(12) STANDARD PATENT (11) Application No. **AU 2017241837 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Substituted aminopurine compounds, compositions thereof, and methods of treatment therewith

(51) International Patent Classification(s)
C07D 473/02 (2006.01) ***A61K 31/52*** (2006.01)
A61K 31/505 (2006.01) ***C07D 473/26*** (2006.01)
A61K 31/519 (2006.01) ***C07D 473/32*** (2006.01)

(21) Application No: **2017241837** (22) Date of Filing: **2017.03.31**

(87) WIPO No: **WO17/173206**

(30) Priority Data

(31) Number	(32) Date	(33) Country
62/317,412	**2016.04.01**	**US**

(43) Publication Date: **2017.10.05**
(44) Accepted Journal Date: **2021.07.22**

(71) Applicant(s)
Signal Pharmaceuticals, LLC

(72) Inventor(s)
Boylan, John F.;Bray, Gordon L.;Filvaroff, Ellen;Hubbard, Robert;Mikolon, David;Raymon, Heather;Shi, Tao;Tran, Tam M.;Tsuji, Toshiya;Wong, Lilly L.;Xu, Suichan;Zhu, Dan

(74) Agent / Attorney
FB Rice Pty Ltd, Level 23 44 Market Street, Sydney, NSW, 2000, AU

(56) Related Art
WO 2006076595 A1
WO 2016057370 A1

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 October 2017 (05.10.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/173206 A1

(51) International Patent Classification:
A61K 31/52 (2006.01) *C07D 473/02* (2006.01)
A61K 31/505 (2006.01) *C07D 473/26* (2006.01)
A61K 31/519 (2006.01) *C07D 473/32* (2006.01)

(21) International Application Number:
PCT/US2017/025252

(22) International Filing Date:
31 March 2017 (31.03.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/317,412 1 April 2016 (01.04.2016) US

(71) Applicant: **SIGNAL PHARMACEUTICALS, LLC** [US/US]; 10300 Campus Point Drive, Suite 100, San Diego, CA 92121 (US).

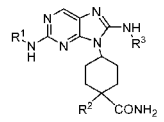
(72) Inventors: **BOYLAN, John, F.**; 10486 Harvest View Way, San Diego, CA 92128 (US). **BRAY, Gordon, L.**; 301 Main Street, Unit 8c, San Francisco, CA 94105 (US). **FILVAROFF, Ellen**; 538 18th Avenue, San Francisco, CA 94121 (US). **HUBBARD, Robert**; 7684 Marker Road, San Diego, CA 92087 (US). **MIKOLON, David**; 6140 Calle Empinada, San Diego, CA 92120 (US). **RAYMON, Heather**; 3520 Vista de la Orilla, San Diego, CA 92117 (US). **SHI, Tao**; 4650 Tarantella Lane, San Diego, CA 92130 (US). **TRAN, Tam, M.**; 8953 Libra Drive, San Diego, CA 92126 (US). **TSUJI, Toshiya**; 4171 Donald Court, San Diego, CA 92117 (US). **WONG, Lilly, L.**; 871 Viva Court, Solana Beach, CA 92075 (US). **XU, Suichan**; 9650 Deer Trail Place, San Diego, CA 92127 (US). **ZHU, Dan**; 4432 Calle Mar De Armonia, San Diego, CA 92130 (US).

(74) Agents: **BRUNER, Michael, J.** et al.; Jones Day, 250 Vesey Street, New York, NY 10281-1047 (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, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG,

[Continued on next page]

(54) Title: SUBSTITUTED AMINOPURINE COMPOUNDS, COMPOSITIONS THEREOF, AND METHODS OF TREATMENT THEREWITH



(I)

(57) Abstract: Provided herein are methods for treating or preventing a cancer, including solid tumors and hematological cancers, comprising administering an effective amount of aminopurine compounds of formula (I), and compositions comprising an effective amount of such compounds.

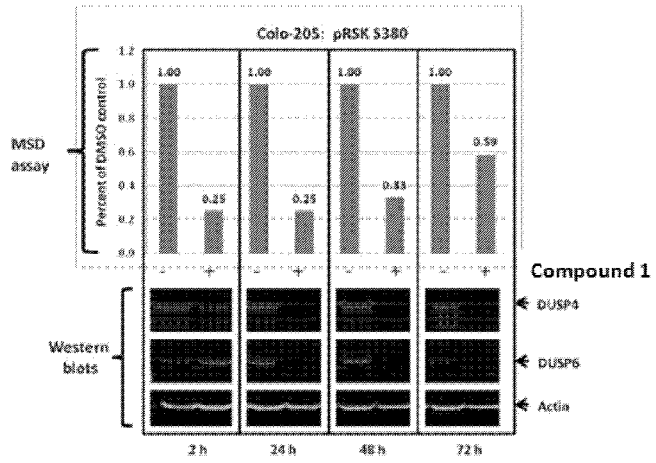


FIG. 1

WO 2017/173206 A1

NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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

Published:

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

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

SUBSTITUTED AMINOPURINE COMPOUNDS, COMPOSITIONS THEREOF, AND METHODS OF TREATMENT THEREWITH

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Application No. 62/317,412, filed April 1, 2016, which is incorporated herein by reference in its entirety and for all purposes.

FIELD

[0002] Provided herein are methods for treating or preventing a cancer, including solid tumors and hematological cancers, comprising administering an effective amount of certain aminopurine compounds described herein, and compositions comprising an effective amount of such compounds.

BACKGROUND

[0003] Cancer is characterized primarily by an increase in the number of abnormal cells derived from a given normal tissue, invasion of adjacent tissues by these abnormal cells, or lymphatic or blood-borne spread of malignant cells to regional lymph nodes and to distant sites (metastasis). Clinical data and molecular biologic studies indicate that cancer is a multistep process that begins with minor preneoplastic changes, which may under certain conditions progress to neoplasia. The neoplastic lesion may evolve clonally and develop an increasing capacity for invasion, growth, metastasis, and heterogeneity, especially under conditions in which the neoplastic cells escape the host's immune surveillance (Roitt, I., Brostoff, J and Kale, D., Immunology, 17.1-17.12 (3rd ed., Mosby, St. Louis, Mo., 1993)).

[0004] Cancers figure among the leading causes of death worldwide, accounting for 8.2 million deaths in 2012. It is expected that annual cancer cases will rise from 14 million in 2012 to 22 million within the next two decades (See Cancer Fact sheet No 297, World Health Organization, February 2014, retrieved 10 June 2014 and Globocan 2012, IARC).

[0005] The current drugs used in cancer treatment are highly toxic and often non-specific. Current anticancer therapy strategies are typically focused on rapid proliferating cells, which can

shrink primary and metastatic tumors, but such effects are usually transient and tumor relapse of most metastatic cancers frequently occur. One possible reason for failure is the existence of cancer stem cells. Unlike most cells within the tumor, cancer stem cells are resistant to well-defined chemotherapy, and after treatment, they can regenerate all the cell types in the tumor through their stem cell-like behavior of largely quiescent nature and their abundant expression of drug transporters.

[0006] There is an enormous variety of cancers which are described in detail in the medical literature. The incidence of cancer continues to climb as the general population ages, as new cancers develop, and as susceptible populations (e.g., people infected with AIDS or excessively exposed to sunlight) grow. However, options for the treatment of cancer are limited. A tremendous demand therefore exists for new methods and compositions that can be used to treat patients with cancer

[0007] Citation or identification of any reference in Section of this application is not to be construed as an admission that the reference is prior art to the present application.

SUMMARY

[0008] Provided herein are Aminopurine Compounds, including compositions (e.g. pharmaceutical compositions) comprising such Aminopurine Compounds, that can be used in the methods provided herein.

[0009] Provided herein are methods of treating a cancer, in particular a solid tumor or a hematological cancer. The Aminopurine Compound provided herein can be used in the methods for treating or preventing a cancer, in particular a solid tumor or a hematological cancer, as described herein. The methods comprise administering to a subject in need thereof an effective amount of Aminopurine Compound 1. Also provided herein are methods for treating and preventing cancer metastasis, comprising administering to a subject in need thereof an effective amount of an Aminopurine Compound as provided herein. The Aminopurine Compound provided herein can be used in the methods for treating and preventing cancer metastasis. Additionally, provided herein are methods of eradicating cancer stem cells in a subject, comprising administering to a subject in need thereof an effective amount of an Aminopurine Compound as provided herein. The Aminopurine Compound provided herein can be used in the

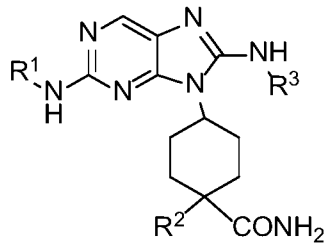
methods of eradicating cancer stem cells in a subject. Also provided are methods of inducing differentiation in cancer stem cells in a subject, comprising administering to a subject in need thereof an effective amount of an Aminopurine Compound as provided herein. The Aminopurine Compound provided herein can be used in the methods of inducing differentiation in cancer stem cells in a subject. In another aspect, provided are methods of inducing cancer stem cell death in a subject, comprising administering to a subject in need thereof an effective amount of an Aminopurine Compound as provided herein. The Aminopurine Compound provided herein can be used in the methods of inducing cancer stem cell death in a subject.

[0010] Provided herein are methods of treating a cancer, in particular a solid tumor or a hematological cancer using a pharmaceutical composition that includes an Aminopurine Compound described herein. The Aminopurine Compound pharmaceutical composition provided herein can be used in the methods for treating or preventing a cancer, in particular a solid tumor or a hematological cancer, as described herein. The methods comprise administering to a subject in need thereof an effective amount of a pharmaceutical composition that includes Aminopurine Compound 1. Also provided herein are methods for treating and preventing cancer metastasis, comprising administering to a subject in need thereof an effective amount of a pharmaceutical composition that includes an Aminopurine Compound as provided herein. The Aminopurine Compound pharmaceutical composition provided herein can be used in the methods for treating and preventing cancer metastasis. Additionally, provided herein are methods of eradicating cancer stem cells in a subject, comprising administering to a subject in need thereof an effective amount of a pharmaceutical composition that includes an Aminopurine Compound as provided herein. The Aminopurine Compound pharmaceutical composition provided herein can be used in the methods of eradicating cancer stem cells in a subject. Also provided are methods of inducing differentiation in cancer stem cells in a subject, comprising administering to a subject in need thereof an effective amount of a pharmaceutical composition that includes an Aminopurine Compound as provided herein. The Aminopurine Compound pharmaceutical composition provided herein can be used in the methods of inducing differentiation in cancer stem cells in a subject. In another aspect, provided are methods of inducing cancer stem cell death in a subject, comprising administering to a subject in need thereof an effective amount of a pharmaceutical composition that includes an Aminopurine Compound as provided herein. The Aminopurine

Compound pharmaceutical composition provided herein can be used in the methods of inducing cancer stem cell death in a subject.

[0011] Compounds useful in the methods disclosed herein are Aminopurine Compounds as described herein, such as, for example, in Table 1, or a pharmaceutically acceptable salt, tautomer, stereoisomer, enantiomer, or isotopologue thereof and pharmaceutical compositions of Aminopurine Compounds.

[0011A] According to the invention there is provided herein a method for treating a cancer, the method comprising administering to a subject having the cancer an effective amount of an Aminopurine Compound of formula (I):



(I)

or a pharmaceutically acceptable salt, tautomer, stereoisomer, or enantiomer thereof, wherein:

R^1 is substituted or unsubstituted non-aromatic heterocyclyl;

R^2 is H or substituted or unsubstituted C_{1-3} alkyl; and

R^3 is phenyl, substituted with one or more halogen, optionally further substituted with one or more substituents independently selected from substituted or unsubstituted C_{1-3} alkyl, CN, and -OR', wherein each R' is independently substituted or unsubstituted C_{1-3} alkyl;

wherein when a C_{1-3} alkyl group is substituted, the C_{1-3} alkyl group is substituted with halogen, alkyl, hydroxyl, alkoxy, alkoxyalkyl, amino, alkylamino, carboxy, nitro, cyano, thiol, thioether, imine, imide, amidine, guanidine, enamine, aminocarbonyl, acylamino, phosphonate, phosphine, thiocarbonyl, sulfinyl, sulfone, sulfonamide, ketone, aldehyde, ester, urea, urethane, oxime, hydroxyl amine, alkoxyamine, aryloxyamine, aralkoxyamine, N-oxide, hydrazine, hydrazide, hydrazone, azide, isocyanate, isothiocyanate, cyanate, thiocyanate, $B(OH)_2$, or O(alkyl)aminocarbonyl;

wherein when a group, other than a C_{1-3}alkyl group, is substituted, the group is substituted with halogen, C_{1-10}alkyl, hydroxyl, C_{1-10}alkoxy, C_{1-10} alkoxy C_{1-10}alkyl, amino, C_{1-10}alkylamino, carboxy, nitro, cyano, thiol, thioether, imine, imide, amidine, guanidine, enamine, aminocarbonyl, acylamino, phosphonate, phosphine, thiocarbonyl, sulfinyl, sulfone, sulfonamide, ketone, aldehyde, ester, urea, urethane, oxime, hydroxyl amine, C_{1-10}alkoxyamine, C_{6-14}aryloxyamine, C_{6-14}arC_{1-10}alkoxyamine, N-oxide, hydrazine, hydrazide, hydrazone, azide, isocyanate, isothiocyanate, cyanate, thiocyanate, oxygen (=O), $B(OH)_2$, O(C_{1-10}alkyl)aminocarbonyl, C_{3-10}cycloalkyl, heterocyclyl, aryl, heteroaryl, C_{6-14}aryloxy, C_{6-14}arC_{1-10}alkyloxy, heterocyclyloxy, or heterocyclyl C_{1-10}alkoxy;

wherein the cancer is colorectal cancer, colon cancer, renal cell carcinoma, gastric cancer, stomach cancer, hepatocellular carcinoma, liver cancer, lung cancer, pancreatic cancer, leukemia, or multiple myeloma;

wherein an alkyl group is a saturated straight chain or branched non-cyclic hydrocarbon having from 1 to 10 carbon atoms;

wherein a heterocyclyl group is an aromatic or non-aromatic cycloalkyl having from 1 to 2 rings in which one to four of the ring carbon atoms are independently replaced with a heteroatom selected from the group consisting of O, S and N;

wherein an aryl group is an aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring or multiple condensed rings;

wherein a heteroaryl group is an aromatic cycloalkyl of from 3 to 10 carbon atoms having a single cyclic ring or multiple condensed or bridged rings in which one to four of the ring carbon atoms are independently replaced with a heteroatom selected from the group consisting of O, S and N.

[0011B] According to the invention there is provided herein a method for treating a cancer, the method comprising administering to a subject having the cancer an effective amount of an Aminopurine Compound, wherein the cancer is selected from the group consisting of colorectal cancer, colon cancer, renal cell carcinoma, gastric cancer, stomach cancer, hepatocellular carcinoma, liver cancer, lung cancer, pancreatic cancer, leukemia, and multiple myeloma; and wherein the Aminopurine compound is selected from the group consisting of

(1s,4s)-4-(2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(3-chlorophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-chlorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclopentylamino)-8-(2,4-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-chlorophenylamino)-2-(4-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-difluorophenylamino)-2-(3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-difluorophenylamino)-2-(1-methylcyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(tert-butylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-difluorophenylamino)-2-((3R,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(4-methyltetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-chloro-2-fluorophenylamino)-2-(4-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(tetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((3R,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-difluorophenylamino)-2-((3R,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-6-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-chlorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3,4-dichlorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(5-chloro-2-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-chloro-2-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,5-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-chloro-2-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(tetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,3-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichlorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-5-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-fluoro-2-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-bromo-2-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-fluoro-4-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-(trifluoromethyl)phenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-fluoro-2-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(tetrahydro-2H-pyran-4-ylamino)-8-(2,3,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-1-methyl-4-(2-(tetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclobutylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclobutylamino)-8-(2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-(cyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclopentylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclopentylamino)-8-(2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-difluorophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclobutylamino)-8-(2,6-dichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclopentylamino)-8-(2,6-dichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(oxetan-3-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-(oxetan-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-(oxetan-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(tetrahydro-2H-pyran-4-ylamino)-8-(2,4,5-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(isopropylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-3-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,3-dichlorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-fluoro-6-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(5-chloro-2,4-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(tetrahydro-2H-pyran-4-ylamino)-8-(2,4,5-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(tetrahydro-2H-pyran-4-ylamino)-8-(2,3,4-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-chloro-2,6-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclopentylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-3-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,5-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2-fluoro-5-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(tetrahydro-2H-pyran-4-ylamino)-8-(2,3,4-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-fluoro-6-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2-fluoro-6-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-tetrahydrofuran-3-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1r,4r)-4-methoxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1r,4r)-4-hydroxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-chloro-6-fluoro-2-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,5-dichloro-4-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,3-dichloro-4-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-3-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,3-difluoro-4-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-3-fluoro-4-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,3-dichloro-4-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-difluoro-6-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((S)-tetrahydrofuran-3-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(4,4-difluorocyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-3-fluoro-2-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-3,6-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-6-fluoro-3-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino)-8-((2,4,6-trichlorophenyl)amino)-9H-purin-9-yl)cyclohexane-1-carboxamide;

(1s,4s)-4-(8-(2-chlorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclopentylamino)-8-(2,4-dichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2-fluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichlorophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-fluorophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,5-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,5-dimethylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2-fluoro-3-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,3-dichloro-6-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-5-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,5-difluoro-4-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-(1-(pyridin-3-yl)piperidin-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-(1-phenylpiperidin-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4,6-trichlorophenylamino)-2-(2,2,2-trifluoroethylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclobutylmethylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-tetrahydro-2H-pyran-3-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3,4-dichloro-2-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(6-chloro-2,3-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-(1-(methylsulfonyl)piperidin-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-difluoro-4-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(cyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclobutylamino)-8-(2,6-dichloro-4-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclopentylamino)-8-(2,6-dichloro-4-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclopentylamino)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((R)-1-hydroxybutan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(3R,4S)-tert-butyl 4-(9-((1s,4r)-4-carbamoylcyclohexyl)-8-(2,4,6-trifluorophenylamino)-9H-purin-2-ylamino)-3-fluoropiperidine-1-carboxylate;

(3R,4S)-tert-butyl 4-(9-((1s,4r)-4-carbamoylcyclohexyl)-8-(2,6-difluorophenylamino)-9H-purin-2-ylamino)-3-fluoropiperidine-1-carboxylate;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(cyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclobutylamino)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((R)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((R)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((R)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((R)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-1-hydroxybutan-2-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((3R,4S)-3-fluoropiperidin-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclopentylamino)-8-(2,3-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-chloro-2-fluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclopentylamino)-8-(2,3,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((S)-1-methoxypropan-2-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((S)-1-hydroxybutan-2-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-((S)-1-hydroxybutan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((S)-1-hydroxybutan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((S)-1-hydroxybutan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((S)-1-hydroxybutan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((S)-1-hydroxybutan-2-ylamino)-8-(2,3,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,4-dichlorophenylamino)-2-((S)-1-hydroxybutan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(3-chloro-2-fluorophenylamino)-2-((S)-1-hydroxybutan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((S)-1-hydroxybutan-2-ylamino)-8-(2,3,4-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-2-hydroxypropylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichlorophenylamino)-2-((S)-1-hydroxybutan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((S)-1-hydroxybutan-2-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(3R,4S)-tert-butyl 4-(9-((1s,4r)-4-carbamoylcyclohexyl)-8-(4-chloro-2,6-difluorophenylamino)-9H-purin-2-ylamino)-3-fluoropiperidine-1-carboxylate;

(1s,4s)-4-(8-((4-chloro-2,6-difluorophenyl)amino)-2-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino)-9H-purin-9-yl)cyclohexane-1-carboxamide;

(1s,4s)-4-(8-((2,4-dichloro-6-fluorophenyl)amino)-2-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino)-9H-purin-9-yl)cyclohexane-1-carboxamide;

(R)-tert-butyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4,6-trifluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-tert-butyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-difluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-tert-butyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-dichlorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-tert-butyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2-chloro-4,6-difluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-tert-butyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(4-chloro-2,6-difluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-tert-butyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4,6-trichlorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(1r,4s)-4-(2-((S)-1-hydroxypropan-2-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((S)-1-hydroxypropan-2-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-difluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichlorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,4-dichlorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(5-chloro-2-fluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(3-chloro-2-fluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(2,6-dichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(2-chloro-4,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(4-chloro-2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(4-hydroxytetrahydrofuran-3-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-(4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(4-hydroxytetrahydrofuran-3-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((R)-tetrahydro-2H-pyran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((R)-tetrahydro-2H-pyran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((R)-tetrahydro-2H-pyran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((R)-tetrahydro-2H-pyran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichlorophenylamino)-2-(4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-chloro-2-fluorophenylamino)-2-(4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(2,6-dichloro-4-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(4-chloro-2,3-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(3-chloro-2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(1-acetylpiperidin-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(1-acetylpiperidin-4-ylamino)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((R)-tetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((S)-tetrahydro-2H-pyran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((S)-tetrahydro-2H-pyran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((S)-tetrahydro-2H-pyran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1-(hydroxymethyl)cyclopropyl)methylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1-(hydroxymethyl)cyclopropyl)methylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3R)-3-hydroxycyclopentylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3R)-3-hydroxycyclopentylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-chloro-2,6-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3R)-3-hydroxycyclopentylamino)-8-(2,3,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichlorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3R)-3-hydroxycyclopentylamino)-8-(2,3,4-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((R)-tetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((R)-tetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((R)-tetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(3,3-difluorocyclobutylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(3,3-difluorocyclobutylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(3,3-difluorocyclobutylamino)-8-(2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(3,3-difluorocyclobutylamino)-8-(2,3,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-chloro-2,6-difluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-chloro-2-fluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,5-difluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(4,4-difluorocyclohexylamino)-8-(2,3,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichlorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((S)-tetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((S)-tetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((S)-tetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((S)-tetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((S)-tetrahydro-2H-pyran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((3R,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-difluorophenylamino)-2-((3R,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyanophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,2R)-2-hydroxycyclopentylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-difluorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,2R)-2-hydroxycyclopentylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-chloro-2,6-difluorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,2R)-2-hydroxycyclopentylamino)-8-(2,3,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichlorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(5-chloro-2-fluorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-chloro-2-fluorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,2R)-2-hydroxycyclopentylamino)-8-(2,3,4-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,5-difluorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((1S,2S)-2-hydroxycyclopentylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-difluorophenylamino)-2-((1S,2S)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichlorophenylamino)-2-((1S,2S)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1S,2S)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((1S,2S)-2-hydroxycyclopentylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1S,2S)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1S,2S)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(3-chloro-2,6-difluorophenylamino)-2-((1S,2S)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-difluorophenylamino)-2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((3R,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1r,3r)-3-hydroxycyclobutylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-((1r,3r)-3-hydroxycyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-((1r,3r)-3-hydroxycyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1r,3r)-3-hydroxycyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1r,3r)-3-hydroxycyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1r,3r)-3-hydroxycyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-((1r,3r)-3-hydroxycyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-chloro-2,6-difluorophenylamino)-2-((1r,3r)-3-hydroxycyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-chloro-2,5-difluorophenylamino)-2-((1r,3r)-3-hydroxycyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(4,4-difluorocyclohexylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(4,4-difluorocyclohexylamino)-8-(2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-chloro-2,6-difluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(1-(methylsulfonyl)piperidin-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-(1-(methylsulfonyl)piperidin-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(1-(methylsulfonyl)piperidin-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(1-(methylsulfonyl)piperidin-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(1-(methylsulfonyl)piperidin-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(1-(methylsulfonyl)piperidin-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-(1-(methylsulfonyl)piperidin-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichlorophenylamino)-2-(1-(methylsulfonyl)piperidin-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1r,3r)-3-hydroxycyclobutylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1r,3r)-3-hydroxycyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((3R,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-difluorophenylamino)-2-((3R,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-difluorophenylamino)-2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((3R,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-((1s,3s)-3-hydroxycyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((3S,4R)-4-hydroxytetrahydrofuran-3-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((3S,4R)-4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((3S,4R)-4-hydroxytetrahydrofuran-3-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((3R,4S)-4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((3R,4S)-4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((3R,4S)-4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-((3S,4R)-4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(3-chloro-2,6-difluorophenylamino)-2-((3S,4R)-4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,4-dichlorophenylamino)-2-((3S,4R)-4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(5-chloro-2-fluorophenylamino)-2-((3S,4R)-4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,5-difluorophenylamino)-2-((3R,4S)-4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1s,3s)-3-hydroxycyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1s,3s)-3-hydroxycyclobutylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1s,3s)-3-hydroxycyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-((1S,3S)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-difluorophenylamino)-2-((1S,3S)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichlorophenylamino)-2-((1S,3S)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,3S)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1S,3S)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((1S,3S)-3-hydroxycyclopentylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((1S,3S)-3-hydroxycyclopentylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3S)-3-hydroxycyclopentylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3S)-3-hydroxycyclopentylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-(sec-butylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-(sec-butylamino)-8-(2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-(sec-butylamino)-8-(2,6-dichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-(sec-butylamino)-8-(2-chloro-6-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-(sec-butylamino)-8-(2-chloro-4,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-(sec-butylamino)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-(sec-butylamino)-8-(3-chloro-2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-difluorophenylamino)-2-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3S)-3-hydroxycyclohexylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-difluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3S)-3-hydroxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-chloro-2,6-difluorophenylamino)-2-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-8-(2,3,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-chloro-2,6-difluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,5-difluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3S)-3-hydroxycyclohexylamino)-8-(2,3,4-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-(trifluoromethoxy)phenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclopentylamino)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-(cyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichlorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((1S,3R)-3-hydroxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(3-chloro-2,6-difluorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-cyano-2,3-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,3-difluoro-4-methoxyphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3R)-3-hydroxy-4,4-dimethylcyclohexylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-difluorophenylamino)-2-((1R,3R)-3-hydroxy-4,4-dimethylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-((1R,3R)-3-hydroxy-4,4-dimethylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-((1R,3R)-3-hydroxy-4,4-dimethylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1R,3R)-3-hydroxy-4,4-dimethylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,3R)-3-hydroxy-4,4-dimethylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3R)-3-hydroxy-4,4-dimethylcyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1R,3R)-3-hydroxy-4,4-dimethylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1R,3R)-3-hydroxy-4,4-dimethylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-chloro-2,6-difluorophenylamino)-2-((1R,3R)-3-hydroxy-4,4-dimethylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichlorophenylamino)-2-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclobutylamino)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(cyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-6-fluoro-4-(trifluoromethyl)phenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-((S)-1-hydroxybutan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4,6-trifluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-difluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-dichlorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2-chloro-6-fluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2-chloro-4,6-difluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(4-chloro-2,6-difluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4,6-trichlorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-dichloro-4-fluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(4-chloro-2,3-difluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(3-chloro-2,6-difluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,3,4-trifluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(1s,4s)-4-(2-((1R,3R)-3-hydroxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3R)-3-hydroxycyclohexylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-((1R,3S)-3-hydroxy-3-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1R,3S)-3-hydroxy-3-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,3S)-3-hydroxy-3-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1R,3S)-3-hydroxy-3-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1R,3S)-3-hydroxy-3-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-fluorophenylamino)-2-((1R,3S)-3-hydroxy-3-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((S)-1-hydroxybutan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((S)-1-hydroxybutan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3S)-3-hydroxycycloheptylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-((1R,3S)-3-hydroxycycloheptylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-((1R,3S)-3-hydroxycycloheptylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1R,3S)-3-hydroxycycloheptylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,3S)-3-hydroxycycloheptylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3S)-3-hydroxycycloheptylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-((1R,3S)-3-hydroxycycloheptylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-3-cyanophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((1S,3R)-3-hydroxycycloheptylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((2S,4R)-2-(hydroxymethyl)tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((2S,4R)-2-(hydroxymethyl)tetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-cyano-2,6-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1S,3S)-3-hydroxycycloheptylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((1S,3S)-3-hydroxycycloheptylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(2,2-difluoro-3-hydroxypropylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(2,2-difluoro-3-hydroxypropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(2,2-difluoro-3-hydroxypropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(2,2-difluoro-3-hydroxypropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((1S,3S)-3-hydroxycyclohexylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((1S,3S)-3-hydroxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,5-difluorophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1R,2R)-2-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,2R)-2-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,2R)-2-hydroxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1R,2R)-2-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1R,2R)-2-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((R)-1,1,1-trifluoro-3-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((R)-1,1,1-trifluoro-3-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4r)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4r)-1-methyl-4-(2-(tetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4r)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4r)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4r)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4r)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4r)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1S,4r)-4-(8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1S,4r)-4-(2-((S)-1-hydroxypropan-2-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(3-hydroxy-2,2-dimethylpropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,2S)-2-hydroxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1R,4r)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4r)-4-(2-(cyclopentylamino)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4r)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4r)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4r)-4-(2-(cyclopentylamino)-8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4r)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4r)-4-(2-(cyclopentylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4r)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4r)-4-(2-(cyclopentylamino)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4r)-4-(2-(cyclopentylamino)-8-(2,6-dichloro-4-fluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4r)-4-(2-(cyclopentylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((3S,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((3R,4S)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((3R,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((3S,4S)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((3S,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((3R,4S)-3-methyltetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((3R,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((3S,4S)-3-methyltetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((3S,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((3R,4S)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((3R,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((3S,4S)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((3R,4S)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((3R,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((3S,4S)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((3R,4S)-3-methyltetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((3S,4S)-3-methyltetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((1S,2R)-2-hydroxycyclohexylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1S,2R)-2-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((1S,2R)-2-hydroxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1S,2R)-2-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1S,2R)-2-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1S,2R)-2-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((R)-tetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((1S,2R)-2-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((R)-tetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-1-methyl-4-(2-(tetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-2-((R)-tetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-((R)-tetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-tetrahydrofuran-3-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(1-morpholinopropan-2-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((3S,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((3S,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-(oxepan-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(oxepan-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(oxepan-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(oxepan-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(oxepan-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(oxepan-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-(oxepan-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(oxepan-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-2-(oxepan-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-3,3-difluorocyclopentylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((S)-1-hydroxypropan-2-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(2-((S)-1-hydroxypropan-2-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(oxepan-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclopentylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclopentylamino)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclopentylamino)-8-(2,6-dichloro-4-fluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclopentylamino)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclopentylamino)-8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3S)-3-hydroxycyclohexylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3S)-3-hydroxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(2-chloro-4-cyano-6-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(4-cyano-2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclopentylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-(3,3-difluorocyclobutylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-(3,3-difluorocyclobutylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((S)-3,3-difluorocyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((R)-3,3-difluorocyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((S)-3,3-difluorocyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((R)-3,3-difluorocyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((S)-3,3-difluorocyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((R)-3,3-difluorocyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((S)-3,3-difluorocyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((R)-3,3-difluorocyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((S)-3,3-difluorocyclopentylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((S)-3,3-difluorocyclopentylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-(trifluoromethoxy)phenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-(trifluoromethoxy)phenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclopentylamino)-8-(2,6-dichloro-4-(trifluoromethoxy)phenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclobutylamino)-8-(2,6-dichloro-4-(trifluoromethoxy)phenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclobutylamino)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(cyclobutylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-(cyclobutylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclobutylamino)-8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclobutylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(cyclobutylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclobutylamino)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclobutylamino)-8-(2,6-dichloro-4-fluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclobutylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(cyclobutylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(2-((1S,3S)-3-hydroxycyclohexylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(2-((1S,3S)-3-hydroxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3R)-3-hydroxycyclohexylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3R)-3-hydroxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(2-((1S,3R)-3-hydroxycyclohexylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(2-((1S,3R)-3-hydroxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3R)-3-hydroxycyclopentylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3R)-3-hydroxycyclopentylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(2-((1S,3S)-3-hydroxycyclopentylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1S,3S)-3-hydroxycyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(2-((1S,3S)-3-hydroxycyclopentylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1S,3S)-3-hydroxycyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1S,3S)-3-hydroxycyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1S,3S)-3-hydroxycyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1S,3S)-3-hydroxycyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((1S,3S)-3-hydroxycyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(2-(((1S,2S)-2-hydroxycyclohexyl)methylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(((1S,2S)-2-hydroxycyclohexyl)methylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-(((1S,2S)-2-hydroxycyclohexyl)methylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(((1S,2S)-2-hydroxycyclohexyl)methylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(((1S,2S)-2-hydroxycyclohexyl)methylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(((1S,2S)-2-hydroxycyclohexyl)methylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(((1S,2S)-2-hydroxycyclohexyl)methylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(((1S,2S)-2-hydroxycyclohexyl)methylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(((1S,2R)-2-hydroxycyclohexyl)methylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-(((1S,2R)-2-hydroxycyclohexyl)methylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(((1S,2R)-2-hydroxycyclohexyl)methylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(((1S,2R)-2-hydroxycyclohexyl)methylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(((1S,2R)-2-hydroxycyclohexyl)methylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(((1S,2R)-2-hydroxycyclohexyl)methylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(4-(2,5-dioxopyrrolidin-1-yl)cyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(4-(2,5-dioxopyrrolidin-1-yl)cyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-(4-(1,2,4-oxadiazol-5-yl)cyclohexylamino)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(4-(1,2,4-oxadiazol-5-yl)cyclohexylamino)-8-(2-chloro-4,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(4-(1,2,4-oxadiazol-5-yl)cyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(4-(1,2,4-oxadiazol-5-yl)cyclohexylamino)-8-(2,6-dichloro-4-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(4-(1,2,4-oxadiazol-5-yl)cyclohexylamino)-8-(2-chloro-4-cyano-6-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(4-(1,2,4-oxadiazol-5-yl)cyclohexylamino)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-bromo-2,6-dichlorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-bromo-2,6-dichlorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclopentylamino)-8-(2,3-dichloro-4-cyanophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,3-dichloro-4-cyanophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,3-dichloro-4-cyanophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,3-dichloro-4-cyanophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-((R)-3,3-difluorocyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((R)-3,3-difluorocyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((R)-3,3-difluorocyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-1-(methylsulfonyl)piperidin-3-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((R)-1-(methylsulfonyl)piperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((R)-1-(methylsulfonyl)piperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((R)-1-(methylsulfonyl)piperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((R)-1-(methylsulfonyl)piperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(R)-3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4,6-trichlorophenylamino)-9H-purin-2-ylamino)-N-methylpiperidine-1-carboxamide;

(R)-3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-2-ylamino)-N-methylpiperidine-1-carboxamide;

(R)-3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-2-ylamino)-N-methylpiperidine-1-carboxamide;

(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2-chloro-4-cyano-6-fluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(1s,4s)-4-(2-((R)-1-acetylpiperidin-3-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-1-acetylpiperidin-3-ylamino)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-1-acetylpiperidin-3-ylamino)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-1-acetylpiperidin-3-ylamino)-8-(4-chloro-2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((3S,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((3S,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((3S,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((3S,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-1-methyl-4-(2-((3S,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(3-(methylsulfonyl)cyclobutylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(3-(methylsulfonyl)cyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(3-(methylsulfonyl)cyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-1-ethylpiperidin-3-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((R)-1-ethylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((R)-1-ethylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-2-(3-(methylsulfonyl)cyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(3-(methylsulfonyl)cyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-2-((R)-1-ethylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-1-isopropylpiperidin-3-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((R)-1-isopropylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((R)-1-isopropylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((R)-1-isopropylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((R)-1-phenylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-1-phenylpiperidin-3-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((R)-1-phenylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-((R)-1-phenylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-1-phenylpiperidin-3-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((R)-1-phenylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((R)-1-phenylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((R)-1-phenylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((R)-1-phenylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-1-benzylpiperidin-3-ylamino)-8-(2-chloro-4,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-1-benzylpiperidin-3-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-1-benzylpiperidin-3-ylamino)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-1-benzylpiperidin-3-ylamino)-8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-1-benzylpiperidin-3-ylamino)-8-(4-cyano-2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-1-benzylpiperidin-3-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-1-benzylpiperidin-3-ylamino)-8-(4-chloro-2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-1-benzylpiperidin-3-ylamino)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-1-benzylpiperidin-3-ylamino)-8-(2,6-dichloro-4-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((3S,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((R)-3,3-dimethyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-3,3-dimethyltetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(R)-isopropyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2-chloro-4,6-difluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-isopropyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4,6-trichlorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-isopropyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-isopropyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-isopropyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(4-cyano-2,6-difluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-isopropyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4,6-trifluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-isopropyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(4-chloro-2,6-difluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-isopropyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-isopropyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-dichloro-4-fluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-isopropyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2-chloro-4-cyano-6-fluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(1s,4s)-4-(2-((R)-1-benzylpiperidin-3-ylamino)-8-(2-chloro-4-cyano-6-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(R)-3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2-chloro-4,6-difluorophenylamino)-9H-purin-2-ylamino)-N-phenylpiperidine-1-carboxamide;

(R)-3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4,6-trichlorophenylamino)-9H-purin-2-ylamino)-N-phenylpiperidine-1-carboxamide;

(R)-3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-2-ylamino)-N-phenylpiperidine-1-carboxamide;

(R)-3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4,6-trifluorophenylamino)-9H-purin-2-ylamino)-N-phenylpiperidine-1-carboxamide;

(R)-3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(4-chloro-2,6-difluorophenylamino)-9H-purin-2-ylamino)-N-phenylpiperidine-1-carboxamide;

(R)-3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-2-ylamino)-N-phenylpiperidine-1-carboxamide;

(R)-3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-dichloro-4-fluorophenylamino)-9H-purin-2-ylamino)-N-phenylpiperidine-1-carboxamide;

(R)-3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2-chloro-4-cyano-6-fluorophenylamino)-9H-purin-2-ylamino)-N-phenylpiperidine-1-carboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((R)-3,3-dimethyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((R)-1-tosylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-1-tosylpiperidin-3-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((R)-1-tosylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-((R)-1-tosylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-1-tosylpiperidin-3-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((R)-1-tosylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((R)-1-tosylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((R)-1-tosylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((R)-1-tosylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(R)-3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-9H-purin-2-ylamino)-N-methylpiperidine-1-carboxamide;

(1s,4s)-4-(2-((R)-1-acetylpiperidin-3-ylamino)-8-(2-chloro-4,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-1-acetylpiperidin-3-ylamino)-8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

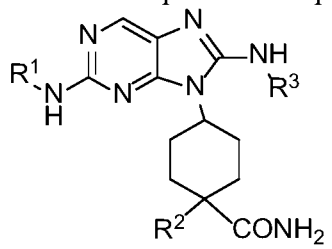
(1s,4s)-4-(2-((R)-1-acetylpiperidin-3-ylamino)-8-(2,6-dichloro-4-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-1-acetylpiperidin-3-ylamino)-8-(2,6-dichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide; or

(1r,4s)-4-(2-(((3R,4S)-3-fluorotetrahydro-2H-pyran-4-yl)amino)-8-((2,4,6-trichlorophenyl)amino)-9H-purin-9-yl)-1-methylcyclohexane-1-carboxamide or a pharmaceutically acceptable salt thereof.

[0011C] Provided herein is use of an Aminopurine Compound of formula (I):



(I)

or a pharmaceutically acceptable salt, tautomer, stereoisomer, or enantiomer thereof, wherein:

R^1 is substituted or unsubstituted non-aromatic heterocyclyl;

R^2 is H or substituted or unsubstituted C_{1-3} alkyl; and

R^3 is phenyl, substituted with one or more halogen, optionally further substituted with one or more substituents independently selected from substituted or unsubstituted C_{1-3} alkyl, CN, and -OR', wherein each R' is independently substituted or unsubstituted C_{1-3} alkyl;

wherein when a C_{1-3} alkyl group is substituted, the C_{1-3} alkyl group is substituted with halogen, alkyl, hydroxyl, alkoxy, alkoxyalkyl, amino, alkylamino, carboxy, nitro, cyano, thiol, thioether, imine, imide, amidine, guanidine, enamine, aminocarbonyl, acylamino, phosphonate, phosphine, thiocarbonyl, sulfinyl, sulfone, sulfonamide, ketone, aldehyde, ester, urea, urethane, oxime, hydroxyl amine, alkoxyamine, aryloxyamine, aralkoxyamine, N-oxide, hydrazine, hydrazide, hydrazone, azide, isocyanate, isothiocyanate, cyanate, thiocyanate, $B(OH)_2$, or O(alkyl)aminocarbonyl;

wherein when a group, other than a C_{1-3}alkyl group, is substituted, the group is substituted with halogen, C_{1-10}alkyl, hydroxyl, C_{1-10}alkoxy, C_{1-10} alkoxy C_{1-10}alkyl, amino, C_{1-10}alkylamino, carboxy, nitro, cyano, thiol, thioether, imine, imide, amidine, guanidine, enamine, aminocarbonyl, acylamino, phosphonate, phosphine, thiocarbonyl, sulfinyl, sulfone, sulfonamide, ketone, aldehyde, ester, urea, urethane, oxime, hydroxyl amine, C_{1-10}alkoxyamine, C_{6-14}aryloxyamine, C_{6-14}arC_{1-10}alkoxyamine, N-oxide, hydrazine, hydrazide, hydrazone, azide, isocyanate, isothiocyanate, cyanate, thiocyanate, oxygen (=O), $B(OH)_2$, O(C_{1-10}alkyl)aminocarbonyl, C_{3-10}cycloalkyl, heterocyclyl, aryl, heteroaryl, C_{6-14}aryloxy, C_{6-14}arC_{1-10}alkyloxy, heterocyclyloxy, or heterocyclyl C_{1-10}alkoxy;

wherein an alkyl group is a saturated straight chain or branched non-cyclic hydrocarbon having from 1 to 10 carbon atoms;

wherein a heterocyclyl group is an aromatic or non-aromatic cycloalkyl having from 1 to 2 rings in which one to four of the ring carbon atoms are independently replaced with a heteroatom selected from the group consisting of O, S and N;

wherein an aryl group is an aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring or multiple condensed rings;

wherein a heteroaryl group is an aromatic cycloalkyl of from 3 to 10 carbon atoms having a single cyclic ring or multiple condensed or bridged rings in which one to four of the ring carbon atoms are independently replaced with a heteroatom selected from the group consisting of O, S and N;

in the manufacture of a medicament for the treatment of a cancer selected from colorectal cancer, colon cancer, renal cell carcinoma, gastric cancer, stomach cancer, hepatocellular carcinoma, liver cancer, lung cancer, pancreatic cancer, leukemia, or multiple myeloma.

[0011D] Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

[0011E] Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present disclosure as it existed before the priority date of each of the appended claims.

[0012] The present embodiments can be understood more fully by reference to the detailed description and examples, which are intended to exemplify non-limiting embodiments.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] **FIG. 1** illustrates Compound 1 Treatment Causes Sustained Inhibition of the ERK Substrate pRSK1 S380 in Colo 205 (mut BRAFV600E) Cells. Colo 205 cells were treated with DMSO or 0.5 μM Compound 1 for indicated time. pRSK1 S380 was measured by MSD assay (Top). DUSP4 and DUSP6 were detected by Western blotting (Bottom).

[0015] **FIGs. 2A-2I** illustrates Compound 1 potently inhibits MAP kinase signaling and downstream target genes in Colo 205. Colon cancer cell line Colo 205 (BRAF V600E) cultures were treated with DMSO or increasing concentrations of Compound 1 for 2, 8 or 24 h. **FIG.2A** illustrates proteins extracted from treated cells and analyzed by Western blot using antibodies against DUSP4, DUSP6, cyclin D1, c-Myc, YAP or β-actin. **FIGs. 2B-2C** illustrate RNAs extracted using Cell-To-CT kit and quantitative PCR was performed with probes specific for DUSP4, DUSP6, SPRY2, c-Myc and cyclin D1. Specific probes for β-actin were used for normalization. **FIGs. 2D-2I** illustrate Compound 1 Treatment modulates MAPK-driven mRNA levels in Colo 205 (mut BRAFV600E) and HT-29 (mut BRAFV600E) Cells. Colo 205 or HT-29 cells were treated with DMSO or 0.3 or 1 μM Compound 1 for 6 h. mRNA was extracted using MagMAX Total RNA Isolation kit and quantitative PCR was performed.

[0016] **FIG. 3A** illustrates Compound 1 effects on WNT/beta-catenin and HIPPO/YAP signaling pathway target genes in Colo 205. Colon cancer cell line Colo 205 (BRAF V600E) cultures were treated with DMSO or increasing concentrations of Compound 1 for 2, 8 or 24 h. RNAs were extracted using Cell-To-CT kit and quantitative PCR was performed with probes specific for Axin2, CTGF, and AREG. Specific probes for β-actin were used for normalization.

FIGs. 3B-3E illustrate Compound 1 treatment regulates YAP-driven mRNA levels in Colo 205 (mut BRAFV600E) and HT-29 (mut BRAFV600E) Cells. Colo 205 or HT-29 cells were treated with DMSO or 0.3 or 1 μM Compound 1 for 6 h. RNAs were extracted using MagMAX Total RNA Isolation kit and quantitative PCR was performed.

[0016] **FIGs. 4A-4B** illustrate Compound 1 down-regulates PD-L1 level in multiple cancer cell lines. FIG. 4A illustrates Western blotting of total PD-L1 in Hop66, Karpas-299, and LOX-IMVI. Cells were cultured in presence or absence of Compound 1 for indicated time before expression levels of PD-L1, DUSP4 and α-tubulin or α-actin were measured by Western blot. FIG. 4B illustrates surface staining of PD-L1 with the Fluorescence-Activated Cell Sorter (FACS). Cells were treated with DMSO or Compound 1 at indicated concentrations for 48 h and cell surface expression of PD-L1 was detected using the FACS analysis with an APC-labeled antibody to PD-L1 (clone 29E.1A3.; BioLegend, San Diego, CA). Geometric mean of PD-L1 positive cells was determined by FlowJo 10 (Treestar, Ashland, OR).

[0017] **FIGs. 5A-5B** illustrate Compound 1-treated KARPAS-299 cells increase production of IL-2 (FIG. 5A) and IFNγ (FIG. 5B) by PBMC-derived T cells stimulated with superantigen (SEB) in vitro. KARPAS-299 cells were treated with DMSO (D) or Compound 1 at indicated concentrations for 48 h. PBMC from healthy donors were treated with or without 20 ng/ml SEB for 48 h. After wash with PBS, the PBMCs were incubated with the cancer cells for 24 h and the supernatants were collected to measure IL-2 and IFNγ using MSD assays. **FIG. 5C** illustrates the effect of Compound 1 treatment on levels of IL-8 were determined in PBMC culture media. PBMCs were isolated from whole blood and cultured in RPMI media plus 10% FBS. PBMCs were plated at $1x10^6$ per milliliter in 10 cm^2 dishes. The PBMCs were treated with 0.1% DMSO or 0.5 μM Compound 1. Treatments were taken down at designated time points. PBMCs were pelleted and used for Western blot analysis and 1 mL of culture media was taken for IL-8 analysis. The IL-8 analysis was performed with a Mesoscale V-Plex Human IL-8 kit according to the manufacturer's instructions. Compound 1 was shown to inhibit IL-8 levels at different time-points.

[0018] **FIG. 6** illustrates antitumor activity of Compound 1 in the LOX-IMVI Xenograft Model. Female SCID mice were inoculated with 1×10^6 LOX-IMVI tumor cells into the right flank. Mice were randomized into treatment groups (n=9/group) at the time of treatment

initiation. Test article treatment started on Day 13 when the tumors were approximately 240 mm^3.

[0019] **FIG. 7** illustrates antitumor activity of Compound 1 in the LOX IMVI Xenograft Model. Female severe-combined immunodeficient (SCID) mice were inoculated with 1 x 10^6 LOX-IMVI tumor cells into the right flank. Mice were randomized into treatment groups (n=10/group) at the time of treatment initiation. Test article treatment started on Day 13 when the tumors were approximately 300 mm^3. Percent inhibition is calculated relative to the vehicle control on the last study day and is in parentheses next to the respective tumor volume for the treatment groups. Dotted line is the tumor volume at the initiation of dosing.

[0020] **FIG. 8** illustrates antitumor activity of Compound 1 in the Colo 205 Xenograft Model. Female SCID mice were inoculated with 2 x 10^6 Colo 205 tumor cells into the right flank. Mice were randomized into treatment groups (n=10/group) at the time of treatment initiation. Test article treatment started on Day 10 when the tumors were approximately 160 mm^3. Percent inhibition is calculated relative to the vehicle control on the last study day and is in parentheses next to the respective tumor volume for the treatment groups. Dotted line is the tumor volume at the initiation of dosing.

[0021] **FIG. 9** illustrates antitumor activity of Compound 1 in the Colo 205 Xenograft Model. Female SCID mice were inoculated with 2 x 10^6 Colo 205 tumor cells into the right flank. Mice were randomized into treatment groups (n=10/group) at the time of treatment initiation. Test article treatment started on Day 10 when the tumors were approximately 130 or 160 mm^3. Percent inhibition is calculated relative to the vehicle control on the last study day and is in parentheses next to the respective tumor volume for the treatment groups. Dotted line is the tumor volume at the initiation of dosing.

[0022] **FIGs. 10A-10B** illustrates antitumor activity of Compound 1 in the PDX146 Xenograft Model. Female NSG mice were inoculated with 25 μg of PDX146 tumor in a cell slurry into the right flank. Mice were randomized into treatment groups (n = 8-10/group) at the time of treatment initiation. Test article treatment started on Day 19 when the tumors were approximately 100 - 110 mm^3. FIG. 10A illustrates tumor volume as a function of time.FIG. 10B illustrates individual tumor volume on the last study day, day 40. Percent inhibition is calculated relative to the vehicle control on the last study day and is in parentheses next to the respective

tumor volume for the treatment groups. Dotted line is the tumor volume at the initiation of dosing. Camp = camptosar.

[0023] **FIG. 11** illustrates tumor Growth Delay with Continuous Compound 1 Treatment in the PDX146 Xenograft Model . Female NSG mice were inoculated with 25 μg of PDX146 tumor in a cell slurry into the right flank. Mice were randomized into treatment groups (n=8-10/group) at the time of treatment initiation. Test article treatment started on Day 16 when the tumors were approximately 100 - 110 mm^3. Black dotted line is the tumor volume at the initiation of dosing and the red dotted line is the tumor volume on Day 43 when the vehicle control group was terminated.

[0024] **FIGs. 12A-12D** illustrates Single doses of Compound 1 inhibit biomarkers in the MAPK, Wnt and Hippo signaling pathways in the PDX146 Xenograft Model**:** Modulation of MAPK, Wnt and Hippo pathways in PDX146 tumors treated with Compound 1. qRT-PCR assays were performed on RNA extracted from PDX146 tumors at the indicated timepoint post-dose. Data are expressed as mean ± SEM. P values are derived from a one-way ANOVA with a Dunnet's post-hoc analysis.

[0025] **FIGs. 13A-13D** illustrate Compound 1 inhibits biomarkers in the MAPK, Wnt and Hippo signaling pathways from PDX146 tumors following a single dose administration**:** Modulation of MAPK, Wnt and Hippo pathways in PDX146 tumors treated with Compound 1. qRT-PCR assays were performed on RNA extracted from PDX146 tumors at the indicated time point post-dose. YAP data is generated from western blot analysis of tumors from the 5 mg/kg treatment group and is expressed as a ratio of YAP to β-actin protein expression. Data are expressed as mean ± SEM. P values are derived from a one-way ANOVA with a Dunnet's post-hoc analysis.

[0026] **FIGs. 14A-14D** illustrate phospho-RSK (pRSK) and phospho-ERK (pERK) protein levels, biomarkers of the MAPK signaling pathway, were modulated by a single dose administration of Compound 1. Western blot (pRSK) or Mesoscale (pERK) assays were performed on protein extracted from PDX146 tumors at the indicated time point post-dose. Phospho-RSK data is expressed as a % of the vehicle control. Phospho-ERK data is expressed as mean ± SEM.

[0027] **FIGs. 15A-15B** illustrate antitumor activity of Compound 1 in the β-catenin mutant SW48 colorectal xenograft model. Female SCID mice were inoculated with 2 x 10^6 SW48 tumor cells into the right flank. Mice were randomized into treatment groups (n=10/group) at the time of treatment initiation. Test article treatment started on Day 10 when the tumors were approximately 110 and 105 mm^3 (FIG. 15A and FIG. 15B, respectively). Black dotted line is the tumor volume at the initiation of dosing. Graph on the left is a dose-response study (graph A). FIG. 15B illustrates a time to progression study where animals were maintained on drug during the course of the study (graph B). Dotted line is the tumor volume on Day 28 when the vehicle control group was terminated.

[0028] **FIG. 16.** illustrates antitumor activity in the orthotopic Hep3B2.1-7 hepatocellular carcinoma xenograft. Female SCID mice were orthotopically inoculated with 2 x 10^6 Hep3B2.1-7 tumor cells per animal. Seven days post-inoculation animals were randomized into treatment groups based on body weight and treatment commenced (Study day 0). Take rate assessment of a satellite group confirmed the presence of tumor in the liver in 100% of the animals. Compound 1 was dosed orally, QD for 21 days. On the day of study termination, tumors were removed and weighed. Individual tumor weights and the mean tumor weight ± SEM of each group are plotted. Percent inhibition is calculated relative to the vehicle control and is above the respective tumor weight for the treatment groups. P values are derived from a one-way ANOVA with a Dunnet's post-hoc analysis. *** = $p<0.001$. Compound 1 showed a statistically signficant reduction in tumor weight compared to vehicle controls.

[0029] **FIG. 17.** illustrates antitumor activity of Compound 1 in the C-Met amplified hepatocellular carcinoma patient-derived xenograft model, LI0612. Female SCID mice were inoculated with hepatocellular carcinoma PDX model LI0612 tumor fragments (2 – 4 mm in diameter) into the right flank. Mice were randomized into treatment groups (n=10/group) at the time of treatment initiation. Test article treatment started on Day 18 when the tumors were approximately 150 mm^3. Tumor growth progressed in the vehicle control and Compound 1 treatment groups over the dosing period. A change in the growth kinetics was noted with Compound 1 administration resulting in significant tumor growth inhibition (TGI) with 30 mg/kg treatment ($p=0.038$, compared to the vehicle control).

[0030] **FIG. 18.** illustrates sensitivity of cell lines having β-catenin mutations to Compound 1 treatment and shows that cell lines with mutated β-catenin are generally more sensitive to Compound 1 treatment.

[0031] **FIGs. 19A-19E.** illustrate cell line sensitivity and resistance to treatment with Compound 1. FIGs 19A-19C show that cell lines containing BRAF and CTNNB1 mutations are more sensitive to treatment with Compound 1 than cell lines with wild type BRAF and CTNNB1. FIG. 19D and FIG. 19E show that cell lines with mutations in RB and the PI3K/PTEN pathway are associated with resistance to Compound 1 treatment in vitro.

[0032] **FIG 20**. illustrates Compound 1 modulates MAPK, β-catenin, and YAP in the BRAF and CTNNB1 mutant cell line SW48.

[0033] **FIGs. 21A-21B.** illustrate Compound 1 modulates target gene expression controlled by MAPK, β-catenin, and YAP in the BRAF and CTNNB1 mutant cell line SW48.

[0034] **FIG. 22.** illustrates that Compound 1 inhibits Axin2 expression in human bronchial epithelial cells. Gene expression was measured at 24 hours.

[0035] **FIGs. 23A-23D.** illustrate that Compound 1 inhibits colony formation of β-catenin mutant cells at a level greater than MEK inhibitors (trametinib) and ERK inhibitors (GDC0994). FIG. 23A shows inhibition of colony formation of SW48 (colo) cells. FIG. 23B shows inhibition of colony formation of HCT-116 (colo) cells. FIG. 23C shows inhibition of colony formation of AGS (gastric) cells. FIG. 23D shows inhibition of colony formation of Hep3B (HCC) cells.

[0036] **FIG. 24** illustrates that AGS cells resistant to the MEK inhibitor trametinib are sensitive to Compound 1 in a colony formation assay.

[0037] **FIG. 25** illustrates TEAD reporter activity in 8xGTIIC-luciferase WI38 VA13 cells treated with Compound 1 and trametinib for 72 hours. Luciferase activity was analyzed using the Bright Glo luciferase assay (Promega). Compound 1 inhibited TEAD reporter activity, with an average IC_{50} of >10 μM in the 24 hour assay and an average IC_{50} of 1.85 μM in the 72 hour assay (cumulative data of three experiments). Viability was not reproducibly affected by Compound 1 across the three assays. Trametinib did not inhibit TEAD reporter activity at 24 or 72 hours.

DETAILED DESCRIPTION

DEFINITIONS

[0038] An "alkyl" group is a saturated, partially saturated, or unsaturated straight chain or branched non-cyclic hydrocarbon having from 1 to 10 carbon atoms, typically from 1 to 8 carbons or, in some embodiments, from 1 to 6, 1 to 4, or 2 to 6 or carbon atoms. Representative alkyl groups include -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl and -n-hexyl; while saturated branched alkyls include -isopropyl, -*sec*-butyl, -isobutyl, -*tert*-butyl, -isopentyl, -neopentyl, *tert*-pentyl, -2-methylpentyl, -3-methylpentyl, -4-methylpentyl, -2,3-dimethylbutyl and the like. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, allyl, $-CH=CH(CH_3)$, $-CH=C(CH_3)_2$, $-C(CH_3)=CH_2$, $-C(CH_3)=CH(CH_3)$, $-C(CH_2CH_3)=CH_2$, $-C\equiv CH$, $-C\equiv C(CH_3)$, $-C\equiv C(CH_2CH_3)$, $-CH_2C\equiv CH$, $-CH_2C\equiv C(CH_3)$ and $-CH_2C\equiv C(CH_2CH_3)$, among others. An alkyl group can be substituted or unsubstituted. When the alkyl groups described herein are said to be "substituted," they may be substituted with any substituent or substituents as those found in the exemplary compounds and embodiments disclosed herein, as well as halogen (chloro, iodo, bromo, or fluoro); alkyl; hydroxyl; alkoxy; alkoxyalkyl; amino; alkylamino; carboxy; nitro; cyano; thiol; thioether; imine; imide; amidine; guanidine; enamine; aminocarbonyl; acylamino; phosphonate; phosphine; thiocarbonyl; sulfinyl; sulfone; sulfonamide; ketone; aldehyde; ester; urea; urethane; oxime; hydroxyl amine; alkoxyamine; aryloxyamine, aralkoxyamine; N-oxide; hydrazine; hydrazide; hydrazone; azide; isocyanate; isothiocyanate; cyanate; thiocyanate; $B(OH)_2$, or O(alkyl)aminocarbonyl.

[0039] A "cycloalkyl" group is a saturated, or partially saturated cyclic alkyl group of from 3 to 10 carbon atoms having a single cyclic ring or multiple condensed or bridged rings which can be optionally substituted with from 1 to 3 alkyl groups. In some embodiments, the cycloalkyl group has 3 to 8 ring members, whereas in other embodiments the number of ring carbon atoms ranges from 3 to 5, 3 to 6, or 3 to 7. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 1-methylcyclopropyl, 2-methylcyclopentyl, 2-methylcyclooctyl, and the like, or multiple or bridged ring structures such as 1-bicyclo[1.1.1]pentyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, adamantyl and the like. Examples of unsaturared cycloalkyl groups include cyclohexenyl, cyclopentenyl, cyclohexadienyl, butadienyl, pentadienyl, hexadienyl, among

others. A cycloalkyl group can be substituted or unsubstituted. Such substituted cycloalkyl groups include, by way of example, cyclohexanol and the like.

[0040] An "aryl" group is an aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (*e.g.*, phenyl) or multiple condensed rings (*e.g.*, naphthyl or anthryl). In some embodiments, aryl groups contain 6-14 carbons, and in others from 6 to 12 or even 6 to 10 carbon atoms in the ring portions of the groups. Particular aryls include phenyl, biphenyl, naphthyl and the like. An aryl group can be substituted or unsubstituted. The phrase "aryl groups" also includes groups containing fused rings, such as fused aromatic-aliphatic ring systems (e.g., indanyl, tetrahydronaphthyl, and the like).

[0041] A "heteroaryl" group is an aryl ring system having one to four heteroatoms as ring atoms in a heteroaromatic ring system, wherein the remainder of the atoms are carbon atoms. In some embodiments, heteroaryl groups contain 3 to 6 ring atoms, and in others from 6 to 9 or even 6 to 10 atoms in the ring portions of the groups. Suitable heteroatoms include oxygen, sulfur and nitrogen. In certain embodiments, the heteroaryl ring system is monocyclic or bicyclic. Non-limiting examples include but are not limited to, groups such as pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, benzisoxazolyl (e.g., benzo[d]isoxazolyl), thiazolyl, pyrolyl, pyridazinyl, pyrimidyl, pyrazinyl, thiophenyl, benzothiophenyl, furanyl, benzofuranyl, indolyl (e.g., indolyl-2-onyl or isoindolin-1-onyl), azaindolyl (pyrrolopyridyl or 1H-pyrrolo[2,3-b]pyridyl), indazolyl, benzimidazolyl (e.g., 1H-benzo[d]imidazolyl), imidazopyridyl (e.g., azabenzimidazolyl or 1H-imidazo[4,5-b]pyridyl), pyrazolopyridyl, triazolopyridyl, benzotriazolyl (e.g., 1H-benzo[d][1,2,3]triazolyl), benzoxazolyl (e.g., benzo[d]oxazolyl), benzothiazolyl, benzothiadiazolyl, isoxazolopyridyl, thianaphthalenyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl (e.g., 3,4-dihydroisoquinolin-1(2H)-onyl), tetrahydroquinolinyl, quinoxalinyl, and quinazolinyl groups.

[0042] A "heterocyclyl" is an aromatic (also referred to as heteroaryl) or non-aromatic cycloalkyl in which one to four of the ring carbon atoms are independently replaced with a heteroatom from the group consisting of O, S and N. In some embodiments, heterocyclyl groups include 3 to10 ring members, whereas other such groups have 3 to 5, 3 to 6, or 3 to 8 ring members. Heterocyclyls can also be bonded to other groups at any ring atom (i.e., at any carbon atom or heteroatom of the heterocyclic ring). A heterocycloalkyl group can be substituted or

unsubstituted. Heterocyclyl groups encompass unsaturated, partially saturated and saturated ring systems, such as, for example, imidazolyl, imidazolinyl and imidazolidinyl (e.g., imidazolidin-4-one or imidazolidin-2,4-dionyl) groups. The phrase heterocyclyl includes fused ring species, including those comprising fused aromatic and non-aromatic groups, such as, for example, 1-and 2-aminotetraline, benzotriazolyl (e.g., 1H-benzo[d][1,2,3]triazolyl), benzimidazolyl (e.g., 1H-benzo[d]imidazolyl), 2,3-dihydrobenzo[l,4]dioxinyl, and benzo[l,3]dioxolyl. The phrase also includes bridged polycyclic ring systems containing a heteroatom such as, but not limited to, quinuclidyl. Representative examples of a heterocyclyl group include, but are not limited to, aziridinyl, azetidinyl, azepanyl, oxetanyl, pyrrolidyl, imidazolidinyl (e.g., imidazolidin-4-onyl or imidazolidin-2,4-dionyl), pyrazolidinyl, thiazolidinyl, tetrahydrothiophenyl, tetrahydrofuranyl, dioxolyl, furanyl, thiophenyl, pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, benzisoxazolyl (e.g., benzo[d]isoxazolyl), thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, piperidyl, piperazinyl (e.g., piperazin-2-onyl), morpholinyl, thiomorpholinyl, tetrahydropyranyl (e.g., tetrahydro-2H-pyranyl), tetrahydrothiopyranyl, oxathianyl, dioxyl, dithianyl, pyranyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, triazinyl, dihydropyridyl, dihydrodithiinyl, dihydrodithionyl, 1,4-dioxaspiro[4.5]decanyl, homopiperazinyl, quinuclidyl, indolyl (e.g., indolyl-2-onyl or isoindolin-1-onyl), indolinyl, isoindolyl, isoindolinyl, azaindolyl (pyrrolopyridyl or 1H-pyrrolo[2,3-b]pyridyl), indazolyl, indolizinyl, benzotriazolyl (e.g. 1H-benzo[d][1,2,3]triazolyl), benzimidazolyl (e.g., 1H-benzo[d]imidazolyl or 1H-benzo[d]imidazol-2(3H)-onyl), benzofuranyl, benzothiophenyl, benzothiazolyl, benzoxadiazolyl, benzoxazinyl, benzodithiinyl, benzoxathiinyl, benzothiazinyl, benzoxazolyl (i.e., benzo[d]oxazolyl), benzothiazolyl, benzothiadiazolyl, benzo[l,3]dioxolyl, pyrazolopyridyl (for example, 1H-pyrazolo[3,4-b]pyridyl, 1H-pyrazolo[4,3-b]pyridyl), imidazopyridyl (e.g., azabenzimidazolyl or 1H-imidazo[4,5-b]pyridyl), triazolopyridyl, isoxazolopyridyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl (e.g., 3,4-dihydroisoquinolin-1(2H)-onyl), quinolizinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalazinyl, naphthyridinyl, pteridinyl, thianaphthalenyl, dihydrobenzothiazinyl, dihydrobenzofuranyl, dihydroindolyl, dihydrobenzodioxinyl, tetrahydroindolyl, tetrahydroindazolyl, tetrahydrobenzimidazolyl, tetrahydrobenzotriazolyl, tetrahydropyrrolopyridyl, tetrahydropyrazolopyridyl, tetrahydroimidazopyridyl, tetrahydrotriazolopyridyl, tetrahydropyrimidin-2(1H)-one and tetrahydroquinolinyl groups.

Representative non-aromatic heterocyclyl groups do not include fused ring species that comprise a fused aromatic group. Examples of non-aromatic heterocyclyl groups include aziridinyl, azetidinyl, azepanyl, pyrrolidyl, imidazolidinyl (e.g., imidazolidin-4-onyl or imidazolidin-2,4-dionyl), pyrazolidinyl, thiazolidinyl, tetrahydrothiophenyl, tetrahydrofuranyl, piperidyl, piperazinyl (e.g., piperazin-2-onyl), morpholinyl, thiomorpholinyl, tetrahydropyranyl (e.g., tetrahydro-2H-pyranyl), tetrahydrothiopyranyl, oxathianyl, dithianyl, 1,4-dioxaspiro[4.5]decanyl, homopiperazinyl, quinuclidyl, or tetrahydropyrimidin-2(1H)-one. Representative substituted heterocyclyl groups may be mono-substituted or substituted more than once, such as, but not limited to, pyridyl or morpholinyl groups, which are 2-, 3-, 4-, 5-, or 6-substituted, or disubstituted with various substituents such as those listed below.

[0043] A "cycloalkylalkyl" group is a radical of the formula: -alkyl-cycloalkyl, wherein alkyl and cycloalkyl are as defined above. Substituted cycloalkylalkyl groups may be substituted at the alkyl, the cycloalkyl, or both the alkyl and the cycloalkyl portions of the group. Representative cycloalkylalkyl groups include but are not limited to methylcyclopropyl, methylcyclobutyl, methylcyclopentyl, methylcyclohexyl, ethylcyclopropyl, ethylcyclobutyl, ethylcyclopentyl, ethylcyclohexyl, propylcyclopentyl, propylcyclohexyl and the like.

[0044] An "aralkyl" group is a radical of the formula: -alkyl-aryl, wherein alkyl and aryl are defined above. Substituted aralkyl groups may be substituted at the alkyl, the aryl, or both the alkyl and the aryl portions of the group. Representative aralkyl groups include but are not limited to benzyl and phenethyl groups and fused (cycloalkylaryl)alkyl groups such as 4-ethyl-indanyl.

[0045] An "heterocyclylalkyl" group is a radical of the formula: -alkyl-heterocyclyl, wherein alkyl and heterocyclyl are defined above. Substituted heterocyclylalkyl groups may be substituted at the alkyl, the heterocyclyl, or both the alkyl and the heterocyclyl portions of the group. Representative heterocylylalkyl groups include but are not limited to 4-ethyl-morpholinyl, 4-propylmorpholinyl, furan-2-yl methyl, furan-3-yl methyl, pyridin-3-yl methyl, tetrahydrofuran-2-yl ethyl, and indol-2-yl propyl.

[0046] A "halogen" is chloro, iodo, bromo, or fluoro.

[0047] A "hydroxyalkyl" group is an alkyl group as described herein substituted with one or more hydroxy groups.

[0048] An "alkoxy" group is -O-(alkyl), wherein alkyl is defined herein.

[0049] An "alkoxyalkyl" group is -(alkyl)-O-(alkyl), wherein alkyl is defined herein.

[0050] An "amine" group is a radical of the formula: $-NH_2$.

[0051] A "hydroxyl amine" group is a radical of the formula: $-N(R^{\#})OH$ or -NHOH, wherein $R^{\#}$ is a substituted or unsubstituted alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl or heterocyclylalkyl group as defined herein.

[0052] An "alkoxyamine" group is a radical of the formula: $-N(R^{\#})O$-alkyl or -NHO-alkyl, wherein $R^{\#}$ and alkyl are as defined herein.

[0053] An "aryloxyamine" group is a radical of the formula: $-N(R^{\#})O$-aryl or -NHO-aryl, wherein $R^{\#}$ and aryl are as defined herein.

[0054] An "aralkoxyamine" group is a radical of the formula: $-N(R^{\#})O$-aralkyl or -NHO-aralkyl, wherein $R^{\#}$ and aralkyl as defined herein.

[0055] An "alkylamine" group is a radical of the formula: -NH-alkyl or $-N(alkyl)_2$, wherein each alkyl is independently as defined herein.

[0056] An "aminocarbonyl" group is a radical of the formula: $-C(=O)N(R^{\#})_2$, $-C(=O)NH(R^{\#})$ or $-C(=O)NH_2$, wherein each $R^{\#}$ is as defined herein.

[0057] An "acylamino" group is a radical of the formula: $-NHC(=O)(R^{\#})$ or $-N(alkyl)C(=O)(R^{\#})$, wherein each alkyl and $R^{\#}$ are independently as defined herein.

[0058] An "O(alkyl)aminocarbonyl" group is a radical of the formula: $-O(alkyl)C(=O)N(R^{\#})_2$, $-O(alkyl)C(=O)NH(R^{\#})$ or $-O(alkyl)C(=O)NH_2$, wherein each $R^{\#}$ and alkyl are independently as defined herein.

[0059] An "N-oxide" group is a radical of the formula: $-N^{+}-O^{-}$.

[0060] A "carboxy" group is a radical of the formula: -C(=O)OH.

[0061] A "ketone" group is a radical of the formula: $-C(=O)(R^{\#})$, wherein $R^{\#}$ is as defined herein.

[0062] An "aldehyde" group is a radical of the formula: -CH(=O).

[0063] An "ester" group is a radical of the formula: $-C(=O)O(R^{\#})$ or $-OC(=O)(R^{\#})$, wherein $R^{\#}$ is as defined herein.

[0064] A "urea" group is a radical of the formula: $-N(alkyl)C(=O)N(R^{\#})_2$, $-N(alkyl)C(=O)NH(R^{\#})$, $-N(alkyl)C(=O)NH_2$, $-NHC(=O)N(R^{\#})_2$, $-NHC(=O)NH(R^{\#})$, or $-NHC(=O)NH_2{}^{\#}$, wherein each alkyl and $R^{\#}$ are independently as defined herein.

[0065] An "imine" group is a radical of the formula: $-N=C(R^{\#})_2$ or $-C(R^{\#})=N(R^{\#})$, wherein each $R^{\#}$ is independently as defined herein.

[0066] An "imide" group is a radical of the formula: $-C(=O)N(R\#)C(=O)(R^{\#})$ or $-N((C=O)(R^{\#}))_2$, wherein each $R^{\#}$ is independently as defined herein.

[0067] A "urethane" group is a radical of the formula: $-OC(=O)N(R^{\#})_2$, $-OC(=O)NH(R^{\#})$, $-N(R^{\#})C(=O)O(R^{\#})$, or $-NHC(=O)O(R^{\#})$, wherein each $R^{\#}$ is independently as defined herein.

[0068] An "amidine" group is a radical of the formula: $-C(=N(R^{\#}))N(R^{\#})_2$, $-C(=N(R^{\#}))NH(R^{\#})$, $-C(=N(R^{\#}))NH_2$, $-C(=NH)N(R^{\#})_2$, $-C(=NH)NH(R^{\#})$, $-C(=NH)NH_2$, $-N=C(R^{\#})N(R^{\#})_2$, $-N=C(R^{\#})NH(R^{\#})$, $-N=C(R^{\#})NH_2$, $-N(R^{\#})C(R^{\#})=N(R^{\#})$, $-NHC(R^{\#})=N(R^{\#})$, $-N(R^{\#})C(R^{\#})=NH$, or $-NHC(R^{\#})=NH$, wherein each $R^{\#}$ is independently as defined herein.

[0069] A "guanidine" group is a radical of the formula: $-N(R^{\#})C(=N(R^{\#}))N(R^{\#})_2$, $-NHC(=N(R^{\#}))N(R^{\#})_2$, $-N(R^{\#})C(=NH)N(R^{\#})_2$, $-N(R^{\#})C(=N(R^{\#}))NH(R^{\#})$, $-N(R^{\#})C(=N(R^{\#}))NH_2$, $-NHC(=NH)N(R^{\#})_2$, $-NHC(=N(R^{\#}))NH(R^{\#})$, $-NHC(=N(R^{\#}))NH_2$, $-NHC(=NH)NH(R^{\#})$, $-NHC(=NH)NH_2$, $-N=C(N(R^{\#})_2)_2$, $-N=C(NH(R^{\#}))_2$, or $-N=C(NH_2)_2$, wherein each $R^{\#}$ is independently as defined herein.

[0070] A "enamine" group is a radical of the formula: $-N(R^{\#})C(R^{\#})=C(R^{\#})_2$, $-NHC(R^{\#})=C(R^{\#})_2$, $-C(N(R^{\#})_2)=C(R^{\#})_2$, $-C(NH(R^{\#}))=C(R^{\#})_2$, $-C(NH_2)=C(R^{\#})_2$, $-C(R^{\#})=C(R^{\#})(N(R^{\#})_2)$, $-C(R^{\#})=C(R^{\#})(NH(R^{\#}))$ or $-C(R^{\#})=C(R^{\#})(NH_2)$, wherein each $R^{\#}$ is independently as defined herein.

[0071] An "oxime" group is a radical of the formula: $-C(=NO(R^{\#}))(R^{\#})$, $-C(=NOH)(R^{\#})$, $-CH(=NO(R^{\#}))$, or $-CH(=NOH)$, wherein each $R^{\#}$ is independently as defined herein.

[0072] A "hydrazide" group is a radical of the formula: $-C(=O)N(R^{\#})N(R^{\#})_2$, $-C(=O)NHN(R^{\#})_2$, $-C(=O)N(R^{\#})NH(R^{\#})$, $-C(=O)N(R^{\#})NH_2$, $-C(=O)NHNH(R^{\#})_2$, or $-C(=O)NHNH_2$, wherein each $R^{\#}$ is independently as defined herein.

[0073] A "hydrazine" group is a radical of the formula: $-N(R^{\#})N(R^{\#})_2$, $-NHN(R^{\#})_2$, $-N(R^{\#})NH(R^{\#})$, $-N(R^{\#})NH_2$, $-NHNH(R^{\#})_2$, or $-NHNH_2$, wherein each $R^{\#}$ is independently as defined herein.

[0074] A "hydrazone" group is a radical of the formula: $-C(=N-N(R^{\#})_2)(R^{\#})_2$, $-C(=N-NH(R^{\#}))(R^{\#})_2$, $-C(=N-NH_2)(R^{\#})_2$, $-N(R^{\#})(N=C(R^{\#})_2)$, or $-NH(N=C(R^{\#})_2)$, wherein each $R^{\#}$ is independently as defined herein.

[0075] An "azide" group is a radical of the formula: $-N_3$.

[0076] An "isocyanate" group is a radical of the formula: -N=C=O.

[0077] An "isothiocyanate" group is a radical of the formula: -N=C=S.

[0078] A "cyanate" group is a radical of the formula: -OCN.

[0079] A "thiocyanate" group is a radical of the formula: -SCN.

[0080] A "thioether" group is a radical of the formula; $-S(R^{\#})$, wherein $R^{\#}$ is as defined herein.

[0081] A "thiocarbonyl" group is a radical of the formula: $-C(=S)(R^{\#})$, wherein $R^{\#}$ is as defined herein.

[0082] A "sulfinyl" group is a radical of the formula: $-S(=O)(R^{\#})$, wherein $R^{\#}$ is as defined herein.

[0083] A "sulfone" group is a radical of the formula: $-S(=O)_2(R^{\#})$, wherein $R^{\#}$ is as defined herein.

[0084] A "sulfonylamino" group is a radical of the formula: $-NHSO_2(R^{\#})$ or $-N(alkyl)SO_2(R^{\#})$, wherein each alkyl and $R^{\#}$ are defined herein.

[0085] A "sulfonamide" group is a radical of the formula: $-S(=O)_2N(R^{\#})_2$, or $-S(=O)_2NH(R^{\#})$, or $-S(=O)_2NH_2$, wherein each $R^{\#}$ is independently as defined herein.

[0086] A "phosphonate" group is a radical of the formula: $-P(=O)(O(R^{\#}))_2$, $-P(=O)(OH)_2$, $-OP(=O)(O(R^{\#}))(R^{\#})$, or $-OP(=O)(OH)(R^{\#})$, wherein each $R^{\#}$ is independently as defined herein.

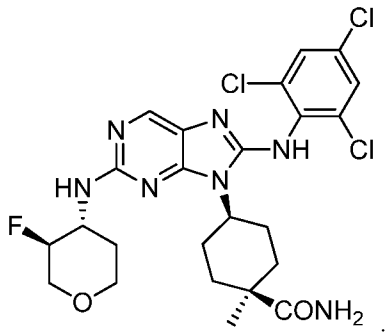
[0087] A "phosphine" group is a radical of the formula: $-P(R^{\#})_2$, wherein each $R^{\#}$ is independently as defined herein.

[0088] When the groups described herein, with the exception of alkyl group, are said to be "substituted," they may be substituted with any appropriate substituent or substituents. Illustrative examples of substituents are those found in the exemplary compounds and embodiments disclosed herein, as well as halogen (chloro, iodo, bromo, or fluoro); alkyl; hydroxyl; alkoxy; alkoxyalkyl; amino; alkylamino; carboxy; nitro; cyano; thiol; thioether; imine; imide; amidine; guanidine; enamine; aminocarbonyl; acylamino; phosphonate; phosphine; thiocarbonyl; sulfinyl; sulfone; sulfonamide; ketone; aldehyde; ester; urea; urethane; oxime; hydroxyl amine; alkoxyamine; aryloxyamine, aralkoxyamine; N-oxide; hydrazine; hydrazide; hydrazone; azide; isocyanate; isothiocyanate; cyanate; thiocyanate; oxygen (=O); $B(OH)_2$, O(alkyl)aminocarbonyl; cycloalkyl, which may be monocyclic or fused or non-fused polycyclic (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl), or a heterocyclyl, which may be monocyclic or fused or non-fused polycyclic (*e.g.*, pyrrolidyl, piperidyl, piperazinyl, morpholinyl, or thiazinyl); monocyclic or fused or non-fused polycyclic aryl or heteroaryl (*e.g.*, phenyl, naphthyl, pyrrolyl, indolyl, furanyl, thiophenyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, tetrazolyl, pyrazolyl, pyridinyl, quinolinyl, isoquinolinyl, acridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, benzimidazolyl, benzothiophenyl, or benzofuranyl) aryloxy; aralkyloxy; heterocyclyloxy; and heterocyclyl alkoxy.

[0089] As used herein, the term "Aminopurine Compound" refers to compounds of formula (I) as well as to further embodiments provided herein. In one embodiment, an "Aminopurine Compound" is a compound set forth in Table 1. In one embodiment, an "Aminopurine Compound" is a compound having the formula of Compound 1. The term "Aminopurine Compound" includes pharmaceutically acceptable salts, tautomers, isotopologues, and stereoisomers of the compounds provided herein.

[0090] "Compound 1" refers to a compound (including pharmaceutically acceptable salts, tautomers, isotopologues, and stereoisomers thereof) having the name: cis-4-[2-{[(3S,4R)-3-fluorooxan-4-yl]amino}-8-(2,4,6-trichloroanilino)-9H-purin-9-yl]-1-methylcyclohexane-1-

carboxamide and having an alternative name of; (1s,4s)-4-(2-(((3S,4R)-3-fluorotetrahydro-2H-pyran-4-yl)amino)-8-((2,4,6-trichlorophenyl)amino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide; and as provided below:



[0091] As used herein, the term "pharmaceutically acceptable salt(s)" refers to a salt prepared from a pharmaceutically acceptable non-toxic acid or base including an inorganic acid and base and an organic acid and base. Suitable pharmaceutically acceptable base addition salts of the compounds of formula (I) include, but are not limited to metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from lysine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methyl-glucamine) and procaine. Suitable non-toxic acids include, but are not limited to, inorganic and organic acids such as acetic, alginic, anthranilic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, formic, fumaric, furoic, galacturonic, gluconic, glucuronic, glutamic, glycolic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phenylacetic, phosphoric, propionic, salicylic, stearic, succinic, sulfanilic, sulfuric, tartaric acid, and p-toluenesulfonic acid. Specific non-toxic acids include hydrochloric, hydrobromic, maleic, phosphoric, sulfuric, and methanesulfonic acids. Examples of specific salts thus include hydrochloride and mesylate salts. Others are well-known in the art, see for example, *Remington's Pharmaceutical Sciences*, 18th eds., Mack Publishing, Easton PA (1990) or *Remington: The Science and Practice of Pharmacy*, 19th eds., Mack Publishing, Easton PA (1995).

[0092] As used herein and unless otherwise indicated, the term "stereoisomer" or "stereomerically pure" means one stereoisomer of an Aminopurine Compound that is substantially free of other stereoisomers of that compound. For example, a stereomerically pure compound having one chiral center will be substantially free of the opposite enantiomer of the

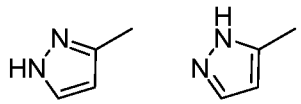
compound. A stereomerically pure compound having two chiral centers will be substantially free of other diastereomers of the compound. A typical stereomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and less than about 20% by weight of other stereoisomers of the compound, greater than about 90% by weight of one stereoisomer of the compound and less than about 10% by weight of the other stereoisomers of the compound, greater than about 95% by weight of one stereoisomer of the compound and less than about 5% by weight of the other stereoisomers of the compound, or greater than about 97% by weight of one stereoisomer of the compound and less than about 3% by weight of the other stereoisomers of the compound. The Aminopurine Compounds can have chiral centers and can occur as racemates, individual enantiomers or diastereomers, and mixtures thereof. All such isomeric forms are included within the embodiments disclosed herein, including mixtures thereof.

[0093] The use of stereomerically pure forms of such Aminopurine Compounds, as well as the use of mixtures of those forms, is encompassed by the embodiments disclosed herein. For example, mixtures comprising equal or unequal amounts of the enantiomers of a particular Aminopurine Compound may be used in methods and compositions disclosed herein. These isomers may be asymmetrically synthesized or resolved using standard techniques such as chiral columns or chiral resolving agents. *See, e.g.*, Jacques, J., *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley-Interscience, New York, 1981); Wilen, S. H., *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, E. L., *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, S. H., *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN, 1972).

[0094] It should also be noted the Aminopurine Compounds can include E and Z isomers, or a mixture thereof, and cis and trans isomers or a mixture thereof. In certain embodiments, the Aminopurine Compounds are isolated as either the E or Z isomer. In other embodiments, the Aminopurine Compounds are a mixture of the E and Z isomers.

[0095] "Tautomers" refers to isomeric forms of a compound that are in equilibrium with each other. The concentrations of the isomeric forms will depend on the environment the compound is found in and may be different depending upon, for example, whether the compound

is a solid or is in an organic or aqueous solution. For example, in aqueous solution, pyrazoles may exhibit the following isomeric forms, which are referred to as tautomers of each other:



[0096] As readily understood by one skilled in the art, a wide variety of functional groups and other structures may exhibit tautomerism and all tautomers of compounds of formula (I) are within the scope of the present invention.

[0097] It should also be noted the Aminopurine Compounds can contain unnatural proportions of atomic isotopes at one or more of the atoms. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I), sulfur-35 (^{35}S), or carbon-14 (^{14}C), or may be isotopically enriched, such as with deuterium (^{2}H), carbon-13 (^{13}C), or nitrogen-15 (^{15}N). As used herein, an "isotopologue" is an isotopically enriched compound. The term "isotopically enriched" refers to an atom having an isotopic composition other than the natural isotopic composition of that atom. "Isotopically enriched" may also refer to a compound containing at least one atom having an isotopic composition other than the natural isotopic composition of that atom. The term "isotopic composition" refers to the amount of each isotope present for a given atom. Radiolabeled and isotopically enriched compounds are useful as therapeutic agents, e.g., cancer and inflammation therapeutic agents, research reagents, e.g., binding assay reagents, and diagnostic agents, e.g., in vivo imaging agents. All isotopic variations of the Aminopurine Compounds as described herein, whether radioactive or not, are intended to be encompassed within the scope of the embodiments provided herein. In some embodiments, there are provided isotopologues of the Aminopurine Compounds, for example, the isotopologues are deuterium, carbon-13, or nitrogen-15 enriched Aminopurine Compounds.

[0098] "Treating" as used herein, means an alleviation, in whole or in part, of a disorder, disease or condition, or one or more of the symptoms associated with a disorder, disease, or condition, or slowing or halting of further progression or worsening of those symptoms, or alleviating or eradicating the cause(s) of the disorder, disease, or condition itself. In one embodiment, the disorder is a cancer, in particular, a solid tumor or hematological cancer. In some embodiments, "treating" means an alleviation, in whole or in part, of a cancer, or

symptoms associated with a cancer, in particular, a solid tumor or hematological cancer, or a slowing, or halting of further progression or worsening of those symptoms.

[0099] "Preventing" as used herein, means a method of delaying and/or precluding the onset, recurrence or spread, in whole or in part, of a cancer, in particular, a solid tumor or hematological cancer; barring a subject from acquiring a cancer, in particular, a solid tumor or hematological cancer; or reducing a subject's risk of acquiring a cancer, in particular, a solid tumor or hematological cancer.

[00100] The term "effective amount" in connection with an Aminopurine Compound means an amount capable of treating or preventing a cancer, in particular, a solid tumor or hematological cancer, or symptoms thereof, as disclosed herein. The effective amount of Aminopurine Compound, for example in a pharmaceutical composition, may be at a level that will exercise the desired effect; for example, about 0.005 mg/kg of a subject's body weight to about 100 mg/kg of a patient's body weight in unit dosage for parenteral administration. As will be apparent to those skilled in the art, it is to be expected that the effective amount of an Aminopurine Compound disclosed herein may vary depending on the severity of the indication being treated.

[00101] The terms "patient" and "subject" as used herein include an animal, including, but not limited to, an animal such a cow, monkey, horse, sheep, pig, chicken, turkey, quail, cat, dog, mouse, rat, rabbit or guinea pig, in one embodiment a mammal, in another embodiment a human. In one embodiment, a subject is a human having or at risk for having cancer, in particular, a solid tumor or hematological cancer, or symptoms thereof. In one embodiment, a patient is a human having histologically or cytologically-confirmed solid tumor or hematological cancer, including subjects who have progressed on (or not been able to tolerate) standard anticancer therapy or for whom no standard anticancer therapy exists.

[00102] As used herein, and unless otherwise specified, the terms "cancer" refers to or describes the physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer include solid tumors and hematological cancer. In some embodiments, the cancer is a primary cancer, in others, the cancer is metastasized.

[00103] As used herein "solid tumors" includes, but is not limited to, bladder cancer (including, but not limited to, superficial bladder cancer), breast cancer (including, but not

limited to, luminal B type, ER+, PR+ and Her2+ breast cancer), central nervous system cancer (including, but not limited to, glioblastoma multiforme (GBM), glioma, medulloblastoma, and astrocytoma), colorectal cancer, gastrointestinal cancer (including, but not limited to, stomach cancer, esophageal cancer, and rectum cancer), endocrine cancer (including, but not limited to, thyroid cancer, and adrenal gland cancer), eye cancer (including, but not limited to, retinoblastoma), female genitourinary cancer (including, but not limited to, cancer of the placenta, uterus, vulva, ovary, cervix), head and neck cancer (including, but not limited to, cancer of the pharynx, esophageal, and tongue), liver cancer, lung cancer (including, but not limited to, non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), mucoepidermoid, bronchogenic, squamous cell carcinoma (SQCC), and analplastic/NSCLC), skin cancer (including, but not limited to, melanoma, and SQCC), soft tissue cancer (including but not limited to, sarcoma, Ewing's sarcoma, and rhabdomyosarcoma), bone cancer (including, but not limited to, sarcoma, Ewing's sarcoma, and osteosarcoma), squamous cell cancer (including, but not limited to, lung, esophageal, cervical, and head and neck cancer), pancreas cancer, kidney cancer (including, but not limited to, renal Wilm's tumor and renal cell carcinoma), and prostate cancer. In one embodiment, the solid tumor is not triple negative breast cancer (TNBC). In some embodiments, the solid tumor is breast cancer, colon cancer, lung cancer or bladder cancer. In one such embodiment, the solid tumor is superficial bladder cancer. In another, the solid tumor is lung squamous cell carcinoma. In yet another embodiment, the solid tumor is luminal B type breast cancer.

[00104] As used herein "hematological cancer" includes, but is not limited to, leukemia (including, but not limited to, acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML), acute T-cell leukemia, B cell precursor leukemia, acute promyelocytic leukemia (APML), plasma cell leukemia, myelomonoblastic/T-ALL, B myelomonocytic leukemia, erythroleukemia, and acute myeloid leukemia (AML)), lymphoma (including but not limited to Hodgkin's lymphoma, non-Hodgkin's lymphoma (NHL), Burkitt's lymphoma (BL), B cell lymphoma, lymphoblastic lymphoma, follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), large cell immunoblastic lymphoma), and multiple myeloma.

[00105] In the context of a cancer, inhibition may be assessed by inhibition of disease progression, inhibition of tumor growth, reduction of primary tumor, relief of tumor-related

symptoms, inhibition of tumor secreted factors (including tumor secreted hormones, such as those that contribute to carcinoid syndrome), delayed appearance of primary or secondary tumors, slowed development of primary or secondary tumors, decreased occurrence of primary or secondary tumors, slowed or decreased severity of secondary effects of disease, arrested tumor growth and regression of tumors, increased Time To Progression (TTP), increased Progression Free Survival (PFS), increased Overall Survival (OS), among others. OS as used herein means the time from treatment onset until death from any cause. TTP as used herein means the time from treatment onset until tumor progression; TTP does not include deaths. As used herein, PFS means the time from treatment onset until tumor progression or death. In one embodiment, PFS rates will be computed using the Kaplan-Meier estimates. In the extreme, complete inhibition, is referred to herein as prevention or chemoprevention. In this context, the term "prevention" includes either preventing the onset of clinically evident cancer altogether or preventing the onset of a preclinically evident stage of a cancer. Also intended to be encompassed by this definition is the prevention of transformation into malignant cells or to arrest or reverse the progression of premalignant cells to malignant cells. This includes prophylactic treatment of those at risk of developing a cancer.

[00106] In certain embodiments, the treatment of lymphoma may be assessed by the International Workshop Criteria (IWC) for non-Hodgkin lymphoma (NHL) (*see* Cheson BD, Pfistner B, Juweid, ME, et. al. Revised Response Criteria for Malignant Lymphoma. J. Clin. Oncol: 2007: (25) 579-586), using the response and endpoint definitions shown below:

Response	Definition	Nodal Masses	Spleen, liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative

Response	Definition	Nodal Masses	Spleen, liver	Bone Marrow
PR	Regression of measurable disease and no new sites	≥50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
PD or relapsed disease	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) ≥1.5 cm in any axis, ≥50% increase in SPD of more than one node, or ≥50% increase in longest diameter of a previously identified node ≥1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	≥50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

[00107] Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

End point	Patients	Definition	Measured from
Primary			
Overall survival	All	Death as a result of any cause	Entry onto study
Progression-free survival	All	Disease progression or death as a result of any cause	Entry onto study
Secondary			
Event-free survival	All	Failure of treatment or death as result of any cause	Entry onto study
Time to progression	All	Time to progression or death as a result of lymphoma	Entry onto study
Disease-free survival	In CR	Time to relapse or death as a result of lymphoma or acute toxicity of treatment	Documentation of response
Response duration	In CR or PR	Time to relapse or progression	Documentation of response
Lymphoma-specific survival	All	Time to death as a result of lymphoma	Entry onto study
Time to next treatment	All	Time to new treatment	End of primary treatment

Abbreviations: CR: complete remission; PR: partial remission.

[00108] In one embodiment, the end point for lymphoma is evidence of clinical benefit. Clinical benefit may reflect improvement in quality of life, or reduction in patient symptoms, transfusion requirements, frequent infections, or other parameters. Time to reappearance or progression of lymphoma-related symptoms can also be used in this end point.

[00109] In certain embodiments, the treatment of lymphoma may be assessed by the International Workshop Criteria (IWC) for non-Hodgkin lymphoma (NHL) (*see* Cheson BD, Pfistner B, Juweid, ME, et. al. Revised Response Criteria for Malignant Lymphoma. J. Clin. Oncol: 2007: (25) 579-586), using the response and endpoint definitions shown below:

Response	Definition	Nodal Masses	Spleen, liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
PD or relapsed disease	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) ≥1.5 cm in any axis, ≥50% increase in SPD of more than one node, or ≥50% increase in longest diameter of a previously identifed node ≥1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	≥50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

[00110] Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

End point	Patients	Definition	Measured from
Primary			
Overall survival	All	Death as a result of any cause	Entry onto study
Progression-free survival	All	Disease progression or death as a result of any cause	Entry onto study
Secondary			
Event-free survival	All	Failure of treatment or death as result of any cause	Entry onto study
Time to progression	All	Time to progression or death as a result of lymphoma	Entry onto study
Disease-free survival	In CR	Time to relapse or death as a result of lymphoma or acute toxicity of treatment	Documentation of response
Response duration	In CR or PR	Time to relapse or progression	Documentation of response
Lymphoma-specific survival	All	Time to death as a result of lymphoma	Entry onto study
Time to next treatment	All	Time to new treatment	End of primary treatment

Abbreviations: CR: complete remission; PR: partial remission.

[00111] In one embodiment, the end point for lymphoma is evidence of clinical benefit. Clinical benefit may reflect improvement in quality of life, or reduction in patient symptoms, transfusion requirements, frequent infections, or other parameters. Time to reappearance or progression of lymphoma-related symptoms can also be used in this end point.

[00112] In certain embodiments, the treatment of CLL may be assessed by the International Workshop Guidelines for CLL (*see* Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood, 2008; (111) 12: 5446-5456) using the response and endpoint definitions shown therein and in particular:

Parameter	CR	PR	PD
Group A			
Lymphadenopathy†	None > 1.5 cm	Decrease ≥ 50%	Increase ≥ 50%
Hepatomegaly	None	Decrease ≥ 50%	Increase ≥ 50%
Splenomegaly	None	Decrease ≥ 50%	Increase ≥ 50%
Blood lymphocytes	< 4000/μL	Decrease ≥ 50% from baseline	Increase ≥ 50% over baseline
Marrow‡	Normocellular, < 30% lymphocytes, no B-lymphoid nodules. Hypocellular marrow defines CRi (5.1.6).	50% reduction in marrow infiltrate, or B-lymphoid nodules	
Group B			
Platelet count	> 100 000/μL	> 100 000/μL or increase ≥ 50% over baseline	Decrease of ≥ 50% from baseline secondary to CLL
Hemoglobin	> 11.0 g/dL	> 11 g/dL or increase ≥ 50% over baseline	Decrease of > 2 g/dL from baseline secondary to CLL
Neutrophils‡	> 1500/μL	> 1500/μL or > 50% improvement over baseline	

[00113] Group A criteria define the tumor load; Group B criteria define the function of the hematopoietic system (or marrow). CR (complete remission): all of the criteria have to be met, and patients have to lack disease-related constitutional symptoms; PR (partial remission): at least two of the criteria of group A plus one of the criteria of group B have to be met; SD is absence of progressive disease (PD) and failure to achieve at least a PR; PD: at least one of the above criteria of group A or group B has to be met. Sum of the products of multiple lymph nodes (as evaluated by CT scans in clinical trials, or by physical examination in general practice). These parameters are irrelevant for some response categories.

[00114] In certain embodiments, the treatment of multiple myeloma may be assessed by the International Uniform Response Criteria for Multiple Myeloma (IURC) (*see* Durie BGM, Harousseau J-L, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia, 2006; (10) 10: 1-7), using the response and endpoint definitions shown below:

Response Subcategory	Response Criteria[a]
sCR	CR as defined below plus Normal FLC ratio and Absence of clonal cells in bone marrow[b] by immunohistochemistry or immunofluorescence[c]
CR	Negative immunofixation on the serum and urine and Disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow[b]
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level <100mg per 24 h
PR	≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by≥90% or to <200mg per 24 h If the serum and urine M-protein are unmeasurable,[d] a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30% In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required
SD (not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates)	Not meeting criteria for CR, VGPR, PR or progressive disease

[00115] Abbreviations: CR, complete response; FLC, free light chain; PR, partial response; SD, stable disease; sCR, stringent complete response; VGPR, very good partial response; [a]All response categories require two consecutive assessments made at anytime before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements; [b]Confirmation with repeat bone marrow biopsy not needed; [c]Presence/absence of clonal cells is based upon the κ/λ ratio. An abnormal κ/λ ratio by

immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of >4:1 or <1:2.[d]Measurable disease defined by at least one of the following measurements: Bone marrow plasma cells ≥30%; Serum M-protein ≥1 g/dl (≥10 gm/l)[10 g/l]; Urine M-protein ≥200 mg/24 h; Serum FLC assay: Involved FLC level ≥10 mg/dl (≥100 mg/l); provided serum FLC ratio is abnormal.

[00116] In certain embodiments, the treatment of a cancer may be assessed by Response Evaluation Criteria in Solid Tumors (RECIST 1.1) (*see* Thereasse P., et al. New Guidelines to Evaluate the Response to Treatment in Solid Tumors. J. of the National Cancer Institute; 2000; (92) 205-216 and Eisenhauer E.A., Therasse P., Bogaerts J., et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European J. Cancer; 2009; (45) 228–247). Overall responses for all possible combinations of tumor responses in target and non-target lesions with our without the appearance of new lesions are as follows:

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; PR = partial response; SD = stable disease; and PD = progressive disease.

[00117] With respect to the evaluation of target lesions, complete response (CR) is the disappearance of all target lesions, partial response (PR) is at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter, progressive disease (PD) is at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions and stable disease (SD) is neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started.

[00118] With respect to the evaluation of non-target lesions, complete response (CR) is the disappearance of all non-target lesions and normalization of tumor marker level; incomplete response/stable disease (SD) is the persistence of one or more non-target lesion(s) and/or the maintenance of tumor marker level above the normal limits, and progressive disease (PD) is the appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

[00119] The procedures, conventions, and definitions described below provide guidance for implementing the recommendations from the Response Assessment for Neuro-Oncology (RANO) Working Group regarding response criteria for high-grade gliomas (Wen P., Macdonald, DR., Reardon, DA., et al. Updated response assessment criteria for high-grade gliomas: Response assessment in neuro-oncology working group. J Clin Oncol 2010; 28: 1963-1972). Primary modifications to the RANO criteria for Criteria for Time Point Responses (TPR) can include the addition of operational conventions for defining changes in glucocorticoid dose, and the removal of subjects' clinical deterioration component to focus on objective radiologic assessments. The baseline MRI scan is defined as the assessment performed at the end of the post-surgery rest period, prior to initiating or re-initiating compound treatment. The baseline MRI is used as the reference for assessing complete response (CR) and partial response (PR). Whereas, the smallest SPD (sum of the products of perpendicular diameters) obtained either at baseline or at subsequent assessments will be designated the nadir assessment and utilized as the reference for determining progression. For the 5 days preceding any protocol-defined MRI scan, subjects receive either no glucocorticoids or are on a stable dose of glucocorticoids. A stable dose is defined as the same daily dose for the 5 consecutive days preceding the MRI scan. If the prescribed glucocorticoid dose is changed in the 5 days before the baseline scan, a new baseline scan is required with glucocorticoid use meeting the criteria described above. The following definitions will be used.

[00120] Measurable Lesions: Measurable lesions are contrast-enhancing lesions that can be measured bi-dimensionally. A measurement is made of the maximal enhancing tumor diameter (also known as the longest diameter, LD). The greatest perpendicular diameter is measured on the same image. The cross hairs of bi-dimensional measurements should cross and the product of these diameters will be calculated.

[00121] Minimal Diameter: T1-weighted image in which the sections are 5 mm with 1 mm skip. The minimal LD of a measurable lesion is set as 5 mm by 5 mm. Larger diameters may be required for inclusion and/or designation as target lesions. After baseline, target lesions that become smaller than the minimum requirement for measurement or become no longer amenable to bi-dimensional measurement will be recorded at the default value of 5 mm for each diameter below 5 mm. Lesions that disappear will be recorded as 0 mm by 0 mm.

[00122] Multicentric Lesions: Lesions that are considered multicentric (as opposed to continuous) are lesions where there is normal intervening brain tissue between the two (or more) lesions. For multicentric lesions that are discrete foci of enhancement, the approach is to separately measure each enhancing lesion that meets the inclusion criteria. If there is no normal brain tissue between two (or more) lesions, they will be considered the same lesion.

[00123] Nonmeasurable Lesions: All lesions that do not meet the criteria for measurable disease as defined above will be considered non-measurable lesions, as well as all nonenhancing and other truly nonmeasurable lesions. Nonmeasurable lesions include foci of enhancement that are less than the specified smallest diameter (i.e., less than 5 mm by 5 mm), nonenhancing lesions (e.g., as seen on T1-weighted post-contrast, T2-weighted, or fluid-attenuated inversion recovery (FLAIR) images), hemorrhagic or predominantly cystic or necrotic lesions, and leptomeningeal tumor. Hemorrhagic lesions often have intrinsic T1-weighted hyperintensity that could be misinterpreted as enhancing tumor, and for this reason, the pre-contrast T1-weighted image may be examined to exclude baseline or interval sub-acute hemorrhage.

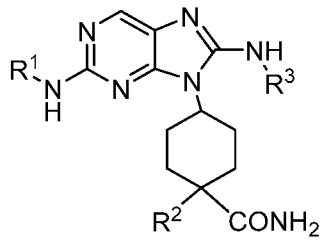
[00124] At baseline, lesions will be classified as follows: Target lesions: Up to 5 measurable lesions can be selected as target lesions with each measuring at least 10 mm by 5 mm, representative of the subject's disease; Non-target lesions: All other lesions, including all nonmeasurable lesions (including mass effects and T2/FLAIR findings) and any measurable lesion not selected as a target lesion. At baseline, target lesions are to be measured as described in the definition for measurable lesions and the SPD of all target lesions is to be determined. The presence of all other lesions is to be documented. At all post-treatment evaluations, the baseline classification of lesions as target and non-target lesions will be maintained and lesions will be documented and described in a consistent fashion over time (*e.g.*, recorded in the same order on source documents and eCRFs). All measurable and nonmeasurable lesions must be assessed

using the same technique as at baseline (e.g., subjects should be imaged on the same MRI scanner or at least with the same magnet strength) for the duration of the study to reduce difficulties in interpreting changes. At each evaluation, target lesions will be measured and the SPD calculated. Non-target lesions will be assessed qualitatively and new lesions, if any, will be documented separately. At each evaluation, a time point response will be determined for target lesions, non-target lesions, and new lesion. Tumor progression can be established even if only a subset of lesions is assessed. However, unless progression is observed, objective status (stable disease, PR or CR) can only be determined when all lesions are assessed.

[00125] Confirmation assessments for overall time point responses of CR and PR will be performed at the next scheduled assessment, but confirmation may not occur if scans have an interval of < 28 days. Best response, incorporating confirmation requirements, will be derived from the series of time points.

AMINOPURINE COMPOUNDS

[00126] Provided herein are compounds having the following formula (I):



(I)

and pharmaceutically acceptable salts, tautomers, stereoisomers, enantiomers, and isotopologues thereof,

wherein:

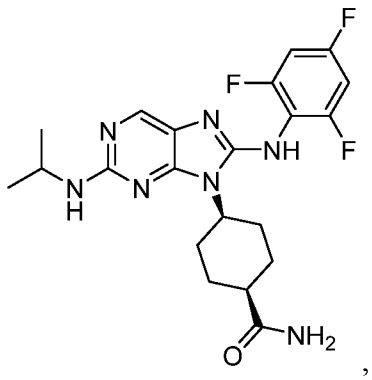
R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, or substituted or unsubstituted non-aromatic heterocyclyl;

R^2 is H or substituted or unsubstituted C_{1-3} alkyl; and

R^3 is phenyl, substituted with one or more halogen, optionally further substituted with one or more substituents independently selected from substituted or

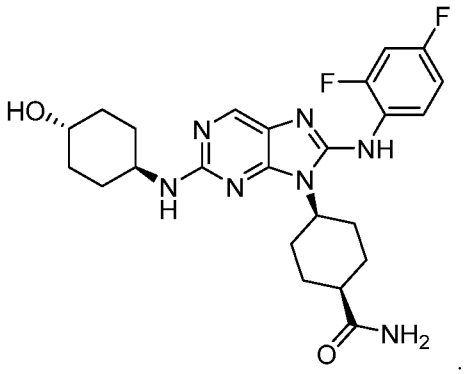
unsubstituted C_{1-3} alkyl, CN, and -OR', wherein each R' is independently substituted or unsubstituted C_{1-3} alkyl.

[00127] In some embodiments, the compound is not 4-[2-[(1-methylethyl)amino]-8-[(2,4,6-trifluorophenyl)amino]-9*H*-purin-9-yl]-*cis*-cyclohexanecarboxamide



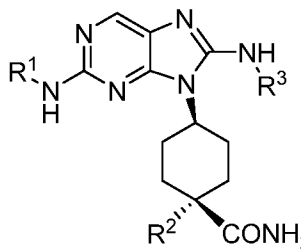
,

or 4-[8-[(2,4-difluorophenyl)amino]-2-[(*trans*-4-hydroxycyclohexyl)amino]-9*H*-purin-9-yl]-*cis*-cyclohexanecarboxamide



.

[00128] In one embodiment, the compound is a compound of formula (II):

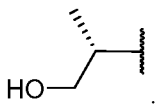


(II).

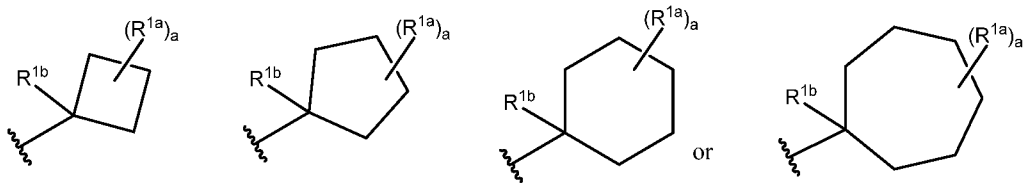
[00129] In some embodiments or compounds of formula (I), R^1 is substituted or unsubstituted C_{1-8} alkyl. In some embodiments, R^1 is substituted or unsubstituted methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, 2-methylpentyl, 3-methylpentyl,

isopentyl, or neopentyl. In some embodiments, R^1 is substituted with one or more substituents independently selected from halogen and OR, wherein each R is independently H or substituted or unsubstituted C_{1-3} alkyl. For example, R^1 is substituted with one or more substituents independently selected from F, OH, and OCH_3. In some embodiments, R^1 is ethyl, isopropyl, isobutyl, tert-butyl, CH_2CH_2F, CH_2CHF_2, CH_2CF_3, $CH_2CH(CH_3)OH$, $CH_2CH(CH_3)OCH_3$, $CH(CH_3)CH_2OH$, $CH(CH_3)CH_2OCH_3$, $CH_2C(F_2)CH_2OH$, $CH_2C(F_2)CH_2OCH_3$, $CH(CF_3)CH_2OH$, $CH(CF_3)CH_2OCH_3$, $CH(CH_2OH)CH_2CH_3$, $CH(CH_2OCH_3)CH_2CH_3$, $CH_2C(CH_3)_2CH_2OH$, or $CH_2C(CH_3)_2CH_2OCH_3$. For example, R^1 is isopropyl, isobutyl, tert-butyl, CH_2CF_3, $CH_2CH(CH_3)OH$, $CH(CH_3)CH_2OH$, $CH(CH_3)CH_2OCH_3$, $CH_2C(F_2)CH_2OH$, $CH(CF_3)CH_2OH$, $CH(CH_2OH)CH_2CH_3$, or $CH_2C(CH_3)_2CH_2OH$.

[00130] In one embodiment, R^1 is isopropyl, $CH(CH_3)CH_2OH$, or $CH(CH_2OH)CH_2CH_3$. In some embodiments, R^1 is (S)-2-propan-1-ol:



[00131] In some embodiments, R^1 is substituted or unsubstituted cycloalkyl. In some embodiments, R^1 is substituted or unsubstituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl. In some embodiments, R^1 is substituted with one or more substituents independently selected from halogen, OR, SO_2R', substituted or unsubstituted C_{1-3} alkyl, and substituted or unsubstituted heterocyclyl, wherein each R is independently H or substituted or unsubstituted C_{1-3} alkyl, and each R' is independently substituted or unsubstituted C_{1-3} alkyl. In some embodiments, R^1 is substituted with one or more substituents independently selected from F, OH, OCH_3, SO_2CH_3, methyl, and substituted or unsubstituted 5-membered heterocyclyl, for example, pyrrolidinedionyl, or oxadiazolyl. In some other embodiments, R^1 is cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl, optionally substituted with one or more substituents independently selected from F, OH, OCH_3, SO_2CH_3, methyl, pyrrolidinedionyl, and oxadiazolyl. In some embodiments, R^1 is



wherein

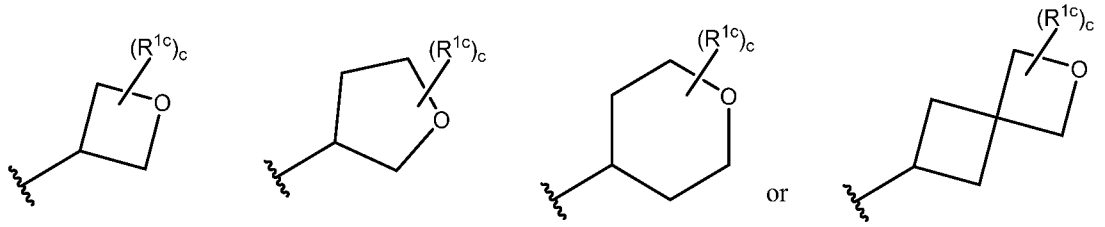
each R^{1a} is independently F, OH, OCH_3, SO_2CH_3, or methyl;

R^{1b} is H or CH_3;

and a is 0-4.

[00132] In some embodiments, R^1 is substituted or unsubstituted cycloalkylalkyl. In some embodiments, R^1 is substituted or unsubstituted (C_{1-3} alkyl)-(C_{1-8} cycloalkyl), for example, R^1 is substituted or unsubstituted CH_2-cyclopropyl, CH_2-cyclobutyl, CH_2-cyclopentyl, CH_2-cyclohexyl, or CH_2-cycloheptyl. In some embodiments, R^1 is substituted with one or more substituents independently selected from (C_{1-3} alkyl)OR or OR, wherein each R is independently H or substituted or unsubstituted C_{1-3} alkyl. For example, R^1 is CH_2-cyclopropyl, CH_2-cyclobutyl, CH_2-cyclopentyl, or CH_2-cyclohexyl, optionally substituted with one or more CH_2OH or OH.

[00133] In some embodiments, R^1 is substituted or unsubstituted non-aromatic heterocyclyl. In some embodiments, R^1 is substituted or unsubstituted oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydro-thiopyrandioxide, piperidyl, oxepanyl, or oxaspiroheptyl. In some embodiments, R^1 is substituted with one or more substituents independently selected from halogen, OR, SO_2R^4, $C(=O)R^5$, $C(=O)OR^6$, $C(=O)NRR^7$, substituted or unsubstituted C_{1-3} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted or alkylaryl, wherein each R is independently H or substituted or unsubstituted C_{1-3} alkyl; R^4 is substituted or unsubstituted C_{1-3} alkyl, or substituted or unsubstituted aryl; R^5 is substituted or unsubstituted C_{1-3} alkyl; R^6 is substituted or unsubstituted C_{1-6} alkyl; and R^7 is substituted or unsubstituted C_{1-3} alkyl, or substituted or unsubstituted aryl. For example, R^1 is oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydro-thiopyrandioxide, piperidyl, oxepanyl, or oxaspiroheptyl, optionally substituted with one or more substituents independently selected from F, OH, SO_2CH_3, SO_2-tosyl, $C(=O)CH_3$, $C(=O)OCH_3$, C(=O)O-tert-butyl, C(=O)O-isopropyl, $C(=O)NHCH_3$, C(=O)NH-phenyl, methyl, ethyl, isopropyl, CH_2OH, phenyl, pyridyl, or benzyl. In one embodiment, R^1 is



wherein each R^{1c} is independently F, OH, methyl, or CH_2OH;

and c is 0-3.

[00134] In some such embodiments, R^{1c} is F or methyl and c is 1 or 2.

[00135] In some embodiments of compounds of formula (I), R^2 is H. In others, R^2 is CH_3.

[00136] In some embodiments of compounds of formula (I), R^3 is ortho-halogen substituted phenyl. In one embodiment R^3 is o-fluoro or o-chloro substituted phenyl. In some embodiments, the phenyl is additionally para substituted, for example, the phenyl is additionally substituted with p-chloro, p-bromo, p-fluoro, p-CN, p-methyl, p-CF_3, or p-OCH_3. In other embodiments, R^3 is para-halogen substituted phenyl. In some embodiments, R^3 is p-fluoro or p-chloro substituted phenyl. In some embodiments, the phenyl is additionally ortho substituted, for example, the phenyl is additionally substituted with o-chloro, o-fluoro, or o-methyl. In other embodiments, R^3 is para-CN substituted phenyl. In some embodiments, the phenyl is additionally ortho substituted, for example, the phenyl is additionally substituted with o-chloro, or o-fluoro. In yet other embodiments, R^3 is ortho, ortho-dihalogen substituted phenyl. In one embodiment R^3 is o,o-difluoro or o,o-dichloro substituted phenyl. In some embodiments, the phenyl is additionally para substituted, for example, the phenyl is additionally substituted with p-chloro, p-bromo, p-fluoro, p-CN, p-methyl, p-CF_3, or p-OCH_3. In yet other embodiments, R^3 is ortho, para-dihalogen substituted phenyl. In one embodiment R^3 is o,p-difluoro substituted phenyl or o,p-dichloro substituted phenyl. In some embodiments, the phenyl is additionally ortho substituted, for example, the phenyl is additionally substituted with o-chloro, o-fluoro, or o-methyl. In still other embodiments, R^3 is 2,4,6-trihalogen substituted phenyl. In one embodiment R^3 is 2,4,6-trifluoro substituted phenyl, 4-chloro-2,6-difluoro substituted phenyl, or 2,4,6-trichloro substituted phenyl. In yet another embodiment, R^3 is ortho-halogen, para-CN substituted phenyl. In one embodiment R^3 is o-fluoro-p-CN substituted phenyl, or o-chloro-para-CN substituted phenyl. In some embodiments, the phenyl is additionally ortho substituted, for example, the phenyl is additionally substituted with o-chloro, or o-fluoro.

[00137] Further embodiments provided herein include combinations of one or more of the particular embodiments set forth above.

[00138] **Table 1**: Representative compounds of formula (I).

Compound	Compound Name
1	(1s,4s)-4-(2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide
2	(1s,4s)-4-(8-(3-chlorophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
3	(1s,4s)-4-(8-(3-chlorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
4	(1s,4s)-4-(2-(cyclopentylamino)-8-(2,4-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
5	(1s,4s)-4-(8-(3-chlorophenylamino)-2-(4-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
6	(1s,4s)-4-(8-(2,4-difluorophenylamino)-2-(3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
7	(1s,4s)-4-(8-(2,4-difluorophenylamino)-2-(1-methylcyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
8	(1s,4s)-4-(2-(tert-butylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
9	(1s,4s)-4-(8-(2,4-difluorophenylamino)-2-((3R,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
10	(1s,4s)-4-(2-(4-methyltetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
11	(1s,4s)-4-(8-(3-chloro-2-fluorophenylamino)-2-(4-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
12	(1s,4s)-4-(2-(tetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
13	(1s,4s)-4-(8-(2,6-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
14	(1s,4s)-4-(8-(2-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
15	(1s,4s)-4-(2-((3R,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
16	(1s,4s)-4-(8-(2,6-difluorophenylamino)-2-((3R,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
17	(1s,4s)-4-(8-(2-chloro-6-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

Compound	Compound Name
18	(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
19	(1s,4s)-4-(8-(3-chlorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
20	(1s,4s)-4-(8-(2,4-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
21	(1s,4s)-4-(8-(3,4-dichlorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
22	(1s,4s)-4-(8-(5-chloro-2-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
23	(1s,4s)-4-(8-(3-chloro-2-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
24	(1s,4s)-4-(8-(2,5-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
25	(1s,4s)-4-(8-(3-chloro-2-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
26	(1s,4s)-4-(2-(tetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
27	(1s,4s)-4-(8-(2,3-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
28	(1s,4s)-4-(8-(2,4-dichlorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
29	(1s,4s)-4-(8-(2-chloro-5-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
30	(1s,4s)-4-(8-(2-chloro-4-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
31	(1s,4s)-4-(8-(2-chloro-4-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
32	(1s,4s)-4-(8-(3-fluoro-2-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
33	(1s,4s)-4-(8-(4-bromo-2-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
34	(1s,4s)-4-(8-(2-fluoro-4-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
35	(1s,4s)-4-(8-(2-chloro-4-(trifluoromethyl)phenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
36	(1s,4s)-4-(8-(2,6-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

Compound	Compound Name
37	(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
38	(1s,4s)-4-(8-(4-fluoro-2-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
39	(1s,4s)-4-(2-(tetrahydro-2H-pyran-4-ylamino)-8-(2,3,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
40	(1s,4s)-1-methyl-4-(2-(tetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
41	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
42	(1s,4s)-4-(2-(cyclobutylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
43	(1s,4s)-4-(2-(cyclobutylamino)-8-(2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
44	(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-(cyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
45	(1s,4s)-4-(2-(cyclopentylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
46	(1s,4s)-4-(2-(cyclopentylamino)-8-(2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
47	(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
48	(1s,4s)-4-(8-(2,6-difluorophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
49	(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
50	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
51	(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
52	(1s,4s)-4-(2-(cyclobutylamino)-8-(2,6-dichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
53	(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
54	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
55	(1s,4s)-4-(2-(cyclopentylamino)-8-(2,6-dichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

Compound	Compound Name
56	(1s,4s)-4-(2-(oxetan-3-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
57	(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-(oxetan-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
58	(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-(oxetan-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
59	(1s,4s)-4-(2-(tetrahydro-2H-pyran-4-ylamino)-8-(2,4,5-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
60	(1s,4s)-4-(2-(isopropylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
61	(1s,4s)-4-(8-(4-chloro-2-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
62	(1s,4s)-4-(8-(2-chloro-3-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
63	(1s,4s)-4-(8-(2,3-dichlorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
64	(1s,4s)-4-(8-(2-fluoro-6-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
65	(1s,4s)-4-(8-(5-chloro-2,4-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
66	(1s,4s)-4-(2-(tetrahydro-2H-pyran-4-ylamino)-8-(2,4,5-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
67	(1s,4s)-4-(2-(tetrahydro-2H-pyran-4-ylamino)-8-(2,3,4-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
68	(1s,4s)-4-(8-(3-chloro-2,6-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
69	(1s,4s)-4-(2-(cyclopentylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
70	(1s,4s)-4-(8-(2-chloro-3-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
71	(1s,4s)-4-(8-(4-chloro-2,5-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
72	(1s,4s)-4-(8-(4-chloro-2-fluoro-5-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
73	(1s,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
74	(1s,4s)-4-(2-(tetrahydro-2H-pyran-4-ylamino)-8-(2,3,4-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

Compound	Compound Name
75	(1s,4s)-4-(8-(2-chloro-4-fluoro-6-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
76	(1s,4s)-4-(8-(4-chloro-2-fluoro-6-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
77	(1s,4s)-4-(2-((R)-tetrahydrofuran-3-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
78	(1s,4s)-4-(2-((1r,4r)-4-methoxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
79	(1s,4s)-4-(2-((1r,4r)-4-hydroxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
80	(1s,4s)-4-(8-(3-chloro-6-fluoro-2-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
81	(1s,4s)-4-(8-(2,5-dichloro-4-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
82	(1s,4s)-4-(8-(2,3-dichloro-4-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
83	(1s,4s)-4-(8-(2,4-dichloro-3-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
84	(1s,4s)-4-(8-(2,3-difluoro-4-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
85	(1s,4s)-4-(8-(2-chloro-3-fluoro-4-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
86	(1s,4s)-4-(8-(2,3-dichloro-4-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
87	(1s,4s)-4-(8-(2,4-difluoro-6-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
88	(1r,4s)-4-(2-((S)-tetrahydrofuran-3-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
89	(1s,4s)-4-(2-(4,4-difluorocyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
90	(1s,4s)-4-(8-(4-chloro-3-fluoro-2-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
91	(1s,4s)-4-(8-(2-chloro-3,6-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
92	(1s,4s)-4-(8-(2-chloro-6-fluoro-3-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
93	(1s,4s)-4-(2-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino)-8-((2,4,6-trichlorophenyl)amino)-9H-purin-9-yl)cyclohexane-1-carboxamide;

Compound	Compound Name
94	(1s,4s)-4-(8-(2-chlorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
95	(1s,4s)-4-(2-(cyclopentylamino)-8-(2,4-dichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
96	(1s,4s)-4-(8-(4-chloro-2-fluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
97	(1s,4s)-4-(8-(2,4-dichlorophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
98	(1s,4s)-4-(8-(2-chloro-4-fluorophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
99	(1s,4s)-4-(2-(isopropylamino)-8-(2,3,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
100	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
101	(1s,4s)-4-(8-(2-chloro-4,5-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
102	(1s,4s)-4-(8-(2-chloro-4,5-dimethylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
103	(1s,4s)-4-(8-(4-chloro-2-fluoro-3-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
104	(1s,4s)-4-(8-(2,4-dichloro-6-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
105	(1s,4s)-4-(8-(2,3-dichloro-6-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
106	(1s,4s)-4-(8-(2,4-dichloro-5-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
107	(1s,4s)-4-(8-(2,5-difluoro-4-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
108	(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-(1-(pyridin-3-yl)piperidin-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
109	(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-(1-phenylpiperidin-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
110	(1s,4s)-4-(8-(2,4,6-trichlorophenylamino)-2-(2,2,2-trifluoroethylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
111	(1s,4s)-4-(2-(cyclobutylmethylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
112	(1s,4s)-4-(2-((R)-tetrahydro-2H-pyran-3-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

Compound	Compound Name
113	(1s,4s)-4-(8-(3,4-dichloro-2-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
114	(1s,4s)-4-(8-(6-chloro-2,3-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
115	(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-(1-(methylsulfonyl)piperidin-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
116	(1s,4s)-4-(8-(2,6-difluoro-4-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
117	(1s,4s)-4-(8-(2,6-dichloro-4-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
118	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(cyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
119	(1s,4s)-4-(2-(cyclobutylamino)-8-(2,6-dichloro-4-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
120	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
121	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
122	(1s,4s)-4-(2-(cyclopentylamino)-8-(2,6-dichloro-4-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
123	(1s,4s)-4-(2-(cyclopentylamino)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
124	(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
125	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
126	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
127	(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((R)-1-hydroxybutan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
128	(3R,4S)-tert-butyl 4-(9-((1s,4r)-4-carbamoylcyclohexyl)-8-(2,4,6-trifluorophenylamino)-9H-purin-2-ylamino)-3-fluoropiperidine-1-carboxylate;
129	(3R,4S)-tert-butyl 4-(9-((1s,4r)-4-carbamoylcyclohexyl)-8-(2,6-difluorophenylamino)-9H-purin-2-ylamino)-3-fluoropiperidine-1-carboxylate;
130	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(cyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
131	(1s,4s)-4-(2-(cyclobutylamino)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

Compound	Compound Name
132	(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((R)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
133	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((R)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
134	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((R)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
135	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((R)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
136	(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
137	(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
138	(1s,4s)-4-(2-((R)-1-hydroxybutan-2-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
139	(1r,4s)-4-(2-((3R,4S)-3-fluoropiperidin-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
140	(1s,4s)-4-(2-(cyclopentylamino)-8-(2,3-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
141	(1s,4s)-4-(8-(3-chloro-2-fluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
142	(1s,4s)-4-(2-(cyclopentylamino)-8-(2,3,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
143	(1r,4s)-4-(2-((S)-1-methoxypropan-2-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
144	(1r,4s)-4-(2-((S)-1-hydroxybutan-2-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
145	(1r,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-((S)-1-hydroxybutan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
146	(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((S)-1-hydroxybutan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
147	(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((S)-1-hydroxybutan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
148	(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((S)-1-hydroxybutan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
149	(1r,4s)-4-(2-((S)-1-hydroxybutan-2-ylamino)-8-(2,3,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
150	(1r,4s)-4-(8-(2,4-dichlorophenylamino)-2-((S)-1-hydroxybutan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

Compound	Compound Name
151	(1r,4s)-4-(8-(3-chloro-2-fluorophenylamino)-2-((S)-1-hydroxybutan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
152	(1r,4s)-4-(2-((S)-1-hydroxybutan-2-ylamino)-8-(2,3,4-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
153	(1s,4s)-4-(2-((R)-2-hydroxypropylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
154	(1r,4s)-4-(8-(2,6-dichlorophenylamino)-2-((S)-1-hydroxybutan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
155	(1r,4s)-4-(2-((S)-1-hydroxybutan-2-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
156	(3R,4S)-tert-butyl 4-(9-((1s,4r)-4-carbamoylcyclohexyl)-8-(4-chloro-2,6-difluorophenylamino)-9H-purin-2-ylamino)-3-fluoropiperidine-1-carboxylate;
157	(1s,4s)-4-(8-((4-chloro-2,6-difluorophenyl)amino)-2-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino)-9H-purin-9-yl)cyclohexane-1-carboxamide;
158	(1s,4s)-4-(8-((2,4-dichloro-6-fluorophenyl)amino)-2-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino)-9H-purin-9-yl)cyclohexane-1-carboxamide;
159	(R)-tert-butyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4,6-trifluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;
160	(R)-tert-butyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-difluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;
161	(R)-tert-butyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-dichlorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;
162	(R)-tert-butyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2-chloro-4,6-difluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;
163	(R)-tert-butyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(4-chloro-2,6-difluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;
164	(R)-tert-butyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4,6-trichlorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;
165	(1r,4s)-4-(2-((S)-1-hydroxypropan-2-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
166	(1r,4s)-4-(2-((S)-1-hydroxypropan-2-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
167	(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
168	(1r,4s)-4-(8-(2,6-difluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
169	(1r,4s)-4-(8-(2,6-dichlorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

Compound	Compound Name
170	(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
171	(1r,4s)-4-(8-(2,4-dichlorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
172	(1r,4s)-4-(8-(5-chloro-2-fluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
173	(1r,4s)-4-(8-(3-chloro-2-fluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
174	(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
175	(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(2,6-dichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
176	(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(2-chloro-4,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
177	(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(4-chloro-2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
178	(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
179	(1s,4s)-4-(2-(4-hydroxytetrahydrofuran-3-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
180	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
181	(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-(4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
182	(1s,4s)-4-(2-(4-hydroxytetrahydrofuran-3-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
183	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
184	(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
185	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
186	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
187	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
188	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((R)-tetrahydro-2H-pyran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

Compound	Compound Name
189	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((R)-tetrahydro-2H-pyran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
190	(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((R)-tetrahydro-2H-pyran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
191	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((R)-tetrahydro-2H-pyran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
192	(1s,4s)-4-(8-(2,4-dichlorophenylamino)-2-(4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
193	(1s,4s)-4-(8-(3-chloro-2-fluorophenylamino)-2-(4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
194	(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(2,6-dichloro-4-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
195	(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(4-chloro-2,3-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
196	(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
197	(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(3-chloro-2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
198	(1s,4s)-4-(2-(1-acetylpiperidin-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
199	(1s,4s)-4-(2-(1-acetylpiperidin-4-ylamino)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
200	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((R)-tetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
201	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
202	(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
203	(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((S)-tetrahydro-2H-pyran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
204	(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((S)-tetrahydro-2H-pyran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
205	(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((S)-tetrahydro-2H-pyran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
206	(1s,4s)-4-(2-((1-(hydroxymethyl)cyclopropyl)methylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
207	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1-(hydroxymethyl)cyclopropyl)methylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

Compound	Compound Name
208	(1s,4s)-4-(2-((1R,3R)-3-hydroxycyclopentylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
209	(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
210	(1s,4s)-4-(8-(2,6-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
211	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
212	(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
213	(1s,4s)-4-(2-((1R,3R)-3-hydroxycyclopentylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
214	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
215	(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
216	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
217	(1s,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
218	(1s,4s)-4-(8-(3-chloro-2,6-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
219	(1s,4s)-4-(2-((1R,3R)-3-hydroxycyclopentylamino)-8-(2,3,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
220	(1s,4s)-4-(8-(2,4-dichlorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
221	(1s,4s)-4-(2-((1R,3R)-3-hydroxycyclopentylamino)-8-(2,3,4-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
222	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((R)-tetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
223	(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((R)-tetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
224	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((R)-tetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
225	(1s,4s)-4-(2-(3,3-difluorocyclobutylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
226	(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

Compound	Compound Name
227	(1s,4s)-4-(2-(3,3-difluorocyclobutylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
228	(1s,4s)-4-(2-(3,3-difluorocyclobutylamino)-8-(2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
229	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
230	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
231	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
232	(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
233	(1s,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
234	(1s,4s)-4-(2-(3,3-difluorocyclobutylamino)-8-(2,3,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
235	(1s,4s)-4-(8-(3-chloro-2,6-difluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
236	(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
237	(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
238	(1s,4s)-4-(8-(3-chloro-2-fluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
239	(1s,4s)-4-(8-(4-chloro-2,5-difluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
240	(1s,4s)-4-(2-(4,4-difluorocyclohexylamino)-8-(2,3,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
241	(1s,4s)-4-(8-(2,4-dichlorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
242	(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((S)-tetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
243	(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((S)-tetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
244	(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((S)-tetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
245	(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((S)-tetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

Compound	Compound Name
246	(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((S)-tetrahydro-2H-pyran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
247	(1r,4s)-4-(2-((3R,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
248	(1r,4s)-4-(8-(2,6-difluorophenylamino)-2-((3R,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
249	(1s,4s)-4-(8-(2-chloro-4-cyanophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
250	(1s,4s)-4-(2-((1R,2R)-2-hydroxycyclopentylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
251	(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
252	(1s,4s)-4-(8-(2,6-difluorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
253	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
254	(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
255	(1s,4s)-4-(2-((1R,2R)-2-hydroxycyclopentylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
256	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
257	(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
258	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
259	(1s,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
260	(1s,4s)-4-(8-(3-chloro-2,6-difluorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
261	(1s,4s)-4-(2-((1R,2R)-2-hydroxycyclopentylamino)-8-(2,3,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
262	(1s,4s)-4-(8-(2,4-dichlorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
263	(1s,4s)-4-(8-(5-chloro-2-fluorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
264	(1s,4s)-4-(8-(3-chloro-2-fluorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

Compound	Compound Name
265	(1s,4s)-4-(2-((1R,2R)-2-hydroxycyclopentylamino)-8-(2,3,4-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
266	(1s,4s)-4-(8-(4-chloro-2,5-difluorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
267	(1r,4s)-4-(2-((1S,2S)-2-hydroxycyclopentylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
268	(1r,4s)-4-(8-(2,6-difluorophenylamino)-2-((1S,2S)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
269	(1r,4s)-4-(8-(2,6-dichlorophenylamino)-2-((1S,2S)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
270	(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1S,2S)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
271	(1r,4s)-4-(2-((1S,2S)-2-hydroxycyclopentylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
272	(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1S,2S)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
273	(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1S,2S)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
274	(1r,4s)-4-(8-(3-chloro-2,6-difluorophenylamino)-2-((1S,2S)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
275	(1s,4s)-4-(2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
276	(1s,4s)-4-(8-(2,6-difluorophenylamino)-2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
277	(1s,4s)-4-(2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
278	(1r,4s)-4-(2-((3R,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
279	(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
280	(1s,4s)-4-(2-((1r,3r)-3-hydroxycyclobutylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
281	(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-((1r,3r)-3-hydroxycyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
282	(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-((1r,3r)-3-hydroxycyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
283	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1r,3r)-3-hydroxycyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

Compound	Compound Name
284	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1r,3r)-3-hydroxycyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
285	(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1r,3r)-3-hydroxycyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
286	(1s,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-((1r,3r)-3-hydroxycyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
287	(1s,4s)-4-(8-(3-chloro-2,6-difluorophenylamino)-2-((1r,3r)-3-hydroxycyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
288	(1s,4s)-4-(8-(3-chloro-2,5-difluorophenylamino)-2-((1r,3r)-3-hydroxycyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
289	(1s,4s)-4-(2-(4,4-difluorocyclohexylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
290	(1s,4s)-4-(2-(4,4-difluorocyclohexylamino)-8-(2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
291	(1s,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
292	(1s,4s)-4-(8-(3-chloro-2,6-difluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
293	(1s,4s)-4-(2-(1-(methylsulfonyl)piperidin-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
294	(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-(1-(methylsulfonyl)piperidin-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
295	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(1-(methylsulfonyl)piperidin-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
296	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(1-(methylsulfonyl)piperidin-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
297	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(1-(methylsulfonyl)piperidin-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
298	(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(1-(methylsulfonyl)piperidin-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
299	(1s,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-(1-(methylsulfonyl)piperidin-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
300	(1s,4s)-4-(8-(2,4-dichlorophenylamino)-2-(1-(methylsulfonyl)piperidin-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
301	(1s,4s)-4-(2-((1r,3r)-3-hydroxycyclobutylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
302	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1r,3r)-3-hydroxycyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

Compound	Compound Name
303	(1s,4s)-4-(2-((3R,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
304	(1r,4s)-4-(2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
305	(1s,4s)-4-(8-(2,6-difluorophenylamino)-2-((3R,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
306	(1r,4s)-4-(8-(2,6-difluorophenylamino)-2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
307	(1r,4s)-4-(2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
308	(1s,4s)-4-(2-((3R,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
309	(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
310	(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
311	(1s,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-((1s,3s)-3-hydroxycyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
312	(1r,4s)-4-(2-((3S,4R)-4-hydroxytetrahydrofuran-3-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
313	(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((3S,4R)-4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
314	(1r,4s)-4-(2-((3S,4R)-4-hydroxytetrahydrofuran-3-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
315	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((3R,4S)-4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
316	(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((3R,4S)-4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
317	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((3R,4S)-4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
318	(1r,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-((3S,4R)-4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
319	(1r,4s)-4-(8-(3-chloro-2,6-difluorophenylamino)-2-((3S,4R)-4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
320	(1r,4s)-4-(8-(2,4-dichlorophenylamino)-2-((3S,4R)-4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
321	(1r,4s)-4-(8-(5-chloro-2-fluorophenylamino)-2-((3S,4R)-4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

Compound	Compound Name
322	(1s,4s)-4-(8-(4-chloro-2,5-difluorophenylamino)-2-((3R,4S)-4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
323	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1s,3s)-3-hydroxycyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
324	(1s,4s)-4-(2-((1s,3s)-3-hydroxycyclobutylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
325	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1s,3s)-3-hydroxycyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
326	(1r,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-((1S,3S)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
327	(1r,4s)-4-(8-(2,6-difluorophenylamino)-2-((1S,3S)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
328	(1r,4s)-4-(8-(2,6-dichlorophenylamino)-2-((1S,3S)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
329	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,3S)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
330	(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1S,3S)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
331	(1r,4s)-4-(2-((1S,3S)-3-hydroxycyclopentylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
332	(1r,4s)-4-(2-((1S,3S)-3-hydroxycyclopentylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
333	(1s,4s)-4-(2-((1R,3S)-3-hydroxycyclopentylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
334	(1s,4s)-4-(2-((1R,3S)-3-hydroxycyclopentylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
335	(1r,4s)-4-(2-(sec-butylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
336	(1r,4s)-4-(2-(sec-butylamino)-8-(2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
337	(1r,4s)-4-(2-(sec-butylamino)-8-(2,6-dichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
338	(1r,4s)-4-(2-(sec-butylamino)-8-(2-chloro-6-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
339	(1r,4s)-4-(2-(sec-butylamino)-8-(2-chloro-4,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
340	(1r,4s)-4-(2-(sec-butylamino)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

Compound	Compound Name
341	(1r,4s)-4-(2-(sec-butylamino)-8-(3-chloro-2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
342	(1s,4s)-4-(2-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
343	(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
344	(1s,4s)-4-(8-(2,6-difluorophenylamino)-2-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
345	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
346	(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
347	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
348	(1s,4s)-4-(2-((1R,3S)-3-hydroxycyclohexylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
349	(1s,4s)-4-(8-(2,6-difluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
350	(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
351	(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
352	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
353	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
354	(1s,4s)-4-(2-((1R,3S)-3-hydroxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
355	(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
356	(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
357	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
358	(1s,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
359	(1s,4s)-4-(8-(3-chloro-2,6-difluorophenylamino)-2-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

Compound	Compound Name
360	(1s,4s)-4-(2-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-8-(2,3,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
361	(1s,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
362	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
363	(1s,4s)-4-(8-(3-chloro-2,6-difluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
364	(1s,4s)-4-(8-(4-chloro-2,5-difluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
365	(1s,4s)-4-(2-((1R,3S)-3-hydroxycyclohexylamino)-8-(2,3,4-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
366	(1s,4s)-4-(8-(2,6-dichloro-4-(trifluoromethoxy)phenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
367	(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
368	(1s,4s)-4-(2-(cyclopentylamino)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
369	(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-(cyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
370	(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
371	(1r,4s)-4-(8-(2,6-dichlorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
372	(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
373	(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
374	(1r,4s)-4-(2-((1S,3R)-3-hydroxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
375	(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
376	(1r,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
377	(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
378	(1r,4s)-4-(8-(3-chloro-2,6-difluorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

Compound	Compound Name
379	(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
380	(1s,4s)-4-(8-(4-cyano-2,3-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
381	(1s,4s)-4-(8-(2,3-difluoro-4-methoxyphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
382	(1s,4s)-4-(2-((1R,3R)-3-hydroxy-4,4-dimethylcyclohexylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
383	(1s,4s)-4-(8-(2,6-difluorophenylamino)-2-((1R,3R)-3-hydroxy-4,4-dimethylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
384	(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-((1R,3R)-3-hydroxy-4,4-dimethylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
385	(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-((1R,3R)-3-hydroxy-4,4-dimethylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
386	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1R,3R)-3-hydroxy-4,4-dimethylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
387	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,3R)-3-hydroxy-4,4-dimethylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
388	(1s,4s)-4-(2-((1R,3R)-3-hydroxy-4,4-dimethylcyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
389	(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1R,3R)-3-hydroxy-4,4-dimethylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
390	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1R,3R)-3-hydroxy-4,4-dimethylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
391	(1s,4s)-4-(8-(3-chloro-2,6-difluorophenylamino)-2-((1R,3R)-3-hydroxy-4,4-dimethylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
392	(1s,4s)-4-(8-(2,4-dichlorophenylamino)-2-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
393	(1s,4s)-4-(2-(cyclobutylamino)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
394	(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(cyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
395	(1r,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
396	(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
397	(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

Compound	Compound Name
398	(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
399	(1s,4s)-4-(8-(2-chloro-6-fluoro-4-(trifluoromethyl)phenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
400	(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
401	(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
402	(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
403	(1r,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-((S)-1-hydroxybutan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
404	(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4,6-trifluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;
405	(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-difluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;
406	(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-dichlorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;
407	(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2-chloro-6-fluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;
408	(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2-chloro-4,6-difluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;
409	(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(4-chloro-2,6-difluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;
410	(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4,6-trichlorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;
411	(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-dichloro-4-fluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;
412	(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(4-chloro-2,3-difluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;
413	(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;
414	(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(3-chloro-2,6-difluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;
415	(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,3,4-trifluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;
416	(1s,4s)-4-(2-((1R,3R)-3-hydroxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

Compound	Compound Name
417	(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
418	(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
419	(1s,4s)-4-(2-((1R,3R)-3-hydroxycyclohexylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
420	(1s,4s)-4-(8-(2,6-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
421	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
422	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
423	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
424	(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
425	(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-((1R,3S)-3-hydroxy-3-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
426	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1R,3S)-3-hydroxy-3-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
427	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,3S)-3-hydroxy-3-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
428	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1R,3S)-3-hydroxy-3-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
429	(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1R,3S)-3-hydroxy-3-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
430	(1s,4s)-4-(8-(2-chloro-4-fluorophenylamino)-2-((1R,3S)-3-hydroxy-3-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
431	(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
432	(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
433	(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((S)-1-hydroxybutan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
434	(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((S)-1-hydroxybutan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
435	(1s,4s)-4-(2-((1R,3S)-3-hydroxycycloheptylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

Compound	Compound Name
436	(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-((1R,3S)-3-hydroxycycloheptylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
437	(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-((1R,3S)-3-hydroxycycloheptylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
438	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1R,3S)-3-hydroxycycloheptylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
439	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,3S)-3-hydroxycycloheptylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
440	(1s,4s)-4-(2-((1R,3S)-3-hydroxycycloheptylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
441	(1s,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-((1R,3S)-3-hydroxycycloheptylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
442	(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
443	(1s,4s)-4-(8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
444	(1s,4s)-4-(8-(2,6-dichloro-3-cyanophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
445	(1r,4s)-4-(2-((1S,3R)-3-hydroxycycloheptylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
446	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((2S,4R)-2-(hydroxymethyl)tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
447	(1s,4s)-4-(2-((2S,4R)-2-(hydroxymethyl)tetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
448	(1s,4s)-4-(8-(3-cyano-2,6-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
449	(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1S,3S)-3-hydroxycycloheptylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
450	(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((1S,3S)-3-hydroxycycloheptylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
451	(1s,4s)-4-(2-(2,2-difluoro-3-hydroxypropylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
452	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(2,2-difluoro-3-hydroxypropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
453	(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(2,2-difluoro-3-hydroxypropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
454	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(2,2-difluoro-3-hydroxypropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

Compound	Compound Name
455	(1s,4s)-4-(8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
456	(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
457	(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
458	(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
459	(1r,4s)-4-(2-((1S,3S)-3-hydroxycyclohexylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
460	(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
461	(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
462	(1r,4s)-4-(2-((1S,3S)-3-hydroxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
463	(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
464	(1r,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
465	(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
466	(1r,4s)-4-(8-(4-chloro-2,5-difluorophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
467	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1R,2R)-2-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
468	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,2R)-2-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
469	(1s,4s)-4-(2-((1R,2R)-2-hydroxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
470	(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1R,2R)-2-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
471	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1R,2R)-2-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
472	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((R)-1,1,1-trifluoro-3-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
473	(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((R)-1,1,1-trifluoro-3-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

Compound	Compound Name
474	(1r,4r)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
475	(1r,4r)-1-methyl-4-(2-(tetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
476	(1r,4r)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
477	(1r,4r)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
478	(1r,4r)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
479	(1r,4r)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
480	(1r,4r)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
481	(1S,4r)-4-(8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
482	(1S,4r)-4-(2-((S)-1-hydroxypropan-2-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
483	(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(3-hydroxy-2,2-dimethylpropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
484	(1s,4s)-4-(2-((1R,2S)-2-hydroxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
485	(1R,4r)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
486	(1r,4r)-4-(2-(cyclopentylamino)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
487	(1r,4r)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
488	(1r,4r)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
489	(1r,4r)-4-(2-(cyclopentylamino)-8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
490	(1r,4r)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
491	(1r,4r)-4-(2-(cyclopentylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
492	(1r,4r)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

Compound	Compound Name
493	(1r,4r)-4-(2-(cyclopentylamino)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
494	(1r,4r)-4-(2-(cyclopentylamino)-8-(2,6-dichloro-4-fluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
495	(1r,4r)-4-(2-(cyclopentylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
496	(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((3S,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
497	(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((3R,4S)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
498	(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((3R,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
499	(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((3S,4S)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
500	(1s,4s)-4-(2-((3S,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
501	(1r,4s)-4-(2-((3R,4S)-3-methyltetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
502	(1s,4s)-4-(2-((3R,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
503	(1r,4s)-4-(2-((3S,4S)-3-methyltetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
504	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((3S,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
505	(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((3R,4S)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
506	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((3R,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
507	(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((3S,4S)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
508	(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((3R,4S)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
509	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((3R,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
510	(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((3S,4S)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
511	(1r,4s)-4-(2-((3R,4S)-3-methyltetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

Compound	Compound Name
512	(1r,4s)-4-(2-((3S,4S)-3-methyltetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
513	(1r,4s)-4-(2-((1S,2R)-2-hydroxycyclohexylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
514	(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1S,2R)-2-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
515	(1r,4s)-4-(2-((1S,2R)-2-hydroxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
516	(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1S,2R)-2-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
517	(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1S,2R)-2-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
518	(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1S,2R)-2-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
519	(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((R)-tetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
520	(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((1S,2R)-2-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
521	(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((R)-tetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
522	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
523	(1s,4s)-1-methyl-4-(2-(tetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
524	(1s,4s)-4-(8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-2-((R)-tetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
525	(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
526	(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
527	(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
528	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
529	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
530	(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-((R)-tetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

Compound	Compound Name
531	(1s,4s)-4-(2-((R)-tetrahydrofuran-3-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
532	(1s,4s)-4-(2-(1-morpholinopropan-2-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
533	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((3S,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
534	(1s,4s)-4-(2-((3S,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
535	(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
536	(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
537	(1s,4s)-4-(2-(oxepan-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
538	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(oxepan-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
539	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(oxepan-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
540	(1s,4s)-4-(2-(oxepan-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
541	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(oxepan-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
542	(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(oxepan-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
543	(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-(oxepan-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
544	(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(oxepan-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
545	(1s,4s)-4-(8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-2-(oxepan-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
546	(1s,4s)-4-(2-((R)-3,3-difluorocyclopentylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
547	(1r,4s)-4-(2-((S)-1-hydroxypropan-2-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
548	(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
549	(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

Compound	Compound Name
550	(1r,4s)-4-(2-((S)-1-hydroxypropan-2-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
551	(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
552	(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
553	(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
554	(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
555	(1r,4s)-4-(8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
556	(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(oxepan-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
557	(1s,4s)-4-(2-(cyclopentylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
558	(1s,4s)-4-(2-(cyclopentylamino)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
559	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
560	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
561	(1s,4s)-4-(2-(cyclopentylamino)-8-(2,6-dichloro-4-fluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
562	(1s,4s)-4-(2-(cyclopentylamino)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
563	(1s,4s)-4-(2-(cyclopentylamino)-8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
564	(1s,4s)-4-(2-((1R,3S)-3-hydroxycyclohexylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
565	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
566	(1s,4s)-4-(2-((1R,3S)-3-hydroxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
567	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
568	(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

Compound	Compound Name
569	(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
570	(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
571	(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
572	(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
573	(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(2-chloro-4-cyano-6-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
574	(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(4-cyano-2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
575	(1s,4s)-4-(2-(cyclopentylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
576	(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
577	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
578	(1s,4s)-4-(8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
579	(1s,4s)-4-(2-(3,3-difluorocyclobutylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
580	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
581	(1s,4s)-4-(2-(3,3-difluorocyclobutylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
582	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
583	(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
584	(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
585	(1s,4s)-4-(8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
586	(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((S)-3,3-difluorocyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
587	(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((R)-3,3-difluorocyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

Compound	Compound Name
588	(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((S)-3,3-difluorocyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
589	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((R)-3,3-difluorocyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
590	(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((S)-3,3-difluorocyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
591	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((R)-3,3-difluorocyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
592	(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((S)-3,3-difluorocyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
593	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((R)-3,3-difluorocyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
594	(1r,4s)-4-(2-((S)-3,3-difluorocyclopentylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
595	(1r,4s)-4-(2-((S)-3,3-difluorocyclopentylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
596	(1s,4s)-4-(8-(2,6-dichloro-4-(trifluoromethoxy)phenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
597	(1s,4s)-4-(8-(2,6-dichloro-4-(trifluoromethoxy)phenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
598	(1s,4s)-4-(2-(cyclopentylamino)-8-(2,6-dichloro-4-(trifluoromethoxy)phenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
599	(1s,4s)-4-(2-(cyclobutylamino)-8-(2,6-dichloro-4-(trifluoromethoxy)phenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
600	(1s,4s)-4-(2-(cyclobutylamino)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
601	(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(cyclobutylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
602	(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-(cyclobutylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
603	(1s,4s)-4-(2-(cyclobutylamino)-8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
604	(1s,4s)-4-(2-(cyclobutylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
605	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(cyclobutylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
606	(1s,4s)-4-(2-(cyclobutylamino)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

Compound	Compound Name
607	(1s,4s)-4-(2-(cyclobutylamino)-8-(2,6-dichloro-4-fluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
608	(1s,4s)-4-(2-(cyclobutylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
609	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(cyclobutylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
610	(1r,4s)-4-(2-((1S,3S)-3-hydroxycyclohexylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
611	(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
612	(1r,4s)-4-(2-((1S,3S)-3-hydroxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
613	(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
614	(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
615	(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
616	(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
617	(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
618	(1s,4s)-4-(2-((1R,3R)-3-hydroxycyclohexylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
619	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
620	(1s,4s)-4-(2-((1R,3R)-3-hydroxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
621	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
622	(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
623	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
624	(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
625	(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

Compound	Compound Name
626	(1r,4s)-4-(2-((1S,3R)-3-hydroxycyclohexylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
627	(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
628	(1r,4s)-4-(2-((1S,3R)-3-hydroxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
629	(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
630	(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
631	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
632	(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
633	(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
634	(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
635	(1s,4s)-4-(2-((1R,3R)-3-hydroxycyclopentylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
636	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
637	(1s,4s)-4-(2-((1R,3R)-3-hydroxycyclopentylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
638	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
639	(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
640	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
641	(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
642	(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
643	(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
644	(1r,4s)-4-(2-((1S,3S)-3-hydroxycyclopentylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

Compound	Compound Name
645	(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1S,3S)-3-hydroxycyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
646	(1r,4s)-4-(2-((1S,3S)-3-hydroxycyclopentylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
647	(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1S,3S)-3-hydroxycyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
648	(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1S,3S)-3-hydroxycyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
649	(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1S,3S)-3-hydroxycyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
650	(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1S,3S)-3-hydroxycyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
651	(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((1S,3S)-3-hydroxycyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
652	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
653	(1r,4s)-4-(2-(((1S,2S)-2-hydroxycyclohexyl)methylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
654	(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(((1S,2S)-2-hydroxycyclohexyl)methylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
655	(1r,4s)-4-(2-(((1S,2S)-2-hydroxycyclohexyl)methylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
656	(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(((1S,2S)-2-hydroxycyclohexyl)methylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
657	(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(((1S,2S)-2-hydroxycyclohexyl)methylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
658	(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(((1S,2S)-2-hydroxycyclohexyl)methylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
659	(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(((1S,2S)-2-hydroxycyclohexyl)methylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
660	(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(((1S,2S)-2-hydroxycyclohexyl)methylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
661	(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(((1S,2R)-2-hydroxycyclohexyl)methylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
662	(1r,4s)-4-(2-(((1S,2R)-2-hydroxycyclohexyl)methylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
663	(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(((1S,2R)-2-hydroxycyclohexyl)methylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

Compound	Compound Name
664	(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(((1S,2R)-2-hydroxycyclohexyl)methylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
665	(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(((1S,2R)-2-hydroxycyclohexyl)methylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
666	(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(((1S,2R)-2-hydroxycyclohexyl)methylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
667	(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
668	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(4-(2,5-dioxopyrrolidin-1-yl)cyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
669	(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(4-(2,5-dioxopyrrolidin-1-yl)cyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
670	(1r,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
671	(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
672	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
673	(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
674	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
675	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
676	(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
677	(1s,4s)-4-(2-(4-(1,2,4-oxadiazol-5-yl)cyclohexylamino)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
678	(1s,4s)-4-(2-(4-(1,2,4-oxadiazol-5-yl)cyclohexylamino)-8-(2-chloro-4,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
679	(1s,4s)-4-(2-(4-(1,2,4-oxadiazol-5-yl)cyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
680	(1s,4s)-4-(2-(4-(1,2,4-oxadiazol-5-yl)cyclohexylamino)-8-(2,6-dichloro-4-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
681	(1s,4s)-4-(2-(4-(1,2,4-oxadiazol-5-yl)cyclohexylamino)-8-(2-chloro-4-cyano-6-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
682	(1s,4s)-4-(2-(4-(1,2,4-oxadiazol-5-yl)cyclohexylamino)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

Compound	Compound Name
683	(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
684	(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
685	(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
686	(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
687	(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
688	(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
689	(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
690	(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
691	(1s,4s)-4-(8-(4-bromo-2,6-dichlorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
692	(1s,4s)-4-(8-(4-bromo-2,6-dichlorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
693	(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
694	(1s,4s)-4-(2-(cyclopentylamino)-8-(2,3-dichloro-4-cyanophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
695	(1r,4s)-4-(8-(2,3-dichloro-4-cyanophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
696	(1s,4s)-4-(8-(2,3-dichloro-4-cyanophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
697	(1s,4s)-4-(8-(2,3-dichloro-4-cyanophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
698	(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-((R)-3,3-difluorocyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
699	(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((R)-3,3-difluorocyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
700	(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((R)-3,3-difluorocyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
701	(1s,4s)-4-(2-((R)-1-(methylsulfonyl)piperidin-3-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

Compound	Compound Name
702	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((R)-1-(methylsulfonyl)piperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
703	(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((R)-1-(methylsulfonyl)piperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
704	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((R)-1-(methylsulfonyl)piperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
705	(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((R)-1-(methylsulfonyl)piperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
706	(R)-3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4,6-trichlorophenylamino)-9H-purin-2-ylamino)-N-methylpiperidine-1-carboxamide;
707	(R)-3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-2-ylamino)-N-methylpiperidine-1-carboxamide;
708	(R)-3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-2-ylamino)-N-methylpiperidine-1-carboxamide;
709	(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;
710	(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2-chloro-4-cyano-6-fluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;
711	(1s,4s)-4-(2-((R)-1-acetylpiperidin-3-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
712	(1s,4s)-4-(2-((R)-1-acetylpiperidin-3-ylamino)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
713	(1s,4s)-4-(2-((R)-1-acetylpiperidin-3-ylamino)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
714	(1s,4s)-4-(2-((R)-1-acetylpiperidin-3-ylamino)-8-(4-chloro-2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
715	(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
716	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
717	(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
718	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((3S,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
720	(1r,4s)-4-(2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
721	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

Compound	Compound Name
722	(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
723	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((3S,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
724	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((3S,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
725	(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
726	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((3S,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
727	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
728	(1s,4s)-1-methyl-4-(2-((3S,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
729	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
730	(1s,4s)-4-(2-(3-(methylsulfonyl)cyclobutylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
731	(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(3-(methylsulfonyl)cyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
732	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(3-(methylsulfonyl)cyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
733	(1s,4s)-4-(2-((R)-1-ethylpiperidin-3-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
734	(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((R)-1-ethylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
735	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((R)-1-ethylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
736	(1s,4s)-4-(8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-2-(3-(methylsulfonyl)cyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
737	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(3-(methylsulfonyl)cyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
738	(1s,4s)-4-(8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-2-((R)-1-ethylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
739	(1s,4s)-4-(2-((R)-1-isopropylpiperidin-3-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
740	(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((R)-1-isopropylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

Compound	Compound Name
741	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((R)-1-isopropylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
742	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((R)-1-isopropylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
743	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((R)-1-phenylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
744	(1s,4s)-4-(2-((R)-1-phenylpiperidin-3-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
745	(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((R)-1-phenylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
746	(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-((R)-1-phenylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
747	(1s,4s)-4-(2-((R)-1-phenylpiperidin-3-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
748	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((R)-1-phenylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
749	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((R)-1-phenylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
750	(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((R)-1-phenylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
751	(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((R)-1-phenylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
752	(1s,4s)-4-(2-((R)-1-benzylpiperidin-3-ylamino)-8-(2-chloro-4,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
753	(1s,4s)-4-(2-((R)-1-benzylpiperidin-3-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
754	(1s,4s)-4-(2-((R)-1-benzylpiperidin-3-ylamino)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
755	(1s,4s)-4-(2-((R)-1-benzylpiperidin-3-ylamino)-8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
756	(1s,4s)-4-(2-((R)-1-benzylpiperidin-3-ylamino)-8-(4-cyano-2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
757	(1s,4s)-4-(2-((R)-1-benzylpiperidin-3-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
758	(1s,4s)-4-(2-((R)-1-benzylpiperidin-3-ylamino)-8-(4-chloro-2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
759	(1s,4s)-4-(2-((R)-1-benzylpiperidin-3-ylamino)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

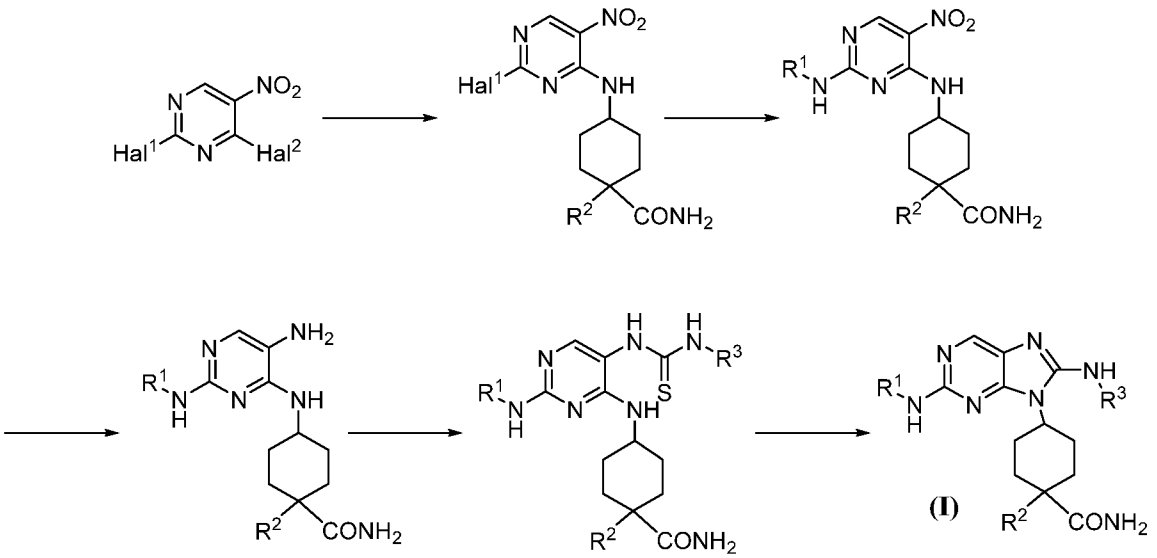
Compound	Compound Name
760	(1s,4s)-4-(2-((R)-1-benzylpiperidin-3-ylamino)-8-(2,6-dichloro-4-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
761	(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
762	(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
763	(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
764	(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((3S,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
765	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((R)-3,3-dimethyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
766	(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
767	(1s,4s)-4-(2-((R)-3,3-dimethyltetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
768	(R)-isopropyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2-chloro-4,6-difluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;
769	(R)-isopropyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4,6-trichlorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;
770	(R)-isopropyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;
771	(R)-isopropyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;
772	(R)-isopropyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(4-cyano-2,6-difluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;
773	(R)-isopropyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4,6-trifluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;
774	(R)-isopropyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(4-chloro-2,6-difluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;
775	(R)-isopropyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;
776	(R)-isopropyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-dichloro-4-fluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;
777	(R)-isopropyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2-chloro-4-cyano-6-fluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;
778	(1s,4s)-4-(2-((R)-1-benzylpiperidin-3-ylamino)-8-(2-chloro-4-cyano-6-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

Compound	Compound Name
779	(R)-3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2-chloro-4,6-difluorophenylamino)-9H-purin-2-ylamino)-N-phenylpiperidine-1-carboxamide;
780	(R)-3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4,6-trichlorophenylamino)-9H-purin-2-ylamino)-N-phenylpiperidine-1-carboxamide;
781	(R)-3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-2-ylamino)-N-phenylpiperidine-1-carboxamide;
782	(R)-3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4,6-trifluorophenylamino)-9H-purin-2-ylamino)-N-phenylpiperidine-1-carboxamide;
783	(R)-3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(4-chloro-2,6-difluorophenylamino)-9H-purin-2-ylamino)-N-phenylpiperidine-1-carboxamide;
784	(R)-3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-2-ylamino)-N-phenylpiperidine-1-carboxamide;
785	(R)-3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-dichloro-4-fluorophenylamino)-9H-purin-2-ylamino)-N-phenylpiperidine-1-carboxamide;
786	(R)-3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2-chloro-4-cyano-6-fluorophenylamino)-9H-purin-2-ylamino)-N-phenylpiperidine-1-carboxamide;
787	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((R)-3,3-dimethyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
788	(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((R)-1-tosylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
789	(1s,4s)-4-(2-((R)-1-tosylpiperidin-3-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
790	(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((R)-1-tosylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
791	(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-((R)-1-tosylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
792	(1s,4s)-4-(2-((R)-1-tosylpiperidin-3-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
793	(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((R)-1-tosylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
794	(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((R)-1-tosylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
795	(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((R)-1-tosylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
796	(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((R)-1-tosylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
797	(R)-3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-9H-purin-2-ylamino)-N-methylpiperidine-1-carboxamide;

Compound	Compound Name
798	(1s,4s)-4-(2-((R)-1-acetylpiperidin-3-ylamino)-8-(2-chloro-4,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
799	(1s,4s)-4-(2-((R)-1-acetylpiperidin-3-ylamino)-8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
800	(1s,4s)-4-(2-((R)-1-acetylpiperidin-3-ylamino)-8-(2,6-dichloro-4-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
801	(1s,4s)-4-(2-((R)-1-acetylpiperidin-3-ylamino)-8-(2,6-dichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
802	(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide; or
803	(1r,4s)-4-(2-(((3R,4S)-3-fluorotetrahydro-2H-pyran-4-yl)amino)-8-((2,4,6-trichlorophenyl)amino)-9H-purin-9-yl)-1-methylcyclohexane-1-carboxamide.

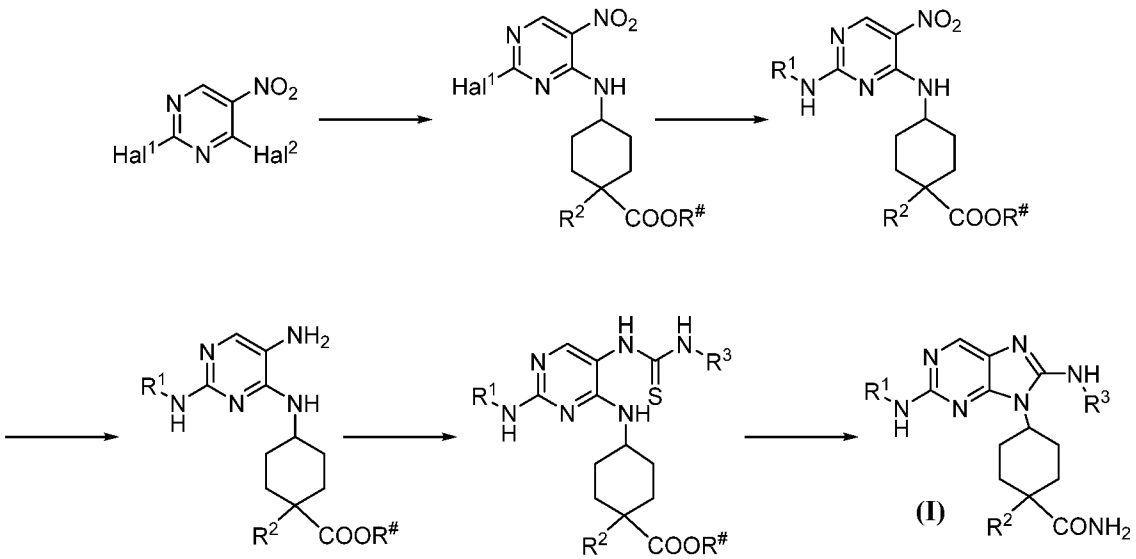
METHODS FOR MAKING AMINOPURINE COMPOUNDS

[00139] The Aminopurine Compounds can be made using conventional organic syntheses and commercially available starting materials. By way of example and not limitation, Aminopurine Compounds of formula (I) can be prepared as described in U.S. Patent No. 7,723,340, U.S. Patent No. 8,158,635, and U.S. Patent Application No. 14/874,513 , or as outlined in Scheme 1, shown below, as well as in the examples set forth herein. It should be noted that one skilled in the art would know how to modify the procedures set forth in the illustrative schemes and examples to arrive at the desired products.



Scheme 1

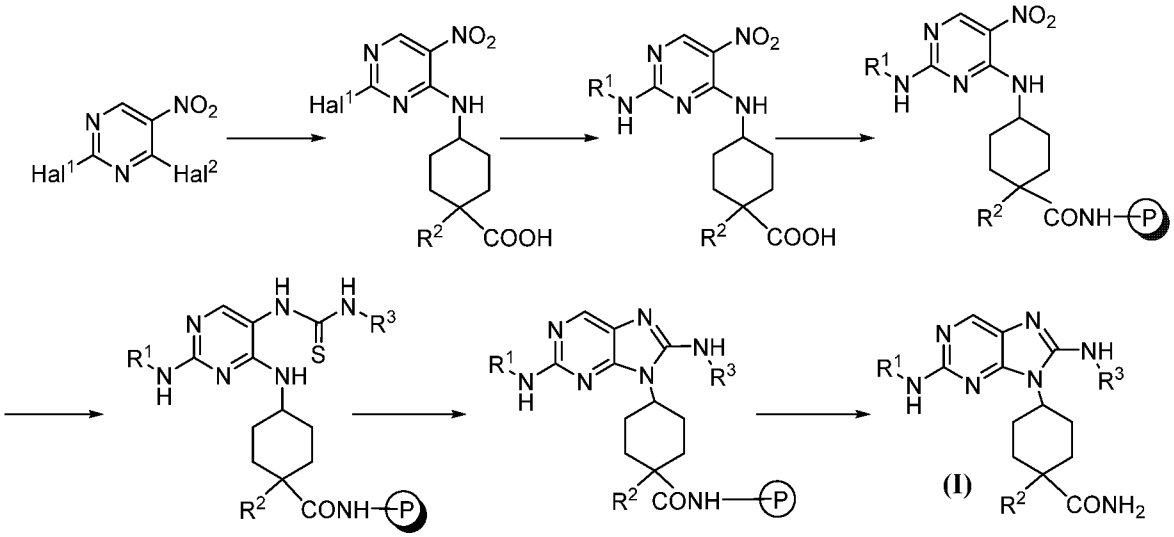
[00140] As shown in Scheme 1, compounds of formula (I), wherein R^1, R^2 and R^3 are as defined herein, can be prepared starting from an appropriately derivatized nitropyrimidine, wherein Hal^1 is Cl, and Hal^2 is Cl. Treatment of the dihalogenated nitropyrimidine with the appropriate 4-aminocyclohexane-1-carboxamide derivative, in the presence of a base, such as, for example, DIEA, TEA, or pyridine, in a solvent, such as for example, DCM or THF, at reduced temperature (for example, -78 °C), provided incorporation of the cyclohexylamide sidechain. Treatment of this product with R^1NH_2, in the presence of a base, such as DIEA, TEA, or pyridine, in a solvent such as DCM, THF, dioxane or DMF, at elevated temperature (for example 25 – 80 °C), resulted in incorporation of the R^1 sidechain. Reduction of the nitro moiety, using, for example hydrogen in the presence of a catalyst such as Pd/C, in a solvent, such as MeOH or ethyl acetate, provided the aminopyrimidine derivative. The aminopyrimidine derivative was treated with R^3NCS, in a solvent, such as THF, DMF, NMP, dioxane, or EtOH, to obtain the (optionally isolated) thiourea derivative, which was cyclized, using for example, EDC or DIC, in a solvent, for example, THF, dioxane, NMP or DMF, optionally at elevated temperature (for example, 40- 80 °C), to provide compounds of formula (I).



Scheme 2

[00141] Alternatively, as shown in Scheme 2, compounds of formula (I), wherein R^1, R^2 and R^3 are as defined herein, and $R^{\#}$ is $C_{1\text{-}2}$ alkyl, can be prepared starting from, as before, an appropriately derivatized nitropyrimidine, wherein Hal^1 is Cl, and Hal^2 is Cl. Treatment of the

dihalogenated nitropyrimidine with the appropriate 4-aminocyclohexane-1-carboxylate alkyl ester derivative, in the presence of a base, such as DIEA, TEA or pyridine, in a solvent, such as DCM or THF, at reduced temperature (for example, -78 °C), provided incorporation of the cyclohexylalkyl ester sidechain. Treatment of this product with R^1NH_2, in the presence of a base, such as DIEA, TEA, or pyridine, in a solvent such as DCM, THF, dioxane or DMF, at elevated temperature (for example 25- 80 °C), resulted in incorporation of the R^1 sidechain. Reduction of the nitro moiety, using, for example hydrogen in the presence of a catalyst such as Pd/C, in a solvent, such as MeOH or ethyl acetate, provided the aminopyrimidine derivative. The aminopyrimidine derivative was treated with R^3NCS, in a solvent, such as THF, DMF, NMP, dioxane, or EtOH, to obtain the (optionally isolated) thiourea derivative, which was cyclized, using for example, EDC or DIC, in a solvent, for example, THF, NMP, dioxane, or DMF, optionally at elevated temperature (for example, 40 °C to 80 °C), to provide the derivatized diaminopurine derivative. Saponification of the alkyl ester, using a base (such as lithium hydroxide, sodium hydroxide, or potassium hydroxide), in a solvent (such as aqueous THF, MeOH, or EtOH), optionally at elevated temperature (for example, 40 - 80 °C), followed by amide formation, via treatment with NH_4Cl, in the presence of a coupling agent (such as, for example, HATU, CDI, HBTU, EDC, optionally in combination with HOBt, or ethyl chloroformate) and a base (such as DIEA, TEA, pyridine, DBU, or NMM), in a solvent, for example, DMF, provided the compounds of formula (I).



Scheme 3

[00142] In a third approach, compounds of formula (I), wherein R^1, R^2 and R^3 are as defined herein, and P is a solid support, such as a resin, can be prepared starting from, as before, an appropriately derivatized nitropyrimidine, wherein Hal^1 is Cl, and Hal^2 is Cl. Treatment of the dihalogenated nitropyrimidine with the appropriate 4-aminocyclohexane-1-carboxylate derivative, in the presence of a base, such as DIEA, TEA or pyridine, in a solvent, such as DCM or THF, at reduced temperature (for example, -78 °C), provided incorporation of the cyclohexylalkyl carboxylate sidechain. Treatment of this product with R^1NH_2, in the presence of a base, such as DIEA, TEA, or pyridine, in a solvent such as DCM, THF, dioxane or DMF, at elevated temperature (for example 25 - 80 °C), resulted in incorporation of the R^1 sidechain. This intermediate was coupled to a solid support, such as a polymeric resin (for example, Rink-H resin) using a coupling agent (for example, HATU, CDI, HBTU, EDC, optionally in combination with HOBt, or ethyl chloroformate), in a solvent, for example DMF, at elevated temperature, for example 50 °C. Treatment of the resin-bound intermediate with a reducing agent (such as chromium(II) chloride), in a solvent (such as DMF/MeOH mixture), resulted in reduction of the nitro group. The resulting amine moiety was reacted with R^3NCS, in a solvent, for example, EtOH, at elevated temperature, for example, 40 °C to 60 °C, providing the thiourea derivative intermediate. This intermediate was cyclized using, for example, EDC or DIC, in a solvent, for example, THF, NMP, dioxane, or DMF, optionally at elevated temperature (for example, 40 °C to 80 °C), to provide the resin-bound diaminopurine derivative. Finally, acid treatment (for example, treatment with TFA in a solvent such as DCM), resulted in cleavage of compounds of formula (I) from the resin.

METHODS OF USE

[00143] The Aminopurine Compounds have utility as pharmaceuticals to treat, prevent or improve conditions in animals or humans. Accordingly, provided herein are Aminopurine Compounds and pharmaceutical compositions thereof that can be used in all the methods as provided herein. Particularly, the Aminopurine Compounds as provided herein are for uses in the treatment or prevention of a cancer. The methods provided herein comprise the administration of an effective amount of one or more Aminopurine Compound(s) to a subject in need thereof. It is to be understood that the methods described herein also include treatment with a pharmaceutical composition, such as those provided below, where the pharmaceutical composition includes an

Aminopurine Compound described herein and optionally at least one pharmaceutically acceptable excipient.

[00144] In another aspect, provided herein are methods for treating or preventing a cancer, comprising administering to a subject in need thereof an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof, as described herein. In some embodiments, the cancer is a solid tumor or a hematological tumor. In some embodiments, the cancer is not melanoma.

[00145] In some embodiments, the solid tumor is melanoma, colorectal cancer, stomach cancer, head and neck cancer, thyroid cancer, bladder cancer, CNS cancer, lung cancer, pancreatic cancer, and soft tissue cancer. In one embodiment, the solid tumor is endocrine cancer, bladder cancer, breast cancer, cervix cancer, colon cancer, duodenum cancer, glioma, head and d neck cancer, kidney cancer, liver cancer, lung cancer (e.g. non-small cell lung cancer NSCLC), esophageal cancer, thyroid cancer, or pancreatic cancer.

[00146] In other embodiment, the cancer is bladder cancer, breast cancer (for example Her positive, Her negative, or EGFR positive), CNS cancer (including neuroblastoma, and glioma), colon cancer, gastrointestinal cancer (for example, stomach cancer, and colon cancer), endocrine cancer (for example, thyroid cancer, or adrenal gland cancer), female genitoureal cancer (for example, cervix cancer, ovary clear cell cancer, vulva cancer, uterus cancer, or ovary cancer), head and neck cancer, hematopoietic cancer (for example, leukemia or myeloma), kidney cancer, liver cancer, lung cancer (for example, NSCLC, or SCLC), melanoma, pancreas cancer, prostate cancer, or soft tissue cancer (for example, sarcoma, or osteosarcoma).

[00147] In another embodiment, the cancer is bladder cancer, breast cancer (for example Her positive, Her negative, or EGFR positive), CNS cancer (for example, glioma, or neuroblastoma), colon cancer, gastrointestinal cancer (for example, stomach cancer), endocrine cancer (for example, thyroid cancer or adrenal gland cancer), female genitoureal cancer (for example, cancer of the uterus, cervix, ovary clear cell, or vulva), head and neck cancer, hematopoietic cancer (for example, leukemia or myeloma), kidney cancer, liver cancer, lung cancer (for example, NSCLC, or SCLC), melanoma, pancreas cancer, prostate cancer, or soft tissue cancer (for example, sarcoma or osteosarcoma).

[00148] In still another embodiment, the cancer is a cancer set forth in Table 3.

[00149] Also provided herein are methods for treating or preventing hepatocellular carcinoma (HCC), comprising administering to a subject in need thereof an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof, as described herein.

[00150] Also provided herein are methods for treating or preventing colorectal cancer (CRC), melanoma, gastric cancer, HCC, lung cancer, pancreatic cancer, leukemia, or multiple myeloma, comprising administering to a subject in need thereof an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof, as described herein. In one embodiment, the CRC, gastric, or HCC is a cancer characterized by a β-catenin mutation. Also provided herein are methods for treating or preventing colorectal cancer (CRC), gastric cancer, HCC, lung cancer, pancreatic cancer, leukemia, and multiple myeloma, comprising administering to a subject in need thereof an effective amount of an Aminopurine Compound, as described herein.

[00151] In another embodiment provided herein are methods of treating leukemia comprising administering an Aminopurine Compound or a pharmaceutical composition thereof. The leukemia can be chronic myelogenous leukemia (CML). In another embodiment, the leukemia is acute myelogenous leukemia (AML). In one embodiment, the leukemia is FLT-3 mutated AML.

[00152] In another embodiment provided herein are methods of treating lymphoma comprising administering an Aminopurine Compound or a pharmaceutical composition thereof. The lymphoma can be Burkitt's lymphoma. In one embodiment, the leukemia is Hodgkin's lymphoma. In another embodiment, the leukemia is a B-cell lymphoma. In another embodiment, the leukemia is a T-cell lymphoma. In still another embodiment, the lymphoma is primary effusion lymphoma (PEL).

[00153] Aminopurine Compounds (exemplified by Compound 1) show anti-proliferative activity in a variety of cancer cell lines. (Table 3) Anti-proliferative activity in these cancer cell lines indicates that the Aminopurine Compounds are useful in the treatment of cancers, including hematopoietic and solid tumors. In one embodiment, the hematopoietic and solid tumors are selected from bladder cancer, breast cancer, CNS cancer (for example, neuroblastoma, medulloblastoma and glioma), colon cancer, duodenum cancer, endocrine cancer (for example, thyroid cancer and adrenal gland cancer), female genitourinary cancer (for example, uterus cancer, cervix cancer, ovary cancer and vulva cancer), head and neck cancer (for example, esophageal cancer), hematopoietic and lymphoid cancer (for example, lymphoma, leukemia, and

myeloma), kidney cancer, liver cancer, lung cancer (for example, NSCLC and SCLC), pancreas cancer, prostate cancer, skin cancer (for example, melanoma and carcinoma), soft tissue cancer (for example, sarcoma and osteosarcoma), stomach cancer, and testis cancer. In one embodiment, the hematopoietic and solid tumors are selected from bladder cancer, breast cancer, CNS cancer (for example, neuroblastoma, medulloblastoma and glioma), colon cancer, duodenum cancer, endocrine cancer (for example, thyroid cancer and adrenal gland cancer), female genitourinary cancer (for example, uterus cancer, cervix cancer, and vulva cancer), head and neck cancer, hematopoietic and lymphoid cancer (for example, lymphoma, leukemia, and myeloma), kidney cancer, liver cancer, lung cancer (for example, NSCLC and SCLC), pancreas cancer, prostate cancer, skin cancer (for example, melanoma and carcinoma), soft tissue cancer (for example, sarcoma and osteosarcoma), stomach cancer, and testis cancer. In one embodiment, the cancer is HCC. In one embodiment, the cancer is gastric cancer. In one embodiment, the cancer is CRC. Such cancers can be characterized by a β-catenin mutation. In still another embodiment, such cancers can be characterized by a BRAF mutation. In still another embodiment, such cancers are characterized by having both a β-catenin mutation and a BRAF mutation.

[00154] In another embodiment, Aminopurine Compounds (exemplified by Compound 1) induce apoptosis in a variety of cancer cell lines. Induction of apoptosis indicates that the Aminopurine compounds are useful in the treatment of cancers, including hematopoietic and solid tumors. In one embodiment, the hematopoietic and solid tumors are selected from bladder cancer, breast cancer, CNS cancer (for example, neuroblastoma, and glioma), colon cancer, duodenum cancer, endocrine cancer (for example, thyroid cancer and adrenal gland cancer), female genitourinary cancer (for example, uterus cancer, cervix cancer, ovary cancer and vulva cancer), head and neck cancer (for example, esophageal cancer), hematopoietic and lymphoid cancer (for example, lymphoma, leukemia, and myeloma), kidney cancer, liver cancer, lung cancer (for example, NSCLC and SCLC), pancreas cancer, prostate cancer, skin cancer (for example, melanoma and carcinoma), soft tissue cancer (for example, sarcoma and osteosarcoma), stomach cancer, and testis cancer. In one embodiment, the hematopoietic and solid tumors are selected from bladder cancer, breast cancer, CNS cancer (for example, neuroblastoma, and glioma), colon cancer, duodenum cancer, endocrine cancer (for example, thyroid cancer and adrenal gland cancer), female genitourinary cancer (for example, vulva

cancer), head and neck cancer (for example, esophageal cancer), hematopoietic and lymphoid cancer (for example, lymphoma, and leukemia), kidney cancer, liver cancer, lung cancer (for example, NSCLC and SCLC), pancreas cancer, prostate cancer, skin cancer (for example, melanoma), soft tissue cancer (for example, sarcoma and osteosarcoma), stomach cancer, and testis cancer. In one embodiment, the hematopoietic and solid tumors are selected from bladder cancer, breast cancer, CNS cancer (for example, medulloblastoma, neuroblastoma, and glioma), colon cancer, duodenum cancer, endocrine cancer (for example, thyroid cancer and adrenal gland cancer), female genitourinary cancer (for example, placenta cancer, uterus cancer, cervix cancer, ovary cancer and vulva cancer), head and neck cancer (for example, esophageal cancer), hematopoietic and lymphoid cancer (for example, lymphoma, leukemia, and myeloma), kidney cancer, liver cancer, lung cancer (for example, NSCLC and SCLC), pancreas cancer, prostate cancer, skin cancer (for example, melanoma and carcinoma), soft tissue cancer (for example, sarcoma and osteosarcoma), stomach cancer, and testis cancer.

[00155] Also provided herein are methods for treating or preventing a cancer characterized by a BRAF mutation and/or a beta-catenin mutation (alternatively referred to as CTNNB1 mutation), comprising administering to a subject in need thereof an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof, as described herein. In some such embodiments, the cancer is characterized by a BRAF mutation. In another embodiment, the cancer is characterized by a beta-catenin mutation. In yet another embodiment, the cancer is characterized by an activated beta-catenin pathway. In some such embodiments, the cancer is CRC or melanoma characterized by a BRAF mutation. In other embodiments, the cancer is CRC characterized by a beta-catenin mutation, additionally comprising an EGFR mutation or increased EGFR activity (for example, CRC characterized by an activated beta-catenin pathway and an EGFR mutation, or CRC characterized by an activated beta-catenin pathway and increased EGFR activity). In still other embodiments, the cancer is gastric cancer characterized by a beta-catenin mutation, additionally comprising a KRAS mutation (i.e. gastric cancer characterized by an activated beta-catenin pathway and a KRAS mutation). In another embodiment the cancer is HCC, characterized by an activated beta-catenin pathway. In some such embodiments, the BRAF mutation is BRAF V660E. In other embodiments, the BRAF mutation is one or more of BRAF V600E, BRAF T119S, or BRAF G596R. In some such embodiments, the beta-catenin mutation is one or more of beta-catenin S33Y, G34E, S45del, or

S33C. In some such embodiments, the EGFR mutation is one or more of EGFR E282K, G719S, P753S, or V1011M. In some such embodiments, the KRAS mutation is A146T, G12C, G12D, G12V, G13D, or Q61L.

[00156] Provided herein are methods of treating CRC characterized by a beta-catenin mutation where the beta-catenin mutation is one or more of beta-catenin S33Y, G34E, S45del, or S33C comprising administering to a subject in need thereof an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof, as described herein. In one embodiment, the Aminopurine Compound is Compound 1. Further provided herein are methods of treating CRC characterized by a beta-catenin mutation, additionally comprising an EGFR mutation or increased EGFR activity where the beta-catenin mutation is one or more of beta-catenin S33Y, G34E, S45del, or S33C and the EGFR mutation is one or more of EGFR E282K, G719S, P753S, or V1011M comprising administering to a subject in need thereof an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof, as described herein. In one embodiment, the Aminopurine Compound is Compound 1.

[00157] Also provided herein are methods for treating or preventing a cancer expressing PD-L1, comprising administering to a subject in need thereof an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof, as described herein. In some such embodiments, the PD-L1 expressing cancer is melanoma, lung cancer, renal cell carcinoma (RCC), or HCC.

[00158] Also provided herein are methods for treating or preventing a cancer characterized by a BRAF mutation, comprising administering to a subject in need thereof an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof, as described herein. In some such embodiments, the cancer characterized by a BRAF mutation is CRC, thyroid cancer, melanoma or lung cancer. In some such embodiments, the cancer characterized by a BRAF mutation is CRC, thyroid cancer, or lung cancer. In some such embodiments, the BRAF mutation is BRAF V660E. In other embodiments, the BRAF mutation is one or more of BRAF V600E, BRAF T119S, or BRAF G596R.

[00159] Also provided herein are methods for treating or preventing a cancer characterized by an NRAS mutation, comprising administering to a subject in need thereof an effective amount of

an Aminopurine Compound or a pharmaceutical composition thereof, as described herein. In some such embodiments, the cancer characterized by an NRAS mutation is melanoma.

[00160] Also provided herein are methods for treating or preventing a cancer characterized by a KRAS mutation, comprising administering to a subject in need thereof an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof, as described herein. In some such embodiments, the cancer characterized by a KRAS mutation is CRC, pancreas cancer or lung cancer. The KRAS mutation can be a KRAS mutation as described above.

[00161] Also provided herein are methods for treating or preventing a cancer characterized by a beta-catenin mutation, comprising administering to a subject in need thereof an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof, as described herein. Also provided herein are methods for treating or preventing a cancer characterized by an activated beta-catenin pathway, comprising administering to a subject in need thereof an effective amount of an Aminopurine Compound, as described herein. In some such embodiments, the cancer characterized by a beta-catenin mutation is CRC, stomach cancer, HCC or sarcoma. In some such embodiments, the cancer characterized by an activated beta-catenin pathway is CRC, stomach cancer, HCC or sarcoma. The beta-catenin mutation can be a mutation as described herein.

[00162] Also provided herein are methods for treating or preventing hepatocellular carcinoma (HCC), comprising administering to a subject in need thereof an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof, as described herein. In some such embodiments, the HCC is characterized by a beta-catenin mutation and/or increased YAP expression. In some such embodiments, the HCC is characterized by an activated beta-catenin pathway and/or increased YAP amplification expression. In some embodiments, the increased YAP expression is due to amplification or a mutation.

[00163] Also provided herein are methods for treating or preventing colorectal cancer (CRC), comprising administering to a subject in need thereof an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof, as described herein. In some such embodiments, the CRC is characterized by a BRAF mutation and/or beta-catenin mutation. In some such embodiments, the CRC is characterized by a BRAF mutation and/or an activated beta-catenin pathway.

[00164] Also provided herein are methods for treating or preventing gastric cancer, comprising administering to a subject in need thereof an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof, as described herein. In some such embodiments, the gastric cancer is characterized by a beta-catenin mutation. In some such embodiments, the gastric cancer is characterized by activated beta-catenin activation. The beta-catenin mutation can be a mutation as described herein.

[00165] Also provided herein are methods for treating or preventing melanoma, comprising administering to a subject in need thereof an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof, as described herein. In some such embodiments, the melanoma is characterized by a BRAF mutation and/or NRAS mutation.

[00166] Also proved herein are methods of treating or preventing C-Met amplified hepatocellular carcinoma (HCC). In one embodiment, the method comprises treating C-Met amplified HCC by administering an effective amount of an Aminopurine Compound described herein to a subject having C-Met amplified HCC. In another embodiment, the method comprises preventing C-Met amplified HCC by administering a prophylactic amount of an Aminopurine Compound described herein to a subject having C-Met amplified HCC

[00167] Further provided herein are methods for predicting response to treatment with an Aminopurine Compound in a patient having a cancer characterized by a gene mutation, the method comprising: a) obtaining a biological test sample from the patient's cancer; b) obtaining the gene sequence of one or more genes selected from BRAF, NRAS, KRAS, and/or CTNNB1 in said biological test sample; c) comparing said gene sequence(s) to the gene sequence(s) of a biological wild-type sample; wherein the presence of a mutation indicates an increased likelihood of response to Aminopurine Compound treatment of said patient's cancer. In some such embodiments, the method additionally comprises administering an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof, as described herein.

[00168] Further provided herein are methods for predicting therapeutic efficacy of Aminopurine Compound treatment of a patient having a cancer characterized by a gene mutation, the method comprising: a) obtaining a biological test sample from the patient's cancer; b) obtaining the gene sequence(s) of one or more genes selected from BRAF, NAS, KRAS, and/or CTNNB1 in said biological test sample; c) comparing said gene sequence(s) to the gene

sequence(s) of a biological wild-type sample; wherein the presence of a mutation indicates an increased likelihood of therapeutic efficacy of said Aminopurine Compound treatment for said patient. In some such embodiments, the method additionally comprises administering an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof, as described herein.

[00169] In some embodiments, provided herein are methods for treating and preventing cancer metastasis, comprising administering to a subject in need thereof an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof, as described herein. In some embodiments, the cancer is a metastatic cancer, in particular, a metastatic solid tumor or metastatic hematologic cancer, wherein the solid tumor and hematologic cancer is as described herein. In other embodiments, provided herein are methods of treating and preventing cancer metastasis, comprising administering to a subject in need thereof an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof, as described herein.

[00170] In yet another aspect, provided herein is methods of eradicating cancer stem cells in a subject, comprising administering to a subject in need thereof an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof, as described herein.

[00171] In still another aspect, provided herein are methods of inducing differentiation in cancer stem cells in a subject, comprising administering to a subject in need thereof an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof, as described herein. In other embodiments, provided herein are methods of inducing cancer stem cell death in a subject, comprising administering to a subject in need thereof an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof, as described herein. In some such embodiments, the cancer is a solid tumor or a hematological cancer, as described herein .

[00172] In one embodiment, provided herein are methods for achieving a Response Evaluation Criteria in Solid Tumors (RECIST 1.1) of complete response, partial response or stable disease in a patient comprising administering an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof to a patient having a cancer, in particular a solid tumor as described herein. In another embodiment, provided herein are methods to increase Progression Free Survival rates, as determined by Kaplan-Meier estimates. Such methods are applicable and can be in addition to the methods of treating cancers as described herein.

[00173] In one embodiment, provided herein are methods for preventing or delaying a Response Evaluation Criteria in Solid Tumors (RECIST 1.1) of progressive disease in a patient, comprising administering an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof to a patient having a solid tumor as described herein. In one embodiment the prevention or delaying of progressive disease is characterized or achieved by a change in overall size of the target lesions, of for example, between -30% and +20% compared to pre-treatment. In another embodiment, the change in size of the target lesions is a reduction in overall size of more than 30%, for example, more than 50% reduction in target lesion size compared to pre-treatment. In another, the prevention is characterized or achieved by a reduction in size or a delay in progression of non-target lesions compared to pre-treatment. In one embodiment, the prevention is achieved or characterized by a reduction in the number of target lesions compared to pre-treatment. In another, the prevention is achieved or characterized by a reduction in the number or quality of non-target lesions compared to pre-treatment. In one embodiment, the prevention is achieved or characterized by the absence or the disappearance of target lesions compared to pre-treatment. In another, the prevention is achieved or characterized by the absence or the disappearance of non-target lesions compared to pre-treatment. In another embodiment, the prevention is achieved or characterized by the prevention of new lesions compared to pre-treatment. In yet another embodiment, the prevention is achieved or characterized by the prevention of clinical signs or symptoms of disease progression compared to pre-treatment, such as cancer-related cachexia or increased pain. In one embodiment, the cancer is cancer set forth in Table 3. Such methods are applicable and can be in addition to the methods of treating cancers as described herein.

[00174] In certain embodiments, provided herein are methods for decreasing the size of target lesions in a patient compared to pre-treatment, comprising administering an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof to a patient having a cancer, in particular a solid tumor as described herein. Such methods are applicable and can be in addition to the methods of treating cancers as described herein.

[00175] In certain embodiments, provided herein are methods for decreasing the size of a non-target lesion in a patient compared to pre-treatment, comprising administering an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof to a patient

having a cancer, in particular a solid tumor as described herein. Such methods are applicable and can be in addition to the methods of treating cancers as described herein.

[00176] In certain embodiments, provided herein are methods for achieving a reduction in the number of target lesions in a patient compared to pre-treatment, comprising administering an effective amount of an Aminopurine Compound to a patient having a cancer, in particular a solid tumor as described herein. Such methods are applicable and can be in addition to the methods of treating cancers as described herein.

[00177] In certain embodiments, provided herein are methods for achieving a reduction in the number of non-target lesions in a patient compared to pre-treatment, comprising administering an effective amount an Aminopurine Compound or a pharmaceutical composition thereof to a patient having a cancer, in particular a solid tumor as described herein. Such methods are applicable and can be in addition to the methods of treating cancers as described herein.

[00178] In certain embodiments, provided herein are methods for achieving a disappearance of all target lesions in a patient, comprising administering an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof to a patient having a cancer, in particular a solid tumor as described herein. Such methods are applicable and can be in addition to the methods of treating cancers as described herein.

[00179] In certain embodiments, provided herein are methods for achieving a disappearance of all non-target lesions in a patient, comprising administering an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof to a patient having a cancer, in particular a solid tumor as described herein. Such methods are applicable and can be in addition to the methods of treating cancers as described herein.

[00180] In certain embodiments, provided herein are methods for treating a cancer, in particular a solid tumor as described herein, the methods comprising administering an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof to a patient having a cancer, in particular a solid tumor, wherein the treatment results in a complete response, partial response or stable disease, as determined by Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Such methods are applicable and can be in addition to the methods of treating cancers as described herein.

[00181] In certain embodiments, provided herein are methods for treating a cancer, in particular a solid tumor as described herein, the methods comprising administering an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof to a patient having a cancer, in particular a solid tumor as described herein, wherein the treatment results in a reduction in target lesion size, a reduction in non-target lesion size and/or the absence of new target and/or non-target lesions, compared to pre-treatment. In one embodiment, the cancer is a cancer set forth in Table 3. Such methods are applicable and can be in addition to the methods of treating cancers as described herein.

[00182] In certain embodiments, provided herein are methods for treating a cancer, in particular a solid tumor as described herein, the methods comprising administering an effective amount an Aminopurine Compound or a pharmaceutical composition thereof to a patient having a cancer, in particular a solid tumor as described herein, wherein the treatment results in prevention or retarding of clinical progression, such as cancer-related cachexia or increased pain.

[00183] In another embodiment, provided herein are methods for inducing a therapeutic response characterized with the International Workshop Criteria (IWC) for NHL (*see* Cheson BD, Pfistner B, Juweid, ME, et. al. Revised Response Criteria for Malignant Lymphoma. J. Clin. Oncol: 2007: (25) 579-586) of a patient, comprising administering an effective amount an Aminopurine Compound or a pharmaceutical composition thereof to a patient having a cancer, in particular hematological cancers such as lymphoma, as described herein. In another embodiment, provided herein are methods for achieving complete remission, partial remission or stable disease, as determined by the International Workshop Criteria (IWC) for NHL in a patient, comprising administering an effective amount of an Aminopurine Compound to a patient having a cancer, in particular hematological cancers such as lymphoma, as described herein. In another embodiment, provided herein are methods for achieving an increase in overall survival, progression-free survival, event-free survival, time to progression, disease-free survival or lymphoma-free survival as determined by the International Workshop Criteria (IWC) for NHL in a patient, comprising administering an effective amount of an Aminopurine Compound to a patient having a cancer, in particular hematological cancers such as lymphoma, as described herein. Such methods are applicable and can be in addition to the methods of treating cancers as described herein.

[00184] In another embodiment, provided herein are methods for inducing a therapeutic response assessed with the International Uniform Response Criteria for Multiple Myeloma (IURC) (*see* Durie BGM, Harousseau J-L, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia, 2006; (10) 10: 1-7) of a patient, comprising administering an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof to a patient having a cancer, in particular multiple myeloma. In another embodiment, provided herein are methods for achieving a stringent complete response, complete response, very good partial response, or partial response, as determined by the International Uniform Response Criteria for Multiple Myeloma (IURC) in a patient, comprising administering an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof to a patient having a cancer, in particular multiple myeloma. In another embodiment, provided herein are methods for achieving an increase in overall survival, progression-free survival, event-free survival, time to progression, or disease-free survival in a patient, comprising administering an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof to a patient having a cancer, in particular multiple myeloma. Such methods are applicable and can be in addition to the methods of treating cancers as described herein.

[00185] In another embodiment, provided herein are methods for inducing a therapeutic response assessed with the Response Assessment for Neuro-Oncology (RANO) Working Group for GBM (*see* Wen P., Macdonald, DR., Reardon, DA., et al. Updated response assessment criteria for high-grade gliomas: Response assessment in neuro-oncology working group. J. Clin. Oncol. 2010; 28: 1963-1972) of a patient, comprising administering an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof to a patient having a cancer, in particular glioblastoma multiforme (GBM). In one embodiment, RANO will be used to establish the proportion of subjects progression-free at 6 months from Day 1 of treatment relative to efficacy evaluable subjects in the GBM type. Such methods are applicable and can be in addition to the methods of treating cancers as described herein.

[00186] In another embodiment, provided herein are methods for improving the Eastern Cooperative Oncology Group Performance Status (ECOG) of a patient, comprising administering an effective amount an Aminopurine Compound or a pharmaceutical composition thereof to a patient having a cancer, in particular a solid tumor or hematological cancer as

described herein. Such methods are applicable and can be in addition to the methods of treating cancers as described herein.

[00187] In another embodiment, provided herein are methods for inducing a therapeutic response assessed by Positron Emission Tomography (PET) outcome of a patient, comprising administering an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof to a patient having a cancer, in particular a solid tumor or hematological cancer as described herein. In certain embodiments, provided herein are methods for treating a cancer, in particular a solid tumor or hematological cancer as described herein, the methods comprising administering an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof to a patient having a cancer, in particular a solid tumor or hematological cancer as described herein, wherein the treatment results in a reduction in tumor metabolic activity, for example, as measured by PET imaging. Such methods are applicable and can be in addition to the methods of treating cancers as described herein.

[00188] In some embodiments of the methods described herein, the Aminopurine Compound is a compound as described herein. In one embodiment, the Aminopurine Compound is a compound of formula (I). In another embodiment, the Aminopurine Compound is a compound from Table 1. In one embodiment, the Aminopurine Compound is an Aminopurine Compound set forth herein having molecular formula $C_{24}H_{27}N_7O_2FCl_3$. In one embodiment, the Aminopurine Compound is (1s,4s)-4-(2-(((3S,4R)-3-fluorotetrahydro-2H-pyran-4-yl)amino)-8-((2,4,6-trichlorophenyl)amino)-9H-purin-9-yl)-1-methylcyclohexane-1-carboxamide, alternatively named cis-4-[2-{[(3S,4R)-3-fluorooxan-4-yl]amino}-8-(2,4,6-trichloroanilino)-9H-purin-9-yl]-1-methylcyclohexane-1-carboxamide (Compound 1).

[00189] Further provided herein are methods for treating patients who have been previously treated for a cancer, in particular a solid tumor or a hematological cancer as described herein, as well as those who have not previously been treated. In one embodiment, the cancer is a cancer provided in Table 3. Such cancers can be treated using the Aminopurine Compounds described herein, including compounds set forth in Table 1 and/or Compound 1. Because patients with a cancer have heterogeneous clinical manifestations and varying clinical outcomes, the treatment given to a patient may vary, depending on his/her prognosis. The skilled clinician will be able to readily determine without undue experimentation specific secondary agents, types of surgery,

and types of non-drug based standard therapy that can be effectively used to treat an individual patient with a cancer.

BIOMARKERS

[00190] In one embodiment, provided herein are methods for modulating the levels of a biomarker in a subject having a cancer as described herein, comprising administering an effective amount of a Aminopurine Compound or a pharmaceutical composition thereof, to said subject. In some such embodiments, the modulation of the biomarker is assessed in a biological sample of the subject, such as in circulating blood, skin biopsies, tumor biopsies, circulating tumor cells, hair, and/or urine. In one embodiment, the biological sample is peripheral blood mononuclear cells (PBMC). In such embodiments, the amount of biomarker modulation is assessed by comparison of the amount of biomarker before and after administration of the Aminopurine Compound or pharmaceutical composition thereof. In some embodiments, the modulation in biomarker is a reduction of about 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, or about 100% compared to baseline levels. In some other embodiments, the modulation in biomarker is an increase of about 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, or about 100% compared to baseline levels.

[00191] In some embodiments, the biomarker is ERK, RSK1, DUSP4, DUSP5, DUSP6, BMF, EFNA1, EGR1, ETV5, FOS, FOSL1, GJA1, IL-8, cMyc, Cyclin D1, YAP, SPRY2, SPRY4, Axin2, CTGF, AREG, CYR61, CXCL1, HAS2, HES1, MAFF, CITED2, ELF3, or PD-L1. In some such embodiments, the modulation is measured by measurement of the reduction of phosphorylation levels of one or more of ERK and RSK1. In some embodiments, the modulation in biomarker is a reduction of about 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, or about 100% compared to baseline levels. In some other embodiments, the modulation in biomarker is an increase of about 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, or about 100% compared to baseline levels.

[00192] In some embodiments, the biomarker is one or more of DUSP4, DUSP6, cyclin D1, c-Myc, SPRY2, and YAP. In some such embodiments, the modulation is measured by measurement of the reduction in mRNA and/or protein expression levels of one or more of DUSP4, DUSP6, cyclin D1, c-Myc, and YAP. In some such embodiments, the modulation is measured by measurement of the reduction in mRNA and/or protein expression levels of one or

more of DUSP4, DUSP6, SPRY2, c-Myc and cyclin D1. In some embodiments, the modulation in biomarker is a reduction of about 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, or about 100% compared to baseline levels.

[00193] In some embodiments, the biomarker is one or more of DUSP4, DUSP6, cyclin D1, c-Myc, SPRY2, and YAP. In some such embodiments, the modulation is measured by measurement of the reduction in mRNA and/or protein expression levels of one or more of DUSP4, DUSP6, cyclin D1, c-Myc, and YAP. In some such embodiments, the modulation is measured by measurement of the reduction in mRNA and/or protein expression levels of one or more of DUSP4, DUSP6, SPRY2, c-Myc and cyclin D1. In some embodiments, the modulation in biomarker is a reduction of about 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, or about 100% compared to baseline levels.

[00194] In some embodiments, the biomarker is one or more of DUSP5, DUSP6, EGR1, ETV5, FOS, FOSL1, IL-8, SPRY2, and SPRY4. In some such embodiments, the modulation is measured by measurement of the reduction in mRNA and/or protein expression levels of one or more of DUSP5, DUSP6, EGR1, ETV5, FOS, FOSL1, IL-8, SPRY2, and SPRY4. In some embodiments, the modulation in biomarker is a reduction of about 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, or about 100% compared to baseline levels.

[00195] In some embodiments, the biomarker is one or more of BMF and EFNA. In some such embodiments, the modulation is measured by measurement of the increase in mRNA and/or protein expression levels of one or more of BMF and EFNA1. In some embodiments, the modulation in biomarker is an increase of about 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, or about 100% compared to baseline levels.

[00196] In some embodiments, the biomarker is GJA1. In some such embodiments, the modulation is measured by measurement of the modulation in mRNA and/or protein expression levels of one or more of GJA1. In some such embodiments, the modulation in biomarker is a reduction of about 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, or about 100% compared to baseline levels. In some embodiments, the modulation in biomarker is an increase of about 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, or about 100% compared to baseline levels.

[00197] In some embodiments, the biomarker is one or more of Axin2, CTGF, Cur61 and AREG. In some such embodiments, the modulation is measured by measurement of the reduction in mRNA and/or protein expression levels of one or more of Axin2, CTGF, and AREG. In some embodiments, the modulation in biomarker is a reduction of about 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, or about 100% compared to baseline levels.

[00198] In some embodiments, the biomarker is one or more of CYR61, CXCL1, HAS2, HES1 and MAFF. In some such embodiments, the modulation is measured by measurement of the reduction in mRNA and/or protein expression levels of one or more of CYR61, CXCL1, HAS2, HES1 and MAFF. In some embodiments, the modulation in biomarker is a reduction of about 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, or about 100% compared to baseline levels.

[00199] In some embodiments, the biomarker is one or more of CITED2 and ELF3. In some such embodiments, the modulation is measured by measurement of the increase in mRNA and/or protein expression levels of one or more of CITED2 and ELF3. In some embodiments, the modulation in biomarker is an increase of about 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, or about 100% compared to baseline levels.

[00200] In some embodiments, the biomarker is PD-L1. In some embodiments, the modulation in the levels of biomarker is a reduction in cell surface expression levels of PD-L1. In some embodiments, the modulation in biomarker is a reduction of about 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, or about 100% compared to baseline levels.

[00201] In another embodiment, the biomarker is IFNγ or IL-2. In some such embodiments, the modulation in the levels of biomarker is an increase in mRNA and/or protein expression levels of IFNγ or IL-2. In some such embodiments, the modulation in mRNA and/or protein expression levels of IFNγ or IL-2 is an increase of about 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, or about 100% compared to baseline levels.

[00202] In another embodiment, the biomarker is IL-8. In some such embodiments, the modulation in the levels of biomarker is a decrease in mRNA and/or protein expression levels of IL-8. In some such embodiments, the modulation in mRNA and/or protein expression levels of

IL-8 is an decrease of about 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, or about 100% compared to baseline levels.

[00203] In one embodiment, provided herein are methods for inhibiting phosphorylation of ERK and/or RSK1 in a subject having a cancer as described herein, comprising administering an effective amount of an Aminopurine compound or a pharmaceutical composition thereof as described herein to said subject. In some such embodiments, the inhibition of phosphorylation is assessed in a biological sample of the subject, such as in circulating blood and/or tumor cells, skin biopsies and/or tumor biopsies or aspirate. In such embodiments, the amount of inhibition of phosphorylation is assessed by comparison of the amount of phospho- ERK and/or RSK1 before and after administration of the Aminopurine Compound or a pharmaceutical composition thereof provided herein. In certain embodiments, provided herein are methods for measuring inhibition of phosphorylation of ERK and/or RSK1, in a subject having a cancer as described herein, comprising administering an effective amount of Aminopurine Compound or a pharmaceutical composition thereof provided herein to said subject, measuring the amount of phosphorylated ERK and/or RSK1 in said subject, and comparing said amount of phosphorylated ERK and/or RSK to that of said subject prior to administration of an effective amount of the Aminopurine Compound or a pharmaceutical composition thereof provided herein. In some embodiments, the biological sample is a tumor biopsy. In another embodiment, the biological sample is PBMC. In still another embodiment, the biological sample is circulating tumor cells.

[00204] In certain embodiments, provided herein are methods for inhibiting phosphorylation of ERK and/or RSK1 in a biological sample of a subject having a cancer as described herein, comprising administering an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof provided herein to said subject and comparing the amount of phosphorylated ERK and/or RSK1 in a biological sample of a subject obtained prior to and after administration of said Aminopurine Compound or a pharmaceutical composition thereof provided herein, wherein less phosphorylated ERK and/or RSK1 in said biological sample obtained after administration of said Aminopurine Compound provided herein relative to the amount of phosphorylated ERK and/or RSK1 in said biological sample obtained prior to administration of said Aminopurine Compound or a pharmaceutical composition thereof provided herein indicates inhibition. In some embodiments, the biological sample is a tumor

biopsy. In another embodiment, the biological sample is PBMC. In still another embodiment, the biological sample is circulating tumor cells.

[00205] Further provided herein are methods for determining whether a patient is sensitive to an Aminopurine Compound or a pharmaceutical composition thereof, comprising administering said patient said Aminopurine Compound or a pharmaceutical composition thereof and determining whether or not ERK and/or RSK1 phosphorylation is inhibited in said patient by measuring the amount of phosphorylated ERK and/or RSK1 in a biological sample from said patient prior to and after the administration of Aminopurine Compound or a pharmaceutical composition thereof to said patient, wherein inhibition of ERK and/or RSK1 phosphorylation indicates that said patient is sensitive to said Aminopurine Compound. In some such embodiments, the method additionally comprises administering an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof, as described herein. In some embodiments, the biological sample is a tumor biopsy. In another embodiment, the biological sample is PBMC. In still another embodiment, the biological sample is circulating tumor cells.

[00206] Further provided herein are methods for determining the effective amount of an Aminopurine Compound or a pharmaceutical composition thereof for the treatment of a cancer treatable by inhibition of phosphorylation of ERK and/or RSK1 in a patient, comprising administering said patient varying doses of said Aminopurine Compound or a pharmaceutical composition thereof and determining the amount of ERK and/or RSK1 phosphorylation inhibition in said patient resulting from each dose of said Aminopurine Compound or a pharmaceutical composition thereof by measuring the amount of phosphorylated ERK and/or RSK1 in a biological sample from said patient prior to and after the administration of each dose of Aminopurine Compound to said patient, wherein inhibition of ERK and/or RSK1 phosphorylation by at least about 10%, about 20%, about 30%, about 40%, about 50% or greater than about 50% ,corresponds to an effective amount of an Aminopurine compound. In some such embodiments, the method additionally comprises administering an effective amount of an Aminopurine Compound or a pharmaceutical composition thereof, as described herein. In some embodiments, the biological sample is a tumor biopsy. In another embodiment, the biological sample is PBMC. In still another embodiment, the biological sample is circulating tumor cells.

[00207] Further provided herein are methods for predicting response to treatment with an Aminopurine Compound in a patient having a cancer, the method comprising: a) obtaining a biological test sample from the patient's cancer; b) obtaining the mRNA and/or protein expression levels of one or more of DUSP4, DUSP5, DUSP6, EGR1, ETV5, FOS, FOSL1, IL-8, cMyc, Cyclin D1, YAP, SPRY2, SPRY4, Axin2, CTGF, AREG, CYR61, CXCL1, HAS2, HES1, and MAFF in said biological test sample; c) comparing said mRNA and/or protein expression levels to the mRNA and/or protein expression levels of a biological wild-type sample; wherein a reduction in mRNA and/or protein expression levels in said patient's biological test sample relative to said biological wild-type sample, indicates an increased likelihood of response to Aminopurine Compound treatment of said patient's cancer. In some such embodiments, the method additionally comprises administering an effective amount of an Aminopurine Compound, as described herein. In some embodiments, the biological sample is a tumor biopsy. In another embodiment, the biological sample is PBMC. In still another embodiment, the biological sample is circulating tumor cells.

[00208] Further provided herein are methods for predicting therapeutic efficacy of Aminopurine Compound treatment of a patient having a cancer, the method comprising: a) obtaining a biological test sample from the patient's cancer; b) obtaining the mRNA and/or protein expression levels of one or more of DUSP4, DUSP5, DUSP6, EGR1, ETV5, FOS, FOSL1, IL-8, cMyc, Cyclin D1, YAP, SPRY2, SPRY4, Axin2, CTGF, AREG, CYR61, CXCL1, HAS2, HES1, and MAFF in said biological test sample; c) comparing said mRNA and/or protein expression levels to the mRNA and/or protein expression levels of a biological wild-type sample; wherein a reduction in mRNA and/or protein expression levels indicates an increased likelihood of therapeutic efficacy of said Aminopurine Compound treatment for said patient. In some such embodiments, the method additionally comprises administering an effective amount of an Aminopurine Compound, as described herein. In some embodiments, the biological sample is a tumor biopsy. In another embodiment, the biological sample is PBMC. In still another embodiment, the biological sample is circulating tumor cells.

[00209] Further provided herein are methods for determining whether a patient is sensitive to an Aminopurine Compound, comprising administering said patient said Aminopurine Compound and determining whether or not mRNA and/or protein expression levels of one or more of

DUSP4, DUSP5, DUSP6, EGR1, ETV5, FOS, FOSL1, IL-8, cMyc, Cyclin D1, YAP, SPRY2, SPRY4, Axin2, CTGF, AREG, CYR61, CXCL1, HAS2, HES1, and MAFF, are inhibited in said patient, by measuring the amount of mRNA and/or protein expression levels of one or more of DUSP4, DUSP5, DUSP6, EGR1, ETV5, FOS, FOSL1, IL-8, cMyc, Cyclin D1, YAP, SPRY2, SPRY4, Axin2, CTGF, AREG, CYR61, CXCL1, HAS2, HES1, and MAFF in a biological sample from said patient, prior to and after the administration of Aminopurine Compound to said patient. In some such embodiments, the method additionally comprises administering an effective amount of an Aminopurine Compound, as described herein. In some embodiments, the biological sample is a tumor biopsy. In another embodiment, the biological sample is PBMC. In still another embodiment, the biological sample is circulating tumor cells.

[00210] Further provided herein are methods for determining the effective amount of an Aminopurine Compound for the treatment of a cancer treatable by inhibition of mRNA and/or protein expression levels of one or more of DUSP4, DUSP5, DUSP6, EGR1, ETV5, FOS, FOSL1, IL-8, cMyc, Cyclin D1, YAP, SPRY2, SPRY4, Axin2, CTGF, AREG, CYR61, CXCL1, HAS2, HES1, and MAFF in a patient, comprising administering said patient varying doses of said Aminopurine Compound and determining the amount of mRNA and/or protein expression levels of one or more of DUSP4, DUSP5, DUSP6, EGR1, ETV5, FOS, FOSL1, IL-8, cMyc, Cyclin D1, YAP, SPRY2, SPRY4, Axin2, CTGF, AREG, CYR61, CXCL1, HAS2, HES1, and MAFF inhibition in said patient, resulting from each dose of said Aminopurine Compound by measuring the amount of mRNA and/or protein expression levels of one or more of DUSP4, DUSP5, DUSP6, EGR1, ETV5, FOS, FOSL1, IL-8, cMyc, Cyclin D1, YAP, SPRY2, SPRY4, Axin2, CTGF, AREG, CYR61, CXCL1, HAS2, HES1, and MAFF in a biological sample from said patient, prior to and after the administration of each dose of Aminopurine Compound to said patient. In some such embodiments, the method additionally comprises administering an effective amount of an Aminopurine Compound, as described herein. In some embodiments, the biological sample is a tumor biopsy. In another embodiment, the biological sample is PBMC. In still another embodiment, the biological sample is circulating tumor cells.

[00211] Further provided herein are methods for predicting response to treatment with an Aminopurine Compound in a patient having a cancer, the method comprising: a) obtaining a biological test sample from the patient's cancer; b) obtaining the mRNA and/or protein

expression levels of one or more of BMF, EFNA1, CITED2, and ELF3 in said biological test sample; c) comparing said mRNA and/or protein expression levels to the mRNA and/or protein expression levels of a biological wild-type sample; wherein an increase in mRNA and/or protein expression levels in said patient's biological test sample relative to said biological wild-type sample, indicates an increased likelihood of response to Aminopurine Compound treatment of said patient's cancer. In some such embodiments, the method additionally comprises administering an effective amount of an Aminopurine Compound, as described herein. In some embodiments, the biological sample is a tumor biopsy. In another embodiment, the biological sample is PBMC. In still another embodiment, the biological sample is circulating tumor cells.

[00212] Further provided herein are methods for predicting therapeutic efficacy of Aminopurine Compound treatment of a patient having a cancer, the method comprising: a) obtaining a biological test sample from the patient's cancer; b) obtaining the mRNA and/or protein expression levels of one or more of BMF, EFNA1, CITED2, and ELF3 in said biological test sample; c) comparing said mRNA and/or protein expression levels to the mRNA and/or protein expression levels of a biological wild-type sample; wherein an increase in mRNA and/or protein expression levels indicates an increased likelihood of therapeutic efficacy of said Aminopurine Compound treatment for said patient. In some such embodiments, the method additionally comprises administering an effective amount of an Aminopurine Compound, as described herein. In some embodiments, the biological sample is a tumor biopsy. In another embodiment, the biological sample is PBMC. In still another embodiment, the biological sample is circulating tumor cells.

[00213] Further provided herein are methods for determining whether a patient is sensitive to an Aminopurine Compound, comprising administering said patient said Aminopurine Compound and determining whether or not mRNA and/or protein expression levels of one or more of BMF, EFNA1, CITED2, and ELF3 are increased in said patient, by measuring the amount of mRNA and/or protein expression levels of one or more of BMF, EFNA1, CITED2, and ELF3 in a biological sample from said patient, prior to and after the administration of Aminopurine Compound to said patient. In some such embodiments, the method additionally comprises administering an effective amount of an Aminopurine Compound, as described herein. In some

embodiments, the biological sample is a tumor biopsy. In another embodiment, the biological sample is PBMC. In still another embodiment, the biological sample is circulating tumor cells.

[00214] Further provided herein are methods for determining the effective amount of an Aminopurine Compound for the treatment of a cancer treatable by an increase of mRNA and/or protein expression levels of one or more of BMF, EFNA1, CITED2, and ELF3 in a patient, comprising administering said patient varying doses of said Aminopurine Compound, and determining the amount of mRNA and/or protein expression levels of one or more of BMF, EFNA1, CITED2, and ELF3 increase in said patient resulting from each dose of said Aminopurine Compound by measuring the amount of mRNA and/or protein expression levels of one or more of BMF, EFNA1, CITED2, and ELF3 in a biological sample from said patient, prior to and after the administration of each dose of Aminopurine Compound to said patient. In some such embodiments, the method additionally comprises administering an effective amount of an Aminopurine Compound, as described herein. In some embodiments, the biological sample is a tumor biopsy. In another embodiment, the biological sample is PBMC. In still another embodiment, the biological sample is circulating tumor cells.

[00215] Further provided herein are methods for predicting response to treatment with an Aminopurine Compound or a pharmaceutical composition thereof in a patient having a cancer, the method comprising: a) obtaining a biological test sample from the patient's cancer; b) obtaining the mRNA and/or protein expression levels of GJA1 in said biological test sample; c) comparing said mRNA and/or protein expression levels to the mRNA and/or protein expression levels of a biological wild-type sample; wherein a reduction in mRNA and/or protein expression levels in said patient's biological test sample relative to said biological wild-type sample, indicates an increased likelihood of response to Aminopurine Compound treatment of said patient's cancer. In some such embodiments, the method additionally comprises administering an effective amount of an Aminopurine Compound, as described herein. In some embodiments, the biological sample is a tumor biopsy. In another embodiment, the biological sample is PBMC. In still another embodiment, the biological sample is circulating tumor cells.

[00216] Further provided herein are methods for predicting therapeutic efficacy of Aminopurine Compound treatment of a patient having a cancer, the method comprising: a) obtaining a biological test sample from the patient's cancer; b) obtaining the mRNA and/or

protein expression levels of GJA1 in said biological test sample; c) comparing said mRNA and/or protein expression levels to the mRNA and/or protein expression levels of a biological wild-type sample; wherein a reduction in mRNA and/or protein expression levels indicates an increased likelihood of therapeutic efficacy of said Aminopurine Compound treatment for said patient. In some such embodiments, the method additionally comprises administering an effective amount of an Aminopurine Compound, as described herein. In some embodiments, the biological sample is a tumor biopsy. In another embodiment, the biological sample is PBMC. In still another embodiment, the biological sample is circulating tumor cells.

[00217] Further provided herein are methods for determining whether a patient is sensitive to an Aminopurine Compound, comprising administering said patient said Aminopurine Compound and determining whether or not mRNA and/or protein expression levels of GJA1 are inhibited in said patient, by measuring the amount of mRNA and/or protein expression levels of GJA1 in a biological sample from said patient, prior to and after the administration of Aminopurine Compound to said patient. In some such embodiments, the method additionally comprises administering an effective amount of an Aminopurine Compound, as described herein. In some embodiments, the biological sample is a tumor biopsy. In another embodiment, the biological sample is PBMC. In still another embodiment, the biological sample is circulating tumor cells.

[00218] Further provided herein are methods for determining the effective amount of an Aminopurine Compound for the treatment of a cancer treatable by inhibition of mRNA and/or protein expression levels of GJA1 in a patient, comprising administering said patient varying doses of said Aminopurine Compound and determining the amount of mRNA and/or protein expression levels of GJA1 inhibition in said patient, resulting from each dose of said Aminopurine Compound by measuring the amount of mRNA and/or protein expression levels of GJA1 in a biological sample from said patient, prior to and after the administration of each dose of Aminopurine Compound to said patient. In some such embodiments, the method additionally comprises administering an effective amount of an Aminopurine Compound, as described herein. In some embodiments, the biological sample is a tumor biopsy. In another embodiment, the biological sample is PBMC. In still another embodiment, the biological sample is circulating tumor cells.

[00219] Further provided herein are methods for predicting response to treatment with an Aminopurine Compound in a patient having a cancer, the method comprising: a) obtaining a biological test sample from the patient's cancer; b) obtaining the mRNA and/or protein expression levels of GJA1 in said biological test sample; c) comparing said mRNA and/or protein expression levels to the mRNA and/or protein expression levels of a biological wild-type sample; wherein an increase in mRNA and/or protein expression levels in said patient's biological test sample relative to said biological wild-type sample, indicates an increased likelihood of response to Aminopurine Compound treatment of said patient's cancer. In some such embodiments, the method additionally comprises administering an effective amount of an Aminopurine Compound, as described herein. In some embodiments, the biological sample is a tumor biopsy. In another embodiment, the biological sample is PBMC. In still another embodiment, the biological sample is circulating tumor cells.

[00220] Further provided herein are methods for predicting therapeutic efficacy of Aminopurine Compound treatment of a patient having a cancer, the method comprising: a) obtaining a biological test sample from the patient's cancer; b) obtaining the mRNA and/or protein expression levels of GJA1 in said biological test sample; c) comparing said mRNA and/or protein expression levels to the mRNA and/or protein expression levels of a biological wild-type sample; wherein an increase in mRNA and/or protein expression levels indicates an increased likelihood of therapeutic efficacy of said Aminopurine Compound treatment for said patient. In some such embodiments, the method additionally comprises administering an effective amount of an Aminopurine Compound, as described herein. In some embodiments, the biological sample is a tumor biopsy. In another embodiment, the biological sample is PBMC. In still another embodiment, the biological sample is circulating tumor cells.

[00221] Further provided herein are methods for determining whether a patient is sensitive to an Aminopurine Compound, comprising administering said patient said Aminopurine Compound and determining whether or not mRNA and/or protein expression levels of GJA1 are increased in said patient, by measuring the amount of mRNA and/or protein expression levels of GJA1 in a biological sample from said patient, prior to and after the administration of Aminopurine Compound to said patient. In some such embodiments, the method additionally comprises administering an effective amount of an Aminopurine Compound, as described herein. In some

embodiments, the biological sample is a tumor biopsy. In another embodiment, the biological sample is PBMC. In still another embodiment, the biological sample is circulating tumor cells.

[00222] Further provided herein are methods for determining the effective amount of an Aminopurine Compound for the treatment of a cancer treatable by an increase of mRNA and/or protein expression levels of GJA1 in a patient, comprising administering said patient varying doses of said Aminopurine Compound, and determining the amount of mRNA and/or protein expression levels of GJA1 increase in said patient resulting from each dose of said Aminopurine Compound by measuring the amount of mRNA and/or protein expression levels of GJA1 in a biological sample from said patient, prior to and after the administration of each dose of Aminopurine Compound to said patient. In some such embodiments, the method additionally comprises administering an effective amount of an Aminopurine Compound, as described herein. In some embodiments, the biological sample is a tumor biopsy. In another embodiment, the biological sample is PBMC. In still another embodiment, the biological sample is circulating tumor cells.

[00223] Further provided herein are methods for predicting response to treatment with an Aminopurine Compound in a patient having a cancer, the method comprising: a) obtaining a biological test sample from the patient's cancer; b) obtaining the cell surface expression levels of PD-L1 in said biological test sample; c) comparing said cell surface expression levels of PD-L1 to the cell surface expression levels of PD-L1 of a biological wild-type sample; wherein a reduction in cell surface expression levels of PD-L1 indicates an increased likelihood of response to Aminopurine Compound treatment of said patient's cancer. In some such embodiments, the method additionally comprises administering an effective amount of an Aminopurine Compound, as described herein. In some embodiments, the biological sample is a tumor biopsy. In another embodiment, the biological sample is PBMC. In still another embodiment, the biological sample is circulating tumor cells.

[00224] Further provided herein are methods for predicting therapeutic efficacy of Aminopurine Compound treatment of a patient having a cancer, the method comprising: a) obtaining a biological test sample from the patient's cancer; b) obtaining the cell surface expression levels of PD-L1 in said biological test sample; c) comparing said cell surface expression levels of PD-L1 to the cell surface expression levels of PD-L1 of a biological

wild-type sample; wherein a reduction in cell surface expression levels of PD-L1 indicates an increased likelihood of therapeutic efficacy of said Aminopurine Compound treatment for said patient. In some such embodiments, the method additionally comprises administering an effective amount of an Aminopurine Compound, as described herein. In some embodiments, the biological sample is a tumor biopsy. In another embodiment, the biological sample is PBMC. In still another embodiment, the biological sample is circulating tumor cells.

[00225] Further provided herein are methods for determining whether a patient is sensitive to an Aminopurine Compound, comprising administering said patient said Aminopurine Compound and determining whether or not cell surface expression levels of PD-L1 are inhibited in said patient by measuring the amount of cell surface expression levels of PD-L1 in a biological sample from said patient prior to and after the administration of Aminopurine Compound to said patient. In some such embodiments, the method additionally comprises administering an effective amount of an Aminopurine Compound, as described herein. In some embodiments, the biological sample is a tumor biopsy. In another embodiment, the biological sample is PBMC. In still another embodiment, the biological sample is circulating tumor cells.

[00226] Further provided herein are methods for determining the effective amount of an Aminopurine Compound for the treatment of a cancer treatable by cell surface expression levels of PD-L1 in a patient, comprising administering said patient varying doses of said Aminopurine Compound and determining the amount of cell surface expression levels of PD-L1 inhibition in said patient resulting from each dose of said Aminopurine Compound by measuring the amount of cell surface expression levels of PD-L1 in a biological sample from said patient prior to and after the administration of each dose of Aminopurine Compound to said patient. In some such embodiments, the method additionally comprises administering an effective amount of an Aminopurine Compound, as described herein. In some embodiments, the biological sample is a tumor biopsy. In another embodiment, the biological sample is PBMC. In still another embodiment, the biological sample is circulating tumor cells.

COMBINATION THERAPY

[00227] Aminopurine Compounds provided herein can also be combined or used in combination with other therapeutic agents useful in the treatment and/or prevention of cancer described herein.

[00228] In one embodiment, provided herein is a method of treating, preventing, or managing cancer, comprising administering to a patient an Aminopurine Compound provided herein in combination with one or more second active agents, and optionally in combination with radiation therapy, blood transfusions, or surgery. Examples of second active agents are disclosed herein.

[00229] As used herein, the term "in combination" includes the use of more than one therapy (*e.g.*, one or more prophylactic and/or therapeutic agents). However, the use of the term "in combination" does not restrict the order in which therapies (*e.g.*, prophylactic and/or therapeutic agents) are administered to a patient with a disease or disorder. A first therapy (*e.g.*, a prophylactic or therapeutic agent such as an Aminopurine Compound provided herein, can be administered prior to (*e.g.*, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (*e.g.*, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of a second therapy (*e.g.*, a prophylactic or therapeutic agent) to the subject. Triple therapy is also contemplated herein.

[00230] Administration of an Aminopurine Compound provided herein and one or more second active agents to a patient can occur simultaneously or sequentially by the same or different routes of administration. The suitability of a particular route of administration employed for a particular active agent will depend on the active agent itself (*e.g.*, whether it can be administered orally without decomposing prior to entering the blood stream) and the cancer being treated.

[00231] The route of administration of an Aminopurine Compound is independent of the route of administration of a second therapy. Thus, in accordance with these embodiments, an Aminopurine Compound is administered intravenously, and the second therapy can be administered orally, parenterally, intraperitoneally, intravenously, intraarterially, transdermally, sublingually, intramuscularly, rectally, transbuccally, intranasally, liposomally, via inhalation, vaginally, intraoccularly, via local delivery by catheter or stent, subcutaneously, intraadiposally, intraarticularly, intrathecally, or in a slow release dosage form. In one embodiment, an Aminopurine Compound and a second therapy are administered by the same mode of

administration, for example, orally. In another embodiment, an Aminopurine Compound is administered by one mode of administration, *e.g.*, orally, whereas the second agent (an anticancer agent) is administered by another mode of administration, *e.g.*, IV.

[00232] In one embodiment, the second active agent is administered, for example, orally, intravenously or subcutaneously, and once or twice daily in an amount of from about 1 to about 1000 mg, from about 5 to about 500 mg, from about 10 to about 350 mg, from about 50 to about 200 mg, from about 1 to about 100 mg, from about 1 to about 200 mg, from about 1 to about 300 mg, from about 1 to about 400 mg, or from about 1 to about 500 mg. The specific amount of the second active agent will depend on the specific agent used, the type of disease being treated or managed, the severity and stage of disease, and the amount of Aminopurine Compound described herein and any optional additional active agents concurrently administered to the patient. In one embodiment, dosing amounts described herein are for human patients.

[00233] One or more second active ingredients or agents can be used together with an Aminopurine Compound in the methods and compositions provided herein. Second active agents can be large molecules *(e.g.*, proteins) or small molecules *(e.g.*, synthetic inorganic, organometallic, or organic molecules).

[00234] Examples of large molecule active agents include, but are not limited to, hematopoietic growth factors, cytokines, and monoclonal and polyclonal antibodies, particularly, therapeutic antibodies to cancer antigens. Typical large molecule active agents are biological molecules, such as naturally occurring or synthetic or recombinant proteins. Proteins that are particularly useful in the methods and compositions provided herein include proteins that stimulate the survival and/or proliferation of hematopoietic precursor cells lymphopoietic cells *in vitro* or *in vivo*. Other useful proteins stimulate the division and differentiation of committed hematopoietic progenitors in cells *in vitro* or *in vivo*. Particular proteins include, but are not limited to: interleukins, such as IL-2 (including recombinant IL-2 ("rIL2") and canarypox IL-2), IL-10, IL-12, and IL-18; interferons, such as interferon alfa-2a, interferon alfa-2b, interferon alfa-n1, interferon alfa-n3, interferon beta-Ia, and interferon gamma-I b; GM-CF and GM-CSF; and EPO.

[00235] In certain embodiments, GM-CSF, G-CSF, SCF or EPO is administered subcutaneously during about five days in a four or six week cycle in an amount ranging from

about 1 to about 750 mg/m^2/day, from about 25 to about 500 mg/m^2/day, from about 50 to about 250 mg/m^2/day, or from about 50 to about 200 mg/m^2/day. In certain embodiments, GM-CSF may be administered in an amount of from about 60 to about 500 mcg/m^2 intravenously over 2 hours or from about 5 to about 12 mcg/m^2/day subcutaneously. In certain embodiments, G-CSF may be administered subcutaneously in an amount of about 1 mcg/kg/day initially and can be adjusted depending on rise of total granulocyte counts. The maintenance dose of G-CSF may be administered in an amount of about 300 (in smaller patients) or 480 mcg subcutaneously. In certain embodiments, EPO may be administered subcutaneously in an amount of 10,000 Unit 3 times per week.

[00236] Particular proteins that can be used in the methods and compositions include, but are not limited to: filgrastim, sargramostim, and recombinant EPO.

[00237] Recombinant and mutated forms of GM-CSF can be prepared as described in U.S. patent Nos. 5,391,485; 5,393,870; and 5,229,496; all of which are incorporated herein by reference. Recombinant and mutated forms of G-CSF can be prepared as described in U.S. patent Nos. 4,810,643; 4,999,291; 5,528,823; and 5,580,755; the entireties of which are incorporated herein by reference.

[00238] Also provided for use in combination with an Aminopurine Compound provided herein are native, naturally occurring, and recombinant proteins. Further encompassed are mutants and derivatives (*e.g.*, modified forms) of naturally occurring proteins that exhibit, *in vivo*, at least some of the pharmacological activity of the proteins upon which they are based. Examples of mutants include, but are not limited to, proteins that have one or more amino acid residues that differ from the corresponding residues in the naturally occurring forms of the proteins. Also encompassed by the term "mutants" are proteins that lack carbohydrate moieties normally present in their naturally occurring forms (*e.g.*, nonglycosylated forms). Examples of derivatives include, but are not limited to, pegylated derivatives and fusion proteins, such as proteins formed by fusing IgG1 or IgG3 to the protein or active portion of the protein of interest. *See, e.g.*, Penichet, M.L. and Morrison, S.L., *J. Immunol. Methods* 248:91-101 (2001).

[00239] Antibodies that can be used in combination with an Aminopurine Compound provided herein include monoclonal and polyclonal antibodies. Examples of antibodies include, but are not limited to, trastuzumab, rituximab, bevacizumab, pertuzumab, tositumomab,

edrecolomab, and G250. Aminopurine Compounds can also be combined with, or used in combination with, anti-TNF-α antibodies, and/or anti-EGFR antibodies, such as, for example, cetuximab or panitumumab.

[00240] Antibodies that can be used in combination with an Aminopurine Compound provided herein include immune checkpoint inhibitors, such as, anti-CTLA4, anti-PD1, anti-PD-L1, anti-Tim-3, anti-Lag-3 antibodies. In some such embodiments, the PD-1 or PD-L1 antibodies are, for example, avelumab, durvalumab, MEDI0680, atezolizumab, BMS-936559, nivolumab, pembrolizumab, pidilizumab, or PDR-001. In one such embodiment, the anti-Lag-3 antibody is BMS-986016.

[00241] Additional antibodies that can be used in combination with an Aminopurine compound provided herein include anti-RSPO antibodies.

[00242] Large molecule active agents may be administered in the form of anti-cancer vaccines. For example, vaccines that secrete, or cause the secretion of, cytokines such as IL-2, G-CSF, and GM-CSF can be used in the methods and pharmaceutical compositions provided. *See, e.g.*, Emens, L.A., *et al.*, *Curr. Opinion Mol. Ther.* 3(1):77-84 (2001).

[00243] Second active agents that are small molecules can also be used to alleviate adverse effects associated with the administration of an Aminopurine Compound provided herein. However, like some large molecules, many are believed to be capable of providing an additive or synergistic effect when administered with (*e.g.*, before, after or simultaneously) an Aminopurine Compound provided herein. Examples of small molecule second active agents include, but are not limited to, anti-cancer agents, antibiotics, immunosuppressive agents, and steroids.

[00244] In certain embodiments, the second agent is a BRAF inhibitor, an HSP inhibitor, a proteasome inhibitor, a FLT3 inhibitor, a MEK inhibitor, a PI3K inhibitor, an EGFR inhibitor, an immunomodulatory compound, or a TOR kinase inhibitor. In some such embodiments, the BRAF inhibitor is sorafenib, dabrafenib, encorafenib, or vemurafenib. In some such embodiment, the HSP inhibitor is geldanamycin, gamitrinib, luminespib, or radicicol. In some embodiments, the proteasome inhibitor is bortezomib, carfilzomib, ixazomib, disulfiram, oprozomib, delanzomib, or ixazomib. In other embodiments, the FLT3 inhibitor is quizartinib, midostaurin, sorafenib , sunitinib, or lestaurtinib. In some such embodiments, the MEK inhibitor is trametinib, cobimetinib, binimetinib, selumetinib, PD-325901, CI-1040 (PD184352) or

TAK-733. In some other embodiments, the PI3K inhibitor is AT7867, AZD 8055, BX-912, silmitasertib, pictilisib, MK-2206, or pilaralisib. In another embodiment, the EGFR inhibitor is gefitinib, erlotinib, afatinib, osimertinib (TAGRISSO), rociletinib, or lapatinib. In some other embodiments, the TOR kinase inhibitor is CC-115, CC-223, OSI-027, AZD8055, sapanisertib, dactolisib, BGT226, voxtalisib (SAR-245409), apitolisib, omipalisib (GSK-2126458), PF-04691502, gedatolisib or PP242. In some embodiments, the immunomodulatory compound is thalidomide, lenalidomide, pomalidomide, CC-220, or CC-122.

[00245] Examples of additional anti-cancer agents to be used within the methods or compositions described herein include, but are not limited to: acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; celecoxib (COX-2 inhibitor); chlorambucil; cirolemycin; cisplatin; cladribine; clofarabine; crisnatol mesylate; cyclophosphamide; arabinoxylcytosine; dacarbazine; dabrafenib; dactinomycin; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; docetaxel; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; flurocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; ilmofosine; iproplatin; irinotecan; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazole; nogalamycin; omacetaxine; ormaplatin;

oxisuran; paclitaxel; paclitaxel protein-bound particles for injectable suspension, albumin bound (ABRAXANE®); pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; safingol; safingol hydrochloride; semustine; simtrazene; sorafenib; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; docetaxel; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; vemurafenib; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; and zorubicin hydrochloride.

[00246] Other anti-cancer drugs to be included within the methods or compositions include, but are not limited to: 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogens, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorlns; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B;

combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; dihydrotaxol, 9-; dioxamycin; diphenyl spiromustine; docetaxel; docosanol; dolasetron; doxifluridine; doxorubicin; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imatinib; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; cetuximab, human chorionic gonadotrophin; monophosphoryl lipid A+mycobacterium cell wall sk; mopidamol; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; nilutamide; nisamycin; nitric oxide modulators;

nitroxide antioxidant; nitrullyn; oblimersen; O^6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; paclitaxel; paclitaxel analogues; paclitaxel derivatives; paclitaxel protein-bound particles for injectable suspension, albumin bound (ABRAXANE®); palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; sarmustine; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; and zinostatin stimalamer.

[00247] Specific second active agents particularly useful in the methods or compositions include, but are not limited to, rituximab, oblimersen, infliximab, docetaxel, celecoxib, melphalan, dexamethasone, steroids, gemcitabine, cisplatinum, temozolomide, etoposide, cyclophosphamide, temodar, carboplatin, procarbazine, carmustine, tamoxifen, topotecan, methotrexate, gefitinib, paclitaxel, fluorouracil, leucovorin, irinotecan, capecitabine, interferon alpha, pegylated interferon alpha, cisplatin, thiotepa, fludarabine, carboplatin, liposomal daunorubicin, cytarabine, vinblastine, IL-2, GM-CSF, dacarbazine, vinorelbine, zoledronic acid, palmitronate, clarithormycin, busulphan, prednisone, bisphosphonate, arsenic trioxide, vincristine, doxorubicin, ganciclovir, estramustine sodium phosphate, clinoril, and etoposide.

[00248] Other specific second active agents particularly useful in the methods or compositions include, but are not limited to, sorafenib, dabrafenib, vemurafenib, trametinib, cobimetinib, binimetinib, selumetinib, PD-325901, CI-1040 (PD184352), TAK-733, AT7867, AZD 8055, BX-912, silmitasertib, pictilisib, MK-2206, pilaralisib, gefitinib, erlotinib, lapatinib, osimertinib, CC-115, CC-223, OSI-027, AZD8055, sapanisertib, dactolisib, BGT226, voxtalisib, apitolisib, omipalisib, PF-04691502, gedatolisib, PP242, lenalidomide, pomalidomide, or CC-122.

[00249] Other specific second active agents particularly useful in the methods or compositions include, but are not limited to, avelumab, durvalumab, MEDI0680, atezolizumab, BMS-936559, nivolumab, pembrolizumab, pidilizumab, PDR-001, sorafenib, cetuximab, panatumumab, erlotinib, trametinib, trastuzumab, CC-223, CC-122 or lapatinib.

[00250] In certain embodiments of the methods provided herein, use of a second active agent in combination with an Aminopurine Compound provided herein may be modified or delayed during or shortly following administration of an Aminopurine Compound provided herein as deemed appropriate by the practitioner of skill in the art. In certain embodiments, subjects being administered an Aminopurine Compound provided herein alone or in combination with other therapies may receive supportive care including antiemetics, myeloid growth factors, and transfusions of blood products, when appropriate. In some embodiments, subjects being administered an Aminopurine Compound provided herein may be administered a growth factor as a second active agent according to the judgment of the practitioner of skill in the art.

[00251] In certain embodiments, an Aminopurine Compound provided herein is administered with gemcitabine, cisplatinum, 5-fluorouracil, mitomycin, methotrexate, vinblastine,

doxorubicin, carboplatin, thiotepa, paclitaxel, paclitaxel protein-bound particles for injectable suspension-albumin bound (ABRAXANE®), or docetaxel to patients with locally advanced or metastatic urothelial carcinoma.

[00252] In certain embodiments, an Aminopurine Compound provided herein is administered in combination with a second active ingredient as follows: temozolomide to pediatric patients with relapsed or progressive brain tumors or recurrent neuroblastoma; celecoxib, etoposide and cyclophosphamide for relapsed or progressive CNS cancer; temozolomide to patients with recurrent or progressive meningioma, malignant meningioma, hemangiopericytoma, multiple brain metastases, relapsed brain tumors, or newly diagnosed glioblastoma multiforme; irinotecan to patients with recurrent glioblastoma; carboplatin to pediatric patients with brain stem gliomas; procarbazine to pediatric patients with progressive malignant gliomas; cyclophosphamide to patients with poor prognosis malignant brain tumors, newly diagnosed or recurrent glioblastoma multiforms; carmustine for high grade recurrent malignant gliomas; temozolomide and tamoxifen for anaplastic astrocytoma; or topotecan for gliomas, glioblastoma, anaplastic astrocytoma or anaplastic oligodendroglioma.

[00253] In certain embodiments, an Aminopurine Compound provided herein is administered with methotrexate, cyclophosphamide, 5-fluorouracil, everolimus, paclitaxel, paclitaxel protein-bound particles for injectable suspension-albumin bound (ABRAXANE®), lapatinib, trastuzumab, pamidronate disodium, eribulin mesylate, everolimus, gemcitabine, palbociclib, ixabepilone, ado-trastuzumab emtansine, pertuzumab, thiotepa, aromatase inhibitors, exemestane, selective estrogen modulators, estrogen receptor antagonists, anthracyclines, emtansine, and/or pexidartinib to patients with metastatic breast cancer.

[00254] In certain embodiments, an Aminopurine Compound provided herein is administered with temozolomide, doxorubicin, everolimus, fluorouracil, 5-fluorouracil, or streptozocin to patients with neuroendocrine tumors.

[00255] In certain embodiments, an Aminopurine Compound provided herein is administered with methotrexate, gemcitabine, cisplatin, cetuximab, 5-fluorouracil, bleomycin, docetaxel or carboplatin to patients with recurrent or metastatic head or neck cancer. In one embodiment, an Aminopurine Compound provided herein is administered with cetuximab, to patients with head or neck cancer.

[00256] In certain embodiments, an Aminopurine Compound provided herein is administered with gemcitabine, paclitaxel, paclitaxel protein-bound particles for injectable suspension-albumin bound (ABRAXANE®), 5-fluorouracil, everolimus, irinotecan, mitomycin C, sunitinib or erlotinib to patients with pancreatic cancer.

[00257] In certain embodiments, an Aminopurine Compound provided herein is administered to patients with colon cancer in combination with getfitinib, erlotinib, oxaliplatin, 5-fluorouracil, irinotecan, capecitabine, cetuximab, ramucirumab, panitumumab, bevacizumab, leucovorin calcium, LONSURF, regorafenib, ziv-aflibercept, trametinib, paclitaxel, paclitaxel protein-bound particles for injectable suspension-albumin bound (ABRAXANE®), and/or docetaxel. In certain embodiments, an Aminopurine Compound provided herein is administered to patients with colon cancer in combination with bevacizumab, irinotecan hydrochloride, capecitabine, cetuximab, ramucirumab, oxaliplatin, cetuximab, fluorouracil, leucovorin calcium, trifluridine and tipiracil hydrochloride, panitumumab, regorafenib, or ziv-aflibercept. In some embodiments, an Aminopurine Compound provided herein is administered to patients with colon cancer in combination with an EGFR inhibitor (for example cetuximab or erlotinib) and/or a BRAF inhibitor (for example, sorafenib, dabrafenib, or vemurafenib).

[00258] In certain embodiments, an Aminopurine Compound provided herein is administered with capecitabine, cetuximab, erlotinib, trametinib, and/or vemurafenib to patients with refractory colorectal cancer or patients who fail first line therapy or have poor performance in colon or rectal adenocarcinoma. In some embodiments, an Aminopurine Compound provided herein is administered to patients with refractory colorectal cancer or patients who fail first line therapy or have poor performance in colon or rectal adenocarcinoma in combination with an EGFR inhibitor (for example cetuximab or erlotinib) and a BRAF inhibitor (for example, sorafenib, dabrafenib, or vemurafenib). In some embodiments, an Aminopurine Compound provided herein is administered to patients with refractory colorectal cancer or patients who fail first line therapy or have poor performance in colon or rectal adenocarcinoma in combination with an anti-RSPO antibody.

[00259] In certain embodiments, an Aminopurine Compound provided herein is administered in combination with fluorouracil, leucovorin, trametinib and/or irinotecan to patients with Stage IIIa to IV colorectal cancer or to patients who have been previously treated for metastatic

colorectal cancer. In some embodiments, an Aminopurine Compound provided herein is administered to patients with Stage IIIa to IV colorectal cancer or to patients who have been previously treated for metastatic colorectal cancer, in combination with an EGFR inhibitor (for example cetuximab or erlotinib) and a BRAF inhibitor (for example, sorafenib, dabrafenib, or vemurafenib). In certain embodiments, an Aminopurine Compound provided herein is administered to patients with refractory colorectal cancer in combination with capecitabine, xeloda, trametinib, oxaliplatin and/or irinotecan. In some embodiments, an Aminopurine Compound provided herein is administered to patients with refractory colorectal cancer , in combination with an EGFR inhibitor (for example cetuximab or erlotinib) and a BRAF inhibitor (for example, sorafenib, dabrafenib, or vemurafenib). In certain embodiments, an Aminopurine Compound provided herein is administered with capecitabine, trametinib, and/or irinotecan to patients with refractory colorectal cancer or to patients with unresectable or metastatic colorectal carcinoma. In some embodiments, an Aminopurine Compound provided herein is administered to patients with refractory colorectal cancer or to patients with unresectable or metastatic colorectal carcinoma, in combination with an EGFR inhibitor (for example cetuximab or erlotinib) and a BRAF inhibitor (for example, sorafenib, dabrafenib, or vemurafenib).

[00260] In certain embodiments, an Aminopurine Compound provided herein is administered alone or in combination with interferon alpha, 5-fluorouracil/leucovorin or capecitabine to patients with unresectable or metastatic hepatocellular carcinoma; or with cisplatin and thiotepa, or with sorafenib to patients with primary or metastatic liver cancer. In certain embodiments, an Aminopurine Compound provided herein is administered alone or in combination with sorafenib, sunitinib, erlotinib, and/or sirolimus, to patients with unresectable or metastatic hepatocellular carcinoma; or with sorafenib, sunitinib, erlotinib, and/or rapamycin to patients with primary or metastatic liver cancer. In some embodiments, an Aminopurine Compound provided herein is administered to patients with primary, unresectable, or metastatic liver cancer, in combination with an immune checkpoint inhibitor (for example, an anti-CTLA4, anti-PD1, anti-PD-L1, anti-Tim-3, or anti-Lag-3 antibody) or a BRAF inhibitor (for example, sorafenib, dabrafenib, or vemurafenib). In some such embodiments, the anti-PD-1 or anti-PD-L1 antibody is avelumab, durvalumab, MEDI0680, atezolizumab, BMS-936559, nivolumab, pembrolizumab, pidilizumab, or PDR-001. In certain embodiments, an Aminopurine Compound provided herein is administered alone or in combination with lenalidomide, pomalidomide or CC-122 to patients

with primary, unresectable or metastatic hepatocellular carcinoma. In certain embodiments, an Aminopurine Compound provided herein is administered alone or in combination CC-223 to patients with primary, unresectable or metastatic hepatocellular carcinoma.

[00261] In certain embodiments, an Aminopurine Compound provided herein is administered in combination with cisplatin/5-fluorouracil, ramucirumab, docetaxel, doxorubicin hydrochloride, fluorouracil injection, trastuzumab, and/or mitomycin C to patients with gastric (stomach) cancer.

[00262] In certain embodiments, an Aminopurine Compound provided herein is administered in combination with an immune checkpoint inhibitor (for example, an anti-CTLA4, anti-PD1, anti-PD-L1, anti-Tim-3, or anti-Lag-3 antibody) and/or a BRAF inhibitor (for example, sorafenib, dabrafenib, or vemurafenib) to patients with various types or stages of melanoma. In some embodiments, an Aminopurine Compound provided herein is administered in combination with aldesleukin, cobimetinib, dabrafenib, dacarbazine, IL-2, talimogene laherparepvec, recombinant interferon alfa-2b, ipilimumab, pembrolizumab, lapatinib, trametinib, nivolumab, peginterferon alfa-2b, aldesleukin, dabrafenib, and/or vemurafenib to patients with various types or stages of melanoma.

[00263] In certain embodiments, an Aminopurine Compound provided herein is administered in combination with doxorubicin, paclitaxel, paclitaxel protein-bound particles for injectable suspension-albumin bound (ABRAXANE®), vinblastine or pegylated interferon alpha to patients with Kaposi's sarcoma.

[00264] In certain embodiments, an Aminopurine Compound provided herein is administered in combination with methotrexate, mechlorethamine hydrochloride, afatinib dimaleate, pemetrexed, bevacizumab, carboplatin, cisplatin, ceritinib, crizotinib, ramucirumab, pembrolizumab, docetaxel, vinorelbine tartrate, gemcitabine, paclitaxel, paclitaxel protein-bound particles for injectable suspension-albumin bound (ABRAXANE®), erlotinib, geftinib, and/or irinotecan to patients with non-small cell lung cancer.

[00265] In certain embodiments, an Aminopurine Compound provided herein is administered in combination with carboplatin and irinotecan to patients with non-small cell lung cancer.

[00266] In certain embodiments, an Aminopurine Compound provided herein is administered with docetaxel to patients with non-small cell lung cancer who have been previously treated with carboplatin/etoposide and radiotherapy.

[00267] In certain embodiments, an Aminopurine Compound provided herein is administered in combination with carboplatin and/or docetaxel, or in combination with carboplatin, pacilitaxel, paclitaxel protein-bound particles for injectable suspension-albumin bound (ABRAXANE®), and/or thoracic radiotherapy to patients with non-small cell lung cancer.

[00268] In certain embodiments, an Aminopurine Compound provided herein is administered in combination with docetaxel to patients with stage IIIB or IV non-small cell lung cancer.

[00269] In certain embodiments, an Aminopurine Compound provided herein is administered in combination with oblimersen, methotrexate, mechlorethamine hydrochloride, etoposide, topotecan or doxorubicin to patients with small cell lung cancer.

[00270] In certain embodiments, an Aminopurine Compound provided herein and doxetaxol are administered to patients with small cell lung cancer who were previously treated with carbo/VP 16 and radiotherapy.

[00271] In certain embodiments, an Aminopurine Compound provided herein is administered to patients with various types or stages of ovarian cancer such as peritoneal carcinoma, papillary serous carcinoma, refractory ovarian cancer or recurrent ovarian cancer, in combination with carboplatin, doxorubicin, gemcitabine, cisplatin, capecitabine, paclitaxel, paclitaxel protein-bound particles for injectable suspension-albumin bound (ABRAXANE®), dexamethasone, avastin, cyclophosphamide, topotecan, olaparib, thiotepa, or a combination thereof.

[00272] In certain embodiments, an Aminopurine Compound provided herein is administered to patients with various types or stages of prostate cancer, in combination with capecitabine, 5-fluorouracil plus leucovorin, gemcitabine, irinotecan plus gemcitabine, cyclophosphamide, vincristine, dexamethasone, GM-CSF, celecoxib, ganciclovir, paclitaxel, paclitaxel protein-bound particles for injectable suspension-albumin bound (ABRAXANE®), docetaxel, estramustine, denderon, abiraterone, bicalutamide, cabazitaxel, degarelix, enzalutamide, goserelin, leuprolide acetate, mitoxantrone hydrochloride, prednisone, sipuleucel-T, radium 223 dichloride, or a combination thereof.

[00273] In certain embodiments, an Aminopurine Compound provided herein is administered to patients with various types or stages of renal cell cancer, in combination with capecitabine, IFN, tamoxifen, IL-2, GM-CSF, celecoxib, or a combination thereof.

[00274] In certain embodiments, an Aminopurine Compound provided herein is administered to patients with various types or stages of gynecologic, uterus or soft tissue sarcoma cancers in combination with IFN, dactinomycin, doxorubicin, imatinib mesylate, pazopanib, hydrochloride, trabectedin, a COX-2 inhibitor such as celecoxib, and/or sulindac.

[00275] In certain embodiments, an Aminopurine Compound provided herein is administered to patients with various types or stages of solid tumors in combination with celecoxib, etoposide, cyclophosphamide, docetaxel, apecitabine, IFN, tamoxifen, IL-2, GM-CSF, or a combination thereof.

[00276] In certain embodiments, an Aminopurine Compound provided herein is administered alone or in combination with vinorelbine to patients with malignant mesothelioma, or stage IIIB non-small cell lung cancer with pleural implants or malignant mesothelioma syndrome.

[00277] In certain embodiments, an Aminopurine Compound provided herein is administered in combination with navitoclax, venetoclax and/or obatoclax to patients with lymphoma and other blood cancers.

[00278] In certain embodiments, an Aminopurine Compound provided herein is administered in combination with arsenic trioxide, fludarabine, carboplatin, daunorubicin, cyclophosphamide, cytarabine, doxorubicin, idarubicin, mitoxantrone hydrochloride, thioguanine, vincristine, and/or topotecan to patients with acute myeloid leukemia, including refractory or relapsed or high-risk acute myeloid leukemia.

[00279] In certain embodiments, an Aminopurine Compound provided herein is administered in combination with liposomal daunorubicin, topotecan and/or cytarabine to patients with unfavorable karotype acute myeloblastic leukemia.

[00280] In certain embodiments, an Aminopurine Compound provided herein is administered alone or in combination with a second active ingredient such as vinblastine or fludarabine, chlorambucil, bleomycin, brentuximab vedotin, carmustine, chlorambucil, cyclophosphamide, dacarbazine, doxorubicin, lomustine, mechlorethamine hydrochloride, prednisone, procarbazine

hydrochloride or vincristine to patients with various types of lymphoma, including, but not limited to, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cutaneous T-Cell lymphoma, cutaneous B-Cell lymphoma, diffuse large B-Cell lymphoma or relapsed or refractory low grade follicular lymphoma.

[00281] In certain embodiments, an Aminopurine Compound provided herein is administered to patients with various types or stages of multiple myeloma in combination with dexamethasone, zoledronic acid, pamitronate, GM-CSF, clarithromycin, vinblastine, melphalan, busulphan, cyclophosphamide, IFN, prednisone, bisphosphonate, celecoxib, arsenic trioxide, peginterferon alfa-2b, vincristine, carmustine, bortezomib, carfilzomib, doxorubicin, panobinostat, lenalidomide, pomalidomide, thalidomide, plerixafor or a combination thereof.

[00282] In certain embodiments, an Aminopurine Compound provided herein is administered to patients with various types or stages of multiple myeloma in combination with chimeric antigen receptor (CAR) T-cells.

[00283] In certain embodiments, an Aminopurine Compound provided herein is administered to patients with relapsed or refractory multiple myeloma in combination with doxorubicin, vincristine and/or dexamethasone.

[00284] In certain embodiments, an Aminopurine Compound provided herein is administered to patients with scleroderma or cutaneous vasculitis in combination with celecoxib, etoposide, cyclophosphamide, docetaxel, capecitabine, IFN, tamoxifen, IL-2, GM-CSF, or a combination thereof.

[00285] Also encompassed herein is a method of increasing the dosage of an anti-cancer drug or agent that can be safely and effectively administered to a patient, which comprises administering to the patient (*e.g.*, a human) an Aminopurine Compound provided herein. Patients that can benefit by this method are those likely to suffer from an adverse effect associated with anti-cancer drugs for treating a specific cancer of the skin, subcutaneous tissue, lymph nodes, brain, lung, liver, bone, intestine, colon, heart, pancreas, adrenal, kidney, prostate, breast, colorectal, or combinations thereof. The administration of an Aminopurine Compound provided herein alleviates or reduces adverse effects which are of such severity that it would otherwise limit the amount of anti-cancer drug.

[00286] In one embodiment, an Aminopurine Compound provided herein is administered daily in an amount ranging from about 0.1 to about 150 mg, from about 1 to about 100 mg, from about 2 to about 50 mg, or from about 1 to about 10 mg prior to, during, or after the occurrence of the adverse effect associated with the administration of an anti-cancer drug to a patient. In certain embodiments, an Aminopurine Compound provided herein is administered in combination with specific agents such as heparin, aspirin, coumadin, anti-Factor Xa, or G-CSF to avoid adverse effects that are associated with anti-cancer drugs such as but not limited to thromboembolism, neutropenia or thrombocytopenia.

[00287] In one embodiment, an Aminopurine Compound provided herein is administered to patients with diseases and disorders associated with or characterized by, undesired angiogenesis in combination with additional active ingredients, including, but not limited to, anti-cancer drugs, anti-inflammatories, antihistamines, antibiotics, and steroids.

[00288] In another embodiment, encompassed herein is a method of treating, preventing and/or managing cancer, which comprises administering an Aminopurine Compound provided herein in conjunction with (*e.g.* before, during, or after) conventional therapy including, but not limited to, surgery, immunotherapy, biological therapy, radiation therapy, or other non-drug based therapy presently used to treat, prevent or manage cancer. The combined use of the compound provided herein and conventional therapy may provide a unique treatment regimen that is unexpectedly effective in certain patients. Without being limited by theory, it is believed that an Aminopurine Compound provided herein may provide additive or synergistic effects when given concurrently with conventional therapy.

[00289] As discussed elsewhere herein, encompassed herein is a method of reducing, treating and/or preventing adverse or undesired effects associated with conventional therapy including, but not limited to, surgery, chemotherapy, radiation therapy, hormonal therapy, biological therapy and immunotherapy. An Aminopurine Compound provided herein and other active ingredient can be administered to a patient prior to, during, or after the occurrence of the adverse effect associated with conventional therapy.

CYCLING THERAPY

[00290] In certain embodiments, the prophylactic or therapeutic agents provided herein are cyclically administered to a patient. Cycling therapy involves the administration of an active agent for a period of time, followed by a rest for a period of time, and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or more of the therapies, avoid, or reduce the side effects of one of the therapies, and/or improves the efficacy of the treatment.

[00291] Consequently, in certain embodiments, an Aminopurine Compound provided herein is administered daily in a single or divided dose in a four to six week cycle with a rest period of about a week or two weeks. In certain embodiments, an Aminopurine Compound provided herein is administered daily in a single or divided doses for one to ten consecutive days of a 28 day cycle, then a rest period with no administration for rest of the 28 day cycle. The cycling method further allows the frequency, number, and length of dosing cycles to be increased. Thus, encompassed herein in certain embodiments is the administration of an Aminopurine Compound provided herein for more cycles than are typical when it is administered alone. In certain embodiments, an Aminopurine Compound provided herein is administered for a greater number of cycles that would typically cause dose-limiting toxicity in a patient to whom a second active ingredient is not also being administered.

[00292] In one embodiment, an Aminopurine Compound provided herein is administered daily and continuously for three or four weeks at a dose of from about 0.1 to about 150 mg/day followed by a break of one or two weeks.

[00293] In another embodiment, an Aminopurine Compound provided herein is administered intravenously and a second active ingredient is administered orally, with administration of Aminopurine Compounds occurring 30 to 60 minutes prior to a second active ingredient, during a cycle of four to six weeks. In certain embodiments, the combination of an Aminopurine Compound provided herein and a second active ingredient is administered by intravenous infusion over about 90 minutes every cycle. In certain embodiments, one cycle comprises the administration from about 0.1 to about 150 mg/day of an Aminopurine Compound provided herein and from about 50 to about 200 mg/m^2/day of a second active ingredient daily for three to four weeks and then one or two weeks of rest. In certain embodiments, the number of cycles

during which the combinatorial treatment is administered to a patient is ranging from about one to about 24 cycles, from about two to about 16 cycles, or from about four to about three cycles.

PHARMACEUTICAL COMPOSITIONS AND ROUTES OF ADMINISTRATION

[00294] The Aminopurine Compounds can be administered to a subject orally, topically or parenterally in the conventional form of preparations, such as capsules, microcapsules, tablets, granules, powder, troches, pills, suppositories, injections, suspensions, syrups, patches, creams, lotions, ointments, gels, sprays, solutions and emulsions. Suitable formulations can be prepared by methods commonly employed using conventional, organic or inorganic additives, such as an excipient *(e.g.,* sucrose, starch, mannitol, sorbitol, lactose, glucose, cellulose, talc, calcium phosphate or calcium carbonate), a binder *(e.g.,* cellulose, methylcellulose, hydroxymethylcellulose, polypropylpyrrolidone, polyvinylpyrrolidone, gelatin, gum arabic, polyethyleneglycol, sucrose or starch), a disintegrator *(e.g.,* starch, carboxymethylcellulose, hydroxypropylstarch, low substituted hydroxypropylcellulose, sodium bicarbonate, calcium phosphate or calcium citrate), a lubricant *(e.g.,* magnesium stearate, light anhydrous silicic acid, talc or sodium lauryl sulfate), a flavoring agent *(e.g.,* citric acid, menthol, glycine or orange powder), a preservative *(e.g.,* sodium benzoate, sodium bisulfite, methylparaben or propylparaben), a stabilizer *(e.g.,* citric acid, sodium citrate or acetic acid), a suspending agent *(e.g.,* methylcellulose, polyvinyl pyrrolidone or aluminum stearate), a dispersing agent *(e.g.,* hydroxypropylmethylcellulose), a diluent *(e.g.,* water), and base wax *(e.g.,* cocoa butter, white petrolatum or polyethylene glycol). The effective amount of the Aminopurine Compounds in the pharmaceutical composition may be at a level that will exercise the desired effect; for example, about 0.005 mg/kg of a subject's body weight to about 10 mg/kg of a subject's body weight in unit dosage for both oral and parenteral administration.

[00295] The dose of an Aminopurine Compound to be administered to a subject is rather widely variable and can be subject to the judgment of a health-care practitioner. In general, the Aminopurine Compounds can be administered one to four times a day in a dose of about 0.005 mg/kg of a subject's body weight to about 10 mg/kg of a subject's body weight in a subject, but the above dosage may be properly varied depending on the age, body weight and medical condition of the subject and the type of administration. In one embodiment, the dose is about

0.01 mg/kg of a subject's body weight to about 10 mg/kg of a subject's body weight, about 0.1 mg/kg of a subject's body weight to about 10 mg/kg of a subject's body weight, about 1 mg/kg of a subject's body weight to about 10 mg/kg of a subject's body weight or about 1 mg/kg of a subject's body weight to about 5 mg/kg of a subject's body weight. In one embodiment, one dose is given per day. In any given case, the amount of the Aminopurine Compound administered will depend on such factors as the solubility of the active component, the formulation used and the route of administration. In one embodiment, application of a topical concentration provides intracellular exposures or concentrations of about 0.01 – 10 μM.

[00296] In another embodiment, provided herein are methods for the treatment or prevention of a disease or disorder comprising the administration of about 1 mg/day to about 1000 mg/day, about 1 mg/day to about 750 mg/day, about 1 mg/day to about 500 mg/day, about 1 mg/day to about 250 mg/day or about 100 mg/day to about 1000 mg/day of an Aminopurine Compound to a subject in need thereof.

[00297] In another embodiment, provided herein are unit dosage formulations that comprise between about 1 mg and 1000 mg, about 5 mg and about 1000 mg, about 10 mg and about 1000 mg, about 25 mg and about 1000 mg, about 50 mg and about 1000 mg, about 100 mg and about 1000 mg, or about 250 mg and about 1000 mg of an Aminopurine Compound.

[00298] An Aminopurine Compound can be administered once, twice, three, four or more times daily. In a particular embodiment, doses of 600 mg or less are administered as a once daily dose and doses of more than 600 mg are administered twice daily in an amount equal to one half of the total daily dose.

[00299] An Aminopurine Compound can be administered orally for reasons of convenience. In one embodiment, when administered orally, an Aminopurine Compound is administered with a meal and water. In another embodiment, the Aminopurine Compound is dispersed in water or juice (*e.g.*, apple juice or orange juice) and administered orally as a suspension.

[00300] The Aminopurine Compound can also be administered intradermally, intramuscularly, intraperitoneally, percutaneously, intravenously, subcutaneously, intranasally, epidurally, sublingually, intracerebrally, intravaginally, transdermally, rectally, mucosally, by inhalation, or topically to the ears, nose, eyes, or skin. The mode of administration is left to the

discretion of the health-care practitioner, and can depend in part upon the site of the medical condition.

[00301] In one embodiment, provided herein are capsules containing an Aminopurine Compound without an additional carrier, excipient or vehicle.

[00302] In another embodiment, provided herein are compositions comprising an effective amount of an Aminopurine Compound and a pharmaceutically acceptable carrier or vehicle, wherein a pharmaceutically acceptable carrier or vehicle can comprise an excipient, diluent, or a mixture thereof. In one embodiment, the composition is a pharmaceutical composition.

[00303] The compositions can be in the form of tablets, chewable tablets, capsules, solutions, parenteral solutions, troches, suppositories and suspensions and the like. Compositions can be formulated to contain a daily dose, or a convenient fraction of a daily dose, in a dosage unit, which may be a single tablet or capsule or convenient volume of a liquid. In one embodiment, the solutions are prepared from water-soluble salts, such as the hydrochloride salt. In general, all of the compositions are prepared according to known methods in pharmaceutical chemistry. Capsules can be prepared by mixing an Aminopurine Compound with a suitable carrier or diluent and filling the proper amount of the mixture in capsules. The usual carriers and diluents include, but are not limited to, inert powdered substances such as starch of many different kinds, powdered cellulose, especially crystalline and microcrystalline cellulose, sugars such as fructose, mannitol and sucrose, grain flours and similar edible powders.

[00304] Tablets can be prepared by direct compression, by wet granulation, or by dry granulation. Their formulations usually incorporate diluents, binders, lubricants and disintegrators as well as the compound. Typical diluents include, for example, various types of starch, lactose, mannitol, kaolin, calcium phosphate or sulfate, inorganic salts such as sodium chloride and powdered sugar. Powdered cellulose derivatives are also useful. Typical tablet binders are substances such as starch, gelatin and sugars such as lactose, fructose, glucose and the like. Natural and synthetic gums are also convenient, including acacia, alginates, methylcellulose, polyvinylpyrrolidine and the like. Polyethylene glycol, ethylcellulose and waxes can also serve as binders.

[00305] A lubricant might be necessary in a tablet formulation to prevent the tablet and punches from sticking in the dye. The lubricant can be chosen from such slippery solids as talc,

magnesium and calcium stearate, stearic acid and hydrogenated vegetable oils. Tablet disintegrators are substances that swell when wetted to break up the tablet and release the compound. They include starches, clays, celluloses, algins and gums. More particularly, corn and potato starches, methylcellulose, agar, bentonite, wood cellulose, powdered natural sponge, cation-exchange resins, alginic acid, guar gum, citrus pulp and carboxymethyl cellulose, for example, can be used as well as sodium lauryl sulfate. Tablets can be coated with sugar as a flavor and sealant, or with film-forming protecting agents to modify the dissolution properties of the tablet. The compositions can also be formulated as chewable tablets, for example, by using substances such as mannitol in the formulation.

[00306] When it is desired to administer an Aminopurine Compound as a suppository, typical bases can be used. Cocoa butter is a traditional suppository base, which can be modified by addition of waxes to raise its melting point slightly. Water-miscible suppository bases comprising, particularly, polyethylene glycols of various molecular weights are in wide use.

[00307] The effect of the Aminopurine Compound can be delayed or prolonged by proper formulation. For example, a slowly soluble pellet of the Aminopurine Compound can be prepared and incorporated in a tablet or capsule, or as a slow-release implantable device. The technique also includes making pellets of several different dissolution rates and filling capsules with a mixture of the pellets. Tablets or capsules can be coated with a film that resists dissolution for a predictable period of time. Even the parenteral preparations can be made long-acting, by dissolving or suspending the Aminopurine Compound in oily or emulsified vehicles that allow it to disperse slowly in the serum.

EXAMPLES

[00308] The following Examples are presented by way of illustration, not limitation. Compounds are named using the automatic name generating tool provided in Chemdraw Ultra 9.0 (Cambridgesoft), which generates systematic names for chemical structures, with support for the Cahn-Ingold-Prelog rules for stereochemistry.

CELL ASSAYS

[00309] **Multiplexed Cytotoxicity Assay.** Cells are grown in RPMI1640, 10% FBS, 2 mM L-alanyl-L-Glutamine, 1 mM Na pyruvate or a special medium in a humidified atmosphere of 5%

CO_2 at 37 °C. Cells are seeded into 384-well plates and incubated in a humidified atmosphere of 5% CO_2 at 37 °C. Compounds are added 24 h post cell seeding. At the same time, a time zero untreated cell plate is generated. After a 72 hour incubation period, cells are fixed and stained with fluorescently labeled antibodies and nuclear dye to allow visualization of nuclei, apoptotic cells and mitotic cells. Apoptotic cells are detected using an anti-active caspase-3 antibody. Mitotic cells are detected using an anti phospho-histone-3 antibody. Compounds are serially diluted 3.16-fold and assayed over 10 concentrations in a final assay concentration of 0.1% DMSO from the highest test concentration of 10 μM. Automated fluorescence microscopy was carried out using a Molecular Devices ImageXpress Micro XL high-content imager, and images are collected with a 4X objective.

[00310] **Data Analysis.** Sixteen-bit TIFF images are acquired and analyzed with MetaXpress 5.1.0.41 software. Cell proliferation is measured by the signal intensity of the incorporated nuclear dye. The cell proliferation assay output is referred to as the relative cell count. To determine the cell proliferation end point, the cell proliferation data output is transformed to percentage of control (POC) using the following formula:

[00311] POC = relative cell count (compound wells)/relative cell count (vehicle wells)x100

[00312] Relative cell count IC_{50} is the test compound concentration at 50% of maximal possible response relative to the DMSO control. GI_{50} is the concentration needed to reduce the observed growth by half. This is the concentration that inhibits the growth to the level midway between growth in untreated cells and the number of cells seeded in the well (Time zero value). The IC_{50} values are calculated using nonlinear regression to fit data to a sigmoidal 4 point, 4 parameter One-Site dose response model, where :

$$y\ (fit) = A + [(B - A)/(1 + ((C/x)\ \hat{}\ D))].$$

[00313] The activated caspase-3 marker labels cells from early to late stage apoptosis. Concentrations of test compound that cause a 5-fold induction in the caspase-3 signal (Cal_X5) indicate significant apoptosis induction. The maximal induction of caspase 3 by compound in comparison with DMSO control is reported as Max_Fold_Change.

[00314] **Table 2**: Cell lines used in multiplexed cytotoxicity assays

Cell Line	Type	Subtype
SW-13	Endocrine	Adrenal gland
NCI-H295R	Endocrine	Adrenal gland
639-V	Bladder	Bladder
BFTC-905	Bladder	Bladder
HT1376	Bladder	Bladder
SCaBER	Bladder	Bladder
T24	Bladder	Bladder
5637	Bladder	Bladder
647-V	Bladder	Bladder
HT-1197	Bladder	Bladder
TCCSUP	Bladder	Bladder
J82	Bladder	Bladder
UM-UC-3	Bladder	Bladder
MDA-MB-436	Breast	Breast
Hs 578T	Breast	Breast
AU565	Breast	Breast
BT20	Breast	Breast
SK-BR-3	Breast	Breast
BT474	Breast	Breast
CAMA-1	Breast	Breast
EFM-19	Breast	Breast
KPL-1	Breast	Breast
MDA MB 231	Breast	Breast
MDA MB 453	Breast	Breast
MCF7	Breast	Breast
T47D	Breast	Breast
MDA-MB-415	Breast	Breast
ZR-75-1	Breast	Breast
BT-549	Breast	Breast
MDA MB 468	Breast	Breast
C-33A	Female GU	Cervix
C-4 I	Female GU	Cervix
C-4 II	Female GU	Cervix
HeLa	Female GU	Cervix
SiHa	Female GU	Cervix
DoTc2 4510	Female GU	Cervix
HT-3	Female GU	Cervix

Cell Line	Type	Subtype
LS513	Colon	Colon
LS411N	Colon	Colon
SNU-C2B	Colon	Colon
LS123	Colon	Colon
MT-3	Colon	Colon
SW403	Colon	Colon
RKO-AS45-1	Colon	Colon
SW480	Colon	Colon
SW948	Colon	Colon
Colo 320 HSR	Colon	Colon
HCT-15	Colon	Colon
HCT-116	Colon	Colon
RKOE6	Colon	Colon
SW48	Colon	Colon
SW837	Colon	Colon
SW1463	Colon	Colon
Colo 320DM	Colon	Colon
HT-29	Colon	Colon
LS1034	Colon	Colon
Colo 201	Colon	Colon
Colo 205	Colon	Colon
NCI-H747	Colon	Colon
RKO	Colon	Colon
SW1417	Colon	Colon
DLD-1	Colon	Colon
NCI-H508	Colon	Colon
SW620	Colon	Colon
WiDr	Colon	Colon
HRT-18	Colon	Colon
LS-174T	Colon	Colon
HuTu 80	Duodenum	Duodenum
Y79	Eye	Eye
Hs 683	Central Nervous System	Glioma
U-118 MG	Central Nervous System	Glioma
M059J	Central Nervous System	Glioma
PFSK-1	Central Nervous System	Glioma
SW1783	Central Nervous System	Glioma
SW1088	Central Nervous System	Glioma

Cell Line	Type	Subtype
T98G	Central Nervous System	Glioma
CCF-STTG1	Central Nervous System	Glioma
A172	Central Nervous System	Glioma
DBTRG-05MG	Central Nervous System	Glioma
H4	Central Nervous System	Glioma
SNB-19	Central Nervous System	Glioma
U-138MG	Central Nervous System	Glioma
U-87 MG	Central Nervous System	Glioma
DK-MG	Central Nervous System	Glioma
A-253	Head and Neck	Head and Neck
A388	Head and Neck	Head and Neck
Detroit 562	Head and Neck	Head and Neck
A431	Head and Neck	Head and Neck
Cal 27	Head and Neck	Head and Neck
OE19	Head and Neck	Head and Neck
OE33	Head and Neck	Head and Neck
SCC-4	Head and Neck	Head and Neck
FaDu	Head and Neck	Head and Neck
OE21	Head and Neck	Head and Neck
SCC-25	Head and Neck	Head and Neck
SCC-9	Head and Neck	Head and Neck
A-704	Kidney	Kidney
769-P	Kidney	Kidney
786-O	Kidney	Kidney
G-402	Kidney	Kidney
ACHN	Kidney	Kidney
Caki-1	Kidney	Kidney
Caki-2	Kidney	Kidney
SK-NEP-1	Kidney	Kidney
G-401	Kidney	Kidney
A498	Kidney	Kidney
KG-1	Hematopoietic	Leukemia
RS4;11	Hematopoietic	Leukemia
KU812	Hematopoietic	Leukemia
TF-1	Hematopoietic	Leukemia
MX1	Hematopoietic	Leukemia
NALM-6	Hematopoietic	Leukemia
MOLT-3	Hematopoietic	Leukemia

Cell Line	Type	Subtype
MOLT-16	Hematopoietic	Leukemia
MEG01	Hematopoietic	Leukemia
MHH-PREB-1	Hematopoietic	Leukemia
MV-4-11	Hematopoietic	Leukemia
Thp1	Hematopoietic	Leukemia
BV-173	Hematopoietic	Leukemia
CCRFCEM	Hematopoietic	Leukemia
CML-T1	Hematopoietic	Leukemia
HEL-92-1-7	Hematopoietic	Leukemia
J-RT3-T3-5	Hematopoietic	Leukemia
Jurkat	Hematopoietic	Leukemia
CEM-C1	Hematopoietic	Leukemia
EM-2	Hematopoietic	Leukemia
K562	Hematopoietic	Leukemia
HuCCT1	Liver	Liver
HLE	Liver	Liver
HUH-6 Clone 5	Liver	Liver
HepG2	Liver	Liver
HLF	Liver	Liver
OCUG-1	Liver	Liver
SNU-423	Liver	Liver
Hs 611.T	Hematopoietic	Lymphoma
EB2	Hematopoietic	Lymphoma
GA-10	Hematopoietic	Lymphoma
H9	Hematopoietic	Lymphoma
JeKo-1	Hematopoietic	Lymphoma
SU-DHL-8	Hematopoietic	Lymphoma
SUP-T1	Hematopoietic	Lymphoma
TUR	Hematopoietic	Lymphoma
Hs 445	Hematopoietic	Lymphoma
BCP-1	Hematopoietic	Lymphoma
CA46	Hematopoietic	Lymphoma
Jiyoye	Hematopoietic	Lymphoma
MC116	Hematopoietic	Lymphoma
NAMALWA	Hematopoietic	Lymphoma
REC-1	Hematopoietic	Lymphoma
SU-DHL-4	Hematopoietic	Lymphoma
SU-DHL-5	Hematopoietic	Lymphoma

Cell Line	Type	Subtype
SU-DHL-10	Hematopoietic	Lymphoma
DB	Hematopoietic	Lymphoma
DOHH-2	Hematopoietic	Lymphoma
HT	Hematopoietic	Lymphoma
RPMI 6666	Hematopoietic	Lymphoma
Raji	Hematopoietic	Lymphoma
SR	Hematopoietic	Lymphoma
ST486	Hematopoietic	Lymphoma
BC-1	Hematopoietic	Lymphoma
Daudi	Hematopoietic	Lymphoma
L-428	Hematopoietic	Lymphoma
EB-3	Hematopoietic	Lymphoma
Ramos (RA 1)	Hematopoietic	Lymphoma
CRO-AP2	Hematopoietic	Lymphoma
D341 Med	Central Nervous System	Medulloblastoma
D283 Med	Central Nervous System	Medulloblastoma
Daoy	Central Nervous System	Medulloblastoma
Hs 852.T	Skin (Melanoma)	Melanoma
WM-266-4	Skin (Melanoma)	Melanoma
Hs 934.T	Skin (Melanoma)	Melanoma
A2058	Skin (Melanoma)	Melanoma
G-361	Skin (Melanoma)	Melanoma
Hs 688(A).T	Skin (Melanoma)	Melanoma
Hs 936.T(C1)	Skin (Melanoma)	Melanoma
Hs 895.T	Skin (Melanoma)	Melanoma
A7	Skin (Melanoma)	Melanoma
C32	Skin (Melanoma)	Melanoma
CHL-1	Skin (Melanoma)	Melanoma
SK-MEL-28	Skin (Melanoma)	Melanoma
SH-4	Skin (Melanoma)	Melanoma
RPMI-7951	Skin (Melanoma)	Melanoma
MALME3M	Skin (Melanoma)	Melanoma
MeWo	Skin (Melanoma)	Melanoma
SK-MEL-1	Skin (Melanoma)	Melanoma
SK-MEL-3	Skin (Melanoma)	Melanoma
C32TG	Skin (Melanoma)	Melanoma
Hs 294T	Skin (Melanoma)	Melanoma
Hs 695T	Skin (Melanoma)	Melanoma

Cell Line	Type	Subtype
A101D	Skin (Melanoma)	Melanoma
A375	Skin (Melanoma)	Melanoma
COLO 829	Skin (Melanoma)	Melanoma
HMCB	Skin (Melanoma)	Melanoma
IM-9	Hematopoietic	Myeloma
SKO-007	Hematopoietic	Myeloma
U266B1	Hematopoietic	Myeloma
RPMI 8226	Hematopoietic	Myeloma
ARH-77	Hematopoietic	Myeloma
BE(2)C	Central Nervous System	Neuroblastoma
SK-N-FI	Central Nervous System	Neuroblastoma
CHP-212	Central Nervous System	Neuroblastoma
SK-N-AS	Central Nervous System	Neuroblastoma
MC-IXC	Central Nervous System	Neuroblastoma
SK-N-DZ	Central Nervous System	Neuroblastoma
Hs 229.T	Lung	NSCLC
NCI-H661	Lung	NSCLC
A427	Lung	NSCLC
Calu6	Lung	NSCLC
NCI-H460	Lung	NSCLC
NCI-H520	Lung	NSCLC
NCI-H596	Lung	NSCLC
NCIH441	Lung	NSCLC
A549	Lung	NSCLC
ChaGoK1	Lung	NSCLC
Calu1	Lung	NSCLC
COR-L23	Lung	NSCLC
SKMES1	Lung	NSCLC
NCI-H292	Lung	NSCLC
COR-L105	Lung	NSCLC
G-292, clone A141B1	Soft Tissue	Osteosarcoma
Hs 888.Sk	Soft Tissue	Osteosarcoma
HOS	Soft Tissue	Osteosarcoma
MG-63	Soft Tissue	Osteosarcoma
SJSA1	Soft Tissue	Osteosarcoma
SW1353	Soft Tissue	Osteosarcoma
SaOS2	Soft Tissue	Osteosarcoma
U2OS	Soft Tissue	Osteosarcoma

Cell Line	Type	Subtype
KHOS-240S	Soft Tissue	Osteosarcoma
ME-180	Female GU	Ovary
PA-1	Female GU	Ovary
Ca Ski	Female GU	Ovary
MS751	Female GU	Ovary
CaOV3	Female GU	Ovary
OVCAR3	Female GU	Ovary
SKOV3	Female GU	Ovary
PSN-1	Pancreas	Pancreas
AsPC-1	Pancreas	Pancreas
PANC-1	Pancreas	Pancreas
Hs 766T	Pancreas	Pancreas
Mia PaCa-2	Pancreas	Pancreas
SU.86.86	Pancreas	Pancreas
YAPC	Pancreas	Pancreas
BxPC-3	Pancreas	Pancreas
CFPAC-1	Pancreas	Pancreas
Capan-1	Pancreas	Pancreas
Capan-2	Pancreas	Pancreas
HPAF-II	Pancreas	Pancreas
HuP-T4	Pancreas	Pancreas
BeWo	Placenta	Placenta
JAR	Placenta	Placenta
JEG-3	Placenta	Placenta
22Rv1	Prostate	Prostate
DU145	Prostate	Prostate
PC-3	Prostate	Prostate
LNCaP	Prostate	Prostate
BM-1604	Prostate	Prostate
BPH1	Prostate	Prostate
Hs 729	Soft Tissue	Sarcoma
VA-ES-BJ	Soft Tissue	Sarcoma
Hs 821.T	Soft Tissue	Sarcoma
TE 125.T	Soft Tissue	Sarcoma
RD	Soft Tissue	Sarcoma
SK-UT-1	Soft Tissue	Sarcoma
A-673	Soft Tissue	Sarcoma
SW684	Soft Tissue	Sarcoma

Cell Line	Type	Subtype
A204	Soft Tissue	Sarcoma
SW872	Soft Tissue	Sarcoma
SW982	Soft Tissue	Sarcoma
HT-1080	Soft Tissue	Sarcoma
MES-SA	Soft Tissue	Sarcoma
SJRH30	Soft Tissue	Sarcoma
SK-LMS-1	Soft Tissue	Sarcoma
TE 381.T	Soft Tissue	Sarcoma
NCI-H510A	Lung	SCLC
NCIH446	Lung	SCLC
SHP-77	Lung	SCLC
DMS114	Lung	SCLC
SW900	Lung	SCLC
DMS53	Lung	SCLC
NCI-H69	Lung	SCLC
DMS273	Lung	SCLC
SK-PN-DW	Stomach	Stomach
AGS	Stomach	Stomach
HS 746T	Stomach	Stomach
SNU-1	Stomach	Stomach
KATO III	Stomach	Stomach
SNU-16	Stomach	Stomach
SNU-5	Stomach	Stomach
NTERA-2 cl.D1	Testis	Testis
TT	Endocrine	Thyroid
BHT-101	Endocrine	Thyroid
CAL-62	Endocrine	Thyroid
CGTH-W-1	Endocrine	Thyroid
SW579	Endocrine	Thyroid
HEC-1-A	Female GU	Uterus
RL95-2	Female GU	Uterus
KLE	Female GU	Uterus
AN3 CA	Female GU	Uterus
SW962	Female GU	Vulva
SW954	Female GU	Vulva

[00315] Aminopurine Compounds (exemplified by Compound 1) show or will be shown to have anti-proliferative activity in a variety of cancer cell lines. Anti-proliferative activity in

these cancer cell lines indicates that the Aminopurine compounds may be useful in the treatment of cancers, including solid tumors, as exemplified by melanoma, colorectal cancer, stomach cancer, head and neck cancer, thyroid cancer, bladder cancer, CNS cancer, lung cancer, pancreatic cancer, and soft tissue cancer.

[00316] In another embodiment, Aminopurine Compounds (exemplified by Compound 1) show or will be shown to induce apoptosis in a variety of cancer cell lines. Induction of apoptosis indicates that the Aminopurine compounds may be useful in the treatment of cancers, including solid tumors, as exemplified by bladder cancer, breast cancer, CNS cancer (including neuroblastoma and glioma), colon cancer, gastrointestinal cancer (for example, stomach cancer or colon cancer), endocrine cancer (for example, thyroid cancer or adrenal gland cancer), female genitoureal cancer (for example, cervix cancer or ovary clear cell cancer, vulva cancer, uterus cancer, or ovary cancer), head and neck cancer, hematopoietic cancer (for example, leukemia or myeloma), kidney cancer, liver cancer, lung (for example, NSCLC or SCLC), melanoma, pancreas cancer, prostate cancer, or soft tissue cancer (for example, sarcoma or osteosarcoma).

[00317] In another embodiment, Aminopurine Compounds (exemplified by Compound 1) show or will be shown to cause G1/S arrest in a variety of cancer cell lines. Causing G1/S arrest in these cancer cell lines indicates that the Aminopurine compounds may be useful in the treatment of cancers, including solid tumors, as exemplified by bladder cancer, breast cancer, CNS cancer (for example, glioma or neuroblastoma), colon cancer, gastrointestinal cancer (for example, stomach cancer), endocrine cancer (for example, thyroid cancer or adrenal gland cancer), female genitoureal cancer (for example, uterus cancer, cervix cancer, ovary clear cell cancer, or vulva cancer), head and neck cancer, hematopoietic cancer (for example, leukemia or myeloma), kidney cancer, liver cancer, lung cancer (for example, NSCLC or SCLC), melanoma, pancreas cancer, prostate cancer, or soft tissue cancer (sarcoma or osteosarcoma).

[00318] **Multiplexed Cytotoxicity Assay.** In another experiment, cells were grown in RPMI1640, 10% FBS, 2 mM L-alanyl-L-Glutamine, 1 mM Na pyruvate or a special medium in a humidified atmosphere of 5% CO_2 at 37 °C. Cells were seeded into 384-well plates and incubated in a humidified atmosphere of 5% CO_2 at 37 °C. Compounds were added 24 h post cell seeding. At the same time, a time zero untreated cell plate was generated. After a 72 hour incubation period, cells were fixed and stained with fluorescently labeled antibodies and nuclear

dye to allow visualization of nuclei, apoptotic cells and mitotic cells. Apoptotic cells were detected using an anti-active caspase-3 antibody. Mitotic cells were detected using an anti phospho-histone-3 antibody. Compounds were serially diluted 3.16-fold and assayed over 10 concentrations in a final assay concentration of 0.1% DMSO from the highest test concentration of 10 μM. Automated fluorescence microscopy was carried out using a Molecular Devices ImageXpress Micro XL high-content imager, and images were collected with a 4X objective.

[00319] **Data Analysis.** Sixteen-bit TIFF images were acquired and analyzed with MetaXpress 5.1.0.41 software. Cell proliferation was measured by the signal intensity of the incorporated nuclear dye. The cell proliferation assay output was referred to as the relative cell count. To determine the cell proliferation end point, the cell proliferation data output was transformed to percentage of control (POC) using the following formula:

POC = relative cell count (compound wells)/relative cell count (vehicle wells)x100

[00320] Relative cell count IC_{50} was the test compound concentration at 50% of maximal possible response relative to the DMSO control. GI_{50} refers to the concentration needed to reduce the observed growth by half. This corresponds to the concentration that inhibits the growth to the level midway between growth in untreated cells and the number of cells seeded in the well (Time zero value). The IC_{50} values were calculated using nonlinear regression to fit data to a sigmoidal 4 point, 4 parameter One-Site dose response model, where:

$$y\ (fit) = A + [(B - A)/(1 + ((C/x) \wedge D))].$$

[00321] The activated caspase-3 marker labels cells from early to late stage apoptosis. Concentrations of test compound that cause a 2-fold (Cal-X2) or 5-fold induction in the caspase-3 signal (Cal_X5) indicated significant apoptosis induction. The maximal induction of caspase 3 by compound in comparison with DMSO control was reported as Max_Fold_Change.

[00322] **Table 3**. Results of Cytotoxicity Assays

Cell line	Tumor Type	Subtype	GI50 (μM)	IC50 (μM)	CalX2 (μM)	CalX5 (μM)	Max fold change
NCIH295R	Endocrine	Adrenal gland	10	10	10	10	1.74
SW13	Endocrine	Adrenal gland	0.0711	0.135	0.04	0.535	8.74
5637	Bladder	Bladder	6.85	9.77	10	10	2.12
639V	Bladder	Bladder	0.184	0.206	0.0841	0.465	6.33

Cell line	Tumor Type	Subtype	GI50 (μM)	IC50 (μM)	CalX2 (μM)	CalX5 (μM)	Max fold change
647V	Bladder	Bladder	6.93	7.82	2.7413	4.45	19.29
BFTC905	Bladder	Bladder	0.0515	0.0546	0.0179	0.0414	45.3
HT1197	Bladder	Bladder	0.444	10	0.1601	10	4.16
HT1376	Bladder	Bladder	0.792	3.48	0.0524	0.167	10.87
J82	Bladder	Bladder	10	10	2.4365	10	3.17
SCABER	Bladder	Bladder	0.0665	0.0772	0.0086	0.0506	29.47
T24	Bladder	Bladder	0.233	0.274	4.5443	10	2.61
TCCSUP	Bladder	Bladder	2.21	6.59	5.6435	10	3.67
UMUC3	Bladder	Bladder	0.149	0.201	2.7934	5.76	6.56
AU565	Breast	Breast	8.15	8.77	3.8749	7.14	14.18
BT20	Breast	Breast	8.36	10	10	10	1.81
BT474	Breast	Breast	10	10	10	10	0.94
BT549	Breast	Breast	10	10	5.4537	10	3.14
CAMA1	Breast	Breast	0.298	2.24	6.4981	10	2.85
EFM19	Breast	Breast	4.2	10	10	10	2.1
HS578T	Breast	Breast	0.153	0.837	2.6723	6.58	5.94
KPL1	Breast	Breast	10	10	0.0481	10	2.63
MCF7	Breast	Breast	0.636	3.47	6.5592	9.74	5.78
MDAMB231	Breast	Breast	0.0339	0.0624	0.0242	0.257	5.94
MDAMB415	Breast	Breast	0.729	10	10	10	1.85
MDAMB436	Breast	Breast	0.262	10	5.118	10	4.25
MDAMB453	Breast	Breast	0.656	2.82	10	10	1.07
MDAMB468	Breast	Breast	0.0363	0.0721	0.0969	10	3.81
MT3	Breast	Breast	0.674	1.08	7.6544	10	2.81
SKBR3	Breast	Breast	6.81	8.45	3.2211	6.2	12.79
T47D	Breast	Breast	10	10	10	10	2
ZR751	Breast	Breast	0.0943	7.7	5.9055	6.44	7.36
A431	Skin	Carcinoma	0.228	0.311	0.0801	1.76	5.11
C33A	Female GU	Cervix	0.191	0.407	3.6798	5.39	9.45
C4I	Female GU	Cervix	10	10	5.7177	7.94	7.38
C4II	Female GU	Cervix	10	10	0.044	10	3.7
DOTC24510	Female GU	Cervix	0.04	0.132	0.0268	10	5.03
HELA	Female GU	Cervix	6.75	8.71	7.0794	10	3.65
HT3	Female GU	Cervix	0.856	3.21	0.2906	3.74	7.49
SIHA	Female GU	Cervix	10	10	7.6882	8.82	5.49
COLO201	Colon	Colon	0.0128	0.0172	0.0225	0.267	6.09
COLO205	Colon	Colon	0.0095	0.0117	0.0102	0.0248	9.86

Cell line	Tumor Type	Subtype	GI50 (μM)	IC50 (μM)	CalX2 (μM)	CalX5 (μM)	Max fold change
COLO320DM	Colon	Colon	9.11	10	6.1862	9.53	5.28
COLO320HSR	Colon	Colon	4.19	4.44	2.0186	3.53	49.73
DLD1	Colon	Colon	0.162	0.197	0.0474	0.104	21.95
HCT116	Colon	Colon	0.0194	0.0204	0.0196	0.0448	45.43
HCT15	Colon	Colon	1.97	2.23	5.1211	7.03	7.97
HRT18	Colon	Colon	0.0775	0.0819	0.0657	0.147	11.1
HT29	Colon	Colon	0.0129	0.0167	0.0092	0.0318	61.59
LS1034	Colon	Colon	0.224	0.676	1.4781	10	2.52
LS123	Colon	Colon	0.061	0.188	0.0766	10	4.74
LS174T	Colon	Colon	0.194	0.259	0.2846	0.412	5.63
LS411N	Colon	Colon	0.0358	0.053	0.0575	10	5.58
LS513	Colon	Colon	0.0353	0.0386	0.0233	0.0356	64.31
NCIH508	Colon	Colon	0.0288	0.0481	0.0778	1.25	5.37
NCIH747	Colon	Colon	0.012	0.0445	0.0226	0.0756	8.21
RKO	Colon	Colon	0.0353	0.0405	0.0407	0.378	11.14
RKOAS451	Colon	Colon	0.0405	0.0449	0.1873	1.16	10.06
RKOE6	Colon	Colon	0.0753	0.107	1.6988	3.6	29.26
SNUC2B	Colon	Colon	0.0544	0.722	10	10	1.67
SW1417	Colon	Colon	0.0088	0.0351	0.0221	0.0693	6.76
SW1463	Colon	Colon	0.135	0.181	2.4138	10	2.82
SW403	Colon	Colon	0.0476	0.173	0.1084	10	4.02
SW48	Colon	Colon	0.0018	0.0031	0.0047	0.0266	13.66
SW480	Colon	Colon	0.0184	0.0311	0.0638	0.248	6.26
SW620	Colon	Colon	0.0492	0.0798	1.4774	3.88	14.66
SW837	Colon	Colon	0.172	0.348	0.325	10	4.34
SW948	Colon	Colon	0.195	0.327	10	10	1.57
WIDR	Colon	Colon	0.0104	0.0133	0.0085	0.021	79.03
HUTU80	Duodenum	Duodenum	0.057	0.0695	0.0161	0.354	9.27
Y79	Eye-retinoblastoma	Eye	10	10	7.8739	10	2.58
A172	CNS	Glioma	0.0649	0.139	0.1174	2.36	5.95
CCFSTTG1	CNS	Glioma	10	10	10	10	1.03
DBTRG05MG	CNS	Glioma	0.0432	0.0984	0.1963	10	3.94
DKMG	CNS	Glioma	0.0207	0.126	0.0463	0.16	10.86
H4	CNS	Glioma	0.758	0.943	1.7285	3.78	14.47
HS683	CNS	Glioma	0.148	0.305	10	10	2.54
M059J	CNS	Glioma	0.612	3.31	4.9633	10	2.8

Cell line	Tumor Type	Subtype	GI50 (μM)	IC50 (μM)	CalX2 (μM)	CalX5 (μM)	Max fold change
PFSK1	CNS	Glioma	0.0234	10	10	10	1.06
SNB19	CNS	Glioma	0.163	0.244	0.4478	10	3.29
SW1088	CNS	Glioma	3.35	5.98	5.2615	7.5	9.59
SW1783	CNS	Glioma	5.92	9.85	9.0994	10	2.49
T98G	CNS	Glioma	10	10	5.4225	10	3.16
U118MG	CNS	Glioma	0.175	10	10	10	1.92
U138MG	CNS	Glioma	0.053	10	0.1598	0.417	8.01
U87MG	CNS	Glioma	0.0692	0.101	9.3615	10	2.14
A253	Head and Neck	Head and Neck	0.171	10	8.7811	10	2.85
A388	Head and Neck	Head and Neck	0.422	1.12	0.0902	3.52	6.48
CAL27	Head and Neck	Head and Neck	0.0592	0.0661	0.0877	0.46	7.98
DETROIT562	Head and Neck	Head and Neck	0.347	10	4.9484	7.16	6.02
FADU	Head and Neck	Head and Neck	0.435	0.787	4.0608	5.64	8.64
SCC25	Head and Neck	Head and Neck	0.0439	0.051	0.1187	0.304	6.72
SCC4	Head and Neck	Head and Neck	0.0512	0.108	0.0317	0.065	7.38
SCC9	Head and Neck	Head and Neck	0.117	0.28	0.6679	3.86	9.58
769P	Kidney	Kidney	0.194	0.255	0.2023	5.11	5.67
786O	Kidney	Kidney	2.04	6.92	10	10	0.83
A498	Kidney	Kidney	0.522	0.808	0.5562	10	4.72
A704	Kidney	Kidney	10	10	10	10	0.96
ACHN	Kidney	Kidney	0.306	0.55	0.78	10	2.97
CAKI1	Kidney	Kidney	0.0914	0.151	0.2015	10	4.12
CAKI2	Kidney	Kidney	0.139	0.193	0.1631	0.449	6.26
G401	Kidney	Kidney	0.0774	0.086	0.0717	0.179	30.87
G402	Kidney	Kidney	0.0504	0.0925	0.0162	0.637	7.34
SKNEP1	Kidney	Kidney	10	10	10	10	1.15
BV173	Hematopoietic and lymphoid	Leukemia	1.1	10	0.4959	10	2.91
CCRFCEM	Hematopoietic and lymphoid	Leukemia	5.03	6.05	3.4279	6.95	12.74
CEMC1	Hematopoietic and lymphoid	Leukemia	10	10	4.1828	5.22	11.27
CMLT1	Hematopoietic and lymphoid	Leukemia	0.149	10	0.0948	10	4.85
EM2	Hematopoietic and lymphoid	Leukemia	0.0481	0.0936	10	10	1.55
HEL9217	Hematopoietic and lymphoid	Leukemia	4.62	8.23	3.2991	6.57	6.23

Cell line	Tumor Type	Subtype	GI50 (μM)	IC50 (μM)	CalX2 (μM)	CalX5 (μM)	Max fold change
JRT3T35	Hematopoietic and lymphoid	Leukemia	3.58	4.78	2.6364	3.8	14.26
JURKAT	Hematopoietic and lymphoid	Leukemia	3.34	3.73	1.6173	3.28	14.48
K562	Hematopoietic and lymphoid	Leukemia	10	10	2.9298	4.86	51.89
KG1	Hematopoietic and lymphoid	Leukemia	0.0017	0.0325	2.5811	10	2.5
KU812	Hematopoietic and lymphoid	Leukemia	0.003	0.0159	0.03	8.02	5.63
MEG01	Hematopoietic and lymphoid	Leukemia	0.0818	0.221	0.5718	10	2.77
MHHPREB1	Hematopoietic and lymphoid	Leukemia	6.69	6.97	5.1142	7.66	11.43
MOLT16	Hematopoietic and lymphoid	Leukemia	2.88	3.35	2.4102	4.97	8.06
MOLT3	Hematopoietic and lymphoid	Leukemia	0.946	3.03	5.88	10	3.63
MV411	Hematopoietic and lymphoid	Leukemia	0.107	0.184	0.0933	1.15	8.12
MX1	Hematopoietic and lymphoid	Leukemia	0.0401	0.0619	1.1016	10	3.78
NALM6	Hematopoietic and lymphoid	Leukemia	10	10	0.1241	10	5
RS411	Hematopoietic and lymphoid	Leukemia	0.359	2.96	3.8025	8.4	5.83
TF1	Hematopoietic and lymphoid	Leukemia	0.0015	0.0095	0.006	0.0296	16.1
THP1	Hematopoietic and lymphoid	Leukemia	0.0251	0.0495	0.132	3.9	6.3
HEPG2	Liver	Liver	0.0224	0.0643	0.0041	0.0108	62.47
HLE	Liver	Liver	0.683	1.04	0.8174	10	2.5
HLF	Liver	Liver	4.76	6.47	10	10	1.95
HUCCT1	Liver	Liver	0.0537	0.0633	0.0222	0.0406	11.54
HUH6CLONE5	Liver	Liver	0.145	0.354	0.0631	0.302	8.25
OCUG1	Liver	Liver	0.464	1.29	0.0848	0.49	5.49
SNU423	Liver	Liver	0.192	0.276	0.0909	1.65	7.32
BC1	Hematopoietic and lymphoid	Lymphoma	10	10	5.1005	6.54	8.72
BCP1	Hematopoietic	Lymphoma	0.0205	0.0797	4.8663	7.36	6.56

Cell line	Tumor Type	Subtype	GI50 (μM)	IC50 (μM)	CalX2 (μM)	CalX5 (μM)	Max fold change
	and lymphoid						
CA46	Hematopoietic and lymphoid	Lymphoma	0.0146	0.0213	3.2395	8.08	9.46
CROAP2	Hematopoietic and lymphoid	Lymphoma	0.996	2.58	2.9603	4.2	50.79
DAUDI	Hematopoietic and lymphoid	Lymphoma	0.0177	10	3.9392	5.33	10.08
DB	Hematopoietic and lymphoid	Lymphoma	0.0131	10	6.1153	6.5	7.11
DOHH2	Hematopoietic and lymphoid	Lymphoma	5.54	5.79	2.4833	3.99	20.41
EB2	Hematopoietic and lymphoid	Lymphoma	0.389	0.55	5.7381	10	4.16
EB3	Hematopoietic and lymphoid	Lymphoma	1.63	2.15	6.1469	7.66	5.5
GA10	Hematopoietic and lymphoid	Lymphoma	0.0468	0.0567	0.6477	1.94	6.49
H9	Hematopoietic and lymphoid	Lymphoma	0.0232	0.039	0.0222	0.4	7.33
HS445	Hematopoietic and lymphoid	Lymphoma	0.0143	0.0377	4.9128	7.7	5.65
HS611T	Hematopoietic and lymphoid	Lymphoma	0.0106	0.0123	2.8507	10	3.84
HT	Hematopoietic and lymphoid	Lymphoma	8.3	10	8.6354	10	2.44
JEKO1	Hematopoietic and lymphoid	Lymphoma	0.461	0.83	4.3369	10	3.11
JIYOYE	Hematopoietic and lymphoid	Lymphoma	0.0814	0.21	4.4004	5.35	11.1
L428	Hematopoietic and lymphoid	Lymphoma	1.63	3.46	4.2384	5.88	7.51
MC116	Hematopoietic and lymphoid	Lymphoma	6.02	6.49	2.8763	5.18	9.46
NAMALWA	Hematopoietic and lymphoid	Lymphoma	0.0181	0.0239	5.9431	10	2.68
RAJI	Hematopoietic and lymphoid	Lymphoma	0.179	10	2.5564	4.07	24.81
RAMOSRA1	Hematopoietic and lymphoid	Lymphoma	3.66	3.84	4.5496	7.39	25.1
REC1	Hematopoietic and lymphoid	Lymphoma	0.0053	0.193	10	10	1.86

Cell line	Tumor Type	Subtype	GI50 (μM)	IC50 (μM)	CalX2 (μM)	CalX5 (μM)	Max fold change
RPMI6666	Hematopoietic and lymphoid	Lymphoma	0.0801	0.37	3.0419	4.37	26.35
SR	Hematopoietic and lymphoid	Lymphoma	1.42	1.84	1.2842	3.07	33.52
ST486	Hematopoietic and lymphoid	Lymphoma	5.02	6.14	4.2422	6.11	10.85
SUDHL10	Hematopoietic and lymphoid	Lymphoma	1.23	1.4	3.611	4.87	11.63
SUDHL4	Hematopoietic and lymphoid	Lymphoma	0.168	0.332	2.5668	4.83	10.75
SUDHL5	Hematopoietic and lymphoid	Lymphoma	0.0011	0.0013	1.6359	4.54	10.37
SUDHL8	Hematopoietic and lymphoid	Lymphoma	0.0193	0.0406	1.2344	4.19	10.79
SUPT1	Hematopoietic and lymphoid	Lymphoma	0.0196	0.0466	4.5476	9.21	5.76
TUR	Hematopoietic and lymphoid	Lymphoma	0.0415	0.0539	0.6984	3.45	17.35
D283MED	CNS	Medulloblastoma	2.56	7.55	8.3456	10	2.23
D341MED	CNS	Medulloblastoma	10	0.0219	7.7855	10	2.14
DAOY	CNS	Medulloblastoma	0.749	1.09	3.2773	5.22	16.68
A101D	Skin	Melanoma	0.0424	0.0815	0.4207	3.71	7.93
A2058	Skin	Melanoma	0.212	0.288	0.065	0.204	11.68
A375	Skin	Melanoma	0.0065	0.0072	0.0673	0.0827	103.79
A7	Skin	Melanoma	1.72	7.27	5.0814	9.4	5.51
C32	Skin	Melanoma	0.0289	0.111	0.0451	0.0778	110.9
C32TG	Skin	Melanoma	0.0408	0.109	0.0608	0.117	42.82
CHL1	Skin	Melanoma	0.103	0.117	1.2376	10	3.46
COLO829	Skin	Melanoma	0.0121	0.0343	0.0421	0.125	24.28
G361	Skin	Melanoma	0.102	0.15	0.0428	0.12	24.48
HMCB	Skin	Melanoma	0.0724	0.113	10	10	1.8
HS294T	Skin	Melanoma	0.0507	0.0706	0.154	2.15	5.74
HS688AT	Skin	Melanoma	0.0822	10	10	10	1.61
HS695T	Skin	Melanoma	0.0363	0.16	0.0253	0.0727	22.05
HS852T	Skin	Melanoma	0.0564	0.715	0.05	0.234	6.51
HS895T	Skin	Melanoma	10	10	10	10	1.52
HS934T	Skin	Melanoma	0.0052	10	0.3638	1.4	5.1
HS936TC1	Skin	Melanoma	0.0184	0.0258	0.0084	0.0224	134.98
MALME3M	Skin	Melanoma	0.0034	0.012	0.0025	0.0045	102.73

Cell line	Tumor Type	Subtype	GI50 (μM)	IC50 (μM)	CalX2 (μM)	CalX5 (μM)	Max fold change
MEWO	Skin	Melanoma	0.102	0.159	0.167	0.373	14.34
RPMI7951	Skin	Melanoma	0.0716	0.0945	0.1237	1.29	28.15
SH4	Skin	Melanoma	0.0208	0.029	0.0157	0.0382	66.44
SKMEL1	Skin	Melanoma	0.001	0.0291	0.1019	0.194	7.63
SKMEL28	Skin	Melanoma	0.0279	0.0571	0.2907	0.344	16.64
SKMEL3	Skin	Melanoma	0.0284	0.0625	10	10	1.74
WM2664	Skin	Melanoma	0.012	0.0354	0.0023	0.0151	83.29
ARH77	Hematopoietic and lymphoid	Myeloma	10	10	10	10	1.86
IM9	Hematopoietic and lymphoid	Myeloma	0.0911	0.143	0.043	10	4.85
RPMI8226	Hematopoietic and lymphoid	Myeloma	1.09	2.48	3.3103	5.34	8.35
SKO007	Hematopoietic and lymphoid	Myeloma	0.0274	0.482	0.1758	2.79	7.24
U266B1	Hematopoietic and lymphoid	Myeloma	0.0133	0.109	0.0493	10	4.36
BE2C	CNS	Neuroblastoma	0.146	0.21	0.1223	10	5.47
CHP212	CNS	Neuroblastoma	0.0066	0.0165	0.019	0.341	5.97
MCIXC	CNS	Neuroblastoma	2.04	2.33	1.9309	4.62	5.15
SKNAS	CNS	Neuroblastoma	0.0489	0.132	0.0675	0.227	8.86
SKNDZ	CNS	Neuroblastoma	7.4	10	10	10	1.23
SKNFI	CNS	Neuroblastoma	0.0151	0.135	0.0897	10	3.51
A427	Lung	NSCLC	0.0475	0.0763	0.0018	10	3.34
A549	Lung	NSCLC	0.102	0.128	0.0297	0.0946	13.03
CALU1	Lung	NSCLC	0.0967	0.149	0.2575	10	3.73
CALU6	Lung	NSCLC	0.0463	0.083	0.11	10	4.86
CHAGOK1	Lung	NSCLC	10	10	10	10	1.23
CORL105	Lung	NSCLC	0.0165	0.0414	0.0583	0.571	6.55
CORL23	Lung	NSCLC	0.0238	0.0283	0.0176	0.0569	12.96
HS229T	Lung	NSCLC	0.415	10	0.8448	7.22	5.29
NCIH292	Lung	NSCLC	0.278	0.686	2.4602	4.85	10.26
NCIH441	Lung	NSCLC	0.271	1.25	7.7406	10	4.32
NCIH460	Lung	NSCLC	10	10	10	10	0.98
NCIH520	Lung	NSCLC	0.991	2.13	3.637	5.03	13.95
NCIH596	Lung	NSCLC	2.75	10	10	10	1.11
NCIH661	Lung	NSCLC	1.44	2.64	0.0833	10	4.58
SKMES1	Lung	NSCLC	0.103	0.122	0.0384	0.212	27.03

Cell line	Tumor Type	Subtype	GI50 (μM)	IC50 (μM)	CalX2 (μM)	CalX5 (μM)	Max fold change
OE19	Head and Neck	Esophageal	0.34	10	10	10	1.79
OE21	Head and Neck	Esophageal	0.0939	0.124	0.0221	0.948	5.91
OE33	Head and Neck	Esophageal	0.063	0.0969	0.0317	0.495	5.9
G292CLONEA141B1	Soft Tissue	Osteosarcoma	0.0272	0.0493	0.0401	0.211	7.61
HOS	Soft Tissue	Osteosarcoma	2.57	3.69	6.2324	8.81	7.12
HS888SK	Soft Tissue	Osteosarcoma	0.111	10	0.1023	0.175	15.7
KHOS240S	Soft Tissue	Osteosarcoma	10	10	4.3797	4.93	18.16
MG63	Soft Tissue	Osteosarcoma	0.108	0.115	4.1626	5.71	17.21
SAOS2	Soft Tissue	Osteosarcoma	3.57	6.88	3.2386	5.98	6.35
SJSA1	Soft Tissue	Osteosarcoma	1.16	2.46	2.9744	6.21	62.65
SW1353	Soft Tissue	Osteosarcoma	0.184	0.292	0.404	10	4.79
U2OS	Soft Tissue	Osteosarcoma	0.23	0.373	0.0332	0.0801	20.57
CAOV3	Female GU	Ovary	0.429	10	2.0076	10	2.95
CASKI	Female GU	Ovary	6.76	10	0.9719	10	2.61
ME180	Female GU	Ovary	10	10	5.1674	6.32	12.19
MS751	Female GU	Ovary	6.91	9.51	5.4363	10	3.62
OVCAR3	Female GU	Ovary	10	10	10	10	1.19
PA1	Female GU	Ovary	0.471	2.62	3.6547	5.1	11.55
SKOV3	Female GU	Ovary	0.547	10	0.2939	10	2.65
ASPC1	Pancreas	Pancreas	0.0308	10	0.0471	10	4.08
BXPC3	Pancreas	Pancreas	0.0369	0.0455	0.025	10	4.98
CAPAN1	Pancreas	Pancreas	0.105	10	10	10	1.97
CAPAN2	Pancreas	Pancreas	0.136	0.291	10	0.209	6.62
CFPAC1	Pancreas	Pancreas	10	10	10	10	1.46
HPAFII	Pancreas	Pancreas	0.013	0.0175	0.0034	0.0093	52.77
HS766T	Pancreas	Pancreas	0.0343	0.0793	0.0646	0.632	6.36
HUPT4	Pancreas	Pancreas	0.0434	0.0505	0.0998	10	5.3
MIAPACA2	Pancreas	Pancreas	0.0357	0.0396	0.0387	0.578	15.16
PANC1	Pancreas	Pancreas	0.0416	0.08	0.0227	0.173	10.76
PSN1	Pancreas	Pancreas	0.0083	0.0092	0.036	0.0701	8.75
SU8686	Pancreas	Pancreas	0.0635	0.132	10	10	2.09
YAPC	Pancreas	Pancreas	0.183	0.67	10	10	1.59
BEWO	Female GU	Placenta	5.16	5.69	3.9778	6.42	10.1
JAR	Female GU	Placenta	3.17	3.21	1.0062	2.99	102.66
JEG3	Female GU	Placenta	6.34	7.75	5.8823	7.95	6.39
22RV1	Prostate	Prostate	2.66	5.58	3.0283	4.45	18.69
BM1604	Prostate	Prostate	0.141	0.401	10	10	1.8

Cell line	Tumor Type	Subtype	GI50 (μM)	IC50 (μM)	CalX2 (μM)	CalX5 (μM)	Max fold change
BPH1	Prostate	Prostate	0.0578	0.0675	0.0577	0.116	35.09
DU145	Prostate	Prostate	0.0738	0.0965	5.1233	8.37	6.15
LNCAP	Prostate	Prostate	2.43	5.07	4.1807	10	3.85
PC3	Prostate	Prostate	7.82	8.54	10	10	3.64
A204	Soft Tissue	Sarcoma	10	10	0.2906	10	3.48
A673	Soft Tissue	Sarcoma	3.75	3.87	3.411	4.59	27.78
HS729	Soft Tissue	Sarcoma	0.54	10	10	10	1.87
HS821T	Soft Tissue	Sarcoma	0.169	10	10	10	1.53
HT1080	Soft Tissue	Sarcoma	0.0648	0.0727	0.0509	0.107	63.63
MESSA	Soft Tissue	Sarcoma	0.81	1.1	4.196	5.47	8.03
RD	Soft Tissue	Sarcoma	0.0367	0.0443	0.0297	0.0581	14.86
SJRH30	Soft Tissue	Sarcoma	0.219	1.47	0.039	10	5.61
SKLMS1	Soft Tissue	Sarcoma	0.146	0.166	0.1405	0.876	12.5
SKUT1	Soft Tissue	Sarcoma	10	10	6.5345	10	4.63
SW684	Soft Tissue	Sarcoma	0.0869	0.37	0.256	0.308	16.88
SW872	Soft Tissue	Sarcoma	0.105	0.136	0.0538	0.434	9.48
SW982	Soft Tissue	Sarcoma	0.0156	0.0614	10	10	1.94
TE125T	Soft Tissue	Sarcoma	1.09	10	3.9673	10	2.5
TE381T	Soft Tissue	Sarcoma	0.0076	0.0128	0.0048	0.0143	15.88
VAESBJ	Soft Tissue	Sarcoma	0.336	0.58	3.1752	10	3.26
DMS114	Lung	SCLC	0.0688	0.6	0.9142	10	3.38
DMS273	Lung	SCLC	5.96	6.79	6.5676	8.53	6.76
DMS53	Lung	SCLC	0.998	10	0.0661	1.4	7.01
NCIH446	Lung	SCLC	0.327	10	10	10	1.63
NCIH510A	Lung	SCLC	3.7	6.61	3.8517	8.62	6.44
NCIH69	Lung	SCLC	5	10	10	10	1.7
SHP77	Lung	SCLC	4.79	5.82	6.8591	10	3.64
SW900	Lung	SCLC	0.0216	0.0399	0.0162	0.0849	10.26
AGS	Stomach	Stomach	0.0086	0.0098	0.0075	0.0131	31.12
HS746T	Stomach	Stomach	0.0396	0.122	0.0471	10	4.41
KATOIII	Stomach	Stomach	0.0612	0.0787	0.0137	0.123	29.59
SKPNDW	Stomach	Stomach	3.6	10	7.8388	10	2.58
SNU1	Stomach	Stomach	0.0355	0.0631	0.041	2.57	5.5
SNU16	Stomach	Stomach	10	10	3.2968	5.11	10.66
SNU5	Stomach	Stomach	0.0368	0.0943	0.1664	10	3.21
NTERA2CLD1	Testis	Testis	0.044	0.0507	0.0707	0.0957	9.95
BHT101	Endocrine	Thyroid	0.0376	0.0412	0.0438	0.0864	22.52

Cell line	Tumor Type	Subtype	GI50 (μM)	IC50 (μM)	CalX2 (μM)	CalX5 (μM)	Max fold change
CAL62	Endocrine	Thyroid	0.0836	0.0936	0.0795	0.129	6.49
CGTHW1	Endocrine	Thyroid	0.0547	0.0605	0.065	0.103	91.55
SW579	Endocrine	Thyroid	0.0477	0.0708	0.1374	0.256	51.22
TT	Endocrine	Thyroid	0.0863	10	0.5946	10	2.79
AN3CA	Female GU	Uterus	0.713	7.03	8.777	10	2.75
HEC1A	Female GU	Uterus	1.8	2.81	1.6552	3.7	30.12
KLE	Female GU	Uterus	10	10	10	10	1.37
RL952	Female GU	Uterus	0.009	0.0599	0.1762	10	4.12
SW954	Female GU	Vulva	0.114	0.142	0.1749	0.521	9.14
SW962	Female GU	Vulva	0.0828	0.232	0.0686	10	3.39

[00323] **Effect on HCC Proliferation.** HCC cell lines were treated with DMSO or increasing concentrations of Compound 1 for 72 h. Specifically, Compound 1 at various concentrations in dimethyl sulfoxide (DMSO) was spotted via an acoustic dispenser (EDC ATS-100) into an empty 384-well plate. Compound 1 was spotted in a 10-point serial dilution fashion (3-fold dilution) in duplicate within the plate. Replicates of plates spotted with Compound 1 were made for use with different cell lines. After compound plate replication, all plates were sealed (Agilent ThermoLoc) and stored at -20 °C for up to 1 month. When ready for testing, plates were removed from the freezer, thawed, and unsealed just prior to the addition of the test cells.

[00324] Prior to testing, cells were grown and expanded in culture flasks to provide sufficient amounts of starting material. Cells were then diluted to the appropriate densities and added directly to the compound-spotted 384-well plates. Cells were allowed to grow for 72 h at 37 °C/5% CO_2. At the time when compound was added (t_0), initial cell number was assessed via a viability assay (Cell Titer-Glo) by quantifying the level of luminescence generated by ATP present in viable cells. After 72 h, cell viability of compound-treated cells was assessed via Cell Titer-Glo and luminescence measurement. The apoptotic response to Compound 1 was assessed by quantifying the activities of caspase 3 and caspase 7 (Caspase 3/7-Glo) in treated cells and DMSO control cells.

[00325] **Determination of GI_{50} and IC_{50} Values.** A Four Parameter Logistic Model (Sigmoidal Dose-Response Model) was used to determine the compound's GI_{50} value.

$y = (A+ ((B-A)/ (1+ ((C/x)^D))))$

$A = Y_{Min}$

$B = Y_{Max}$

$C = EC_{50}$

D = Hill Slope

GI_{50} is the concentration of the compound when $Y = (Y_{Max}+Yt_0)/2$

IC_{50} is the concentration of the compound when Y = 50% of DMSO control

Y = Cell viability measured as luminescence unit

t_0 = time when compound was added

[00326] Proliferation and apoptosis were measured using CellTiter-Glo and Caspase 3/7-Glo. CalX2 values are the lowest concentration at which Compound 1 induces a 2-fold increase of cleaved caspase 3/7 compared to DMSO control. Proliferation and apoptosis data is the average of 3 experiments.

[00327] **Table 4:** Effect of Compound 1 on HCC cell line proliferation

Cell Line	GI_{50}	IC_{50}	Cal_X2
JHH-1	0.0016	0.0946	0.0427
JHH-5	0.0045	0.0072	0.0139
Hep3B	0.0053	0.0147	0.0028
HuH-7	0.0212	0.4894	0.0118
HuCCT1	0.0253	1.3033	0.0213
HuH-6-Clone5	0.0291	1.2236	1.5813
SNU-387	0.0332	0.1041	0.0046
HepG2	0.0346	1.2420	0.0129
SNU-182	0.0764	4.9775	5.2385
JHH-7	0.0834	0.5476	4.7601
JHH-2	0.1289	4.4850	0.2806
HuH-1	0.2351	7.2643	6.5641
SNU-398	0.2652	1.9653	0.0378
JHH-4	0.3627	2.3178	0.0588
PLC-PRF-5	0.8884	4.0089	3.8310
FOCUS	1.4994	4.2962	3.8562

Cell Line	GI_{50}	IC_{50}	Cal_X2
HepG2/C3A	4.6211	10.0000	0.8273
HLE	4.8451	9.6157	10.0000
SNU-423	6.2355	10.0000	10.0000
HLF	6.6814	7.3878	7.2156
SK-HEP-1	7.0390	10.0000	10.0000
SNU-475	9.9879	10.0000	10.0000
JHH-6	10.0000	10.0000	10.0000
SNU-449	10.0000	10.0000	10.0000

[00328] Compound 1 inhibits proliferation and induces apoptosis in multiple HCC lines.

[00329] **Anti-proliferative Activity across a Panel of 64 cancer cell Lines.** Cells were treated with DMSO or increasing concentrations of Compound 1 for 72 h. Proliferation was measured using CellTiter-Glo as described. Results are shown in Table 5.

[00330] **Table 5**: Anti-proliferative activity of Compound 1 across a panel of 64 cancer cell lines

Cell line	Tumor Type	GI_{50} (μM)	IC_{50} (μM)
SW48	Colon	0.0057	0.088
MALME-3M	Melanoma	0.0011	0.0038
HT29/219	Colon	0.0017	0.0045
HCT-116	Colon	0.017	0.022
LOX-IMVI	Melanoma	0.022	0.025
HT29	Colon	0.016	0.025
A375	Melanoma	0.021	0.024
Colo 205	Colon	0.025	0.040
AGS	Stomach	0.023	0.028
JHH-5	Liver	0.0045	0.007
SW620	Colon	0.047	0.092

Cell line	Tumor Type	GI_{50} (μM)	IC_{50} (μM)
MiaPaCa-2	Pancreas	0.047	0.80
JHH-5	Liver	0.0045	0.0072
SW620	Colon	0.0474	0.0918
MiaPaCa-2	Pancreas	0.0471	0.0798
JHH-1	Liver	0.0016	0.0946
NCI-H2122	Lung	0.0318	0.0427
Hep3B	Liver	0.0053	0.0147
NCI-H1755	Lung	0.0404	0.0584
92-1	Melanoma	0.0102	0.0316
BxPC-3	Pancreas	0.0368	0.0708
SW1417	Colon	0.0005	0.0169
HOP92	Lung	0.1077	0.1173
NCI-H23	Lung	0.0364	0.1821
PC-9	Lung	0.2167	0.3791
HuH-7	Liver	0.0212	0.4894
MEL-202	Melanoma	0.0385	0.0968
SW900	Lung	0.0048	0.0217
NCI-H1299	Lung	0.2336	0.4982
A549	Lung	0.0402	0.0822
LOVO	Colon	0.0630	0.1256
NCI-H460	Lung	0.2441	0.6445
SNU-387	Liver	0.0332	0.1041
HuCCT1	Liver	0.0253	1.3033
HOP62	Lung	0.3390	3.4861

Cell line	Tumor Type	GI_{50} (μM)	IC_{50} (μM)
HuH-6-Clone5	Liver	0.0291	1.2236
JHH-7	Liver	0.0834	0.5476
NCI-H838	Lung	0.5670	9.1808
NCI-H226	Lung	1.6266	6.1499
NCI-H28	Lung	1.2797	2.3574
MDA-MB-231	Breast	0.0353	3.3333
JHH-2	Liver	0.1289	4.4850
HepG2	Liver	0.0346	1.2420
RPMI-8226	Multiple myeloma	3.2365	9.7392
K-562	Leukemia	5.4223	6.0279
SNU-182	Liver	0.0764	4.9775
HuH-1	Liver	0.2351	7.2643
SNU-398	Liver	0.2652	1.9653
JHH-4	Liver	0.3627	2.3178
PLC-PRF-5	Liver	0.8884	4.0089
FOCUS	Liver	1.4994	4.2962
HepG2/C3A	Liver	4.6211	10.0000
HLE	Liver	4.8451	9.6157
SNU-423	Liver	6.2355	10.0000
HLF	Liver	6.6814	7.3878
SK-HEP-1	Liver	7.0390	10.0000
SNU-475	Liver	9.9879	10.0000
JHH-6	Liver	10.0000	10.0000
SNU-449	Liver	10.0000	10.0000

Cell line	Tumor Type	GI_{50} (μM)	IC_{50} (μM)
NCI-H441	Lung	0.1838	6.3503
NCI-H1703	Lung	1.3513	1.6795
NCI-H1975	Lung	2.0476	3.1940
NCI-H520	Lung	5.2445	8.3699
CFPAC-1	Pancreas	1.9512	7.3967
PANC-1	Pancreas	5.4360	10.0000
KATOIII	Stomach	7.0455	8.0240

[00331] Compound 1 was shown to inhibit the proliferation of multiple cancer cell lines derived from CRC, melanoma, gastric cancer, HCC, lung cancer, pancreatic cancer, leukemia, and multiple myeloma.

[00332] **Anti-proliferative and apoptotic activity in BRAF mutant and beta-catenin mutant or active cancer cell lines**. The mutation status of BRAF, CTNNB1, KRAS, and EGFR in five cell lines evaluated was based on public data (COSMIC and CCLE) and confirmed internally. β-catenin status was evaluated using TOP Flash reporter system by transient transfection. A cell line was defined as β-catenin active if a ratio of Top Flash reporter over Fop Flash reporter is greater than 2. N/A: Not available. Transfection efficiency in Colo 205 (BRAF V600E) was too low to access its β-catenin activity using this approach. Antiproliferative and apoptotic activity of Compound 1 in the five cell lines were measured as described above.

[00333] **Table 6:** Antiproliferative and apoptosis activity of Compound 1 in BRAF mutant and beta-catenin mutant and active cell lines.

Cell lines	Tumor type	Mutation status of key genes	β-catenin status	Proliferation IC_{50} (μM)	Apoptosis induction CalX2 (μM)
Colo 205	CRC	BRAF (V600E)	N/A	0.036 +/- 0.023	0.053 +/- 0.039
LOX-IMVI	Melanoma	BRAF (V600E)	Inactive	0.025 +/- 0.008	0.034 +/- 0.028
SW48	CRC	CTNNB1 (S33Y); EGFR (G179S)	Active	0.009 +/- 0.007	0.005 +/- 0.001
AGS	Gastric	CTNNB1 (G43E); KRAS (G12D)	Active	0.028 +/- 0.021	0.004 +/- 0.002
Hep3B	HCC	-	Active	0.014 +/- 0.006	0.002 +/- 0.002

[00334] Compound 1 potently inhibits proliferation and induces apoptosis in both BRAF mutant and beta-catenin mutant or active cancer cell lines, including BRAF mutant CRC, BRAF mutant melanoma, beta-catenin mutant/EGFR mutant CRC (i.e. beta-catenin active/EGFR mutant CRC), beta-catenin mutant/KRAS mutant gastric cancer (i.e. beta-catenin active/KRAS mutant gastric cancer), and HCC.

[00335] **Oncogenic pathway inhibition. Effect on MAPK signaling**. Cancer cells were seeded at a density of 25,000 cells per well in 96-well tissue culture plates and incubated at 37 °C in a CO_2 incubator overnight. After treatment with Compound 1 at 37 °C for 2 h, the cells were lysed with Mesoscale lysis buffer and pRSK S380 levels in each lysate were measured via Mesoscale ELISA technology.

[00336] **Conclusion**. Compound 1 potently inhibited pRSK1 in multiple cancer cell lines (Table 7).

[00337] **Table 7**: Compound 1 pRSK1 S380 IC_{50} Values in BRAF Mutant LOX-IMVI and Colo 205 Cancer Cell Lines

Cell line (n=3)	pRSK1 S380 IC_{50} (μM)
LOX-IMVI	0.038 +/- 0.009
Colo 205	0.047 +/- 0.01
SW48	0.021 +/- 0.001
AGS	0.020 +/- 0.001

[00338] In a time course experiment, Colo-205 cancer cells were treated with 0.5 μM Compound 1 for various time periods. The effect of Compound 1 on pRSK S380 was measured as described. The effect of Compound 1 on other MAPK pathway markers (DUSP4 and DUSP6) was measured via Western blotting with specific antibodies. The time course data in **FIG. 1** indicates Compound 1 causes sustained inhibition (up to 72 hr) of the following ERK targets: pRSK1, DUSP4 and DUSP6. BRAF inhibitors (BRAFi) do not cause sustained ERK inhibition in BRAF mutant CRC lines (Corcoran *et al., Cancer Discov.* 2012, 2:227-35). Sufficient and sustained inhibition of ERK seems to be critical for clinical efficacy of BRAFi and MEK inhibitors (MEKi) in BRAF mutant melanoma (Bollag *et al.*, *Nat Rev Drug Disc.* 2012; 11, 873-886) and CRC patients (Corcoran *et al., Cancer Discov.* 2012, 2:227-35). Lack of sustained inhibition of ERK by BRAFi may contribute to the lack of clinical activity of BRAFi in BRAF mutant CRC patients. The sustained inhibition of ERK by Compound 1 may provide an advantage over BRAFi in BRAF mutant CRC patients.

[00339] The ability of Compound 1 to inhibit MAPK signaling was assessed by determining the DUSP4 and DUSP6 protein expression. Colon cancer cell line Colo 205 (BRAF V600E) cultures were treated with DMSO or increasing concentrations of Compound 1 for 2, 8 or 24 h. Proteins were extracted from treated cells and analyzed by Western blot using antibodies against DUSP4, DUSP6, cyclin D1, c-Myc, YAP or β-actin. RNAs were extracted using Cell-To-CT kit and quantitative PCR was performed with probes specific for DUSP4, DUSP6, SPRY2, c-Myc and cyclin D1. Specific probes for β-actin were used for normalization.

[00340] In Colo 205 (BRAF V600E), DUSP4 and DUSP6 were significantly reduced by Compound 1 as early as 2 h and the reduction was sustained through 24 h (**FIG. 2A**). Compound 1 treatment led to the reduction of SPRY2 transcription in a concentration-dependent manner in Colo 205 (**FIG. 2B**), consistent with potent ERK inhibition. Levels of cyclin D1 and c-Myc, which are downstream of both canonical Wnt and MAPK signaling, were assessed. Compound 1 significantly decreased cyclin D1 and c-Myc RNA and protein levels in Colo 205 cells (**FIG. 2A-2C**). Compound 1 treatment resulted in decreased YAP protein at 24 h in Colo 205 (**FIG. 2A**). Taken together, our cellular data is consistent with strong, sustained MAPK pathway inhibition.

[00341] To further evaluate the ability of Compound 1 to inhibit MAPK signaling, RNA expression was assessed of additional MAPK targets (BMF, DUSP5, DUSP6, EFNA1, EGR1, ETV5, FOS, FOSL1, GJA1, IL-8, SPRY2, and SPRY4). Cultures of the colon cancer cell lines Colo 205 (characterized by a BRAF V600E mutation) and HT-29 (characterized by a BRAF V600E mutation) were treated with DMSO or Compound 1 at 0.3 or 1 μM for 6 h. RNAs were extracted using MagMAX Total RNA Isolation kit and quantitative PCR was performed with probes specific for BMF, DUSP5, DUSP6, EFNA1, EGR1, ETV5, FOS, FOSL1, GJA1, IL-8, SPRY2, SPRY4. Specific probes for 18S rRNA were used for normalization.

[00342] In both cell lines, mRNA levels of DUSP5, DUSP6, EGR1, ETV5, FOS, FOSL1, IL-8, SPRY2, SPRY4 were reduced by Compound 1 (**FIGs. 2D-2I**), consistent with ERK inhibition. The finding that mRNA levels of GJA1 are reduced in Colo205 cells and increased in HT29 may be related to our finding that Compound 1 is cytotoxic in Colo205 and cytostatic in HT29. Compound 1 treatment resulted in increased mRNA levels of BMF and EFNA1 at 6 h in Colo 205 and HT-29. Taken together, our cellular data is consistent with MAPK pathway inhibition.

[00343] **Effect on beta-catenin and YAP signaling**. Cellular activity against beta-catenin and YAP target genes by Compound 1 was evaluated. Colon cancer cell line Colo 205 (BRAF V600E) cultures were treated with DMSO or increasing concentrations of Compound 1 for 2, 8 or 24 h. RNAs were extracted using Cell-To-CT kit and quantitative PCR was performed with probes specific for Axin2, CTGF, and AREG. Specific probes for β-actin were used for normalization.

[00344] Compound 1 treatment led to increased Axin2 RNA (**FIG. 3A**). Compound 1 significantly reduced the expression of Hippo/YAP target genes (CTGF, AREG) in Colo 205 (BRAF V600E) at 2, 8 and 24 hr (**FIG. 3A**). Taken together, these data suggest that Compound 1 impacts Wnt signaling and blocks Hippo signaling in Colo 205 cancer cells.

[00345] Cellular activity against additional YAP target genes by Compound 1 was evaluated (**FIGs. 3B-3E**). Cultures of the colon cancer cell lines Colo 205 and HT-29 were treated with DMSO or Compound 1 at 0.3 or 1 μM for 6 h. RNAs were extracted using MagMAX Total RNA Isolation kit and quantitative PCR was performed with probes specific for CYR61, CITED2, CXCL1, ELF3, HAS2, HES1, and MAFF. Specific probes for 18S rRNA were used for normalization.

[00346] In both cell lines, mRNA levels of CYR61, CXCL1, HAS2, HES1 and MAFF were reduced by Compound 1. The finding that CYR61 mRNA levels are reduced in Colo205 cells but not in HT29 and that mRNA levels of CITED2 are increased in HT29, but not in Colo205, may be related to our finding that Compound 1 is cytotoxic in Colo205 and cytostatic in HT29. Compound 1 treatment resulted in increased mRNA levels for CITED2 and ELF3 mRNA at 6 h in Colo 205 and HT-29. **(FIG. 3B)** Taken together, our cellular data is consistent with YAP pathway inhibition.

[00347] **Evaluation of sensitivity in cell lines having beta-catenin mutations**. The effect of Compound 1 on cell lines having β-catenin mutations was evaluated. (FIG. 18 and FIGs. 19A-19B). Compound 1 showed efficacy against cell lines with mutated β-catenin. Such cell lines demonstrate that cancers characterized by mutated β-catenin are more sensitive to treatment with Compound 1. Compound 1 was further shown to modulate β-catenin, and YAP in BRAF and CTNNB1 mutant cell lines as shown in FIG. 20. Compound 1 also modulates target gene expression controlled by MAPK, β-catenin, and YAP in BRAF and CTNNB1 mutant cell lines as provided in FIG. 21A and FIG. 21B..

[00348] **Western Blot**. Compound 1 modulation of MAPK, WNT/β-catenin, and Hippo/YAP pathway markers was evaluated by standard Western blotting . LOX-IMVI, SW48, and Colo-205 cells were plated in 6-well plates at a density of 250,000 cells per well and were allowed to attach overnight. Compound 1 was added to cells at concentrations of 0.03, 0.1, 0.3, 1, and 3 μM for durations of 2, 8, and 24 hours. Cells were harvested and lysed in RIPA buffer (50 mM Tris-HCl, pH 7.4, 150 mM sodium chloride [NaCl], 0.25% deoxycholic acid, 1% Nonidet P-40, 1 mM ethylenediaminetetraacetic acid [EDTA], protease and phosphatase inhibitors). The cell lysates were heated in sodium dodecyl sulfate (SDS)-sample buffer and 40 μg of cell lysate per condition were loaded onto gels and separated using SDS polyacrylamide gel electrophoresis (PAGE). Protein was transferred to nitrocellulose membrane, and immunoblotted with anti DUSP4, DUSP6, cMyc, Cyclin D1, YAP, AXIN2, HDAC5 (phospho S498), and β-actin antibodies. Membranes were scanned on the Licor Odyssey system.

[00349] **Quantitative Polymerase Chain Reaction**. Compound 1 modulation of MAPK, WNT/β-catenin, and Hippo/YAP pathway genes was evaluated by real-time (RT)-qPCR. Lysyl oxidase IMVI, SW48, and Colo-205 cells were plated in 96-well plates at a density of 20,000

cells per well and were allowed to attach overnight. Compound 1 was added to cells at half log concentrations from 1 nM to 10 μM for durations of 2, 8, and 24 hours. Cells were harvested using the TaqMan Gene Expression Cells-to-CT Kit according to the product manual. Next, RT-PCR was performed and the resulting cDNA was used in qPCR reactions on the ViiA7 Real-Time PCR System (Thermo Fisher Scientific). TaqMan probes were used to monitor changes in DUSP4, DUSP6, SPRY2, MYC, CCND1, AXIN2, CTGF, Cyr61, AREG, and ACTB genes. All genes were normalized to ACTB expression and reported as percentage of DMSO-only control.

[00350] Gene Expression Analysis: Human bronchial epithelial cells were cultured in T-150 flasks in BEpiCM growth medium and allowed to reach 80% confluency. Cells were plated in 12-well plastic culture plates at 150,000 cells per well in BEpiCM medium for 24 hours. After a 24-hour incubation, cells were treated with dimethyl sulfoxide (DMSO) as a control, Compound 1 at 0.1, 1, 10 uM, for 30 minutes. Cells were then stimulated with 100 ng/ml recombinant Wnt3a (formulated in phosphate buffered saline [PBS]), 350 pM RSPO3 (formulated in PBS) or a combination of Wnt3 and RSPO3 for 24 hours. Ribonucleic acid (RNA) was isolated using a Qiagen Rneasy Mini Kit according to manufacturer's instruction. Axin2 and gene expression was determined using reverse transcription polymerase chain reaction (RT-PCR) Taq-Man assays. Quantitative PCR (qPCR) was performed using SuperScript® III One-Step RT-PCR System and ran on a Viia 7 Real-Time PCR System. Data was normalized to glyceraldehyde 3-phosphate dehydrogenase.Compound 1 inhibits Axin2 expression in human bronchial epithelial cells. Gene expression was measured at 24 hours. From these results it was shown that Compound 1 inhibits Axin2 expression in human bronchial epithelial cells. (FIG. 22).

[00351] Long Term Colony Assay. Compound 1 was assessed for its ability to inhibit the colony formation of cancer cells via a long-term colony forming assay. Cells and compounds were added to 96-well plates and were monitored for up to 8 weeks for the formation of colonies. Compound and media were replenished every 1 week throughout the course of the assay. Colony formation was detected via imaging at 4x on the IncuCyte ZOOM System. Compound 1 demonstrated inhibition of colony formation of β-catenin mutant cells at a level greater than MEK inhibitors (trametinib) and ERK inhibitors (GDC0994). SW48 (colo) cells, HCT-116 (colo) cells, AGS (gastric) cells, and Hep3B (HCC) cells were treated with Compound 1 and showed greater levels of inhibition than seen with treatment with MEK inhibitors or ERK

inhibitors. (FIG. 23A-23D). Compound 1 was further shown to surprisingly inhibit colony formation of AGS cells that are resistant to MEK inhibitor treatment with trametinib. Such results suggest Aminopurine Compounds described herein, such as Compound 1, can be useful in treating cancers resistant to other treatments.

[00352] Evaluation of Immunomodulatory Effects. The effect of Compound 1 was evaluated on PD-L1 expression levels. Cells were cultured in presence or absence of Compound 1 for indicated time before expression levels of PD-L1, DUSP4 and α-tubulin or α-actin were measured by Western blot. To detect surface levels of PD-L1, cells were treated with DMSO or Compound 1 at indicated concentrations for 48 h and cell surface expression of PD-L1 was detected using flow cytometry analysis (FACS) with an APC-labeled antibody to PD-L1 (clone 29E.1A3.; BioLegend, San Diego, CA). Geometric mean of PD-L1 positive cells was determined by FlowJo 10 (Treestar, Ashland, OR).

[00353] Conclusion. Compound 1 directly inhibits PD-L1 expression in multiple cancer cells including HOP62, KARPAS-299, and LOX-IMVI (BRAF V600E) (**FIG. 4A**). FACS analysis indicates that surface PD-L1 levels are also inhibited by Compound 1 in multiple cancer cell lines (**FIG. 4B**).

[00354] To determine if Compound 1 down-regulation of PD-L1 enhances T cell activation, compound-treated KARPAS-299 cancer cells were co-cultured with PBMC-derived T cells stimulated with low concentrations of super antigen (SEB). KARPAS-299 cells were treated with DMSO (D) or Compound 1 at indicated concentrations for 48 h. PBMC from healthy donors were treated with or without 20 ng/ml SEB for 48 h. After wash with PBS, the PBMCs were incubated with the cancer cells for 24 h and the supernatants were collected to measure IL-2 and IFNγ using Mesoscale assays.

[00355] Supernatant levels of IL-2 and IFNγ were used as functional markers of T cell activation. In the absence of SEB, PBMC co-cultured with Compound-1-treated KARPAS-299 cells produced little IL-2 or IFNγ. In the presence of low concentrations of SEB (20 ng/ml), Compound 1-treated cancer cells co-cultured with PBMC demonstrated increased levels of both IL-2 and IFNγ production (**FIGs. 5A-5B**). The increased levels of IL-2 and IFNγ in Compound 1-treated cancer cells were similar to the levels observed with treatment of anti-PD-L1 (Ultra-LEAFTM from Biolegend).

[00356] The effect of Compound 1 treatment on levels of IL-8 was determined in PBMC culture media. PBMCs were isolated from whole blood and cultured in RPMI media plus 10% FBS. PBMCs were plated at $1x10^6$ per milliliter in 10 cm^2 dishes. The PBMCs were treated with 0.1% DMSO or 0.5 μM Compound 1. Treatments were taken down at the designated time points. The culture media (1mL) was used for IL-8 analysis. The IL-8 analysis was performed with a Mesoscale V-Plex Human IL-8 kit according to the manufacturer's instructions. Compound 1 was shown to inhibit IL-8 levels at different time-points (**FIG. 5C).**

[00357] **TEAD reporter assay**. TEAD reporter activity was analyzed using WI38 VA13 cells stably expressing a YAP/TAZ responsive synthetic promoter driving luciferase expression (8xGTIIC-luciferase). 10,000 cells per well were seeded on a white-walled 96-well plate and left overnight. After 16-20 hours, cells were treated with compound and TEAD reporter activity was measured 24 or 72 hours later using Bright Glo luciferase assay (Promega) according to the manufacturers instructions. This assay was performed 3 times for Compound 1 and twice for Trametinib. See FIG. 25.

[00358] **Viability assay**. In parallel 10,000 WI38 VA13 cells expressing 8xGTIIC-luciferase were seeded in each well of a black-walled 96-well plate. After 16-20 hours cells were treated with compound for 24 or 72 hours. At this time the serum and compound containing media was removed and replaced with 100 μl serum free media and 100 μl Cell Titer Fluor (Promega). The plate was incubated for 2 hours at 37 °C before reading fluorescence output. This assay is based on measurement of live-cell protease activity. The viability assay was performed to confirm that any effects of compounds on TEAD reporter were not the result of compound effects on viability. This assay was performed 3 times for Compound 1 and twice for Trametinib.

[00359] **Conclusion.** These data provide an additional therapeutic hypothesis suggesting that treatment with Compound 1 will potentiate T cell activation. The in vitro data suggests that Compound 1 may enhance T cell immunity against cancer cells by inhibiting key oncogenic pathways such as the MAPK pathway and down-regulating the immune checkpoint molecule PD-L1 expression in tumor microenvironment. Cancer types that express high levels of PD-L1 (for example, melanoma, lung, RCC, or HCC) may therefore be sensitive to Compound 1.

ANIMAL MODELS

[00360] **Xenograft models.** For xenograft model studies human cancer cell lines were injected into SCID (severe combined immunodeficiency) mice. Cancer cell lines were propagated in culture *in vitro*. Tumor bearing animals were generated by injecting precisely determined numbers of cells into mice. Following inoculation of animals, the tumors were allowed to grow to a certain size prior to randomization. The mice bearing xenograft tumors ranging between pre-determined sizes were pooled together and randomized into various treatment groups. A typical efficacy study design involved administering one or more compounds at various dose levels to tumor-bearing mice. Additionally, reference chemotherapeutic agents (positive control) and negative controls were similarly administered and maintained. Tumor measurements and body weights were taken over the course of the study.

[00361] Mice were anesthetized with inhaled isoflurane and then inoculated with LOX-IMVI tumor cells subcutaneously above the right hind leg with 0.1 mL of a single cell suspension in PBS using a sterile 1 mL syringe fitted with a 26-gauge needle. Following inoculation of the animals, tumors were allowed to grow to approximately 75-125 mm^3 or in some cases 250-400 mm^3 prior to randomization of the mice. The tumor of each animal was measured and animals with tumors in the appropriate range were included in the study. Animals from the study pool were then distributed randomly into various cages and the cages were randomly assigned to vehicle, positive control, or test article groups. All of the mice were tagged with metal ear tags on the right ear. A typical group consisted of 8-10 animals. For a typical xenograft study, SCID mice bearing tumors were randomized and dosed with compounds ranging from, for example, 100 mg/kg to 0.1 mg/kg with different dose scheduling, including, but not limited to, qd, q2d, q3d, q5d, q7d and bid. The mice were dosed for 1-4 weeks. Tumors were measured twice a week using calipers and tumor volumes were calculated using the formula of $W^2 \times L / 2$.

[00362] The purpose of these studies was to test the efficacy of Compound 1 in the cell line-derived xenograft models, LOX-IMVI (melanoma) and Colo205 (colorectal) and the PDX1994060146 (patient-derived xenograft [PDX146]) colorectal xenograft model. These models were chosen because they harbor the V600E BRAF mutation. Additional PK/PD analysis was performed to examine the Compound 1-mediated inhibition of pathway biomarkers in the PDX146 xenograft model.

[00363] **LOX-IMVI Subcutaneous Melanoma Xenograft Model.** The purpose of this study was to confirm the efficacy of Compound 1 in the LOX-IMVI melanoma xenograft model. One study (**FIG. 6**) in the LOX-IMVI xenograft model testing two dose levels of Compound 1 (15 and 30 mg/kg) demonstrated significant tumor volume reduction compared to the vehicle control ($p<0.001$ for both dose levels). Tumor regression was observed in 9 out of 9 animals for both dose levels and 1 out of 9 animals from each group was tumor free at study end.

[00364] In a separate experiment, Compound 1 was administered orally, QD for 8 days at 0.2, 1, 5, 10, and 15 mg/kg. Dose-dependent antitumor activity was observed with Compound 1 treatment in the LOX-IMVI xenograft model (**FIG. 7**). Tumor regression was observed at the 10 and 15 mg/kg dose levels.

[00365] **Colo 205 Subcutaneous Colorectal Xenograft Model.** The purpose of these studies was to test the efficacy of Compound 1 in the Colo 205 colorectal cancer xenograft model, and determine whether twice daily dosing (BID) had an impact on antitumor activity. In the first experiment Compound 1 was administered orally, QD for 15 days at 0.2, 1, 5, 10, and 15 mg/kg. Dose-dependent antitumor activity was observed with Compound 1 treatment in the Colo 205 xenograft model (**FIG. 8**). A scheduling study was conducted to determine whether BID dosing increased the antitumor activity of Compound 1. Dose-dependent antitumor activity was observed with Compound 1 treatment in the Colo 205 xenograft model (**FIG. 9**).

[00366] **PDX1994060146 Subcutaneous Colorectal Patient-Derived Xenograft Model.** The purpose of these studies was to test the efficacy of Compound 1 in the PDX1994060146 (PDX146) colorectal cancer xenograft model and determine whether BID dosing had an impact on antitumor activity. A time to progression (TTP) study was performed to determine the effect of longer treatment duration on tumor growth.

[00367] In the first experiment Compound 1 was administered orally, QD at 1, 5, and 15 mg/kg or 5 and 15 mg/kg BID for 22 days. Dose- dependent antitumor activity was observed with Compound 1 treatment in the PDX146 xenograft model (**FIGs. 10A-10B**). Dosing 15 mg/kg BID appeared to increase the antitumor activity of Compound 1 compared to the administration of 15 mg/kg QD.

[00368] In the TTP study, Compound 1 was administered orally, 1, 5, and 15 mg/kg BID for 49-77 days. Compound 1 treatment groups were dosed throughout the duration of the study until

the group mean reached the predetermined endpoint of approximately 1200 mm^3 or study termination. Tumor growth delay (TGD) was calculated as the time between the termination of the vehicle control group (on day 43) and the Compound 1 treatment groups. The TGD was 8, 12 and >37 days for the 1, 5 and 15 mg/kg treatment groups, respectively. **(FIG. 11)**

[00369] Biomarkers representing the activity of three different pathways, MAPK, Wnt, and Hippo, were inhibited in the PDX146 xenograft model. Sustained inhibition of these pathway biomarkers was observed through 24 h.

[00370] Antitumor Activity of Compound 1 in the β-catenin Mutant SW48 Colorectal Xenograft Model. Female SCID mice were inoculated with 2 x 10^6 SW48 tumor cells into the right flank. Mice were randomized into treatment groups (n=10/group) at the time of treatment initiation. Test article treatment started on Day 10 when the tumors were approximately 110 and 105 mm^3. (See FIGs. 15A-15B.) Black dotted line is the tumor volume at the initiation of dosing. Graph on the left is a dose-response study. Graph on the right is a time to progression study where animals were maintained on drug during the course of the study. Dotted line is the tumor volume on Day 28 when the vehicle control group was terminated.

[00371] Antitumor Activity in the Orthotopic Hep3B2.1-7 Hepatocellular Carcinoma Xenograft. Female SCID mice were orthotopically inoculated with 2 x 10^6 Hep3B2.1-7 tumor cells per animal. Seven days post-inoculation the animals were randomized into treatment groups based on body weight and the treatment commenced (Study day 0). Take rate assessment of a satellite group confirmed the presence of tumor in the liver in 100% of the animals. Treatment with Compound 1 was started and Compound 1 was dosed orally, QD for 21 days. Significant mean body weight loss expected with this model was observed in the vehicle control group. Animals treated with 15 mg/kg Compound 1 showed minimal body weight loss and a significant mean body weight gain was observed in the 30 mg/kg Compound 1 treatment group. On the day of study termination, the tumors were removed and weighed. Individual tumor weights and the mean tumor weight ± SEM of each group was plotted (FIG. 16). Percent inhibition was calculated relative to the vehicle control. P values were derived from a one-way ANOVA with a Dunnet's post-hoc analysis. *** = $p<0.001$.

[00372] Antitumor Activity of Compound 1 in the C-Met Amplified Hepatocellular Carcinoma Patient-derived Xenograft Model, LI0612. Female SCID mice were inoculated

with hepatocellular carcinoma PDX model LI0612 tumor fragments (2 – 4 mm in diameter) into the right flank. The mice were randomized into treatment groups (n=10/group) at the time of treatment initiation. Test article treatment started on Day 18 when the tumors were approximately 150 mm^3 in size. Tumor growth progressed in the vehicle control and Compound 1 treatment groups over the dosing period. A change in the growth kinetics was noted with Compound 1 administration resulting in significant tumor growth inhibition (TGI) with 30 mg/kg treatment (p=0.038, compared to the vehicle control). See FIG. 17.

[00373] Pharmacokinetic/Pharmacodynamic Data in a BRAF Mutant Patient-Derived Xenograft Model. Based on the known kinases (ERK 1/2, NLK and SIK) that are inhibited by Compound 1, the impact of compound treatment was evaluated on MAPK, β-catenin and Hippo pathway biomarkers in PDX146 tumors from xenografted mice. Tumor-bearing mice (tumors were ~400 mm^3) were treated with a single dose of 1 or 5 mg/kg Compound 1. Tumor tissue was collected at 1, 2, 4, 8, and 24 h post-dose.

[00374] The modulation of the MAPK pathway was evaluated by examination of tumor DUSP4, DUSP6 and Sprouty (SPRY2) mRNA levels and pRSK and pERK protein levels. DUSP6 mRNA levels were significantly decreased with compound treatment starting 2 hr post-dose and remained suppressed through 24 h at both dose levels (**FIG. 12A**). A similar pattern was observed with DUSP4 and SPRY2 mRNA levels (**FIGs. 13A-13B**). Phospho-RSK (pRSK) and phospho-ERK (pERK) protein levels were modulated by Compound 1 treatment in a dose- and time-dependent manner (**FIGs. 14A-14D**). Levels of cMyc (**FIG. 12B**) and cyclin D1 (**FIG. 13C**), which are downstream of both the MAPK and Wnt signaling pathways, were inhibited with Compound 1 treatment. Compound 1 treatment upregulated the Wnt target gene, Axin2. Treatment with Compound 1 at both dose levels demonstrated a significant increase in Axin2 mRNA levels 24 h post-dose. Sustained inhibition of AREG (a downstream target gene in the Hippo pathway) mRNA levels was observed through 24 h. Additionally Compound 1 inhibited YAP protein levels in a time-dependent manner (not statistically significant (see **FIG. 13D**), which could be due to SIK inhibition and Hippo pathway regulation or an indirect effect as a result of MAPK inhibition.

[00375] These data suggest that Compound 1 impacts three different pathways, MAPK, Wnt and Hippo, in this BRAF mutant colorectal PDX model following a single dose administration.

[00376] **Conclusion**: Significant dose-dependent antitumor activity was observed in all three BRAF mutant xenograft models (See **FIGs. 15A-15B, FIG. 16**, and **FIG.17**). Tumor regression was observed with Compound 1 treatment across the models and there was a significant growth delay with long term treatment in the PDX146 model.

[00377] **Patient Enrichment and Tumor Indications.** Based upon the in vitro and in vivo data of Compound 1, the patient enrichment hypotheses and tumor indications are outlined in Table 8 and Table 9.

[00378] **Table 8**: Patient enrichment biomarkers and tumor indications

Patient Enrichment Biomarkers	Tumor indications
BRAF mutant	CRC, Thyroid, Melanoma, Lung
NRAS mutant	Melanoma
KRAS mutant	Lung, CRC, Pancreas
CTNNB1 (β-catenin mutant and/or active)	CRC, Stomach, HCC, Sarcoma

[00379] **Table 9**.

Molecular Alterations	Pathways	Clinical Indications
CTNNB1 mutant, YAP amplification	Wnt/b-catenin// Hippo	HCC
BRAF mutant, CTNNB1	MAPK//Wnt/b-catenin	CRC
CTNNB1 mutant	Wnt/b-catenin	Gastric
BRAF mutant, NRAS mutant	MAPK	Melanoma

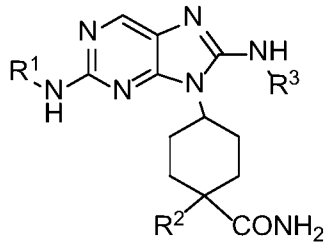
[00380] A number of references have been cited, the disclosures of which are incorporated herein by reference in their entirety.

[00381] Although the invention has been described with reference to the disclosed embodiments, those skilled in the art will readily appreciate that the specific examples and studies detailed above are only illustrative of the invention. It should be understood that various modifications can be made without departing from the spirit of the invention. Accordingly, the invention is limited only by the following claims.

2017241837 11 Nov 2020

CLAIMS:

1. A method for treating a cancer, the method comprising administering to a subject having the cancer an effective amount of an Aminopurine Compound of formula (I):



(I)

or a pharmaceutically acceptable salt, tautomer, stereoisomer, or enantiomer thereof,

wherein:

R^1 is substituted or unsubstituted non-aromatic heterocyclyl;

R^2 is H or substituted or unsubstituted C_{1-3} alkyl; and

R^3 is phenyl, substituted with one or more halogen, optionally further substituted with one or more substituents independently selected from substituted or unsubstituted C_{1-3} alkyl, CN, and -OR', wherein each R' is independently substituted or unsubstituted C_{1-3} alkyl;

wherein when a C_{1-3} alkyl group is substituted, the C_{1-3} alkyl group is substituted with halogen, alkyl, hydroxyl, alkoxy, alkoxyalkyl, amino, alkylamino, carboxy, nitro, cyano, thiol, thioether, imine, imide, amidine, guanidine, enamine, aminocarbonyl, acylamino, phosphonate, phosphine, thiocarbonyl, sulfinyl, sulfone, sulfonamide, ketone, aldehyde, ester, urea, urethane, oxime, hydroxyl amine, alkoxyamine, aryloxyamine, aralkoxyamine, N-oxide, hydrazine, hydrazide, hydrazone, azide, isocyanate, isothiocyanate, cyanate, thiocyanate, $B(OH)_2$, or O(alkyl)aminocarbonyl;

wherein when a group, other than a C_{1-3}alkyl group, is substituted, the group is substituted with halogen, C_{1-10}alkyl, hydroxyl, C_{1-10}alkoxy, C_{1-10} alkoxy C_{1-10}alkyl, amino, C_{1-10}alkylamino, carboxy, nitro, cyano, thiol, thioether, imine, imide, amidine, guanidine, enamine, aminocarbonyl, acylamino, phosphonate, phosphine, thiocarbonyl, sulfinyl, sulfone, sulfonamide, ketone, aldehyde, ester, urea, urethane, oxime, hydroxyl amine, C_{1-10}alkoxyamine, C_{6-14}aryloxyamine, C_{6-14}arC_{1-10}alkoxyamine, N-oxide, hydrazine, hydrazide, hydrazone, azide, isocyanate, isothiocyanate, cyanate, thiocyanate, oxygen (=O), $B(OH)_2$, O(C_{1-10}alkyl)aminocarbonyl, C_{3-10}cycloalkyl,

heterocyclyl, aryl, heteroaryl, C_{6-14}aryloxy, C_{6-14}arC_{1-10}alkyloxy, heterocyclyloxy, or heterocyclyl C_{1-10}alkoxy;

wherein the cancer is colorectal cancer, colon cancer, renal cell carcinoma, gastric cancer, stomach cancer, hepatocellular carcinoma, liver cancer, lung cancer, pancreatic cancer, leukemia, or multiple myeloma;

wherein an alkyl group is a saturated straight chain or branched non-cyclic hydrocarbon having from 1 to 10 carbon atoms;

wherein a heterocyclyl group is an aromatic or non-aromatic cycloalkyl having from 1 to 2 rings in which one to four of the ring carbon atoms are independently replaced with a heteroatom selected from the group consisting of O, S and N;

wherein an aryl group is an aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring or multiple condensed rings;

wherein a heteroaryl group is an aromatic cycloalkyl of from 3 to 10 carbon atoms having a single cyclic ring or multiple condensed or bridged rings in which one to four of the ring carbon atoms are independently replaced with a heteroatom selected from the group consisting of O, S and N.

2. A method for treating a cancer, the method comprising administering to a subject having the cancer an effective amount of an Aminopurine Compound, wherein the cancer is selected from the group consisting of colorectal cancer, colon cancer, renal cell carcinoma, gastric cancer, stomach cancer, hepatocellular carcinoma, liver cancer, lung cancer, pancreatic cancer, leukemia, and multiple myeloma; and wherein the Aminopurine compound is selected from the group consisting of

(1s,4s)-4-(2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(3-chlorophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-chlorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclopentylamino)-8-(2,4-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-chlorophenylamino)-2-(4-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,4-difluorophenylamino)-2-(3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,4-difluorophenylamino)-2-(1-methylcyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-(tert-butylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,4-difluorophenylamino)-2-((3R,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-(4-methyltetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(3-chloro-2-fluorophenylamino)-2-(4-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-(tetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,6-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-((3R,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,6-difluorophenylamino)-2-((3R,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2-chloro-6-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-chlorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,4-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(3,4-dichlorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(5-chloro-2-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(3-chloro-2-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,5-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(3-chloro-2-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-(tetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,3-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,4-dichlorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2-chloro-5-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2-chloro-4-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2-chloro-4-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(3-fluoro-2-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-bromo-2-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-fluoro-4-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-(trifluoromethyl)phenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-fluoro-2-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(tetrahydro-2H-pyran-4-ylamino)-8-(2,3,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-1-methyl-4-(2-(tetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclobutylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclobutylamino)-8-(2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-(cyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclopentylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclopentylamino)-8-(2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-difluorophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclobutylamino)-8-(2,6-dichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclopentylamino)-8-(2,6-dichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(oxetan-3-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-(oxetan-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-(oxetan-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(tetrahydro-2H-pyran-4-ylamino)-8-(2,4,5-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(isopropylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-3-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,3-dichlorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-fluoro-6-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(5-chloro-2,4-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(tetrahydro-2H-pyran-4-ylamino)-8-(2,4,5-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(tetrahydro-2H-pyran-4-ylamino)-8-(2,3,4-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-chloro-2,6-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclopentylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-3-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,5-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2-fluoro-5-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(tetrahydro-2H-pyran-4-ylamino)-8-(2,3,4-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-fluoro-6-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2-fluoro-6-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-tetrahydrofuran-3-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1r,4r)-4-methoxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1r,4r)-4-hydroxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-chloro-6-fluoro-2-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,5-dichloro-4-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,3-dichloro-4-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-3-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,3-difluoro-4-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-3-fluoro-4-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,3-dichloro-4-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-difluoro-6-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((S)-tetrahydrofuran-3-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(4,4-difluorocyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(4-chloro-3-fluoro-2-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2-chloro-3,6-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2-chloro-6-fluoro-3-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino)-8-((2,4,6-trichlorophenyl)amino)-9H-purin-9-yl)cyclohexane-1-carboxamide;
(1s,4s)-4-(8-(2-chlorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-(cyclopentylamino)-8-(2,4-dichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(4-chloro-2-fluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,4-dichlorophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2-chloro-4-fluorophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2-chloro-4,5-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2-chloro-4,5-dimethylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(4-chloro-2-fluoro-3-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,3-dichloro-6-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-5-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,5-difluoro-4-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-(1-(pyridin-3-yl)piperidin-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-(1-phenylpiperidin-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4,6-trichlorophenylamino)-2-(2,2,2-trifluoroethylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclobutylmethylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-tetrahydro-2H-pyran-3-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3,4-dichloro-2-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(6-chloro-2,3-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-(1-(methylsulfonyl)piperidin-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-difluoro-4-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-methylphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(cyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclobutylamino)-8-(2,6-dichloro-4-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclopentylamino)-8-(2,6-dichloro-4-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclopentylamino)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((R)-1-hydroxybutan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(3R,4S)-tert-butyl 4-(9-((1s,4r)-4-carbamoylcyclohexyl)-8-(2,4,6-trifluorophenylamino)-9H-purin-2-ylamino)-3-fluoropiperidine-1-carboxylate;

(3R,4S)-tert-butyl 4-(9-((1s,4r)-4-carbamoylcyclohexyl)-8-(2,6-difluorophenylamino)-9H-purin-2-ylamino)-3-fluoropiperidine-1-carboxylate;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(cyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclobutylamino)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((R)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((R)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((R)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((R)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-1-hydroxybutan-2-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((3R,4S)-3-fluoropiperidin-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclopentylamino)-8-(2,3-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-chloro-2-fluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclopentylamino)-8-(2,3,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((S)-1-methoxypropan-2-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((S)-1-hydroxybutan-2-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-((S)-1-hydroxybutan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((S)-1-hydroxybutan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((S)-1-hydroxybutan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((S)-1-hydroxybutan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((S)-1-hydroxybutan-2-ylamino)-8-(2,3,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,4-dichlorophenylamino)-2-((S)-1-hydroxybutan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(3-chloro-2-fluorophenylamino)-2-((S)-1-hydroxybutan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((S)-1-hydroxybutan-2-ylamino)-8-(2,3,4-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-2-hydroxypropylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichlorophenylamino)-2-((S)-1-hydroxybutan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((S)-1-hydroxybutan-2-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(3R,4S)-tert-butyl 4-(9-((1s,4r)-4-carbamoylcyclohexyl)-8-(4-chloro-2,6-difluorophenylamino)-9H-purin-2-ylamino)-3-fluoropiperidine-1-carboxylate;

(1s,4s)-4-(8-((4-chloro-2,6-difluorophenyl)amino)-2-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino)-9H-purin-9-yl)cyclohexane-1-carboxamide;

(1s,4s)-4-(8-((2,4-dichloro-6-fluorophenyl)amino)-2-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino)-9H-purin-9-yl)cyclohexane-1-carboxamide;

(R)-tert-butyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4,6-trifluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-tert-butyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-difluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-tert-butyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-dichlorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-tert-butyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2-chloro-4,6-difluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-tert-butyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(4-chloro-2,6-difluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-tert-butyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4,6-trichlorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(1r,4s)-4-(2-((S)-1-hydroxypropan-2-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((S)-1-hydroxypropan-2-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-difluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichlorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,4-dichlorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(5-chloro-2-fluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(3-chloro-2-fluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(2,6-dichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(2-chloro-4,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(4-chloro-2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-(4-hydroxytetrahydrofuran-3-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-(4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-(4-hydroxytetrahydrofuran-3-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((R)-tetrahydro-2H-pyran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((R)-tetrahydro-2H-pyran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((R)-tetrahydro-2H-pyran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((R)-tetrahydro-2H-pyran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichlorophenylamino)-2-(4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-chloro-2-fluorophenylamino)-2-(4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(2,6-dichloro-4-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(4-chloro-2,3-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(3-chloro-2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(1-acetylpiperidin-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(1-acetylpiperidin-4-ylamino)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((R)-tetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((S)-tetrahydro-2H-pyran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((S)-tetrahydro-2H-pyran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((S)-tetrahydro-2H-pyran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1-(hydroxymethyl)cyclopropyl)methylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1-(hydroxymethyl)cyclopropyl)methylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3R)-3-hydroxycyclopentylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3R)-3-hydroxycyclopentylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-chloro-2,6-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3R)-3-hydroxycyclopentylamino)-8-(2,3,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichlorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3R)-3-hydroxycyclopentylamino)-8-(2,3,4-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((R)-tetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((R)-tetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((R)-tetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(3,3-difluorocyclobutylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(3,3-difluorocyclobutylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(3,3-difluorocyclobutylamino)-8-(2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-(3,3-difluorocyclobutylamino)-8-(2,3,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(3-chloro-2,6-difluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(3-chloro-2-fluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(4-chloro-2,5-difluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-(4,4-difluorocyclohexylamino)-8-(2,3,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,4-dichlorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((S)-tetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((S)-tetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((S)-tetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((S)-tetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((S)-tetrahydro-2H-pyran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((3R,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-difluorophenylamino)-2-((3R,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyanophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,2R)-2-hydroxycyclopentylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-difluorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,2R)-2-hydroxycyclopentylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-chloro-2,6-difluorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,2R)-2-hydroxycyclopentylamino)-8-(2,3,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichlorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(5-chloro-2-fluorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-chloro-2-fluorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,2R)-2-hydroxycyclopentylamino)-8-(2,3,4-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,5-difluorophenylamino)-2-((1R,2R)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((1S,2S)-2-hydroxycyclopentylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-difluorophenylamino)-2-((1S,2S)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichlorophenylamino)-2-((1S,2S)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1S,2S)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((1S,2S)-2-hydroxycyclopentylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1S,2S)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1S,2S)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(3-chloro-2,6-difluorophenylamino)-2-((1S,2S)-2-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-difluorophenylamino)-2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((3R,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1r,3r)-3-hydroxycyclobutylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-((1r,3r)-3-hydroxycyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-((1r,3r)-3-hydroxycyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1r,3r)-3-hydroxycyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1r,3r)-3-hydroxycyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1r,3r)-3-hydroxycyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-((1r,3r)-3-hydroxycyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-chloro-2,6-difluorophenylamino)-2-((1r,3r)-3-hydroxycyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-chloro-2,5-difluorophenylamino)-2-((1r,3r)-3-hydroxycyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(4,4-difluorocyclohexylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(4,4-difluorocyclohexylamino)-8-(2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-chloro-2,6-difluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(1-(methylsulfonyl)piperidin-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-(1-(methylsulfonyl)piperidin-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(1-(methylsulfonyl)piperidin-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(1-(methylsulfonyl)piperidin-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(1-(methylsulfonyl)piperidin-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(1-(methylsulfonyl)piperidin-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-(1-(methylsulfonyl)piperidin-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichlorophenylamino)-2-(1-(methylsulfonyl)piperidin-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1r,3r)-3-hydroxycyclobutylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1r,3r)-3-hydroxycyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((3R,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-difluorophenylamino)-2-((3R,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-difluorophenylamino)-2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((3R,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-((1s,3s)-3-hydroxycyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((3S,4R)-4-hydroxytetrahydrofuran-3-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((3S,4R)-4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((3S,4R)-4-hydroxytetrahydrofuran-3-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((3R,4S)-4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((3R,4S)-4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((3R,4S)-4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-((3S,4R)-4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(8-(3-chloro-2,6-difluorophenylamino)-2-((3S,4R)-4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(8-(2,4-dichlorophenylamino)-2-((3S,4R)-4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(8-(5-chloro-2-fluorophenylamino)-2-((3S,4R)-4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(4-chloro-2,5-difluorophenylamino)-2-((3R,4S)-4-hydroxytetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1s,3s)-3-hydroxycyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-((1s,3s)-3-hydroxycyclobutylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1s,3s)-3-hydroxycyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-((1S,3S)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(8-(2,6-difluorophenylamino)-2-((1S,3S)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichlorophenylamino)-2-((1S,3S)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,3S)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1S,3S)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((1S,3S)-3-hydroxycyclopentylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((1S,3S)-3-hydroxycyclopentylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3S)-3-hydroxycyclopentylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3S)-3-hydroxycyclopentylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-(sec-butylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-(sec-butylamino)-8-(2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-(sec-butylamino)-8-(2,6-dichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-(sec-butylamino)-8-(2-chloro-6-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-(sec-butylamino)-8-(2-chloro-4,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-(sec-butylamino)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-(sec-butylamino)-8-(3-chloro-2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,6-difluorophenylamino)-2-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-((1R,3S)-3-hydroxycyclohexylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,6-difluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-((1R,3S)-3-hydroxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(3-chloro-2,6-difluorophenylamino)-2-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-8-(2,3,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(3-chloro-2,6-difluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(4-chloro-2,5-difluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-((1R,3S)-3-hydroxycyclohexylamino)-8-(2,3,4-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,6-dichloro-4-(trifluoromethoxy)phenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-(cyclopentylamino)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-(cyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichlorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((1S,3R)-3-hydroxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(3-chloro-2,6-difluorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-cyano-2,3-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,3-difluoro-4-methoxyphenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3R)-3-hydroxy-4,4-dimethylcyclohexylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-difluorophenylamino)-2-((1R,3R)-3-hydroxy-4,4-dimethylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-((1R,3R)-3-hydroxy-4,4-dimethylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-((1R,3R)-3-hydroxy-4,4-dimethylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1R,3R)-3-hydroxy-4,4-dimethylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,3R)-3-hydroxy-4,4-dimethylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-((1R,3R)-3-hydroxy-4,4-dimethylcyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1R,3R)-3-hydroxy-4,4-dimethylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1R,3R)-3-hydroxy-4,4-dimethylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(3-chloro-2,6-difluorophenylamino)-2-((1R,3R)-3-hydroxy-4,4-dimethylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,4-dichlorophenylamino)-2-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-(cyclobutylamino)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(cyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-6-fluoro-4-(trifluoromethyl)phenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-((S)-1-hydroxybutan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4,6-trifluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-difluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-dichlorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2-chloro-6-fluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2-chloro-4,6-difluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(4-chloro-2,6-difluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4,6-trichlorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-dichloro-4-fluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(4-chloro-2,3-difluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(3-chloro-2,6-difluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,3,4-trifluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(1s,4s)-4-(2-((1R,3R)-3-hydroxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3R)-3-hydroxycyclohexylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-((1R,3S)-3-hydroxy-3-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1R,3S)-3-hydroxy-3-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,3S)-3-hydroxy-3-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1R,3S)-3-hydroxy-3-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1R,3S)-3-hydroxy-3-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2-chloro-4-fluorophenylamino)-2-((1R,3S)-3-hydroxy-3-methylcyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((S)-1-hydroxybutan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((S)-1-hydroxybutan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-((1R,3S)-3-hydroxycycloheptylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,6-dichlorophenylamino)-2-((1R,3S)-3-hydroxycycloheptylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2-chloro-6-fluorophenylamino)-2-((1R,3S)-3-hydroxycycloheptylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1R,3S)-3-hydroxycycloheptylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,3S)-3-hydroxycycloheptylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3S)-3-hydroxycycloheptylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-((1R,3S)-3-hydroxycycloheptylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-(isopropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-3-cyanophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((1S,3R)-3-hydroxycycloheptylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((2S,4R)-2-(hydroxymethyl)tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((2S,4R)-2-(hydroxymethyl)tetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(3-cyano-2,6-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1S,3S)-3-hydroxycycloheptylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((1S,3S)-3-hydroxycycloheptylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(2,2-difluoro-3-hydroxypropylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(2,2-difluoro-3-hydroxypropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(2,2-difluoro-3-hydroxypropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(2,2-difluoro-3-hydroxypropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((1S,3S)-3-hydroxycyclohexylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((1S,3S)-3-hydroxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,3-difluorophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,5-difluorophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1R,2R)-2-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,2R)-2-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,2R)-2-hydroxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1R,2R)-2-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1R,2R)-2-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((R)-1,1,1-trifluoro-3-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((R)-1,1,1-trifluoro-3-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4r)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4r)-1-methyl-4-(2-(tetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4r)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4r)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4r)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4r)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4r)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1S,4r)-4-(8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1S,4r)-4-(2-((S)-1-hydroxypropan-2-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(3-hydroxy-2,2-dimethylpropylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,2S)-2-hydroxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1R,4r)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4r)-4-(2-(cyclopentylamino)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4r)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4r)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4r)-4-(2-(cyclopentylamino)-8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4r)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4r)-4-(2-(cyclopentylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4r)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4r)-4-(2-(cyclopentylamino)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4r)-4-(2-(cyclopentylamino)-8-(2,6-dichloro-4-fluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4r)-4-(2-(cyclopentylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((3S,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((3R,4S)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((3R,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((3S,4S)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((3S,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((3R,4S)-3-methyltetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((3R,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((3S,4S)-3-methyltetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((3S,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((3R,4S)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((3R,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((3S,4S)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((3R,4S)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((3R,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((3S,4S)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(2-((3R,4S)-3-methyltetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(2-((3S,4S)-3-methyltetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(2-((1S,2R)-2-hydroxycyclohexylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1S,2R)-2-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(2-((1S,2R)-2-hydroxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1S,2R)-2-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1S,2R)-2-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1S,2R)-2-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((R)-tetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((1S,2R)-2-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((R)-tetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
(1s,4s)-1-methyl-4-(2-(tetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-2-((R)-tetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-((R)-tetrahydrofuran-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-((R)-tetrahydrofuran-3-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-(1-morpholinopropan-2-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((3S,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-((3S,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
(1s,4s)-4-(2-(oxepan-4-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(oxepan-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(oxepan-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(oxepan-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(oxepan-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(oxepan-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-(oxepan-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(oxepan-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-2-(oxepan-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-3,3-difluorocyclopentylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((S)-1-hydroxypropan-2-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(2-((S)-1-hydroxypropan-2-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(oxepan-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclopentylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclopentylamino)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclopentylamino)-8-(2,6-dichloro-4-fluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclopentylamino)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclopentylamino)-8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3S)-3-hydroxycyclohexylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3S)-3-hydroxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(2-chloro-4-cyano-6-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-(2-oxaspiro[3.3]heptan-6-ylamino)-8-(4-cyano-2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-(cyclopentylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(cyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
(1s,4s)-4-(8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
(1s,4s)-4-(2-(3,3-difluorocyclobutylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-(3,3-difluorocyclobutylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((S)-3,3-difluorocyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((R)-3,3-difluorocyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((S)-3,3-difluorocyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((R)-3,3-difluorocyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((S)-3,3-difluorocyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((R)-3,3-difluorocyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((S)-3,3-difluorocyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((R)-3,3-difluorocyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((S)-3,3-difluorocyclopentylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(2-((S)-3,3-difluorocyclopentylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-(trifluoromethoxy)phenylamino)-2-((1R,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-(trifluoromethoxy)phenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclopentylamino)-8-(2,6-dichloro-4-(trifluoromethoxy)phenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclobutylamino)-8-(2,6-dichloro-4-(trifluoromethoxy)phenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclobutylamino)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(cyclobutylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-(cyclobutylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclobutylamino)-8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclobutylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(cyclobutylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclobutylamino)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclobutylamino)-8-(2,6-dichloro-4-fluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclobutylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(cyclobutylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(2-((1S,3S)-3-hydroxycyclohexylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(2-((1S,3S)-3-hydroxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3R)-3-hydroxycyclohexylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3R)-3-hydroxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(2-((1S,3R)-3-hydroxycyclohexylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(2-((1S,3R)-3-hydroxycyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3R)-3-hydroxycyclopentylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(2-((1R,3R)-3-hydroxycyclopentylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(2-((1S,3S)-3-hydroxycyclopentylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((1S,3S)-3-hydroxycyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(2-((1S,3S)-3-hydroxycyclopentylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((1S,3S)-3-hydroxycyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((1S,3S)-3-hydroxycyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((1S,3S)-3-hydroxycyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1S,3S)-3-hydroxycyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((1S,3S)-3-hydroxycyclopentylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
(1r,4s)-4-(2-(((1S,2S)-2-hydroxycyclohexyl)methylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(((1S,2S)-2-hydroxycyclohexyl)methylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(2-(((1S,2S)-2-hydroxycyclohexyl)methylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(((1S,2S)-2-hydroxycyclohexyl)methylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(((1S,2S)-2-hydroxycyclohexyl)methylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(((1S,2S)-2-hydroxycyclohexyl)methylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(((1S,2S)-2-hydroxycyclohexyl)methylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(((1S,2S)-2-hydroxycyclohexyl)methylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(((1S,2R)-2-hydroxycyclohexyl)methylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(2-(((1S,2R)-2-hydroxycyclohexyl)methylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(((1S,2R)-2-hydroxycyclohexyl)methylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(((1S,2R)-2-hydroxycyclohexyl)methylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-(((1S,2R)-2-hydroxycyclohexyl)methylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(((1S,2R)-2-hydroxycyclohexyl)methylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(3,3-difluorocyclobutylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(4-(2,5-dioxopyrrolidin-1-yl)cyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(4-(2,5-dioxopyrrolidin-1-yl)cyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
(1s,4s)-4-(2-(4-(1,2,4-oxadiazol-5-yl)cyclohexylamino)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(4-(1,2,4-oxadiazol-5-yl)cyclohexylamino)-8-(2-chloro-4,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-(4-(1,2,4-oxadiazol-5-yl)cyclohexylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-(4-(1,2,4-oxadiazol-5-yl)cyclohexylamino)-8-(2,6-dichloro-4-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-(4-(1,2,4-oxadiazol-5-yl)cyclohexylamino)-8-(2-chloro-4-cyano-6-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-(4-(1,2,4-oxadiazol-5-yl)cyclohexylamino)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((1R,3R)-3-hydroxycyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1R,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1S,3R)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((1S,3S)-3-hydroxycyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(4-bromo-2,6-dichlorophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-bromo-2,6-dichlorophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(cyclopentylamino)-8-(2,3-dichloro-4-cyanophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,3-dichloro-4-cyanophenylamino)-2-((S)-1-hydroxypropan-2-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,3-dichloro-4-cyanophenylamino)-2-(4,4-difluorocyclohexylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,3-dichloro-4-cyanophenylamino)-2-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-((R)-3,3-difluorocyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((R)-3,3-difluorocyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((R)-3,3-difluorocyclopentylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-1-(methylsulfonyl)piperidin-3-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((R)-1-(methylsulfonyl)piperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((R)-1-(methylsulfonyl)piperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((R)-1-(methylsulfonyl)piperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((R)-1-(methylsulfonyl)piperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(R)-3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4,6-trichlorophenylamino)-9H-purin-2-ylamino)-N-methylpiperidine-1-carboxamide;
(R)-3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-2-ylamino)-N-methylpiperidine-1-carboxamide;
(R)-3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-2-ylamino)-N-methylpiperidine-1-carboxamide;
(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;
(R)-methyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2-chloro-4-cyano-6-fluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;
(1s,4s)-4-(2-((R)-1-acetylpiperidin-3-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-((R)-1-acetylpiperidin-3-ylamino)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-((R)-1-acetylpiperidin-3-ylamino)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-((R)-1-acetylpiperidin-3-ylamino)-8-(4-chloro-2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
(1r,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((3S,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
(1r,4s)-4-(2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1r,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((3S,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((3S,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((3S,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-1-methyl-4-(2-((3S,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-(3-(methylsulfonyl)cyclobutylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-(3-(methylsulfonyl)cyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-(3-(methylsulfonyl)cyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-1-ethylpiperidin-3-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((R)-1-ethylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((R)-1-ethylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-2-(3-(methylsulfonyl)cyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-(3-(methylsulfonyl)cyclobutylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-2-((R)-1-ethylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-1-isopropylpiperidin-3-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((R)-1-isopropylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((R)-1-isopropylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((R)-1-isopropylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((R)-1-phenylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-1-phenylpiperidin-3-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((R)-1-phenylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-((R)-1-phenylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-1-phenylpiperidin-3-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((R)-1-phenylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((R)-1-phenylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((R)-1-phenylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((R)-1-phenylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-((R)-1-benzylpiperidin-3-ylamino)-8-(2-chloro-4,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-((R)-1-benzylpiperidin-3-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-((R)-1-benzylpiperidin-3-ylamino)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-((R)-1-benzylpiperidin-3-ylamino)-8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-((R)-1-benzylpiperidin-3-ylamino)-8-(4-cyano-2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-((R)-1-benzylpiperidin-3-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-((R)-1-benzylpiperidin-3-ylamino)-8-(4-chloro-2,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-((R)-1-benzylpiperidin-3-ylamino)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-((R)-1-benzylpiperidin-3-ylamino)-8-(2,6-dichloro-4-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;
(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((3S,4R)-3-methyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)-1-methylcyclohexanecarboxamide;

(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((R)-3,3-dimethyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1r,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((3S,4S)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-3,3-dimethyltetrahydro-2H-pyran-4-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(R)-isopropyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2-chloro-4,6-difluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-isopropyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4,6-trichlorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-isopropyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-isopropyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-isopropyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(4-cyano-2,6-difluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-isopropyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4,6-trifluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-isopropyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(4-chloro-2,6-difluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-isopropyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-isopropyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-dichloro-4-fluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(R)-isopropyl 3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2-chloro-4-cyano-6-fluorophenylamino)-9H-purin-2-ylamino)piperidine-1-carboxylate;

(1s,4s)-4-(2-((R)-1-benzylpiperidin-3-ylamino)-8-(2-chloro-4-cyano-6-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(R)-3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2-chloro-4,6-difluorophenylamino)-9H-purin-2-ylamino)-N-phenylpiperidine-1-carboxamide;

(R)-3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4,6-trichlorophenylamino)-9H-purin-2-ylamino)-N-phenylpiperidine-1-carboxamide;

(R)-3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-dichloro-4-cyanophenylamino)-9H-purin-2-ylamino)-N-phenylpiperidine-1-carboxamide;

(R)-3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4,6-trifluorophenylamino)-9H-purin-2-ylamino)-N-phenylpiperidine-1-carboxamide;

(R)-3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(4-chloro-2,6-difluorophenylamino)-9H-purin-2-ylamino)-N-phenylpiperidine-1-carboxamide;

(R)-3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,4-dichloro-6-fluorophenylamino)-9H-purin-2-ylamino)-N-phenylpiperidine-1-carboxamide;

(R)-3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-dichloro-4-fluorophenylamino)-9H-purin-2-ylamino)-N-phenylpiperidine-1-carboxamide;

(R)-3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2-chloro-4-cyano-6-fluorophenylamino)-9H-purin-2-ylamino)-N-phenylpiperidine-1-carboxamide;

(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((R)-3,3-dimethyltetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2-chloro-4,6-difluorophenylamino)-2-((R)-1-tosylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(2-((R)-1-tosylpiperidin-3-ylamino)-8-(2,4,6-trichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(2,6-dichloro-4-cyanophenylamino)-2-((R)-1-tosylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;

(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-((R)-1-tosylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-((R)-1-tosylpiperidin-3-ylamino)-8-(2,4,6-trifluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(4-chloro-2,6-difluorophenylamino)-2-((R)-1-tosylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,4-dichloro-6-fluorophenylamino)-2-((R)-1-tosylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2,6-dichloro-4-fluorophenylamino)-2-((R)-1-tosylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(2-chloro-4-cyano-6-fluorophenylamino)-2-((R)-1-tosylpiperidin-3-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(R)-3-(9-((1s,4s)-4-carbamoylcyclohexyl)-8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-9H-purin-2-ylamino)-N-methylpiperidine-1-carboxamide;
(1s,4s)-4-(2-((R)-1-acetylpiperidin-3-ylamino)-8-(2-chloro-4,6-difluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-((R)-1-acetylpiperidin-3-ylamino)-8-(2,6-dichloro-4-(trifluoromethyl)phenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-((R)-1-acetylpiperidin-3-ylamino)-8-(2,6-dichloro-4-fluorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(2-((R)-1-acetylpiperidin-3-ylamino)-8-(2,6-dichlorophenylamino)-9H-purin-9-yl)cyclohexanecarboxamide;
(1s,4s)-4-(8-(4-cyano-2,6-difluorophenylamino)-2-((3S,4R)-3-fluorotetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl)cyclohexanecarboxamide; or
(1r,4s)-4-(2-(((3R,4S)-3-fluorotetrahydro-2H-pyran-4-yl)amino)-8-((2,4,6-trichlorophenyl)amino)-9H-purin-9-yl)-1-methylcyclohexane-1-carboxamide or a pharmaceutically acceptable salt thereof.

3. The method of claim 1, wherein the cancer is colorectal cancer, stomach cancer, colon cancer, or gastric cancer.

4. The method of claim 1, wherein the cancer is liver cancer, lung cancer, or pancreatic cancer.

5. The method of claim 1, wherein the cancer is leukemia, or multiple myeloma.

6. The method of claim 1, wherein the cancer is hepatocellular carcinoma.

7. The method of claim 1, wherein the cancer is a cancer expressing PD-L1.

8. The method of claim 7, wherein the PD-L1 expressing cancer is lung cancer, renal cell carcinoma, or hepatocellular carcinoma.

9. The method of claim 1, wherein the cancer is characterized by a BRAF mutation.

10. The method of claim 9, wherein the cancer characterized by a BRAF mutation is colorectal cancer, or lung cancer.

11. The method of claim 9, wherein the BRAF mutation is BRAF V600E.

12. The method of claim 1, wherein the cancer is characterized by an NRAS mutation.

13. The method of claim 1, wherein the cancer is characterized by a KRAS mutation.

14. The method of claim 13, wherein the cancer characterized by a KRAS mutation is colorectal cancer, pancreatic cancer or lung cancer.

15. The method of claim 1, wherein the cancer is characterized by an activated beta-catenin pathway.

16. The method of claim 15, wherein the cancer is colorectal cancer, stomach cancer, or hepatocellular carcinoma.

17. The method of claim 1, wherein the Aminopurine Compound is administered as a pharmaceutical composition comprising at least one pharmaceutically acceptable excipient.

18. The method of claim 15, wherein the cancer is hepatocellular carcinoma, gastric cancer, or melanoma.

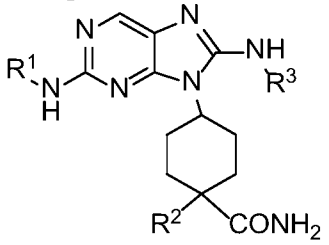
19. The method of claim 15, wherein the cancer is further characterized by an EGFR mutation or increased EGFR activity.

20. The method of claim 19, wherein the EGFR mutation is one or more of EGFR E282K, G719S, P753S, or V1011M.

21. The method of claim 15, wherein the cancer is further characterized by a BRAF mutation.

22. The method of claim 21, wherein the BRAF mutation comprises a BRAF V600E, BRAF T119S, or BRAF G596R mutation.

23. Use of an Aminopurine Compound of formula (I):



(I)

or a pharmaceutically acceptable salt, tautomer, stereoisomer, or enantiomer thereof,

wherein:

R^1 is substituted or unsubstituted non-aromatic heterocyclyl;

R^2 is H or substituted or unsubstituted C_{1-3} alkyl; and

R^3 is phenyl, substituted with one or more halogen, optionally further substituted with one or more substituents independently selected from substituted or unsubstituted C_{1-3} alkyl, CN, and -OR', wherein each R' is independently substituted or unsubstituted C_{1-3} alkyl;

wherein when a C_{1-3} alkyl group is substituted, the C_{1-3} alkyl group is substituted with halogen, alkyl, hydroxyl, alkoxy, alkoxyalkyl, amino, alkylamino, carboxy, nitro, cyano, thiol, thioether, imine, imide, amidine, guanidine, enamine, aminocarbonyl, acylamino, phosphonate, phosphine, thiocarbonyl, sulfinyl, sulfone, sulfonamide, ketone, aldehyde, ester, urea, urethane, oxime, hydroxyl amine, alkoxyamine, aryloxyamine, aralkoxyamine, N-oxide, hydrazine, hydrazide, hydrazone, azide, isocyanate, isothiocyanate, cyanate, thiocyanate, $B(OH)_2$, or O(alkyl)aminocarbonyl;

wherein when a group, other than a C_{1-3}alkyl group, is substituted, the group is substituted with halogen, C_{1-10}alkyl, hydroxyl, C_{1-10}alkoxy, C_{1-10} alkoxy C_{1-10}alkyl, amino, C_{1-10}alkylamino, carboxy, nitro, cyano, thiol, thioether, imine, imide, amidine, guanidine, enamine, aminocarbonyl, acylamino, phosphonate, phosphine, thiocarbonyl, sulfinyl, sulfone, sulfonamide, ketone, aldehyde, ester, urea, urethane, oxime, hydroxyl amine, C_{1-10}alkoxyamine, C_{6-14}aryloxyamine, C_{6-14}arC_{1-10}alkoxyamine, N-oxide, hydrazine, hydrazide, hydrazone, azide, isocyanate, isothiocyanate, cyanate, thiocyanate, oxygen (=O), $B(OH)_2$, O(C_{1-10}alkyl)aminocarbonyl, C_{3-10}cycloalkyl, heterocyclyl, aryl, heteroaryl, C_{6-14}aryloxy, C_{6-14}arC_{1-10}alkyloxy, heterocyclyloxy, or heterocyclyl C_{1-10}alkoxy;

wherein an alkyl group is a saturated straight chain or branched non-cyclic hydrocarbon having from 1 to 10 carbon atoms;

wherein a heterocyclyl group is an aromatic or non-aromatic cycloalkyl having from 1 to 2 rings in which one to four of the ring carbon atoms are independently replaced with a heteroatom selected from the group consisting of O, S and N;

wherein an aryl group is an aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring or multiple condensed rings;

wherein a heteroaryl group is an aromatic cycloalkyl of from 3 to 10 carbon atoms having a single cyclic ring or multiple condensed or bridged rings in which one to four of the ring carbon atoms are independently replaced with a heteroatom selected from the group consisting of O, S and N;

in the manufacture of a medicament for the treatment of a cancer selected from colorectal cancer, colon cancer, renal cell carcinoma, gastric cancer, stomach cancer,

hepatocellular carcinoma, liver cancer, lung cancer, pancreatic cancer, leukemia, or multiple myeloma.

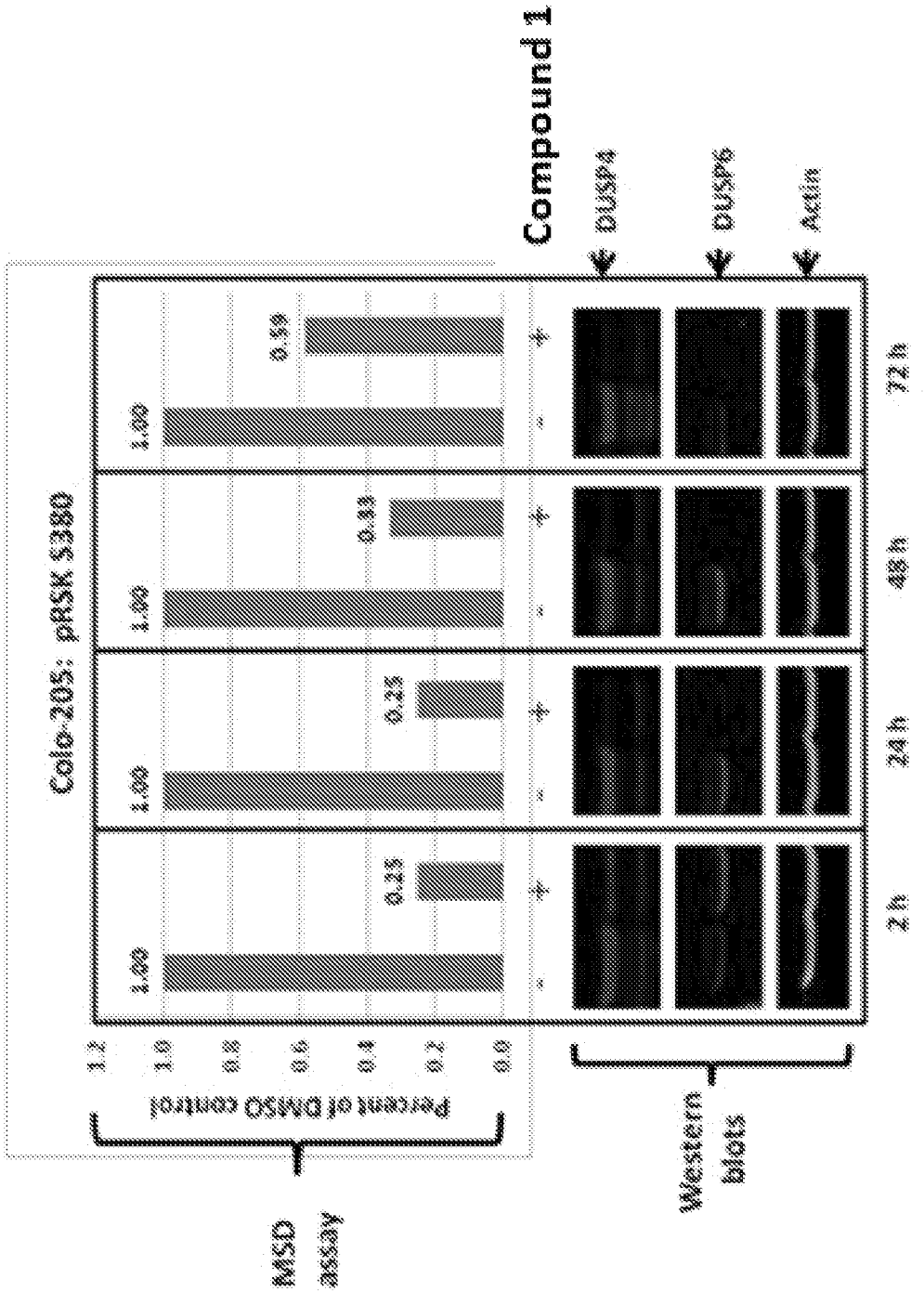

Compound 1
DUSP4
DUSP6
Actin
Colo-205; pRSK S380
Percent of DMSO control
1.2
1.0
0.8
0.6
0.4
0.2
0.0
1.00
0.35
0.59
1.00
0.25
0.33
1.00
0.11
0.39
1.00
+
-
2 h
24 h
48 h
72 h
MSD assay
Western blots

FIG. 1

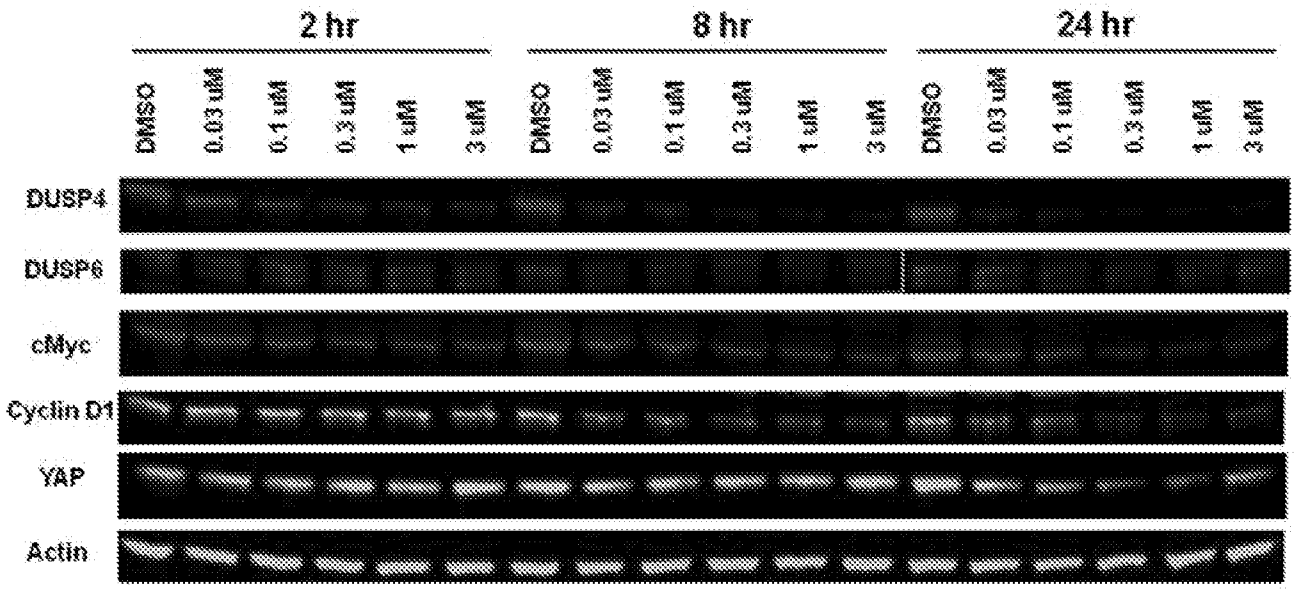

2 hr
8 hr
24 hr
DMSO
0.03 uM
0.1 uM
0.3 uM
1 uM
3 uM
DUSP4
DUSP6
cMyc
Cyclin D1
YAP
Actin

FIG. 2A

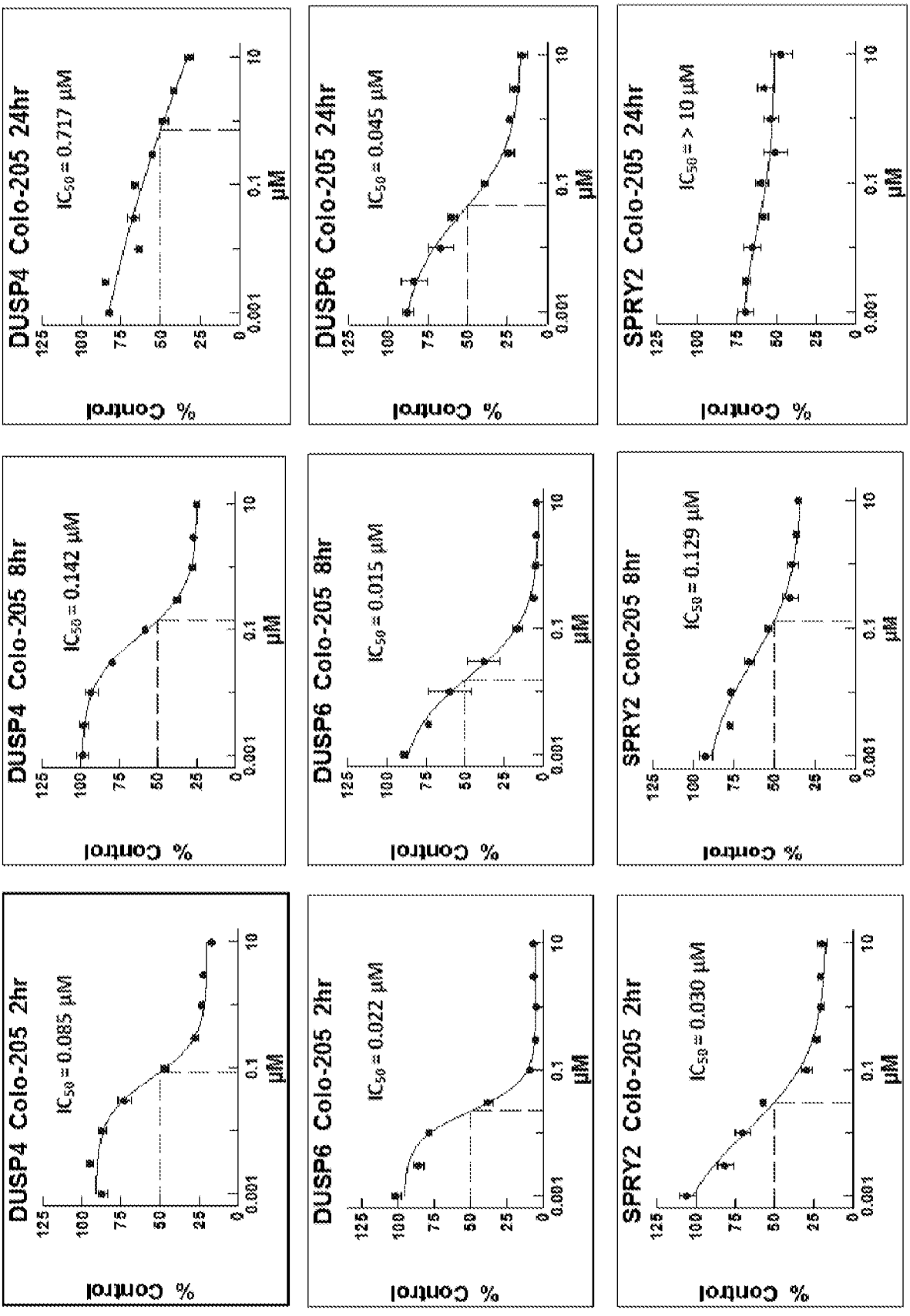

2 Hours
8 Hours
24 Hours
DUSP4
DUSP6
SPRY2
DUSP4 Colo-205 2hr
IC50 = 0.085 µM
DUSP4 Colo-205 8hr
IC50 = 0.142 µM
DUSP4 Colo-205 24hr
IC50 = 0.717 µM
DUSP6 Colo-205 2hr
IC50 = 0.022 µM
DUSP6 Colo-205 8hr
IC50 = 0.015 µM
DUSP6 Colo-205 24hr
IC50 = 0.045 µM
SPRY2 Colo-205 2hr
IC50 = 0.030 µM
SPRY2 Colo-205 8hr
IC50 = 0.129 µM
SPRY2 Colo-205 24hr
IC50 = > 10 µM
% Control
µM

FIG. 2B

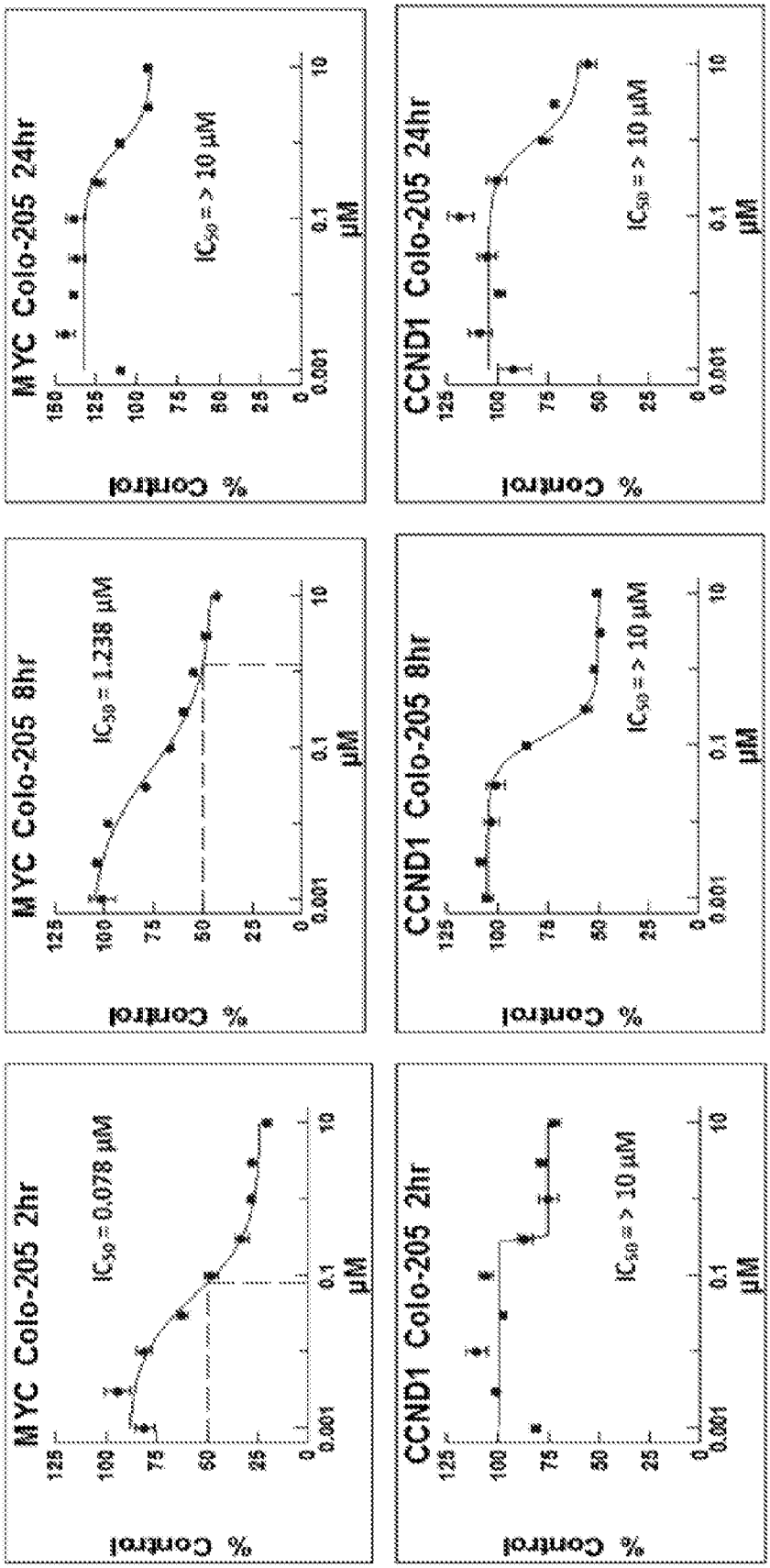

2 Hours
8 Hours
24 Hours
MYC
CCND1
MYC Colo-205 2hr
IC50 = 0.078 µM
MYC Colo-205 8hr
IC50 = 1.238 µM
MYC Colo-205 24hr
IC50 = > 10 µM
CCND1 Colo-205 2hr
IC50 = > 10 µM
CCND1 Colo-205 8hr
IC50 = > 10 µM
CCND1 Colo-205 24hr
IC50 = > 10 µM
% Control
µM

FIG. 2C

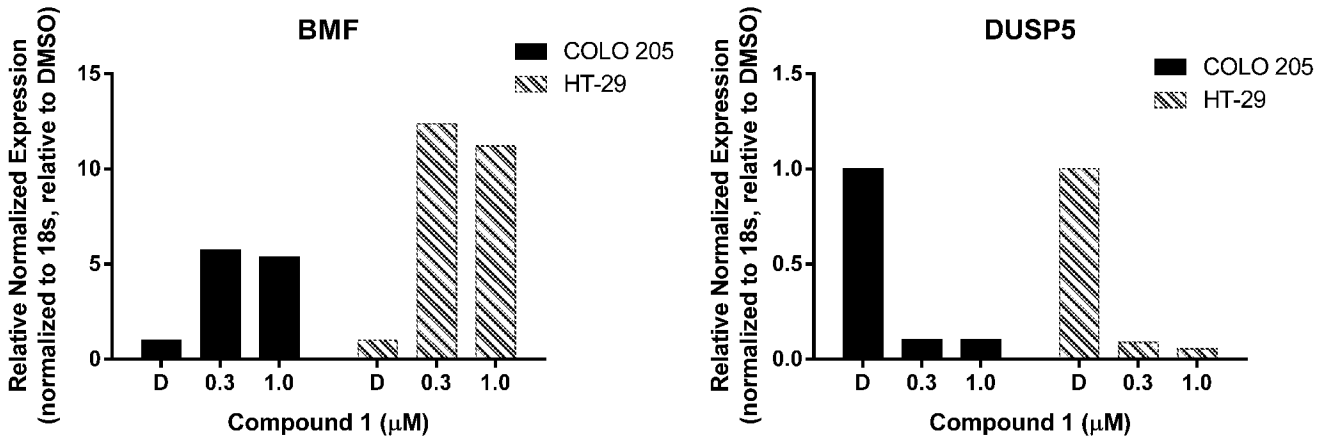


FIG. 2D

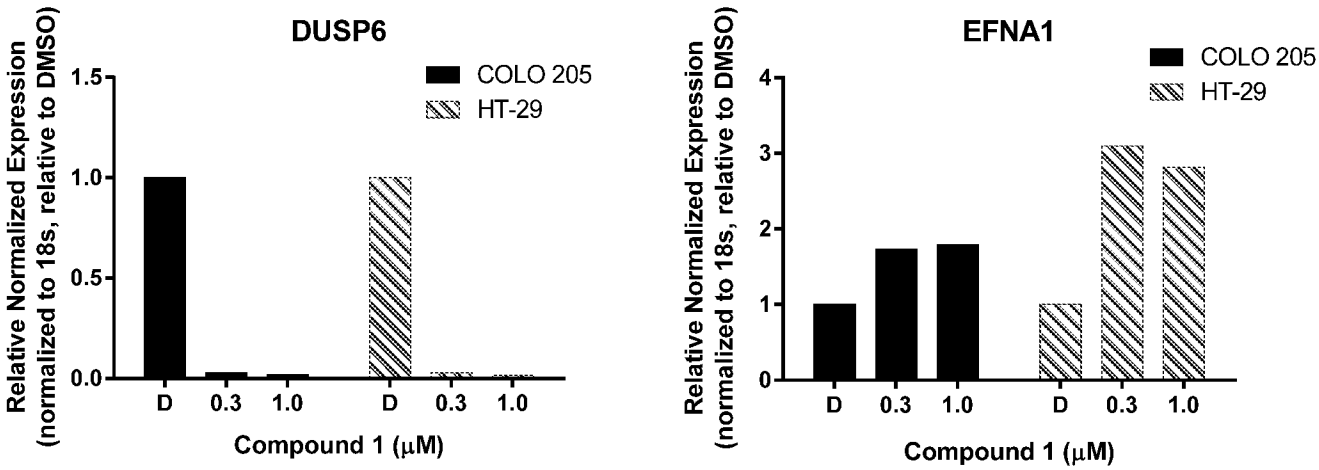


FIG. 2E

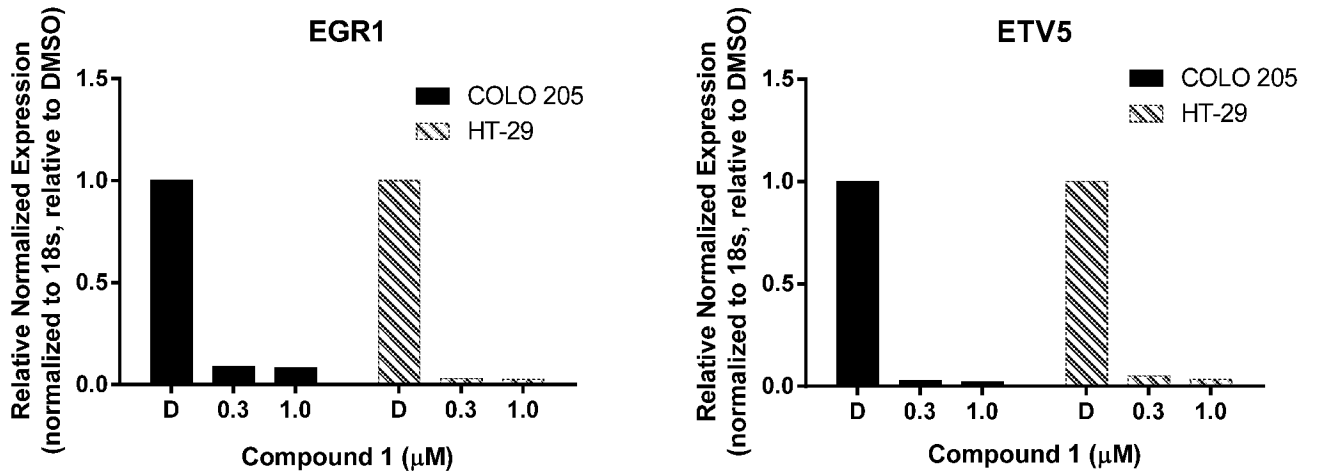


FIG. 2F

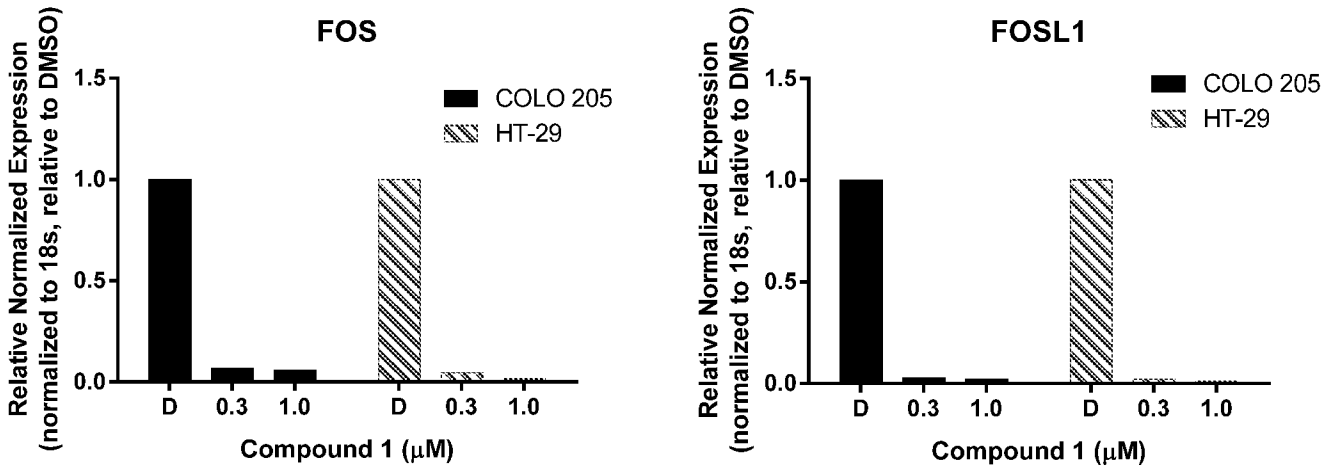


FIG. 2G

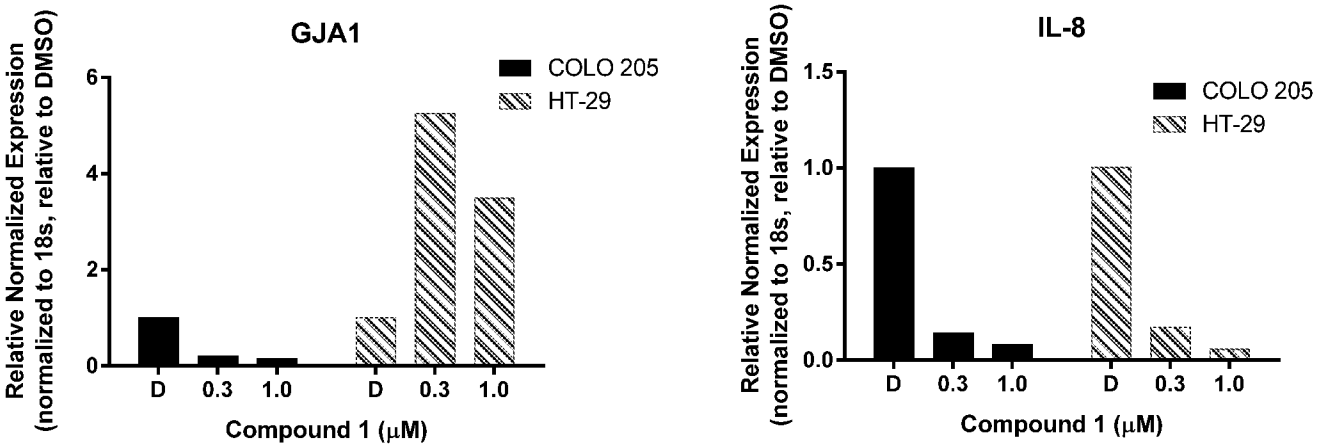


FIG. 2H

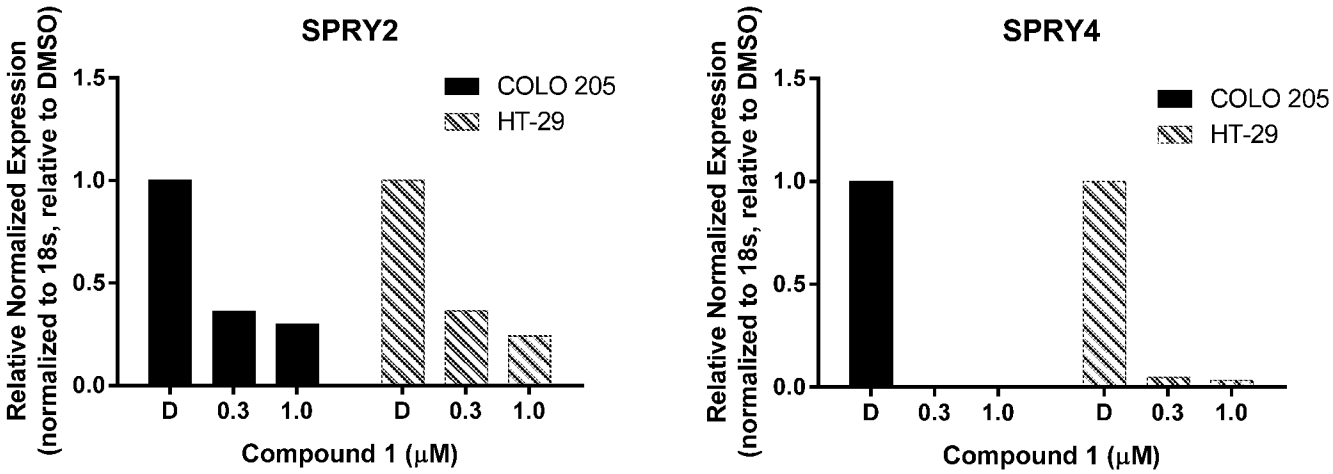


FIG. 2I

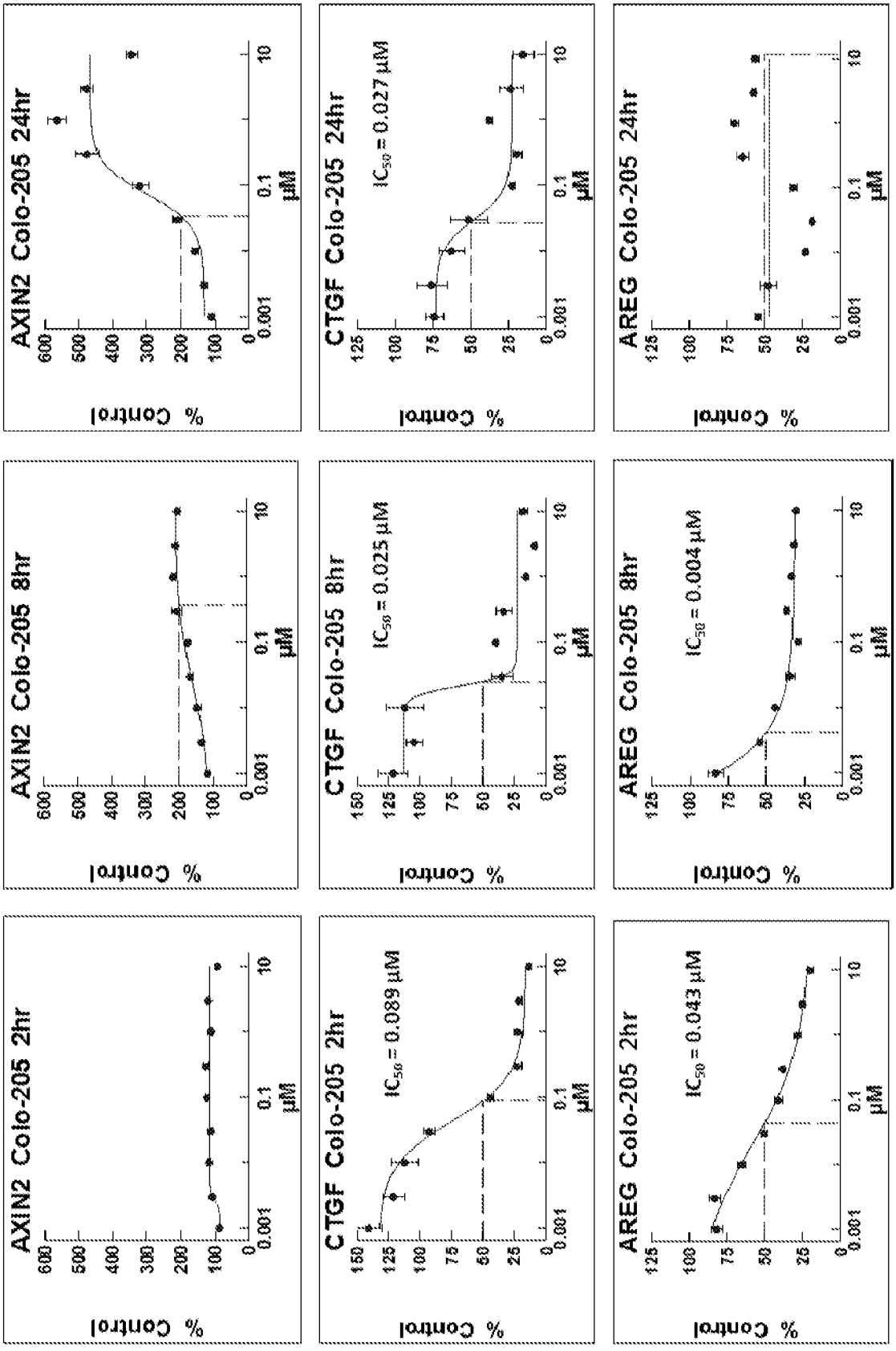

2 Hours
8 Hours
24 Hours
Axin2
CTGF
AREG
AXIN2 Colo-205 2hr
AXIN2 Colo-205 8hr
AXIN2 Colo-205 24hr
CTGF Colo-205 2hr
CTGF Colo-205 8hr
CTGF Colo-205 24hr
AREG Colo-205 2hr
AREG Colo-205 8hr
AREG Colo-205 24hr
IC50 = 0.089 µM
IC50 = 0.025 µM
IC50 = 0.027 µM
IC50 = 0.043 µM
IC50 = 0.004 µM
% Control
µM

FIG. 3A

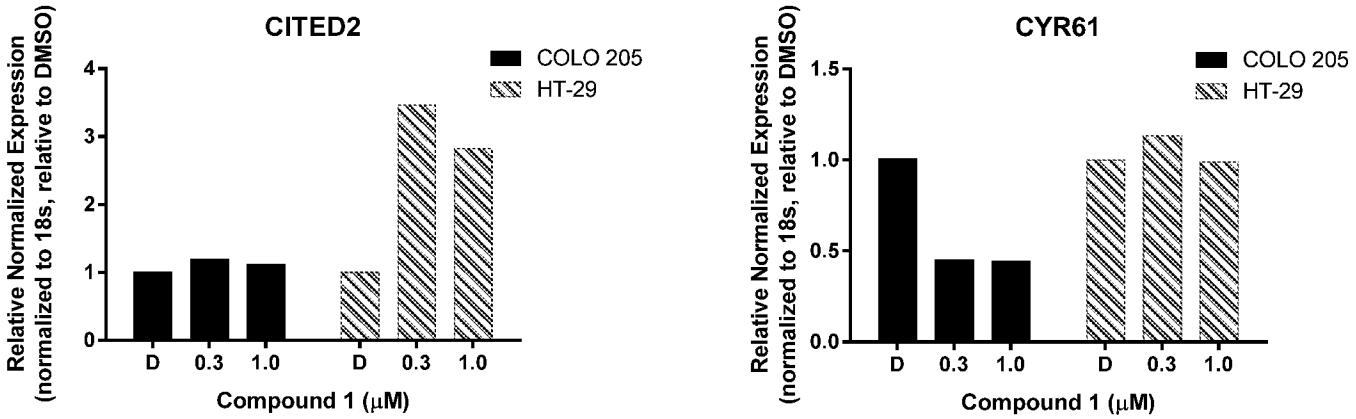

CITED2
Relative Normalized Expression (normalized to 18s, relative to DMSO)
COLO 205
HT-29
0
1
2
3
4
D
0.3
1.0
D
0.3
1.0
Compound 1 (μM)
CYR61
Relative Normalized Expression (normalized to 18s, relative to DMSO)
COLO 205
HT-29
0.0
0.5
1.0
1.5
D
0.3
1.0
D
0.3
1.0
Compound 1 (μM)

FIG. 3B

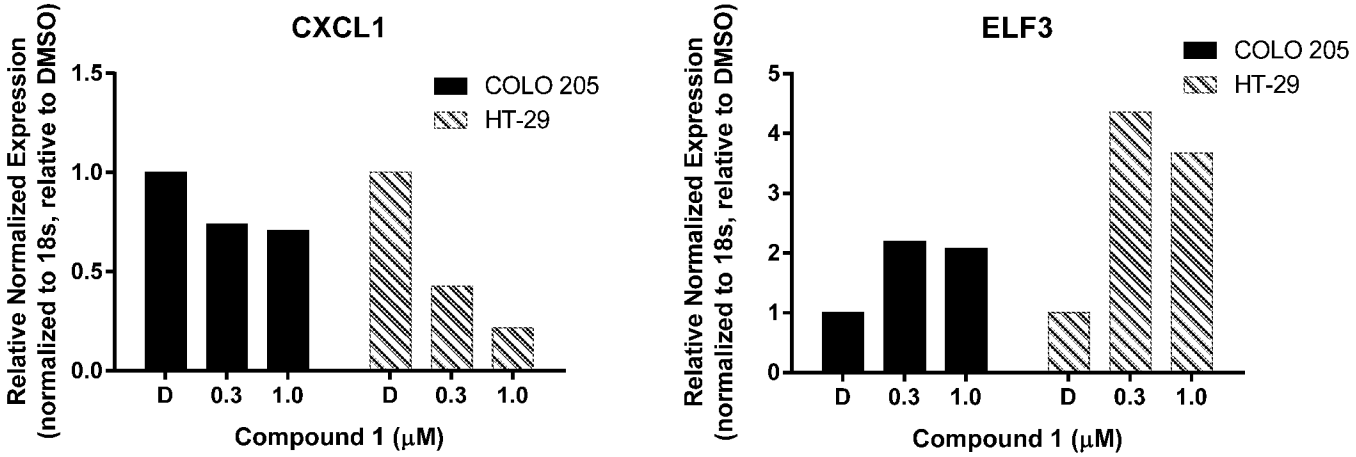

CXCL1
Relative Normalized Expression (normalized to 18s, relative to DMSO)
COLO 205
HT-29
0.0
0.5
1.0
1.5
D
0.3
1.0
D
0.3
1.0
Compound 1 (μM)
ELF3
Relative Normalized Expression (normalized to 18s, relative to DMSO)
COLO 205
HT-29
0
1
2
3
4
5
D
0.3
1.0
D
0.3
1.0
Compound 1 (μM)

FIG. 3C

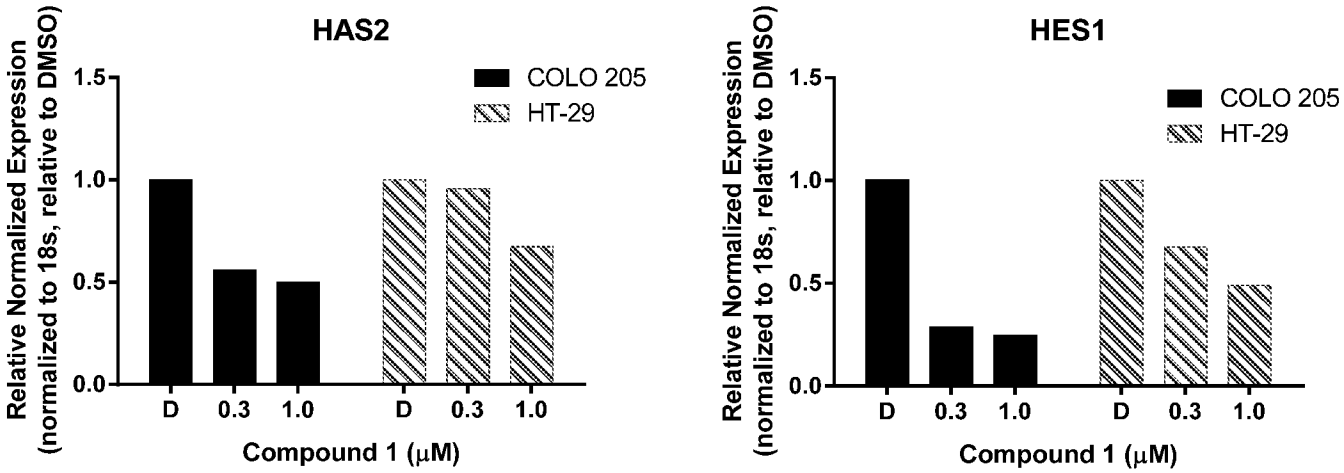

HAS2
HES1
COLO 205
HT-29
Relative Normalized Expression
(normalized to 18s, relative to DMSO)
1.5
1.0
0.5
0.0
D
0.3
1.0
Compound 1 (μM)

FIG. 3D

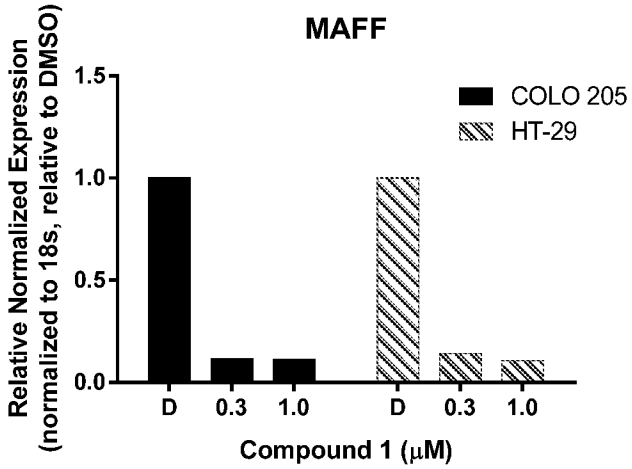

MAFF
COLO 205
HT-29
Relative Normalized Expression
(normalized to 18s, relative to DMSO)
1.5
1.0
0.5
0.0
D
0.3
1.0
Compound 1 (μM)

FIG. 3E

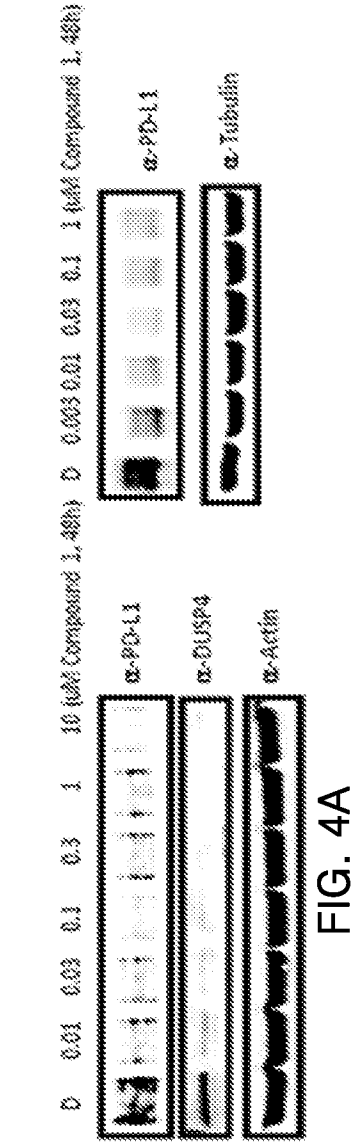

HOP62 (NSCLC)
Karpas-299 (Lymphoma)
Lox-IMVI (Melanoma)
Total PD-L1 (Western)
0 0.03 0.01 0.3 0.1 10 (uM) Compound 1, 48h)
α-PD-L1
α-DUSP4
α-Tubulin
0 0.01 0.03 0.1 0.3 1 10 (uM) Compound 1, 48h)
α-PD-L1
α-DUSP4
α-Actin
0 0.003 0.01 0.03 0.1 1 (uM) Compound 1, 48h)
α-PD-L1
α-Tubulin

FIG. 4A

Cell surface PD-L1 (FACS)
Stain
No
0
0.03
0.1
0.3
1
(uM) Compound 1
Stain
No
0
0.03
0.1
0.3
1
10
50
(uM) Compound 1 (ng/mL) PD-L1Ab
Stain
No
0
0.001
0.003
0.01
0.03
(uM) Compound 1

FIG. 4B

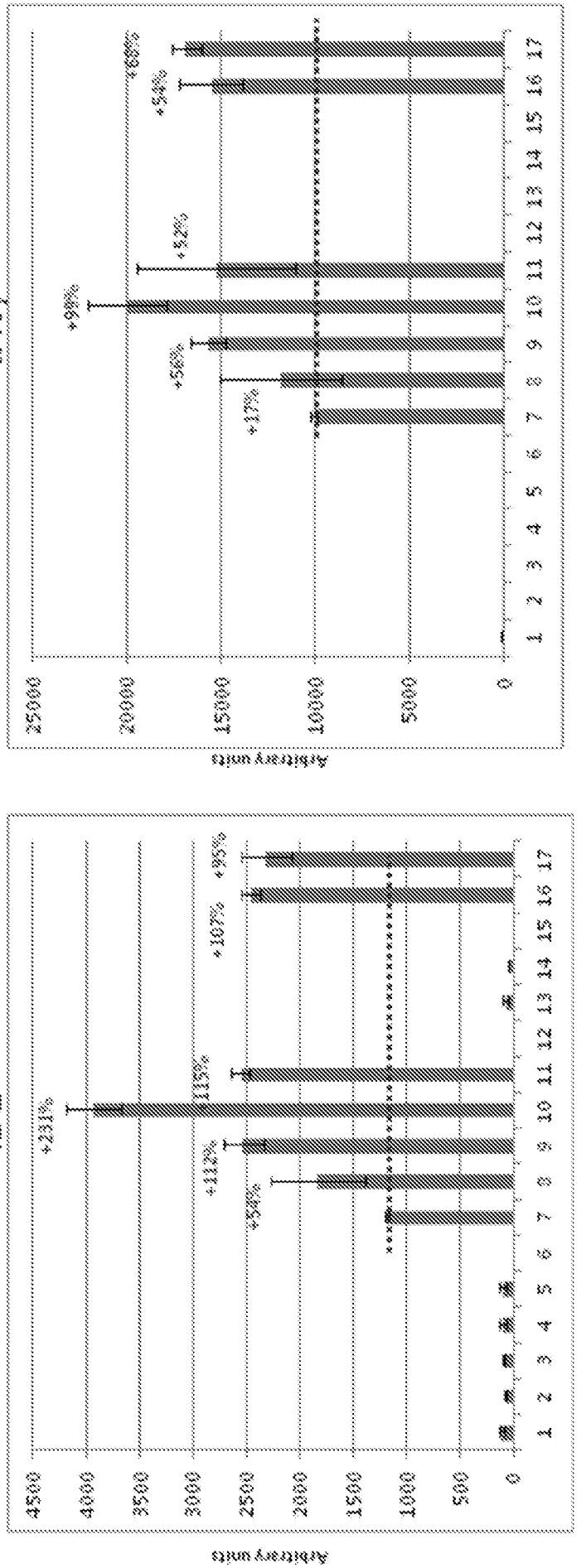

IL-2
Arbitrary units
4500
4000
3500
3000
2500
2000
1500
1000
500
0
+231%
+112%
+58%
115%
+107%
+95%
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
PBMC + + + + + + + + + + + + + + + + +
SEB - - - - - + + + + + + - - - + + +
Karpas299 + + + + + + + + + + + + + + + + +
Treatment D 0.03 0.1 0.3 1 D 0.03 0.1 0.3 1 10 50 10 50
Compound 1 (μM)
α-PD-L1 (ng/ml)

FIG. 5A

IFNγ
Arbitrary units
25000
20000
15000
10000
5000
0
+98%
+52%
+68%
+54%
+58%
+17%
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
PBMC + + + + + + + + + + + + + + + + +
SEB - - - - - + + + + + + - - - + + +
Karpas299 + + + + + + + + + + + + + + + + +
Treatment D 0.03 0.1 0.3 1 D 0.03 0.1 0.3 1 10 50 10 50
Compound 1 (μM)
α-PD-L1 (ng/ml)

FIG. 5B

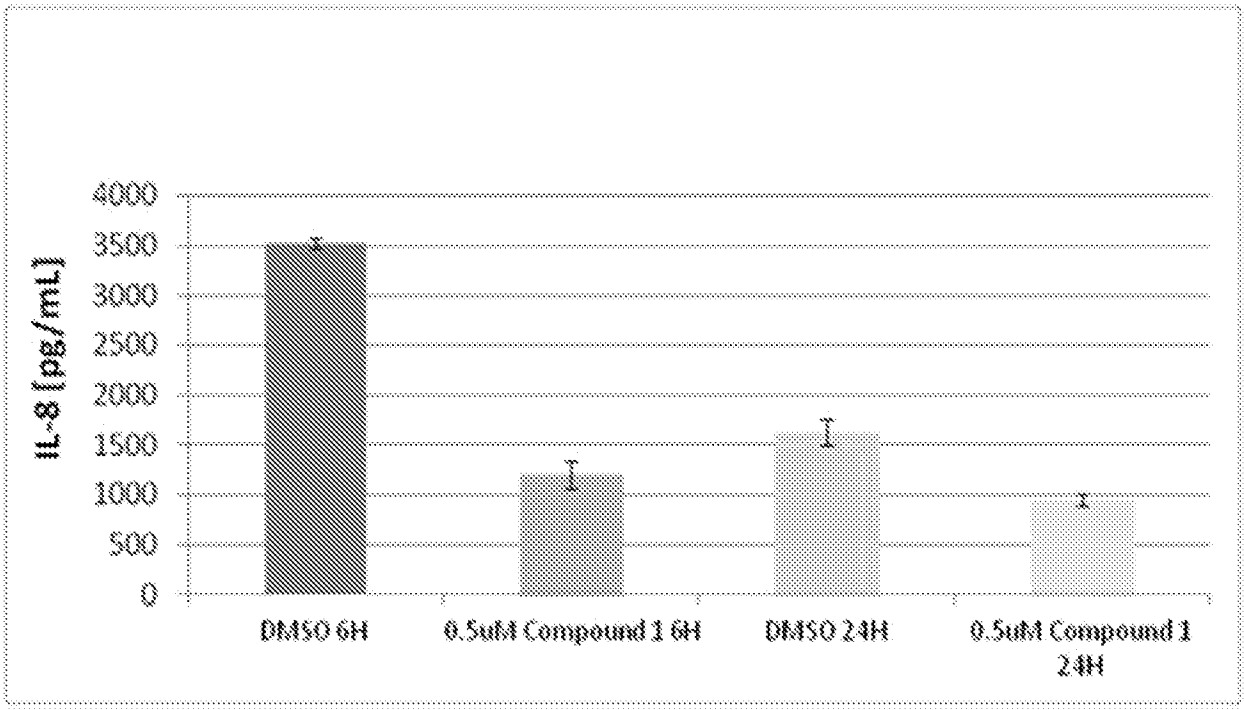

IL-8 [pg/mL]
4000
3500
3000
2500
2000
1500
1000
500
0
DMSO 6H
0.5uM Compound 1 6H
DMSO 24H
0.5uM Compound 1 24H

FIG. 5C

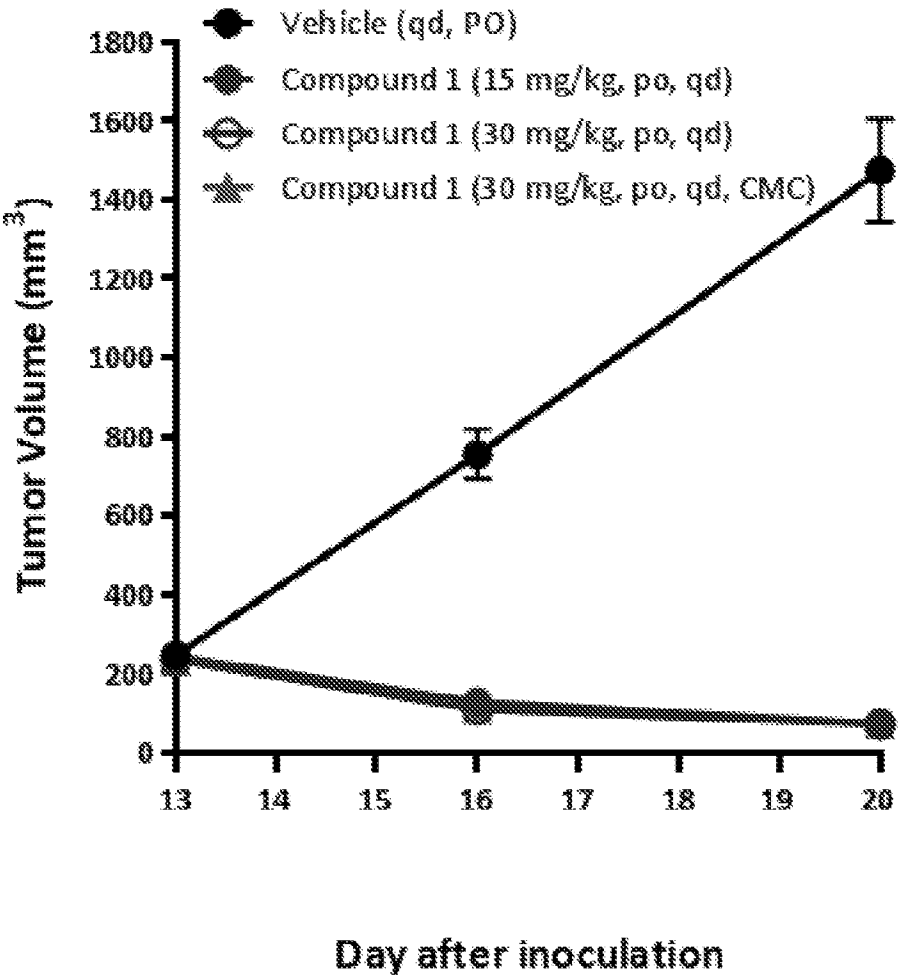

Vehicle (qd, PO)
Compound 1 (15 mg/kg, po, qd)
Compound 1 (30 mg/kg, po, qd)
Compound 1 (30 mg/kg, po, qd, CMC)
Tumor Volume (mm3)
1800
1600
1400
1200
1000
800
600
400
200
0
13
14
15
16
17
18
19
20
Day after inoculation

FIG. 6

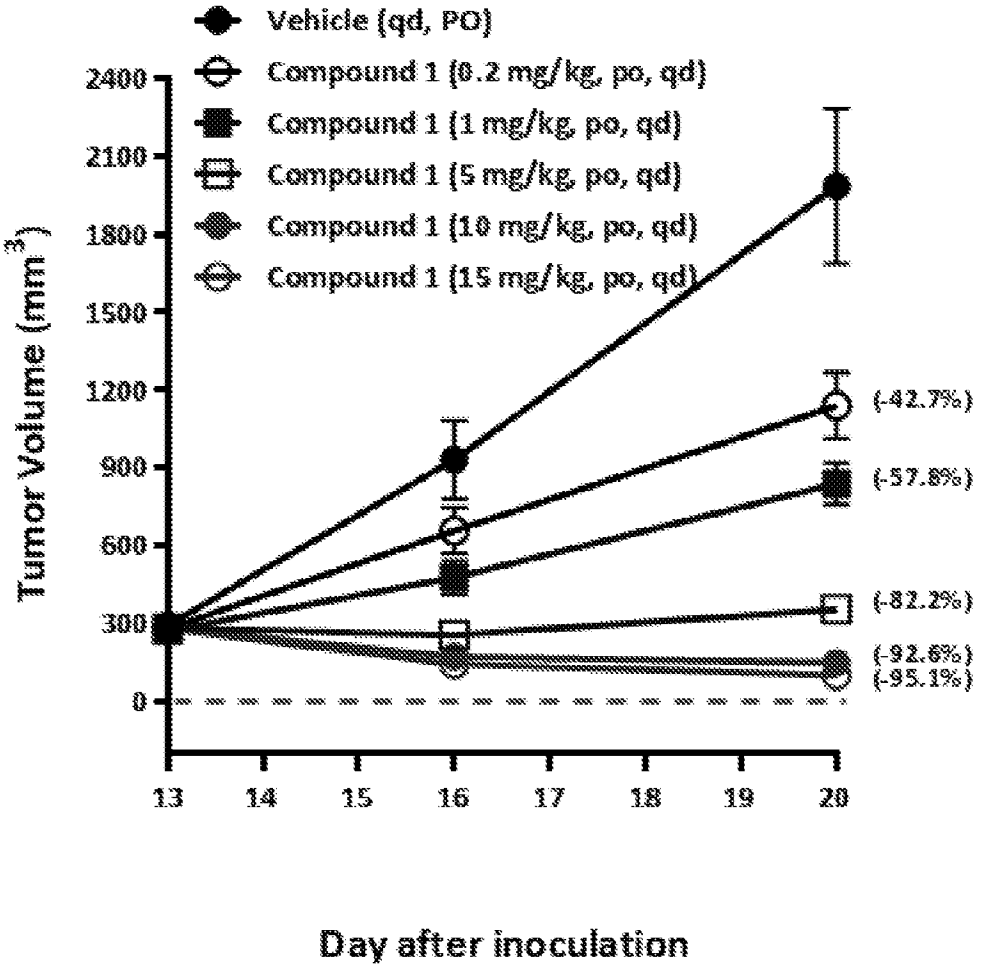

Vehicle (qd, PO)
Compound 1 (0.2 mg/kg, po, qd)
Compound 1 (1 mg/kg, po, qd)
Compound 1 (5 mg/kg, po, qd)
Compound 1 (10 mg/kg, po, qd)
Compound 1 (15 mg/kg, po, qd)
Tumor Volume (mm3)
2400
2100
1800
1500
1200
900
600
300
0
13
14
15
16
17
18
19
20
(-42.7%)
(-57.8%)
(-82.2%)
(-92.6%)
(-95.1%)
Day after inoculation

FIG. 7

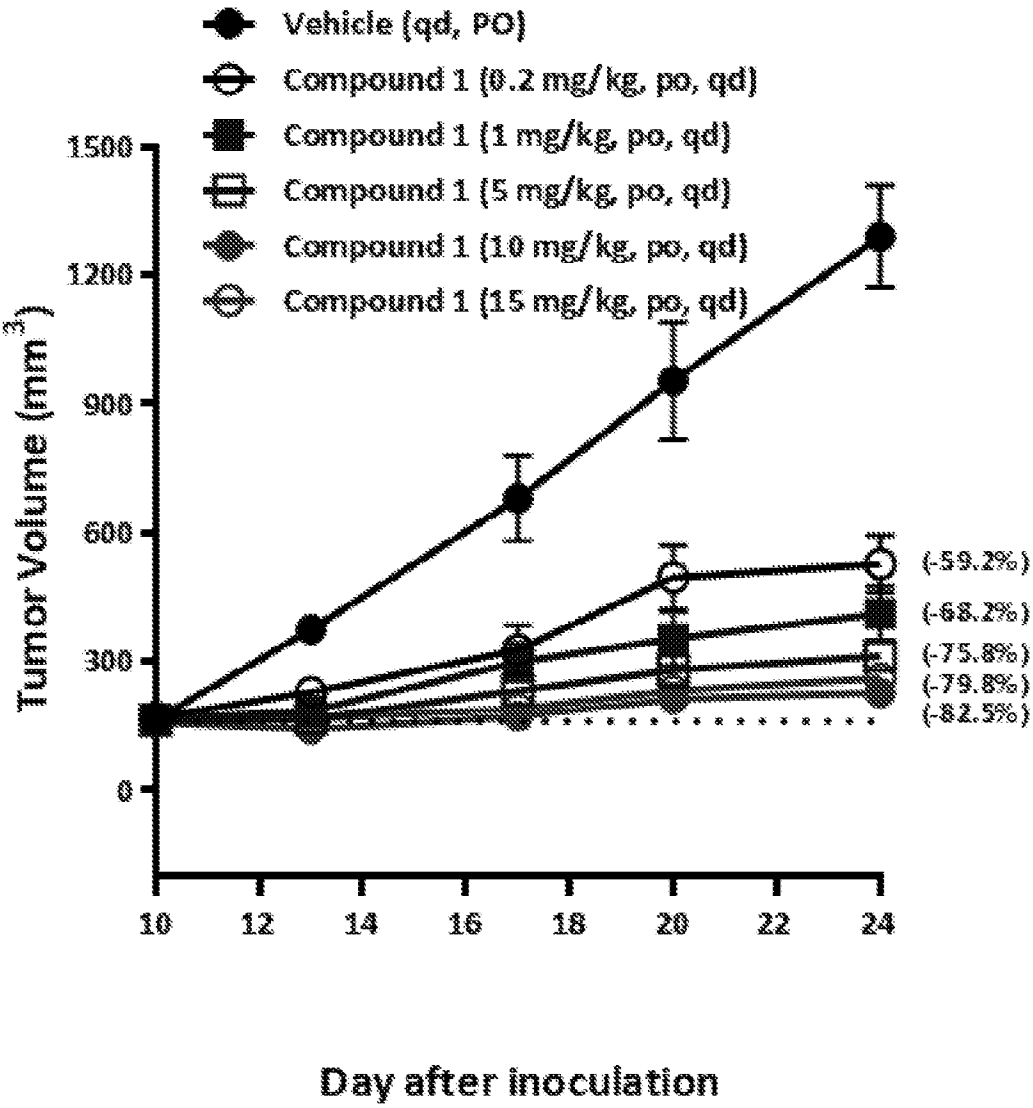

Vehicle (qd, PO)
Compound 1 (0.2 mg/kg, po, qd)
Compound 1 (1 mg/kg, po, qd)
Compound 1 (5 mg/kg, po, qd)
Compound 1 (10 mg/kg, po, qd)
Compound 1 (15 mg/kg, po, qd)
Tumor Volume (mm3)
1500
1200
900
600
300
0
10
12
14
16
18
20
22
24
(-59.2%)
(-68.2%)
(-75.8%)
(-79.8%)
(-82.5%)
Day after inoculation

FIG. 8

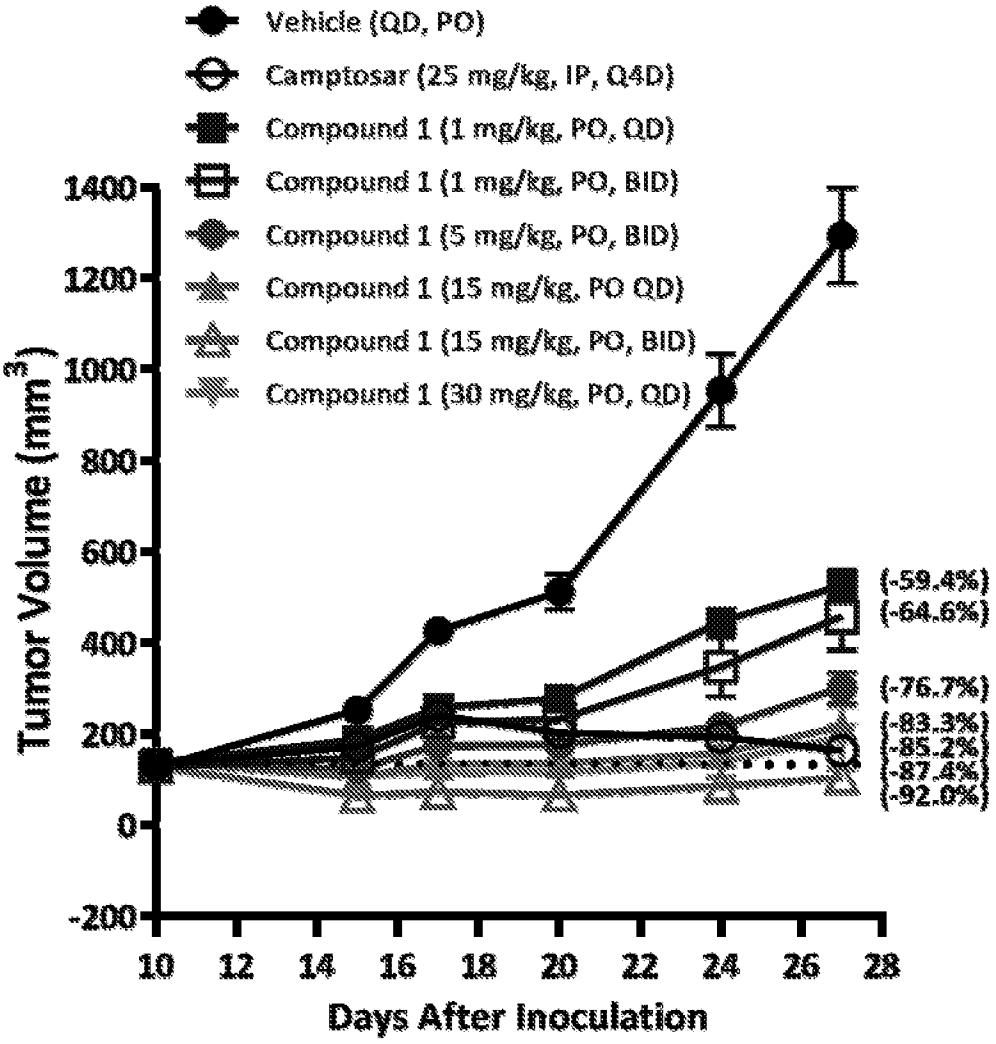

Vehicle (QD, PO)
Camptosar (25 mg/kg, IP, Q4D)
Compound 1 (1 mg/kg, PO, QD)
Compound 1 (1 mg/kg, PO, BID)
Compound 1 (5 mg/kg, PO, BID)
Compound 1 (15 mg/kg, PO QD)
Compound 1 (15 mg/kg, PO, BID)
Compound 1 (30 mg/kg, PO, QD)
Tumor Volume (mm3)
1400
1200
1000
800
600
400
200
0
-200
10
12
14
16
18
20
22
24
26
28
Days After Inoculation
(-59.4%)
(-64.6%)
(-76.7%)
(-83.3%)
(-85.2%)
(-87.4%)
(-92.0%)

FIG. 9

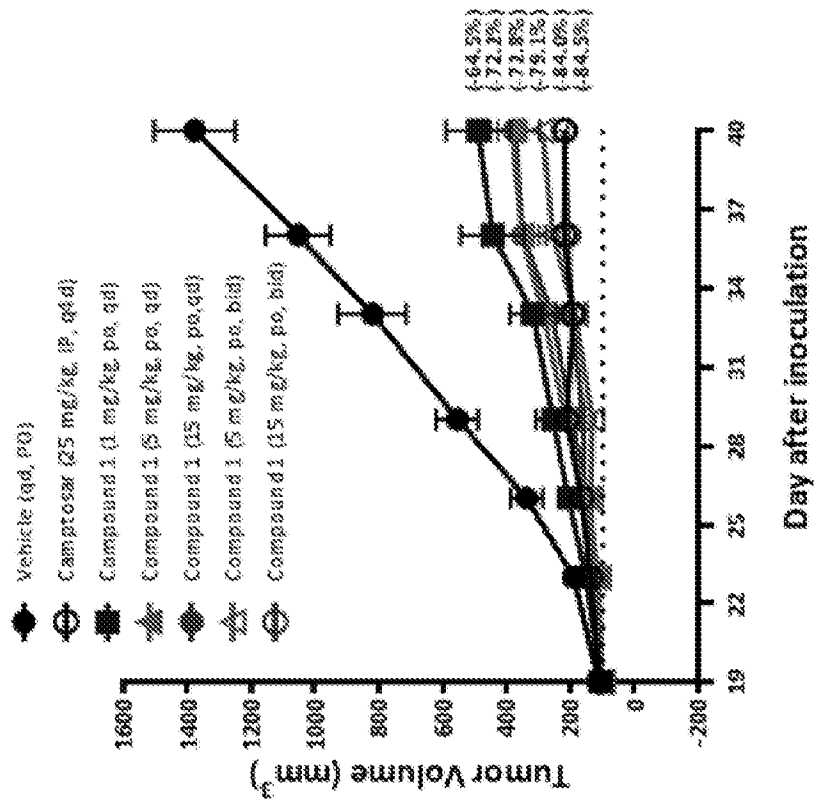


FIG. 10A

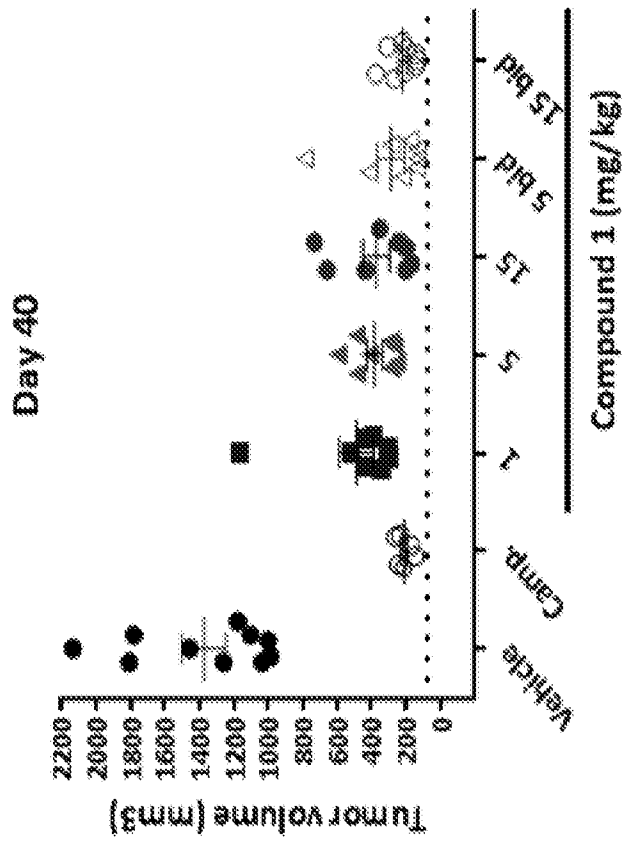


FIG. 10B

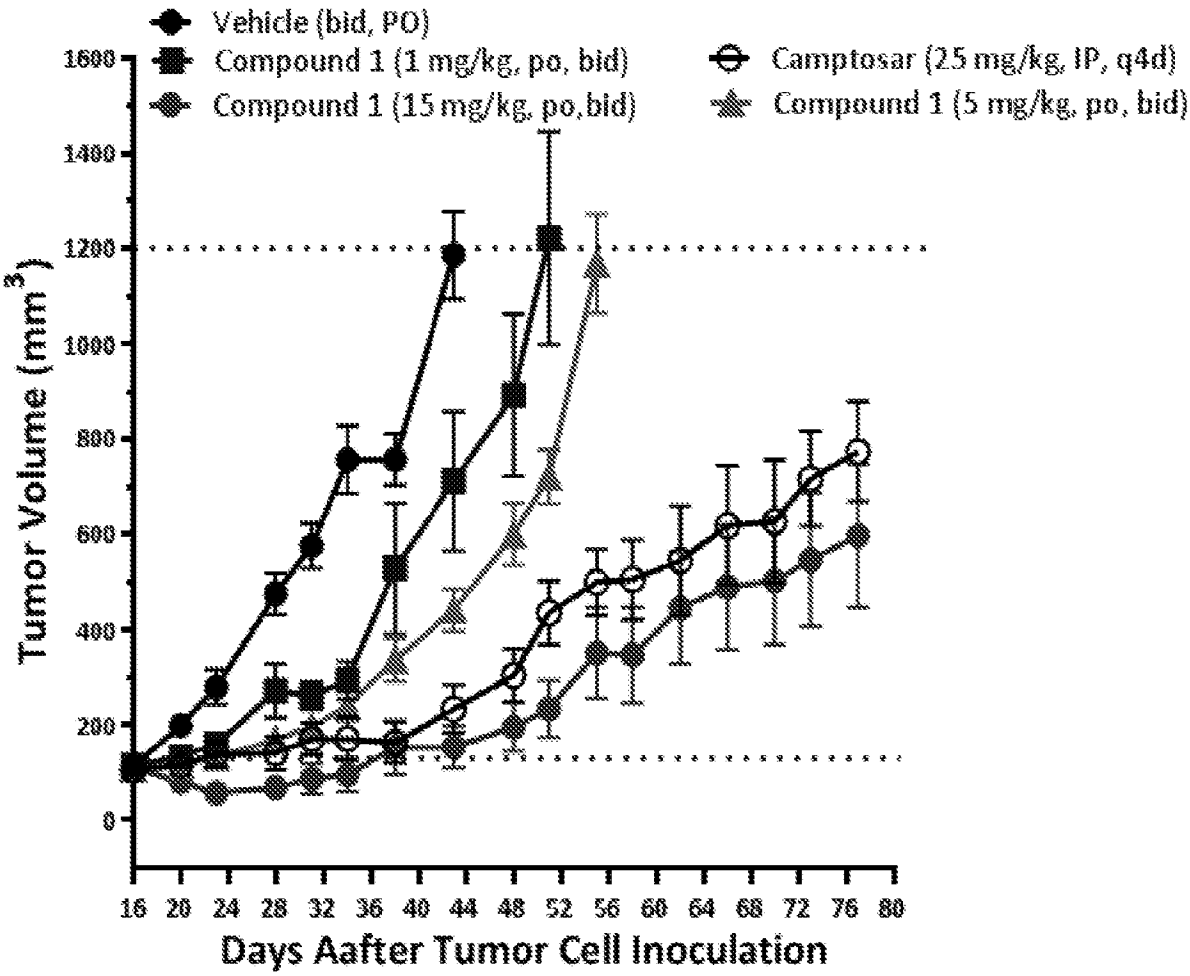

Vehicle (bid, PO)
Compound 1 (1 mg/kg, po, bid)
Compound 1 (15 mg/kg, po, bid)
Camptosar (25 mg/kg, IP, q4d)
Compound 1 (5 mg/kg, po, bid)
Tumor Volume (mm3)
1600
1400
1200
1000
800
600
400
200
0
16 20 24 28 32 36 40 44 48 52 56 60 64 68 72 76 80
Days Aafter Tumor Cell Inoculation

FIG.11

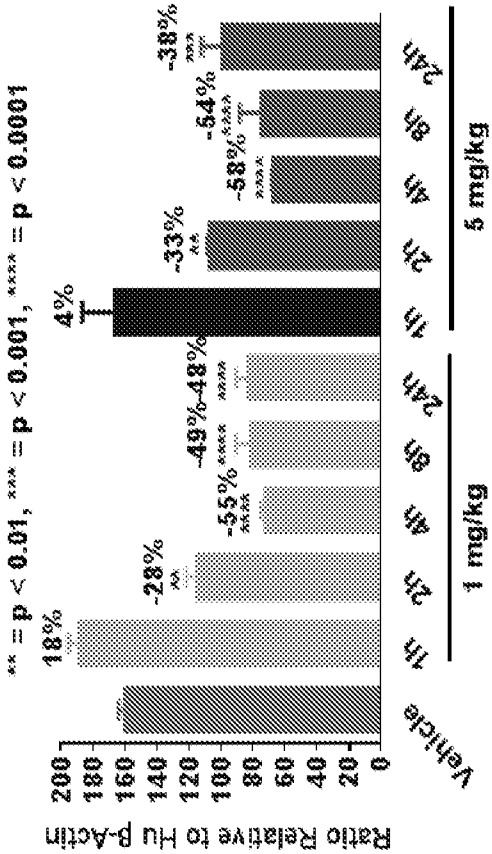


FIG. 12A

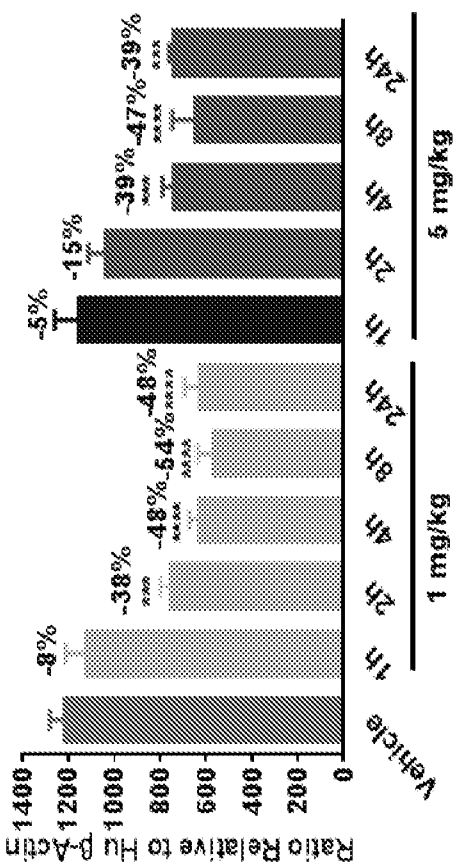


FIG. 12B

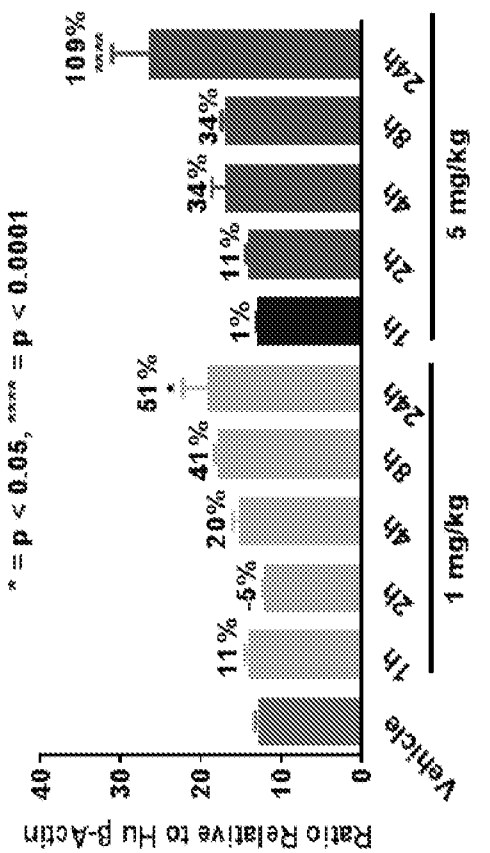


FIG. 12C

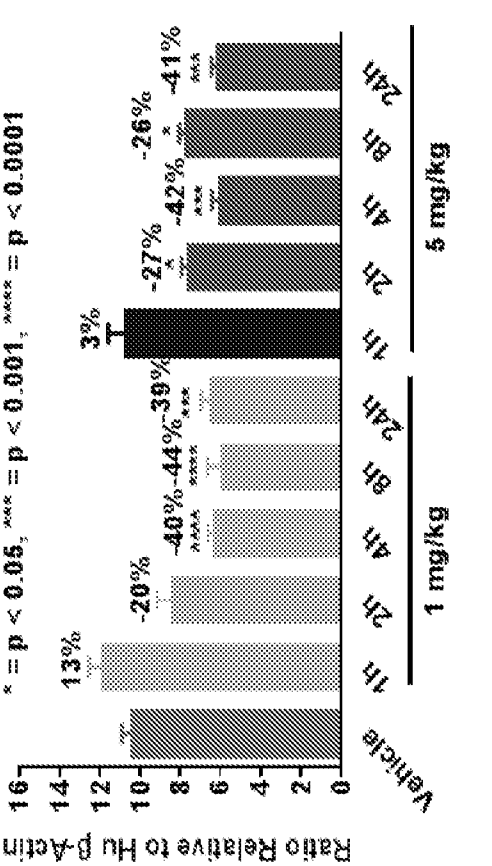


FIG. 12D

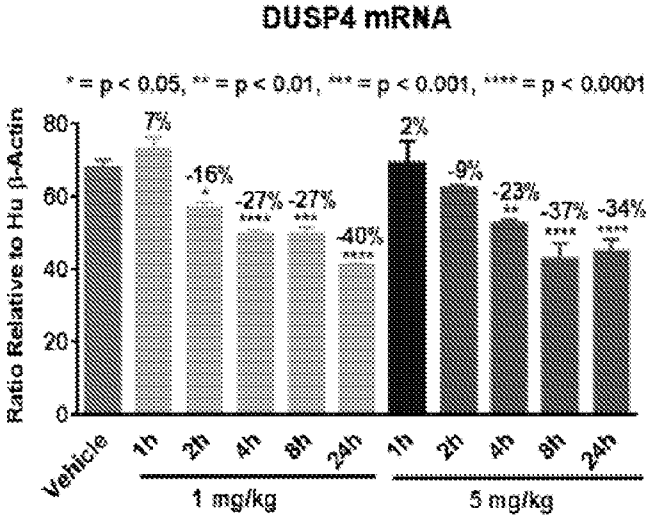


FIG. 13A

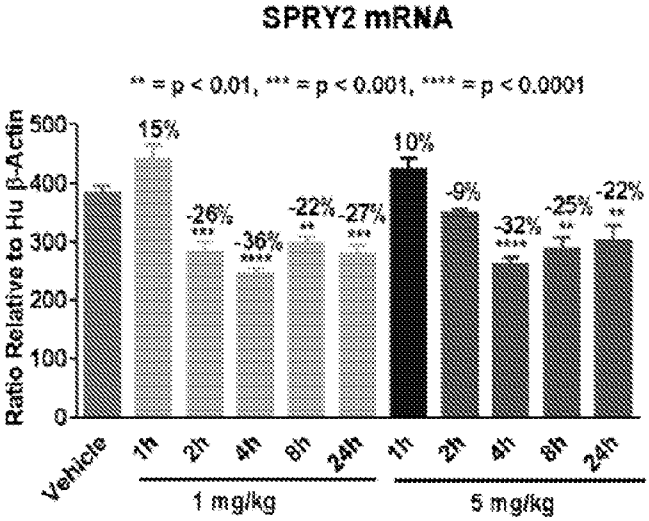


FIG. 13B

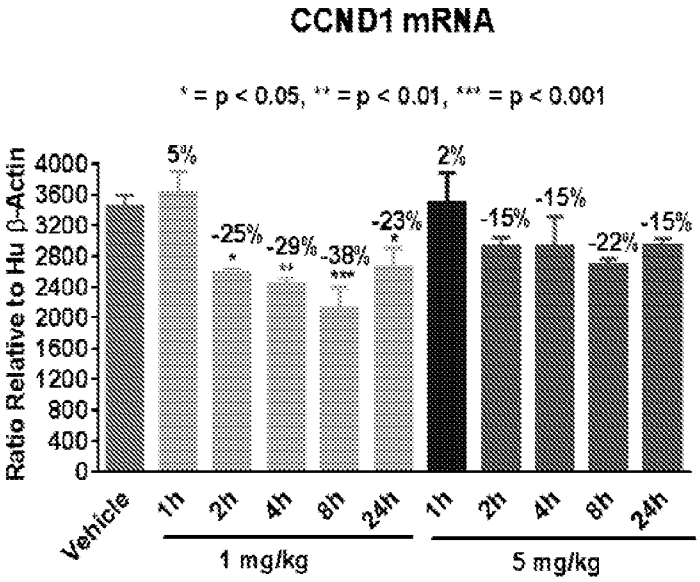


FIG. 13C

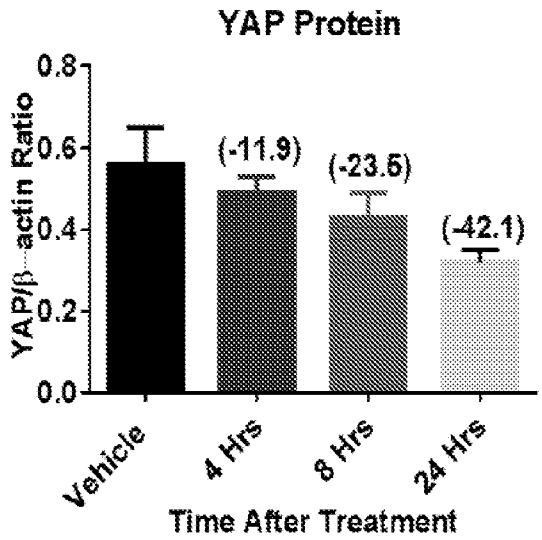


FIG. 13D

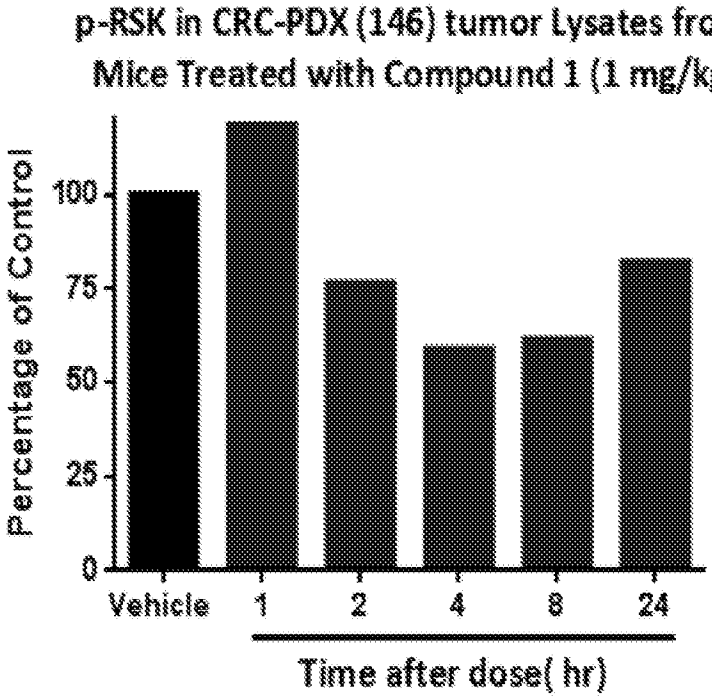


FIG. 14A

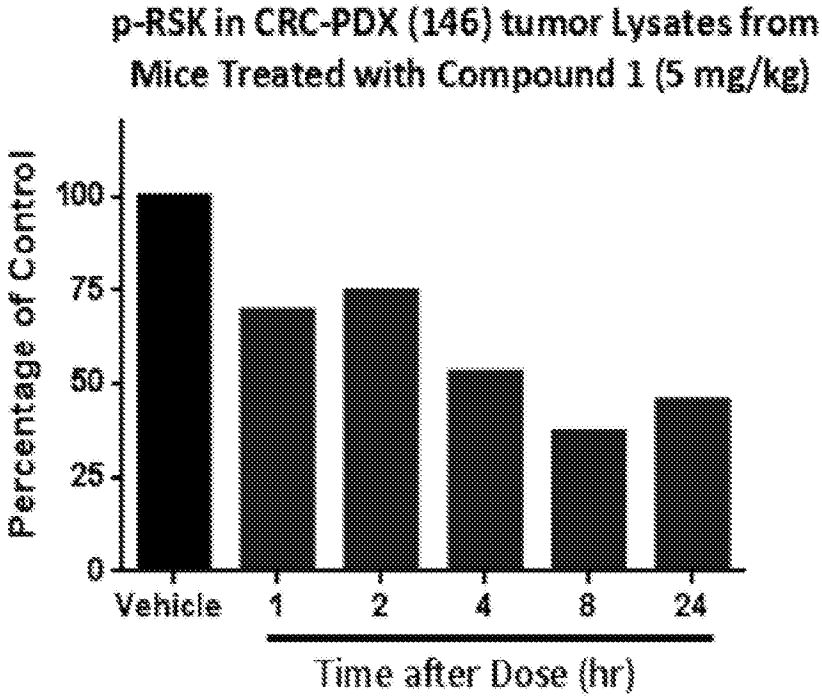


FIG. 14B

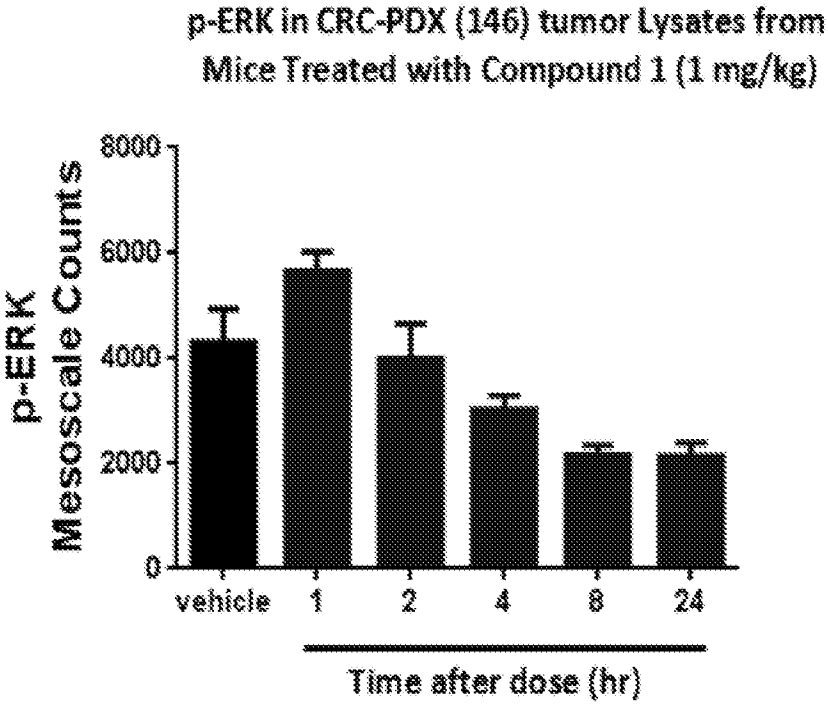


FIG. 14C

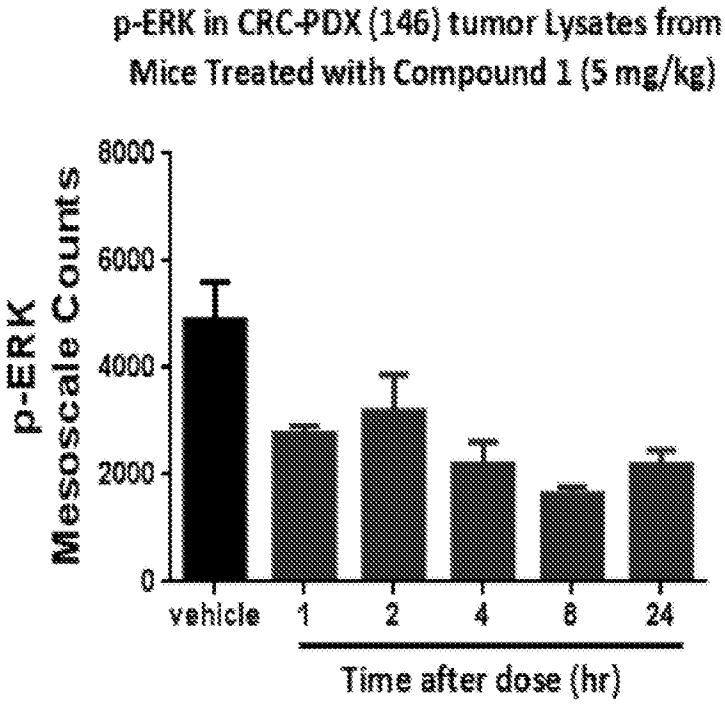


FIG. 14D

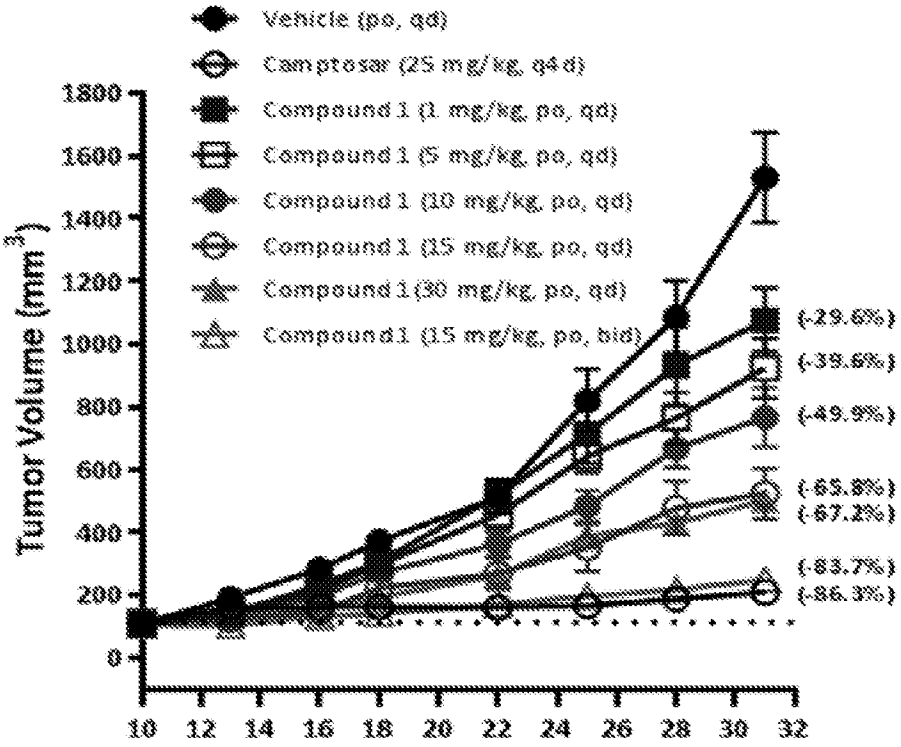


FIG. 15A

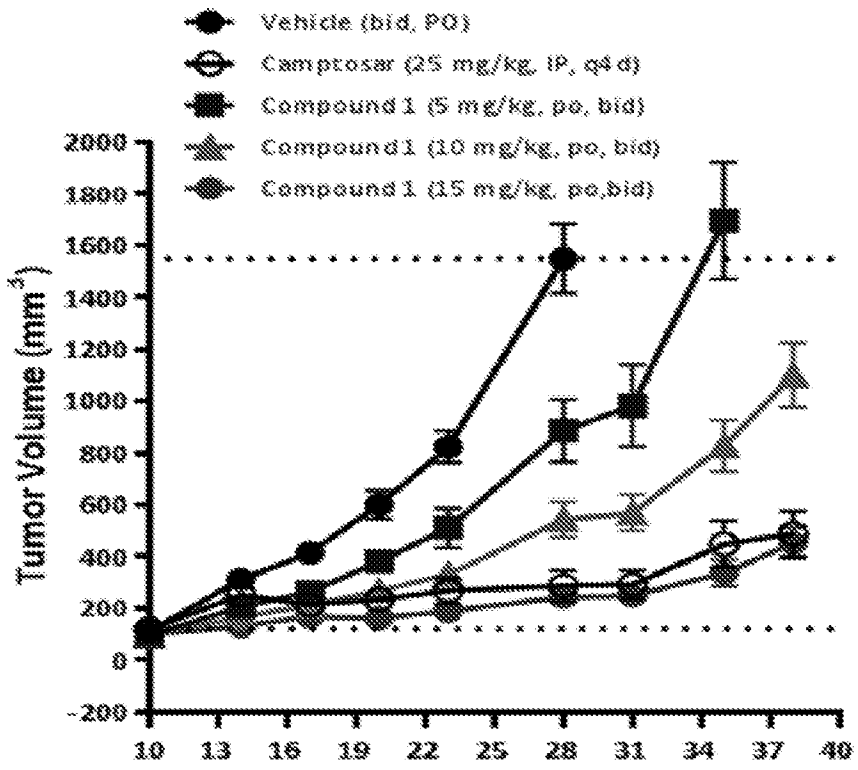


FIG. 15B

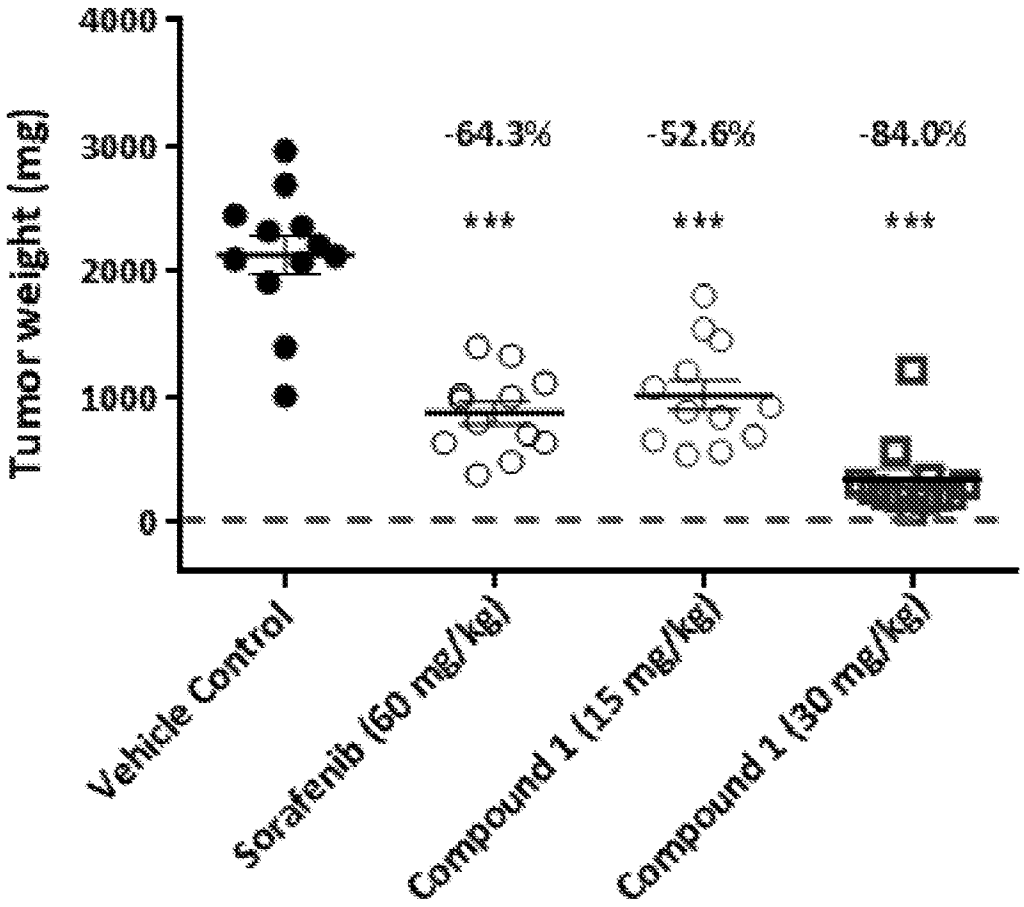

Tumor weight (mg)
4000
3000
2000
1000
0
-64.3%
-52.6%
-84.0%
***
***
***
Vehicle Control
Sorafenib (60 mg/kg)
Compound 1 (15 mg/kg)
Compound 1 (30 mg/kg)

FIG. 16

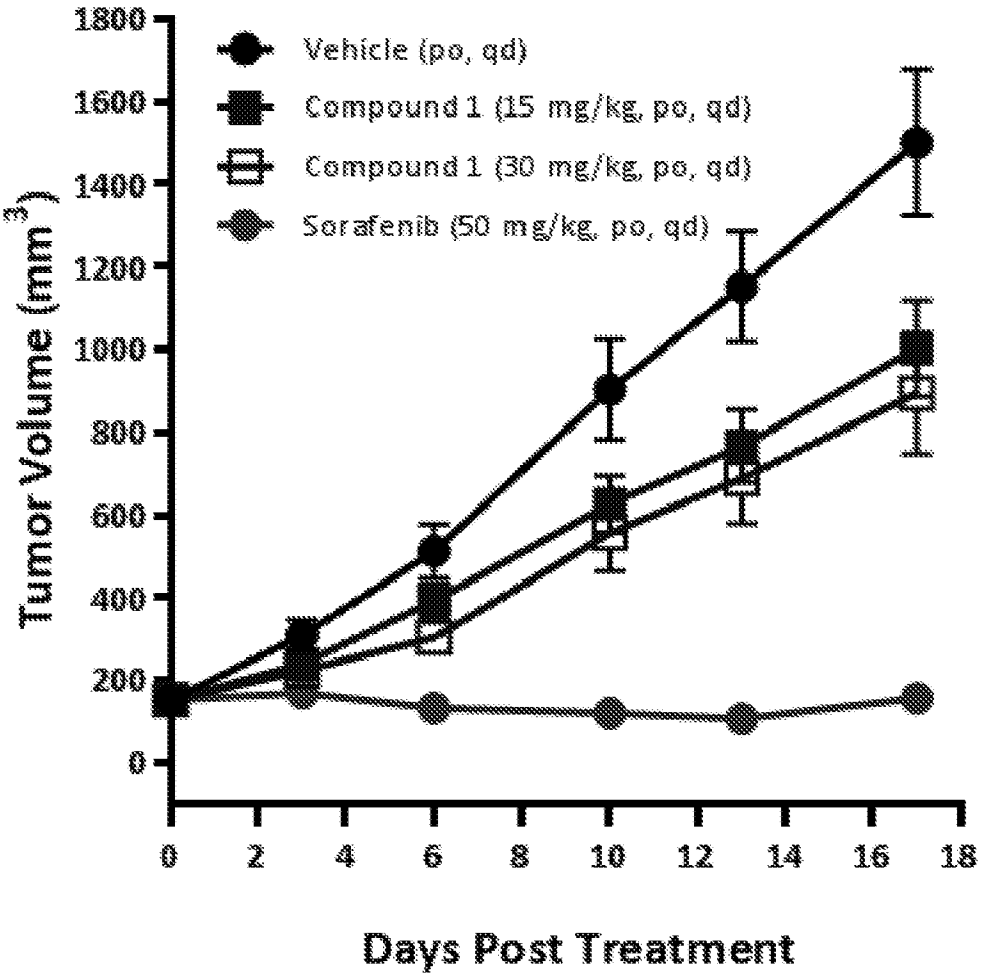

Vehicle (po, qd)
Compound 1 (15 mg/kg, po, qd)
Compound 1 (30 mg/kg, po, qd)
Sorafenib (50 mg/kg, po, qd)
Tumor Volume (mm3)
1800
1600
1400
1200
1000
800
600
400
200
0
0
2
4
6
8
10
12
14
16
18
Days Post Treatment

FIG. 17

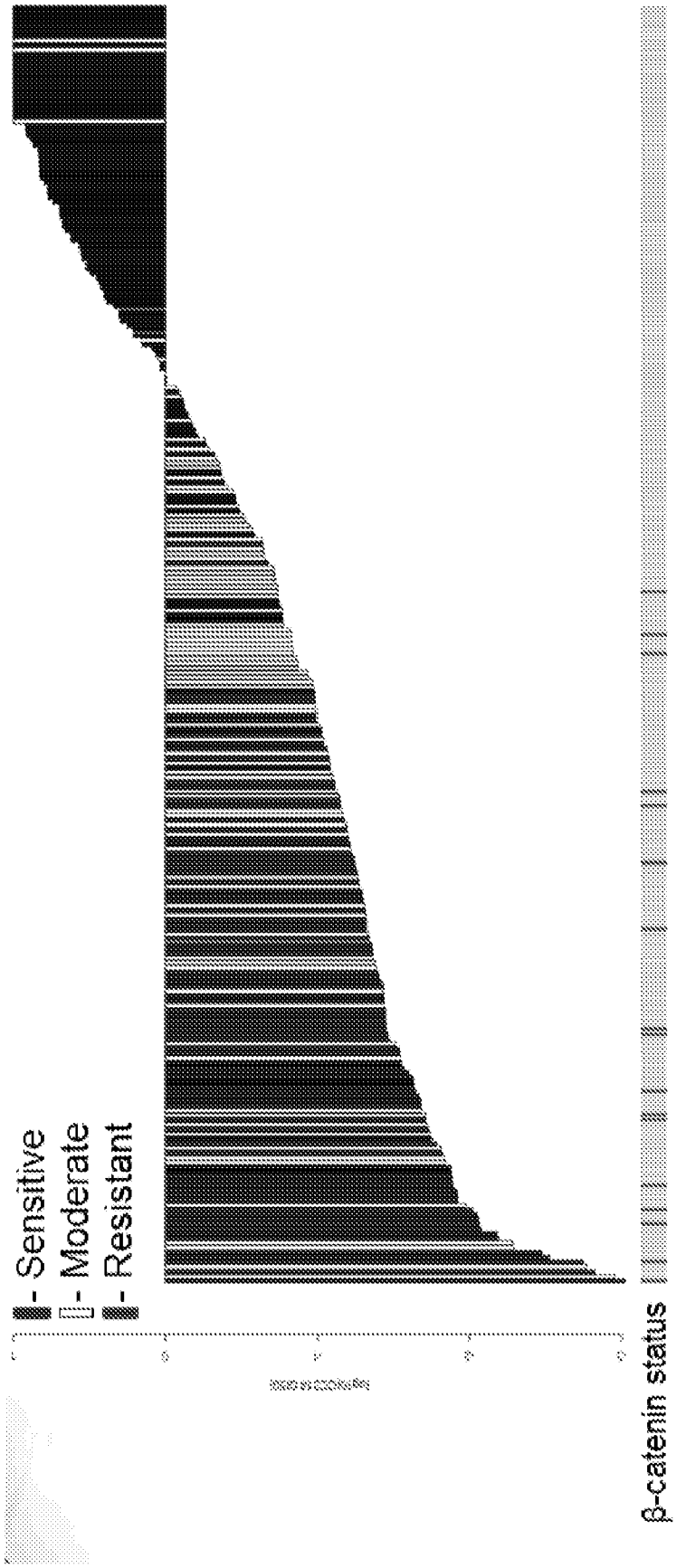

- Sensitive
- Moderate
- Resistant
β-catenin status
l = mutant
l =WT or unknown

FIG. 18

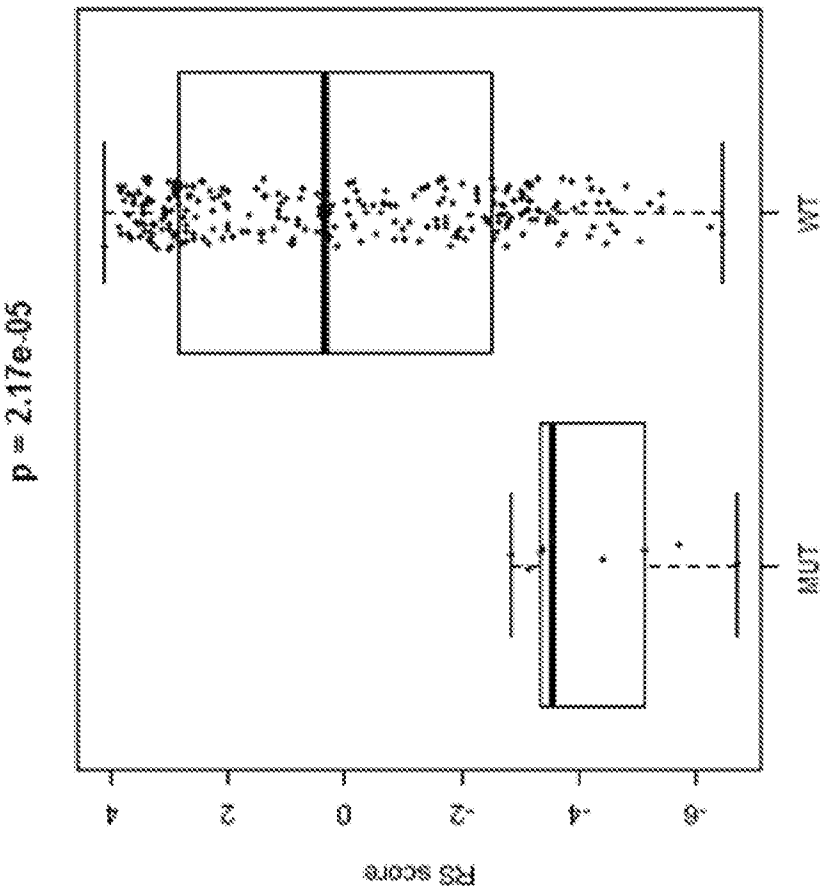


FIG. 19B

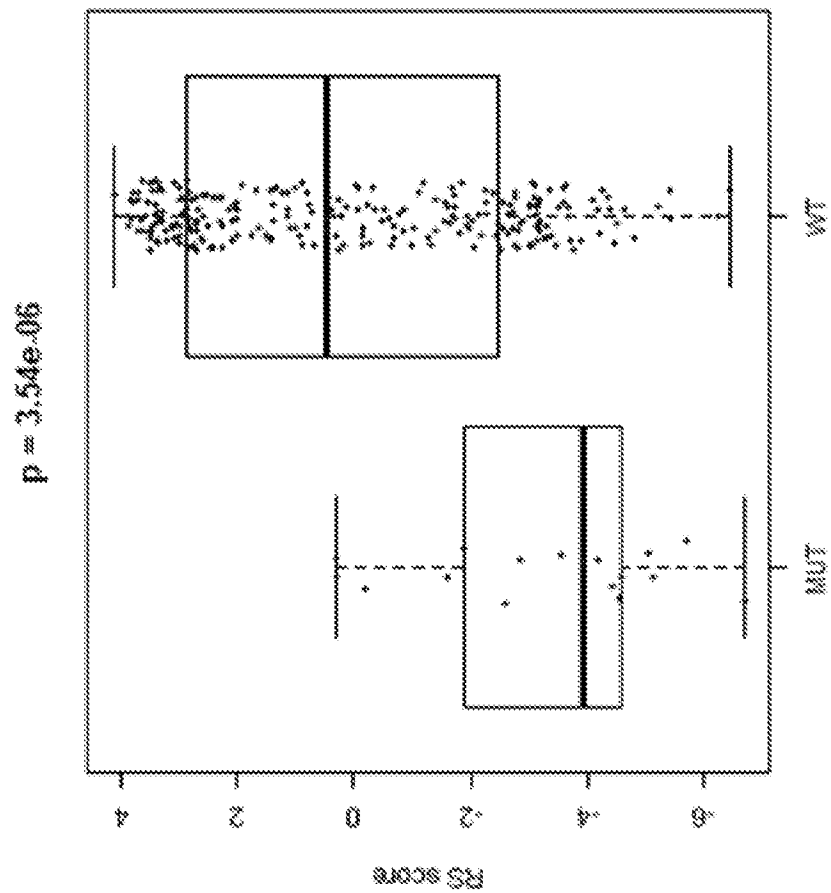


FIG. 19A

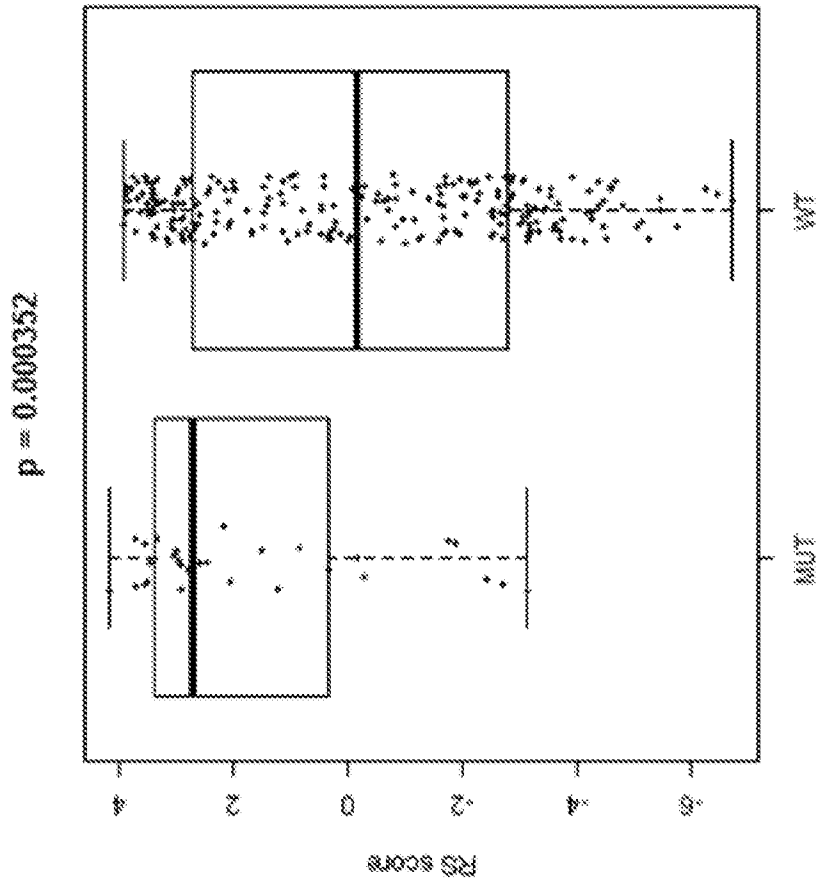


FIG. 19D

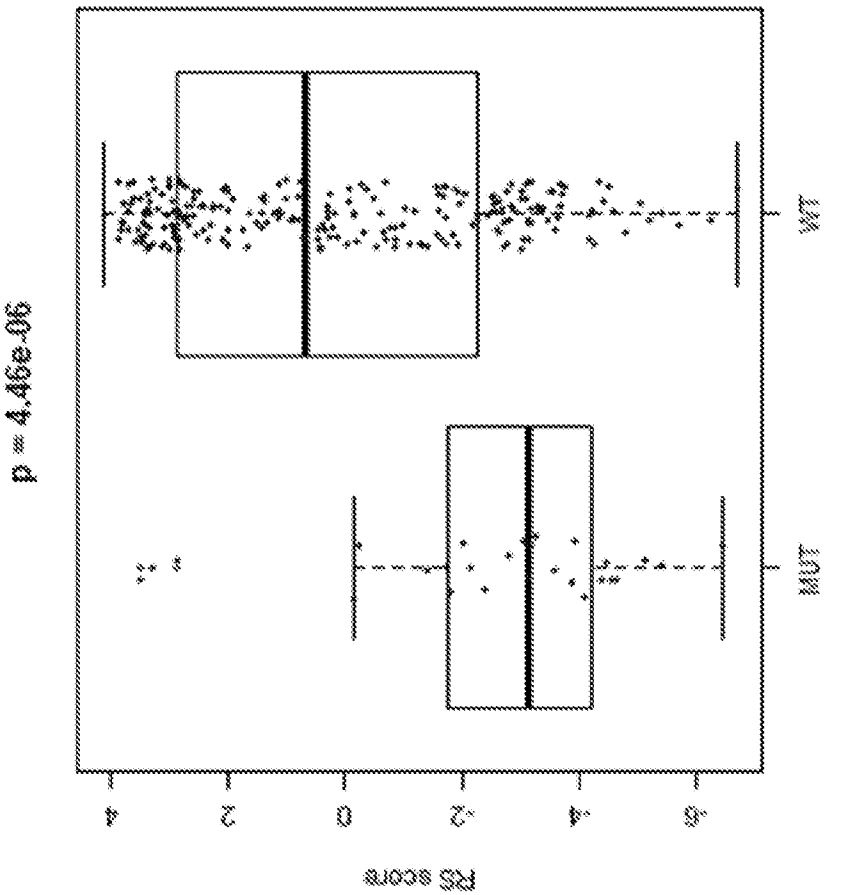


FIG. 19C

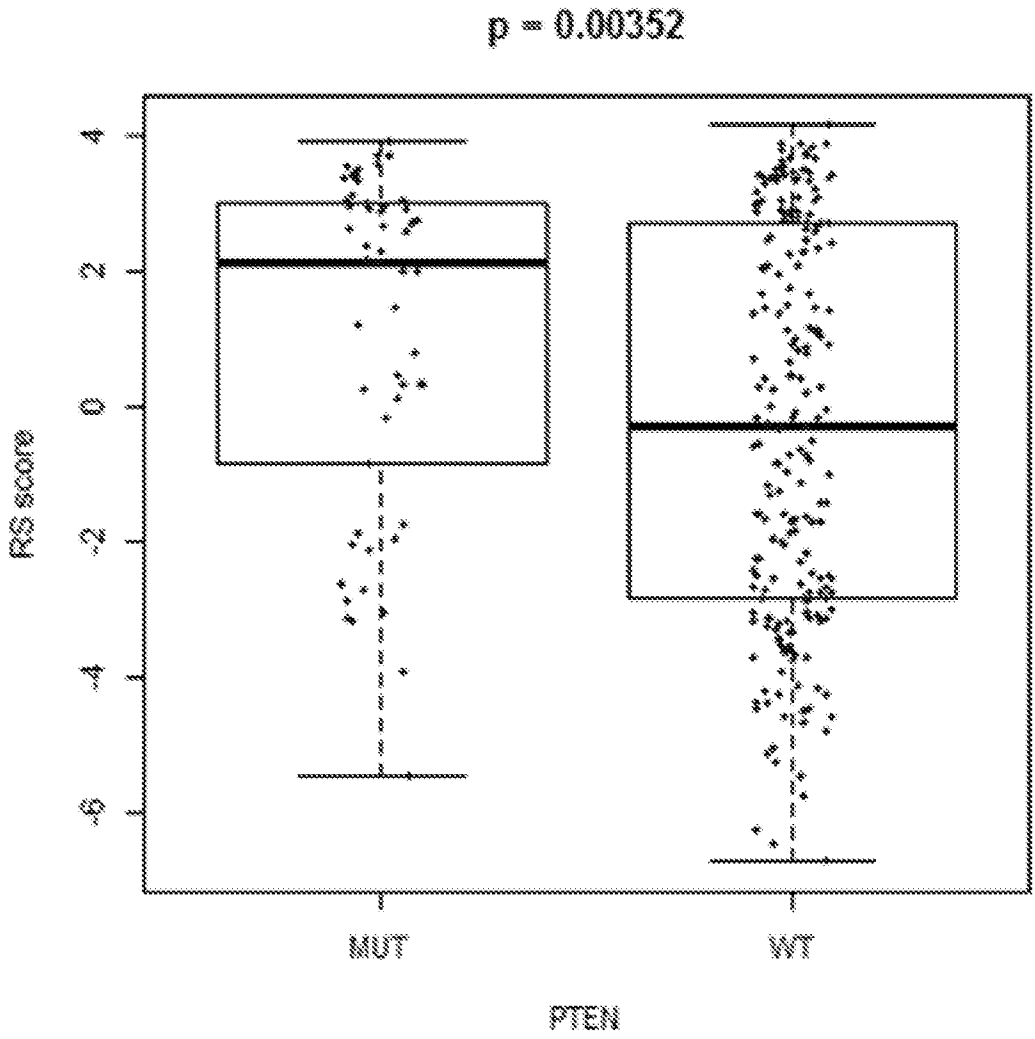


FIG. 19E

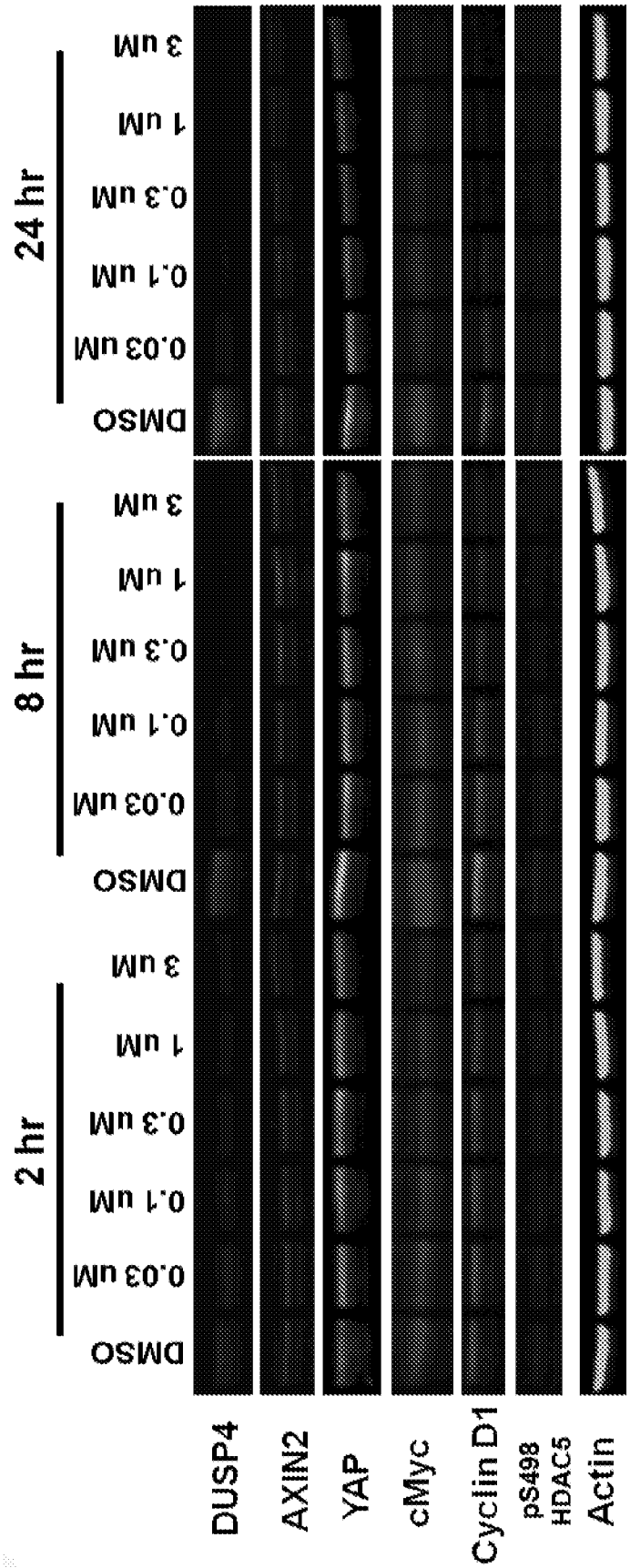

DUSP4
AXIN2
YAP
cMyc
Cyclin D1
pS498 HDAC5
Actin
2 hr
8 hr
24 hr
DMSO
0.03 uM
0.1 uM
0.3 uM
1 uM
3 uM

FIG. 20

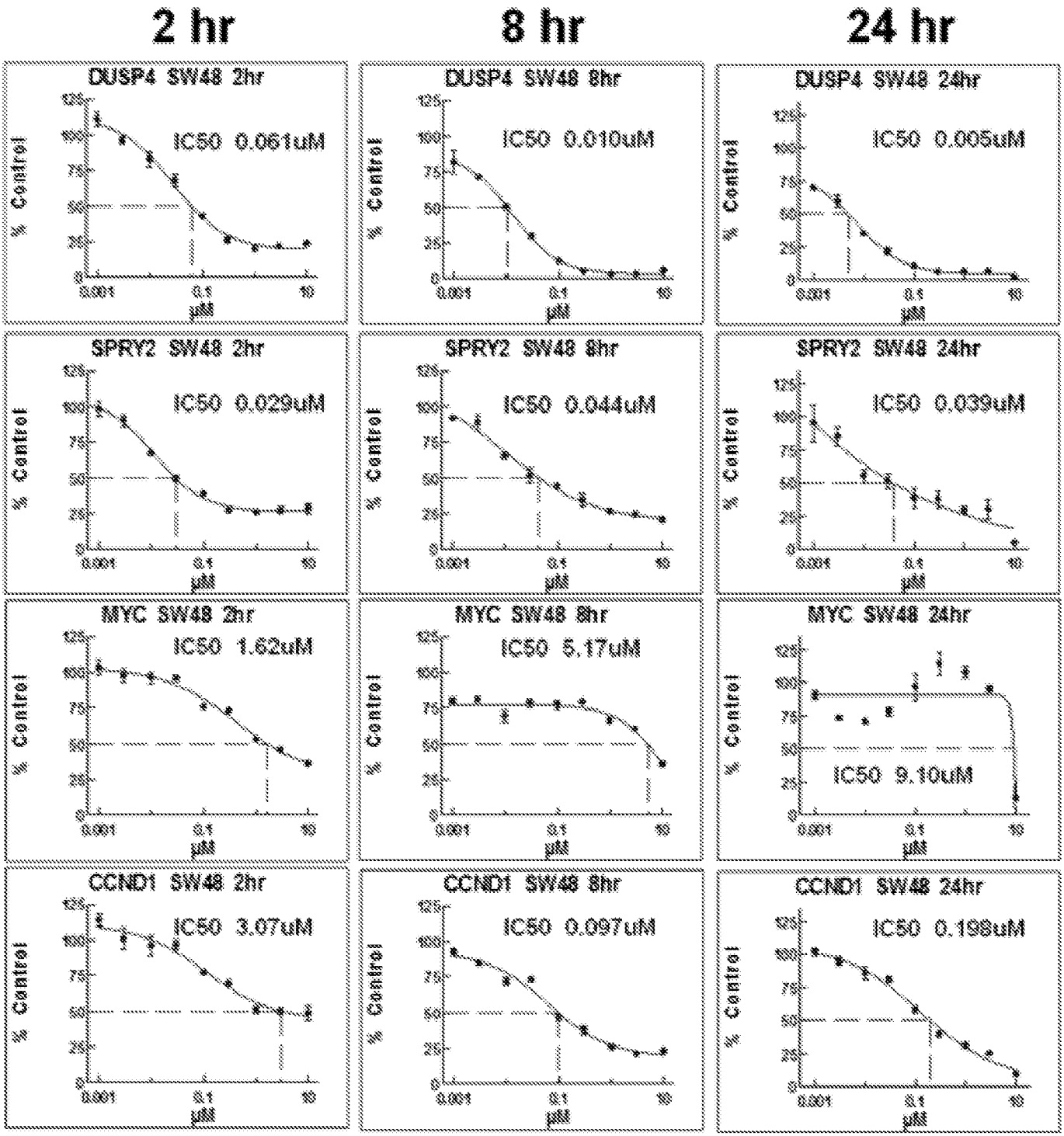

2 hr
8 hr
24 hr
DUSP4 SW48 2hr
IC50 0.061uM
DUSP4 SW48 8hr
IC50 0.010uM
DUSP4 SW48 24hr
IC50 0.005uM
SPRY2 SW48 2hr
IC50 0.029uM
SPRY2 SW48 8hr
IC50 0.044uM
SPRY2 SW48 24hr
IC50 0.039uM
MYC SW48 2hr
IC50 1.62uM
MYC SW48 8hr
IC50 5.17uM
MYC SW48 24hr
IC50 9.10uM
CCND1 SW48 2hr
IC50 3.07uM
CCND1 SW48 8hr
IC50 0.097uM
CCND1 SW48 24hr
IC50 0.198uM
% Control
μM

FIG. 21A

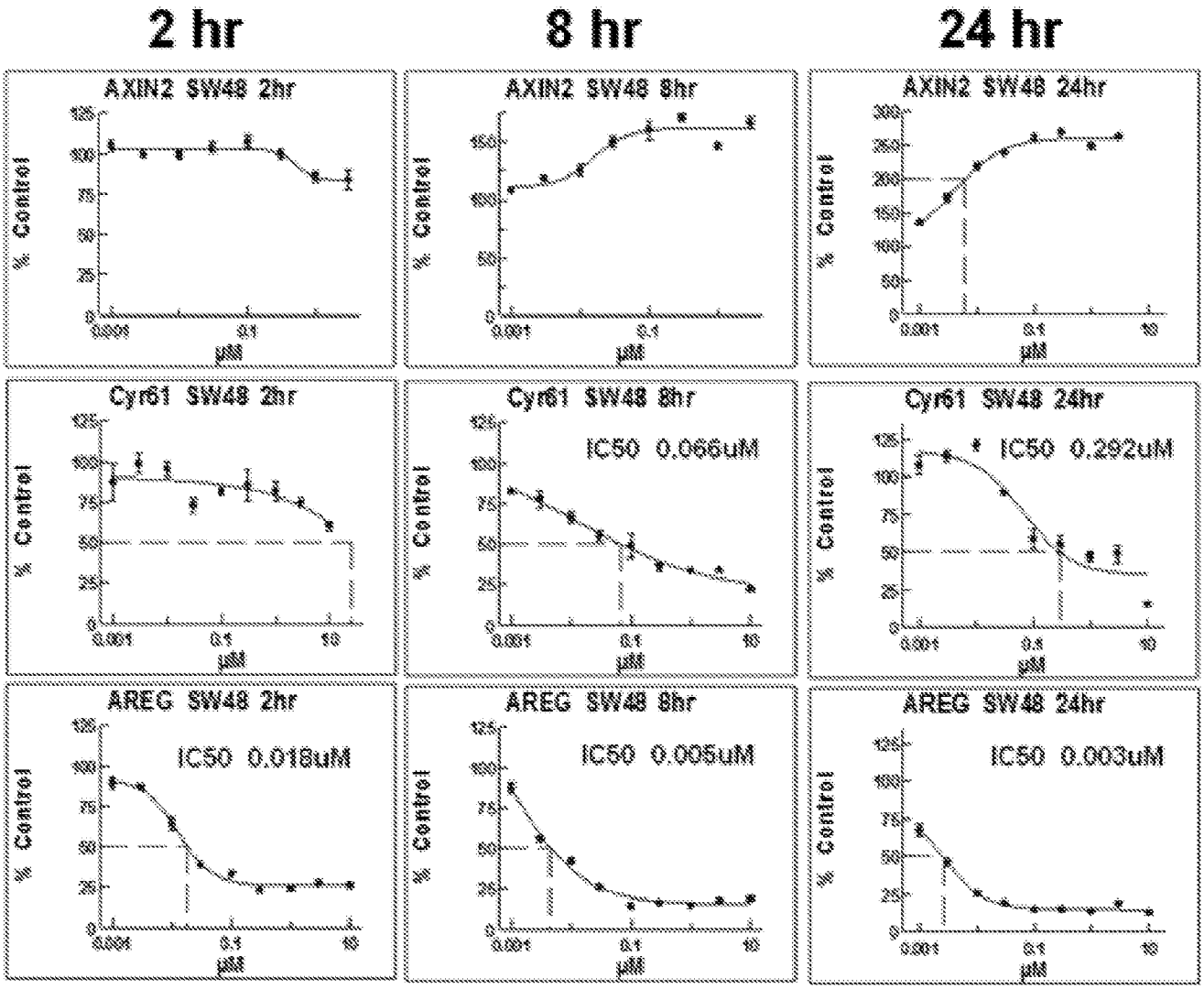
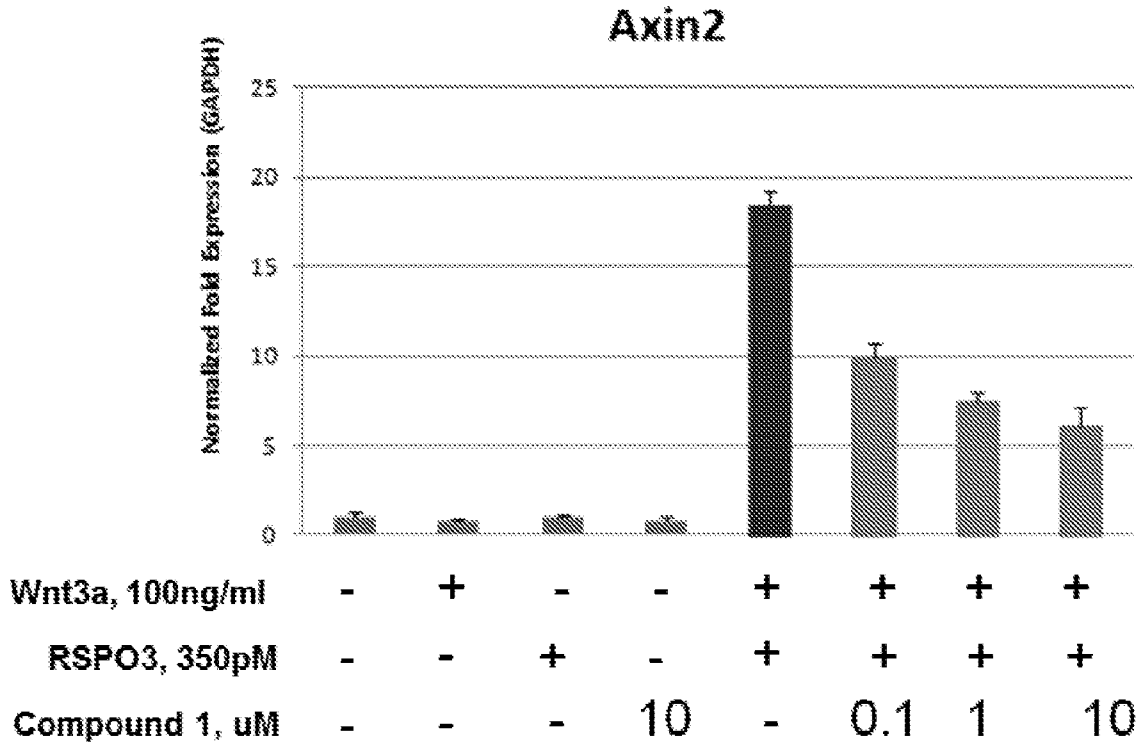

2 hr
8 hr
24 hr
AXIN2 SW48 2hr
AXIN2 SW48 8hr
AXIN2 SW48 24hr
Cyr61 SW48 2hr
Cyr61 SW48 8hr
IC50 0.066uM
Cyr61 SW48 24hr
IC50 0.292uM
AREG SW48 2hr
IC50 0.018uM
AREG SW48 8hr
IC50 0.005uM
AREG SW48 24hr
IC50 0.003uM
% Control
μM

FIG. 21B



Human Bronchial Epithelial cell gene expression at 24hrs

FIG. 22

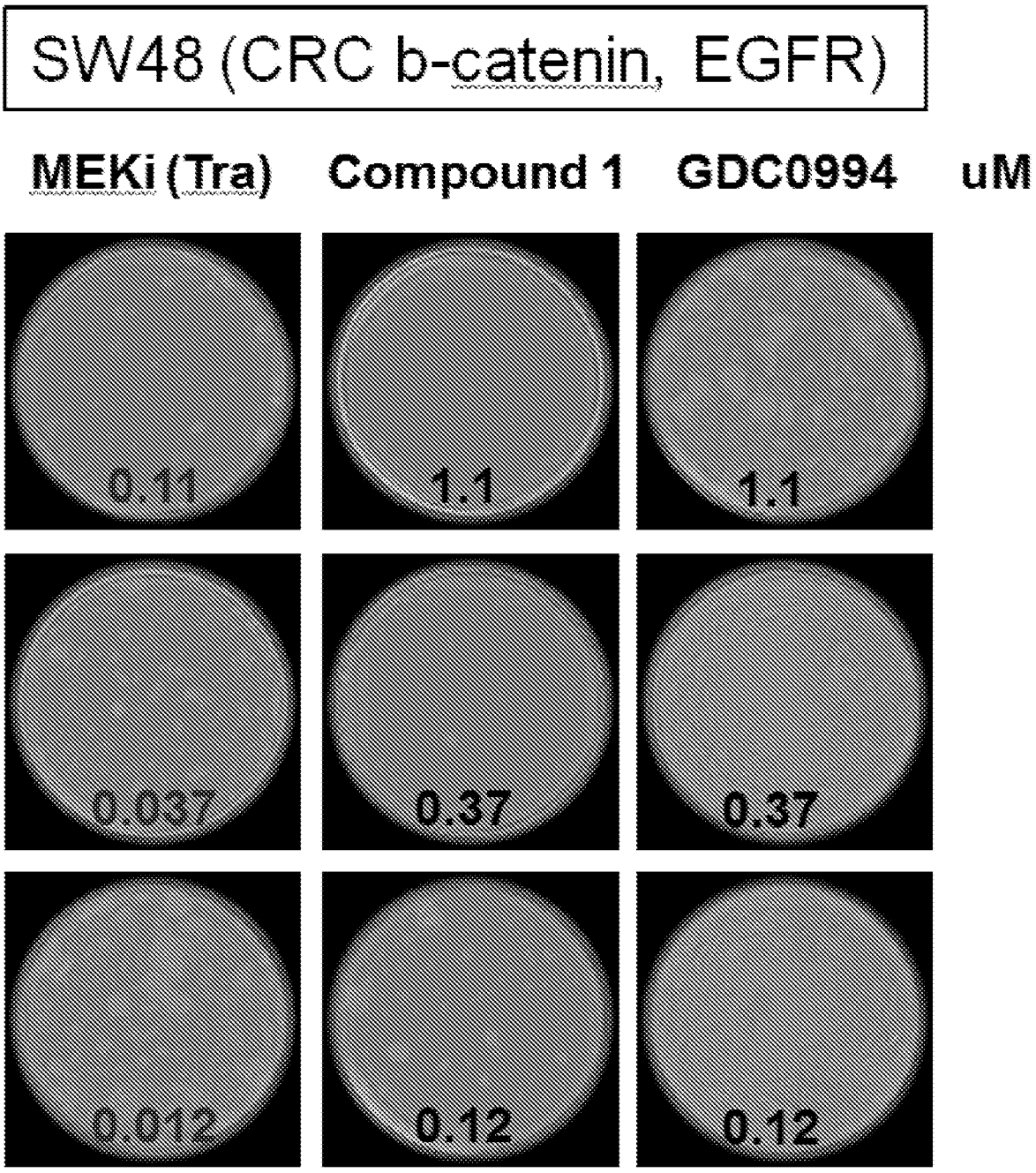

SW48 (CRC b-catenin, EGFR)
MEKi (Tra)
Compound 1
GDC0994
uM
0.11
1.1
1.1
0.037
0.37
0.37
0.012
0.12
0.12

FIG. 23A

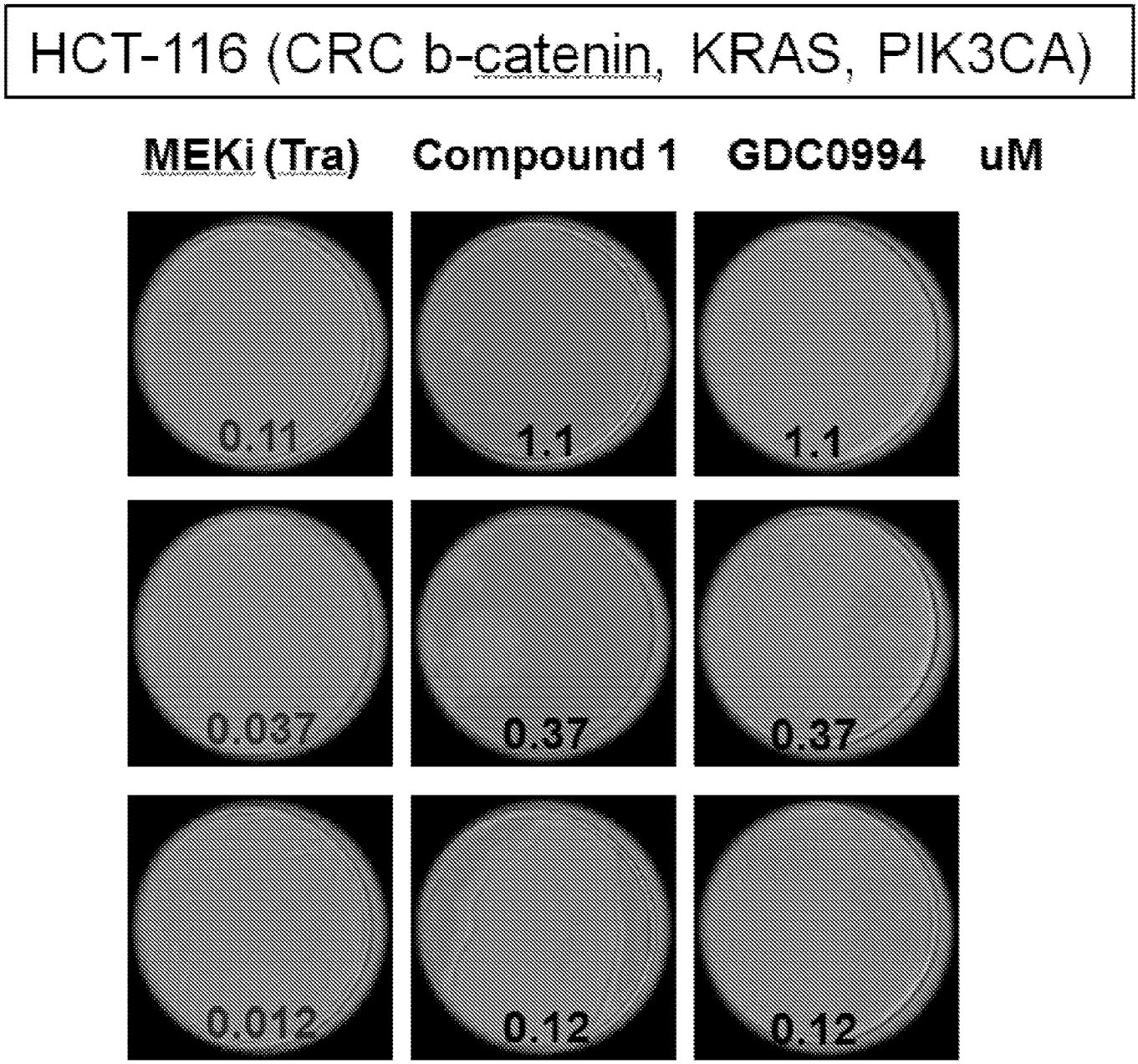

HCT-116 (CRC b-catenin, KRAS, PIK3CA)
MEKi (Tra)
Compound 1
GDC0994
uM
0.11
1.1
1.1
0.037
0.37
0.37
0.012
0.12
0.12

FIG. 23B

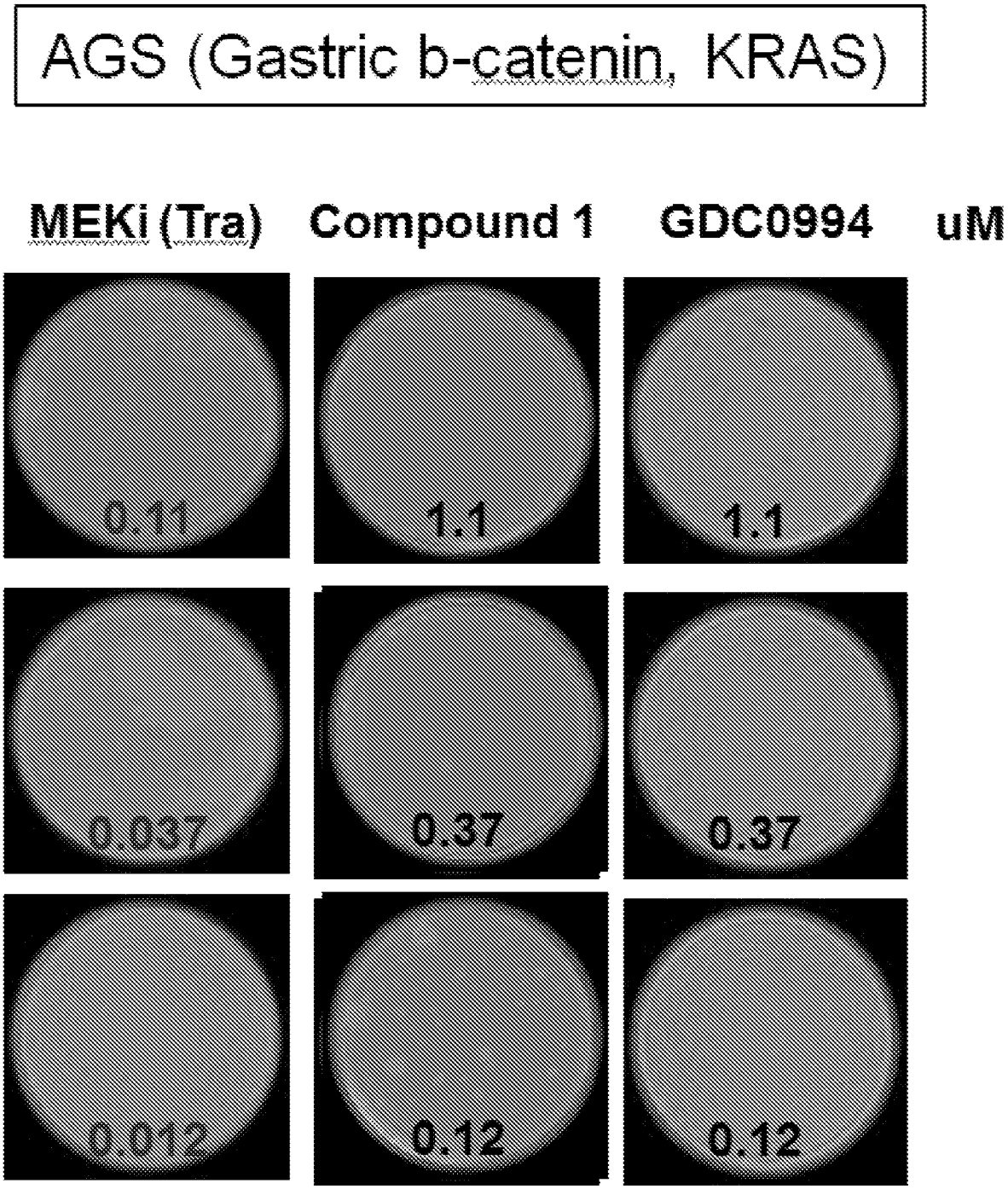

AGS (Gastric b-catenin, KRAS)
MEKi (Tra)
Compound 1
GDC0994
uM
0.11
1.1
1.1
0.037
0.37
0.37
0.012
0.12
0.12

FIG. 23C

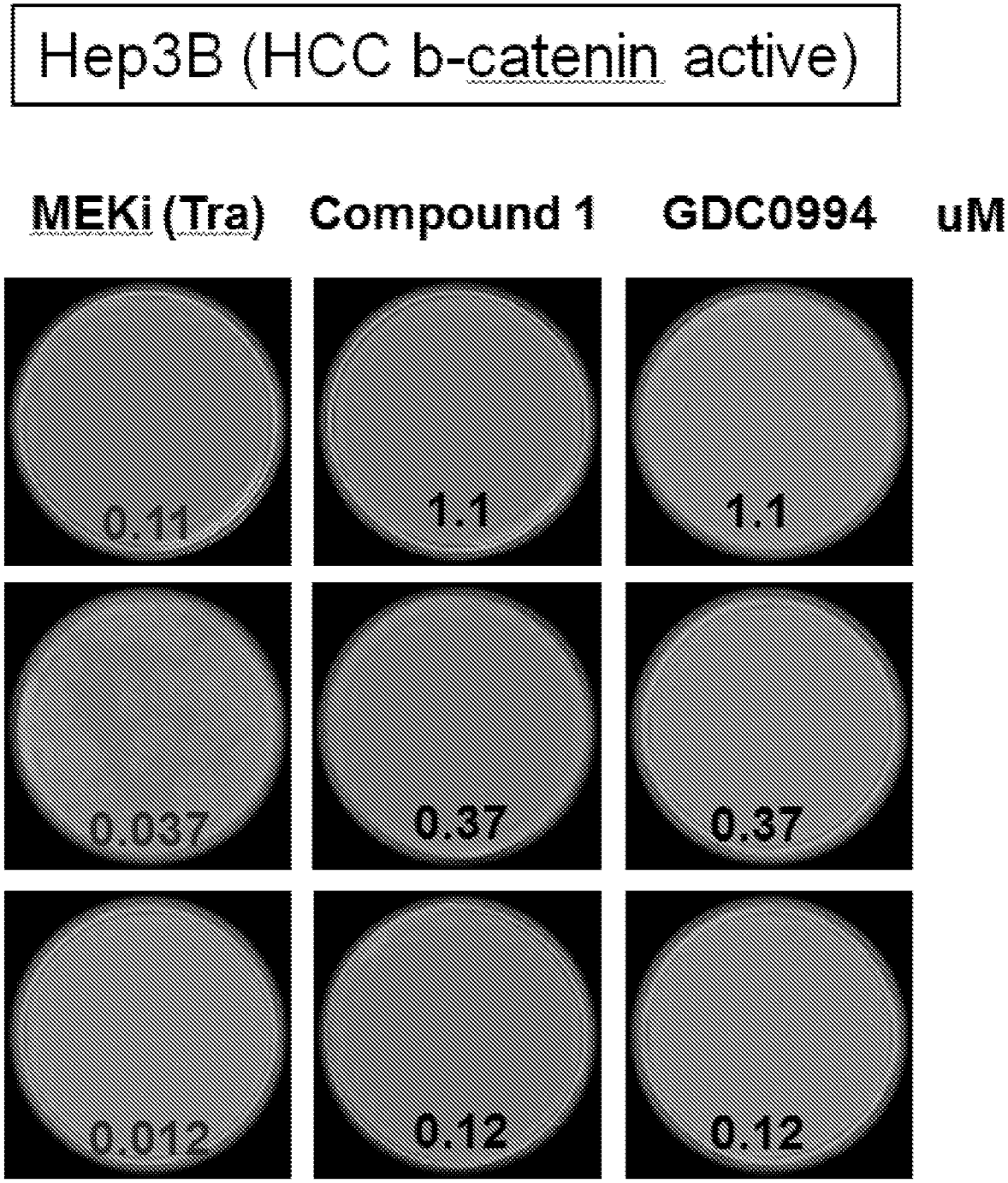

Hep3B (HCC b-catenin active)
MEKi (Tra)
Compound 1
GDC0994
uM
0.11
1.1
1.1
0.037
0.37
0.37
0.012
0.12
0.12

FIG. 23D

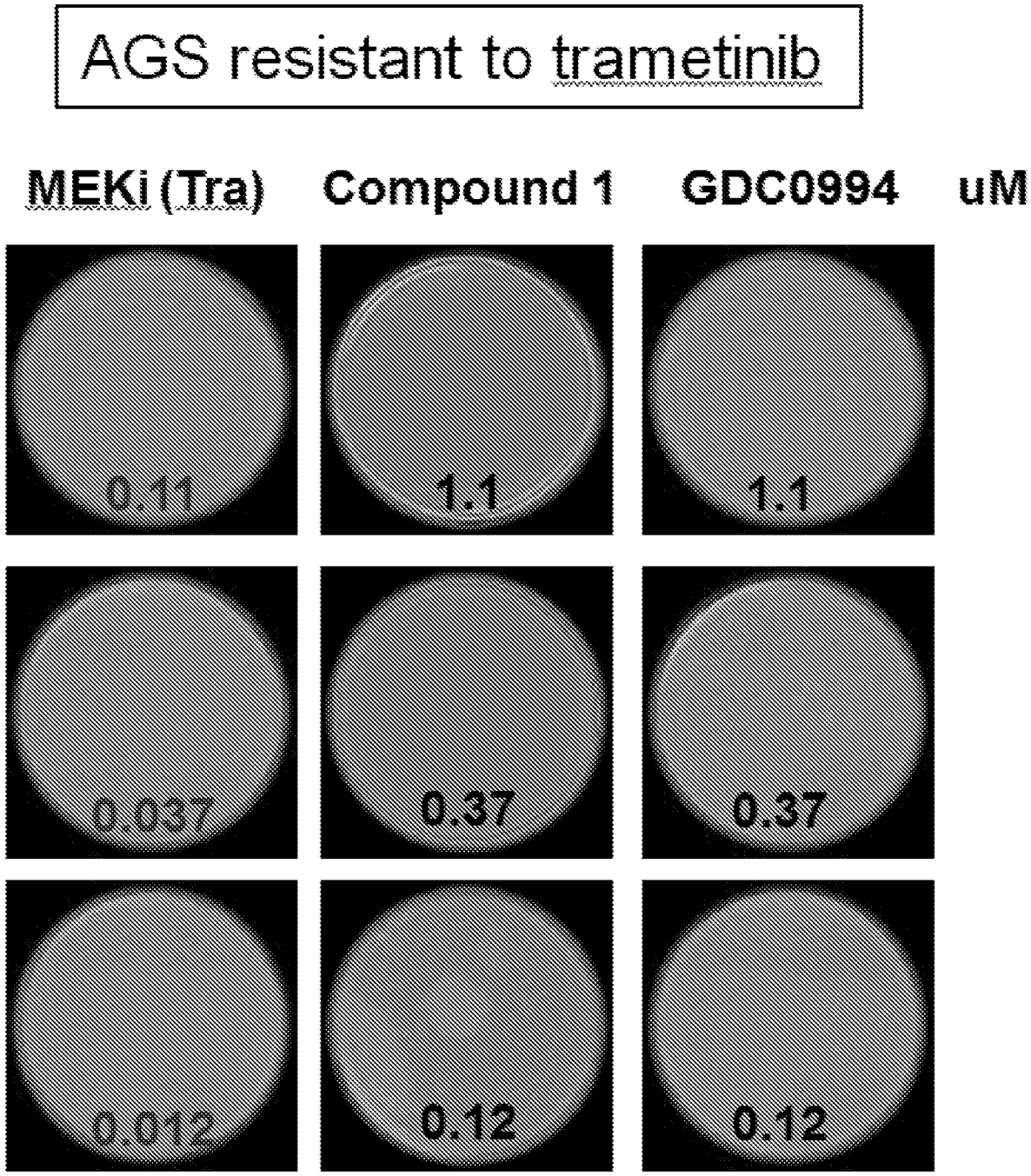

AGS resistant to trametinib
MEKi (Tra)
Compound 1
GDC0994
uM
0.11
1.1
1.1
0.037
0.37
0.37
0.012
0.12
0.12

FIG. 24

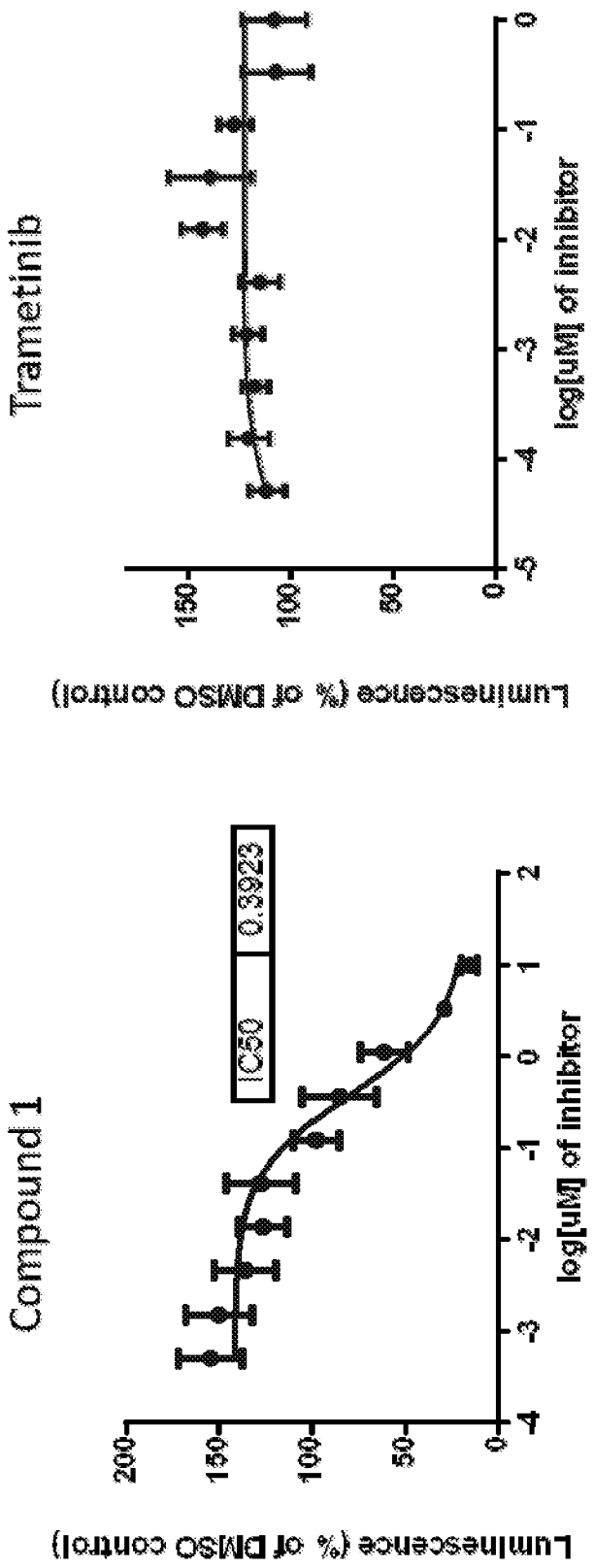

Trametinib
Luminescence (% of DMSO control)
150
100
50
0
-5
-4
-3
-2
-1
0
log[uM] of inhibitor
Compound 1
IC50
0.3923
Luminescence (% of DMSO control)
200
150
100
50
0
-4
-3
-2
-1
0
1
2
log[uM] of inhibitor

FIG. 25