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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 August 2008 (07.08.2008)

PCT

(10) International Publication Number
WO 2008/094602 A2

(51) International Patent Classification:
C07D 487/04 (2006.01) *A61P 35/00* (2006.01)
A61K 31/505 (2006.01)

(21) International Application Number:
PCT/US2008/001230

(22) International Filing Date: 30 January 2008 (30.01.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/898,300	30 January 2007 (30.01.2007)	US
60/898,382	30 January 2007 (30.01.2007)	US

(71) Applicant *(for all designated States except US)*: **BIOGEN IDEC MA INC.** [US/US]; 14 Cambridge Center, Cambridge, MA 02142 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KASIBHATLA, Srinivas, Rao** [US/US]; 13073 Dressage Lane, San Diego, CA 92130 (US). **HONG, Kevin** [US/US]; 5734 Redwood Street, San Diego, CA 92129 (US). **ZHANG, Lin** [US/US]; 12455 Brickellia Street, San Diego, CA 92104 (US). **BOEHM, Marcus, F.** [US/US]; 2811 Maple Street, San Diego, CA 92104 (US). **FAN, Junhua** [CN/US]; 12217 Caminito Mira Del Mar, San Diego, CA 92130 (US). **LE BRAZIDEC, Jean-yves** [FR/US]; 10170 Wateridge Circle, Unit 142, San Diego, CA 92121 (US).

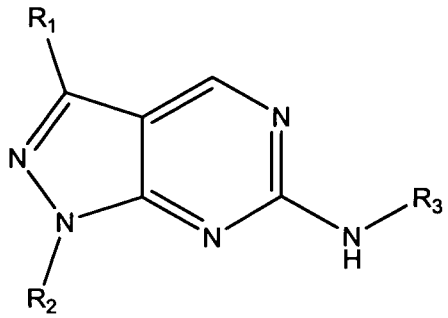
(74) Agent: **O'BRIEN, Jonathan, P.**; Miller, Canfield, Paddock And Stone, P.L.C., 444 West Michigan Avenue, Kalamazoo, MI 49007 (US).

(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, BR, BW, BY, BZ, CA, CH, 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, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, 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, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

(54) Title: MODULATORS OF MITOTIC KINASES



(I)

(57) Abstract: The invention relates to compounds of Formula (I), a prodrug, a polymorph, a tautomer, an enantiomer, a stereoisomer, a solvate, an N-oxide derivatve, or a pharmaceutically acceptable salt thereof: Formula (I); which have inhibitory effect on one or more protein kinases that are involved in cell mitosis.

WO 2008/094602 A2

MODULATORS OF MITOTIC KINASES

CROSS-REFERENCE

[001] This application claims priority to U.S. Application No. 60/898,300, filed on January 30, 2007, and U.S. Application No. 60/898,382, also filed on January 30, 2007. Both of these applications are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

[002] Mitosis is an extraordinarily complex biological process in which a complete copy of the duplicated genome is precisely segregated by the microtubule spindle apparatus into two daughter cells. Since the survival of a cell depends on the accuracy of mitosis, multiple fidelity monitoring checkpoint systems have evolved to ensure correct temporal and spatial coordination of this process. Errors in these mechanisms can lead to genomic instability, an important aspect of tumorigenesis. As a result, it is not surprising that these regulatory systems are frequently found to be abnormal in tumor cells when compared to normal cells. See, e.g., Keen, N. et al., *Nature Rev. Cancer*, 4: 927-936 (2004); Lengauer, C. et al., *Nature*, 396, 643-649 (1998).

[003] The onset and end of mitosis are tightly regulated by the phosphorylation and dephosphorylation of numerous proteins. The mitotic phosphorylations are carried out by multiple mitotic serine/threonine kinases such as Aurora kinases, polo-like kinases, cyclin-dependent kinases, and MIMA. See, e.g., Nigg, E.A., *Nature Rev. Mol. Cell Biol.*, 2: 21-32 (2001); Toji, S. et al., *Genes to Cells*, 9: 383-397 (2004).

[004] Eleven forms of cyclin-dependent kinases (CDKs) are known to exist and are named as CDK1 through CDK11. Most of the CDKs were originally discovered as being involved in the regulation of the cell cycle. CDKs are also involved in the regulation of transcription and mRNA processing. CDKs are considered a potential target for anti-cancer medication. Cell death may be caused by interfering with CDK action selectively to interrupt the cell cycle regulation in cancer cells. Currently, some CDK inhibitors such as Seliciclib are undergoing clinical trials. See, e.g., Loyer, P. et al., *Cellular Signalling*, 17 (9): 1033-51 (2005); Adriano G Rossi, *Nature Medicine*, 12: 1056-1064 (2006).

[005] Aurora kinases are protein serine/threonine kinases essential to mitotic progression. In mammalian cells, the Aurora kinase family consists of three members, namely, Aurora A, Aurora B, and Aurora C. These kinases share a conserved catalytic domain and participate in regulating mitotic processes although there exist some differences in their subcellular

localization and mitotic functions. See, e.g., Brown, J.R. et al., *BMC Evol. Biol.*, 4: 39 (2004). Aurora A is localized to duplicated centrosomes and spindle poles during mitosis. Functional studies show that this protein is required for centrosome maturation, separation and mitotic spindle formation. Suppression of Aurora A expression by RNA interference (RNAi) delays mitotic entry in human cells and over-expression of this kinase compromises spindle-checkpoint function and inhibits cytokinesis. Aurora B is a chromosome passenger protein, which is localized to the centromeric region of chromosomes in early stages of mitosis; it translocates to the spindle equator and the spindle midzone during anaphase A, and to the midbody between anaphase B and cytokinesis. It is believed that this protein is actively involved in regulating chromosome alignment and segregation, spindle-checkpoint function, and cytokinesis. Over-expression of kinase dead Aurora B protein blocks the attachment of chromosomes to mitotic spindles, strongly suggestive of defective kinetochores. In addition, impaired functions of Aurora B as the result of RNAi or antibody injection result in spindle checkpoint failure because the cells are unable to undergo mitotic arrest in response to exposure to nocodazole and paclitaxel. Aurora C is a centrosome-associated kinase that may also play a role in the development and progression of cancer. See Jiang, N. et al., *Mini-Reviews in Medicianl Chemistry*, 6: 885-895 (2006). Deregulated expression of Aurora kinases is closely associated with tumorigenesis. Many studies show that Aurora A and Aurora B genes are either over-expressed or amplified in a broad range of tumors. See, e.g., Keen, N. et al., *supra*; Anand, S. et al., Cancer *Cell*, 3: 51 (2003); Warner, S.L. et al., *Mol. Cancer Ther.*, 2: 589 (2003). Due to the important role of Aurora kinases in the mitosis as well as tumorigenesis, great efforts have been directed to the development of compounds targeting these molecules.

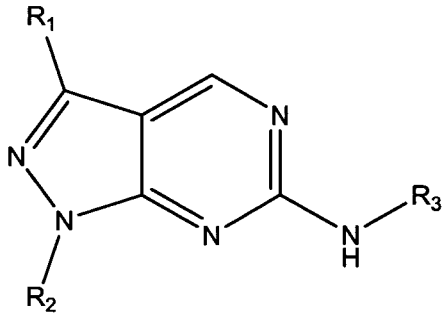
[006] Polo-like kinases (PLKs) are a family of protein serine/threonine kinases highly conserved among eukaryotes. In mammals, the PLK family consists of four members, namely, PLK1, PLK2, PLK3, and PLK4. In addition to the conserved kinase domain, PLKs share unique motifs termed Polo box domains (PBDs) that are present in the C-terminus of this group of proteins. See, e.g., Xie, S.Q. et al., *Oncogene*, 24: 277 (2005). Several studies show that PBDs play a critical role in regulation of the subcellular localization probably through interaction with certain phosphorylated proteins critical for cell proliferation. See, e.g., Lowery, D.M. et al., *Oncogene*, 24: 248 (2005). PLKs have multiple functions in regulating the cell cycle, especially during mitosis. See, Xie, S.Q. et al., supra. PLKs are able to activate the Cdk1/cyclinB complex, which is the key molecule to initiation of mitosis entry. PLK1 also phosphorylates components of the anaphase-promoting complex such as Cdc16 and Cdc27,

suggesting that PLK1 is an important regulator of metaphase and anaphase transition. PLKs are also required for completion of mitosis since point mutations or N-terminal truncation cause cytokinesis failure. See, e.g., van Vugt, M.A. et al., *Oncogene*, 24: 2844 (2005). Over-expression of PLK1 is detected in a majority of human tumor cells and tumor cell lines. See, e.g., Eckerdt, F. et al., *Oncogene*, 24, 267 (2005); Takai, N. et al., *Oncogene*, 24: 287 (2005). In addition, elevated PLK1 expression is closely associated with poor prognosis in cancer patients as well as the metastatic potential of certain tumors. Thus, it is believed that PLK1 plays a causative role in oncogenic transformation. See Takai, N. et al., *supra*.

[007] In view of the roles that multiple mitotic kinases play in tumor cell division and proliferation, it is desireable to have compounds that can inhibt one or more of these multiple mitotic kinases for treating cancer.

SUMMARY OF THE INVENTION

[008] The present invention provides compounds of Formula (I),



I

or prodrugs, polymorphs, tautomers, enantiomers, stereoisomers, solvates, N-oxide derivatves, or pharmaceutically acceptable salts thereof.

[009] Referring to Formula (I),

R_1 is hydrogen or halo;

R_2 is $-L_1-R_a$, wherein

L_1 is a bond or alkyl, and

R_a is cyclohexyl, cycloheptyl, piperidinyl, pyrrolidinyl, furyl, thienyl, morpholinyl, pyridinyl, or pyrimidinyl, each of which is optionally substituted with 1 to 3 substituents; or R_a is substituted phenyl;

R_3 is $-R_b-L_2-R_c$; wherein

R_b is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, and is optionally substituted with 1 to 3 substituents; wherein two of the substituents when adjacent, together

with the atom or atoms to which they are attached, can form a 5- to 16-membered ring with 0 to 6 hetero ring atoms,

L_2 is a bond, $-(CR_xR_y)_n-$, $-N=$, $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-CO-$, $-CO-O-$, $-O-CO-$, $-NR_x-$, $-NR_x-CO-$, $-NR_x-SO_2-$, $-CO-NR_x-$, $-SO_2-NR_x-$, $-NR_x-CO-O-$, $-NR_x-SO_2-O-$, $-NR_x-CO-NR_y-$, $-NR_x-SO_2-NR_y-$, $-CO-NR_x-NR_y-$, $-SO_2-NR_x-NR_y-$, $-NR_x-CO-CO-O-$,

$-NR_x-SO_2-SO_2-O-$, $-S(O)_2-N_x-CO-R_y-$, $-CO-N_x-S(O)_2-R_y-$, or $-(NR_xR_y)C=N-O-$;

R_c is hydrogen, alkyl, alkenyl, alkynyl, guanidinyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, aryl, heteroaryl, (cycloalkyl)alkyl, (heterocycloalkyl)alkyl, (cycloalkenyl)alkyl, (heterocycloalkenyl)alkyl, aralkyl, or heteroaralkyl, and except when being hydrogen, is optionally substituted with 1 to 3 substituents; and

each of R_x and R_y, independently, is hydrogen, hydroxy, alkyl, alkoxy, amino, –CO–alkyl, –CO–aryl, $-SO_2-$alkyl, $-SO_2-$aryl, $-SO_2-$heteroaryl, or $-P(O)(O-alkyl)_2$, wherein the alkyl or aryl moiety in R_x or R_y is optionally substituted with 1 to 3 substituents; and

n is 0, 1, 2, or 3.

[0010] Note that the orientation of L_2 is as shown above, i.e., the left bond of each Markush member links to R_b and the right bond links to R_c. For instance, when L_2 is –CO-O-, R_3 is $-R_b$-CO-O-R_c.

[0011] In some embodiments, each of the 1 to 3 optional substituents on R_a, R_b, R_c, R_x, and R_y, independently, is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, -OR, -SR, -NRR', oxo, -C(O)-OR, -C(O)-NRR', halo, CN, NO_2, N_3, -C(O)R",

-P(O)(OR)(OR'), -O-P(O)(OR)(OR'), -NR-P(O)(OR)(OR'), $-S(O)_2$-OR, -O-$S(O)_2$-OR, -NR-$S(O)_2$-OR', -NR-C(O)-OR", -NR-C(O)-NRR', -NR-C(S)-NRR', -C(S)-NRR', and thioalkyl; wherein each of R and R', independently, is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, or heteroaralkyl; and R" is alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, or heteroaralkyl.

[0012] In some embodiments, R_1 is hydrogen.

[0013] In some embodiments, L_1 is a bond.

[0014] In some embodiments, R_a is cycloheptyl.

[0015] In some embodiments, R_a is phenyl.

[0016] In some embodiments, R_a is phenyl with at least one substituent (e.g., with at least one

substituent at the *para* position).

[0017] In some embodiments, R_2 is 1-(biphenyl-2-yl), 4-hydroxyphenyl, 4-(hydroxymethyl)phenyl, 3-(hydroxyethyl)phenyl, 4-(chloromethyl)phenyl, 4-(tert-butoxycarbonyl)phenyl, 2-(tert-butoxycarboxamido)phenyl, 4-(tert-butoxycarboxamido)phenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 4-iodophenyl, 4-methoxy-2-methylphenyl, 4-methoxy-3-methylphenyl, 4-acetylphenyl, 3-acetylphenyl, 4-(diethoxyphosphoryloxy)phenyl, 4-aminophenyl, 4-nitrophenyl, 4-acetamidophenyl, 3-acetamidophenyl, 2-acetamidophenyl, 4-(tert-butoxycarboxamido)phenyl, 4-(dimethylaminoethoxy)phenyl, 5-methoxy-2,4-dinitrophenyl, 3-methoxy-2,4-dinitrophenyl, 4-(morpholin-4-ylcarbonyl)phenyl, 4-(dimethylamino)phenyl, 4-methoxycarbonyl-3-flurophenyl, 4-(di(cyclopropylcarbonyl)amino)phenyl, 2-methylthiophenyl, 2-ethylthiophenyl, 3-(isopropyloxy)phenyl, 4-isopropylphenyl, 4-(methoxyacetamido)phenyl, 4-(isopropylacetamido)phenyl, 4-(dimethylaminoacetamido)phenyl, 4-methoxy-3-(trifluoromethyl)phenyl, 4-(acrylamido)phenyl, 4-(di(2-furanylcarbox)amido)phenyl, 4-(2-furanyl)carboxamidophenyl, 4-((ethoxycarbonyl)methylcarboxamido)phenyl, 4-(cyclopropylcarboxamido)phenyl, 4-(trifluoromethoxy)phenyl, 4-(2-(piperidin-1-yl)acetamido)phenyl, 4-((tert-butoxycarboxamido)methylcarboxyamido)phenyl, 2-vinylphenyl, 2-(methylsulfonyl)phenyl, 4-(2-(2-methyl-imidazol-1-yl)acetamido)phenyl, 4-(2-(imidazol-1-yl)acetamido)phenyl, 4-(2-(pyrrolidin-1-yl)acetamido)phenyl, 4-(3-(pyrrolidin-1-yl)propanamido)phenyl, 4-(2-(pyrrolidin-1-yl)acetamido)phenyl, 4-(2-(4-methylpiperazin-1-yl)acetamido)phenyl, 4-(3-(4-methylpiperazin-1-yl)propanamido)phenyl, 4-(3-(imidazol-yl)propanamido)phenyl, 4-((4-methoxycarbonyl)butanamido)phenyl, 4-((2-bis(2-hydroxyethyl)amino)acetamido)phenyl, 4-(cyclohexylcarboxamido)phenyl, 4-(bis(cyclohexylcarbonyl)amino)phenyl, 4-((N-morpholinyl)carboxamido)phenyl, 4-(2-(pyridin-3-yl)acetamido)phenyl, 4-(2-(methyl(pyridin-3-ylmethyl)amino)acetamido)phenyl, 4-(3-(N-morpholinyl)propanamido)phenyl, 4-(3-bromopropanamido)phenyl, 4-(2-(thiophen-2-yl)acetamido)phenyl, 4-(2-(2-oxopyrrolidin-1-yl)acetamido)phenyl, 4-(2-(2-oxooxazolidin-3-yl)acetamido)phenyl, 4-((dimethylaminoethyl)aminomethyl)phenyl, 4-((methoxycarbonyl)ethyl)phenyl, 4-((3-(diethylamino)pyrrolidin-1-yl)methyl)phenyl, 2-(ethoxymethyl)phenyl, 4-((N-(tert-butoxycarbonyl)piperidin-4-yl)carboxamido)phenyl, 4-(2-(pyrrolidin-1-yl)acetamido)phenyl, 4-(2-(1H-pyrazol-1-yl)ethoxy)phenyl, 2-(3-hydroxypropylamino)phenyl, 4-(3-hydroxypropylamino)phenyl, 4-(2-aminoacetamido)phenyl, 4-((N-methylpiperdin-4-yl)carboxamido)phenyl, 4-(2-

hydroxyacetamido)phenyl, 2-(hydroxyethylamino)phenyl, 2-(bis(hydroxyethyl)amino)phenyl, 4-(hydroxyethylamino)phenyl, 4-(bis(hydroxyethyl)amino)phenyl, 4-(bis(hydroxypropyl)amino)phenyl, or 4-(((1,1-dioxo)tetrahydrothien-3-yl)(methyl)aminoacetamido)phenyl.

[0018] In some embodiments, R_3 is thioanisol-4-yl, 4-(N'-methanesulfonyl)piperizinylphenyl, 4-bis(methanesulfonyl)aminophenyl, 4-methoxy-3-(methylamino)phenyl, 4-methoxy-3-acetoxyphenyl, 4-methoxy-3-acetamidophenyl, 4-methoxy-3-(methyoxycarbonylamino)phenyl, 4-methoxy-3-(cyclopropanecarboxamido)phenyl, 4-methoxy-3-(cyclopropanecarboxy)phenyl, 4-methoxy-3-((ethylamino)carbonyl)aminophenyl, 4-methoxy-3-aminophenyl, 4-methoxy-3-ethylcarboxyphenyl, 3-aminophenyl, 4-(methanesulfonyl)aminophenyl, 4-aminophenyl, 3-bis(methanesulfonyl)aminophenyl, 3-(methanesulfonyl)aminophenyl, 2-oxo-2,3-dihydrobenzoimidizol-5-yl, 4-(pyrrolidine-1-ylsulfonyl)phenyl, 4-amino-3-bromophenyl, 4-amino-3-hydroxyphenyl, 4-amino-2-hydroxyphenyl, 4-((methanesulfonyl)methylsulfonyl)aminophenyl, 4-amino-3-methoxyphenyl, 4-(N'-methyl)piperazinylphenyl, methanesulfonyl, piperidin-4-yl, 1-(tert-butoxycarbonyl)piperidin-4-yl, or 1-(methanesulfonyl)piperidin-4-yl.

[0019] In some embodimentys, L_1 is alkyl.

[0020] In some embodiments, L_1 is methyl and R_a is phenyl with at least one substituent. In some embodiments, R_2 is 4-acetoxybenzyl, 4-hydroxybenzyl, 3-hydroxybenzyl, 2-(2-imidazol-N-yl)acetamidobenzyl, 2-acetamidobenzyl, 2-aminobenzyl, 2-nitrobenzyl, 4-((2-imidazol-N-yl)acetamido)benzyl, 4-(2-bromo)acetamidobenzyl, 4-aminobenzyl, 3-(2-pyrrolidin-N-yl)acetamidobenzyl, 3-(2-morpholin-N-yl)acetamidobenzyl, 3-(2-(N'-methyl)piperazin-N-yl)acetamidobenzyl, 3-(2-((2-hydroxyethyl)(methyl)amino)acetamido)benzyl, 3-(2-imidazol-N-yl)acetamidobenzyl, 3-((2-bromo)acetamido)benzyl, 3-(2-dimethylamino)acetamidobenzyl, 3-acetamidobenzyl, 3-aminobenzyl, 4-methanesulfonyloxybenzyl, 3-(2-amino)acetamidobenzyl, 4-acetamidobenzyl, 3-(chloromethyl)benzyl, 3-(hydroxymethyl)benzyl, or 3-(acetoxymethyl)benzyl.

[0021] In some embodiments, R_3 is 4-(bis(methanesulfonyl)amino)phenyl.

[0022] In some embodiments, L_1 is ethyl; and R_a is piperidinyl, pyrrolidinyl, furyl, thienyl, or morpholinyl.

[0023] In some embodiments, R_2 is 2-morpholinoethyl.

[0024] In some embodiments, L_1 is a bond; R_a is cycloheptyl, pyridinyl, pyrimidinyl, or

phenyl.

[0025] In some embodiments, R_3 is 4-(ethoxycarbonyl)methylphenyl, 4-(1-methylpiperidin-4-yl)methylphenyl, 4-carboxymethylphenyl, ((4-ethylpiperizin-1-yl)carbonyl)methylphenyl, 4-((methylcarboxamido)methyl)phenyl, 4-((isopropylcarboxamido)methyl)phenyl, 4-((ethoxycarbonyl)isopropyl)phenyl, 4-(carboxyisopropyl)phenyl, 4-(4-methylpiperazin-1-yl)carbonyl)isopropylphenyl, 4-(methanesulfonyl)methylphenyl, 3-chloro-4-(methanesulfonyl)methylphenyl, 4-(methanesulfonyl)(2-morpholinoethyl)aminophenyl, 4-(methanesulfonyl)(2-piperidinoethyl)aminophenyl, 4-(methanesulfonyl)(2-hydroxyethyl)aminophenyl, 4-(methanesulfonyl)isopropylaminophenyl, 4-(methanesulfonyl)(2-hydroxy-3-(piperidin-1-yl)propyl)aminophenyl, 4-(methanesulfonyl)(2-(pyrrolidin-1-yl)ethyl)aminophenyl, 4-(propanesulfonyl)carbamoylphenyl, 4-(tert-butanesulfonyl)carbamoylphenyl, or 4-(ethanesulfonyl)carbamoylphenyl.

[0026] In some embodiments, R_2 is 1-(biphenyl-2-yl), 1-(phenanthren-4-yl), 3-methoxyphenyl, 4-methoxyphenyl, or cycloheptyl.

[0027] In some embodiments, R_b is phenyl.

[0028] In some embodiments, L_2 is a bond; and R_c is cycloalkyl, heterocycloalkyl, aryl, heteroaryl, (cycloalkyl)alkyl, (heterocycloalkyl)alkyl, aralkyl, or heteroaralkyl.

[0029] In some embodiments, L_2 is a bond; and R_c is heterocycloalkyl, heteroaryl, (heterocycloalkyl)alkyl, or heteroaralkyl.

[0030] In some embodiments, L_2 is a bond; and R_c is tetrazolyl, morpholino, or piperazinyl.

[0031] In some embodiments, L_2 is –O–, –S–, $–SO_2–$, –CO–, –CO–O–, $–NR_x–$, $–NR_x–CO–$, $–NR_x–SO_2–$, $–NR_x–CO–O–$, $–NR_x–CO–NR_y–$, or $–NR_x–CO–CO–O–$.

[0032] In some embodiments, L_2 is –CO–O–, $–NR_x–$, $–NR_x–SO_2–$, $–NR_x–CO–O–$, or $–NR_x–CO–NR_y–$, with R_x being hydrogen, alkyl, –CO–alkyl, $–SO_2–$alkyl, $–SO_2–$heteroaryl, or $–SO_2–$aryl.

[0033] In some embodiments, R_c is hydrogen, alkyl, or aryl.

[0034] R_x is hydrogen, alkyl, –CO–alkyl, or $–SO_2–$alkyl; and R_c is hydrogen, alkyl, or aryl.

[0035] In some embodiments, L_1 is a bond; R_a is cycloheptyl, pyridinyl, pyrimidinyl, or phenyl; R_b is phenyl; L_2 is a bond; and R_c is cycloalkyl, heterocycloalkyl, aryl, heteroaryl, (cycloalkyl)alkyl, (heterocycloalkyl)alkyl, aralkyl, or heteroaralkyl.

[0036] In some embodiments, L_1 is a bond; R_a is cycloheptyl or phenyl; R_b is phenyl; L_2 is a bond; and R_c is tetrazolyl, morpholino, or piperazinyl.

[0037] In some embodiments, R_a is phenyl with at least one substituent at the *para* position.

[0038] In some embodiments, R_a is *p*-methoxyphenyl.

[0039] In some embodiments, L_1 is a bond; R_a is cycloheptyl, pyridinyl, pyrimidinyl or phenyl substituted with alkoxy; R_b is phenyl; L_2 is –O–, –S–, $–SO_2–$, –CO–, –CO–O–, $–NR_x–$, $–NR_x–CO–$, $–NR_x–SO_2–$, $–NR_x–CO–O–$, $–NR_x–CO–NR_y–$, or $–NR_x–CO–CO–O–$; with R_x being hydrogen, alkyl, –CO–alkyl, $–SO_2–$alkyl, or $–SO_2–$aryl; and R_c is hydrogen, alkyl, or aryl.

[0040] In some embodiments, L_1 is a bond; R_a is cycloheptyl or phenyl; R_b is phenyl; L_2 is –CO–O–, $–NR_x–$, $–NR_x–SO_2–$, $–NR_x–CO–O–$, or $–NR_x–CO–NR_y–$, with R_x being hydrogen, alkyl,

–CO–alkyl, $–SO_2–$alkyl, or $–SO_2–$aryl; and R_c is hydrogen, alkyl, or aryl.

[0041] In some embodiments, R_x is $–SO_2–$alkyl; and R_c is alkyl.

[0042] In some embodiments, R_a is phenyl with at least one substituent at the *para* position.

[0043] In some embodiments, R_a is *p*-methoxyphenyl.

[0044] In some embodiments, L_1 is alkyl; R_a is phenyl; R_b is phenyl; L_2 is –CO–O–, $–NR_x–$, $–NR_x–SO_2–$, $–NR_x–CO–O–$, or $–NR_x–CO–NR_y$ with each of R_x and R_y, independently, being hydrogen, alkyl, –CO–alkyl, $–SO_2–$alkyl, or $–SO_2–$aryl; and R_c is hydrogen, alkyl, or aryl.

[0045] In some embodiments, L_1 is methyl substituted with phenyl.

[0046] In some embodiments, R_a is cyclohexyl optionally substituted with 1-3 substitutnets. Examples of suitable substitutents include alkoxycarbonyl, hydroxyalkyl, hyroxycarbonyl, alkoxycarbonylamino, and hydroxycarbonylamino. In some further embodiments, R_a is ethoxycarbonyl, hydroxymethyl, hydroxycarbonyl, or tert-butoxycarbonylamino.

[0047] In some embodiments, R_b is phenyl; L_2 is a bond or $–NR_x–SO_2–$; R_x is hydrogen or $–SO_2–$alkyl; and R_c is hydrogen, alkyl, heterocycloalkyl, heteroaryl, heterocycloalkyl–alkyl, or heteroaralkyl.

[0048] In some embodiments, R_x is $–SO_2–$alkyl; and R_c is alkyl.

[0049] In some embodiments, R_3 is 4-(4-methylpiperazin-1-yl)phenyl), 4-(piperazin-1-yl)phenyl, 4-aminophenyl, 4-benzoic acid, 4-morpholinophenyl, 4-N,N-dimethylsulfonylphenyl, or 4-(methanesulfonamide)phenyl.

[0050] In some embodiments, the compound is

N-(4-(1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)cyclopropanesulfonamide,

1-(4-methoxyphenyl)-N-(3-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

2-hydroxy-5-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)benzaldehyde,

ethyl2-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenylamino)-2-oxoacetate,

N-(2,3,5,6,8,9,11,12,14,15-decahydrobenzo[b]-[1,4,7,10,13,16]hexaoxacyclooctadecin-18-yl)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(4-methoxyphenyl)-N-(2,3,5,6,8,9,11,12-octahydrobenzo[b]-[1,4,7,10,13]pentaoxacyclopentadecin-15-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-1-(methylsulfonyl)methanesulfonamide,

3,3,3-trifluoro-N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)propane-1-sulfonamide,

1-(4-methoxyphenyl)-N-(4-morpholinophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(4-(1H-1,2,4-triazol-1-yl)phenyl)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

2-methoxy-4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenol,

N-(3,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(3-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)ethanol,

N^1-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,4-diamine,

N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide,

4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenol,

1-(4-methoxyphenyl)-N-(3,4,5-trimethoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(4-methoxyphenyl)-N-(4-(4-(methylsulfonyl)piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

methyl-3-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenylamino)-3-oxopropanoate,

2-methoxy-N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)acetamide,

N-(3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

2-ethoxy-5-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenol,

2-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)ethanol,

N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)acetamide,

2-(2-methoxyethoxy)-N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)acetamide,

diethyl4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)benzylphosphonate,

1-(3-methoxyphenyl)-N-(4-(4-(methylsulfonyl)piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

dimethyl4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenylphosphoramidate,

N^1-(1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,4-diamine,

1-(4-methoxyphenyl)-N-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(3-methoxyphenyl)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

3-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenol,

1-(4-methoxyphenyl)-N-(4-(piperidin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N^1-bis(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

methyl4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenylcarbamate,

2-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenylamino)-2-oxoethylacetate,

N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

2-methoxy-5-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenol,

1-(4-methoxyphenyl)-N-(4-(methylthio)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-2-methylphenol,

2-methoxy-4-(1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenol,

N-(3,4-dimethoxyphenyl)-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

2-(2-methoxyethoxy)-N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)acetamide,

(E)-N'-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N,N-dimethylformimidamide,

2-methoxy-5-(1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenol,

N-(2,2-dimethylbenzo[d][1,3]dioxol-5-yl)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

methyl2-hydroxy-5-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)benzoate,

1-(4-methoxyphenyl)-N-(4-(methylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

3-(1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenol,

1-(3-methoxyphenyl)-N-(2,3,5,6,8,9,11,12-octahydrobenzo[b]-[1,4,7,10,13]pentaoxacyclopentadecin-15-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(benzo[d][1,3]dioxol-5-yl)-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-methylmethanesulfonamide,

4-methoxy-N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)benzamide,

N-(2,4-dimethoxyphenyl)-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(4-methoxyphenyl)-N-(naphthalen-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

N-(4-(1H-tetrazol-5-yl)phenyl)-1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N,N-dimethyl 4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenylsulfamide,

N^1-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,4-diamine,

3-chloro-N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)propane-1-sulfonamide,

3-chloro-N(-4(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-propyl-1,3-sultam,

1-cycloheptyl-N-(4-(4-(methylsulfonyl)piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)benzoicacid,

1-cycloheptyl-N-(4-morpholinophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

3-chloro-N-(3-chloropropylsulfonyl)-N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)propane-1-sulfonamide,

(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)(morpholino)methanone,

N^1-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,3-diamine,

1-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)guanidine,

N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide,

dimethyl4-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)piperazin-1-ylphosphonate,

(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)(4-ethylpiperazin-1-yl)methanone,

1-cycloheptyl-N-(4-thiomorpholinophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

dimethyl4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenylphosphoramidate,

1-cycloheptyl-N-(4-(piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-cycloheptyl-N-(4-(1-methyl-1H-tetrazol-5-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

2-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)ethanol,

1-allyl-3-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)urea,

N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)acetamide,

1-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-3-ethylurea,

1-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-3-propylurea,

1-cycloheptyl-N-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-cycloheptyl-N-(4-(2-methyl-2H-tetrazol-5-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(4-(2-(2-chloroethyl)-2H-tetrazol-5-yl)phenyl)-1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)thiophene-2-sulfonamide,

4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)benzonitrile,

N-(3-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

1-cycloheptyl-N-(4-(piperidin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-1-(methylsulfonyl)-N-(methylsulfonylmethylsulfonyl)methanesulfonamide,

1-cycloheptyl-N-(4-(2-morpholinoethoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(4-(1H-pyrazol-1-yl)phenyl)-1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(phenylsulfonyl)benzenesulfonamide,

N-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-1,1,1-trifluoro-N-(4-(1,1,1-trifluoro-N-(trifluoromethylsulfonyl)methylsulfonamido)phenyl)methane-sulfonamide,

N-(benzo[d][1,3]dioxol-5-yl)-1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

2-(4-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)piperazin-1-yl)ethanol,

1-cycloheptyl-N-phenyl-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-cycloheptyl-N-(4-(2-vinyl-2H-tetrazol-5-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

ethyl 4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)benzoate,

tert-butyl 4-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)piperazine-1-carboxylate,

N-(4-(1-(4-methoxy-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

1-(4-methoxy-2-methylphenyl)-N-(4-(4-(methylsulfonyl)piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(4-methoxy-2-methylphenyl)-N-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(4-(1-(4-methoxy-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide,

1-(4-methoxy-2-methylphenyl)-N-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(4-methoxy-2-methylphenyl)-N-(4-(trifluoromethoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(4-methoxy-2-methylphenyl)-N-(4-(methylthio)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

2-methoxy-5-(1-(4-methoxy-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenol,

3-(6-(4-aminophenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenol,

4-(6-(4-aminophenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenol,

4-(6-(4-morpholinophenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenol,

5-(1-(3-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-2-methoxyphenol,

5-(1-(4-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-2-methoxyphenol,

N^1-(1-(4-iodophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,4-diamine,

4-(4-(6-(4-aminophenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)but-3-yn-1-ol,

4-(4-(6-(3,4-dimethoxyphenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)but-3-yn-1-ol,

N-(3,4-dimethoxyphenyl)-1-(4-iodophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

5-(1-(4-iodophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-2-methoxyphenol,

1-(4-ethylphenyl)-N-(4-(piperidin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(4-iodophenyl)-N-(4-(piperidin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-benzyl-N-(4-(piperidin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(3-methoxybenzyl)-N-(4-(piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(3,4-dimethoxybenzyl)-N-(4-(piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

tert-butyl 4-(4-(1-(3,5-dimethoxybenzyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)piperazine-1-carboxylate,

1-(3,5-dimethoxybenzyl)-N-(4-(piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

tert-butyl 4-(4-(3-bromo-1-(3,4-dimethoxybenzyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)piperazine-1-carboxylate,

tert-butyl 4-(4-(1-(3,4-dimethoxybenzyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)piperazine-1-carboxylate,

1-(4-methoxybenzyl)-N-(4-(piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

tert-butyl 4-(4-(1-(4-methoxybenzyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)piperazine-1-carboxylate,

1-(2,3-dihydro-1H-inden-2-yl)-N-(4-morpholinophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

ethyl 2-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)acetate,

1-cycloheptyl-N-(4-((4-methylpiperazin-1-yl)methyl)phenyl)-1h-pyrazolo[3,4-d]pyrimidin-6-amine,

2-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)acetic acid,

2-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-1-(4-ethylpiperazin-1-yl)ethanone,

2-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-methylacetamide,

2-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-isopropylacetamide,

ethyl 2-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-2-methylpropanoate,

2-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-2-methylpropanoic acid,

ethyl 2-(2-chloro-4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)acetate,

2-(2-chloro-4-(1-cycloheptyl-1H-pyrazolo[3,4d]pyrimidin-6-ylamino)phenyl)acetic acid,

2-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-2-methyl-1-(4-methylpiperazin-1-yl)propan-1-one,

1-cycloheptyl-N-(4-(methylsulfonylmethyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(3-chloro-4-(methylsulfonylmethyl)phenyl)-1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(2-morpholinoethyl)methanesulfonamide,

N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(2-(piperidin-1-yl)ethyl)methanesulfonamide,

N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(2-hydroxyethyl)methanesulfonamide,

N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-isopropylmethanesulfonamide,

N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(2-hydroxy-3-(piperidin-1-yl)propyl)methanesulfonamide,

N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(2-(pyrrolidin-1-yl)ethyl)methanesulfonamide,

N-(4-(1-(4-hydroxy-2,3-dihydro-1H-inden-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

(S)-N-(4-(1-(2,3-dihydro-1H-inden-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(ethylsulfonyl)ethanesulfonamide,

1-(6-(4-(4-methylpiperazin-1-yl)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2,3-dihydro-1H-inden-4-ol,

1-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2,3-dihydro-1H-inden-4-yl benzoate,

1-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2,3-dihydro-1H-inden-4-yl dihydrogen phosphate,

(S)-1-chloro-N-(chloromethylsulfonyl)-N-(4-(1-(2,3-dihydro-1H-inden-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide,

N-(4-(1-(6,7-dihydro-5H-indeno[5,6-d][1,3]dioxol-5-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

N-(1-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2,3-dihydro-1H-inden-5-yl)acetamide,

N-(4-(1-(4-hydroxy-2,3-dihydro-1H-inden-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide,

1-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2,3-dihydro-1H-inden-5-yl benzoate,

(S,Z)-4-(1-(2,3-dihydro-1H-inden-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-N'-hydroxybenzimidamide,

1-(6-(4-(4-methylpiperazin-1-yl)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2,3-dihydro-1H-inden-4-yl benzoate,

1-(6-(4-aminophenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2,3-dihydro-1H-inden-4-ol,

1-(6-(4-aminophenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2,3-dihydro-1H-inden-4-yl benzoate,

di-tert-butyl 1-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2,3-dihydro-1H-inden-4-yl phosphate,

(S)-4-(1-(2,3-dihydro-1H-inden-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-N-(methylsulfonyl)benzamide,

N-(4-(1-(5-((2-methoxyethoxy)methoxy)-2,3-dihydro-1H-inden-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

N-(1-(6-(4-aminophenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2,3-dihydro-1H-inden-5-yl)acetamide,

(S)-4-(1-(2,3-dihydro-1H-inden-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)benzonitrile,

(S)-N-(4-(1H-tetrazol-5-yl)phenyl)-1-(2,3-dihydro-1H-inden-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N1-(1-(5-methoxy-2,3-dihydro-1H-inden-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,4-diamine,

N-(4-(1-(5-methoxy-2,3-dihydro-1H-inden-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

(S)-1-(2,3-dihydro-1H-inden-1-yl)-N-(4-nitrophenethyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

(S)-N-(4-aminophenethyl)-1-(2,3-dihydro-1H-inden-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

(S)-N-(4-(2-(1-(2,3-dihydro-1H-inden-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)ethyl)phenyl)-N-(methylsulfonyl)methanesulfonamide,

N-(4-(1-(1H-indol-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

N-(4-(1-(1H-indol-6-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

N-(4-(1-(1H-indol-5-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

N-(4-(1-(benzo[d][1,3]dioxol-5-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

1-(1H-indol-4-yl)-N-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(4-(1-(1-methyl-1H-indol-5-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

1-(7-methyl-1H-indol-4-yl)-N-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

tert-butyl 7-methyl-4-(6-(4-(4-methylpiperazin-1-yl)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1H-indole-1-carboxylate,

tert-butyl 4-(6-(4-(4-methylpiperazin-1-yl)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1H-indole-1-carboxylate,

N-(4-morpholinophenyl)-1-(naphthalen-1-ylmethyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-butyl-N-(4-(piperidin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-isopropyl-N-(4-(piperidin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(cyclopentylmethyl)-N-(4-(piperidin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

(S)-N-(4-morpholinophenyl)-1-(1-phenylethyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-((6-fluoro-4H-benzo[d][1,3]dioxin-8-yl)methyl)-N-(4-morpholinophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(furan-2-ylmethyl)-N-(4-(piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

ethyl 2-(6-(4-(piperidin-1-yl)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)acetate,

N-(4-morpholinophenyl)-1-(pyridin-2-ylmethyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-methyl-N-(4-(piperidin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(4-morpholinophenyl)-1-(1,2,3,4-tetrahydronaphthalen-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(1-benzylpiperidin-4-yl)-N-(4-morpholinophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine, or

1-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-N-(4-morpholinophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine.

[0051] In some embodiments, the compound is

N-(4-(1H-tetrazol-5-yl)phenyl)-1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(4-(1H-tetrazol-5-yl)phenyl)-1-(biphenyl-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(4-(1H-tetrazol-5-yl)phenyl)-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(4-(1H-tetrazol-5-yl)phenyl)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-cycloheptyl-N-(4-morpholinophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(biphenyl-2-yl)-N-(4-morpholinophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(4-morpholinophenyl)-1-(phenanthren-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(3-methoxyphenyl)-N-(4-morpholinophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(4-methoxyphenyl)-N-(4-morpholinophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-cycloheptyl-N-(4-(piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(biphenyl-2-yl)-N-(4-(piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(3-methoxyphenyl)-N-(4-(piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(4-methoxyphenyl)-N-(4-(piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)benzoic acid,

4-(1-(biphenyl-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)benzoic acid,

4-(1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)benzoic acid,

4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)benzoic acid,

N^1-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,4-diamine,

N^1-(1-(biphenyl-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,4-diamine,

N^1-(1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,4-diamine,

N^1-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,4-diamine,

N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

N-(4-(1-(biphenyl-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

N-(4-(1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide,

N-(4-(1-(biphenyl-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide,

N-(4-(1-(phenanthren-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide,

N-(4-(1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide,

N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide,

1-cycloheptyl-N-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(biphenyl-2-yl)-N-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(3-methoxyphenyl)-N-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(4-methoxyphenyl)-N-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

5-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-2-methoxyphenol,

5-(1-(biphenyl-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-2-methoxyphenol,

2-methoxy-5-(1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenol,

2-methoxy-5-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenol,

1-(cyclopentylmethyl)-N-(4-(piperidin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

(S)-N-(4-morpholinophenyl)-1-(1-phenylethyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-((6-fluoro-4H-benzo[d][1,3]dioxin-8-yl)methyl)-N-(4-morpholinophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(furan-2-ylmethyl)-N-(4-(piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(4-morpholinophenyl)-1-(pyridin-2-ylmethyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(1-benzylpiperidin-4-yl)-N-(4-morpholinophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-N-(4-morpholinophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(5-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)pyridine-2yl)-N-(methylsulfonyl)methanesulfonamide,

N-(5-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)pyridin-2-yl)methanesulfonamide,

N-(5-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)pyridin-2-yl)-N-(2-hydroxyethyl)methanesulfonamide,

N-(4-(6-(6-(N-(methylsulfonyl)methylsulfonamido)pyridin-3-ylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)-2-(pyrrolidin-1-yl)acetamide,

N-(4-(6-(6-(methylsulfonamido)pyridin-3-ylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)-2-(pyrrolidin-1-yl)acetamide,

N-(5-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)pyridin-2-yl)-N-(2-morpholinoethyl)methanesulfonamide,

N-(5-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)pyridin-2-yl)-N-(2,3-dihydroxypropyl)methanesulfonamide,

N-(4-(6-(6-(N-(2,3-dihydroxypropyl)methylsulfonamido)pyridin-3-ylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)-2-(pyrrolidin-1-yl)acetamide,

tert-butyl 4-(6-(6-(N-(2,3-dihydroxypropyl)methylsulfonamido)pyridin-3-ylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenylcarbamate,

tert-butyl 4-(6-(6-(N-(2-morpholinoethyl)methylsulfonamido)pyridin-3-ylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenylcarbamate,

N-(5-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)pyrimidin-2-yl)methanesulfonamide,

N-(5-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)pyrimidin-2-yl)-N-(2,3-dihydroxypropyl)methanesulfonamide,

tert-butyl 4-(6-(2-(N-(2,3-dihydroxypropyl)methylsulfonamido)pyrimidin-5-ylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenylcarbamate,

N-(5-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)pyrimidin-2-yl)-N-(2-morpholinoethyl)methanesulfonamide,

N-(4-(6-(2-(N-(2,3-dihydroxypropyl)methylsulfonamido)pyrimidin-5-ylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)-2-(pyrrolidin-1-yl)acetamide,

tert-butyl 4-(6-(2-(N-(2-morpholinoethyl)methylsulfonamido)pyrimidin-5-ylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenylcarbamate,

tert-butyl 5-(6-(2-(N-(2-morpholinoethyl)methylsulfonamido)pyrimidin-5-ylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyridin-2-ylcarbamate,

N-(5-(6-(2-(N-(2,3-dihydroxypropyl)methylsulfonamido)pyrimidin-5-ylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyridin-2-yl)-2-(pyrrolidin-1-yl)acetamide,

N-(5-(6-(6-(N-(2,3-dihydroxypropyl)methylsulfonamido)pyridin-3-ylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyridin-2-yl)-2-(pyrrolidin-1-yl)acetamide,

tert-butyl 5-(6-(6-(N-(2-morpholinoethyl)methylsulfonamido)pyridin-3-ylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyridin-2-ylcarbamate,

tert-butyl 6-(6-(6-(N-(2-morpholinoethyl)methylsulfonamido)pyridin-3-ylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyridin-3-ylcarbamate,

N-(6-(6-(6-(N-(2,3-dihydroxypropyl)methylsulfonamido)pyridin-3-ylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyridin-3-yl)-2-(pyrrolidin-1-yl)acetamide,

tert-butyl 6-(6-(2-(N-(2,3-dihydroxypropyl)methylsulfonamido)pyrimidin-5-ylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyridin-3-ylcarbamate,

tert-butyl 6-(6-(6-(N-(2,3-dihydroxypropyl)methylsulfonamido)pyridin-3-ylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyridin-3-ylcarbamate,

N-(5-(1-(3-hydroxybenzyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)pyridin-2-yl)methanesulfonamide,

N-(2,3-dihydroxypropyl)-N-(5-(1-(3-hydroxybenzyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)pyridin-2-yl)methanesulfonamide,

N-(2,3-dihydroxypropyl)-N-(5-(1-((2-hydroxypyridin-4-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)pyridin-2-yl)methanesulfonamide,

N-(5-(1-(3-hydroxybenzyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)pyridin-2-yl)-N-(2-morpholinoethyl)methanesulfonamide,

N-(2,3-dihydroxypropyl)-N-(4-(1-((2-hydroxypyridin-4-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide, or

N-(5-(1-((2-hydroxypyridin-4-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)pyridin-2-yl)-N-(2-morpholinoethyl)methanesulfonamide.

[0052] The present invention includes within its scope prodrugs. In general, such prodrugs will be functional derivatives of the compounds of Formula (I) which are readily convertible in vivo into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various conditions

described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound in vivo after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs," ed. H. Bundgaard, Elsevier, 1985, which is incorporated by reference herein in its entirety. Metabolites of these compounds include active species produced upon introduction of compounds of this invention into the biological milieu.

[0053] Also within the scope of this invention are *N*-oxide derivatives or pharmaceutically acceptable salts of the compounds of Formula (I). For example, a nitrogen ring atom of the imidazole core ring or a nitrogen-containing heterocyclyl substituent can form an oxide in the presence of a suitable oxidizing agent such as *m*-chloroperbenzoic acid or H_2O_2.

[0054] A compound of Formula (I) that is acidic in nature (e.g., having a carboxyl or phenolic hydroxyl group) can form a pharmaceutically acceptable salt such as a sodium, potassium, calcium, or gold salt. Also within the scope of the invention are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, and N-methylglycamine. A compound of Formula (I) can be treated with an acid to form acid addition salts. Examples of such acids include hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, methanesulfonic acid, phosphoric acid, *p*-bromophenyl-sulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, oxalic acid, malonic acid, salicylic acid, malic acid, fumaric acid, ascorbic acid, maleic acid, acetic acid, and other mineral and organic acids well known to those skilled in the art. The acid addition salts can be prepared by treating a compound of Formula (I) in its free base form with a sufficient amount of an acid (e.g., hydrochloric acid) to produce an acid addition salt (e.g., a hydrochloride salt). The acid addition salt can be converted back to its free base form by treating the salt with a suitable dilute aqueous basic solution (e.g., sodium hydroxide, sodium bicarbonate, potassium carbonate, or ammonia). Compounds of Formula (I) can also be, e.g., in a form of achiral compounds, racemic mixtures, optically active compounds, pure diastereomers, or a mixture of diastereomers.

[0055] The compounds described above exhibit inhibitory effect on one or more protease kinases that are involved in the motitic cycle of a cell, e.g., a tumor cell, and also referred to as "mitotic kinases." Examples of such protease kianses include, among others, all exising forms of Aurora kinase, cyclin-dependent kinase, or polo-like kinase.

[0056] As such, also within the scope of this invention are pharmaceutical compositions each including at least one of the compounds described above and a carrier. These pharmaceutical

compositions can be used to treat diseases or conditions mediated by one or more mitotic kineses.

[0057] Accordingly, another aspect of this invention relates to a method of treating a subject with a protein kinase-mediated disease. The method includes administering to said subject a pharmaceutically effective amount of one of the compounds described abvoe.

[0058] The compounds of this invention also exhibit inhibitory effect on one or more kinases involved in the phosphorylation process in the cells. Exampels of such kinases also include all forms of Aurora kinase, cyclin-dependent kinase, or polo-like kinase. Thus, the invention is further directed to a method for decreasing the phosphorylation of one or more such protease kinases in a cell, which includes contacting the cell with one of the compounds of this invention.

[0059] Another aspect of this invention further relates to a method of inhibiting a protease kinase in a cell, which includes contacting the cell with one of the compounds described abvoe. Such protease kinase is one or more protease kinases involved in cell mitosis and examples of which include, among others, all exising forms of Aurora kinase, cyclin-dependent kinase, or polo-like kinase.

[0060] This invention further provides a method for inhibiting the abnormal growth of cells, including transformed cells, by administering an effective amount of a compound of the invention. Abnormal growth of cells refers to cell growth independent of normal regulatory mechanisms (e.g. loss of contact inhibition).

[0061] This invention may also provide a method for inhibiting proliferative diseases (i.e., diseases worsened due to the reproduction of cells), both benign and malignant, with said inhibition being accomplished by the administration of an effective amount of the compounds described herein, to a subject in need of such a treatment.

[0062] The invention still further provides a method of treating or preventing tumor or cancer with a compound of Formula (I) to a subject, e.g. a mammal (and more particularly a human) in need of such treatment. The tumor or cancer can be, e.g., bone cancer (e.g., Ewing's sarcoma, osteosarcoma, chondrosarcoma, or orthopaedics links), brain and CNS tumor (e.g., acoustic neuroma, spinal cord tumor, brain tumor ring of hope), breast cancer, breast cancer, colorectal cancer (e.g., anal cancer), endocrine cancer (e.g., adrenocortical carcinoma, pancreatic cancer(e.g. pancreatic carcinoma such as exocrine pancreatic carcinoma), pituitary cancer, thyroid cancer, parathyroid cancer, thymus cancer, multiple endocrine neoplasia, or other endocrine cancer), gastrointestinal cancer (e.g., stomach cancer, esophageal cancer, small intestine cancer, gall bladder cancer, liver cancer, extra-hepatic bile duct cancer, or

gastrointestinal carcinoid tumor), genitourinary cancer (e.g., testicular cancer, penile cancer, or prostate cancer), gynaecological cancer (e.g., cervical cancer, ovarian cancer, vaginal cancer, uterus/endometrium cancer, vulva cancer, gestational trophoblastic cancer, fallopian tube cancer, or uterine sarcoma), head and neck cancer (e.g., oral cavity, lip, salivary gland cancer, larynx, hypopharynx, oropharynx cancer, nasal, paranasal, or nasopharynx cancer), leukaemia (e.g., acute lymphocytic leukaemia, acute myeloid leukaemia, chronic lymphocytic leukaemia, chronic myeloid leukaemia, hairy cell leukaemia, acute promyelocytic leukemia, plasma cell leukaemia), lung cancer (e.g., adenocarcinoma, small cell lung cancer, or non-small cell lung cancer), lymphoma (e.g., Hodgkin's Disease, Non-Hodgkin's Lymphoma, AIDS-related Lymphoma), eye cancer (e.g., retinoblastoma or intraocular melanoma), skin cancer (e.g., melanoma, non-melanoma skin cancer or Merkel cell cancer), soft tissue sarcoma (e.g., Kaposi's Sarcoma), urinary system cancer (e.g., kidney cancer, Wilm's tumor, bladder cancer, urethral cancer, or transitional cell cancer), and other types or related disorders (e.g., histiocytosis, mesothelioma, metastatic cancer, carcinoid tumors, neurofibromatosis, germ cell tumors, desmoplasic small round cell tumor, malignant rhabdoid tumor, desmoid tumor, ataxia-telangiectasia, Nijmegen breakage syndrome, Rothmund-Thomson syndrome, Li-Fraumeni Syndrome, von Hipple-Lindau Disease, Beckwith-Wiedemann syndrome, Down's syndrome, Denys-Drash syndrome, WAGR syndrome, or CIN cervical intraepithelial neoplas). The compound can be administered in a suitable manner, e.g., intravenously, subcutenously, orally, parenterally, or topically.

[0063] In some other embodiments, the compound is administered in combination with a second therapeutic agent. Examples of such a second therapeutic agent include alkylating agents (e.g., Asaley, AZQ, BCNU, Busulfan, carboxyphthalatoplatinum, CBDCA, CCNU, CHIP, chlorambucil, chlorozotocin, cis-platinum, clomesone, cyanomorpholinodoxorubicin, cyclodisone, dianhydrogalactitol, fluorodopan, hepsulfam, hycanthone, melphalan, methyl CCNU, mitomycin C, mitozolamide, nitrogen mustard, PCNU, piperazine, piperazinedione, pipobroman, porfiromycin, spirohydantoin mustard, teroxirone, tetraplatin, thio-tepa, triethylenemelamine, uracil nitrogen mustard, or Yoshi-864), anitmitotic agents (e.g., allocolchicine, Halichondrin B, colchicines, colchicine derivative, dolastatin 10, maytansine, rhizoxin, taxol, taxol derivative, thiocolchicine, trityl cysteine, vinblastine sulfate, or vincristine sulfate), Topoisomerase I inhibitors (e.g., camptothecin, camptothecin sodium, aminocamptothecin, or camptothecin derivatives), Topoisomerase II inhibitors (e.g., doxorubicin, amonafide, m-AMSA, anthrapyrazole derivative, pyrazoloacridine, bisantrene HCl, daunorubicin, deoxydoxorubicin, mitoxantrone, menogaril, N,N-dibenzyl daunomycin,

oxanthrazole, rubidazone, VM-26, VP-16), RNA/DNA antimetabolite (e.g., L-alanosine, 5-azacytidine, 5-fluorouracil, acivicin, aminopterin derivative, aminopterin derivative, aminopterin derivative, an antifol, Baker's soluble antifol, dichlorallyl lawsone, brequinar, ftorafur (pro-drug), 5,6-dihydro-5-azacytidine, methotrexate, methotrexate derivative, N-(phosphonoacetyl)-L-aspartate (PALA), pyrazofurin, or trimetrexate), DNA antimetabolites (e.g., 3-HP, 2'-deoxy-5-fluorouridine, 5-HP, alpha-TGDR, aphidicolin glycinate, ara-C, 5-aza-2'-deoxycytidine, beta-TGDR, cyclocytidine, guanazole, hydroxyurea, inosine glycodialdehyde, macbecin II, pyrazoloimidazole, thioguanine, or thiopurine).

[0064] For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described by Thomas Sorrell in Organic Chemistry, University Science Books, Sausalito (1999); and by M.B. Smith and J. March in Advanced Organic Chemistry, 5th Ed., John Wiley & Sons, New York (2001), the entire contents of which are hereby incorporated by reference.

[0065] The term "modulating" as used herein means increasing or decreasing, e.g. activity, by a measurable amount. Compounds that modulate the function of protease kinases by increasing their activity or their roles in protein phosphorylation are called agonists. Compounds that modulate the function of protease kinases by decreasing their activity or their roles in protein phsophorylaton are called antagonists or inhibitors.

[0066] As described herein, compounds of the invention may optionally be substituted with one or more substituents, such as those as generally illustrated above, or as specifically exemplified by particular classes, subclasses, and species of the invention.

[0067] As used herein, the term "aliphatic" encompasses alkyl, alkenyl, and alkynyl, each of which is optionally substituted as set forth below. Unless otherwise specified, it encompasses both a branched group (e.g., tert-alkyl such as tert-butyl) or a straight aliphatic chain (e.g., *n*-alkyl groups, alkenyl groups, or alkynyl groups). A straight aliphatic chain has the basic structure of $-(CH_2)_v-$, wherein v can be any integer, e.g., from 1 to 12 (such as 1 to 6). A branched aliphatic chain is a straight aliphatic chain that is substituted with one or more aliphatic groups. A branched aliphatic chain has the structure $-[CQQ']_v-$ wherein at least one of Q and Q' is an aliphatic group.

[0068] As used herein, an "alkyl" group refers to a saturated aliphatic hydrocarbon group containing 1-8 (e.g., 1-6 or 1-4) carbon atoms. An alkyl group can be straight or branched. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-heptyl, and 2-ethylhexyl. An alkyl group can

be substituted (i.e., optionally substituted) with one or more substituents. Examples of the substituents include, but are not limited to, halo; cycloaliphatic (e.g., cycloalkyl or cycloalkenyl); heterocycloaliphatic (e.g., heterocycloalkyl or heterocycloalkenyl); aryl; heteroaryl; alkoxy; alkoxycarbonyl; alkylcarboxy; aroyl; heteroaroyl; acyl (e.g., (aliphatic)carbonyl, (cycloaliphatic)carbonyl, or (heterocycloaliphatic)carbonyl); nitro; cyano; amido (e.g., (cycloalkylalkyl)amido, arylamidoo, aralkylamido, (heterocycloalkyl)amido, (heterocycloalkylalkyl)amido, heteroarylamido, heteroaralkylamido alkylamido, cycloalkylamido, heterocycloalkylamido, arylamido, or heteroarylamido); amino (e.g., aliphaticamino, cycloaliphaticamino, or heterocycloaliphaticamino); oxime; sulfonyl (e.g., aliphatic-$S(O)_2$-); sulfinyl; sulfanyl; sulfoxy; urea; thiourea; sulfonamide; sulfamide; oxo (thus forming a carbonyl group, i.e., -CO-); carboxy; carbamoyl; cycloaliphaticoxy; heterocycloaliphaticoxy; aryloxy; heteroaryloxy; aralkyloxy; heteroarylalkoxy; alkoxycarbonyl; alkylcarbonyloxy; hydroxyl; or cycloaliphatic (alkoxy)phosphoryl. Without limitation, examples of substituted alkyls include carboxyalkyl (such as HOOC-alkyl, alkoxycarbonylalkyl, and alkylcarbonyloxyalkyl); cyanoalkyl; hydroxyalkyl; alkoxyalkyl; acylalkyl; aralkyl; (alkoxyaryl)alkyl; (sulfonylamino)alkyl (e.g., alkyl-$S(O)_2$-aminoalkyl); aminoalkyl; amidoalkyl; (cycloaliphatic)alkyl; silyl (e.g. trialkylsilyl); and haloalkyl.

[0069] As used herein, an "alkenyl" group refers to an aliphatic carbon group that contains 2 to 8 (e.g., 2 to 6 or 2 to 4) carbon atoms and at least one double bond. Like an alkyl group, an alkenyl group can be straight or branched. Examples of an alkenyl group include, but are not limited to, allyl, isoprenyl, 2-butenyl, and 2-hexenyl. An alkenyl group can be optionally substituted with one or more substituents, such as halo; cycloaliphatic (e.g., cycloalkyl or cycloalkenyl); heterocycloaliphatic (e.g., heterocycloalkyl or heterocycloalkenyl); aryl; heteroaryl; alkoxy; aroyl; heteroaroyl; acyl (e.g., (aliphatic)carbonyl, (cycloaliphatic)carbonyl, or (heterocycloaliphatic)carbonyl); nitro; cyano; amido (e.g., (cycloalkylalkyl)amido, arylamido, aralkylamido, (heterocycloalkyl)amido, (heterocycloalkylalkyl)amido, heteroarylamido, heteroaralkylamido alkylaminocarbonyl, cycloalkylaminocarbonyl, heterocycloalkylaminocarbonyl, arylaminocarbonyl, or heteroarylaminocarbonyl); amino (e.g., aliphaticamino, cycloaliphaticamino, heterocycloaliphaticamino, or aliphaticsulfonylamino); oxime; sulfonyl (e.g., alkyl-$S(O)_2$-, cycloaliphatic-$S(O)_2$-, or aryl-$S(O)_2$-); sulfinyl; sulfanyl; sulfoxy; urea; thiourea; sulfonamide; sulfamide; oxo; carboxy; carbamoyl; cycloaliphaticoxy; heterocycloaliphaticoxy; aryloxy; heteroaryloxy; aralkyloxy; heteroaralkoxy; alkoxycarbonyl; alkylcarbonyloxy; or hydroxy. Without limitation, some examples of

substituted alkenyls include cyanoalkenyl, alkoxyalkenyl, acylalkenyl, hydroxyalkenyl, aralkenyl, (alkoxyaryl)alkenyl, (sulfonylamino)alkenyl (such as (alkyl-$S(O)_2$-aminoalkenyl), aminoalkenyl, amidoalkenyl, (cycloaliphatic)alkenyl, and haloalkenyl.

[0070] As used herein, an "alkynyl" group refers to an aliphatic carbon group that contains 2 to 8 (e.g., 2 to 6 or 2 to 4) carbon atoms and has at least one triple bond. An alkynyl group can be straight or branched. Examples of an alkynyl group include, but are not limited to, propargyl and butynyl. An alkynyl group can be optionally substituted with one or more substituents such as aroyl; heteroaroyl; alkoxy; cycloalkyloxy; heterocycloalkyloxy; aryloxy; heteroaryloxy; aralkyloxy; nitro; carboxy; cyano; halo; hydroxy; sulfo; mercapto; sulfanyl (e.g., aliphatic-S- or cycloaliphatic-S-); sulfinyl (e.g., aliphatic-S(O)- or cycloaliphatic-S(O)-); sulfonyl (e.g., aliphatic-$S(O)_2$-, aliphaticamino-$S(O)_2$-, or cycloaliphatic-$S(O)_2$-); amido (e.g., alkylamido, alkylamido, cycloalkylamido, heterocycloalkylamido, cycloalkylamido, arylamido, arylamido, aralkylamido, (heterocycloalkyl)amido, (cycloalkylalkyl)amido, heteroaralkylamido, heteroarylamido or heteroarylamido); urea; thiourea; sulfonamide; sulfamide; alkoxycarbonyl; alkylcarbonyloxy; cycloaliphatic; heterocycloaliphatic; aryl; heteroaryl; acyl (e.g., (cycloaliphatic)carbonyl or (heterocycloaliphatic)carbonyl); amino (e.g., aliphaticamino); sulfoxy; oxo; carbamoyl; (cycloaliphatic)oxy; (heterocycloaliphatic)oxy; or (heteroaryl)alkoxy.

[0071] As used herein, an "amido" encompasses both "aminocarbonyl" and "carbonylamino." Each of these terms, when used alone or in connection with another group, refers to an amido group such as -$N(R_X)$-C(O)-R_Y or -C(O)-$N(R_X)_2$, when used terminally; or -C(O)-$N(R_X)$- or -$N(R_X)$-C(O)- when used internally, wherein R_X and R_Y are defined below. Examples of amido groups include alkylamido (such as alkylcarbonylamino or alkylaminocarbonyl), (heterocycloaliphatic)amido, (heteroaralkyl)amido, (heteroaryl)amido, (heterocycloalkyl)alkylamido, arylamido, aralkylamido, (cycloalkyl)alkylamido, and cycloalkylamido.

[0072] As used herein, an "amino" group refers to -NR_XR_Y wherein each of R_X and R_Y is independently hydrogen (or sometimes "H" hereinafter), alkyl, cycloaliphatic, (cycloaliphatic)aliphatic, aryl, araliphatic, heterocycloaliphatic, (heterocycloaliphatic)aliphatic, heteroaryl, carboxy, sulfanyl, sulfinyl, sulfonyl, (aliphatic)carbonyl, (cycloaliphatic)carbonyl, ((cycloaliphatic)aliphatic)carbonyl, arylcarbonyl, (araliphatic)carbonyl, (heterocycloaliphatic)carbonyl, ((heterocycloaliphatic)aliphatic)carbonyl, (heteroaryl)carbonyl, or

(heteroaraliphatic)carbonyl, each of which being defined herein and being optionally substituted. Examples of amino groups include alkylamino, dialkylamino, arylamino, and diarylamino. When the term "amino" is not the terminal group (e.g., alkylcarbonylamino), it is represented by $-NR_X-$ in which R_X has the same meaning as defined above.

[0073] As used herein, an "aryl" group, used alone or as part of a larger moiety such as in "aralkyl", "aralkoxy," or "aryloxyalkyl," refers to monocyclic (e.g., phenyl); bicyclic (e.g., indenyl, naphthalenyl, tetrahydronaphthyl, benzimidazole, benzothiazole, or tetrahydroindenyl); and tricyclic (e.g., fluorenyl tetrahydrofluorenyl, tetrahydroanthracenyl, or anthracenyl) ring systems in which the monocyclic ring system is aromatic or at least one of the rings in a bicyclic or tricyclic ring system is aromatic. The bicyclic and tricyclic groups include benzofused 2- or 3-membered carbocyclic rings. For instance, a benzofused group includes phenyl fused with two or more C_{4-8} carbocyclic moieties. An aryl is optionally substituted with one or more substituents. Examples of such substitutents include, but are not limited to, aliphatic (e.g., alkyl, alkenyl, or alkynyl); arylaliphatic (e.g., arylalkyl), cycloaliphatic; (cycloaliphatic)aliphatic; heterocycloaliphatic; (heterocycloaliphatic)aliphatic; aryl; heteroaryl; heteroarylaliphatic (e.g., heteroarylalkyl); alkoxy; (cycloaliphatic)oxy; (heterocycloaliphatic)oxy; aryloxy; heteroaryloxy; (araliphatic)oxy; (heteroaraliphatic)oxy; aroyl; heteroaroyl; amino; oxo (on a non-aromatic carbocyclic ring of a benzofused bicyclic or tricyclic aryl); azide (i.e., $-N_3$), nitro; carboxy (e.g., alkoxy-C(O)-); amido; amidoamino (e.g., -NR-C(O)-NRR'); thioamido (e.g., -C(S)-NRR'); thioamidoamino (e.g., -NR-C(S)-NRR'); alkoxyamido (e.g., -NR-C(O)-alkoxy or -C(O)-NR-alkoxy); acyl (e.g., aliphaticcarbonyl, (cycloaliphatic)carbonyl, ((cycloaliphatic)aliphatic)carbonyl, (araliphatic)carbonyl, (heterocycloaliphatic)carbonyl, ((heterocycloaliphatic)aliphatic)carbonyl, or (heteroaraliphatic)carbonyl); sulfonyl (e.g., aliphatic-$S(O)_2$-, (aliphatic-O)-$S(O)_2$-O-, or amino-$S(O)_2$-); sulfonylamino (e.g., -NR-$S(O)_2$-OR'); sulfinyl (e.g., aliphatic-S(O)- or cycloaliphatic-S(O)-); sulfinylamino; sulfanyl (e.g., aliphatic-S-); cyano; halo; hydroxy; mercapto; sulfoxy; urea; thiourea; sulfonamide; sulfamide; carbamoyl; phosphinio (e.g., -P(O)(OR)R'); phosphonio (e.g., -O-P(O)(OR)R'); phosphinioamino (e.g., -NR-P(O)(OR')R"); or phosphonioamino (e.g., -NR-P(O)(OR)(OR')). Each of R, R' and R" in the just-mentioned examples can be independently an aliphatic. Alternatively, an aryl can be unsubstituted.

[0074] Non-limiting examples of substituted aryls include haloaryl (e.g., mono-, di- (e.g., p,m-dihaloaryl), and (trihalo)aryl); (carboxy)aryl (e.g., (alkoxycarbonyl)aryl, ((aralkyl)carbonyloxy)aryl, and (alkoxycarbonyl)aryl); (amido)aryl (e.g.,

(aminocarbonyl)aryl, (((alkylamino)alkyl)aminocarbonyl)aryl, (alkylcarbonyl)aminoaryl, (arylaminocarbonyl)aryl, and (((heteroaryl)amino)carbonyl)aryl); aminoaryl (e.g., ((alkylsulfonyl)amino)aryl or ((dialkyl)amino)aryl); (cyanoalkyl)aryl; (alkoxy)aryl; (sulfonamide)aryl (e.g., (aminosulfonyl)aryl); (alkylsulfonyl)aryl; (cyano)aryl; (hydroxyalkyl)aryl; ((alkoxy)alkyl)aryl; (hydroxy)aryl, ((carboxy)alkyl)aryl; (((dialkyl)amino)alkyl)aryl; (nitroalkyl)aryl; (((alkylsulfonyl)amino)alkyl)aryl; ((heterocycloaliphatic)carbonyl)aryl; ((alkylsulfonyl)alkyl)aryl; (cyanoalkyl)aryl; (hydroxyalkyl)aryl; (alkylcarbonyl)aryl; alkylaryl; (trihaloalkyl)aryl; p-amino-m-alkoxycarbonylaryl; p-amino-m-cyanoaryl; p-halo-m-aminoaryl; and (m-(heterocycloaliphatic)-o-(alkyl))aryl.

[0075] As used herein, an "araliphatic" such as an "aralkyl" group refers to an aliphatic group (e.g., a C_{1-4} alkyl group) that is substituted with an aryl group. "Aliphatic," "alkyl," and "aryl" are as defined herein. An example of an araliphatic such as an aralkyl group is benzyl.

[0076] As used herein, an "aralkyl" group refers to an alkyl group (e.g., a C_{1-4} alkyl group) that is substituted with an aryl group. Both "alkyl" and "aryl" have been defined above. An example of an aralkyl group is benzyl. An aralkyl is optionally substituted with one or more substituents.

[0077] Each of the one or more substituents independent can be, e.g., aliphatic (e.g., alkyl, alkenyl, or alkynyl, including carboxyalkyl, hydroxyalkyl, or haloalkyl such as trifluoromethyl); cycloaliphatic (e.g., cycloalkyl or cycloalkenyl); (cycloalkyl)alkyl; heterocycloalkyl; (heterocycloalkyl)alkyl; aryl; heteroaryl; alkoxy; cycloalkyloxy; heterocycloalkyloxy; aryloxy; heteroaryloxy; aralkyloxy; heteroaralkyloxy; aroyl; heteroaroyl; nitro; carboxy; alkoxycarbonyl; alkylcarbonyloxy; amido (e.g., alkylamido, cycloalkylamido, (cycloalkylalkyl)amido, arylamido, aralkylamido, (heterocycloalkyl)amido, (heterocycloalkylalkyl)amido, heteroarylamido, or heteroaralkylamido); cyano; halo; hydroxy; acyl; mercapto; alkylsulfanyl; sulfoxy; urea; thiourea; sulfonamide; sulfamide; oxo; or carbamoyl.

[0078] As used herein, a "bicyclic ring system" includes 8- to 12- (e.g., 9-, 10-, or 11-) membered structures that form two rings, wherein the two rings have at least one atom in common (e.g., 2 atoms in common). Bicyclic ring systems include bicycloaliphatics (e.g., bicycloalkyl or bicycloalkenyl), bicycloheteroaliphatics, bicyclic aryls, and bicyclic heteroaryls.

[0079] As used herein, a "cycloaliphatic" group encompasses a "cycloalkyl" group and a "cycloalkenyl" group, each of which being optionally substituted as set forth below.

[0080] As used herein, a "cycloalkyl" group refers to a saturated carbocyclic mono- or bi-cyclic (fused or bridged) ring of 3 to 10 (e.g., 5 to 10) carbon atoms. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, norbornyl, cubyl, octahydro-indenyl, decahydro-naphthyl, bicyclo[3.2.1]octyl, bicyclo[2.2.2]octyl, bicyclo[3.3.1]nonyl, bicyclo[3.3.2.]decyl, bicyclo[2.2.2]octyl, adamantyl, azacycloalkyl, or ((aminocarbonyl)cycloalkyl)cycloalkyl. A "cycloalkenyl" group, as used herein, refers to a non-aromatic carbocyclic ring of 3-10 (e.g., 4-8) carbon atoms having one or more double bonds. Examples of cycloalkenyl groups include cyclopentenyl, 1,4-cyclohexa-di-enyl, cycloheptenyl, cyclooctenyl, hexahydro-indenyl, octahydro-naphthyl, cyclohexenyl, cyclopentenyl, bicyclo[2.2.2]octenyl, or bicyclo[3.3.1]nonenyl. A cycloalkyl or cycloalkenyl group can be optionally substituted with one or more substituents such as aliphatic (e.g., alkyl, alkenyl, or alkynyl); cycloaliphatic; (cycloaliphatic)aliphatic; heterocycloaliphatic; (heterocycloaliphatic) aliphatic; aryl; heteroaryl; alkoxy; (cycloaliphatic)oxy; (heterocycloaliphatic)oxy; aryloxy; heteroaryloxy; (araliphatic)oxy; (heteroaraliphatic)oxy; aroyl; heteroaroyl; amino; amido (e.g., (aliphatic)carbonylamino, (cycloaliphatic)carbonylamino, ((cycloaliphatic)aliphatic)carbonylamino, (aryl)carbonylamino, (araliphatic)carbonylamino, (heterocycloaliphatic)carbonylamino, ((heterocycloaliphatic)aliphatic)carbonylamino, (heteroaryl)carbonylamino, or (heteroaraliphatic)carbonylamino); nitro; carboxy (e.g., HOOC-, alkoxycarbonyl, or alkylcarbonyloxy); acyl (e.g., (cycloaliphatic)carbonyl, ((cycloaliphatic) aliphatic)carbonyl, (araliphatic)carbonyl, (heterocycloaliphatic)carbonyl, ((heterocycloaliphatic)aliphatic)carbonyl, or (heteroaraliphatic)carbonyl); cyano; halo; hydroxy; mercapto; sulfonyl (e.g., alkyl-$S(O)_2$- and aryl-$S(O)_2$-); sulfinyl (e.g., alkyl-S(O)-); sulfanyl (e.g., alkyl-S-); sulfoxy; urea; thiourea; sulfonamide; sulfamide; oxo; or carbamoyl.

[0081] As used herein, "cyclic moiety" includes cycloaliphatic, heterocycloaliphatic, aryl, or heteroaryl, each of which has been defined previously.

[0082] As used herein, the term "heterocycloaliphatic" encompasses a heterocycloalkyl group and a heterocycloalkenyl group, each of which being optionally substituted as set forth below.

[0083] As used herein, a "heterocycloalkyl" group refers to a 3-10 membered mono- or bicylic (fused or bridged) (e.g., 5- to 10-membered mono- or bicyclic) saturated ring structure, in which one or more of the ring atoms is a heteroatom (e.g., N, O, S, or combinations thereof). Examples of a heterocycloalkyl group include piperidyl, piperazyl, tetrahydropyranyl, tetrahydrofuryl, 1,4-dioxolanyl, 1,4-dithianyl, 1,3-dioxolanyl, oxazolidyl,

isoxazolidyl, morpholinyl, thiomorpholyl, octahydrobenzofuryl, octahydrochromenyl, octahydrothiochromenyl, octahydroindolyl, octahydropyrindinyl, decahydroquinolinyl, octahydrobenzo[b]thiopheneyl, 2-oxa-bicyclo[2.2.2]octyl, 1-aza-bicyclo[2.2.2]octyl, 3-aza-bicyclo[3.2.1]octyl, and 2,6-dioxa-tricyclo[3.3.1.03,7]nonyl. A monocyclic heterocycloalkyl group can be fused with a phenyl moiety such as tetrahydroisoquinoline.

[0084] A "heterocycloalkenyl" group, as used herein, refers to a mono- or bicylic (e.g., 5- to 10-membered mono- or bicyclic) non-aromatic ring structure having one or more double bonds, and wherein one or more of the ring atoms is a heteroatom (e.g., N, O, or S). Monocyclic and bicycloheteroaliphatics are numbered according to standard chemical nomenclature.

[0085] A heterocycloalkyl or heterocycloalkenyl group can be optionally substituted with one or more substituents. Examples of such substitutents include, but are not limited to, aliphatic (e.g., alkyl, alkenyl, or alkynyl); arylaliphatic (e.g., arylalkyl), cycloaliphatic; (cycloaliphatic)aliphatic; heterocycloaliphatic; (heterocycloaliphatic)aliphatic; aryl; heteroaryl; heteroarylaliphatic (e.g., heteroarylalkyl); alkoxy; (cycloaliphatic)oxy; (heterocycloaliphatic)oxy; aryloxy; heteroaryloxy; (araliphatic)oxy; (heteroaraliphatic)oxy; aroyl; heteroaroyl; amino; oxo (on a non-aromatic carbocyclic ring of a benzofused bicyclic or tricyclic aryl); azide (i.e., $-N_3$), nitro; carboxy (e.g., alkoxy-C(O)-); amido; amidoamino (e.g., -NR-C(O)-NRR'); thioamido (e.g., -C(S)-NRR'); thioamidoamino (e.g., -NR-C(S)-NRR'); alkoxyamido (e.g., -NR-C(O)-alkoxy or -C(O)-NR-alkoxy); acyl (e.g., aliphaticcarbonyl, (cycloaliphatic)carbonyl, ((cycloaliphatic)aliphatic)carbonyl, (araliphatic)carbonyl, (heterocycloaliphatic)carbonyl, ((heterocycloaliphatic)aliphatic)carbonyl, or (heteroaraliphatic)carbonyl); sulfonyl (e.g., aliphatic-$S(O)_2$-, (aliphatic-O)-$S(O)_2$-O-, or amino-$S(O)_2$-); sulfonylamino (e.g., -NR-$S(O)_2$-OR'); sulfinyl (e.g., aliphatic-S(O)- or cycloaliphatic-S(O)-); sulfinylamino; sulfanyl (e.g., aliphatic-S-); cyano; halo; hydroxy; mercapto; sulfoxy; urea; thiourea; sulfonamide; sulfamide; carbamoyl; phosphinio (e.g., -P(O)(OR)R'); phosphonio (e.g., -O-P(O)(OR)R'); phosphinioamino (e.g., -NR-P(O)(OR')R"); or phosphonioamino (e.g., -NR-P(O)(OR)(OR')). Each of R, R' and R" in the just-mentioned examples can be independently an aliphatic.

[0086] A "heteroaryl" group, as used herein, refers to a monocyclic, bicyclic, or tricyclic ring system having 4 to 15 ring atoms wherein at least one of the ring atoms is a heteroatom (e.g., N, O, S, or combinations thereof and in which the monocyclic ring system is aromatic or at least one of the rings in the bicyclic or tricyclic ring systems is aromatic. A heteroaryl group

includes a benzofused ring system having 2 to 3 rings. For example, a benzofused group includes benzo fused with one or two 4- to 8-membered heterocycloaliphatic moieties (e.g., indolizyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furyl, benzo[b]thiophenyl, quinolinyl, or isoquinolinyl). Some examples of heteroaryl are azetidinyl, pyridyl, 1H-indazolyl, furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, imidazolyl, tetrazolyl, benzofuryl, isoquinolinyl, benzthiazolyl, xanthene, thioxanthene, phenothiazine, dihydroindole, benzo[1,3]dioxole, benzo[b]furyl, benzo[b]thiophenyl, indazolyl, benzimidazolyl, benzthiazolyl, puryl, cinnolyl, quinolyl, quinazolyl,cinnolyl, phthalazyl, quinazolyl, quinoxalyl, isoquinolyl, 4H-quinolizyl, benzo-1,2,5-thiadiazolyl, and 1,8-naphthyridyl.

[0087] Without limitation, examples of monocyclic heteroaryls include furyl, thiophenyl, 2H-pyrrolyl, pyrrolyl, oxazolyl, thazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,3,4-thiadiazolyl, 2H-pyranyl, 4-H-pranyl, pyridyl, pyridazyl, pyrimidyl, pyrazolyl, pyrazyl, and 1,3,5-triazyl. Monocyclic heteroaryls are numbered according to standard chemical nomenclature.

[0088] Without limitation, examples of bicyclic heteroaryls include indolizyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furyl, benzo[b]thiophenyl, quinolinyl, isoquinolinyl, indolizyl, isoindolyl, indolyl, benzo[b]furyl, bexo[b]thiophenyl, indazolyl, benzimidazyl, benzthiazolyl, purinyl, 4H-quinolizyl, quinolyl, isoquinolyl, cinnolyl, phthalazyl, quinazolyl, quinoxalyl, 1,8-naphthyridyl, and pteridyl. Bicyclic heteroaryls are numbered according to standard chemical nomenclature.

[0089] A heteroaryl is optionally substituted with one or more substituents. Examples of such substitutents include, but are not limited to, aliphatic (e.g., alkyl, alkenyl, or alkynyl); arylaliphatic (e.g., arylalkyl), cycloaliphatic; (cycloaliphatic)aliphatic; heterocycloaliphatic; (heterocycloaliphatic)aliphatic; aryl; heteroaryl; heteroarylaliphatic (e.g., heteroarylalkyl); alkoxy; (cycloaliphatic)oxy; (heterocycloaliphatic)oxy; aryloxy; heteroaryloxy; (araliphatic)oxy; (heteroaraliphatic)oxy; aroyl; heteroaroyl; amino; oxo (on a non-aromatic carbocyclic ring of a benzofused bicyclic or tricyclic aryl); azide (i.e., $-N_3$), nitro; carboxy (e.g., alkoxy-C(O)-); amido; amidoamino (e.g., -NR-C(O)-NRR'); thioamido (e.g., -C(S)-NRR'); thioamidoamino (e.g., -NR-C(S)-NRR'); alkoxyamido (e.g., -NR-C(O)-alkoxy or -C(O)-NR-alkoxy); acyl (e.g., aliphaticcarbonyl, (cycloaliphatic)carbonyl, ((cycloaliphatic)aliphatic)carbonyl, (araliphatic)carbonyl, (heterocycloaliphatic)carbonyl, ((heterocycloaliphatic)aliphatic)carbonyl, or (heteroaraliphatic)carbonyl); sulfonyl (e.g., aliphatic-$S(O)_2$-, (aliphatic-O)-$S(O)_2$-O-, or amino-$S(O)_2$-); sulfonylamino (e.g., -NR-$S(O)_2$-OR'); sulfinyl (e.g., aliphatic-S(O)- or cycloaliphatic-S(O)-); sulfinylamino; sulfanyl (e.g.,

aliphatic-S-); cyano; halo; hydroxy; mercapto; sulfoxy; urea; thiourea; sulfonamide; sulfamide; carbamoyl; phosphinio (e.g., -P(O)(OR)R'); phosphonio (e.g., -O-P(O)(OR)R'); phosphinioamino (e.g., -NR-P(O)(OR')R"); or phosphonioamino (e.g., -NR-P(O)(OR)(OR')). Each of R, R' and R" in the just-mentioned examples can be independently an aliphatic. Alternatively, a heteroaryl can be unsubstituted.

[0090] Non-limiting examples of substituted heteroaryls include (halo)heteroaryl (e.g., mono- and di-(halo)heteroaryl), (carboxy)heteroaryl (e.g., (alkoxycarbonyl)heteroaryl), cyanoheteroaryl, aminoheteroaryl (e.g., ((alkylsulfonyl)amino)heteroaryl and((dialkyl)amino)heteroaryl), (amido)heteroaryl (e.g., aminocarbonylheteroaryl, ((alkylcarbonyl)amino)heteroaryl, ((((alkyl)amino)alkyl)aminocarbonyl)heteroaryl, (((heteroaryl)amino)carbonyl)heteroaryl, ((heterocycloaliphatic)carbonyl)heteroaryl, or ((alkylcarbonyl)amino)heteroaryl), (cyanoalkyl)heteroaryl, (alkoxy)heteroaryl, (sulfonamide)heteroaryl (e.g., (aminosulfonyl)heteroaryl), (sulfonyl)heteroaryl (e.g., (alkylsulfonyl)heteroaryl), (hydroxyalkyl)heteroaryl, (alkoxyalkyl)heteroaryl, (hydroxy)heteroaryl, ((carboxy)alkyl)heteroaryl, (((dialkyl)amino)alkyl)heteroaryl, (heterocycloaliphatic)heteroaryl, (cycloaliphatic)heteroaryl, (nitroalkyl)heteroaryl, (((alkylsulfonyl)amino)alkyl)heteroaryl, ((alkylsulfonyl)alkyl)heteroaryl, (cyanoalkyl)heteroaryl, (acyl)heteroaryl (e.g., (alkylcarbonyl)heteroaryl), (alkyl)heteroaryl, and (haloalkyl)heteroaryl (e.g., trihaloalkylheteroaryl).

[0091] A "heteroaraliphatic" group (e.g., a heteroaralkyl group) as used herein, refers to an aliphatic group (e.g., a C_{1-4} alkyl group) that is substituted with a heteroaryl group. "Aliphatic," "alkyl," and "heteroaryl" have been defined above.

[0092] A "heteroaralkyl" group, as used herein, refers to an alkyl group (e.g., a C_{1-4} alkyl group) that is substituted with a heteroaryl group. Both "alkyl" and "heteroaryl" have been defined above. A heteroaralkyl is optionally substituted with one or more substituents. Examples of such substitutents include, but are not limited to, aliphatic (e.g., alkyl, alkenyl, or alkynyl); arylaliphatic (e.g., arylalkyl), cycloaliphatic; (cycloaliphatic)aliphatic; heterocycloaliphatic; (heterocycloaliphatic)aliphatic; aryl; heteroaryl; heteroarylaliphatic (e.g., heteroarylalkyl); alkoxy; (cycloaliphatic)oxy; (heterocycloaliphatic)oxy; aryloxy; heteroaryloxy; (araliphatic)oxy; (heteroaraliphatic)oxy; aroyl; heteroaroyl; amino; oxo (on a non-aromatic carbocyclic ring of a benzofused bicyclic or tricyclic aryl); azide (i.e., $-N_3$), nitro; carboxy (e.g., alkoxy-C(O)-); amido; amidoamino (e.g., -NR-C(O)-NRR'); thioamido (e.g., -C(S)-NRR'); thioamidoamino (e.g., -NR-C(S)-NRR'); alkoxyamido (e.g., -NR-C(O)-alkoxy or -C(O)-NR-alkoxy); acyl (e.g., aliphaticcarbonyl, (cycloaliphatic)carbonyl,

((cycloaliphatic)aliphatic)carbonyl, (araliphatic)carbonyl, (heterocycloaliphatic)carbonyl, ((heterocycloaliphatic)aliphatic)carbonyl, or (heteroaraliphatic)carbonyl); sulfonyl (e.g., aliphatic-$S(O)_2$-, (aliphatic-O)-$S(O)_2$-O-, or amino-$S(O)_2$-); sulfonylamino (e.g., -NR-$S(O)_2$-OR'); sulfinyl (e.g., aliphatic-S(O)- or cycloaliphatic-S(O)-); sulfinylamino; sulfanyl (e.g., aliphatic-S-); cyano; halo; hydroxy; mercapto; sulfoxy; urea; thiourea; sulfonamide; sulfamide; carbamoyl; phosphinio (e.g., -P(O)(OR)R'); phosphonio (e.g., -O-P(O)(OR)R'); phosphinioamino (e.g., -NR-P(O)(OR')R"); or phosphonioamino (e.g., -NR-P(O)(OR)(OR')). Each of R, R' and R" in the just-mentioned examples can be independently an aliphatic.

[0093] As used herein, an "acyl" group refers to a formyl group or R_X-C(O)- (such as -alkyl-C(O)-, also referred to as "alkylcarbonyl") where R_X and "alkyl" have been defined previously. Acetyl and pivaloyl are examples of acyl groups.

[0094] As used herein, an "aroyl" or "heteroaroyl" group refers to an aryl-C(O)- or a heteroaryl-C(O)-. The aryl and heteroaryl portion of the aroyl or heteroaroyl is optionally substituted as previously defined.

[0095] As used herein, an "alkoxy" group refers to an alkyl-O- group wherein "alkyl" has been defined previously.

[0096] As used herein, a "carbamoyl" group refers to a group having the structure -O-C(O)-NR_XR_Y or -NR_X-C(O)-O-R_Z, wherein R_X and R_Y are as defined above and R_Z can be aliphatic, aryl, araliphatic, heterocycloaliphatic, heteroaryl, or heteroaraliphatic.

[0097] As used herein, a "carboxy" group refers to -COOH, -$COOR_X$, -OC(O)H, -$OC(O)R_X$ when used as a terminal group; or -OC(O)- or -C(O)O- when used as an internal group.

[0098] As used herein, a "haloaliphatic" group refers to an aliphatic group substituted with 1-3 halogen atoms. For instance, the term haloalkyl includes the group -CF_3.

[0099] As used herein, a "mercapto" group refers to -SH.

[00100] As used herein, a "sulfonic" group refers to -$S(O)_2OH$ or -$S(O)_2OR_X$ when used terminally.

[00101] As used herein, a "sulfamide" group refers to the structure -NR_X-$S(O)_2$-NR_YR_Z when used terminally and -NR_X-$S(O)_2$-NR_Y- when used internally, wherein R_X, R_Y, and R_Z have been defined above.

[00102] As used herein, a "sulfonamide" group refers to the structure -$S(O)_2$-NR_XR_Y or -NR_X-$S(O)_2$-R_Z when used terminally; or -$S(O)_2$-NR_X- or -NR_X-$S(O)_2$- when used internally, wherein Rx, Ry, and R_Z are defined above.

[00103] As used herein a "sulfanyl" group refers to -S-R_X when used terminally and -S-

when used internally, wherein R_X has been defined above. Examples of sulfanyls include aliphatic-S-, cycloaliphatic-S-, aryl-S-, or the like.

[00104] As used herein a "sulfinyl" group refers to -S(O)-R_X when used terminally and -S(O)- when used internally, wherein RX has been defined above. Exemplary sulfinyl groups include aliphatic-S(O)-, aryl-S(O)-, (cycloaliphatic(aliphatic))-S(O)-, cycloalkyl-S(O)-, heterocycloaliphatic-S(O)-, heteroaryl-S(O)-, or the like.

[00105] As used herein, a "sulfonyl" group refers to-$S(O)_2$-R_X when used terminally and -$S(O)_2$- when used internally, wherein R_X has been defined above. Exemplary sulfonyl groups include aliphatic-$S(O)_2$-, aryl-$S(O)_2$-, (cycloaliphatic(aliphatic))-$S(O)_2$-, cycloaliphatic-$S(O)_2$-, heterocycloaliphatic-$S(O)_2$-, heteroaryl-$S(O)_2$-, (cycloaliphatic(amido(aliphatic)))-$S(O)_2$-or the like.

[00106] As used herein, a "sulfoxy" group refers to -O-SO-R_X or -SO-O-R_X, when used terminally and -O-S(O)- or -S(O)-O- when used internally, where RX has been defined above.

[00107] As used herein, a "halogen" or "halo" group refers to fluorine, chlorine, bromine or iodine.

[00108] As used herein, an "alkoxycarbonyl," which is encompassed by the term carboxy, used alone or in connection with another group refers to a group such as alkyl-O-C(O)-.

[00109] As used herein, an "alkoxyalkyl" refers to an alkyl group such as alkyl-O-alkyl-, wherein alkyl has been defined above.

[00110] As used herein, a "carbonyl" refers to -C(O)-.

[00111] As used herein, an "oxo" refers to =O.

[00112] As used herein, an "aminoalkyl" refers to the structure $(R_X)_2$N-alkyl-.

[00113] As used herein, a "cyanoalkyl" refers to the structure (NC)-alkyl-.

[00114] As used herein, a "urea" group refers to the structure -NR_X-CO-NR_YR_Z and a "thiourea" group refers to the structure -NR_X-CS-NR_YR_Z when used terminally and -NRX-CO-NR_Y- or

-NR_X-CS-NR_Y- when used internally, wherein R_X, R_Y, and R_Z have been defined above.

[00115] As used herein, a "guanidine" group refers to the structure -N=C(N(R_XR_Y))N(R_XR_Y) or

-N(R_X)C=(N(R_X))N(R_XR_Y), wherein R_X and R_Y have been defined above.

[00116] As used herein, the term "amidino" group refers to the structure -C=(NR_X)N(R_XR_Y) wherein R_X and R_Y have been defined above.

[00117] In general, the term "vicinal" refers to the placement of substituents on a group that

includes two or more carbon atoms, wherein the substituents are attached to adjacent carbon atoms.

[00118] In general, the term "geminal" refers to the placement of substituents on a group that includes two or more carbon atoms, wherein the substituents are attached to the same carbon atom.

[00119] The terms "terminally" and "internally" refer to the location of a group within a substituent. A group is terminal when the group is present at the end of the substituent not further bonded to the rest of the chemical structure. Carboxyalkyl, i.e., $R_XO(O)C$-alkyl, is an example of a carboxy group being used terminally. A group is internal when the group is present in the middle of a substituent to at the end of the substituent bound to the rest of the chemical structure. Alkylcarboxy (e.g., alkyl-C(O)O- or alkyl-OC(O)-) and alkylcarboxyaryl (e.g., alkyl-C(O)O-aryl- or alkyl-O(CO)-aryl-) are examples of carboxy groups used internally.

[00120] As used herein, the term "cyclic group" encompasses mono-, bi-, and tri-cyclic ring systems including cycloaliphatic, heterocycloaliphatic, aryl, or heteroaryl, each of which has been previously defined.

[00121] As used herein, the term "bridged bicyclic ring system" refers to a bicyclic heterocyclicalipahtic ring system or bicyclic cycloaliphatic ring system in which the rings have at least two common atoms. Examples of bridged bicyclic ring systems include, but are not limited to, adamantanyl, norbornanyl, bicyclo[3.2.1]octyl, bicyclo[2.2.2]octyl, bicyclo[3.3.1]nonyl, bicyclo[3.2.3]nonyl, 2-oxabicyclo[2.2.2]octyl, 1-azabicyclo[2.2.2]octyl, 3-azabicyclo[3.2.1]octyl, and 2,6-dioxatricyclo[3.3.1.03,7]nonyl. A bridged bicyclic ring system can be optionally substituted with one or more substituents such as alkyl (including carboxyalkyl, hydroxyalkyl, and haloalkyl such as trifluoromethyl), alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, (heterocycloalkyl)alkyl, aryl, heteroaryl, alkoxy, cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aroyl, heteroaroyl, nitro, carboxy, alkoxycarbonyl, alkylcarbonyloxy, aminocarbonyl, alkylcarbonylamino, cycloalkylcarbonylamino, (cycloalkylalkyl)carbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkylalkyl)carbonylamino, heteroarylcarbonylamino, heteroaralkylcarbonylamino, cyano, halo, hydroxy, acyl, mercapto, alkylsulfanyl, sulfoxy, urea, thiourea, sulfonamide, sulfamide, oxo, or carbamoyl.

[00122] The phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted." As described herein, compounds of the invention can

optionally be substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species of the invention. As described herein, the variables R_1, R_2, or R_3, and other variables contained therein Formula (I) encompass specific groups, such as alkyl and aryl. Unless otherwise noted, each of the specific groups for the variables R_1, R_2, and R_3, and other variables contained therein can be optionally substituted with one or more substituents described herein. Each substituent of a specific group is further optionally substituted with one to three of halo, cyano, oxoalkoxy, hydroxy, amino, nitro, aryl, haloalkyl, and alkyl. For instance, an alkyl group can be substituted with alkylsulfanyl and the alkylsulfanyl can be optionally substituted with one to three of halo, cyano, oxoalkoxy, hydroxy, amino, nitro, aryl, haloalkyl, and alkyl. As an additional example, the cycloalkyl portion of a (cycloalkyl)carbonylamino can be optionally substituted with one to three of halo, cyano, alkoxy, hydroxy, nitro, haloalkyl, and alkyl. When two alkoxy groups are bound to the same atom or adjacent atoms, the two alkxoy groups can form a ring together with the atom(s) to which they are bound.

[00123] In general, the term "substituted," whether preceded by the term "optionally" or not, refers to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent. Specific substituents are described above in the definitions and below in the description of compounds and examples thereof. Unless otherwise indicated, an optionally substituted group can have a substituent at each substitutable position of the group, and when more than one position in any given structure can be substituted with more than one substituent selected from a specified group, the substituent can be either the same or different at every position. A ring substituent, such as a heterocycloalkyl, can be bound to another ring, such as a cycloalkyl, to form a spiro-bicyclic ring system, e.g., both rings share one common atom. As one of ordinary skill in the art will recognize, combinations of substituents envisioned by this invention are those combinations that result in the formation of stable or chemically feasible compounds.

[00124] The phrase "stable or chemically feasible," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and preferably their recovery, purification, and use for one or more of the purposes disclosed herein. In some embodiments, a stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40 °C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

[00125] As used herein, a "subject" for treatment genrally refers and thus may be interchangeable with a "patient," such as an animal (e.g., a mammal such as a human).

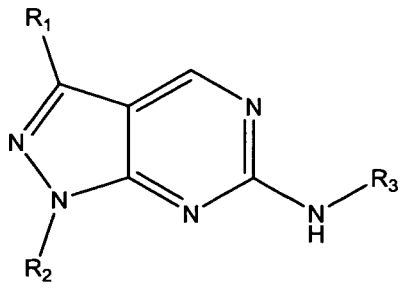
[00126] As used herein, an "effective amount" is defined as the amount required to confer a therapeutic effect on the treated patient, and is typically determined based on age, surface area, weight, and condition of the patient. The interrelationship of dosages for animals and humans (based on milligrams per meter squared of body surface) is described by Freireich et al., *Cancer Chemother. Rep.*, 50: 219 (1966). Body surface area may be approximately determined from height and weight of the patient. See, e.g., Scientific Tables, Geigy Pharmaceuticals, Ardsley, New York, 537 (1970).

[00127] Unless otherwise specified, all cyclic radical moieties identified herein can be bonded to another moiety in Formula (I) at any of its ring atoms.

[00128] Unless otherwise stated, the structures depicted herein are 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 except for 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 or probes in biological assays.

DETAILED DESCRIPTION OF THE INVENTION

[00129] In general, the invention features compounds of Formula (I), or prodrugs, polymorphs, tautomers, enantiomers, stereoisomers, solvates, N-oxide derivatves, or pharmaceutically acceptable salts thereof. These compounds are capable of modulating (e.g., inhibiting) the function of protein kinases involved in cell mitosis.



I

[00130] In Formula (I),

R_1 is hydrogen or halo;

R_2 is $-L_1-R_a$, wherein

L_1 is a bond or alkyl, and

R_a is cyclohexyl, cycloheptyl, piperidinyl, pyrrolidinyl, furyl, thienyl, morpholinyl, pyridinyl, or pyrimidinyl, each of which is optionally substituted with 1 to 3 substituents; or R_a is substituted phenyl;

R_3 is $-R_b-L_2-R_c$; wherein

R_b is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, and is optionally substituted with 1 to 3 substituents; wherein two of the substituents when adjacent, together with the atom or atoms to which they are attached, can form a 5- to 16-membered ring with 0 to 6 hetero ring atoms,

L_2 is a bond, $-(CR_xR_y)_n-$, $-N=$, $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-CO-$, $-CO-O-$, $-O-CO-$, $-NR_x-$, $-NR_x-CO-$, $-NR_x-SO_2-$, $-CO-NR_x-$, $-SO_2-NR_x-$, $-NR_x-CO-O-$, $-NR_x-SO_2-O-$, $-NR_x-CO-NR_y-$, $-NR_x-SO_2-NR_y-$, $-CO-NR_x-NR_y-$, $-SO_2-NR_x-NR_y-$, $-NR_x-CO-CO-O-$, $-NR_x-SO_2-SO_2-O-$, $-S(O)_2-N_x-CO-R_y-$, $-CO-N_x-S(O)_2-R_y-$, or $-(NR_xR_y)C=N-O-$;

R_c is hydrogen, alkyl, alkenyl, alkynyl, guanidinyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, aryl, heteroaryl, (cycloalkyl)alkyl, (heterocycloalkyl)alkyl, (cycloalkenyl)alkyl, (heterocycloalkenyl)alkyl, aralkyl, or heteroaralkyl, and except when being hydrogen, is optionally substituted with 1 to 3 substituents; and

each of R_x and R_y, independently, is hydrogen, hydroxy, alkyl, alkoxy, amino, –CO–alkyl, –CO–aryl, $-SO_2-$alkyl, $-SO_2-$aryl, $-SO_2-$heteroaryl, or $-P(O)(O-alkyl)_2$, wherein the alkyl or aryl moiety in R_x or R_y is optionally substituted with 1 to 3 substituents; and

n is 0, 1, 2, or 3.

[00131] Each of the 1 to 3 optional substituents on R_a, R_b, R_c, R_x, and R_y, independently, can be alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl,

-OR, -SR, -NRR', oxo, -C(O)-OR, -C(O)-NRR', halo, CN, NO_2, N_3, -C(O)R", -P(O)(OR)(OR'), -O-P(O)(OR)(OR'), -NR-P(O)(OR)(OR'), $-S(O)_2$-OR, -O-$S(O)_2$-OR, -NR-$S(O)_2$-OR', -NR-C(O)-OR", -NR-C(O)-NRR', -NR-C(S)-NRR', -C(S)-NRR', or thioalkyl;

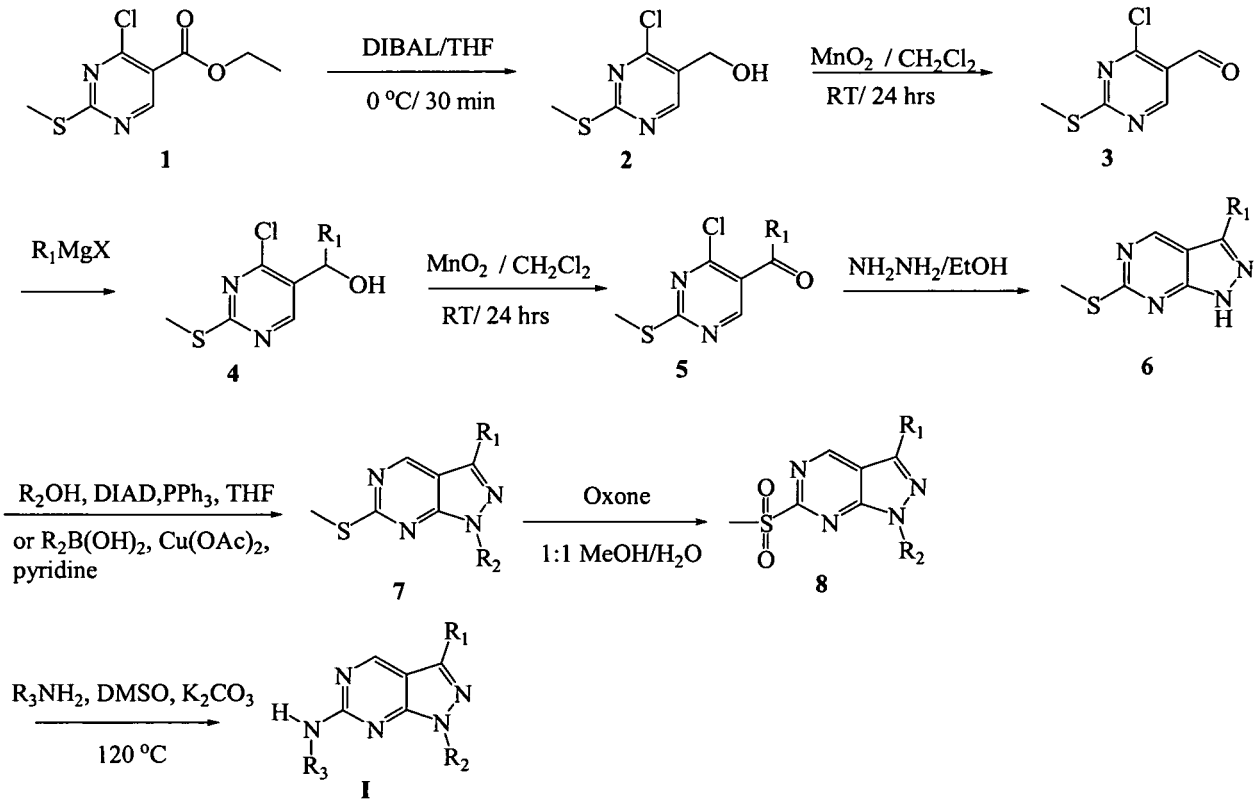
wherein each of R and R', independently, is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, or heteroaralkyl; and R" is alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, or heteroaralkyl.

SYNTHESIS OF COMPOUNDS OF FORMULA (I)

[00132] Compounds of Formula (I) may be synthesized from commercially available or known starting materials by known methods. Exemplary synthetic routes to produce compounds of Formula (I) are provided in Schemes 1-4 below. The generic schemes are not limiting and can be applied to preparation of other compounds that include different variables than those explicitly shown below.

[00133] One method for preparing compounds of Formula (I) is illustrated in Scheme 1.

Scheme 1

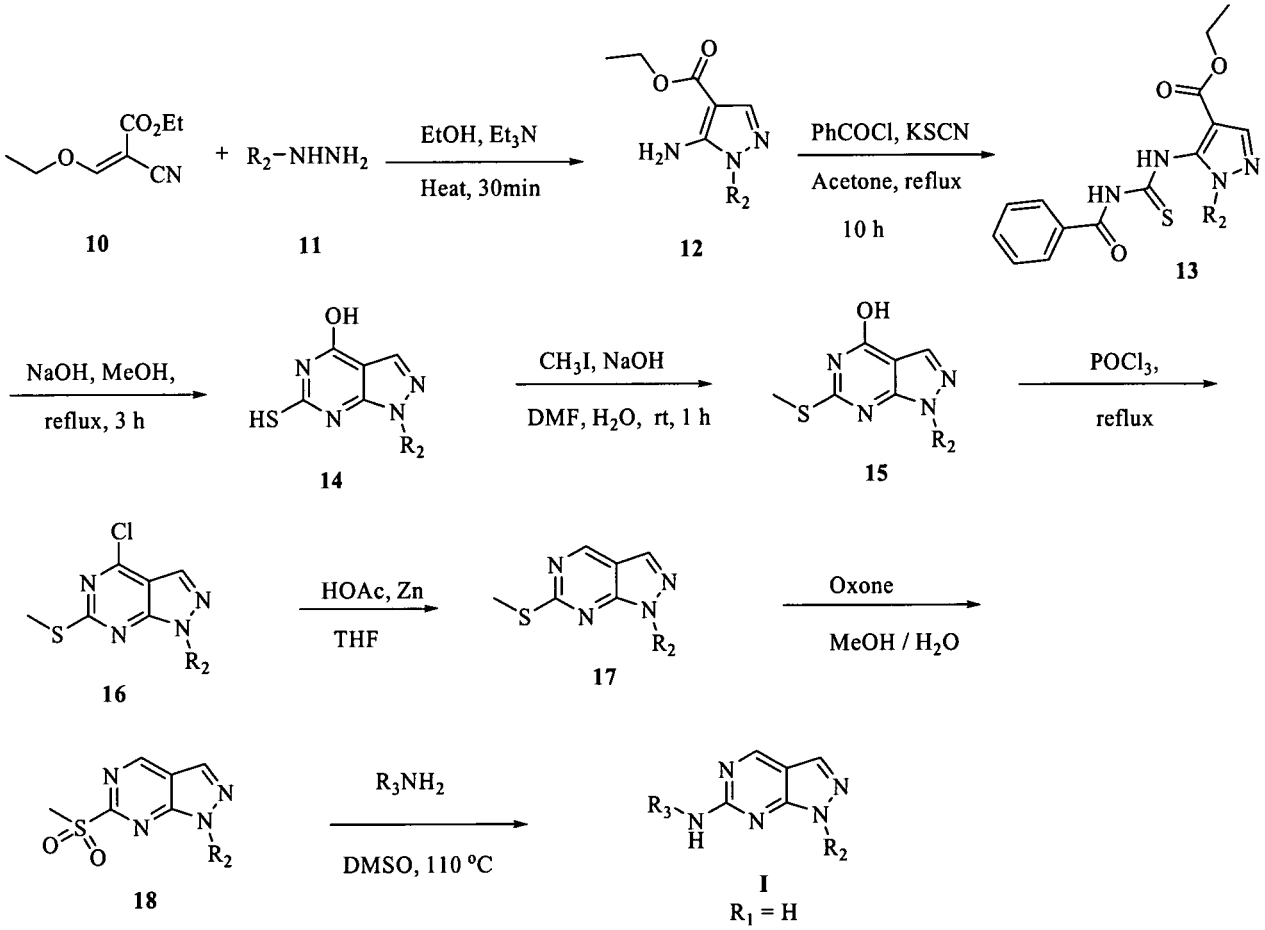


[00134] Referring to Scheme 1, the pyrimidine ester **1** is reduced to the corresponding alcohol **2** with, for example, diisobutylaluminum hydride (DIBAL). Oxidation of **2** with, for example, manganese dioxide provides the corresponding aldehyde 3. The aldehyde **3** may be reacted with hydrazine to provide compounds of formula 6 wherein R_1 is H. Alternatively, the aldehyde **3** may be reacted with, for example, a Grignard reagent R_1MgX to provide the intermediate alcohol **4** wherein R_1 is other than H. Oxidation of **4** provides a ketone **5** which

may be reacted with hydrazine to provide the pyrazolopyrimidine **6**. Alkylation of 6 with, for example, an alkyl halide such as R_2X provides the intermediate **7**. Alternatively, treatment of 6 with, for example, an arylboronic acid such as $R_2B(OH)_2$ in presence of $Cu(OAc)_2$ provides the intermediate 7 (R_2 = aryl). Oxidation of the thioether of 7 with, for example, Oxone® provides the sulfone **8**. Reaction of **8** with an amine R_3NH_2 provides compounds of Formula (I).

[00135] Another method of preparing compounds of Formula (I), wherein R_1 is H, is illustrated in Scheme 2.

Scheme 2

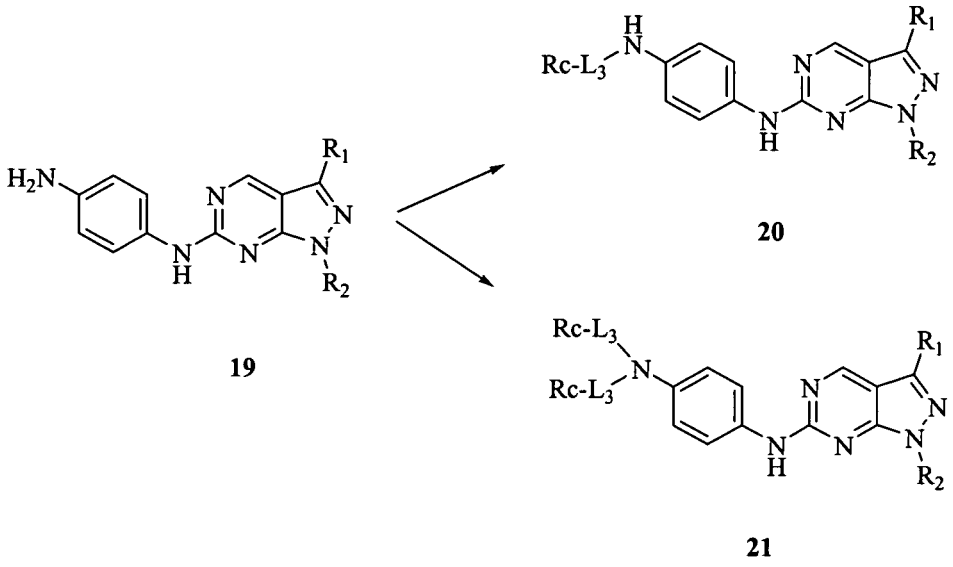


[00136] Referring to Scheme 2, reaction of the cyanoacrylate 10 with a hydrazine 11 provides the aminopyrazole 12. Reaction of 12 with benzoyl chloride and potassium thiocyanate provides the benzoylthio urea 13 which on treatment with sodium hydroxide in methanol provides the pyrrazolopyrimidine 14. Alkylation of 14 with methyl iodied in the presence of soium hydroxide provides the thioether 15. Reaction of 15 with phosphorousoxychloride provides the chloro pyrimidine 16 which is reduced to the pyrazolopyrimidine 17 with zinc in the presence of acetic acid. Oxidation of 17 with Oxone® provides the sulfone 18 which reacts with an amine R_3NH_2 to provide compounds of Formula

(I) wherein R_1 is H.

[00137] In some embodiments where R_3 is, for example, an amino-substituted aryl, further examples of compounds of Formula (I) may be prepared as illustrated in Scheme 3.

Scheme 3

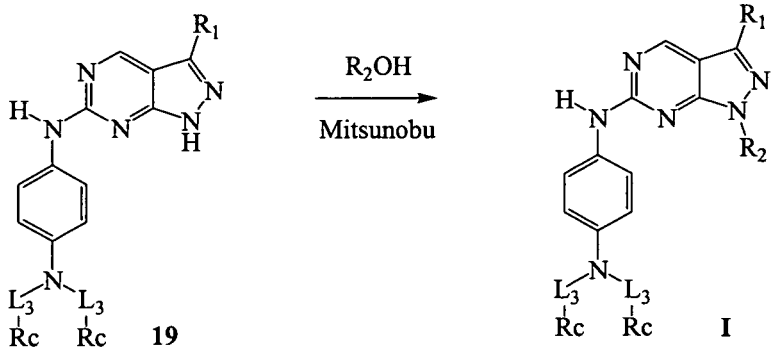


19 20 21

[00138] Referring to Scheme 3, the amino substituted compound 19 may be reacted with a compound of formula Rc-L_3 -Q wherein L_3 is -C(O)-, -SO_2- or -$P(OR^X)_2$- and Q represents a halide, or Rc-L_3 -Q represents an acid anhydride, to provide monosubstituted compounds of formula 20 or disubstituted compounds of formula 21.

[00139] Another method of preparing compounds of formula I, wherein, for example, R_3 is an amino-substituted aryl, is illustrated in Scheme 4.

Scheme 4

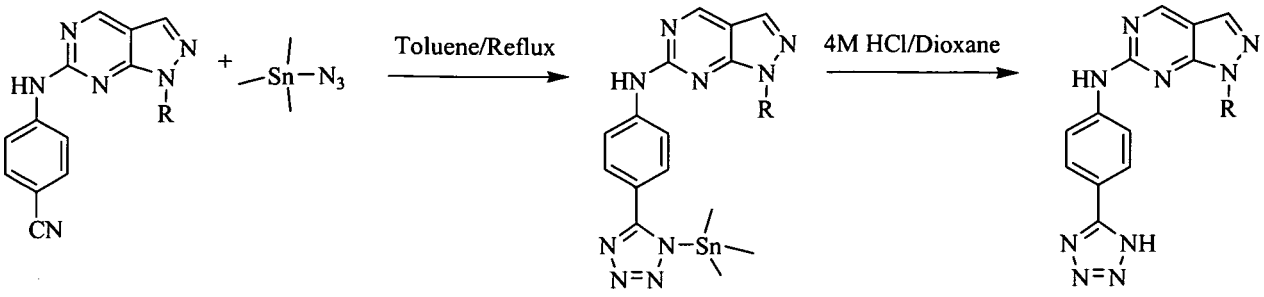


19 I

[00140] Referring to Scheme 4, the amino substituted compound 19 may be reacted with a compound of formula R_2OH to provide compounds of formula I.

[00141] In a further embodiment, compounds of Formula (I) wherein R_3 is an aryl-tetrazole may be prepared as illustrated in Scheme 5.

Scheme 5



22 23 24

[00142] Referring to Scheme 4, the cyanosubstituted compound 22 is reacted with a trialkyltin azide, e.g. trimethyltin azide, to provide the intermediate tin-tetrazole 23. Hydrolysis in the presence of mineral acid, e.g. hydrochloric acid, provides compounds of the invention of formula 24.

ADMINISTRATION OF COMPOSITIONS CONTAINING COMPOUNDS OF FORMULA (I)

[00143] As defined above, an effective amount is the amount required to confer a therapeutic effect on the treated patient. For a compound of Formula (I), an effective amount can range, for example, from about 1 mg/kg to about 150 mg/kg (e.g., from about 1 mg/kg to about 100 mg/kg). The effective amount may also vary, as recognized by those skilled in the art, dependant on route of administration, excipient usage, and the possibility of co-usage with other therapeutic treatments including use of other therapeutic agents and/or radiation therapy.

[00144] The amount of the compounds of the present invention that may be combined with the carrier materials to produce a composition in a single dosage form will vary depending upon the host treated, the particular mode of administration. For instance, the compositions may be formulated so that a dosage of between 0.01-100 mg/kg body weight/day of the modulator can be administered to a patient receiving these compositions.

[00145] It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of a compound of the present invention in the composition will also depend upon the particular compound in the composition.

[00146] Depending upon the particular condition, or disease, to be treated or prevented, additional therapeutic agents, which are normally administered to treat or prevent that condition, may also be present in the compositions of this invention. As used herein,

additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated."

[00147] Compounds of Formula (I) can be administered in any manner suitable for the administration of pharmaceutical compounds, including, but not limited to, pills, tablets, capsules, aerosols, suppositories, liquid formulations for ingestion or injection or for use as eye or ear drops, dietary supplements, and topical preparations. The pharmaceutically acceptable compositions include aqueous solutions of the active agent, in an isotonic saline, 5% glucose or other well-known pharmaceutically acceptable excipient. Solubilizing agents such as cyclodextrins, or other solubilizing agents well-known to those familiar with the art, can be utilized as pharmaceutical excipients for delivery of the therapeutic compounds. As to route of administration, the compositions can be administered orally, intranasally, transdermally, intradermally, vaginally, intraaurally, intraocularly, buccally, rectally, transmucosally, or via inhalation, implantation (e.g., surgically), or intravenous administration. The compositions can be administered to an animal (e.g., a mammal such as a human, non-human primate, horse, dog, cow, pig, sheep, goat, cat, mouse, rat, guinea pig, rabbit, hamster, gerbil, or ferret, or a bird, or a reptile such as a lizard).

[00148] Controlled release of therapeutic agents can utilize various technologies. Devices are known having a monolithic layer or coating incorporating a heterogeneous solution and/or dispersion of an active agent in a polymeric substance, where the diffusion of the agent is rate limiting, as the agent diffuses through the polymer to the polymer-fluid interface and is released into the surrounding fluid. In some devices, a soluble substance is also dissolved or dispersed in the polymeric material, such that additional pores or channels are left after the material dissolves. A matrix device is generally diffusion limited as well, but with the channels or other internal geometry of the device also playing a role in releasing the agent to the fluid. The channels can be pre-existing channels or channels left behind by released agent or other soluble substances.

[00149] Erodible or degradable devices typically have the active agent physically immobilized in the polymer. The active agent can be dissolved and/or dispersed throughout the polymeric material. The polymeric material is often hydrolytically degraded over time through hydrolysis of labile bonds, allowing the polymer to erode into the fluid, releasing the active agent into the fluid. Hydrophilic polymers have a generally faster rate of erosion relative to hydrophobic polymers. Hydrophobic polymers are believed to have almost purely surface diffusion of active agent, having erosion from the surface inwards. Hydrophilic polymers are believed to allow water to penetrate the surface of the polymer, allowing

hydrolysis of labile bonds beneath the surface, which can lead to homogeneous or bulk erosion of polymer.

[00150] The implantable device coating can include a blend of polymers each having a different release rate of the therapeutic agent. For instance, the coating can include a polylactic acid/polyethylene oxide (PLA-PEO) copolymer and a polylactic acid/polycaprolactone (PLA-PCL) copolymer. The polylactic acid/polyethylene oxide (PLA-PEO) copolymer can exhibit a higher release rate of therapeutic agent relative to the polylactic acid/polycaprolactone (PLA-PCL) copolymer. The relative amounts and dosage rates of therapeutic agent delivered over time can be controlled by controlling the relative amounts of the faster releasing polymers relative to the slower releasing polymers. For higher initial release rates the proportion of faster releasing polymer can be increased relative to the slower releasing polymer. If most of the dosage is desired to be released over a long time period, most of the polymer can be the slower releasing polymer. The stent can be coated by spraying the stent with a solution or dispersion of polymer, active agent, and solvent. The solvent can be evaporated, leaving a coating of polymer and active agent. The active agent can be dissolved and/or dispersed in the polymer. In some embodiments, the co-polymers can be extruded over the stent body.

USES OF COMPOUNDS OF FORMULA (I)

[00151] The compounds of this invention have inhibitory effect on protein kinases such as one or more of multiple mitotic kinases (e.g., Aurora kinase, polo-like kinase, or cyclin-dependent kinase) as found in cell mitosis, e.g., abnormal growth of cells of proliferation of tumor cells.

[00152] Accordingly, the compounds of this invention can be used for inhibiting the abnormal growth of cells, including transformed cells, by administering an effective amount of a compound of the invention. Abnormal growth of cells refers to cell growth independent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes the abnormal growth of: (1) tumor cells (tumors) expressing an activated ras oncogene; (2) tumor cells in which the ras protein is activated as a result of oncogenic mutation of another gene; (3) benign and malignant cells of other proliferative diseases in which aberrant ras activation occurs. Furthermore, it has been suggested in literature that ras oncogenes not only contribute to the growth of tumors in vivo by a direct effect on tumor cell growth but also indirectly, i.e. by facilitating tumor-induced angiogenesis (see, e.g., Rak, J. et al, *Cancer Research*, 55: 4575-4580, 1995). Hence, pharmacologically targeting mutant ras oncogenes could

conceivably suppress solid tumor growth in vivo, in part, by inhibiting tumor-induced angiogenesis.

[00153] Examples of tumors which may be inhibited by the compounds of this invention include, but are not limited to, lung cancer (e.g. adenocarcinoma), pancreatic cancers (e.g. pancreatic carcinoma such as, for example exocrine pancreatic carcinoma), colon cancers (e.g. colorectal carcinomas, such as, for example, colon adenocarcinoma and colon adenoma), hematopoietic tumors of lymphoid lineage (e.g. acute lymphocytic leukemia, B-cell lymphoma, Burkitt's lymphoma), myeloid leukemias (for example, acute myelogenous leukemia (AML)), thyroid follicular cancer, myelodysplastic syndrome (MDS), tumors of mesenchymal origin (e.g. fibrosarcomas and rhabdomyosarcomas), melanomas, teratocarcinomas, neuroblastomas, gliomas, benign tumor of the skin (e.g. keratoacanthomas), breast carcinoma, kidney carcinoma, ovary carcinoma, bladder carcinoma and epidermal carcinoma. The compound can be administered in a suitable manner, e.g., intravenously, subcutenously, orally, parenterally, or topically.

[00154] This invention may also provide a method for inhibiting proliferative diseases, both benign and malignant, wherein ras proteins are aberrantly activated as a result of oncogenic mutation in genes. With said inhibition being accomplished by the administration of an effective amount of the compounds described herein, to a subject in need of such a treatment. For example, the benign proliferative disorder neuro-fibromatosis, or tumors in which ras is activated due to mutation or overexpression of tyrosine kinase oncogenes, may be inhibited by the compounds of this invention.

[00155] All references cited herein are incorporated herein in their entirety by reference.

[00156] The following examples are set forth to enable the invention described herein being more readily understood. These examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

GENERAL EXPERIMENTAL

[00157] 1H-NMR spectra were determined on a Bruker 400 MHz instrument. Mass spectra were recorded on an Agilent ESI-TOF mass spectrometer. HPLC was performed on Agilent 1100 instruments. The HPLC method used for these compounds is as follows:

Column: Agilent Zorbax 300 SB C18, 4.6 X 150 mm, 5 μm;

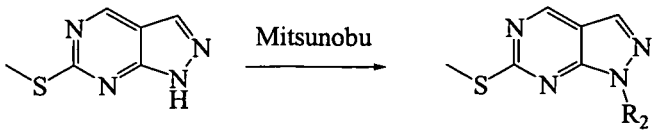
Column Temperature: ambient;

Flow Rate: 1.0 ml/min,

Gradient: 5 % acetonitrile (0.05 % TFA) in water (0.1 % TFA) to 100 % acetonitrile (0.05 % TFA) in 7 minutes, hold at 100 % for 2 minutes.

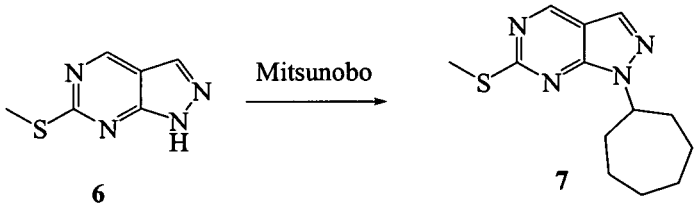
General Procedures to Prepare Pyrazolo[3,4-d]pyrimidines

General Procedure 1-1: Synthesis of 1-alkyl-6-(methylthio)-1H-pyrazolo[3,4-d] pyrimidine



[00158] Synthesis of this compound was conducted according to procedures described by J. Adams in WO03/029209A2. Specifically, to a solution of triphenyl phosphine in THF at -78 °C under nitrogen, diisopropylazodicarboxylate (DIAD) was added dropwise. The reaction mixture was stirred for five minutes before an alchol R_2OH (R_2 is alkyl) was added. The mixture was stirred for another 5 minutes then 6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidine was added. The resultant reaction mixture was stirred at room temperature for 2 hours. The solvent was rotavaped, diethyl ether was added, the mixture was filtered and the filtrate was rotavaped. The crude material was purified by flash chromatography (EtOAc/Hexane) to provide the title compound.

General Procedure 1-2: Synthesis of 1-cycloheptyl-6-(methylthio)-1H-pyrazolo[3,4-d] pyrimidine



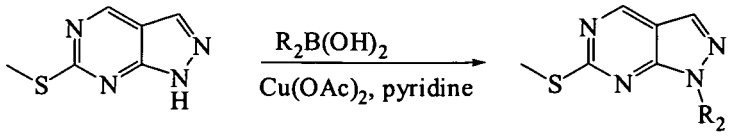
6 7

[00159] To a solution of triphenyl phosphine (3.05 g, 11.6 mmol) in 20 mL THF at -78 °C under nitrogen, diisopropylazodicarboxylate (DIAD) (2.36 g, 11.6 mmol) was added dropwise. The reaction mixture was allowed to stir for five minutes before cycloheptanol (1.34g, 11.7 mmol) was added. The mixture was stirred for 5 minutes then 6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidine (1.6 g, 9.6 mmol) was added. The reaction mixture was stirred at RT for 2 hours. The mixture was chromatographed over silica gel (10% EtOAc/Hexanes) to provide 2.32 g solid (90.6% yield) of 1-cycloheptyl-6-(methylthio)-1H-pyrazolo[3,4-d] pyrimidine.

Rf (25% EtOAc/Hexanes): 0.5.

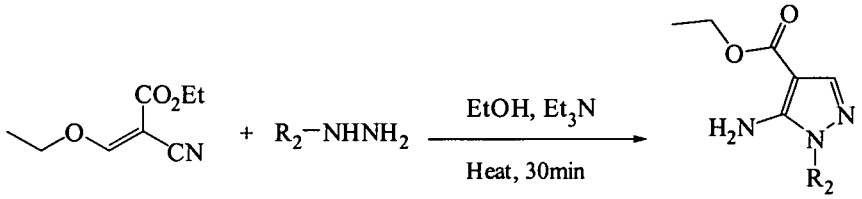
HPLC *t*R : 7.69 minutes.

General Procedure 1-3: Synthesis of 1-Aryl-6-(methylthio)-1H-pyrazolo[3,4-d] pyrimidine



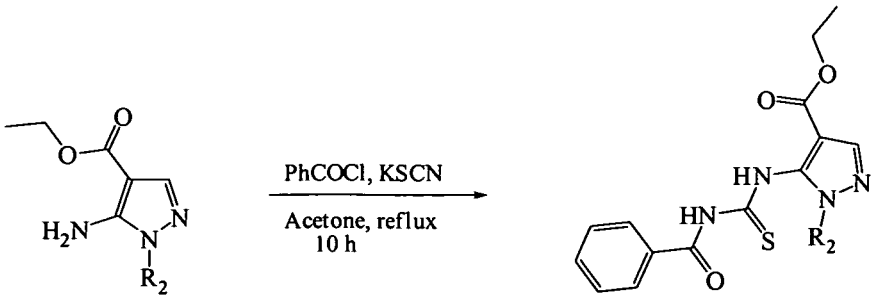
[00160] Synthesis of this compound was conducted accotding to procedures described by P. Y. S. Lam in *Tetrahedron Lett.*, 1998, 39, 2941. Specifically, to activated molecular serive MS4Å were added DCM, copper acetate, and pyridine. After the mixture was stirred for 15 minutes at the room temperature, 6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidine and $R_2B(OH)_2$ (R_2 is aryl) were added to the mixture. After stirring for 2 days at the room temperature, the reaction mixture was filtered, washed with a mixture of water, Brine, and ammonium hydroxide, and then dried over sodium sulfate. The crude material thus obtained was purified by flash chromatography (Ethyl acetate or acetone/hexane) to give the title compound.

General Procedure 1-4: Synthesis of ethyl 5-amino-1-substituted-1H-pyrazole-4-carboxylates



[00161] The synthesis of this compound was performed according to procedures described by M. Kopp in *J. Heterocyclic Chem.*, 2001, 38, 1045-1050. Specifically, to a round-bottom flask was added an optionally substituted hydrazine hydrochloride in ethanol and triethylamine. The mixture was stirred for 15 minutes at the room temperature before being it was heated at 90 °C and (Z)-2-cyano-3-ethoxycarboxylic acid ethyl ester was added. The reaction mixture thus obtained was heated for 1 hour at 90 °C and then cooled to the room temperature. The precipitate was filtered and washed with ether, and then dried over high vacuum to give the title compound.

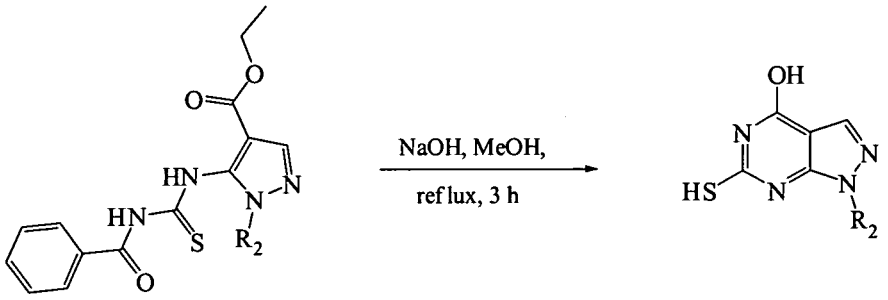
General Procedure 1-5: Synthesis of ethyl 5-(3-benzoylthioureido)-1-substituted-1H-pyrazole-4-carboxylate



[00162] The title compound was synthesized accortding to procedures described by F.

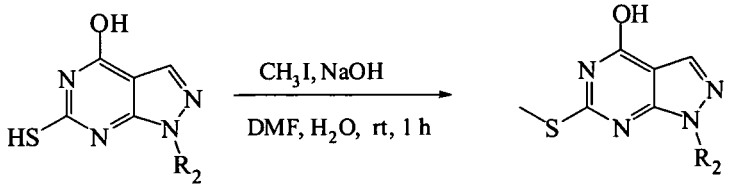
Carraro et al. in *J. Med. Chem.*, 2006, 49, 1549-1561. Specifcally, to a round bottom flask was added potassium thiocyanate in acetone followed by benzoyl chloride at the room temperature. The reaction mixture was stirred for 10 minutes before ethyl 5-amino-1-substituted-1H-pyrazole-4-carboxylate was added to the mixture. The restulant mixture was heated to reflux overnight and cooled to the room temperature. The solvent was removed by rotary evaporation. The residue was extracted with ethyl acetate and washed with water, brine, dried over $MgSO_4$, and concentrated to give the title compound.

General Procedure 1-6: Synthesis of 6-mercapto-1-substituted-1H-pyrazolo[3,4-d]pyrimidin-4-ol



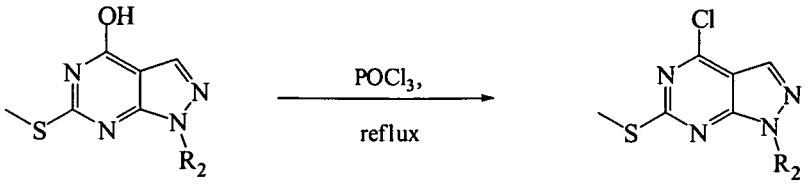
[00163] Synthesis of the title compound was conducted according to procedures described by F. Carraro et al. in *J. Med. Chem.*, 2006, 49, 1549-1561. Specifically, to ethyl 5-(3-benzoylthioureido)-1-substituted-1H-pyrazole-4-carboxylate in methanol was added sodium hydroxide in water at the room temperature and the resultant reaction mixture was heated under reflux for 3 hours. The reaction mixture was then cooled to the room temperature and acidified with saturated NH_4Cl. The resultant precipitate was filtered to give the title compound.

General Procedure 1-7: Synthesis of 1-substituted-6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidin-4-ol



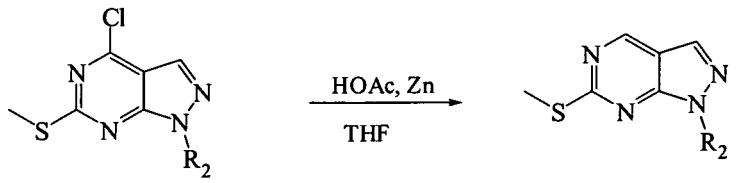
[00164] Synthesis of the title compound was conducted according to procedures described by F. Carraro et al. in the *Journal of Medicinal Chemistry*, 2006, 49, 1549-1561. Specifically, to 6-mercapto-1-substituted-1H-pyrazolo[3,4-d]pyrimidin-4-ol in DMF was added NaOH in water and an alkyl iodide (e.g. methyl iodide) at room temperature. The reaction mixture was stirred for 1 hour and neutralized with saturated NH_4Cl. The resultant precipitate was filtered to give the title compound.

General Procedure 1-8: Synthesis of 4-chloro-1substituted-6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidine



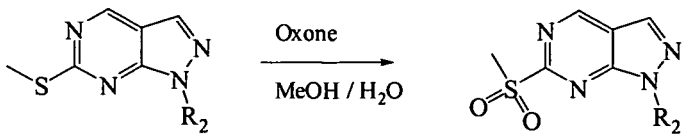
[00165] Synthesis of the title compound was conducted according to procedures described by F. Carraro et al. in the *Journal of Medicinal Chemistry*, 2006, 49, 1549-1561. Specifically, to 1-substituted-6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidin-4-ol was added $POCl_3$ at the room temperature and the restulant mixture was heated under reflux for 1 hour. The reaction mixture was cooled to the room temperature and a precipitate was formed and filtered to give the title compound.

General Procedure 1-9: Synthesis of 6-(methylthio)-1-substituted-1H-pyrazolo[3,4-d]pyrimidine



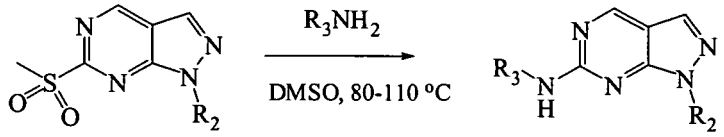
[00166] To 4-chloro-1substituted-6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidine in THF and acetic acid was added Rieke zinc at the room temperature. The reaction mixture was heated at 80 °C for 20 minutes and then cooled to the room temperature. The cooled reaction mixture was then filtered through celite and the filtrate was concentrated and extracted with EtOAc, washed with water, brine, dried, and concentrated to give a crude product. The crude material was purified by flash chromatography (EtOAc/Hexane) to give the title compound.

General Procedure 1-10: Synthesis of 3-optionally substituted-6-(methylsulfonyl)-1-substituted-1H-pyrazolo[3,4-d]pyrimidine.



[00167] To 6-(methylthio)-1-substituted-1H-pyrazolo[3,4-d]pyrimidine in methanol was added Oxone® (5 eq.) in water and the mixture stirred at the room temperature overnight. The reaction mixture was concentrated and then extracted with EtOAc, washed with water, brine, dried, and concentrated. The crude material was was purified by flash chromatography (Ethyl acetate/Hexane) to give the title compound.

General Procedure 1-11: Synthesis of compounds of Formula (I).



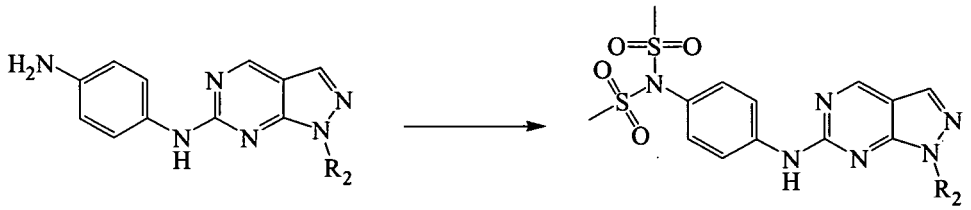
I

[00168] To a sealed tube was added 1-substituted-6-(methylsulfonyl)-1H-pyrazolo[3,4-d]pyrimidine and optionally substituted aniline (5 eq.) in DMSO at the room temperature. The reaction mixture was heated to about 110 °C from 30 minutes to overnight and then cooled to the room temperature. The mixture was quenched with water and extracted with EtOAc, washed with water, brine, dried, and concentrated to give a crude product. The crude material was purified by flash chromatography (Ethyl acetate/Hexane or DCM/MeOH) to give the compounds of Formula **(I)**.

General Procedure 1-12: Synthesis of N-(4-(1-substituted-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide.

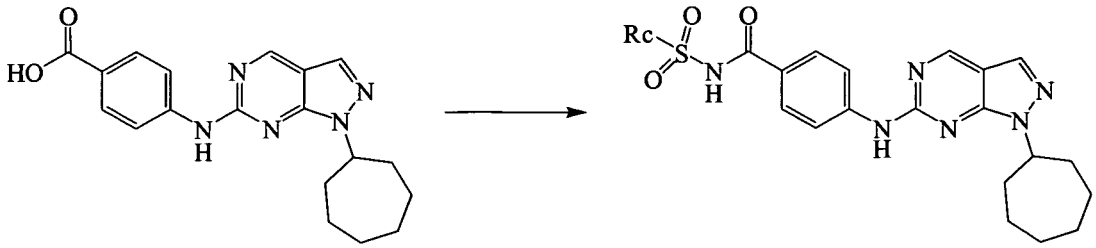
[00169] To N1-(1-substituted-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,4-diamine in $CHCl_3$ was added methanesulfonyl chloride (1 eq.) or methanesulfonic anhydride and DIEA (1.5 eq.) at the room temperature. The reaction mixture was stirred for 15 minutes at the room temperature and then purified by flash chromatography (Ethyl acetate/Hexane or DCM/MeOH) to give the title compound.

General Procedure 1-13: Synthesis of N-(4-(1-substituted-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide.



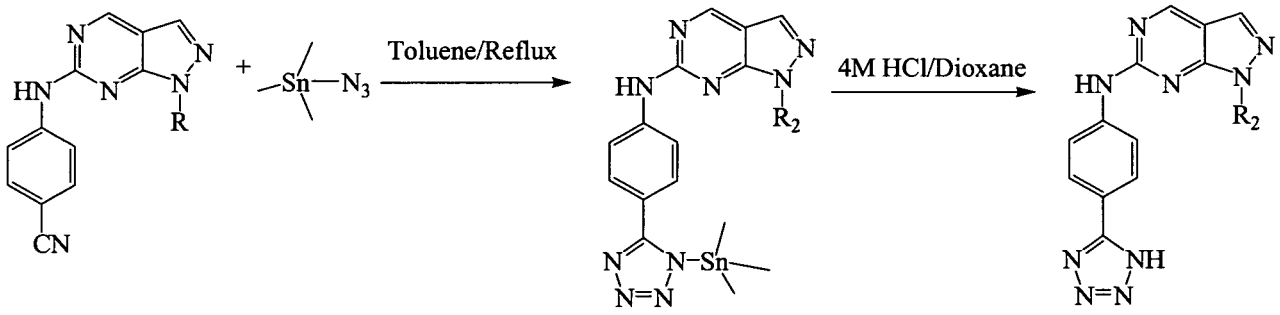
[00170] To N1-(1-substituted-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,4-diamine in $CHCl_3$ was added methanesulfonyl chloride (5 eq.) or methanesulfonic anhydride and DIEA (7.5 eq.) at the room temperature. The reaction mixture was stirred for 15 minutes at the room temperature and then purified by flash chromatography (Ethyl acetate/Hexane or DCM/MeOH) to give the title compound.

General Procedure 1-14: Synthesis of 4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-N-(substituted-sulfonyl)benzamide.



[00171] The synthesis of the title compound was conducted according to procedures described by C.F. Sturino et al. in *Tetrahedron Lett.*, 1998, 39, 5891. Specifically, to 4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)benzoic acid in a 1/1/1/ mixture of t-BuOH/1,2-dichloroethane/DMF were added N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (5eq.), DMAP (10 eq.) and S-substituted-sulfonamide (10 eq). After the reaction mixture was stirred for 2 hours at the room temperature, 2.0 M HCl was added to it. The resultant mixture was extracted with EtOAc, washed with water, dried over sodium sulfate, and concentrated under reduce pressure to give a crude product. After trituration of the crude in DCM, the title compound was isolated as a white solid.

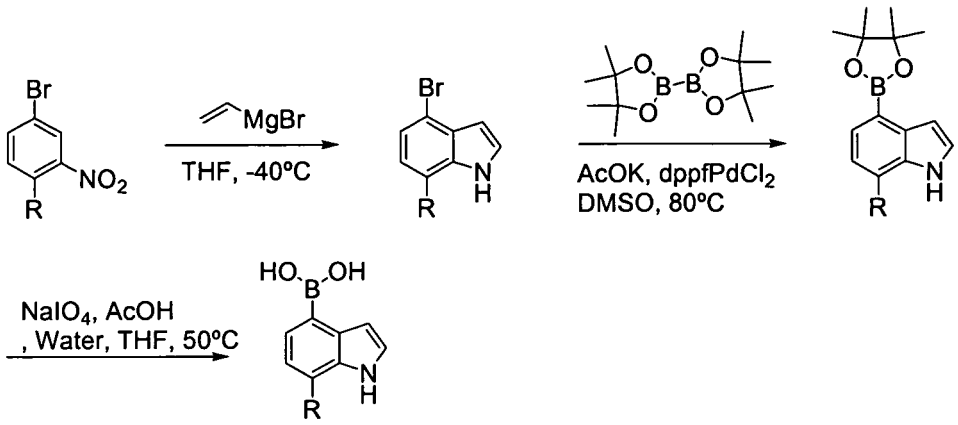
General Procedure 1-15: Synthesis of N-(4-(1H-tetrazol-5-yl)phenyl)-1-substituted-1H-pyrazolo[3,4-d]pyrimidin-6-amine.



[00172] Synthesis of the title compound was conducted according to procedures described by J.V. Duncia in *J. Org. Chem.*, 1991, 56, 2395-2400. Specifically, a suspension of 4-(1-substituted-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)benzonitrile (1.0 mmol) and trimethyltin azide (2.00 mmol) were heated under reflux in 5 mL toluene for 40-60 hours under the nitrogen atmosphere, which gave a crude trimethyltin intermediate. The crude intermediate was dissolved into 5 mL of dioxane and was stirred for 30 minutes in the presence of 4.0 M HCl to give the title compound.

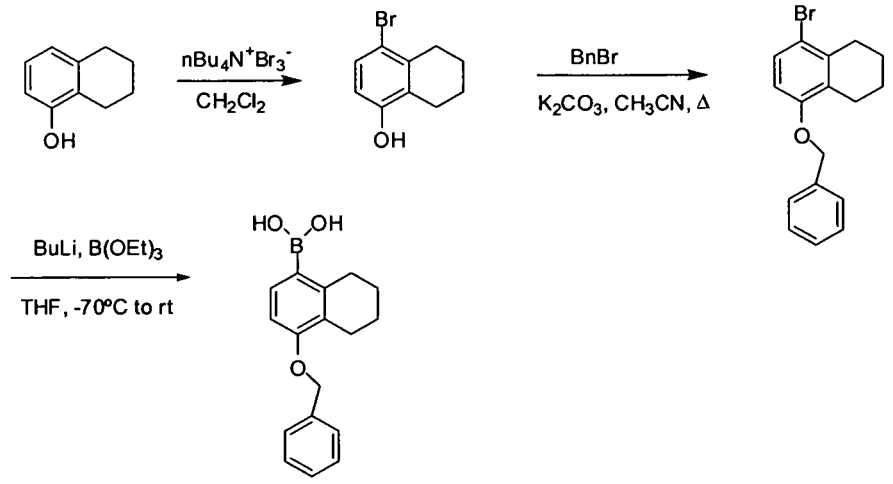
General Procedures to Prepare 1H-indol-4-ylboronic acid and 5,6,7,8-tetrahydronaphthalen-1-ylboronic acid

General Procedure 2-1: Synthesis of 7-substituted-1H-indol-4-yl-boronic acids.



[00173] Synthesis of the title compound was conducted according to procedures described by L. Li in *Tetrahedron Lett.*, 2003, 44, 5987-5990. Specifically, a solution of 6-substituted-3-bromo-nitrobenzene was treated with vinylmagnesium bromide to give a 7-substituted indole which was purified by flash chromatography. The 7-substituted indole then reacted with bis (pinacolato)diboron in presence of palladium (0) to afford a 7-substituted-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole which was hydrolyzed into the title compound using sodium metaperiodate in Acetic/water/THF.

General Procedure 2-2: Synthesis of 4-(benzyloxy)-5,6,7,8-tetrahydronaphthalen-1-ylboronic acid

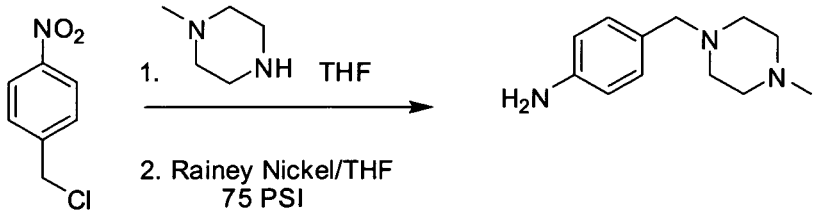


[00174] Synthesis of the title compound was conducted according to procedures described by John A. Lowe, III, in *J. Med. Chem.*, 2004, 47, 1575-1586. Specifically, 4-bromo-1-naphthol was prepared from 1-napthol by treating with 1 equivalent of tributylammonium tribromide. It was then dissolved in acetonitrile, treated with benzyl bromide and potassium carbonate, and heated under reflux for 14 hours to provide 4-bromo-1-benzyloxynaphthalene. The

compound 4-bromo-1-benzyloxynaphthalene then reacted with n-butyllithium and triethyl borate to afford the title compound.

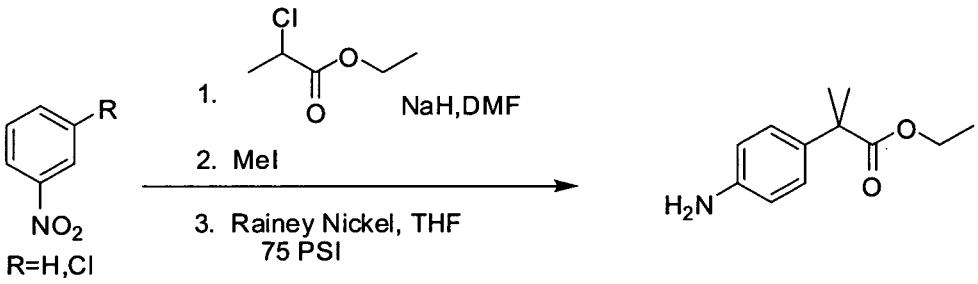
General Procedures to Prepare 3,4-Substituted Anilines

General Procedure 3-1: Synthesis of (4-((4-methylpiperazin-1-yl)methyl)aniline)



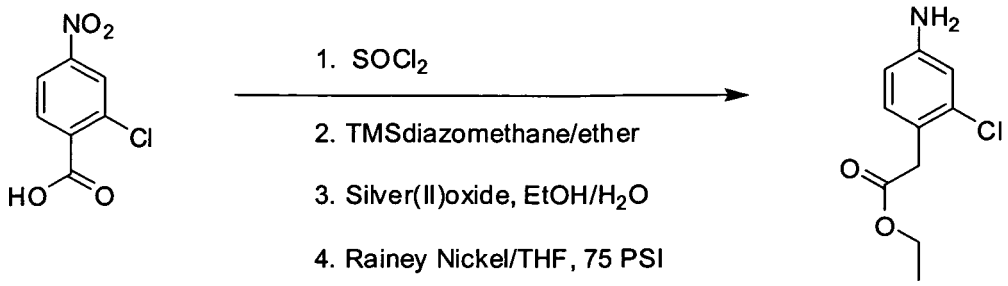
[00175] The synthesis of the title compound was conducted as described in U.S. Pat. Appl. Publ. No. 2006058341 (March 16, 2006). Specifically, to a solution of 4-nitrobenzyl chloride in THF at the room temperature was added 1-methyl piperazine. The solution was stirred for 3 hours after which time the crude reaction was diluted with ethyl acetate and washed repeatedly with water. The dried organics were concentrated to give directly the 4-nitrobenzylamine adduct. This was subsequently treated with Rainey Nickel in THF at 75PSI for 12 hours to give the title compound.

General Procedure 3-2: Synthesis of ethyl 2-(4-aminophenyl)-2-methylpropanoate analogues



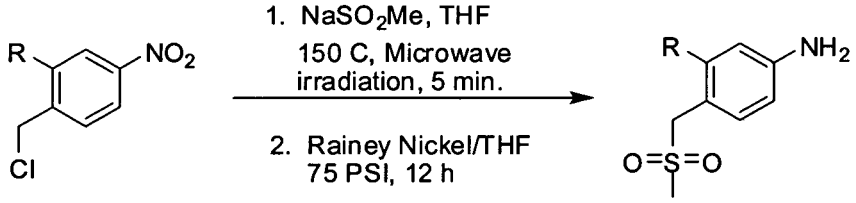
[00176] The synthesis of the title compound was conducted according to procedures described by Lawrence et al. in *J. Org. Chem.*, 2002, 67, 457-464. To a suspension of sodium hydride in DMF at 0 °C was added dropwise a premixed solution of ethyl-2-chloropropionate and nitrobenzene in DMF. This was stirred at 0 °C for 30 minutes then warmed to 25 °C. To this solution was then added methyl iodide and the mixture was stirred for 2 more hours. The reaction solution was quenched with 1 M HCl and diluted with methylene chloride. The organics were washed with saturated aqueous sodium bicarbonate solution and dried over sodium sulfate. The concentrated organics gave the title compound as a viscous brown oil without need for purification. When R is chlorine, flash chromatography is necessary.

General Procedure 3-3: Synthesis of ethyl 2-(4-amino-2-chlorophenyl)acetate



[00177] The synthesis of the title compound was conducted according to procedures described by G. Nannini in *Arzneimittel-Forschung,* 1973, 23, 1090-1100. Specifically, 2-chloro-4-nitrobenzoic acid was taken up into neat thionyl chloride and refluxed for 1 hour. The solvent was removed under reduced pressure to give 2-chloro-4-nitrobenzoyl chloride as a yellow oil. This was treated with trimethylsilyldiazomethane in diethyl ether at the room temperature. The resulting amber oil was purified via flash chromatography to give the dizaoketone as a crystalline yellow solid. This was taken up into a wet ethanol solution and treated with an aqueous slurry of silver(II)oxide. After filtering off the catalyst the mother liquor was diluted with water and extracted with ethyl acetate. Drying of the organics with sodium sulfate followed by concentration afforded the title compound as a viscous yellow oil without need for chromatography.

General procedure 3-4: Synthesis of 4-(methylsulfonylmethyl)anline analogues:

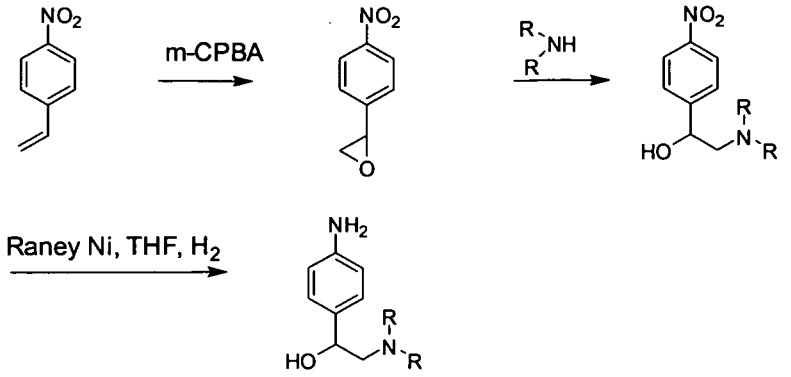


R=H, Cl

[00178] The synthesis of the title compound was conducted according to procedures described by G. Huiping in *Bioorganic & Medicinal Chemistry Letters*, 2004, 14, 187-190. Specifically, a 4-nitro-benzylchloride was taken up into THF to which was added sodium methylsulfinate. The reaction was irradiated with microwaves for 5 minutes at 150 °C. The crude reaction solution was diluted with water and extracted with ethyl acetate. The dried organics were concentrated to give the displacement adduct as a tan solid. This latter material was treated with Rainey Nickel in THF at 75 PSI for 12 hours to give the title compound as a tan solid.

General Procedure to Prepare 1-(4-Aminophenyl)-2-(dialkylamino)ethanol and 1-(3-

Aminophenyl)-2-(dialkylamino)ethanol



Step1: Synthesis 2-(4-nitrophenyl)oxirane

[00179] Synthesis of the title compound was conducted according to procedures described by K. Takai in *Angewandte Chemie*, 1981, 93 (8), 707. A solution of p-Nitrostyrene (1.40 g, 9.4 mmol.) and chloroperbenzoic acid (2.50 g, 11.2 mmol.) in chloroform (21.0 ml) was refluxed in an oil bath for 4 hrs., monitored by TLC (40% ethyl acetate in hexanes solution). Reaction mixture was cooled down to room temperature and filtered. The white precipitate was discarded and the remaining solution was concentrated, absorbed on 3.0 gram silica gel and purified via flash chromatography, eluted with 25% ethyl acetate in hexanes solutions to give the title compound, 2-(4-nitro-phenyl)-oxirane, in 43% yield (2.20 g).

Step2: Synthesis of 1-(4-nitrophenyl)-2-(piperidin-1-yl)ethanol

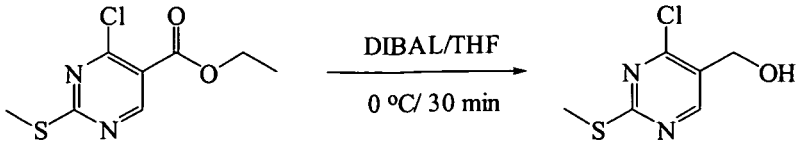
[00180] Synthesis of the title compound was conducted according to procedures described by U.M. Teotino in Farmaco, Edizione Scientifica 1962, *17*, 252-65. A solution of 2-(4-nitrophenyl)-oxirane (0.80 g, 3.0 mmol.) and piperidine (1.00 ml, 10.1 mmol.) in absolute ethanol (100.0 ml) was refluxed in an oil bath for 4 hrs., monitored by TLC (5% methanol in dichloromethane solutions). Reaction solution was cooled down to room temperature, absorbed on 1.50 gram silica gel and purified via flash chromatography, eluted with 2% and 4% methanol in dichloromethane solutions to give the title compound, 1-(4-nitro-phenyl)-2-piperidin-1-yl-ethanol, in 86% yield (0.65 g).

Step3: Synthesis of 1-(4-aminophenyl)-2-(piperidin-1-yl)ethanol

[00181] To a solution of 1-(4-nitro-phenyl)-2-piperidin-1-yl-ethanol (0.60 g, 2.4 mmol.) in tetrahydrofuran (25.0 ml), slurry solution of raney- nickel in water (2.5 ml) was added and hydrogenation was carried on at 75 psi for 12 hrs. The residue was filtered cautiously through celite and then evaporated to dryness to give the title compound, 1-(4-amino-phenyl)-2-piperidin-1-yl-ethanol in 90% yield (0.47 g).

General Procedures to Prepare Other Intermediates

General Procedure 5-1: (4-Chloro-2-(methylthio)pyrimidin-5-yl)methanol

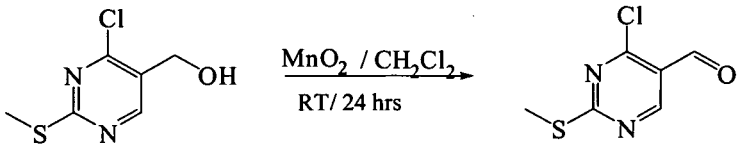


[00182] To a solution of ethyl 4-chloro-2-(methylthio)pyrimidine-5-carboxylate (10.7 g, 46 mmol), in dry THF (50 mL), on an ice-bath, DIBAL (185 mL, 1 M in THF, Aldrich Cat. No. 214981, 185 mmol) was added dropwise over 30 minutes (via pressure equalizing dropping funnel) under the nitrogen atomosphere. The resulting yellow transparent solution was stirred for additional 30 minutes before being transferred to a dry 1 L Erlenmeyer flask. On an ice bath, the reaction mixture was then quenched carefully, added dropwise with saturated solution of Na_2SO4 to give a yellow warm gel-like solid mixture. To this solid mixture, EtOAc (200 mL) was added, followed by dropwise addition of 6.0 N aqueous HCl to dissolve the solid into an aqueous solution of pH 3-4. The EtOAc layer was collected. The aqueous layer was again extracted twice with EtOAc (twice, 200 mL each). The combined EtOAc layers were washed with water (twice, 200 mL each time), dried with $MgSO_4$, and concentrated to give an off-white solid which was suspended in 75 mL petroleum ether and refluxed for 10 minutes. The mixture was cooled to the ambient temperature and then filtered to give the title compound (4.67 g, 53%, HPLC: 97% pure).

HPLC Rt: 4.72 min.

^{1}H-NMR ($CDCl_3$): δ 8.54 (s, 1H), 4.74 (d, 2H), 2.57 (s, 3H), 2.10 (t, 1H).

General Procedure 5-2: 4-Chloro-2-(methylthio)pyrimidine-5-carbaldehyde



[00183] A mixture of (4-chloro-2-(methylthio)pyrimidin-5-yl) methanol (9.0 g, 47 mmol) and activated MnO_2 (70 g, 800 mmol, Aldrich Cat. No. 217646) in 120 mL CH_2Cl_2 was stirred at the room temperature for 24 hours. The mixture was filtered through Celite (Acros Celite 521, Cat. No. 206350010). The filter cake was washed with CH_2Cl_2 until no UV-active material was seen. The combined CH_2Cl_2 solution was concentrated and passed through a thin silica gel plug, using 25% EtOAc/Hexanes. The filtrate was concentrated to give an off white solid (6.37 g, 71.6% yield).

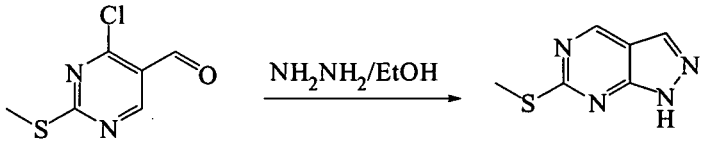
HPLC Rt: 5.53 min.

^{1}H-NMR ($CDCl_3$): δ 10.32 (s, 1H), 8.88 (s, 1H), 2.65 (s, 3H).

[00184] Set forth below are methods for preparing some intermediates and examples of the

compounds of this invention. Also provided below are methods for testing and using the compounds of this invention for inhibiting mitotic kinases and for treating disorders associated with these kinases. These examples are for illustration purposes only and not intended to limit the scope of this invention in any way.

Example 1: 6-(Methylthio)-1H-pyrazolo[3,4-d]pyrimidine.



[00185] A solution of 4-chloro-2-(methylthio) pyrimidine-5-carbaldehyde (6.3 g, 33 mmol) in 160 mL of EtOH and DIEA (6.6 g, 52 mmol) was cooled on an ice-bath before adding hydrazine (1.8 g, 56 mmol, Alfa Aesar P/N 32728) during 5 minutes. The reaction was left stirring at 0 °C for an additional one hour before placing on an oil bath at 50 °C for another hour. Solvents were removed and the residue washed with water then dried under high vacuum to give a crude product (5.05 g, 91% yield). The compound could be recrystalized from mixture of a methanol and water.

HPLC Rt: 3.91 min.

^{1}H-NMR ($CDCl_3$): δ 10.95 (br, s, 1H), 9.00 (s, 1H), 8.10 (s, 1H), 2.66 (s, 3H).

Example 2: 1-(1,2-Dihydroacenaphthylen-1-yl)-6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidine

[00186] The title compound was synthesized by Mitsunobu coupling between 1,2-dihydroacenaphthylen-1-ol and 6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidine according to General Procedure 1-1.

HPLC Rt: 7.47 min.

^{1}H-NMR ($CDCl_3$): δ 8.93 (s, 1H), 7.99 (s, 1H), 7.77 (m, 2H), 7.47 (m, 1H), 7.40 (m, 1H), 7.17 (d, 1H), 6.95 (m, 1H), 4.99 (m, 1H), 4.11 (m, 1H), 3.92(m, 1H), 2.3 (s, 3H).

Example 3: 1-(1,2-Dihydroacenaphthylen-1-yl)-6-(methylsulfonyl)-1H-pyrazolo[3,4-d]pyrimidine

[00187] The title compound was synthesized by oxidation of 1-(1,2-dihydroacenaphthylen-1-yl)-6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidine according to General Procedure 1-10.

HPLC Rt: 6.36 min.

^{1}H-NMR (DMSO-d_6): δ 9.35 (s, 1H), 8.30 (s, 1H), 7.78 (d, 1H), 7.75 (d, 1H), 7.61 (t, 1H), 7.44 (m, 2H), 7.09 (m, 2H), 4.18 (m, 1H), 3.86 (m, 1H), 3.24 (s, 3H).

Example 4: 6-(Methylthio)-1-(2-nitrobenzyl)-1H-pyrazolo[3,4-d]pyrimidine

[00188] The title compound was synthesized by Mitsunobu coupling between 2-nitro-

benzylalcohol and 6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidine according to General Procedure 1.1.

HPLC Rt: 6.79 min.

LC/MS: 302 (M+1).

Example 5: 6-(Methylsulfonyl)-1-(2-nitrobenzyl)-1H-pyrazolo[3,4-d]pyrimidine

[00189] The title compound was synthesized by oxidation of 6-(methylthio)-1-(2-nitrobenzyl)-1H-pyrazolo[3,4-d]pyrimidine according to General Procedure 1-10.

HPLC Rt: 5.79 min.

LC/MS: 334 (M+1).

Example 6: 6-(Methylthio)-1-(4-nitrobenzyl)-1H-pyrazolo[3,4-d]pyrimidine

[00190] The title compound was synthesized by Mitsunobu coupling between 4-nitro-benzylalcohol and 6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidine according to General Procedure 1-1.

HPLC Rt: 6.81 min.

LC/MS: 302 (M+1).

Example 7: 6-(Methylsulfonyl)-1-(4-nitrobenzyl)-1H-pyrazolo[3,4-d]pyrimidine

[00191] The title compound was synthesized by oxidation of 6-(methylsulfonyl)-1-(4-nitrobenzyl)-1H-pyrazolo[3,4-d]pyrimidine according to General Procedure 1-10.

HPLC Rt: 5.854 min.

LC/MS: 334 (M+1).

Example 8: *(S)*-6-(Methylthio)-1-(1-phenylethyl)-1H-pyrazolo[3,4-d]pyrimidine

[00192] The title compound was synthesized by Mitsunobu coupling between (S)-1-phenylethanol and 6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidine according to General Procedure 1-1.

HPLC Rt: 6.98 min.

^{1}H-NMR ($CDCl_3$): δ 8.89 (s, 1H), 8.02 (s, 1H), 7.36 (m, 5H), 6.18 (q, 1H), 2.64 (s, 3H), 2.01 (d, 3H).

Example 9: *(S)*-6-(Methylsulfonyl)-1-(1-phenylethyl)-1H-pyrazolo[3,4-d]pyrimidine

[00193] The title compound was synthesized by oxidation of (S)-6-(methylthio)-1-(1-phenylethyl)-1H-pyrazolo[3,4-d]pyrimidine according to General Procedure 1-10.

HPLC Rt: 5.79 min.

^{1}H-NMR ($CDCl_3$) δ 9.30 (s, 1H), 8.34 (s, 1H), 7.35 (m, 5H), 6.35 (q, 1H), 3.43 (s, 3H), 2.06 (d, 3H).

Example 10: 1-(6-(Methylthio)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2,3-dihydro-1H-inden-4-yl benzoate

[00194] The title compound was synthesized by Mitsunobu coupling between 1-hydroxy-2,3-dihydro-1H-inden-4-yl benzoate and 6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidine according to General Procedure 1-1.

HPLC Rt: 8.21 min.

LC/MS is 403(M+1).

Eample 11: 1-(6-(Methylsulfonyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2,3-dihydro-1H-inden-4-yl benzoate

[00195] The title compound was synthesized by oxidation of 1-(6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2,3-dihydro-1H-inden-4-yl benzoate according to General Procedure 1-10.

HPLC Rt: 7.20 min.

LC/MS: 435(M+1).

Example 12: N-(1-(6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2,3-dihydro-1H-inden-4-yl)acetamide

[00196] The title compound was synthesized by Mitsunobu coupling between N-(1-hydroxy-2,3-dihydro-1H-inden-4-yl)acetamide and 6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidine according to General Procedure 1-1.

HPLC Rt: 6.10 min.

LC/MS: 340(M+1).

Example 13: N-(1-(6-(methylsulfonyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2,3-dihydro-1H-inden-4-yl)acetamide

[00197] The title compound was synthesized by oxidation of N-(1-(6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2,3-dihydro-1H-inden-4-yl)acetamide according to General Procedure 1-10.

HPLC Rt: 5.22 min.

LC/MS: 372(M+1).

Example 14: 1-(4-methoxybenzyl)-6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidine

[00198] The title compound was synthesized by Mitsunobu coupling between 4-methoxy-benzylalcohol and 6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidine according to General Procedure 1-1.

HPLC Rt: 6.55 min.

^{1}H-NMR ($CDCl_3$): δ 8.90 (s, 1H), 7.99 (s, 1H), 7.32 (m, 2H), 6.84 (d, 2H), 5.53 (s, 2H), 3.77

(s, 3H), 2.66 (s, 3H).

Example 15: 1-(4-Methoxybenzyl)-6-(methylsulfonyl)-1H-pyrazolo[3,4-d]pyrimidine

[00199] The title compound was synthesized by oxidation of 1-(4-methoxybenzyl)-6-(methylsulfonyl)-1H-pyrazolo[3,4-d]pyrimidine according to General Procedure 1-10.

HPLC Rt: 5.54 min.

^{1}H-NMR ($CDCl_3$) δ 9.32 (s, 1H), 8.32 (s, 1H), 7.38 (m, 2H), 6.88 (d, 2H), 5.70 (s, 2H), 3.80 (s, 3H), 3.48 (s, 3H).

Example 16: *(S)*-1-(2,3-dihydro-1H-inden-1-yl)-6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidine

[00200] The title compound was synthesized by Mitsunobu coupling between (R)-2,3-dihydro-1H-inden-1-ol and 6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidine according to General Procedure 1-1.

HPLC Rt: 7.15 min.

^{1}H-NMR ($CDCl_3$): δ 8.95 (s, 1H), 8.01 (s, 1H), 7.36 (d, 1H), 7.28 (q, 1H), 7.16 (t, 1H), 7.01 (d, 1H), 6.55 (t, 1H), 3.39 (m, 1H), 3.10 (m, 1H), 2.76 (m, 1H), 2.66 (m, 1H), 2.63 (s, 3H).

Example 17: *(S)*-1-(2,3-dihydro-1H-inden-1-yl)-6-(methylsulfonyl)-1H-pyrazolo[3,4-d]pyrimidine

[00201] The title compound was synthesized by oxidation of *(S)*-1-(2,3-dihydro-1H-inden-1-yl)-6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidine according to General Procedure 1-10.

HPLC Rt: 5.99 min.

^{1}H-NMR ($CDCl_3$): δ 9.34 (s, 1H), 8.31 (s, 1H), 7.39 (d, 1H), 7.31 (q, 1H), 7.17 (t, 1H), 7.00 (d, 1H), 6.69 (t, 1H), 3.45 (s, 1H), 3.43 (m, 3H), 3.13 (m, 1H), 2.80 (m, 1H), 2.66 (m, 1H).

Example 18: 6-(Methylthio)-1-(3-nitrobenzyl)-1H-pyrazolo[3,4-d]pyrimidine

[00202] The title compound was synthesized by Mitsunobu coupling between 3-nitro-benzylalcohol and 6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidine according to General Procedure 1.1.

HPLC Rt: 6.63 min.

^{1}H-NMR ($CDCl_3$): δ 8.93 (s, 1H), 8.27 (m, 1H), 8.16 (m, 1H), 8.05 (s, 1H), 7.69 (d, 1H), 7.52 (t, 1H), 5.70 (s, 2H), 2.65 (s, 3H).

Example 19: 6-(Methylsulfonyl)-1-(3-nitrobenzyl)-1H-pyrazolo[3,4-d]pyrimidine

[00203] The title compound was synthesized by oxidation of 6-(methylthio)-1-(3-nitrobenzyl)-1H-pyrazolo[3,4-d]pyrimidine according to General Procedure 1-10.

HPLC Rt: 5.83 min.

LC/MS: 334(M+1).

Example 20: 1-(5-Methoxy-2,3-dihydro-1H-inden-1-yl)-6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidine

[00204] The title compound was synthesized by Mitsunobu coupling between 5-methoxy-2,3-dihydro-1H-inden-1-ol and 6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidine according to General Procedure 1-1.

HPLC Rt: 7.41 min.

LC/MS: 313(M+1).

Example 21: 1-(5-Methoxy-2,3-dihydro-1H-inden-1-yl)-6-(methylsulfonyl)-1H-pyrazolo[3,4-d]pyrimidine

[00205] The title compound was synthesized by oxidation of 1-(5-methoxy-2,3-dihydro-1H-inden-1-yl)-6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidine according to General Procedure 1-10.

HPLC Rt: 6.32 min.

LC/MS: 345.0(M+1).

Example 22: ethyl 5-amino-1-(3-methoxyphenyl)-1H-pyrazole-4-carboxylate

[00206] The title compound was obtained by condensation of (3-methoxyphenyl)hydrazine with (Z)-ethyl 2-cyano-3-ethoxyacrylateaccording to General Procedure 1-4.

HPLC Rt: 6.10 min.

^{1}H-NMR (DMSO-D_6): δ 7.71 (s 1H), 7.45(t, 1H), 7.15m, 2H), 6.95 (m 1H), 6.35 (s, 2H), 4.22 (q, 2H), 3.82 (s, 3H), 1.28 (t, 3H).

Example 23: Ethyl 5-amino-1-(4-methoxyphenyl)-1H-pyrazole-4-carboxylate

[00207] The title compound was obtained by condensation of (4-methoxyphenyl)hydrazine with (Z)-ethyl 2-cyano-3-ethoxyacrylateaccording to the general procedure 1-4.

HPLC Rt: 5.96 min.

^{1}H-NMR (DMSO-D_6): δ 7.77 (s 1H), 7.45(d, 2H), 7.03d, 2H), 5.20 (s, 2H), 4.22 (q, 2H), 3.82 (s, 3H), 1.28 (t, 3H).

Example 24: Ethyl 5-amino-1-(naphthalen-1-yl)-1H-pyrazole-4-carboxylate

[00208] The title compound was obtained by condensation of naphthalen-1-ylhydrazine with (Z)-ethyl 2-cyano-3-ethoxyacrylateaccording to General Procedure 1-4.

HPLC Rt: 6.53 min.

^{1}H-NMR (DMSO-D_6): δ 8.03(d, 2H), 7.86(s, 1H), 7.53(d, 2H), 7.37(d, 2H), 6.71(s, 1H), 4.22 (q, 2H), 1.28 (t, 3H).

Example 25: Ethyl 5-(3-benzoylthioureido)-1-(3-methoxyphenyl)-1H-pyrazole-4-carboxylate

[00209] The title compound was obtained from ethyl 5-amino-1-(3-methoxyphenyl)-1H-pyrazole-4-carboxylate according to General Procedure 1-5.

HPLC Rt: 7.14 min.

LC/MS: 425.0(M+1).

Example 26: Ethyl 5-(3-benzoylthioureido)-1-(4-methoxyphenyl)-1H-pyrazole-4-carboxylate

[00210] The title compound was obtained from ethyl 5-amino-1-(4-methoxyphenyl)-1H-pyrazole-4-carboxylate according to the general procedure 1-5.

[00211] HPLC Rt: 7.02 min.

^{1}H-NMR ($CDCl_3$): δ 12.15 (s, 3H), 1.35 (t, 3H).

Example 27: Ethyl 5-(3-benzoylthioureido)-1-(naphthalen-1-yl)-1H-pyrazole-4-carboxylate

[00212] The title compound was obtained from ethyl 5-amino-1-(naphthalene-1-yl)-1H-pyrazole-4-carboxylate according to General Procedure 1-5.

HPLC Rt: 7.51 min.

^{1}H-NMR (DMSO): δ 12.08(s, 1H), 11.86(s, 1H), 8.28(s, 1H), 7.89(m, 3H), 7.64(m, 3H), 7.40(m, 6H), 4.24(q, 2H), 1.28 (t, 3H).

Example 28: 6-Mercapto-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol

[00213] The title compound was obtained by cyclelization of ethyl 5-(3-benzoylthioureido)-1-(3-methoxyphenyl)-1H-pyrazole-4-carboxylate in basic condition according to General Procedure 1-6.

HPLC Rt: 4.96 min.

LC/MS: 275.0 (M+1).

Example 29: 6-Mercapto-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol

[00214] The title compound was obtained by cyclelization of ethyl 5-(3-benzoylthioureido)-1-(4-methoxyphenyl)-1H-pyrazole-4-carboxylate in basic condition according to General Procedure 1-6.

HPLC Rt: 4.89 min.

^{1}H-NMR (DMSO): δ 10.25 (s, 1H), 8.11(d, 2H), 7.82 (s, 1H), 7.06d, 2H), 3.80 (s, 3H).

Example 30: 6-Mercapto-1-(naphthalen-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol

[00215] The title compound was obtained by cyclelization of ethyl 5-(3-benzoylthioureido)-1-(naphthalen-1-yl)-1H-pyrazole-4-carboxylate in basic condition according to General Procedure 1-6.

HPLC Rt: 5.59 min.

^{1}H-NMR (DMSO-D_6): δ 10.21(s, 1H), 8.09(t, 2H), 8.05(s, 1H), 7.96 (t, 1H), 7.63 (m, 2H), 7.50 (m, 1H), 7.39d, 1H).

Example 31: 1-(3-Methoxyphenyl)-6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidin-4-ol

[00216] The title compound was obtained from 6-mercapto-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol according to General Procedure 1-7.

HPLC Rt: 6.14 min.

^{1}H-NMR (DMSO-D_6): δ 8.23 (s 1H), 7.95(s, 2H), 7.87s, 1H), 7.79 (d, 1H), 7.46 (t, 1), 6.95 (d, 1H), 3.82 (s, 3H), 2.56 (s, 3H).

Example 32: 1-(4-Methoxyphenyl)-6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidin-4-ol

[00217] The title compound was obtained from 6-mercapto-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol according to General Procedure 1-7.

HPLC Rt: 6.00 min.

^{1}H-NMR (DMSO-D_6): δ 8.10 (d, 2H), 7.72 (s, 1H), 7.03d, 2H), 3.78 (s, 3H), 2.39 (s, 3H).

Example 33: 1-(Naphthalen-1-yl)-6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidin-4-ol

[00218] The title compound was obtained from 6-mercapto-1-(naphthalen-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol according to General Procedure 1-7.

HPLC Rt: 6.39 min.

^{1}H-NMR (DMSO-D_6): δ 12.65(s 1H), 8.34 (s, 1H), 8.13 (dd, 2H), 7.67 (m, 2H), 7.57 (m, 1H), 7.30m, 2H), 2.23 (s, 3H).

Example 34: 4-Chloro-1-(3-methoxyphenyl)-6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidine

[00219] The title compound was obtained from 1-(3-methoxyphenyl)-6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidin-4-ol with $POCl_3$ according to General Procedure 1-8.

HPLC Rt: 8.26 min.

^{1}H-NMR (DMSO-D_6): δ 8.61 (s 1H), 7.85(s, 1H), 7.76d, 1H), 7.50 (t, 1H), 6.98 (d, 1H), 3.85 (s, 3H), 2.67 (s, 3H).

Example 35: 4-Chloro-1-(4-methoxyphenyl)-6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidine

[00220] The title compound was obtained from 1-(4-methoxyphenyl)-6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidin-4-ol with $POCl_3$ according to General Procedure 1-8.

HPLC Rt: 8.06 min.

^{1}H-NMR (DMSO): δ 8.59 (s 1H), 8.02 (d, 2H), 7.18 (d, 2H), 3.82 (s, 3H), 2.67 (s, 3H).

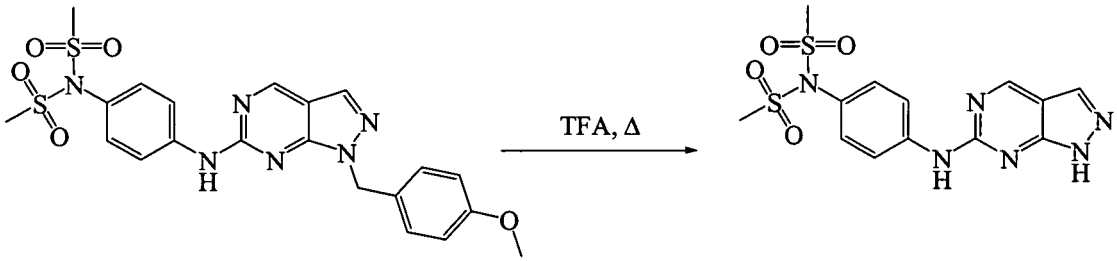
Example 36: 4-Chloro-1-(naphthalen-1-yl)-6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidine

[00221] The title compound was obtained from 1-(naphthalen-1-yl)-6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidin-4-ol with $POCl_3$ according to the general procedure 1-8.

HPLC Rt: 8.27 min.

^{1}H-NMR (DMSO): δ 8.73 (s 1H), 8.21 (d, 1H), 8.13 (d, 1H), 7.78 (m, 3H), 7.55 (m, 2H), 2.39 (s, 3H).

Example 37: N-(4-(1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide



[00222] Synthesis of the title compound was conducted according to procedure described by R.N. Misra in *Bioorg. Med. Chem. Lett. EN,* 2006, 13 (6), 1133-1136. Specifically, N-(4-(1-(4-methoxybenzyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide (0.34g, 0.68 mmol) was dissolved in 5 ml TFA and the solution heated under reflux for 16 hours. TFA was then removed under reduced pressure to give a greenish oily residue which converted to a solid product upon adding ice-cold water. The solud was filtered, washed with a generous amount of DCM before it was washed again with ether to give 0.248 g (yield 96%) of the title product.

[00223] Provided below in Tables 1-7 are additional specific examples of the compounds of Formula (I) which were prepared according to the procedures described anove and tested by the methods described hereinafter.

TABLE 1. COMPOUNDS CONTAINING SUBSTITUTED PHENYL GROUP AS R_2 IN FORMULA (I)

Example No.	Compound Name	HPLC data (RT, mins.)	LC/MS	^{1}H-NMR (in $CDCl_3$ unless noted)
38	N-(4-(1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]-pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	6.94	487 (M-1)	
39	N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl) methanesulfonamide	6.82		(MDSO-d6) 3.53 (s, 6H), 3.85 (s, 3H), 7.18 (d, J=8.88 Hz, 2H), 7.49 (d, J=8.88 Hz, 2H), 7.96 (d, J=8.88 Hz, 2H), 8.36 (s, 1H), 9.20 (s, 1H), 10.32 (s, 1H).

40	N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)cyclopropanesulfonamide	6.60	437 (M+1)	
41	1-(4-methoxyphenyl)-N-(3-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	5.67	416 (M+1)	
42	2-hydroxy-5-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)benzaldehyde	6.92		3.91 (s, 3H), 7.05 (m, 4H), 7.34 (d, J=8.84Hz, 1H), 8.05 (m, 3H), 8.38 (s, 1H), 8.92 (s, 1H), 9.93 (s, 1H), 10.85 (s, 1H).
43	ethyl 2-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenylamino)-2-oxoacetate	6.78	455 (M+23)	
44	N-(2,3,5,6,8,9,11,12,14,15-decahydrobenzo[b][1,4,7,10,13,16]hexaoxacyclooctadecin-18-yl)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	6.47	552 (M+1)	
45	1-(4-methoxyphenyl)-N-(2,3,5,6,8,9,11,12-octahydrobenzo[b][1,4,7,10,13]pentaoxacyclopentadecin-15-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	6.29	508 (M+1)	
46	N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-1-(methylsulfonyl)methanesulfonamide	6.45	487 (M-1)	
47	3,3,3-trifluoro-N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)propane-1-sulfonamide	7.05	515 (M+23)	
48	1-(4-methoxyphenyl)-N-(4-morpholinophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	5.82	401 (M-1)	
49	N-(4-(1H-1,2,4-triazol-1-yl)phenyl)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	6.63	385 (M+1)	
50	2-methoxy-4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenol	6.16	364 (M+1)	
51	N-(3,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	6.76		(DMSO-d6) 3.71 (s, 3H), 3.72 (s, 3H), 3.83 (s, 3H), 6.95 (s, 1H), 7.12 (d, J=8.85Hz, 2H), 7.26 (d, J=8.84Hz,1H), 7.36 (d, J=8.84Hz, 1H), 7.81 (d, J=8.85Hz, 2H), 8.28 (s, 1H), 9.05 (s, 1H), 9.86 (s, 1H).

52	1-(3-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)ethanol	6.45		(DMSO-d6) 1.36 (d, J=6.4 Hz, 3H), 3.88 (s, 3H), 4.73 (m, 1H), 5.20 (d, J=6.4 Hz, 1H), 6.95 (d, J=8.84Hz, 1H), 7.14 (d, J=8.84Hz, 2H, 7,27 (t, J=8.84Hz, 1H), 7.52 (d, D=8.84Hz, 1H), 8.10 (m, 3H), 8.12 (s, 1H), 9.08 (s, 1H), 10.03 (s, 1H).
53	N1-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,4-diamine	5.18		(DMSO-d6) 3.83 (s, 3H), 4.88 (s, 2H), 6.58 (d, J=8.84Hz, 2H), 7.16 (d, J=8.84Hz, 2H), 7.44 (d, J=8.84Hz, 2H), 8.08 (d, J=8.84Hz, 2H), 8.22 (s, 1H), 8.97 (s,1H), 9.58 (s, 1H).
54	N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide	6.34	411 (M+1)	
55	4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenol	6.03	334 (M+1)	
56	1-(4-methoxyphenyl)-N-(3,4,5-trimethoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	6.91	430 (M+23)	
57	1-(4-methoxyphenyl)-N-(4-(4-(methylsulfonyl)piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	6.38	480 (M+1)	
58	methyl 3-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenylamino)-3-oxopropanoate	6.27	431 (M-1))	
59	2-methoxy-N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)acetamide	6.35		3.55 (s,3H), 3.91 (s, 3H), 4.06 (s, 2H), 7.07 (d, J=8.85Hz, 2H), 7.28 (s,1H), 7.60 (d, J=8.84Hz, 2H), 7.74 (d, J=8.84Hz, 2H), 8.09 (d, J=8.84Hz,2H), 8.10(s,1H), 8.26 (s,1H), 8.90 (s,1H).
60	N-(3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	7.20	390 (M+1)	
61	2-ethoxy-5-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenol	6.69		1.47 (t, 3H), 3.90 (s, 1H), 4.15 (dd, 2H), 5.70 (s, 1H), 6.84 (d, J=8.84Hz, 1H), 7.07 (d, J=8.84Hz, 2H), 7.09 (d, J=8.84Hz, 1H), 7.48 (s, 1H), 8.07 *s, 1H), 8.13 (d, J=8.84Hz, 2H), 8.88 (s, 1H).
62	2-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)ethanol	6.27	384 (M+23)	

63	N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)acetamide	6.05	397 (M+23)	
64	2-(2-methoxyethoxy)-N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)acetamide	6.45	447 (M-1)	
65	diethyl 4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)benzylphosphonate	6.75		1.27 (m, 6H), 3.14 (s, 1H), 3.20 (s, 1H), 4.07 (s, 3H), 4.14 (m, 4H), 7.06 9d, J=8.85Hz, 2H0, 7.26(d, J=8.85Hz, 2H), 7.28(s, 1H), 7.71 (d, J=8.85Hz, 2H), 8.09 (d, J=8.85Hz, 2H), 8.10 (s, 1H), 8.91 (s, 1H).
66	1-(3-methoxyphenyl)-N-(4-(4-(methylsulfonyl)piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	6.53	480 (M-1)	
67	dimethyl 4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenylphosphoramidate	5.98	463 (M+23)	
68	N^1-(1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,4-diamine	5.27		(DMSO-d6) 3.81 (s, 3H), 6.56 (d, J=8.85Hz, 2H), 6.90 (d, J=8.85Hz, 1H), 7.41 (m, 3H), 7.76 (d, J=8.84Hz, 1H), 7.89(s, 1H), 8.26 (s, 1H), 8.98 (s, 1H), 9.61 (s, 1H).
69	1-(4-methoxyphenyl)-N-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	5.46	416 (M+1)	
70	N-(3-methoxyphenyl)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	7.32		3.82 (s, 3H0, 3.90(s, 3H), 6.67 (d, J=8.85Hz, 1H), 7.05 (d, J=8.84Hz, 2H), 7.14 (d, J=8.85Hz, 1H), 7.27 (d, J=8.85Hz, 2H), 7.54 (s, 1H), 7.64 (s, 1H), 8.09 (d, J=8.85Hz, 2H), 8.10 (s, 1H), 8.91 (s, 1H).
71	3-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenol	6.35	334 (M+1)	
72	1-(4-methoxyphenyl)-N-(4-(piperidin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	5.85	401 (M+1)	
73	N^1-bis(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	7.08	347.9 (M+1)	3.85 (s, 3H), 3.90 (s, 3H), 6.93 9d, J=8.85Hz, 2H), 7.04 (d, J=8.85Hz, 2H), 7.36 (s, 1H), 7.62 (d, J=8.85Hz, 2H), 8.06 (s, 1H), 8.11 (d, J=8.85Hz, 2H), 8.87 (s, 1H).
74	methyl 4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenylcarbamate	6.59	389 (M-1)	

75	2-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenylamino)-2-oxoethyl acetate	6.30	433 (M+1)	
76	N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	7.04		3.83 (s, 3H), 4.25 (m, 4H), 6.90(d, J=8.84Hz, 1H), 7.13 (d, J=8.84Hz, 2H), 7.23 (d, J=8.84Hz, 1H), 7.52 (s, 1H), 8.08 (d, J=8.84Hz, 2H), 8.28 (s, 1H),9.00 (s, 1H), 9.89 (s, 1H).
77	2-methoxy-5-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenol	6.29	364 (M+1)	
78	1-(4-methoxyphenyl)-N-(4-(methylthio)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	7.71	362 (M-1)	
79	4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-2-methylphenol	6.36		(DMSO-d6) 2.08 (s, 3H), 3.83 (s, 3H), 6.72 (d, J=8.85Hz, 1H), 7.07 (d, J=8.84Hz, 2H), 7.12 (d, J=8.85Hz, 1H), 7.72 (s, 1H), 8.03 (d, J=8.85Hz, 2H), 8.25(s, 1H), 9.00 (s, 2H), 9.77 (s, 1H).
80	2-methoxy-4-(1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenol	6.35	364 (M+1)	
81	N-(3,4-dimethoxyphenyl)-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	6.91	378 (M+1)	
82	2-(2-methoxyethoxy)-N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)acetamide	7.11		3.98(s, 3H), 6.13(s, 2H), 6.82(d, J=8.85Hz, 1H), 6.99(d, J=8.85Hz, 1H), 7.08(d, J=8.88Hz, 2H), 7.28(s, 1H), 7.45(s, 1H), 8.07(d, J=8.88Hz, 2H), 8.10(s, 1H), 8.89(s, 1H).
83	(E)-N'-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N,N-dimethylformimidamide	5.64	388 (M+1)	
84	2-methoxy-5-(1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenol	6.48	362 (M-1)	
85	N-(2,2-dimethylbenzo[d][1,3]dioxol-5-yl)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	7.54	390 (M+1)	
86	methyl 2-hydroxy-5-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)benzoate	7.33		(DMSO-d6) 3.83 (s, 3H), 3.86 (s, 3H), 7.02(d, J=8.52Hz, 1H), 7.11 (d, J=8.56Hz, 2H), 7.81 (d, J=8.52Hz, 1H), 8.00 (d, J=8.56Hz, 2H), 8.30 (s, 1H), 8.43(s, 1H), 9.07(s, 1H), 10.00 (s, 1H). 1029 (s, 1H).

87	1-(4-methoxyphenyl)-N-(4-(methylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	6.60	396 (M+1)	
88	3-(1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenol	6.55		3.98(s, 3H), 6.00(s, 1H), 6.64(d, J=8.65Hz, 1H), 6.71(d, J=8.65Hz, 1H), 6.90(d, J=8.52Hz, 1H), 7.21(m, 2H), 7.48(m, 2H), 7.70(d, J=8.52Hz, 1H), 8.10(s, 1H), 8.26(s, 1H), 8.39(s, 1H), 8.89(s, 1H).
89	1-(3-methoxyphenyl)-N-(2,3,5,6,8,9,11,12-octahydrobenzo[b][1,4,7,10,13]pentaoxacyclopentadecin-15-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	6.48	508 (M+1)	
90	N-(benzo[d][1,3]dioxol-5-yl)-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	7.25	362 (M+1	
91	N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-methylmethanesulfonamide	6.64		3.09(s, 3H), 3.67(s, 3H), 3.88(s, 3H), 6.49(s, 1H), 7.01(d, J=8.65Hz, 2H), 7.32(d, J=8.65Hz, 2H), 7.42(d, J=8.64Hz, 2H), 8.04(s, 1H), 8.13(d, J=8.64Hz, 2H), 8.82(s, 1H).
92	4-methoxy-N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)benzamide	7.14	465 (M-1)	
93	N-(2,4-dimethoxyphenyl)-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	7.49	378 (M+1)	
94	1-(4-methoxyphenyl)-N-(naphthalen-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	7.51	368 (M+1)	
95	4-methoxy-N1-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,3-diamine	5.45	363 (M+1)	
96	4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl acetate	6.72	517 (M+1)	
97	1-(4-methoxy-2-methylphenyl)-N-(4-(methylthio)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	7.395	378 (M+1)	
98	1-(4-methoxy-2-methylphenyl)-N-(4-(4-(methylsulfonyl)piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	6.192	495 (M+1)	

99	4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl acetate	6.73	517 (M+1)	
100	4-methoxy-N1-(1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-N3-methylbenzene-1,3-diamine	5.87	377 (M+1)	
101	2-methoxy-5-(1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl acetate	7.066	406 (M+1)	
102	N-(2-methoxy-5-(1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)acetamide	6.447	405 (M+1)	
103	methyl 2-methoxy-5-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenylcarbamate	6.843	421 (M+1)	
104	N-(2-methoxy-5-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)cyclopropanecarboxamide	6.737	431 (M+1)	
105	2-methoxy-5-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl cyclopropanecarboxylate	7.293	432 (M+1)	
106	4-(6-(3-amino-4-methoxyphenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenol	4.771	349 (M+1)	
107	methyl 2-methoxy-5-(1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenylcarbamate	7.010	421 (M+1)	
108	4-(6-(3-amino-4-methoxyphenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl acetate	5.413	391 (M+1)	
109	1-ethyl-3-(2-methoxy-5-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)urea	6.377	434 (M+1)	

110	4-(6-(4-aminophenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl diethyl phosphate	5.471	455 (M+1)	
111	N1-(1-(4-aminophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,4-diamine	4.096	318 (M+1)	
112	4-methoxy-N1-(1-(4-nitrophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,3-diamine	5.904	378 (M+1)	
113	N-(4-(1-(4-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	6.268	475 (M+1)	
114	2-methoxy-5-(1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl propionate	7.411	420 (M+1)	
115	2-methoxy-5-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl propionate	7.269	420 (M+1)	
116	N-(4-(6-(3-amino-4-methoxyphenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)acetamide	4.790	390 (M+1)	
117	N1-(1-(4-methoxy-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,3-diamine	5.309	347 (M+1)	
118	3-(6-(4-aminophenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl acetate	5.280	361 (M+1)	
119	N1-(1-(4-(2-(dimethylamino)ethoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,4-diamine	4.401	390 (M+1)	
120	3-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl acetate	6.796	517 (M+1)	

121	N-(4-(6-(4-(methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)acetamide	5.549	438 (M+1)	
122	N-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)acetamide	6.012	516 (M+1)	
123	N-(4-(6-(4-aminophenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)acetamide	4.694	360 (M+1)	
124	3-(6-(4-(methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl acetate	6.367	439 (M+1)	
125	N-(3-(1-(4-methoxy-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	6.630	503 (M+1)	
126	N-(3-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide	6.449	409 (M-1)	
127	5-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-1H-benzo[d]imidazol-2(3H)-one	5.427	372 (M-1)	
128	1-(4-methoxyphenyl)-N-(4-(pyrrolidin-1-ylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	7.396	451 (M+1)	
129	3-bromo-N1-(1-(4-methoxy-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,4-diamine	6.126	427 (M+2)	
130	N1-(1-(5-methoxy-2,4-dinitrophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,4-diamine	5.412	423.0 (M+1)	
131	N1-(1-(3-methoxy-2,4-dinitrophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,4-diamine	5.338	423.9 (M+1)	

132	2-amino-5-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenol	5.146	349 (M+1)	
133	5-amino-2-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenol	5.059	349 (M+1)	
134	N-(4-(6-(4-(methylsulfonylmethylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)acetamide	5.609	514 (M-1)	
135	3-methoxy-N1-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,4-diamine	5.232	363 (M+1)	
136	N-(4-(1-(5-methoxy-2,4-dinitrophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide	6.441	501 (M+1)	
137	N-(4-(1-(3-methoxy-2,4-dinitrophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	6.668	579 (M+1)	
138	N-(4-(1-(3-methoxy-2,4-dinitrophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide	6.28	500.9 (M+1)	
139	N-(4-(1-(4-iodophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	7.656	585 (M+1)	
140	N-(4-(1-(4-iodophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide	7.275	507 (M+1)	
141	tert-butyl 4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenylcarbamate	7.287	596 (M+23)	
142	tert-butyl 4-(6-(4-aminophenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenylcarbamate	5.779	418 (M+1)	

143	N-(4-(1-(4-aminophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	5.129	474 (M+1)	
144	N-(3-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)acetamide	5.794	516 (M+1)	
145	ethyl 4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)benzoate	7.378	531 (M+1)	
146	N-(methylsulfonyl)-N-(4-(1-(4-(morpholine-4-carbonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide	6.011	572 (M+1)	
147	N,N-dimethyl-4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)benzamide	6.059	530 (M+1)	
148	methyl 2-fluoro-4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)benzoate	7.146	535 (M+1)	
149	N-(cyclopropanecarbonyl)-N-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)cyclopropanecarboxamide	6.628	610 (M+1)	
150	N-(methylsulfonyl)-N-(4-(1-(2-(methylthio)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide	6.653	505 (M+1)	
151	N-(4-(1-(3-isopropylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	7.630	501 (M+1)	
152	2-methoxy-N-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)acetamide	6.210	546 (M+1)	
153	2-(dimethylamino)-N-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)acetamide	5.289	560 (M+2)	

154	N-(4-(1-(3-(2-hydroxyethyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	6.187	503 (M+1)	
155	N-(4-(1-(4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	7.376	517 (M+1)	
156	N-(4-(1-(4-methoxy-3-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	7.305	557 (M+1)	
157	N-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)isobutyramide	6.574	544 (M+1)	
158	N-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)acrylamide	6.278	550 (M+23)	
159	N-(furan-2-carbonyl)-N-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)furan-2-carboxamide	6.744	662 (M+1)	
160	N-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)furan-2-carboxamide	6.565	590 (M+23)	
161	ethyl 3-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenylamino)-3-oxopropanoate	6.420	610 (M+23)	
162	N-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)cyclopropanecarboxamide	6.460	542 (M+1)	
163	N-(methylsulfonyl)-N-(4-(1-(4-(trifluoromethoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide	7.597	543 (M+1)	
164	N-(methylsulfonyl)-N-(4-(2-(4-(trifluoromethoxy)phenyl)-2H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide	7.192	543 (M+1)	

165	N-(4-(1-(4-acetylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	6.750	501 (M+1)	
166	N-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)-2-(piperidin-1-yl)acetamide	5.567	599 (M+1)	
167	tert-butyl methyl(2-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenylamino)-2-oxoethyl)carbamate	6.768	645 (M+1)	
168	N-(4-(1-(4-(hydroxymethyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	5.942	489 (M+1)	
169	N-(methylsulfonyl)-N-(4-(1-(2-vinylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide	6.799	485 (M+1)	
170	N-(methylsulfonyl)-N-(4-(1-(2-(methylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide	6.144	537 (M+1)	
171	N-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)-2-morpholinoacetamide	5.353	601 (M+1)	
172	2-(2-methyl-1H-imidazol-1-yl)-N-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)acetamide	5.431	596 (M+1)	
173	N-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)-2-(pyrrolidin-1-yl)acetamide	5.450	585 (M+1)	
174	2-(4-methylpiperazin-1-yl)-N-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)acetamide	5.187	614 (M+1)	
175	3-(4-methylpiperazin-1-yl)-N-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)propanamide	5.037	628 (M+1)	

176	3-(1H-imidazol-1-yl)-N-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)propanamide	5.359	596 (M+1)	
177	2-(1H-imidazol-1-yl)-N-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)acetamide	5.351	582 (M+1)	
178	methyl 5-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenylamino)-5-oxopentanoate	6.360	602 (M+1)	
179	dimethyl 5,5'-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenylazanediyl)bis(5-oxopentanoate)	6.514	730 (M+1)	
180	2-(bis(2-hydroxyethyl)amino)-N-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)acetamide	5.195	619 (M+1)	
181	N-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)cyclohexanecarboxamide	7.216	584 (M+1)	
182	N-(cyclohexanecarbonyl)-N-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)cyclohexanecarboxamide	8.135	694 (M+1)	
183	N-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)morpholine-4-carboxamide	5.955	587 (M+1)	
184	tert-butyl 4-(6-(4-(methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenylcarbamate	6.829	496 (M+1)	
185	N-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)-2-(pyridin-3-yl)acetamide	5.368	593 (M+1)	
186	tert-butyl 4-(6-(3-amino-4-methoxyphenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenylcarbamate	5.973	448 (M+1)	

187	2-(methyl(pyridin-3-ylmethyl)amino)-N-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)acetamide	5.096	636 (M+1)	
188	2-(methyl(tetrahydrothiophen 1,1-dioxide-3-yl)amino)-N-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)acetamide	5.500	663 (M+1)	
189	N-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)-3-morpholinopropanamide	5.363	615 (M+1)	
190	N-(4-(1-(4-(chloromethyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	7.198	507 (M+1)	
191	3-bromo-N-(4-(6-(4-(methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)propanamide	5.418	529 (M+1)	
192	N-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)-3-(pyrrolidin-1-yl)propanamide	5.704	599 (M+1)	
193	N-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)-2-(thiophen-2-yl)acetamide	6.841	597 (M+1)	
194	N-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)-2-(2-oxopyrrolidin-1-yl)acetamide	5.770	599 (M+1)	
195	N-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)-2-(2-oxooxazolidin-3-yl)acetamide	5.812	601 (M+1)	
196	N-(4-(1-(2-(ethylthio)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	6.883	519 (M+1)	

197	N-(4-(1-(4-(bromomethyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	7.300	552 (M+1)	
198	tert-butyl 4-(6-(4-(4-methylpiperazin-1-yl)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenylcarbamate		501 (M+1)	
199	N-(4-(1-(4-methoxy-3-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	7.154	503 (M+1)	
200	N-(4-(1-(4-((2-(dimethylamino)ethylamino)methyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	4.897	559 (M+1)	
201	methyl 3-(4-(6-(4-aminophenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)propanoate	5.442	389 (M+1)	
202	methyl 3-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)propanoate	6.976	545 (M+1)	
203	methyl 3-(4-(6-(4-(methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)propanoate	6.539	467 (M+1)	
204	N-(4-(1-(4-((3-(diethylamino)pyrrolidin-1-yl)methyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	5.513	613	
205	N-(4-(1-(2-(ethoxymethyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	6.811	517 (M+1)	
206	N-(4-(1-(4-aminophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide	4.674	396 (M+1)	
207	tert-butyl 4-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenylcarbamoyl)piperidine-1-carboxylate	7.118	685 (M+1)	

208	N-(4-(6-(4-(methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)-2-(pyrrolidin-1-yl)acetamide	5.070	507 (M+1)	
209	tert-butyl 4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)benzoate	7.970	559 (M+1)	
210	tert-butyl 2-(6-(methylsulfonyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenylcarbamate	6.552	390 (M+1)	
211	tert-butyl 2-(6-(4-aminophenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenylcarbamate	5.717	418 (M+1)	
212	1-(4-aminophenyl)-N-(piperidin-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	3.703	310 (M+1)	
213	tert-butyl 4-(1-(4-acetamidophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)piperidine-1-carboxylate	6.025	452 (M+1)	
214	tert-butyl 4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)piperidine-1-carboxylate	7.072	425 (M+1)	
215	1-(4-methoxyphenyl)-N-(piperidin-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	4.791	325 (M+1)	
216	1-(4-methoxyphenyl)-N-(1-(methylsulfonyl)piperidin-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	5.903	403 (M+1)	
217	N-(4-(1-(2-aminophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	6.019	474 (M+1)	
218	N-(2-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)-2-(pyrrolidin-1-yl)acetamide	5.506	585 (M+1)	

219	N-(2-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)acetamide	6.012	516 (M+1)	
220	N-(4-(1-(4-(dimethylamino)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	5.579	502 (M+1)	
221	N-(4-(1-(4-(2-(1H-pyrazol-1-yl)ethoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	6.541	569 (M+1)	
222	N-(4-(1-(2-(3-hydroxypropylamino)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	5.946	532 (M+1)	
223	N-(4-(1-(4-(3-hydroxypropylamino)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	5.240	532 (M+1)	
224	2-amino-N-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)acetamide	5.194	531 (M+1)	
225	tert-butyl 2-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenylamino)-2-oxoethylcarbamate	6.616	631 (M+1)	
226	N-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)pivalamide	6.902	558 (M+1)	
227	1-methyl-N-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)piperidine-4-carboxamide	5.352	599 (M+1)	
228	2-hydroxy-N-(4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)acetamide	5.678	554 (M+23)	
229	N-(4-(1-(4-(bis(2-hydroxyethyl)amino)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	5.293	562 (M+1)	

230	N-(4-(1-(2-(2-hydroxyethylamino)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	5.939	540 (M+23)	
231	N-(4-(1-(2-(bis(2-hydroxyethyl)amino)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	5.321	562 (M+1)	
232	N-(4-(1-(4-(bis(3-hydroxypropyl)amino)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	5.171	590 (M+1)	
233	N-(4-(1-(4-(2-hydroxyethylamino)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	5.302	540 (M+23)	
234	N1-(1-(4-iodophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,4-diamine	5.89		4.70 (s, 2H), 6.75(d, J=8.46Hz, 2H), 7.47 (d, J=8.46Hz, 2H), 7.82 (d, J=8.65Hz, 2H), 8.07 (d, J=8.65Hz, 2H), 8.10 (s, 1H), 8.85 (s, 1H).
235	4-(4-(6-(4-aminophenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)but-3-yn-1-ol	5.17	371 (M+1)	
236	4-(4-(6-(3,4-dimethoxyphenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)but-3-yn-1-ol	6.50	416 (M+1)	
237	N-(3,4-dimethoxyphenyl)-1-(4-iodophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	7.88		(DMSO-D6) 3.76(s, 3H), 3.94(s, 3H), 6.98(d, J=8.54Hz, 1H), 7.31(d, J=8.54Hz, 1H), 7.33(s, 1H), 7.90(d, J=8.42Hz, 2H), 8.03(d, J=8.42Hz, 2H), 8.34(s, 1H), 9.06(s, 1H), 9.92(s, 1H).
238	5-(1-(4-iodophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-2-methoxyphenol	7.35	460 (M+1)	
239	1-(4-ethylphenyl)-N-(4-(piperidin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	6.48		1.32(t, J=4.56Hz, 3H), 1.76(m, 6H), 2.80(dd, J=4.56Hz, 2H), 3.16(m, 4H), 7.00(d, J=8.54Hz, 2H), 7.28(d, J=8.54Hz, 2H), 7.60(d, J=8.45Hz, 2H), 8.01(s, 1H), 8.10(d, J=8.45Hz, 2H), 8.90(s, 1H).

240	1-(4-iodophenyl)-N-(4-(piperidin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	6.67		(DMSO-D6) 1.62(m, 2H), 1.65(m, 4H), 3.10(m, 4H), 6.97(d, J=8.62Hz, 2H), 7.63(d, J=8.62Hz, 2H), 7.96(d, J=8.45Hz, 2H), 8.08(d, J=8.45Hz, 2H), 8.32(s, 1H), 9.00(s, 1H), 9.93(s, 1H).

TABLE 2. COMPOUNDS CONTAINING 4-METHOXY-2-METHYLPHENYL GROUP AS R_2 IN FORMULA (I)

Example No.	Compound Name	HPLC data (Rt, mins.)	LC/MS	^{1}H-NMR (in $CDCl_3$ unless noted)
241	N-(4-(1-(4-methoxy-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	6.69	503 (M+1)	
242	1-(4-methoxy-2-methylphenyl)-N-(4-(4-(methylsulfonyl)piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	6.19		2.20 (s, 3H, CH_3), 2.85 (s, 3H, CH_3), 3.24 (t, J=5.16Hz, 4H, $2CH_2$), 3.41 (t, J=5.16Hz, 4H, $2CH_2$), 3.91(s, 3H, CH_3), 6.92 (m,5H, 4CH, NH), 7.37 (d, J=8.55Hz, 1H, CH), 7.55 (d, J=8.50Hz, 2H, 2CH), 8.14 (s, 1H, CH), 8.95 (s, 1H, CH).
243	1-(4-methoxy-2-methylphenyl)-N-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	5.37		2.19 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.63 (t, J=5.16Hz, 4H, $2CH_2$), 3.19 (t, J=5.16Hz, 4H, $2CH_2$), 3.90(s, 3H, CH_3), 6.92 (m,4H, 4CH), 7.23 (s, 1H, NH), 7.37 (d, J=8.55Hz, 1H, CH), 7.51 (d, J=8.50Hz, 2H, 2CH), 8.14 (s, 1H, CH), 8.95 (s, 1H, CH).
244	N-(4-(1-(4-methoxy-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide	6.17	447 (M+23)	
245	1-(4-methoxy-2-methylphenyl)-N-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	6.77		2.21(s, 3H), 3.80(s, 3H), 3.88(s, 3H), 6.84~6.91(m, 3H), 7.34(d, J=8.46Hz, 2H), 7.36(s, 1H), 7.53(d, J=8.46Hz, 2H), 8.16(s, 1H), 8.89(s, 1H).
246	1-(4-methoxy-2-methylphenyl)-N-(4-(trifluoromethoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	7.82		2.19 (s, 3H, CH_3), 3.91(s, 3H, CH_3), 6.90 (d, J=8.55Hz, 1H, CH), 6.94 (s, 1H, CH), 7.16 (d, J=8.50Hz, 2H, 2CH), 7.37 (d, J=8.55Hz, 1H, CH), 7.46 (s, 1H, NH), 7.67 (d, J=8.50Hz, 2H, 2CH), 8.14 (s, 1H, CH), 8.95 (s, 1H, CH).

247	1-(4-methoxy-2-methylphenyl)-N-(4-(methylthio)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	7.39		2.19 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 3.93(s, 3H, CH_3), 6.90 (d, J=8.55Hz, 1H, CH), 6.94 (s, 1H, CH), 7.16 (d, J=8.50Hz, 2H, CH), 7.37 (d, J=8.55Hz, 1H, CH), 7.39 (s, 1H, NH), 7.67 (d, J=8.50Hz, 2H, 2CH), 8.12 (s, 1H, CH), 8.92 (s, 1H, CH).
248	2-methoxy-5-(1-(4-methoxy-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenol	6.06		2.19 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 3.89 (s, 3H, CH_3), 5.69 (s, 1H, OH), 6.78 (d, J=8.50Hz, 1H, CH), 6.92 (m,2H, CH, NH), 7.10 (d, J=8.50Hz, 1H, CH), 7.25 (m, 2H, 2CH), 7.37 (d, J=8.55Hz, 1H, CH), 8.14 (s, 1H, CH), 8.89 (s, 1H, CH).

TABLE 3. COMPOUNDS CONTAINING PHENOL GROUP AS R_2 IN FORMULA (I)

Example No.	Compound Name	HPLC data (Rt: mins.)	LC/MS	^{1}H-NMR ($CDCl_3$ unless noted)
249	3-(6-(4-aminophenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenol	4.75		4.85 (s, 2H), 6.56 (d, J=8.46Hz, 2H), 6.74 (d, J=8.52Hz, 1H), 7.30 (t, J=8.52Hz, 1H), 7.48 (d, J=8.46Hz, 2H), 7.60 (s, 1H), 7.73 (d, J=8.52Hz, 1H), 8.23 (s, 1H), 8.96 (s, 1H), 9.60 (s, 1H), 9.74 (s, 1H).
250	4-(6-(4-aminophenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenol	4.65	341 (M+23)	
251	4-(6-(4-morpholinophenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenol	5.06	389 (M+1)	
252	5-(1-(3-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-2-methoxyphenol	5.65		(CD_3OD) 3.87 (s, 3H), 6.76 (d, J=8.42Hz, 1H), 6.93 (d, J=8.42Hz, 1H), 7.25 (d, J=8.42Hz, 1H), 7.34 (t, J=8.46Hz, 2H), 7.78 (s, 1H), 7.81 (d, J=8.46Hz, 1H), 8.15(s, 1H), 8.91(s, 1H).
253	5-(1-(4-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-2-methoxyphenol	5.39	350 (M+1)	

TABLE 4. COMPOUNDS CONTAINING BENZYL GROUP AS R_2 IN FORMULA (I)

Example No.	Compound Name	HPLC data (Rt:	LC/MS	^{1}H-NMR ($CDCl_3$ unless noted)

		Mins.)		
254	1-benzyl-N-(4-(piperidin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	5.38		8.80 (s, 1H), 7.91 (s, 1H), 7.60(d, 2H), 7.40 (s, 1H), 7.46(m, 2H), 7.33 (m, 3H), 7.00 (m, 2H), 5.53 (s, 2H), 3.15 (t, 4H), 1.77(m, 4H), 1.61 (m, 2H).
255	1-(3-methoxybenzyl)-N-(4-(piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	4.98		8.78 (s, 1H), 7.91 (s, 1H), 7.64(d, 2H), 7.36 (s, 1H), 7.26(d, 1H), 6.99 (d, 2H), 6.95 (m, 2H), 6.81 (dd, 1H),5.49 (s, 2H), 3.75(s, 3H) 3.16 (t, 4H), 3.07(t, 4H).
256	1-(3,4-dimethoxybenzyl)-N-(4-(piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	4.97		8.78 (s, 1H), 7.91 (s, 1H), 7.64(d, 2H), 7.26 (s, 1H), 7.02(d, 1H), 6.99 (d, 2H), 6.86 (dd, 1H), 6.81(dd, 1H),5.60(s, 2H), 3.88(s, 3H) 3.83(s, 3H), 3.16(t, 4H), 3.07(t, 4H).
257	*tert*-butyl 4-(4-(1-(3,5-dimethoxybenzyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)piperazine-1-carboxylate	6.52		8.78 (s, 1H), 7.91 (s, 1H), 7.69(d, 2H), 7.32(s, 1H), 7.13(d, 1H), 6.99 (d, 2H), 6.52 (s, 1H), 6.48(d, 1H),5.51(s, 2H), 3.81 (s, 3H) 3.79 (s, 3H), 3.63(t, 4H), 3.10(t, 4H), 1.50 (s, 9H).
258	1-(3,5-dimethoxybenzyl)-N-(4-(piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	5.02		8.78 (s, 1H), 7.91 (s, 1H), 7.69(d, 2H), 7.30 (d,2H), 7.13(d, 1H), 6.99 (d, 2H), 6.48(s, 1H), 6.48 (d, 1H), 5.51 (s, 2H), 3.81 (s, 3H), 3.78 (s, 3H), 3.20(t, 4H), 3.10(t, 4H).
259	*tert*-butyl 4-(4-(3-bromo-1-(3,4-dimethoxybenzyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)piperazine-1-carboxylate	7.25		8.64 (s, 1H), 7.57(d, 2H), 7.28(s, 1H), 6.99 (d, 2H), 6.55(d, 2H), 6.39 (d, 1H), 5.37 (s, 2H), 3.74 (s, 6H) 3.60 (t, 4H), 3.13(t, 4H), 1.48 (s, 9H).
290	*tert*-butyl 4-(4-(1-(3,4-dimethoxybenzyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)piperazine-1-carboxylate	7.27		8.80 (s, 1H), 7.92(s, 1H), 7.61(d, 2H), 7.28(d, 2H), 6.99 (d, 2H), 6.55(d, 2H), 6.39 (d, 1H), 5.45 (s, 2H), 3.74 (s, 6H) 3.63 (t, 4H), 3.13(t, 4H), 1.50 (s, 9H).
291	1-(4-methoxybenzyl)-N-(4-(piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	4.93		8.78 (s, 1H), 7.89 (s, 1H), 7.63(d, 2H), 7.46 (s, 1H), 7.36(d, 2H), 6.99 (d, 2H), 6.85(d, 2H), 5.45 (s, 2H), 3.77 (s, 3H) 3.15(t, 4H), 3.10(t, 4H), 1.50 (s, 9H).
292	*tert*-butyl 4-(4-(1-(4-methoxybenzyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)piperazine-1-carboxylate	6.43		8.75 (s, 1H), 8.68(s, 1H), 7.89 (s, 1H), 7.72(d, 2H), 7.36(d, 2H), 6.99 (d, 2H), 6.85(d, 2H),5.45 (s, 2H), 3.77 (s, 3H) 3.63 (t, 4H), 3.13(t, 4H), 1.50 (s, 9H).

293	4-((6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)phenyl acetate	6.462	531 (M+1)	
294	N-(4-(1-(4-hydroxybenzyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	5.935	489 (M+1)	
295	N-(4-(1-(3-hydroxybenzyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	6.000	489 (M+1)	
296	2-(1H-imidazol-1-yl)-N-(2-((6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)phenyl)acetamide	5.360	596 (M+1)	
297	N-(2-((6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)phenyl)acetamide	5.858	530 (M+1)	
298	N-(4-(1-(2-aminobenzyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	5.668	488 (M+1)	
299	N-(methylsulfonyl)-N-(4-(1-(2-nitrobenzyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide	6.561	518 (M+1)	
300	2-(1H-imidazol-1-yl)-N-(4-((6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)phenyl)acetamide	5.324	596 (M+1)	
301	2-bromo-N-(4-((6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)phenyl)acetamide	6.203	609 (M+1)	
302	N-(4-(1-(4-aminobenzyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	5.134	488 (M+1)	

303	N-(3-((6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)phenyl)-2-(pyrrolidin-1-yl)acetamide	5.481	599 (M+1)	
304	N-(3-((6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)phenyl)-2-morpholinoacetamide	5.377	615 (M+1)	
305	2-(4-methylpiperazin-1-yl)-N-(3-((6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)phenyl)acetamide	5.228	628 (M+1)	
306	2-((2-hydroxyethyl)(methyl)amino)-N-(3-((6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)phenyl)acetamide	5.250	603 (M+1)	
307	2-(1H-imidazol-1-yl)-N-(3-((6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)phenyl)acetamide	5.186	596 (M+1)	
308	2-bromo-N-(3-((6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)phenyl)acetamide	6.236	609 (M+1)	
309	2-(dimethylamino)-N-(3-((6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)phenyl)acetamide	5.332	573 (M+1)	
310	N-(3-((6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)phenyl)acetamide	5.627	530 (M+1)	
311	N-(4-(1-(3-aminobenzyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	5.128	488 (M+1)	
312		6.582	518 (M+1)	

313	4-((6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)phenyl methanesulfonate	6.348	566	
314		5.296	546 (M+1)	
315	N-(4-((6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)phenyl)acetamide5.	5.555		8.86 (s, 1H); 7.98 (s, 1H), 7.79 (d, 2H), 7.51(m, 3H), 7.33 (m, 4H), 7.16 (s, 1H), 5.53 (s,2H), 344 (s, 6H), 2.16 (s,3H).
316	N-(4-(1-(3-(chloromethyl)benzyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	6.812	520 (M-1)	
317	N-(4-(1-(3-(hydroxymethyl)benzyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	5.841	503 (M+1)	
318	3-((6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)benzyl acetate	6.508	545 (M+1)	

TABLE 5. COMPOUNDS CONTAINING CYCLOHEPTYL GROUP AS R_2 IN FORMULA (I)

Example No.	**compound name**	**HPLC data (Rt: Mins.)**	**LC/MS**	**^{1}H-NMR (in $CDCl_3$, unless noted)**
319	N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	6.86	478.8 (M+1)	
320	N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(propylsulfonyl)propane-1-sulfonamide	7.81		8.83(s, 1H), 7.94 (s, 1H), 7.89 (d, 2H), 7.50(s, 1H), 7.38(d, 2H), 4.89(m, 1H), 3.54(m, 4H), 2.25 (m, 2H), 2.10 (m, 2H), 1.96 (m, 6H), 1.65 (m, 6H), 1.10 (t, 6H).
321	N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-1,1,1-trifluoromethanesulfonamide	7.31	455.3 (M+1)	

322	N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-1,1,1-trifluoro-N-(trifluoromethylsulfonyl)methanesulfonamide	8.54	587 (M+1)	
323	N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-1-(methylsulfonyl)methanesulfonamide	6.41	479 (M+1)	
324	N-(4-(1H-tetrazol-5-yl)phenyl)-1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-amine	6.44		(d6-DMSO) 10.28 (s, 1H), 9.04 (s, 1H), 8.13(s, 1H), 8.11(d, 2H), 8.01 (d, 2H), 4.85 (m, 1H), 3.10(s, 1H), 2.16 (m, 2H), 1.85 (m, 2H), 1.71 (m, 2H), 1.58 (m, 6H).
325	N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-dimethylaminosulfamide	6.66		8.82 (s, 1H), 7.92 (s, 1H), 7.78(d, 2H), 7.45 (s, 1H), 7.27d, 2H), 6.57 (s, 1H), 4.86 (m, 1H), 2.90 (s, 6H), 2.77 (m, 2H), 2.07 (m, 2H), 1.76 (m, 2H), 1.61 (m, 6H).
326	N1-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,4-diamine	5.27		8.77 (s, 1H), 7.85 (s, 1H), 7.57 (d, 2H), 6.76 (d, 2H), 4.86(m, 1H), 3.61(s, 2H), 2.22 (m, 2H), 2.06 (m, 2H), 1.89 (m, 2H), 1.71 (m, 6H).
327	3-chloro-N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)propane-1-sulfonamide	6.94		8.92(s, 1H), 8.00 (s, 1H), 7.81 (d, 2H), 7.54 (s, 1H), 7.30 (d, 2H),6.38 (s, 1H), 3.67(t, 2H), 3.32(t, 2H), 2.36 (m, 2H), 2.20(m, 2H), 2.07 (m, 2H), 1.93(m, 2H), 1.69(m, 6H).
328	3-chloro-N(-4(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-propyl-1,3-sultam	6.63		8.81 (s, 1H), 7.91 (s, 1H), 7.79 (d, 2H), 7.41(s, 1H), 7.34 (d, 2H), 4.86 (s, 1H), 3.86(t, 2H), 3.41(t, 2H), 2.24 (m, 2H), 2.09(m, 2H), 1.91 (m, 2H), 1.65(m, 6H).
329	1-cycloheptyl-N-(4-(4-(methylsulfonyl)piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	6.49		8.79 (s, 1H), 7.91 (s, 1H), 7.69 (d, 2H), 7.36 (s, 1H), 7.01(d, 2H),4.86 (s, 1H), 3.44 (t, 4H), 3.27 (t, 4H), 2.86 (s, 3H), 2.24 (m, 2H), 2.09 (m, 2H), 1.89 (m, 2H), 1.65 (m, 6H).
330	4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)benzoic acid	7.81	352 (M+1)	
331	1-cycloheptyl-N-(4-morpholinophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	6.08		8.77 (s, 1H), 7.87 (s, 1H), 7.65 (d, 2H), 7.52 (s, 1H), 6.97 (d, 2H), 4.82 (m, 1H), 3.90 (t, 4H), 3.16 (t, 4H), 2.22 (m, 2H), 2.06 (m, 2H), 1.86 (m, 2H), 1.61 (m, 6H).
332	3-chloro-N-(3-chloropropylsulfonyl)-N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)propane-1-sulfonamide	7.84		8.84 (s, 1H), 7.95 (s, 1H), 7.84(d, 2H), 7.57(s, 1H), 7.39(d, 2H), 4.90 (m, 1H), 3.79(t, 4H), 3.67 (t, 4H), 2.45 (m, 4H), 2.22 (m, 2H), 1.95(m, 2H), 1.86 (m, 2H), 1.64(m, 6H).

333	(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)(morpholino)methanone	6.97		8.81 (s, 1H), 7.91 (s, 1H), 7.37 (s, 1H), 7.18 (t, 1H), 7.08 (d, 1H), 6.45 (dd, 1H), 4.90 (m, 1H), 3.70 (b, 1H), 2.22 (m, 2H), 1.95(m, 2H), 1.86 (m, 2H), 1.64 (m, 6H).
334	N^1-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,3-diamine	5.34		(DMSO-d6) 10.1 (s, 1H), 9.01 (s, 1H),8.08 (s, 1H), 7.97 (d, 2H), 7.41(d, 2H), 4.86 (m, 1H), 3.61(m, 4H), 3.52(m, 4H),2.12 (m, 2H), 1.95(m, 2H), 1.86 (m, 2H), 1.64(m, 6H).
335	1-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)guanidine	5.68		(DMSO-d6) 9.68 (s, 1H), 8.91 (s, 1H), 8.38 (s, 1H), 8.00 (s, 1H), 7.72 (d, 2H), 7.31 (d, 2H), 5.77 (s, 1H), 3.29 (s, 1H), 2.15 (m, 2H), 2.01 (m, 2H), 1.85 (m, 2H), 1.6 (m, 6H).
336	N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide	6.38	401.9 (M+1)	
337	dimethyl 4-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)piperazin-1-ylphosphonate	6.06		8.77 (s, 1H), 7.89 (s, 1H), 7.65(d, 2H), 7.20(s, 1H), 6.97(d, 2H), 4.87 (m, 1H), 3.77 (s, 3H), 3.73 (s, 3H) 3.37(t, 4H), 3.31 (t, 4H), 2.27 (m, 2H), 2.08 (m, 2H), 1.90 (m, 2H), 1.64 (m, 6H).
338	(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)(4-ethylpiperazin-1-yl)methanone	5.92	448 (M+1)	
339	1-cycloheptyl-N-(4-thiomorpholinophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	6.08		8.77 (s, 1H), 7.89 (s, 1H), 7.65(d, 2H), 7.20(s, 1H), 6.97(d, 2H), 4.87 (m, 1H), 3.51(t, 4H), 2.81 (t, 4H), 2.27 (m, 2H), 2.08 (m, 2H), 1.90 (m, 2H), 1.64 (m, 6H).
340	dimethyl 4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenylphosphoramidate	6.11	431 (M+1)	
341	1-cycloheptyl-N-(4-(piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	5.37	392 (M+1)	8.78 (s, 1H), 7.89 (s, 1H), 7.65 (d, 2H), 7.17 (s, 1H), 6.99 (d, 2H), 4.86 (m, 1H), 3.16 (m, 4H), 3.10 (m, 4H), 2.25 (m, 2H), 2.10 (m, 2H), 1.90 (m, 2H), 1.74 (m, 4H), 1.61 (m, 2H).
342	1-cycloheptyl-N-(4-(1-methyl-1H-tetrazol-5-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	6.91		8.88 (s, 1H), 8.02 (s, 1H), 8.00 (d, 2H), 7.88 (d, 2H), 7.54 (s, 1H), 4.86 (m, 1H), 4.24 (s, 3H), 2.25 (m, 2H), 2.10 (m, 2H), 1.90 (m, 2H), 1.74 (m, 4H), 1.61 (m, 2H).

343	2-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)ethanol	6.45		8.80(s, 1H), 7.90(s, 1H),7.70 (d, 2H), 7.51 (s, 1H), 7.27 (d, 2H), 4.86 (m, 1H), 3.88(t, 2H), 2.91(t, 2H), 2.25 (m, 2H), 2.10 (m, 2H), 1.90 (m, 2H), 1.74 (m, 6H),
344	1-allyl-3-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)urea	6.41		(d6-DMSO) 9.68 (s, 1H), 8.91 (s, 1H), 8.38 (s, 1H), 8.08 (s, 1H), 7.72 (d, 2H), 7.31 (d, 2H), 6.17 (t, 1H), 5.92 (m, 1H), 5.19 (m, 2H), 4.79 (m, 1H), 3.73 (t,2H),2.15 (m, 2H), 2.01 (m, 2H), 1.6 (m, 6H).
345	N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)acetamide	6.18		8.81 (s, 1H), 7.91 (s, 1H), 7.74 (d, 2H), 7.51 (d, 2H), 8.00 (s, 1H), 7.35 (s, 1H), 7.20 (s, 1H), 4.88 (m, 1H), 2.25 (m, 2H), 2.15 (m, 2H), 1.95 (m, 2H), 1.6 (m, 6H).
346	1-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-3-ethylurea	6.23		(DMSO-d6) 9.68 (s, 1H), 8.91 (s, 1H), 8.27 (s, 1H), 8.00 (s, 1H), 7.72 (d, 2H), 7.31 (d, 2H), 6.02 (t, 1H), 4.77 (m, 1H), 3.08 (m, 2H), 2.15 (m, 2H), 2.01 (m, 2H), 1.6(m, 6H), 1.03 (t, 3H).
347	1-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-3-propylurea	6.52		(d6-DMSO) 9.68 (s, 1H), 8.91 (s, 1H), 8.27 (s, 1H), 8.00 (s, 1H), 7.72 (d, 2H), 7.31 (d, 2H), 6.07 (t, 1H), 4.77 (m, 1H), 3.06 (m, 2H), 2.15 (m, 2H), 2.01 (m, 2H), 1.6 (m, 6H), 0.8 (t, 3H).
348	1-cycloheptyl-N-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	5.14	406 (M+1)	8.78 (s, 1H), 7.88 (s, 1H), 7.64(d, 2H), 7.34(s, 1H), 6.99 (d, 2H), 4.85 (m, 1H), 3.23 (m, 4H), 2.63 (m, 4H), 2.38 (s, 3H), 2.21 (m, 2H), 2.09(m, 2H), 1.90 (m, 2H), 1.72 (m, 6H).
345	1-cycloheptyl-N-(4-(2-methyl-2H-tetrazol-5-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	7.34		8.85(s, 1H), 8.18 (d, 2H), 7.95 (d, 2H), 7.62 (s, 1H), 4.900 (m, 1H), 4.42 (s, 3H), 2.25 (m, 2H), 2.10 (m, 2H), 1.90 (m, 2H), 1.74 (m, 4H), 1.61 (m, 2H).
346	N-(4-(2-(2-chloroethyl)-2H-tetrazol-5-yl)phenyl)-1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-amine	7.67		8.85 (s, 1H), 8.18 (d, 2H), 7.93 (m, 3H), 7.82 (s, 1H), 5.00 (t, 2H), 4.85 (m, 1H), 4.13 (m, 2H), 2.26 (m, 2H), 2.15 (m, 2H), 1.92m, 2H), 1.90 (m, 2H), 1.69 (m, 6H).
347	N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)thiophene-2-sulfonamide	5.18		8.84 (s, 1H), 8.66 (s, 1H), 7.81 (d, 2H), 7.49 (m, 2H), 7.45 (s,1H), 7.33 (d, 2H), 6.96 (t, 1H), 4.90(m, 1H), 2.27(m, 2H), 2.09 (m, 2H), 1.91 (m, 2H), 1.72 (m, 6H)

348	4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)benzonitrile	7.57	333.4 (M+1)	
349	N-(3-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	6.82		8.84 (s, 1H), 8.32 (t, 1H), 7.95 (s, 1H),7.56(dd, 1H), 7.49 (s, 1H), 7.45 (t, 1H), 7.09 (dd, 1H), 4.92(m, 1H), 4.48 (s, 6H), 2.25 (m, 2H), 2.09 (m, 2H), 1.91 (m, 2H), 1.72 (m, 6H).
350	1-cycloheptyl-N-(4-(piperidin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	5.98		8.75 (s, 1H), 8.15(s, 1H), 7.59 (d, 2H), 7.23 (s, 1H), 6.98 (d, 2H), 4.88 (m, 1H), 3.11(t, 4H), 2.25 (m, 2H), 2.09 (m, 2H), 1.75 (m, 2H), 1.57 (m, 10H).
351	N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-1-(methylsulfonyl)-N-(methylsulfonylmethylsulfonyl)methanesulfonamide	5.61	657.5 M+Na	
352	1-cycloheptyl-N-(4-(2-morpholinoethoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine			8.80 (s, 1H), 7.90 (s, 1H), 7.71(d, 2H), 7.23 (s, 1H), 6.98 (d, 2H), 4.88(m, 1H), 4.15 (t, 2H), 3.79(t, 4H), 2.85 (t, 2H), 2.63 (t, 4H), 2.25 (m, 2H), 2.09 (m, 2H), 1.75 (m, 2H), 1.65 (m, 6H).
353	N-(4-(1H-pyrazol-1-yl)phenyl)-1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-amine	7.38		8.84 (s, 1H), 7.94 (d, 2H), 7.87 (d, 2H), 7.75 (d, 1H), 7.73 (d, 2H), 7.60 (s, 1H), 6.49 (t, 1H), 4.88 (m, 1H), 2.25 (m, 2H), 2.09 (m, 2H), 1.75 (m, 2H), 1.65 (m, 6H).
354	N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(phenylsulfonyl)benzenesulfonamide	8.15		8.80 (s, 1H), 8.00 (d, 4H), 7.94 (s, 1H), 7.82 (d, 2H), 7.71 (s, 1H), 7.69 (t, 2H), 7.57 (t, 3H), 7.038 (d, 2H), 4.88 (m, 1H), 2.25 (m, 2H), 2.09 (m, 2H), 1.75 (m, 2H), 1.65 (m, 6H).
355	N-(benzo[d][1,3]dioxol-5-yl)-1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-amine	7.16		8.79 (s, 1H), 7.89 (s, 1H), 7.55(d, 1H), 7.32 (s, 1H), 7.00 (dd, 1H), 6.83 (d, 1H), 5.50 (broad s, 1H), 4.85 (m, 1H), 2.25 (m, 2H), 2.11 (m, 2H), 1.90 (m, 2H), 1.64 (m, 6H).
356	2-(4-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)piperazin-1-yl)ethanol	5.36	436.0 (M+1)	8.79 (s, 1H), 7.89 (s, 1H), 7.65(d, 2H), 7.20 (s, 1H), 7.00(d, 2H), 5.50 (broad s, 1H), 4.85(m, 1H), 3.70 (t, 2H), 3.22 (t, 4H), 2.74 (t, 3H), 2.65 (m, 2H), 2.25 (m, 2H), 2.05 (m, 2H), 1.85 (m, 2H), 1.74 (m, 6H).

357	1-cycloheptyl-N-phenyl-1H-pyrazolo[3,4-d]pyrimidin-6-amine	7.48		8.82 (s, 1H), 7.91 (s, 1H), 7.78 (d, 2H), 7.37 (s, 1H), 7.42 (d, 2H), 7.07 (t, 1H), 4.85 (m, 1H), 2.25 (m, 2H), 2.05 (m, 2H), 1.85 (m, 2H), 1.74 (m, 6H).
358	1-cycloheptyl-N-(4-(2-vinyl-2H-tetrazol-5-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	8.05	402.3 (M+1)	11.68 (s, 1H), 8.75 (s, 1H), 8.27(d, 2H), 8.18 (s, 1H), 8.04(d, 2H),7.6 (q, 1H), 6.33 (d, 1H), 5.45 (d, 1H), 4.85(m, 1H), 2.25 (m, 2H), 2.05 (m, 2H), 1.85 (m, 2H) 1.74 (m, 6H).
359	ethyl 4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)benzoate	5.39	380.3 (M+1)	
360	*tert*-butyl 4-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)piperazine-1-carboxylate	7.13		9.52 (b, 1H), 8.67 (s, 1H), 7.91 (s, 1H),7.71 (d, 2H), 7.04 (d, 2H), 4.85 (m, 1H), 3.62 (t, 4H) 3.13 (t, 4H) 2.25 (m, 2H), 2.05 (m, 2H), 1.95 (m, 2H), 1.74 (m, 6H), 1.48 (s, 9H).
361	Ethyl 2-(4-(1-cycloheptyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-ylamino)phenyl)acetate	7.78	394.4 (M+1)	
362	1-cycloheptyl-*N*-(4-((4-methylpiperazin-1-yl)methyl)phenyl)-1h-pyrazolo[3,4-*d*]pyrimidin-6-amine	5.49	420.5 (M+1)	
363	2-(4-(1-cycloheptyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-ylamino)phenyl)acetic acid	6.40	366.4 (M+1)	
364	2-(4-(1-cycloheptyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-ylamino)phenyl)-1-(4-ethylpiperazin-1-yl)ethanone	5.63	462.6 (M+1)	
365	2-(4-(1-cycloheptyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-ylamino)phenyl)-*N*-methylacetamide	6.18	379.4 (M+1)	
366	2-(4-(1-cycloheptyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-ylamino)phenyl)-*N*-isopropylacetamide	8.30	422.5 (M+1)	
367	Ethyl 2-(4-(1-cycloheptyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-ylamino)phenyl)-2-methylpropanoate	6.70	407.5 (M+1)	
368	2-(4-(1-cycloheptyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-ylamino)phenyl)-2-methylpropanoic acid	7.00	394.4 (M+1)	
369	Ethyl 2-(2-chloro-4-(1-cycloheptyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-ylamino)phenyl)acetate	8.39	428.9 (M+1)	

370	2-(2-chloro-4-(1-cycloheptyl-1*H*-pyrazolo[3,4*d*]pyrimidin-6-ylamino)phenyl)acetic acid	6.98	400.8 (M+1)	
371	2-(4-(1-cycloheptyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-ylamino)phenyl)-2-methyl-1-(4-methylpiperazin-1-yl)propan-1-one	6.77	490.6 (M+1)	
372	1-cycloheptyl-N-(4-(methylsulfonylmethyl)phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-amine	6.50	400.5 (M+1)	
273	*N*-(3-chloro-4-(methylsulfonylmethyl)phenyl)-1-cycloheptyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-amine	7.22	434.9 (M+1)	
374	N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(2-morpholinoethyl)methanesulfonamide	5.971	514 (M+1)	
375	N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(2-(piperidin-1-yl)ethyl)methanesulfonamide	6.291	512 (M+1)	
376	N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(2-hydroxyethyl)methanesulfonamide	6.402	445 (M+1)	
377	N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-isopropylmethanesulfonamide	7.734	443 (M+1)	
378	N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(2-hydroxy-3-(piperidin-1-yl)propyl)methanesulfonamide	6.066	542 (M+1)	
379	N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(2-(pyrrolidin-1-yl)ethyl)methanesulfonamide	6.096	498 (M+1)	
380	4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-N-(propylsulfonyl)benzamide	7.40	457 (M+1)	
381	N-(tert-butylsulfonyl)-4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)benzamide	7.48	471 (M+1)	
382	4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-N-(methylsulfonyl)benzamide	6.87	429 (M+1)	

383	4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-N-(ethylsulfonyl)benzamide	7.10	443 (M+1)	
384	2-(2-chloro-4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-1-(4-ethylpiperazin-1-yl)ethanone	6.05	497.0 (M+1)	
385	2-(2-chloro-4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(2-methoxyethyl)acetamide	6.92	457.9 (M+1)	
386	2-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(2-methoxyethyl)acetamide	6.31	423.5 (M+1)	
387	N-((1s,4s)-4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)cyclohexyl)methanesulfonamide	6.3	407 (M+1)	
388	4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-N-(2-sulfamoylethyl)benzamide	6.18	458.0 (M+1)	
389	1-[3-(1-cyclohept-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-phenyl]-2-morpholin-1-yl-ethanol	5.92	437.2 (M+1)	
390	1-[4-(1-cyclohept-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-phenyl]-2-morpholin-1-yl-ethanol	5.66	437.2 (M+1)	
391	1-[4-(1-cyclohept-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-phenyl]-2-piperidin-1-yl-ethanol	5.91	435.2 (M+1)	

Table6. Compounds Containing Substituted Cyclohexyl as R2

Example No.	Compound Name	HPLC data (Rt, min)	LC/ MS	^{1}H-NMR ($CDCl_3$ unless noted)
392	Ethyl 4-(6-(4-(4-methylpiperazin-1-yl)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexanecarboxylate	5.51	464.1 (M+1)	
393	(4-(6-(4-(4-methylpiperazin-1-yl)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)methanol	4.46	422.2 (M+1)	

394	4-(6-(4-(4-methylpiperazin-1-yl)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexanecarboxylic acid	4.55	436.2 (M+1)	
395	tert-butyl (1r,4r)-4-(6-(4-(4-methylpiperazin-1-yl)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexylcarbamate	5.63	507.2 (M+1)	

TABLE 6. COMPOUNDS CONTAINING OTHER GROUPS AS R_2 IN FORMULA (I)

Example No.	Compound Name	HPLC data (Rt: min.)	LC/MS	^{1}H-NMR (in $CDCl_3$ unelss noted)
396	1-(cyclopentylmethyl)-N-(4-(piperidin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	5.69		8.76 (s, 1H), 7.86 (s, 1H), 7.60(d, 2H), 7.29 (s, 1H), 6.97 (d, 2H), 4.25 (d, 2H), 3.13(t, 4H), 2.61 (m, 1H), 1.68 (m, 8H), 1.58 (m, 4H), 1.37(m, 2H).
397	(S)-N-(4-morpholinophenyl)-1-(1-phenylethyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	5.87		8.80 (s, 1H), 7.93 (s, 1H), 7.60(d, 2H), 7.40 (s, 1H), 7.35 (m, 2H), 7.30 (m, 2H), 6.96(d, 2H), 6.09(q, 1H), 3.95 (t, 3H), 3.19 (t, 4H), 2.03 (d, 3H).
398	1-(furan-2-ylmethyl)-N-(4-(piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	4.57		8.80 (s, 1H), 7.93 (s, 1H), 7.66(d, 2H), 7.39 (d, 1H), 7.34 (s, 1H), 6.96(d, 2H), 6.43(d, 1H), 6.36 (m, 1H), 5.51 (s, 2H), 3.17 (t, 3H), 3.09 (t, 4H).
399	ethyl 2-(6-(4-(piperidin-1-yl)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)acetate	4.78		8.80 (s, 1H), 7.93 (s, 1H), 7.55(d, 2H), 7.25 (d, 1H), 6.96(d, 2H), 5.11 (s, 2H), 4.27 (m, 2H), 3.15 (t, 4H), 1.76 (t, 4H), 1.60 (m, 2H), 1.31 (m, 5H).
400	N-(4-morpholinophenyl)-1-(pyridin-2-ylmethyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	2.86		8.84 (s, 1H), 8.63 (m, 1H), 7.98 (s, 1H), 7.66(dd, 1H), 7.59 (m, 2H), 7.34 (s, 1H), 7.20 (m, 1H), 6.96(d, 1H), 6.94(d, 2H), 5.71 (s, 2H), 3.90 (t, 3H), 3.15 (t, 4H).
401	1-methyl-N-(4-(piperidin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	4.62		1.30 (t, J=7.12Hz, 2H, CH_2), 1.75 (m, 4H, $2CH_2$), 3.15 (t, J=5.30Hz, 4H, $2CH_2$), 4.00 (s, 3H, CH_3), 6.99 (d, J=8.50Hz, 2H, CH), 7.20 (s, 1H, NH7.17 (d, J=8.50Hz, 2H, 2CH), 7.89 (s, 1H, CH), 8.79 (s, 1H, CH).

402	N-(4-morpholinophenyl)-1-(1,2,3,4-tetrahydronaphthalen-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	5.96		8.80 (s, 1H), 7.90 (s, 1H), 7.52(d, 2H), 7.39 (s, 1H), 7.15 (m, 2H), 7.00 (t, 1H), 6.91(d, 2H), 6.69(d, 1H), 6.09 (m, 1H), 3.89 (t, 3H), 3.13 (t, 4H), 3.01 (m, 1H), 2.92 (m, 1H), 2.48 (m, 1H), 2.17 (m, 2H), 1.96 (m, 1H).
403	1-(1-benzylpiperidin-4-yl)-N-(4-morpholinophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	4.58		8.80 (s, 1H), 7.90 (s, 1H), 7.66(d, 2H), 7.42 (m, 2H), 7.34 (t,2H), 7.28(m, 2H), 7.00(d, 2H), 4.66 (m, 1H), 3.92 (t, 3H), 3.62 (s, 2H), 3.18 (t, 4H), 3.07 (d,2H), 2.52 (m, 2H), 2.26(m, 2H), 2.01 (m, 2H).
404	1-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-N-(4-morpholinophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine	4.17		8.94 (s, 1H), 8.25 (s, 1H), 7.96 (s, 1H), 7.66(d, 2H), 7.72 (d, 2H), 7.20(s, 1H), 6.94 (d, 2H), 5.60 (s, 2H), 3.92 (t, 4H), 3.77 (s, 3H), 3.14 (t, 4H), 2.37(s, 3H), 2.27 (s, 3H).
405	N-(4-(1-(benzo[d][1,3]dioxol-5-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	6.72	503 (M+1)	
406	N-(methylsulfonyl)-N-(4-(1-(2-morpholinoethyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide	4.93	496 (M+1)	
407	N-(4-(1-(6-bromopyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	6.964	539 (M+1)	
408	N-(4-(1-(6-methoxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	6.636	490 (M+1)	
409	N-(4-(1-(6-fluoropyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	6.611	478 (M+1)	
410	N-(methylsulfonyl)-N-(4-(1-(thiophen-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide	6.811	464	
411	N-(methylsulfonyl)-N-(4-(1-(pyridin-4-ylmethyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide	4.862	474 (M+1)	
412	N-(4-(1-((6-chloropyridin-3-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	6.292	507	

413	N-(4-(1-((5,6-dichloropyridin-3-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide	6.786	541 (M-1)	

Example 414: Aurora Kinase A (AKA) Kinase Assay

[00224] The assay was conducted as described by Toji, S. et al. in *Genes to Cells*, 9: 383-397 (2004), which is incorporated herein by reference in its entirety.

[00225] 6His-tagged Lats2 substrate (5 ug/mL in PBS) was coated onto a 96-well HisGrab plate (Catalog No. 15142, Pierce Chemical, Rockford, Illinois, USA) previously blocked with TBST containing 5% BSA and 1% milk powder. Aurora kinase A (MBL International, Woburn, Massachusetts, USA, # CY-E1165-1) was diluted (1:200) in a kinase reaction buffer (20 mM HEPES, 1 mM DTT, 50 mM $MgCl_2$, 50 uM ATP, pH 7.5) and autoactivated at 30 °C for 60 minutes. A compound of this invention was then added and the mixture was incubated at 30 °C for 60 minutes. After the incubation, Aurora kinase A was added to the Lats2 coated HisGrab plate and incubated for one hour at 30 °C, then washed twice with PBS containing 0.05% Tween-20 (PBST). Anti-Phospho-Lats2-Ser83 monoclonal antibody (MBL International, #ST-3B11) was diluted (1:500) in antibody dilution buffer (TBST with 5% BSA and 1% milk powder), added to each well, and then incubated at room temperature for 30 minutes. Each well was then washed twice with PBST. Horse radish peroxidase (HRP) conjugated goat anti-mouse IgG (Jackson Immunoresearch, West Grove, Pennsylvania, USA, #115-035-003) was diluted (1:4000) in TBST with BSA and milk, added to each well, and then incubated at room temperature for 30 minutes. Each well was washed 5 times with PBST, and then to it was added 100 uL of TMB Ultra HRP substrate (Pierce Chemical, #34028), and the mixture incubated for 5 minutes at room temperature. To each well was then added 100 uL of 1N H_2SO_4, and the absorbance was measured at a wavelength of 450 nM using a spectrophotometric plate reader. Aurora kinase incubated with DMSO as the inhibitor (control) is defined as 100% activity. EC_{50} is defined as the concentration of compound which gives 50% inhibition of Aurora Kinase A.

[00226] Most of the tested compounds exhibited an IC_{50} value of less than 2 μM, some less than 0.2 μM, some less than 0.08 μM, and some even less than 0.01 μM.

[00227] The results show that the tested compounds of formula (I) exhibited high inhibitory effect on the Aurora Kinase A.

Example 415: Aurora Kinase A (AKA) Kinase Assay

[00228] The assay was similar to the assay described in Example 77 above. Specifically, a Z-Lyte Kinase Assay Ser/Thr 1 Peptide Kit (Invitrogen, # PV3174) and a synthetic peptide substrate Ser-Thr 1 peptide labeled with a donor fluorophore (coumarin) (Invitrogen, # PV3196) and an acceptor fluorophore (fluorescein) that made up a FRET pair were used. All dilutions were performed in 1X Reaction Buffer (50 mM HEPES-pH 7.5, 10 mM MgCl2, 1 mM EGTA, 0.01% Brij-35 from 5X stock (Invitrogen, PV3189).

[00229] The primary 10 uL reaction involved Auronra Kinase B (Invitrogen # PV3970), 64 uM ATP (PV3227), 2 uM Ser-Thr 1 Peptide, and a compound of this invention (1% in DMSO). The reaction was incubated for 1 hour at the room temperature.

[00230] Also used was a 0% control which consisted of 64 uM ATP, 2 uM Ser-Thr 1 Peptide, without Aurora Kinase B, and a 100% control which consisted of 64 uM ATP, 2 uM Phospho Ser-Thr 1 Peptide (Invitrogen # PV3211), without Aurora Kinase B.

[00231] In the secondary reaction, 5 uL of a site-specific protease (the Development Reagent A, Invitrogen, # PV3295) was added at a 1:2048 dilution into Development Buffer (Invotrigen, # P3127) for 1 hour at the room temperature. The protease cleaved non-Phosphorylated peptide disrupting FRET interaction of the two fluorophores, while phosphorylated peptide was uncleaved which maintained the FRET interaction. The reaction was read on an M5 spectrophotometer at Excitation 400 nm, and Emission 445 nm and 520 nm.

[00232] The Emission ratio (Em) = coumarin (C) emission signal (at 445 nm)/Fluorescein (F) emission signal (at 520 nm).

[00233] Percent Phosphorylation = [1 - ((Em ratio X F100%)-C100%)/ ((C0%-C100%) + (Em ratio X (F100% - F0%)))].

[00234] The testes compounds also showed effective inhibition of Aurora Kinase B. Most of the tested compounds exhibited an IC_{50} value of less than 2.0 μM, some less than 0.6 μM, some less than 0.2 μM, and some even less than 0.005 μM.

Example 416: CDK1 Kinase Assay

[00235] A Z-Lyte Kinase Assay Ser/Thr 18 Peptide Kit (Invitrogen, Carlsbad, California, USA, #PV4319) was used for this assay and the assay was performed as per manufacturer's instructions. The assay uses a synthetic peptide substrate (Ser-Thr 18 peptide, Invitrogen # PV4320) that was labeled with a donor fluorophore (coumarin) and an acceptor fluorophore (fluorescein) that make up a FRET pair. All dilutions were performed with a 1X Reaction Buffer made of 50 mM HEPES-pH 7.5, 10 mM $MgCl_2$, 1 mM EGTA, 0.01% Brij-35.

[00236] The primary 10 µl reaction involved 0.62 ug/ml CDK1/Cyclin B (Invitrogen, # PV3292), 34 uM ATP, 2 uM Ser-Thr 18 Peptide. A compound of this invention was dissolved in DMSO to 1%. A 0% control was included with 34 uM ATP, 2 uM Ser-Thr 18 Peptide, no enzyme; and a 100% control contained 34 uM ATP, 2 uM Phospho Ser-Thr 18 Peptide (Invitrogen, # PV4321), no enzyme. The reaction was incubated at the room temperature for 1 hour.

[00237] In the secondary reaction, 5 uL of a site-specific protease (the Development Reagent A, Invitrogen, # PV3295) was diluted (1:1024) in Development Buffer (#P3127) at the room temperature over 1 hour. The protease cleaved non-Phosphorylated peptide disrupting FRET interaction of the two fluorophores, while phosphorylated peptide was uncleaved which maintains FRET interaction. The reaction mixture was read on an M5 spectrophotometer at Excitation 400 nm, and Emission 445 nm and 520 nm.

[00238] The Emission ratio (Em) = coumarin (C) emission signal (at 445 nm)/Fluorescein (F) emission signal (at 520 nm).

[00239] Percent Phosphorylation = [1 - ((Em ratio X F100%)-C100%)/ ((C0%-C100%) + (Em ratio X (F100% - F0%)))].

[00240] IC_{50} is defined as the concentration of compound which gives 50% inhibition of CDK1 kinase activity. Most of the tested compounds exhibited an IC_{50} value of less than 2 µM, some less than 0.4 µM, some less than 0.1 µM, and some even less than 0.01 µM.

[00241] The results show that the tested compounds exhibited high inhibitory effect on the CDK1 kinase activity.

Example 417: G2M Cell Cycle Arrest Assay

[00242] 100,000 K562 leukemia cells were incubated with increasing concentrations (0-0.001-0.003-0.01-0.03 uM or 0.1-0.3-1-3-30-100 uM) of a compound of this invention in Dulbecco's Modified Eagle Media containing 10% FBS at 37 °C in 10% CO_2 for 24 hours in 200 uL culture volumes in 96-well plates. The cells were washed once in DPBS and then fixed in ice cold 70% ethanol at 4 °C for 30 minutes. After washing once in DPBS, the cells were resuspended in DPBS containing 0.2% Tween-20 for 30 minutes. The cells were washed once again in DPBS, resupsended in a solution of 25 ug/mL propidium iodide, 0.002% NP-40, and 12.5 ug/mL RNAse A. The cellular DNA content was measured on a FACSCALIBUR flow cytometer equipped with an Argon-ion laser that emits 15 mW of 488 nm light for excitation of the propidium iodide fluorescent DNA intercalating dye. The minimum effective concentration was defined as the concentration of inhibitor at which the

percentage of cells in G2M exceeded the percentage of cells in G1.

[00243] Results are shown as G2M in the tables and showed that the mimimum effective concentrations ranged from 0.03nM to 100uM to cause G2M cell cycle arrest in K562 leukemia cells.

[00244] Most of the tested compounds exhibited an IC_{50} value of less than 10 μM, some less than 3 μM, some some even less than 0.3 μM.

Example 418: HCT116 growth inhibition assay

[00245] HCT116 (colon) carcinoma cells were dispensed into 96-well plates (100 uL per well, 20000 cells per mL) and allowed to adhere overnight using standard cell culture conditions. The cultures were then incubated with a compound of this invention under standard culture conditions for 5 days. 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium inner salt (MTS), a novel tetrazolium compound (Promega, Madison, Wisconsin, USA, G1111) was added at a concentration of 2 mg/mL and phenazine methyl sulfate at a concentration of 50 ug/mL were mixed 20:1, and 20 uL of the mixture was added to the cultures and allowed to develop for several hours. The color change was used to measure viability at OD490 nm on a 96-well plate spectrophotometric plate reader.

[00246] The IC_{50} was defined as the concentration of compound which gives a 50% inhibition of growth of the HCT116 tumor cell line.

[00247] The tested compounds typically exhibited an IC50 value of less than 6.0 μM, some less than 0.8 μM, some less than 0.2 μM, and even some less than 0.08 μM.

Example 13: *In Vivo* Protocol

[00248] Six- to eight-week old Balb/C and nu/nu athymic female mice were obtained from Charles River Laboratories The mice were maintained in ventilated caging in a room with a 12 hour light/dark cycle. Food and water were provided ad libitum. Animals were identified by the use of bar coded chips. Experiments were carried out under Biogen Idec IACUC protocol SD34-07 and the guidelines for the proper and human use of animals in research established by the Institute for Laboratory Animal Research (ILAR).

Example 419: Mouse Tumor Study

[00249] Tumor fragments (approximately $2mm^3$) or 5 x 10^6 tumor cells were inoculated

subcutaneously in the right or left flank of the animal. Mice with established tumors (50-200mm^3) were selected for study (n=7-10/treatment group). Tumor dimensions were measured using calipers and tumor volumes were calculated using the equation for an ellipsoid sphere ($l \times w^2)/2 = mm^3$, where l and w refer to the larger and smaller dimensions collected at each measurement.

[00250] The test compounds were formulated and administered orally (p.o.) or via the intraperitoneal cavity (IP) at a dose volume of 10mL/kg. The vehicle alone was administered to control groups. Animals were dosed five days per week (Monday through Friday) for four to six consecutive weeks. Animals were weighed and the tumors were measured twice per week.

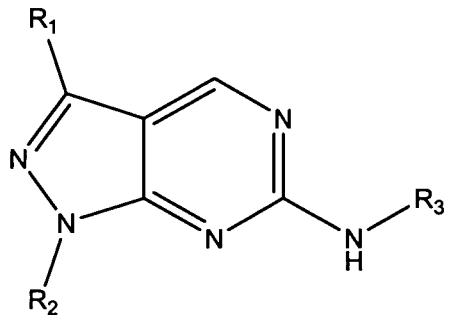
[00251] Mice were followed until tumor volumes in the control group reached approximately 1000mm^3 and were sacrificed by CO_2 euthanasia. The mean tumor volumes of each group were calculated. The change in mean treated tumor volume was divided by the change in mean control tumor volume, multiplied by 100 and subtracted from 100% to give the tumor growth inhibition for each group. Statistical analysis was performed using the standard T-test and using GraphPad Prism© Software. The results showed that the tested compound effectively reduced the tumor volume.

OTHER EMBODIMENTS

[00252] It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A compound of Formula (I), a prodrug, a polymorph, a tautomer, an enantiomer, a stereoisomer, a solvate, an N-oxide derivatve, or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R_1 is hydrogen or halo;

R_2 is $-L_1-R_a$, wherein

L_1 is a bond or alkyl, and

R_a is cyclohexyl, cycloheptyl, piperidinyl, pyrrolidinyl, furyl, thienyl, morpholinyl, pyridinyl, or pyrimidinyl, each of which is optionally substituted with 1 to 3 substituents; or R_a is substituted phenyl;

R_3 is $-R_b-L_2-R_c$; wherein

R_b is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, and is optionally substituted with 1 to 3 substituents; wherein two of the substituents when adjacent, together with the atom or atoms to which they are attached, can form a 5- to 16-membered ring with 0 to 6 hetero ring atoms,

L_2 is a bond, $-(CR_xR_y)_n-$, $-N=$, $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-CO-$, $-CO-O-$, $-O-CO-$, $-NR_x-$, $-NR_x-CO-$, $-NR_x-SO_2-$, $-CO-NR_x-$, $-SO_2-NR_x-$, $-NR_x-CO-O-$, $-NR_x-SO_2-O-$, $-NR_x-CO-NR_y-$, $-NR_x-SO_2-NR_y-$, $-CO-NR_x-NR_y-$, $-SO_2-NR_x-NR_y-$, $-NR_x-CO-CO-O-$, $-NR_x-SO_2-SO_2-O-$, $-S(O)_2-N_x-CO-R_y-$, $-CO-N_x-S(O)_2-R_y-$, or $-(NR_xR_y)C=N-O-$;

R_c is hydrogen, alkyl, alkenyl, alkynyl, guanidinyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, aryl, heteroaryl, (cycloalkyl)alkyl, (heterocycloalkyl)alkyl, (cycloalkenyl)alkyl, (heterocycloalkenyl)alkyl, aralkyl, or heteroaralkyl, and except when being hydrogen, is optionally substituted with 1 to 3 substituents; and

each of R_x and R_y, independently, is hydrogen, hydroxy, alkyl, alkoxy, amino, –CO–alkyl, –CO–aryl, $–SO_2–$alkyl, $–SO_2–$aryl, $–SO_2–$heteroaryl, or $–P(O)(O–alkyl)_2$, wherein the alkyl or aryl moiety in R_x or R_y is optionally substituted with 1 to 3 substituents; and

n is 0, 1, 2, or 3.

2. The compound of claim 1, wherein each of the 1 to 3 optional substituents on R_a, R_b, R_c, R_x, and R_y, independently, is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, -OR, -SR, -NRR', oxo, -C(O)-OR, -C(O)-NRR', halo, CN, NO_2, N_3, -C(O)R", -P(O)(OR)(OR'), -O-P(O)(OR)(OR'), -NR-P(O)(OR)(OR'), $-S(O)_2$-OR, -O-$S(O)_2$-OR, -NR-$S(O)_2$-OR', -NR-C(O)-OR", -NR-C(O)-NRR', -NR-C(S)-NRR', -C(S)-NRR', and thioalkyl,

each of R and R', independently, is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, or heteroaralkyl; and

R" is alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, or heteroaralkyl

3. The compound of claim 1, wherein R_1 is hydrogen.

4. The compound of claim 1, wherein L_1 is a bond.

5. The compound of claim 4, wherein R_a is cycloheptyl.

6. The compound of claim 4, wherein R_a is phenyl substituted with 1 to 3 substituents.

7. The compound of claim 6, wherein R_a is phenyl with at least one substituent at the *para* position.

8. The compound of claim 1, wherein R_2 is 1-(biphenyl-2-yl), 4-hydroxyphenyl, 4-(hydroxymethyl)phenyl, 3-(hydroxyethyl)phenyl, 4-(chloromethyl)phenyl, 4-(tert-butoxycarbonyl)phenyl, 2-(tert-butoxycarboxamido)phenyl, 4-(tert-butoxycarboxamido)phenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 4-iodophenyl, 4-methoxy-2-methylphenyl, 4-methoxy-3-methylphenyl, 4-acetylphenyl, 3-acetylphenyl, 4-(diethoxyphosphoryloxy)phenyl, 4-aminophenyl, 4-nitrophenyl, 4-

acetamidophenyl, 3-acetamidophenyl, 2-acetamidophenyl, 4-(tert-butoxycarboxamido)phenyl, 4-(dimethylaminoethoxy)phenyl, 5-methoxy-2,4-dinitrophenyl, 3-methoxy-2,4-dinitrophenyl, 4-(morpholin-4-ylcarbonyl)phenyl, 4-(dimethylamino)phenyl, 4-methoxycarbonyl-3-flurophenyl, 4-(di(cyclopropylcarbonyl)amino)phenyl, 2-methylthiophenyl, 2-ethylthiophenyl, 3-(isopropyloxy)phenyl, 4-isopropylphenyl, 4-(methoxyacetamido)phenyl, 4-(isopropylacetamido)phenyl, 4-(dimethylaminoacetamido)phenyl, 4-methoxy-3-(trifluoromethyl)phenyl, 4-(acrylamido)phenyl, 4-(di(2-furanylcarbox)amido)phenyl, 4-(2-furanyl)carboxamidophenyl, 4-((ethoxycarbonyl)methylcarboxamido)phenyl, 4-(cyclopropylcarboxamido)phenyl, 4-(trifluoromethoxy)phenyl, 4-(2-(piperidin-1-yl)acetamido)phenyl, 4-((tert-butoxycarboxamido)methylcarboxyamido)phenyl, 2-vinylphenyl, 2-(methylsulfonyl)phenyl, 4-(2-(2-methyl-imidazol-1-yl)acetamido)phenyl, 4-(2-(imidazol-1-yl)acetamido)phenyl, 4-(2-(pyrrolidin-1-yl)acetamido)phenyl, 4-(3-(pyrrolidin-1-yl)propanamido)phenyl, 4-(2-(pyrrolidin-1-yl)acetamido)phenyl, 4-(2-(4-methylpiperazin-1-yl)acetamido)phenyl, 4-(3-(4-methylpiperazin-1-yl)propanamido)phenyl, 4-(3-(imidazol-yl)propanamido)phenyl, 4-((4-methoxycarbonyl)butanamido)phenyl, 4-((2-bis(2-hydroxyethyl)amino)acetamido)phenyl, 4-(cyclohexylcarboxamido)phenyl, 4-(bis(cyclohexylcarbonyl)amino)phenyl, 4-((N-morpholinyl)carboxamido)phenyl, 4-(2-(pyridin-3-yl)acetamido)phenyl, 4-(2-(methyl(pyridin-3-ylmethyl)amino)acetamido)phenyl, 4-(3-(N-morpholinyl)propanamido)phenyl, 4-(3-bromopropanamido)phenyl, 4-(2-(thiophen-2-yl)acetamido)phenyl, 4-(2-(2-oxopyrrolidin-1-yl)acetamido)phenyl, 4-(2-(2-oxooxazolidin-3-yl)acetamido)phenyl, 4-((dimethylaminoethyl)aminomethyl)phenyl, 4-((methoxycarbonyl)ethyl)phenyl, 4-((3-(diethylamino)pyrrolidin-1-yl)methyl)phenyl, 2-(ethoxymethyl)phenyl, 4-((N-(tert-butoxycarbonyl)piperidin-4-yl)carboxamido)phenyl, 4-(2-(pyrrolidin-1-yl)acetamido)phenyl, 4-(2-(1H-pyrazol-1-yl)ethoxy)phenyl, 2-(3-hydroxypropylamino)phenyl, 4-(3-hydroxypropylamino)phenyl, 4-(2-aminoacetamido)phenyl, 4-((N-methylpiperdin-4-yl)carboxamido)phenyl, 4-(2-hydroxyacetamido)phenyl, 2-(hydroxyethylamino)phenyl, 2-(bis(hydroxyethyl)amino)phenyl, 4-(hydroxyethylamino)phenyl, 4-(bis(hydroxyethyl)amino)phenyl, 4-(bis(hydroxypropyl)amino)phenyl, or 4-(((1,1-dioxo)tetrahydrothien-3-yl)(methyl)aminoacetamido)phenyl.

9. The compound of claim 7, wherein R_3 is thioanisol-4-yl, 4-(N'-methanesulfonyl)piperizinylphenyl, 4-bis(methanesulfonyl)aminophenyl, 4-methoxy-3-(methylamino)phenyl, 4-methoxy-3-acetoxyphenyl, 4-methoxy-3-acetamidophenyl, 4-methoxy-3-(methyoxycarbonylamino)phenyl, 4-methoxy-3-(cyclopropanecarboxamido)phenyl, 4-methoxy-3-(cyclopropanecarboxy)phenyl, 4-methoxy-3-((ethylamino)carbonyl)aminophenyl, 4-methoxy-3-aminophenyl, 4-methoxy-3-ethylcarboxyphenyl, 3-aminophenyl, 4-(methanesulfonyl)aminophenyl, 4-aminophenyl, 3-bis(methanesulfonyl)aminophenyl, 3-(methanesulfonyl)aminophenyl, 2-oxo-2,3-dihydrobenzoimidizol-5-yl, 4-(pyrrolidine-1-ylsulfonyl)phenyl, 4-amino-3-bromophenyl, 4-amino-3-hydroxyphenyl, 4-amino-2-hydroxyphenyl, 4-((methanesulfonyl)methylsulfonyl)aminophenyl, 4-amino-3-methoxyphenyl, 4-(N'-methyl)piperazinylphenyl, methanesulfonyl, piperidin-4-yl, 1-(tert-butoxycarbonyl)piperidin-4-yl, or 1-(methanesulfonyl)piperidin-4-yl.

10. The compound of claim 1, wherein L_1 is alkyl.

11. The compound of claim 10, wherein R_a is phenyl optioanlly substituted with 1 to 3 substituents.

12. The compound of claim 11, wherein L_1 is methyl and R_a is phenyl with at least one substituent.

13. The compound of claim 12, wherein R_2 is 4-acetoxybenzyl, 4-hydroxybenzyl, 3-hydroxybenzyl, 2-(2-imidazol-N-yl)acetamidobenzyl, 2-acetamidobenzyl, 2-aminobenzyl, 2-nitrobenzyl, 4-((2-imidazol-N-yl)acetamido)benzyl, 4-(2-bromo)acetamidobenzyl, 4-aminobenzyl, 3-(2-pyrrolidin-N-yl)acetamidobenzyl, 3-(2-morpholin-N-yl)acetamidobenzyl, 3-(2-(N'-methyl)piperazin-N-yl)acetamidobenzyl, 3-(2-((2-hydroxyethyl)(methyl)amino)acetamido)benzyl, 3-(2-imidazol-N-yl)acetamidobenzyl, 3-((2-bromo)acetamido)benzyl, 3-(2-dimethylamino)acetamidobenzyl, 3-acetamidobenzyl, 3-aminobenzyl, 4-methanesulfonyloxybenzyl, 3-(2-amino)acetamidobenzyl, 4-acetamidobenzyl, 3-(chloromethyl)benzyl, 3-(hydroxymethyl)benzyl, or 3-(acetoxymethyl)benzyl.

14. The compound of claim 13, wherein R_3 is 4-(bis(methanesulfonyl)amino)phenyl.

15. The compound of claim 14, wherein L_1 is ethyl; and R_a is piperidinyl, pyrrolidinyl, furyl, thienyl, or morpholinyl.

16. The compound of claim 15, wherein R_2 is 2-morpholinoethyl.

17. The compound of claim 1, wherein R_b is phenyl.

18. The compound of claim 17, wherein L_2 is a bond; and R_c is cycloalkyl, heterocycloalkyl, aryl, heteroaryl, (cycloalkyl)alkyl, (heterocycloalkyl)alkyl, aralkyl, or heteroaralkyl.

19. The compound of claim 17, wherein L_2 is a bond; and R_c is heterocycloalkyl, heteroaryl, (heterocycloalkyl)alkyl, or heteroaralkyl.

20. The compound of claim 17, wherein L_2 is a bond; and R_c is tetrazolyl, morpholino, or piperazinyl, and is optionally substituted.

21. The compound of claim 17, wherein L_2 is –O–, –S–, $–SO_2–$, –CO–, –CO–O–, $–NR_x–$, $–NR_x–CO–$, $–NR_x–SO_2–$, $–NR_x–CO–O–$, $–NR_x–CO–NR_y–$, or $–NR_x–CO–CO–O–$.

22. The compound of claim 21, wherein L_2 is –CO–O–, $–NR_x–$, $–NR_x–SO_2–$, $–NR_x–CO–O–$, or
$–NR_x–CO–NR_y–$, with R_x being hydrogen, alkyl, –CO–alkyl, $–SO_2–$alkyl, $–SO_2–$heteroaryl, or $–SO_2–$aryl.

23. The compound of claim 22, wherein R_c is hydrogen, alkyl, aryl, or heteroaryl.

24. The compound of claim 22, wherein R_x is hydrogen, alkyl, –CO–alkyl, or $–SO_2–$alkyl; and R_c is hydrogen, alkyl, or aryl.

25. The compound of claim 1, wherein R_b is phenyl substituted with 1 to 3 substituents each independently selected from the group consisting of -NRR'and -C(O)OR; L_2 is a bond; and R_c is hydrogen.

26. The compound of claim 1, wherein L_1 is a bond; R_a is cycloheptyl, pyridinyl, pyrimidinyl, or phenyl.

27. The compound of claim 26, wherein R_a is cycloheptyl.

28. The compound of claim 27, wherein R_3 is 4-(ethoxycarbonyl)methylphenyl, 4-(1-methylpiperidin-4-yl)methylphenyl, 4-carboxymethylphenyl, ((4-ethylpiperizin-1-yl)carbonyl)methylphenyl, 4-((methylcarboxamido)methyl)phenyl, 4-((isopropylcarboxamido)methyl)phenyl, 4-((ethoxycarbonyl)isopropyl)phenyl, 4-(carboxyisopropyl)phenyl, 4-(4-methylpiperazin-1-yl)carbonyl)isopropylphenyl, 4-(methanesulfonyl)methylphenyl, 3-chloro-4-(methanesulfonyl)methylphenyl, 4-(methanesulfonyl)(2-morpholinoethyl)aminophenyl, 4-(methanesulfonyl)(2-piperidinoethyl)aminophenyl, 4-(methanesulfonyl)(2-hydroxyethyl)aminophenyl, 4-(methanesulfonyl)isopropylaminophenyl, 4-(methanesulfonyl)(2-hydroxy-3-(piperidin-1-yl)propyl)aminophenyl, 4-(methanesulfonyl)(2-(pyrrolidin-1-yl)ethyl)aminophenyl, 4-(propanesulfonyl)carbamoylphenyl, 4-(tert-butanesulfonyl)carbamoylphenyl, or 4-(ethanesulfonyl)carbamoylphenyl.

29. The compound of claim 3, wherein L_1 is a bond; R_a is cycloheptyl, pyridinyl, pyrimidinyl, or phenyl; R_b is phenyl; L_2 is a bond; and R_c is cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkyl–alkyl, heterocycloalkyl–alkyl, aralkyl, or heteroaralkyl.

30. The compound of claim 3, wherein L_1 is a bond; R_a is cycloheptyl or phenyl; R_b is phenyl; L_2 is a bond; and R_c is tetrazolyl, morpholino, or piperazinyl, and is optionally substituted.

31. The compound of claim 30, wherein R_a is phenyl with at least one substituent at the *para* position.

32. The compound of claim 31, wherein R_a is *p*-methoxyphenyl or *p*-hydroxyphenyl.

33. The compound of claim 3, wherein L_1 is a bond; R_a is cycloheptyl, pyridinyl, pyrimidinyl or-phenyl substituted with alkoxy; R_b is phenyl; L_2 is –O–, –S–, –SO_2–, –CO–, –CO–O–, –NR_x–, –NR_x–CO–, –NR_x–SO_2–, –NR_x–CO–O–, –NR_x–CO–NR_y–, or –NR_x–CO–CO–

O–, with R_x being hydrogen, alkyl, –CO–alkyl, $–SO_2–$alkyl, or $–SO_2–$aryl; and R_c is hydrogen, alkyl, or aryl.

34. The compound of claim 3, wherein L_1 is a bond; R_a is cycloheptyl or phenyl; R_b is phenyl; L_2 is –CO–O–, $–NR_x–$, $–NR_x–SO_2–$, $–NR_x–CO–O–$, or $–NR_x–CO–NR_y–$, with R_x being hydrogen, alkyl, –CO–alkyl, $–SO_2–$alkyl, or $–SO_2–$aryl; and R_c is hydrogen, alkyl, or aryl.

35. The compound of claim 34, wherein R_x is $–SO_2–$alkyl; and R_c is alkyl.

36. The compound of claim 34, wherein R_a is phenyl with at least one substituent at the *para* position.

37. The compound of claim 36, wherein R_a is *p*-methoxyphenyl or *p*-hydroxyphenyl.

38. The compound of claim 3, wherein L_1 is alkyl; R_a is phenyl; R_b is phenyl; L_2 is –CO–O–, $–NR_x–$, $–NR_x–SO_2–$, $–NR_x–CO–O–$, or $–NR_x–CO–NR_y$ with each of R_x and R_y, independently, being hydrogen, alkyl, –CO–alkyl, $–SO_2–$alkyl, or $–SO_2–$aryl; and R_c is hydrogen, alkyl, or aryl.

39. The compound of claim 38, wherein L_1 is methyl substituted with phenyl.

40. The compound of claim 38, wherein L_1 is methyl; R_x is $–SO_2–$alkyl; and R_c is an optionally substituted alkyl.

41. The compound of claim 1, wherein R_b is phenyl; L_2 is a bond or $–NR_x–SO_2–$; R_x is hydrogen or $–SO_2–$alkyl; and R_c is hydrogen, alkyl, heterocycloalkyl, heteroaryl, (heterocycloalkyl)alkyl, or heteroaralkyl.

42. The compound of claim 41, wherein R_x is $–SO_2–$alkyl; and R_c is alkyl.

43. The compound of claim 1, wherein R_a is cyclohexyl optionally substituted with 1-3 substitutnets.

44. The compound of claim 43, wherein the optional substituents are each selected from the group consisting of alkoxycarbonyl, hydroxyalkyl, hyroxycarbonyl, alkoxycarbonylamino, and hydroxycarbonylamino.

45. The compound of claim 44, wherein R_a is ethoxycarbonyl, hydroxymethyl, hydroxycarbonyl, or tert-butoxycarbonylamino.

46. The compound of claim 1, wherein R_3 is 4-(4-methylpiperazin-1-yl)phenyl), 4-(piperazin-1-yl)phenyl, 4-aminophenyl, 4-benzoic acid, 4-morpholinophenyl, 4-N,N-dimethylsulfonylphenyl, or 4-(methanesulfonamide)phenyl.

47. The compound of claim 1, wherein said compound is

N-(4-(1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)cyclopropanesulfonamide,

1-(4-methoxyphenyl)-N-(3-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

2-hydroxy-5-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)benzaldehyde,

ethyl2-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenylamino)-2-oxoacetate,

N-(2,3,5,6,8,9,11,12,14,15-decahydrobenzo[b]-[1,4,7,10,13,16]hexaoxacyclooctadecin-18-yl)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(4-methoxyphenyl)-N-(2,3,5,6,8,9,11,12-octahydrobenzo[b]-[1,4,7,10,13]pentaoxacyclopentadecin-15-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-1-(methylsulfonyl)methanesulfonamide,

3,3,3-trifluoro-N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)propane-1-sulfonamide,

1-(4-methoxyphenyl)-N-(4-morpholinophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(4-(1H-1,2,4-triazol-1-yl)phenyl)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

2-methoxy-4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenol,

N-(3,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(3-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)ethanol,

N^1-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,4-diamine,

N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide,

4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenol,

1-(4-methoxyphenyl)-N-(3,4,5-trimethoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(4-methoxyphenyl)-N-(4-(4-(methylsulfonyl)piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

methyl-3-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenylamino)-3-oxopropanoate,

2-methoxy-N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)acetamide,

N-(3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

2-ethoxy-5-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenol,

2-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)ethanol,

N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)acetamide,

2-(2-methoxyethoxy)-N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)acetamide,

diethyl4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)benzylphosphonate,

1-(3-methoxyphenyl)-N-(4-(4-(methylsulfonyl)piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

dimethyl4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenylphosphoramidate,

N1-(1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,4-diamine,

1-(4-methoxyphenyl)-N-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(3-methoxyphenyl)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

3-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenol,

1-(4-methoxyphenyl)-N-(4-(piperidin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N^1-bis(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

methyl4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenylcarbamate,

2-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenylamino)-2-oxoethylacetate,

N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

2-methoxy-5-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenol,

1-(4-methoxyphenyl)-N-(4-(methylthio)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-2-methylphenol,

2-methoxy-4-(1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenol,

N-(3,4-dimethoxyphenyl)-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

2-(2-methoxyethoxy)-N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)acetamide,

(E)-N'-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N,N-dimethylformimidamide,

2-methoxy-5-(1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenol,

N-(2,2-dimethylbenzo[d][1,3]dioxol-5-yl)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

methyl2-hydroxy-5-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)benzoate,

1-(4-methoxyphenyl)-N-(4-(methylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

3-(1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenol,

1-(3-methoxyphenyl)-N-(2,3,5,6,8,9,11,12-octahydrobenzo[b]-[1,4,7,10,13]pentaoxacyclopentadecin-15-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(benzo[d][1,3]dioxol-5-yl)-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-methylmethanesulfonamide,

4-methoxy-N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)benzamide,

N-(2,4-dimethoxyphenyl)-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(4-methoxyphenyl)-N-(naphthalen-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

N-(4-(1H-tetrazol-5-yl)phenyl)-1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N,N-dimethyl 4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenylsulfamide,

N^1-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,4-diamine,

3-chloro-N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)propane-1-sulfonamide,

3-chloro-N(-4(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-propyl-1,3-sultam,

1-cycloheptyl-N-(4-(4-(methylsulfonyl)piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)benzoicacid,

1-cycloheptyl-N-(4-morpholinophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

3-chloro-N-(3-chloropropylsulfonyl)-N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)propane-1-sulfonamide,

(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)(morpholino)methanone,

N^1-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,3-diamine,

1-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)guanidine,

N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide,

dimethyl4-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)piperazin-1-ylphosphonate,

(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)(4-ethylpiperazin-1-yl)methanone,

1-cycloheptyl-N-(4-thiomorpholinophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

dimethyl4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenylphosphoramidate,

1-cycloheptyl-N-(4-(piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-cycloheptyl-N-(4-(1-methyl-1H-tetrazol-5-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

2-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)ethanol,

1-allyl-3-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)urea,

N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)acetamide,

1-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-3-ethylurea,

1-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-3-propylurea,

1-cycloheptyl-N-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-cycloheptyl-N-(4-(2-methyl-2H-tetrazol-5-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(4-(2-(2-chloroethyl)-2H-tetrazol-5-yl)phenyl)-1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)thiophene-2-sulfonamide,

4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)benzonitrile,

N-(3-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

1-cycloheptyl-N-(4-(piperidin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-1-(methylsulfonyl)-N-(methylsulfonylmethylsulfonyl)methanesulfonamide,

1-cycloheptyl-N-(4-(2-morpholinoethoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(4-(1H-pyrazol-1-yl)phenyl)-1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(phenylsulfonyl)benzenesulfonamide,

N-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-1,1,1-trifluoro-N-(4-(1,1,1-trifluoro-N-(trifluoromethylsulfonyl)methylsulfonamido)phenyl)methane-sulfonamide,

N-(benzo[d][1,3]dioxol-5-yl)-1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

2-(4-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)piperazin-1-yl)ethanol,

1-cycloheptyl-N-phenyl-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-cycloheptyl-N-(4-(2-vinyl-2H-tetrazol-5-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

ethyl 4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)benzoate,

tert-butyl 4-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)piperazine-1-carboxylate,

N-(4-(1-(4-methoxy-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

1-(4-methoxy-2-methylphenyl)-N-(4-(4-(methylsulfonyl)piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(4-methoxy-2-methylphenyl)-N-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(4-(1-(4-methoxy-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide,

1-(4-methoxy-2-methylphenyl)-N-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(4-methoxy-2-methylphenyl)-N-(4-(trifluoromethoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(4-methoxy-2-methylphenyl)-N-(4-(methylthio)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

2-methoxy-5-(1-(4-methoxy-2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenol,

3-(6-(4-aminophenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenol,

4-(6-(4-aminophenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenol,

4-(6-(4-morpholinophenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenol,

5-(1-(3-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-2-methoxyphenol,

5-(1-(4-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-2-methoxyphenol,

N^1-(1-(4-iodophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,4-diamine,

4-(4-(6-(4-aminophenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)but-3-yn-1-ol,

4-(4-(6-(3,4-dimethoxyphenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)but-3-yn-1-ol,

N-(3,4-dimethoxyphenyl)-1-(4-iodophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

5-(1-(4-iodophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-2-methoxyphenol,

1-(4-ethylphenyl)-N-(4-(piperidin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(4-iodophenyl)-N-(4-(piperidin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-benzyl-N-(4-(piperidin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(3-methoxybenzyl)-N-(4-(piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(3,4-dimethoxybenzyl)-N-(4-(piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

tert-butyl 4-(4-(1-(3,5-dimethoxybenzyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)piperazine-1-carboxylate,

1-(3,5-dimethoxybenzyl)-N-(4-(piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

tert-butyl 4-(4-(3-bromo-1-(3,4-dimethoxybenzyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)piperazine-1-carboxylate,

tert-butyl 4-(4-(1-(3,4-dimethoxybenzyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)piperazine-1-carboxylate,

1-(4-methoxybenzyl)-N-(4-(piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

tert-butyl 4-(4-(1-(4-methoxybenzyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)piperazine-1-carboxylate,

1-(2,3-dihydro-1H-inden-2-yl)-N-(4-morpholinophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

ethyl 2-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)acetate,

1-cycloheptyl-N-(4-((4-methylpiperazin-1-yl)methyl)phenyl)-1h-pyrazolo[3,4-d]pyrimidin-6-amine,

2-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)acetic acid,

2-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-1-(4-ethylpiperazin-1-yl)ethanone,

2-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-methylacetamide,

2-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-isopropylacetamide,

ethyl 2-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-2-methylpropanoate,

2-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-2-methylpropanoic acid,

ethyl 2-(2-chloro-4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)acetate,

2-(2-chloro-4-(1-cycloheptyl-1H-pyrazolo[3,4d]pyrimidin-6-ylamino)phenyl)acetic acid,

2-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-2-methyl-1-(4-methylpiperazin-1-yl)propan-1-one,

1-cycloheptyl-N-(4-(methylsulfonylmethyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(3-chloro-4-(methylsulfonylmethyl)phenyl)-1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(2-morpholinoethyl)methanesulfonamide,

N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(2-(piperidin-1-yl)ethyl)methanesulfonamide,

N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(2-hydroxyethyl)methanesulfonamide,

N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-isopropylmethanesulfonamide,

N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(2-hydroxy-3-(piperidin-1-yl)propyl)methanesulfonamide,

N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(2-(pyrrolidin-1-yl)ethyl)methanesulfonamide,

N-(4-(1-(4-hydroxy-2,3-dihydro-1H-inden-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

(S)-N-(4-(1-(2,3-dihydro-1H-inden-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(ethylsulfonyl)ethanesulfonamide,

1-(6-(4-(4-methylpiperazin-1-yl)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2,3-dihydro-1H-inden-4-ol,

1-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2,3-dihydro-1H-inden-4-yl benzoate,

1-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2,3-dihydro-1H-inden-4-yl dihydrogen phosphate,

(S)-1-chloro-N-(chloromethylsulfonyl)-N-(4-(1-(2,3-dihydro-1H-inden-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide,

N-(4-(1-(6,7-dihydro-5H-indeno[5,6-d][1,3]dioxol-5-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

N-(1-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2,3-dihydro-1H-inden-5-yl)acetamide,

N-(4-(1-(4-hydroxy-2,3-dihydro-1H-inden-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide,

1-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2,3-dihydro-1H-inden-5-yl benzoate,

(S,Z)-4-(1-(2,3-dihydro-1H-inden-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-N'-hydroxybenzimidamide,

1-(6-(4-(4-methylpiperazin-1-yl)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2,3-dihydro-1H-inden-4-yl benzoate,

1-(6-(4-aminophenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2,3-dihydro-1H-inden-4-ol,

1-(6-(4-aminophenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2,3-dihydro-1H-inden-4-yl benzoate,

di-tert-butyl 1-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2,3-dihydro-1H-inden-4-yl phosphate,

(S)-4-(1-(2,3-dihydro-1H-inden-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-N-(methylsulfonyl)benzamide,

N-(4-(1-(5-((2-methoxyethoxy)methoxy)-2,3-dihydro-1H-inden-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

N-(1-(6-(4-aminophenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2,3-dihydro-1H-inden-5-yl)acetamide,

(S)-4-(1-(2,3-dihydro-1H-inden-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)benzonitrile,

(S)-N-(4-(1H-tetrazol-5-yl)phenyl)-1-(2,3-dihydro-1H-inden-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N1-(1-(5-methoxy-2,3-dihydro-1H-inden-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,4-diamine,

N-(4-(1-(5-methoxy-2,3-dihydro-1H-inden-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

(S)-1-(2,3-dihydro-1H-inden-1-yl)-N-(4-nitrophenethyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

(S)-N-(4-aminophenethyl)-1-(2,3-dihydro-1H-inden-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

(S)-N-(4-(2-(1-(2,3-dihydro-1H-inden-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)ethyl)phenyl)-N-(methylsulfonyl)methanesulfonamide,

N-(4-(1-(1H-indol-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

N-(4-(1-(1H-indol-6-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

N-(4-(1-(1H-indol-5-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

N-(4-(1-(benzo[d][1,3]dioxol-5-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

1-(1H-indol-4-yl)-N-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(4-(1-(1-methyl-1H-indol-5-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

1-(7-methyl-1H-indol-4-yl)-N-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

tert-butyl 7-methyl-4-(6-(4-(4-methylpiperazin-1-yl)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1H-indole-1-carboxylate,

tert-butyl 4-(6-(4-(4-methylpiperazin-1-yl)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1H-indole-1-carboxylate,

N-(4-morpholinophenyl)-1-(naphthalen-1-ylmethyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-butyl-N-(4-(piperidin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-isopropyl-N-(4-(piperidin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(cyclopentylmethyl)-N-(4-(piperidin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

(S)-N-(4-morpholinophenyl)-1-(1-phenylethyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-((6-fluoro-4H-benzo[d][1,3]dioxin-8-yl)methyl)-N-(4-morpholinophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(furan-2-ylmethyl)-N-(4-(piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

ethyl2-(6-(4-(piperidin-1-yl)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)acetate,

N-(4-morpholinophenyl)-1-(pyridin-2-ylmethyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-methyl-N-(4-(piperidin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(4-morpholinophenyl)-1-(1,2,3,4-tetrahydronaphthalen-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(1-benzylpiperidin-4-yl)-N-(4-morpholinophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine, or

1-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-N-(4-morpholinophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine.

48. The compound of claim 1, wherein the compound is

N-(4-(1H-tetrazol-5-yl)phenyl)-1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(4-(1H-tetrazol-5-yl)phenyl)-1-(biphenyl-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(4-(1H-tetrazol-5-yl)phenyl)-1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(4-(1H-tetrazol-5-yl)phenyl)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-cycloheptyl-N-(4-morpholinophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(biphenyl-2-yl)-N-(4-morpholinophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(4-morpholinophenyl)-1-(phenanthren-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(3-methoxyphenyl)-N-(4-morpholinophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(4-methoxyphenyl)-N-(4-morpholinophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-cycloheptyl-N-(4-(piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(biphenyl-2-yl)-N-(4-(piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(3-methoxyphenyl)-N-(4-(piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(4-methoxyphenyl)-N-(4-(piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)benzoic acid,

4-(1-(biphenyl-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)benzoic acid,

4-(1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)benzoic acid,

4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)benzoic acid,

N^1-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,4-diamine,

N^1-(1-(biphenyl-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,4-diamine,

N^1-(1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,4-diamine,

N^1-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,4-diamine,

N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

N-(4-(1-(biphenyl-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

N-(4-(1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

N-(4-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide,

N-(4-(1-(biphenyl-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide,

N-(4-(1-(phenanthren-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide,

N-(4-(1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide,

N-(4-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide,

1-cycloheptyl-N-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(biphenyl-2-yl)-N-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(3-methoxyphenyl)-N-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(4-methoxyphenyl)-N-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

5-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-2-methoxyphenol,

5-(1-(biphenyl-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-2-methoxyphenol,

2-methoxy-5-(1-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenol,

4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl dihydrogen phosphate

4-methoxy-N1-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzene-1,3-diamine

4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl acetate

4-(6-(4-(N-(methylsulfonyl)methylsulfonamido)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl sulfamate

N-(4-(1-(4-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)-N-(methylsulfonyl)methanesulfonamide,

2-methoxy-5-(1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenol,

1-(cyclopentylmethyl)-N-(4-(piperidin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

(S)-N-(4-morpholinophenyl)-1-(1-phenylethyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-((6-fluoro-4H-benzo[d][1,3]dioxin-8-yl)methyl)-N-(4-morpholinophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(furan-2-ylmethyl)-N-(4-(piperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(4-morpholinophenyl)-1-(pyridin-2-ylmethyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-(1-benzylpiperidin-4-yl)-N-(4-morpholinophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

1-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-N-(4-morpholinophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine,

N-(5-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)pyridine-2yl)-N-(methylsulfonyl)methanesulfonamide,

N-(5-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)pyridin-2-yl)methanesulfonamide,

N-(5-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)pyridin-2-yl)-N-(2-hydroxyethyl)methanesulfonamide,

N-(4-(6-(6-(N-(methylsulfonyl)methylsulfonamido)pyridin-3-ylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)-2-(pyrrolidin-1-yl)acetamide,

N-(4-(6-(6-(methylsulfonamido)pyridin-3-ylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)-2-(pyrrolidin-1-yl)acetamide,

N-(5-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)pyridin-2-yl)-N-(2-morpholinoethyl)methanesulfonamide,

N-(5-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)pyridin-2-yl)-N-(2,3-dihydroxypropyl)methanesulfonamide,

N-(4-(6-(6-(N-(2,3-dihydroxypropyl)methylsulfonamido)pyridin-3-ylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)-2-(pyrrolidin-1-yl)acetamide,

tert-butyl 4-(6-(6-(N-(2,3-dihydroxypropyl)methylsulfonamido)pyridin-3-ylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenylcarbamate,

tert-butyl 4-(6-(6-(N-(2-morpholinoethyl)methylsulfonamido)pyridin-3-ylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenylcarbamate,

N-(5-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)pyrimidin-2-yl)methanesulfonamide,

N-(5-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)pyrimidin-2-yl)-N-(2,3-dihydroxypropyl)methanesulfonamide,

tert-butyl 4-(6-(2-(N-(2,3-dihydroxypropyl)methylsulfonamido)pyrimidin-5-ylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenylcarbamate,

N-(5-(1-cycloheptyl-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)pyrimidin-2-yl)-N-(2-morpholinoethyl)methanesulfonamide,

N-(4-(6-(2-(N-(2,3-dihydroxypropyl)methylsulfonamido)pyrimidin-5-ylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenyl)-2-(pyrrolidin-1-yl)acetamide,

tert-butyl 4-(6-(2-(N-(2-morpholinoethyl)methylsulfonamido)pyrimidin-5-ylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)phenylcarbamate,

tert-butyl 5-(6-(2-(N-(2-morpholinoethyl)methylsulfonamido)pyrimidin-5-ylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyridin-2-ylcarbamate,

N-(5-(6-(2-(N-(2,3-dihydroxypropyl)methylsulfonamido)pyrimidin-5-ylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyridin-2-yl)-2-(pyrrolidin-1-yl)acetamide,

N-(5-(6-(6-(N-(2,3-dihydroxypropyl)methylsulfonamido)pyridin-3-ylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyridin-2-yl)-2-(pyrrolidin-1-yl)acetamide,

tert-butyl 5-(6-(6-(N-(2-morpholinoethyl)methylsulfonamido)pyridin-3-ylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyridin-2-ylcarbamate,

tert-butyl 6-(6-(6-(N-(2-morpholinoethyl)methylsulfonamido)pyridin-3-ylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyridin-3-ylcarbamate,

N-(6-(6-(6-(N-(2,3-dihydroxypropyl)methylsulfonamido)pyridin-3-ylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyridin-3-yl)-2-(pyrrolidin-1-yl)acetamide,

tert-butyl 6-(6-(2-(N-(2,3-dihydroxypropyl)methylsulfonamido)pyrimidin-5-ylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyridin-3-ylcarbamate,

tert-butyl 6-(6-(6-(N-(2,3-dihydroxypropyl)methylsulfonamido)pyridin-3-ylamino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyridin-3-ylcarbamate,

N-(5-(1-(3-hydroxybenzyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)pyridin-2-yl)methanesulfonamide,

N-(2,3-dihydroxypropyl)-N-(5-(1-(3-hydroxybenzyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)pyridin-2-yl)methanesulfonamide,

N-(2,3-dihydroxypropyl)-N-(5-(1-((2-hydroxypyridin-4-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)pyridin-2-yl)methanesulfonamide,

N-(5-(1-(3-hydroxybenzyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)pyridin-2-yl)-N-(2-morpholinoethyl)methanesulfonamide,

N-(2,3-dihydroxypropyl)-N-(4-(1-((2-hydroxypyridin-4-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)methanesulfonamide, or

N-(5-(1-((2-hydroxypyridin-4-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)pyridin-2-yl)-N-(2-morpholinoethyl)methanesulfonamide.

49. A pharmaceutical composition comprising a compound of any of claims 1 to 48 and a pharmaceutically acceptable carrier.

50. A method of treating a subject with a protein kinase-mediated disease, comprising administering to said subject a pharmaceutically effective amount of a compound of any of claims 1 to 48.

51. A method of inhibiting a protease kinase in a cell, comprising contacting the cell with a compound of any of claims 1 to 48.

52. The method of claim 51, wherein the protease kinase is one or more protease kinases involved in cell mitosis.

53. The method of claim 52, wherein the protease kinase is an Aurora kinase or a cyclin-dependant kinase.

54. A method of treating a tumor or a cancer in a subject, comprising administering to the subject in need thereof a compound of any of claims 1 to 48.

55. The method of claim 54, wherein the tumor or cancer is a bone cancer, brain and CNS tumor, breast cancer, breast cancer, colorectal cancer, endocrine cancer, gastrointestinal cancer, genitourinary cancer, gynaecological cancer, head and neck cancer, leukaemia, lung cancer, lymphoma, eye cancer, skin cancer, soft tissue sarcoma, urinary system cancer, and other types or related disorders.