(12) STANDARD PATENT (11) Application No. **AU 2014337122 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Heteroaromatic compounds useful for the treatment of proliferative diseases

(51) International Patent Classification(s)
C07D 401/14 (2006.01) ***A61P 35/02*** (2006.01)
A61K 31/506 (2006.01)

(21) Application No: **2014337122** (22) Date of Filing: **2014.10.17**

(87) WIPO No: **WO15/058126**

(30) Priority Data

(31) Number	(32) Date	(33) Country
61/892,842	**2013.10.18**	**US**

(43) Publication Date: **2015.04.23**
(44) Accepted Journal Date: **2019.01.03**

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(56) Related Art
WO 2013074986 A1

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 April 2015 (23.04.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/058126 A1

(51) International Patent Classification:
C07D 401/14 (2006.01) *A61P 35/02* (2006.01)
A61K 31/506 (2006.01)

(21) International Application Number:
PCT/US2014/061206

(22) International Filing Date:
17 October 2014 (17.10.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/892,842 18 October 2013 (18.10.2013) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

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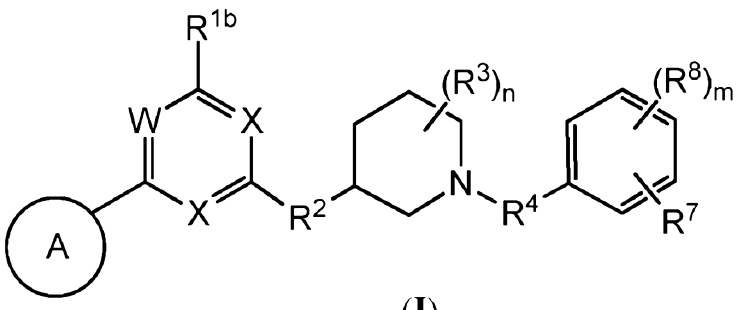
(54) Title: HETEROAROMATIC COMPOUNDS USEFUL FOR THE TREATMENT OF PROLFERATIVE DISEASES



(I)

(57) Abstract: The present invention provides novel compounds of Formula (I), and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers, isotopically labeled derivatives, and compositions thereof. Also provided are methods and kits involving the compounds or compositions for treating or preventing proliferative diseases (e.g., cancers (e.g., leukemia, melanoma, multiple myeloma), benign neoplasms, angiogenesis, inflammatory diseases, autoinflammatory diseases, and autoimmune diseases) in a subject. Treatment of a subject with a proliferative disease using a compound or composition of the invention may inhibit the aberrant activity of a kinase, such as a cyclin-dependent kinase (CDK) (e.g., cyclin-dependent kinase 7 (CDK7)), and therefore, induce cellular apoptosis and/or inhibit transcription in the subject.

WO 2015/058126 A1

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

HETEROAROMATIC COMPOUNDS USEFUL FOR THE TREATMENT OF PROLFERATIVE DISEASES

BACKGROUND OF THE INVENTION

[1] The members of the cyclin-dependent kinase (CDK) family play critical regulatory roles in proliferation. Unique among the mammalian CDKs, CDK7 has consolidated kinase activities, regulating both the cell cycle and transcription. In the cytosol, CDK7 exists as a heterotrimeric complex and is believed to function as a CDK1/2-activating kinase (CAK), whereby phosphorylation of conserved residues in CDK1/2 by CDK7 is required for full catalytic CDK activity and cell cycle progression. In the nucleus, CDK7 forms the kinase core of the RNA polymerase (RNAP) II general transcription factor complex and is charged with phosphorylating the C-terminal domain (CTD) of RNAP II, a requisite step in gene transcriptional initiation Together, the two functions of CDK7, *i.e.*, CAK and CTD phosphorylation, support critical facets of cellular proliferation, cell cycling, and transcription.

[2] Disruption of RNAP II CTD phosphorylation has been shown to preferentially affect proteins with short half-lives, including those of the anti-apoptotic BCL-2 family. Cancer cells have demonstrated the ability to circumvent pro-cell death signaling through upregulation of BCL-2 family members. Therefore, inhibition of human CDK7 kinase activity is likely to result in anti-proliferative activity.

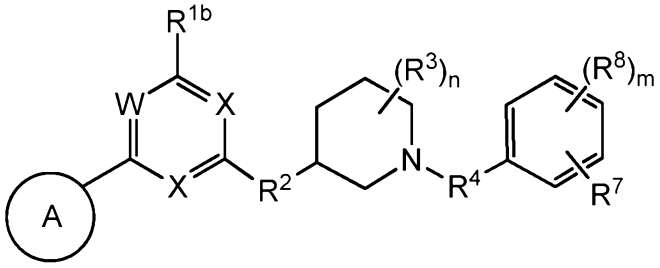
[3] The discovery of selective inhibitors of CDK7 has been hampered by the high sequence and structural similarities of the kinase domain of CDK family members. Therefore, there is a need for the discovery and development of selective CDK7 inhibitors. Such CKD7 inhibitors hold promise as a therapeutic agent for the treatment of CLL and other cancers.

SUMMARY OF THE INVENTION

[4] The present invention provides CDK inhibitors, more particularly CDK7, CDK12, and CDK13 inhibitors, and in particular selective CDK7 inhibitors of Formula (**I**), and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers, isotopically labeled derivatives, and compositions thereof. The present invention further provides methods of using the compounds of the invention, and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers, isotopically labeled derivatives, and compositions thereof, to study the inhibition of CDK7 and other CDK family members, and as therapeutics for the prevention

and/or treatment of diseases associated with overexpression and/or aberrant activity of CDK7 and other CDK family members. In certain embodiments, the inventive compounds are used for the prevention and/or treatment of proliferative diseases (*e.g.*, cancers (*e.g.*, leukemia, melanoma, multiple myeloma), benign neoplasms, angiogenesis, inflammatory diseases, autoinflammatory diseases, and autoimmune diseases) in a subject.

[5] In one aspect, the present invention provides compounds of Formula (**I**):



(**I**),

and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers, and isotopically labeled derivatives thereof, wherein Ring A, W, X, R^{1b}, R^2, R^3, R^4, R^7, R^8, m, n and subvariables thereof are as defined herein.

[6] In another aspect, the present invention provides pharmaceutical compositions comprising a compound of Formula (**I**), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer, or isotopically labeled derivative thereof, and optionally a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical compositions described herein include a therapeutically effective amount of a compound of Formula (**I**), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer, or isotopically labeled derivative thereof. The pharmaceutical composition may be useful for treating and/or preventing a proliferative or infectious disease.

[7] In another aspect, the present invention provides methods for treating and/or preventing proliferative diseases. Exemplary proliferative diseases include cancer (*e.g.*, leukemia, melanoma, multiple myeloma), benign neoplasm, angiogenesis, inflammatory diseases, autoinflammatory diseases, and autoimmune diseases. In other embodiments, the present invention provides methods for treating and/or preventing an infectious disease (*e.g.*, a viral infection).

[8] In still another aspect, the present invention provides methods of down-regulating the expression of a CDK in a biological sample or subject, more specifically CDK7.

[9] Another aspect of the invention relates to methods of inhibiting the activity of CDK7 in a

biological sample or subject.

[10] The present invention also provides methods of inhibiting cell growth in a biological sample or subject.

[11] In still another aspect, the present invention provides methods of inducing apoptosis of a cell in a biological sample or a subject.

[12] In yet another aspect, the present invention provides compounds of Formula (**I**), and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers, isotopically labeled derivatives, and compositions thereof, for use in the treatment of a proliferative disease in a subject.

[13] In yet another aspect, the present invention provides compounds of Formula (**I**), and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers, isotopically labeled derivatives, and compositions thereof, for use in the treatment or prevention of an infectious disease in a subject. In certain embodiments, the infectious disease is a viral infection.

[14] Another aspect of the present invention relates to kits comprising a container with a compound of Formula (**I**), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer, or isotopically labeled derivative thereof, or a pharmaceutical composition thereof. In certain embodiments, the kits described herein further include instructions for administering the compound of Formula (**I**), or the pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer, or isotopically labeled derivative thereof, or the pharmaceutical composition thereof.

[15] The details of one or more embodiments of the invention are set forth herein. Other features, objects, and advantages of the invention will be apparent from the Detailed Description, the Figures, the Examples, and the Claims.

DEFINITIONS

[16] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March,

March's Advanced Organic Chemistry, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

[17] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, Z and E double bond isomers, and Z and E conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures including the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present invention.

[18] Where a particular enantiomer is preferred, it may, in some embodiments be provided substantially free of the corresponding enantiomer, and may also be referred to as "optically enriched." "Optically-enriched," as used herein, means that the compound is made up of a significantly greater proportion of one enantiomer. In certain embodiments the compound is made up of at least about 90% by weight of a preferred enantiomer. In other embodiments the compound is made up of at least about 95%, 98%, or 99% by weight of a preferred enantiomer. Preferred enantiomers may be isolated from racemic mixtures by any method known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts or prepared by asymmetric syntheses. See, for example, Jacques et al., *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen, et al., *Tetrahedron* 33:2725 (1977); Eliel, E.L. *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); Wilen, S.H. *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972).

[19] The term "aliphatic" or "aliphatic group", as used herein, denotes a hydrocarbon moiety that may be straight-chain (i.e., unbranched), branched, or cyclic (including fused, bridging, and spiro-fused polycyclic) and may be completely saturated or may contain one or more units of unsaturation, but which is not aromatic. Unless otherwise specified, aliphatic groups contain 1-6 carbon atoms. In some embodiments, aliphatic groups contain 1-4 carbon atoms, and in yet other embodiments aliphatic groups contain 1-3 carbon atoms. Suitable aliphatic groups include, but are not limited to, linear or branched, alkyl, alkenyl, and alkynyl groups, and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[20] The term "alkyl," as used herein, refers to a monovalent saturated, straight- or branched-chain hydrocarbon such as a straight or branched group of 1-12, 1-10, or 1-6 carbon atoms, referred to herein as C_1-C_{12} alkyl, C_1-C_{10} alkyl, and C_1-C_6 alkyl, respectively. Examples of alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, sec-pentyl, iso-pentyl, tert-butyl, n-pentyl, neopentyl, n-hexyl, sec-hexyl, and the like.

[21] The terms "alkenyl" and "alkynyl" are art-recognized and refer to unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond, respectively. Exemplary alkenyl groups include, but are not limited to, $-CH=CH_2$ and $-CH_2CH=CH_2$.

[22] The term "alkylene" refers to the diradical of an alkyl group.

[23] The terms "alkenylene" and "alkynylene" refer to the diradicals of an alkenyl and an alkynyl group, respectively.

[24] The term "methylene unit" refers to a divalent $-CH_2-$ group present in an alkyl, alkenyl, alkynyl, alkylene, alkenylene, or alkynylene moiety.

[25] The term "carbocyclic ring system", as used herein, means a monocyclic, bicyclic or polycyclic hydrocarbon ring system, wherein each ring is either completely saturated or contains one or more units of unsaturation, but where no ring is aromatic.

[26] The term "carbocyclyl" refers to a radical of a carbocyclic ring system as defined above. Representative carbocyclyl groups include cycloalkyl groups (e.g., cyclopentyl, cyclobutyl, cyclopentyl, cyclohexyl and the like), and cycloalkenyl groups (e.g., cyclopentenyl, cyclohexenyl, cyclopentadienyl, and the like).

[27] The term "aromatic ring system" is art-recognized and refers to a monocyclic, bicyclic or polycyclic hydrocarbon ring system, wherein at least one ring is aromatic.

[28] The term "aryl" refers to a radical of an aromatic ring system. Representative aryl groups include fully aromatic ring systems, such as phenyl, naphthyl, and anthracenyl, and ring systems where an aromatic carbon ring is fused to one or more non-aromatic carbon rings, such as indanyl, phthalimidyl, naphthimidyl, or tetrahydronaphthyl, and the like.

[29] The term "heteroaromatic ring system" is art-recognized and refers to monocyclic, bicyclic or polycyclic ring system wherein at least one ring is both aromatic and comprises a heteroatom; and wherein no other rings are heterocyclyl (as defined below). In certain instances, a ring which is aromatic and comprises a heteroatom contains 1, 2, 3, or 4 independently selected ring heteroatoms in such ring.

[30] The term "heteroaryl" refers to a radical of a heteroaromatic ring system. Representative heteroaryl groups include ring systems where (i) each ring comprises a heteroatom and is aromatic, e.g., imidazolyl, oxazolyl, thiazolyl, triazolyl, pyrrolyl, furanyl, thiophenyl pyrazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, indolizinyl, purinyl, naphthyridinyl, and pteridinyl; (ii) each ring is aromatic or carbocyclyl, at least one aromatic ring comprises a heteroatom and at least one other ring is a hydrocarbon ring or e.g., indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, pyrido[2,3-b]-1,4-oxazin-3(4H)-one, 5,6,7,8-tetrahydroquinolinyl and 5,6,7,8-tetrahydroisoquinolinyl; and (iii) each ring is aromatic or carbocyclyl, and at least one aromatic ring shares a bridgehead heteroatom with another aromatic ring, e.g., 4H-quinolizinyl. In certain embodiments, the heteroaryl is a monocyclic or bicyclic ring, wherein each of said rings contains 5 or 6 ring atoms where 1, 2, 3, or 4 of said ring atoms are a heteroatom independently selected from N, O, and S.

[31] The term "heterocyclic ring system" refers to monocyclic, bicyclic and polycyclic ring systems where at least one ring is saturated or partially unsaturated (but not aromatic) and comprises a heteroatom. A heterocyclic ring system can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be optionally substituted.

[32] The term "heterocyclyl" refers to a radical of a heterocyclic ring system. Representative heterocyclyls include ring systems in which (i) every ring is non-aromatic and at least one ring comprises a heteroatom, e.g., tetrahydrofuranyl, tetrahydrothienyl, pyrrolidinyl, pyrrolidonyl, piperidinyl, pyrrolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, and quinuclidinyl; (ii) at least one ring is non-aromatic and comprises a heteroatom and at least one other ring is an aromatic carbon ring, e.g., 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl; and (iii) at least one ring is non-aromatic and comprises a heteroatom and at least one other ring is aromatic and comprises a heteroatom, e.g., 3,4-dihydro-1H-pyrano[4,3-c]pyridine, and 1,2,3,4-tetrahydro-2,6-naphthyridine. In certain embodiments, the heterocyclyl is a monocyclic or bicyclic ring, wherein each of said rings contains 3-7 ring atoms where 1, 2, 3, or 4 of said ring atoms are a heteroatom independently selected from N, O, and S.

[33] The term "saturated heterocyclyl" refers to a radical of heterocyclic ring system wherein every ring is saturated, e.g., tetrahydrofuran, tetrahydro-2H-pyran, pyrrolidine, piperidine and piperazine.

[34] "Partially unsaturated" refers to a group that includes at least one double or triple bond. A "partially unsaturated" ring system is further intended to encompass rings having multiple sites of unsaturation, but is not intended to include aromatic groups (*e.g.,* aryl or heteroaryl groups) as herein defined. Likewise, "saturated" refers to a group that does not contain a double or triple bond, *i.e.*, contains all single bonds.

[35] As described herein, compounds of the invention may contain "optionally substituted" moieties. In general, the term "substituted", whether preceded by the term "optionally" or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an "optionally substituted" group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at each position. Combinations of substituents envisioned under this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable", as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production,

detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

[36] Suitable monovalent substituents on a substitutable carbon atom of an "optionally substituted" group (such as an alkyl, alkenyl, alkynyl, alkylene, alkenylene, alkynylene or the carbon atom of a carbocyclyl, aryl, heterocyclyl or heteroaryl) are independently deuterium; halogen; $-(CH_2)_{0-4}R°$; $-(CH_2)_{0-4}OR°$; $-O-(CH_2)_{0-4}C(O)OR°$; $-(CH_2)_{0-4}CH(OR°)_2$; $-(CH_2)_{0-4}SR°$; $-(CH_2)_{0-4}Ph$ (where "Ph" is phenyl), which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R°; -CH=CHPh, which may be substituted with -R°; $-NO_2$; -CN; $-N_3$; $-(CH_2)_{0-4}N(R°)_2$; $-(CH_2)_{0-4}N(R°)C(O)R°$; $-N(R°)C(S)R°$; $-(CH_2)_{0-4}N(R°)C(O)NR°_2$; $-N(R°)C(S)NR°_2$; $-(CH_2)_{0-4}N(R°)C(O)OR°$; $-N(R°)N(R°)C(O)R°$; $-N(R°)N(R°)C(O)NR°_2$; $-N(R°)N(R°)C(O)OR°$; $-(CH_2)_{0-4}C(O)R°$; $-C(S)R°$; $-(CH_2)_{0-4}C(O)OR°$; $-(CH_2)_{0-4}C(O)SR°$; $-(CH_2)_{0-4}C(O)OSiR°_3$; $-(CH_2)_{0-4}-C(O)-N(R^o)-S(O)_2-R^o$, $-(CH_2)_{0-4}OC(O)R°$; $-OC(O)(CH_2)_{0-4}SR°$-, $-SC(S)SR°$; $-(CH_2)_{0-4}SC(O)R°$; $-(CH_2)_{0-4}C(O)NR°_2$; $-C(S)NR°_2$; $-C(S)SR°$; $-(CH_2)_{0-4}OC(O)NR°_2$; $-C(O)N(OR°)R°$; $-C(O)C(O)R°$; $-C(O)CH_2C(O)R°$; $-C(NOR°)R°$; $-(CH_2)_{0-4}SSR°$; $-(CH_2)_{0-4}S(O)_2R°$; $-(CH_2)_{0-4}S(O)_2OR°$; $-(CH_2)_{0-4}OS(O)_2R°$; $-S(O)_2NR°_2$; $-(CH_2)_{0-4}S(O)R°$; $-N(R°)S(O)_2NR°_2$; $-N(R°)S(O)_2R°$; $-N(OR°)R°$; $-C(NH)NR°_2$; $-P(O)_2R°$; $-P(O)R°_2$; $-OP(O)R°_2$; $-OP(O)(OR°)_2$; $-SiR°_3$; $-(C_{1-4}$ straight or branched alkylene$)O-N(R°)_2$; or $-(C_{1-4}$ straight or branched alkylene$)C(O)O-N(R°)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, deuterium, C_{1-6} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R°, taken together with their intervening atom(s), form a 3-12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

[37] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently deuterium, halogen, $-(CH_2)_{0-2}R^•$, -(haloR$^•$), $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^•$, $-(CH_2)_{0-2}CH(OR^•)_2$; -O(haloR$^•$), -CN, $-N_3$, $-(CH_2)_{0-2}C(O)R^•$, $-(CH_2)_{0-2}C(O)OH$, $-(CH_2)_{0-2}C(O)OR^•$, $-(CH_2)_{0-2}SR^•$, $-(CH_2)_{0-2}SH$, $-(CH_2)_{0-2}NH_2$, $-(CH_2)_{0-2}NHR^•$, $-(CH_2)_{0-2}NR^•_2$, $-NO_2$, $-SiR^•_3$, $-OSiR^•_3$, $-C(O)SR^•$, $-(C_{1-4}$ straight

or branched alkylene)C(O)OR•, or -SSR• wherein each R• is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of R° include =O and =S.

[38] Suitable divalent substituents on a saturated carbon atom of an "optionally substituted" group include the following: =O, =S, $=NNR^*_2$, $=NNHC(O)R^*$, $=NNHC(O)OR^*$, $=NNHS(O)_2R^*$, $=NR^*$, $=NOR^*$, $-O(C(R^*_2))_{2-3}O-$, or $-S(C(R^*_2))_{2-3}S-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an "optionally substituted" group include: $-O(CR^*_2)_{2-3}O-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[39] Suitable substituents on the aliphatic group of R^* include deuterium, halogen, $-R^•$, $-(haloR^•)$, -OH, $-OR^•$, $-O(haloR^•)$, -CN, -C(O)OH, $-C(O)OR^•$, $-NH_2$, $-NHR^•$, $-NR^•_2$, or $-NO_2$, wherein each $R^•$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[40] Suitable substituents on a substitutable nitrogen of an "optionally substituted" group include $-R^†$, $-NR^†_2$, $-C(O)R^†$, $-C(O)OR^†$, $-C(O)C(O)R^†$, $-C(O)CH_2C(O)R^†$, $-S(O)_2R^†$, $-S(O)_2NR^†_2$, $-C(S)NR^†_2$, $-C(NH)NR^†_2$, or $-N(R^†)S(O)_2R^†$; wherein each $R^†$ is independently hydrogen, C_{1-6} aliphatic which may be substituted as defined below, unsubstituted -OPh, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of $R^†$, taken together with their intervening atom(s) form an unsubstituted 3-12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[41] Suitable substituents on the aliphatic group of $R^{\dagger}$ are independently deuterium, halogen, $-R^{\bullet}$, -(halo$R^{\bullet}$), -OH, $-OR^{\bullet}$, -O(halo$R^{\bullet}$), -CN, -C(O)OH, $-C(O)OR^{\bullet}$, $-NH_2$, $-NHR^{\bullet}$, $-NR^{\bullet}_2$, or $-NO_2$, wherein each $R^{\bullet}$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4}aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

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

[43] The term "one or more methylene units of the alkylene, alkenylene or alkynylene is optionally replaced with -O-, -S-, $-S(=O)_2$, or $-NR^X-$" as used herein means that none, one, more than one, or all of the methylene units present may be so replaced. Thus, for example, the moieties, -O-, -S-, and $-NR^X-$ are included in this definition because in each case they represent a C_1 alkylene (i.e., methylene) replaced with -O-, -S-, or $-NR^X-$, respectively.

[44] It should also be understood that reference to a variable or subvariable in Formula I (e.g., R^2, R^4 or R^5) being "an optionally substituted C_1-C_4 alkylene, and an optionally substituted C_2-C_4 alkenylene or alkynylene, wherein: one or more methylene units of the alkylene, alkenylene or alkynylene other than a methylene unit bound to a nitrogen atom is optionally and independently replaced with -O-, -S-, $-N(R^6)-$, or $-S(=O)_2-$" is only intended to encompass chemically stable combinations of optionally substitutions and replacements.

[45] As used herein, the term "leaving group" is given its ordinary meaning in the art of synthetic organic chemistry and refers to an atom or a group capable of being displaced by a nucleophile. Examples of suitable leaving groups include, but are not limited to, halogen (such as F, Cl, Br, or I (iodine)), alkoxycarbonyloxy, aryloxycarbonyloxy, alkanesulfonyloxy, arenesulfonyloxy, alkyl-carbonyloxy (*e.g.*, acetoxy), arylcarbonyloxy, aryloxy, methoxy, *N*,*O*-dimethylhydroxylamino, pixyl, and haloformates. In some cases, the leaving group is a sulfonic acid ester, such as toluenesulfonate (tosylate, –OTs), methanesulfonate (mesylate, –OMs), *p*-bromobenzenesulfonyloxy (brosylate, –OBs), or trifluoromethanesulfonate (triflate, –OTf). In some cases, the leaving group is a brosylate, such as *p*-bromobenzenesulfonyloxy. In some cases, the leaving group is a nosylate, such as 2-nitrobenzenesulfonyloxy. In some embodiments, the leaving group is a sulfonate-containing group. In some embodiments, the leaving group is a tosylate group. The leaving group may also be a phosphineoxide (*e.g.*, formed

during a Mitsunobu reaction) or an internal leaving group such as an epoxide or cyclic sulfate. Other non-limiting examples of leaving groups are water, ammonia, alcohols, ether moieties, thioether moieties, zinc halides, magnesium moieties, diazonium salts, and copper moieties.

[46] These and other exemplary substituents are described in more detail in the Detailed Description, Figures, Examples, and Claims. The invention is not intended to be limited in any manner by the above exemplary listing of substituents.

Other definitions

[47] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge *et al.*, describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1–19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other methods known in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}\ \text{alkyl})_4^-$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further

pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate.

[48] The term "solvate" refers to forms of the compound that are associated with a solvent, usually by a solvolysis reaction. This physical association may include hydrogen bonding. Conventional solvents include water, methanol, ethanol, acetic acid, DMSO, THF, diethyl ether, and the like. The compounds of Formula (**I**) may be prepared, *e.g.*, in crystalline form, and may be solvated. Suitable solvates include pharmaceutically acceptable solvates and further include both stoichiometric solvates and non-stoichiometric solvates. In certain instances, the solvate will be capable of isolation, for example, when one or more solvent molecules are incorporated in the crystal lattice of a crystalline solid. "Solvate" encompasses both solution-phase and isolable solvates. Representative solvates include hydrates, ethanolates, and methanolates.

[49] The term "hydrate" refers to a compound which is associated with water. Typically, the number of the water molecules contained in a hydrate of a compound is in a definite ratio to the number of the compound molecules in the hydrate. Therefore, a hydrate of a compound may be represented, for example, by the general formula $R \cdot x\ H_2O$, wherein R is the compound and wherein x is a number greater than 0. A given compound may form more than one type of hydrates, including, *e.g.*, monohydrates (x is 1), lower hydrates (x is a number greater than 0 and smaller than 1, *e.g.*, hemihydrates ($R \cdot 0.5\ H_2O$)), and polyhydrates (x is a number greater than 1, *e.g.*, dihydrates ($R \cdot 2\ H_2O$) and hexahydrates ($R \cdot 6\ H_2O$)).

[50] The term "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 phenylnitromethane that are likewise formed by treatment with acid or base.

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

[52] 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".

[53] 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".

[54] A "subject" to which administration is contemplated includes, but is not limited to, humans (*i.e.*, a male or female of any age group, *e.g.*, a pediatric subject (*e.g.*, infant, child, adolescent) or adult subject (*e.g.*, young adult, middle–aged adult, or senior adult)) and/or other non–human animals, for example, mammals (*e.g.*, primates (*e.g.*, cynomolgus monkeys, rhesus monkeys); commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs) and birds (*e.g.*, commercially relevant birds such as chickens, ducks, geese, and/or turkeys). In certain embodiments, the animal is a mammal. The animal may be a male or female and at any stage of development. A non–human animal may be a transgenic animal.

[55] The terms "administer," "administering," or "administration," as used herein refers to implanting, absorbing, ingesting, injecting, inhaling, or otherwise introducing an inventive compound, or a pharmaceutical composition thereof.

[56] As used herein, the terms "treatment," "treat," and "treating" refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a "pathological condition" (*e.g.*, a disease, disorder, or condition, or one or more signs or symptoms thereof) described herein. In some embodiments, "treatment," "treat," and "treating" require that signs or symptoms of the disease disorder or condition have developed or have been observed. In other embodiments, treatment may be administered in the absence of signs or symptoms of the disease or condition. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (*e.g.*, in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved, for example, to delay or prevent recurrence.

[57] As used herein, the terms "condition," "disease," and "disorder" are used interchangeably.

[58] An "effective amount" of a compound of Formula (**I**) refers to an amount sufficient to elicit the desired biological response, *i.e.*, treating the condition. As will be appreciated by those of ordinary skill in this art, the effective amount of a compound of Formula (**I**) may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the condition being treated, the mode of administration, and the age and health of the subject. An effective amount encompasses therapeutic and prophylactic treatment. For example, in treating cancer, an effective amount of an inventive compound may reduce the tumor burden or stop the growth or spread of a tumor.

[59] A "therapeutically effective amount" of a compound of Formula (**I**) is an amount sufficient to provide a therapeutic benefit in the treatment of a condition or to delay or minimize one or more symptoms associated with the condition. In some embodiments, a therapeutically effective amount is an amount sufficient to provide a therapeutic benefit in the treatment of a condition or to minimize one or more symptoms associated with the condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment of the condition. The term "therapeutically effective amount" can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of the condition, or enhances the therapeutic efficacy of another therapeutic agent.

[60] A "prophylactically effective amount" of a compound of Formula (**I**) is an amount sufficient to prevent a condition, or one or more symptoms associated with the condition or prevent its recurrence. A prophylactically effective amount of a compound means an amount of a therapeutic agent, alone or in combination with other agents, which provides a prophylactic benefit in the prevention of the condition. The term "prophylactically effective amount" can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent.

[61] A "proliferative disease" refers to a disease that occurs due to abnormal growth or extension by the multiplication of cells (Walker, *Cambridge Dictionary of Biology*; Cambridge University Press: Cambridge, UK, 1990). A proliferative disease may be associated with: 1) the pathological proliferation of normally quiescent cells; 2) the pathological migration of cells from

their normal location (*e.g.*, metastasis of neoplastic cells); 3) the pathological expression of proteolytic enzymes such as the matrix metalloproteinases (*e.g.*, collagenases, gelatinases, and elastases); or 4) the pathological angiogenesis as in proliferative retinopathy and tumor metastasis. Exemplary proliferative diseases include cancers (*i.e.*, "malignant neoplasms"), benign neoplasms, angiogenesis, inflammatory diseases, autoinflammatory diseases, and autoimmune diseases.

[62] The terms "neoplasm" and "tumor" are used herein interchangeably and refer to an abnormal mass of tissue wherein the growth of the mass surpasses and is not coordinated with the growth of a normal tissue. A neoplasm or tumor may be "benign" or "malignant," depending on the following characteristics: degree of cellular differentiation (including morphology and functionality), rate of growth, local invasion, and metastasis. A "benign neoplasm" is generally well differentiated, has characteristically slower growth than a malignant neoplasm, and remains localized to the site of origin. In addition, a benign neoplasm does not have the capacity to infiltrate, invade, or metastasize to distant sites. Exemplary benign neoplasms include, but are not limited to, lipoma, chondroma, adenomas, acrochordon, senile angiomas, seborrheic keratoses, lentigos, and sebaceous hyperplasias. In some cases, certain "benign" tumors may later give rise to malignant neoplasms, which may result from additional genetic changes in a subpopulation of the tumor's neoplastic cells, and these tumors are referred to as "pre-malignant neoplasms." An exemplary pre-malignant neoplasm is a teratoma. In contrast, a "malignant neoplasm" is generally poorly differentiated (anaplasia) and has characteristically rapid growth accompanied by progressive infiltration, invasion, and destruction of the surrounding tissue. Furthermore, a malignant neoplasm generally has the capacity to metastasize to distant sites.

[63] As used herein, the term "cancer" refers to a malignant neoplasm (*Stedman's Medical Dictionary*, 25th ed.; Hensyl ed.; Williams & Wilkins: Philadelphia, 1990). Exemplary cancers include, but are not limited to, acoustic neuroma; adenocarcinoma; adrenal gland cancer; anal cancer; angiosarcoma (*e.g.,* lymphangiosarcoma, lymphangioendotheliosarcoma, hemangiosarcoma); appendix cancer; benign monoclonal gammopathy; biliary cancer (*e.g.,* cholangiocarcinoma); bladder cancer; breast cancer (*e.g.,* adenocarcinoma of the breast, papillary carcinoma of the breast, mammary cancer, medullary carcinoma of the breast); brain cancer (*e.g.,* meningioma, glioblastomas, glioma (*e.g.,* astrocytoma, oligodendroglioma), medulloblastoma); bronchus cancer; carcinoid tumor; cervical cancer (*e.g.,* cervical adenocarcinoma);

choriocarcinoma; chordoma; craniopharyngioma; colorectal cancer (*e.g.,* colon cancer, rectal cancer, colorectal adenocarcinoma); connective tissue cancer; epithelial carcinoma; ependymoma; endotheliosarcoma (*e.g.,* Kaposi's sarcoma, multiple idiopathic hemorrhagic sarcoma); endometrial cancer (*e.g.,* uterine cancer, uterine sarcoma); esophageal cancer (*e.g.,* adenocarcinoma of the esophagus, Barrett's adenocarcinoma); Ewing's sarcoma; eye cancer (*e.g.,* intraocular melanoma, retinoblastoma); familiar hypereosinophilia; gall bladder cancer; gastric cancer (*e.g.,* stomach adenocarcinoma); gastrointestinal stromal tumor (GIST); germ cell cancer; head and neck cancer (*e.g.,* head and neck squamous cell carcinoma, oral cancer (*e.g.,* oral squamous cell carcinoma), throat cancer (*e.g.,* laryngeal cancer, pharyngeal cancer, nasopharyngeal cancer, oropharyngeal cancer)); hematopoietic cancers (*e.g.,* leukemia such as acute lymphocytic leukemia (ALL) (*e.g.,* B-cell ALL, T-cell ALL), acute myelocytic leukemia (AML) (*e.g.,* B-cell AML, T-cell AML), chronic myelocytic leukemia (CML) (*e.g.,* B-cell CML, T-cell CML), and chronic lymphocytic leukemia (CLL) (*e.g.,* B-cell CLL, T-cell CLL)); lymphoma such as Hodgkin lymphoma (HL) (*e.g.,* B-cell HL, T-cell HL) and non-Hodgkin lymphoma (NHL) (*e.g.*, B-cell NHL such as diffuse large cell lymphoma (DLCL) (*e.g.,* diffuse large B-cell lymphoma), follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), marginal zone B-cell lymphomas (*e.g.,* mucosa-associated lymphoid tissue (MALT) lymphomas, nodal marginal zone B-cell lymphoma, splenic marginal zone B-cell lymphoma), primary mediastinal B-cell lymphoma, Burkitt lymphoma, lymphoplasmacytic lymphoma (*i.e.,* Waldenström's macroglobulinemia), hairy cell leukemia (HCL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma and primary central nervous system (CNS) lymphoma; and T-cell NHL such as precursor T-lymphoblastic lymphoma/leukemia, peripheral T-cell lymphoma (PTCL) (*e.g.,* cutaneous T-cell lymphoma (CTCL) (*e.g.,* mycosis fungoides, Sezary syndrome), angioimmunoblastic T-cell lymphoma, extranodal natural killer T-cell lymphoma, enteropathy type T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, and anaplastic large cell lymphoma); a mixture of one or more leukemia/lymphoma as described above; and multiple myeloma (MM)), heavy chain disease (*e.g.*, alpha chain disease, gamma chain disease, mu chain disease); hemangioblastoma; hypopharynx cancer; inflammatory myofibroblastic tumors; immunocytic amyloidosis; kidney cancer (*e.g.,* nephroblastoma *a.k.a.* Wilms' tumor, renal cell carcinoma); liver cancer (*e.g.,* hepatocellular cancer (HCC), malignant hepatoma); lung cancer (*e.g.,*

bronchogenic carcinoma, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), adenocarcinoma of the lung); leiomyosarcoma (LMS); mastocytosis (*e.g.,* systemic mastocytosis); muscle cancer; myelodysplastic syndrome (MDS); mesothelioma; myeloproliferative disorder (MPD) (*e.g.,* polycythemia vera (PV), essential thrombocytosis (ET), agnogenic myeloid metaplasia (AMM) *a.k.a.* myelofibrosis (MF), chronic idiopathic myelofibrosis, chronic myelocytic leukemia (CML), chronic neutrophilic leukemia (CNL), hypereosinophilic syndrome (HES)); neuroblastoma; neurofibroma (*e.g.,* neurofibromatosis (NF) type 1 or type 2, schwannomatosis); neuroendocrine cancer (*e.g.,* gastroenteropancreatic neuroendocrine tumor (GEP-NET), carcinoid tumor); osteosarcoma (*e.g.,* bone cancer); ovarian cancer (*e.g.,* cystadenocarcinoma, ovarian embryonal carcinoma, ovarian adenocarcinoma); papillary adenocarcinoma; pancreatic cancer (*e.g.,* pancreatic adenocarcinoma, intraductal papillary mucinous neoplasm (IPMN), Islet cell tumors); penile cancer (*e.g.,* Paget's disease of the penis and scrotum); pinealoma; primitive neuroectodermal tumor (PNT); plasma cell neoplasia; paraneoplastic syndromes; intraepithelial neoplasms; prostate cancer (*e.g.,* prostate adenocarcinoma); rectal cancer; rhabdomyosarcoma; salivary gland cancer; skin cancer (*e.g.,* squamous cell carcinoma (SCC), keratoacanthoma (KA), melanoma, basal cell carcinoma (BCC)); small bowel cancer (*e.g.,* appendix cancer); soft tissue sarcoma (*e.g.,* malignant fibrous histiocytoma (MFH), liposarcoma, malignant peripheral nerve sheath tumor (MPNST), chondrosarcoma, fibrosarcoma, myxosarcoma); sebaceous gland carcinoma; small intestine cancer; sweat gland carcinoma; synovioma; testicular cancer (*e.g.,* seminoma, testicular embryonal carcinoma); thyroid cancer (*e.g.,* papillary carcinoma of the thyroid, papillary thyroid carcinoma (PTC), medullary thyroid cancer); urethral cancer; vaginal cancer; and vulvar cancer (*e.g.,* Paget's disease of the vulva).

[64] The term "angiogenesis" refers to the formation and the growth of new blood vessels. Normal angiogenesis occurs in the healthy body of a subject for healing wounds and for restoring blood flow to tissues after injury. The healthy body controls angiogenesis through a number of means, *e.g.*, angiogenesis-stimulating growth factors and angiogenesis inhibitors. Many disease states, such as cancer, diabetic blindness, age-related macular degeneration, rheumatoid arthritis, and psoriasis, are characterized by abnormal (*i.e.*, increased or excessive) angiogenesis. Abnormal angiogenesis refers to angiogenesis greater than that in a normal body, especially angiogenesis in an adult not related to normal angiogenesis (*e.g.*, menstruation or

wound healing). Abnormal angiogenesis can provide new blood vessels that feed diseased tissues and/or destroy normal tissues, and in the case of cancer, the new vessels can allow tumor cells to escape into the circulation and lodge in other organs (tumor metastases).

[65] As used herein, an "inflammatory disease" refers to a disease caused by, resulting from, or resulting in inflammation. The term "inflammatory disease" may also refer to a dysregulated inflammatory reaction that causes an exaggerated response by macrophages, granulocytes, and/or T-lymphocytes leading to abnormal tissue damage and/or cell death. An inflammatory disease can be either an acute or chronic inflammatory condition and can result from infections or non-infectious causes. Inflammatory diseases include, without limitation, atherosclerosis, arteriosclerosis, autoimmune disorders, multiple sclerosis, systemic lupus erythematosus, polymyalgia rheumatica (PMR), gouty arthritis, degenerative arthritis, tendonitis, bursitis, psoriasis, cystic fibrosis, arthrosteitis, rheumatoid arthritis, inflammatory arthritis, Sjogren's syndrome, giant cell arteritis, progressive systemic sclerosis (scleroderma), ankylosing spondylitis, polymyositis, dermatomyositis, pemphigus, pemphigoid, diabetes (*e.g.*, Type I), myasthenia gravis, Hashimoto's thyroiditis, Graves' disease, Goodpasture's disease, mixed connective tissue disease, sclerosing cholangitis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, pernicious anemia, inflammatory dermatoses, usual interstitial pneumonitis (UIP), asbestosis, silicosis, bronchiectasis, berylliosis, talcosis, pneumoconiosis, sarcoidosis, desquamative interstitial pneumonia, lymphoid interstitial pneumonia, giant cell interstitial pneumonia, cellular interstitial pneumonia, extrinsic allergic alveolitis, Wegener's granulomatosis and related forms of angiitis (temporal arteritis and polyarteritis nodosa), inflammatory dermatoses, hepatitis, delayed-type hypersensitivity reactions (*e.g.*, poison ivy dermatitis), pneumonia, respiratory tract inflammation, Adult Respiratory Distress Syndrome (ARDS), encephalitis, immediate hypersensitivity reactions, asthma, hayfever, allergies, acute anaphylaxis, rheumatic fever, glomerulonephritis, pyelonephritis, cellulitis, cystitis, chronic cholecystitis, ischemia (ischemic injury), reperfusion injury, allograft rejection, host-versus-graft rejection, appendicitis, arteritis, blepharitis, bronchiolitis, bronchitis, cervicitis, cholangitis, chorioamnionitis, conjunctivitis, dacryoadenitis, dermatomyositis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, gingivitis, ileitis, iritis, laryngitis, myelitis, myocarditis, nephritis, omphalitis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, pharyngitis, pleuritis, phlebitis,

pneumonitis, proctitis, prostatitis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, testitis, tonsillitis, urethritis, urocystitis, uveitis, vaginitis, vasculitis, vulvitis, vulvovaginitis, angitis, chronic bronchitis, osteomyelitis, optic neuritis, temporal arteritis, transverse myelitis, necrotizing fasciitis, and necrotizing enterocolitis.

[66] As used herein, an "autoimmune disease" refers to a disease arising from an inappropriate immune response of the body of a subject against substances and tissues normally present in the body. In other words, the immune system mistakes some part of the body as a pathogen and attacks its own cells. This may be restricted to certain organs (*e.g.*, in autoimmune thyroiditis) or involve a particular tissue in different places (*e.g.*, Goodpasture's disease which may affect the basement membrane in both the lung and kidney). The treatment of autoimmune diseases is typically with immunosuppression, *e.g.*, medications which decrease the immune response. Exemplary autoimmune diseases include, but are not limited to, glomerulonephritis, Goodpasture's syndrome, necrotizing vasculitis, lymphadenitis, peri-arteritis nodosa, systemic lupus erythematosis, rheumatoid, arthritis, psoriatic arthritis, systemic lupus erythematosis, psoriasis, ulcerative colitis, systemic sclerosis, dermatomyositis/polymyositis, anti-phospholipid antibody syndrome, scleroderma, pemphigus vulgaris, ANCA-associated vasculitis (*e.g.*, Wegener's granulomatosis, microscopic polyangiitis), uveitis, Sjogren's syndrome, Crohn's disease, Reiter's syndrome, ankylosing spondylitis, Lyme arthritis, Guillain-Barré syndrome, Hashimoto's thyroiditis, and cardiomyopathy.

[67] The term "autoinflammatory disease" refers to a category of diseases that are similar but different from autoimmune diseases. Autoinflammatory and autoimmune diseases share common characteristics in that both groups of disorders result from the immune system attacking a subject's own tissues and result in increased inflammation. In autoinflammatory diseases, a subject's innate immune system causes inflammation for unknown reasons. The innate immune system reacts even though it has never encountered autoantibodies or antigens in the subject. Autoinflammatory disorders are characterized by intense episodes of inflammation that result in such symptoms as fever, rash, or joint swelling. These diseases also carry the risk of amyloidosis, a potentially fatal buildup of a blood protein in vital organs. Autoinflammatory diseases include, but are not limited to, familial Mediterranean fever (FMF), neonatal onset multisystem inflammatory disease (NOMID), tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS), deficiency of the interleukin-1 receptor antagonist (DIRA), and

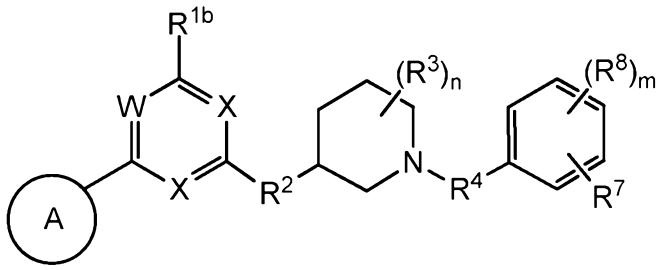
Behçet's disease.

[68] The term "biological sample" refers to any sample including tissue samples (such as tissue sections and needle biopsies of a tissue); cell samples (*e.g.*, cytological smears (such as Pap or blood smears) or samples of cells obtained by microdissection); samples of whole organisms (such as samples of yeasts or bacteria); or cell fractions, fragments or organelles (such as obtained by lysing cells and separating the components thereof by centrifugation or otherwise). Other examples of biological samples include blood, serum, urine, semen, fecal matter, cerebrospinal fluid, interstitial fluid, mucus, tears, sweat, pus, biopsied tissue (*e.g.*, obtained by a surgical biopsy or needle biopsy), nipple aspirates, milk, vaginal fluid, saliva, swabs (such as buccal swabs), or any material containing biomolecules that is derived from a first biological sample. Biological samples also include those biological samples that are transgenic, such as transgenic oocyte, sperm cell, blastocyst, embryo, fetus, donor cell, or cell nucleus.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS OF THE INVENTION

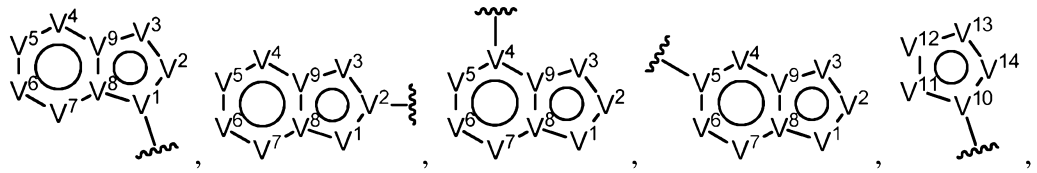
Compounds

[69] In one aspect of the present invention, provided are compounds of Formula (**I**):

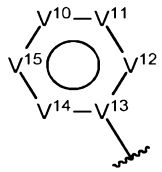


(**I**), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein:

ring A is an optionally substituted heteroaryl ring of any one of the Formulae (**i-1**)-(**i-6**):



(**i-1**) (**i-2**) (**i-3**) (**i-4**) (**i-5**)



(**i-6**), wherein:

each instance of V^1, V^2, V^3, V^4, V^5, V^6, V^7, V^8, V^9, V^{10}, V^{11}, V^{12}, V^{13}, V^{14} and V^{15} is independently O, S, N, $N(R^{A1})$, C, or $C(R^{A2})$;

each instance of R^{A1} is independently selected from hydrogen, deuterium, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

each instance of R^{A2} is independently selected from hydrogen, deuterium, halogen, -CN, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, $-OR^{A2a}$, $-N(R^{A2a})_2$, and $-SR^{A2a}$, wherein each occurrence of R^{A2a} is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or

any two R^{A1}, any two R^{A2}, or one R^{A1} and one R^{A2} are joined to form an optionally substituted carbocyclic, optionally substituted heterocyclic, optionally substituted aryl, or optionally substituted heteroaryl ring;

each X is independently selected from N and CH, wherein at least one X is N;

W is selected from N and $C(R^{1a})$;

each of R^{1a}, if present, and R^{1b} is independently selected from hydrogen, deuterium, halogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, -CN, $-OR^{B1a}$, $-N(R^{B1a})_2$, and $-SR^{B1a}$, wherein each occurrence of R^{B1a} is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or

R^{1a} and R^{1b} are joined to form an optionally substituted carbocyclic, optionally substituted heterocyclic, optionally substituted aryl, or optionally substituted heteroaryl ring;

R^2 is an optionally substituted C_1-C_4 alkylene or an optionally substituted C_2-C_4 alkenylene or alkynylene, wherein one or more methylene units of the alkylene, alkenylene or alkynylene are optionally and independently replaced with -O-, -S-, or -N(R^6)-;

each instance of R^3, if present, is independently selected from deuterium, halogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, -OR^{C1}, -$N(R^{C1})_2$, and -SR^{C1}, wherein each occurrence of R^{C1} is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or

two R^3 groups bound to the same ring carbon atom are taken together to form =O, or

two R^3 groups bound to the same or different ring carbon atoms are joined to form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl ring;

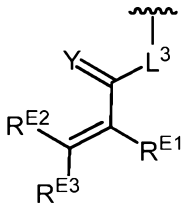
R^4 is selected from a bond, an optionally substituted C_1-C_4 alkylene, and an optionally substituted C_2-C_4 alkenylene or alkynylene, wherein:

one or more methylene units of the alkylene, alkenylene or alkynylene other than a methylene unit bound to a nitrogen atom is optionally and independently replaced with -O-, -S-, -N(R^6)-, or -$S(=O)_2$-, and

two substituents on either the same or adjacent carbon atoms in the alkylene, alkenylene or alkynylene are taken together to form an optionally substituted carbocyclic or optionally substituted heterocyclic ring;

each R^6 is independently selected from hydrogen, and -C_1-C_6 alkyl;

R^7 is any one of the Formulae (**ii-1**)-(**ii-20**):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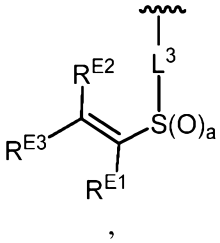
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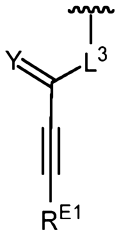
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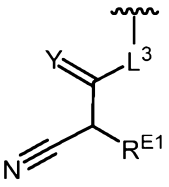
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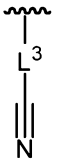
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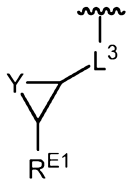
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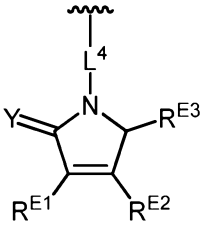
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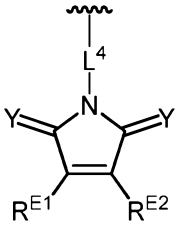
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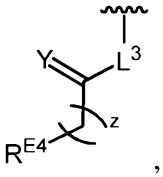
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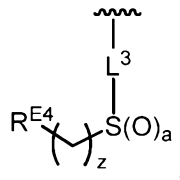
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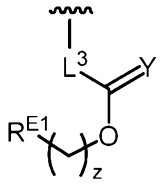
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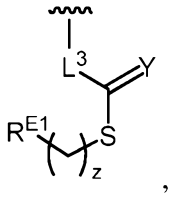
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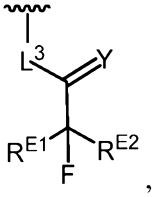
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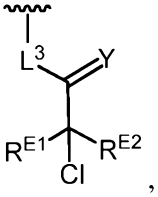
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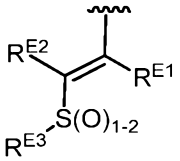
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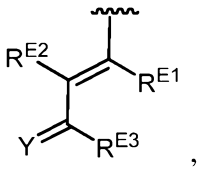
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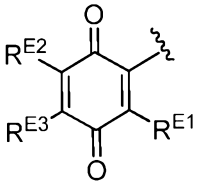
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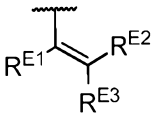
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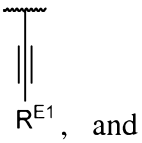
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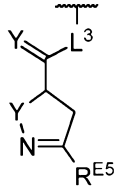

(ii-20)

wherein:

L^3 is a bond, an optionally substituted C_1-C_4 alkylene, or an optionally substituted C_2-C_4 alkenylene or alkynylene, wherein one or more methylene units of the alkylene, alkenylene or alkynylene are optionally and independently replaced with -O-, -S-, or -N(R^6)-;

L^4 is a bond, an optionally substituted C_1-C_4 alkylene, or an optionally substituted C_2-C_4 alkenylene or alkynylene;

R^{E1} is selected from the group consisting of hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally

substituted heteroaryl, –CN, $–CH_2OR^{E1a}$, $–CH_2N(R^{E1a})_2$, $–CH_2SR^{E1a}$, $–OR^{E1a}$, $–N(R^{E1a})_2$, $–Si(R^{E1a})_3$, and $–SR^{E1a}$, wherein each occurrence of R^{E1a} is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or two R^{E1a} groups are joined to form an optionally substituted heterocyclic ring;

R^{E2} is selected from the group consisting of hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, –CN, $–CH_2OR^{E2a}$, $–CH_2N(R^{E2a})_2$, $–CH_2SR^{E2a}$, $–OR^{E2a}$, $–N(R^{E2a})_2$, and $–SR^{E2a}$, wherein each occurrence of R^{E2a} is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or two R^{E2a} groups are joined to form an optionally substituted heterocyclic ring;

R^{E3} is selected from the group consisting of hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, –CN, $–CH_2OR^{E3a}$, $–CH_2N(R^{E3a})_2$, $–CH_2SR^{E3a}$, $–OR^{E3a}$, $–N(R^{E3a})_2$, and $–SR^{E3a}$, wherein each occurrence of R^{E3a} is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or two R^{E3a} groups are joined to form an optionally substituted heterocyclic ring;

optionally R^{E1} and R^{E3}, or R^{E2} and R^{E3}, or R^{E1} and R^{E2} are joined to form an optionally substituted carbocyclic or optionally substituted heterocyclic ring;

R^{E4} is a leaving group;

R^{E5} is selected from the group consisting of hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, –CN, $–CH_2OR^{E5a}$, $–CH_2N(R^{E5a})_2$, $–CH_2SR^{E5a}$, $–OR^{E5a}$, $–N(R^{E5a})_2$, and –

SR^{E5a}, wherein each occurrence of R^{E5a} is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or two R^{E5a} groups are joined to form an optionally substituted heterocyclic ring;

Y is O, S, or NR^{E6}, wherein R^{E6} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

a is 1 or 2;

z is 0, 1, 2, 3, 4, 5, or 6.

each instance of R^8, if present, is independently selected from deuterium, halogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, $-OR^{D1}$, $-N(R^{D1})_2$, and $-SR^{D1}$, wherein each occurrence of R^{D1} is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, and optionally substituted aryl, optionally substituted heteroaryl, or

two R^8 groups are joined to form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl ring;

m is 0, 1, 2, 3 or 4; and

n is 0, 1, 2, 3, 4, 5 or 6.

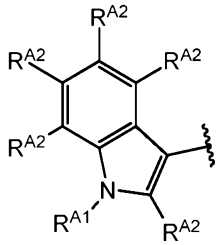
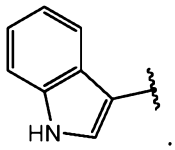
[70] In certain embodiments, provided in the present invention are compounds of Formula **(I)**, and pharmaceutically acceptable salts thereof.

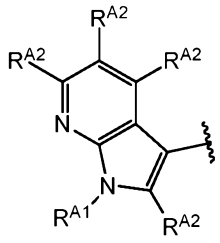
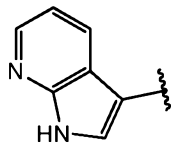
[71] In certain embodiments, no more than three of V^1, V^2, V^3, V^4, V^5, V^6, V^7, V^8, and V^9 are each independently selected from the group consisting of O, S, N, and $N(R^{A1})$.

[72] In certain embodiments, two of V^1, V^2, V^3, V^4, V^5, V^6, V^7, V^8, and V^9 are each independently selected from the group consisting of N and $N(R^{A1})$ and the rest of V^1, V^2, V^3, V^4, V^5, V^6, V^7, V^8, and V^9 are each independently C or $C(R^{A2})$. In one aspect of these embodiments, one of V^1, V^2, or V^3 is $N(R^{A1})$; one of V^1, V^2, or V^3 is C; one of V^1, V^2, and V^3 is $C(R^{A2})$; one of V^4, V^5, V^6, or V^7 is N, the rest of V^4, V^5, V^6, and V^7 are $C(R^{A2})$; and V^8 and V^9 are C.

[73] In certain embodiments, one of V^1, V^2, V^3, V^4, V^5, V^6, V^7, V^8, and V^9 is N or $N(R^{A1})$ and

the rest of V^1, V^2, V^3, V^4, V^5, V^6, V^7, V^8, and V^9 are each independently C or C(R^{A2}). In one aspect of these embodiments, one of V^1, V^2, or V^3 is N(R^{A1}); one of V^1, V^2, or V^3 is C; one of V^1, V^2, and V^3 is C(R^{A2}); each of V^4, V^5, V^6, and V^7 are C(R^{A2}); and V^8 and V^9 are C.

[74] In certain embodiments ring A is  . In one aspect of these embodiments, ring A is  .

[75] In certain embodiments ring A is  . In one aspect of these embodiments, ring A is  .

[76] In certain embodiments, each R^{A1} is independently selected from hydrogen, or C_{1-6} alkyl. In certain embodiments, all instances of R^{A1} are hydrogen.

[77] In certain embodiments, each R^{A2} is independently selected from hydrogen, halogen, and optionally substituted C_1-C_6 alkyl, and optionally substituted aryl. In one aspect of these embodiments, all instances of R^{A2} are hydrogen.

[78] In certain embodiments, W is N.

[79] In certain embodiments, W is C(R^{1a}).

[80] In certain embodiments, each X is nitrogen. In one aspect of these embodiments, each X is nitrogen and W is C(R^{1a}).

[81] In certain embodiments, R^{1a} is selected from selected from hydrogen, halo, -OH, -C_1-C_3 alkyl, halo-substituted -C_1-C_3 alkyl, -O-C_1-C_3 alkyl, halo-substituted -O-C_1-C_3 alkyl, -CN, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, and C_3-C_6 cycloalkyl. In one aspect of these embodiments,

R^{1a} is selected from halo, -CN and C_1-C_3 alkyl. In a more specific aspect of these embodiments, R^{1a} is selected from chloro, -CN and -CH_3. In an even more specific aspect of these embodiments, R^{1a} is chloro.

[82] In certain embodiments, R^{1b} is selected from selected from hydrogen, halo, -OH, -C_1-C_3 alkyl, halo-substituted -C_1-C_3 alkyl, -O-C_1-C_3 alkyl, halo-substituted -O-C_1-C_3 alkyl, -CN, -NH_2, -NH(C_1-C_3 alkyl), and -N(C_1-C_3 alkyl)$_2$. In one aspect of these embodiments, R^{1b} is hydrogen.

[83] In certain embodiments, R^2 is selected from -NH-; -N(C_1-C_3 alkyl)-; -NH-CH_2- **; and C_1-C_2 alkylene optionally substituted with 1 to 4 substituents independently selected from halo, -OH, -C_1-C_3 alkyl, halo-substituted -C_1-C_3 alkyl, -O-C_1-C_3 alkyl, halo-substituted -O-C_1-C_3 alkyl, -CN, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, wherein "**" represents a portion of R^2 bound to piperidin-1,3-diyl. In a more specific aspect of these embodiments, R^2 is selected from -NH- and -NH-CH_2- **. In an even more specific aspect of these embodiments, R^2 is -NH-.

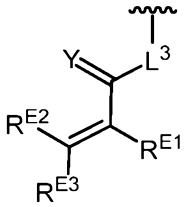
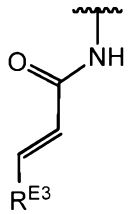
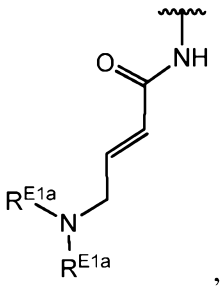
[84] In certain embodiments, R^4 is selected from -S(=O)$_2$-, or C_1-C_2 alkylene optionally substituted with 1 to 4 substituents independently selected from halo, =O, -OH, -C_1-C_3 alkyl, halo-substituted -C_1-C_3 alkyl, -O-C_1-C_3 alkyl, halo-substituted -O-C_1-C_3 alkyl, -CN, -NH_2, -NH(C_1-C_3 alkyl), and -N(C_1-C_3 alkyl)$_2$, wherein one methylene unit in the alkylene is optionally replaced with -N(R^6)-. In a more specific aspect of these embodiments, R^4 is -C(O)- or ††-C(O)-NH-, wherein "††" represents a portion of R^4 bound to piperidin-1,3-diyl. In another specific aspect of these embodiments, R^4 is –(CH_2)-.

[85] In certain embodiments, R^3 is absent (i.e., n is 0), or is selected from halo, -OH, -C_1-C_3 alkyl, halo-substituted -C_1-C_3 alkyl, -O-C_1-C_3 alkyl, halo-substituted -O-C_1-C_3 alkyl, -CN, -NH_2, -NH(C_1-C_3 alkyl), and -N(C_1-C_3 alkyl)$_2$, or two R^3 bound to the same ring carbon atom are taken together to form =O. In a more specific aspect, R^3 is absent (i.e., n is 0).

[86] In certain embodiments, each R^6 present in a compound of Formula (**I**) is selected from hydrogen and -CH_3. In a more specific aspect of these embodiments, each R^6 is hydrogen.

[87] In certain embodiments, R^7 is located *para* or *meta* to R^4. In certain embodiments, R^7 is located *para* to R^4. In one aspect of these embodiments, R^7 comprises L^3 and L^3 is -NR^{L3a}-. In a more specific aspect of these embodiments, R^7 comprises L^3 and L^3 is -NH-. In another aspect of these embodiments, R^7 comprises Y, and Y is =O. In still another aspect of these embodiments, R^7 comprises at least one of R^{E1}, R^{E2} and R^{E3} and one of the R^{E1}, R^{E2} or R^{E3} that is present is -$CH_2N(R^{E1a})_2$. In a more specific aspect of these embodiments, R^7 comprises at least

one of R^{E1}, R^{E2} and R^{E3}; one of the R^{E1}, R^{E2} or R^{E3} that is present is $-CH_2N(R^{E1a})_2$; and each R^{E1a} is independently an optionally substituted C_1-C_4 alkyl, or the two R^{E1a} are taken together with the nitrogen atom to which they are bound to form an optionally substituted heterocyclyl or an optionally substituted heteroaryl.

[88] In certain embodiments, R^7 is  (**ii-1**). In a more specific aspect of these embodiments, R^7 is  . In an even more specific aspect of these embodiments, R^7 is  , wherein each R^{E1a} is independently an optionally substituted C_1-C_4 alkyl, or the two R^{E1a} are taken together with the nitrogen atom to which they are bound to form an optionally substituted heterocyclyl or an optionally substituted heteroaryl. In a further more specific aspect of these embodiments, R^7 is *para* to R^4 and is selected from 4-dimethylaminobut-2-enamido, 4-morpholin-4-ylbut-2-enamido, 4-pyrrolidin-1-ylbut-2-enamido, 4-1H-imidazo-1-ylbut-2-enamido, 4-(4-methylpiperazin-1-yl)but-2-enamido, 4-(2-hydroxyethyl)(methyl)aminobut-2-enamido, 4-dimethylaminobut-2-enamido, 4-dimethylaminobut-2-enamido, 4-dimethylaminobut-2-enamido, and 4-dimethylaminobut-2-enamido. In an even more specific aspect of these embodiments, R^7 is *para* to R^4 and is 4-dimethylaminobut-2-enamido.

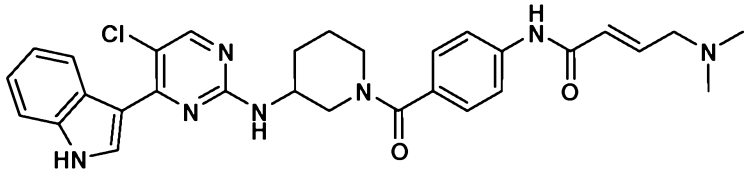
[89] In certain embodiments, m is 0 or 1; and the single R^8, if present, is selected C_1-C_4 alkyl and halogen. In a more specific aspect of these embodiments, R^8 is absent (i.e., m is 0).

[90] Although, as indicated above, various embodiments and aspects thereof for a variable in Formula (**I**) may be selected from a group of chemical moieties, the invention also encompasses

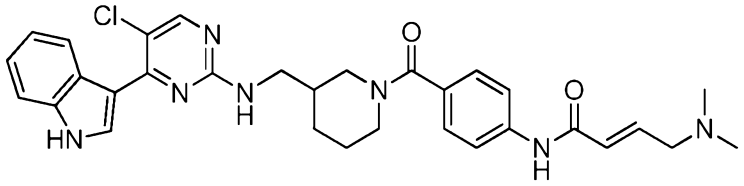
as further embodiments and aspects thereof situations where such variable is: a) selected from any subset of chemical moieties in such a group; and b) any single member of such a group.

[91] Although various embodiments and aspects thereof are set forth (or implied, as discussed in the preceding paragraph) individually for each variable in Formula (**I**) above, the invention encompasses all possible combinations of the different embodiments and aspects for each of the variables in Formula (**I**).

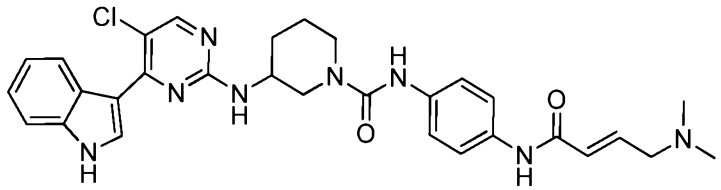
[92] In certain embodiments, the compound of Formula (**I**) is selected from:



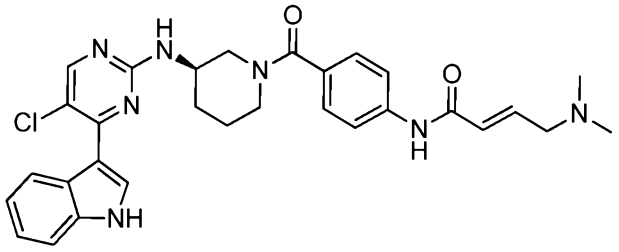
(Compound 100),



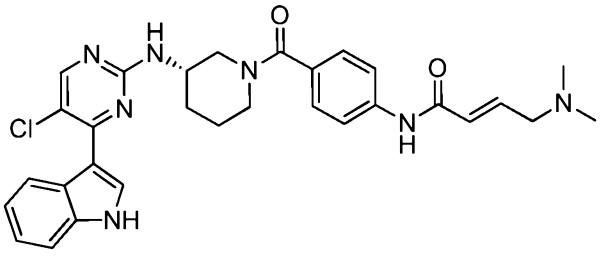
(Compound 101),



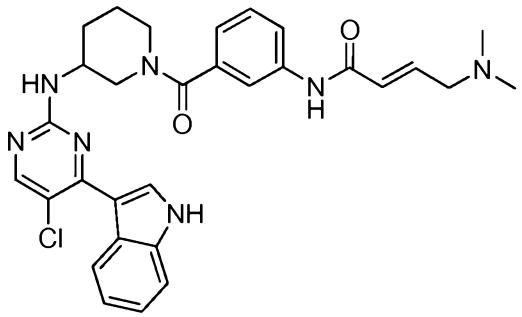
(Compound 102),



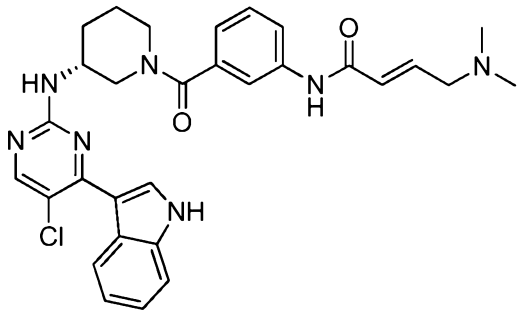
(Compound 103),



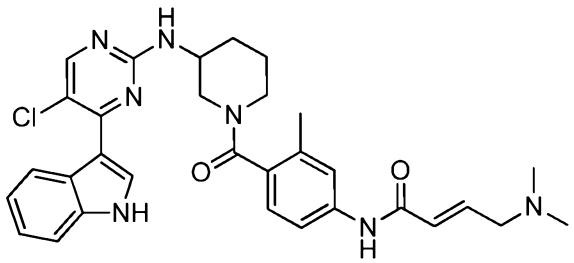
(Compound 104),



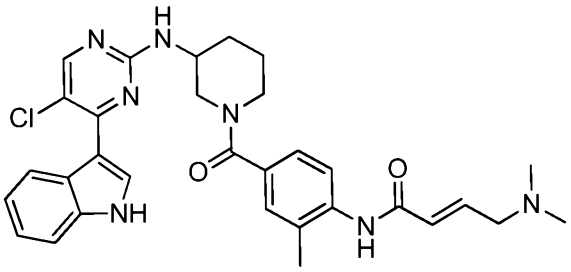
(Compound 105),



(Compound 106),



(Compound 107),



(Compound 108),

and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers, and

isotopically labeled derivatives of the foregoing.

Pharmaceutical Compositions, Kits, and Administration

[93] The present invention provides pharmaceutical compositions comprising a compound of Formula (**I**), *e.g.*, a compound of Formula (**I**), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer, or isotopically labeled derivative thereof, as described herein, and optionally a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical composition of the invention comprises a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable excipient. In certain embodiments, the compound of Formula (**I**), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer, or isotopically labeled derivative thereof, is provided in an effective amount in the pharmaceutical composition. In certain embodiments, the effective amount is a therapeutically effective amount. In certain embodiments, the effective amount is a prophylactically effective amount.

[94] Pharmaceutical compositions described herein can be prepared by any method known in the art of pharmacology. In general, such preparatory methods include the steps of bringing the compound of Formula (**I**) (the "active ingredient") into association with a carrier and/or one or more other accessory ingredients, and then, if necessary and/or desirable, shaping and/or packaging the product into a desired single- or multi-dose unit.

[95] Pharmaceutical compositions can be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a "unit dose" is a discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage.

[96] Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition of the invention will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. By way of example, the composition may comprise between 0.1% and 100% (w/w) active ingredient.

[97] The term "pharmaceutically acceptable excipient" refers to a non-toxic carrier, adjuvant,

diluent, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable excipients useful in the manufacture of the pharmaceutical compositions of the invention are any of those that are well known in the art of pharmaceutical formulation and include inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Pharmaceutically acceptable excipients useful in the manufacture of the pharmaceutical compositions of the invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[98] Compositions of the present invention may be administered orally, parenterally (including subcutaneous, intramuscular, intravenous and intradermal), by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. In some embodiments, provided compounds or compositions are administrable intravenously and/or orally.

[99] The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intraocular, intravitreal, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intraperitoneal intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, subcutaneously, intraperitoneally or intravenously. Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

[100] Pharmaceutically acceptable compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added. In some embodiments, a provided oral formulation is formulated for immediate release or sustained/delayed release. In some embodiments, the composition is suitable for buccal or sublingual administration, including tablets, lozenges and pastilles. A provided compound can also be in micro-encapsulated form.

[101] Alternatively, pharmaceutically acceptable compositions of this invention may be administered in the form of suppositories for rectal administration. Pharmaceutically acceptable compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

[102] Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

[103] For ophthalmic use, provided pharmaceutically acceptable compositions may be formulated as micronized suspensions or in an ointment such as petrolatum.

[104] Pharmaceutically acceptable compositions of this invention may also be administered by nasal aerosol or inhalation.

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

[106] Although the descriptions of pharmaceutical compositions provided herein are principally

directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to animals of all sorts. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with ordinary experimentation.

[107] Compounds provided herein are typically formulated in dosage unit form, e.g., single unit dosage form, for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of the compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular subject or organism will depend upon a variety of factors including the disease being treated and the severity of the disorder; the activity of the specific active ingredient employed; the specific composition employed; the age, body weight, general health, sex and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific active ingredient employed; the duration of the treatment; drugs used in combination or coincidental with the specific active ingredient employed; and like factors well known in the medical arts.

[108] The exact amount of a compound required to achieve an effective amount will vary from subject to subject, depending, for example, on species, age, and general condition of a subject, severity of the side effects or disorder, identity of the particular compound(s), mode of administration, and the like. The desired dosage can be delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, or every four weeks. In certain embodiments, the desired dosage can be delivered using multiple administrations (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations).

[109] In certain embodiments, an effective amount of a compound for administration one or more times a day to a 70 kg adult human may comprise about 0.0001 mg to about 3000 mg, about 0.0001 mg to about 2000 mg, about 0.0001 mg to about 1000 mg, about 0.001 mg to about 1000 mg, about 0.01 mg to about 1000 mg, about 0.1 mg to about 1000 mg, about 1 mg to about 1000 mg, about 1 mg to about 100 mg, about 10 mg to about 1000 mg, or about 100 mg to about 1000 mg, of a compound per unit dosage form.

[110] In certain embodiments, the compounds of Formula (**I**) may be at dosage levels sufficient to deliver from about 0.001 mg/kg to about 100 mg/kg, from about 0.01 mg/kg to about 50 mg/kg, preferably from about 0.1 mg/kg to about 40 mg/kg, preferably from about 0.5 mg/kg to about 30 mg/kg, from about 0.01 mg/kg to about 10 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, and more preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[111] It will be appreciated that dose ranges as described herein provide guidance for the administration of provided pharmaceutical compositions to an adult. The amount to be administered to, for example, a child or an adolescent can be determined by a medical practitioner or person skilled in the art and can be lower or the same as that administered to an adult.

[112] It will be also appreciated that a compound or composition, as described herein, can be administered in combination with one or more additional pharmaceutical agents. The compounds or compositions can be administered in combination with additional pharmaceutical agents that improve their bioavailability, reduce and/or modify their metabolism, inhibit their excretion, and/or modify their distribution within the body. It will also be appreciated that the therapy employed may achieve a desired effect for the same disorder, and/or it may achieve different effects.

[113] The compound or composition can be administered concurrently with, prior to, or subsequent to, one or more additional pharmaceutical agents, which may be useful as, *e.g.*, combination therapies. Pharmaceutical agents include therapeutically active agents. Pharmaceutical agents also include prophylactically active agents. Each additional pharmaceutical agent may be administered at a dose and/or on a time schedule determined for that pharmaceutical agent. The additional pharmaceutical agents may also be administered together with each other and/or with the compound or composition described herein in a single dose or administered separately in different doses. The particular combination to employ in a regimen will take into account compatibility of the inventive compound with the additional pharmaceutical agents and/or the desired therapeutic and/or prophylactic effect to be achieved. In general, it is expected that the additional pharmaceutical agents utilized in combination be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually.

[114] Exemplary additional pharmaceutical agents include, but are not limited to, anti-proliferative agents, anti-cancer agents, anti-diabetic agents, anti-inflammatory agents, immunosuppressant agents, and a pain-relieving agent. Pharmaceutical agents include small organic molecules such as drug compounds (*e.g.*, compounds approved by the U.S. Food and Drug Administration as provided in the Code of Federal Regulations (CFR)), peptides, proteins, carbohydrates, monosaccharides, oligosaccharides, polysaccharides, nucleoproteins, mucoproteins, lipoproteins, synthetic polypeptides or proteins, small molecules linked to proteins, glycoproteins, steroids, nucleic acids, DNAs, RNAs, nucleotides, nucleosides, oligonucleotides, antisense oligonucleotides, lipids, hormones, vitamins, and cells.

[115] Also encompassed by the invention are kits (*e.g.*, pharmaceutical packs). The inventive kits may be useful for preventing and/or treating a proliferative disease (*e.g.*, cancer (*e.g.*, leukemia, melanoma, multiple myeloma), benign neoplasm, angiogenesis, inflammatory disease, autoinflammatory disease, or autoimmune disease). The kits provided may comprise an inventive pharmaceutical composition or compound and a container (*e.g.*, a vial, ampule, bottle, syringe, and/or dispenser package, or other suitable container). In some embodiments, provided kits may optionally further include a second container comprising a pharmaceutical excipient for dilution or suspension of an inventive pharmaceutical composition or compound. In some embodiments, the inventive pharmaceutical composition or compound provided in the container and the second container are combined to form one unit dosage form.

[116] Thus, in one aspect, provided are kits including a first container comprising a compound described herein, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer, and isotopically labeled derivative, or a pharmaceutical composition thereof. In certain embodiments, the kit of the invention includes a first container comprising a compound described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. In certain embodiments, the kits are useful in preventing and/or treating a proliferative disease in a subject. In certain embodiments, the kits further include instructions for administering the compound, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer, isotopically and labeled derivative thereof, or a pharmaceutical composition thereof, to a subject to prevent and/or treat a proliferative disease.

Methods of Treatment and Uses

[117] The present invention also provides methods for the treatment or prevention of a proliferative disease (*e.g.*, cancer, benign neoplasm, angiogenesis, inflammatory disease, autoinflammatory disease, or autoimmune disease) or an infectious disease (*e.g.*, a viral disease) in a subject. Such methods comprise the step of administering to the subject in need thereof an effective amount of a compound of Formula (**I**), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer, or isotopically labeled derivative thereof, or a pharmaceutical composition thereof. In certain embodiments, the methods described herein include administering to a subject an effective amount of a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

[118] In certain embodiments, the subject being treated is a mammal. In certain embodiments, the subject is a human. In certain embodiments, the subject is a domesticated animal, such as a dog, cat, cow, pig, horse, sheep, or goat. In certain embodiments, the subject is a companion animal such as a dog or cat. In certain embodiments, the subject is a livestock animal such as a cow, pig, horse, sheep, or goat. In certain embodiments, the subject is a zoo animal. In another embodiment, the subject is a research animal such as a rodent, dog, or non-human primate. In certain embodiments, the subject is a non-human transgenic animal such as a transgenic mouse or transgenic pig.

[119] The proliferative disease to be treated or prevented using the compounds of Formula (**I**) will typically be associated with aberrant activity of a CDK, and more specifically CDK7. Aberrant activity of CDK7 may be an elevated and/or an inappropriate (e.g., abnormal) activity of CDK7. In certain embodiments, CDK7 is not overexpressed, and the activity of CDK7 is elevated and/or inappropriate. In certain other embodiments, CDK7 is overexpressed, and the activity of CDK7 is elevated and/or inappropriate. The compounds of Formula (**I**), and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers, isotopically labeled derivatives, and compositions thereof, may inhibit the activity of CDK7 and be useful in treating and/or preventing proliferative diseases.

[120] In other embodiments, the proliferative disease to be treated or prevented using the compounds of Formula (**I**) will typically be associated with aberrant activity of CDK12. Aberrant activity of CDK12 may be an elevated and/or an inappropriate (e.g., abnormal) activity of CDK12. In certain embodiments, CDK12 is not overexpressed, and the activity of CDK12 is elevated and/or inappropriate. In certain other embodiments, CDK12 is overexpressed, and the

activity of CDK12 is elevated and/or inappropriate. The compounds of Formula (**I**), and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers, isotopically labeled derivatives, and compositions thereof, may inhibit the activity of CDK12 and be useful in treating and/or preventing proliferative diseases.

[121] In other embodiments, the proliferative disease to be treated or prevented using the compounds of Formula (**I**) will typically be associated with aberrant activity of CDK13. Aberrant activity of CDK13 may be an elevated and/or an inappropriate (e.g., abnormal) activity of CDK13. In certain embodiments, CDK13 is not overexpressed, and the activity of CDK13 is elevated and/or inappropriate. In certain other embodiments, CDK13 is overexpressed, and the activity of CDK13 is elevated and/or inappropriate. The compounds of Formula (**I**), and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers, isotopically labeled derivatives, and compositions thereof, may inhibit the activity of CDK13 and be useful in treating and/or preventing proliferative diseases.

[122] A proliferative disease may also be associated with inhibition of apoptosis of a cell in a biological sample or subject. All types of biological samples described herein or known in the art are contemplated as being within the scope of the invention. Inhibition of the activity of CDK7 is expected to cause cytotoxicity via induction of apoptosis. The compounds of Formula (**I**), and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers, isotopically labeled derivatives, and compositions thereof, may induce apoptosis, and therefore, be useful in treating and/or preventing proliferative diseases.

[123] In certain embodiments, the proliferative disease to be treated or prevented using the compounds of Formula (**I**) is cancer. All types of cancers disclosed herein or known in the art are contemplated as being within the scope of the invention. In certain embodiments, the proliferative disease is a cancer associated with dependence on BCL-2 anti-apoptotic proteins (*e.g.*, MCL-1 and/or XIAP). In certain embodiments, the proliferative disease is a cancer associated with overexpression of MYC (a gene that codes for a transcription factor). In certain embodiments, the proliferative disease is a hematological malignancy. In certain embodiments, the proliferative disease is a blood cancer. In certain embodiments, the proliferative disease is leukemia. In certain embodiments, the proliferative disease is chronic lymphocytic leukemia (CLL). In certain embodiments, the proliferative disease is acute lymphoblastic leukemia (ALL). In certain embodiments, the proliferative disease is T-cell acute lymphoblastic leukemia

(T-ALL). In certain embodiments, the proliferative disease is chronic myelogenous leukemia (CML). In certain embodiments, the proliferative disease is acute myelogenous leukemia (AML). In certain embodiments, the proliferative disease is lymphoma. In certain embodiments, the proliferative disease is melanoma. In certain embodiments, the proliferative disease is multiple myeloma. In certain embodiments, the proliferative disease is a bone cancer. In certain embodiments, the proliferative disease is osteosarcoma. In some embodiments, the proliferative disease is Ewing's sarcoma. In some embodiments, the proliferative disease is triple-negative breast cancer (TNBC). In some embodiments, the proliferative disease is a brain cancer. In some embodiments, the proliferative disease is neuroblastoma. In some embodiments, the proliferative disease is a lung cancer. In some embodiments, the proliferative disease is small cell lung cancer (SCLC). In some embodiments, the proliferative disease is large cell lung cancer. In some embodiments, the proliferative disease is a benign neoplasm. All types of benign neoplasms disclosed herein or known in the art are contemplated as being within the scope of the invention.

[124] In some embodiments, the proliferative disease is associated with angiogenesis. All types of angiogenesis disclosed herein or known in the art are contemplated as being within the scope of the invention.

[125] In certain embodiments, the proliferative disease is an inflammatory disease. All types of inflammatory diseases disclosed herein or known in the art are contemplated as being within the scope of the invention. In certain embodiments, the inflammatory disease is rheumatoid arthritis. In some embodiments, the proliferative disease is an autoinflammatory disease. All types of autoinflammatory diseases disclosed herein or known in the art are contemplated as being within the scope of the invention. In some embodiments, the proliferative disease is an autoimmune disease. All types of autoimmune diseases disclosed herein or known in the art are contemplated as being within the scope of the invention.

[126] The cell described herein may be an abnormal cell. The cell may be *in vitro* or *in vivo*. In certain embodiments, the cell is a proliferative cell. In certain embodiments, the cell is a blood cell. In certain embodiments, the cell is a lymphocyte. In certain embodiments, the cell is a cancer cell. In certain embodiments, the cell is a leukemia cell. In certain embodiments, the cell is a CLL cell. In certain embodiments, the cell is a melanoma cell. In certain embodiments, the cell is a multiple myeloma cell. In certain embodiments, the cell is a benign neoplastic cell. In

certain embodiments, the cell is an endothelial cell. In certain embodiments, the cell is an immune cell.

[127] In another aspect, the present invention provides methods of down-regulating the expression of a CDK (*e.g.*, CDK7, CDK1, CDK2, CDK5, CDK8, CDK9, CDK12, CDK13) in a biological sample or subject. In certain embodiments, the present invention provides methods of down-regulating the expression of CDK7 in a biological sample or subject.In another aspect, the present invention provides methods of down-regulating the expression of IRAK1, JNK1, JNK2, or MLK3 in a biological sample or subject.

[128] Another aspect of the invention relates to methods of inhibiting the activity of a kinase in a biological sample or subject. In certain embodiments, the kinase is CDK. In certain embodiments, the kinase is CDK7. In other embodiments, the kinase is CDK12 or CDK13. In certain embodiments, the activity of the kinase is aberrant activity of the kinase. In certain embodiments, the inhibition of the activity of the kinase is irreversible. In other embodiments, the inhibition of the activity of the kinase is reversible. In certain embodiments, the methods of inhibiting the activity of the kinase include attaching a compound of Formula (**I**) to the kinase.

[129] In certain embodiments, the methods described herein comprise the additional step of administering one or more additional pharmaceutical agents in combination with the compound of Formula (**I**), a pharmaceutically acceptable salt thereof, or compositions comprising such compound or pharmaceutically acceptable salt thereof. Such additional pharmaceutical agents include, but are not limited to, anti-proliferative agents, anti-cancer agents, anti-diabetic agents, anti-inflammatory agents, immunosuppressant agents, and a pain-relieving agent. The additional pharmaceutical agent(s) may synergistically augment inhibition of CDK7, CDK12, or CDK13 induced by the inventive compounds or compositions of this invention in the biological sample or subject. In certain embodiments, the additional pharmaceutical agent is flavopiridol, triptolide , SNS-032 (BMS-387032), PHA-767491, PHA-793887, BS-181, (*S*)-CR8, (*R*)-CR8, or NU6140. In certain embodiments, the additional pharmaceutical agent is an inhibitor of a mitogen-activated protein kinase (MAPK). In certain embodiments, the additional pharmaceutical agent is an inhibitor of a glycogen synthase kinase 3 (GSK3). In certain embodiments, the additional pharmaceutical agent is an inhibitor of an AGC kinase. In certain embodiments, the additional pharmaceutical agent is an inhibitor of a CaM kinase. In certain embodiments, the additional pharmaceutical agent is an inhibitor of a casein kinase 1. In certain embodiments, the additional

pharmaceutical agent is an inhibitor of a STE kinase. In certain embodiments, the additional pharmaceutical agent is an inhibitor of a tyrosine kinase. Thus, the combination of the inventive compounds or compositions and the additional pharmaceutical agent(s) may be useful in treating proliferative diseases resistant to a treatment using the additional pharmaceutical agent(s) without the inventive compounds or compositions.

[130] In some embodiments, the one or more additional pharmaceutical agents are independently selected from a topoisomerase inhibitor, a MCL1 inhibitor, a BCL-2 inhibitor, a BCL-xL inhibitor, a BRD4 inhibitor, a CDK9 inhibitor, a Jumonji histone demethylase inhibitor, and a DNA damage inducer. In a more specific aspect of these embodiments, the one or more additional agents is selected from etoposide, obatoclax, navitoclax, JQ1, 4-(((5'-chloro-2'-(((1*R*,4*R*)-4-(((*R*)-1-methoxypropan-2-yl)amino)cyclohexyl)amino)-[2,4'-bipyridin]-6-yl)amino)methyl)tetrahydro-2H-pyran-4-carbonitrile, JIB04 and cisplatin. In an even more specific aspect of these embodiments, the additional agent is selected from etoposide, obatoclax, and navitoclax and the disease to be treated is breast cancer, e.g., triple-negative breast cancer, HER2 positive breast cancer, ER-positive breast cancer, or ER/PR-positive breast cancer. In another even more specific aspect of these embodiments, the additional agent is selected from etoposide, JIB04 and cisplatin and the disease to be treated is Ewing's sarcoma. In still another even more specific aspect of these embodiments, the additional agent is selected from JQ1 and NVP2, and the disease to be treated is leukemia, e.g., acute myelogenous leukemia, myeloblastic leukemia, promyelocytic leukemia, myelomonocytic leukemia, monocytic leukemia, monoblastic leukemia, or megakaryoblastic leukemia.

[131] In yet another aspect, the present invention provides the compounds of Formula (**I**), and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers, isotopically labeled derivatives, and compositions thereof, for use in the treatment of a proliferative disease in a subject. In certain embodiments, provided by the invention are the compounds described herein, and pharmaceutically acceptable salts and compositions thereof, for use in the treatment of a proliferative disease in a subject. In certain embodiments, provided by the invention are the compounds described herein, and pharmaceutically acceptable salts and compositions thereof, for use in inhibiting cell growth. In certain embodiments, provided by the invention are the compounds described herein, and pharmaceutically acceptable salts and compositions thereof, for use in inducing apoptosis in a cell. In certain embodiments, provided by the invention are the

compounds described herein, and pharmaceutically acceptable salts and compositions thereof, for use in inhibiting transcription.

EXAMPLES

[132] In order that the invention described herein may be more fully understood, the following examples are set forth. The synthetic and biological examples described in this application are offered to illustrate the compounds, pharmaceutical compositions, and methods provided herein and are not to be construed in any way as limiting their scope.

[133] The compounds provided herein can be prepared from readily available starting materials using modifications to the specific synthesis protocols set forth below that would be well known to those of skill in the art. It will be appreciated that where typical or preferred process conditions (*i.e.*, reaction temperatures, times, mole ratios of reactants, solvents, pressures, *etc.*) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvents used, but such conditions can be determined by those skilled in the art by routine optimization procedures.

[134] Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions for protection and deprotection are well known in the art. For example, numerous protecting groups, and their introduction and removal, are described in Greene *et al.*, *Protecting Groups in Organic Synthesis*, Second Edition, Wiley, New York, 1991, and references cited therein.

[135] ABBREVIATIONS

Ac	acetyl
ACN	acetonitrile
aq.	aqueous
atm	atmospheres
Boc	*tert*-butoxy carbonyl
Boc_2O	Di-*t*-butyl dicarbonate
DCC	N,N'-Dicyclohexylcarbodiimide
DCM	dichloromethane
DIPEA	N,N-Diisopropyl ethylamine
DMF	Dimethylformamide
DMSO	dimethylsulfoxide

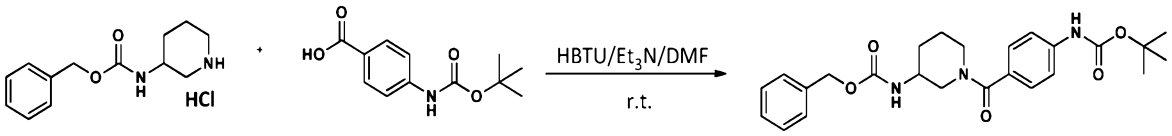
EDTA	ethylenediamine tetraacetic acid
eq(s).	equivalent(s)
Et	Ethyl
EtOAc	ethyl acetate
EtOH	ethanol
Et_3N	triethylamine
g	gram(s)
H; H	hour(s)

HATU	(Dimethylamino)-*N*,*N*-dimethyl(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yloxy)methaniminium hexafluorophosphate
HBTU	O-Benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate
Hex	hexane
HPLC	High pressure liquid chromatography
IPA	isopropanol
LCMS; LC-MS	liquid chromatography mass spectrometry
MeOH	methanol
mg	milligram(s)
min	Minute(s)

mL; ml	milliliter(s)
MS	mass spectrometry
mW	microwave
NMP	N-Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
Ph	phenyl
r.t.; rt; RT	Room temperature
S.; sat.	saturated
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	Thin layer chromatography
X-Phos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

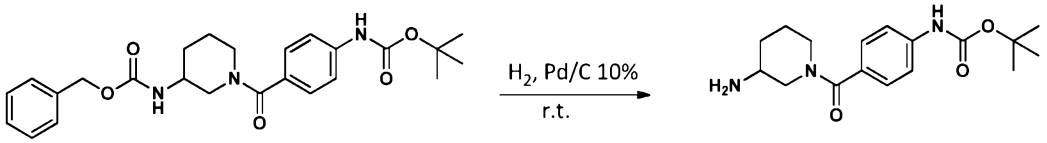
[136] **Example 1. Synthesis of (E)-N-(4-(3-(5-chloro-4-(1H-indol-3-yl)pyrimidin-2-ylamino)piperidine-1-carbonyl)phenyl)-4-(dimethylamino)but-2-enamide (Compound 100)**

[137] *p-{[3-(Benzyloxycarbonylamino)-1-piperidyl]carbonyl}phenylamino 2,2-dimethylpropionate*



[138] To a solution of 4-(tert-butoxycarbonylamino)benzoic acid (438mg, 1.8mmol), 3-CBz-aminopiperidine.HCl (500mg, 1.8mmol) and Et_3N (0.89ml, 5.5mmol) in DMF (10mL) was added HBTU (1.05g, 2.8mmol). The mixture was stirred 5h at rt before being diluted with EtOAc (100ml), washed with water (100mL), brine (3 x 100mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The mixture was purified by SiO_2 chromatography (Hex/EtOAc 20 to 100% gradient) and afforded the title compound (765mg, 1.69mmol, 94%) as a colorless oil.

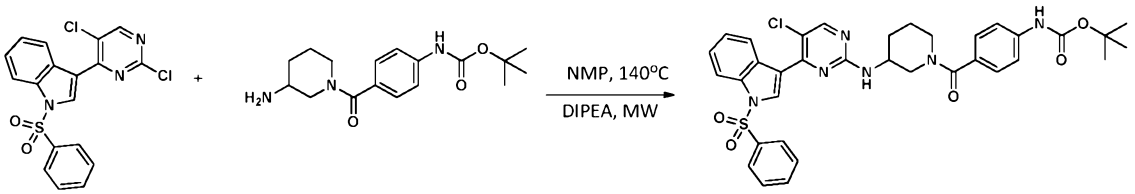
[139] *tert-butyl 4-(3-aminopiperidine-1-carbonyl)phenylcarbamate*



[140] To a degassed solution of *p*-{[3-(Benzyloxycarbonylamino)-1-

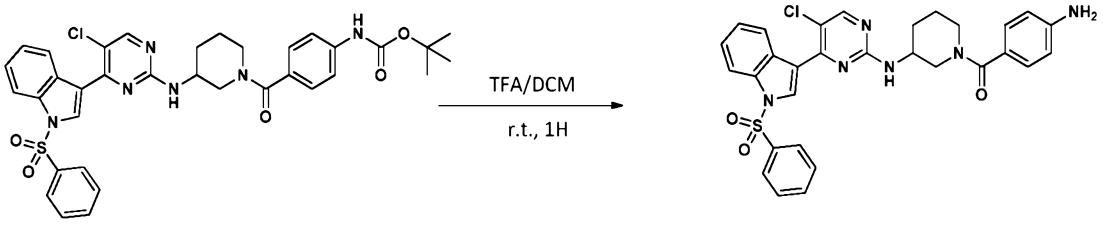
piperidyl]carbonyl}phenylamino 2,2-dimethylpropionate (765mg, 1.69mmol) in MeOH (25mL) was added 10% Pd/C (60mg). The mixture was stirred 1h under H_2 (1atm) before being filtered over Celite® (MeOH). The volatiles were removed under reduced pressure to afford the title compound (510mg, 1.60mmol, 94.7%) as a white solid which was used in the next step without further purification.

[141] *tert-butyl 4-(3-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)piperidine-1-carbonyl)phenylcarbamate*



[142] A suspension of 3-(2,5-dichloropyrimidin-4-yl)-1-(phenylsulfonyl)-1H-indole (0.524g, 1.3mmol), tert-butyl 4-(3-aminopiperidine-1-carbonyl)phenylcarbamate (414mg, 1.3mmol) andDIPEA (452uL, 2.59mmol) in NMP (5 mL) was heated at 140°C (mW) for 20min. The cooled mixture was diluted with EtOAc (20mL), washed with sat. $NaHCO_3$ (5mL), brine (5mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by SiO_2 chromatography (Hex/EtOAc 35 to 100% gradient) to afford the title compound (570mg, 0.83mmol, 64%) as a white solid.

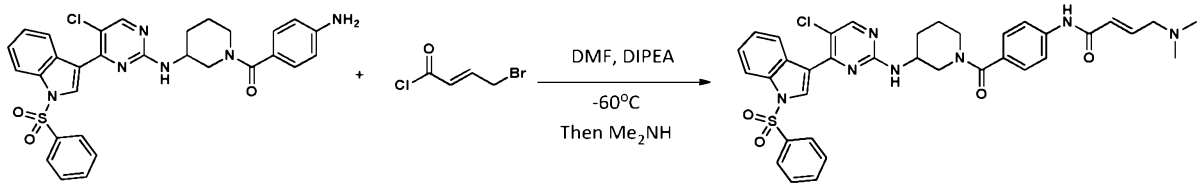
[143] *(4-aminophenyl)(3-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)piperidin-1-yl)methanone*



[144] A solution of tert-butyl 4-(3-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)piperidine-1-carbonyl)phenylcarbamate (570mg, 0.829mmol) in DCM (5mL) was treated with TFA (2mL). The mixture was stirred 30min at rt before being concentrated under reduced pressure and diluted with DCM (10mL), washed with sat. $NaHCO_3$ (5mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford the title compound (461mg, 0.785mmol, 95%) as white solid.

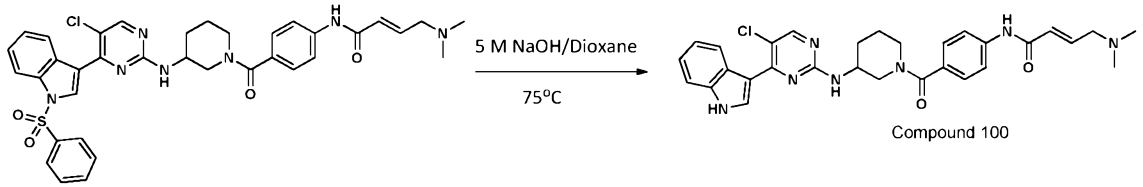
[145] *(E)-N-(4-(3-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-*

ylamino)piperidine-1-carbonyl)phenyl)-4-(dimethylamino)but-2-enamide



[146] To a -60°C solution of (4-aminophenyl)(3-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)piperidin-1-yl)methanone (60mg, 0.102mmol) and DIPEA (53ul, 0.310mmol) in DMF (1mL) was slowly added a 74mg/mL solution of (E)-4-bromobut-2-enoyl chloride in DCM (256uL, 0.102mmol). After 30 min at -60°C, a 2M solution of dimethylamine in THF (60uL, 0.120mmol) was added and the resulting mixture was warmed to room temp and stirred for 1hr. The solution was diluted with $CHCl_3$ (25ml), washed with water (5mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the title compound (71mg, 0.102mmol, 100%) as a yellowish solid which was used in the next step without further purification.

[147] *(E)-N-(4-(3-(5-chloro-4-(1H-indol-3-yl)pyrimidin-2-ylamino)piperidine-1-carbonyl)phenyl)-4-(dimethylamino)but-2-enamide (Compound 100)*

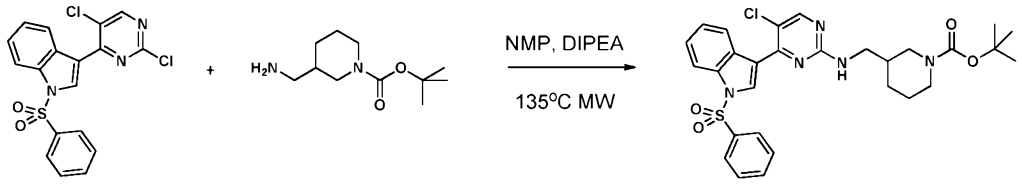


[148] A solution of (E)-N-(4-(3-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)piperidine-1-carbonyl)phenyl)-4-(dimethylamino)but-2-enamide (71mg, 0.102mmol) in dioxane (2mL) and 5M NaOH (500uL, 2.55mmol) was heated 3h at 75°C. The cooled mixture was diluted with DCM (10mL), washed with water (3mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The mixture was purified by reverse phase chromatography (C18, water/ACN, 20 to 100% gradient) to afford Compound 100 (5mg, 0.009mmol, 10%) as a white solid after lyophilisation. ^{1}H NMR (500 MHz, DMSO) δ 11.87 (s, 1H), 10.42 – 10.02 (m, 2H), 8.82 – 8.59 (m, 1H), 8.47 (s, 1H), 8.30 (s, 1H), 7.87 – 7.59 (m, 2H), 7.49 (t, J = 19.2 Hz, 1H), 7.37 (m, 2H), 7.27 – 7.04 (m, 2H), 6.80 (dt, J = 15.7, 12.9 Hz, 2H), 6.30 (d, J = 16.3 Hz, 2H), 4.19 – 3.66 (m, 4H), 3.87 (s, 1H), 3.10 (d, J = 5.9 Hz, 2H), 2.21 (s, 3H), 2.14 – 2.03 (m, 1H), 1.80 – 1.63 (m, 1H), 1.59 (m, 1H); MS (m/z): 558.66 $[M+1]^+$.

[149] **Example 2. Synthesis of (E)-N-(4-(3-((5-chloro-4-(1H-indol-3-yl)pyrimidin-2-**

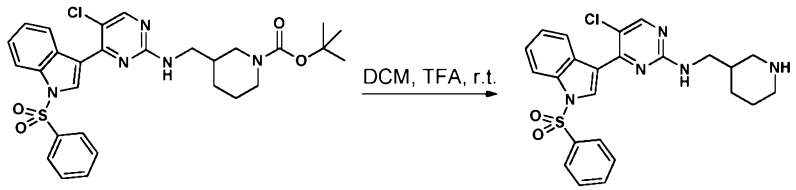
ylamino)methyl)piperidine-1-carbonyl)phenyl)-4-(dimethylamino)but-2-enamide (Compound 101)

[150] *tert-butyl 3-((5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)methyl)piperidine-1-carboxylate*



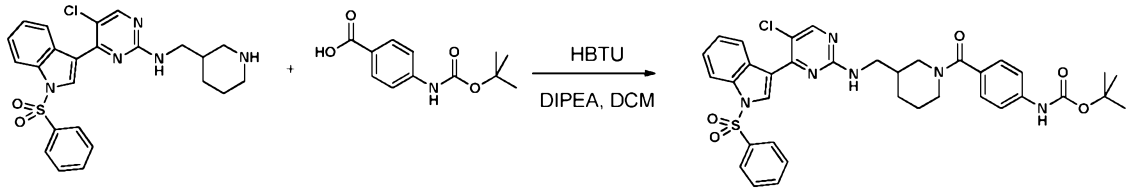
[151] A solution of 3-(2,5-dichloropyrimidin-4-yl)-1-(phenylsulfonyl)-1H-indole (300mg, 0.74mmol), 1-Boc-3-(aminomethyl)piperidine (159mg, 0.74mmol) and diisopropylethylamine (0.13 mL, 0.74 mmol) in NMP (2.0mL) was heated 25min at 135°C (mW). The mixture was diluted with EtOAc (30mL), washed with water (3x5mL), brine (5mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by SiO_2 chromatography (DCM/EtOAc 0 to 15% gradient), and afforded the title compound (355mg, 0.67mmol, 85%) as a white solid.

[152] *5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)-N-(piperidin-3-ylmethyl)pyrimidin-2-amine*



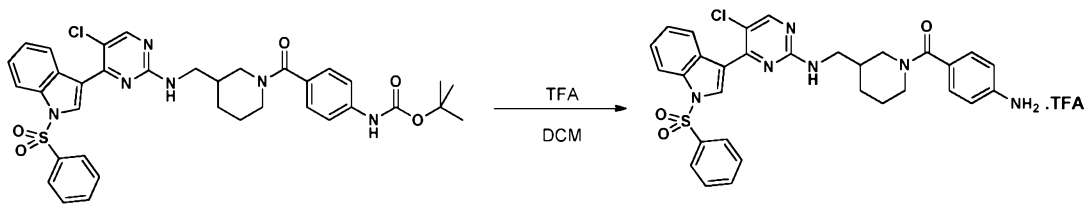
[153] Trifluoroacetic acid (0.93mL, 12.2mmol) was added to a stirring solution of tert-butyl 3-((5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)methyl)piperidine-1-carboxylate (355mg, 0.67mmol) in DCM (2.7mL) at 0°C. The resulting solution was stirred 1h at rt, concentrated under reduced pressure, and diluted with DCM (20mL) and sat $NaHCO_3$ (10mL). The phases were separated and the aqueous layer was extracted with DCM (2x15mL). The combined organics layers were dried ($MgSO_4$), filtered, and concentrated to afford the title compound (324g, 0.67mmol, 100%) as a yellow foam which was used in the next step without further purification.

[154] *tert-butyl 4-(3-((5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)methyl)piperidine-1-carbonyl)phenylcarbamate*



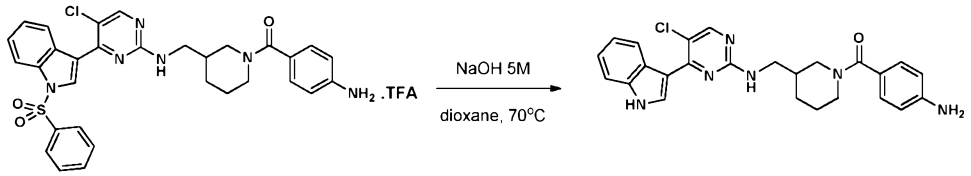
[155] A solution of 5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)-N-(piperidin-3-ylmethyl)pyrimidin-2-amine (273mg, 0.57mmol), 4-(tert-butoxycarbonylamino)benzoic acid (134mg, 0.57mmol), HBTU (644mg, 1.7mmol), and diisopropylethylamine (0.30mL, 1.70mmol) in DCM (2.5mL) was stirred overnight at rt. The mixture was concentrated under reduced pressure and the residue was used in the next step without further purification.

[156] *(4-aminophenyl)(3-((5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)methyl)piperidin-1-yl)methanone trifluoroacetic acid salt*



[157] A solution of crude tert-butyl 4-(3-((5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)methyl)piperidine-1-carbonyl)phenylcarbamate (349mg, 0.498mmol) DCM (5mL) was treated with TFA (381uL, 4.98mmol) and stirred overnight at rt. The mixture was concentrated under reduced pressure, diluted with toluene (5mL), and concentrated under reduced pressure again. The same process was repeated three times and afforded the title compound as a pale orange foam which was used in the next step without further purification.

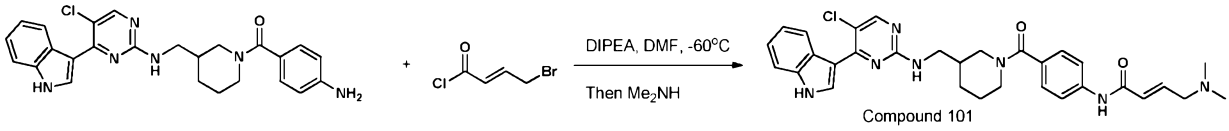
[158] *(4-aminophenyl)(3-((5-chloro-4-(1H-indol-3-yl)pyrimidin-2-ylamino)methyl)piperidin-1-yl)methanone*



[159] A solution of (4-aminophenyl)(3-((5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)methyl)piperidin-1-yl)methanone trifluoroacetic acid salt (356mg, 0.498mmol) and 5M NaOH (1.49mL, 7.47mmol) in dioxane (8.0mL) was heated 3.5h at 70°C. The cooled mixture was diluted with DCM/MeOH 10/1 (15mL) and washed with water (5mL). The water layer was extracted with DCM/MeOH 10:1 (3x10mL) andthe combined organics

were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by reverse phase chromatography (H_2O/ACN +0.1% formic acid 15 to 60% gradient), and afforded the title compound (219mg, 0.48mmol, 83% over 3 steps) as a white solid.

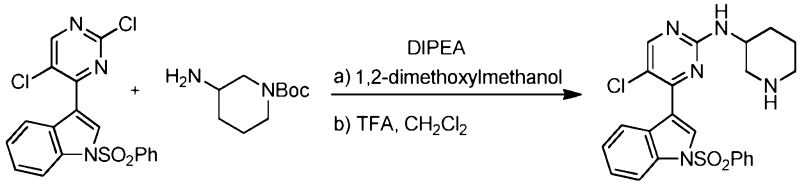
[160] *(E)-N-(4-(3-((5-chloro-4-(1H-indol-3-yl)pyrimidin-2-ylamino)methyl)piperidine-1-carbonyl)phenyl)-4-(dimethylamino)but-2-enamide*



[161] To a cold solution (-60°C) of (4-aminophenyl)(3-((5-chloro-4-(1H-indol-3-yl)pyrimidin-2-ylamino)methyl)piperidin-1-yl)methanone (185mg, 0.401mmol) and DIPEA (210 µL, 1.20mmol) in THF (2.5mL) was added a 55.6mg/mL solution of (E)-4-bromobut-2-enoyl chloride (547uL, 0.401mmol) in THF. After 1.5h at (-60°C), a 2M solution of dimethylamine in THF (802uL, 1.61mmol) was added and the mixture was stirred 24h at -30°C. NMP (2mL) was added, followed by removal of the THF under reduced pressure. The residue was purified by reverse phase chromatography (0.1% HCOOH, H_2O/ACN 15 to 60% gradient) and afforded Compound 101 (53mg, 0.093mmol, 23%) as a light yellow solid after lyophilisation. ^{1}H NMR (500 MHz, DMSO) δ 11.83 (s, 1H), 10.20 (s, 1H), 8.56 (br s, 1H), 8.46 (s, 1H), 8.24 (s, 1H), 7.72 – 7.55 (m, 2H), 7.49 (d, J = 7.9 Hz, 2H), 7.38 – 6.97 (m, 4H), 6.74 (dd, J = 13.6, 7.4 Hz, 1H), 6.28 (d, J = 15.6 Hz, 1H), 4.46 (br s, 1H), 4.15 (br s, 1H), 3.16 (d, J = 4.3 Hz, 2H), 3.04 – 2.86 (m, 2H), 2.74– 2.56 (m, 1H), 2.37 (d, J = 9.0 Hz, 1H), 2.25 (s, 6H), 2.03 – 1.81 (m, 2H), 1.76 – 1.59 (m, 1H), 1.46 – 1.22 (m, 2H); MS (m/z): 572.65 $[M+1]^+$.

[162] Example 3. Synthesis of (E)-3-((5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-yl)amino)-N-(4-(4-(dimethylamino)but-2-enamido)phenyl)piperidine-1-carboxamide (Compound 102)

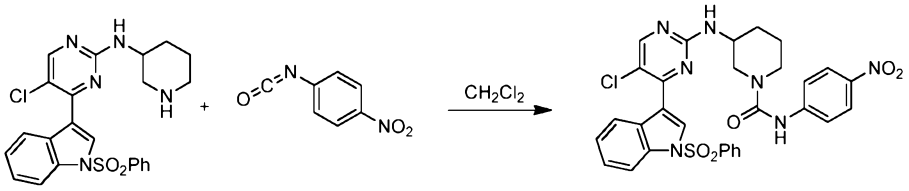
5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)-N-(piperidin-3-yl)pyrimidin-2-amine



[163] To a solution of 3-(2, 5-dichloropyrimidin-4-yl)-1-(phenylsulfonyl)-1H-indole (402mg) in 1, 2-dimethoxylmethanol was added tert-butyl 3-aminopiperidine-1-carboxylate (200mg, 1.0 equiv) and diisopropylethylamine (129 mg, 1.0 equiv). The solution was heated for

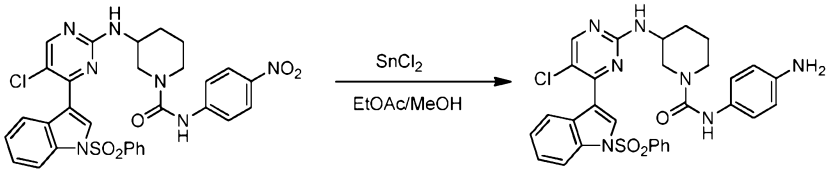
2 h at 120 ℃.The cooled solution was diluted with 100mL of $CHCl_3$ and *i*-PrOH(4:1) and then washed with water. After removing solvent, the crude product was dissolved in 10 mL $CHCl_3$ and treated with 5mL TFA. After stirring for 30min at room temperature, the solvent was removed and the product was purified byby silica gel chromatography with CH_2Cl_2/methanol (10:1) to give the product (350 mg, 76%) .

[164] *3-((5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-yl)amino)-N-(4-nitrophenyl)piperidine-1-carboxamide*



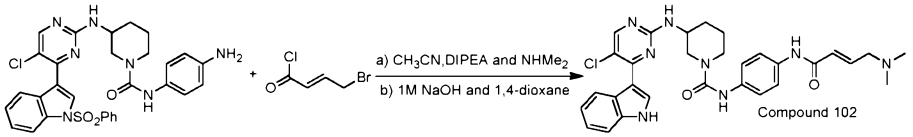
[165] To a stirred solution of the 5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)-N-(piperidin-3-yl)pyrimidin-2-amine (350 mg) in 10 mL CH_2Cl_2 was added 1-isocyanato-4-nitrobenzene (123mg, 1.0 equiv) at room temperature. The reaction mixture was stirred for 2 h and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography with CH_2Cl_2/methanol (10:1) to provide the title compound (375 mg, 80%).

[166] *N-(4-aminophenyl)-3-((5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxamide*



[167] The nitro compound (375 mg) was suspended in 30 mL of ethyl acetate/methanol (5:1) and treated with $SnCl_2$ (280 mg, 2.5 equiv). After stirring for 2 h at 80 ℃, the reaction mixture was cooled to room temperature and poured into saturated aqueous $NaHCO_3$. The mixture was stirred for 10 min and the aqueous phase was then extracted with 100 mL chloroform and 2-propanol (4:1). The combined organic layer was washed with water and brine, dried over $MgSO_4$, filtered through a pad of Celite® and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography with CH_2Cl_2/methanol (10:1) to provide the title compound (210 mg, 60%).

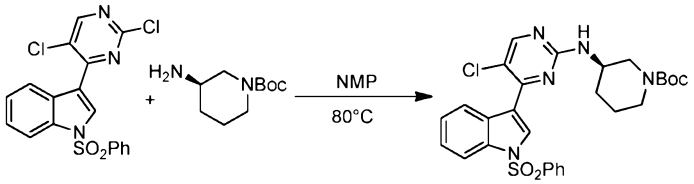
[168] *(E)-3-((5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-yl)amino)-N-(4-(4-(dimethylamino)but-2-enamido)phenyl)piperidine-1-carboxamide (Compound 102)*



[169] To the solution of the aniline (60 mg) in 10 mL of acetonitrile was added diisopropylethylamine (13 mg, 1.0 equiv). The reaction mixture was cooled to 0 ℃ and then treated with 4-chlorobut-2-enoyl chloride (54 mg, 3.0 equiv) in CH_2Cl_2. The reaction mixture was stirred for 10 min at 0 °C and then treated with a solution of dimethylamine in THF. The reaction mixture was then warmed to room temperature, stirred for 1 h, and concentrated under reduced pressure. The resulting crude product was purified by preparative HPLC. The resulting product then was dissolved in 5mL 1,4-dioxane and 5 mL 1M NaOH. The solution was allowed to stir at room temperature for 2h and then 5mL 1M HCl was added. The solution was then diluted with 30 mL of chloroform and 2-propanol (4:1), followed by washing the organic layer with water. The removal of solvent provided the crude product, which was purified by HPLC to give the final product Compound 102 (25 mg, 43%). MS (m/z): 573 $[M+1]^+$.

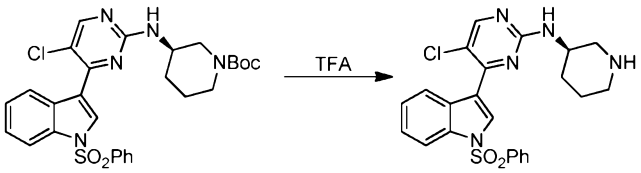
[170] **Example 4. Synthesis of (R,E)-N-(4-(3-((5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl)amino)piperidine-1-carbonyl)phenyl)-4-(dimethylamino)but-2-enamide (Compound 103)**

[171] *(R)-tert-butyl 3-((5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate*



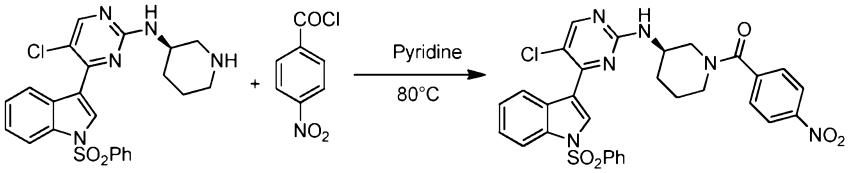
[172] 3-(2,5-dichloropyrimidine-4-yl)-1-1-(phenylsulfonyl)-1H-indole (403 mg, 1.0 mmol) and (R)-tert-butyl 3-aminopiperidine-1-carboxylate (400 mg, 2.0 equiv) were dissolved in NMP (5 mL). After heating at 80°C for 3 hours, the solution was cooled to room temperature and then diluted with ethyl acetate (100 mL). The resulted solution was washed with saturated $NaHCO_3$, water, and brine. After drying with $MgSO_4$, the solvent was removed and the product was obtained by flash chromatography with dichloromethane/methanol (10:1) as eluent. (397.0 mg, yield 70%) MS (m/z): 568 $[M+1]^+$.

[173] *(R)-5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)-N-(piperidin-3-yl)pyrimidin-2-amine*



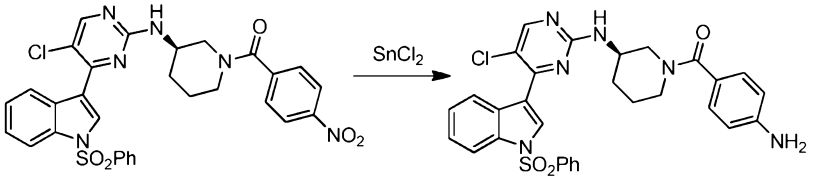
[174] (R)-tert-butyl 3-((5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate was dissolved in 4mL of dichloromethane and 2mL of trifluoroacetic acid. The solvent was removed with reduced pressure to give the crude product which was used in next step directly.

[175] *(R)-(3-((5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2- yl)amino)piperidin-1-yl)(4-nitrophenyl)methanone*



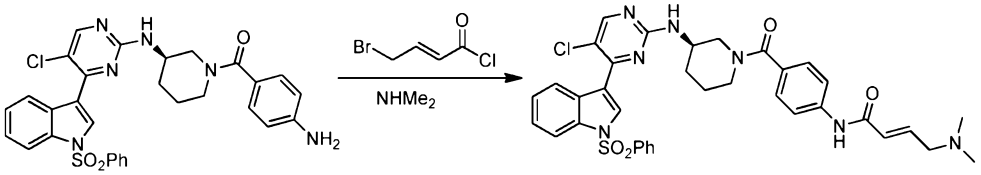
[176] To a pyridine solution of the free amine (47.0 mg, 0.1 mmol) was added benzoyl chloride (22.0 mg, 1.2 equiv). After stirring for 2 hours at 80°C, the reaction mixture was concentrated and the crude was purified by HPLC to give the pure product as a TFA salt. (52 mg, 80%) MS (m/z): 617 $[M+1]^+$.

[177] *(R)-(4-aminophenyl)(3-((5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-yl)amino)piperidin-1-yl)methanone*



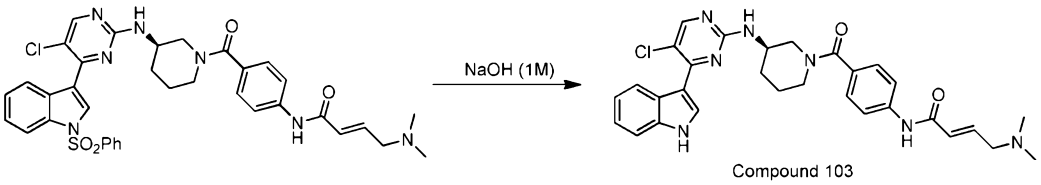
[178] The nitro compound (52 mg, 0.080 mmol) was suspended in ethyl acetate/methanol (5:1, vol/vol, 10 mL) and the resulted suspension was treated with $SnCl_2$ (40 mg, 2.5 equiv). After stirring for 2 hours at 80°C, the reaction mixture was cooled to room temperature and then was poured into a saturated $NaHCO_3$ solution (10 mL). The mixture was stirred for 10 minutes and then was extracted with chloroform/2-propanol (4:1, vol/vol, 50 mL). The organic layer was washed with water and brine, dried over $MgSO_4$, filtered through a pad of Celite® and concentrated under reduced pressure. The crude was purified by HPLC to provide the product (32 mg, 61%). MS (m/z): 587 $[M+1]^+$.

[179] *(R,E)-N-(4-(3-((5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-yl)amino)piperidine-1-carbonyl)phenyl)-4-(dimethylamino)but-2-enamide*



[180] To a solution of the free amine (60 mg, 0.11 mmol) in acetonitrile (5 mL) was added *N,N*-diisopropylethylamine (40 uL) and (*E*)-4-bromobut-2-enoyl chloride (40 mg, 2.0 equiv) in dichloromethane (1 mL) at 0°C dropwise. After stirring for 5 minutes, dimethylamine (1M in THF, 2 mL) was added and the solution was allowed to stir at room temperature for 2 hours. The solvent was then removed and the crude was purified by HPLC to give the product (58 mg, 82%). MS (m/z): 698 $[M+1]^+$.

[181] *(R,E)-N-(4-(3-((5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl)amino)piperidine-1-carbonyl)phenyl)-4-(dimethylamino)but-2-enamide*



Compound 103

[182] To a solution of (R,E)-N-(4-(3-((5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-yl)amino)piperidine-1-carbonyl)phenyl)-4-(dimethylamino)but-2-enamide (58 mg, 0.08 mmol) in 1,4-dioxane (2 mL) was added 1.0 M NaOH (2 mL). The solution was stirred at room temperature for 2 hours and then was quenched with 1.0 M HCl (2 mL). The solution was extracted with chloroform/2-propanol (4/1, vol/vol, 20 mL) and the organic layer was washed with water, brine and dried with $MgSO_4$. The sovlent was removed under reduced pressure and the crude was purified by HPLC to provide Compound 103 as a TFA salt. (33 mg, 72%) ^{1}H NMR (600 MHz, DMSO-*d6*): 11.83 (s, 1H), 10.44 (s, 1H), 9.82 (s, 1H), 8.60-8.20(m, 2H), 7.64 (m, 2H), 7.47 (d, J = 8.4 Hz, 1H), 7.35 (m, 2H), 7.18 (m, 1H), 7.12 (s, 1H), 6.74 (m, 1H) 6.43 (d, J = 14.4 Hz, 1H), 3.90 (d, J = 7.2 Hz, 2H), 3.80-3.50 (m, 3H), 3.20-3.08 (m, 2H), 2.66 (s, 6H), 2.05 (s, 1H), 2.00-1.70 (m, 1H), 1,64 (s, 1H), 1.52 (m, 1H). MS (m/z): 558 $[M+1]^+$.

[183] **Example 5. Synthesis of Additional Compounds of the Invention**. Additional compounds of the invention were synthesized in the manner outlined in Example 4. The ^{1}H

NMR and MS characterization data for these compounds are indicated in the table below.

[184]

Compound Number	^{1}H NMR	$[M+1]^+$
104		558
105		558
106	^{1}H NMR (600 MHz, DMSO-*d6*) 11.82 (s, 1H), 10.47 (s, 1H), 9.82 (s, 1H), 8.65-8.28 (m, 2H), 8.01-7.55 (m, 2H), 7.46 (d, *J* = 7.8 Hz, 1 H), 7.45-7.25 (m, 2H), 7.17 (m, 1H), 7.13 (m, 1H), 6.72 (m, 1H), 6.43 (m, 1H), 3.92 (m, 2H), 3.90-3.50 (m, 3H), 3.20-3.00 (m, 2H) 2.78 (s, 6H), 2.09-1.50 (m, 4H)	588
107		572
108		572

[185] **Example 6 Kinase Activity.** Compounds of the invention were assayed for activity against a variety of different kinases at Life Technologies™ (Grand Island, New York) using their commercially available Adapta® (for CDK7, CDK9/cyclin T1, and IRAK1 kinases), Z'-Lyte® (for CDK1, CDK2, CDK5/p25, CDK5/p35, JNK1 and JNK2 kinases) and LanthaScreen Eu® (for CDK8, CDK9/cyclin K and MLK3) kinase assay services. Test compounds were tested at 100 nM and 1μM final concentrations in 1% DMSO against all kinases except CDK7. For CDK7, test compounds were tested at concentrations ranging from 10 μM down to 0.514 nM in a series of 3-fold serial dilutions. Details of these assays, including substrates used for each kinase, are available on the Life Technologies web site (http://www.lifetechnologies.com/us/en/home/life-science/drug-discovery/target-and-lead-identification-and-validation/kinasebiology/kinase-activity-assays.html) . The results of the assay are shown below in Tables 2A and 2B. In Tables 2A and 2B, for CDK7 activity, "A" represents a calculated IC_{50} of less than 100 nM; "B" represents a calculated IC_{50} of between 100

nM and 1 μM; and "C" represents a calculated IC_{50} of greater than 1 μM. For all other tested kinases, "A" represents greater than a 70% inhibition of that kinase by the test compound, "B" represents between a 50% and 70% inhibition; and "C" represents less than a 50% inhibition. The co-factors used for each kinase in the assays were as follows CDK1 - cyclin B; CDK2 - cyclin A; CDK5 - p25 or p35 as indicated; CDK7 - cyclin H and MNAT1; CDK8 - cyclin C; CDK9 - cyclin K or cyclin T1 as indicated; IRAK1 - Histone H3 (1-20) peptide; JNK1 - none required; JNK2 - none required; MLK3 - none required.

[186] Table 2A. Activity of Selected Compounds of the Invention Against Various Kinases

Compound No.	**CDK7**	CDK1[a]	CDK1[b]	CDK2[a]	CDK2[b]	CDK5[a,c]	CDK5[b,c]	CDK5[a,d]	CDK5[b,d]	CDK8[a]	CDK8[b]
100	**B**										
101	**B**	C	C	C	C	C	C	C	C	C	C
102	**B**										

Table 2B. Activity of Selected Compounds of the Invention Against Various Kinases

Compound No.	CDK9[a,e]	CDK9[b,e]	CDK9[a,f]	CDK9[b,f]	JNK1[a]	JNK1[b]	JNK2[a]	JNK2[b]	MLK3[a]	MLK3[b]
100										
101	C	C	C	C	B	A	C	A		

[a] Compound tested at 100 nM
[b] Compound tested at 1 μM
[c] CDK5 tested using p25 co-factor
[d] CDK5 tested using p35 co-factor
[e] CDK9 tested using cyclin T1 co-factor
[f] CDK9 tested using cyclin K co-factor

Compound 100 was tested against CDK5 using p25 as a co-factor and against MLK3. Although a percent inhibition was not determined, Compound 100 was calculated to have a 3.0 μM IC_{50} against CDK5 and a 3.2 μM C_{50} against MLK3.

Example 7 Inhibition of Cell Proliferation. Representative compounds of the invention were tested at different concentrations (from 10 μM to 316 pM; 0.5 log serial dilutions) for their ability to inhibit the proliferation of Jurkat cells. Cells were grown in RPMI 1640 + 10% FBS + 1% Glutamax supplemented with FBS (Life Technologies) and 100 $U \cdot mL^{-1}$ penicillin, 100 $\mu g \cdot mL^{-1}$ streptomycin (Invitrogen) and cultured at 37 °C in a humidified chamber in the presence of 5% CO_2. Proliferation assays were conducted over a 72 hour time period. CellTiter-Glo®

(Promega Corporation, Madison, WI USA) was used to assess the anti-proliferative effects of the compounds following manufacturer's directions and utilizing the reagents supplied with the CellTiter-Glo® kit. The results of these assays are set forth in Tables 3, below. In this table, "A" represents an IC_{50} of less than 500 nM; "B" an IC_{50} of between 500 nM and 5 μM; and "C" an IC_{50} of greater than 5 μM.

Table 3. Inhibition of Proliferation of Jurkat Cells by Compounds of the Invention.

Compound	Jurkat
100	A

Compound	Jurkat
101	B

Equivalents and Scope

[187] In the claims articles such as "a," "an," and "the" may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include "or" between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The invention includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process.

[188] Furthermore, the invention encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, and descriptive terms from one or more of the listed claims is introduced into another claim. For example, any claim that is dependent on another claim can be modified to include one or more limitations found in any other claim that is dependent on the same base claim. Where elements are presented as lists, *e.g.*, in Markush group format, each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should it be understood that, in general, where the invention, or aspects of the invention, is/are referred to as comprising particular elements and/or features, certain embodiments of the invention or aspects of the invention consist, or consist essentially of, such elements and/or features. For purposes of simplicity, those embodiments have not been specifically set forth *in haec verba* herein. It is also noted that the terms "comprising" and "containing" are intended to be open and permits the inclusion of additional elements or steps.

Where ranges are given, endpoints are included. Furthermore, unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or sub–range within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[189] This application refers to various issued patents, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference. If there is a conflict between any of the incorporated references and the instant specification, the specification shall control. In addition, any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims. Because such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the invention can be excluded from any claim, for any reason, whether or not related to the existence of prior art.

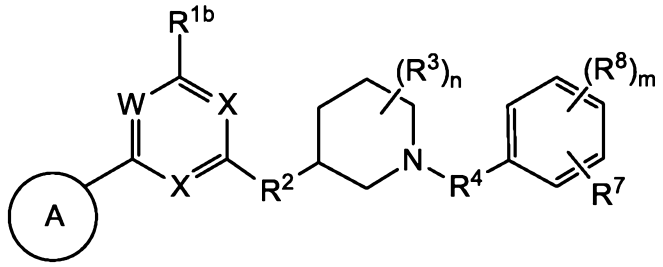
[190] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The scope of the present embodiments described herein is not intended to be limited to the above Description, but rather is as set forth in the appended claims. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present invention, as defined in the following claims.

[191] The term "comprise" and variants of the term such as "comprises" or "comprising" are used herein to denote the inclusion of a stated integer or stated integers but not to exclude any other integer or any other integers, unless in the context or usage an exclusive interpretation of the term is required.

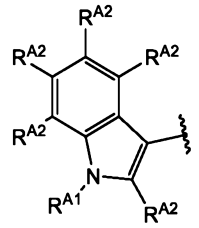
[192] Any reference to publications cited in this specification is not an admission that the disclosures constitute common general knowledge in Australia.

CLAIMS:

1. A compound having the structural formula I:



(I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein:

ring A is  ;

wherein:

each instance of R^{A1} is independently selected from hydrogen and C_{1-6} alkyl;

each instance of R^{A2} is independently selected from hydrogen, halogen, C_{1-6} alkyl, and aryl;

each X is N;

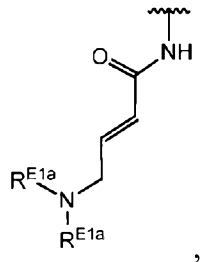
W is $C(R^{1a})$;

R^{1a} is selected from hydrogen, halogen, -OH, -C_1-C_3 alkyl, halo-substituted -C_1-C_3 alkyl, -O-C_1-C_3 alkyl, halo-substituted -O-C_1-C_3 alkyl, -CN, -NH_2, -NH(C_1-C_3alkyl), -N(C_1-C_3 alkyl)$_2$, and C_3-C_6-cycloalkyl;

R^{1b} is selected from hydrogen, halogen, -OH, -C_1-C_3 alkyl, halo-substituted -C_1-C_3 alkyl, -O-C_1-C_3 alkyl, halo-substituted -O-C_1-C_3 alkyl, -CN, -NH_2, -NH(C_1-C_3alkyl), and -N(C_1-C_3 alkyl)$_2$;

R^2 is selected from -NH- and -NH-CH_2-**, wherein "**" represents a portion of R^2 bound to piperidin-1,3-diyl;

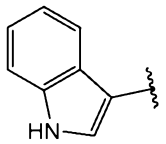
R^4 is -C(O)-, ††-C(O)-NH, or -CH_2-, wherein "††" represents a portion of R^4 bound to piperidin-1,3-diyl;

R^7 is  , wherein each occurrence of R^{E1a} is independently selected from the group consisting of hydrogen, and alkyl optionally substituted with hydroxy, or two R^{E1a} groups are joined to form a heterocyclic ring optionally substituted with methyl;

R^8, if present, is halogen, or C_1-C_4 alkyl;

m is 0 or 1; and

n is 0.

2. The compound of claim 1, wherein ring A is  .

3. The compound of claim 1 or 2, wherein R^{1a} is chloro.

4. The compound of any one of claims 1-3, wherein R^{1b} is hydrogen.

5. The compound of any one of claims 1-3, wherein R^2 is -NH.

6. The compound of any one of claims 1-5, wherein R^4 is -C(O)- or $-CH_2$.

7. The compound of any one of claims 1-6, wherein R^7 is located *para* or *meta* to R^4.

8. The compound of claim 7, wherein R^7 is located *para* to R^4.

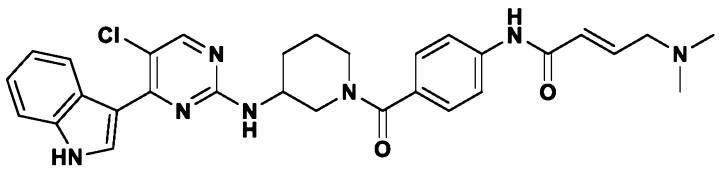
9. The compound of claim 7, wherein R^7 is located *meta* to R^4.

10. The compound of any one of claims 1-9, wherein R^7 is 4-dimethylaminobut-2-enamido.

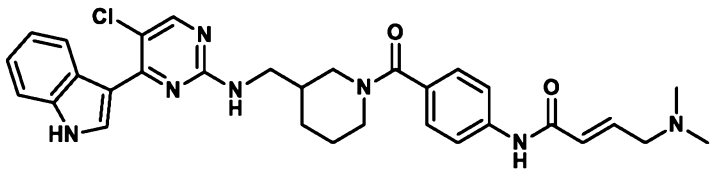
11. The compound of any one of claims 1-10, wherein R^8, if present, is C_1-C_4 alkyl.

12. The compound of claim 11, wherein R^8 is methyl.

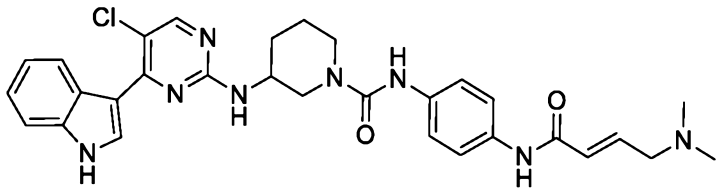
13. The compound of claim 1, selected from any one of:



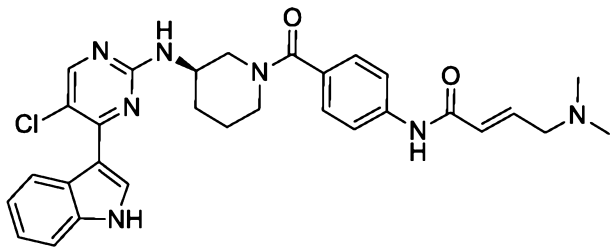
(Compound 100),



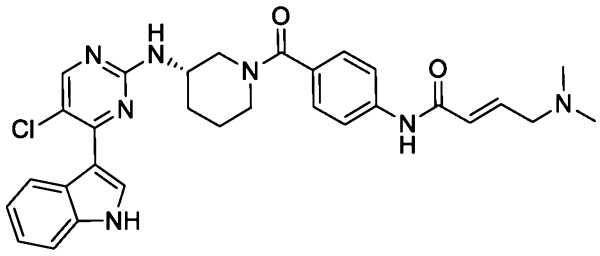
(Compound 101),



(Compound 102),



(Compound 103),



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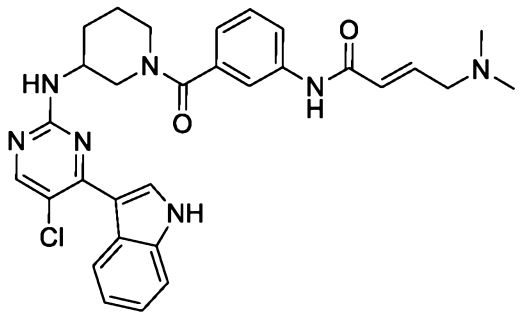
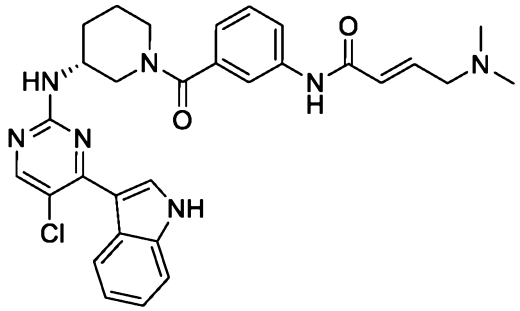
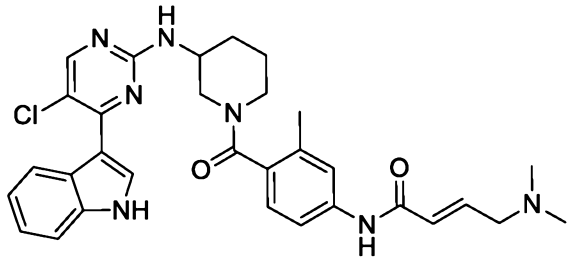


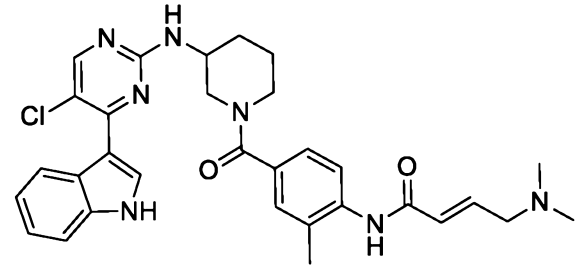
(Compound 105),



(Compound 106),



(Compound 107),



(Compound 108),

and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers, and isotopically labeled derivatives of the foregoing.

14. A pharmaceutical composition comprising a compound of any one of claims 1-13 and a pharmaceutically acceptable excipient.

15. A method of treating a subject suffering from a disease or condition associated with aberrant activity of a cyclin-dependent kinase 7 (CDK7) comprising the step of administering to the subject in need thereof a compound of any one of claims 1-13, or a composition of claim 14.

16. The method of claim 15, wherein the disease or condition is a proliferative disease or an infectious disease.

17. The method of claim 15 or 16, wherein the subject is a mammal.

18. The method of claim 16 or 17, wherein the proliferative disease is cancer.

19. The method of claim 18, wherein the cancer is a blood cancer, melanoma, a bone cancer, a breast cancer, a brain cancer, or a lung cancer.

20. The method of claim 19, wherein the cancer is a blood cancer selected from chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), T-cell acute lymphoblastic leukemia (T-ALL), chronic myelogenous leukemia (CML), acute myelogenous leukemia (AML), lymphoma, and multiple myeloma.

21. The method of claim 19, wherein the bone cancer is osteosarcoma or Ewing's sarcoma.

22. The method of claim 19, wherein the breast cancer is triple-negative breast cancer (TNBC).

23. The method of claim 19, wherein the brain cancer is neuroblastoma.

24. The method of claim 19, wherein the lung cancer is small cell lung cancer (SCLC).

25. The method of any one of claims 15-24, comprising the additional step of administering to the subject in need thereof one or more additional agents independently selected from anti-proliferative agents, anti-cancer agents, immunosuppressant agents, and pain-relieving agents.

26. The method of any one of claims 15-24, comprising the additional step of administering to the subject in need thereof one or more additional agents independently selected from a topoisomerase inhibitor, a MCL1 inhibitor, a BCL-2 inhibitor, a BCL-xL inhibitor, a BRD4 inhibitor, a CDK9 inhibitor, a Jumonji histone demethylase inhibitor, and a DNA damage inducer.

Date: 13 December 2018