with C₁₋₆haloalkyl, for example, C₁₋₅haloalkyl, C₁₋₄haloalkyl, C₁₋₃haloalkyl, C₁₋₂haloalkyl, or C₁haloalkyl, including CF₃, CH₂CH₂F, and the like. Preferred substituents wherein A is pyridyl include C₁₋₆alkyl, with C₁alkyl being most preferred, and with one C₁alkyl substituent being more preferred. Other preferred substituents include halogen, in particular F and Cl.

[00166] In some aspects, A is phenyl. Preferably, the phenyl is substituted with one or two substituents, preferably one substituent. The phenyl can be substituted at any available ring carbon atom with C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl. The phenyl can be substituted at any available ring carbon atom with halogen, for example F or Cl. The phenyl can be substituted at any available ring carbon atom with -SF₅. The phenyl can be substituted at any available ring carbon atom with OC₁₋₆alkyl, for example, OC₁₋₅alkyl, OC₁₋₄alkyl, OC₁₋₃alkyl, OC₁₋₂alkyl, or OC₁alkyl. The phenyl can be substituted at any available ring carbon atom with C(O)-C₁₋₆alkyl, for example, C(O)-C₁₋₅alkyl, C(O)-C₁₋₄alkyl, C(O)-C₁₋₃alkyl, C(O)-C₁₋₂alkyl, or C(O)-C₁alkyl. The phenyl can be substituted at any available ring carbon atom with C₁₋₆haloalkyl, for example, C₁₋₅haloalkyl, C₁₋₄haloalkyl, C₁₋₃haloalkyl, C₁₋₂haloalkyl, or C₁haloalkyl, including CF₃, CH₂CH₂F, and the like. The phenyl's substituent can be attached to any ring carbon atom of the phenyl ring, preferably ortho to the phenyl moiety's point of attachment to the compound of Formula (I). Preferred substituents wherein A is phenyl include C₁₋₆alkyl, with C₁alkyl being most preferred. Other preferred substituents include halogen, in particular F and Cl.

[00167] In some aspects, A is naphthalenyl. Preferably, the naphthalenyl is substituted with one or two substituents, preferably one substituent. The naphthalenyl can be substituted at any available ring carbon atom with C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl. The naphthalenyl can be substituted at any available ring carbon atom with halogen, for example F or Cl. The naphthalenyl can be substituted at any available ring carbon atom with SF₅. The naphthalenyl can be substituted at any available ring carbon atom with OC₁₋

alkyl, for example, OC₁₋₅alkyl, OC₁₋₄alkyl, OC₁₋₃alkyl, OC₁₋₂alkyl, or OC₁alkyl. The naphthalenyl can be substituted at any available ring carbon atom with C(O)-C₁₋₆alkyl, for example, C(O)-C₁₋₅alkyl, C(O)-C₁₋₄alkyl, C(O)-C₁₋₃alkyl, C(O)-C₁₋₂alkyl, or C(O)-C₁alkyl. The naphthalenyl can be substituted at any available ring carbon atom with C₁₋₆haloalkyl, for example, C₁₋₅haloalkyl, C₁₋₄haloalkyl, C₁₋₃haloalkyl, C₁₋₂haloalkyl, or C₁haloalkyl, including CF₃, CH₂CH₂F, and the like. The naphthalenyl can be attached through any of its carbon atoms to the compound of Formula (I). The naphthalenyl substituent can be attached to any ring carbon atom of the naphthalenyl ring, preferably ortho to the naphthalenyl moiety's point of attachment to the compound of Formula (I). Preferred substituents wherein A is naphthalenyl include C₁₋₆alkyl, with C₁alkyl being most preferred. Other preferred substituents include halogen, in particular F and Cl.

[00168] In some aspects, A is pyrimidinyl. The pyrimidinyl can be attached to any of the compounds of Formula (I) (or its subgenera) through any ring carbon atom through any ring carbon atom. Preferably, the pyrimidinyl is substituted with one or two substituents, preferably one substituent. The pyrimidinyl can be substituted at any available ring carbon atom with C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl. The pyrimidinyl can be substituted at any available ring carbon atom with halogen, for example F or Cl. The pyrimidinyl can be substituted at any available ring carbon atom with SF₅. The pyrimidinyl can be substituted at any available ring carbon atom with OC₁₋₆alkyl, for example, OC₁₋₅alkyl, OC₁₋₄alkyl, OC₁₋₃alkyl, OC₁₋₂alkyl, or OC₁alkyl. The pyrimidinyl can be substituted at any available ring carbon atom with C(O)-C₁₋₆alkyl, for example, C(O)-C₁₋₅alkyl, C(O)-C₁₋₄alkyl, C(O)-C₁₋₃alkyl, C(O)-C₁₋₂alkyl, or C(O)-C₁alkyl. The pyrimidinyl can be substituted at any available ring carbon atom with C₁₋₆haloalkyl, for example, C₁₋₅haloalkyl, C₁₋₄haloalkyl, C₁₋₃haloalkyl, C₁₋₂haloalkyl, or C₁haloalkyl, including CF₃, CH₂CH₂F, and the like. Preferred substituents wherein A is pyrimidinyl include C₁₋₆alkyl, with C₁alkyl being most preferred. Other preferred substituents include halogen, in particular F and Cl.

[00169] In some aspects, A is pyrazinyl. The pyrazinyl can be attached to any of the compounds of Formula (I) (or its subgenera) through any ring carbon atom. Preferably, the pyrazinyl is substituted with one or two substituents, preferably one substituent. The pyrazinyl can be substituted at any available ring carbon atom with C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl. The pyrazinyl can be substituted at any available ring carbon atom with halogen, for example F or Cl. The pyrazinyl can be substituted at any available ring carbon atom with SF₅. The pyrazinyl can be substituted at any available ring

carbon atom with OC₁₋₆alkyl, for example, OC₁₋₅alkyl, OC₁₋₄alkyl, OC₁₋₃alkyl, OC₁₋₂alkyl, or OC₁alkyl. The pyrazinyl can be substituted at any available ring carbon atom with C(O)-C₁₋₆alkyl, for example, C(O)-C₁₋₅alkyl, C(O)-C₁₋₄alkyl, C(O)-C₁₋₃alkyl, C(O)-C₁₋₂alkyl, or C(O)-C₁alkyl. The pyrazinyl can be substituted at any available ring carbon atom with C₁₋₆haloalkyl, for example, C₁₋₅haloalkyl, C₁₋₄haloalkyl, C₁₋₃haloalkyl, C₁₋₂haloalkyl, or C₁haloalkyl, including CF₃, CH₂CH₂F, and the like. Preferred substituents wherein A is pyrazinyl include C₁₋₆alkyl, with C₁alkyl being most preferred. Other preferred substituents include halogen, in particular F and Cl.

[00170] In some aspects, A is pyridazinyl. The pyridazinyl can be attached to any of the compounds of Formula (I) (or its subgenera) through any ring carbon atom. Preferably, the pyridazinyl is substituted with one or two substituents, preferably one substituent. The pyridazinyl can be substituted at any available ring carbon atom with C₁₋₆alkyl, for example, -C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl. The pyridazinyl can be substituted at any available ring carbon atom with halogen, for example F or Cl. The pyridazinyl can be substituted at any available ring carbon atom with SF₅. The pyridazinyl can be substituted at any available ring carbon atom with OC₁₋₆alkyl, for example, OC₁₋₅alkyl, OC₁₋₄alkyl, OC₁₋₃alkyl, OC₁₋₂alkyl, or OC₁alkyl. The pyridazinyl can be substituted at any available ring carbon atom with C(O)-C₁₋₆alkyl, for example, C(O)-C₁₋₅alkyl, C(O)-C₁₋₄alkyl, C(O)-C₁₋₃alkyl, C(O)-C₁₋₂alkyl, or C(O)-C₁alkyl. The pyridazinyl can be substituted at any available ring carbon atom with C₁₋₆haloalkyl, for example, C₁₋₅haloalkyl, C₁₋₄haloalkyl, C₁₋₃haloalkyl, C₁₋₂haloalkyl, or C₁haloalkyl, including CF₃, CH₂CH₂F, and the like. Preferred substituents wherein A is pyridazinyl include C₁₋₆alkyl, with C₁alkyl being most preferred. Other preferred substituents include halogen, in particular F and Cl.

[00171] In some aspects, A is benzo[d][1,3]dioxolyl. The benzo[d][1,3]dioxolyl can be attached to any of the compounds of Formula (I) (or its subgenera) through any ring carbon atom. The benzo[d][1,3]dioxolyl can be unsubstituted or can be substituted with one or two halogen, preferably F. Preferably, the benzo[d][1,3]dioxolyl is substituted with one or two other substituents. The benzo[d][1,3]dioxolyl can be substituted at any available ring carbon atom with C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl. The benzo[d][1,3]dioxolyl can be substituted at any available ring carbon atom with halogen, for example F or Cl. The benzo[d][1,3]dioxolyl can be substituted at any available ring carbon atom with -SF₅. The benzo[d][1,3]dioxolyl can be substituted at any available ring carbon atom with OC₁₋₆alkyl, for example, OC₁₋₅alkyl, OC₁₋₄alkyl, OC₁₋₃alkyl, OC₁₋₂alkyl, or OC₁alkyl. The

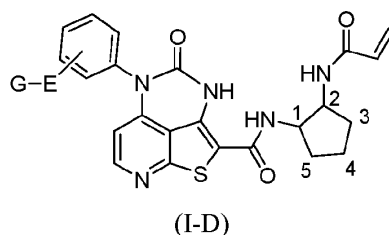
benzo[d][1,3]dioxolyl can be substituted at any available ring carbon atom with C(O)-C₁₋₆alkyl, for example, C(O)-C₁₋₅alkyl, C(O)-C₁₋₄alkyl, C(O)-C₁₋₃alkyl, C(O)-C₁₋₂alkyl, or C(O)-C₁alkyl. The benzo[d][1,3]dioxolyl can be substituted at any available ring carbon atom with C₁₋₆haloalkyl, for example, C₁₋₅haloalkyl, C₁₋₄haloalkyl, C₁₋₃haloalkyl, C₁₋₂haloalkyl, or C₁haloalkyl, including CF₃, CH₂CH₂F, and the like.

[00172] In some aspects, A is benzothiophenyl. The benzothiophenyl can be attached to any of the compounds of Formula (I) (or its subgenera) through any ring carbon atom. Preferably, the benzothiophenyl is substituted with one or two substituents, preferably one substituent. The benzothiophenyl can be substituted at any available ring carbon atom with C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl. The benzothiophenyl can be substituted at any available ring carbon atom with halogen, for example F or Cl. The benzothiophenyl can be substituted at any available ring carbon atom with SF₅. The benzothiophenyl can be substituted at any available ring carbon atom with OC₁₋₆alkyl, for example, OC₁₋₅alkyl, OC₁₋₄alkyl, OC₁₋₃alkyl, OC₁₋₂alkyl, or OC₁alkyl. The benzothiophenyl can be substituted at any available ring carbon atom with C(O)-C₁₋₆alkyl, for example, C(O)-C₁₋₅alkyl, C(O)-C₁₋₄alkyl, C(O)-C₁₋₃alkyl, C(O)-C₁₋₂alkyl, or C(O)-C₁alkyl. The benzothiophenyl can be substituted at any available ring carbon atom with C₁₋₆haloalkyl, for example, C₁₋₅haloalkyl, C₁₋₄haloalkyl, C₁₋₃haloalkyl, C₁₋₂haloalkyl, or C₁haloalkyl, including CF₃, CH₂CH₂F, and the like.

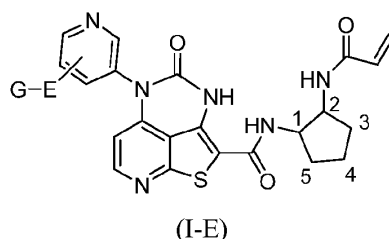
[00173] In some aspects, A is pyrazolyl. The pyrazolyl can be attached to any of the compounds of Formula (I) (or its subgenera) through any ring carbon atom. Preferably, the pyrazolyl is substituted with one or two substituents, preferably one substituent. The pyrazolyl can be substituted at any available ring carbon atom with C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl. The pyrazolyl can be substituted at any available ring carbon atom with halogen, for example F or Cl. The pyrazolyl can be substituted at any available ring carbon atom with SF₅. The pyrazolyl can be substituted at any available ring carbon atom with OC₁₋₆alkyl, for example, OC₁₋₅alkyl, OC₁₋₄alkyl, OC₁₋₃alkyl, OC₁₋₂alkyl, or OC₁alkyl. The pyrazolyl can be substituted at any available ring carbon atom with C(O)-C₁₋₆alkyl, for example, C(O)-C₁₋₅alkyl, C(O)-C₁₋₄alkyl, C(O)-C₁₋₃alkyl, C(O)-C₁₋₂alkyl, or C(O)-C₁alkyl. The pyrazolyl can be substituted at any available ring carbon atom with C₁₋₆haloalkyl, for example, C₁₋₅haloalkyl, C₁₋₄haloalkyl, C₁₋₃haloalkyl, C₁₋₂haloalkyl, or C₁haloalkyl, including CF₃, CH₂CH₂F, and the like.

[00174] In preferred aspects, A is an unsubstituted or substituted phenyl, pyridyl, pyrimidyl, or pyrazinyl moiety, with pyridyl being particularly preferred. In those aspects wherein the phenyl, pyridyl, pyrimidyl, or pyrazinyl moiety is substituted, the preferred substituents include C₁₋₆alkyl (e.g., methyl) and halogen (e.g., F or Cl).

5 [00175] Additional preferred subgenera of Formula (I) are:

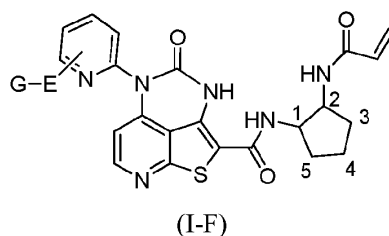


wherein the phenyl moiety can be unsubstituted or substituted with 1 or 2 substituents at any available carbon atom.



10

wherein the pyridyl moiety can be unsubstituted or substituted with 1 or 2 substituents at any available carbon atom.



15

wherein the pyridyl moiety can be unsubstituted or substituted with 1 or 2 substituents at any available carbon atom.

[00176] According to the disclosure, E is O, a bond, C(O)-NH, CH₂, or CH₂-O. The E moiety can be attached through any available carbon atom on the A moiety. The E moiety can also be attached through any available carbon atom on the G moiety.

20

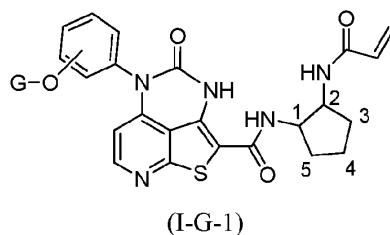
[00177] In some aspects, E is O, a bond, or CH₂. In preferred aspects, E is O. In other preferred aspects, E is a bond.

[00178] In some aspects of the disclosure, E is C(O)-NH, wherein the A-E-G moiety is A-C(O)-NH-G.

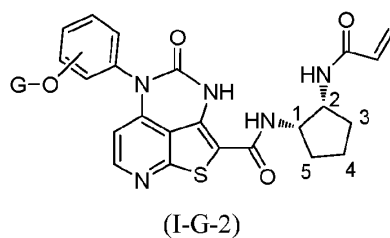
[00179] In other aspects of the disclosure, E is CH₂.

[00180] In yet other aspects of the disclosure, E is CH₂-O, wherein the A-E-G moiety is
5 A-CH₂-O-G.

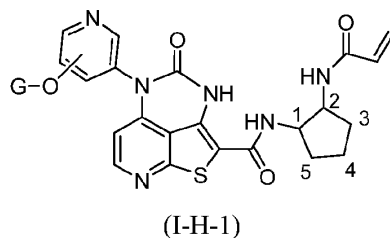
[00181] Additional preferred subgenera of Formula (I) are:



wherein the phenyl moiety can be unsubstituted or substituted with 1 or 2 substituents at
10 any available carbon atom.

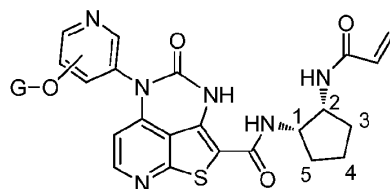


wherein the phenyl moiety can be unsubstituted or substituted with 1 or 2 substituents at
any available carbon atom.



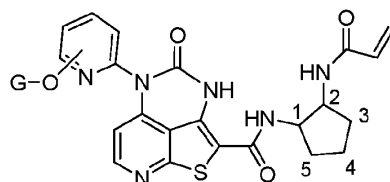
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wherein the pyridyl moiety can be unsubstituted or substituted with 1 or 2 substituents at
any available carbon atom.



(I-H-2)

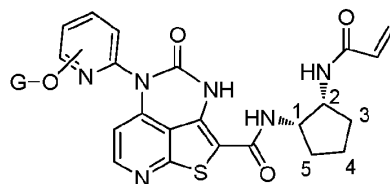
wherein the pyridyl moiety can be unsubstituted or substituted with 1 or 2 substituents at any available carbon atom.



5

(I-J-1)

wherein the pyridyl moiety can be unsubstituted or substituted with 1 or 2 substituents at any available carbon atom.

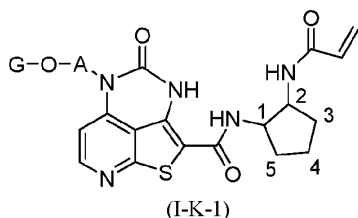


(I-J-2)

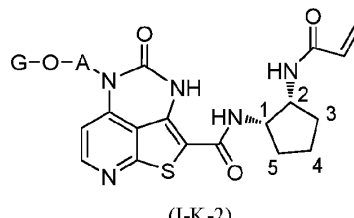
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wherein the pyridyl moiety can be unsubstituted or substituted with 1 or 2 substituents at any available carbon atom.

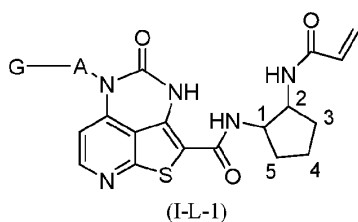
[00182] Other preferred subgenera of Formula (I) are:



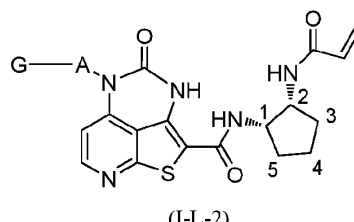
(I-K-1)



(I-K-2)



(I-L-1)



(I-L-2)

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[00183] According to the disclosure, G is H; halogen; C₁₋₆alkyl; C₁₋₆haloalkyl; NH(C₁₋₆alkyl); C₃₋₆cycloalkyl; phenyl; pyrimidinyl; pyridyl; pyridazinyl; pyridin-2(1H)-one; heterocycloalkyl that contains an oxygen heteroatom; and phenyl-CH₂-O-phenyl, wherein the -O-phenyl is substituted with CN; wherein the phenyl; pyridyl; pyridazinyl; and pyridin-2(1H)-

one is optionally substituted with 1, 2, or 3 substituents each independently selected from the group consisting of: halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, OC₁₋₆haloalkyl, and OC₁₋₆alkyl,

[00184] Also according to the disclosure, G is H; C₃₋₆cycloalkyl; phenyl; thiophenyl; C₁₋₆alkyl; pyrimidinyl; pyridyl; pyridazinyl; benzofuranyl; C₁₋₆haloalkyl; heterocycloalkyl that
5 contains an oxygen heteroatom; phenyl-CH₂-O-phenyl; C₁₋₆alk-O-C₁₋₆alkyl; NR⁶R⁷; SO₂C₁₋₆alkyl; or OH; wherein the phenyl; pyridyl; pyridazinyl; pyrimidinyl; benzofuranyl; or thiophenyl is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen; C₁₋₆alkyl; C₁₋₆haloalkyl; OC₁₋₆haloalkyl; C₃₋₆cycloalkyl; OC₁₋₆alkyl; CN; OH; C₁₋₆alk-O-C₁₋₆alkyl; C(O)-NR⁶R⁷; and C(O)-C₁₋₆alkyl.

10 **[00185]** In some aspects, G is H.

[00186] In other aspects, G is C₃₋₆cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

[00187] In some aspects, G is C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl.

15 **[00188]** In some aspects, G is C₁₋₆haloalkyl, for example, C₁₋₅haloalkyl, C₁₋₄haloalkyl, C₁₋₃haloalkyl, C₁₋₂haloalkyl, or C₁haloalkyl, including CF₃, CH₂CH₂F, and the like.

[00189] In other aspects, G is a heterocycloalkyl that contains an oxygen heteroatom, for example, tetrahydropyranyl, tetrahydrofuranyl, or oxetanyl.

20 **[00190]** In preferred aspects, G is phenyl-CH₂-O-phenyl. In these aspects, the phenyl-CH₂-O-phenyl can be unsubstituted or substituted with 1, 2, or 3 substituents, preferably 1 or 2 substituents, more preferably 1 substituent, independently selected from the group consisting of halogen; C₁₋₆alkyl; C₁₋₆haloalkyl; OC₁₋₆haloalkyl; C₃₋₆cycloalkyl; OC₁₋₆alkyl; CN; OH; C₁₋₆alk-O-C₁₋₆alkyl; C(O)-NR⁶R⁷; and C(O)-C₁₋₆alkyl. The one or both of the phenyl
25 rings of the phenyl-CH₂-O-phenyl moiety can be substituted with halogen, for example F or Cl. The one or both of the phenyl rings of the -phenyl-CH₂-O-phenyl moiety can be substituted with C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl. The one or both of the phenyl rings of the phenyl-CH₂-O-phenyl moiety can be substituted with C₁₋₆haloalkyl, for example, C₁₋₅haloalkyl, C₁₋₄haloalkyl, C₁₋₃haloalkyl, C₁₋₂haloalkyl, or
30 C₁haloalkyl. The one or both of the phenyl rings of the phenyl-CH₂-O-phenyl moiety can be substituted with OC₁₋₆haloalkyl, for example, OC₁₋₅haloalkyl, OC₁₋₄haloalkyl, OC₁₋₃haloalkyl, OC₁₋₂haloalkyl, or OC₁haloalkyl. The one or both of the phenyl rings of the phenyl-CH₂-O-phenyl moiety can be substituted with C₃₋₆cycloalkyl, for example, cyclopropyl,

cyclobutyl, cyclopentyl, or cyclohexyl. The one or both of the phenyl rings of the phenyl-CH₂-O-phenyl moiety can be substituted with OC₁₋₆alkyl, for example, OC₁₋₅alkyl, OC₁₋₄alkyl, OC₁₋₃alkyl, OC₁₋₂alkyl, or OC₁alkyl. The one or both of the phenyl rings of the phenyl-CH₂-O-phenyl moiety can be substituted with CN. The one or both of the phenyl rings of the phenyl-CH₂-O-phenyl moiety can be substituted with OH. The one or both of the phenyl rings of the phenyl-CH₂-O-phenyl moiety can be substituted with C₁₋₆alk-O-C₁₋₆alkyl, for example, C₁₋₅alk-O-C₁₋₅alkyl, C₁₋₄alk-O-C₁₋₄alkyl, C₁₋₃alk-O-C₁₋₃alkyl, C₁₋₂alk-O-C₁₋₂alkyl, or C₁alk-O-C₁alkyl. The one or both of the phenyl rings of the phenyl-CH₂-O-phenyl moiety can be substituted with C(O)-NR⁶R⁷, wherein R⁶ and R⁷ are preferably each independently H; C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl; or C₃₋₆cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. More preferably, R⁶ and R⁷ are each independently H or C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl. The one or both of the phenyl rings of the phenyl-CH₂-O-phenyl moiety can be substituted with C(O)-C₁₋₆alkyl, for example, C(O)-C₁₋₆alkyl, C(O)-C₁₋₄alkyl, C(O)-C₁₋₃alkyl, C(O)-C₁₋₂alkyl, or C(O)-C₁alkyl.

[00191] In some aspects, G is C₁₋₆alk-O-C₁₋₆alkyl, for example, C₁₋₅alk-O-C₁₋₅alkyl, C₁₋₄alk-O-C₁₋₄alkyl, C₁₋₃alk-O-C₁₋₃alkyl, C₁₋₂alk-O-C₁₋₂alkyl, or C₁alk-O-C₁alkyl.

[00192] In other aspects, G is NR⁶R⁷, wherein R⁶ and R⁷ are each independently H; C₁₋₆alkyl; C₃₋₆cycloalkyl; C(O)H, or CN. In these aspects, R⁶ and R⁷ are preferably each independently H; C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl; or C₃₋₆cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. More preferably, R⁶ and R⁷ are each independently H or C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl.

[00193] In some aspects, G is SO₂C₁₋₆alkyl, for example, SO₂C₁₋₅alkyl, SO₂C₁₋₄alkyl, -SO₂C₁₋₃alkyl, SO₂C₁₋₂alkyl, or SO₂C₁alkyl.

[00194] In some aspects, G is OH.

[00195] In preferred aspects, G is phenyl. In these aspects, the phenyl can be unsubstituted or substituted with 1, 2, or 3 substituents, preferably 1 or 2 substituents, more preferably 1 substituent, independently selected from the group consisting of halogen; C₁₋₆alkyl; C₁₋₆haloalkyl; OC₁₋₆haloalkyl; C₃₋₆cycloalkyl; OC₁₋₆alkyl; CN; OH; C₁₋₆alk-O-C₁₋₆alkyl; C(O)-NR⁶R⁷; and C(O)-C₁₋₆alkyl. The phenyl can be substituted with halogen, for example F or Cl. The phenyl can be substituted with C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl. The phenyl can be substituted with C₁₋₆haloalkyl, for example,

C₁₋₅haloalkyl, C₁₋₄haloalkyl, C₁₋₃haloalkyl, C₁₋₂haloalkyl, or C₁haloalkyl. The phenyl can be substituted with OC₁₋₆haloalkyl, for example, OC₁₋₅haloalkyl, OC₁₋₄haloalkyl, OC₁₋₃haloalkyl, OC₁₋₂haloalkyl, or OC₁haloalkyl. The phenyl can be substituted with C₃₋₆cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. The phenyl can be substituted with OC₁₋₆alkyl, for example, OC₁₋₅alkyl, OC₁₋₄alkyl, OC₁₋₃alkyl, OC₁₋₂alkyl, or OC₁alkyl. The phenyl can be substituted with CN. The phenyl can be substituted with OH. The phenyl can be substituted with C₁₋₆alk-O-C₁₋₆alkyl, for example, C₁₋₅alk-O-C₁₋₅alkyl, C₁₋₄alk-O-C₁₋₄alkyl, C₁₋₃alk-O-C₁₋₃alkyl, C₁₋₂alk-O-C₁₋₂alkyl, or C₁alk-O-C₁alkyl. The phenyl can be substituted with C(O)-NR⁶R⁷, wherein R⁶ and R⁷ are preferably each independently H; C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl; or C₃₋₆cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. More preferably, R⁶ and R⁷ are each independently H or C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl. The phenyl can be substituted with C(O)-C₁₋₆alkyl, for example, C(O)-C₁₋₅alkyl, C(O)-C₁₋₄alkyl, C(O)-C₁₋₃alkyl, C(O)-C₁₋₂alkyl, or C(O)-C₁alkyl.

[00196] In some aspects, G is pyridyl. In these aspects, the pyridyl can be unsubstituted or substituted with 1, 2, or 3 substituents, preferably 1 or 2 substituents, more preferably 1 substituent, independently selected from the group consisting of halogen; C₁₋₆alkyl; C₁₋₆haloalkyl; OC₁₋₆haloalkyl; C₃₋₆cycloalkyl; OC₁₋₆alkyl; CN; OH; C₁₋₆alk-O-C₁₋₆alkyl; C(O)-NR⁶R⁷; and C(O)-C₁₋₆alkyl. The pyridyl can be substituted with halogen, for example F or Cl. The pyridyl can be substituted with C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl. The pyridyl can be substituted with C₁₋₆haloalkyl, for example, C₁₋₅haloalkyl, C₁₋₄haloalkyl, C₁₋₃haloalkyl, C₁₋₂haloalkyl, or C₁haloalkyl. The pyridyl can be substituted with OC₁₋₆haloalkyl, for example, OC₁₋₅haloalkyl, OC₁₋₄haloalkyl, OC₁₋₃haloalkyl, OC₁₋₂haloalkyl, or OC₁haloalkyl. The pyridyl can be substituted with C₃₋₆cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. The pyridyl can be substituted with OC₁₋₆alkyl, for example, OC₁₋₅alkyl, OC₁₋₄alkyl, OC₁₋₃alkyl, OC₁₋₂alkyl, or OC₁alkyl. The pyridyl can be substituted with CN. The pyridyl can be substituted with -OH. The pyridyl can be substituted with C₁₋₆alk-O-C₁₋₆alkyl, for example, C₁₋₅alk-O-C₁₋₅alkyl, C₁₋₄alk-O-C₁₋₄alkyl, C₁₋₃alk-O-C₁₋₃alkyl, C₁₋₂alk-O-C₁₋₂alkyl, or C₁alk-O-C₁alkyl. The pyridyl can be substituted with C(O)-NR⁶R⁷, wherein R⁶ and R⁷ are preferably each independently H; C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl; or C₃₋₆cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. More

preferably, R^6 and R^7 are each independently H or C_{1-6} alkyl, for example, C_{1-5} alkyl, C_{1-4} alkyl, C_{1-3} alkyl, C_{1-2} alkyl, or C_1 alkyl. The pyridyl can be substituted with $C(O)-C_{1-6}$ alkyl, for example, $C(O)-C_{1-5}$ alkyl, $C(O)-C_{1-4}$ alkyl, $C(O)-C_{1-3}$ alkyl, $C(O)-C_{1-2}$ alkyl, or $C(O)-C_1$ alkyl.

- 5 **[00197]** In some aspects, G is pyridazinyl. In these aspects, the pyridazinyl can be unsubstituted or substituted with 1, 2, or 3 substituents, preferably 1 or 2 substituents, more preferably 1 substituent, independently selected from the group consisting of halogen; C_{1-6} alkyl; C_{1-6} haloalkyl; OC_{1-6} haloalkyl; C_{3-6} cycloalkyl; OC_{1-6} alkyl; CN; OH; C_{1-6} alk-O- C_{1-6} alkyl; $C(O)-NR^6R^7$; and $C(O)-C_{1-6}$ alkyl. The pyridazinyl can be substituted with halogen, for example
- 10 F or Cl. The pyridazinyl can be substituted with C_{1-6} alkyl, for example, C_{1-5} alkyl, C_{1-4} alkyl, C_{1-3} alkyl, C_{1-2} alkyl, or C_1 alkyl. The pyridazinyl can be substituted with C_{1-6} haloalkyl, for example, C_{1-5} haloalkyl, C_{1-4} haloalkyl, C_{1-3} haloalkyl, C_{1-2} haloalkyl, or C_1 haloalkyl. The pyridazinyl can be substituted with OC_{1-6} haloalkyl, for example, OC_{1-5} haloalkyl, OC_{1-4} haloalkyl, OC_{1-3} haloalkyl, OC_{1-2} haloalkyl, or OC_1 haloalkyl. The pyridazinyl
- 15 can be substituted with C_{3-6} cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. The pyridazinyl can be substituted with OC_{1-6} alkyl, for example, OC_{1-5} alkyl, OC_{1-4} alkyl, OC_{1-3} alkyl, OC_{1-2} alkyl, or OC_1 alkyl. The pyridazinyl can be substituted with CN. The pyridazinyl can be substituted with OH. The pyridazinyl can be substituted with C_{1-6} alk-O- C_{1-6} alkyl, for example, C_{1-5} alk-O- C_{1-5} alkyl, C_{1-4} alk-O- C_{1-4} alkyl,
- 20 C_{1-3} alk-O- C_{1-3} alkyl, C_{1-2} alk-O- C_{1-2} alkyl, or C_1 alk-O- C_1 alkyl. The pyridazinyl can be substituted with $C(O)-NR^6R^7$, wherein R^6 and R^7 are preferably each independently H; C_{1-6} alkyl, for example, C_{1-5} alkyl, C_{1-4} alkyl, C_{1-3} alkyl, C_{1-2} alkyl, or C_1 alkyl; or C_{3-6} cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. More preferably, R^6 and R^7 are each independently H or C_{1-6} alkyl, for example, C_{1-5} alkyl, C_{1-4} alkyl, C_{1-3} alkyl, C_{1-2} alkyl, or C_1 alkyl.
- 25 The pyridazinyl can be substituted with $C(O)-C_{1-6}$ alkyl, for example, $C(O)-C_{1-5}$ alkyl, $C(O)-C_{1-4}$ alkyl, $C(O)-C_{1-3}$ alkyl, $C(O)-C_{1-2}$ alkyl, or $C(O)-C_1$ alkyl.

- [00198]** In some aspects, G is pyrimidinyl. In these aspects, the pyrimidinyl can be unsubstituted or substituted with 1, 2, or 3 substituents, preferably 1 or 2 substituents, more preferably 1 substituent, independently selected from the group consisting of halogen; C_{1-6} alkyl;
- 30 C_{1-6} haloalkyl; OC_{1-6} haloalkyl; C_{3-6} cycloalkyl; OC_{1-6} alkyl; CN; OH; C_{1-6} alk-O- C_{1-6} alkyl; $C(O)-NR^6R^7$; and $C(O)-C_{1-6}$ alkyl. The pyrimidinyl can be substituted with halogen, for example F or Cl. The pyrimidinyl can be substituted with C_{1-6} alkyl, for example, C_{1-5} alkyl, C_{1-4} alkyl, C_{1-3} alkyl, C_{1-2} alkyl, or C_1 alkyl. The pyrimidinyl can be substituted with

C₁₋₆haloalkyl, for example, C₁₋₅haloalkyl, C₁₋₄haloalkyl, C₁₋₃haloalkyl, C₁₋₂haloalkyl, or C₁haloalkyl. The pyrimidinyl can be substituted with OC₁₋₆haloalkyl, for example, OC₁₋₅haloalkyl, OC₁₋₄haloalkyl, OC₁₋₃haloalkyl, OC₁₋₂haloalkyl, or OC₁haloalkyl. The pyrimidinyl can be substituted with C₃₋₆cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. The pyrimidinyl can be substituted with OC₁₋₆alkyl, for example, OC₁₋₅alkyl, OC₁₋₄alkyl, OC₁₋₃alkyl, OC₁₋₂alkyl, or OC₁alkyl. The pyrimidinyl can be substituted with CN. The pyrimidinyl can be substituted with OH. The pyrimidinyl can be substituted with C₁₋₆alk-O-C₁₋₆alkyl, for example, C₁₋₅alk-O-C₁₋₅alkyl, C₁₋₄alk-O-C₁₋₄alkyl, C₁₋₃alk-O-C₁₋₃alkyl, C₁₋₂alk-O-C₁₋₂alkyl, or C₁alk-O-C₁alkyl. The pyrimidinyl can be substituted with C(O)-NR⁶R⁷, wherein R⁶ and R⁷ are preferably each independently H; C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl; or C₃₋₆cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. More preferably, R⁶ and R⁷ are each independently H or C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl. The pyrimidinyl can be substituted with C(O)-C₁₋₆alkyl, for example, C(O)-C₁₋₅alkyl, C(O)-C₁₋₄alkyl, C(O)-C₁₋₃alkyl, C(O)-C₁₋₂alkyl, or C(O)-C₁alkyl.

[00199] In some aspects, G is benzofuranyl. In these aspects, the benzofuranyl can be unsubstituted or substituted with 1, 2, or 3 substituents, preferably 1 or 2 substituents, more preferably 1 substituent, independently selected from the group consisting of halogen; C₁₋₆alkyl; C₁₋₆haloalkyl; OC₁₋₆haloalkyl; C₃₋₆cycloalkyl; OC₁₋₆alkyl; CN; OH; C₁₋₆alk-O-C₁₋₆alkyl; C(O)-NR⁶R⁷; and C(O)-C₁₋₆alkyl. The benzofuranyl can be substituted with halogen, for example F or Cl. The benzofuranyl can be substituted with C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl. The benzofuranyl can be substituted with C₁₋₆haloalkyl, for example, C₁₋₅haloalkyl, C₁₋₄haloalkyl, C₁₋₃haloalkyl, C₁₋₂haloalkyl, or C₁haloalkyl. The benzofuranyl can be substituted with OC₁₋₆haloalkyl, for example, OC₁₋₅haloalkyl, OC₁₋₄haloalkyl, OC₁₋₃haloalkyl, OC₁₋₂haloalkyl, or OC₁haloalkyl. The benzofuranyl can be substituted with C₃₋₆cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. The benzofuranyl can be substituted with OC₁₋₆alkyl, for example, OC₁₋₅alkyl, OC₁₋₄alkyl, OC₁₋₃alkyl, OC₁₋₂alkyl, or OC₁alkyl. The benzofuranyl can be substituted with CN. The benzofuranyl can be substituted with OH. The benzofuranyl can be substituted with C₁₋₆alk-O-C₁₋₆alkyl, for example, C₁₋₅alk-O-C₁₋₅alkyl, C₁₋₄alk-O-C₁₋₄alkyl, C₁₋₃alk-O-C₁₋₃alkyl, C₁₋₂alk-O-C₁₋₂alkyl, or C₁alk-O-C₁alkyl. The benzofuranyl can be substituted with C(O)-NR⁶R⁷, wherein R⁶ and R⁷ are preferably each independently H; C₁₋₆alkyl, for example, C₁₋₅alkyl, C₁₋₄alkyl, C₁₋₃alkyl, C₁₋₂alkyl, or C₁alkyl; or C₃₋₆cycloalkyl, for example,

cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. More preferably, R^6 and R^7 are each independently H or C_{1-6} alkyl, for example, C_{1-5} alkyl, C_{1-4} alkyl, C_{1-3} alkyl, C_{1-2} alkyl, or C_1 alkyl. The benzofuranyl can be substituted with $C(O)-C_{1-6}$ alkyl, for example, $C(O)-C_{1-6.5}$ alkyl, $C(O)-C_{1-4}$ alkyl, $C(O)-C_{1-3}$ alkyl, $C(O)-C_{1-2}$ alkyl, or $C(O)-C_1$ alkyl.

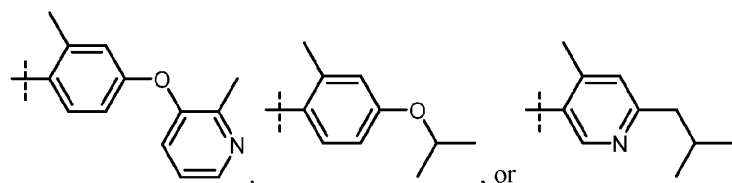
- 5 **[00200]** In some aspects, G is thiophenyl. In these aspects, the thiophenyl can be unsubstituted or substituted with 1, 2, or 3 substituents, preferably 1 or 2 substituents, more preferably 1 substituent, independently selected from the group consisting of halogen; C_{1-6} alkyl; C_{1-6} haloalkyl; OC_{1-6} haloalkyl; C_{3-6} cycloalkyl; OC_{1-6} alkyl; CN; OH; $C_{1-6}alk-O-C_{1-6}alkyl$; $C(O)-NR^6R^7$; and $C(O)-C_{1-6}alkyl$. The thiophenyl can be substituted with halogen, for example
- 10 F or Cl. The thiophenyl can be substituted with C_{1-6} alkyl, for example, C_{1-5} alkyl, C_{1-4} alkyl, C_{1-3} alkyl, C_{1-2} alkyl, or C_1 alkyl. The thiophenyl can be substituted with C_{1-6} haloalkyl, for example, $C_{1-5}haloalkyl$, $C_{1-4}haloalkyl$, $C_{1-3}haloalkyl$, $C_{1-2}haloalkyl$, or $C_1haloalkyl$. The thiophenyl can be substituted with OC_{1-6} haloalkyl, for example, $OC_{1-5}haloalkyl$, $OC_{1-4}haloalkyl$, $OC_{1-3}haloalkyl$, $OC_{1-2}haloalkyl$, or $OC_1haloalkyl$. The
- 15 thiophenyl can be substituted with C_{3-6} cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. The thiophenyl can be substituted with OC_{1-6} alkyl, for example, OC_{1-5} alkyl, OC_{1-4} alkyl, OC_{1-3} alkyl, OC_{1-2} alkyl, or OC_1 alkyl. The thiophenyl can be substituted with CN. The thiophenyl can be substituted with OH. The thiophenyl can be substituted with $C_{1-6}alk-O-C_{1-6}alkyl$, for example, $C_{1-5}alk-O-C_{1-5}alkyl$, $C_{1-4}alk-O-C_{1-4}alkyl$,
- 20 $C_{1-3}alk-O-C_{1-3}alkyl$, $C_{1-2}alk-O-C_{1-2}alkyl$, or $C_1alk-O-C_1alkyl$. The thiophenyl can be substituted with $C(O)-NR^6R^7$, wherein R^6 and R^7 are preferably each independently H; C_{1-6} alkyl, for example, C_{1-5} alkyl, C_{1-4} alkyl, C_{1-3} alkyl, C_{1-2} alkyl, or C_1 alkyl; or C_{3-6} cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. More preferably, R^6 and R^7 are each independently H or C_{1-6} alkyl, for example, C_{1-5} alkyl, C_{1-4} alkyl, C_{1-3} alkyl, C_{1-2} alkyl, or C_1 alkyl.
- 25 The thiophenyl can be substituted with $C(O)-C_{1-6}alkyl$, for example, $C(O)-C_{1-6.5}alkyl$, $C(O)-C_{1-4}alkyl$, $C(O)-C_{1-3}alkyl$, $C(O)-C_{1-2}alkyl$, or $C(O)-C_1alkyl$.

- [00201]** In preferred aspects, G is unsubstituted or substituted pyridyl, pyridizynyl, or pyrazynyl. In those aspects wherein G is substituted pyridyl, pyridizynyl, or pyrazynyl, preferred substituents include C_{1-6} alkyl (e.g., methyl). In other preferred aspects, G is C_{1-6} alkyl (e.g.,
- 30 isopropyl).

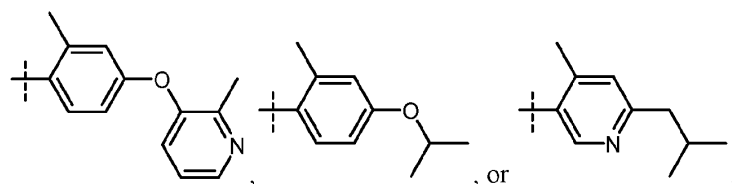
[00202] In preferred aspects, G is unsubstituted or substituted pyridyl, pyridizynyl, or pyrazynyl and E is CH_2 or O. In those aspects wherein G is substituted pyridyl, pyridizynyl, or

pyrazinyl and E is CH₂ or O, preferred substituents include C₁₋₆alkyl (e.g., methyl). In other preferred aspects, G is C₁₋₆alkyl (e.g., isopropyl) and E is CH₂ or O.

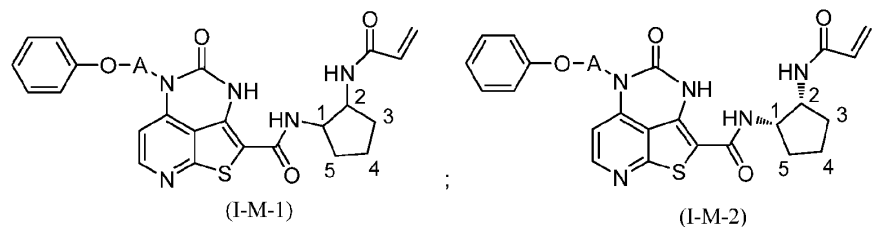
[00203] In some preferred aspects, A-E-G is:

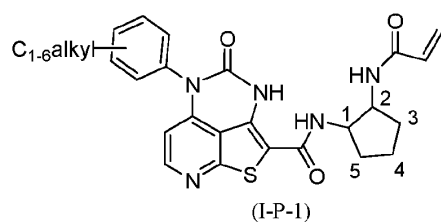
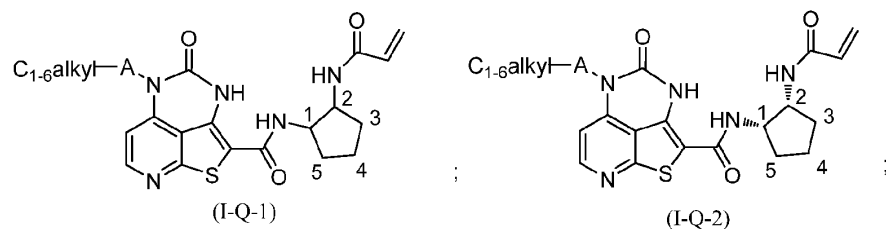
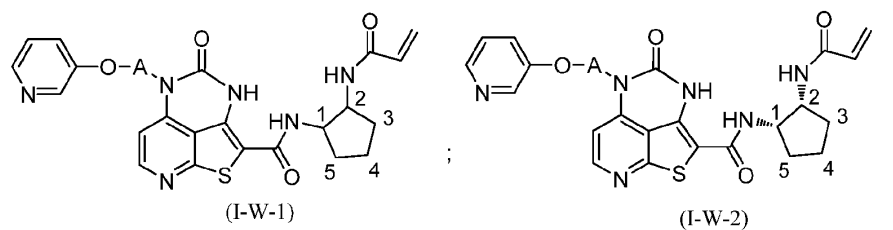
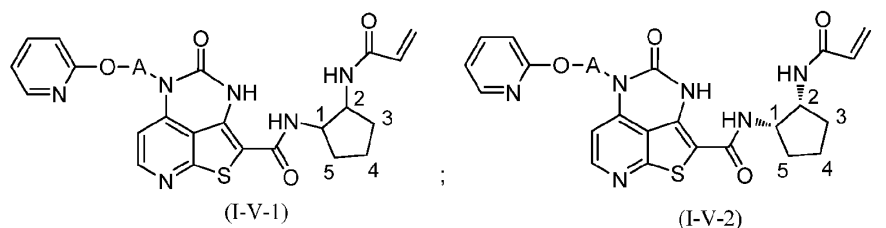


5 [00204] Preferred compounds of the Formula I include those wherein R¹ is H; R² is cyclopentyl substituted with 1 or 2 substituents wherein one of the substituents is NR⁸-C(O)-C(R³)=CR⁴(R⁵), wherein R³, R⁴, and R⁵ are each H; A is phenyl or pyridyl, wherein the phenyl or pyridyl is substituted with CH₃; E is O or a bond; and G is phenyl or C₁₋₆alkyl. In more preferred aspects, R² is substituted with 1 substituent that is NR⁸-C(O)-C(R³)=CR⁴(R⁵). In
10 preferred aspects, A-E-G is

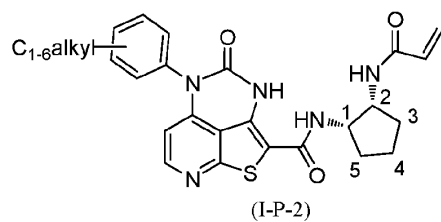


Preferred subgenera of Formula (I) include:

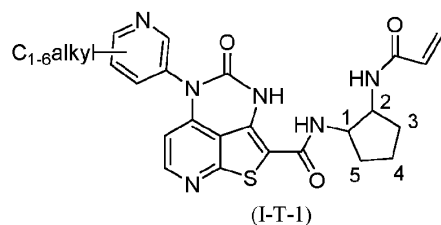




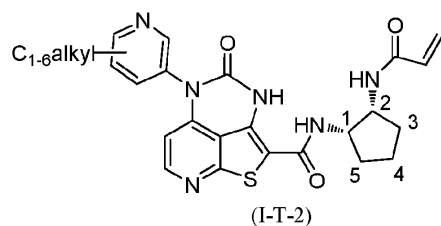
5 wherein the A phenyl is unsubstituted or substituted, preferably with C₁₋₆alkyl;



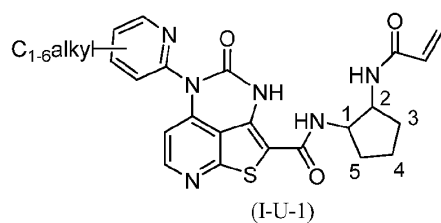
wherein the A phenyl is unsubstituted or substituted, preferably with C₁₋₆alkyl;



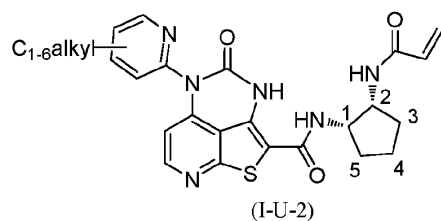
wherein the A pyridyl is unsubstituted or substituted, preferably with C₁₋₆alkyl;



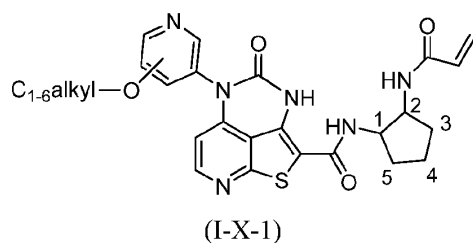
wherein the A pyridyl is unsubstituted or substituted, preferably with C₁₋₆alkyl;



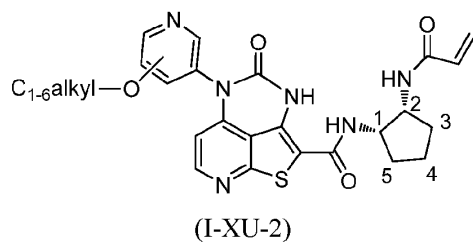
5 wherein the A pyridyl is unsubstituted or substituted, preferably with C₁-alkyl;

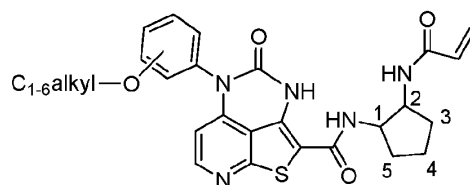


wherein the A pyridyl is unsubstituted or substituted, preferably with C₁₋₆alkyl;



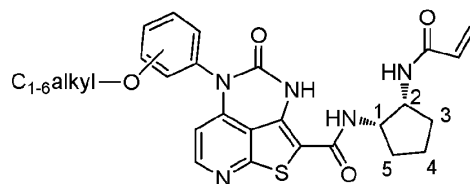
10 wherein the A pyridyl is unsubstituted or substituted, preferably with C₁₋₆alkyl;





(I-Y-1)

wherein the A phenyl is unsubstituted or substituted, preferably with C₁₋₆alkyl; and



(I-Y-2)

wherein the A phenyl is unsubstituted or substituted, preferably with C₁₋₆alkyl.

[00205] An additional aspect of the invention is a compound selected from the group consisting of:

- 10 N-((1S,4S)-4-Acrylamidocyclohexyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,3S)-3-Acrylamidocyclohexyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,4S)-4-Acrylamidocyclohexyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 15 1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2R)-2-Hydroxycyclopentyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Aminocyclohexyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 20 N-((1R,2S)-2-Hydroxycyclopentyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-(Dimethylamino)cyclohexyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 25 N-((1R,2S)-2-Hydroxycyclopentyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

- N-((1R,2R)-2-Hydroxycyclopentyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Aminocyclohexyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5 N-((1R,2R)-2-Acetamidocyclopentyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Aminocyclopentyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,4R)-4-Acrylamidocyclohexyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 10 N-((1R,2S)-2-(Dimethylamino)cyclohexyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,4R)-4-Hydroxycyclohexyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 15 N-((1S,4S)-4-Hydroxycyclohexyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-(Dimethylamino)cyclopentyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,4R)-4-Methoxycyclohexyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 20 N-((1S,4S)-4-((E)-2-Cyano-3-cyclopropylacrylamido)cyclohexyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,2S)-2-Hydroxycyclopentyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 25 5-(2-Methyl-4-phenoxyphenyl)-N-((1R,2R)-2-(methylamino)cyclopentyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2R)-2-Aminocyclopentyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 30 N-((1S,4S)-4-Cyanamidocyclohexyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,3S)-3-(Dimethylamino)cyclohexyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

- N-((1S,4S)-4-Aminocyclohexyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-((1R,2R)-2-propionamidocyclopentyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5 N-((1RS,2RS)-2-Hydroxycyclohexyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-Cyclopentyl-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 10 N-((1R,2R)-2-(Dimethylamino)cyclopentyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,3S,5R,7S)-3-Hydroxyadamantan-1-yl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-(2-Methyl-4-phenoxyphenyl)-N-(2-(methylamino)cyclohexyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 15 N-((1S,2S)-2-(Dimethylamino)cyclopentyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acetamidocyclohexyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-((1R,2S)-2-propionamidocyclopentyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 20 5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-((1R,2S)-2-propionamidocyclohexyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1RS,2RS)-2-Hydroxycyclohexyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 25 N-((1R,2S)-2-Acetamidocyclopentyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2R)-2-Aminocyclohexyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 30 N-((1S,2R)-2-Hydroxycyclopentyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,2S)-2-Acetamidocyclopentyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

- N-((1S,2S)-2-Aminocyclopentyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-((1S,2R)-2-propionamidocyclohexyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5 N-((1R,2R)-2-(Dimethylamino)cyclohexyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,2R)-2-Acetamidocyclohexyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-((1S,2S)-2-propionamidocyclopentyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 10 5-(2-Methyl-4-phenoxyphenyl)-N-((1S,2S)-2-(methylamino)cyclopentyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2R)-2-Acetamidocyclohexyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 15 N-((1S,2R)-2-(Dimethylamino)cyclohexyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,2R)-2-Aminocyclohexyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-(2-Methyl-4-phenoxyphenyl)-N-((1S,2R)-2-(methylamino)cyclohexyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 20 N-((1S,2R)-2-(Dimethylamino)cyclopentyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-((1R,2R)-2-propionamidocyclohexyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 25 N-((1S,2R)-2-Aminocyclopentyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,2S)-2-Formamidocyclohexyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,2S)-2-Acetamidocyclohexyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 30 N-((1S,2S)-2-Acrylamidocyclopentyl)-5-(*)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

- N-((1S,2R)-2-Acetamidocyclopentyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,2S)-2-Aminocyclohexyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5 5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-((1S,2R)-2-propionamidocyclopentyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-((1S,2S)-2-propionamidocyclohexyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2R)-2-Hydroxycyclopentyl)-5-(^{*}R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 10 N-((1S,2S)-2-(Dimethylamino)cyclohexyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-(2-Methyl-4-phenoxyphenyl)-N-(4-(methylamino)cyclohexyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 15 N-((1S,4S)-4-Acetamidocyclohexyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-((1S,4S)-4-propionamidocyclohexyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,4S)-4-(Dimethylamino)cyclohexyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 20 N-((1R,2R)-2-Acetamidocyclopentyl)-5-(^{*}S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,3R)-3-acrylamidocyclopentyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 25 5-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-((1S,3R)-3-propionamidocyclopentyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,3R)-3-Acetamidocyclopentyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,3R)-3-(2-(Dimethylamino)acetamido)cyclopentyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 30 5-(2-Methyl-4-phenoxyphenyl)-N-((1S,3R)-3-(2-(methylamino)acetamido)cyclopentyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

- N-((1S,3R)-3-(Dimethylamino)cyclopentyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,3R)-3-Hydroxycyclopentyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5 N-((1S,3R)-3-(2-Aminoacetamido)cyclopentyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,3R)-3-Aminocyclopentyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 10 N-((1S,4S)-4-((E)-4-(Dimethylamino)but-2-enamido)cyclohexyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-(2-Methyl-4-phenoxyphenyl)-N-((1S,4S)-4-((E)-4-(methylamino)but-2-enamido)cyclohexyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 15 N-((1S,4S)-4-((E)-4-Aminobut-2-enamido)cyclohexyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-(2-Methyl-4-phenoxyphenyl)-N-((1S)-3-(methylamino)cyclopentyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-Cyclopentyl-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 20 N-Cyclopentyl-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,4S)-4-Hydroxycyclohexyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 25 N-((1S,4S)-4-Hydroxycyclohexyl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,4R)-4-Hydroxycyclohexyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 30 N-((1R,4R)-4-Hydroxycyclohexyl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-((1S,3R)-3-propionamidocyclopentyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

- N-((1S,3R)-3-Acetamidocyclopentyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,4S)-4-((*E)-2-Cyano-3-cyclopropylacrylamido)cyclohexyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5 N-((1S,4S)-4-((*E)-2-Cyano-3-cyclopropylacrylamido)cyclohexyl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2R)-2-Aminocyclopentyl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 10 5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-((1S,4S)-4-propionamidocyclohexyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-(*R)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-((1S,4S)-4-propionamidocyclohexyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 15 N-((1S,4S)-4-Acetamidocyclohexyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,4S)-4-Acetamidocyclohexyl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-(rac-(1,3-cis)-3-Aminocyclopentyl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 20 N-((1R,2S)-2-Aminocyclopentyl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,2R)-2-Aminocyclopentyl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 25 N-((1S,4S)-4-(Dimethylamino)cyclohexyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,4S)-4-(Dimethylamino)cyclohexyl)-5-(*R)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,3R)-3-Acrylamidocyclopentyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 30 N-((1S,3R)-3-(2-(dimethylamino)acetamido)cyclopentyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

- 5-(*S)-(2-Methyl-4-phenoxyphenyl)-N-((1S,3R)-3-(2-(methylamino)acetamido)cyclopentyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5 N-((1R,2S)-2-acrylamidocyclopentyl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2R)-2-Acrylamidocyclopentyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-([1,1'-Biphenyl]-3-yl)-N-((1R,2S)-2-acrylamidocyclohexyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 10 N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclohexyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,3R)-3-Acrylamidocyclopentyl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 15 N-((1S,3R)-3-Acrylamidocyclopentyl)-5-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2R)-2-(2-(Dimethylamino)acetamido)cyclopentyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 20 5-(*S)-(2-Methyl-4-phenoxyphenyl)-N-((1R,2R)-2-(2-(methylamino)acetamido)cyclopentyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2R)-2-(2-Aminoacetamido)cyclopentyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 25 N-((1S,2R)-2-Acrylamidocyclopentyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Aminocyclopentyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 30 N-((1S,2S)-2-Acrylamidocyclopentyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,3R)-3-Acrylamidocyclopentyl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

- N-((1R,2S)-2-Acrylamidocyclohexyl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,4S)-4-Acrylamidocyclohexyl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5 N-((1R,2R)-2-Aminocyclopentyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,3S)-3-Acrylamidocyclopentyl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-(*S)-(2-Methyl-4-phenoxyphenyl)-N-((1R,2S)-2-(2-
- 10 (methylamino)acetamido)cyclopentyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,2S)-2-(2-(Dimethylamino)acetamido)cyclopentyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 15 N-((1S,2R)-2-Acrylamidocyclohexyl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-(*S)-(2-Methyl-4-phenoxyphenyl)-N-((1R,2S)-2-(2-(methylamino)acetamido)cyclohexyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Aminocyclohexyl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-
- 20 triazaacenaphthylene-2-carboxamide;
- N-((1S,2R)-2-Acrylamidocyclopentyl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-(2-(Dimethylamino)acetamido)cyclopentyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-
- 25 carboxamide;
- N-((1R,2S)-2-(2-Aminoacetamido)cyclohexyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,2S)-2-(2-Aminoacetamido)cyclopentyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 30 N-((1R,2S)-2-(2-Aminoacetamido)cyclopentyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

- N-((1R,2S)-2-(2-(Dimethylamino)acetamido)cyclohexyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5 5-(*S)-(2-Methyl-4-phenoxyphenyl)-N-((1S,2S)-2-(2-(methylamino)acetamido)cyclopentyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,2S)-2-Acetamidocyclopentyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 10 N-((1S,2S)-2-Aminocyclopentyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acetamidocyclohexyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 15 N-((1R,2S)-2-Aminocyclohexyl)-5-(3-chloro-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acetamidocyclopentyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 20 N-((1R,3R)-3-Hydroxycyclohexyl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Hydroxycyclopentyl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 25 5-([1,1'-Biphenyl]-3-yl)-N-((1R,2S)-2-aminocyclohexyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,3S)-3-Hydroxycyclohexyl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 30 N-((1S,3S)-3-Hydroxycyclohexyl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-([1,1'-Biphenyl]-3-yl)-N-((1R,2R)-2-hydroxycyclopentyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,4S)-4-Aminocyclohexyl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- trans-N-((1R,4R)-4-Aminocyclohexyl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- trans-N-((1R,3R)-3-Aminocyclopentyl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

- N-((1S,2S)-2-Aminocyclopentyl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2R)-2-Aminocyclohexyl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5 tert-Butyl ((1R,3S)-3-(4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)cyclopentyl)carbamate;
- tert-Butyl trans-((1R,4R)-4-(4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)cyclohexyl)carbamate;
- N-((1-Hydroxycyclohexyl)methyl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 10 N-((1S,3R)-3-((E)-4-(Dimethylamino)but-2-enamido)cyclopentyl)-5-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,2R)-2-(2-Aminoacetamido)cyclopentyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 15 N-((1S,2R)-2-(2-(Dimethylamino)acetamido)cyclopentyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-(*S)-(2-Methyl-4-phenoxyphenyl)-N-((1S,2R)-2-(2-(methylamino)acetamido)cyclopentyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 20 N-((1S,3R)-3-Hydroxycyclohexyl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,3R)-3-(2-(Dimethylamino)acetamido)cyclopentyl)-5-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 25 4-Oxo-5-(2-phenylpyridin-4-yl)-N-((1S,2R)-2-propionamidocyclopentyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Aminocyclohexyl)-5-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-(4-Isopropoxy-2-methylphenyl)-N-((1S,3R)-3-(2-(methylamino)acetamido)cyclopentyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 30 N-((1S,2R)-2-Acetamidocyclopentyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

- tert-Butyl ((1S,4S)-4-(4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)cyclohexyl)carbamate;
- N-((1S,3R)-3-Aminocyclopentyl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5 N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(*R)-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(*S)-(4-methyl-2-phenoxy-pyrimidin-5-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-4-oxo-5-(6-phenylpyrimidin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 10 N-((1R,2S)-2-Acrylamidocyclohexyl)-4-oxo-5-(2-phenylpyridin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-4-oxo-5-(2-phenylpyridin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 15 N-((1R,2S)-2-Aminocyclopentyl)-5-(*S)-(4-methyl-6-phenoxy-pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(*S)-(4-methyl-6-phenoxy-pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclohexyl)-4-oxo-5-(6-phenoxy-pyridin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 20 N-((1R,2S)-2-Acrylamidocyclohexyl)-5-(*S)-(4-methyl-6-phenoxy-pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclohexyl)-5-(*R)-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 25 N-((1R,3R)-3-Acrylamidocyclopentyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,3R)-3-Acrylamidocyclohexyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2R)-2-Acrylamidocyclopentyl)-4-oxo-5-(6-phenoxy-pyridin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 30 N-((1R,2S)-2-Acrylamidocyclopentyl)-4-oxo-5-(6-phenoxy-pyridin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

- N-((1R,2S)-2-Acrylamidocyclopentyl)-4-oxo-5-(5-phenoxy pyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,3R)-3-Acetamidocyclohexyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5 N-((1R,3R)-3-Aminocyclohexyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,3R)-3-Acrylamidocyclohexyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 10 N-((1R,2S)-2-Acrylamidocyclohexyl)-5-(6-cyclobutoxy-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,3R)-3-Acrylamidocyclopentyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2R)-2-Acrylamidocyclopentyl)-4-oxo-5-(5-phenoxy pyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 15 N-((1S,3R)-3-Acrylamidocyclopentyl)-5-(*R)-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclohexyl)-5-(6-cyclobutoxy-2-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,3S)-3-Acrylamidocyclopentyl)-4-oxo-5-(6-phenoxy pyridin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 20 N-((1R,2S)-2-Acrylamidocyclopentyl)-4-oxo-5-(4-phenylpyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,3R)-3-Acrylamidocyclohexyl)-5-(*R)-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 25 N-((1S,3R)-3-Acrylamidocyclopentyl)-5-(3-chloro-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-4-oxo-5-(5-phenylpyridin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-([1,1'-Biphenyl]-3-yl)-N-((1R,2S)-2-acrylamidocyclopentyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 30 N-((1R,2S)-2-Acrylamidocyclopentyl)-4-oxo-5-(3-(pyridin-2-yl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

- N-((1R,3R)-3-Acetamidocyclohexyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,3S)-3-Acrylamidocyclopentyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5 N-((1R,2R)-2-Acrylamidocyclopentyl)-4-oxo-5-(2-phenylpyridin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,3R)-3-Acrylamidocyclopentyl)-4-oxo-5-(2-phenylpyridin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(2-methyl-4-(pyridin-3-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 10 N-((1R,2R)-2-Acrylamidocyclopentyl)-5-(*S)-(4-methyl-6-phenoxy-pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-4-oxo-5-(5-phenoxy-pyrazin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 15 N-((1R,2S)-2-Acrylamidocyclopentyl)-4-oxo-5-(3-(pyridin-3-yl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-4-oxo-5-(6-phenylpyridazin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclohexyl)-5-(*S)-(6-cyclobutoxy-2-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 20 N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(4-isopropoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(2-methyl-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 25 N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(2-isopropylpyridin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,3S)-3-Acrylamidocyclopentyl)-4-oxo-5-(2-phenylpyridin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclohexyl)-5-(*S)-(6-isopropoxy-2-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 30 N-((1R,2S)-2-(3-Chloropropanamido)cyclopentyl)-5-(*S)-(4-methyl-6-phenoxy-pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

- N-((1R,2S)-2-Acrylamidocyclohexyl)-5-(6-isopropoxy-2-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,3R)-3-Acrylamidocyclopentyl)-4-oxo-5-(2-phenylpyridin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5 N-((1R,2R)-2-Acrylamidocyclohexyl)-5-(*S)-(4-methyl-6-phenoxy-pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,3R)-3-Acrylamidocyclopentyl)-4-oxo-5-(5-phenoxy-pyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 10 N-((1R,3R)-3-Acrylamidocyclohexyl)-5-(*R)-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,3R)-3-Acrylamidocyclohexyl)-4-oxo-5-(5-phenoxy-pyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,3R)-3-(2-(Dimethylamino)acetamido)cyclopentyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 15 N-((1R,2R)-2-Acrylamidocyclohexyl)-4-oxo-5-(5-phenoxy-pyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2R)-2-Acrylamidocyclopentyl)-5-(*S)-(4-methyl-2-phenoxy-pyrimidin-5-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(2-methyl-4-(pyridin-2-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 20 N-((1R,2S)-2-Acrylamidocyclohexyl)-5-(*S)-(6-cyclobutoxy-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclohexyl)-5-(6-isopropoxy-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 25 N-((1R,2S)-2-Acrylamidocyclohexyl)-5-(6-(cyclopentyloxy)-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(2-methyl-4-(pyrimidin-2-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclohexyl)-5-(6-isobutoxy-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 30 N-((1S,3S)-3-Acrylamidocyclopentyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

- N-((1R,2R)-2-Acrylamidocyclohexyl)-4-oxo-5-(2-phenylpyridin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,3R)-3-Acetamidocyclopentyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5 5-(2-Methyl-4-phenoxyphenyl)-N-((1R,3R)-3-(2-(methylamino)acetamido)cyclopentyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,3R)-3-Aminocyclohexyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,3S)-3-Acrylamidocyclohexyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 10 N-((1R,3R)-3-Acrylamidocyclohexyl)-4-oxo-5-(2-phenylpyridin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2R)-2-Aminocyclopentyl)-5-(4-methyl-6-phenoxy-pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 15 N-((1R,2S)-2-Acrylamidocyclopentyl)-4-oxo-5-(4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,3R)-3-(2-Aminoacetamido)cyclopentyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,3R)-3-Aminocyclopentyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 20 N-((1R,3S)-3-Acrylamidocyclohexyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclohexyl)-5-(*R)-(6-isopropoxy-2-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 25 N-((1R,2R)-2-Acrylamidocyclohexyl)-4-oxo-5-(6-phenoxy-pyridin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,3S)-3-Aminocyclopentyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,3S)-3-Acetamidocyclopentyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 30 N-((1R,2S)-2-Acrylamidocyclohexyl)-5-(*R)-(6-cyclobutoxy-2-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

- N-((1S,3S)-3-Acetamidocyclohexyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,3S)-3-Acetamidocyclopentyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5 N-((1S,3S)-3-(2-(Dimethylamino)acetamido)cyclopentyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-(2-Methyl-4-phenoxyphenyl)-N-((1S,3S)-3-(2-(methylamino)acetamido)cyclopentyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,3S)-3-Aminocyclohexyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 10 1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-(3-Chloro-4-phenoxyphenyl)-N-((1S,3R)-3-((E)-4-(dimethylamino)but-2-enamido)cyclopentyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-([1,1'-Biphenyl]-3-yl)-N-((1R,2S)-2-aminocyclopentyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 15 5-(*S)-(2-Methyl-4-phenoxyphenyl)-N-((1R,3S)-3-(2-(methylamino)acetamido)cyclohexyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,3S)-3-(2-Aminoacetamido)cyclohexyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 20 N-((1R,3S)-3-(2-(Dimethylamino)acetamido)cyclohexyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,3S)-3-Acetamidocyclohexyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 25 N-((1R,2S)-2-Aminocyclopentyl)-5-(*S)-(4-methyl-2-phenoxy-pyrimidin-5-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2R)-2-Aminocyclohexyl)-5-(*S)-(4-methyl-6-phenoxy-pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2R)-2-Aminocyclopentyl)-5-(*S)-(4-methyl-2-phenoxy-pyrimidin-5-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 30 N-((1R,2S)-2-Aminocyclohexyl)-4-oxo-5-(6-phenoxy-pyridin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

- N-((1S,2R)-2-Acetamidocyclopentyl)-4-oxo-5-(2-phenylpyridin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,3S)-3-Aminocyclopentyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5 N-((1R,2S)-2-Aminocyclohexyl)-4-oxo-5-(2-phenylpyridin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,3S)-3-Aminocyclohexyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 10 N-((1R,2S)-2-Aminocyclopentyl)-5-(*R)-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Aminocyclopentyl)-4-oxo-5-(2-phenylpyridin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2R)-2-Acrylamidocyclohexyl)-5-(*R)-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 15 N-((1R,2S)-2-Aminocyclopentyl)-4-oxo-5-(6-phenoxy-pyridin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclohexyl)-5-(*R)-(6-cyclobutoxy-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Aminocyclopentyl)-4-oxo-5-(4-phenylpyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 20 N-((1R,2R)-2-Hydroxycyclopentyl)-4-oxo-5-(2-phenylpyridin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2R)-2-Aminocyclopentyl)-4-oxo-5-(6-phenoxy-pyridin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 25 N-((1R,2S)-2-Aminocyclopentyl)-5-(2-isopropylpyridin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Aminocyclopentyl)-5-(4-isopropoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,2S)-2-Acrylamidocyclohexyl)-5-(*R)-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 30 N-((1R,2R)-2-Acrylamidocyclohexyl)-5-(*S)-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

- N-((1S, S)-3-Acrylamidocyclohexyl)-5-(*R)-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,3S)-3-Acrylamidocyclohexyl)-5-(*R)-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5 N-((1R,3S)-3-Acrylamidocyclopentyl)-5-(*R)-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2R)-2-Aminocyclohexyl)-4-oxo-5-(6-phenoxy pyridin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Aminocyclopentyl)-4-oxo-5-(6-phenylpyridazin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 10 N-((1S,3S)-3-Acrylamidocyclohexyl)-4-oxo-5-(2-phenylpyridin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acetamidocyclopentyl)-4-oxo-5-(2-phenylpyridin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 15 N-((1R,2S)-2-Aminocyclopentyl)-4-oxo-5-(6-phenylpyrimidin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,3S)-3-Acrylamidocyclopentyl)-4-oxo-5-(2-phenylpyridin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,3S)-3-Acrylamidocyclohexyl)-4-oxo-5-(2-phenylpyridin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 20 N-((1R,2S)-2-Aminocyclopentyl)-4-oxo-5-(5-phenylpyridin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Aminocyclopentyl)-4-oxo-5-(3-(pyridin-2-yl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 25 N-((1S,2R)-2-(2-(Methylamino)acetamido)cyclopentyl)-4-oxo-5-(2-phenylpyridin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Aminocyclopentyl)-5-(2-methyl-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Aminocyclopentyl)-4-oxo-5-(4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 30 racemic cisN-((1RS,3RS)-3-Aminocyclopentyl)-4-oxo-5-(6-phenoxy pyridin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

- racemic transN-((1R,3R)-3-Aminocyclopentyl)-4-oxo-5-(6-phenoxy-pyridin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclohexyl)-4-oxo-5-(5-phenoxy-pyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5 N-((1R,2R)-2-Acrylamidocyclopentyl)-5-(2-methyl-6-phenoxy-pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,3R)-3-Aminocyclopentyl)-5-(4-methyl-6-phenoxy-pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 10 N-((1R,3R)-3-Acrylamidocyclopentyl)-4-oxo-5-(6-phenoxy-pyridin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclohexyl)-4-oxo-5-(5-phenoxy-pyrazin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-acrylamidocyclopentyl)-4-oxo-5-(5-phenoxy-pyrimidin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 15 N-((1R,2S)-2-Acrylamidocyclohexyl)-4-oxo-5-(5-phenoxy-pyrimidin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclohexyl)-5-(*S)-(6-isopropoxy-4-methyl-pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-4-oxo-5-(*S)-(4-(pyridin-3-yloxy)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 20 N-((1R,2R)-2-Acrylamidocyclopentyl)-5-(*S)-(2-methyl-6-phenoxy-pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclohexyl)-4-oxo-5-(2-phenoxy-pyrimidin-5-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 25 N-((1R,2S)-2-Acrylamidocyclohexyl)-5-(*S)-(2-methyl-6-phenoxy-pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(*S)-(2-methyl-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(2-methyl-4-(pyridazin-3-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 30 N-((1*S,3*S)-3-Acrylamidocyclopentyl)-5-(*S)-(4-methyl-6-phenoxy-pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

- N-((1R,2R)-2-Acrylamidocyclopentyl)-4-oxo-5-(5-phenoxy pyrimidin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1*S,3*S)-3-Acrylamidocyclohexyl)-5-(*S)-(4-methyl-6-phenoxy pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5 N-((1R,2S)-2-Acrylamidocyclohexyl)-5-(*S)-(6-(cyclopentyloxy)-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-4-oxo-5-(2-phenoxy pyrimidin-5-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2R)-2-Acrylamidocyclopentyl)-4-oxo-5-(5-phenoxy pyrazin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 10 N-((1R,2S)-2-Acrylamidocyclohexyl)-5-(*S)-(6-isobutoxy-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,3R)-3-Acrylamidocyclopentyl)-4-oxo-5-(5-phenoxy pyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 15 N-((1R,2R)-2-Acrylamidocyclopentyl)-4-oxo-5-(2-phenoxy pyrimidin-5-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1*S,3*S)-3-Acrylamidocyclohexyl)-4-oxo-5-(5-phenoxy pyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2R)-2-Acrylamidocyclopentyl)-5-(*S)-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 20 5-([2,3'-Bipyridin]-4-yl)-N-((1R,2S)-2-acrylamidocyclopentyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1*R,2*S)-2-Aminocyclopentyl)-5-(*S)-(2-methyl-6-phenoxy pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 25 N-((1S,3R)-3-Acrylamidocyclopentyl)-4-oxo-5-(2-phenoxy pyrimidin-5-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-4-oxo-5-(5-phenylpyridazin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1*S,3*S)-3-Acrylamidocyclopentyl)-4-oxo-5-(6-phenoxy pyridin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 30 N-((1R,2R)-2-Acrylamidocyclohexyl)-5-(*S)-(2-methyl-6-phenoxy pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

- N-((1S,3S)-3-Acrylamidocyclohexyl)-4-oxo-5-(6-phenoxy pyridin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2R)-2-Acrylamidocyclopentyl)-4-oxo-5-(3-(pyridin-3-yl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5 5-([2,2'-Bipyridin]-4-yl)-N-((1R,2S)-2-acrylamidocyclopentyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-([2,3'-Bipyridin]-4-yl)-N-((1R,2R)-2-acrylamidocyclopentyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2R)-2-Acrylamidocyclopentyl)-4-oxo-5-(3-(pyridin-2-yl)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 10 N-((1*R,3*S)-3-Acrylamidocyclopentyl)-4-oxo-5-(5-phenoxy pyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1*R,3*R)-3-Acrylamidocyclopentyl)-5-(4-methyl-6-phenoxy pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 15 N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(6-(isopropylamino)-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1*R,3*R)-3-Acrylamidocyclohexyl)-4-oxo-5-(6-phenoxy pyridin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1*R,3*R)-3-Acrylamidocyclohexyl)-5-(4-methyl-6-phenoxy pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 20 N-((1R,2S)-2-Aminocyclohexyl)-5-(4-methyl-6-phenoxy pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1*R,3*R)-3-Acrylamidocyclopentyl)-4-oxo-5-(6-phenoxy pyridin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 25 N-((1R,2S)-2-Aminocyclohexyl)-5-(6-isobutyl-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2R)-2-Aminocyclopentyl)-5-(2-isopropylpyridin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2R)-2-Acrylamidocyclopentyl)-5-(2-isopropylpyridin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 30 N-((1R,2R)-2-Acrylamidocyclohexyl)-4-oxo-5-(2-phenoxy pyrimidin-5-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

- N-((1R,2R)-2-Aminocyclopentyl)-5-(*S)-(2-methyl-6-phenoxy pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acetamidocyclohexyl)-5-(*S)-(2-methyl-6-phenoxy pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5 N-((1R,2S)-2-Acrylamidocyclohexyl)-5-(*R)-(6-(cyclopentyloxy)-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-([2,2'-Bipyridin]-4-yl)-N-((1R,2R)-2-acrylamidocyclopentyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-(*S)-(2-Methyl-6-phenoxy pyridin-3-yl)-4-oxo-N-((1R,2S)-2-propionamidocyclohexyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 10 N-((1R,2S)-2-Acetamidocyclopentyl)-5-(*S)-(2-methyl-6-phenoxy pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acetamidocyclohexyl)-4-oxo-5-(5-phenoxy pyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acetamidocyclopentyl)-5-(*S)-(2-methyl-6-phenoxy pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 15 5-(*S)-(2-Methyl-6-phenoxy pyridin-3-yl)-4-oxo-N-((1R,2S)-2-propionamidocyclopentyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(*R)-(2-methyl-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclohexyl)-5-(*R)-(6-isopropoxy-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 20 N-((1R,2S)-2-Aminocyclopentyl)-4-oxo-5-(5-phenylpyridazin-3-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2R)-2-Aminocyclohexyl)-5-(*S)-(2-methyl-6-phenoxy pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 25 N-((1S,3R)-3-Acrylamidocyclohexyl)-4-oxo-5-(2-phenylpyridin-4-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclohexyl)-5-(*R)-(6-isobutoxy-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-(*S)-(2-Methyl-6-phenoxy pyridin-3-yl)-4-oxo-N-((1R,2R)-2-propionamidocyclopentyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 30 N-((1R,2S)-2-Aminocyclopentyl)-5-(*S)-(6-isobutyl-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

- N-((1R,3S)-3-Aminocyclopentyl)-5-(*S)-(4-methyl-6-phenoxy pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,3S)-3-Aminocyclohexyl)-5-(*S)-(4-methyl-6-phenoxy pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5 N-((1R,2S)-2-Acrylamidocyclohexyl)-5-(*S)-(6-isobutyl-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2R)-2-Acetamidocyclopentyl)-5-(*S)-(2-methyl-6-phenoxy pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,3S)-3-Acrylamidocyclopentyl)-5-(*S)-(4-methyl-6-phenoxy pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 10 N-((1R,3S)-3-Acetamidocyclohexyl)-5-(*S)-(4-methyl-6-phenoxy pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-(*S)-(4-Methyl-6-phenoxy pyridin-3-yl)-4-oxo-N-((1R,3S)-3-propionamidocyclopentyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 15 N-((1R,2R)-2-Acetamidocyclohexyl)-5-(*S)-(2-methyl-6-phenoxy pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,3S)-3-Acrylamidocyclohexyl)-5-(*S)-(4-methyl-6-phenoxy pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-(*S)-(2-Methyl-6-phenoxy pyridin-3-yl)-4-oxo-N-((1R,2R)-2-propionamidocyclohexyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 20 N-((1R,3S)-3-Acrylamidocyclopentyl)-5-(6-isobutoxy-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,3S)-3-Acrylamidocyclopentyl)-5-(*S)-(6-(cyclopentyl oxy)-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 25 N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(2-methyl-4-((2-methylpyridin-3-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(2-methyl-4-((6-methylpyridin-2-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(4-((6-methylpyridin-2-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 30 N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(4-((6-methylpyridin-3-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

- N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(*S)-(6-(cyclopentyloxy)-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(4-((2-methylpyridin-3-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5 N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(*S)-(6-isobutoxy-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Aminocyclopentyl)-5-(*S)-(6-(cyclopentyloxy)-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Aminocyclohexyl)-5-(*S)-(4-methyl-6-phenoxy-pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 10 N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(2-cyclobutylpyridin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acetamidocyclohexyl)-5-(*S)-(4-methyl-6-phenoxy-pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 15 N-((1R,2S)-2-Acetamidocyclopentyl)-5-(*S)-(4-methyl-6-phenoxy-pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2R)-2-Acrylamidocyclopentyl)-5-(2-cyclobutylpyridin-4-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-(*S)-(2-Methyl-4-phenoxyphenyl)-4-oxo-N-((1R,2S)-2-propionamidocyclohexyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 20 5-(*S)-(4-Methyl-6-phenoxy-pyridin-3-yl)-4-oxo-N-((1R,2S)-2-propionamidocyclohexyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2R)-2-Acrylamidocyclopentyl)-5-(*S)-(6-isobutyl-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 25 N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(2-methyl-4-(((S)-tetrahydrofuran-3-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(2-methyl-4-((6-methylpyridin-3-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-(*S)-(4-Methyl-6-phenoxy-pyridin-3-yl)-4-oxo-N-((1R,3S)-3-propionamidocyclohexyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 30 N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(2-methyl-4-(((R)-tetrahydrofuran-3-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

- N-((1R,2S)-2-Acrylamidocyclopentyl)-4-oxo-5-(4-(pyridazin-3-yloxy)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-(*S)-(4-Methyl-6-phenoxy pyridin-3-yl)-4-oxo-N-((1R,3R)-3-propionamidocyclopentyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5 N-((1S,4S)-4-Acetamidocyclohexyl)-5-(*S)-(4-methyl-6-phenoxy pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-(*S)-(4-Methyl-6-phenoxy pyridin-3-yl)-4-oxo-N-((1S,3R)-3-propionamidocyclopentyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 10 N-((1S,3R)-3-Acetamidocyclopentyl)-5-(*S)-(4-methyl-6-phenoxy pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,3R)-3-Acetamidocyclopentyl)-5-(*S)-(4-methyl-6-phenoxy pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2R)-2-Hydroxycyclopentyl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 15 N-((1R,3S)-3-Aminocyclopentyl)-5-(*S)-(6-(cyclopentyl oxy)-4-methyl pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,3S)-3-Acetamidocyclopentyl)-5-(*S)-(4-methyl-6-phenoxy pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acetamidocyclopentyl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 20 N-((1R,2S)-2-Aminocyclopentyl)-5-(*S)-(6-isobutoxy-4-methyl pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 4-Oxo-5-(4-phenoxyphenyl)-N-((1R,2S)-2-propionamidocyclopentyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 25 5-(*S)-(4-Methyl-6-phenoxy pyridin-3-yl)-4-oxo-N-((1S,3S)-3-propionamidocyclopentyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,3S)-3-Acetamidocyclohexyl)-5-(*S)-(4-methyl-6-phenoxy pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclohexyl)-5-(2-methyl-4-(pyridin-2-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 30 5-(*S)-(4-Methyl-6-phenoxy pyridin-3-yl)-4-oxo-N-((1S,3S)-3-propionamidocyclohexyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

- N-((1R,3S)-3-Acetamidocyclopentyl)-5-(*S)-(4-methyl-6-phenoxy-pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2R)-2-Acrylamidocyclohexyl)-5-(*S)-(6-isobutyl-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5 N-((1R,3S)-3-Aminocyclopentyl)-5-(*S)-(6-isobutoxy-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclohexyl)-5-(2-methyl-4-(pyridazin-3-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,3R)-3-Acetamidocyclohexyl)-5-(*S)-(4-methyl-6-phenoxy-pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 10 N-((1R,2S)-2-Acrylamidocyclohexyl)-4-oxo-5-(4-(pyridazin-3-yloxy)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-(*S)-(2-Methyl-6-phenoxy-pyridin-3-yl)-4-oxo-N-((1S,3S)-3-propionamidocyclopentyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 15 N-((1S,3S)-3-Acetamidocyclopentyl)-5-(*S)-(2-methyl-6-phenoxy-pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,3R)-3-Acrylamidocyclohexyl)-5-(*S)-(2-methyl-6-phenoxy-pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-(*S)-(2-Methyl-6-phenoxy-pyridin-3-yl)-4-oxo-N-((1S,3R)-3-propionamidocyclohexyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 20 N-((1S,3R)-3-Acetamidocyclohexyl)-5-(*S)-(2-methyl-6-phenoxy-pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,3R)-3-Aminocyclohexyl)-5-(*S)-(2-methyl-6-phenoxy-pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 25 N-((1S,3S)-3-Aminocyclopentyl)-5-(*S)-(2-methyl-6-phenoxy-pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-(*S)-(4-Methyl-6-phenoxy-pyridin-3-yl)-4-oxo-N-((1S,3R)-3-propionamidocyclohexyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- (S)-5-(2-Methyl-4-phenoxyphenyl)-2-(3-(methylamino)pyrrolidine-1-carbonyl)-3H-1-thia-3,5,8-triazaacenaphthylene-4(5H)-one;
- 30 (S)-N-(1-(5-(2-Methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carbonyl)pyrrolidin-3-yl)propionamide;

- (S)-N-(1-(5-(2-Methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carbonyl)pyrrolidin-3-yl)acetamide;
- (S)-2-(3-Aminopyrrolidine-1-carbonyl)-5-(2-methyl-4-phenoxyphenyl)-3H-1-thia-3,5,8-triazaacenaphthylene-4(5H)-one;
- 5 (S)-2-(3-(Dimethylamino)pyrrolidine-1-carbonyl)-5-(2-methyl-4-phenoxyphenyl)-3H-1-thia-3,5,8-triazaacenaphthylene-4(5H)-one;
- N-((1R,3R)-3-Acetamidocyclohexyl)-5-(*)-(4-methyl-6-phenoxy-pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-(*)-(4-Methyl-6-phenoxy-pyridin-3-yl)-4-oxo-N-((1R,3R)-3-propionamidocyclohexyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 10 N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(*)-(2-methyl-4-(pyridazin-3-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(*)-(2-methyl-4-(pyridazin-3-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 15 N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(*)-(6-isopropoxy-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,3S)-3-Acrylamidocyclopentyl)-5-(*)-(6-isopropoxy-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Aminocyclopentyl)-5-(*)-(6-isopropoxy-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 20 N-((1R,3S)-3-Aminocyclopentyl)-5-(*)-(6-isopropoxy-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,3R)-3-Acrylamidocyclopentyl)-5-(*)-(4-methyl-6-phenoxy-pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 25 N-((1S,3R)-3-Aminocyclopentyl)-5-(*)-(4-methyl-6-phenoxy-pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1r,4r)-4-Acetamidocyclohexyl)-5-(*)-(4-methyl-6-phenoxy-pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- (S)-N-(1-(5-(2-Methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carbonyl)pyrrolidin-3-yl)acrylamide;
- 30 (R)-N-(1-(5-(2-Methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carbonyl)pyrrolidin-3-yl)acrylamide;

- (S,E)-2-Cyano-3-cyclopropyl-N-(1-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carbonyl)pyrrolidin-3-yl)acrylamide;
- (R,E)-2-Cyano-3-cyclopropyl-N-(1-(5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carbonyl)pyrrolidin-3-yl)acrylamide;
- 5 N-((1R,2S)-2-Acrylamidocyclopentyl)-4-oxo-5-(4-(pyridin-2-yloxy)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(3-isopropylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 10 N-((1R,2R)-2-Acrylamidocyclohexyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2R)-2-Aminocyclohexyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2R)-2-(2-Aminoacetamido)cyclohexyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 15 N-((1R,2S)-2-Acrylamidocyclohexyl)-4-oxo-5-(4-(pyridin-2-yloxy)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-(*S)-(2-Methyl-4-phenoxyphenyl)-N-((1S,2R)-2-(2-(methylamino)acetamido)cyclohexyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,2R)-2-(2-Aminoacetamido)cyclohexyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 20 N-((1R,2R)-2-Acetamidocyclohexyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,2R)-2-Acetamidocyclohexyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 25 N-((1R,2R)-2-(2-(Dimethylamino)acetamido)cyclohexyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5-(*S)-(2-Methyl-4-phenoxyphenyl)-N-((1R,2R)-2-(2-(methylamino)acetamido)cyclohexyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 30 N-((1S,2R)-2-(2-(Dimethylamino)acetamido)cyclohexyl)-5-(*S)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

- N-((1S,2R)-2-Aminocyclohexyl)-5-(*S*)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,2R)-2-Acrylamidocyclohexyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5 N-((1S,2R)-2-Aminocyclopentyl)-5-(*S*)-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Aminocyclopentyl)-5-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,3R)-3-Acetamidocyclopentyl)-5-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 10 N-((1R,2S)-2-Aminocyclopentyl)-5-(3-isopropylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2R)-2-Hydroxycyclopentyl)-5-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 15 N-((1S,2R)-2-Aminocyclohexyl)-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,2S)-2-Acrylamidocyclopentyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1S,2R)-2-Acrylamidocyclopentyl)-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 20 5-(4-(3-((2-Cyanophenoxy)methyl)phenoxy)-2-methylphenyl)-N-cyclohexyl-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-(5-(4-(3-((2-Cyanophenoxy)methyl)phenoxy)-2-methylphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-yl)cyclopropanecarboxamide;
- 25 N-Cyclohexyl-5-(2-methyl-4-phenoxyphenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-Cyclohexyl-4-oxo-5-(4-phenoxyphenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N1-((E)-4-(((1S,2R)-2-(5-(6-isobutyl-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)cyclopentyl)amino)-4-oxobut-2-en-1-yl)-N5-(15-oxo-19-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1H-thieno[3,4-*d*]imidazol-4-yl)-4,7,10-trioxa-14-azanonadecyl)glutaramide;
- 30

- N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(4-methyl-6-(pyrimidin-2-yloxy)pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-((E)-2-Cyano-3-cyclopropylacrylamido)cyclopentyl)-5-(*S)-(6-isobutyl-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5 N-((1R,2S)-2-Acrylamidocyclohexyl)-5-(4-methyl-6-(pyridazin-3-yloxy)pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(2-methyl-6-(pyrimidin-2-yloxy)pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 10 N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(*S)-(4-methyl-6-oxo-1-(pyridazin-3-yl)-1,6-dihydropyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(*R)-(4-methyl-6-oxo-1-(pyridazin-3-yl)-1,6-dihydropyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 15 N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(4-methyl-6-(pyridazin-3-yloxy)pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclohexyl)-5-(2-methyl-6-(pyridazin-3-yloxy)pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 20 N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(2-methyl-6-(pyridazin-3-yloxy)pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(2-methyl-6-((2-methylpyridin-3-yl)oxy)pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclohexyl)-4-oxo-5-(5-(pyridazin-3-yloxy)pyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 25 N-((1R,2S)-2-Acrylamidocyclopentyl)-4-oxo-5-(5-(pyridazin-3-yloxy)pyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(6'-methyl-2-oxo-2H-[1,2'-bipyridin]-5'-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 30 N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(2-methyl-6-(pyridin-2-yloxy)pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(5-((6-methylpyridin-2-yl)oxy)pyridin-2-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

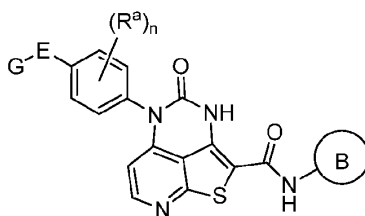
- N-((1R,2S)-2-Acrylamidocyclopentyl)-4-oxo-5-(5-(pyridin-2-yloxy)pyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(5-((6-methylpyridin-3-yl)oxy)pyridin-2-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 5 N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(2-methyl-4-(pyrimidin-5-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(4-methyl-6-((6-methylpyridin-2-yl)oxy)pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-4-oxo-5-(5-(pyrimidin-2-yloxy)pyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 10 N-((1R,2S)-2-Acrylamidocyclopentyl)-4-oxo-5-(5-(pyrimidin-5-yloxy)pyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(4-methyl-6-(pyrimidin-5-yloxy)pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 15 N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(4-methyl-6-((6-methylpyridin-3-yl)oxy)pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(4-methyl-6-(pyridin-2-yloxy)pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(4-methyl-6-((2-methylpyridin-3-yl)oxy)pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide ;
- 20 N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(4-methyl-6-(pyridin-3-yloxy)pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-4-oxo-5-(5-(pyridin-3-yloxy)pyridin-2-yl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 25 N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(2-methyl-6-(pyrimidin-5-yloxy)pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(5-((2-methylpyridin-3-yl)oxy)pyridin-2-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(2-methyl-6-(pyridin-3-yloxy)pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 30 N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(2-methyl-6-((6-methylpyridin-3-yl)oxy)pyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;

- N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(*S)-(2-methyl-4-((6-methylpyridin-2-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(*R)-(2-methyl-4-((6-methylpyridin-2-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
5 N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(*S)-(2-methyl-4-((6-methylpyridin-3-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(*R)-(2-methyl-4-((6-methylpyridin-3-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(*S)-(2-methyl-4-((2-methylpyridin-3-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
10 N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(*R)-(2-methyl-4-((2-methylpyridin-3-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(*S)-(2-methyl-4-(pyrimidin-2-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
15 N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(*R)-(2-methyl-4-(pyrimidin-2-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(*S)-(2-methyl-4-(pyridin-2-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
N-((1R,2S)-2-Acrylamidocyclopentyl)-5-(*R)-(2-methyl-4-(pyridin-2-yloxy)phenyl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
20 N-((1R,2S)-2-((E)-2-Cyano-3-(3-methyloxetan-3-yl)acrylamido)cyclopentyl)-5-(*S)-(6-isobutyl-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
N-((1R,2S)-2-((E)-2-Cyano-4-ethoxy-4-methylpent-2-enamido)cyclopentyl)-5-(*S)-(6-isobutyl-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
25 N-1-((E)-4-(((1S,2R)-2-(5-(6-isobutyl-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamido)cyclopentyl)amino)-4-oxobut-2-en-1-yl)-N5-(15-oxo-19-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)-4,7,10-trioxa-14-azanonadecyl)glutaramide; and
30 N-((1R,2S)-2-acrylamidocyclopentyl)-4-oxo-5-(4-(pyrimidin-5-yloxy)phenyl)-4,5-dihydro-3H-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide; and isotopic variants, and pharmaceutically acceptable salts, hydrates, polymorph or solvates thereof.

[00206] An additional aspect of the invention is a compound selected from the group consisting of:

- 5 *N*-((1*R*,2*S*)-2-Acrylamidocyclopentyl)-5-(**R*)-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N*-((1*R*,2*S*)-2-Acrylamidocyclopentyl)-5-(**S*)-(4-methyl-2-phenoxy pyrimidin-5-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N*-((1*R*,2*S*)-2-Acrylamidocyclohexyl)-4-oxo-5-(2-phenylpyridin-4-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 10 *N*-((1*R*,2*S*)-2-Acrylamidocyclohexyl)-4-oxo-5-(6-phenoxy pyridin-3-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N*-((1*R*,2*S*)-2-Acrylamidocyclohexyl)-5-(**R*)-(4-isopropoxy-2-methylphenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N*-((1*R*,2*R*)-2-Acrylamidocyclopentyl)-5-(**S*)-(4-methyl-2-phenoxy pyrimidin-5-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 15 *N*-((1*R*,2*S*)-2-Acrylamidocyclopentyl)-4-oxo-5-(5-phenoxy pyrazin-2-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- N*-((1*R*,2*S*)-2-Acrylamidocyclohexyl)-4-oxo-5-(5-phenoxy pyrimidin-2-yl)-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 20 *N*-((1*R*,2*S*)-2-Acrylamidocyclohexyl)-5-(**S*)-(6-isobutyl-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide; and
- N*-((1*R*,2*S*)-2-Acrylamidocyclopentyl)-5-(**S*)-(2-methyl-4-((2-methylpyridin-3-yl)oxy)phenyl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide;
- 25 isotopic variants, and pharmaceutically acceptable salts, hydrates, polymorph or solvates thereof.

[00207] An additional aspect of the invention is a compound of Formula (I) having the Formula (IIa):



(IIa)

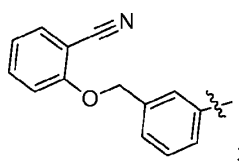
wherein

R^a is selected from the group consisting of: H, Cl and CH_3 ;

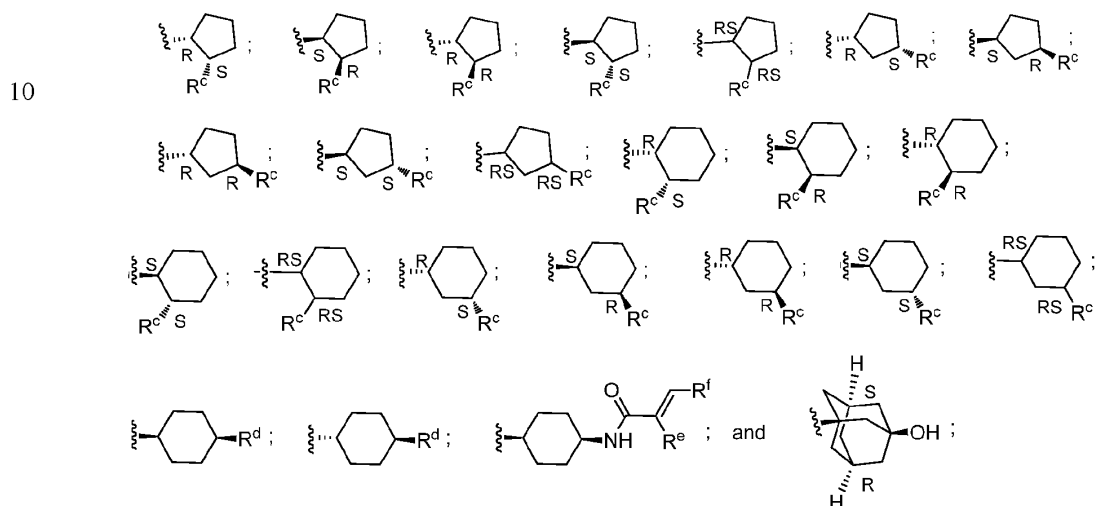
n is 0 or 1;

5 E is O;

G is selected from the group consisting of: C_{1-6} alkyl, phenyl, pyridyl, pyridyl substituted with CH_3 , pyrimidinyl, pyridazinyl, tetrahydrofuranyl, tetrahydropyranyl, and



Ring B is selected from the group consisting of:



15 R^c is selected from the group consisting of: OH, OCH_3 , NH_2 , $NH(CH_3)$, $N(CH_3)_2$, $NH(CO_2-$
tert-butyl), $NH(C=O)C_{1-3}alkyl$, $NH(C=O)CH=CH_2$, $NH(C=O)CH_2NH_2$,

$NH(C=O)CH_2NH(CH_3)$, $NH(C=O)CH_2N(CH_3)_2$, and $NH(C=O)CH=CHCH_2N(CH_3)_2$;

R^d is selected from the group consisting of: OH, OCH_3 , CN, NH_2 , $NH(CH_3)$, $N(CH_3)_2$,

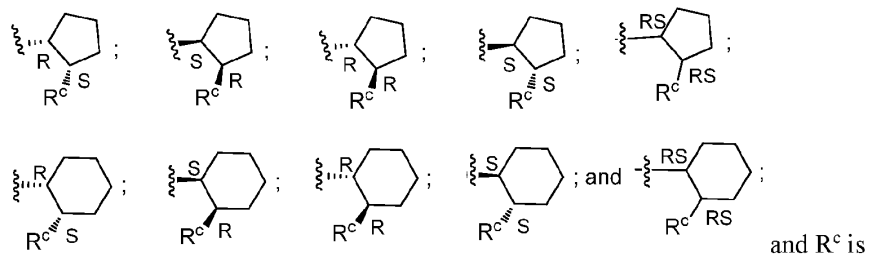
$NH(CO_2-$ *tert*-butyl), $NH(C=O)C_{1-3}alkyl$, and $NH(C=O)CH=CH_2$;

R^e is H or CN; and

20 R^f is selected from the group consisting of: CH_2NH_2 , $CH_2NH(CH_3)$, $CH_2N(CH_3)_2$, and cyclopropyl.

[00208] An additional aspect of the invention is a compound of Formula (I) having the Formula (IIa) wherein: R^a is H or CH_3 ; n is 1; E is O; G is selected from the group consisting of:

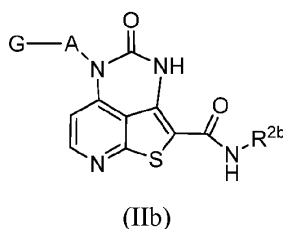
C₁₋₃alkyl, phenyl, pyridyl, and pyridyl substituted with CH₃; Ring B is selected from the group consisting of:



NH(C=O)CH=CH₂.

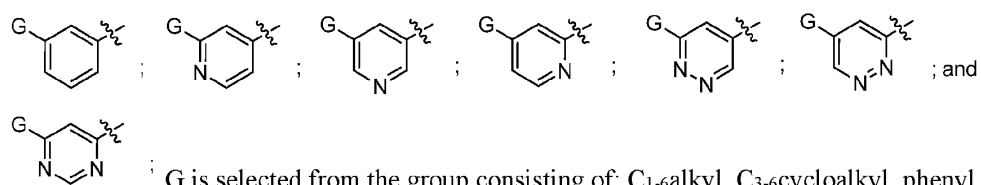
5

[00209] An additional aspect of the invention is a compound of Formula (I) having the Formula (IIb):



10 wherein

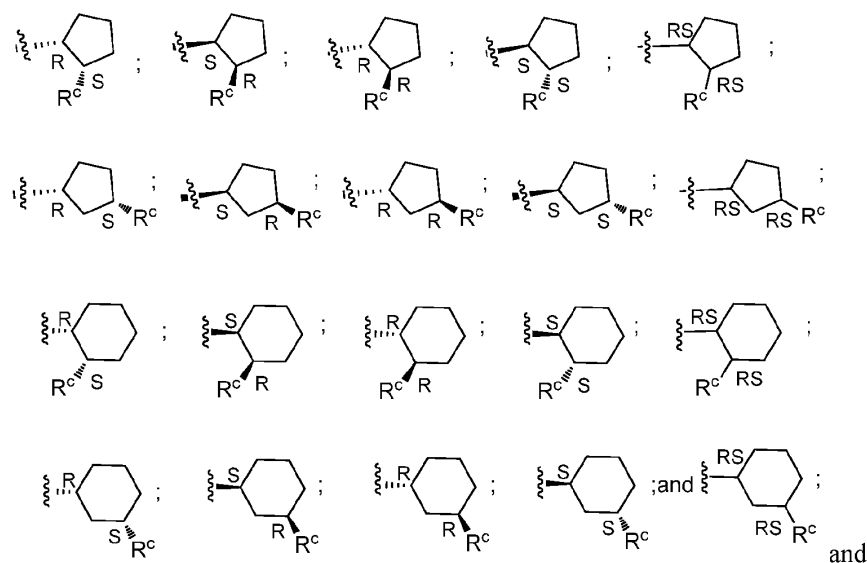
G-A is selected from the group consisting of:



G is selected from the group consisting of: C₁₋₆alkyl, C₃₋₆cycloalkyl, phenyl,

and pyridyl.

15 R^{2b} is selected from the group consisting of:

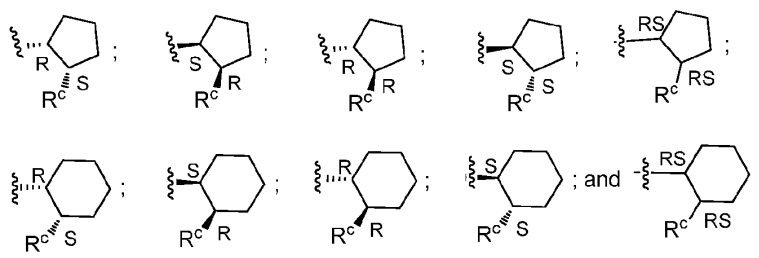


R^c is selected from the group consisting of: OH, OCH₃, NH₂, NH(CH₃), N(CH₃)₂, NH(CO₂-*tert*-butyl), NH(C=O)C₁₋₃alkyl, NH(C=O)CH=CH₂, NH(C=O)CH₂NH₂, NH(C=O)CH₂NH(CH₃), NH(C=O)CH₂N(CH₃)₂, and NH(C=O)CH=CHCH₂N(CH₃)₂.

5

[00210] An additional aspect of the invention is a compound of Formula (I) having the

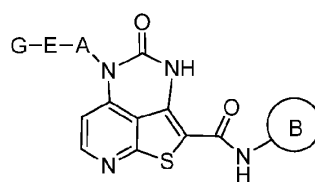
Formula (IIb) wherein: G-A is ; or ; G is phenyl or pyridyl; R^{2b} is selected from the group consisting of:



and R^c is

10 NH(C=O)CH=CH₂.

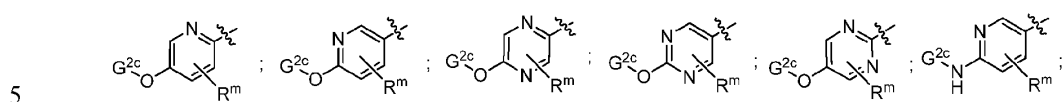
[00211] An additional aspect of the invention is a compound of Formula (I) having the Formula (IIc):



(IIc)

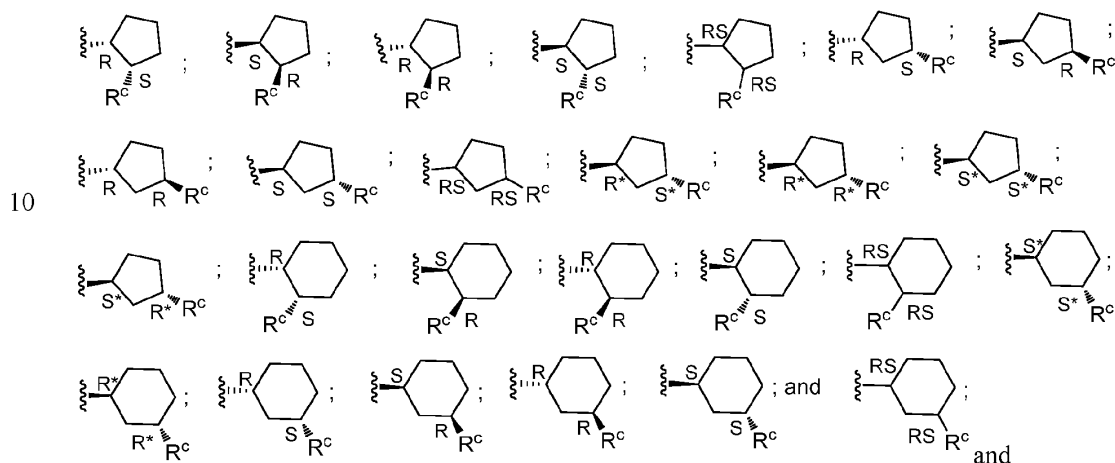
wherein

G-E-A is selected from the group consisting of:



and ; where G^{2c} is selected from the group consisting of: C₁₋₆alkyl, phenyl, pyrimidinyl, pyridyl, pyridyl substituted with CH₃, and C₃₋₆cycloalkyl; and R^m is H or CH₃;

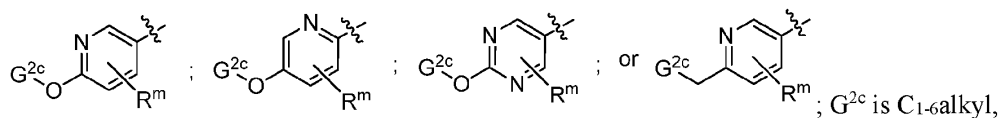
Ring B is selected from the group consisting of:



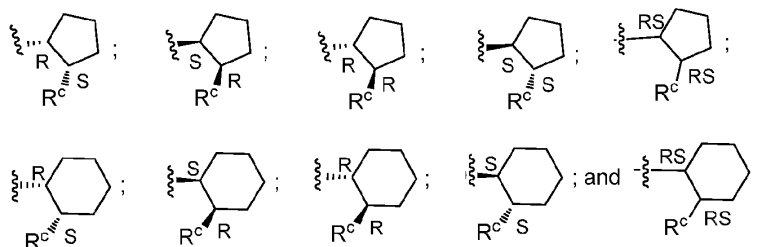
15 R^c is selected from the group consisting of: OH, OCH₃, NH₂, NH(CH₃), N(CH₃)₂, NH(CO₂-*tert*-butyl), NH(C=O)C₁₋₃alkyl, NH(C=O)CH=CH₂, NH(C=O)CH₂NH₂, NH(C=O)CH₂NH(CH₃), NH(C=O)CH₂N(CH₃)₂, and NH(C=O)CH=CHCH₂N(CH₃)₂.

[00212] An additional aspect of the invention is a compound of Formula (I) having the Formula (IIc) wherein:

20 [00213] An additional aspect of the invention is a compound of Formula (I) having the Formula (IIc): wherein G-E-A is



phenyl, or pyridyl; R^m is H or CH_3 ; Ring B is



$NH(C=O)CH=CH_2$.

5

Method of Treatment

[00214] The disclosure also relates to methods of using the compounds described herein to treat subjects diagnosed with or suffering from a disease, disorder, or condition mediated by Bruton's tyrosine kinase. These methods are accomplished by administering to the subject a compound of the disclosure in an amount sufficient to inhibit Bruton's tyrosine kinase.

10 In a further aspect, provided herein are methods for inhibiting Bruton's tyrosine kinase in a subject in need of treatment by administering to the subject a composition containing a therapeutically effective amount of the compound of Formula (III). Some aspects of the disclosure are directed to methods of treating a subject suffering from a malignancy by administering to the subject a composition containing a therapeutically effective amount of the compound of Formula (III). In some aspects, the malignancy is, e.g., a lymphoma, a leukemia, a carcinoma, or a sarcoma. In some aspects the lymphoma includes, but is not limited to non-Hodgkin's lymphoma (NHL (including B-cell NHL)), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), mucosa-associated lymphoid tissue

20 (MALT) lymphoma, marginal zone lymphoma (MZL), T-cell lymphoma, Hodgkin's lymphoma, small lymphocytic lymphoma (SLL), Waldenström macroglobulinemia, and Burkitt's lymphoma. In some aspects, the leukemia includes, but is not limited to chronic lymphocytic leukemia (CLL), lymphoblastic T cell leukemia, chronic myelogenous leukemia (CML), hairy-cell leukemia, acute lymphoblastic T cell leukemia, plasmacytoma, immunoblastic large cell

25 leukemia, megakaryoblastic leukemia, acute megakaryocyte leukemia, promyelocytic leukemia, erythroleukemia and multiple myeloma. In some aspects, the malignancy includes but is not

limited to brain (gliomas), glioblastomas, breast cancer, colorectal/colon cancer, prostate cancer, lung cancer, non-small-cell lung cancer, gastric cancer, endometrial cancer, melanoma, pancreatic cancer, liver cancer, kidney cancer, squamous cell carcinoma, ovarian cancer, sarcoma, osteosarcoma, thyroid cancer, bladder cancer, head & neck cancer, testicular cancer, Ewing's sarcoma, rhabdomyosarcoma, medulloblastoma, neuroblastoma, cervical cancer, renal cancer, urothelial cancer, vulval cancer, esophageal cancer, salivary gland cancer, nasopharyngeal cancer, buccal cancer, cancer of the mouth, Chronic graft versus host disease, and gastrointestinal stromal tumor. When used for the treatment of a malignancy, the compound of Formula (III) can be administered as a single agent. Alternatively, when used for the treatment of an malignancy, the compound of Formula (III) can be administered in combination with other agents known to be useful for the treatment of autoimmune diseases. In a further aspect, provided herein are methods for inhibiting Bruton's tyrosine kinase in a subject in need of treatment by administering to the subject a composition containing a therapeutically effective amount of the compound of Formula (I). Some aspects of the disclosure are directed to methods of treating a subject suffering from a malignancy by administering to the subject a composition containing a therapeutically effective amount of the compound of Formula (I). In some aspects, the malignancy is a lymphoma, a leukemia, a carcinoma, or a sarcoma. In some aspects the lymphoma includes, but is not limited to, non-Hodgkin's lymphoma (NHL (including B-cell NHL)), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), mucosa-associated lymphoid tissue (MALT) lymphoma, marginal zone lymphoma (MZL), T-cell lymphoma, Hodgkin's lymphoma, small lymphocytic lymphoma (SLL), Waldenström macroglobulinemia, and Burkitt's lymphoma. In some aspects, the leukemia includes, but is not limited to chronic lymphocytic leukemia (CLL), lymphoblastic T cell leukemia, chronic myelogenous leukemia (CML), hairy-cell leukemia, acute lymphoblastic T cell leukemia, plasmacytoma, immunoblastic large cell leukemia, megakaryoblastic leukemia, acute megakaryocyte leukemia, promyelocytic leukemia, erythroleukemia and multiple myeloma. In some aspects, the malignancy includes, but is not limited to brain (gliomas), glioblastomas, breast cancer, colorectal/colon cancer, prostate cancer, lung cancer, non-small-cell lung cancer, gastric cancer, endometrial cancer, melanoma, pancreatic cancer, liver cancer, kidney cancer, squamous cell carcinoma, ovarian cancer, sarcoma, osteosarcoma, thyroid cancer, bladder cancer, head & neck cancer, testicular cancer, Ewing's sarcoma, rhabdomyosarcoma, medulloblastoma, neuroblastoma, cervical cancer, renal cancer, urothelial cancer, vulval cancer, esophageal cancer, salivary gland cancer, nasopharyngeal cancer, buccal cancer, cancer of the

mouth, and gastrointestinal stromal tumor. In some aspects, provided herein are methods for the treatment of chronic graft versus host disease in a subject in need thereof. When used for the treatment of a malignancy or other disease or condition, the compound of Formula (I) can be administered as a single agent. Alternatively, when used for the treatment of a malignancy or other disease or condition, the compound of Formula (I) can be administered in combination with one or more other agents known to be useful for the treatment of malignancies.

[00215] The present invention also provides a compound of Formula (III) or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof, for use in treating a malignancy, comprising administering a therapeutically effective amount of said compound or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof to an individual in need thereof. The present invention also provides a compound of Formula (III) or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof for use in treating chronic graft versus host disease in an individual in need thereof, comprising administering a therapeutically effective amount of said compound of Formula (III) or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof. The present invention also provides the use of a compound of Formula (III) or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof, for the manufacture of a medicament for treating a malignancy, in an individual in need thereof. The present invention also provides the use of a compound of Formula (III) or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof, for the manufacture of a medicament for treating chronic graft versus host disease in an individual in need thereof.

[00216] Other aspects of the disclosure are directed to methods of treating a subject suffering from a malignancy by administering to the subject a composition containing a therapeutically effective amount of a compound of Formula (III). In one aspect, the malignancy is diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), marginal zone lymphoma (MZL), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), Waldenström macroglobulinemia, and Chronic graft versus host disease. Malignancies that are particularly suited to being treated with compounds of the disclosure include diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), marginal zone lymphoma (MZL), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), Waldenström macroglobulinemia, and Chronic graft versus host disease. Other aspects of the disclosure are directed to methods of treating a subject suffering from chronic graft versus host disease by administering to the subject a composition containing a therapeutically effective amount of a compound of Formula (III).

[00217] In preferred aspects, the compound of Formula (III) can be used to treat diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), marginal zone lymphoma (MZL), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), Waldenström macroglobulinemia, and Chronic graft versus host disease.

5 [00218] The compound of Formula (III) can also be used to treat malignancies including, but not limited to, lymphomas, leukemias, carcinomas, and sarcomas, e.g. non-Hodgkin's lymphoma (NHL (including B-cell NHL)), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), mucosa-associated lymphoid tissue (MALT) lymphoma, marginal zone lymphoma, T-cell lymphoma, Hodgkin's lymphoma,
10 Burkitt's lymphoma, multiple myeloma, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), Waldenström macroglobulinemia, lymphoblastic T cell leukemia, chronic myelogenous leukemia (CML), hairy-cell leukemia, acute lymphoblastic T cell leukemia, plasmacytoma, immunoblastic large cell leukemia, megakaryoblastic leukemia, acute megakaryocyte leukemia, promyelocytic leukemia, erythroleukemia, brain (gliomas),
15 glioblastomas, breast cancer, colorectal/colon cancer, prostate cancer, lung cancer including non-small-cell, gastric cancer, endometrial cancer, melanoma, pancreatic cancer, liver cancer, kidney cancer, squamous cell carcinoma, ovarian cancer, sarcoma, osteosarcoma, thyroid cancer, bladder cancer, head & neck cancer, testicular cancer, Ewing's sarcoma, rhabdomyosarcoma, medulloblastoma, neuroblastoma, cervical cancer, renal cancer, urothelial cancer, vulval cancer,
20 esophageal cancer, salivary gland cancer, nasopharyngeal cancer, buccal cancer, cancer of the mouth, and GIST (gastrointestinal stromal tumor) as well as chronic graft versus host disease.

[00219] In treatment methods according to the disclosure, a therapeutically effective amount of a pharmaceutical agent according to the disclosure is administered to a subject suffering from or diagnosed as having such a disease, disorder, or condition. Therapeutically
25 effective amounts or doses of the compounds of the present disclosure may be ascertained by routine methods such as modeling, dose escalation studies or clinical trials, and by taking into consideration routine factors, e.g., the mode or route of administration or drug delivery, the pharmacokinetics of the compound, the severity and course of the disease, disorder, or condition, the subject's previous or ongoing therapy, the subject's health status and response to drugs, and
30 the judgment of the treating physician. An example of a dose is in the range of from about 0.0001 to about 1,000 mg of compound per kg of subject's body weight per day, preferably about 0.05 to 100 mg/kg/day, or about 1 to 35 mg/kg/day, in single or divided dosage units (e.g., BID,

TID, QID). For a 70-kg human, an illustrative range for a suitable dosage amount is from about 0.05 to about 7 g/day, or about 0.2 to about 2.5 g/day.

[00220] In some aspects, the therapeutically effective amount of the compound of Formula (III) is from about 0.0001 mg to about 10,000 mg. In some aspects, the therapeutically effective amount of the compound of Formula (III) is from about 0.0001 mg to about 1,000 mg. In some aspects, the therapeutically effective amount of the compound of Formula (III) is from about 0.0001 mg to about 100 mg. In some aspects, the therapeutically effective amount of the compound of Formula (III) is from about 100 mg to about 200 mg. In some aspects, the therapeutically effective amount of the compound of Formula (III) is from about 100 mg to about 300 mg. In some aspects, the therapeutically effective amount of the compound of Formula (III) is from about 100 mg to about 400 mg. In some aspects, the therapeutically effective amount of the compound of Formula (III) is from about 100 mg to about 500 mg. In some aspects, the therapeutically effective amount of the compound of Formula (III) is from about 100 mg to about 600 mg. In some aspects, the therapeutically effective amount of the compound of Formula (III) is from about 100 mg to about 700 mg. In some aspects, the therapeutically effective amount of the compound of Formula (III) is from about 100 mg to about 800 mg. In some aspects, the therapeutically effective amount of the compound of Formula (III) is from about 100 mg to about 900 mg. In some aspects, the therapeutically effective amount of the compound of Formula (III) is from about 100 mg to about 1,000 mg. In some aspects, the therapeutically effective amount of the compound of Formula (III) is from about 140 mg to about 560 mg. In some aspects, the therapeutically effective amount of the compound of Formula (III) is about 140 mg. In some aspects, the therapeutically effective amount of the compound of Formula (III) is about 280 mg. In some aspects, the therapeutically effective amount of the compound of Formula (III) is about 560 mg.

[00221] The present invention also relates to the use of a therapeutically effective amount ranging from about 100 mg to about 1000 mg, alternatively from about 100 mg to about 600 mg, alternatively from about 140 mg to about 560 mg of a compound of Formula (III) or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof, for treating a malignancy as described herein.

[00222] The present invention also relates to the use of a therapeutically effective amount ranging from about 100 mg to about 1000 mg, alternatively from about 100 mg to about 600 mg, alternatively from about 140 mg to about 560 mg of a compound of Formula (III) or a

pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof, for treating a malignancy that is affected by the inhibition of BTK.

[00223] The present invention also relates to a therapeutically effective amount ranging from about 100 mg to about 1000 mg, alternatively from about 100 mg to about 600 mg, 5 alternatively from about 140 mg to about 560 mg of a compound of Formula (III) or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof, for use in treating a malignancy as described herein.

[00224] The present invention also relates to a therapeutically effective amount ranging from about 100 mg to about 1000 mg, alternatively from about 100 mg to about 600 mg, 10 alternatively from about 140 mg to about 560 mg of a compound of Formula (III) or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof, for use in treating a malignancy that is affected by the inhibition of BTK.

[00225] The present invention also relates to a therapeutically effective amount ranging from about 100 mg to about 1000 mg, alternatively from about 100 mg to about 600 mg, 15 alternatively from about 140 mg to about 560 mg of a compound of Formula (III) or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof, for use in a method of treating a malignancy as described herein.

[00226] The present invention also relates to a therapeutically effective amount ranging from about 100 mg to about 1000 mg, alternatively from about 100 mg to about 600 mg, 20 alternatively from about 140 mg to about 560 mg of a compound of Formula (III) or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof, for use in a method of treating a malignancy that is affected by the inhibition of BTK.

[00227] The present invention also relates to the use of a therapeutically effective amount ranging from about 100 mg to about 1000 mg, alternatively from about 100 mg to about 25 600 mg, alternatively from about 140 mg to about 560 mg of a compound of Formula (III) or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof, for the manufacture of a medicament for the treatment of a malignancy as described herein.

[00228] The present invention also relates to the use of a therapeutically effective amount ranging from about 100 mg to about 1000 mg, alternatively from about 100 mg to about 30 600 mg, alternatively from about 140 mg to about 560 mg of a compound of Formula (III) or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof, for the manufacture of a medicament for the treatment of a malignancy that is affected by the inhibition of BTK.

[00229] In some aspects, the therapeutically effective amount of a compound of Formula (III) is determined by the resulting effect in the patient such as a particular pharmacokinetic or pharmacodynamic profile following administration. In some aspects, therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,day1)}$ (maximum concentration at day 1) of about 50 ng/ml to about 2,500 ng/ml. In some aspects, therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,day1)}$ of about 59.992 ng/ml to about 2,377.2 ng/ml. In some aspects, therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,day1)}$ of about 0.0001 ng/ml to about 10,000 ng/ml. In some aspects, therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,day1)}$ of about 0.0001 ng/ml to about 5,000 ng/ml. In some aspects, therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,day1)}$ of about 0.0001 ng/ml to about 2,500 ng/ml. In some aspects, therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,day1)}$ of about 0.0001 ng/ml to about 2,000 ng/ml. In some aspects, therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,day1)}$ of about 0.0001 ng/ml to about 1,500 ng/ml. In some aspects, therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,day1)}$ of about 0.0001 ng/ml to about 1,000 ng/ml. In some aspects, therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,day1)}$ of about 0.0001 ng/ml to about 750 ng/ml. In some aspects, therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,day1)}$ of about 0.0001 ng/ml to about 500 ng/ml. In some aspects, therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,day1)}$ of about 0.0001 ng/ml to about 250 ng/ml. In some aspects, therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,day1)}$ of about 0.0001 ng/ml to about 200 ng/ml. In some aspects, therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,day1)}$ of about 0.0001 ng/ml to about 100 ng/ml. In some aspects, therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,day1)}$ of about 0.0001 ng/ml to about 50 ng/ml. In some aspects, therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,day1)}$ of about 0.0001 ng/ml to about 10 ng/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,day1)}$ of about 200 ng/ml to about 10,000 ng/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an

amount that results in a $C_{(max,day1)}$ of about 239.97 to about 9,509 ng/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,day1)}$ of about 429.75 ng/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,day1)}$ of about 1,719 ng/ml.

- 5 **[00230]** In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ (maximum concentration at steady state) of about 0.0001 ng/ml to about 10,000 ng/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 0.0001 ng/ml to about 5,000 ng/ml. In some aspects, the therapeutically effective amount of the compound of
- 10 Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 0.0001 ng/ml to about 4,000 ng/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 0.0001 ng/ml to about 3,000 ng/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 0.0001 ng/ml to about 2,500 ng/ml. In some aspects, the therapeutically
- 15 effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 0.0001 ng/ml to about 2,000 ng/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 0.0001 ng/ml to about 1,000 ng/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 0.0001 ng/ml to about 750 ng/ml. In
- 20 some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 0.0001 ng/ml to about 500 ng/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 0.0001 ng/ml to about 250 ng/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 0.0001
- 25 ng/ml to about 100 ng/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 0.0001 ng/ml to about 50 ng/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 0.0001 ng/ml to about 10 ng/ml. In some aspects, therapeutically effective amount of the compound of Formula (III) is an amount that results in a
- 30 $C_{(max,day1)}$ of about 50 ng/ml to about 2,500 ng/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 66.855 ng/ml to about 2,395.4 ng/ml. In some aspects, therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,day1)}$ of about 250 ng/ml to

about 10,000 ng/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 267.42 to about 9,581.5 ng/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 435.1 ng/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 1,740.4 ng/ml.

[00231] In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ (area under the curve at day 1) of about 0.0001 ng.hr/ml to about 100,000 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 0.0001 ng.hr/ml to about 75,000 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 0.0001 ng.hr/ml to about 50,000 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 0.0001 ng.hr/ml to about 25,000 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 0.0001 ng.hr/ml to about 20,000 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 0.0001 ng.hr/ml to about 15,000 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 0.0001 ng.hr/ml to about 10,000 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 0.0001 ng.hr/ml to about 5,000 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 0.0001 ng.hr/ml to about 2,500 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 0.0001 ng.hr/ml to about 2,000 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 0.0001 ng.hr/ml to about 1,500 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 0.0001 ng.hr/ml to about 1,000 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 0.0001 ng.hr/ml to about 750 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 0.0001 ng.hr/ml to about 500

ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 0.0001 ng.hr/ml to about 250 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 0.0001 ng.hr/ml to about 200 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 0.0001 ng.hr/ml to about 100 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 0.0001 ng.hr/ml to about 10 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 300 ng.hr/ml to about 15,000 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 312.1 to about 11,517 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 1,000 ng.hr/ml to about 50,000 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 1,248.4 to about 46,068 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 2,157.5 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 8,629.9 ng.hr/ml.

[00232] In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ (area under the curve at steady state) of about 0.0001 ng.hr/ml to about 100,000 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 0.0001 ng.hr/ml to about 75,000 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 0.0001 ng.hr/ml to about 50,000 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 0.0001 ng.hr/ml to about 40,000 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 0.0001 ng.hr/ml to about 30,000 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 0.0001 ng.hr/ml to about 20,000 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 0.0001 ng.hr/ml to about 15,000 ng.hr/ml. In some aspects, the

therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 0.0001 ng.hr/ml to about 10,000 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 0.0001 ng.hr/ml to about 5,000 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 0.0001 ng.hr/ml to about 2,500 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 0.0001 ng.hr/ml to about 2,000 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 0.0001 ng.hr/ml to about 1,000 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 0.0001 ng.hr/ml to about 750 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 0.0001 ng.hr/ml to about 500 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 0.0001 ng.hr/ml to about 250 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 0.0001 ng.hr/ml to about 200 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 0.0001 ng.hr/ml to about 100 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 0.0001 ng.hr/ml to about 10 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 300 ng.hr/ml to about 15,000 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 312.27 ng.hr/ml to about 13,015 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 0.0001 ng.hr/ml to about 20,000 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 1,249.1 ng.hr/ml to about 52,061 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 1,000 ng.hr/ml to about 55,000 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 2,249.7 ng.hr/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 8,998.9 ng.hr/ml.

[illegible]

In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day1)}$ of greater than about 25 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day1)}$ of greater than about 20 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day1)}$ of greater than about 15 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day1)}$ of greater than about 10 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day1)}$ of greater than about 5 % occupancy.

[00234] In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day1)}$ of about 0.0001 % occupancy to about 100 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day1)}$ of about 0.0001 % occupancy to about 99.9 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day1)}$ of about 0.0001 % occupancy to about 99.95 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day1)}$ of about 0.0001 % occupancy to about 99 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day1)}$ of about 0.0001 % occupancy to about 98 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day1)}$ of about 0.0001 % occupancy to about 95 % occupancy.

[00235] In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day1)}$ of about 0.0001 % occupancy to about 90 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day1)}$ of about 0.0001 % occupancy to about 85 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day1)}$ of about 0.0001 % occupancy to about 80 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day1)}$ of about 0.0001 % occupancy to about 75 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day1)}$ of about 0.0001 % occupancy to about 70 % occupancy. In some aspects, the therapeutically effective amount of the compound of

Formula (III) is an amount that results in a $BTkO_{(max/day1)}$ of about 0.0001 % occupancy to about 60 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(max/day1)}$ of about 0.0001 % occupancy to about 50 % occupancy. In some aspects, the therapeutically effective amount of the compound of

5 Formula (III) is an amount that results in a $BTkO_{(max/day1)}$ of about 0.0001 % occupancy to about 40 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(max/day1)}$ of about 0.0001 % occupancy to about 30 % occupancy. In some aspects, the therapeutically effective amount of the compound of

10 Formula (III) is an amount that results in a $BTkO_{(max/day1)}$ of about 0.0001 % occupancy to about 20 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(max/day1)}$ of about 0.0001 % occupancy to about 10 % occupancy. In some aspects, the therapeutically effective amount of the compound of

Formula (III) is an amount that results in a $BTkO_{(max/day1)}$ of about 0.0001 % occupancy to about 1 % occupancy. In some aspects, the therapeutically effective amount of the compound of

15 Formula (III) is an amount that results in a $BTkO_{(max/day1)}$ of about 30.9 % occupancy to about 99.8 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(max/day1)}$ of about 87.1 % occupancy to about 100 % occupancy. In some aspects, the therapeutically effective amount of the compound of

Formula (III) is an amount that results in a $BTkO_{(max/day1)}$ of about 90.4 % occupancy. In some

20 aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(max/day1)}$ of about 95.9 % occupancy.

[00236] In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(max/ss)}$ (maximum BTK occupancy at steady state) of about 100 % occupancy. In some aspects, the therapeutically effective amount of the

25 compound of Formula (III) is an amount that results in a $BTkO_{(max/ss)}$ of greater than about 99.95 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(max/ss)}$ of greater than about 99 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(max/ss)}$ of greater than about 98 % occupancy. In some aspects, the

30 therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(max/ss)}$ of greater than about 95 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(max/ss)}$ of greater than about 90 % occupancy. In some aspects, the therapeutically effective amount of the

compound of Formula (III) is an amount that results in a $BTKO_{(max/ss)}$ of greater than about 85 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/ss)}$ of greater than about 80 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that

5 results in a $BTKO_{(max/ss)}$ of greater than about 75 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/ss)}$ of greater than about 70 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/ss)}$ of greater than about 65 % occupancy. In some aspects, the therapeutically effective amount of the

10 compound of Formula (III) is an amount that results in a $BTKO_{(max/ss)}$ of greater than about 60 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/ss)}$ of greater than about 55% occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/ss)}$ of greater than about 50 % occupancy. In some aspects, the

15 therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/ss)}$ of greater than about 45 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/ss)}$ of greater than about 40 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/ss)}$ of greater than about 35 %

20 occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/ss)}$ of greater than about 30 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/ss)}$ of greater than about 25 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a

25 $BTKO_{(max/ss)}$ of greater than about 20 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/ss)}$ of greater than about 15 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/ss)}$ of greater than about 10 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula

30 (III) is an amount that results in a $BTKO_{(max/ss)}$ of greater than about 5 % occupancy.

[00237] In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/ss)}$ of about 0.0001 % occupancy to about 100 % occupancy. In some aspects, the therapeutically effective amount of the compound of

(III) is an amount that results in a $BTKO_{(max/ss)}$ of about 0.0001 % occupancy to about 1 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/ss)}$ of about 59.4 % occupancy to about 99.9 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/ss)}$ of about 90.2 % occupancy to about 100 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/ss)}$ of about 99.8 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/ss)}$ of about 99.8 % occupancy.

10 **[00239]** In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day\ 1)}$ (trough BTK occupancy at day 1) of about 100 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day\ 1)}$ of greater than about 99.95 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day\ 1)}$ of greater than about 99 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day\ 1)}$ of greater than about 98 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day\ 1)}$ of greater than about 95 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day\ 1)}$ of greater than about 90 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day\ 1)}$ of greater than about 85 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day\ 1)}$ of greater than about 80 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day\ 1)}$ of greater than about 75 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day\ 1)}$ of greater than about 70 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day\ 1)}$ of greater than about 65 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day\ 1)}$ of greater than about 60 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day\ 1)}$ of greater than

about 55% occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day\ 1)}$ of greater than about 50 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day\ 1)}$ of greater than about 45 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day\ 1)}$ of greater than about 40 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day\ 1)}$ of greater than about 35 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day\ 1)}$ of greater than about 30 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day\ 1)}$ of greater than about 25 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day\ 1)}$ of greater than about 20 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day\ 1)}$ of greater than about 15 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day\ 1)}$ of greater than about 10 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day\ 1)}$ of greater than about 5 % occupancy.

[00240] In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day\ 1)}$ of about 0.0001 % occupancy to about 100 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day\ 1)}$ of about 0.0001 % occupancy to about 99.9 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day\ 1)}$ of about 0.0001 % occupancy to about 99.95 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day\ 1)}$ of about 0.0001 % occupancy to about 99 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day\ 1)}$ of about 0.0001 % occupancy to about 98 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day\ 1)}$ of about 0.0001 % occupancy to about 95 % occupancy.

[00241] In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/day\ 1)}$ of about 0.0001 % occupancy to about 90 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/day\ 1)}$ of about 0.0001 % occupancy to about 85 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/day\ 1)}$ of about 0.0001 % occupancy to about 80 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/day\ 1)}$ of about 0.0001 % occupancy to about 75 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/day\ 1)}$ of about 0.0001 % occupancy to about 70 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/day\ 1)}$ of about 0.0001 % occupancy to about 60 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/day\ 1)}$ of about 0.0001 % occupancy to about 50 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/day\ 1)}$ of about 0.0001 % occupancy to about 40 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/day\ 1)}$ of about 0.0001 % occupancy to about 30 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/day\ 1)}$ of about 0.0001 % occupancy to about 20 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/day\ 1)}$ of about 0.0001 % occupancy to about 10 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/day\ 1)}$ of about 0.0001 % occupancy to about 1 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/day\ 1)}$ of about 63.9 % occupancy to about 97.3 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/day\ 1)}$ of about 23.3 % occupancy to about 91.3 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/day\ 1)}$ of about 77.4 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/day\ 1)}$ of about 85.4 % occupancy.

[00242] In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ (trough BTK occupancy at steady state) of about 100 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of greater than about 99.95 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of greater than about 99 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of greater than about 98 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of greater than about 95 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of greater than about 90 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of greater than about 85 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of greater than about 80 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of greater than about 75 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of greater than about 70 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of greater than about 65 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of greater than about 60 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of greater than about 55 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of greater than about 50 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of greater than about 45 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of greater than about 40 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of greater than about 35 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of greater than about 30 % occupancy.

In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of greater than about 25 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of greater than about 20 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of greater than about 15 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of greater than about 10 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of greater than about 5 % occupancy.

10 **[00243]** In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of about 50.2 % occupancy to about 95.4 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of about 0.0001 % occupancy to about 100 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of about 0.0001 % occupancy to about 99.9 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of about 0.0001 % occupancy to about 99.95 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of about 0.0001 % occupancy to about 99 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of about 0.0001 % occupancy to about 98 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of about 0.0001 % occupancy to about 95 % occupancy.

25 **[00244]** In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of about 0.0001 % occupancy to about 90 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of about 0.0001 % occupancy to about 85 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of about 0.0001 % occupancy to about 80 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of about 0.0001 % occupancy to about 75 % occupancy. In some aspects, the therapeutically effective amount of the compound of

Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of about 0.0001 % occupancy to about 70 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of about 0.0001 % occupancy to about 60 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of about 0.0001 % occupancy to about 50 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of about 0.0001 % occupancy to about 40 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of about 0.0001 % occupancy to about 30 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of about 0.0001 % occupancy to about 20 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of about 0.0001 % occupancy to about 10 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of about 0.0001 % occupancy to about 1 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of about 75.5 % occupancy to about 99.3 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of about 80.7 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of about 86.0 % occupancy. In some aspects, the therapeutically effective amount of the compound of Formula (III) is administered once a day. In some aspects, the therapeutically effective amount of the compound of Formula (III) is administered twice a day. In some aspects, the therapeutically effective amount of the compound of Formula (III) is administered three times a day. In some aspects the therapeutically effective amount of the compound of formula (III) is administered orally.

[00245] In some aspects, the the compound of Formula (III) is used as a front line therapy, second line therapy, third line therapy, fourth line therapy, fifth line therapy, or sixth line therapy. In some aspects, the compound of Formula (III) treats a refractory hematological malignancy. In some aspects, the compound of Formula (III) is used as a maintenance therapy. In some aspects, the compound of Formula (III) is administered until disease progression, unacceptable toxicity, or individual choice.

[00246] In addition, the compounds of the disclosure may be used in combination with additional active ingredients in the treatment of the above conditions. The additional active ingredients may be coadministered separately with a compound of the disclosure or included with such an agent in a pharmaceutical composition according to the disclosure. The combination may serve to increase efficacy (e.g., by including in the combination a compound potentiating the potency or effectiveness of an active agent according to the disclosure), decrease one or more side effects, or decrease the required dose of the active agent according to the disclosure.

[00247] The compounds of the disclosure are used, alone or in combination with one or more additional active ingredients, to formulate pharmaceutical compositions of the disclosure. A pharmaceutical composition of the disclosure comprises: (a) an effective amount of at least one compound in accordance with the disclosure; and (b) a pharmaceutically acceptable excipient.

[00248] In some aspects, the compound of Formula (III) can be administered in combination with one or more additional therapeutic agent. In some aspects, the one of more additional therapeutic agent is a Bcl2 inhibitor. In some aspects, the Bcl2 inhibitor is 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin5-yloxy)benzamide) also known as venetoclax. In some aspects, 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin5-yloxy)benzamide) is administered according to a weekly ramp up dosage regimen comprising administering about 20mg/day for the first week, about 50 mg/day for the second week, about 100 mg/day for the third week, 200 mg/day for the third week, and 400 mg/day for the fourth week and beyond. In some aspects, the 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin5-yloxy)benzamide) is administered orally. In some aspects, the compound of Formula (III) can be administered in combination with 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin5-yloxy)benzamide) and rituximab. In some aspects, the compound of Formula (III) can be administered in combination with 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-

b]pyridin5-yloxy)benzamide) and obinutuzumab. In some aspects, the compound of Formula (III) and Bcl2 inhibitor can be administered simultaneously, concurrently or sequentially with no specific intervening time limits.

5 [00249] In some aspects, the compound of Formula (III) can be administered in combination with one or more additional therapeutic agent. In some aspects, the one of more additional therapeutic agents are cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab (R-CHOP).

10 [00250] In some aspects, a method of treating non-Hodgkin's lymphoma (NHL) in a subject comprises administering a therapeutically effective dose of about 140 mg to about 560 mg of compound of Formula (III). In some aspects, therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max, day1)}$ of about 429.75 ng/ml to about 1,719 ng/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max, ss)}$ of about 435.1 ng/ml to about 1,740.4 ng/ml. In some aspects, the administration of the compound of Formula (III) is once daily or twice
15 daily. In some aspects, the compound of Formula (III) is administered in combination with R-CHOP. In some aspects, the compound of Formula (III) is administered in combination with venetoclax. The venetoclax is administered according to a weekly ramp up dosage regimen comprising administering about 20mg/day for the first week, about 50 mg/day for the second week, about 100 mg/day for the third week, 200 mg/day for the third week, and 400 mg/day for
20 the fourth week and beyond. In some aspects, the NHL is relapsed or refractory NHL.

[00251] In some aspects, a method of treating diffuse large B-cell lymphoma (DLBCL) in a subject comprises administering a therapeutically effective dose of about 140 mg to about 560 mg of compound of Formula (III). In some aspects, therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max, day1)}$ of about 429.75 ng/ml to
25 about 1,719 ng/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max, ss)}$ of about 435.1 ng/ml to about 1,740.4 ng/ml. In some aspects, the administration of the compound of Formula (III) is once daily or twice daily. In some aspects, the compound of Formula (III) is administered in combination with R-CHOP. In some aspects, the compound of Formula (III) is administered in combination with
30 venetoclax. The venetoclax is administered according to a weekly ramp up dosage regimen comprising administering about 20mg/day for the first week, about 50 mg/day for the second week, about 100 mg/day for the third week, 200 mg/day for the third week, and 400 mg/day for the fourth week and beyond. In some aspects, the DLBCL is relapsed or refractory DLBCL.

[00252] In some aspects, a method of treating mantle cell lymphoma (MCL) in a subject comprises administering a therapeutically effective dose of about 140 mg to about 560 mg of compound of Formula (III). In some aspects, therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,day1)}$ of about 429.75 ng/ml to about 1,719 ng/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 435.1 ng/ml to about 1,740.4 ng/ml. In some aspects, the administration of the compound of Formula (III) is once daily or twice daily. In some aspects, the compound of Formula (III) is administered in combination with R-CHOP. In some aspects, the compound of Formula (III) is administered in combination with venetoclax. The venetoclax is administered according to a weekly ramp up dosage regimen comprising administering about 20mg/day for the first week, about 50 mg/day for the second week, about 100 mg/day for the third week, 200 mg/day for the third week, and 400 mg/day for the fourth week and beyond. In some aspects, the MCL is relapsed or refractory MCL.

[00253] In some aspects, a method of treating follicular lymphoma (FL) in a subject comprises administering a therapeutically effective dose of about 140 mg to about 560 mg of compound of Formula (III). In some aspects, therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,day1)}$ of about 429.75 ng/ml to about 1,719 ng/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 435.1 ng/ml to about 1,740.4 ng/ml. In some aspects, the administration of the compound of Formula (III) is once daily or twice daily. In some aspects, the compound of Formula (III) is administered in combination with R-CHOP. In some aspects, the compound of Formula (III) is administered in combination with venetoclax. The venetoclax is administered according to a weekly ramp up dosage regimen comprising administering about 20mg/day for the first week, about 50 mg/day for the second week, about 100 mg/day for the third week, 200 mg/day for the third week, and 400 mg/day for the fourth week and beyond. In some aspects, the FL is relapsed or refractory FL.

[00254] In some aspects, a method of treating marginal zone lymphoma (MZL) in a subject comprises administering a therapeutically effective dose of about 140 mg to about 560 mg of compound of Formula (III). In some aspects, therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,day1)}$ of about 429.75 ng/ml to about 1,719 ng/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 435.1 ng/ml to about 1,740.4 ng/ml. In some aspects, the administration of the compound of Formula (III) is once daily or twice

daily. In some aspects, the compound of Formula (III) is administered in combination with R-CHOP. In some aspects, the compound of Formula (III) is administered in combination with venetoclax. The venetoclax is administered according to a weekly ramp up dosage regimen comprising administering about 20mg/day for the first week, about 50 mg/day for the second week, about 100 mg/day for the third week, 200 mg/day for the third week, and 400 mg/day for the fourth week and beyond. In some aspects, the MZL is relapsed or refractory MZL.

[00255] In some aspects, a method of treating chronic lymphocytic leukemia (CLL) in a subject comprises administering a therapeutically effective dose of about 140 mg to about 560 mg of compound of Formula (III). In some aspects, therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,day1)}$ of about 429.75 ng/ml to about 1,719 ng/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 435.1 ng/ml to about 1740.4 ng/ml. In some aspects, the administration of the compound of Formula (III) is once daily or twice daily. In some aspects, the compound of Formula (III) is administered in combination with R-CHOP. In some aspects, the compound of Formula (III) is administered in combination with venetoclax. The venetoclax is administered according to a weekly ramp up dosage regimen comprising administering about 20mg/day for the first week, about 50 mg/day for the second week, about 100 mg/day for the third week, 200 mg/day for the third week, and 400 mg/day for the fourth week and beyond. In some aspects, the CLL is relapsed or refractory CLL.

[00256] In some aspects, a method of treating small lymphocytic lymphoma (SLL) in a subject comprises administering a therapeutically effective dose of about 140 mg to about 560 mg of compound of Formula (III). In some aspects, therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,day1)}$ of about 429.75 ng/ml to about 1,719 ng/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 435.1 ng/ml to about 1,740.4 ng/ml. In some aspects, the administration of compound of Formula (III) is once daily or twice daily. In some aspects, the compound of Formula (III) is administered in combination with R-CHOP. In some aspects, the compound of Formula (III) is administered in combination with venetoclax. The venetoclax is administered according to a weekly ramp up dosage regimen comprising administering about 20mg/day for the first week, about 50 mg/day for the second week, about 100 mg/day for the third week, 200 mg/day for the third week, and 400 mg/day for the fourth week and beyond. In some aspects, the SLL is relapsed or refractory SLL.

[00257] In some aspects, a method of treating Waldenström macroglobulinemia (WM) in a subject comprises administering a therapeutically effective dose of about 140 mg to about 560 mg of compound of Formula (III). In some aspects, therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,day1)}$ of about 429.75 ng/ml to about 1,719 ng/ml. In some aspects, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 435.1 ng/ml to about 1,740.4 ng/ml. In some aspects, the administration of compound of Formula (III) is once daily or twice daily. In some aspects, the compound of Formula (III) is administered in combination with R-CHOP. In some aspects, the compound of Formula (III) is administered in combination with venetoclax. The venetoclax is administered according to a weekly ramp up dosage regimen comprising administering about 20mg/day for the first week, about 50 mg/day for the second week, about 100 mg/day for the third week, 200 mg/day for the third week, and 400 mg/day for the fourth week and beyond. In some aspects, the WM is relapsed or refractory WM.

[00258] In some aspects, the compound of Formula (III) can be administered in combination with one or more additional therapeutic agents selected from the group consisting of a chemotherapeutic agent, a steroid, an immunotherapeutic agent, a targeted therapy, and any combination thereof. In some aspects, the one or more additional therapeutic agent includes, but is not limited to a B cell receptor pathway inhibitor B cell receptor signaling inhibitor, a PI3K inhibitor, an IAP inhibitor, an mTOR inhibitor, a radioimmunotherapeutic, a DNA damaging agent, a proteasome inhibitor, a histone deacetylase inhibitor, a protein kinase inhibitor, a hedgehog inhibitor, an Hsp90 inhibitor, a telomerase inhibitor, a Jak1/2 inhibitor, a protease inhibitor, a PKC inhibitor, a PARP inhibitor, and any combination thereof. In some aspects, the B cell receptor pathway inhibitor includes, but is not limited to a CD79A inhibitor, a CD79B inhibitor, a CD 19 inhibitor, a Lyn inhibitor, a Syk inhibitor, a PI3K inhibitor, a Blnk inhibitor, a PLCy inhibitor, a PKCP inhibitor, or an inhibitor of mitogen-activated protein kinase signaling, (e.g., U0126, PD98059, PD184352, PD0325901, ARRY-142886, SB239063, SP600125, BAY 43-9006, wortmannin, LY294002) or a combination thereof. In some aspects, the one or more additional therapeutic agents include, but are not limited to chlorambucil, ifosfamide, doxorubicin, mesalazine, thalidomide, lenalidomide, temsirolimus, everolimus, fludarabine, fostamatinib, paclitaxel, docetaxel, ofatumumab, rituximab, dexamethasone, prednisone, CAL-101, ibritumomab, tositumomab, bortezomib, pentostatin, endostatin, cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone, rituximab, bendamustine, etoposide, prednisolone, and any combination thereof. In some aspects, the one or more therapeutic agents is a nitrogen

mustard including but not limited to bendamustine, chlorambucil, chlormethine, cyclophosphamide, ifosfamide, melphalan, prednimustine, trofosfamide; Alkyl Sulfonates such as, but not limited to busulfan, mannosulfan, treosulfan; Ethylene Imines, carboquone, thiotepa, triaziquone; Nitrosoureas such as, but not limited to carmustine, fotemustine, lomustine, 5 nimustine, ranimustine, semustine, streptozocin; Epoxides such as, but not limited to etoglucid; Other Alkylating Agents such as, but not limited to dacarbazine, mitobronitol, pipobroman, temozolomide, Folic Acid Analogues such as, but not limited to methotrexate, perimetrexed, pralatrexate, raltitrexed; Purine Analogs such as, but not limited to cladribine, clofarabine, fludarabine, mercaptopurine, nelarabine, tioguanine; Pyrimidine Analogs such as, but not limited 10 to azacitidine, capecitabine, carmofur, cytarabine, decitabine, fluorouracil, gemcitabine, tegafur; Vinca; Alkaloids such as for example vinblastine, vincristine, vindesine, vinflunine, vinorelbine; Podophyllotoxin Derivatives such as, but not limited to etoposide, teniposide; Colchicine derivatives such as, but not limited to demecolcine; Taxanes such as, but not limited to docetaxel, paclitaxel, paclitaxel poliglumex; Other Plant Alkaloids and Natural Products such as, 15 but not limited to trabectedin; Actinomycines such as, but not limited to dactinomycin; Anthracyclines such as for example aclarubicin, daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone, pirarubicin, valrubicin, zorubicin; Other Cytotoxic Antibiotics such as, but not limited to bleomycin, ixabepilone, mitomycin, plicamycin; Platinum Compounds such as for example carboplatin, cisplatin, oxaliplatin, satraplatin; Methylhydrazines such as, but not limited 20 to procarbazine; Sensitizers such as, but not limited to aminolevulinic acid, efaproxiral, methyl aminolevulinate, porfimer sodium, temoporfin; Protein Kinase Inhibitors such as, but not limited to dasatinib, erlotinib, everolimus, gefitinib, imatinib, lapatinib, nilotinib, pazopanib, sorafenib, sunitinib, temsirolimus; Other Antineoplastic Agents such as, but not limited to alitretinoin, altretamine, amzacrine, anagrelide, arsenic trioxide, asparaginase, bexarotene, bortezomib, 25 celecoxib, denileukin diftitox, estramustine, hydroxycarbamide, irinotecan, lonidamine, masoprocol, miltefosine, mitoguazone, mitotane, oblimersen, pegaspargase, pentostatin, romidepsin, sitimagene ceradenovec, tiazofurine, topotecan, tretinoin, vorinostat; Estrogens such as, but not limited to diethylstilbenol, ethinylestradiol, fosfestrol, polyestradiol phosphate; Progestogens such as, but not limited to gestonorone, medroxyprogesterone, megestrol; 30 Gonadotropin Releasing Hormone Analogs such as, but not limited to buserelin, goserelin, leuporelin, triptorelin; Anti-Estrogens such as, but not limited to fulvestrant, tamoxifen, toremifene; Anti- Androgens such as, but not limited to bicalutamide, flutamide, nilutamide, , Enzyme Inhibitors, aminoglutethimide, anastrozole, exemestane, formestane, letrozole, vorozole;

Other Hormone Antagonists such as, but not limited to abarelix, degarelix; Immunostimulants such as, but not limited to histamine dihydrochloride, mifamurtide, pidotimod, plerixafor, roquinimex, thymopentin; Immunosuppressants such as, but not limited to everolimus, gusperimus, leflunomide, mycophenolic acid, sirolimus; Calcineurin Inhibitors such as, but not limited to ciclosporin, tacrolimus; Other Immunosuppressants such as, but not limited to azathioprine, lenalidomide, methotrexate, thalidomide; and Radiopharmaceuticals such as, but not limited to, iobenguane, interferons, interleukins, Tumor Necrosis Factors, Growth Factors, or the like., immunostimulants such as, but not limited to ancestim, filgrastim, lenograstim, molgramostim, pegfilgrastim, sargramostim; Interferons such as, but not limited to interferon alfa natural, interferon alfa-2a, interferon alfa-2b, interferon alfacon-1, interferon alfa-n1, interferon beta natural, interferon beta-1a, interferon beta-1b, interferon gamma, peginterferon alfa-2a, peginterferon alfa-2b; Interleukins such as, but not limited to aldesleukin, oprelvekin; Other Immunostimulants such as, but not limited to BCG vaccine, glatiramer acetate, histamine dihydrochloride, immunocyanin, lentinan, melanoma vaccine, mifamurtide, pegademase, pidotimod, plerixafor, poly I:C, poly ICLC, roquinimex, tasonermin, thymopentin; Immunosuppressants such as, but not limited to abatacept, abetimus, alefacept, antilymphocyte immunoglobulin (horse), antithymocyte immunoglobulin (rabbit), eculizumab, efalizumab, everolimus, gusperimus, leflunomide, muromab-CD3, mycophenolic acid, natalizumab, sirolimus; TNF alpha Inhibitors such as for example adalimumab, afelimomab, certolizumab pegol, etanercept, golimumab, infliximab; Interleukin Inhibitors such as, but not limited to anakinra, basiliximab, canakinumab, daclizumab, mepolizumab, rilonacept, tocilizumab, ustekinumab; Calcineurin Inhibitors such as, but not limited to ciclosporin, tacrolimus; Other Immunosuppressants such as, but not limited to azathioprine, lenalidomide, methotrexate, thalidomide, Adalimumab, Alemtuzumab, Basiliximab, Bevacizumab, Cetuximab, Certolizumab pegol, Daclizumab, Eculizumab, Efalizumab, Gemtuzumab, Ibritumomab tiuxetan, Infliximab, Muromonab-CD3, Natalizumab, Panitumumab, Ranibizumab, Rituximab, Tositumomab, Trastuzumab, Additional cancer treatment regimens include Monoclonal Antibodies such as, but not limited to alemtuzumab, bevacizumab, catumaxomab, cetuximab, edrecolomab, gemtuzumab, ofatumumab, panitumumab, rituximab, trastuzumab, Immunosuppressants, eculizumab, efalizumab, muromab-CD3, natalizumab; TNF alpha Inhibitors such as, but not limited to adalimumab, afelimomab, certolizumab pegol, golimumab, infliximab, Interleukin Inhibitors, basiliximab, canakinumab, daclizumab, mepolizumab, tocilizumab, ustekinumab, Radiopharmaceuticals, ibritumomab tiuxetan, tositumomab; Others Monoclonal Antibodies such

as, but not limited to abagovomab, adecatumumab, alemtuzumab, anti-CD30 monoclonal antibody Xmab2513, anti-MET monoclonal antibody MetMab, apolizumab, apomab, arcitumomab, basiliximab, bispecific antibody 2B1, blinatumomab, brentuximab vedotin, capromab pendetide, cixutumumab, claudiximab, conatumumab, dacetuzumab, denosumab, 5 eculizumab, epratuzumab, epratuzumab, ertumaxomab, etaracizumab, figitumumab, fresolimumab, galiximab, ganitumab, gemtuzumab ozogamicin, glembatumumab, ibritumomab, inotuzumab ozogamicin, ipilimumab, lexatumumab, lintuzumab, lintuzumab, lucatumumab, mapatumumab, matuzumab, milatuzumab, monoclonal antibody CC49, necitumumab, nimotuzumab, ofatumumab, oregovomab, pertuzumab, ramacurimab, ranibizumab, sipilizumab, 10 sonepcizumab, tanezumab, tositumomab, trastuzumab, tremelimumab, tucotuzumab celmoleukin, veltuzumab, visilizumab, volociximab, zalutumumab. Additional cancer treatment regimens include agents that affect the tumor micro- environment such as, but not limited to cellular signaling network (e.g. phosphatidylinositol 3-kinase (PI3K) signaling pathway, signaling from the B-cell receptor and the IgE receptor). In some aspects, the one or more 15 therapeutic agent is a PI3K signaling inhibitor or a syk kinase inhibitor. In one aspect, the syk inhibitor is R788. In another aspect is a PKCy inhibitor such as, but not limited to, enzastaurin. Examples of agents that affect the tumor micro-environment include but are not limited to PI3K signaling inhibitor, syk kinase inhibitor, Protein Kinase Inhibitors such as, but not limited to dasatinib, erlotinib, everolimus, gefitinib, imatinib, lapatinib, nilotinib, pazopanib, sorafenib, 20 sunitinib, temsirolimus; Other Angiogenesis Inhibitors such as, but not limited to GT-111, JI-101, R1530; Other Kinase Inhibitors such as for example AC220, AC480, ACE-041, AMG 900, AP24534, Arry- 614, AT7519, AT9283, AV-951, axitinib, AZD1 152, AZD7762, AZD8055, AZD8931, bafetinib, BAY 73-4506, BGJ398, BGT226, BI 811283, BI6727, BIBF 1120, BIBW 2992, BMS-690154, BMS-777607, BMS-863233, BSK-461364, CAL-101, CEP-11981, 25 CYC116, DCC-2036, dinaciclib, dovitinib lactate, E7050, EMD 1214063, ENMD-2076, fostamatinib disodium, GSK2256098, GSK690693, INCB18424, INNO-406, JNJ-26483327, JX-594, KX2- 391, linifanib, LY2603618, MGCD265, MK-0457, MK1496, MLN8054, MLN8237, MP470, NMS-1116354, NMS-1286937, ON 01919.Na, OSI-027, OSI-930, Btk inhibitor, PF-00562271, PF-02341066, PF-03814735, PF-04217903, PF-04554878, PF-04691502, PF- 30 3758309, PHA- 739358, PLC3397, progenipoiectin, R547, R763, ramucirumab, regorafenib, R05185426, SAR103168, S3333333CH 727965, SGI-1176, SGX523, SNS-314, TAK-593, TAK-901, TKI258, TLN-232, TTP607, XL147, XL228, XL281R05126766, XL418, XL765, inhibitors of mitogen-activated protein kinase signaling such as, but not limited to U0126,

- PD98059, PD184352, PD0325901, ARRY-142886, SB239063, SP600125, BAY 43- 9006, wortmannin, or LY294002; Syk inhibitors; mTOR inhibitors; and antibodies (e.g., rituxan), Adriamycin, Dactinomycin, Bleomycin, Vinblastine, Cisplatin, acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate;
- 5 aminogluthethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; broprimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cladribine; crisnatol mesylate;
- 10 cyclophosphamide; cytarabine; dacarbazine; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine
- 15 phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; flurocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; ifimofosine; interleukin II (including recombinant interleukin II, or rIL2), interferon alfa-2a; interferon alfa-2b; interferon alfa-n1;
- 20 interferon alfa-n3; interferon beta-1 a; interferon gamma-1 b; iproplatin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedopa; mitindomide;
- 25 mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazole; nogalamycin; ormaplatin; oxisuran; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; pipsulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride;
- 30 pyrazofurin; riboprine; rogletimide; safngol; safngol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spiro germanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfm; teniposide; teroxirone; testolactone; thiamiprine; thioguanine;

- thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate;
- 5 vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; zorubicin hydrochloride; 20-epi-1, 25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic
- 10 protein- 1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstauropine;
- 15 beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3, CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS);
- 20 castanospermine; cecropin B; cetrorelix; chlornls; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentantraquinones, cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; daclicimab; decitabine;
- 25 dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylmorspermine; dihydro-5-azacytidine; 9- dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists;
- 30 etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorubicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam;

- heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-such as for example growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole;
- 5 isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarazole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone;
- 10 lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguanzone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin;
- 15 mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+mycobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1 -based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim;
- 20 nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; 06-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan
- 25 polysulfate sodium; pentostatin; pentozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexin; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based
- 30 immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP

inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII
retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol;
saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence
derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction
5 modulators; single chain antigen-binding protein; sizofiran; sobuzoxane; sodium borocaptate;
sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid;
spicamycin D; spionmustine; splenopentin; spongistatin I; squalamine; stem cell inhibitor; stem-
cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive
intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans;
10 tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur;
tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide;
tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin
mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone;
tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem
15 cell factor; translation inhibitors; tretinoin; triacetylluridine; triciribine; trimetrexate; triptorelin;
tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex;
urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide;
variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin;
vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; and zinostatin
20 stimalamer. Yet other anticancer agents that can be employed in combination with the compound
of Formula (III) include alkylating agents, antimetabolites, natural products, or hormones, such
as, but not limited to nitrogen mustards (such as, but not limited to mechloroethamine,
cyclophosphamide, chlorambucil, etc.), alkyl sulfonates (such as, but not limited to busulfan),
nitrosoureas (such as, but not limited to carmustine, lomustine, etc.), or triazenes (decarbazine,
25 etc.). Examples of antimetabolites include but are not limited to folic acid analog (such as, but
not limited to methotrexate), or pyrimidine analogs (such as, but not limited to Cytarabine),
purine analogs (such as, but not limited to mercaptopurine, thioguanine, pentostatin). Examples
of alkylating agents that can be employed in combination the compounds of Formula (III)
include, but are not limited to, nitrogen mustards (such as, but not limited to mechloroethamine,
30 cyclophosphamide, chlorambucil, meiphalan, etc.), ethylenimine and methylmelamines (such as,
but not limited to hexamethylmelamine, thiotepa), alkyl sulfonates (such as, but not limited to
busulfan), nitrosoureas (such as, but not limited to carmustine, lomustine, semustine,
streptozocin, etc.), or triazenes (decarbazine, etc.). Examples of antimetabolites include, but are

not limited to folic acid analog (such as, but not limited to methotrexate), or pyrimidine analogs (such as, but not limited to fluorouracil, floxouridine, Cytarabine), purine analogs (such as, but not limited to mercaptopurine, thioguanine, pentostatin. Examples of anti-cancer agents which act by arresting cells in the G2-M phases due to stabilized microtubules and which can be used in combination with a Btk inhibitor compound include without limitation the following marketed drugs and drugs in development: Erbulozole (also known as R-55104), Dolastatin 10 (also known as DLS-10 and NSC-376128), Mivobulin isethionate (also known as CI-980), Vincristine, NSC-639829, Discodermolide (also known as NVP-XX-A-296), ABT-751 (Abbott, also known as E-7010), Altorhyrtins (such as Altorhyrtin A and Altorhyrtin C), Spongistatins (such as Spongistatin 1, Spongistatin 2, Spongistatin 3, Spongistatin 4, Spongistatin 5, Spongistatin 6, Spongistatin 7, Spongistatin 8, and Spongistatin 9), Cemadotin hydrochloride (also known as LU- 103793 and NSC-D-669356), Epothilones (such as Epothilone A, Epothilone B, Epothilone C (also known as desoxyepothilone A or dEpoA), Epothilone D (also referred to as KOS-862, dEpoB, and desoxyepothilone B), Epothilone E, Epothilone F, Epothilone B N-oxide, Epothilone A N- oxide, 16-aza-epothilone B, 21-aminoepothilone B (also known as BMS-310705), 21- hydroxyepothilone D (also known as Desoxyepothilone F and dEpoF), 26-fluoroepothilone), Auristatin PE (also known as NSC-654663), Soblidotin (also known as TZT-1027), LS-4559-P (Pharmacia, also known as LS-4577), LS-4578 (Pharmacia, also known as LS-477-P), LS-4477 (Pharmacia), LS-4559 (Pharmacia), RPR-112378 (Aventis), Vincristine sulfate, DZ-3358 (Daiichi), FR- 182877 (Fujisawa, also known as WS-9885B), GS-164 (Takeda), GS-198 (Takeda), KAR-2 (Hungarian Academy of Sciences), BSF-223651 (BASF, also known as ILX- 651 and LU-223651), SAH-49960 (Lilly/Novartis), SDZ-268970 (Lilly/Novartis), AM-97 (Armad/Kyowa Hakko), AM-132 (Armad), AM-138 (Armad/Kyowa Hakko), IDN-5005 (Indena), Cryptophycin 52 (also known as LY-355703), AC-7739 (Ajinomoto, also known as AVE-8063A and CS-39.HCl), AC-7700 (Ajinomoto, also known as AVE-8062, AVE-8062A, CS-39-L-Ser HCl, and RPR-258062A), Vitilevuamide, Tubulysin A, Canadensol, Centaureidin (also known as NSC- 106969), T- 138067 (Tularik, also known as T-67, TL- 138067 and TI-138067), COBRA- 1 (Parker Hughes Institute, also known as DDE-261 and WHI-261), H10 (Kansas State University), H16 (Kansas State University), Oncocidin A1 (also known as BTO-956 and DIME), DDE-313 (Parker Hughes Institute), Fijianolide B, Laulimalide, SPA-2 (Parker Hughes Institute), SPA-1 (Parker Hughes Institute, also known as SPIKET-P), 3-IAABU (Cytoskeleton/Mt. Sinai School of Medicine, also known as MF-569), Narcosine (also known as NSC-5366), Nascapine, D-24851 (Asta Medica), A-105972 (Abbott), Hemiasterlin, 3 -B A ABU

(Cytoskeleton/Mt. Sinai School of Medicine, also known as MF-191), TMPN (Arizona State University), Vanadocene acetylacetonate, T- 138026 (Tularik), Monsatrol, Inanocine (also known as NSC-698666), 3-1AABE (Cytoskeleton/Mt. Sinai School of Medicine), A-204197 (Abbott), T-607 (Tularik, also known as T-900607), RPR- 115781 (Aventis), Eleutherobins
5 (such as Desmethyleleutherobin, Desacetyeleutherobin, Isoeleutherobin A, and Z-Eleutherobin), Caribaeoside, Caribaeolin, Halichondrin B, D-64131 (Asta Medica), D-68144 (Asta Medica), Diazonamide A, A-293620 (Abbott), NPI-2350 (Nereus), Taccalonolide A, TUB-245 (Aventis), A-259754 (Abbott), Diozostatin, (-)-Phenylahistin (also known as NSCL-96F037), D-68838 (Asta Medica), D-68836 (Asta Medica), Myoseverin B, D-43411 (Zentaris, also known as D-
10 81862), A-289099 (Abbott), A-318315 (Abbott), HTI-286 (also known as SPA-110, trifluoroacetate salt) (Wyeth), D-82317 (Zentaris), D-82318 (Zentaris), SC- 12983 (NCI), Resverastatin phosphate sodium, BPR-OY-007 (National Health Research Institutes), and SSR- 250411 (Sanofi).

[00259] In some aspects, the compound of Formula (III) and additional therapeutic
15 agent can be administered simultaneously, concurrently or sequentially with no specific intervening time limits.

[00260] Delivery forms of the pharmaceutical compositions containing one or more dosage units of the active agents may be prepared using suitable pharmaceutical excipients and compounding techniques known or that become available to those skilled in the art. The
20 compositions may be administered in the inventive methods by a suitable route of delivery, e.g., oral, parenteral, rectal, topical, or ocular routes, or by inhalation.

[00261] The preparation may be in the form of tablets, capsules, sachets, dragees, powders, granules, lozenges, powders for reconstitution, liquid preparations, or suppositories. Preferably, the compositions are formulated for intravenous infusion, topical administration, or
25 oral administration.

[00262] For oral administration, the compounds of the disclosure can be provided in the form of tablets or capsules, or as a solution, emulsion, or suspension. To prepare the oral compositions, the compounds may be formulated to yield a dosage of, e.g., from about 0.05 to about 100 mg/kg daily, or from about 0.05 to about 35 mg/kg daily, or from about 0.1 to about
30 10 mg/kg daily. For example, a total daily dosage of about 5 mg to 5 g daily may be accomplished by dosing once, twice, three, or four times per day.

[00263] Oral tablets may include a compound according to the disclosure mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding

agents, lubricating agents, sweetening agents, flavoring agents, coloring agents and preservative agents. Suitable inert fillers include sodium and calcium carbonate, sodium and calcium phosphate, lactose, starch, sugar, glucose, methyl cellulose, magnesium stearate, mannitol, sorbitol, and the like. Exemplary liquid oral excipients include ethanol, glycerol, water, and the like. Starch, polyvinyl-pyrrolidone (PVP), sodium starch glycolate, microcrystalline cellulose, and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin. The lubricating agent, if present, may be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate to delay absorption in the gastrointestinal tract, or may be coated with an enteric coating.

10 **[00264]** Capsules for oral administration include hard and soft gelatin capsules. To prepare hard gelatin capsules, compounds of the disclosure may be mixed with a solid, semi-solid, or liquid diluent. Soft gelatin capsules may be prepared by mixing the compound of the disclosure with water, an oil such as peanut oil or olive oil, liquid paraffin, a mixture of mono and di-glycerides of short chain fatty acids, polyethylene glycol 400, or propylene glycol.

15 **[00265]** Liquids for oral administration may be in the form of suspensions, solutions, emulsions or syrups or may be lyophilized or presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid compositions may optionally contain: pharmaceutically-acceptable excipients such as suspending agents (for example, sorbitol, methyl cellulose, sodium alginate, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminum stearate gel and the like); non-aqueous vehicles, e.g., oil (for example, almond oil or fractionated coconut oil), propylene glycol, ethyl alcohol, or water; preservatives (for example, methyl or propyl p-hydroxybenzoate or sorbic acid); wetting agents such as lecithin; and, if desired, flavoring or coloring agents.

25 **[00266]** The active agents of this disclosure may also be administered by non-oral routes. For example, the compositions may be formulated for rectal administration as a suppository. For parenteral use, including intravenous, intramuscular, intraperitoneal, or subcutaneous routes, the compounds of the disclosure may be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity or in parenterally acceptable oil. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride.

30 Such forms will be presented in unit-dose form such as ampules or disposable injection devices, in multi-dose forms such as vials from which the appropriate dose may be withdrawn, or in a solid form or pre-concentrate that can be used to prepare an injectable formulation. Illustrative

infusion doses may range from about 1 to 1000 µg/kg/minute of compound, admixed with a pharmaceutical carrier over a period ranging from several minutes to several days.

[00267] For topical administration, the compounds may be mixed with a pharmaceutical carrier at a concentration of about 0.1% to about 10% of drug to vehicle. Another mode of administering the compounds of the disclosure may utilize a patch formulation to affect transdermal delivery.

[00268] Compounds of the disclosure may alternatively be administered in methods of this disclosure by inhalation, via the nasal or oral routes, e.g., in a spray formulation also containing a suitable carrier.

[00269] Compounds of the disclosure can be prepared using the knowledge of one skilled in the art in combination with the present disclosure. For example, compounds of the disclosure can be prepared according to the schemes and examples disclosed in U.S. Patent No. 10,717,745, U.S. Patent No. 10,934,310 and PCT application publication WO2017100662, each of which is hereby incorporated in its entirety.

[00270] Aspects of the present disclosure also include the use of BTK binding assays to determine efficacy and dosing regimens for the use of BTK inhibitors including, but not limited to the compounds disclosed herein. In some aspects, a BTK binding assay is used to determine the level of BTK occupancy by a BTK inhibitor including the compounds of the present disclosure. In some aspects, the BTK inhibitor is a compound of Formula (I) or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof. In some aspects, the BTK inhibitor is a compound of Formula (III) or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof.

[00271] Aspects of the present disclosure are directed to companion diagnostic methods and kits for use in combination with a therapy comprising administration of a BTK inhibitor such as the compound of Formula (III) or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof. Such methods and kits are described in WO 2014/059368 which is hereby incorporated by reference in its entirety.

[00272] Described herein are companion diagnostic methods and kits for use in combination with a therapy comprising administration of a BTK inhibitor. In some aspects, the companion diagnostic methods provided involve protein occupancy assays for one or more inhibitors of BTK. Accordingly, described herein are protein occupancy assays for BTK inhibitors. Described herein in certain aspects is protein occupancy assay that is an ELISA probe assay. In some aspects, the ELISA probe assay is plate based electrochemilumnescent assay to

determine the relative amount of a BTK that has not been bound by a BTK inhibitor. For example, in some aspects, the BTK inhibitor binds to the active site of the BTK and forms a disulfide bond with a cysteine residue. In some aspects, the assays involves binding an activity probe to free BTK that have not been bound by the BTK inhibitor. In some aspects, the activity probe comprises a BTK inhibitor attached to a detectable label (e.g., biotin) via a linker (e.g., a long chain linker). Labeling of samples with the probe allows for the detection of BTK not occupied by drug. In some aspects, the probe conjugated with the BTK is captured by a streptavidin coated plate. In some aspects, excess un-conjugated probe competes with probe labeled BTK for binding to streptavidin. Also described herein are methods for determining the efficacy of inhibitors of the BTK. Further described herein are methods for using the protein occupancy assays in the diagnosis, prognosis, and determination and modification of therapeutic regimens in the treatment of diseases associated with activation of BTK, including diseases wherein inhibition of BTK provides therapeutic benefit to a patient having the disease. In some aspects, the patient is diagnosed as having a disease or disorder associated with aberrant activation of BTK, such as, for example, a malignancy. Further disclosed herein are diagnostic assays for diagnosing, prognosing, and monitoring a disease or condition benefitting from treatment with a BTK inhibitor. Also disclosed herein are diagnostic assays for identifying responders to BTK inhibitor therapy, determining therapeutic regimens, and detecting resistance to BTK inhibitor therapy. Some aspects are methods for determining the efficacy of a protein modulator (e.g., inhibitor drug) on a target (e.g., target protein kinase). In some aspects, methods are provided for determining the efficacy of a BTK inhibitor on a target kinase (e.g., BTK). In some aspects, the method comprises: (a) contacting a sample comprising a BTK with a probe to form a probe-bound target kinase; (b) detecting the amount of the probe-bound target kinase in the sample; and (c) determining the efficacy of the BTK inhibitor based on the amount of probe-bound target kinase. In some aspects, the method further comprises contacting the sample with the BTK inhibitor prior to step (a) (e.g., combining the sample with the probe). In some aspects, detecting the amount of the probe-bound target kinase comprises administering a compound, reagent or buffer to detect the probe-bound kinase. In some aspects, the compound, reagent or buffer comprises horseradish peroxidase (HRP), detection antibody buffer, read buffer, wash buffer. In some aspects, detecting the presence or absence of the probe-bound target kinase comprises quantifying the amount of probe-bound target kinase. In some aspects, the quantifying step comprises fluorescence, immunofluorescence, chemiluminescence, or electrochemiluminescence. In some aspects, determining the efficacy of the BTK inhibitor

comprises determining occupancy of the target kinase by the BTK inhibitor. In some aspects, the amount of probe-bound target kinase inversely correlates with the efficacy of the BTK inhibitor. For example, if a drug-treated sample (e.g., a sample that is contacted with the drug prior to contact with the probe such as a blood sample or tumor tissue) is contacted with the probe, then as the amount of probe-bound target kinases (e.g., unoccupied target kinases) detected increases, the efficacy of the drug decreases. In another example, if a drug-treated sample is contacted with the probe, then as the amount of probe-bound target kinase (e.g., unoccupied target kinases) detected decreases, the efficacy of the drug increases. In some aspects, the amount of probe-bound target kinases directly correlates with the efficacy of the drug. For example, if an untreated sample (e.g., a sample that is not contacted with the drug prior to contact with the probe) is contacted with the probe, then as the amount of probe-bound target kinase detected increases, the efficacy of the drug also increases. In another example, if an untreated sample (e.g., a sample that is not contacted with the drug prior to contact with the probe) is contacted with the probe, then as the amount of probe-bound target kinase detected decreases, the efficacy of the drug decreases. In some aspects, a drug is determined to be effective when the drug binds at least about 50% of the target kinases. Alternatively, a drug is determined to be effective when the drug binds at least about 60% of the target kinases. In some aspects, a drug is determined to be effective when the drug binds at least about 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, or 99% of the targets. In some aspects, the assay is performed on a sample obtained from a patient that has been administered a BTK inhibitor. In some aspects, the sample is obtained about 1 hour, 2 hours, 4 hours, 6 hours, 8 hours, 10 hours, 12 hours, 14 hours, 16 hours, 18 hours, 20 hours, 22 hours, 24 hours, 30 hours, 36 hours, 42 hours, 48 hours, 3 days, 4 days, 5 days, 6 days, 1 week, 2 weeks or longer after administration of the BTK inhibitor. In some aspects, the probe comprises an agent and a label. In some instances, the agent is fused to the label. In other instances, the agent is attached to the label. In another instance, the agent is attached to the label by a linker. In some aspects, the agent and the drug are essentially the same. In some aspects, the probe comprises a label. In some aspects, the probe comprises a label and a linker. In some aspects, the agent and the drug are at least about 20% identical, at least about 30% identical, at least about 40% identical, at least about 50% identical, at least about 60% identical, at least about 70% identical, at least about 80% identical, at least about 90% identical, or at least about 95% identical. In other aspects, the agent and the drug are different. In some aspects, the agent and the drug are at least about 5% different, at least about 10% different, at least about 20% different, at least about 30% different, at least about 40% different, at least about 50% different, at least about

60%) different, at least about 70% different, at least about 80% different, at least about 90% different, or at least about 95% different.

[00273] Disclosed herein are protein occupancy assay kits comprising a linker, a label, an agent, or any combination thereof. In one aspect is a protein occupancy assay kit comprising a linker and a label, wherein the linker is capable of attaching the label to an agent and the agent is a protein modulator. In another aspect is a protein occupancy assay kit comprising an agent, a linker, and a label, wherein the linker is capable of attaching to the agent and the label, thereby attaching the agent to the label. In some aspects is a protein occupancy assay kit comprising a probe, wherein the probe comprises an agent attached to a label. In some aspects is a protein occupancy assay kit comprising a probe, wherein the probe comprises an agent attached to a linker. In some aspects is a protein occupancy assay kit comprising an agent and a solid support, wherein the agent is attached to the solid support. In another aspect is a protein occupancy assay kit comprising a label and a solid support, wherein the label is attached to the solid support. In another aspect is a protein occupancy assay kit comprising a probe and a solid support, wherein the probe comprises an agent, a linker, a label, or any combination thereof. In some aspects is a protein occupancy assay kit comprising a target (e.g., protein) and a solid support, wherein the target is attached to the solid support. In some aspects, any of the kits disclosed herein further comprise a label. In some aspects, any of the kits disclosed herein further comprise a linker. In some aspects, any of the kits disclosed herein further comprise an agent. In some aspects, any of the kits disclosed herein further comprise a plurality of linkers, wherein the linkers are capable of attaching to another linker, an agent, a label, or any combination thereof. In some aspects, any of the kits disclosed herein further comprise a probe. In some aspects the probe comprises an agent, a linker, a label, or any combination thereof. In some aspects, any of the kits disclosed herein further comprise a target (e.g., protein). Exemplary aspects of agents, linkers, labels, probes, solid supports, and targets are disclosed herein. Further disclosed herein are exemplary methods for attaching probes or targets to solid supports.

[00274] In some aspects, the methods, kits, and compositions disclosed herein comprise a probe. In some aspects, the probe comprises an agent and a label. In some aspects, the agent and label are attached. In other aspects, the probe comprises an agent and a linker. In some aspects, the agent and linker are attached. In another aspect, the probe comprises an agent, a linker, and a label. In some aspects, the agent, linker and/or label are attached to each other. In some aspects, the probe comprises a label. In another aspect, the probe comprises a label and a linker. In some aspects, the label and the linker are attached. In some aspects, attachment is by

chemical methods, enzymatic methods, or crosslinking methods. In some aspects, the probe is attached to a solid support. Exemplary aspects of agents, linkers, labels, and solid supports are disclosed herein.

5 **[00275]** Any of the assays and systems disclosed herein can be useful in researching and validating drugs. Provided herein are methods for validating a drug comprising (a) contacting a sample comprising a target with a probe to form a probe-bound target; (b) detecting the presence or absence of the probe-bound target; and (c) determining occupancy of the target by a drug based on the presence or absence of the probe-bound target, thereby validating the drug.

10 **[00276]** Further provided herein are methods for determining occupancy of a target comprising: a) combining a sample comprising a target with a probe; b) detecting the presence or absence of a probe-bound target; and c) determining occupancy of the target by a drug based on the presence or absence of the probe-bound target.

15 **[00277]** In some aspects, the method further comprises capturing the target prior to step (a) contacting the sample with the probe. In some aspects, the target is captured by an antibody. In some aspects, the antibody is an anti-target antibody. In some aspects, the antibody is attached to a solid support. In some aspects, the solid support is a microplate. In some aspects, the microplate is a MSD microplate.

20 **[00278]** In yet other aspects, the method further comprises contacting the probe-bound target with a primary detection agent. In some aspects, the primary detection agent comprises an antibody, a bead, a dye, or a fluorophore. In some aspects, the primary detection agent comprises an antibody. In some aspects, the antibody is an anti-BTK antibody. In some aspects, the method further comprises contacting the detection agent with a secondary detection agent. In some aspects, the secondary detection agent comprises an antibody, a bead, a dye, or a fluorophore. In
25 some aspects, the primary detection agent is labeled. In some aspects, the secondary detection agent is labeled. In some aspects, the label is an electrochemiluminescent tag. In some aspects, the electrochemiluminescent tag comprises Tris(bipyridine)ruthenium(II) dicloride. In some aspects, the electrochemiluminescent tag is Ruthenium (II) tris-bipyridine, N-hydroxysuccinimide. In some aspects, the label is a SULFO TAG.

30 **[00279]** In some aspects, detecting the presence or absence of the probe-bound target comprises contacting the sample with a solid support. In some aspects, the solid support comprises a bead. In some aspects, the bead is a streptavidin bead. In some aspects, the bead is a magnetic bead. In some aspects, the bead is a labeled bead. In some aspects, the bead is a labeled

streptavidin bead. In some aspects, the bead is a labeled with an electrochemiluminescent tag. In some aspects, the electrochemiluminescent tag comprises Tris(bipyridine)ruthenium(II) dicloride. In some aspects, the electrochemiluminescent tag is Ruthenium (II) tris-bipyridine, N- hydroxysuccinimide. In some aspects, the bead is a SULFO TAG bead. In some aspects, the bead is a SULFO TAG streptavidin bead.

[00280] In some aspects, the bead interacts with the probe. In some aspects, the probe comprises a label. In some aspects, the label comprises biotin. In some aspects, the bead interacts with biotin. In some aspects, the bead forms a conjugate with the probe-bound target. In some aspects, the bead is conjugated to the probe.

[00281] In some aspects, detecting the presence or absence of the probe-bound target comprises detecting the probe-bound target or a portion thereof. In some aspects, detecting the presence or absence of the probe-bound target comprises detecting the bead or a portion thereof. In some aspects, detecting the presence or absence of the probe-bound target comprises detecting the labeled bead. In some aspects, detecting the presence or absence of the probe-bound target comprises detecting an electrochemiluminescent tag. In some aspects, the electrochemiluminescent tag comprises Tris(bipyridine)ruthenium(II) dichloride. In some aspects, the electrochemiluminescent tag is Ruthenium (II) tris- bipyridine, N- hydroxysuccinimide. In some aspects, detecting the presence or absence of the probe-bound target comprises detecting a SULFO TAG. In some aspects, the detecting step comprises luminescence. In some aspects, the detecting step comprises electrochemiluminescence.

[00282] In some aspects, the method further comprises purification of the probe-bound target. In some aspects, the probe-bound target is an unoccupied target. In some aspects, the probe-bound target is a drug-occupied target. In another aspect, purification of the probe-bound target comprises magnetic separation of probe-bound targets from non-probe-bound targets.

[00283] In some aspects, the sample is a pre -treated sample, wherein the pre-treated sample is contacted with a drug prior to contact with the probe. In some aspects, the sample is a non-treated sample, wherein the sample is not contacted with a drug prior to contact with the label.

[00284] In some aspects, the probe comprises an agent. In some aspects, the probe comprises an agent and a linker. In some aspects, the probe comprises a label. In some aspects, the probe comprises a label and a linker. In some aspects, the agent is a BTK inhibitor. In some aspects, the agent is a compound of Formula (III). In some aspects, the BTK inhibitor is a reversible BTK inhibitor. In some aspects, the agent is a, the BTK inhibitor is an irreversible

BTK inhibitor. In some aspects, the agent is a, the BTK inhibitor is a selective, covalent BTK inhibitor. In some aspects, the agent is a, the BTK inhibitor forms a covalent bond with a cysteine residue of a Bruton's tyrosine kinase (BTK). In some aspects, the cysteine residue is cysteine 481. In some aspects, the agent is a, the BTK inhibitor is a compound of Formula (III).

5 **[00285]** In some aspects, validating the drug comprises determining the efficacy of the drug on a target. In some aspects, determining occupancy of the target by the drug comprises quantifying the presence or absence of probe-bound targets. In some aspects, the drug is effective when the occupancy of the target is at least about 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, or 99%.

10 **[00286]** Any of the methods, assays and systems can be used to inform therapeutic treatment and the over-all health care management of a subject informing method for determining a therapeutic regimen. In some aspects, is a method for determining a therapeutic regimen comprising: (a) combining a sample comprising a target with a probe; (b) detecting the presence or absence of a probe-bound target; and (c) determining a therapeutic regimen based on
15 the presence or absence of the probe-bound target. Further disclosed herein is a method for determining efficacy of a test agent comprising: (a) combining a sample comprising a target with a probe; (b) detecting the presence or absence of a probe-bound target; and (c) determining efficacy of a test agent based on the presence or absence of the probe-bound target. Further disclosed herein is a method for identifying drug responders comprising: (a) combining a sample
20 comprising a target with a probe; (b) detecting the presence or absence of a probe-bound target; and (c) identifying drug responders based on the presence or absence of the probe-bound target. Further disclosed herein is a method for identifying BTK inhibitors comprising: (a) combining a sample comprising a target with a probe; (b) detecting the presence or absence of a probe-bound target; and (c) identifying kinase modulators based on the presence or absence of the probe-
25 bound target. Disclosed herein is a method for determining drug resistance comprising: (a) combining a sample comprising a target with a probe; (b) detecting the presence or absence of a probe-bound target; and (c) determining drug resistance based on the presence or absence of the probe-bound target.

[00287] In some aspects, the methods, assays, and systems disclosed herein comprise
30 contacting sample comprising a target with a probe. Suitable samples for use in any of the methods, assays, and systems disclosed herein comprise, but are not limited to, a whole blood sample, peripheral blood sample, lymph sample, tissue sample, tumor biopsy sample, bone marrow sample, or other bodily fluid sample. In some aspects, the sample is a sample containing

one or more cell types, or a lysate thereof, derived from a whole blood sample, peripheral blood sample, lymph sample, tissue sample, tumor biopsy sample, bone marrow sample, or other bodily fluid sample. Examples of bodily fluids include, but are not limited to, smears, sputum, biopsies, secretions, cerebrospinal fluid, bile, blood, lymph fluid, saliva, and urine. In some aspects, cells of the sample are isolated from other components of the sample prior to use in the methods provided. In some aspects, particular cell types of the sample are isolated from other cell types of the sample prior to use in the methods provided. For example, in some aspects, peripheral blood mononuclear cells (PBMCs, e.g., lymphocytes, monocytes and macrophages) of a blood sample are isolated from other cell types of the blood sample prior to use in the methods provided. For example, in some aspects, lymphocytes (e.g., B cells, T cells or NK cells) of the sample are isolated from other cell types of the sample prior to use in the methods provided. For example, in some aspects, B cells of the sample are isolated from other cell types of the sample prior to use in the methods provided. In some aspects, cells of the sample are lysed prior to use in the methods provided. For example, in some aspects, cancer cells are isolated from normal cells of the sample prior to use in the methods provided.

[00288] Any of the samples disclosed herein comprises complex populations of cells, which can be assayed as a population, or separated into sub-populations. Such cellular and acellular samples can be separated by centrifugation, elutriation, density gradient separation, apheresis, affinity selection, panning, FACS, filtration, centrifugation with Hypaque, etc. By using antibodies specific for markers identified with particular cell types, a relatively homogeneous population of cells can be obtained. Alternatively, a heterogeneous cell population can be used.

[00289] Once a sample is obtained, it can be used directly, frozen, or maintained in appropriate culture medium for short periods of time. Methods to isolate one or more cells for use according to the methods of this invention are performed according to standard techniques and protocols well-established in the art. In some aspects, the sample is obtained from a subject. Such subject can be a human or a domesticated animal such as a cow, chicken, pig, horse, rabbit, dog, cat, or goat. In some aspects, the cells used in the present invention are taken from a patient. Samples derived from an animal, e.g., human, can include, for example whole blood, sweat, tears, saliva, ear flow, sputum, lymph, bone marrow suspension, lymph, urine, saliva, semen, vaginal flow, cerebrospinal fluid, brain fluid, ascites, milk, secretions of the respiratory, intestinal or genitourinary tracts fluid, a lavage of a tissue or organ (e.g., lung) or tissue which

has been removed from organs, such as breast, lung, intestine, skin, cervix, prostate, pancreas, heart, liver and stomach.

[00290] To obtain a blood sample, any technique known in the art can be used, e.g., a syringe or other vacuum suction device. A sample can be optionally pre-treated or processed prior to enrichment. Examples of pre-treatment steps include the addition of a reagent such as a stabilizer, a preservative, a fixant, a lysing reagent, a diluent, a drug, an anti-apoptotic reagent, an anti-coagulation reagent, an anti-thrombotic reagent, magnetic property regulating reagent, a buffering reagent, an osmolality regulating reagent, a pH regulating reagent, and/or a cross-linking reagent. For example, when a blood sample is obtained, a preservative such an anticoagulation agent and/or a stabilizer can be added to the sample prior to enrichment.

[00291] A sample, such as a blood sample, can be analyzed under any of the methods, assays and systems disclosed herein within 1 week, 6 days, 5 days, 4 days, 3 days, 2 days, 1 day, 12 hrs, 6 hrs, 3 hrs, 2 hrs, or 1 hr from the time the sample is obtained.

[00292] In some aspects, a sample can be combined with an enzyme or compound that selectively lyses one or more cells or components in the sample. For example, in a blood sample, platelets and/or enucleated red blood cells are selectively lysed to generate a sample enriched in nucleated cells. The cells of interest can subsequently be separated from the sample using methods known in the art.

[00293] When obtaining a sample from a subject (e.g., blood sample), the amount can vary depending upon subject size and the condition being screened. In some aspects, up to 50, 40, 30, 20, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 mL of a sample is obtained. In some aspects, 1 -50, 2-40, 3-30, or 4-20 mL of sample is obtained. In some aspects, more than 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 100 mL of a sample is obtained.

[00294] Aspects of the present disclosure include methods of modifying the dose and/or frequency of dosing of a BTK inhibitor. Aspects of the present disclosure include methods of determining a BTK inhibitor treatment regimen in a subject. Aspects of the present disclosure include methods of monitoring the efficacy of BTK inhibitor therapy in a subject. In some aspects, a BTK occupancy of greater than about 75% is indicative that the BTK inhibitor is therapeutically effective. In some aspects, a BTK occupancy of greater than about 80% is indicative that the BTK inhibitor is therapeutically effective. In some aspects, a BTK occupancy of greater than about 90% is indicative that the BTK inhibitor is therapeutically effective. In some aspects, a BTK occupancy of greater than about 95% is indicative that the BTK inhibitor is therapeutically effective. In some aspects, a BTK occupancy of greater than

about 99% is indicative that the BTK inhibitor is therapeutically effective. In some aspects, a BTK occupancy of greater than about 100% is indicative that the BTK inhibitor is therapeutically effective. Aspects of the present disclosure include methods of predicting a subjects' response to BTK inhibitor therapy. In some aspects, a BTK occupancy of greater than about 75% is indicative that a patient will response to a particular BTK inhibitor. Aspects of the present disclosure also include methods for determining drug target occupancy in a patient.

[00295] Aspects of the present disclosure include the use of a A BTK lanthascreen binding assay to determine the BTK occupancy by a BTK inhibitor. In some aspects, a BTK lanthascreen binding assay monitors compound binding to unphosphorylated-BTK kinase domain (UP-BTK), by competing with a fluorescent labeled tracer. In some aspects, UP-BTK, consisting of the kinase domain of non-phosphorylated BTK protein (389-659aa), is produced in a Baculovirus/insect cell expression system. In some aspects, into a 384-well plate, 2 ng of GST-tagged human BTK (389-659aa) is incubated with a BTK inhibitor compound, 50 nM of Tracer 236 and 2 nM anti-GST antibody for 60 minutes using an optimized Lanthascreen™ assay. In some aspects, after 60 minutes, plates are read at 340 nM and 615/665 nM in a multifunctional plate reader such as an Infinite F500 (Tecan). In some aspects, data is analyzed using Xlfit™ version 5.3 from ID Business Solutions (Guildford), Microsoft Excel add-in.

[00296] In some aspects, binding of a BTK inhibitor to BTK in the assay described herein may be indicative of the the BTK inhibitors' function when used to treat a disease or condition in a patient in need thereof. In some aspects, a BTK occupancy of greater than about 75% is indicative that the BTK inhibitor is therapeutically effective. In yet other aspects, binding of a BTK inhibitor to BTK in the assay described herein may provide insight into the optimal dosage and frequency of administration of a BTK inhibitor. In some aspects, a BTK occupancy of greater than about 75% is indicative that the BTK inhibitor is being administered at an optimal dose and/or frequency. In some aspects, binding of a BTK inhibitor to BTK in the assay described herein may be predictive of a compounds ability to inhibit BTK and thereby treat a disease or condition disclosed herein. In some aspects, a BTK occupancy of greater than about 75% is indicative that the BTK inhibitor is effectively ingibiting BTK. In yet other aspects binding of a BTK inhibitor to BTK in the assay described herein may be predictive of the *in vivo* activity of a particular BTK inhibitor based on having similar BTK occupancy in the assay. In some aspects, a BTK occupancy of greater than about 75% is indicative that the BTK inhibitor is therapeutically effective *in vivo*.

EXAMPLES**Example 1: : A Phase I First In Human Pharmacokinetic and Pharmacodynamic Study of the Compound of Formula (III), A Potent and Selective Covalent Inhibitor of the Bruton's Tyrosine Kinase**

5 Introduction

[00297] Bruton's tyrosine kinase (BTK) is a nonreceptor tyrosine kinase expressed in most hematopoietic cells except for T cells, natural killer cells, and plasma cells. BTK activity is critical to the development and differentiation of B cells and acts as a modulator of signaling via the B-cell receptor (BCR). Given the key role of BTK in oncogenic BCR signaling and the fact
10 that BCR signaling is necessary to sustain B-cell malignancies, recent efforts have focused on developing BTK inhibitors for the treatment of these malignancies.

[00298] Currently, four small-molecule, irreversible, covalent, variably selective BTK inhibitors are approved as oral monotherapy for the treatment of B-cell malignancies. Ibrutinib (IMBRUVICA®), the first-in-class and most potent of the currently approved BTK inhibitors, is
15 approved in numerous countries around the world for treatment of mantle-cell lymphoma, chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), Waldenström macroglobulinemia, and marginal zone lymphoma, as well as chronic graft vs host disease. Subsequently, several selective second-generation BTK inhibitors like acalabrutinib, zanubrutinib, and tirabrutinib have been developed. Acalabrutinib and zanubrutinib have
20 received United States Food and Drug Administration approval for the treatment of mantle-cell lymphoma. Additionally, acalabrutinib is approved for treating patients with CLL/SLL and zanubrutinib is approved for marginal zone lymphoma and Waldenström macroglobulinemia. Whereas, tirabrutinib has been approved in Japan for the treatment of recurrent or refractory primary central nervous system lymphoma. All four BTK inhibitors bind to cysteine-481 in the
25 adenosine triphosphate binding site. Acalabrutinib and tirabrutinib are the most selective for BTK followed by zanubrutinib and then ibrutinib. With a shorter half-life than ibrutinib, acalabrutinib and zanubrutinib are dosed twice-daily, to maintain >95% BTK occupancy (BTKO), with a lower risk of off-target effects. However, side effects such as infection, atrial fibrillation and bleeding can limit the clinical benefits of these agents. Thus, there is a clinical
30 need for novel, more specific BTK inhibitors with less toxicity that might improve efficacy with a shorter duration of therapy.

[00299] Compound of Formula (III) is being developed as an orally active, potent, covalent, and highly selective BTK inhibitor as a potential treatment for patients with B-cell

malignancies or autoimmune disorders. This first-in-human (FIH) study was designed to assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD; BTKO) of compound of Formula (III) when orally administered as either single-ascending doses (SAD) or multiple-ascending doses (MAD) in healthy participants. The effects of gender, food, and solid capsule formulation on the safety, tolerability, PK, and PD BTKO of a single oral dose of compound of Formula (III) were also evaluated.

[00300] Data from this study have also been used to investigate the currently accepted paradigm that meaningful BTK inhibitor efficacy requires >90-95% BTKO. The dynamics of BTKO depend both on PK exposure and on the kinetics of target turnover, which is best captured with a quantitative PK/PD model.

METHODS

[00301] Study Participants - Volunteers aged 18-58 years, with a body mass index (BMI) of 18-30 kg/m², body weight ≥50 kg, and who were considered healthy based on medical history, physical examination, clinical laboratory evaluation, and 12-lead electrocardiogram (ECG) were enrolled in this study. Females were required to be surgically sterile or postmenopausal. Key exclusion criteria were history of, or current, clinically significant medical illness and history of malignancy within 5 years.

[00302] The Independent Ethics Committee associated with the study site reviewed and approved the study protocol and amendments. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Conference on Harmonization for Good Clinical Practices guidelines and applicable local and regulatory requirements. Written informed consent was obtained prior to study enrollment.

[00303] Study Design - This phase 1, randomized, double-blind, placebo-controlled, single-center study (NCT03607513; EudraCT 2018-000428-32) was conducted between July 2018 and August 2019 at the Janssen Clinical Pharmacology Unit in Merksem, Belgium. The study comprised two distinct parts; Part 1 examined SAD of compound of Formula (III) and Part 2 assessed MAD of compound of Formula (III).

Part 1

[00304] Safety, tolerability, PK, and BTKO were assessed for six doses of compound of Formula (III) oral solution (4, 12, 36, 100, 200, 400 mg) in participants under fasted conditions. The SAD part comprised 10 cohorts of 8 participants each (Figure 1). In each cohort receiving compound of Formula (III) oral solution (Cohorts 1-9), 6 participants were randomized

to receive compound of Formula (III) and 2 to receive placebo. All participants in Cohort 10 received compound of Formula (III) as an oral capsule. All 10 cohorts included 2 sentinel participants who were dosed ~24 hours prior to the rest of the cohort. In cohorts receiving compound of Formula (III) oral solution, 1 sentinel participant received compound of Formula (III) and the other received placebo.

[00305] Six male escalating dose cohorts received a single oral dose of 4, 12, 36, 100, 200, 400 mg compound of Formula (III) or placebo solution under fasted conditions. Gender effects were assessed in 2 female cohorts whose participants received either a 36 or 100 mg dose of compound of Formula (III) or placebo as an oral solution under fasted conditions. Food effects were evaluated in a male cohort receiving compound of Formula (III) 100 mg or placebo as an oral solution after a high-fat breakfast.

[00306] Safety, tolerability, and PK of a solid dose formulation of compound of Formula (III) were assessed in an additional male cohort (Cohort 10) that received 3 x 35 mg (105 mg) of compound of Formula (III) in the fasted state. Since all the participants received the same dose of compound of Formula (III), this cohort was not blinded.

Part 2

[00307] Safety, tolerability, PK, and BTKO following multiple compound of Formula (III) doses were evaluated in 3 dose escalation cohorts with a total of 18 participants (males: 9, females: 9) receiving active study drug. In each cohort, 3 males and 3 females were randomized to receive 36 mg once-daily (QD), 100 mg QD, or 200 mg QD compound of Formula (III) oral solution and 3 participants (males: 2; female: 1) to receive placebo. Two male participants in each cohort served as sentinel participants: one received compound of Formula (III) and other received placebo ~48 hours prior to other participants in the cohort. All safety and tolerability data (through the follow-up visit), PK data (through at least 24 hours after last dose administration), and all available PD data were reviewed from each cohort before a decision was made to dose escalate.

[00308] The doses administered during Part 2 were determined based on safety, tolerability, PK, and PD data obtained from preceding cohorts and on data obtained in Part 1 of the study, considering predicted PK and target occupancy of compound of Formula (III) after repeated dosing.

Study Assessments

[00309] Safety - Safety evaluations were based upon the type, incidence, and severity of treatment-emergent adverse events (TEAEs) reported throughout the study, and concomitant

medication reporting, clinical laboratory tests, physical examinations, vital sign measurements, and ECGs assessed at pre-defined time points. The TEAEs and serious TEAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 21.0) and summarized by system-organ class (SOC) and preferred terms.

5 Pharmacokinetics

[00310] Sample collection - For the PK assessment of compound of Formula (III), venous blood samples (2 to 4 mL each) were collected predose and at 15 min, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, and 72 hours post-dose in Part 1. In Part 2, samples were collected predose and at 15 min, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 hours post-dose on day 1, predose and 1
10 hour post-dose on days 2-9, and predose and at 15 min, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 48, and 72 hours after the last dose on day 10. Plasma samples were analyzed to determine concentrations of compound of Formula (III) using a scientific validated, specific, and sensitive liquid chromatography-mass spectrometry (LC-MS/MS) method.

[00311] The PK analysis for the compound of Formula (III) samples was performed
15 using a non-compartmental method with validated Phoenix® WinNonlin® (version 8.0, Certara L.P.). Estimated PK parameters included maximum observed plasma concentration (C_{max}), time to reach C_{max} (t_{max}), minimum observed plasma concentration during dosing interval (C_{min}), area under the plasma concentration-time curve during the 24-hour dosing interval (AUC_{0-24}), AUC from time 0 to time of last measurable concentration (AUC_{last}), AUC from time 0 to
20 infinite time (AUC_{∞}), dominant half-life ($t_{1/2, dom}$), apparent elimination half-life ($t_{1/2, \lambda z}$), the observed accumulation ratio based on C_{max} (ARC_{max}), the observed accumulation ratio based on AUC (AR_{AUC}), amount of drug excreted into the urine as a percent dose, and renal clearance of drug (CL_R).

[00312] Pharmacodynamics (BTKO) - In Part 1, venous blood samples (8 mL) were
25 collected predose and at 1, 2, 4, 8, 12, 24, 48, and 72 hours post-dose for measuring free BTK levels in peripheral blood mononuclear cells (PBMCs) and calculating %BTKO. In Part 2, blood samples were taken on day 1 predose and at 2, 4, and 8 hours after dosing; days 2-10 predose and 4 hours post-dose; and at 24, 48, and 72 hours after the last dose and at the follow-up visit.

[00313] After PBMCs were isolated from whole blood, they were lysed and prepared
30 for the measurement of BTK occupancy using a custom streptavidin-coated Meso Scale Discovery (MSD) immunoassay. Percent occupancy was calculated as $100\% \times ([\text{Baseline free BTK} - \text{Free BTK with treatment}] / \text{Baseline Free BTK})$.

[00314] PK/PD modeling and simulation - In the PK/PD model, a two-compartment population PK (popPK) model with a first-order absorption and elimination was used to fit the PK data. The model was parameterized in terms of apparent clearance (CL/F), apparent volume of distribution of the central compartment (V₂/F), apparent inter-compartmental clearance (Q/F), apparent volume of distribution of the peripheral compartment (V₃/F), and first-order absorption rate constant (K_a). Inter-individual variability was included on CL/F, V₂/F, Q/F, and K_a. Following the development of the popPK model, the PK/PD model was subsequently developed based on individual estimates from the popPK model.

[00315] A mechanistic covalent binding model (Figure 2) was used to describe the receptor occupancy of compound of Formula (III). The equations describing the binding model are shown in equations 1-5.

$$f_u = 1.4 + \frac{4.43 \times C^2}{2076^2 + C^2}$$

(1)

where f_u is the compound of Formula (III) unbound fraction and C is the concentration in nM. Free fraction equation was developed using data from the study that evaluated the concentration dependence of compound of Formula (III) binding to the proteins in human plasma using an equilibrium dialysis technique.

$$\frac{dBTK}{dt} = k_{syn} - k_{on} \times BTK \times C_1 \times f_u - k_{degf} \times BTK + k_{off} \times BTK_b \quad BTK(0) = BTK_0$$

(2)

$$\frac{dBTK_b}{dt} = k_{on} \times BTK \times C_1 \times f_u - k_{off} \times BTK_b - k_{inact} \times BTK_b \quad BTK_b(0) = 0$$

(3)

$$\frac{dBTK_i}{dt} = k_{inact} \times BTK_b - k_{degi} \times BTK_i \quad BTK_i(0) = 0$$

(4)

$$\%BTK \text{ occupancy} = \frac{BTK_b + BTK_i}{BTK + BTK_b + BTK_i}$$

(5)

where symbols represent the free BTK protein concentration (BTK), drug-BTK complex (BTK_b) and covalently bound complex (BTK_i). The rate constants in the equations include zero-order rate of BTK synthesis (k_{syn}); the first-order rate of free BTK degradation (k_{degf}); the first-order rate of covalently bound complex degradation (K_{degi}); association rate drug-BTK binding (k_{on}); dissociation rate drug-BTK binding (k_{off}). C₁ is the concentration in central compartment.

BTK₀ is the baseline value of BTK. The degradation rate of free BTK and covalently bound complex is assumed to be the same.

[00316] In order to refine predictions of %BTKO after multiple dosing for the MAD cohorts and to help select a starting dose for the subsequent first-in-patient oncology study, a prior mechanistic PK/PD model based on *in vitro* and *in vivo* BTKO data was updated with clinical PK/BTKO data collected from SAD cohorts of the FIH study. The semi-mechanistic PK/PD model was used to simulate %BTKO following various dose regimen. The evaluated dosing regimens included 12 mg, 36 mg, 70 mg, 100 mg, 140 mg, 200 mg QD dose. The participants for simulation were randomly sampled from the analysis dataset (n=1000). The BTKO was targeted at 90% as meaningful clinical efficacy. The observed %BTKO in MAD cohort were compared with the model predictions.

[00317] Once MAD data were available, the semi-mechanistic PK/PD model was updated with the acquired data from SAD and MAD cohorts. The covariates assessed in the popPK analysis were shown in Table 4. All covariate effects in the popPK analysis were evaluated on clearance from the central compartment (CL/F) only, except for body weight, food effect, and drug formulation. Body weight was included in the structural model (as a covariate on the CL/F, V₂/F, Q/F). Body weight was investigated as a covariate by using an allometric function with power value of 0.75 for clearance parameters and 1 for volume parameters. Food effect and drug formulation were evaluated on K_a. The covariates model selection was conducted using a full-model approach with backward elimination (nominal p<0.001, i.e., a change in the objective function value of 10.83 with 1 degree of freedom). A covariate model was initially developed using all statistically significant covariates of interest, and was then reduced by removing covariates with effect sizes less than 10% of the typical values of the respective PK parameters. This reduced model was regarded as the final model which was subsequently used for PD model. Model selection was determined by graphical assessment, statistically significant difference in the objective function value between competing models. The performance of the final model was evaluated using a prediction-corrected visual predictive check (pcVPC; n=1000 replicates).

Software

[00318] The semi-mechanistic PK/PD model was performed using NONMEM (version 7.3.0, ICON Development Solutions LLC, Ellicott City, MD, United States). The use of NONMEM, including model qualification procedures, were facilitated within the environment of Perl-speaks-NONMEM (version 4.6.0, a compatible front-end program for NONMEM. Data

management, exploratory analyses, diagnostic graphics, and post processing of the data and NONMEM outputs were performed using R (version 3.4.1, The R Project for Statistical Computing, statistical software). All analyses were performed in a validated environment, High Performance Pharmacometrics Platform System (Rudraya Sonic version 4 or higher), based on Good Automated Manufacturing Practice and in accordance with 21 CFR Part 11 and Good Clinical Practice regulations.

Statistical Analysis

[00319] Considering this was a phase 1 FIH study, formal statistical sample size calculation was not appropriate and was not performed. The number of participants enrolled was consistent with the customary size employed in such early development dose-escalation studies, and was expected to allow clinical judgment of safety and tolerability, and to allow meaningful assessment of the PK and PD profile.

[00320] Compound of Formula (III) plasma concentration data and its derived PK parameters, %BTKO, and safety were summarized using descriptive statistics. The PK analysis set included participants who received at least one dose of compound of Formula (III). The PD analysis set consisted of all participants who received at least 1 dose of compound of Formula (III) or placebo, and had at least 1 post-dose PD assessment. Safety analysis included all participants who received at least one dose of compound of Formula (III) or placebo.

RESULTS

Participant Disposition and Demographics

[00321] In Part 1, 60 participants received a single dose of compound of Formula (III) and 18 received placebo. To assess multiple doses in Part 2, 18 participants received compound of Formula (III) and 9 participants received placebo. Overall, the demographic characteristics were similar across groups in either Part 1 or Part 2. Most participants were Caucasian (Part 1: 74/78 [94.9%]; Part 2: 26/27 [96.3%]). In Part 1, the mean age of participants was 45.8 years (range: 21 to 58 years) and mean body mass index (BMI) was 24.93 kg/m² (range: 19.4 to 29.2 kg/m²). In Part 2, the mean age was 48.6 years (range: 25 to 58 years) and mean BMI was 24.95 kg/m² (range: 19.1 to 29.9 kg/m²).

Safety

[00322] Overall, the nature and incidence of TEAEs were similar in compound of Formula (III) -treated and placebo-treated participants after single and multiple dosing. In Part 1 and Part 2, 24 (40.0%) and 14 (77.8%) participants receiving compound of Formula (III) had at

least 1 TEAE, as compared to 9 (50.0%) and 9 (100.0%) participants in the corresponding placebo groups (Table 1). All TEAEs were rated as mild to moderate in severity.

Table 1. TEAEs Reported for $\geq 10\%$ of Total Population in any Treatment Group
5 (compound of Formula (III) or Placebo; Safety Analysis Set)

PART 1										
TEAEs, n (%)	Placebo n=18	compound of Formula (III)								Total compound of Formula (III) N=60
		Fasted						Solid	Fed	
		4 mg n=6	12 mg n=5	36 mg n=12	100 mg n=11	200 mg n=6	400 mg n=6	105 mg n=6	100 mg n=8	
Patients with ≥1 TEAEs	9 (50.0)	2 (33.3)	3 (60.0)	4 (33.3)	4 (36.4)	4 (66.7)	3 (50.0)	3 (50.0)	1 (12.5)	24 (40.0)
Headache	3 (16.7)	1 (16.7)	2 (40.0)	2 (16.7)	0	1 (16.7)	0	1 (16.7)	1 (12.5)	8 (13.3)
Administration site irritation*	2 (11.1)	1 (16.7)	0	0	0	1 (16.7)	0	0	0	2 (3.3)
PART 2										
	Placebo n=9	compound of Formula (III)				Total compound of Formula (III) N=18				
		36 mg n=6		100 mg n=6		200 mg n=6				
Patients with ≥1 TEAEs	9 (100.0)	4 (66.7)		5 (83.3)		5 (83.3)				14 (77.8)
Administration site irritation*	1 (11.1)	1 (16.7)		2 (33.3)		0				3 (16.7)
Injection site hematoma*	0	0		2 (33.3)		0				2 (11.1)
Injection site reaction*	0	1 (16.7)		1 (16.7)		0				2 (11.1)
Fatigue	3 (33.3)	0		0		1 (16.7)				1 (5.6)
Vessel puncture site hematoma*	1 (11.1)	0		1 (16.7)		0				1 (5.6)
Abdominal discomfort	1 (11.1)	1 (16.7)		1 (16.7)		0				2 (11.1)
Regurgitation	1 (11.1)	1 (16.7)		0		1 (16.7)				2 (11.1)
Abdominal pain	2 (22.2)	0		0		1 (16.7)				1 (5.6)
Diarrhea	4 (44.4)	0		1 (16.7)		0				1 (5.6)
Flatulence	1 (11.1)	1 (16.7)		0		0				1 (5.6)
Nausea	1 (11.1)	0		0		0				0
Oral dysaesthesia	1 (11.1)	0		0		0				0
Paresthesia	0	2 (33.3)		0		0				2 (11.1)
Dizziness	1 (11.1)	0		0		1 (16.7)				1 (5.6)
Headache	2 (22.2)	0		0		1 (16.7)				1 (5.6)
Somnolence	1 (11.1)	0		1 (16.7)		0				1 (5.6)
Dysgeusia	1 (11.1)	0		0		0				0
Back pain	0	1 (16.7)		0		0				1 (16.7)
Myalgia	1 (11.1)	0		1 (16.7)		0				0

Abnormal dreams	1 (11.1)	0	0	0	0
Skin irritation	1 (11.1)	0	0	0	0
Skin reaction	0	1 (16.7)	0	1 (16.7)	2 (11.1)
Hot flush	0	0	1 (16.7)	1 (16.7)	2 (11.1)
Vertigo	1 (11.1)	0	0	0	0
Vision blurred	1 (11.1)	0	0	1 (16.7)	1 (5.6)
Lipase increased	1 (11.1)	0	0	0	0
Dehydration	1 (11.1)	0	0	0	0
Cough	1 (11.1)	0	0	0	0
Increased bronchial secretion	1 (11.1)	0	0	0	0
Oropharyngeal pain	1 (11.1)	0	0	0	0
Nasopharyngitis	1 (11.1)	0	0	0	0

TEAEs = treatment-emergent adverse events

*“Vessel puncture site hematoma” were due to bruising at the site of indwelling catheters for blood draws.

The TEAEs of “skin irritation” and “skin reaction” were due to ECG electrode adhesive.

- 5 **[00323]** In Part 1, among compound of Formula (III) -treated participants, the most common ($\geq 5\%$) TEAEs were headache (13.3% versus 16.7% in placebo) and nasal congestion (5% versus 0 in placebo). In Part 2, administration site irritation (ECG electrode adhesive site irritation) was the most frequently reported TEAE (compound of Formula (III), 16.7% [3/18] versus placebo, 11.1% [0 to 1/9]), followed by abdominal discomfort, back pain, hot flush,
- 10 paresthesia, regurgitation, and skin reaction (reaction at ECG electrode adhesive site) (compound of Formula (III), 11.1% [2/18] versus placebo, 11.1% [0 to 1/9] for each). Only 1 participant from Part 2 (compound of Formula (III) 200 mg group) discontinued after 8 days of dosing due to a TEAE of mild ‘transaminases increased, and levels returned to within the normal range at follow-up, 12 days after administration of the last dose of compound of Formula (III).
- 15 **[00324]** There were no dose-related, gender-related, or food-related differences in TEAEs reported in either of the parts. No serious TEAEs or TEAEs considered probably or very likely related to the study drug were reported. Also, no clinically significant changes were observed in laboratory parameters, vital signs, physical examinations, or ECGs.
- 20 **Table 2. Mean (SD) of compound of Formula (III) Pharmacokinetic Parameters Following Single Dose of compound of Formula (III) in Healthy Participants (PK Analysis Set)**

^aData presented as Median (Minimum-Maximum); ^bn=5; ^cn=4; ^dn=6.

AUC = area under the plasma concentration versus time curve; AUC_{0-24h} = AUC from time 0 to 24 hours post-dose; AUC_{last} = AUC from time 0 to the time corresponding to the last quantifiable concentration;

Formulation Treatment, Condition	N	C _{max} (ng/mL)	C _{max} /Dose (ng/mL)	t _{max} ^a (h)	AUC _{0-24h} (h·ng/mL)	AUC _{last} (h·ng/mL)	AUC _∞ (h·ng/mL)	AUC _∞ /Dose (h·ng/mL/mg)	t _{1/2, λz} (h)	t _{1/2, dom} (h)
Oral Solution										
4 mg, Male Fasted	6	43.5 (9.61)	10.9 (2.40)	1 (1- 1.5)	157 (51.0)	154 (48.9)	155 (49.8)	38.9 (12.5)	1.6 (0.2)	1.6 (0.2)
12 mg, Male Fasted	5	88.0 (18.9)	7.33 (1.58)	1 (1- 1.5)	319 (108)	316 (109)	317 (109)	26.4 (9.07)	1.6 (0.5)	1.5 (0.2)
36 mg, Male Fasted	6	200 (51.8)	5.55 (1.44)	1 (0.5- 1)	649 (213)	649 (214)	644 (239) ^b	17.9 (6.64)	2.1 (0.4) ^b	1.6 (0.1)
100 mg, Male Fasted	6	923 (334)	9.23 (3.34)	0.5 (0.5- 1)	2135 (709)	2145 (718)	2060 (760) ^b	20.6 (7.60)	5.0 (3.3) ^b	1.9 (0.2)
200 mg, Male Fasted	6	1210 (413)	6.06 (2.07)	1 (0.5- 1)	2748 (752)	2773 (763)	2778 (761)	13.9 (3.80)	12.7 (8.4)	1.8 (0.2)
400 mg, Male Fasted	6	1920 (1280)	4.80 (3.20)	0.75 (0.5- 2)	3704 (1639)	3828 (1616)	4197 (1885) ^b	9.11 (4.68)	13.2(11.3) ^c	2.2 (0.3)
36 mg, Female Fasted	6	233 (44.5)	6.46 (1.24)	1 (1- 1.5)	819 (296)	816 (299)	818 (299)	22.7 (8.30)	1.9 (0.5)	1.6 (0.2)
100 mg, Female Fasted	5	650 (199)	6.50 (1.99)	0.5 (0.25- 1)	1420 (519)	1459 (494)	1338 (460) ^c	13.4 (4.60)	11.6 (7.8) ^c	1.6 (0.2)
100 mg, Male Fed	6	277 (81.1)	2.77 (0.811)	2.5 (1-4)	1716 (403)	1752 (420)	1757 (420)	17.6 (4.20)	10.8 (5.2)	2.0 (0.5)
Oral Capsule										
105 mg (3x35 mg), Male Fasted	8	345 (200)	3.28 (1.91)	1.5 (1-2)	1323 (710)	1452 (731)	1505 (797) ^d	14.3 (7.59)	14.2 (4.5) ^d	1.9 (0.3)

AUC_∞ = AUC from time 0 to infinity with extrapolation of the terminal phase; AUC_∞/Dose = AUC_∞ normalized for dose; C_{max} = maximum observed plasma concentration; C_{max}/Dose = C_{max} normalized for dose; SD = standard deviation; t_{1/2, λz} = terminal half-life; t_{1/2, eff} = dominant half-life; t_{max} = time correspondent to the maximum observed plasma concentration

Pharmacokinetics

Part 1

[00325] Following a single dose of compound of Formula (III) oral solution under fasted conditions in healthy males, peak plasma concentrations occurred within 1 hour and then declined in a multi-exponential manner (Figure 3). Compound of Formula (III) was rapidly absorbed into the systemic circulation as indicated by a median t_{max} of 0.5 to 1 hours post-dose.

Mean C_{max}, AUC_{last}, and AUC_∞ of compound of Formula (III) increased over the dose range of 4

to 400 mg but less than dose proportionally with increasing doses (Table 2). Mean $t_{1/2, dom}$ values were similar, ranging from 1.5 to 2.2 hours in the dose range of 4 to 400 mg. Mean $t_{1/2, \lambda z}$ increased with dose, with mean values ranging from 1.6 to 13.2 hours. At the lowest doses (4, 12, and 36 mg), the Mean $t_{1/2, \lambda z}$ was similar to the Mean $t_{1/2, dom}$ as the plasma concentrations were approaching the lower limit of quantitation (LLOQ) between 12 and 24 hours post-dose.

Gender effects

[00326] The PK parameters in male and female participants were overlapping following a single dose of 36 mg and 100 mg of compound of Formula (III) as an oral solution under fasted conditions. For 36 mg dose cohorts, mean C_{max} and AUCs in females were slightly higher than in males by approximately 17-27%; however, in females dosed with the 100 mg dose, these values were lower than in males by approximately 30-35% (Table 2).

[00327] Mean $t_{1/2}$ of the initial fast decay ($t_{1/2, dom}$) was 1.6 hours in fasted females irrespective of the dose of compound of Formula (III) (36 mg or 100 mg) and was comparable to the mean $t_{1/2, dom}$ reported for male participants (36 mg: 1.6 hours; 100 mg: 1.9 hours). The $t_{1/2, \lambda z}$ in female participants increased with dose, with values of 1.9 hours and 11.6 hours for the 36 mg and 100 mg dose groups, respectively.

Food effects

[00328] Administration of a single dose of 100 mg compound of Formula (III) following a high-fat meal delayed peak of the concentration-time profile (median t_{max} : 2.5 hours versus 0.5 hours [100 mg fasted cohort]) (Figure 4), and lowered the plasma C_{max} by approximately 70% without much affecting overall exposure (Table 2). Mean AUCs of the fed cohort were approximately 15 to 20% lower compared with the fasted cohort (Table 2). The rate of decline in plasma concentrations was similar between fasted and fed male cohorts, with mean $t_{1/2, dom}$ of 1.9 and 2.0 hours, respectively. Mean $t_{1/2, \lambda z}$ in fed participants fell within the range of values estimated across the dose range of 4 mg to 400 mg in the fasted cohorts (Table 2).

Capsule formulation

[00329] Following a single dose of 105 mg compound of Formula (III) administered as 3 x 35 mg capsules, the peak of the plasma concentration-time profile was slightly delayed, with a median t_{max} of 1.5 hours versus 0.5 hours for 100 mg oral solution (Table 2). Mean $C_{max}/Dose$ of the capsule formulation was approximately 64% lower while mean AUCs/Dose was approximately 31% to 41% lower compared with the oral solution.

Part 2

[00330] On day 1, the mean PK profiles increased with dose, and compound of Formula (III) was rapidly absorbed with median t_{max} ranging from 1.25 to 1.77 hours post-dose (Table 3). Mean predose and 1-hour post-dose concentrations remained similar across days 2-9 within each dose group, suggesting that compound of Formula (III) plasma concentrations reached steady-state by the second dose (Figure 5). Compared to the profiles observed on day 1, the day 10 plasma concentration-time profiles were similar or slightly higher but subsequently decreased in a multi-exponential manner (Figure 5). No accumulation of compound of Formula (III) was observed following daily dosing of 36 mg and 100 mg, with mean (SD) AR_{AUC} = 0.968 (0.101) and 0.950 (0.237), respectively. Minor accumulation was observed after multiple doses of 200 mg compound of Formula (III) with mean (SD) AR_{AUC} = 1.21 (0.180). Renal elimination of unchanged compound of Formula (III) was negligible following daily oral doses of 200 mg compound of Formula (III) (Table 3).

Table 3. Mean (SD) of compound of Formula (III) Pharmacokinetic Parameters Following Multiple Doses of compound of Formula (III) Oral Solution in Healthy Males and Females under Fed Conditions (PK Analysis set)

Treatment	C_{max} (ng/mL)	t_{max} ^a (h)	AUC_{0-24h} (h-ng/mL)	C_{min} (ng/mL)	$t_{1/2, \lambda_z}$ (h)	$t_{1/2, dom}$ (h)	$AR_{C_{max}}$	AR_{AUC}	$Ae_{\%dose}$	CL_R (L/h)
Day 1										
36 mg QD	193 (39.2)	1.50 (1.00-2.50)	925 (210)	NA	NA	NA	NA	NA	NA	NA
100 mg QD	464 (141)	1.25 (1.00-3.00)	1821 (499)	NA	NA	NA	NA	NA	NA	NA
200 mg QD	719 (299)	1.77 (1.00-3.00)	2565 (577)	NA	NA	NA	NA	NA	0.234 (0.0662)	0.186 (0.0544)
Day 10										
36 mg QD	199 (36.9)	2.00 (1.00-2.50)	889 (182)	0.552 (0.198)	4.9 (3.3) ^b	1.5 (0.1)	1.04 (0.129)	0.968 (0.101)	NA	NA
100 mg QD	424 (70.4)	1.53 (1.00-3.00)	1692 (546)	1.51 (0.545)	9.6 (3.6)	1.8 (0.2)	0.968 (0.234)	0.950 (0.237)	NA	NA
200 mg QD	839 (252)	2.00 (1.50-2.50)	3164 (965)	4.96 (1.85)	23.1 (12.2) ^c	1.9 (0.1)	1.21 (0.614)	1.21 (0.180)	0.231 (0.0723)	0.151 (0.0453)

^aData presented as Median (Minimum-Maximum); ^bn=3; ^cn=4

$Ae_{\%dose}$ = amount excreted into the urine as a percent of dose, calculated as ratio of Ae to the dose administered $\times 100$; AR_{AUC} = the observed accumulation ratio based on AUC; $AR_{C_{max}}$ = the observed accumulation ratio based on C_{max} ; AUC = area under the plasma concentration versus time curve; AUC_{0-24h} = AUC from time 0 to

24 hours post-dose; $C_{\max}$ = maximum observed plasma concentration; $C_{\min}$, minimum observed plasma concentration; CL_R = renal clearance; SD = standard deviation; $t_{1/2, \text{tz}}$ = terminal half-life; $t_{1/2, \text{eff}}$ = dominant half-life; $t_{\max}$ = time correspondent to the maximum observed plasma concentration

5 **Table 4. Covariates Assessed in Population Pharmacokinetic Analysis Using All Data from SAD and MAD**

Categories	Covariates	Type
Demographic characteristics	Weight [BWT], Age [AGE]	Continuous
	Sex [SEX], Race [RACE]	Discrete
Renal Function	Baseline creatinine clearance [CRCL], Estimated glomerular filtration rate [eGFR]	Continuous
Clinical laboratory characteristics	Baseline albumin [BALB], Baseline aspartate aminotransferase [AST], Baseline alanine aminotransferase [ALT], Baseline alkaline phosphatase [ALP], Total bilirubin [TB]	Continuous
Food Effects	Nutritional status [NUTR]	Discrete
Formulation	Dosage form [FORM]	Discrete

MAD, multiple-ascending dose; SAD, single-ascending dose.

Pharmacodynamics

10 **[00331]** BTKO following single oral solution dose in fasted state - In male participants, the %BTKO increased with increasing compound of Formula (III) doses and approached 100% at 4 hours after administration of doses ≥ 100 mg (Figure 6). While plasma concentrations of compound of Formula (III) decreased to <LLOQ 12 hours post-dose, the duration of BTKO was up to 72 hours for cohorts dosed with ≥ 100 mg compound of Formula
 15 (III) (Figure 6). At the follow-up visit (7-14 days post last dose), the mean %BTKO values were $\leq 42\%$ in all treatment groups, with high variability in some groups. The emerging PK and BTKO data demonstrated that BTKO was closely linked with compound of Formula (III) AUCss rather than $C_{\max}$.

[00332] Compared with fasted administration of the solution formulation (100 mg), the
 20 peak mean %BTKO value was delayed and slightly lower following administration of the solution formulation after a high-fat breakfast (100 mg) (fed state: 73% [at 8 hours post-dose]; fasted state: 86% [at 4 hours post-dose]).

[00333] The mean %BTKO values in females receiving 36 mg or 100 mg compound of Formula (III) were similar to male participants receiving the same doses. At 4 hours following
 25 administration of the 36 mg dose, the mean %BTKO values were 39% in males and 55% in females, and were 86% versus 81%, respectively when dosed with 100 mg compound of Formula (III).

[00334] BTKO following single capsule formulation dose in fasted state - The mean %BTKO was reduced in males dosed with 105 mg compound of Formula (III) capsule formulation compared with fasted administration of 100 mg oral solution. At 4 hours post-dose, mean %BTKO was $\approx 37\%$ lower for 105 mg capsule formulation (54%) than the 100 mg oral solution (86%), and $\approx 30\%$ lower at 24 hours post-dose (53% versus 76%, respectively) (Figure 4).

[00335] BTKO following multiple doses of compound of Formula (III) oral solution - Accumulation of %BTKO in PBMCs was observed after multiple once-daily dosing with compound of Formula (III). At 4 hours post-dose, the mean %BTKO increased from 34% (day 1) to 80% (day 10) in the 36 mg dose group and from 61% (day 1) to 91% (day 10) in the 100 mg group. Whereas, in the 200 mg dose group, mean %BTKO was evident from day 1 (94%) and maintained on day 10 (98%). Mean %BTKO at all 3 compound of Formula (III) doses (36, 100, and 200 mg) remained high (68% to 79%) 24 hours after the day 10 dose. At the follow-up visit (7 to 14 days post-dose), the mean %BTKO values were $<40\%$ in all treatment groups with high variability in some groups.

[00336] PK/PD modeling and simulation - compound of Formula (III) plasma concentrations from the first 5 SAD cohorts were best described with a 2-compartment model, including a first-order absorption and first-order elimination with IIV on CL/F, V_1/F , V_2/F , Q/F and K_a . Additionally, correlation terms were included between CL/F and V_1/F . The PK/PD model was subsequently developed based on individual estimates from the popPK model to describe free BTK, with IIV on baseline free BTK and associate rate k_{on} . Parameter estimates are shown in Table 5 and goodness-of-fit plots are shown in Figure 9 and Figure 10. All model parameters were estimated reasonably well with relative standard errors $\leq 20\%$ for all the structural PK/PD parameter estimates. Based on the PK/PD model, simulations were conducted to predict %BTK occupancy in the MAD cohorts (Figure 5). The model-predicted %BTKO in the MAD cohorts based on data from the SAD cohorts was consistent with observed %BTKO (Table 6).

Table 5. Parameter Estimates of the PK/PD Model Using (A) First 5 SAD Cohorts data (B) All SAD and MAD Data

(A)

Parameter, unit	Estimate	RSE (%)	IIV (%CV)	RSE (%)	Shrinkage (%)
popPK parameters^b					
CL/F (L/h)	49.4	8.68	44.0	25.2	1.18
V ₁ /F (L)	108.9	8.62	40.6	25.1	2.93
V ₂ /F (L)	43.0	17.7			
Q/F (L/h)	1.57	12.0	49.1	42.2	21.8
K _a (1/h)	1.94	11.2	44.5	33.7	12.5
Covar(CL/F, V ₁ /F)	0.174	25.4			
Proportional residual error (%CV)	24.5	8.43			
Additive residual error (ng/mL) ^c	0.0289	--			
PD parameters^b					
k _{on} (1/nM/h)	0.0447	13.3	31.6	125.5	64.8
k _{off} (1/h) ^d	5.7×10 ⁻³ ×60×60	--			
k _{inact} (1/s) ^d	7.8×10 ⁻⁴	--			
BTK ₀ (nM)	0.0815	3.63	34.0	29.1	8.82
k _{degi} /k _{degf} (1/h) ^d	0.0116	--			
Additive residual error (nM)	0.0208	12.4			

^aCL/F= apparent clearance; IIV= inter-individual variability, calculated as (variance)^{1/2} × 100%; K_a= first-order absorption rate constant; k_{on}=association rate; k_{off}=dissociate rate; k_{inact}=covalent binding rate; k_{deg}=BTK degradation rate; Q/F= apparent inter-compartmental clearance; RSE=relative standard error; V₁/F= apparent volume of distribution of the central compartment; V₂/F=apparent volume of distribution of the peripheral compartment.

^bpopPK was examined using Cohort 1-5 data, PD was assessed with Cohort 2-5 data.

^cAdditive residual error was fixed to 0.0289 ng/mL based on a calculation of the probability distribution characteristic associated with LLOQ of 0.1 ng/mL.

^dk_{off} was obtained from Woyach Supplemental Data 2014, k_{inact} was from lab measurement, k_{degi}/k_{degf} was calculated with ln(2)/60, assuming BTK turnover half-life was 60 h.

Parameter, unit	Estimate	RSE (%)	IIV (%CV)	RSE (%)	Shrinkage (%)
popPK parameters^b					
CL/F (L/h) ^c	62.4	5.10	46.0	17.4	0.42
BWT on CL/F	0.75	--			
V ₁ /F (L) ^d	129.6	4.92	41.7	19.7	2.76
BWT on V ₁ /F	1	--			
V ₂ /F (L) ^e	49.5	15.2	139.9	19.7	10.1
BWT on V ₂ /F	1	--			
Q/F (L/h) ^f	2.85	13.7	132.5	19.6	8.92
BWT on Q/F	0.75	--			
K _a (1/h) ^g	1.97	8.14	44.3	22.0	11.5
NURT= Fed, standard meal on Ka	0.339	12.3			
FORM= Oral Capsule on Ka	0.325	19.2			
Covar(CL/F, V ₁ /F)	0.185	18.5			
Covar(Q/F, V ₂ /F)	1.74	19.9			
Proportional residual error (%CV)	28.1	2.21			
Additive residual error (ng/mL)	0.0483	33.9			
PD parameters^b					
k _{on} (1/nM/h)	0.0509	10.2	43.2	45.7	50.4
k _{off} (1/h) ^h	5.7×10 ⁻⁵ ×60×60	--			
k _{inact} (1/s) ^h	7.8×10 ⁻⁴	--			
BTK ₀ (nM)	0.0802	3.01	24.6	19.4	11.2
k _{degi} /k _{degf} (1/h) ^h	0.0116	--			
Additive residual error (nM)	0.0220	0.748			

^a BWT= baseline body weight in kilograms; CL/F= apparent clearance; FORM=Dosage form (1=Oral solution, 2= Oral Capsule); IIV= inter-individual variability, calculated as (variance)^{1/2} ×100%; K_a= first-order absorption rate constant; k_{on}=association rate; k_{off}=dissociate rate; k_{inact}=covalent binding rate; k_{deg}=BTK degradation rate; NURT=Nutritional status (0=Fasted, 1=Fed, standard meal); Q/F= apparent inter-compartmental clearance; RSE=relative standard error; V₁/F= apparent volume of distribution of the central compartment; V₂/F=apparent volume of distribution of the peripheral compartment.

^b popPK and PD were examined using data from both SAD and MAD data.

$$^c \frac{CL}{F} (L/h) = 62.4 \times \left(\frac{BWT}{75.5} \right)^{0.75}$$

$$^d \frac{V_1}{F} (L) = 129.6 \times \left(\frac{BWT}{75.5} \right)^1$$

$$^e \frac{V_2}{F} (L) = 49.5 \times \left(\frac{BWT}{75.5} \right)^1$$

$$^f \frac{Q}{F} (L) = 2.85 \times \left(\frac{BWT}{75.5} \right)^{0.75}$$

$$^g K_a \left(\frac{1}{h} \right) = 1.97 \times 0.339^{NURT=Fed, standard meal} \times 0.325^{FORM=Oral Capsule}$$

^h k_{off} was obtained from Woyach Supplemental Data 2014, k_{inact} was from lab measurement, k_{degi}/k_{degf} was calculated with ln(2)/60, assuming BTK turnover half life was 60 h.

Table 6. Comparison of Simulated and Observed Data

Median of Simulations (n=1000) based on Phase 1 SAD Oral Solution data				Median Observed Day 10 Oral Solution Data		
Dose (mg)	BTKO at 24 hr, ss (%) ^b	Max BTKO at ss (%) ^b	Average BTKO (%) ^{b,c}	BTKO at 24 hr, ss (%)	Max BTKO at ss (%)	Calculated Average BTKO (%)
12 QD	43.4	52.0	48.3	-	-	-
36 QD	66.7	79.9	74.3	69.5	78.9	74.2
70 QD	75.6	91.5	84.7	-	-	-

100 QD	78.8	96.0	88.3	84.1	94.1	89.1
105 QD	79.1	96.3	88.7	-	-	-
140 QD	80.3	98.2	90.4	-	-	-
200 QD	81.6	99.3	91.5	78.9	98.8	88.8

^apopPK was examined using Cohort 1-5 data, popPD was assessed with Cohort 2-5 data; ^bThe values are median of 1000 simulations; ^cAverage RO at steady-state (ss) was calculated as $AUMC_{ss}/\tau_u$
 $AUMC_{ss}/\tau_u$ = Area under the first moment of the plasma concentration-time curve for the dosing interval at steady-state; BTKO = Bruton's tyrosine kinase occupancy; PopPK = population pharmacokinetics; popPD = population pharmacodynamics; QD, once daily; SAD = single-ascending dose; ss = steady-state.

[00337] The PK/PD model was updated again with the data acquired from FIH study. The PK/PD dataset contained 1509 compound of Formula (III) concentration-time datapoints and 1335 free BTK datapoints from 105 participants. compound of Formula (III) plasma concentrations from both SAD and MAD cohorts were described with a 2-compartment model, including a first-order absorption and first-order elimination with IIV on CL/F, V_1/F , V_2/F , Q/F and K_a . Additionally, correlation terms were included between CL/F and V_1/F , Q/F and V_2/F . The residual error was best described by a combined additive and proportional error model. The covariate effects retained in the final popPK model were the effects of body weight on CL/F, V_1/F , V_2/F and Q/F, the food effects and drug formulation effects on K_a . Other covariates tested were not statistically significant. pcVPC are shown in Figure 11, the final PKPD model adequately captured the median concentration-time profiles.

DISCUSSION

[00338] In the overall context of pharmacotherapy, the BTK inhibitors are promising novel agents that have significantly expanded the arsenal of therapies available for the treatment of various types of B-cell malignancies. This FIH phase 1 study demonstrated that an oral solution of compound of Formula (III), a novel BTK inhibitor, can be administered as a single dose up to 400 mg and multiple daily doses up to 200 mg for 10 days with no safety signals of concern. A maximum %BTKO of $\geq 90\%$ (mean) was achieved after single and multiple doses of compound of Formula (III) of ≥ 100 mg. The high variability was seen between the reported %BTKO for the same doses in SAD and MAD cohorts. This high variability in BTKO can be attributed to the food effect; in SAD cohorts, participants were dosed in a fasted state, while in MAD cohorts, participants were not fasted.

[00339] The safety profile showed that TEAEs occurred in 40% of participants following single dosing and in 78% participants after multiple dosing of compound of Formula (III). The most common TEAEs after single dosing were headache and nasal congestion, and administration site irritation, abdominal discomfort, back pain, hot flush, paresthesia,

regurgitation, and skin reaction were most common after multiple dosing. All the events were of mild to moderate severity and resolved by the end of the study. All TEAEs reported in both parts of the study resolved by follow-up and there was no apparent increase in frequency or type of TEAEs with increasing dose of compound of Formula (III). Also, no gender- or food-related differences were reported in incidence and severity of TEAEs. There were no clinically relevant ECG changes or relevant cardiac or cardiovascular TEAEs.

[00340] The PK profiles of compound of Formula (III) demonstrated rapid absorption with peak concentrations reached within 1 hour after single doses and 2 hours after multiple doses. After reaching C_{max} , the plasma concentration of compound of Formula (III) declined rapidly in a multiexponential fashion. The PK were linear but less than dose-proportional over a 4 to 400 mg single-dose range and a 36 to 200 mg QD multiple-dose range at steady-state, with little to no accumulation and no time dependency observed after 10 days repeated dosing. Gender did not have a substantial effect on PK of compound of Formula (III). Food delayed the t_{max} and decreased the C_{max} by approximately 70%; and overall exposure was approximately 15 to 20% lower in the fed versus fasted state. The capsule formulation affected the PK profile, showing slower absorption and ~64% lower C_{max} and 31% to 41% lower AUC compared with a similar dose of the oral solution.

[00341] Pharmacodynamics were assessed as %BTKO in PBMCs. Target occupancy was dose-dependent, approaching complete maximal BTKO following single and multiple doses of compound of Formula (III) ≥ 100 mg, typically within 4 hours of administration. The duration of BTKO was long-lasting, remaining detectable 72 hours post dose for cohorts who received ≥ 100 mg compound of Formula (III). Following multiple oral doses of compound of Formula (III), mean BTKO values appeared to reach steady-state by between days 3 and 7. Although little accumulation of plasma concentrations of compound of Formula (III) was observed, lower variability in BTKO was observed following multiple doses compared with single dose administration. This was particularly evident in samples taken within a few hours of dosing, at the time when peak plasma concentrations of compound of Formula (III) would have been achieved. As mean compound of Formula (III) plasma concentrations declined and approached the LLOQ within 24 hours after the last dose on Day 10, mean BTKO in all dose groups remained above 65% and 30% at 24 hours and 72 hours post-dose, respectively. These findings are in line with target occupancy data reported for other covalent BTK inhibitors. Although there are no published target occupancy data in healthy volunteers for ibrutinib, acalabrutinib, and zanubrutinib in healthy volunteers; a median BTKO of $\geq 95\%$ was observed in patients with B-

cell lymphoma or chronic lymphocytic leukemia in peripheral blood. A semi-mechanistic PK/PD model was developed to describe the irreversible BTK inhibition of compound of Formula (III). The PK/PD model with the first 5 SAD cohorts' clinical data was used to predict %BTKO and to aid in the selection of doses for Part 2 (i.e., MAD portion) of this study. The PK/PD model

5 guided the decision of dose-escalation. The model-predicted %BTKO in the MAD cohorts based on data from the SAD cohorts were consistent with observed MAD %BTKO once data became available. Food effects and dosage formulation effects were identified as covariates significantly contributing to the observed compound of Formula (III) PK variability when the PK/PD model was further updated when all the data from the FIH Study was available.

10 **[00342]** Single doses of 4 to 400 mg compound of Formula (III) and multiple-doses of 36 to 200 mg compound of Formula (III) QD x 10 days were safe and well tolerated and had favorable PK/PD properties for continued development. The observed data, PK/BTKO modeling, and data from the oral capsule cohort guided the selection of 140 mg QD as the starting dose regimen for the first-in-patient studies in B-cell non-Hodgkin lymphoma and CLL

15 as a single agent and in combination (NCT04210219 and NCT04657224).

Table 7. Comparison of Simulated and Observed Data

Simulations (n=1000) based on Phase 1 SAD Oral Solution data				Median Observed Day 10 Oral Solution Data		
Dose (mg)	BTKO at 24 hr, ss (%) ^b	Max BTKO at ss (%) ^b	Average BTKO (%) ^{b,c}	BTKO at 24 hr, ss (%)	Max BTKO at ss (%)	Calculated Ave BTKO (%)
12 QD	43.2	51.8	48.0	-	-	-
36 QD	66	79.7	74.1	69.5	78.9	74.2
70 QD	75.6	91.5	84.6	-	-	-
100 QD	78.7	96	88.3	84.1	94.1	89.1
105 QD	79	96.3	88.7	-	-	-
140 QD	80.1	98.3	90.3	-	-	-
200 QD	81.4	99.4	91.49	78.9	98.8	88.8

^apopPK was examined using Cohort 1-5 data, popPD was assessed with Cohort 2-5 data; ^bThe values are median of 1000 simulations; ^cAverage RO at steady state (ss) was calculated as AUMC_{ss}/tau

Example 2 - Discovery and Preclinical Properties of compound of Formula (III), A Potent and Selective Covalent Inhibitor of Bruton's Tyrosine Kinase

5 **[00343]** Introduction – Bruton's tyrosine kinase (BTK), a member of the Tec family of nonreceptor cytoplasmic tyrosine kinases, plays a critical role in B cell activation via the B cell receptor (BCR). Bruton's tyrosine kinase also plays a critical role in macrophage activation via Fcγ receptors, platelet microparticle production in the inflamed joint, and osteoclast activation. The BTK protein is expressed in most hematopoietic cells, with the exception of T cells, plasma
10 cells, and natural killer cells. The upstream Src-family kinases (BLK, LYN, and FYN1,10) and SYK tyrosine kinases activate BTK, which in turn phosphorylates and activates phospholipase-Cγ, leading to calcium mobilization and activation of NF-κB and mitogen-activated protein kinase pathways.

[00344] Given the key role of BTK in oncogenic BCR signaling, BTK inhibitors have
15 been extensively studied in B-cell hematologic malignancies. Multiple lines of evidence suggest that signaling through the BCR is necessary to sustain the viability of B-cell malignancies. For example, expression of a functional BCR is maintained throughout lymphoma progression. Selective knockdown of BCR components by RNA interference results in apoptosis in multiple B-cell lymphoma cell lines. Furthermore, activation of NF-κB via BCR signaling is critical for
20 the survival of several B-cell tumors, including the activated B-cell subtype of diffuse large B-cell lymphoma (ABC-DLBCL). B-cell receptor signaling has also been shown to be the major pathway activated in proliferating chronic lymphocytic leukemia cells and is, therefore, a primary therapeutic target. Finally, BCR signaling may also lead to increased occlusion within the stromal microenvironment in tissues, and blocking this protective interaction can lead to
25 efflux of the tumor cells into the circulation, where they are more easily killed by chemotherapeutic agents.

[00345] Three small-molecule BTK inhibitors—ibrutinib, acalabrutinib, and zanubrutinib (Figure 12) are approved for the treatment of hematologic malignancies. Despite the success of these drugs, the treatment of hematological malignancies remains challenging due
30 to a substantial portion of patients not achieving complete response or experiencing relapse.

Therefore, additional highly selective and safe BTK inhibitors are needed to with the potential to achieve transformational efficacy with synergistic combination therapies.

[00346] The approved BTK inhibiting drugs 1-3 validate covalent targeting BTK as a viable strategy for achieving high kinase selectivity and sustained target occupancy. The BTK Cys481 residue is present in an analogous position for only 10 other human kinases (BMX, TEC, ITK, TXK, EGFR, ERBB2, ERBB4, JAK3, BLK, MKK7), thus providing an opportunity for covalent bond formation with a small fraction of the kinome. Furthermore, an irreversible covalent inhibition mechanism can achieve an extended pharmacodynamic effect with a transient pharmacokinetic exposure when the protein re-synthesis rate is low. The re-synthesis rate of BTK has been estimated at 3.6-31.4% per day in patients with chronic lymphocytic leukemia, and a corresponding extended pharmacodynamic effect with clinical BTK inhibitors has been reported.

[00347] RESULTS AND DISCUSSION – Selectivity –The compound of Formula (III) was evaluated in three selectivity panels to assess the potential for off-target pharmacology (Table 8). In a panel of diverse proteins including receptors, enzymes, and ion channels, The compound of Formula (III) did not bind > 50% at 10 μ M for any of the 54 test targets. The kinase off-target profile of The compound of Formula (III) was assessed in a full human wild-type panel using radiometric kinase activity assays (KinaseProfiler™ and IC₅₀Profiler™, Eurofins Scientific) (Table 9; Figure 23). The compound of Formula (III) inhibited 4/278 kinases >50% at 1 micromolar, identifying BTK and the three other kinases having analogous Cys residues with the potential for covalent inhibition (BMX, TEC, BLK). Subsequence concentration-response experiment confirmed BMX and TEC IC₅₀ < 1 micromolar, however the IC₅₀ does not measure the rate component of a potential covalent interaction with these homologous kinases. The cellular kinase selectivity of The compound of Formula (III) was established in native Ramos B cell kinome assays (KiNativ™, ActivX) confirmed BTK as the primary target with inhibition of BLK and TEC inhibition detected (Table 10).

Table 8. In Vitro Inhibition of Various Receptors at 10 μ M by the compound of Formula (III)

Study 1			
Target	% Inhibition at 10 μ M	Target	% Inhibition at 10 μ M
A1 (h)	–	Y1 (h)	44.4
A2A (h)	–	Y2 (h)	–
A3 (h)	–	NT1 (h) (NTS1)	–

alpha 1	—	delta 2 (h) (DOP)	—
alpha 2	—	kappa (KOP)	—
beta 1 (h)	—	mu (h) (MOP)	—
AT1 (h)	—	ORL1 (h) (NOP)	14.6
BZD (central)	—	5-HT1A (h)	—
B2 (h)	—	5-HT1B	—
CCKA (h) (CCK1)	23.7	5-HT2A (h)	—
D1 (h)	—	5-HT3 (h)	—
D2S (h)	—	5-HT5A (h)	—
ETA (h)	—	5-HT6 (h)	—
GABA	—	5-HT7 (h)	—
GAL2 (h)	—	sst (non-selective)	—
CXCR2 (h) (IL-8B)	—	VIP1 (h) (VPAC1)	—
CCR1 (h)	—	V1a (h)	—
H1 (h)	—	Ca ²⁺ channel	—
H2 (h)	—	K ⁺ V channel	12.2
MC4 (h)	—	SK ⁺ Ca channel	—
MT1 (h)	13.4	Na ⁺ channel (site 2)	—
M1 (h)	—	Cl ⁻ channel	25.1
M2 (h)	—	NE transporter (h)	—
M3 (h)	—	DA transporter (h)	—
NK2 (h)	16	5-HT Transporter (h)	—
NK3 (h)	38.9		

Study 2

Target	% Inhibition at 10 μ M	Target	% Inhibition at 10 μ M
Beta2 (h)	—	GR (h)	—
CB1 (h)	—	AR (h)	—
CB2 (h)	—	Ca channel	—
NMDA	—	PDE3A (h)	—
mGluR5 (h)	—	PDE4D2 (h)	—
MAO-A	14	Ach (h)	11
N neuronal α 4 β 2 (h)	—		

Study 3

Assay	Receptor	Agonist		Antagonist	
		EC ₅₀ ,	Comments	IC ₅₀ , μ M	Comments
ADRB1	Adrenergic beta	ND	ND	>12.5	n = 2
ADRB2	Adrenergic beta	ND	ND	>12.5	n = 2
D2L	Dopamine 2L	ND	ND	>12.5	n = 2
DOP	Opioid delta	ND	ND	>10	n = 2 20%
H1	Histamine H1	>10	n = 2	>10	n = 2

—, no inhibition observed; ND, not determined.

Table 9. Summary of Kinase Selectivity Profiling

Assay [test concentration]	Result
Eurofins KinaseProfiler™ [1 µM] ^a	98% inhibition of BTK; 92% inhibition of BMX; 88% inhibition of TEC; 54% inhibition of BLK;
Eurofins IC ₅₀ Profiler™ [10-point concentration response] ^b	BTK IC ₅₀ = 0.558 µM; BMX IC ₅₀ = 0.172 µM; TEC IC ₅₀ = 0.303 µM; BLK IC ₅₀ = 3.128 µM;

^bDirect filter-binding radiometric kinase activity assay. No other kinases with IC₅₀ < 10 µM

^aDirect filter-binding radiometric kinase activity assay (278 human wild type kinases). No other kinases with > 50% inhibition at 1 µM of the compound of formula (III).

Table 10: Summary of ActivX KiNativ™ Kinase Selectivity Profiling^a

Kinase ^b	% Inhibition
BTK (activation loop labeling)	94.4
BTK (Lys labelling)	90.3
TEC	77.6
BLK (activation loop labelling)	61.9

^aNative cellular kinases: Ramos cell lysates; test concentration, 1 µM.

- 5 **[00348]** In vitro Absorption, Distribution, Metabolism, and Excretion - The compound of Formula (III) was assessed at a concentration of 5 µM in cell permeability models. In the Caco-2 model, the compound of Formula (III) demonstrated moderate-to-high permeability with evidence for efflux (Table 11). In the MDCK cell line over-expressing MDR1 (Pgp), the efflux ratio was > 115, and the A to B permeability increased in the presence of the Pgp inhibitor
- 10 elacridar, indicating that the compound of Formula (III) is a high permeability Pgp substrate. The compound of Formula (III) is highly plasma protein bound with a percent free of 3.1% in human, which was commensurate to free concentrations observed in pre-clinical species. In blood to plasma partitioning studies, the compound of Formula (III) primarily distributes into the blood in rat and resides primarily in plasma for dog and human.
- 15 **[00349]** In human hepatocytes, the compound of Formula (III) is metabolized by CYP3A through mono-oxidations and *N*-dealkylations and by GSH conjugation to its acrylamide

functionality. It bears moderate metabolic stability in hepatocytes across species and is slowly metabolized in human intestinal microsomes fortified with NADPH.

Table 11. Permeability and Efflux Potential of the Compound of Formula (III) in Caco-2 and MDCK MDR1 Cell Lines

Cell Line	P _{app} , 10 ⁻⁶ cm/s		Efflux Ratio (BA/AB)
	A to B	B to A	
Caco-2			
Compound of formula (III)	6.69	54.9	8.2
Propranolol	31.6	30.1	0.95
Atenolol	0.317	0.477	1.5
Talinolol	0.232	8.71	37.5
MDCK-MDR1 (NIH)			
Compound of formula (III) alone	< 0.483	55.4	> 115
compound of formula (III) with elacridar	16.7		
Propranolol ^a	28.6	38.3	1.3
Prazosin alone ^a	1.8	70.1	38.2
Prazosin with elacridar ^a	17.5		

P_{app}, apparent permeability coefficient.

^aValues reported as mean of n = 2.

5

Table 12. ADME Properties of the compound of formula (III)

Assay	Result
Caco-2 permeability, P _{app} , 10 ⁻⁶ cm/sec	6.69 (AB), 54.9 (BA)
Plasma protein binding, % free ^a	2.4 (Ms), 3.7 (R), 6.3 (D), 3.2 (Mk), 3.1 (H)
Blood:plasma ratio	1.37 (R), 0.75 (D), 0.69 (Mk), 0.67 (H)
Hepatocyte metabolic stability, extraction ratio	0.52 (R), 0.67 (D), 0.78 (Mk), 0.51 (H)
Intestinal microsomal stability, CL _{int} μL/min/mg	<3.9 (R), <3.9 (D), 14.1 (H)

ADME, absorption, distribution, metabolism, and excretion; Ms, CD-1 mouse; R, Sprague Dawley rat; D, beagle dog; Mk, cynomolgus monkey; H, Human.

^a2.5 μ M concentration.

^bIntravenous administration.

[00350] The potential of the compound of Formula (III) to inhibit human CYP450s in vitro was investigated up to test concentrations of 50 μ M by incubating the compound of Formula (III) with specific CYP probe substrates in human liver microsomes and measuring probe metabolite formation. The compound of Formula (III) did not show significant inhibition of CYP1A2, 2A6, 2B6, 2C19, or 2E1; moderate inhibition was observed for CYP2C8 (IC₅₀: 16 μ M), 2D6 (26 μ M), and 3A4 (25– μ M for midazolam), and more potent inhibition was observed for CYP2C9 (3.0 μ M for diclofenac and 5.3 μ M for tolbutamide) (Table 13).

Table 13. Inhibition by the compound of formula (III) of Major CYP Isoforms in Human Liver Microsomes

Isoform	CYP Probe Substrate	Compound of
		Formula (III) IC ₅₀ , μ M
1A2	Phenacetin	> 50
2A6	Coumarin	> 50
2B6	Bupropion	> 50
2C8	Amodiaquine	16
2C9	Tolbutamide	5.3
2C9	Diclofenac	3.0
2C19	S-Mephenytoin	> 50
2D6	Dextromethorphan	26
2E1	Chlorzoxazone	> 50
3A4	Testosterone	40
3A4	Midazolam	25
3A4	Nifedipine	> 50

IC₅₀, half maximal inhibitory concentration.

[00351] Preclinical PK Profile - Pharmacokinetics of the compound of Formula (III) in pre-clinical species was characterized by a low (monkey) to moderate (rat and dog) clearance and a moderate volume of distribution (all species) affording a short drug half-life ranging from 0.4 h (rat) to 4.0 h (monkey) (Table 14). It was rapidly absorbed across pre-clinical species with a t_{max} achieved within the first two hours after oral administration from a 20% hydroxy propyl beta cyclodextrin solution and had moderate to high oral bioavailability ranging from 28 – 75%. Notably, commensurate drug exposure of the compound of Formula (III) was achieved from a crystalline suspension relative to solution, whereas the initial lead compound did not achieve significant oral bioavailability when dosed as a crystalline suspension.

Table 14. Rat, Dog, and Monkey PK Data Following Oral and IV Administration of the compound of Formula (III)

Species	CL, mL/min/kg	V _{ss} , L/kg	IV T _{1/2} , h	F, %	Oral C _{max} , ng/mL	Oral AUC _{inf} , ng/mL•h	T _{max} , h
Rat	55 ± 2	1.9 ± 0.2	0.4 ± 0.0	28 ± 6 ^a ; 41 ± 19 ^b	189 ± 81 ^a ; 133 ± 53 ^b	425 ± 96 ^a ; 626 ± 290 ^b	0.5 ± 0.0 ^a ; 1.7 ± 0.6 ^b
Dog	11 ± 3	0.8 ± 0.2	1.1 ± 0.1	51 ± 10	890 ± 286	1964 ± 421	0.8 ± 0.3
Monkey	3.1 ± 0.3	0.7 ± 0.0	4.0 ± 0.2	75 ± 17	1006 ± 94	10044 ± 2273	1.7 ± 0.6

^a5 mg/kg solution PO; formulated from amorphous material in 20% hydroxy propyl beta cyclodextrin solution.

^b5 mg/kg suspension PO; formulated from crystalline material as suspension in 0.5% HPMC suspension.

Data presented as mean ± SD (n = 3 animals).

[00352] In vitro cellular target engagement - The dose-response of BTK occupancy was assessed using a Ramos B cell occupancy assay. Irreversible reaction with Cys491 excludes it from further reaction and enables selective detection of the free (unreacted) BTK with a chemical probe, which utilizes the same binding site and reaction mechanism as the compound of formula (III). The probe carries a biotin sidechain to tag free BTK with an affinity handle to enable detection by ELISA. The mean ± SD IC₅₀ was 0.021 ± 0.007 μM (n = 11) (Figure 13). The kinetics of BTK occupancy in Human B cells were assessed using 5 concentrations of the compound of formula (III) (3, 10, 30, 100, and 300 nM). Occupancy increased in magnitude and speed with increasing concentration, reaching full occupancy within 40 minutes for the 2 highest concentrations (100 and 300 nM) (Figure 14).

[00353] In Vivo BTK Engagement - BTK receptor occupancy and plasma concentrations of the Compound of Formula (III) increased in a dose-dependent manner

following a single oral dose in rat (Figure 15). Doses of 2 mg/kg or higher consistently achieved sustained target occupancy after 8 and 24 hours ($> 75\%$ following a 2 mg/kg dose, $\geq 88\%$ following a 3 mg/kg dose, and $\geq 99\%$ following a 10 mg/kg dose). Target occupancy was maintained at 24 h even after parent drug plasma levels decreased, indicating persistent BTK occupancy, a hallmark of the covalent mechanism. Considering that 70% to 80% BTK target engagement for 7 to 8 hours in a chronic dosing regimen is associated with anti-inflammatory activity in rodent efficacy models, 75% target engagement at 7.5 hours was identified as the desired level of target engagement.

[00354] In vivo activity in collagen-induced arthritis - A rat CIA model in female Wistar rats was used to define the impact of the compound of Formula (III) on chronic inflammation and derive PK-PD correlations (Figure 16). YiSaipu™ (recombinant human tumor necrosis factor- α receptor (type II): IgG1 Fc (rhTNFR:Fc) fusion protein; biogeneric version of Etanercept™) was used as a comparator. The compound of Formula (III) attenuated hind paw inflammation in a dose-dependent manner. A dose of 2 mg/kg/day or higher of the compound of Formula (III) achieved an effect on inflammation equivalent to the anti-TNF α comparator treatment, corresponding to C_{max} of 46.6 ng/mL and AUC_{last} of 324 ng/mL*h. The doses required to achieve meaningful efficacy correlated with a BTK target occupancy threshold of $>75\%$ over 24 hours based on the preceding target engagement studies.

[00355] In Vitro Activity in DLBCL Cell Lines - NF κ B signaling regulates the secretion of multiple cytokines, including interleukin (IL)-6 and IL-10. Secretion of IL-6 and -10 by ABC-DLBCL OCI-LY-10 cells was measured using a MesoScale assay. The mean $\pm$ SEM IC_{50} values of the compound of Formula (III) across 6 independent experiments was determined to be 16 ± 3 nM for IL-6 and 18 ± 7 nM for IL-10. To determine the anti-proliferative activity of the compound of formula (III), several ABC-DLBCL cell lines—OCI-LY-3, OCI-LY-10, TMD8, and HBL-1—were treated for 8 days. In CD79b-mutant ABC-DLBCL cell lines (OCI-LY10, TMD8, HBL-1), the compound of Formula (III) showed antiproliferative activity with IC_{50} values below 100 nM (Figure 17; Table 15). The OCI-LY-3 cell line, which harbors a CARD11 mutation downstream of BTK in the NF- κ B signaling pathway, was completely insensitive to the compound of Formula (III) up to 2 μ M. In 2 experiments, OCI-LY-3 cells were insensitive to the compound of Formula (III) at all concentrations up to 10 μ M. These results support a first in-human trial of the compound of Formula (III) in patients with lymphomas driven by the classical NF- κ B pathway.

Table 15: Antiproliferative Activity of the compound of Formula (III) in ABC-DLBCL Cell Lines (8 Days)

Cell Line	IC ₅₀ , μ M (n = 4)
OCI-LY10 (CD79b/Myd88/A20 mutant)	0.018
TMD8 (CD79b/Myd88/A20 mutant)	0.034
HBL1 (CD79b/Myd88/A20 mutant)	0.080
OCI-LY3 (Myd88/CARD11/A20 mutant)	>2000

IC₅₀, half maximal inhibitory concentration.

- [00356]** In Vivo Efficacy in ABC-DLBCL Xenograft and PDX Mouse Models of Lymphoma- To evaluate the effect of the compound of Formula (III) on NF κ B signaling in vivo, we analyzed circulating human IL-10 levels in serum of NSG mice implanted with OCI-LY10 DLBCL tumors treated with 0, 1, 3, 10, 30 and 100 mg/kg compound of Formula (III) at 2, 4, 8, 12, 16 and 24 hours after single dose administration. Human IL-10 levels dropped to around 50% of vehicle control 2 hours after dosing, lowering even further after 4 hours to below 20%, 10% and 5% of vehicle control IL-10 levels in 10 mg/kg, 30mg/kg and 100mg/kg compound of Formula (III) treatment groups, respectively, and remaining low up to 12 hours. Some rebound to 23% of vehicle control levels for 30 mg/kg and 100 mg/kg and to 39% for the 10mg/kg dosing group are observed 16 hours after compound administration, while IL-10 levels normalize after 24 hours (Figure 18).
- [00357]** To evaluate the duration of signaling shutdown and occupancy of BTK protein after compound administration, we determined the amount of free BTK protein in OCI-LY10 DLBCL tumor lysates harvested using an BTK occupancy assay. No BTK occupancy was observed in OCI-LY10 DLBCL tumor lysates of animals dosed with 1 and 3 mg/kg the compound of Formula (III). However, 54%, 90% and 95% BTK protein occupancy was observed 4 hours after the compound of Formula (III) dosing at dose levels of 10, 30 and 100 mg/kg, respectively. BTK protein occupancy levels remained high with 71%, 94% and 96%, respectively, at 12 hours and 70%, 91% and 85%, respectively after 24 hours. (Figure 19). The antitumor efficacy of compound of Formula (III) was assessed in mice bearing established SC OCI-LY10 human CD79b mutant DLBCL xenografts in female NSG mice, dosed either once (QD) or twice (BID) a day. Analysis of tumor growth inhibition was performed 14 days into the

21-day treatment period (Day 45) as that was the last day when 2/3 of the vehicle controls remained on the study. Compound of Formula (III) induced tumor growth inhibition in the OCI-LY10 model at all dose levels. Treatment with 10, 30 and 100 mg/kg the compound of Formula (III) administered QD inhibited tumor growth by 24%, 35% and 51% TGI (30, 45, and 65% Δ TGI) respectively, as compared with vehicle treated control mice ($p < 0.05$). BID treatments with 5, 15 and 50 mg/kg the compound of Formula (III) elicited slightly more pronounced tumor growth inhibition with 26%, 51% and 78% TGI (34, 66, and 102% Δ TGI) ($p < 0.05$) (Figure 20). In the LY2298 xenograft model (CD79b/MyD88 mut), monotherapy of the compound of Formula (III) treatment moderately inhibits *in vivo* growth of LY2298 DLBCL PDX model while Venetoclax did not show efficacy in this model (Figure 21). The combination therapy of the compound of Formula (III) and Venetoclax showed *in vivo* synergistic efficacy with tumor growth inhibition of 76.6% ($P < 0.001$). Taken together, the *in vivo* data support a first in-human trial of the compound of Formula (III) in combination with Venetoclax in patients with B cell lymphomas.

[00358] The compound of Formula (III) Inhibits B-cell receptor activation - Rat whole blood assays were used to assess the ability of the compound of Formula (III) to inhibit activation of primary B cells in whole blood. The assay used anti-IgD stimulation to trigger B-cell activation. Cell activation in freshly isolated blood was quantified by staining for cell surface expression of B220 to identify B cells and a cell activation marker CD86. The compound of Formula (III) inhibited B-cell activation in rat whole blood with an IC_{50} of $0.0410 \pm 0.0117 \mu M$ ($n=2$) and a 95% CI of 0.0248 to 0.0572 μM (Figure 22).

[00359] CONCLUSIONS - In summary, we have identified a highly selective and potent irreversible BTK inhibitor, the compound of Formula (III). Preclinical characterization predicts a low dose should achieve BTK inactivation based upon potency and pharmacokinetic properties. The molecule demonstrated highly favorable preclinical tolerability and ADME profile. The compound of Formula (III) demonstrated potent effects in cellular assays and efficacy in *in vivo* models of autoimmunity and lymphoma. In addition, *in vivo* efficacy data indicates combination therapy of the compound of Formula (III) together with Venetoclax results in synergistic efficacy. Together, these data suggest that the compound of Formula (III) has potential utility in both autoimmune indications and B cell lymphomas, potentially using combination approaches.

[00360] EXPERIMENTAL SECTION - Experimental Details -All solvents and chemicals were used as purchased without further purification. Nuclear magnetic resonance

spectra were obtained on Bruker model DRX spectrometers. Chemical shifts (δ) are expressed in parts per million, relative to internal tetramethylsilane; coupling constants (J) are in Hz. The following abbreviations are used to describe peak patterns when appropriate: s (singlet), d (doublet), t (triplet), q (quartet), qt (quintet), m (multiplet), app (apparent), and br (broad).

5 HPLC–MS chromatograms and spectra were obtained using one of the following methods: (1) Agilent 1200 HPLC and G6100 system on X-Bridge ShieldRP18 (50×2.1 mm, $5 \mu\text{m}$) and a gradient system of 0.05% NH_4OH in $\text{H}_2\text{O}/\text{CH}_3\text{CN}$, 100:0 to 5:95 over 7.5 min, then 100:0 for 2.5 min at a temperature of 40°C ; (2) Agilent 1200 HPLC and G6100 system on Phenomenex Luna-C18 (50×2 mm, $5 \mu\text{m}$) and a gradient system of 0.1% TFA in $\text{H}_2\text{O}/0.05\%$ TFA in CH_3CN ,
10 100:0 to 15:85 over 7.5 min, then 100:0 for 2.5 min at a temperature of 50°C ; or (3) Agilent 1100 HPLC and G1367A system on X-Bridge C18 (100×3 mm, $3.5 \mu\text{m}$) and a gradient system of 20 mM NH_4OH in $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ 90:10 over 2 min, then 0:100 for 1 min at a flow rate of 2.4 mL/min at a temperature of 45°C . All compounds tested were of a minimum of 95% purity as determined by HPLC.

15 **[00361]** Rat Whole Blood Assay-Anti-rat IgD was purchased from Bio-Rad AbD Serotec, Ltd. (Oxford, United Kingdom). Rat B220-PE and rat CD86-FITC were purchased from eBioscience (San Diego, CA). Lysing buffer was purchased from BD Biosciences (San Diego, CA). To determine the potency of each compound, inhibition of anti-IgD-induced activation of B cells in rat whole blood was assessed by flow cytometry. Heparinized blood was collected from
20 Wistar rats, supplemented with penicillin (100 U/mL) and streptomycin (100 $\mu\text{g}/\text{mL}$), and incubated for 1 hour with a titration of compound in DMSO (0.3% final concentration). The blood was then stimulated and incubated overnight at 37°C with anti-IgD (10 $\mu\text{g}/\text{mL}$). The samples were then stained with fluorescent antibodies against CD86 and B220 for 30 minutes, red blood cells removed with lysing buffer, washed, fixed, and acquired on FACSCalibur. Each
25 sample was gated on forward and side scatter for lymphocytes and on B220+ for B cells. The percentage of activated B cells was defined as the proportion of B220+CD86+ cells over total B220+ cells.

[00362] Inhibition percentage was determined by the following equation: $\text{Inhibition}\% = (\text{ActB}_{\text{stim}} - \text{ActB}_{\text{compound}}) \times 100 / (\text{ActB}_{\text{stim}} - \text{ActB}_{\text{unstim}})$, where $\text{ActB}_{\text{high}}$, $\text{ActB}_{\text{unstim}}$, and
30 $\text{ActB}_{\text{compound}}$ refer to the percentage of activated B cells of the stimulated (no compound), unstimulated (no antibody), and compound treated wells, respectively. The IC_{50} for each compound was then calculated from the inhibition % of the titrations using a 4-PL fit.

BTK Occupancy - Animal Studies - Rat studies were conducted using female Wistar rats (110-140 g for target engagement and PKPD studies, 144-175 g (6-8 weeks of age) for efficacy studies). These rats were supplied by Shanghai SLAC Laboratory Animal Co. Ltd (Shanghai, China) and acclimated at least 4 days following arrival at the animal facility. Rats were multiple housed (3-4 rats/cage). The holding and study rooms were maintained on a 12-hour light/dark cycle (light/dark cycle may be interrupted for study-related activities), within a temperature range of $24 \pm 1^\circ\text{C}$ and a relative humidity of 30-70%. Rats had free access to food (irradiated, Shanghai SLAC Laboratory Animal Co. Ltd., China) and water (filtered by Molanimal ultrapure water machine from the municipal water supply).

10 **[00363]** Test article preparation - The compound of Formula (III) was formulated in 20% HP β CD, pH adjusted to 2.1 using 6 M HCl. YiSaiPu was prepared by dissolving the lyophilized powder into normal saline to a working concentration of 1.5 mg/mL.

15 **[00364]** BTK Occupancy PK/PD Model - Rat in vivo target engagement - Two studies were conducted in which the compound of Formula (III) formulated in 20% HPCD, was administered orally to female Wistar rats. In study 1, compound of Formula (III) was evaluated at oral doses of 0.3, 1, 3 and 10 mg/kg; in study 2, compound of Formula (III) was evaluated at oral doses of 0.1, 0.3, 1, 2 and 3 mg/kg. (n = 4/group for both studies). In both experiments, at assigned time points postdose (0.5, 4, 8 and 24 hr), animals were anesthetized and approximately 140 μL of blood was obtained by retro-orbital bleeding into heparinized tubes. These samples
20 were split into two aliquots, with one aliquot used to measure compound levels by liquid chromatography mass spectrophotometry method and the other aliquot to assess BTK occupancy by a target-site occupancy ELISA.

25 **[00365]** Cell lysates were prepared from the blood samples using cell lysis buffer (BD Pharmingen™, BD Biosciences). Free BTK protein in each sample is tagged by the addition a biotinylated probe (1 μL of a 25 μM working solution per sample, final concentration 250 nM), which is then captured on the surface of a streptavidin coated microtiter plate and detected by ELISA using an antibody specific for BTK (BD Transduction). Samples from rats that were dosed with vehicle alone were used to define the level of total free BTK in the cell lysates and samples from compound of Formula (III) dosed animals were used to define the fraction of total
30 BTK occupied via covalent modification.

[00366] Rat collagen-induced arthritis - An emulsion was prepared on ice from equal volumes of type II collagen (CII; Chondrex) (2 mg/mL in 100 mM acetic acid (Sinopharm

Chemical Reagent Co. Ltd)) and Incomplete Freund's Adjuvant (IFA) (Sigma-Aldrich) by high speed homogenization (28,000 rpm) for 3 min (FLUKO Equipment Shanghai Co. Ltd).

Eighty-two rats were used in the study. Before immunization, 6 rats were randomly selected as a naive group. The other 76 rats were anesthetized with inhalational isoflurane, and injected

5 intradermally at the base of the tail with 0.2 mL of the emulsion (1 mg/mL CII/IFA), 2 to 3 cm from the body on day 0 and day 7. On day 10, the 56 rats with the most developed arthritis based on paw volume measurements out of the 76 rats that were immunized were divided into 7 groups (n = 8) with a stratified random block design according to average hind paw volume of each rat. Each group with similar starting paw inflammation was administered with vehicle or different
10 doses of the compound of Formula (III) (0.3, 1, 2, 3, 10 mg/kg, PO, QD, days 10-17) or YiSaiPu (biosimilar etnarncept) (15 mg/kg, IP, QOD, days 10-16).

[00367] Hind paws volume and body weight were monitored daily for 7 consecutive days (days 10-16) after initiation of test article dosing. Left and right paw volumes in each rat were measured by a Plethysmometer (Catalog No. 7140, Ugo Basile. Italy). Blood (about 300
15 μ L) in the groups treated with the compound of Formula (III) was collected into heparinized tubes via retro-orbital bleeding under isoflurane anesthesia on day 17-18. For groups treated with the compound of Formula (III), the composite collection time points were 0, 0.5, 1, 2, 4, 8, 12 and 24 hrs after last administration of the compound of Formula (III). After collection, blood samples were centrifuged (5,000 rpm for 10 min), plasma collected, and the concentrations of the
20 compound of Formula (III) were determined using liquid chromatography mass spectrophotometry.

[00368] Additional Data on Preclinical PK Profile - Protein binding of the compound of Formula (III) was studied using an equilibrium dialysis method in plasma from human, cynomolgus monkey, beagle dog, Sprague Dawley rat, CD-1 mouse, and guinea pig at 0.25, 2.5,
25 and 25 μ M. Within the quantification limits of the assay, the compound of Formula (III) demonstrated high plasma protein binding across species with the unbound fraction ranging from 1.69% to 6.88% (Table 16). In human and monkey, the plasma protein binding was concentration dependent. Plasma protein binding was also determined by an equilibrium dialysis method in female Wistar rats used for both the PD and efficacy in vivo model; at a concentration
30 of 1 μ M, the free fraction in plasma was 7.54%. In addition, protein binding was examined in RPMI culture media containing 10% FBS used for BTK occupancy studies in Ramos human B cells in order to provide inputs for PK/PD modeling; the compound of Formula (III) was determined to be 31.7% free at an incubated concentration of 1 μ M. Liver microsomal binding of

the compound of Formula (III) (1 μ M) was determined at a microsomal protein concentration of 0.25 and 1.0 mg/mL to provide inputs for human PK predictions. Free fraction of the compound of Formula (III) in liver microsomes from various species ranged from 75.1% to 87.9% at 0.25 mg/mL and from 58.9% to 86.5% at 1.0 mg/mL (Table 17). The blood-to-plasma concentration ratio of the compound of Formula (III) determined in fresh blood at a concentration of 1 μ M was 0.67 in human, 0.69 in monkey, 0.75 in dog, 0.84 in mouse, and 1.37 in rat, suggesting a slightly preferential distribution into plasma (except for rat). In vitro metabolic stability of the compound of Formula (III) was investigated in liver microsomes (1.0 mg/mL; in presence of 1 mM NADPH) and hepatocytes (0.5×10^6 cells/mL) from multiple species. In liver microsomes, the compound of formula (III) demonstrated moderate-to-high turnover with $T_{1/2}$ ranging from 4.9 minutes in mouse to 22.3 minutes in human (Table 18). In hepatocytes, the compound of Formula (III) turnover followed a similar trend, with $T_{1/2}$ ranging from 75.3 minutes in monkey to 278.1 minutes in human.

[00369] To assess the potential of the compound of Formula (III) to be a time-dependent inhibitor of CYP3A, human liver microsomes were preincubated for 30 minutes at 37°C with the compound of Formula (III) at concentrations up to 10 μ M, and CYP3A activity was measured using testosterone as a probe substrate. The results showed that the compound of Formula (III) did not inhibit CYP3A4 in a time-dependent manner at up to concentrations of 10 μ M, with IC_{50} values of 9.81 μ M and $> 10 \mu$ M with and without preincubation, respectively. The potential of the compound of Formula (III) to induce CYPs at the transcriptional level was assessed using Puracyp™ DPX2 (CYP3A4, PXR) and DRE (CYP1A2, AhR) luciferase-reporter cell lines; rifampicin and omeprazole were used as positive controls for CYP3A and CYP1A induction, respectively. The activation by the compound of Formula (III) was $< 20\%$ of positive control values for PXR (6.6% and 14.1% at 1 and 10 μ M change, respectively) or AhR (0.1% and 0.3% change, respectively). Similarly, studies using plated human hepatocytes coincubated for 48 hours with the compound of Formula (III) at 1 and 10 μ M followed by probe reactions with midazolam and phenacetin showed no increase in CYP3A (-0.8% and 0.8% change at 1 and 10 μ M, respectively) or CYP1A (0.2% and 1.0% change, respectively) enzyme activities. Potential involvement of various CYP isoforms in the metabolism of the compound of Formula (III) was investigated by measuring the parent compound remaining after 1-hour incubation with the compound of Formula (III) (1 μ M) with recombinant CYPs (rCYPs) at 100 pmol P450/mL in the presence of 1 mM NADPH at 37°C. The only isozyme that produced notable the compound of Formula (III) turnover with $< 1\%$ parent remaining after 1-hour incubation was CYP3A4

(Figure 24). To confirm CYP3A4 as a major contributor to the compound of Formula (III) metabolism, chemical inhibition studies were conducted; the compound of Formula (III) at 1 μ M was incubated with pooled human liver microsomes (0.5 mg/mL) in the absence or presence of ketoconazole (CYP3A4 inhibitor, 1 μ M). The turnover of the compound of Formula (III) was
 5 completely (> 97%) inhibited by ketoconazole, suggesting that CYP3A4 is a main contributor to its CYP-mediated metabolism (Figure 25).

[00370] The extent of the compound of Formula (III) covalent binding to hepatic proteins was determined in human hepatocytes at 1 and 10 μ M (Table 19). A 14 C label was introduced at the acrylamide carbonyl carbon of the compound of Formula (III). The 1 μ M
 10 incubations were carried out with 0.5×10^6 cells/mL for 4.5 h to correspond with the compound of Formula (III) half-life in test system; The 10 μ M incubations were conducted with 0.75×10^6 cells/mL for 3 h. Troglitazone and pioglitazone served as positive and negative controls, respectively.

15 **Table 16. Protein Binding of The Compound of Formula (III) in Plasma From Various Species**

Species		
Concentration, μ M	% Free	% Recovery
Human		
0.25	1.69	104.8
2.5	3.12	99.1
25	4.63	88.9
Monkey		
0.25	< 0.4 ^a	102.9
2.5	3.21	95.6
25	5.32	87.6
Dog		
0.25	6.88	91.8
2.5	6.33	87.5
25	6.85	91.9
Rat		

0.25	3.73	90.0
2.5	3.65	94.0
25	4.05	92.6
Mouse		
0.25	1.92	101.8
2.5	2.35	97.9
25	3.35	99.1
Guinea Pig		
0.25	3.26	88.9
2.5	3.23	86.1
25	3.72	81.6

^aValue was below 1 nM, the lower limit of quantification in assay. At 1 nM, the calculated % free is 0.4%.

Table 17. Liver Microsomal Binding of the Compound of Formula (III) at 1 μ M in Various Species

Species	% Free	
	0.25 mg/mL	1.0 mg/mL
Human	75.8	64.1
Monkey	75.1	58.9
Dog	87.9	69.4
Rat	84.0	86.5
Mouse	ND	82.0

ND, not determined.

5 Table 18. Metabolic Stability of the compound of formula (III) in Liver Microsomes and Hepatocytes of Various Species

Species	Liver Microsomes			Hepatocytes		
	$T_{1/2}$, min	CL_{int} , μ L/min/mg	Extraction Ratio	$T_{1/2}$, min	CL_{int} , μ L/min/ 10^6 cells	Extraction Ratio
Human	22.3	31.1	0.63	278.1	15.4	0.52

Monkey	11.4	61.0	0.65	75.3	66.3	0.78
Dog	17.1	40.6	0.65	277.4	19.2	0.46
Rat	12.9	53.8	0.58	127.1	52.3	0.53
Mouse	4.9	142.3	0.79	NT	NT	NT

CL_{int}, intrinsic clearance; NT, not tested; T_{1/2}, half-life.

Table 19. [¹⁴C]- Compound of Formula (III) Human Hepatocyte Covalent Binding

Test Compound	Net Covalent Binding, pmol eq/mg protein	Compound Turnover, %	Fraction Covalently Bound (f _{cvb})
1 μM study			
Compound of Formula (III)	46.8 ± 5.1	49.1	0.07 ± 0.01
Pioglitazone	20.1 ± 1.8	57.2	0.0285 ± 0.0026
Troglitazone	83.7 ± 6.7	59.4	0.1071 ± 0.0086
10 μM study			
Compound of Formula (III)	50.0 ± 0.8	70.1	0.00564 ± 0.0001
Pioglitazone	29.5 ± 2.1	52.9	0.00429 ± 0.00031
Troglitazone	98.6 ± 6.4	55.2	0.01393 ± 0.00090

Example 3 – Predicted C_{max} and BTK occupancy values for the compound of Formula

5 **(III).**

Table 20 shows C_{max} and AUC, values are for both 140 mg and 560 mg, at Day 1 and steady state after 5-10 days of continuous dosing. Table 21 shows BTO % occupancy values are shown at Day 1 and steady state after 5-10 days of continuous dosing

10 **Table 20. C_{max} and AUC values for the compound of Formula (III)**

	C _{max,day1} ^a (ng/mL)	C _{max,ss} ^a (ng/mL)	AUC _{day1} ^a (ng· hr/mL)	AUC _{ss} ^a (ng· hr/mL)
140 mg QD Capsule Fasting	429.75 (186.87, 950.72) [59.992, 2377.2]	435.1 (190.24, 966.35) [66.855, 2395.4]	2157.5 (1002, 4641.3) [312.1, 11517]	2249.7 (1030.7, 4919.4) [312.27, 13015]
560 mg QD Capsule Fasting	1719 (747.47, 3802.9) [239.97, 9509]	1740.4 (760.97, 3865.4) [267.42, 9581.5]	8629.9 (4007.9, 18565) [1248.4, 46068]	8998.9 (4122.7, 19678) [1249.1, 52061]

Simulations were conducted using the final population PK model (n=5,000) developed from one Phase 1 study in healthy subjects

^aData shown as median (5th – 95th) [min, max]

Key: $C_{\max, \text{day 1}}$ = max concentration at day 1; $C_{\max, \text{ss}}$ = max concentration at steady state;

$AUC_{\text{day 1}}$ = Area under the curve at day 1; AUC_{ss} = Area under the curve at steady state

Table 21. BTKO % occupancy for the compound of Formula (III)

	$BTKO_{\max, \text{day 1}}$ ^a (%)	$BTKO_{\max, \text{ss}}$ ^a (%)	$BTKO_{\text{trough}, \text{day 1}}$ ^a (%)	$BTKO_{\text{trough}, \text{ss}}$ ^a (%)
140 mg QD Capsule Fasting	90.4 (58.8, 99.2) [30.9, 99.8]	95.9 (83.5, 99.5) [59.4, 99.9]	77.4 (50.9, 86.2) [23.3, 91.3]	80.7 (70.9, 87.8) [50.2, 95.4]
560 mg QD Capsule Fasting	99.8 (98.0, 99.9) [87.1, 100]	99.8 (98.8, 99.9) [90.2, 100]	85.4 (81.4, 92.8) [63.9, 97.3]	86.0 (81.8, 94.4) [75.5, 99.3]

Simulations were conducted using the final population PK model (n=1,000) developed from one Phase 1 study in healthy subjects

^aData shown as median (5th – 95th) [min, max]

Key: $BTKO_{\max, \text{day 1}}$ = max BTKO at day 1; $BTKO_{\max, \text{ss}}$ = max BTKO at steady state;

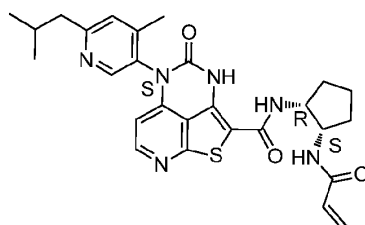
$BTKO_{\text{trough}, \text{day 1}}$ = trough BTKO at day 1; $BTKO_{\text{trough}, \text{ss}}$ = trough BTKO at steady state

5

ASPECTS

The disclosure is also directed to the following aspects:

Aspect 1. A compound of formula (III):



(III)

- Aspect 2. The compound of formula (III) of the preceding aspect that is a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof.
- Aspect 3. A pharmaceutical composition comprising a compound of formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof, and a pharmaceutically acceptable excipient.
- Aspect 4. A method of inhibiting Bruton's tyrosine kinase comprising contacting the kinase with a compound of formula (III).
- Aspect 5. A method of treating a malignancy in a patient comprising administering to the patient a therapeutically effective amount of a compound of formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof.
- Aspect 6. The method of aspect 5, wherein the malignancy is selected from the group consisting of a lymphoma, a leukemia, a carcinoma, and a sarcoma.
- Aspect 7. The method of aspect 6, wherein the lymphoma is selected from the group consisting of non-Hodgkin's lymphoma (NHL (including B-cell NHL)), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), mucosa-associated lymphoid tissue (MALT) lymphoma, marginal zone lymphoma (MZL), T-cell lymphoma, Hodgkin's lymphoma, small lymphocytic lymphoma (SLL), Waldenström macroglobulinemia, and Burkitt's lymphoma.
- Aspect 8. The method of aspect 6, wherein the leukemia is selected from the group consisting of chronic lymphocytic leukemia (CLL), lymphoblastic T cell leukemia, chronic myelogenous leukemia (CML), hairy-cell leukemia, acute lymphoblastic T cell leukemia, plasmacytoma, immunoblastic large cell leukemia, megakaryoblastic leukemia, acute megakaryocyte leukemia, promyelocytic leukemia, erythroleukemia and multiple myeloma.
- Aspect 9. The method of aspect 6, wherein the malignancy is selected from the group consisting of brain (gliomas), glioblastomas, breast cancer, colorectal/colon cancer, prostate cancer, lung cancer, non-small-cell lung cancer, gastric cancer, endometrial cancer, melanoma, pancreatic cancer, liver cancer, kidney cancer, squamous cell carcinoma, ovarian cancer, sarcoma, osteosarcoma, thyroid cancer, bladder cancer, head & neck cancer, testicular cancer, Ewing's sarcoma, rhabdomyosarcoma, medulloblastoma, neuroblastoma,

cervical cancer, renal cancer, urothelial cancer, vulval cancer, esophageal cancer, salivary gland cancer, nasopharyngeal cancer, buccal cancer, cancer of the mouth, Chronic graft versus host disease, and gastrointestinal stromal tumor.

Aspect 10. A method of treating a diffuse large B-cell lymphoma (DLBCL) in a patient
5 comprising administering to the patient a therapeutically effective amount of a compound of formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof.

Aspect 11. The method of aspect 10, wherein the method comprises further administering a Bcl2 inhibitor.

Aspect 12. A method of treating mantle cell lymphoma (MCL) in a patient comprising
10 administering to the patient a therapeutically effective amount of a compound of formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof.

Aspect 13. A method of treating follicular lymphoma (FL) in a patient comprising administering to the patient a therapeutically effective amount of a compound of formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof.

Aspect 14. A method of treating marginal zone lymphoma (MZL) in a patient comprising
15 administering to the patient a therapeutically effective amount of a compound of formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof.

Aspect 15. A method of treating chronic lymphocytic leukemia (CLL) in a patient
20 comprising administering to the patient a therapeutically effective amount of a compound of formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof.

Aspect 16. A method of treating small lymphocytic lymphoma (SLL) in a patient comprising administering to the patient a therapeutically effective amount of a compound of formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof.

Aspect 17. A method of treating Waldenström macroglobulinemia in a patient comprising
25 administering to the patient a therapeutically effective amount of a compound of formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof.

- Aspect 18. A method of treating chronic graft versus host disease in a patient comprising administering to the patient a therapeutically effective amount of a compound of formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof.
- Aspect 19. The method of aspects 5 to 18, wherein the therapeutically effective amount of the compound of Formula (III) is about 140 mg.
- Aspect 20. The method of aspects 5 to 18, wherein the therapeutically effective amount of the compound of Formula (III) is about 280 mg.
- Aspect 21. The method of aspects 5 to 18, wherein the therapeutically effective amount of the compound of Formula (III) is about 560 mg.
- Aspect 22. The method of aspects 5 to 18, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,day1)}$ of about 59.992 ng/ml to about 2,377.2 ng/ml.
- Aspect 23. The method of aspects 5 to 18, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,day1)}$ of about 239.97 ng/ml to about 9,509 ng/ml.
- Aspect 24. The method of aspects 5 to 18, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,day1)}$ of about 429.75 ng/ml.
- Aspect 25. The method of aspects 5 to 18, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,day1)}$ of about 1,719 ng/ml.
- Aspect 26. The method of aspects 5 to 18, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 66.855 ng/ml to about 2,395.4 ng/ml.
- Aspect 27. The method of aspects 5 to 18, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 267.42 ng/ml to about 9,581.5 ng/ml.
- Aspect 28. The method of aspects 5 to 18, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 435.1 ng/ml.

- Aspect 29. The method of aspects 5 to 18, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 1,740.4 ng/ml.
- Aspect 30. The method of aspects 5 to 18, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 312.1 ng.hr/ml to about 11,517 ng.hr/ml.
- Aspect 31. The method of aspects 5 to 18, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 1,248.4 ng.hr/ml to about 46,068 ng.hr/ml.
- Aspect 32. The method of aspects 5 to 18, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 2,157.5 ng.hr/ml.
- Aspect 33. The method of aspects 5 to 18, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 8,629.9 ng.hr/ml.
- Aspect 34. The method of aspects 5 to 18, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 312.27 ng.hr/ml to about 13015 ng.hr/ml.
- Aspect 35. The method of aspects 5 to 18, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 1,249.1 to about 52,061 ng.hr/ml.
- Aspect 36. The method of aspects 5 to 18, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 2,249.7 ng.hr/ml.
- Aspect 37. The method of aspects 5 to 18, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 8,998.9 ng.hr/ml.
- Aspect 38. The method of aspects 5 to 18, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day\ 1)}$ of about 30.9 % occupancy to about 99.8 % occupancy.

- Aspect 39. The method of aspects 5 to 18, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKE_{(max/day1)}$ of about 87.1 % occupancy to about 100 % occupancy.
- 5 Aspect 40. The method of aspects 5 to 18, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKE_{(max/day1)}$ of about 90.4 % occupancy.
- Aspect 41. The method of aspects 5 to 18, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKE_{(max/day1)}$ of about 95.9 % occupancy.
- 10 Aspect 42. The method of aspects 5 to 18, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKE_{(max/ss)}$ of about 59.4 to about 99.9 % occupancy.
- Aspect 43. The method of aspects 5 to 18, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKE_{(max/ss)}$ of about 90.2 to about 15 100 % occupancy.
- Aspect 44. The method of aspects 5 to 18, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKE_{(max/ss)}$ of about 99.8 % occupancy.
- Aspect 45. The method of aspects 5 to 18, wherein the therapeutically effective amount of the 20 compound of Formula (III) is an amount that results in a $BTKE_{(max/ss)}$ of about 99.8 % occupancy.
- Aspect 46. The method of aspects 5 to 18, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKE_{(trough/day1)}$ of about 23.3% occupancy to about 91.3 % occupancy.
- 25 Aspect 47. The method of aspects 5 to 18, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKE_{(trough/day1)}$ of about 63.9 % occupancy to about 97.3 % occupancy.

- Aspect 48. The method of aspects 5 to 18, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/day1)}$ of about 77.4 % occupancy.
- 5 Aspect 49. The method of aspects 5 to 18, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/day1)}$ of about 85.4 % occupancy.
- Aspect 50. The method of aspects 5 to 18, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of about 50.2 % occupancy to about 95.4 % occupancy.
- 10 Aspect 51. The method of aspects 5 to 18, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of about 75.5 % occupancy to about 99.3 % occupancy.
- Aspect 52. The method of aspects 5 to 18, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of about 80.7 %
- 15 occupancy.
- Aspect 53. The method of aspects 5 to 18, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of about 86.0 % occupancy.
- Aspect 54. The method of aspects 5 to 18, wherein the therapeutically effective amount of the
- 20 compound of Formula (III) is administered once a day.
- Aspect 55. The method of aspects 5 to 18, wherein the therapeutically effective amount of the compound of Formula (III) is administered twice a day.
- Aspect 56. The method of aspects 5 to 18, wherein the therapeutically effective amount of the compound of Formula (III) is administered three times a day.
- 25 Aspect 57. The method of aspects 5, wherein the compound of formula (III) is administered orally.

- Aspect 58. The method of aspects 5 to 18, further comprising administering 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide).
- 5 Aspect 59. The method of aspects 5 to 18, further comprising administering cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab.
- Aspect 60. The compound of Formula (III) for use in a method of inhibiting Bruton's tyrosine kinase comprising contacting the kinase with said compound of Formula (III).
- Aspect 61. A compound of Formula (III), or a pharmaceutically acceptable salt, hydrate,
10 polymorph or solvate thereof for use in treating a malignancy in a patient comprising administering to the patient a therapeutically effective amount of said compound of Formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof.
- Aspect 62. The compound of Formula (III), or a pharmaceutically acceptable salt, hydrate,
15 polymorph or solvate thereof according to aspect 61, wherein the malignancy is selected from the group consisting of a lymphoma, a leukemia, a carcinoma, and a sarcoma.
- Aspect 63. The compound of Formula (III), or a pharmaceutically acceptable salt, hydrate,
20 polymorph or solvate thereof according to aspect 62, wherein the lymphoma is selected from the group consisting of non-Hodgkin's lymphoma (NHL (including B-cell NHL)), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), mucosa-associated lymphoid tissue (MALT) lymphoma, marginal zone lymphoma (MZL), T-cell lymphoma, Hodgkin's lymphoma, small lymphocytic lymphoma (SLL), Waldenström macroglobulinemia, and Burkitt's lymphoma.
- Aspect 64. The compound of Formula (III), or a pharmaceutically acceptable salt, hydrate,
25 polymorph or solvate thereof according to aspect 62, wherein the leukemia is selected from the group consisting of chronic lymphocytic leukemia (CLL), lymphoblastic T cell leukemia, chronic myelogenous leukemia (CML), hairy-cell leukemia, acute lymphoblastic T cell leukemia, plasmacytoma, immunoblastic large cell leukemia, megakaryoblastic leukemia, acute megakaryocyte leukemia, promyelocytic leukemia, erythroleukemia and multiple myeloma.

- Aspect 65. The compound of Formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof according to aspect 62, wherein the malignancy is selected from the group consisting of brain (gliomas), glioblastomas, breast cancer, colorectal/colon cancer, prostate cancer, lung cancer, non-small-cell lung cancer, gastric cancer, endometrial cancer, melanoma, pancreatic cancer, liver cancer, kidney cancer, squamous cell carcinoma, ovarian cancer, sarcoma, osteosarcoma, thyroid cancer, bladder cancer, head & neck cancer, testicular cancer, Ewing's sarcoma, rhabdomyosarcoma, medulloblastoma, neuroblastoma, cervical cancer, renal cancer, urothelial cancer, vulval cancer, esophageal cancer, salivary gland cancer, nasopharyngeal cancer, buccal cancer, cancer of the mouth, Chronic graft versus host disease, and gastrointestinal stromal tumor.
- Aspect 66. A compound of Formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof for use in a method of treating a diffuse large B-cell lymphoma (DLBCL) in a patient comprising administering to the patient a therapeutically effective amount of said compound of Formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof.
- Aspect 67. The compound of Formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof for use according to aspect 66, wherein the method comprises further administering a Bcl2 inhibitor.
- Aspect 68. A compound of Formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof for use in a method of treating mantle cell lymphoma (MCL) in a patient comprising administering to the patient a therapeutically effective amount of said compound of Formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof.
- Aspect 69. A compound of Formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof for use in a method of treating follicular lymphoma (FL) in a patient comprising administering to the patient a therapeutically effective amount of said compound of Formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof.
- Aspect 70. A compound of Formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof for use in a method of treating marginal zone lymphoma (MZL)

in a patient comprising administering to the patient a therapeutically effective amount of said compound of Formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof.

- Aspect 71. A compound of Formula (III), or a pharmaceutically acceptable salt, hydrate,
5 polymorph or solvate thereof for use in a method of treating chronic lymphocytic leukemia (CLL) in a patient comprising administering to the patient a therapeutically effective amount of said compound of Formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof.
- Aspect 72. A compound of Formula (III), or a pharmaceutically acceptable salt, hydrate,
10 polymorph or solvate thereof for use in a method of treating small lymphocytic lymphoma (SLL) in a patient comprising administering to the patient a therapeutically effective amount of said compound of Formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof.
- Aspect 73. A compound of Formula (III), or a pharmaceutically acceptable salt, hydrate,
15 polymorph or solvate thereof for use in a method of treating Waldenström macroglobulinemia in a patient comprising administering to the patient a therapeutically effective amount of said compound of Formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof.
- Aspect 74. A compound of Formula (III), or a pharmaceutically acceptable salt, hydrate,
20 polymorph or solvate thereof for use in a method of treating chronic graft versus host disease in a patient comprising administering to the patient a therapeutically effective amount of said compound of Formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof.
- Aspect 75. The compound of Formula (III) for use according to aspects 61-74, wherein the
25 therapeutically effective amount of the compound of Formula (III) is about 140 mg.
- Aspect 76. The compound of Formula (III) for use according to aspects 61-75, wherein the therapeutically effective amount of the compound of Formula (III) is about 280 mg.
- Aspect 77. The compound of Formula (III) for use according to aspects 61-76, wherein the therapeutically effective amount of the compound of Formula (III) is about 560 mg.

- Aspect 78. The compound of Formula (III) for use according to aspects 61-77, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,day1)}$ of about 59.992 ng/ml to about 2,377.2 ng/ml.
- 5 Aspect 79. The compound of Formula (III) for use according to aspects 61-78, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,day1)}$ of about 239.97 ng/ml to about 9,509 ng/ml.
- Aspect 80. The compound of Formula (III) for use according to aspects 61-79, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,day1)}$ of about 429.75 ng/ml.
- 10 Aspect 81. The compound of Formula (III) for use according to aspects 61-80, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,day1)}$ of about 1,719 ng/ml.
- Aspect 82. The compound of Formula (III) for use according to aspects 61-81, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 66.855 ng/ml to about 2,395.4 ng/ml.
- 15 Aspect 83. The compound of Formula (III) for use according to aspects 61-82, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 267.42 ng/ml to about 9,581.5 ng/ml.
- Aspect 84. The compound of Formula (III) for use according to aspects 61-83, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 435.1 ng/ml.
- 20 Aspect 85. The compound of Formula (III) for use according to aspects 61-84, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 1,740.4 ng/ml.
- 25 Aspect 86. The compound of Formula (III) for use according to aspects 61-85, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day 1)}$ of about 312.1 ng.hr/ml to about 11,517 ng.hr/ml.

- Aspect 87. The compound of Formula (III) for use according to aspects 61-86, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 1,248.4 ng.hr/ml to about 46,068 ng.hr/ml.
- 5 Aspect 88. The compound of Formula (III) for use according to aspects 61-87, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 2,157.5 ng.hr/ml.
- Aspect 89. The compound of Formula (III) for use according to aspects 61-88, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 8,629.9 ng.hr/ml.
- 10 Aspect 90. The compound of Formula (III) for use according to aspects 61-89, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 312.27 ng.hr/ml to about 13015 ng.hr/ml.
- Aspect 91. The compound of Formula (III) for use according to aspects 61-90, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results
15 in a $AUC_{(ss)}$ of about 1,249.1 to about 52,061 ng.hr/ml.
- Aspect 92. The compound of Formula (III) for use according to aspects 61-91, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 2,249.7 ng.hr/ml.
- Aspect 93. The compound of Formula (III) for use according to aspects 61-92, wherein the
20 therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 8,998.9 ng.hr/ml.
- Aspect 94. The compound of Formula (III) for use according to aspects 61-93, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day1)}$ of about 30.9 % occupancy to about 99.8 % occupancy.
- 25 Aspect 95. The compound of Formula (III) for use according to aspects 61-94, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day1)}$ of about 87.1 % occupancy to about 100 % occupancy.

- Aspect 96. The compound of Formula (III) for use according to aspects 61-95, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day1)}$ of about 90.4 % occupancy.
- 5 Aspect 97. The compound of Formula (III) for use according to aspects 61-96, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day1)}$ of about 95.9 % occupancy.
- Aspect 98. The compound of Formula (III) for use according to aspects 61-97, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/ss)}$ of about 59.4 to about 99.9 % occupancy.
- 10 Aspect 99. The compound of Formula (III) for use according to aspects 61-98, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/ss)}$ of about 90.2 to about 100 % occupancy.
- Aspect 100. The compound of Formula (III) for use according to aspects 61-99, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results
15 in a $BTKO_{(max/ss)}$ of about 99.8 % occupancy.
- Aspect 101. The compound of Formula (III) for use according to aspects 61-100, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/ss)}$ of about 99.8 % occupancy.
- Aspect 102. The compound of Formula (III) for use according to aspects 61-101, wherein the
20 therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day1)}$ of about 23.3% occupancy to about 91.3 % occupancy.
- Aspect 103. The compound of Formula (III) for use according to aspects 61-102, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day1)}$ of about 63.9 % occupancy to about 97.3 % occupancy.
- 25 Aspect 104. The compound of Formula (III) for use according to aspects 61-103, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day1)}$ of about 77.4 % occupancy.

- Aspect 105. The compound of Formula (III) for use according to aspects 61-104, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/day1)}$ of about 85.4 % occupancy.
- 5 Aspect 106. The compound of Formula (III) for use according to aspects 61-105, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of about 50.2 % occupancy to about 95.4 % occupancy.
- Aspect 107. The compound of Formula (III) for use according to aspects 61-106, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of about 75.5 % occupancy to about 99.3 % occupancy.
- 10 Aspect 108. The compound of Formula (III) for use according to aspects 61-107, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of about 80.7 % occupancy.
- Aspect 109. The compound of Formula (III) for use according to aspects 61-108, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results
- 15 in a $BTkO_{(trough/ss)}$ of about 86.0 % occupancy.
- Aspect 110. The compound of Formula (III) for use according to aspects 61-109, wherein the therapeutically effective amount of the compound of Formula (III) is administered once a day.
- Aspect 111. The compound of Formula (III) for use according to aspects 61-110, wherein the
- 20 therapeutically effective amount of the compound of Formula (III) is administered twice a day.
- Aspect 112. The compound of Formula (III) for use according to aspects 61-111, wherein the therapeutically effective amount of the compound of Formula (III) is administered three times a day.
- 25 Aspect 113. The compound of Formula (III) for use according to aspects 61-112, wherein the compound of Formula (III) is administered orally.
- Aspect 114. The compound of Formula (III) for use according to aspects 61-113, further comprising administering 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-

yl)methyl}piperazin-1-yl)-N-({3- nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin5-yloxy)benzamide).

Aspect 115. The compound of Formula (III) for use according to aspects 61-114, further comprising administering cyclophosphamide, doxorubicin, vincristine, prednisone and
5 rituximab.

Aspect 116. Use of a compound of Formula (III) for the manufacture of a medicament for use in a method of inhibiting Bruton's tyrosine kinase comprising contacting the kinase with a compound of formula (III).

Aspect 117. Use of a compound of Formula (III), or a pharmaceutically acceptable salt,
10 hydrate, polymorph or solvate thereof for the manufacture of a medicament for treating a malignancy in a patient comprising administering to the patient a therapeutically effective amount of said compound of Formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof.

Aspect 118. The use of aspect 117, wherein the malignancy is selected from the group
15 consisting of a lymphoma, a leukemia, a carcinoma, and a sarcoma.

Aspect 119. The use of aspect 118, wherein the lymphoma is selected from the group consisting of non-Hodgkin's lymphoma (NHL (including B-cell NHL)), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), mucosa-associated lymphoid tissue (MALT) lymphoma, marginal zone lymphoma (MZL), T-cell
20 lymphoma, Hodgkin's lymphoma, small lymphocytic lymphoma (SLL), Waldenström macroglobulinemia, and Burkitt's lymphoma.

Aspect 120. The use of aspect 118, wherein the leukemia is selected from the group consisting of chronic lymphocytic leukemia (CLL), lymphoblastic T cell leukemia, chronic myelogenous leukemia (CML), hairy-cell leukemia, acute lymphoblastic T cell leukemia,
25 plasmacytoma, immunoblastic large cell leukemia, megakaryoblastic leukemia, acute megakaryocyte leukemia, promyelocytic leukemia, erythroleukemia and multiple myeloma.

Aspect 121. The use of aspect 118, wherein the malignancy is selected from the group consisting of brain (gliomas), glioblastomas, breast cancer, colorectal/colon cancer, prostate cancer, lung cancer, non-small-cell lung cancer, gastric cancer, endometrial cancer,

melanoma, pancreatic cancer, liver cancer, kidney cancer, squamous cell carcinoma, ovarian cancer, sarcoma, osteosarcoma, thyroid cancer, bladder cancer, head & neck cancer, testicular cancer, Ewing's sarcoma, rhabdomyosarcoma, medulloblastoma, neuroblastoma, cervical cancer, renal cancer, urothelial cancer, vulval cancer, esophageal cancer, salivary gland cancer, nasopharyngeal cancer, buccal cancer, cancer of the mouth, Chronic graft
5 versus host disease, and gastrointestinal stromal tumor.

Aspect 122. Use of a compound of Formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof for the manufacture of a medicament for use in a method of treating a diffuse large B-cell lymphoma (DLBCL) in a patient comprising
10 administering to the patient a therapeutically effective amount of said compound of Formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof.

Aspect 123. The use of aspect 122, wherein the method comprises further administering a Bcl2 inhibitor.

Aspect 124. Use of a compound of Formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof for the manufacture of a medicament for use in a method of treating mantle cell lymphoma (MCL) in a patient comprising administering to the
15 patient a therapeutically effective amount of said compound of Formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof.

Aspect 125. Use of a compound of Formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof for the manufacture of a medicament for use in a method of treating follicular lymphoma (FL) in a patient comprising administering to the
20 patient a therapeutically effective amount of said compound of Formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof.

Aspect 126. Use of a compound of Formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof for the manufacture of a medicament for use in a method of treating marginal zone lymphoma (MZL) in a patient comprising administering to
25 the patient a therapeutically effective amount of said compound of Formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof.

- Aspect 127. Use of a compound of Formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof for the manufacture of a medicament for use in a method of treating chronic lymphocytic leukemia (CLL) in a patient comprising administering to the patient a therapeutically effective amount of said compound of Formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof.
- Aspect 128. Use of a compound of Formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof for the manufacture of a medicament for use in a method of treating small lymphocytic lymphoma (SLL) in a patient comprising administering to the patient a therapeutically effective amount of said compound of Formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof.
- Aspect 129. Use of a compound of Formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof for the manufacture of a medicament for use in a method of treating Waldenström macroglobulinemia in a patient comprising administering to the patient a therapeutically effective amount of said compound of Formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof.
- Aspect 130. Use of a compound of Formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof for the manufacture of a medicament for use in a method of treating chronic graft versus host disease in a patient comprising administering to the patient a therapeutically effective amount of said compound of Formula (III), or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof.
- Aspect 131. Use of aspects 117 to 130, wherein the therapeutically effective amount of the compound of Formula (III) is about 140 mg.
- Aspect 132. Use of aspects 117 to 131, wherein the therapeutically effective amount of the compound of Formula (III) is about 280 mg.
- Aspect 133. Use of aspects 117 to 132, wherein the therapeutically effective amount of the compound of Formula (III) is about 560 mg.
- Aspect 134. Use of aspects 117 to 133, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max, day1)}$ of about 59.992 ng/ml to about 2,377.2 ng/ml.

- Aspect 135. Use of aspects 117 to 134, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,day1)}$ of about 239.97 ng/ml to about 9,509 ng/ml.
- Aspect 136. Use of aspects 117 to 135, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,day1)}$ of about 429.75 ng/ml.
- Aspect 137. Use of aspects 117 to 136, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,day1)}$ of about 1,719 ng/ml.
- Aspect 138. Use of aspects 117 to 137, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 66.855 ng/ml to about 2,395.4 ng/ml.
- Aspect 139. Use of aspects 117 to 138, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 267.42 ng/ml to about 9,581.5 ng/ml.
- Aspect 140. Use of aspects 117 to 139, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 435.1 ng/ml.
- Aspect 141. Use of aspects 117 to 140, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 1,740.4 ng/ml.
- Aspect 142. Use of aspects 117 to 141, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 312.1 ng.hr/ml to about 11,517 ng.hr/ml.
- Aspect 143. Use of aspects 117 to 142, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 1,248.4 ng.hr/ml to about 46,068 ng.hr/ml.
- Aspect 144. Use of aspects 117 to 143, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 2,157.5 ng.hr/ml.
- Aspect 145. Use of aspects 117 to 144, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 8,629.9 ng.hr/ml.

- Aspect 146. Use of aspects 117 to 145, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 312.27 ng.hr/ml to about 13015 ng.hr/ml.
- 5 Aspect 147. Use of aspects 117 to 146, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 1,249.1 to about 52,061 ng.hr/ml.
- Aspect 148. Use of aspects 117 to 147, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 2,249.7 ng.hr/ml.
- 10 Aspect 149. Use of aspects 117 to 148, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 8,998.9 ng.hr/ml.
- Aspect 150. Use of aspects 117 to 149, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day1)}$ of about 30.9 % occupancy to about 99.8 % occupancy.
- 15 Aspect 151. Use of aspects 117 to 150, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day1)}$ of about 87.1 % occupancy to about 100 % occupancy.
- Aspect 152. Use of aspects 117 to 151, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day1)}$ of about 90.4 % occupancy.
- 20 Aspect 153. Use of aspects 117 to 152, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day1)}$ of about 95.9 % occupancy.
- Aspect 154. Use of aspects 117 to 153, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/ss)}$ of about 59.4 to about 99.9 % occupancy.
- 25 Aspect 155. Use of aspects 117 to 154, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/ss)}$ of about 90.2 to about 100 % occupancy.

- Aspect 156. Use of aspects 117 to 155, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(max/ss)}$ of about 99.8 % occupancy.
- 5 Aspect 157. Use of aspects 117 to 156, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(max/ss)}$ of about 99.8 % occupancy.
- Aspect 158. Use of aspects 117 to 157, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/day1)}$ of about 23.3% occupancy to about 91.3 % occupancy.
- 10 Aspect 159. Use of aspects 117 to 158, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/day1)}$ of about 63.9 % occupancy to about 97.3 % occupancy.
- Aspect 160. Use of aspects 117 to 159, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/day1)}$ of about 77.4 %
15 occupancy.
- Aspect 161. Use of aspects 117 to 160, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/day1)}$ of about 85.4 % occupancy.
- Aspect 162. Use of aspects 117 to 161, wherein the therapeutically effective amount of the
20 compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of about 50.2 % occupancy to about 95.4 % occupancy.
- Aspect 163. Use of aspects 117 to 162, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of about 75.5 % occupancy to about 99.3 % occupancy.
- 25 Aspect 164. Use of aspects 117 to 163, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTkO_{(trough/ss)}$ of about 80.7 % occupancy.

Aspect 165. Use of aspects 117 to 164, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/ss)}$ of about 86.0 % occupancy.

Aspect 166. Use of aspects 117 to 165, wherein the therapeutically effective amount of the compound of Formula (III) is administered once a day.

Aspect 167. Use of aspects 117 to 166, wherein the therapeutically effective amount of the compound of Formula (III) is administered twice a day.

Aspect 168. Use of aspects 117 to 167, wherein the therapeutically effective amount of the compound of Formula (III) is administered three times a day.

Aspect 169. Use of aspects 117 to 168, wherein the compound of Formula (III) is administered orally.

Aspect 170. Use of aspects 117 to 169, further comprising administering 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide).

Aspect 171. Use of aspects 117 to 170, further comprising administering cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab.

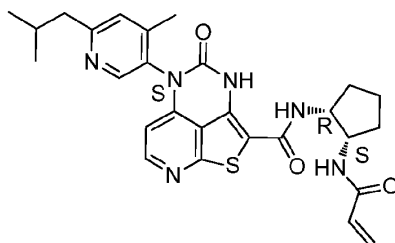
All aspects described herein for methods of treating a malignancy, are also applicable for use in treating said malignancy.

All aspects described herein for methods of treating a malignancy, are also applicable for use in a method of treating said malignancy.

CLAIMS

What is Claimed:

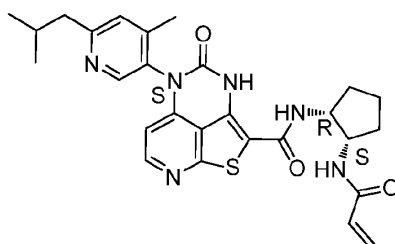
1. A method of treating a malignancy in an individual in need thereof, comprising
 5 administering a therapeutically effective amount of a compound of Formula (III):



(III)

or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof.

2. The method of claim 1, wherein the malignancy is selected from the group consisting of a
 10 diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), marginal zone lymphoma (MZL), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), and Waldenström macroglobulinemia, Chronic graft versus host disease.
3. The method of claim 2, further comprising administering 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide).
4. A method of treating chronic graft versus host disease in an individual in need thereof,
 20 comprising administering a therapeutically effective amount of a compound of Formula (III):



(III)

or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof.

5. The method of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is from about 140 mg to about 560 mg.
6. The method of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is about 140 mg.
7. The method of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is about 280 mg.
8. The method of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is about 560 mg.
9. The method of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max, day1)}$ of about 59.992 ng/ml to about 2,377.2 ng/ml.
10. The method of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max, day1)}$ of about 239.97 ng/ml to about 9,509 ng/ml.
11. The method of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max, ss)}$ of about 66.855 ng/ml to about 2,395.4 ng/ml.

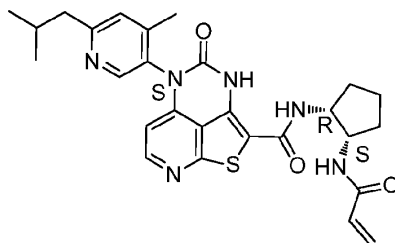
12. The method of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 267.42 ng/ml to about 9,581.5 ng/ml.
13. The method of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 312.1 ng.hr/ml to about 11,517 ng.hr/ml.
14. The method of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 1,248.4 ng.hr/ml to about 46,068 ng.hr/ml.
15. The method of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 312.27 ng.hr/ml to about 13,015 ng.hr/ml.
16. The method of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 1249.1 to about 52061 ng.hr/ml.
17. The method of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day1)}$ of about 30.9 % occupancy to about 99.8 % occupancy.
18. The method of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day1)}$ of about 87.1 % occupancy to about 100 % occupancy.
19. The method of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/ss)}$ of about 59.4 % occupancy to about 99.9 % occupancy.
20. The method of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/ss)}$ of about 90.2 % occupancy to about 100 % occupancy.

21. The method of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day1)}$ of about 23.3 % occupancy to about 91.3 % occupancy.
22. The method of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day1)}$ of about 63.9 % occupancy to about 97.3 % occupancy.
23. The method of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/ss)}$ of about 50.2 % occupancy to about 95.4 % occupancy.
24. The method of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/ss)}$ of about 75.5 % occupancy to about 99.3 % occupancy.
25. The method of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is administered once a day.
26. The method of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is administered twice a day.
27. The method of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is administered three times a day.
28. The method of any one of claims 1-4, wherein the compound of formula (III) is administered orally.
29. The method of any one of claims 1-4, further comprising administering 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide).

30. The method of any one of claims 1-4, further comprising administering cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab.

31. A compound of Formula (III):

5



(III)

or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof, for use in treating a malignancy.

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32. The compound of Formula (III) or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof for use according to claim 31 wherein the malignancy is selected from the group consisting of a diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), marginal zone lymphoma (MZL), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), and Waldenström macroglobulinemia, Chronic graft versus host disease.

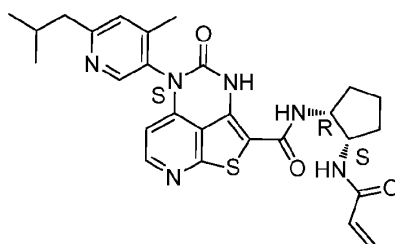
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33. The compound of Formula (III) or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof for use according to claim 32, further comprising administering 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide).

20

34. A compound of Formula (III):

25



(III)

or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof for use in treating chronic graft versus host disease.

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35. The compound of Formula (III) for use according to any one of claims 31-34, wherein the therapeutically effective amount of the compound of Formula (III) is from about 140 mg to about 560 mg.

- 10 36. The compound of Formula (III) for use according to any one of claims 31-34, wherein the therapeutically effective amount of the compound of Formula (III) is about 140 mg.

37. The compound of Formula (III) for use according to any one of claims 31-34, wherein the therapeutically effective amount of the compound of Formula (III) is about 280 mg.

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38. The compound of Formula (III) for use according to any one of claims 31-34, wherein the therapeutically effective amount of the compound of Formula (III) is about 560 mg.

39. The compound of Formula (III) for use according to any one of claims 31-34, wherein the
20 therapeutically effective amount of the compound of Formula (III) is an amount that results
in a $C_{(max, day1)}$ of about 59.992 ng/ml to about 2,377.2 ng/ml.

40. The compound of Formula (III) for use according to any one of claims 31-34, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max, day1)}$ of about 239.97 ng/ml to about 9,509 ng/ml.

41. The compound of Formula (III) for use according to any one of claims 31-34, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 66.855 ng/ml to about 2,395.4 ng/ml.
- 5 42. The compound of Formula (III) for use according to any one of claims 31-34, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 267.42 ng/ml to about 9,581.5 ng/ml.
43. The compound of Formula (III) for use according to any one of claims 31-34, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day 1)}$ of about 312.1 ng.hr/ml to about 11,517 ng.hr/ml.
- 10 44. The compound of Formula (III) for use according to any one of claims 31-34, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day 1)}$ of about 1,248.4 ng.hr/ml to about 46,068 ng.hr/ml.
45. The compound of Formula (III) for use according to any one of claims 31-34, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 312.27 ng.hr/ml to about 13,015 ng.hr/ml.
- 15 46. The compound of Formula (III) for use according to any one of claims 31-34, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 1249.1 to about 52061 ng.hr/ml.
47. The compound of Formula (III) for use according to any one of claims 31-34, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day1)}$ of about 30.9 % occupancy to about 99.8 % occupancy.
- 20 48. The compound of Formula (III) for use according to any one of claims 31-34, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day1)}$ of about 87.1 % occupancy to about 100 % occupancy.
- 25 49. The compound of Formula (III) for use according to any one of claims 31-34, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/ss)}$ of about 59.4 % occupancy to about 99.9 % occupancy.

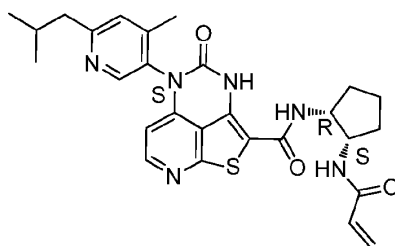
50. The compound of Formula (III) for use according to any one of claims 31-34, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/ss)}$ of about 90.2 % occupancy to about 100 % occupancy.
51. The compound of Formula (III) for use according to any one of claims 31-34, wherein the
5 therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day1)}$ of about 23.3 % occupancy to about 91.3 % occupancy.
52. The compound of Formula (III) for use according to any one of claims 31-34, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day1)}$ of about 63.9 % occupancy to about 97.3 % occupancy.
- 10 53. The compound of Formula (III) for use according to any one of claims 31-34, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/ss)}$ of about 50.2 % occupancy to about 95.4 % occupancy.
54. The compound of Formula (III) for use according to any one of claims 31-34, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results
15 in a $BTKO_{(trough/ss)}$ of about 75.5 % occupancy to about 99.3 % occupancy.
55. The compound of Formula (III) for use according to any one of claims 31-34, wherein the therapeutically effective amount of the compound of Formula (III) is administered once a
20 day.
56. The compound of Formula (III) for use according to any one of claims 31-34, wherein the therapeutically effective amount of the compound of Formula (III) is administered twice a day.
- 25 57. The compound of Formula (III) for use according to any one of claims 31-34, wherein the therapeutically effective amount of the compound of Formula (III) is administered three times a day.
- 30 58. The compound of Formula (III) for use according to any one of claims 31-34, wherein the compound of formula (III) is administered orally.

59. The compound of Formula (III) for use according to any one of claims 31-34, further comprising administering 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide).

60. The compound of Formula (III) for use according to any one of claims 31-34, further comprising administering cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab.

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61. Use of a compound of Formula (III):



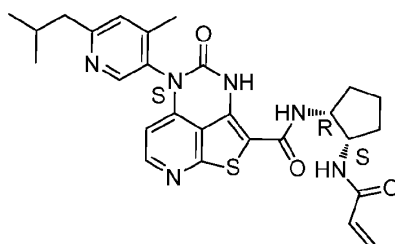
(III)

15 or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof, for the manufacture of a medicament for treating a malignancy.

62. The use of claim 61, wherein the malignancy is selected from the group consisting of a diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), marginal zone lymphoma (MZL), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), and Waldenström macroglobulinemia, Chronic graft versus host disease.

63. The use of claim 62, further comprising administering 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide).

64. Use of a compound of Formula (III):



(III)

or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof, for the manufacture of a medicament for treating chronic graft versus host disease.

- 5 65. The use of any one of claims 61-64, wherein the therapeutically effective amount of the compound of Formula (III) is from about 140 mg to about 560 mg.
66. The use of any one of claims 61-64, wherein the therapeutically effective amount of the compound of Formula (III) is about 140 mg.
- 10 67. The use of any one of claims 61-64, wherein the therapeutically effective amount of the compound of Formula (III) is about 280 mg.
68. The use of any one of claims 61-64, wherein the therapeutically effective amount of the compound of Formula (III) is about 560 mg.
- 15 69. The use of any one of claims 61-64, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max, day1)}$ of about 59.992 ng/ml to about 2,377.2 ng/ml.
- 20 70. The use of any one of claims 61-64, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max, day1)}$ of about 239.97 ng/ml to about 9,509 ng/ml.
71. The use of any one of claims 61-64, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max, ss)}$ of about 66.855 ng/ml to about 2,395.4 ng/ml.
- 25

72. The use of any one of claims 61-64, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $C_{(max,ss)}$ of about 267.42 ng/ml to about 9,581.5 ng/ml.
- 5 73. The use of any one of claims 61-64, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 312.1 ng.hr/ml to about 11,517 ng.hr/ml.
74. The use of any one of claims 61-64, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(day\ 1)}$ of about 1,248.4 ng.hr/ml to about 46,068 ng.hr/ml.
- 10 75. The use of any one of claims 61-64, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 312.27 ng.hr/ml to about 13,015 ng.hr/ml.
76. The use of any one of claims 61-64, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $AUC_{(ss)}$ of about 1249.1 to about
15 52061 ng.hr/ml.
77. The use of any one of claims 61-64, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day1)}$ of about 30.9 % occupancy to about 99.8 % occupancy.
- 20 78. The use of any one of claims 61-64, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day1)}$ of about 87.1 % occupancy to about 100 % occupancy.
79. The use of any one of claims 61-64, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/ss)}$ of about 59.4 % occupancy to about 99.9 % occupancy.
- 25 80. The use of any one of claims 61-64, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/ss)}$ of about 90.2 % occupancy to about 100 % occupancy.

81. The use of any one of claims 61-64, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day1)}$ of about 23.3 % occupancy to about 91.3 % occupancy.
- 5 82. The use of any one of claims 61-64, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day1)}$ of about 63.9 % occupancy to about 97.3 % occupancy.
83. The use of any one of claims 61-64, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/ss)}$ of about 50.2 % occupancy to about 95.4 % occupancy.
- 10 84. The use of any one of claims 61-64, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/ss)}$ of about 75.5 % occupancy to about 99.3 % occupancy.
- 15 85. The use of any one of claims 61-64, wherein the therapeutically effective amount of the compound of Formula (III) is administered once a day.
86. The use of any one of claims 61-64, wherein the therapeutically effective amount of the compound of Formula (III) is administered twice a day.
- 20 87. The use of any one of claims 61-64, wherein the therapeutically effective amount of the compound of Formula (III) is administered three times a day.
88. The use of any one of claims 61-64, wherein the compound of formula (III) is administered orally.
- 25 89. The use of any one of claims 61-64, further comprising administering 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide).
- 30

90. The use of any one of claims 61-64, further comprising administering cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab.