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Eduardo [AR/US]; 804 North Delaware St., San Mateo, CA 94401 (US). **SINDAC, Janice, A.** [US/US]; 7853 Bacadri Drive, San Diego, CA 92126 (US).

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(74) Agents: **INSOGNA, Anthony, M.** et al.; Jones Day, 222 East 41st Street, New York, NY 10017-6702 (US).

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(71) Applicant (for all designated States except US): **AMBIT BIOSCIENCES CORPORATION** [US/US]; 4215 Sorrento Valley Boulevard, San Diego, CA 92121 (US).

(72) Inventors; and

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(75) Inventors/Applicants (for US only): **ABRAHAM, Sunny** [IN/US]; 4215 Sorrento Valley Blvd., San Diego, CA 92121 (US). **BHAGWAT, Shripad, S.** [US/US]; 5015 Ashley Falls Court, San Diego, CA 92130 (US). **HADD, Michael, J.** [US/US]; 4215 Sorrento Valley Blvd., San Diego, CA 92121 (US). **HOLLADAY, Mark, W.** [US/US]; 4215 Sorrento Valley Blvd., San Diego, CA 92121 (US). **LIU, Gang** [US/US]; 4215 Sorrento Valley Blvd., San Diego, CA 92121 (US). **MILANOV, Zdravko, V.** [BG/US]; 3962 Hamilton Street, #25, San Diego, CA 92104 (US). **PATEL, Hitesh, K.** [US/US]; 334 Playa Blanca, Encinitas, CA 92024 (US). **SETTI,**

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(54) Title: AURORA KINASE COMPOUNDS AND METHODS OF THEIR USE

(57) Abstract: Provided herein are pyrrolotriazine compounds for treatment of Aurora kinase mediated diseases. Also provided are pharmaceutical compositions comprising the compounds and methods of using the compounds and compositions.



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AURORA KINASE COMPOUNDS AND METHODS OF THEIR USE

RELATED APPLICATIONS

[0001] This application claims priority to U.S. provisional application no. 61/294,413 filed January 12, 2010, which is incorporated in its entirety by reference.

FIELD

[0002] Provided herein are compounds that are modulators of Aurora kinases, compositions comprising the compounds and methods of use thereof. The compounds provided are useful in the treatment, prevention, and/or amelioration of a disease or disorder related to Aurora kinase activity or one or more symptoms associated with such diseases or disorders. Pharmaceutical compositions comprising the compounds and methods of treating cancer are also provided.

BACKGROUND

[0003] Members of the Aurora-kinase family are key mitiotic regulators required for genome stability. Furthermore, the Aurora kinases have been reported to be over-expressed in a wide range of human tumors. Elevated expression of Aurora-A and Aurora-B has been detected in cancers of breast, including invasive duct adenocarcinomas of the breast, lung, colon, prostate, pancreas, liver, skin, stomach, rectum, oesophagus, endometrium, cervix, bladder, ovary and thyroid, *see, Keen et al., Nature, Cancer Reviews*, vol. 4, 927-936 (2004). High levels of Aurora-A have also been reported in renal, neuroblastoma, melanoma and lymphoma tumor cell lines. Amplification/over-expression of Aurora-A is observed in human bladder cancers, and amplification of Aurora-A is associated with aneuploidy and aggressive clinical behavior. Moreover, amplification of the Aurora-A locus (20q13) correlates with poor prognosis for patients with node-negative breast cancer. In addition, an allelic variant, isoleucine at amino acid position 31, is reported to be a low-penetrance tumor-susceptibility gene. This variant displays greater transforming potential than the phenylalanine-31 variant and is associated with increased risk for advanced and metastatic disease. Aurora-B is also highly expressed in multiple human tumor cell lines, including leukemic cells. Levels of Aurora-B increase as a function of Duke's stage in primary colorectal cancers. Aurora-C, which is normally only found in germ cells, is also over-expressed in a high percentage of primary colorectal cancers and in a variety of tumor cell lines, including cervical adenocarcinoma and breast carcinoma cells.

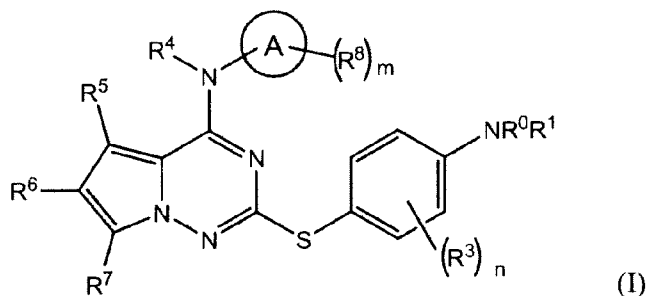
[0004] Research to date supports the hypothesis that *in vitro* an inhibitor of Aurora kinase activity would disrupt mitosis causing cell cycle defects and eventual cell death. Therefore, without being bound to any theory, *in vivo*, an Aurora kinase inhibitor slows tumor growth and induce regression. For example, Hauf *et al.* describe an Aurora B inhibitor, Hesperadin, that causes defects in chromosomal segregation and a block in cytokinesis, thereby resulting in polyploidy [Hauf, S *et al.* *JCB* 161(2), 281-294 (2003)]. Ditchfield *et al.* have described an equipotent inhibitor of Aurora A and B (ZM447439) that causes defects in chromosome alignment, chromosome segregation and cytokinesis, Ditchfield, C. *et al.*, *JCB* 161(2), 267-280 (2003). Furthermore, the authors show that proliferating cells, but not cell-cycle arrested cells, are sensitive to the inhibitor. Efficacy of a potent Aurora A and B inhibitor in mouse and rat xenograft models was recently reported, *see*, Harrington, E. A. *et al.*, *Nature Medicine* 10(3), 262-267, (2004). These results demonstrate that inhibition of Aurora kinases can provide a therapeutic window for the treatment of proliferative disorders such as cancer (*see Nature*, Cancer Reviews, Vol. 4, p927-936, December 2004, for a review by N. Keen and S. Taylor, which outlines the therapeutic potential of Aurora kinase inhibitors for the treatment of cancer). Certain Aurora kinase inhibitor compounds are disclosed in US patent no. 7,442,700 and US publication no. 2006/0084650A1.

[0005] There is a continuing need for compounds that inhibit the activity of Aurora kinases; for compounds that are selective at Aurora kinases or compounds that modulate Aurora kinase activity.

SUMMARY

[0006] Provided herein are compounds of formula (I). Also provided are pharmaceutically acceptable salts, solvates, hydrates, isotopes or clathrates thereof. In certain embodiments, the compounds have activity as Aurora kinase, including Aurora-A, Aurora-B and/or Aurora-C kinase, modulators. The compounds are useful in medical treatments, pharmaceutical compositions and methods for modulating the activity of Aurora kinase, including wildtype and/or mutated forms of Aurora kinase. In one embodiment, the compounds for use in the compositions and methods provided herein are compounds of formula (I).

[0007] The compounds provided herein are pyrrolotriazines with a sulfur linker at 2-position and nitrogen linker at 4-position. In one embodiment, the compounds have formula (I):



or pharmaceutically acceptable salts, solvates, hydrates or clathrates thereof, wherein:

ring A is pyrazolyl;

R^0 and R^1 are selected from (i) and (ii) as follows:

(i) R^0 and R^1 are both hydrogen provided that R^8 is cycloalkyl, haloalkyl or hydroxyalkyl; and

(ii) R^1 is hydrogen, hydroxy, alkoxy, or alkyl and R^0 is $-C(O)R^2$;

R^4 is hydrogen or alkyl;

R^2 is selected from the following:

(i) $-R^9NR^9R^{10}$;

(ii) $-C(O)OH$, haloalkyl, hydroxyalkyl, cycloalkylalkyl, aralkyl optionally substituted with $-OR$, $-C(O)O$

(iii) phenyl, pyrazolyl, isoxazolyl, pyridyl, pyrimidinyl or triazolyl, each independently substituted with one, two or three groups selected from halo, alkyl, haloalkyl, alkoxy and heteroaryl optionally substituted with haloalkyl; and

(iv) cyclopropyl, cyclobutyl or cyclohexyl, each independently unsubstituted or substituted with one or two groups selected from halo, hydroxy, and alkoxy carbonyl;

R^3 is halo or alkyl;

R^5 , R^6 and R^7 are each independently selected from hydrogen, halo, alkyl, alkenyl, alkynyl, hydroxyl, alkoxy, haloalkyl, cycloalkyl, $-R^xNR^{11a}R^{11b}$ and $-R^xNR^{11}C(O)R^{12}$;

R^8 is alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, or halocycloalkyl;

R^y is a direct bond or alkylene;

R^9 and R^{10} are selected as follows:

(i) R^9 and R^{10} are each independently hydrogen, alkyl, cycloalkyl, aralkyl, aryl, and heteroaralkyl, wherein alkyl and cycloalkyl are each optionally substituted with one, two or three groups independently selected from halo, alkyl, cycloalkyl, haloalkyl, hydroxy and alkoxy; and aryl is optionally substituted with OR^{15} ; and

(ii) R^9 and R^{10} , together with the nitrogen atom to which they are attached, form a heterocyclyl optionally containing a second heteroatom selected from N, O and S(O), which heterocyclyl is optionally substituted with 1 to 5 groups each independently selected from halo, cyano, $-R^xOP(O)(OH)_2$, alkyl, haloalkyl, alkenyl, haloalkenyl, alkynyl, haloalkynyl, $=N-OH$, $=CR^yR^y$, $-R^xOR^{16}$, $-R^xS(O)_tR^{16}$, $-R^xC(O)R^{16}$, $-R^xNR^{17}R^{18}$, $-R^xNR^{15}C(O)R^{16}$, $-R^xNR^{15}S(O)_tR^{16}$, $-R^xNR^{15}C(O)NR^{17}R^{18}$, $-R^xC(O)NR^{13}R^{14}$, and $-R^xOP(O)(OH)_2$;

R^{11} , R^{11a} , R^{11b} and R^{15} are each independently hydrogen or alkyl;

R^{12} is $-R^xNR^{19}R^{20}$;

each R^{13} and R^{14} are independently selected from (i) and (ii) as follows:

(i) R^{13} is hydrogen or alkyl; and R^{14} is alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, or heterocyclylalkyl; R^{13} and R^{14} are each optionally substituted with 1 to 5 Q^1 , each Q^1 independently selected from halo, hydroxyl, alkoxy, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, cycloalkyl, aryl, heterocyclyl and heteroaryl; and

(ii) R^{13} and R^{14} , together with the nitrogen atom to which they are attached, form heterocyclyl or heteroaryl; optionally substituted with 1 to 5 Q^1 , each Q^1 independently selected from halo, hydroxyl, alkoxy, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, cycloalkyl, aryl, heterocyclyl and heteroaryl;

each R^x is independently alkylene or a direct bond;

each R^y is independently hydrogen, alkyl or halo;

each R^{15} is independently hydrogen or alkyl;

each R^{16} is independently hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroarylalkyl; wherein R^{16} is optionally substituted with 1 to 3 Q^2 , each Q^2 independently selected from alkyl,

hydroxyl, alkoxy, aryloxy, halo, haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloaryl and alkoxyalkyl;

each R^{17} and R^{18} are independently selected from (i) and (ii) below:

(i) R^{17} and R^{18} are each independently hydrogen, alkyl or aryl, wherein the alkyl and aryl are each optionally substituted with one to five substituents independently selected from the group consisting of halo, alkyl and $-R^xOR^{15}$; and

(ii) R^{17} and R^{18} , together with the nitrogen atom to which they are attached, form heterocyclyl or heteroaryl, where heterocyclyl and heteroaryl are each optionally substituted with one or more substituents independently selected from the group consisting of halo, alkyl, haloalkyl, hydroxyalkyl, and $-R^xOR^{15}$;

each R^{19} and R^{20} are independently selected from (i) and (ii) below:

(i) R^{19} and R^{20} are each independently hydrogen, alkyl, haloalkyl or heterocyclyl; and

(ii) R^{19} and R^{20} , together with the nitrogen atom to which they are attached, form heterocyclyl which is optionally substituted with one or more substituents each independently selected from the group consisting of halo and alkyl;

Q^1 and Q^2 are each independently optionally substituted with 1 to 5 Q^3 , each Q^3 independently selected from alkyl, hydroxyl, alkoxy, aryloxy, halo, haloalkyl and cycloalkyl;

each t is independently 0, 1 or 2;

m is 0, 1 or 2; and

n is 0-4,

with a proviso that when R^2 is unsubstituted cyclopropyl, then R^6 is other than hydrogen.

[0008] Many of the compounds provided herein have one or more chiral centers. The compounds encompassed herein include stereoisomers or chirally pure molecules as well as racemates, and diastereomeric mixtures as described below.

[0009] Also provided are pharmaceutical compositions formulated for administration by an appropriate route and means containing effective concentrations of one or more of the compounds provided herein, or pharmaceutically acceptable salts, solvates and hydrates thereof, and optionally comprising at least one pharmaceutical carrier, excipient or diluant.

[0010] Such pharmaceutical compositions deliver amounts effective for the treatment, prevention, or amelioration of Aurora kinase associated diseases, such as, for example, cancer, bone diseases, inflammatory diseases, autoimmune diseases, metabolic diseases, viral diseases, fungal diseases, neurological and neurodegenerative disorders, Alzheimer's disease, allergies and asthma, cardiovascular diseases, and hormone related diseases.

[0011] The cancers that can be treated with compounds of Formula (I) include, but are not limited to, for example, carcinoma, including, for example, that of the bladder, breast, colon, kidney, liver, lung (including small cell lung cancer), esophagus, gall bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin (including squamous cell carcinoma); hematopoietic tumors of lymphoid lineage, such as, for example, leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma, and Burkett's lymphoma; hematopoietic tumors of myeloid lineage, such as, for example, acute and chronic myelogenous leukemia, myelodysplastic syndrome, and promyelocytic leukemia; tumors of mesenchymal origin, including, for example, fibrosarcoma and rhabdomyosarcoma; tumors of the central and peripheral nervous system, including, for example, astrocytoma, neuroblastoma, glioma, and schwannomas; and other tumors, such as, for example, melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoacanthoma, thyroid follicular cancer, and Kaposi's sarcoma.

[0012] In certain embodiments, provided herein are methods of treating, preventing or ameliorating a disease or disorder that is modulated or otherwise affected by Aurora kinases, including wild type and/or mutant Aurora kinase, or one or more symptoms or causes thereof.

[0013] In practicing the methods, effective amounts of the compounds or compositions containing therapeutically effective concentrations of the compounds, which are formulated for systemic delivery, including parenteral, oral, or intravenous delivery, or for local or topical application are administered to an individual exhibiting the symptoms of the disease or disorder to be treated. The amounts are effective to ameliorate or eliminate one or more symptoms of the disease or disorder.

[0014] Also provided herein are combination therapies using one or more compounds or compositions provided herein, or pharmaceutically acceptable

derivatives thereof, in combination with other pharmaceutically active agents for the treatment of the diseases and disorders described herein.

[0015] In one embodiment, such additional pharmaceutical agents include one or more chemotherapeutic agents, anti-proliferative agents, anti-inflammatory agents, immunomodulatory agents or immunosuppressive agents.

[0016] The compounds or compositions provided herein, or pharmaceutically acceptable derivatives thereof, may be administered simultaneously with, prior to, or after administration of one or more of the above agents. Pharmaceutical compositions containing a compound provided herein and one or more of the above agents are also provided.

DETAILED DESCRIPTION

[0017] Provided herein are compounds of formula (I) that have activity as Aurora kinase modulators. Further provided are methods of treating, preventing or ameliorating diseases that are modulated by Aurora kinase, and pharmaceutical compositions and dosage forms useful for such methods. The methods and compositions are described in detail in the sections below.

A. DEFINITIONS

[0018] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications are incorporated by reference in their entirety. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0019] “Alkyl” refers to a straight or branched hydrocarbon chain group consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to ten, one to eight, one to six or one to four carbon atoms, and which is attached to the rest of the molecule by a single bond, *e.g.*, methyl, ethyl, *n*-propyl, 1-methylethyl (*iso*-propyl), *n*-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl), and the like.

[0020] “Alkenyl” refers to a straight or branched hydrocarbon chain group consisting solely of carbon and hydrogen atoms, containing at least one double bond, having from two to ten carbon atoms, and which is attached to the rest of the molecule by a single bond or a double bond, *e.g.*, ethenyl, prop-1-enyl, but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like.

[0021] “Alkynyl” refers to a straight or branched hydrocarbon chain group consisting solely of carbon and hydrogen atoms, containing at least one triple bond, having from two to ten carbon atoms, and which is attached to the rest of the molecule by a single bond or a triple bond, *e.g.*, ethynyl, prop-1-ynyl, but-1-ynyl, pent-1-ynyl, pent-3-ynyl and the like.

[0022] “Alkylene” and “alkylene chain” refer to a straight or branched divalent hydrocarbon chain consisting solely of carbon and hydrogen, containing no unsaturation and having from one to eight carbon atoms, *e.g.*, methylene, ethylene, propylene, *n*-butylene and the like. The alkylene chain may be attached to the rest of the molecule through any two carbons within the chain.

[0023] “Alkoxy” refers to the group having the formula -OR wherein R is alkyl or haloalkyl. An “optionally substituted alkoxy” refers to the group having the formula -OR wherein R is an optionally substituted alkyl as defined herein.

[0024] “Amine” or “amino” refers to a group having the formula -NR'R'' wherein R' and R'' are each independently hydrogen, alkyl, haloalkyl, hydroxyalkyl or alkoxyalkyl, aminoalkyl, or wherein R' and R'', together with the nitrogen atom to which they are attached form a heterocyclyl optionally substituted with halo, oxo, hydroxyl, alkoxy, or amino.

[0025] “Aryl” refers to a group of carbocyclic ring system, including monocyclic, bicyclic, tricyclic, tetracyclic C₆-C₁₈ ring systems, wherein at least one of the rings is aromatic. The aryl may be fully aromatic, examples of which are phenyl, naphthyl, anthracenyl, acenaphthylenyl, azulenyl, fluorenyl, indenyl and pyrenyl. The aryl may also contain an aromatic ring in combination with a non-aromatic ring, examples of which are acenaphene, indene, and fluorene.

[0026] “Cycloalkyl” refers to a stable monovalent monocyclic or bicyclic hydrocarbon group consisting solely of carbon and hydrogen atoms, having from three to ten carbon atoms, and which is saturated and attached to the rest of the molecule by a single bond, *e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, decalinyl, norbornane, norbornene, adamantyl, bicyclo[2.2.2]octane and the like.

[0027] “Cycloalkylalkyl” refers to a group of the formula -R_aR_d where R_a is an alkyl group as defined above and R_d is a cycloalkyl group as defined above. The alkyl group and the cycloalkyl group may be optionally substituted as defined herein.

[0028] “Halo”, “halogen” or “halide” refers to F, Cl, Br or I.

[0029] “Haloalkyl” refers to an alkyl group, in certain embodiments, C₁₋₆alkyl group in which one or more of the hydrogen atoms are replaced by halogen. Such groups include, but are not limited to, chloromethyl, trifluoromethyl, 1-chloro-2-fluoroethyl, 2,2-difluoroethyl, 2-fluoropropyl, 2-fluoropropan-2-yl, 2,2,2-trifluoroethyl, 1,1-difluoroethyl, 1,3-difluoro-2-methylpropyl, 2,2-difluorocyclopropyl, (trifluoromethyl)cyclopropyl, 4,4-difluorocyclohexyl and 2,2,2-trifluoro-1,1-dimethyl-ethyl.

[0030] “Heterocyclyl” refers to a stable 3- to 15-membered ring group which consists of carbon atoms and from one to five heteroatoms selected from a group consisting of nitrogen, oxygen and sulfur. In one embodiment, the heterocyclic ring system group may be a monocyclic, bicyclic or tricyclic ring or tetracyclic ring system, which may include fused or bridged ring systems; and the nitrogen or sulfur atoms in the heterocyclic ring system group may be optionally oxidized; the nitrogen atom may be optionally quaternized; and the heterocyclyl group may be partially or fully saturated or aromatic. The heterocyclic ring system may be attached to the main structure at any heteroatom or carbon atom which results in the creation of a stable compound. Examples of such heterocyclic groups include, but are not limited to: acridinyl, azepinyl, azetidiny, benzimidazolyl, benzindolyl, benzoisoxazolyl, benzoisoxazinyl, benzo[4,6]imidazo[1,2-*a*]pyridinyl, benzodioxanyl, benzodioxolyl, benzofuranonyl, benzofuranyl, benzonaphthofuranyl, benzopyranonyl, benzopyranyl, benzotetrahydrofuranyl, benzotetrahydrothienyl, benzothiadiazolyl, benzothiazolyl, benzothiophenyl, benzotriazolyl, benzothiopyranyl, benzoxazinyl, benzoxazolyl, benzothiazolyl, β-carbolinyl, carbazolyl, chromanyl, chromonyl, cinnoliny, coumarinyl, decahydroisoquinoliny, dibenzofuranyl, dihydrobenzothiazinyl, dihydrobenzoxazinyl, dihydrofuryl, dihydropyranyl, dioxolanyl, dihydropyrazinyl, dihydropyridinyl, dihydropyrazolyl, dihydropyrimidinyl, dihydropyrrolyl, dioxolanyl, 1,4-dithianyl, furanonyl, furanyl, imidazolidinyl, imidazoliny, imidazolyl, imidazopyridinyl, imidazothiazolyl, indazolyl, indoliny, indoliziny, indolyl, isobenzotetrahydrofuranyl, isobenzotetrahydrothienyl, isobenzothienyl, isochromanyl, isocoumarinyl, isoindoliny, isoindolyl, isoquinoliny, isothiazolidinyl, isothiazolyl, isoxazolidinyl, isoxazolyl, morpholiny, naphthyridinyl, octahydroindolyl, octahydroisoindolyl, oxadiazolyl, oxazolidinonyl, oxazolidinyl, oxazolopyridinyl, oxazolyl, oxiranyl, perimidiny, phenanthridinyl, phenathroliny, phenarsazinyl,

phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, 4-piperidonyl, pteridinyl, purinyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyridinyl, pyridopyridinyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuryl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydropyranyl, tetrahydrothienyl, tetrazolyl, thiadiazolopyrimidinyl, thiadiazolyl, thiamorpholinyl, thiazolidinyl, thiazolyl, thienyl, triazinyl, triazolyl, 1,3,5-trithianyl and 8-azabicyclo[4.3.0]nonyl.

[0031] “Heteroaryl” refers to a heterocyclyl group as defined above which is aromatic. The heteroaryl group may be attached to the main structure at any heteroatom or carbon atom which results in the creation of a stable compound.

Examples of such heteroaryl groups include, but are not limited to: acridinyl, benzimidazolyl, benzindolyl, benzisoxazinyl, benzo[4,6]imidazo[1,2-*a*]pyridinyl, benzofuranyl, benzonaphthofuranyl, benzothiadiaazolyl, benzothiazolyl, benzothiophenyl, benzotriazolyl, benzothiopyranyl, benzoxazinyl, benzoxazolyl, benzothiazolyl, β -carbolinyl, carbazolyl, cinnolinyl, dibenzofuranyl, furanyl, imidazolyl, imidazopyridinyl, imidazothiazolyl, indazolyl, indolizinyl, indolyl, isobenzothienyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, naphthyridinyl, octahydroindolyl, octahydroisoindolyl, oxazolidinonyl, oxazolidinyl, oxazolopyridinyl, oxazolyl, isoxazolyl, oxiranyl, perimidinyl, phenanthridinyl, phenathrolinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyridopyridinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl, triazinyl and triazolyl.

[0032] “Aralkyl” refers to a group of the formula $-R_aR_b$ where R_a is an alkyl group as defined above, substituted with R_b , an aryl group, as defined above, *e.g.*, benzyl. Both the alkyl and aryl groups may be optionally substituted as defined herein.

[0033] “Heteroaralkyl” refers to a group of the formula $-R_aR_f$ where R_a is an alkyl group as defined above and R_f is a heteroaryl group as defined herein. The alkyl group and the heteroaryl group may be optionally substituted as defined herein.

[0034] “Heterocyclylalkyl” refers to a group of the formula $-R_aR_c$ wherein R_a is an alkyl group as defined above and R_c is a heterocyclyl group as defined herein, where the alkyl group R_a may attach at either the carbon atom or the heteroatom of the

heterocyclyl group R_e . The alkyl group and the heterocyclyl group may be optionally substituted as defined herein.

[0035] “ IC_{50} ” refers to an amount, concentration or dosage of a particular test compound that achieves a 50% inhibition of a maximal response, such as cell growth or proliferation measured via any the *in vitro* or cell based assay described herein.

[0036] Unless stated otherwise specifically described in the specification, it is understood that the substitution can occur on any atom of the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl group.

[0037] Pharmaceutically acceptable salts include, but are not limited to, salts of organic acids, such as but not limited to acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates, mesylates, tosylates and fumarates.

[0038] As used herein and unless otherwise indicated, the term “hydrate” means a compound provided herein or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces.

[0039] As used herein and unless otherwise indicated, the term “solvate” means a solvate formed from the association of one or more solvent molecules to a compound provided herein. The term “solvate” includes hydrates (e.g., monohydrate, dihydrate, trihydrate, tetrahydrate and the like).

[0040] As used herein, “substantially pure” means sufficiently homogeneous to appear free of readily detectable impurities as determined by standard methods of analysis, such as thin layer chromatography (TLC), gel electrophoresis, high performance liquid chromatography (HPLC) and mass spectrometry (MS), used by those of skill in the art to assess such purity, or sufficiently pure such that further purification would not detectably alter the physical and chemical properties, such as enzymatic and biological activities, of the substance. Methods for purification of the compounds to produce substantially chemically pure compounds are known to those of skill in the art. A substantially chemically pure compound may, however, be a mixture of stereoisomers. In such instances, further purification might increase the specific activity of the compound.

[0041] Thioxo refers to the group $=S$ attached to a carbon atom.

[0042] Unless specifically stated otherwise, where a compound may assume alternative tautomeric, regioisomeric and/or stereoisomeric forms, all alternative isomers are intended to be encompassed within the scope of the claimed subject matter. For example, where a compound is described as having one of two tautomeric forms, it is intended that the both tautomers be encompassed herein.

[0043] Thus, the compounds provided herein may be enantiomerically pure, or be stereoisomeric or diastereomeric mixtures. In the case of amino acid residues, such residues may be of either the L- or D-form. The configuration for naturally occurring amino acid residues is generally L. When not specified the residue is the L form. As used herein, the term "amino acid" refers to α -amino acids which are racemic, or of either the D- or L-configuration. The designation "d" preceding an amino acid designation (*e.g.*, dAla, dSer, dVal, etc.) refers to the D-isomer of the amino acid. The designation "dl" preceding an amino acid designation (*e.g.*, dlPip) refers to a mixture of the L- and D-isomers of the amino acid. It is to be understood that the chiral centers of the compounds provided herein may undergo epimerization *in vivo*. As such, one of skill in the art will recognize that administration of a compound in its (*R*) form is equivalent, for compounds that undergo epimerization *in vivo*, to administration of the compound in its (*S*) form.

[0044] It is to be understood that the compounds provided herein may contain one or more chiral centers. Such chiral centers may be of either the (*R*) or (*S*) configuration, or may be a mixture thereof.

[0045] Optically active (+) and (-), (*R*)- and (*S*)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, such as reverse phase HPLC.

[0046] As used herein, the term "chirally pure" denotes that the compound comprises more than 75% by weight, more than 80% by weight, more than 85% by weight, more than 90% by weight, more than 91% by weight, more than 92% by weight, more than 93% by weight, more than 94% by weight, more than 95% by weight, more than 96% by weight, more than 97% by weight, more than 98% by weight, more than 98.5% by weight, more than 99% by weight, more than 99.2% by weight, more than 99.5% by weight, more than 99.6% by weight, more than 99.7% by weight, more than 99.8% by weight or more than 99.9% by weight, of the desired enantiomer or diastereomer as measured by chiral high performance liquid

chromatography (HPLC). Other methods of measuring chiral purity include conventional analytical methods, including specific rotation, and conventional chemical methods.

[0047] As used herein, the term “enantiomerically pure” or “pure enantiomer” denotes that the compound comprises more than 75% by weight, more than 80% by weight, more than 85% by weight, more than 90% by weight, more than 91% by weight, more than 92% by weight, more than 93% by weight, more than 94% by weight, more than 95% by weight, more than 96% by weight, more than 97% by weight, more than 98% by weight, more than 98.5% by weight, more than 99% by weight, more than 99.2% by weight, more than 99.5% by weight, more than 99.6% by weight, more than 99.7% by weight, more than 99.8% by weight or more than 99.9% by weight, of the desired enantiomer.

[0048] Where the number of any given substituent is not specified (*e.g.*, haloalkyl), there may be one or more substituents present. For example, “haloalkyl” may include one or more of the same or different halogens.

[0049] In the description herein, if there is any discrepancy between a chemical name and chemical structure, the structure provided herein preferably controls.

[0050] As used herein, “isotopic composition” refers to the amount of each isotope present for a given atom, and “natural isotopic composition” refers to the naturally occurring isotopic composition or abundance for a given atom. Atoms containing their natural isotopic composition may also be referred to herein as “non-enriched” atoms. Unless otherwise designated, the atoms of the compounds recited herein are meant to represent any stable isotope of that atom. For example, unless otherwise stated, when a position is designated specifically as “H” or “hydrogen”, the position is understood to have hydrogen at its natural isotopic composition.

[0051] As used herein, “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.

[0052] As used herein, “isotopic enrichment” refers to the percentage of incorporation of an amount of a specific isotope at a given atom in a molecule in the

place of that atom's natural isotopic abundance. For example, deuterium enrichment of 1% at a given position means that 1% of the molecules in a given sample contain deuterium at the specified position. Because the naturally occurring distribution of deuterium is about 0.0156%, deuterium enrichment at any position in a compound synthesized using non-enriched starting materials is about 0.0156%. The isotopic enrichment of the compounds provided herein can be determined using conventional analytical methods known to one of ordinary skill in the art, including mass spectrometry and nuclear magnetic resonance spectroscopy.

[0053] "Anti-cancer agents" refer to anti-metabolites (e.g., 5-fluoro-uracil, methotrexate, fludarabine), antimicrotubule agents (e.g., vinca alkaloids such as vincristine, vinblastine; taxanes such as paclitaxel, docetaxel), alkylating agents (e.g., cyclophosphamide, melphalan, carmustine, nitrosoureas such as bischloroethylnitrosourea and hydroxyurea), platinum agents (e.g. cisplatin, carboplatin, oxaliplatin, JM-216 or satraplatin, CI-973), anthracyclines (e.g., doxorubicin, daunorubicin), antitumor antibiotics (e.g., mitomycin, idarubicin, adriamycin, daunomycin), topoisomerase inhibitors (e.g., etoposide, camptothecins), anti-angiogenesis agents (e.g. Sutent® and Bevacizumab) or any other cytotoxic agents, (estramustine phosphate, prednimustine), hormones or hormone agonists, antagonists, partial agonists or partial antagonists, kinase inhibitors, and radiation treatment.

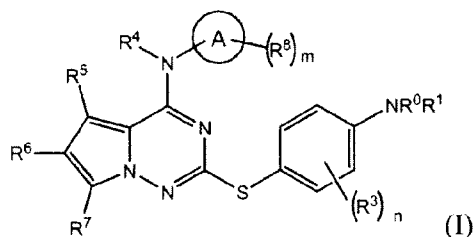
[0054] "Anti-inflammatory agents" refers to matrix metalloproteinase inhibitors, inhibitors of pro-inflammatory cytokines (e.g., anti-TNF molecules, TNF soluble receptors, and IL1) non-steroidal anti-inflammatory drugs (NSAIDs) such as prostaglandin synthase inhibitors (e.g., choline magnesium salicylate, salicylsalicyclic acid), COX-1 or COX-2 inhibitors), or glucocorticoid receptor agonists such as corticosteroids, methylprednisone, prednisone, or cortisone.

[0055] As used herein, the abbreviations for any protective groups, amino acids and other compounds, are, unless indicated otherwise, in accord with their common usage, recognized abbreviations, or the IUPAC-IUB Commission on Biochemical Nomenclature (see, *Biochem.* 1972, 11:942-944).

B. COMPOUNDS

[0056] In one embodiment, the compounds for use in the compositions and methods provided herein are compounds of formula (I).

[0057] The compounds provided herein are pyrrolotriazines with a sulfur linker at 2-position and nitrogen linker at 4-position. In one embodiment, the compounds have formula (I):



or pharmaceutically acceptable salts, solvates, hydrates or clathrates thereof, wherein:

ring A is pyrazolyl;

R^0 and R^1 are selected from (i) and (ii) as follows:

(iv) R^0 and R^1 are both hydrogen provided that R^8 is cycloalkyl; and

(v) R^1 is hydrogen or alkyl and R^0 is $-C(O)R^2$;

R^4 is hydrogen or alkyl;

R^2 is selected from the following:

(i) $-R^yNR^9R^{10}$;

(ii) phenyl or pyrazolyl, each independently substituted with one, two or three groups selected from halo and haloalkyl; and

(iii) cyclopropyl, unsubstituted or substituted with one or two groups selected from halo and alkoxy carbonyl;

R^3 is halo or alkyl;

R^5 , R^6 and R^7 are each independently selected from hydrogen, halo, alkyl, alkenyl, alkynyl, hydroxyl, alkoxy, haloalkyl, cycloalkyl, $-R^xNR^{11a}R^{11b}$ and $-R^xNR^{11}C(O)R^{12}$;

R^8 is alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, or halocycloalkyl;

R^y is alkylene;

R^9 and R^{10} are selected as follows:

(i) R^9 and R^{10} are each independently hydrogen, alkyl or cycloalkyl, wherein alkyl and cycloalkyl are each optionally substituted with one, two or three groups independently selected from halo, alkyl, cycloalkyl, haloalkyl, hydroxy and alkoxy; and

(ii) R^9 and R^{10} , together with the nitrogen atom to which they are attached, form a heterocyclyl which is optionally substituted with 1 to 5 groups each independently selected from halo, cyano, alkyl, haloalkyl, alkenyl, haloalkenyl, alkynyl, haloalkynyl, $=N-OH$, $-R^xOR^{16}$, $-R^xS(O)R^{16}$, $-R^xC(O)R^{16}$, $-R^xNR^{17}R^{18}$, $-R^xNR^{15}C(O)R^{16}$ and $-R^xC(O)NR^{13}R^{14}$

R^{11} , R^{11a} , R^{11b} and R^{15} are each independently hydrogen or alkyl;

R^{12} is $-R^xNR^{19}R^{20}$;

each R^{13} and R^{14} are independently selected from (i) and (ii) as follows:

(i) R^{13} is hydrogen or alkyl; and R^{14} is alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, or heterocyclylalkyl; R^{13} and R^{14} are each optionally substituted with 1 to 5 Q^1 , each Q^1 independently selected from halo, hydroxyl, alkoxy, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, cycloalkyl, aryl, heterocyclyl and heteroaryl; and

(ii) R^{13} and R^{14} , together with the nitrogen atom to which they are attached, form heterocyclyl or heteroaryl; optionally substituted with 1 to 5 Q^1 , each Q^1 independently selected from halo, hydroxyl, alkoxy, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, cycloalkyl, aryl, heterocyclyl and heteroaryl;

each R^x is independently alkylene or a direct bond;

each R^{15} is independently hydrogen or alkyl;

each R^{16} is independently hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroarylalkyl; wherein R^{16} is optionally substituted with 1 to 3 Q^2 , each Q^2 independently selected from alkyl, hydroxyl, alkoxy, aryloxy, halo, haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloaryl and alkoxyalkyl;

each R^{17} and R^{18} are independently selected from (i) and (ii) below:

(i) R^{17} and R^{18} are each independently hydrogen, alkyl or aryl, wherein the alkyl and aryl are each optionally substituted with one to five substituents independently selected from the group consisting of halo, alkyl and $-R^xOR^{15}$; and

(ii) R^{17} and R^{18} , together with the nitrogen atom to which they are attached, form heterocyclyl or heteroaryl, where heterocyclyl and heteroaryl are each optionally substituted with one or more substituents independently selected from the group consisting of halo, alkyl, haloalkyl, hydroxyalkyl, and $-R^xOR^{15}$;

each R^{19} and R^{20} are independently selected from (i) and (ii) below:

(i) R^{19} and R^{20} are each independently hydrogen, alkyl or haloalkyl; and

(ii) R^{19} and R^{20} , together with the nitrogen atom to which they are attached, form heterocyclyl which is optionally substituted with one or more substituents each independently selected from the group consisting of halo and alkyl;

Q^1 and Q^2 are each independently optionally substituted with 1 to 5 Q^3 , each Q^3 independently selected from alkyl, hydroxyl, alkoxy, aryloxy, halo, haloalkyl and cycloalkyl;

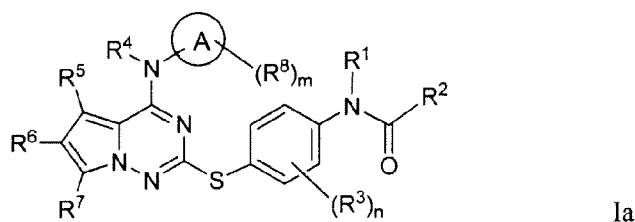
each t is independently 0, 1 or 2;

m is 0, 1 or 2; and

n is 0-4;

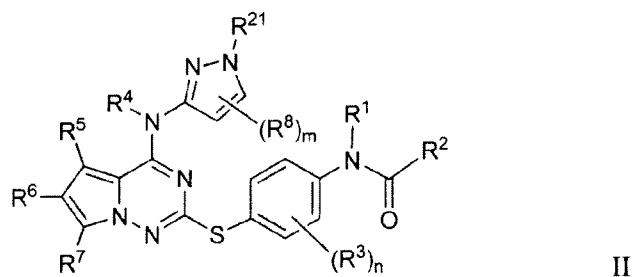
with a proviso that when R^2 is unsubstituted cyclopropyl, then R^6 is other than hydrogen.

[0058] In one embodiment, the compounds have the formula (Ia)



or pharmaceutically acceptable salts, solvates, hydrates or clathrates thereof, wherein the variables are as described elsewhere herein.

[0059] In one embodiment, the compounds have formula (II),



or pharmaceutically acceptable salts, solvates, hydrates or clathrates thereof, wherein

R^1 is hydrogen or alkyl;

R^2 is $-R^yNR^9R^{10}$;

R^3 is halo or alkyl;

R^4 and R^{21} are each independently hydrogen or alkyl;

R^5 , R^6 and R^7 are each independently selected from hydrogen, halo, alkyl, $-R^xNR^{11a}R^{11b}$ and $-R^xNR^{11}C(O)R^{12}$;

R^8 is alkyl, haloalkyl or cycloalkyl;

R^9 and R^{10} are selected as follows:

(i) R^9 and R^{10} are each independently hydrogen, alkyl, hydroxyalkyl, haloalkyl or cycloalkyl; or

(ii) R^9 and R^{10} , together with the nitrogen atom to which they are attached, form a heterocyclyl which is optionally substituted with 1 to 5 groups each independently selected from halo, cyano, alkyl, haloalkyl, alkenyl, haloalkenyl, alkynyl, haloalkynyl, $=N-OH$, $-R^xOR^{16}$, $-R^xS(O)R^{16}$, $-R^xC(O)R^{16}$, $-R^xNR^{17}R^{18}$, $-R^xNR^{15}C(O)R^{16}$, and $-R^xC(O)NR^{13}R^{14}$;

R^{11} , R^{11a} , R^{11b} and R^{15} are each independently hydrogen or alkyl;

R^{12} is $R^xNR^{19}R^{20}$;

each R^{13} and R^{14} are independently selected from (i) and (ii) as follows:

(i) R^{13} is hydrogen or alkyl; and R^{14} is alkyl, cycloalkyl, aryl, arylalkyl or heterocyclylalkyl; R^{13} and R^{14} are each optionally substituted with 1 to 5 groups Q^1 , each Q^1 independently selected from halo, hydroxyl, alkoxy, alkyl, haloalkyl, alkoxyalkyl and hydroxyalkyl; and

(ii) R^{13} and R^{14} , together with the nitrogen atom to which they are attached, form heterocyclyl or heteroaryl, optionally substituted with 1 to 5 groups Q^1 , each Q^1 independently selected from halo, hydroxyl, alkoxy, alkyl, haloalkyl, alkoxyalkyl and hydroxyalkyl;

each R^{15} is independently hydrogen or alkyl;

when Q^1 is selected from alkoxy, alkyl, haloalkyl, alkoxyalkyl and hydroxyalkyl, each Q^1 is independently optionally substituted with 1 to 5 Q^3 , where each Q^3 is independently selected from alkyl, hydroxyl, alkoxy, aryloxy, halo, haloalkyl and cycloalkyl;

each R^x is independently alkylene or a direct bond;

R^y is alkylene;

each R^{16} is independently hydrogen, alkyl, alkoxy, haloalkyl, hydroxyalkyl, alkoxyalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroarylalkyl; wherein R^{16} is optionally substituted with 1 to 3 groups Q^2 , each Q^2 independently selected from

alkyl, hydroxyl, alkoxy, aryloxy, halo, haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloaryl and alkoxyalkyl;

when Q^2 is selected from alkyl, alkoxy, aryloxy, haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloaryl and alkoxyalkyl, each Q^2 is independently optionally substituted with 1 to 5 Q^3 , where each Q^3 is independently selected from alkyl, hydroxyl, alkoxy, aryloxy, halo, haloalkyl and cycloalkyl;

each R^{17} and R^{18} are independently selected from (i) and (ii) below:

(i) R^{17} and R^{18} are each independently hydrogen, alkyl or aryl, wherein the alkyl and aryl may each be optionally substituted with one to five substituents each independently selected from the group consisting of halo, alkyl and $-R^xOR^{15}$; and

(ii) R^{17} and R^{18} , together with the nitrogen atom to which they are attached, form heterocyclyl or heteroaryl which is optionally substituted with one or more substituents independently selected from the group consisting of halo, alkyl, haloalkyl, hydroxyalkyl, and $-R^xOR^{15}$;

each R^{19} and R^{20} are independently selected from (i) and (ii) below:

(i) R^{19} and R^{20} are each independently hydrogen, alkyl or haloalkyl; and

(ii) R^{19} and R^{20} , together with the nitrogen atom to which they are attached, form heterocyclyl which is optionally substituted with one or more substituents independently selected from the group consisting of halo and alkyl;

each t is independently 0, 1 or 2;

m is 0, 1 or 2; and

n is 0-4.

[0060] In one embodiment, the compound provided herein is a compound of formula (I), (Ia) or (II). In one embodiment, the compound provided herein is a pharmaceutically acceptable salt of the compound of formula (I), (Ia) or (II). In one embodiment, the compound provided herein is a solvate of the compound of formula (I), (Ia) or (II). In one embodiment, the compound provided herein is a hydrate of compound of formula (I), (Ia) or (II). In one embodiment, the compound provided herein is a clathrate of the compound of formula (I), (Ia) or (II).

[0061] In one embodiment, the compounds provided herein are selected with a proviso that when R^2 is unsubstituted cyclopropyl, then R^6 is selected from halo, alkyl, alkenyl, alkynyl, hydroxyl, alkoxy, haloalkyl, cycloalkyl, $-R^xNR^{11a}R^{11b}$ and $-R^xNR^{11}C(O)R^{12}$.

[0062] In one embodiment, the compounds provided herein are selected with a proviso that when R^2 is unsubstituted cyclopropyl, then R^6 is selected from - $R^xNR^{11a}R^{11b}$ and $-R^xNR^{11}C(O)R^{12}$.

[0063] In one embodiment, the compounds provided herein are selected with a proviso that when R^2 is unsubstituted cyclopropyl, then R^6 is $-R^xNR^{11}C(O)R^{12}$, R^{11} is hydrogen or alkyl; R^{12} is $-R^xNR^{19}R^{20}$; each R^x is independently alkylene or a direct bond, and R^{19} and R^{20} are each independently selected from (i) and (ii) below:

(i) R^{19} and R^{20} are each independently hydrogen, alkyl or haloalkyl; and

(ii) R^{19} and R^{20} , together with the nitrogen atom to which they are attached, form heterocyclyl which is optionally substituted with one or more substituents each independently selected from the group consisting of halo and alkyl.

[0064] In one embodiment, the compounds provided herein are selected with a proviso that when R^2 is unsubstituted cyclopropyl, then R^6 is $-NR^{11}C(O)R^{12}$, R^{11} is hydrogen; R^{12} is $-NR^{19}R^{20}$; and R^{19} and R^{20} are each independently selected from (i) and (ii) below:

(i) R^{19} and R^{20} are each independently hydrogen, alkyl or haloalkyl; and

(ii) R^{19} and R^{20} , together with the nitrogen atom to which they are attached, form heterocyclyl which is optionally substituted with one or more substituents each independently selected from the group consisting of halo and alkyl.

[0065] In one embodiment, R^y is $-(CH_2)_{n1}-$, where n_1 is 1, 2, 3, or 4. In one embodiment, R^y is $-(CH_2)_{n1}-$, where n_1 is 1 or 2. In one embodiment, R^y is $-(CH_2)_{n1}-$, where n_1 is 1.

[0066] In one embodiment, R^1 is hydrogen.

[0067] In one embodiment, R^3 is fluoro or methyl. In one embodiment, R^3 is fluoro.

[0068] In one embodiment, R^4 is hydrogen.

[0069] In one embodiment, R^5 and R^7 are each independently selected from hydrogen, halo and alkyl. In one embodiment, R^5 and R^7 are each hydrogen.

[0070] In one embodiment, m is 0 or 1. In one embodiment, m is 0. In one embodiment, m is 1. In one embodiment, n is 0, 1 or 2. In one embodiment, n is 0 or 1. In one embodiment, n is 0. In one embodiment, n is 1. In one embodiment, p is 1. In one embodiment, p is 2.

[0071] In one embodiment, R^6 is hydrogen or $-R^xNR^{11}C(O)R^{12}$. In one embodiment, R^6 is hydrogen. In one embodiment, R^6 is hydrogen, or $-NHC(O)R^xNR^{19}R^{20}$, where R^x is a direct bond, methylene or ethylene; R^{19} and R^{20} are independently selected from (i) and (ii) below:

(i) R^{19} and R^{20} are each independently hydrogen, alkyl or haloalkyl; and

(ii) R^{19} and R^{20} , together with the nitrogen atom to which they are attached, form a 5- or 6- membered heterocycle which is optionally substituted with one or more substituents each independently selected from the group consisting of halo and alkyl.

[0072] In one embodiment, R^8 is alkyl, haloalkyl or cycloalkyl. In one embodiment, R^8 is methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, $-CF_3$, or $-CHF_2$.

[0073] In one embodiment, $R^2-CH_2-NR^9R^{10}$. In one embodiment, R^9 and R^{10} are each independently hydrogen, alkyl, hydroxyalkyl, haloalkyl or cycloalkyl. In another embodiment, R^9 and R^{10} are each independently hydrogen, methyl, hydroxyethyl or cyclopropyl.

[0074] In one embodiment, R^9 and R^{10} , together with the nitrogen atom to which they are attached, form a 4- to 7- membered heterocyclyl which is optionally substituted with 1 to 5 groups, each independently selected from halo, cyano, alkyl, haloalkyl, alkenyl, haloalkenyl, alkynyl, haloalkynyl, $=N-OH$, $-R^xOR^{16}$, $-R^xS(O)_tR^{16}$, $-R^xC(O)R^{16}$, $-R^xNR^{17}R^{18}$, $-R^xNR^{15}C(O)R^{16}$ and $-R^xC(O)NR^{13}R^{14}$.

[0075] In one embodiment, R^9 and R^{10} , together with the nitrogen atom to which they are attached, form a 4- to 6- membered heterocyclyl which is optionally substituted with 1 to 5 groups selected from halo, hydroxyl, hydroxyalkyl, $=N-OH$, $-R^xOR^{16}$, and $-C(O)NR^{13}R^{14}$,

each R^{13} and R^{14} are independently selected from (i) and (ii) as follows:

(i) R^{13} is hydrogen or alkyl; and R^{14} is alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, or heterocyclylalkyl; R^{13} and R^{14} are each optionally substituted with 1 to 5 Q^1 , each Q^1 independently selected from halo, hydroxyl, alkoxy, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, cycloalkyl, aryl, heterocyclyl and heteroaryl; and

(ii) R^{13} and R^{14} , together with the nitrogen atom to which they are attached, form heterocyclyl or heteroaryl; optionally substituted with 1 to 5 Q^1 , each

Q^1 independently selected from halo, hydroxyl, alkoxy, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, cycloalkyl, aryl, heterocyclyl and heteroaryl;

each R^x is independently alkylene or a direct bond; and

each R^{16} is independently hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroarylalkyl; wherein R^{16} is optionally substituted with 1 to 3 Q^2 , each Q^2 independently selected from alkyl, hydroxyl, alkoxy, aryloxy, halo, haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloaryl and alkoxyalkyl;

[0076] In one embodiment, R^9 and R^{10} , together with the nitrogen atom to which they are attached, form a 4- to 7- or 5- to 7- membered heterocyclyl which is optionally substituted with 1 to 3 groups selected from cyano, hydroxyl and $-R^xOR^{16}$, where R^{16} is hydrogen, alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroarylalkyl; wherein R^{16} is optionally substituted with 1 to 3 Q^2 , each Q^2 independently selected from alkyl, hydroxyl, alkoxy, aryloxy, halo, haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloaryl and alkoxyalkyl; when Q^2 is selected from alkyl, alkoxy, aryloxy, haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloaryl and alkoxyalkyl, each Q^2 is independently optionally substituted with 1 to 5 Q^3 , where each Q^3 independently selected from alkyl, alkoxy and halo.

In one embodiment, R^9 and R^{10} , together with the nitrogen atom to which they are attached, form azetidiny, piperidiny, or pyrrolidiny, each of which is optionally substituted with 1 to 3 groups selected from hydroxyl, cyano and $-R^xOR^{16}$, where R^{16} is hydrogen, methyl, ethyl, propyl, isopropyl, *t*-butyl, hydroxyethyl, $-CHCF_3CF_3$, cyclopentyl, benzyl, phenyl, tetrahydrofuranyl or pyridiny; wherein R^{16} is optionally substituted with 1 to 3 Q^2 , where each Q^2 independently selected from alkyl, hydroxyl, alkoxy, halo and heterocyclyl and when Q^2 is selected from alkyl, alkoxy, and heterocyclyl, each Q^2 group is independently optionally substituted with 1 to 5 groups Q^3 , each Q^3 independently selected from alkyl and halo.

[0077] In one embodiment, R^9 and R^{10} , together with the nitrogen atom to which they are attached, form azetidiny, piperidiny or pyrrolidiny, each of which is optionally substituted with 1 to 3 groups selected from halo, hydroxyl and $-R^xOR^{16}$, where R^x is a direct bond or alkylene; and R^{16} is hydrogen, methyl, ethyl, propyl,

isopropyl, *t*-butyl, hydroxyethyl, cyclopropylmethyl, $-\text{C}(\text{CH}_3)_2\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{C}(\text{CH}_3)(\text{C}_2\text{H}_5)\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{C}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CF}_3$, $-\text{C}(\text{CH}_3)_2\text{CF}_3$, $-\text{CHCF}_3\text{CF}_3$, cyclopentyl, benzyl, phenyl, tetrahydrofuranyl, piperidinyl, piperazinyl, pyrrolidinyl or pyridinyl; wherein R^{16} is optionally substituted with 1 to 3 Q^2 , each Q^2 independently selected from methyl, ethyl, fluoro, chloro, cyclopropyl, piperidinyl, piperazinyl, pyrrolidinyl, azepanyl, morpholinyl, furanyl and hydroxyl; and when Q^2 is methyl, ethyl, cyclopropyl, piperidinyl, piperazinyl, pyrrolidinyl, azepanyl, morpholinyl, furanyl, each Q^2 group is independently optionally substituted with 1 to 3 Q^3 , each Q^3 independently selected from methyl, fluoro and halo.

[0078] In one embodiment, R^9 and R^{10} , together with the nitrogen atom to which they are attached, form a 4- to 7- membered heterocyclyl which is optionally substituted with 1 to 3 groups selected from halo, hydroxyl, hydroxyalkyl and $-\text{R}^x\text{S}(\text{O})_t\text{R}^{16}$, wherein R^x is a direct bond or alkylene; R^{16} is *t*-butyl and *t* is 0, 1, or 2. In one embodiment, R^9 and R^{10} , together with the nitrogen atom to which they are attached, form a 4- to 7- membered heterocyclyl which is optionally substituted with 1 or 2 groups selected from $-\text{S}(\text{O})_2\text{C}(\text{CH}_3)_3$, $-\text{SC}(\text{CH}_3)_3$ and $-\text{SOC}(\text{CH}_3)_3$.

[0079] In one embodiment, R^9 and R^{10} , together with the nitrogen atom to which they are attached, form a 4- to 7- membered heterocyclyl which is optionally substituted with 1 to 3 groups selected from halo, hydroxyl, hydroxyalkyl and $-\text{R}^x\text{C}(\text{O})\text{R}^{16}$, where R^x is a direct bond or alkylene and R^{16} is alkyl. In another embodiment, R^9 and R^{10} , together with the nitrogen atom to which they are attached, form a 4- to 7- membered heterocyclyl which is optionally substituted with 1 to 3 groups selected from fluoro, hydroxyl, hydroxymethyl, *tert*-butyloxycarbonyl and *tert*-butylcarbonyl.

[0080] In one embodiment, R^9 and R^{10} , together with the nitrogen atom to which they are attached, form a 4- to 7- membered heterocyclyl which is optionally substituted with 1 to 3 groups selected from halo, hydroxyl, hydroxyalkyl and $-\text{R}^x\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, where R^x is a direct bond or alkylene and each R^{13} and R^{14} are independently selected from (i) and (ii) as follows:

(i) R^{13} is hydrogen or alkyl; and R^{14} is alkyl, aryl, cycloalkyl, arylalkyl or heterocyclylalkyl; R^{13} and R^{14} are each optionally substituted with 1 to 5 groups Q^1 , each Q^1 independently selected from halo, hydroxyl, alkoxy, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, cycloalkyl, aryl, heterocyclyl and heteroaryl; and

(ii) R^{13} and R^{14} , together with the nitrogen atom to which they are attached, form heterocyclyl or heteroaryl; each optionally substituted with 1 to 5 groups Q^1 , each Q^1 independently selected from halo, hydroxyl, alkoxy, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, cycloalkyl, aryl, heterocyclyl and heteroaryl.

[0081] In one embodiment, R^9 and R^{10} , together with the nitrogen atom to which they are attached, form a 4- to 7- membered heterocyclyl which is optionally substituted with 1 to 3 groups selected from halo, hydroxyl, hydroxyalkyl and $-R^x C(O)NR^{13}R^{14}$, where R^x is a direct bond; and each R^{13} and R^{14} are independently selected from (i) and (ii) as follows:

(i) R^{13} is hydrogen, methyl or ethyl; and R^{14} is methyl, hydroxyethyl, *tert*-butyl, phenyl, morpholin-1-ylethyl, morpholin-1-ylpropyl, pyrrolidin-1-ylethyl, pyrrolidin-1-ylpropyl, piperidin-1-ylpropyl, piperidin-1-ylethyl, phenyl, cyclohexyl, cyclopropyl or cyclopentyl; where R^{13} and R^{14} are optionally substituted with 1 or 2 groups selected from halo, hydroxyl, hydroxyalkyl, alkoxy, hydroxyalkoxy and alkoxyalkoxy; and

(ii) R^{13} and R^{14} , together with the nitrogen atom to which they are attached, form pyrrolidinyl, piperidinyl or morpholinyl, each optionally substituted with 1 or 2 groups selected from halo, hydroxyl and hydroxyalkyl.

[0082] In one embodiment, R^9 and R^{10} , together with the nitrogen atom to which they are attached, form a 4- to 6- membered heterocyclyl which is optionally substituted with 1 to 3 groups selected from halo, hydroxyl, hydroxyalkyl and $-C(O)NR^{13}R^{14}$, where each R^{13} and R^{14} are independently selected from (i) and (ii) as follows:

(i) R^{13} is hydrogen, methyl or ethyl; and R^{14} is methyl, hydroxyethyl, *tert*-butyl, phenyl, morpholin-1-ylethyl, pyrrolidin-1-ylethyl, piperidin-1-ylpropyl, phenyl, cyclohexyl, cyclopropyl or cyclopentyl; and

(ii) R^{13} and R^{14} , together with the nitrogen atom to which they are attached, form pyrrolidinyl, piperidinyl or morpholinyl, where R^{13} and R^{14} are optionally substituted with 1 or 2 groups selected from fluoro, hydroxyl and hydroxymethyl.

[0083] In one embodiment, R^9 and R^{10} , together with the nitrogen atom to which they are attached, form a 4- to 7- membered heterocyclyl which is optionally substituted with 1 to 3 groups selected from halo, hydroxyl, hydroxyalkyl

$-\text{NR}^{15}\text{C}(\text{O})\text{R}^{16}$ and $-\text{R}^x\text{NR}^{17}\text{R}^{18}$, where R^x is a direct bond or alkylene; each R^{17} and R^{18} are independently selected from (i) and (ii) below:

(i) R^{17} and R^{18} are each independently hydrogen, alkyl or aryl, wherein the alkyl and aryl may each be optionally substituted with one to five substituents independently selected from the group consisting of halo, alkyl and $-\text{R}^x\text{OR}^{15}$; and

(ii) R^{17} and R^{18} , together with the nitrogen atom to which they are attached, form heterocyclyl or heteroaryl which is optionally substituted with one or more substituents independently selected from the group consisting of halo, alkyl, haloalkyl, hydroxyalkyl, and $-\text{R}^x\text{OR}^{15}$;

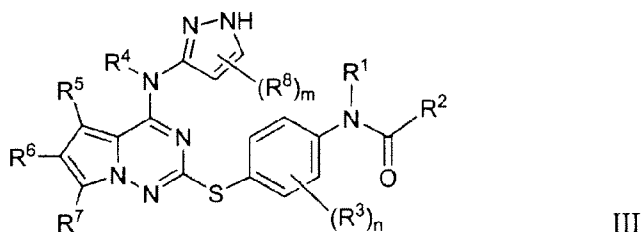
R^{16} is alkyl or alkoxy; and

R^{15} is hydrogen or alkyl.

[0084] In one embodiment, R^9 and R^{10} , together with the nitrogen atom to which they are attached, form a 4- to 7- membered heterocyclyl which is optionally substituted with 1 to 3 groups selected from halo, hydroxyl, hydroxyalkyl, $-\text{NR}^{15}\text{C}(\text{O})\text{R}^{16}$ and $-\text{NR}^{17}\text{R}^{18}$, R^{17} and R^{18} are each independently hydrogen, alkyl, haloaryl, or alkoxyaryl, R^{16} is alkyl or alkoxy, and R^{15} is hydrogen or alkyl.

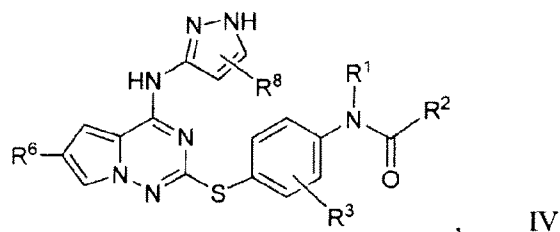
[0085] In one embodiment, R^9 and R^{10} , together with the nitrogen atom to which they are attached, form a 4- to 7- membered heterocyclyl which is optionally substituted with 1 to 3 groups selected from halo, hydroxyl, hydroxyalkyl, *tert*butyloxycarbonylamino, isopropylcarbonylamino, *tert*butylcarbonylamino, 3-chlorophenylamino, 3-fluorophenylamino, 3-methoxyphenylamino, 3,4-difluorophenylamino, 4-fluorophenylamino and 2-fluorophenylamino.

[0086] In one embodiment, the compounds have formula (III),



or pharmaceutically acceptable salts, solvates, hydrates or clathrates thereof, wherein the variables are as described elsewhere herein.

[0087] In one embodiment, the compounds have formula (IV)



wherein

R^1 is hydrogen;

R^3 is halo;

R^8 is alkyl, cycloalkyl, or haloalkyl;

R^6 is hydrogen, or $-NHC(O)R^xNR^{19}R^{20}$;

R^{19} and R^{20} are independently selected from (i) or (ii) below:

(i) R^{19} and R^{20} are each independently hydrogen, alkyl or haloalkyl; or

(ii) R^{19} and R^{20} , together with the nitrogen atom to which they are

attached, form a 5 or 6 membered heterocycle which is optionally substituted with one or more substituents independently selected from the group consisting of halo and alkyl;

R^2 is $-CH_2-NR^9R^{10}$;

R^9 and R^{10} are selected as follows:

i) R^9 and R^{10} are each independently hydrogen, alkyl, hydroxyalkyl, haloalkyl or cycloalkyl; or

ii) R^9 and R^{10} , together with the nitrogen atom to which they are attached, form a 4-7 membered heterocyclyl which is optionally substituted with 1 to 5 groups, each independently selected from halo, cyano, alkyl, haloalkyl, alkenyl, haloalkenyl, alkenyl, haloalkynyl, $=N-OH$, $-R^xOR^{16}$, $-R^xS(O)_tR^{16}$, $-R^xC(O)R^{16}$, $-R^xNR^{17}R^{18}$, $-R^xNR^{15}C(O)R^{16}$, and $-R^xC(O)NR^{13}R^{14}$.

each R^{13} and R^{14} are independently selected from (i) and (ii) as follows:

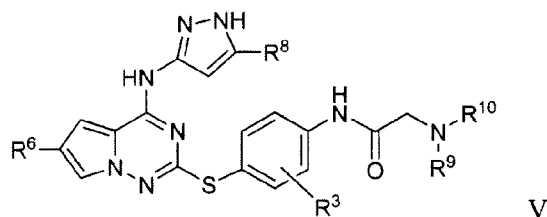
(i) R^{13} is hydrogen or alkyl; and R^{14} is alkyl, aryl, or cycloalkyl; R^{13} and R^{14} are each optionally substituted with 1 to 5 groups Q^1 , each Q^1 independently selected from halo, hydroxyl, alkoxy, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, cycloalkyl, aryl, heterocyclyl and heteroaryl; and

(ii) R^{13} and R^{14} , together with the nitrogen atom to which they are attached, form heterocyclyl or heteroaryl, each optionally substituted with 1 to 5 groups Q^1 , each Q^1 independently selected from halo, hydroxyl, alkoxy, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, cycloalkyl, aryl, heterocyclyl and heteroaryl;

R^{16} is hydrogen, alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroarylalkyl; wherein R^{16} is optionally substituted with 1 to 3 Q^2 , each Q^2 independently selected from alkyl, hydroxyl, alkoxy, aryloxy, halo, haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloaryl and alkoxyalkyl; and when Q^2 is selected from alkyl, alkoxy, aryloxy, haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloaryl and alkoxyalkyl, each Q^2 is independently optionally substituted with 1 to 5 Q^3 , each Q^3 independently selected from alkyl and halo; and

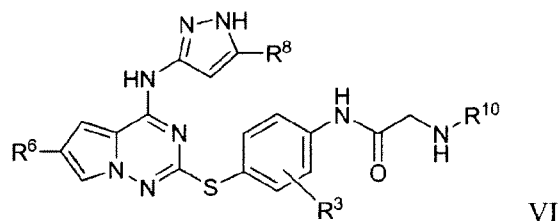
t is 0, 1 or 2.

[0088] In one embodiment, the compounds have formula (V),



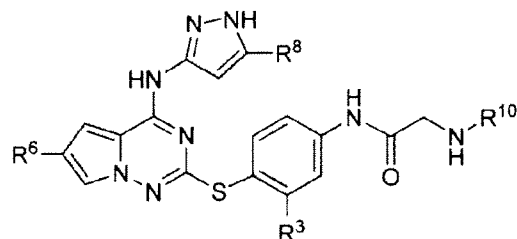
or pharmaceutically acceptable salts, solvates, hydrates or clathrates thereof, wherein the variables are as described elsewhere herein.

[0089] In one embodiment, the compounds have formula (VI),



or pharmaceutically acceptable salts, solvates, hydrates or clathrates thereof, wherein R^{10} is alkyl, hydroxyalkyl, haloalkyl or cycloalkyl and the other variables are as described elsewhere herein.

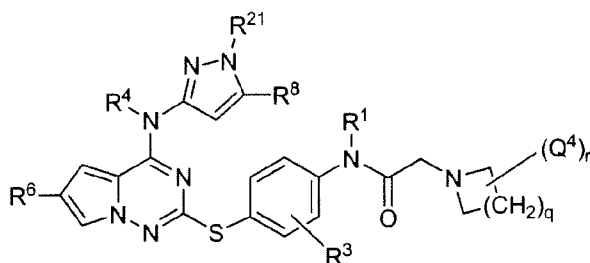
[0090] In one embodiment, the compounds have formula (VIA),



VIA

or pharmaceutically acceptable salts, solvates, hydrates or clathrates thereof, wherein R^{10} is alkyl, hydroxyalkyl, haloalkyl or cycloalkyl and the other variables are as described elsewhere herein.

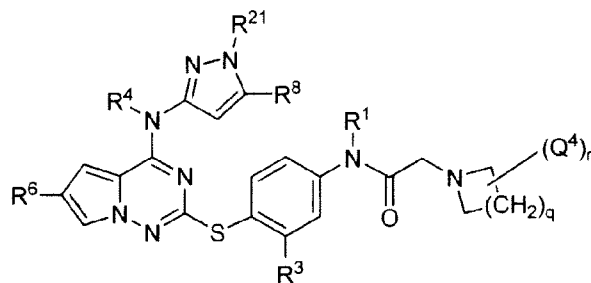
[0091] In one embodiment, the compounds have formula (VII),



VII

or pharmaceutically acceptable salts, solvates, hydrates or clathrates thereof, where q is 1, 2 or 3; r is 0, 1, 2 or 3; each Q^4 is independently selected from halo, cyano, alkyl, haloalkyl, $=N-OH$, $-R^xOR^{16}$, $-R^xS(O)_tR^{16}$, $-R^xC(O)R^{16}$, $-R^xNR^{17}R^{18}$, $-R^xNR^{15}C(O)R^{16}$ and $-R^xC(O)NR^{13}R^{14}$; and other variables are as described elsewhere herein.

[0092] In one embodiment, the compounds have formula (VIIA),

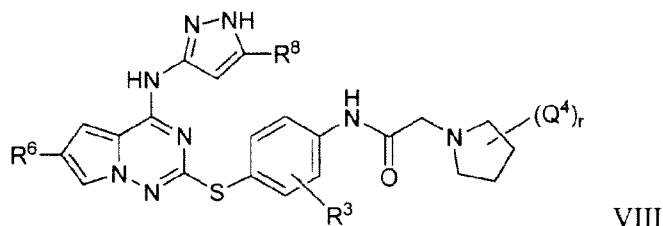


VIIA

or pharmaceutically acceptable salts, solvates, hydrates or clathrates thereof, where q is 1, 2 or 3; r is 0, 1, 2 or 3; each Q^4 is independently selected from halo, cyano, alkyl, haloalkyl, $=N-OH$, $-R^xOR^{16}$, $-R^xS(O)_tR^{16}$, $-R^xC(O)R^{16}$, $-R^xNR^{17}R^{18}$, $-R^xNR^{15}C(O)R^{16}$ and $-R^xC(O)NR^{13}R^{14}$; and other variables are as described elsewhere herein.

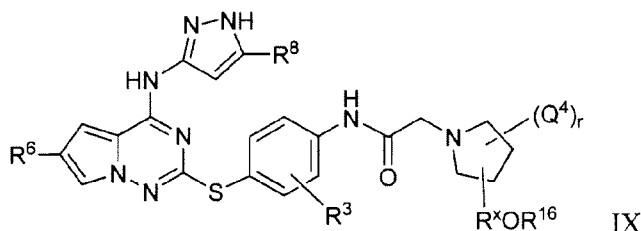
[0093] In one embodiment, each Q^4 is independently selected from halo, hydroxyl, alkoxy, hydroxyalkyl. In one embodiment, each Q^4 is independently selected from fluoro, hydroxyl, hydroxymethyl and hydroxyethyl.

[0094] In one embodiment, the compounds have formula (VIII),



or pharmaceutically acceptable salts, solvates, hydrates or clathrates thereof, wherein each Q^4 is independently selected from halo, hydroxyl, hydroxyalkyl, alkoxy, hydroxyalkoxy and alkoxyalkoxy and the other variables are as described elsewhere herein.

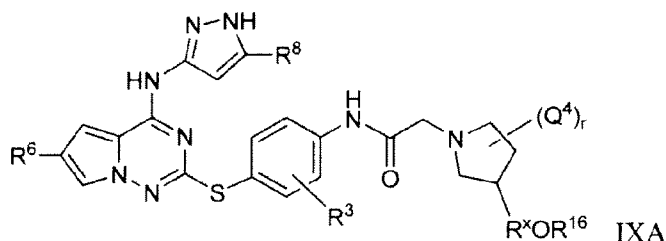
[0095] In one embodiment, the compounds have formula (IX),



or pharmaceutically acceptable salts, solvates, hydrates or clathrates thereof, wherein each Q^4 is independently selected from halo, hydroxyl, alkoxy, and hydroxyalkyl; and the other variables are as described elsewhere herein. In one embodiment, r is 0.

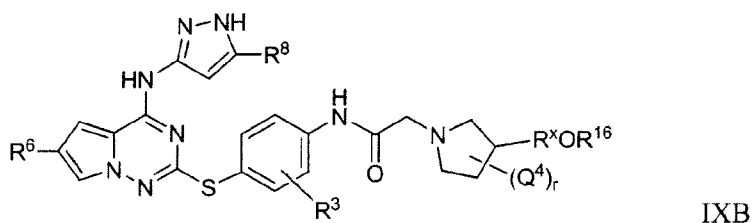
[0096] In one embodiment, the compounds have formula (IX), where R^x is a direct bond or alkylene; R^{16} is hydrogen, alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroarylalkyl; wherein R^{16} is optionally substituted with 1 to 3 Q^2 , each Q^2 independently selected from alkyl, hydroxyl, alkoxy, aryloxy, halo, haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloaryl and alkoxyalkyl; when Q^2 is selected from alkyl, alkoxy, aryloxy, haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloaryl and alkoxyalkyl, each Q^2 is independently optionally substituted with 1 to 5 Q^3 , each Q^3 independently selected from alkyl and halo; each Q^4 is independently selected from halo, hydroxyl and hydroxyalkyl; and other variables are as described elsewhere herein.

[0097] In one embodiment, the compounds have formula (IXA),



or pharmaceutically acceptable salts, solvates, hydrates or clathrates thereof, wherein each Q^4 is independently selected from halo, alkoxy, hydroxyl and hydroxyalkyl; and the other variables are as described elsewhere herein.

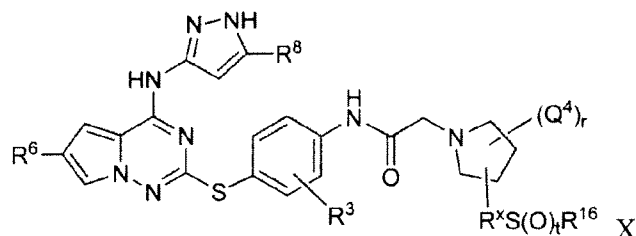
[0098] In one embodiment, the compounds have formula (IXB),



or pharmaceutically acceptable salts, solvates, hydrates or clathrates thereof, wherein each Q^4 is independently selected from halo, hydroxyl, alkoxy and hydroxyalkyl; and the other variables are as described elsewhere herein.

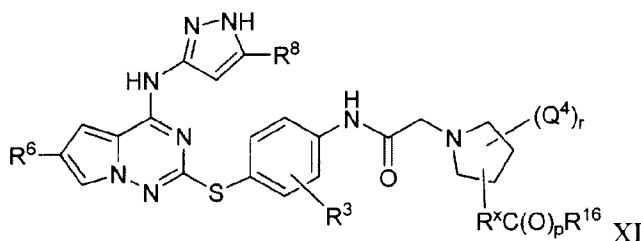
[0099] In one embodiment, the compounds have formula IX, IXA or IXB, where R^x is a direct bond or alkylene; R^{16} is hydrogen, alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroarylalkyl; wherein R^{16} is optionally substituted with 1 to 3 groups Q^2 , each Q^2 independently selected from alkyl, hydroxyl, alkoxy, aryloxy, halo, haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloaryl and alkoxyalkyl; where Q^2 is selected from alkyl, alkoxy, aryloxy, haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloaryl and alkoxyalkyl, each Q^2 group is independently optionally substituted with 1 to 5 groups Q^3 , each Q^3 independently selected from alkyl and halo; each Q^4 is independently selected from halo, hydroxyl, alkoxy and hydroxyalkyl; and other variables are as described elsewhere herein. In one embodiment, R^x is a direct bond.

[0100] In one embodiment, the compounds have formula (X),



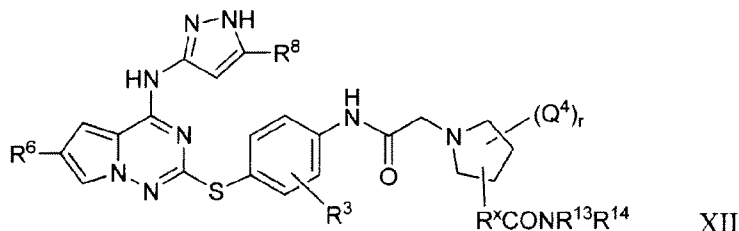
or pharmaceutically acceptable salts, solvates, hydrates or clathrates thereof, where R^x is a direct bond or alkylene; R^{16} is *t*-butyl; *t* is 0, 1, or 2; each Q^4 is independently selected from halo, hydroxyl, alkoxy and hydroxyalkyl; and the other variables are as described elsewhere herein.

[00101] In one embodiment, the compounds have formula (XI),



or pharmaceutically acceptable salts, solvates, hydrates or clathrates thereof, where where R^x is a direct bond or alkylene; R^{16} is alkyl; *p* is 1 or 2; each Q^4 is independently selected from halo, hydroxyl, alkoxy and hydroxyalkyl; and the other variables are as described elsewhere herein.

[00102] In one embodiment, the compounds have formula (XII),



or pharmaceutically acceptable salts, solvates, hydrates or clathrates thereof, where R^x is a direct bond or alkylene and R^{13} and R^{14} are selected as follows:

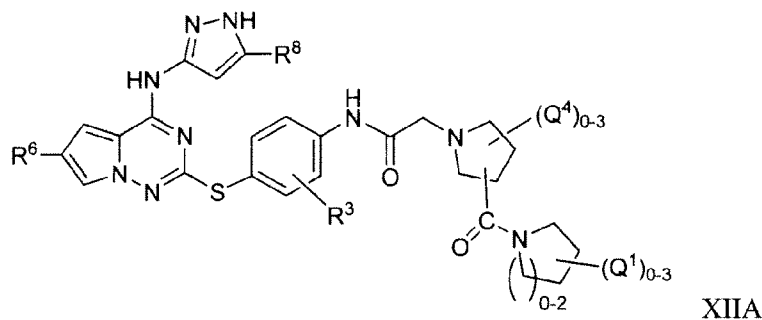
(i) R^{13} is hydrogen or alkyl; and R^{14} is alkyl, aryl, cycloalkyl or heterocyclalkyl; R^{13} and R^{14} are each optionally substituted with 1 to 5 Q^1 , each Q^1 independently selected from halo, hydroxyl, alkoxy, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, cycloalkyl, aryl, heterocyclyl and heteroaryl;

(ii) R^{13} and R^{14} , together with the nitrogen atom to which they are attached, form heterocyclyl or heteroaryl, each optionally substituted with 1 to 5

groups Q^1 , each Q^1 independently selected from halo, hydroxyl, alkoxy, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, cycloalkyl, aryl, heterocyclyl or heteroaryl;

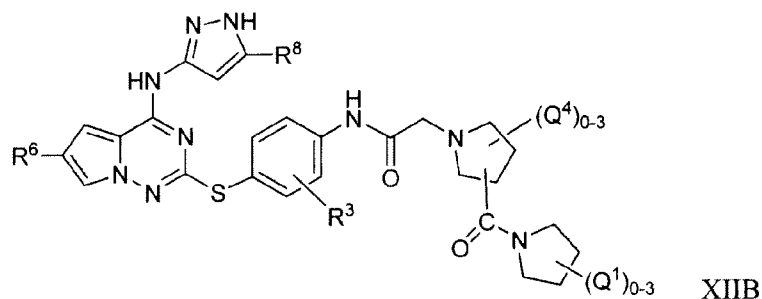
each Q^4 is independently selected from halo, hydroxyl, alkoxy and hydroxyalkyl; and the other variables are as described elsewhere herein.

[00103] In one embodiment, the compounds have formula (XIIA),



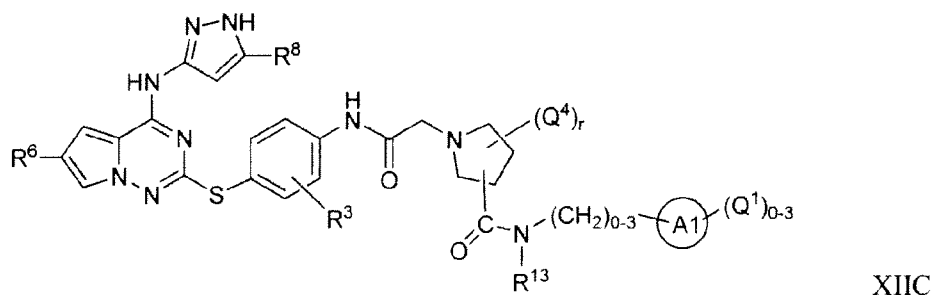
or pharmaceutically acceptable salts, solvates, hydrates or clathrates thereof, where each Q^4 is independently selected from halo, hydroxyl, alkoxy and hydroxyalkyl; each Q^1 is independently selected from halo, hydroxyl, alkoxy, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, cycloalkyl, aryl, heterocyclyl and heteroaryl; and the other variables are as described elsewhere herein.

[00104] In one embodiment, the compounds have formula (XIIB),



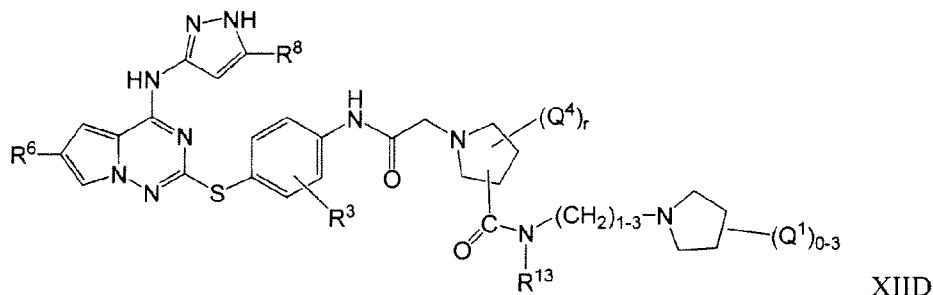
or pharmaceutically acceptable salts, solvates, hydrates or clathrates thereof, where the variables are as described elsewhere herein.

[00105] In one embodiment, the compounds have formula (XIIC),



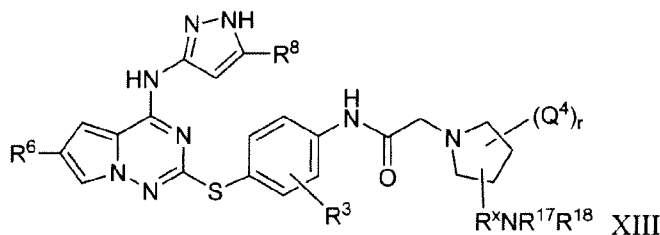
or pharmaceutically acceptable salts, solvates, hydrates or clathrates thereof, wherein A1 is aryl, cycloalkyl or heterocyclyl and each Q¹ is independently selected from halo, hydroxyl, alkoxy, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl and cycloalkyl; and the other variables are as described elsewhere herein.

[00106] In one embodiment, the compounds have formula (XIID),



or pharmaceutically acceptable salts, solvates, hydrates or clathrates thereof, wherein each Q¹ is independently selected from halo, hydroxyl, alkoxy, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl and cycloalkyl; and the other variables are as described elsewhere herein.

[00107] In one embodiment, the compounds have formula (XIII),



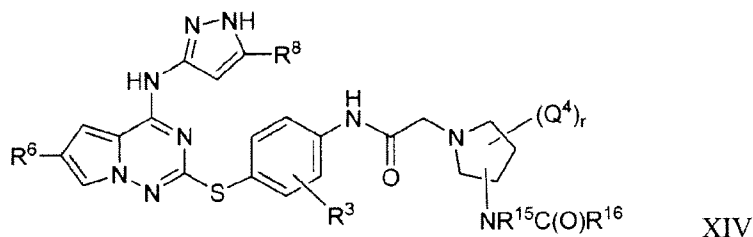
or pharmaceutically acceptable salts, solvates, hydrates or clathrates thereof, where where R^x is a direct bond or alkylene; R¹⁷ and R¹⁸ are independently selected from (i) or (ii) below:

- (i) R¹⁷ and R¹⁸ are each independently hydrogen or alkyl, wherein the alkyl and aryl may each be optionally substituted with one to five substituents independently selected from the group consisting of halo, alkyl and -R^xOR¹⁵; or
- (ii) R¹⁷ and R¹⁸, together with the nitrogen atom to which they are attached, form heterocyclyl or heteroaryl each of which is optionally substituted by one or more substituents independently selected from the group consisting of halo, alkyl, haloalkyl, hydroxyalkyl, and -R^xOR¹⁵;

R¹⁶ is alkyl or alkoxy;

R^{15} is hydrogen or alkyl; each Q^4 is independently selected from halo, hydroxyl, alkoxy and hydroxyalkyl; and the other variables are as described elsewhere herein.

[00108] In one embodiment, the compounds have formula (XIV),



or pharmaceutically acceptable salts, solvates, hydrates or clathrates thereof, where R^{16} is alkyl or alkoxy; R^{15} is hydrogen or alkyl; each Q^4 is independently selected from halo, hydroxyl, alkoxy and hydroxyalkyl; and the other variables are as described elsewhere herein.

[00109] In one embodiment, the compounds have formula (I), wherein:

R^1 and R^4 are each independently hydrogen or alkyl;

R^2 is selected from i) phenyl or pyrazolyl, each substituted with one or two substituents selected from halo and haloalkyl; and ii) cyclopropyl substituted with one or two substituents selected from halo and alkoxycarbonyl;

R^3 is halo or alkyl;

R^5 , R^6 and R^7 are each independently selected from hydrogen, halo, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl and $-R^xNR^{11}C(O)R^{12}$;

R^8 is alkyl, haloalkyl, hydroxyalkyl, cycloalkylalkyl, cycloalkyl or halocycloalkyl;

R^{11} is hydrogen or alkyl;

R^{12} is $R^xNR^{19}R^{20}$;

each R^x is independently an alkylene or a direct bond;

each R^{19} and R^{20} are independently selected from (i) and (ii) below:

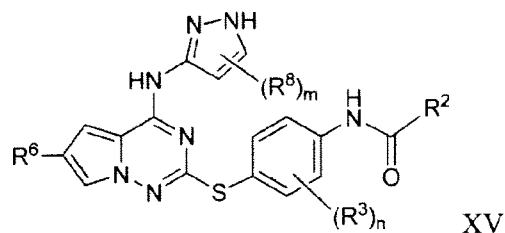
(i) R^{19} and R^{20} are each independently hydrogen, alkyl or haloalkyl; and

(ii) R^{19} and R^{20} , together with the nitrogen atom to which they are attached, form heterocyclyl which is optionally substituted with one, two or three substituents independently selected from the group consisting of halo and alkyl;

m is 0, 1 or 2; and

n is 0-4.

[00110] In one embodiment, the compounds have formula (XV),



or pharmaceutically acceptable salts, solvates, hydrates or clathrates thereof, wherein:

R^2 is selected from

- i) phenyl or pyrazolyl, each substituted with one or two substituents selected from halo and haloalkyl; and
- ii) cyclopropyl substituted with one or two substituents selected from halo and alkoxy carbonyl;

R^3 is halo;

R^6 is selected from hydrogen, halo, alkyl, haloalkyl, cycloalkyl and $-R^xNR^{11}C(O)R^{12}$;

R^8 is alkyl, haloalkyl, hydroxyalkyl, cycloalkylalkyl, cycloalkyl or halocycloalkyl;

R^{11} is hydrogen or alkyl;

R^{12} is $R^xNR^{19}R^{20}$;

each R^x is independently an alkylene or a direct bond;

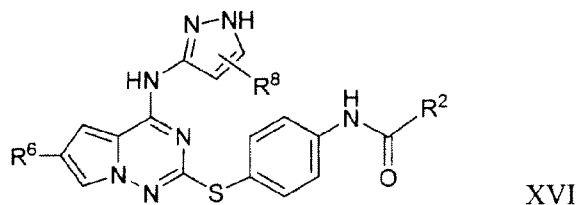
R^{19} and R^{20} are independently selected from (i) or (ii) below:

- (i) R^{19} and R^{20} are each independently hydrogen, alkyl or haloalkyl; or
- (ii) R^{19} and R^{20} , together with the nitrogen atom to which they are attached, form heterocyclyl which is optionally substituted with one, two or three substituents independently selected from the group consisting of halo and alkyl;

m is 0 or 1; and

n is 0 or 1.

[00111] In one embodiment, the compounds have formula (XVI),



or pharmaceutically acceptable salts, solvates, hydrates or clathrates thereof, wherein:

R^2 is selected from

i) phenyl and pyrazolyl, each substituted with one or two substituents selected from halo and haloalkyl; and

ii) cyclopropyl substituted with one or two substituents selected from halo and alkoxy carbonyl;

R^6 is selected from hydrogen and $-R^xNR^{11}C(O)R^{12}$;

R^8 is alkyl or cycloalkyl;

R^{11} is hydrogen;

R^{12} is $R^xNR^{19}R^{20}$;

each R^x is independently a direct bond, methylene or ethylene; and

R^{19} and R^{20} are independently selected from (i) or (ii) below:

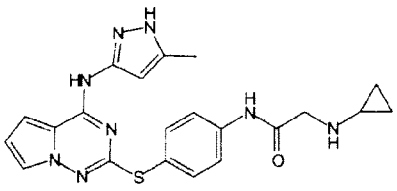
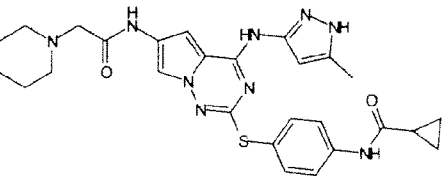
(i) R^{19} and R^{20} are each alkyl; or

(ii) R^{19} and R^{20} , together with the nitrogen atom to which they are attached, form heterocyclyl which is optionally substituted with an alkyl.

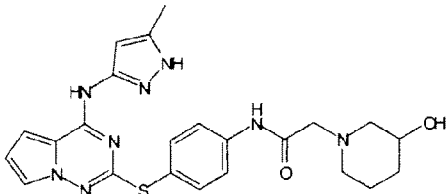
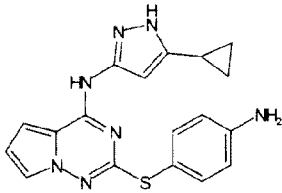
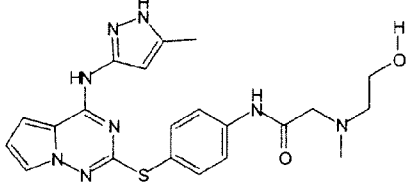
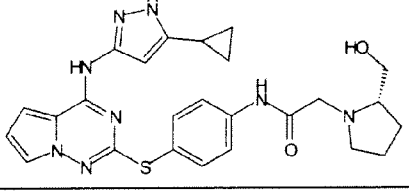
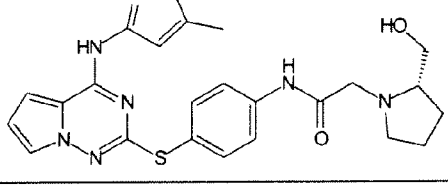
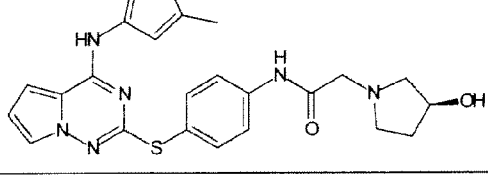
[00112] In another embodiment, the compounds have formula XVI, where R^2 is amino; provided that R^8 is cyclopropyl.

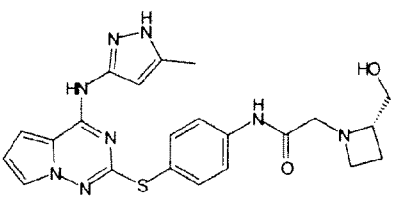
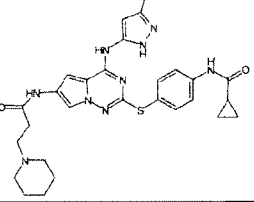
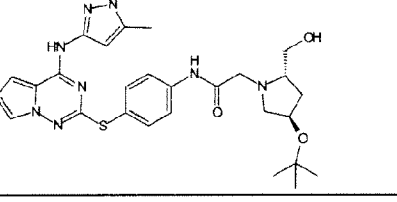
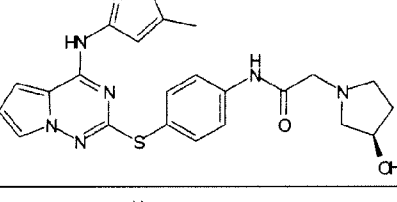
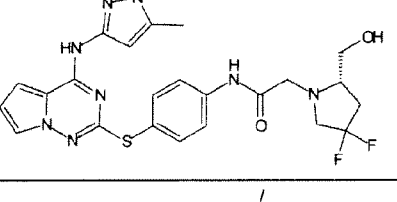
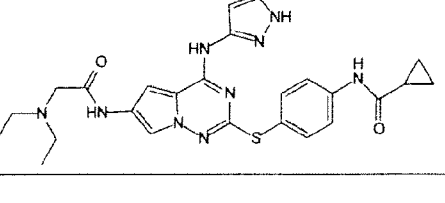
[00113] In another embodiment, the compound provided is selected from Table 1.

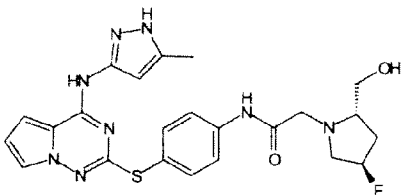
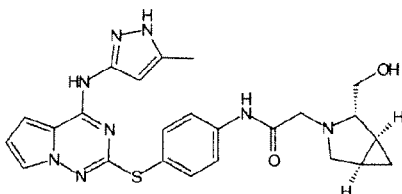
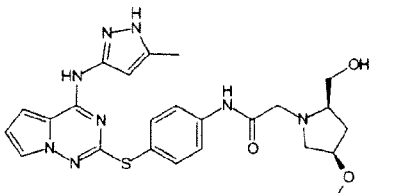
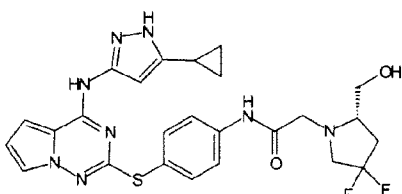
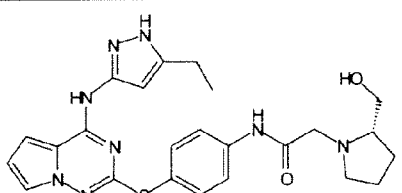
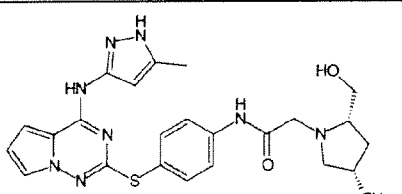
Table 1

Compound	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
	C	D	B	C	A
	B	B	B	A	A

Compound	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
	B	B	B	B	A
	D	B	A	A	A
	D	C	C	C	A
	C	B	B	B	A
	C	C	B	A	A
	C	B	A	A	A
	C	D	B	C	A

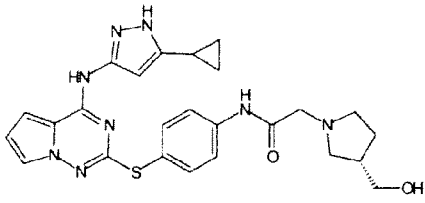
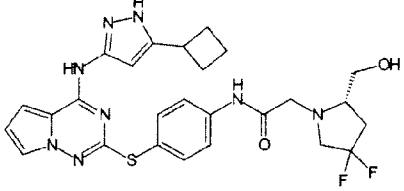
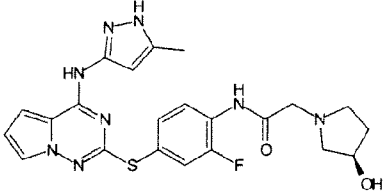
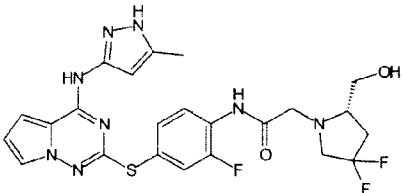
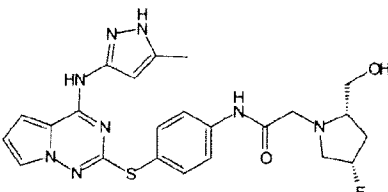
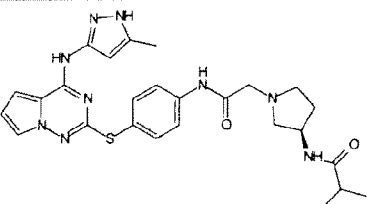
Compound	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
	D	C	A	B	A
	C	E	A	B	A
	C	E	B	B	A
	C	C	A	B	A
	C	C	A	B	A
	D	C	B	C	A

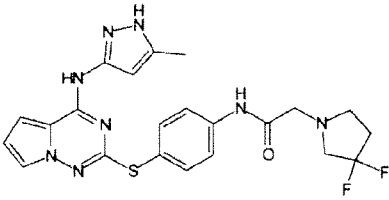
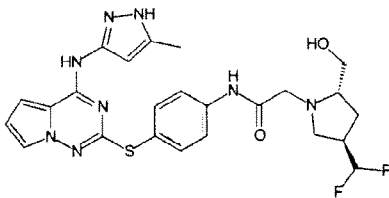
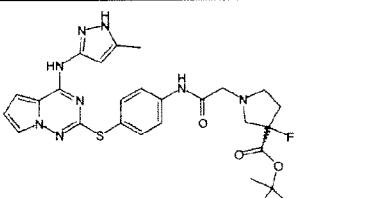
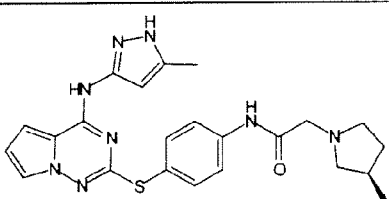
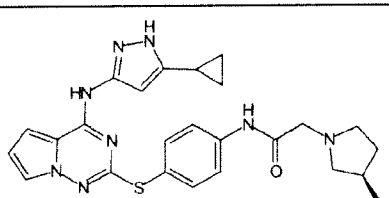
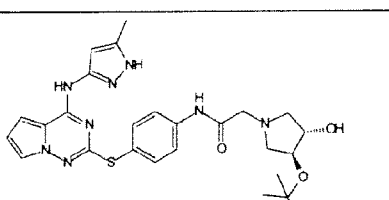
Compound	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
	C	C	A	C	A
	D	B	B	A	A
	A	A	A	B	A
	B	B	A	B	A
	A	A	A	B	A
	B	A	B	A	ND

Compound	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
	B	B	A	B	ND
	C	C	B	B	ND
	C	C	A	C	ND
	A	A	A	C	ND
	C	C	A	C	ND
	C	C	B	C	ND

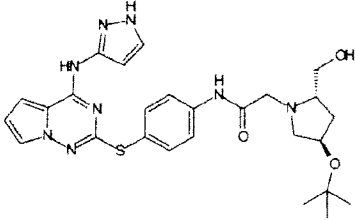
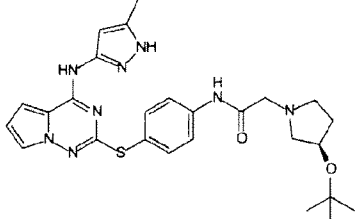
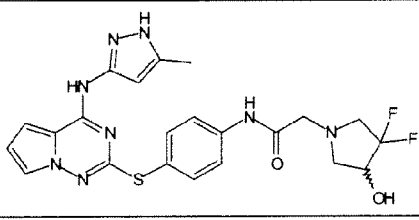
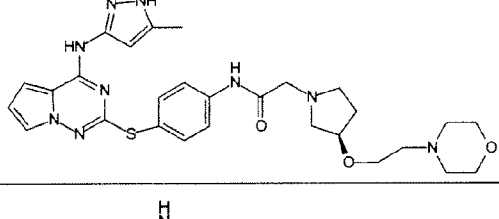
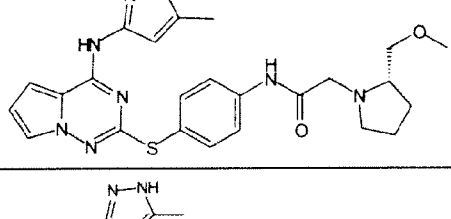
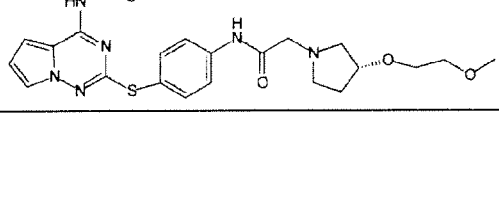
Compound	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
	C	B	A	B	ND
	B	B	B	C	ND
	C	B	A	B	ND
	C	B	B	C	ND
	B	A	A	B	ND
	C	C	C	C	ND

Compound	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
	D	D	B	C	ND
	B	B	A	C	ND
	D	D	A	B	ND
	B	B	A	A	ND
	B	B	A	C	ND
	C	C	B	C	ND

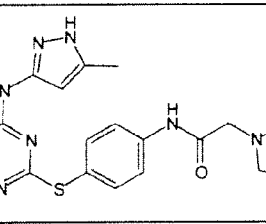
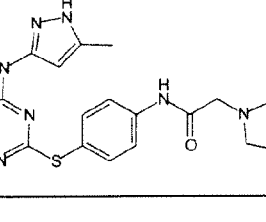
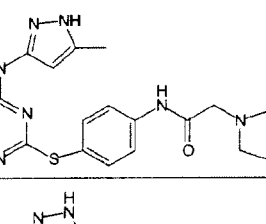
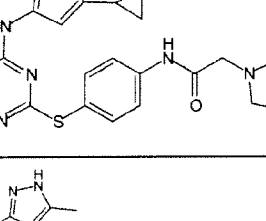
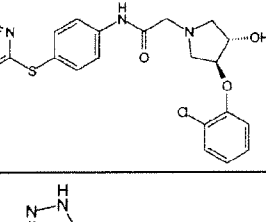
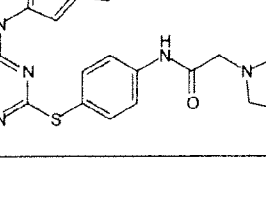
Compound	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
	B	B	B	C	ND
	D	C	C	C	ND
	B	B	A	A	ND
	B	B	A	B	ND
	A	A	A	A	ND
	B	A	A	B	ND

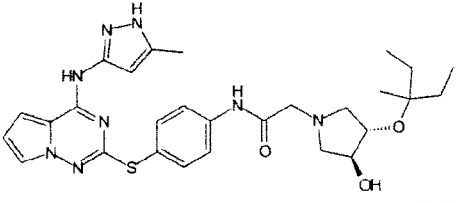
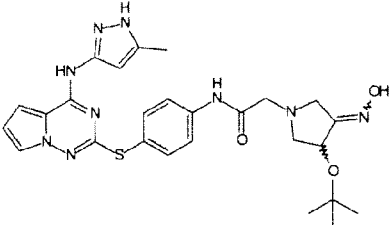
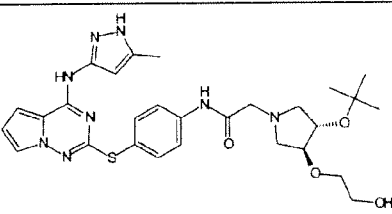
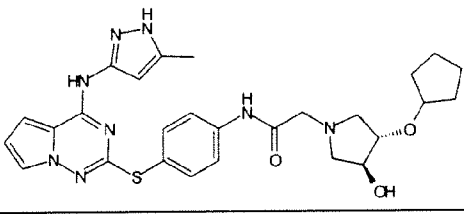
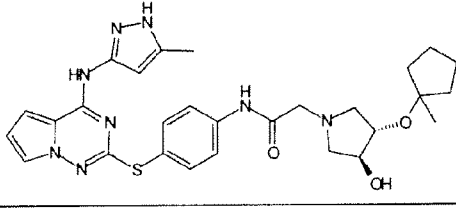
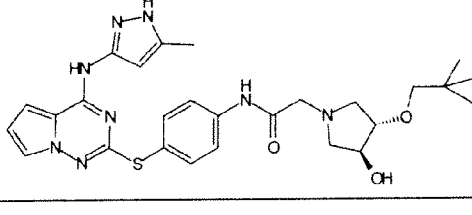
Compound	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
	B	B	A	B	ND
	C	C	A	B	ND
	B	B	B	C	ND
	D	D	B	C	ND
	B	B	A	B	ND
	A	A	A	B	ND

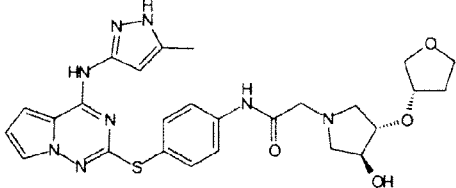
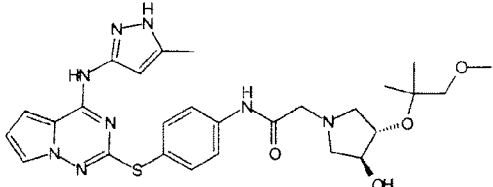
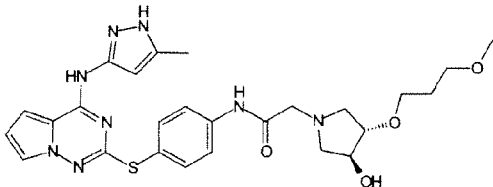
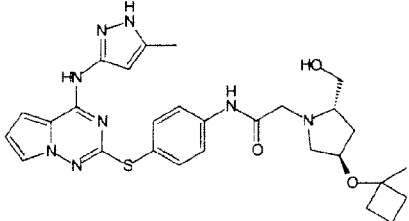
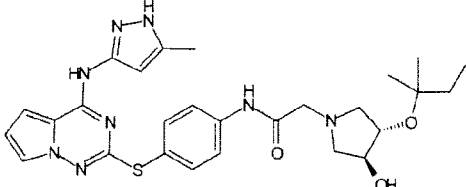
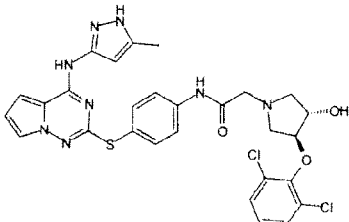
Compound	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
	C	D	C	C	ND
	B	C	B	C	ND
	A	A	A	B	ND
	B	B	A	B	ND
	A	A	A	A	ND
	A	A	A	A	ND

Compound	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
	B	C	A	C	ND
	A	A	A	C	ND
	B	A	A	A	ND
	A	A	A	B	ND
	C	C	A	A	ND
	A	A	A	A	ND

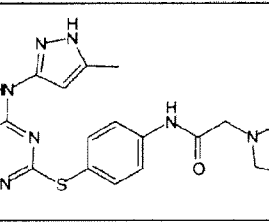
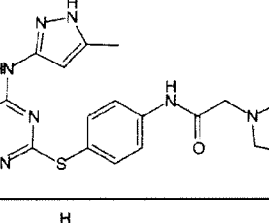
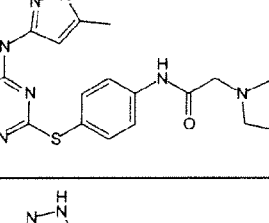
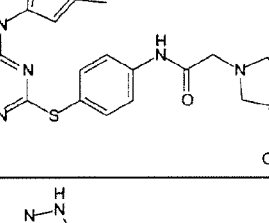
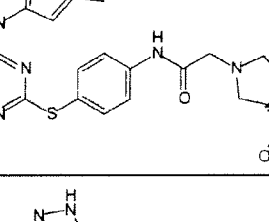
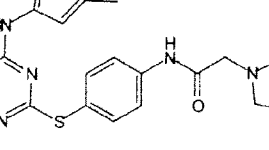
Compound	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
	B	A	C	C	ND
	B	B	A	B	ND
	A	A	C	C	ND
	B	A	A	C	ND
	A	A	A	B	ND
	B	A	B	C	ND

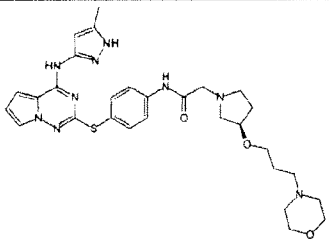
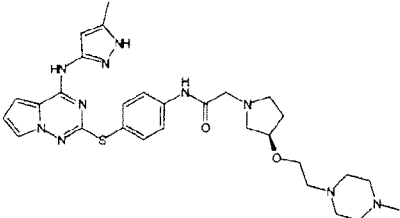
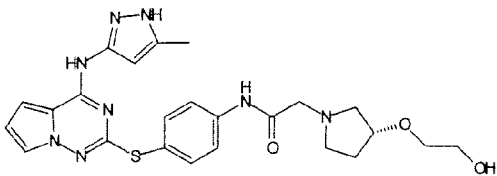
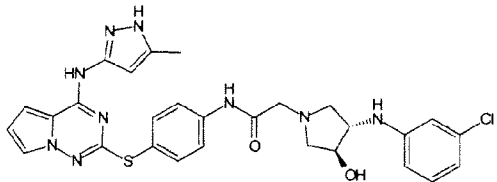
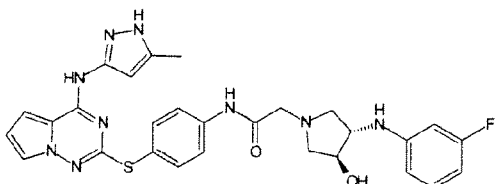
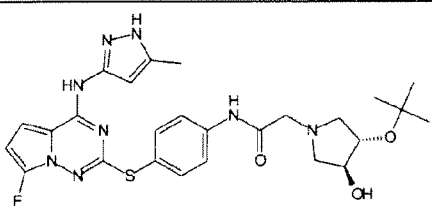
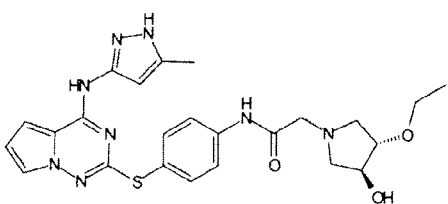
Compound	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
	B	A	B	B	ND
	B	A	C	C	ND
	A	A	A	A	ND
	A	A	A	C	ND
	B	A	C	C	ND
	B	A	B	B	ND

Compound	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
	B	A	B	C	ND
	A	A	A	A	ND
	B	A	A	A	ND
	A	A	A	B	ND
	B	A	A	B	ND
	B	A	B	C	ND

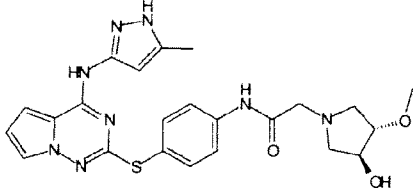
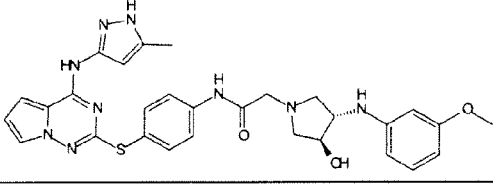
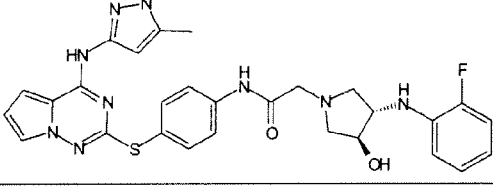
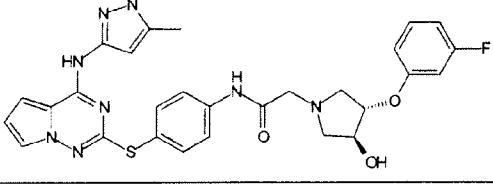
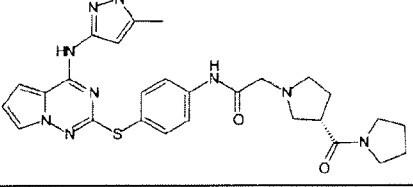
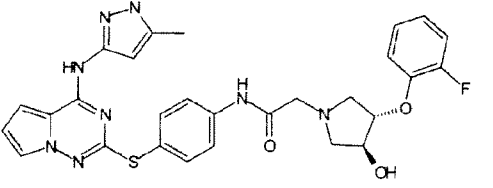
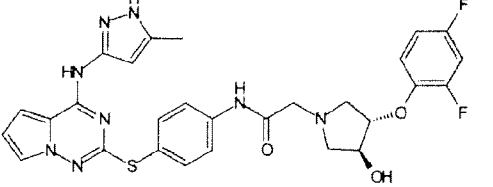
Compound	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
	C	B	A	A	ND
	A	A	A	B	ND
	B	B	A	A	ND
	A	A	A	A	ND
	A	A	A	A	ND
	B	A	B	B	ND

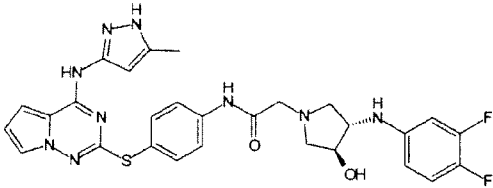
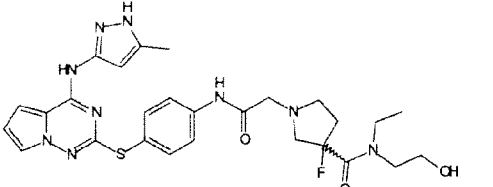
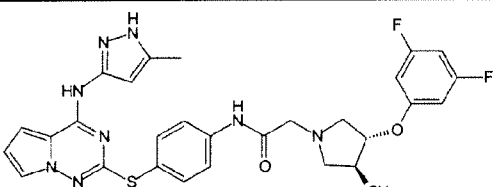
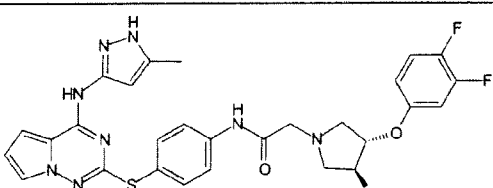
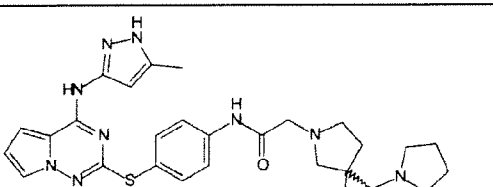
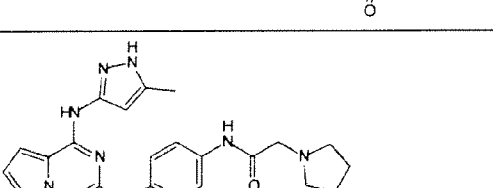
Compound	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
	A	A	A	A	ND
	A	A	A	A	ND
	A	A	A	A	ND
	C	B	A	B	ND
	B	A	B	C	ND
	A	A	A	A	ND

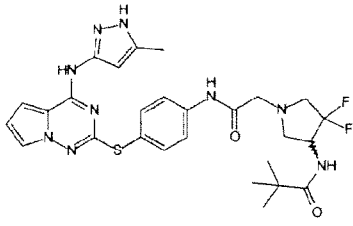
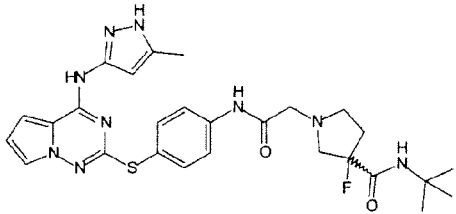
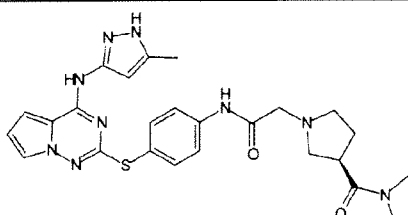
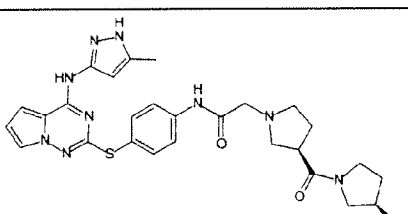
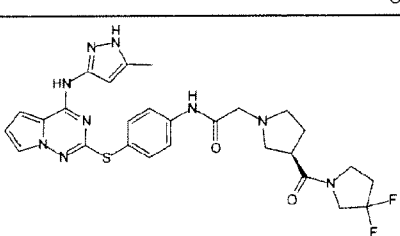
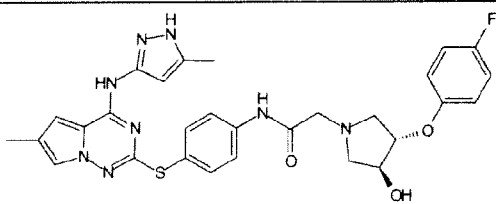
Compound	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
	A	A	A	A	ND
	A	A	A	A	ND
	B	A	A	B	ND
	A	A	A	B	ND
	A	A	A	A	ND
	C	C	A	A	ND

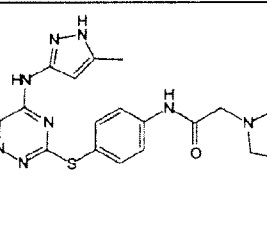
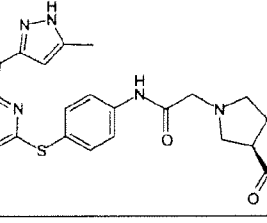
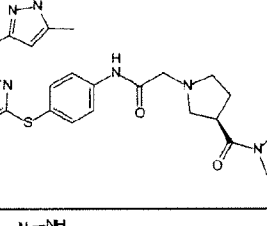
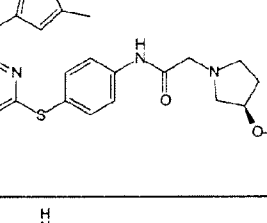
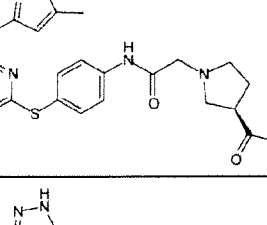
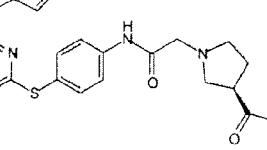
Compound	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
	A	A	A	A	ND
	C	A	A	B	ND
	A	A	A	A	ND
	B	A	A	C	ND
	B	A	A	B	ND
	B	B	A	C	ND
	A	A	A	A	ND

Compound	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
	B	A	A	B	ND
	A	A	A	A	ND
	A	A	B	C	ND
	C	B	B	C	ND
	C	B	B	C	ND
	B	A	A	B	ND

Compound	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
	B	B	A	A	ND
	B	A	A	C	ND
	A	A	A	B	ND
	B	A	A	B	ND
	A	A	A	A	ND
	A	A	A	A	ND
	B	A	B	B	ND

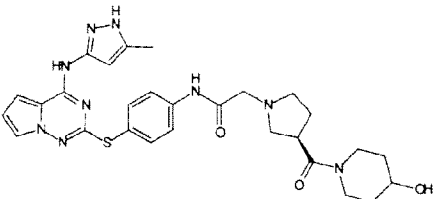
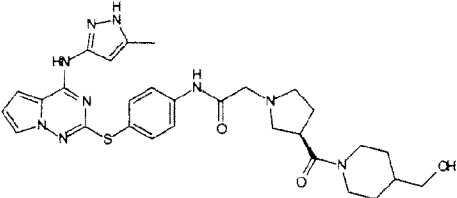
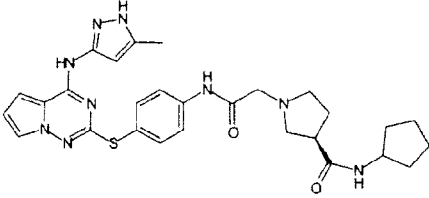
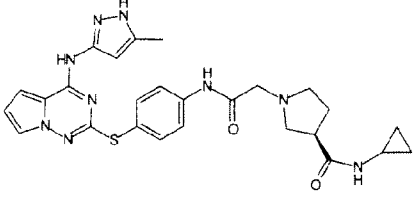
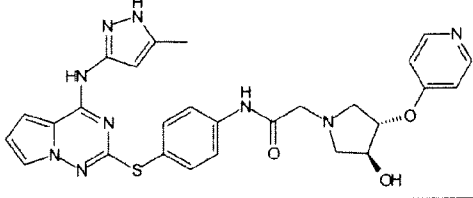
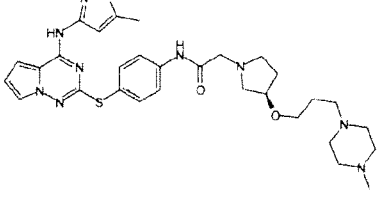
Compound	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
	B	A	B	C	ND
	C	D	A	A	ND
	B	A	C	C	ND
	B	A	C	C	ND
	A	A	A	A	ND
	B	A	B	C	ND

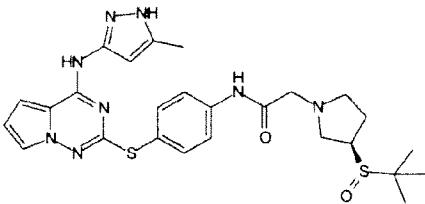
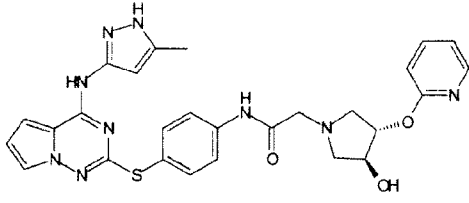
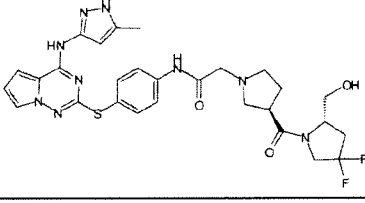
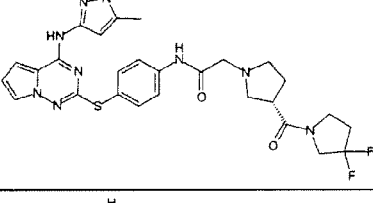
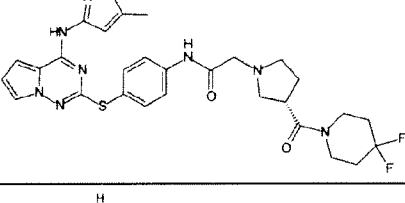
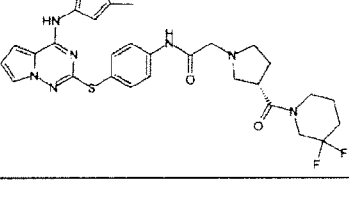
Compound	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
	B	A	A	A	ND
	A	A	A	B	ND
	A	A	A	A	ND
	B	A	A	A	ND
	A	A	A	A	ND
	B	A	C	C	ND

Compound	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
	A	A	A	A	ND
	A	A	A	A	ND
	C	B	A	A	ND
	B	B	A	A	ND
	B	A	A	A	ND
	C	B	A	A	ND

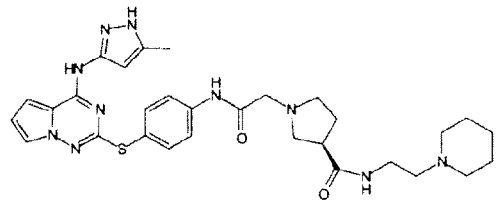
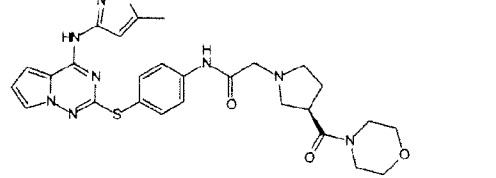
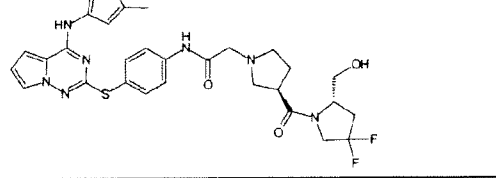
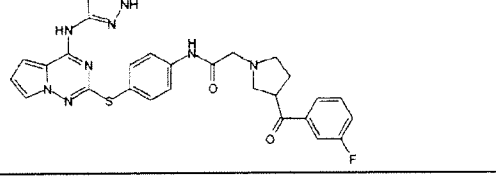
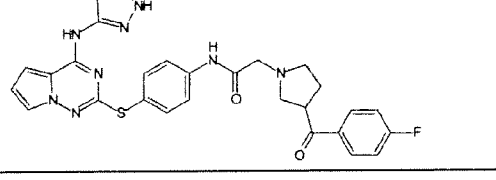
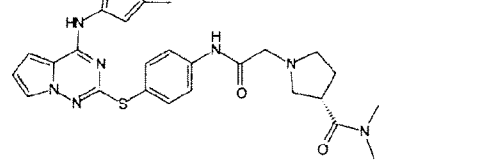
Compound	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
	B	A	A	A	ND
	B	A	A	A	ND
	B	A	A	ND	
	B	A	A	A	ND
	A	A	A	A	ND
	A	A	A	B	ND

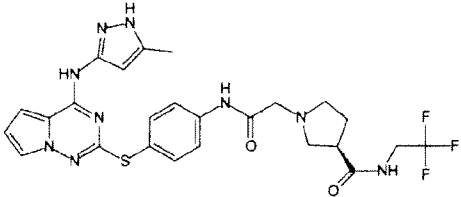
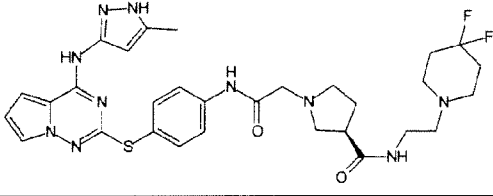
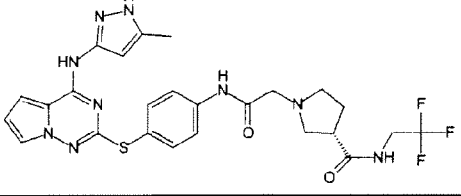
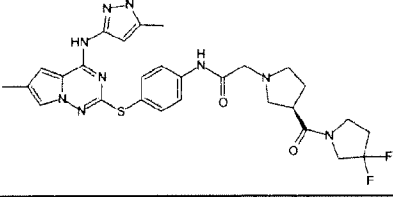
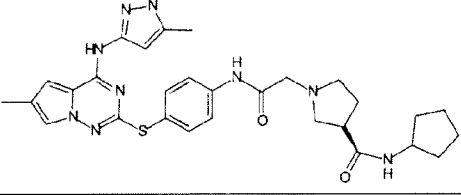
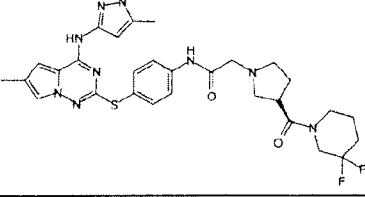
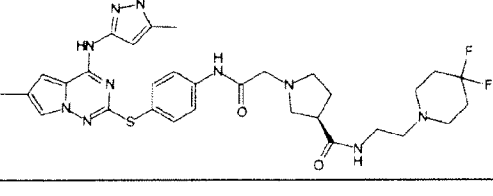
Compound	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
	A	A	A	A	ND
	B	A	A	A	ND
	A	A	A	A	ND
	A	A	A	B	ND
	A	A	A	A	ND
	B	A	A	A	ND

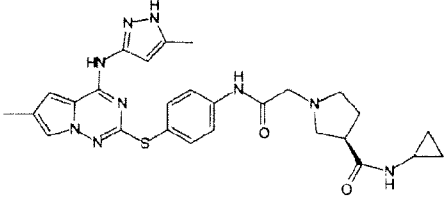
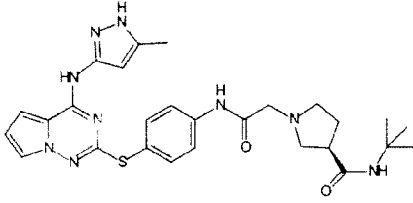
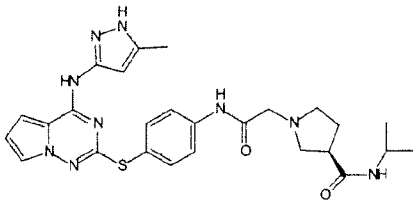
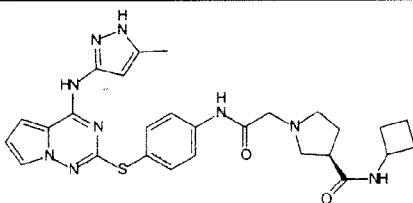
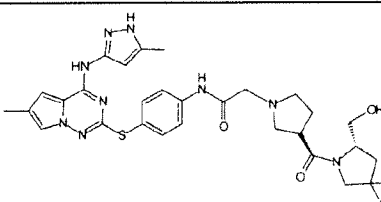
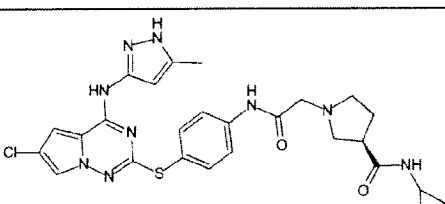
Compound	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
	C	B	A	A	ND
	B	B	A	A	ND
	A	A	A	A	ND
	A	A	A	A	ND
	C	B	A	A	ND
	B	A	A	ND	

Compound	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
	A	A	A	A	ND
	A	A	A	A	ND
	A	A	A	A	ND
	B	A	A	A	ND
	B	B	A	A	ND
	B	B	A	A	ND

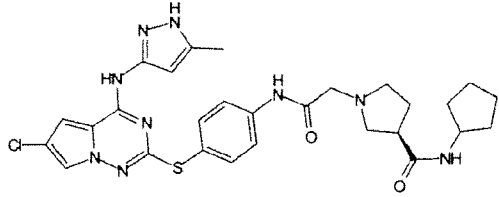
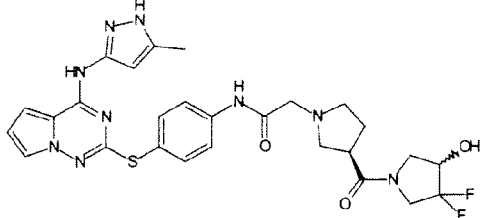
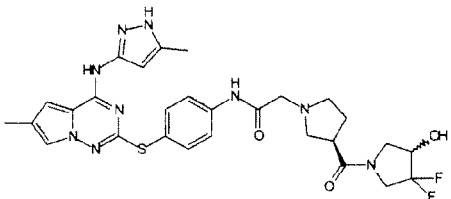
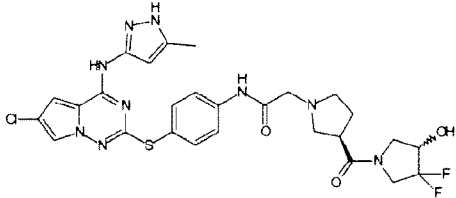
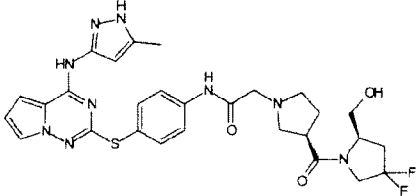
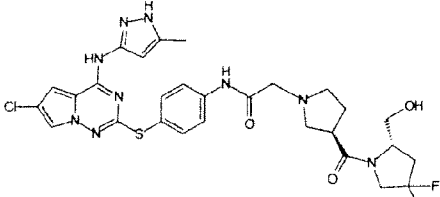
Compound	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
	A	A	A	A	ND
	A	A	A	A	ND
	A	A	A	A	ND
	B	A	A	A	ND
	C	B	A	B	ND
	B	B	A	A	ND

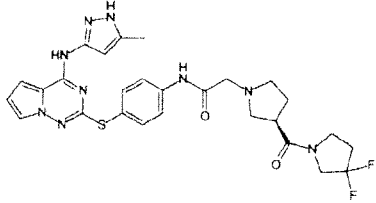
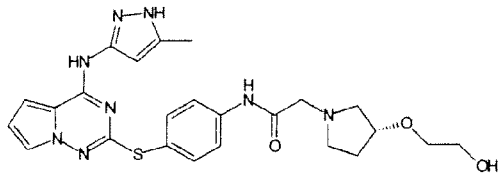
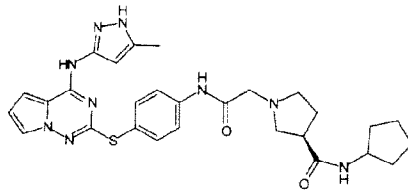
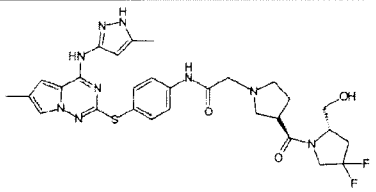
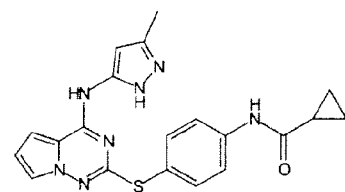
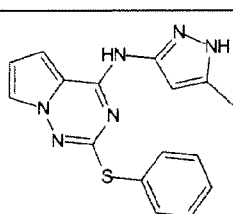
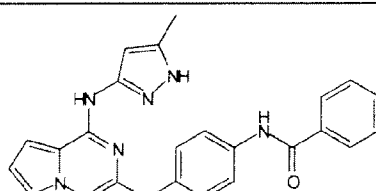
Compound	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
	ND	A	ND	ND	ND
	ND	A	ND	ND	ND
	ND	A	ND	ND	ND
	A	A	A	A	ND
	A	A	A	A	ND
	B	A	A	A	ND

Compound	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
	A	A	A	A	ND
	A	A	A	A	ND
	A	A	A	A	ND
	A	A	A	A	ND
	A	A	A	A	ND
	A	A	A	B	ND
	B	A	B	A	ND

Compound	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
	A	A	A	A	ND
	A	A	A	A	ND
	A	A	A	A	ND
	A	A	A	A	ND
	A	A	A	B	ND
	A	A	B	B	ND

Compound	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
	B	A	C	C	ND
	C	A	C	C	ND
	C	B	A	A	ND
	A	A	A	B	ND
	A	A	A	A	ND
	A	A	B	C	ND
	B	A	B	C	ND

Compound	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
	A	A	A	C	ND
	A	A	A	A	ND
	A	A	A	B	ND
	A	A	A	A	ND
	A	A	A	A	ND
	C	A	B	C	ND

Compound	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
	A	A	A	A	ND
	A	A	A	A	ND
	A	A	A	A	ND
	A	A	A	B	ND
	ND	D	ND	ND	ND
	ND	D	ND	ND	ND
	ND	D	ND	ND	ND

In Table 1, Phosphorylation Histone H3 and BrdU IC₅₀ (nM): A ≤50, 50<B≤150, 150<C≤300, D>300,
Aurora A, Aurora B and Aurora C Kd (nM): A ≤10, 10<B≤20, C>20; and
ND= no data.

[00114] In another embodiment, the compound provided is selected from:

[00115] 2-(diethylamino)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;

[00116] N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-(phenylamino)acetamide;

[00117] 2-(cyclopentylamino)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;

[00118] 2-(benzylamino)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;

[00119] N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-morpholinoacetamide;

[00120] (R)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-((1-phenylethyl)amino)acetamide;

[00121] N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-((1-phenylethyl)amino)acetamide;

[00122] 2-((1-hydroxy-2-methylpropan-2-yl)amino)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;

[00123] (S)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-((1-phenylethyl)amino)acetamide;

[00124] N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-((1-phenylethyl)amino)acetamide;

[00125] 2-((3-methoxyphenyl)amino)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;

[00126] N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-((pyridin-3-ylmethyl)amino)acetamide;

[00127] N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-(5-oxo-1,4-diazepan-1-yl)acetamide;

[00128] N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-(4-methylpiperazin-1-yl)acetamide;

- [00129] 2-(4-hydroxypiperidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00130] 2-(1,1-dioxidothiomorpholino)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00131] 2-(4-(hydroxymethyl)piperidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00132] 2-(4-(2-hydroxyethyl)piperazin-1-yl)-N-(4-((4-((3-methyl-1H-pyrazol-5-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00133] (S)-2-((1-hydroxypropan-2-yl)amino)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00134] 2-((1-hydroxypropan-2-yl)amino)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00135] 2-((2-(2-hydroxyethoxy)ethyl)amino)-N-(4-((4-((3-methyl-1H-pyrazol-5-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00136] 2-(4-(2-hydroxyethyl)piperidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00137] (R)-1-(2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)pyrrolidine-2-carboxamide;
- [00138] 1-(2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)pyrrolidine-2-carboxamide;
- [00139] (R)-2-((1-hydroxypropan-2-yl)amino)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00140] 2-((1-hydroxypropan-2-yl)amino)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00141] 2-(4-aminopiperidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00142] (R)-N-(4-((4-((5-ethyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-(2-(hydroxymethyl)pyrrolidin-1-yl)acetamide;
- [00143] N-(4-((4-((5-ethyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-(2-(hydroxymethyl)pyrrolidin-1-yl)acetamide;
- [00144] 2-((2-(dimethylamino)ethyl)amino)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;

- [00145] 2-((3-(dimethylamino)propyl)amino)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00146] 2-((3-hydroxypropyl)amino)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00147] (S)-2-(2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00148] 2-(2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00149] (R)-2-(2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00150] 2-(2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00151] N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-((2-(1-methylpyrrolidin-2-yl)ethyl)amino)acetamide;
- [00152] (R)-N-(4-((6-(2-(2-(hydroxymethyl)pyrrolidin-1-yl)acetamido)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide;
- [00153] N-(4-((6-(2-(2-(hydroxymethyl)pyrrolidin-1-yl)acetamido)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide;
- [00154] N-(4-((6-(2-(4-(hydroxymethyl)piperidin-1-yl)acetamido)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide;
- [00155] 3-methyl-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)-6-(2-(piperidin-1-yl)acetamido)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)picolinamide;
- [00156] N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)-6-(2-morpholinoacetamido)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide;
- [00157] N-(4-((6-(2-(cyclopropylamino)acetamido)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide;
- [00158] N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)-6-(2-(pyrrolidin-1-yl)acetamido)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide;

- [00159] N-(4-((6-(2-((2-(2-hydroxyethoxy)ethyl)amino)acetamido)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide;
- [00160] (S)-N-(4-((6-(2-(2-(hydroxymethyl)pyrrolidin-1-yl)acetamido)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide;
- [00161] N-(4-((6-(2-(2-(hydroxymethyl)pyrrolidin-1-yl)acetamido)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide;
- [00162] N-(4-((6-(2-(4-hydroxypiperidin-1-yl)acetamido)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide;
- [00163] N-(4-((6-(2-(4-(2-hydroxyethyl)piperidin-1-yl)acetamido)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide;
- [00164] N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)-6-(2-(4-methylpiperazin-1-yl)acetamido)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide;
- [00165] (R)-N-(4-((6-(2-(3-hydroxypyrrolidin-1-yl)acetamido)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide;
- [00166] N-(4-((6-(2-(3-hydroxypyrrolidin-1-yl)acetamido)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide;
- [00167] (S)-N-(4-((6-(2-(3-hydroxypyrrolidin-1-yl)acetamido)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide;
- [00168] N-(4-((6-(2-(3-hydroxypyrrolidin-1-yl)acetamido)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide;
- [00169] N-(4-((6-(2-(4-(2-hydroxyethyl)piperazin-1-yl)acetamido)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide;
- [00170] N-(4-((6-(2-(1,1-dioxidothiomorpholino)acetamido)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide;

- [00171] (R)-2-(2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)-6-(2-(piperidin-1-yl)acetamido)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00172] 2-(2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)-6-(2-(piperidin-1-yl)acetamido)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00173] N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclobutanecarboxamide
- [00174] N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclohexanecarboxamide
- [00175] 2,2,2-trifluoro-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide
- [00176] N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-4-(trifluoromethyl)nicotinamide
- [00177] N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-4-(1H-1,2,4-triazol-1-yl)benzamide
- [00178] N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)quinoline-3-carboxamide
- [00179] N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)picolinamide
- [00180] 6-fluoro-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)picolinamide
- [00181] N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-6-(trifluoromethyl)nicotinamide
- [00182] N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)nicotinamide
- [00183] 2-fluoro-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)nicotinamide
- [00184] N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)isonicotinamide
- [00185] 2-methyl-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)nicotinamide

- [00186] 5-methyl-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)nicotinamide
- [00187] N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)oxazole-5-carboxamide
- [00188] 2-methoxy-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)nicotinamide
- [00189] 2-chloro-6-methyl-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)nicotinamide
- [00190] N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-3-(trifluoromethyl)benzamide
- [00191] 4-methyl-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)nicotinamide
- [00192] 3-methyl-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)picolinamide
- [00193] 6-chloro-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)nicotinamide
- [00194] 2-bromo-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide;
- [00195] 6-methyl-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)picolinamide;
- [00196] 5-methyl-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)picolinamide;
- [00197] 2-cyclopropyl-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00198] 5-chloro-3-ethyl-1-methyl-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-1H-pyrazole-4-carboxamide;
- [00199] 5-chloro-1,3-dimethyl-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-1H-pyrazole-4-carboxamide;
- [00200] 1-methyl-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide;
- [00201] 1,3,5-trimethyl-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-1H-pyrazole-4-carboxamide;

- [00202] 1-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-3-(2-(trifluoromethyl)phenyl)urea;
- [00203] N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide;
- [00204] 3-cyclopropyl-1-methyl-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-1H-pyrazole-4-carboxamide;
- [00205] (1R,2R)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-(morpholinomethyl)cyclopropanecarboxamide;
- [00206] N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-(morpholinomethyl)cyclopropanecarboxamide;
- [00207] 2-chloro-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-6-(trifluoromethyl)benzamide;
- [00208] 1-methyl-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide;
- [00209] methyl 1-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)carbonyl)cyclopropanecarboxylate;
- [00210] 1-(dimethylamino)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide;
- [00211] (1S,2S)-ethyl 2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)carbonyl)cyclopropanecarboxylate;
- [00212] ethyl 2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)carbonyl)cyclopropanecarboxylate;
- [00213] 2-methyl-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-5-(trifluoromethyl)oxazole-4-carboxamide;
- [00214] (S)-2-methoxy-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-phenylacetamide;
- [00215] 2-methoxy-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-phenylacetamide;
- [00216] 1-hydroxy-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide;
- [00217] (1S,2R)-2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)carbonyl)cyclopropanecarboxylic acid;

- [00218] 2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)carbamoyl)cyclopropanecarboxylic acid;
- [00219] 2-amino-2-methyl-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)propanamide;
- [00220] 2-amino-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00221] (1S,2R)-N1-methyl-N2-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropane-1,2-dicarboxamide;
- [00222] N1-methyl-N2-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropane-1,2-dicarboxamide;
- [00223] (1R,2S)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-(morpholine-4-carbonyl)cyclopropanecarboxamide;
- [00224] N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-(morpholine-4-carbonyl)cyclopropanecarboxamide;
- [00225] 1-(5-(tert-butyl)isoxazol-3-yl)-3-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)urea;
- [00226] (R)-1-(2-(methoxymethyl)pyrrolidin-1-yl)-3-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)urea;
- [00227] 1-(2-(methoxymethyl)pyrrolidin-1-yl)-3-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)urea;
- [00228] N-(2-((4-(cyclopropanecarboxamido)phenyl)thio)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-6-yl)morpholine-4-carboxamide;
- [00229] 2-hydroxy-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00230] N-(4-((4-((5-(hydroxymethyl)-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide;
- [00231] 2-((4-aminophenyl)thio)-N-(5-(trifluoromethyl)-1H-pyrazol-3-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine;
- [00232] 2-(3-((2-((4-aminophenyl)thio)pyrrolo[2,1-f][1,2,4]triazin-4-yl)amino)-1H-pyrazol-5-yl)ethanol;

- [00233] 2-((4-aminophenyl)thio)-N-(5-propyl-1H-pyrazol-3-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine;
- [00234] (S)-1-(2-(hydroxymethyl)pyrrolidin-1-yl)-2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)ethanone;
- [00235] 1-(2-(hydroxymethyl)pyrrolidin-1-yl)-2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)ethanone;
- [00236] (S)-2-(hydroxymethyl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)pyrrolidine-1-carboxamide;
- [00237] 2-(hydroxymethyl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)pyrrolidine-1-carboxamide;
- [00238] 1-((1R,2S)-2-(hydroxymethyl)cyclopentyl)-3-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)urea;
- [00239] 1-(-2-(hydroxymethyl)cyclopentyl)-3-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)urea;
- [00240] (R)-2-(hydroxymethyl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)pyrrolidine-1-carboxamide;
- [00241] 2-(hydroxymethyl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)pyrrolidine-1-carboxamide;
- [00242] (R)-3-hydroxy-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)pyrrolidine-1-carboxamide;
- [00243] 3-hydroxy-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)pyrrolidine-1-carboxamide;
- [00244] (S)-1-(2-(methoxymethyl)pyrrolidin-1-yl)-3-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)urea;
- [00245] 1-(2-(methoxymethyl)pyrrolidin-1-yl)-3-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)urea;
- [00246] 2-((4-amino-2-fluorophenyl)thio)-N-(5-methyl-1H-pyrazol-3-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine;
- [00247] 2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoacetic acid;
- [00248] (R)-2-(3-hydroxypyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-oxoacetamide;

- [00249] 2-(3-hydroxypyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-oxoacetamide;
- [00250] N-(4-((4-((5-(hydroxymethyl)-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide;
- [00251] 2-((4-aminophenyl)thio)-N-(5-(trifluoromethyl)-1H-pyrazol-3-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine;
- [00252] 2-(3-((2-((4-aminophenyl)thio)pyrrolo[2,1-f][1,2,4]triazin-4-yl)amino)-1H-pyrazol-5-yl)ethanol;
- [00253] 2-((4-aminophenyl)thio)-N-(5-propyl-1H-pyrazol-3-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine;
- [00254] (S)-1-(2-(hydroxymethyl)pyrrolidin-1-yl)-2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)ethanone;
- [00255] 1-(2-(hydroxymethyl)pyrrolidin-1-yl)-2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)ethanone;
- [00256] (S)-2-(hydroxymethyl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)pyrrolidine-1-carboxamide;
- [00257] 2-(hydroxymethyl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)pyrrolidine-1-carboxamide;
- [00258] 1-((1R,2S)-2-(hydroxymethyl)cyclopentyl)-3-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)urea;
- [00259] 1-(2-(hydroxymethyl)cyclopentyl)-3-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)urea;
- [00260] (R)-2-(hydroxymethyl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)pyrrolidine-1-carboxamide;
- [00261] 2-(hydroxymethyl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)pyrrolidine-1-carboxamide;
- [00262] (R)-3-hydroxy-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)pyrrolidine-1-carboxamide;
- [00263] 3-hydroxy-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)pyrrolidine-1-carboxamide;
- [00264] (S)-1-(2-(methoxymethyl)pyrrolidin-1-yl)-3-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)urea;

- [00265] 1-(2-(methoxymethyl)pyrrolidin-1-yl)-3-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)urea;
- [00266] 2-((4-amino-2-fluorophenyl)thio)-N-(5-methyl-1H-pyrazol-3-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine;
- [00267] 2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoacetic acid;
- [00268] (R)-2-(3-hydroxypyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-oxoacetamide;
- [00269] 2-(3-hydroxypyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-oxoacetamide;
- [00270] (S)-2-(2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-(trifluoromethyl)-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00271] 2-(2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-(trifluoromethyl)-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00272] (R)-2-(3-hydroxypiperidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00273] 2-(3-hydroxypiperidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00274] (S)-2-(3-hydroxypiperidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00275] 2-(3-hydroxypiperidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00276] N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-(piperidin-1-yl)acetamide;
- [00277] 2-(2-(hydroxymethyl)piperidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00278] (S)-2-((R)-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)propanamide;
- [00279] 2-(2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)propanamide;
- [00280] (R)-2-((R)-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)propanamide;

- [00281] 2-(2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)propanamide;
- [00282] 2-((4-(cyclopropanecarboxamido)phenyl)thio)-4-((5-methyl-1H-pyrazol-3-yl)amino)-N-(3-(piperidin-1-yl)propyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- [00283] N-(4-((6-(hydroxymethyl)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide;
- [00284] 2,2,2-trifluoro-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)-6-(2-(piperidin-4-yl)acetamido)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00285] N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)-6-(4-(piperidin-1-yl)butanamido)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide;
- [00286] N-(4-((5-methyl-1H-pyrazol-3-yl)amino)-2-((4-(2,2,2-trifluoroacetamido)phenyl)thio)pyrrolo[2,1-f][1,2,4]triazin-6-yl)-4-(piperidin-1-yl)butanamide;
- [00287] N-(4-((5-methyl-1H-pyrazol-3-yl)amino)-2-((4-(2,2,2-trifluoroacetamido)phenyl)thio)pyrrolo[2,1-f][1,2,4]triazin-6-yl)-3-(4-methylpiperazin-1-yl)propanamide;
- [00288] N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)-6-(3-(piperidin-1-yl)propanamido)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-3-(trifluoromethyl)benzamide;
- [00289] 3-fluoro-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)-6-(3-(piperidin-1-yl)propanamido)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)benzamide;
- [00290] (S)-tert-butyl 2-(2-((2-((4-(cyclopropanecarboxamido)phenyl)thio)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-6-yl)amino)-2-oxoethyl)pyrrolidine-1-carboxylate;
- [00291] N-(4-((6-(4-(dimethylamino)butanamido)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide;
- [00292] (R)-N-(4-((6-(2-aminopropanamido)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide;
- [00293] (S)-N-(4-((6-(2-aminopropanamido)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide;
- [00294] N-(4-((6-(3-(diethylamino)propanamido)-4-((3-methyl-1H-pyrazol-5-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide;

- [00295] 2-((2R,4R)-4-(tert-butoxy)-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00296] 2-((1S,3aS,7aR)-1-(hydroxymethyl)hexahydro-1H-isoindol-2(3H)-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00297] (R)-2-(2-(2-hydroxyethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00298] 2-((3R,4R)-3-(hydroxymethyl)-4-isopropylpyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00299] (S)-1-(2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)pyrrolidine-2-carboxamide;
- [00300] 2-(3-hydroxyazetidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00301] (S)-2-(2-(hydroxymethyl)-2-methylpyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00302] (S)-tert-butyl 3-(hydroxymethyl)-4-(2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)piperazine-1-carboxylate;
- [00303] (R)-2-(3-aminopyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00304] 2-((2R,4S)-4-hydroxy-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00305] 2-((2S,4R)-4-amino-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00306] (S)-2-(2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methoxymethyl)-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00307] N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-(pyrrolidin-1-yl)acetamide;
- [00308] (R)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-(2-methylpyrrolidin-1-yl)acetamide;

- [00309] (R)-1-(2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)ethyl)pyrrolidin-3-ol;
- [00310] (R)-N-(4-((4-((5-cyclobutyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-(3-hydroxypyrrolidin-1-yl)acetamide;
- [00311] (S)-1-(2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)pyrrolidine-2-carboxylic acid;
- [00312] 2-((2S,4R)-4-(tert-butoxy)-2-(2-hydroxypropan-2-yl)pyrrolidin-1-yl)-N-(4-((4-((5-cyclopropyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00313] 2-((2S,4R)-4-(tert-butoxy)-2-(2-hydroxypropan-2-yl)pyrrolidin-1-yl)-N-(4-((4-((5-cyclobutyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00314] 2-((2S,4R)-4-(tert-butoxy)-2-(2-hydroxypropan-2-yl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00315] 2-((3R,4R)-3-(hydroxymethyl)-4-(trifluoromethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00316] (S)-4,4-difluoro-1-(2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)pyrrolidine-2-carboxylic acid;
- [00317] (2S,4R)-4-(tert-butoxy)-1-(2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)pyrrolidine-2-carboxylic acid;
- [00318] (R)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-(3-(methylsulfonamido)pyrrolidin-1-yl)acetamide;
- [00319] (R)-2-(2-(methoxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00320] (R)-2-(3-acetamidopyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00321] (R)-N-(4-((4-((1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-(3-hydroxypyrrolidin-1-yl)acetamide;
- [00322] (S)-2-(2-(1H-tetrazol-5-yl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;

- [00323] (R)-2-(3-(3-isopropylureido)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00324] (R)-isopropyl (1-(2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)pyrrolidin-3-yl)carbamate;
- [00325] (R)-N-(1-(2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)pyrrolidin-3-yl)pivalamide;
- [00326] (R)-3-(3-hydroxypyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)propanamide;
- [00327] (R)-2-((1-(2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)pyrrolidin-3-yl)oxy)ethyl dihydrogen phosphate;
- [00328] (3R)-3-(cyclopentylcarbamoyl)-1-(2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)-1-((phosphonooxy)methyl)pyrrolidin-1-ium;
- [00329] (S)-2-(4,4-difluoro-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00330] (S)-N-(4-((4-((1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-(4,4-difluoro-2-(hydroxymethyl)pyrrolidin-1-yl)acetamide;
- [00331] (S)-1-(2-((4-((4-((5-cyclopropyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)-4,4-difluoropyrrolidine-2-carboxylic acid;
- [00332] (S)-2-(4,4-difluoro-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00333] (S)-N-(4-((4-((1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-(4,4-difluoro-2-(hydroxymethyl)pyrrolidin-1-yl)acetamide;
- [00334] (S)-1-(2-((4-((4-((5-cyclopropyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)-4,4-difluoropyrrolidine-2-carboxylic acid;
- [00335] 2-((2R,4R)-4-hydroxy-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;

- [00336] 2-((2S,4S)-4-hydroxy-2-(hydroxymethyl)-4-(trifluoromethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00337] (S)-2-(4-(difluoromethyl)-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00338] 2-((2S,4S)-4-(difluoromethyl)-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00339] (R)-2-(methoxymethyl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)pyrrolidine-1-carboxamide;
- [00340] 2-((2R,4R)-4-hydroxy-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00341] 2-((2S,4S)-4-hydroxy-2-(hydroxymethyl)-4-(trifluoromethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00342] (S)-2-(4-(difluoromethylene)-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00343] 2-((2S,4S)-4-(difluoromethyl)-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00344] (R)-2-(methoxymethyl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)pyrrolidine-1-carboxamide;
- [00345] 2-((2S,4R)-4-hydroxy-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00346] (R)-2-(3-hydroxypyrrolidin-1-yl)-N-(4-((4-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00347] 2-((3R,4S)-3-hydroxy-4-isopropylpyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;

- [00348] 2-((3R,4S)-3-hydroxy-4-neopentylpyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00349] N-((3R,4R)-4-hydroxy-1-(2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)pyrrolidin-3-yl)-N-methylisobutyramide;
- [00350] N-((3R,4R)-4-hydroxy-1-(2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)pyrrolidin-3-yl)isobutyramide;
- [00351] 2-((3S,4R)-3-(tert-butyl)-4-hydroxypyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00352] 2-((3S,4S)-3-hydroxy-4-((4-(trifluoromethyl)phenyl)amino)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00353] 2-((3S,4S)-3-hydroxy-4-((3-(trifluoromethyl)phenyl)amino)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00354] 2-((3S,4S)-3,4-dihydroxypyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00355] 2-((3S,4S)-3-(tert-butylamino)-4-hydroxypyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00356] 2-((3S,4S)-3-hydroxy-4-(2-morpholinoethoxy)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00357] 2-((3S,4R)-3,4-dihydroxypyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00358] 2-((3S,4S)-3-(diethylamino)-4-hydroxypyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00359] (R)-1-(2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)-N-(3-(pyrrolidin-1-yl)propyl)pyrrolidine-3-carboxamide;
- [00360] (S)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-(3-(4-methylpiperazine-1-carbonyl)pyrrolidin-1-yl)acetamide;

- [00361] (S)-1-(2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)-N-(2-(piperidin-1-yl)ethyl)pyrrolidine-3-carboxamide;
- [00362] 3-fluoro-N-(2-hydroxyethyl)-1-(2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)pyrrolidine-3-carboxamide;
- [00363] (S)-N-(2-(dimethylamino)ethyl)-N-methyl-1-(2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)pyrrolidine-3-carboxamide;
- [00364] 3-fluoro-1-(2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)pyrrolidine-3-carboxylic acid;
- [00365] 2-((2S,4S)-4-(tert-butylthio)-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00366] (2S,4R)-4-(tert-butoxy)-1-(2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)-N-(methylsulfonyl)pyrrolidine-2-carboxamide;
- [00367] (R)-2-(3-(1,1-dioxidothiomorpholine-4-carbonyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00368] (S)-N-(2-(4,4-difluoropiperidin-1-yl)ethyl)-1-(2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)pyrrolidine-3-carboxamide;
- [00369] (3R)-3-(3,3-difluoropyrrolidine-1-carbonyl)-1-(2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)-1-((phosphonoxy)methyl)pyrrolidin-1-ium;
- [00370] (R)-2-(3-(2-hydroxyethoxy)pyrrolidin-1-yl)-N-(4-((6-methyl-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;
- [00371] (S)-2-(3-(4-(hydroxymethyl)piperidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide;

[00372] ((S)-4,4-difluoro-1-((R)-1-(2-((4-((6-methyl-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)pyrrolidine-3-carbonyl)pyrrolidin-2-yl)methyl dihydrogen phosphate;

[00373] (4,4-difluoro-1-(1-(2-((4-((6-methyl-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)pyrrolidine-3-carbonyl)pyrrolidin-2-yl)methyl dihydrogen phosphate;

[00374] (R)-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidin-3-yl dihydrogen phosphate;

[00375] 1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidin-3-yl dihydrogen phosphate;

[00376] (S)-(4,4-difluoro-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidin-2-yl)methyl dihydrogen phosphate;

[00377] (4,4-difluoro-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidin-2-yl)methyl dihydrogen phosphate;

[00378] ((1R)-4,4-difluoro-2-((R)-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carbonyl)cyclopentyl)methyl dihydrogen phosphate;

[00379] (4,4-difluoro-2-(1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carbonyl)cyclopentyl)methyl dihydrogen phosphate;

[00380] ((1R)-4,4-difluoro-2-((R)-1-(2-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carbonyl)cyclopentyl)methyl dihydrogen phosphate; and

[00381] (4,4-difluoro-2-(1-(2-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carbonyl)cyclopentyl)methyl dihydrogen phosphate;

[00382] In certain embodiments, to the best of the knowledge of the inventors, the compounds provided herein are about 2 to 10 times more active than compounds reported in the literature, *i.e.*, for example, compounds are disclosed in US patent no. 7,442,700 and US publication no. 2006/0084650A1. In certain embodiments, the compounds provided herein are about 2 to 10, 2 to 5, or 2, 3, 4, 5, 6, 8 or 10 times

more active in cell assays, such as proliferation assay to determine anti-proliferative activity of the compounds based on the detection of BrdU (bromodeoxyuridine), than compounds reported in the literature.

[00383] In certain embodiment, compounds provided herein have IC_{50} of about 30-370 nM in BrdU assay. In certain embodiment, compounds provided herein have IC_{50} of about 30-200 nM in BrdU assay. In certain embodiment, compounds provided herein have IC_{50} of about 30-150 nM in BrdU assay. In certain embodiment, compounds provided herein have IC_{50} of about 30-100 nM in BrdU assay.

[00384] Also provided herein are isotopically enriched analogs of the compounds provided herein. Isotopic enrichment (for example, deuteration) of pharmaceuticals to improve pharmacokinetics ("PK"), pharmacodynamics ("PD"), and toxicity profiles, has been demonstrated previously with some classes of drugs. See, for example, Lijinsky *et al.*, *Food Cosmet. Toxicol.*, 20: 393 (1982); Lijinsky *et al.*, *J. Nat. Cancer Inst.*, 69: 1127 (1982); Mangold *et al.*, *Mutation Res.* 308: 33 (1994); Gordon *et al.*, *Drug Metab. Dispos.*, 15: 589 (1987); Zello *et al.*, *Metabolism*, 43: 487 (1994); Gately *et al.*, *J. Nucl. Med.*, 27: 388 (1986); Wade D, *Chem. Biol. Interact.* 117: 191 (1999).

[00385] Isotopic enrichment of a drug can be used, for example, to (1) reduce or eliminate unwanted metabolites, (2) increase the half-life of the parent drug, (3) decrease the number of doses needed to achieve a desired effect, (4) decrease the amount of a dose necessary to achieve a desired effect, (5) increase the formation of active metabolites, if any are formed, and/or (6) decrease the production of deleterious metabolites in specific tissues and/or create a more effective drug and/or a safer drug for combination therapy, whether the combination therapy is intentional or not.

[00386] Replacement of an atom for one of its isotopes often will result in a change in the reaction rate of a chemical reaction. This phenomenon is known as the Kinetic Isotope Effect ("KIE"). For example, if a C-H bond is broken during a rate-determining step in a chemical reaction (*i.e.* the step with the highest transition state energy), substitution of a deuterium for that hydrogen will cause a decrease in the reaction rate and the process will slow down. This phenomenon is known as the Deuterium Kinetic Isotope Effect ("DKIE"). (See, *e.g.* Foster *et al.*, *Adv. Drug Res.*, vol. 14, pp. 1-36 (1985); Kushner *et al.*, *Can. J. Physiol. Pharmacol.*, vol. 77, pp. 79-88 (1999)).

[00387] Tritium ("T") is a radioactive isotope of hydrogen, used in research, fusion reactors, neutron generators and radiopharmaceuticals. Tritium is a hydrogen atom that has 2 neutrons in the nucleus and has an atomic weight close to 3. It occurs naturally in the environment in very low concentrations, most commonly found as T₂O. Tritium decays slowly (half-life = 12.3 years) and emits a low energy beta particle that cannot penetrate the outer layer of human skin. Internal exposure is the main hazard associated with this isotope, yet it must be ingested in large amounts to pose a significant health risk. As compared with deuterium, a lesser amount of tritium must be consumed before it reaches a hazardous level. Substitution of tritium ("T") for hydrogen results in yet a stronger bond than deuterium and gives numerically larger isotope effects. Similarly, substitution of isotopes for other elements, including, but not limited to, ¹³C or ¹⁴C for carbon, ³³S, ³⁴S, or ³⁶S for sulfur, ¹⁵N for nitrogen, and ¹⁷O or ¹⁸O for oxygen, will provide a similar kinetic isotope effects.

[00388] In another embodiment, provided herein are methods of using the disclosed compounds and compositions, or pharmaceutically acceptable salts, solvates or hydrates thereof, for the local or systemic treatment or prophylaxis of human and veterinary diseases, disorders and conditions modulated or otherwise affected mediated via Aurora kinase activity.

C. FORMULATION OF PHARMACEUTICAL COMPOSITIONS

[00389] The pharmaceutical compositions provided herein contain therapeutically effective amounts of one or more of compounds provided herein that are useful in the prevention, treatment, or amelioration of Aurora kinase, mediated diseases or one or more of the symptoms thereof.

[00390] The compositions contain one or more compounds provided herein. The compounds can be formulated into suitable pharmaceutical preparations such as solutions, suspensions, tablets, dispersible tablets, pills, capsules, powders, sustained release formulations or elixirs, for oral administration or in sterile solutions or suspensions for parenteral administration, as well as transdermal patch preparation and dry powder inhalers. Typically the compounds described above are formulated into pharmaceutical compositions using techniques and procedures well known in the art.

[00391] In the compositions, effective concentrations of one or more compounds or pharmaceutically acceptable salt, solvate, hydrate or prodrug is (are) mixed with a suitable pharmaceutical carrier or vehicle. The concentrations of the compounds in the compositions are effective for delivery of an amount, upon administration, that treats, prevents, or ameliorates one or more of the symptoms of Aurora kinase mediated diseases.

[00392] Typically, the compositions are formulated for single dosage administration. To formulate a composition, the weight fraction of compound is dissolved, suspended, dispersed or otherwise mixed in a selected vehicle at an effective concentration such that the treated condition is relieved or ameliorated. Pharmaceutical carriers or vehicles suitable for administration of the compounds provided herein include any such carriers known to those skilled in the art to be suitable for the particular mode of administration.

[00393] In addition, the compounds may be formulated as the sole pharmaceutically active ingredient in the composition or may be combined with other active ingredients. These may be prepared according to methods known to those skilled in the art.

[00394] The active compound is included in the pharmaceutically acceptable carrier in an amount sufficient to exert a therapeutically useful effect in the absence of undesirable side effects on the patient treated. The therapeutically effective concentration may be determined empirically by testing the compounds in *in vitro* and *in vivo* systems described herein and then extrapolated therefrom for dosages for humans.

[00395] The concentration of active compound in the pharmaceutical composition will depend on absorption, inactivation and excretion rates of the active compound, the physicochemical characteristics of the compound, the dosage schedule, and amount administered as well as other factors known to those of skill in the art. For example, the amount that is delivered is sufficient to ameliorate one or more of the symptoms of Aurora kinase mediated diseases.

[00396] Typically a therapeutically effective dosage should produce a serum concentration of active ingredient of from about 1 ng/ml to about 50-100 µg/ml. The pharmaceutical compositions typically should provide a dosage of from about 10 mg to about 4000 mg of compound per kilogram of body weight per day. Pharmaceutical

dosage unit forms are prepared to provide from about 10 mg to about 1000 mg and in certain embodiments, from about 10 mg to about 500 mg, from about 20 mg to about 250 mg or from about 25 mg to about 100 mg of the essential active ingredient or a combination of essential ingredients per dosage unit form. In certain embodiments, the pharmaceutical dosage unit forms are prepared to provide about 10 mg, 20 mg, 25 mg, 50 mg, 100 mg, 250 mg, 500 mg, 1000 mg or 2000 mg of the essential active ingredient. The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the disease being treated and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test data. It is to be noted that concentrations and dosage values may also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed compositions.

[00397] Thus, effective concentrations or amounts of one or more of the compounds described herein are mixed with a suitable pharmaceutical carrier or vehicle for systemic, topical or local administration to form pharmaceutical compositions. Compounds are included in an amount effective for ameliorating one or more symptoms of, or for treating or preventing Aurora kinase mediated diseases. The concentration of active compound in the composition will depend on absorption, inactivation, excretion rates of the active compound, the dosage schedule, amount administered, particular formulation as well as other factors known to those of skill in the art.

[00398] The compositions are intended to be administered by a suitable route, including, but not limited to, orally, parenterally, rectally, topically and locally. For oral administration, capsules and tablets can be formulated.

[00399] Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include any of the following components: a sterile diluent, such as water for injection, saline solution, fixed oil, polyethylene glycol, glycerine, propylene glycol, dimethyl acetamide or other synthetic solvent;

antimicrobial agents, such as benzyl alcohol and methyl parabens; antioxidants, such as ascorbic acid and sodium bisulfite; chelating agents, such as ethylenediaminetetraacetic acid (EDTA); buffers, such as acetates, citrates and phosphates; and agents for the adjustment of tonicity such as sodium chloride or dextrose. Parenteral preparations can be enclosed in ampules, disposable syringes or single or multiple dose vials made of glass, plastic or other suitable material.

[00400] In instances in which the compounds exhibit insufficient solubility, methods for solubilizing compounds may be used. Such methods are known to those of skill in this art, and include, but are not limited to, using cosolvents, such as dimethylsulfoxide (DMSO), using surfactants, such as TWEEN®, or dissolution in aqueous sodium bicarbonate.

[00401] Upon mixing or addition of the compound(s), the resulting mixture may be a solution, suspension, emulsion or the like. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. In one embodiment, the effective concentration is sufficient for ameliorating the symptoms of the disease, disorder or condition treated and may be empirically determined.

[00402] The pharmaceutical compositions are provided for administration to humans and animals in unit dosage forms or multiple-dosage forms. Unit-dose forms as used herein refer to physically discrete units suitable for human and animal subjects and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of the therapeutically active compound sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carrier, vehicle or diluent. Examples of unit-dose forms include ampules and syringes and individually packaged tablets, capsules, pills, powders and granules, oral solutions or suspensions, and oil-water emulsions. Unit-dose forms may be administered in fractions or multiples thereof. A multiple-dose form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dose form. Examples of multiple-dose forms include vials, bottles of tablets or capsules or bottles of pints or gallons. Hence, multiple dose form is a multiple of unit-doses which are not segregated in packaging.

[00403] Dosage forms or compositions containing active ingredient in the range of 0.005% to 100% with the balance made up from non-toxic carrier may be

prepared. For oral administration, a pharmaceutically acceptable non-toxic composition is formed by the incorporation of any of the normally employed excipients, such as, for example pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, talcum, cellulose derivatives, sodium crosscarmellose, glucose, sucrose, magnesium carbonate or sodium saccharin. Such compositions include solutions, suspensions, tablets, capsules, powders and sustained release formulations, such as, but not limited to, implants and microencapsulated delivery systems, and biodegradable, biocompatible polymers, such as collagen, ethylene vinyl acetate, polyanhydrides, polyglycolic acid, polyorthoesters, polylactic acid and others. Methods for preparation of these compositions are known to those skilled in the art. The contemplated compositions may contain about 0.001%-100% active ingredient, in certain embodiments, about 0.1-85%, typically about 75-95%.

[00404] The active compounds or pharmaceutically acceptable derivatives may be prepared with carriers that protect the compound against rapid elimination from the body, such as time release formulations or coatings.

1. Compositions for oral administration

[00405] Oral pharmaceutical dosage forms are either solid, gel or liquid. The solid dosage forms are tablets, capsules, granules, and bulk powders. Types of oral tablets include compressed, chewable lozenges and tablets which may be enteric-coated, sugar-coated or film-coated. Capsules may be hard or soft gelatin capsules, while granules and powders may be provided in non-effervescent or effervescent form with the combination of other ingredients known to those skilled in the art.

[00406] In certain embodiments, the formulations are solid dosage forms, such as capsules or tablets. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder; a diluent; a disintegrating agent; a lubricant; a glidant; a sweetening agent; and a flavoring agent.

[00407] Examples of binders include microcrystalline cellulose, gum tragacanth, glucose solution, acacia mucilage, gelatin solution, sucrose and starch paste. Lubricants include talc, starch, magnesium or calcium stearate, lycopodium and stearic acid. Diluents include, for example, lactose, sucrose, starch, kaolin, salt, mannitol and dicalcium phosphate. Glidants include, but are not limited to, colloidal

silicon dioxide. Disintegrating agents include crosscarmellose sodium, sodium starch glycolate, alginic acid, corn starch, potato starch, bentonite, methylcellulose, agar and carboxymethylcellulose. Coloring agents include, for example, any of the approved certified water soluble FD and C dyes, mixtures thereof; and water insoluble FD and C dyes suspended on alumina hydrate. Sweetening agents include sucrose, lactose, mannitol and artificial sweetening agents such as saccharin, and any number of spray dried flavors. Flavoring agents include natural flavors extracted from plants such as fruits and synthetic blends of compounds which produce a pleasant sensation, such as, but not limited to peppermint and methyl salicylate. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene laural ether. Emetic-coatings include fatty acids, fats, waxes, shellac, ammoniated shellac and cellulose acetate phthalates. Film coatings include hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000 and cellulose acetate phthalate.

[00408] If oral administration is desired, the compound could be provided in a composition that protects it from the acidic environment of the stomach. For example, the composition can be formulated in an enteric coating that maintains its integrity in the stomach and releases the active compound in the intestine. The composition may also be formulated in combination with an antacid or other such ingredient.

[00409] When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar and other enteric agents. The compounds can also be administered as a component of an elixir, suspension, syrup, wafer, sprinkle, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

[00410] The active materials can also be mixed with other active materials which do not impair the desired action, or with materials that supplement the desired action, such as antacids, H₂ blockers, and diuretics. The active ingredient is a compound or pharmaceutically acceptable derivative thereof as described herein.

Higher concentrations, up to about 98% by weight of the active ingredient may be included.

[00411] Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Aqueous solutions include, for example, elixirs and syrups. Emulsions are either oil-in-water or water-in-oil.

[00412] Elixirs are clear, sweetened, hydroalcoholic preparations. Pharmaceutically acceptable carriers used in elixirs include solvents. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may contain a preservative. An emulsion is a two-phase system in which one liquid is dispersed in the form of small globules throughout another liquid. Pharmaceutically acceptable carriers used in emulsions are non-aqueous liquids, emulsifying agents and preservatives. Suspensions use pharmaceutically acceptable suspending agents and preservatives. Pharmaceutically acceptable substances used in non-effervescent granules, to be reconstituted into a liquid oral dosage form, include diluents, sweeteners and wetting agents. Pharmaceutically acceptable substances used in effervescent granules, to be reconstituted into a liquid oral dosage form, include organic acids and a source of carbon dioxide. Coloring and flavoring agents are used in all of the above dosage forms.

[00413] Solvents include glycerin, sorbitol, ethyl alcohol and syrup. Examples of preservatives include glycerin, methyl and propylparaben, benzoic acid, sodium benzoate and alcohol. Examples of non-aqueous liquids utilized in emulsions include mineral oil and cottonseed oil. Examples of emulsifying agents include gelatin, acacia, tragacanth, bentonite, and surfactants such as polyoxyethylene sorbitan monooleate. Suspending agents include sodium carboxymethylcellulose, pectin, tragacanth, Veegum and acacia. Diluents include lactose and sucrose. Organic acids include citric and tartaric acid. Sources of carbon dioxide include sodium bicarbonate and sodium carbonate.

[00414] For a solid dosage form, the solution or suspension, in for example propylene carbonate, vegetable oils or triglycerides, is encapsulated in a gelatin capsule. For a liquid dosage form, the solution, *e.g.*, for example, in a polyethylene

glycol, may be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, *e.g.*, water, to be easily measured for administration.

[00415] Alternatively, liquid or semi-solid oral formulations may be prepared by dissolving or dispersing the active compound or salt in vegetable oils, glycols, triglycerides, propylene glycol esters (*e.g.*, propylene carbonate) and other such carriers, and encapsulating these solutions or suspensions in hard or soft gelatin capsule shells. Other useful formulations include, but are not limited to, those containing a compound provided herein, a dialkylated mono- or poly-alkylene glycol, including, but not limited to, 1,2-dimethoxymethane, diglyme, triglyme, tetraglyme, polyethylene glycol-350-dimethyl ether, polyethylene glycol-550-dimethyl ether, polyethylene glycol-750-dimethyl ether wherein 350, 550 and 750 refer to the approximate average molecular weight of the polyethylene glycol, and one or more antioxidants, such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, vitamin E, hydroquinone, hydroxycoumarins, ethanolamine, lecithin, cephalin, ascorbic acid, malic acid, sorbitol, phosphoric acid, thiodipropionic acid and its esters, and dithiocarbamates.

[00416] Other formulations include, but are not limited to, aqueous alcoholic solutions including a pharmaceutically acceptable acetal. Alcohols used in these formulations are any pharmaceutically acceptable water-miscible solvents having one or more hydroxyl groups, including, but not limited to, propylene glycol and ethanol. Acetals include, but are not limited to, di(lower alkyl) acetals of lower alkyl aldehydes such as acetaldehyde diethyl acetal.

[00417] In all embodiments, tablets and capsules formulations may be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient. Thus, for example, they may be coated with a conventional enterically digestible coating, such as phenylsalicylate, waxes and cellulose acetate phthalate.

2. Injectables, solutions and emulsions

[00418] Parenteral administration, generally characterized by injection, either subcutaneously, intramuscularly or intravenously is also contemplated herein. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Suitable excipients are, for example, water, saline, dextrose, glycerol

or ethanol. In addition, if desired, the pharmaceutical compositions to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents, stabilizers, solubility enhancers, and other such agents, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate and cyclodextrins. In one embodiment, the composition is administered as an aqueous solution with hydroxypropyl-beta-cyclodextrin (HPBCD) as an excipient. In one embodiment, the aqueous solution contains about 1% to about 50% HPBCD. In one embodiment, the aqueous solution contains about 1%, 3%, 5%, 10% or about 20% HPBCD.

[00419] Parenteral administration of the compositions includes intravenous, subcutaneous and intramuscular administrations. Preparations for parenteral administration include sterile solutions ready for injection, sterile dry soluble products, such as lyophilized powders, ready to be combined with a solvent just prior to use, including hypodermic tablets, sterile suspensions ready for injection, sterile dry insoluble products ready to be combined with a vehicle just prior to use and sterile emulsions. The solutions may be either aqueous or nonaqueous.

[00420] If administered intravenously, suitable carriers include physiological saline or phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents, such as glucose, polyethylene glycol, and polypropylene glycol and mixtures thereof.

[00421] Pharmaceutically acceptable carriers used in parenteral preparations include aqueous vehicles, nonaqueous vehicles, antimicrobial agents, isotonic agents, buffers, antioxidants, local anesthetics, suspending and dispersing agents, emulsifying agents, sequestering or chelating agents and other pharmaceutically acceptable substances.

[00422] Examples of aqueous vehicles include Sodium Chloride Injection, Ringers Injection, Isotonic Dextrose Injection, Sterile Water Injection, Dextrose and Lactated Ringers Injection. Nonaqueous parenteral vehicles include fixed oils of vegetable origin, cottonseed oil, corn oil, sesame oil and peanut oil. Antimicrobial agents in bacteriostatic or fungistatic concentrations must be added to parenteral preparations packaged in multiple-dose containers which include phenols or cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoic acid esters, thimerosal, benzalkonium chloride and benzethonium chloride. Isotonic agents

include sodium chloride and dextrose. Buffers include phosphate and citrate. Antioxidants include sodium bisulfate. Local anesthetics include procaine hydrochloride. Suspending and dispersing agents include sodium carboxymethylcellulose, hydroxypropyl methylcellulose and polyvinylpyrrolidone. Emulsifying agents include Polysorbate 80 (TWEEN® 80). A sequestering or chelating agent of metal ions include EDTA. Pharmaceutical carriers also include ethyl alcohol, polyethylene glycol and propylene glycol for water miscible vehicles and sodium hydroxide, hydrochloric acid, citric acid or lactic acid for pH adjustment.

[00423] The concentration of the pharmaceutically active compound is adjusted so that an injection provides an effective amount to produce the desired pharmacological effect. The exact dose depends on the age, weight and condition of the patient or animal as is known in the art.

[00424] The unit-dose parenteral preparations are packaged in an ampule, a vial or a syringe with a needle. All preparations for parenteral administration must be sterile, as is known and practiced in the art.

[00425] Illustratively, intravenous or intraarterial infusion of a sterile aqueous solution containing an active compound is an effective mode of administration. Another embodiment is a sterile aqueous or oily solution or suspension containing an active material injected as necessary to produce the desired pharmacological effect.

[00426] Injectables are designed for local and systemic administration. Typically a therapeutically effective dosage is formulated to contain a concentration of at least about 0.1% w/w up to about 90% w/w or more, such as more than 1% w/w of the active compound to the treated tissue(s). The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the tissue being treated and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test data. It is to be noted that concentrations and dosage values may also vary with the age of the individual treated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations, and that the concentration ranges

set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed formulations.

[00427] The compound may be suspended in micronized or other suitable form or may be derivatized to produce a more soluble active product or to produce a prodrug. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the condition and may be empirically determined.

3. Lyophilized powders

[00428] Of interest herein are also lyophilized powders, which can be reconstituted for administration as solutions, emulsions and other mixtures. They may also be reconstituted and formulated as solids or gels.

[00429] The sterile, lyophilized powder is prepared by dissolving a compound provided herein, or a pharmaceutically acceptable derivative thereof, in a suitable solvent. The solvent may contain an excipient which improves the stability or other pharmacological component of the powder or reconstituted solution, prepared from the powder. Excipients that may be used include, but are not limited to, dextrose, sorbital, fructose, corn syrup, xylitol, glycerin, glucose, sucrose, hydroxypropyl-beta-cyclodextrin (HPBCD) or other suitable agent. The solvent may also contain a buffer, such as citrate, sodium or potassium phosphate or other such buffer known to those of skill in the art at, typically, about neutral pH. Subsequent sterile filtration of the solution followed by lyophilization under standard conditions known to those of skill in the art provides the desired formulation. Generally, the resulting solution will be apportioned into vials for lyophilization. Each vial will contain a single dosage (10-1000 mg, 100-500 mg, 10-500 mg, 50-250 mg or 25-100 mg) or multiple dosages of the compound. The lyophilized powder can be stored under appropriate conditions, such as at about 4°C to rt.

[00430] Reconstitution of this lyophilized powder with water for injection provides a formulation for use in parenteral administration. For reconstitution, about 1-50 mg, about 5-35 mg, or about 9-30 mg of lyophilized powder, is added per mL of sterile water or other suitable carrier. The precise amount depends upon the selected compound. Such amount can be empirically determined.

4. Topical administration

[00431] Topical mixtures are prepared as described for the local and systemic administration. The resulting mixture may be a solution, suspension, emulsions or the like and are formulated as creams, gels, ointments, emulsions, solutions, elixirs, lotions, suspensions, tinctures, pastes, foams, aerosols, irrigations, sprays, suppositories, bandages, dermal patches or any other formulations suitable for topical administration.

[00432] The compounds or pharmaceutically acceptable derivatives thereof may be formulated as aerosols for topical application, such as by inhalation. These formulations for administration to the respiratory tract can be in the form of an aerosol or solution for a nebulizer, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case, the particles of the formulation will typically have diameters of less than 50 microns or less than 10 microns.

[00433] The compounds may be formulated for local or topical application, such as for topical application to the skin and mucous membranes, such as in the eye, in the form of gels, creams, and lotions and for application to the eye or for intracisternal or intraspinal application. Topical administration is contemplated for transdermal delivery and also for administration to the eyes or mucosa, or for inhalation therapies. Nasal solutions of the active compound alone or in combination with other pharmaceutically acceptable excipients can also be administered.

[00434] These solutions, particularly those intended for ophthalmic use, may be formulated as 0.01% - 10% isotonic solutions, pH about 5-7, with appropriate salts.

5. Compositions for other routes of administration

[00435] Other routes of administration, such as topical application, transdermal patches, and rectal administration are also contemplated herein.

[00436] For example, pharmaceutical dosage forms for rectal administration are rectal suppositories, capsules and tablets for systemic effect. Rectal suppositories are used herein mean solid bodies for insertion into the rectum which melt or soften at body temperature releasing one or more pharmacologically or therapeutically active ingredients. Pharmaceutically acceptable substances utilized in rectal suppositories are bases or vehicles and agents to raise the melting point. Examples of bases include cocoa butter (theobroma oil), glycerin-gelatin, carbowax (polyoxyethylene glycol) and appropriate mixtures of mono-, di- and triglycerides of fatty acids. Combinations

of the various bases may be used. Agents to raise the melting point of suppositories include spermaceti and wax. Rectal suppositories may be prepared either by the compressed method or by molding. The typical weight of a rectal suppository is about 2 to 3 gm.

[00437] Tablets and capsules for rectal administration are manufactured using the same pharmaceutically acceptable substance and by the same methods as for formulations for oral administration.

D. EVALUATION OF THE ACTIVITY OF THE COMPOUNDS

[00438] Standard physiological, pharmacological and biochemical procedures are available for testing the compounds to identify those that possess biological activities that modulate the activity of Aurora kinases, including wild type and mutant Aurora kinases.

[00439] Such assays include, for example, biochemical assays such as binding assays, radioactivity incorporation assays, as well as a variety of cell based assays.

[00440] Exemplary cell based assay methodologies include, but are not limited to measurement of histone H3 phosphorylation in a cellular assay to determine the compounds' ability to inhibit the ability of the Aurora B kinase to phosphorylate serine 10 of the histone H3 enzyme (HH3) during mitosis in human cells and proliferation assay to determine anti-proliferative activity of the compounds based on the detection of BrdU (bromodeoxyuridine), a synthetic thymidine analog that is incorporated into the genomic DNA of proliferating cells which is then detected with peroxidase-conjugated anti-BrdU antibody (anti-BrdU-POD).

[00441] Cells useful in the assays include cells with wildtype or mutated forms. Suitable cells include those derived through cell culture from patient samples as well as cells derived using routine molecular biology techniques, *e.g.*, retroviral transduction, transfection, mutagenesis, etc.

E. METHODS OF USE OF THE COMPOUNDS AND COMPOSITIONS

[00442] Also provided herein are methods of using the disclosed compounds and compositions, or pharmaceutically acceptable salts, solvates or hydrates thereof, for the treatment, prevention, or amelioration of a disease or disorder that is mediated or otherwise affected via Aurora kinase activity or one or more symptoms of diseases or disorders that are mediated or otherwise affected via Aurora kinase activity, such

as, for example, cancer, bone diseases, inflammatory diseases, autoimmune diseases, metabolic diseases, viral diseases, fungal diseases, neurological and neurodegenerative disorders, Alzheimer's disease, allergies and asthma, cardiovascular diseases, and hormone related diseases. Aurora kinase can be wild type and/or mutant form of Aurora kinase.

[00443] The cancers that can be treated with compounds of Formula (I) include, but are not limited to, for example, carcinoma, including, for example, that of the bladder, breast, colon, kidney, liver, lung (including small cell lung cancer), esophagus, gall bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin (including squamous cell carcinoma); hematopoietic tumors of lymphoid lineage, such as, for example, leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma, and Burkett's lymphoma; hematopoietic tumors of myeloid lineage, such as, for example, acute and chronic myelogenous leukemia, myelodysplastic syndrome, and promyelocytic leukemia; tumors of mesenchymal origin, including, for example, fibrosarcoma and rhabdomyosarcoma; tumors of the central and peripheral nervous system, including, for example, astrocytoma, neuroblastoma, glioma, and schwannomas; and other tumors, such as, for example, melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoacanthoma, thyroid follicular cancer, and Kaposi's sarcoma.

[00444] Further inhibitors of Aurora kinases may act as reversible cytostatic agents, thereby making such inhibitors useful to treat any disease process featuring abnormal cellular proliferation, e.g., benign prostatic hyperplasia, familial adenomatosis polyposis, neuro-fibromatosis, atherosclerosis, pulmonary fibrosis, arthritis, psoriasis, glomerulonephritis, restenosis following angioplasty or vascular surgery, hypertrophic scar formation, inflammatory bowel disease, transplantation rejection, endotoxic shock, and fungal infections.

[00445] In certain embodiments, compounds of Formula (I) modulate apoptosis, and therefore are useful in treating cancer, including but not limited to, for example, the cancers already mentioned herein above; treating viral infections, including but not limited to, for example, herpes virus, pox virus, Epstein-Barr virus, Sindbis virus, and adenovirus; preventing AIDS from developing in HIV-infected individuals; treating autoimmune diseases, including but not limited to, for example,

systemic lupus, erythematosus, autoimmune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and autoimmune diabetes mellitus; treating neurodegenerative disorders, including but not limited to, for example, Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy, and cerebellar degeneration; treating myelodysplastic syndromes; treating aplastic anemia; treating ischemic injury associated with myocardial infarctions, strokes, and reperfusion injury; treating arrhythmias; treating arteriosclerosis; treating toxin-induced or alcohol related liver diseases; treating hematological diseases, including but not limited to, for example, chronic anemia and aplastic anemia; treating degenerative diseases of the musculoskeletal system, including but not limited to, for example, osteoporosis and arthritis; treating aspirin-sensitive rhinosinusitis; treating cystic fibrosis; treating multiple sclerosis; treating kidney diseases; and treating cancer pain.

[00446] In certain embodiments, compounds of Formula (I) are useful in treatment of rheumatoid arthritis.

[00447] In certain embodiments, compounds of Formula (I) modulate the level of cellular RNA and DNA synthesis, and as a result are useful in treating viral infections, including but not limited to, for example, HIV; human papilloma virus; herpes virus; pox virus; Epstein-Barr virus; Sindbis virus; and adenovirus.

[00448] In certain embodiments, compounds of Formula (I) are also useful in the chemoprevention of cancer. Chemoprevention is defined as inhibiting the development of invasive cancer by blocking the initiating mutagenic event, by blocking progression of pre-malignant cells that have already suffered an insult, or by inhibiting tumor relapse.

[00449] In certain embodiments, compounds of Formula (I) are useful in inhibiting tumor angiogenesis and metastasis.

F. COMBINATION THERAPY

[00450] Furthermore, it will be understood by those skilled in the art that the compounds, isomers and pharmaceutically acceptable derivatives provided herein, including pharmaceutical compositions and formulations containing these compounds, can be used in a wide variety of combination therapies to treat the conditions and diseases described above. Thus, also contemplated herein is the use of compounds, isomers and pharmaceutically acceptable derivatives provided herein in

combination with other active pharmaceutical agents for the treatment of the disease/conditions described herein.

[00451] In one embodiment, such additional pharmaceutical agents include without limitation anti-cancer agents, including chemotherapeutic agents and anti-proliferative agents; anti-inflammatory agents and immunomodulatory agents or immunosuppressive agents.

[00452] In certain embodiments, the anti-cancer agents include anti-metabolites (*e.g.*, 5-fluoro-uracil, cytarabine, methotrexate, fludarabine and others), antimicrotubule agents (*e.g.*, vinca alkaloids such as vincristine, vinblastine; taxanes such as paclitaxel and docetaxel), alkylating agents (*e.g.*, cyclophosphamide, melphalan, carmustine, nitrosoureas such as bischloroethylnitrosurca and hydroxyurca), platinum agents (*e.g.* cisplatin, carboplatin, oxaliplatin, satraplatin and CI-973), anthracyclines (*e.g.*, doxorubicin and daunorubicin), antitumor antibiotics (*e.g.*, mitomycin, idarubicin, adriamycin and daunomycin), topoisomerase inhibitors (*e.g.*, etoposide and camptothecins), anti-angiogenesis agents (*e.g.* Sutent®, sorafenib and Bevacizumab) or any other cytotoxic agents, (*e.g.* estramustine phosphate, prednimustine), hormones or hormone agonists, antagonists, partial agonists or partial antagonists, kinase inhibitors (such as imatinib), and radiation treatment.

[00453] In certain embodiments, the anti-inflammatory agents include matrix metalloproteinase inhibitors, inhibitors of pro-inflammatory cytokines (*e.g.*, anti-TNF molecules, TNF soluble receptors, and IL1) non-steroidal anti-inflammatory drugs (NSAIDs) such as prostaglandin synthase inhibitors (*e.g.*, choline magnesium salicylate and salicylsalicylic acid), COX-1 or COX-2 inhibitors, or glucocorticoid receptor agonists such as corticosteroids, methylprednisone, prednisone, or cortisone.

[00454] The compound or composition provided herein, or pharmaceutically acceptable derivative thereof, may be administered simultaneously with, prior to, or after administration of one or more of the above agents.

[00455] Pharmaceutical compositions containing a compound provided herein or pharmaceutically acceptable derivative thereof, and one or more of the above agents are also provided.

[00456] Also provided is a combination therapy that treats or prevents the onset of the symptoms, or associated complications of cancer and related diseases and disorders comprising the administration to a subject in need thereof, of one of the

compounds or compositions disclosed herein, or pharmaceutically acceptable derivatives thereof, with one or more anti-cancer agents.

G. PREPARATION OF COMPOUNDS

[00457] Starting materials in the synthesis examples provided herein are either available from commercial sources or via literature procedures (*e.g.*, March *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, (1992) 4th Ed.; Wiley Interscience, New York). All commercially available compounds were used without further purification unless otherwise indicated. DMSO-*d*₆ (Cambridge Isotope Laboratories), CD₃OD (Aldrich) and CDCl₃ (99.8% D, Cambridge Isotope Laboratories) were used in all experiments as indicated. Proton (¹H) nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 300 MHz NMR spectrometer. Significant peaks are tabulated and typically include: number of protons, and multiplicity (s, singlet; d, double; t, triplet; q, quartet; m, multiplet; br s, broad singlet). Chemical shifts are reported as parts per million (δ) relative to tetramethylsilane. Low resolution mass spectra (MS) were obtained as electrospray ionization (ESI) mass spectra, which were recorded on a Shimadzu HPLC/MS instrument using reverse-phase conditions (acetonitrile/water, 0.05% acetic acid). Preparative HPLC was performed using Varian HPLC systems and Phenomenex columns. Flash chromatography was performed using Merck Silica Gel 60 (230-400 mesh) following standard protocol (Still *et al.* (1978) *J. Org. Chem.* 43:2923).

[00458] It is understood that in the following description, combinations of substituents and/or variables of the depicted formulae are permissible only if such contributions result in stable compounds under standard conditions.

[00459] It will also be appreciated by those skilled in the art that in the process described below the functional groups of intermediate compounds may need to be protected by suitable protecting groups. Such functional groups include hydroxy, amino, mercapto and carboxylic acid. Suitable protecting groups for hydroxy include trialkylsilyl or diarylalkylsilyl (*e.g.*, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl or trimethylsilyl), tetrahydropyranyl, benzyl, and the like. Suitable protecting groups for amino, amidino and guanidino include *t*-butoxycarbonyl, benzyloxycarbonyl, and the like. Suitable protecting groups for mercapto include -C(O)-R (where R is alkyl, aryl or aralkyl), *p*-methoxybenzyl, trityl and the like. Suitable protecting groups for carboxylic acid include alkyl, aryl or aralkyl esters.

[00460] Protecting groups may be added or removed in accordance with standard techniques, which are well-known to those skilled in the art and as described herein. The use of protecting groups is described in detail in Green, T.W. and P.G.M. Wutz, *Protective Groups in Organic Synthesis* (1991), 2nd Ed., Wiley-Interscience.

[00461] One of ordinary skill in the art could easily ascertain which choices for each substituent are possible for the reaction conditions of each Scheme. Moreover, the substituents are selected from components as indicated in the specification heretofore, and may be attached to starting materials, intermediates, and/or final products according to schemes known to those of ordinary skill in the art.

[00462] Also it will be apparent that the compounds provided herein could exist as one or more isomers, that is E/Z isomers, enantiomers and/or diastereomers. Compounds of formula (I) may be generally prepared as depicted in the following schemes, unless otherwise noted, the various substituents are as defined elsewhere herein.

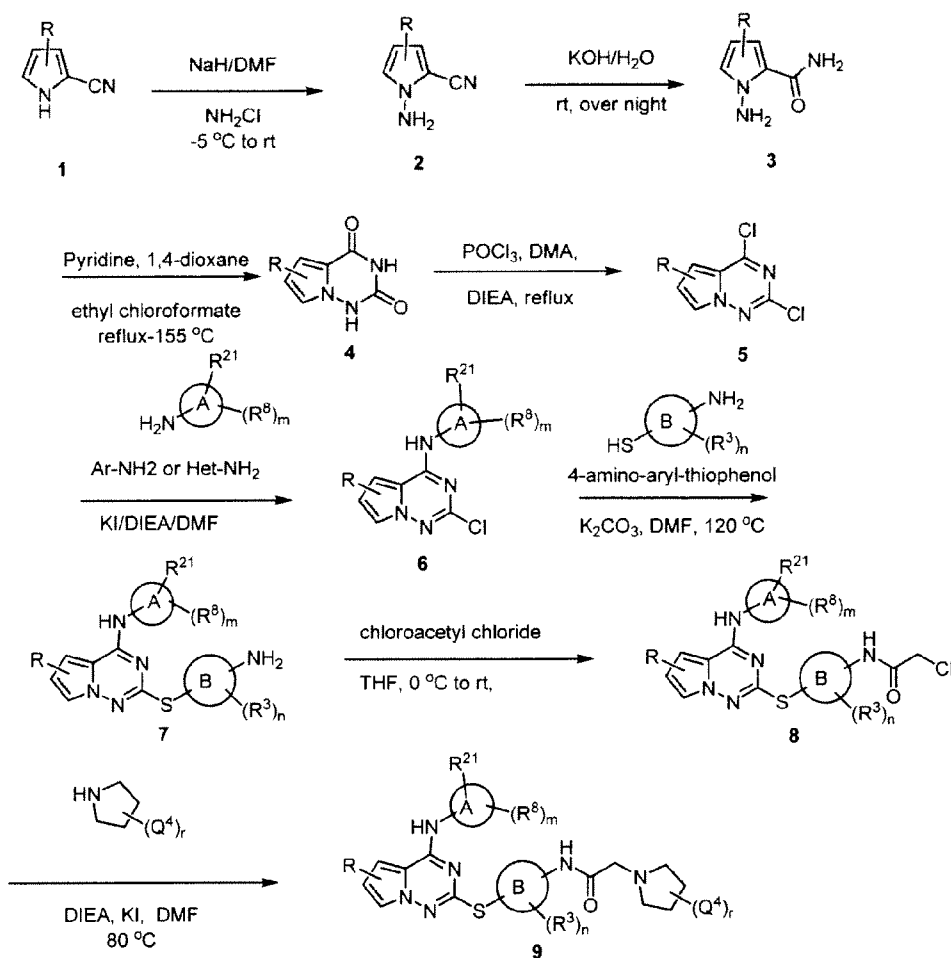
Standard abbreviations and acronyms as defined in *J. Org. Chem.* **2007** 72(1): 23A-24A are used herein. Additional abbreviations are provided below:

DAST	(diethylamino)sulfur trifluoride
DCM	dichloromethane
Deoxo-Fluor	Bis(2-methoxyethyl)aminosulfur trifluoride
Dess-Martin periodinane	1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1h)-one
DIEA	diisopropylethylamine
EDCI	N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride
EtOAc	ethyl acetate
EtOH	ethanol
HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HOAc	acetic acid
HOBt	N-hydroxybenzotriazole
LCMS	Tandem high pressure liquid chromatography-mass spectrometry
MeOH	methanol
TEA	Triethylamine
Trityl	Triphenylmethyl

[00463] In the following schemes, the variables are as described herein for compounds of Formulae I - XVI.

[00464] In certain embodiments, compounds of formula (I) are prepared according to the synthetic routes outlined in Scheme 1. The commercially available 2-cyanopyrrole **1** and substituted 2-cyanopyrroles **1** are aminated by reacting with chloroamine under strong basic condition to give the corresponding 1-amino-2-cyanopyrroles **2**. The cyano group of **2** can be hydrolyzed to carboxamides **3** using an aqueous base, such as potassium hydroxide or sodium hydroxide. Compounds **3** can be cyclized by reacting with alkyl chloroformate and pyridine at elevated temperature to give the pyrrolo[1,2-f][1,2,4]triazine-2,4(1H,3H)-diones (**4**). Chloro-dehydration of **4** using phosphoryl oxychloride catalyzed by N,N-dimethylacetamide with base, such as N,N-diisopropylethylamine, can lead to the formation of 2,4-dichloropyrrolo[1,2-f][1,2,4]triazines (**5**). The 4-position chloride of **5** can be regioselectively displaced by an arylamine or a heteroarylamine in the presence of KI and DIEA as base to give compounds **6**. Under elevated temperature with base, such as potassium carbonate, the 2-position chloride of **6** can be displaced by 4-amino-aryl-mercaptan to give compounds **7**. Compounds **7** can be acylated with chloroacetyl chloride to give compounds **8**. The chloride of **8** can be displaced with a variety of amines, including pyrrolidines, to give compounds **9**.

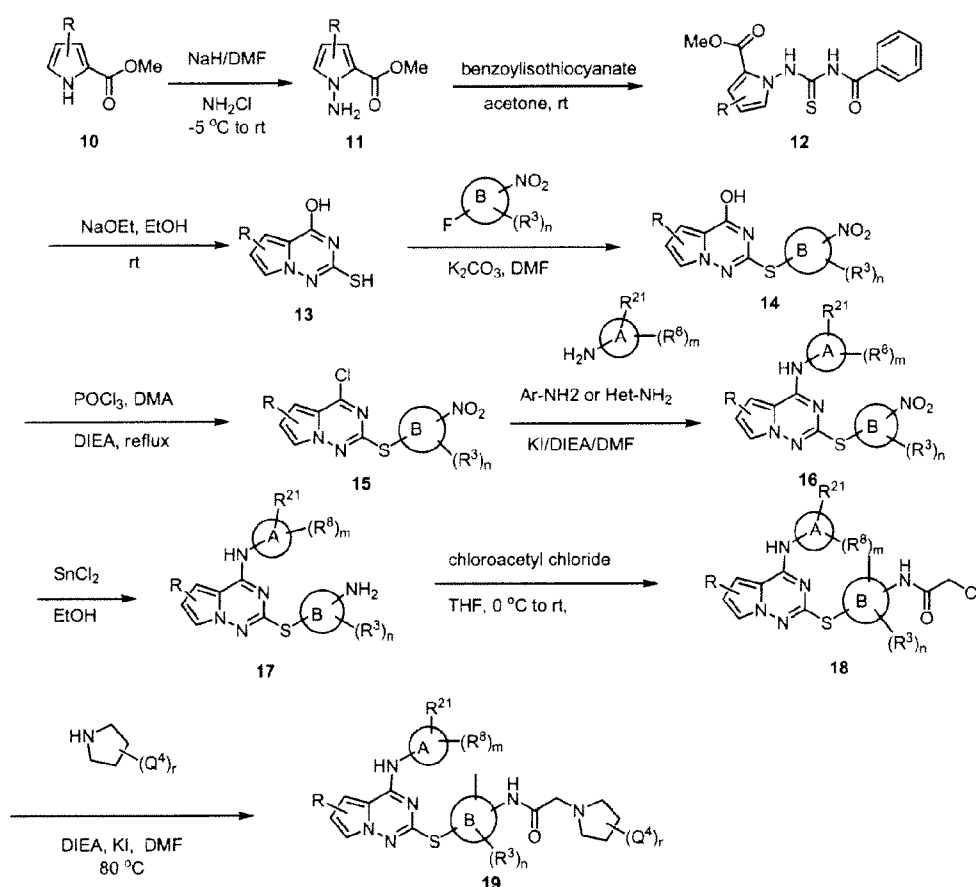
Scheme 1: General synthesis of Aurora compounds:



[00465] In another embodiment, compounds of formula (I) are prepared according to the synthetic routes outlined in Scheme 2 without going through 2,4-dichloropyrrolo[1,2-f][1,2,4]triazines. The commercially available methyl 2-pyrrole carboxylate and readily available substituted methyl 2-pyrrole carboxylates **10** are aminated by reacting with chloroamine under strong basic condition to give the corresponding 1-amino-2-pyrrole carboxylates **11**. Reacting **11** with benzoylisothiocyanate provided 1-(3-benzoylthioureido)-1H-pyrrole-2-carboxylates **12**. Cyclization can be realized under basic condition with bases such as sodium ethoxide to give 2-mercaptopyrrolo[1,2-f][1,2,4]triazin-4-ols **13**. A nucleophilic substitution of mercaptans **13** with fluorine-substituted nitroarenes under basic condition at elevated temperature can generate the diarylsulfides **14**. Chlorodehydration of **14** yield 4-chloropyrrolo[1,2-f][1,2,4]triazines **15**. The 4-chloride of **15** can be displaced by an arylamine or a heteroarylamine using KI as catalyst and DIEA as base to give compounds **16**. Reduction of the nitro group of **16** using a

number of reducing agents, such as tin(II) chloride, in solvents such as EtOH, would provide anilines **17**. Compounds **17** can be acylated with chloroacetyl chloride to give compounds **18**. The chloride of **18** can be displaced with a variety of amines, including pyrrolidines, to give compounds **19**. Alternatively, 2-mercaptopyrrolo[1,2-f][1,2,4]triazin-4-ols **13** may undergo aminolysis to yield the carboxamide **3** and proceed as described in Scheme 1 to produce compounds **9**.

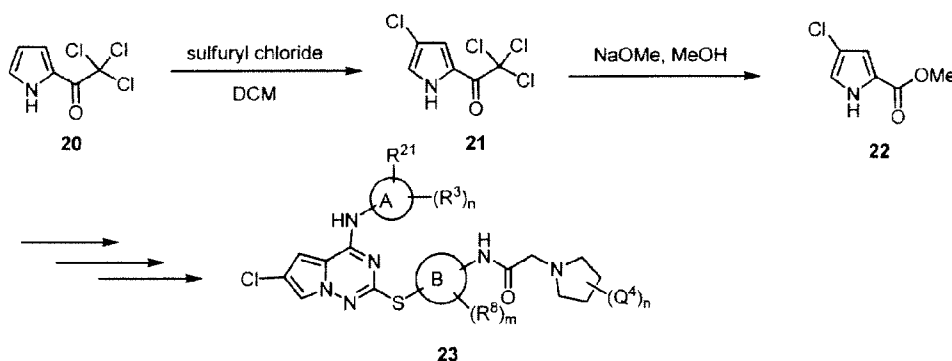
Scheme 2: General synthesis of Aurora compounds without going through 2,4-dichloropyrrolotriazine:



[00466] In an illustrative method, compounds of formula (I), such as 6-chloropyrrolo[1,2-f][1,2,4]triazine analogs may be routinely prepared according to the synthetic route outlined in Scheme 3. The commercially available 2,2,2-trichloro-1-(1H-pyrrol-2-yl)ethanone **20** can be regioselectively chlorinated with chlorination agents, not limited to sulfonyl chloride, to give 2,2,2-trichloro-1-(4-chloro-1H-pyrrol-2-yl)ethanone **21**. Methanolysis of **21** with sodium methoxide can yield methyl

carboxylate **22**, which can then be subsequently transformed to the desired compound **23** as described in Scheme 1 or 2.

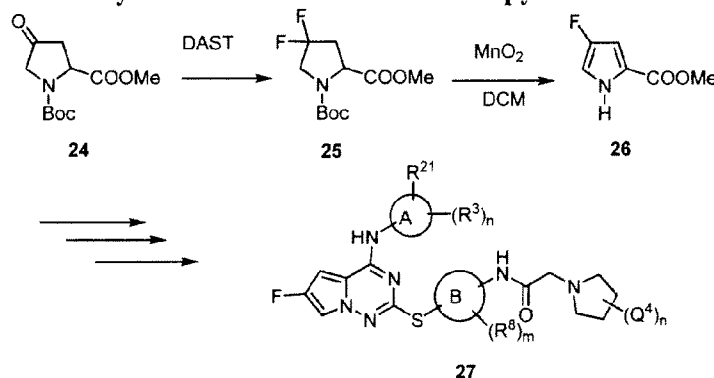
Scheme 3: General synthesis of 6-chloro and 6-bromo substituted pyrrolotriazine analogs:



[00467] A similar sequence can be adapted for making the 6-bromopyrrolotriazine analogs.

[00468] In an illustrative method, compounds of formula (I), such as 6-fluoropyrrolo[1,2-f][1,2,4]triazine analogs may be routinely prepared according to the synthetic routes outlined in Scheme 4. Treatment of methyl N-tert-butyloxycarbonyl-4-oxopyrrolidine-2-carboxylate with DAST or Deoxo-Fluor can lead to difluoropyrrolidine **25**. Oxidation and dehydrofluorination of the pyrrolidine ring of **25** to pyrrole **26** can be realized with oxidizing agents, such as manganese dioxide. Compound **26** can then be transformed to the fluorinated compounds **27** as described in Scheme 1 or 2.

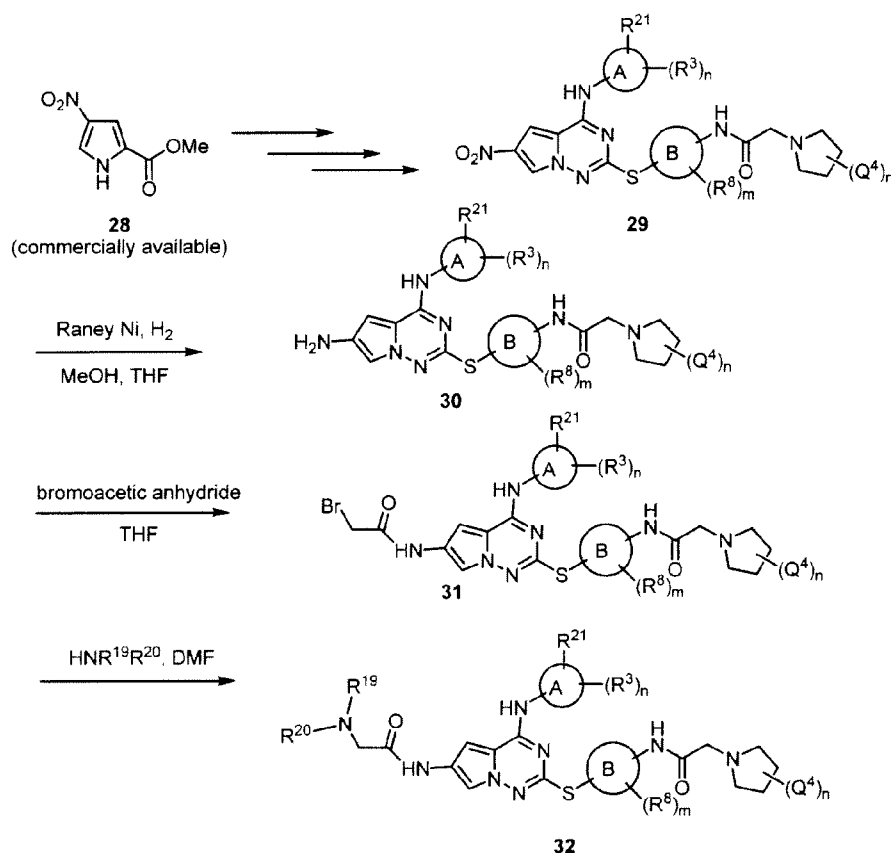
Scheme 4: General synthesis of 6-fluoro substituted pyrrolotriazine analogs:



[00469] In an illustrative method, compounds of formula (I), such as 6-amino-substituted pyrrolo[1,2-f][1,2,4]triazine analogs may be routinely prepared according to the synthetic routes outlined in Scheme 5. The commercially available 2-methyl 4-

nitro-1H-pyrrole-2-carboxylate **28** can be converted to compounds **29** by following the steps described in Scheme 2. The nitro group of **29** can then be reduced to an amino group using a variety of reducing agents, one of which can be Raney Ni under a hydrogen atmosphere to give **30**. The amino group of **30** can then be acylated with bromoacetic anhydride or chloroacetyl chloride to give acetamides **31**. Substitution with a variety of amines can then afford the desired compounds **32**.

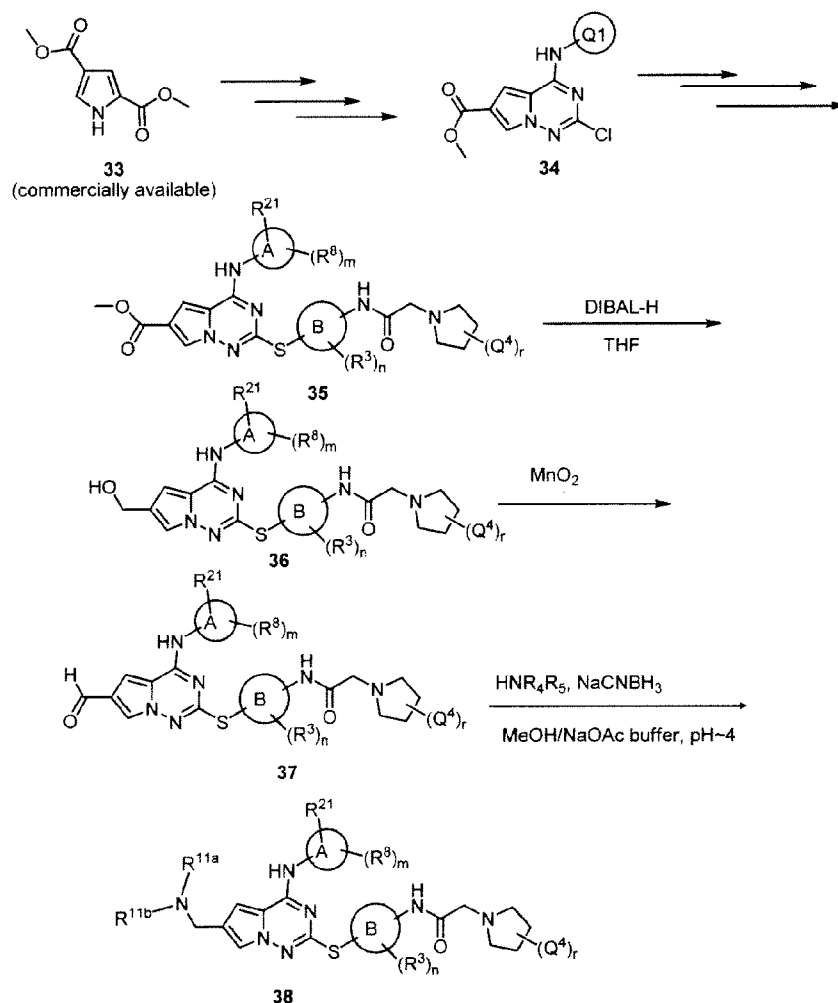
Scheme 5: General synthesis of 6-nitrogen substituted pyrrolotriazine derivatives:



[00470] In an illustrative method, compounds of formula (I), such as 6-hydroxymethyl-substituted pyrrolo[1,2-f][1,2,4]triazine analogs and 6-aminomethyl-substituted pyrrolo[1,2-f][1,2,4]triazine analogs may be routinely prepared according to the synthetic routes outlined in Scheme 6. The commercially available dimethyl 1H-pyrrole-2,4-dicarboxylate **33** can be converted to compounds **34** by following the steps described in Scheme 1. The compounds **34** can be further transformed to compounds **35** by following the steps described in Scheme 1. The carboxylate group

of **35** can then be reduced to give the hydroxymethyl analogs **36**. Oxidation of the hydroxyl group of **36** to aldehyde **37** can be realized with different oxidizing agents, such as manganese dioxide. Reductive amination using a variety of amines, under a variety of conditions, can afford the aminomethyl analogs **38**.

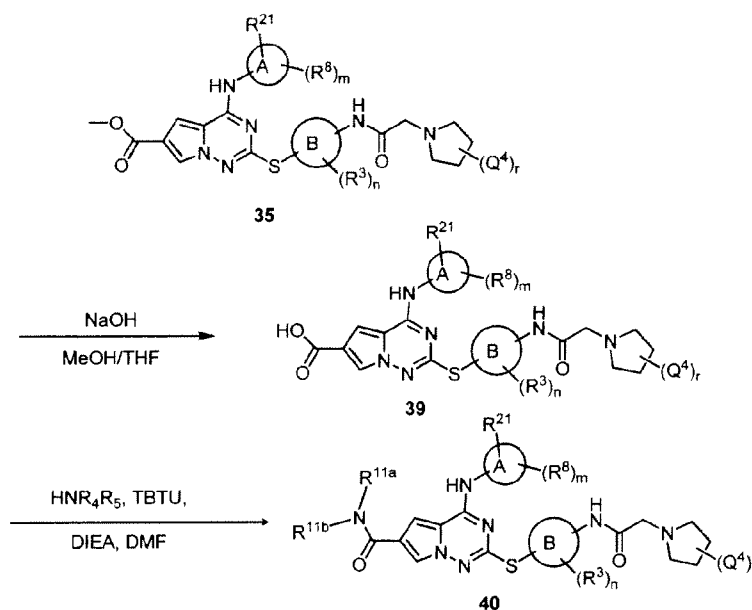
Scheme 6: General synthesis of 6-carbon substituted pyrrolotriazine derivatives-1:



[00471] Similarly, in an illustrative method, compounds of formula (I), such as 6-carboxamide-substituted pyrrolo[1,2-f][1,2,4]triazine analogs may be routinely prepared according to the synthetic routes outlined in Scheme 7. The carboxylate analogs **35** can be hydrolyzed to give the carboxylic acids **39**. Amide bond formation

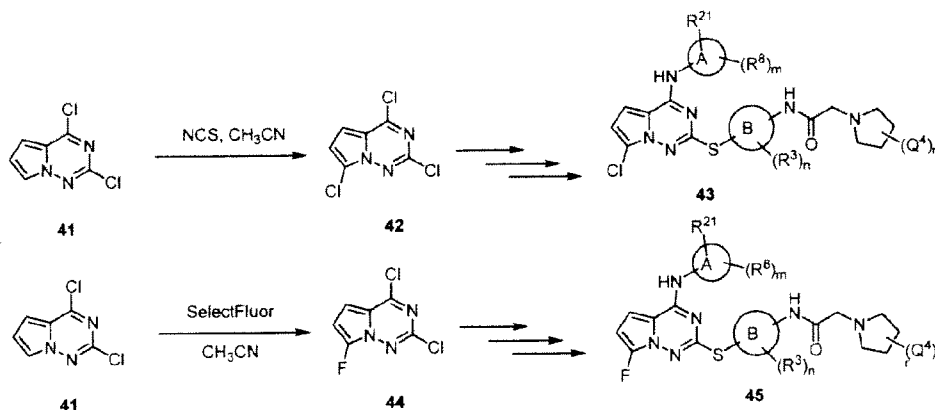
using a variety of coupling reagents, such as TBTU, provides the carboxamide analogs **40**.

Scheme 7: General synthesis of 6-carbon substituted pyrrolotriazine derivatives-2:



[00472] In an illustrative method, compounds of formula (I), such as 7-chloro-substituted or 7-fluoro-substituted-pyrrolo[1,2-f][1,2,4]triazine analogs may be routinely prepared according to the synthetic routes outlined in Scheme 8. The dichloropyrrolotriazine **41** can be chlorinated with NCS in solvents such as acetonitrile to give 7-chloropyrrolotriazine **42**, which can then be transformed to the chlorinated compounds **43** as described in Scheme 1. Similarly, fluorination of **41** can be realized with agents such as SelectFluor to give 7-fluoropyrrolotriazine **44**, which can then be transformed to the fluorinated compounds **45** as described in Scheme 1 or 2.

Scheme 8: General synthesis of 7-substituted pyrrolotriazine derivatives



[00473] The subject matter has been described in an illustrative manner, and it is to be understood that the terminology used is intended to be in the nature of description rather than of limitation. Thus, it will be appreciated by those of skill in the art that conditions such as choice of solvent, temperature of reaction, volumes and reaction time may vary while still producing the desired compounds. In addition, one of skill in the art will also appreciate that many of the reagents provided in the following examples may be substituted with other suitable reagents. *See, e.g., Smith & March, Advanced Organic Chemistry, 5th ed. (2001).* Such changes and modifications, including without limitation those relating to the chemical structures, substituents, derivatives, intermediates, syntheses, formulations and/or methods of use provided herein, may be made without departing from the spirit and scope thereof. U.S. patents and publications referenced herein are incorporated by reference.

EXAMPLES

[00474] The embodiments described above are intended to be merely exemplary, and those skilled in the art will recognize, or will be able to ascertain using no more than routine experimentation, numerous equivalents of specific compounds, materials, and procedures. All such equivalents are considered to be within the scope of the claimed subject matter and are encompassed by the appended claims.

Example 001

Preparation of 2-(cyclopropylamino)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

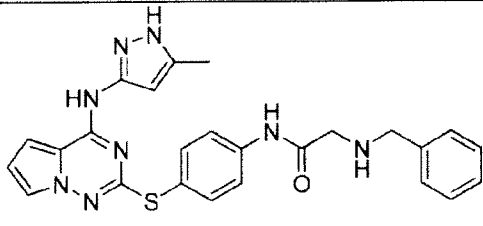
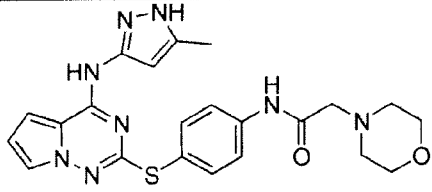
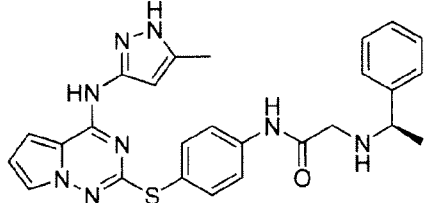
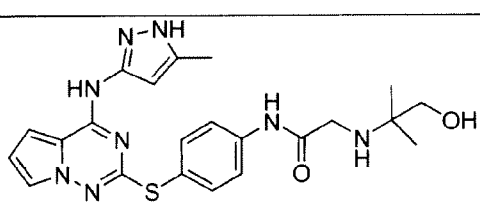
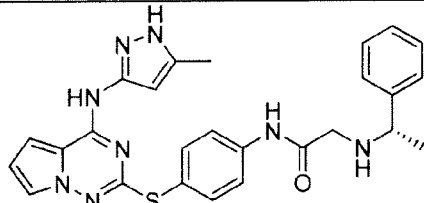
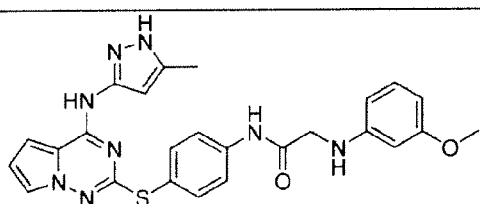
[00475] Example 001A: 2-bromo-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was synthesized

using a procedure analogous to that described in Example 016B, substituting bromoacetic anhydride for the chloroacetyl chloride used in Example 016B.

[00476] Example 001B: To a solution of bromide from Example 001A (50 mg, 0.109 mmol) in DMF (2 mL) was added cyclopropylamine (0.5 mL) and the mixture was heated in a sealed tube at 120°C for 6 h. Formation of the product was determined by LCMS. The crude reaction mixture was purified by preparative HPLC (Phenomenex phenylhexyl reverse phase column) eluting with a gradient of solvent B (0.05% HOAc/CH₃CN) in solvent A (0.05% HOAc/H₂O) to afford 2-(cyclopropylamino)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide as a white solid (21 mg, 44 %). ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.05 (s, 1H), 10.60 (s, 1H), 10.05 (s, 1H), 7.75 (d, 2H), 7.55 (m, 3H), 6.55 (s, 1H), 5.60 (s, 1H), 3.30 (s, 2H), 2.20 (m, 1H), 2.05 (s, 3H), 0.45-0.20 (m, 4H); LCMS (ESI) *m/z* 435 (M+H)⁺.

The following compounds were prepared using a procedure similar to that described in Example 1 optionally with DIEA, KI or TBAI.

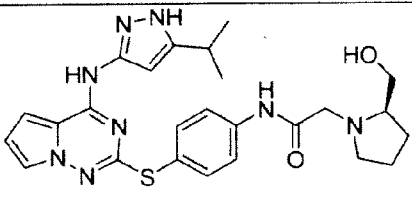
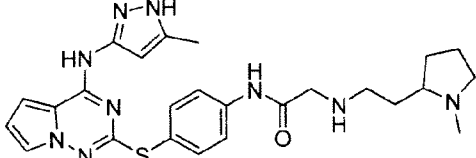
Exam. No.	Structure	Compound name	LC MS
1-I		2-(diethylamino)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	451
1-II		N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-(phenylamino)acetamide	471
1-III		2-(cyclopentylamino)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	463

Exam. No.	Structure	Compound name	LC MS
1-IV		2-((benzylamino)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	485
1-V		N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-morpholinoacetamide	465
1-VI		(R)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-((1-phenylethyl)amino)acetamide	499
1-VII		2-((1-hydroxy-2-methylpropan-2-yl)amino)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	467
1-VIII		(S)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-((1-phenylethyl)amino)acetamide	499
1-IX		2-((3-methoxyphenyl)amino)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	501

Exam. No.	Structure	Compound name	LC MS
1-X		N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-((pyridin-3-ylmethyl)amino)acetamide	486
1-XI		N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-(5-oxo-1,4-diazepan-1-yl)acetamide	492
1-XII		N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-(4-methylpiperazin-1-yl)acetamide	478
1-XIII		2-(4-hydroxypiperidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	479
1-XIV		2-(1,1-dioxidothiomorpholino)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	513
1-XV		2-(4-(hydroxymethyl)piperidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	493

Exam. No.	Structure	Compound name	LC MS
1-XVI		2-(4-(2-hydroxyethyl)piperazin-1-yl)-N-(4-((4-(3-methyl-1H-pyrazol-5-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	508
1-XVII		(S)-2-((1-hydroxypropan-2-yl)amino)-N-(4-((4-(5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	453
1-XVII I		2-((2-(2-hydroxyethoxy)ethyl)amino)-N-(4-((4-(3-methyl-1H-pyrazol-5-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	483
1-XIX		2-(4-(2-hydroxyethyl)piperidin-1-yl)-N-(4-((4-(5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	507
1-XX		(R)-1-(2-((4-((4-(5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)pyrrolidine-2-carboxamide	492
1-XXI		(R)-2-((1-hydroxypropan-2-yl)amino)-N-(4-((4-(5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	453

Exam. No.	Structure	Compound name	LC MS
		f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	
1-XXII		2-(4-aminopiperidin-1-yl)-N-(4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	478
1-XXII I		(R)-N-(4-((4-((5-ethyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-(2-(hydroxymethyl)pyrrolidin-1-yl)acetamide	493
1-XXI V		2-((2-(dimethylamino)ethyl)amino)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	466
1-XXV		2-((3-(dimethylamino)propyl)amino)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	480
1-XXV I		2-((3-hydroxypropyl)amino)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	453
1-XXV II		(S)-2-(2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	507

Exam. No.	Structure	Compound name	LC MS
		f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	
I-XXV III		(R)-2-(2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	507
I-XXI X		N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-((2-(1-methylpyrrolidin-2-yl)ethyl)amino)acetamide	506

Example 002**Preparation of N-(4-(4-(5-Methyl-1H-pyrazol-3-ylamino)-6-(2-(piperidin-1-yl)acetamido)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)cyclopropanecarboxamide**

[00477] **Example 2 Step 1.** Preparation of ethyl 1-amino-4-nitro-1H-pyrrole-2-carboxylate

To a suspension of sodium hydride (2.84 g, 118.6 mmol) in DMF (20 mL) was added ethyl 4-nitro-1H-pyrrole-2-carboxylate (18.2 g, 98.8 mmol) in DMF (20 mL). The mixture was stirred at rt for 1 h. Chloramine (395 mL, 118.6 mmol) was added and the mixture was stirred at rt overnight, and then partitioned between ether (600 mL) and water (700 mL). The ether layer was dried over magnesium sulfate and concentrated. The residue was triturated with EtOAc to give N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)-6-(2-(piperidin-1-yl)acetamido)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)cyclopropanecarboxamide (7.0g, 36%).

[00478] **Example 002 Step 2: Preparation of 1-amino-4-nitro-1H-pyrrole-2-carboxamide.** Ammonia gas was bubbled for 30 min into methanol in a pressure

vessel at -10 °C, and then ethyl 1-amino-4-nitro-1H-pyrrole-2-carboxylate (7.0 g, 35 mmol) was added. The vessel was sealed and heated at 80 °C overnight. The mixture was cooled and a solid was formed. Collection of the solid by filtration gave 1-amino-4-nitro-1H-pyrrole-2-carboxamide (6.0 g, 100%).

[00479] Example 002 Step 3: Preparation of 6-nitropyrrolo[1,2-f][1,2,4]triazine-2,4(1H,3H)-dione To a mixture of 1-amino-4-nitro-1H-pyrrole-2-carboxamide (6.0 g, 35.3 mmol) and pyridine (3.10 mL, 38.4 mmol) in 1,4-dioxane was added slowly ethyl chloroformate (3.67 mL, 38.4 mmol). The mixture was heated at reflux for 1 h, and then concentrated under reduced pressure. The residue was melted and heated at 155 °C overnight. After cooling, the solid was triturated with MeOH to give 6-nitropyrrolo[1,2-f][1,2,4]triazine-2,4(1H,3H)-dione (5.0 g, 72%).

[00480] Example 002 Step 4: Preparation of 2,4-dichloro-6-nitropyrrolo[1,2-f][1,2,4]triazine. To 6-nitropyrrolo[1,2-f][1,2,4]triazine-2,4(1H,3H)-dione (3.0 g, 15.4 mmol) were added phosphoryl chloride (40 mL) and triethylamine (1.09 mL, 7.82 mmol). The mixture was heated at reflux under an argon atmosphere. When completed, the mixture was concentrated under reduced pressure overnight. The residue was triturated with anhydrous diethyl ether several times. The combined ether extracts were concentrated under reduced pressure to give 2,4-dichloro-6-nitropyrrolo[1,2-f][1,2,4]triazine (1.3 g, 37%).

[00481] Example 002 Step 5: Preparation of 2-chloro-N-(5-methyl-1H-pyrazol-3-yl)-6-nitropyrrolo[1,2-f][1,2,4]triazin-4-amine: To a round bottom flask were added potassium iodide (926 mg, 5.58 mmol), DMF, and 2,4-dichloro-6-nitropyrrolo[1,2-f][1,2,4]triazine (1.3 g, 5.58 mmol). The mixture was stirred at rt for 5 min then a solution of 5-methyl-1H-pyrazol-3-amine (650 mg, 6.69 mmol) in DMF was added followed by diisopropylethylamine (0.97 mL, 5.58 mmol). The reaction was stirred at rt for 2 h. The mixture was partitioned between EtOAc and saturated aq sodium chloride, the organic phase was concentrated and the residue was triturated with MeOH to give 2-chloro-N-(5-methyl-1H-pyrazol-3-yl)-6-nitropyrrolo[1,2-f][1,2,4]triazin-4-amine (750 mg, 46%).

[00482] **Example 002 Step 6: Preparation of N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)-6-nitropyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)cyclopropanecarboxamide:** To a suspension of potassium carbonate (236 mg, 1.71 mmol) in DMF was added N-(4-mercaptophenyl)cyclopropanecarboxamide (263 mg, 1.36 mmol) followed by a solution of 2-chloro-N-(5-methyl-1H-pyrazol-3-yl)-6-nitropyrrolo[1,2-f][1,2,4]triazin-4-amine (200 mg, 0.683 mmol) in DMF. The mixture was heated at 60 °C overnight, then diluted with EtOAc and washed with water and brine. The organic layer was concentrated and the crude residue was purified by reverse phase HPLC to give N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)-6-nitropyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)cyclopropanecarboxamide (120 mg, 39%).

[00483] **Example 002 Step 7: Preparation of N-(2-(4-acetamidophenylthio)-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-6-yl)-2-(piperidin-1-yl)acetamide.** To a flask were added N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)-6-nitropyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)cyclopropanecarboxamide (100 mg, 0.222 mmol), Raney nickel in MeOH, and THF, and the mixture was placed under a hydrogen atmosphere. When LCMS showed the reaction was complete, the mixture was concentrated. To the residue in THF was added α -bromoacetic anhydride (39.12 mg, 0.266 mmol) and the mixture was stirred at rt for 3 h under an argon atmosphere. The mixture was concentrated to afford crude N-(4-(6-(2-bromoacetamido)-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)cyclopropanecarboxamide. To this residue in DMF was added piperidine (44 μ L, 0.444 mmol), and the mixture was heated at 120 °C overnight. Purification by HPLC followed by trituration with acetonitrile gave N-(2-(4-acetamidophenylthio)-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-6-yl)-2-(piperidin-1-yl)acetamide (9.5 mg, 8%). ¹H NMR (300 MHz, DMSO-d₆) δ : 10.46 (br. s., 1H), 10.0 (s, 1H), 7.86 (s, 1H), 7.70-7.80 (m, 2H), 7.51-7.61 (m, 4H), 7.23 (s, 1H), 5.57 (s, 1H), 3.0-3.15 (m, 2H), 1.91-2.13 (m, 4H), 1.46-1.67 (m, 4H), 0.69-0.94 (m, 10H); LCMS (ESI) m/z 546 (M + H)⁺.

The following compounds were prepared using a procedure similar to that described in Example 2 optionally with DIEA, KI or TBAI.

Exam. No.	Structure	Compound name	LC MS (M+H) ⁺
2-I		(R)-N-(4-((6-(2-(2-(hydroxymethyl)pyrrolidin-1-yl)acetamido)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide	562
2-II		N-(4-((6-(2-(4-(hydroxymethyl)piperidin-1-yl)acetamido)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide	576
2-III		3-methyl-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)-6-(2-(piperidin-1-yl)acetamido)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)picolinamide	597
2-IV		N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)-6-(2-(morpholinoacetamido)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide	548
2-V		N-(4-((6-(2-(cyclopropylamino)acetamido)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide	518
2-VI		N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)-6-(2-(pyrrolidin-1-yl)acetamido)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide	532

Exam. No.	Structure	Compound name	LC MS (M+H) ⁺
2-VII		N-(4-((6-(2-((2-(2-hydroxyethoxy)ethyl)amino)acetamido)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide	566
2-VIII		(S)-N-(4-((6-(2-(2-(hydroxymethyl)pyrrolidin-1-yl)acetamido)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide	562
2-IX		N-(4-((6-(2-(4-hydroxypiperidin-1-yl)acetamido)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide	562
2-X		N-(4-((6-(2-(4-(2-hydroxyethyl)piperidin-1-yl)acetamido)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide	590
2-XI		N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)-6-(2-(4-methylpiperazin-1-yl)acetamido)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide	561
2-XII		(R)-N-(4-((6-(2-(3-hydroxypyrrolidin-1-yl)acetamido)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide	548

Exam. No.	Structure	Compound name	LC MS (M+H) ⁺
2-XIII		(S)-N-(4-((6-(2-(3-hydroxypyrrolidin-1-yl)acetamido)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide	548
2-XIV		N-(4-((6-(2-(4-(2-hydroxyethyl)piperazin-1-yl)acetamido)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide	591
2-XV		N-(4-((6-(2-(1,1-dioxidothiomorpholino)acetamido)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide	596
2-XVI		(R)-2-(2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)-6-(2-(piperidin-1-yl)acetamido)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	619

Example 003

Preparation of 5-Chloro-1-methyl-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide

[00484] 5-chloro-1-methyl-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide was synthesized using a procedure analogous to that described in Example 004, substituting 5-chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid for the 2-trifluoromethylbenzoic acid used in Example 004. 22 %. ¹H NMR (DMSO-*d*₆)

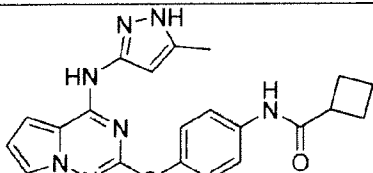
δ 12.10 (br s, 1H), 10.80 (s, 1H), 10.70 (br s, 1H), 7.79 (d, 2H), 7.63 (d, 2H), 7.59 (m, 1H), 7.21 (1H, s), 6.58 (s, 1H), 5.61 (s, 1H), 3.98 (s, 3H), 2.03 (s, 3H); LCMS (ESI) m/z 548 (M + H)⁺.

Example 004

Preparation of N-(4-(4-(5-Methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(trifluoromethyl)benzamide

[00485] To a solution of 2-trifluoromethylbenzoic acid (30.9 mg, 0.162 mmol) in DMA (2 mL) was added PyBrop (89.6 mg, 0.210 mmol) and the mixture was stirred for 10 min at ambient temperature, after which 2-(4-aminophenylthio)-N-(5-methyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine (50 mg, 0.148 mmol) and diisopropylethyl amine (0.05 mL) were added sequentially. The mixture was stirred at ambient temperature for 12 h and completion of the reaction was determined by LCMS. The mixture was purified by preparative HPLC (Phenomenex phenylhexyl reverse phase column) eluting with a gradient of solvent B (0.05% HOAc/CH₃CN) in solvent A (0.05% HOAc/H₂O) to afford N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(trifluoromethyl) benzamide (21 mg, 27 %) as a white solid. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.10 (s, 1H), 10.85 (s, 1H), 10.67 (s, 1H), 7.77-7.55 (m, 9H), 7.23 (s, 1H), 6.59 (s, 1H), 5.72 (s, 1H), 2.15 (s, 3H); LCMS (ESI) m/z 510 (M+H)⁺.

The following compounds were prepared using a procedure similar to that described in Example 4, optionally with HATU in place of PyBrop. In certain cases, where the acid coupling partner contained a Boc-protected amino group an additional deprotection step was required.

Exam. No.	Structure	Compound name	LC MS (M+H) ⁺
4-i		N-(4-(((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclobutanecarboxamide	420

Exam. No.	Structure	Compound name	LC MS (M+H) ⁺
4-ii		N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclohexanecarboxamide	448
4-iii		2,2,2-trifluoro-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	434
4-iv		N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-4-(trifluoromethyl)nicotinamide	511
4-v		N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-4-(1H-1,2,4-triazol-1-yl)benzamide	509
4-vi		N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)quinoline-3-carboxamide	493
4-vii		N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)picolinamide	443
4-viii		6-fluoro-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)picolinamide	461

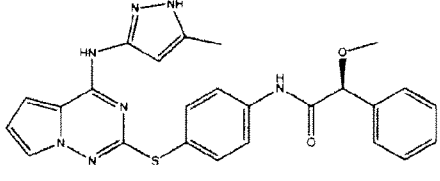
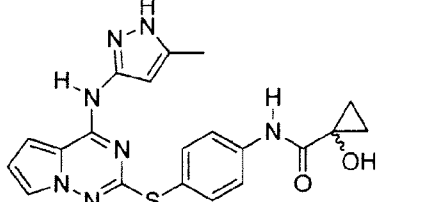
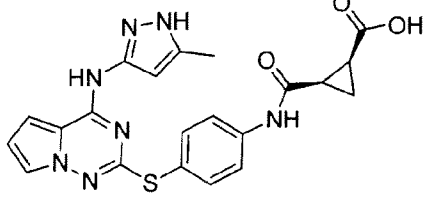
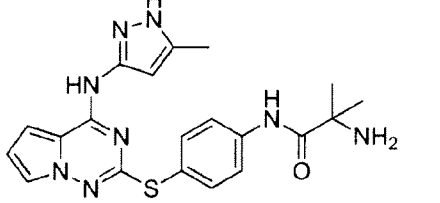
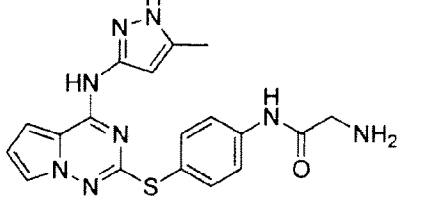
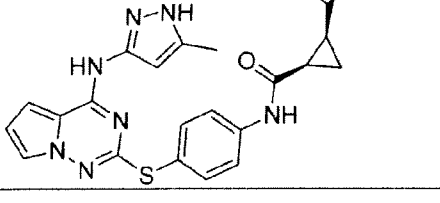
Exam. No.	Structure	Compound name	LC MS (M+H) ⁺
4-ix		N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-6-(trifluoromethyl)nicotinamide	511
4-x		N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)nicotinamide	443
4-xi		2-fluoro-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)nicotinamide	461
4-xii		N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)isonicotinamide	443
4-xiii		2-methyl-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)nicotinamide	457
4-xiv		5-methyl-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)nicotinamide	457
4-xvI		N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)oxazole-5-carboxamide	433

Exam. No.	Structure	Compound name	LC MS (M+H) ⁺
4-xvi		2-methoxy-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)nicotinamide	473
4-xvii		2-chloro-6-methyl-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)nicotinamide	491
4-xviii		N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-3-(trifluoromethyl)benzamide	510
4-xix		4-methyl-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)nicotinamide	457
4-xx		3-methyl-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)picolinamide	457
4-xxi		6-chloro-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)nicotinamide	477
4-xxii		2-bromo-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide	484, 486 Br pattern

Exam. No.	Structure	Compound name	LC MS (M+H) ⁺
4-xxiii		6-methyl-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)picolinamide	457
4-xxiv		5-methyl-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)picolinamide	457
4-xxv		2-cyclopropyl-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	420
4-xxvi		5-chloro-3-ethyl-1-methyl-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-1H-pyrazole-4-carboxamide	508
4-xxvii		5-chloro-1,3-dimethyl-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-1H-pyrazole-4-carboxamide	494
4-xxviii		1-methyl-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide	514

Exam. No.	Structure	Compound name	LC MS (M+H) ⁺
		carboxamide	
4-xxix		1,3,5-trimethyl-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-1H-pyrazole-4-carboxamide	474
4-xxx		1-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-3-(2-(trifluoromethyl)phenyl)urea	525
4-xxxi		N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide	500
4-xxxii		3-cyclopropyl-1-methyl-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-1H-pyrazole-4-carboxamide	486
4-xxxiii		(1R,2R)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-(morpholinomethyl)cyclopropanecarboxamide	505

Exam. No.	Structure	Compound name	LC MS (M+H) ⁺
4-xxxiv		2-chloro-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-6-(trifluoromethyl)benzamide	545
4-xxxv		1-methyl-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide	420
4-xxxvi		methyl 1-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)carbamoyl)cyclopropanecarboxylate	464
4-xxxvi i		1-(dimethylamino)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide	449
4-xxxvi ii		(1S,2S)-ethyl 2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)carbamoyl)cyclopropanecarboxylate	478
4-xxxix		2-methyl-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-5-(trifluoromethyl)oxazole-4-carboxamide	515

Exam. No.	Structure	Compound name	LC MS (M+H) ⁺
4-xl		(S)-2-methoxy-N-(4-(((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-phenylacetamide	486
4-xli		1-hydroxy-N-(4-(((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide	422
4-xlii		(1S,2R)-2-(((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)carbonyl)cyclopropanecarboxylic acid	450
4-xliii		2-amino-2-methyl-N-(4-(((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)propanamide	423
4-xliv		2-amino-N-(4-(((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	395
4-xlv		(1S,2R)-N1-methyl-N2-(4-(((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropane-1,2-dicarboxamide	463

Exam. No.	Structure	Compound name	LC MS (M+H) ⁺
		dicarboxamide	
4-xlvi		(1R,2S)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-(morpholine-4-carbonyl)cyclopropane carboxamide	519
4- xlvi		1-(5-(tert-butyl)isoxazol-3-yl)-3-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)urea	504
4- xlvi		(R)-1-(2-(methoxymethyl)pyrrolidin-1-yl)-3-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)urea	494

Example 005**Preparation of 5-Chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(trifluoromethyl)benzamide**

[00486] 5-Chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(trifluoromethyl)benzamide (15 mg, 18 %) was prepared as a white solid using a procedure analogous to that described in Example 004, substituting 2-trifluoromethyl-5-chlorobenzoic acid for the 2-trifluoromethylbenzoic acid used in Example 004. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.05 (s, 1H), 10.95 (s, 1H), 10.65 (s, 1H), 7.95-7.75 (m, 5H), 7.70-7.50 (m, 3H), 7.20 (s, 1H), 6.55 (s, 1H), 5.70 (s, 1H), 2.05 (s, 3H); LCMS (ESI) *m/z* 544 (M+H)⁺.

Example 006

Preparation of (1R,2S)-Ethyl 2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)benzamido)cyclopropanecarboxylate

[00487] (1R,2S)-ethyl 2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)benzamido)cyclopropanecarboxylate was synthesized using a procedure analogous to that described in Example 004, substituting (1R,2S)-2-(ethoxycarbonyl)cyclopropanecarboxylic acid for the 2-trifluoromethylbenzoic acid used in Example 004. 7.7 %. ¹H NMR (DMSO-*d*₆) δ 12.0 (br s, 1H), 10.55 (s, 2H), 7.71 (d, 2H), 7.53 (m, 3H), 7.15 (br s, 1H), 6.52 (s, 1H), 5.60 (s, 1H), 4.02 (q, 2H), 2.25 (m, 1H), 2.15 (m, 1H), 2.03 (s, 3H), 1.42 (m, 1H), 1.20 (m, 1H), 1.11 (t, 3H); LCMS (ESI) *m/z* 478 (M+H)⁺.

Example 007

Preparation of N-(2,2-Difluorocyclopropyl)-4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)benzamide

[00488] N-(2,2-difluorocyclopropyl)-4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)benzamide was synthesized using a procedure analogous to that described in Example 004, substituting 2,2-difluorocyclopropanecarboxylic acid (obtained by following the procedure described in *J. Fluorine Chem.*, **2005**, 126, 339) for the 2-trifluoromethylbenzoic acid used in Example 004. The crude product was purified by reverse phase HPLC. Yield: 5.5 %. ¹H NMR (DMSO- *d*₆) δ 12.10 (br s, 1H), 10.70 (s, 1H), 10.65 (br s, 1H), 7.75 (d, 2H), 7.60 (m, 3H), 7.20 (s, 1H), 6.55 (m, 1H), 5.58 (s, 1H), 2.90 (m, 2H), 2.50 (d, 1H), 2.02 (s, 3H).; LCMS (ESI) *m/z* 442 (M+H)⁺.

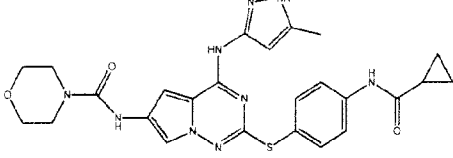
Example 008

Preparation of N-(2-(4-(Cyclopropanecarboxamido)phenylthio)-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-6-yl)-4-methylpiperazine-1-carboxamide

[00489] To a flask were added N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)-6-nitropyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)cyclopropanecarboxamide from Example 002 Step 6 (100 mg, 0.222 mmol), Raney nickel (0.1 g) in MeOH (2 mL) and tetrahydrofuran (20 mL). The mixture was placed under a hydrogen atmosphere for 3 h, then the mixture was filtered and the filtrate was concentrated. To the residue in THF (5 mL) were added sequentially a solution of p-nitrophenylchloroformate (47 mg, 0.22 mmol) in THF (2 mL) and triethylamine (4 drops). The mixture was stirred

at rt for 2 h, then N-methylpiperazine (2 mL) was added and the mixture was stirred overnight. Purification by HPLC followed by trituration with acetonitrile gave N-(2-(4-(cyclopropanecarboxamido)phenylthio)-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-6-yl)-4-methylpiperazine-1-carboxamide (9.5 mg, 8%). ¹H NMR (DMSO-*d*₆) δ 11.99 (br. s., 1H), 10.39 - 10.54 (m, 2H), 8.90 (s, 1H), 7.65 - 7.79 (m, 3H), 7.53 (d, J = 8.5 Hz, 2H), 7.05 (s, 1H), 5.54 (s, 1H), 3.40 - 3.48 (m, 4H), 2.25 - 2.35 (m, 4H), 2.20 (s, 3H), 2.01 (s, 3H), 1.75 - 1.92 (m, 1H), 0.82 (d, J = 6.0 Hz, 4H); LCMS (ESI) *m/z* 547 (M + H)⁺.

[00490] The following compound was also prepared in a similar manner.

Example No.	Structure	Compound name	LC MS (M+H) ⁺
8-i		N-(2-((4-(cyclopropanecarboxamido)phenylthio)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-6-yl)morpholine-4-carboxamide	534

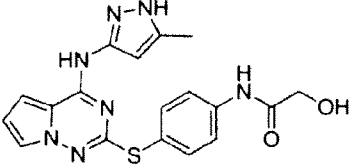
Example 009

Preparation of N-(4-(4-(5-Methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(dimethylamino)acetamide

[00491] To a solution of dimethylamine hydrochloride (82 mg, 1.00 mmol) in DMF (2 mL) under N₂ were added K₂CO₃ (173 mg, 1.25 mmol), KI (42 mg, 0.25 mmol) and N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-chloroacetamide (104 mg, 0.25 mmol). The mixture was stirred overnight at 40 °C, then water (10mL) was added and the mixture was extracted with EtOAc (3 x 15mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give a solid (45 mg, 10% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.05 (s, 1H), 10.62 (s, 1H), 10.00 (s, 1H), 7.81 (d, 2H), 7.55 (m, 3H), 7.19 (s, 1H), 6.55 (s, 1H), 5.62 (s, 1H), 3.09 (s, 3H), 2.26 (s, 6H), 2.01 (s, 3H); MS (ESI) *m/z* 423 (M+H)⁺.

[00492] The following compound was prepared in a similar manner.

Examp	Structure	Compound name	LC MS
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le No.			(M+H) ⁺
9-i		2-hydroxy-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-ylthio)phenyl)acetamide	396

Example 010**Preparation of N-(4-(4-(5-Methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-hydroxypiperidin-1-yl)acetamide**

[00493] To a solution of piperidin-3-ol (101 mg, 1.00 mmol) in DMF (2 mL) under N₂ were added K₂CO₃ (173 mg, 1.25 mmol), KI (42 mg, 0.25 mmol) and N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-chloroacetamide (104 mg, 0.25 mmol). The mixture was stirred overnight at 40 °C, then water (10 mL) was added and the mixture was extracted with EtOAc (3 x 15 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to give N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4] triazin-2-ylthio)phenyl)-2-(3-hydroxypiperidin-1-yl)acetamide as a solid (52 mg, 11% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.05 (s, 1H), 10.62 (s, 1H), 9.96 (s, 1H), 7.78 (d, 2H), 7.59 (m, 3H), 7.21 (s, 1H), 6.58 (s, 1H), 4.74 (s, 1H), 3.13 (s, 1H), 2.68 (m, 2H), 2.22 (m, 1H), 2.00 (s, 3H), 1.71 (m, 2H), 1.51 (m, 1H), 1.23 (m, 2H); MS (ESI) *m/z* 479 (M+H)⁺.

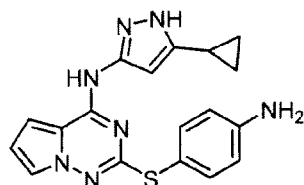
Example 011**Preparation of N-(4-(4-(5-Methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(N-(2-hydroxyethyl)-N-methylamino)acetamide**

[00494] To a solution of 2-(methylamino)ethanol (75 mg, 1.00 mmol) in DMF (2 mL) at rt under N₂ were added K₂CO₃ (138 mg, 1.00 mmol), KI (42 mg, 0.25 mmol), and N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-chloroacetamide (104 mg, 0.25 mmol). The mixture was stirred at 40 °C overnight, then water (10 mL) was added, and the mixture was extracted with EtOAc (3 x 15mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4] triazin-2-ylthio)phenyl)-2-(N-(2-hydroxyethyl)-N-methylamino)acetamide as

a solid (23 mg, 5% yield). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.04 (s, 1H), 10.60 (s, 1H), 10.04 (s, 1H), 7.76 (d, 2H), 7.52 (m, 3H), 7.17 (s, 1H), 6.54 (s, 1H), 5.61 (s, 1H), 4.82 (s, 1H), 3.99 (m, 1H), 3.48 (s, 2H), 3.17 (s, 2H), 2.50 (s, 2H), 2.30 (s, 3H), 2.00 (s, 3H), 1.98 (s, 1H), 1.13 (s, 1H); MS (ESI) m/z 453 ($\text{M}+\text{H}$) $^+$.

Example 012

Preparation of 2-(4-Aminophenylthio)-N-(5-cyclopropyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine



[00495] 2-(4-aminophenylthio)-N-(5-cyclopropyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine was prepared by a procedure analogous to that described in Example 016A, substituting 2-chloro-N-(5-cyclopropyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine (Mastalerz, et al. Publ.: US2007/4731 A1) for the 2-chloro-N-(5-methyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine used in Example 016A. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.01 (s, 1H), 10.54 (s, 1H), 7.55 (s, 1H), 7.23 (m, 3H), 6.61 (m, 2H), 5.97 (s, 1H), 5.52 (s, 2H), 1.87 (m, 1H), 0.95 (m, 2H), 0.66 (m, 2H); LCMS (ESI) m/z 364 ($\text{M} + \text{H}$) $^+$.

Example 013

Preparation of (S)-N-(4-(4-(5-Cyclopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(2-(hydroxymethyl)pyrrolidin-1-yl)acetamide

[00496] **Example 013A:** 2-chloro-N-(4-(4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was prepared using a procedure analogous to that described in Example 016B, substituting 2-(4-aminophenylthio)-N-(5-cyclopropyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine from Example 012 for the 2-(4-aminophenylthio)-N-(5-methyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine used in Example 016B. LCMS (ESI) m/z 440, 442 ($\text{M} + \text{H}$) $^+$.

[00497] **Example 013B:** (S)-N-(4-(4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(2-(hydroxymethyl)pyrrolidin-1-yl)acetamide was prepared using a procedure analogous

to that described in Example 018B, substituting 2-chloro-N-(4-(4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 013A for the 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide used in Example 018B, and substituting (S)-pyrrolidin-(2-yl)methanol for the ((2S,4R)-4-tert-butoxypyrrolidin-2-yl)methanol used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.07 (s, 1H), 10.63 (s, 1H), 9.98 (s, 1H), 7.76 (d, 2H), 7.59 (s, 1H), 7.56 (d, 2H), 7.23 (s, 1H), 6.59 (d, 1H), 5.75 (s, 1H), 4.70 (s, 1H), 3.57 (d, 1H), 3.39 (m, 2H), 3.15 (d, 1H), 3.05 (m, 1H), 2.73 (s, 1H), 1.72 (m, 6H), 0.85 (m, 2H), 0.54 (m, 2H); LCMS (ESI) *m/z* 503 (M-H)⁺.

Example 014

Preparation of N-(4-(4-(5-Methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-((S)-2-(hydroxymethyl)pyrrolidin-1-yl)acetamide

[00498] To a solution of (S)-pyrrolidin-(2-yl)methanol (101 mg, 1.00 mmol) in DMF (2 mL) at rt under N₂ were added K₂CO₃ (173 mg, 1.25 mmol), KI (42 mg, 0.25 mmol) and N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-chloroacetamide (104 mg, 0.25 mmol). The mixture was stirred overnight at 40 °C, then water (10 mL) was added, and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic phases were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4] triazin-2-ylthio)phenyl)-2-((S)-2-(hydroxymethyl)pyrrolidin-1-yl)acetamide as a solid (90 mg, 19% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.05 (s, 1H), 10.62 (s, 1H), 10.02 (s, 1H), 7.77 (d, 2H), 7.59 (m, 3H), 7.22 (s, 1H), 6.58 (s, 1H), 4.70 (s, 1H), 3.57 (d, 1H), 3.40 (s, 2H), 3.19 (m, 1H), 3.15 (m, 1H), 2.72 (m, 1H), 1.85 (s, 3H), 1.23 (m, 4H), 0.88 (m, 1H); MS (ESI) *m/z* 479 (M+H)⁺.

Example 015

Preparation of N-(4-(4-(5-Methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(S)-3-hydroxypyrrolidin-1-yl)acetamide

[00499] To a solution of (S)-pyrrolidin-3-ol (87 mg, 1.00 mmol) in DMF (2 mL) at rt under N₂ were added K₂CO₃ (173 mg, 1.25 mmol), KI (42 mg, 0.25 mmol) and N-(4-

(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-chloroacetamide (104 mg, 0.25 mmol). The mixture was stirred overnight at 40 °C, then water (10 mL) was added, and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic phases were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4] triazin-2-ylthio)phenyl)-2-(S)-3-hydroxypyrrolidin-1-yl)acetamide as a solid (90 mg, 19% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.05 (s, 1H), 10.62 (s, 1H), 9.96 (s, 1H), 7.78 (d, 2H), 7.58 (m, 3H), 7.21 (s, 1H), 6.57 (s, 1H), 5.63 (s, 1H), 4.82 (s, 1H), 4.22 (s, 1H), 3.30 (m, 2H), 3.16 (m, 1H), 2.79 (s, 2H), 2.51 (m, 1H), 2.00 (s, 3H), 1.62 (m, 2H); MS (ESI) *m/z* 465 (M+H)⁺.

Example 016

Preparation of (S)-2-(2-(Hydroxymethyl)azetidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

Example 016A: To a suspension of K₂CO₃ (1.39 g, 10.05 mmol) in DMF (20 mL) under N₂ at rt was added a solution of 4-aminothiophenol (1.00 g, 8.04 mmol) in DMF (1 mL). The mixture was stirred at rt for 10 min, then 2-chloro-N-(5-methyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine, prepared according to Mastalerz, et al. US20070004731A1, (1.00 g, 4.02 mmol) in DMF (5 mL) was added. The mixture was stirred at 120 °C overnight, then allowed to cool to rt and poured into water (100 mL). The solid was collected by filtration, washing with MeOH. The filtrate was extracted with EtOAc, and the organic layer was washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with petroleum ether-EtOAc (3:1 to 1:1) to give 2-(4-aminophenylthio)-N-(5-methyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine as a gray solid (740 mg, 54%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.09 (s, 1H), 10.61 (s, 1H), 7.61 (s, 1H), 7.25-7.31 (m, 3H), 6.61-6.70 (m, 3H), 5.88 (s, 1H), 5.61 (s, 1H), 2.22 (s, 3H); LCMS (ESI) *m/z* 338 (M + H)⁺.

[00500] Example 016B: To 2-(4-aminophenylthio)-N-(5-methyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine (3.30 g, 10.00 mmol) in THF (15 mL) at 0 °C under N₂ was added dropwise 2-chloroacetyl chloride (1.32 g, 12.00 mmol) in THF (5 mL). The mixture was stirred at rt overnight, then EtOAc (150 mL) and 10% NaOH

(5 mL) were added. The mixture was stirred vigorously at rt for 30 min, then the organic layer was then separated, washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 20:1 DCM/methanol to afford 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (4.00 g, 97%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.08 (s, 1H), 10.66 (s, 1H), 7.76 (d, 2H), 7.62 (m, 3H), 7.23 (s, 1H), 6.59 (m, 1H), 5.61 (s, 1H), 4.30 (s, 2H), 2.02 (s, 3H); LCMS (ESI) *m/z* 414 (M + H)⁺.

[00501] Example 016C: (S)-azetidin-2-ylmethanol was prepared using a procedure analogous to that described in Example 018A, substituting L-azetidine carboxylic acid for the (2S,4R)-4-tert-butoxypyrrolidine-2-carboxylic acid used in Example 018A.

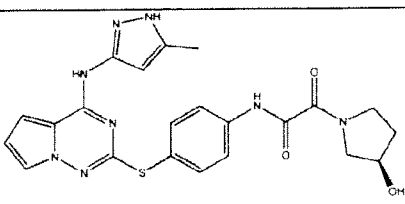
[00502] Example 016D : (S)-2-(2-(hydroxymethyl)azetidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was prepared using a procedure analogous to that described in Example 018B, substituting (S)-azetidin-2-ylmethanol for the ((2S,4R)-4-tert-butoxypyrrolidin-2-yl)methanol used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.08 (s, 1H), 10.63 (s, 1H), 10.04 (s, 1H), 7.79 (d, 2H), 7.59 (s, 1H), 7.58 (d, 2H), 7.22 (s, 1H), 6.59 (d, 1H), 5.76 (s, 1H), 4.76 (s, 1H), 3.46 (s, 2H), 3.18 (m, 1H), 3.05 (m, 4H), 2.04 (s, 3H), 2.04 (m, 2H); LCMS (ESI) *m/z* 463 (M-H)⁻.

The following compounds were prepared using a procedure similar to that described in Example 16A followed by transformation of 2-(4-aminophenylthio)-N-(5-methyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine, so obtained, into the corresponding carbamate or isocyanate derivative by means of standard methods. A final standard coupling procedure afforded the desired compounds.

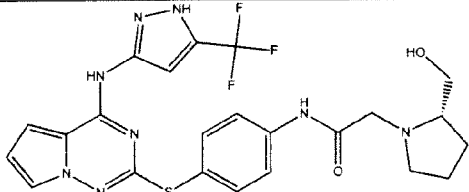
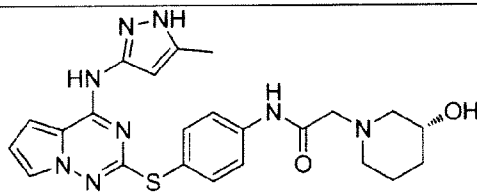
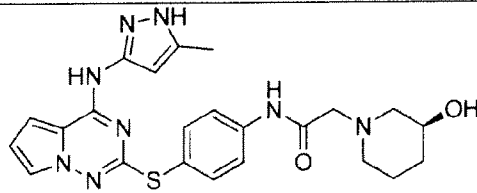
Exam. No.	Structure	Compound name	LC MS
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Exam. No.	Structure	Compound name	LC MS
16A-i		N-(4-((4-((5-(hydroxymethyl)-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropyl)carboxamide	422
16A-ii		2-((4-aminophenyl)thio)-N-(5-(trifluoromethyl)-1H-pyrazol-3-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	392
16A-iii		2-(3-((2-((4-aminophenyl)thio)pyrrolo[2,1-f][1,2,4]triazin-4-yl)amino)-1H-pyrazol-5-yl)ethanol	368
16A-iv		2-((4-aminophenyl)thio)-N-(5-propyl-1H-pyrazol-3-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	366
16A-v		(S)-1-(2-(hydroxymethyl)pyrrolidin-1-yl)-2-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)ethanone	479
16A-vi		(S)-2-(hydroxymethyl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)pyrrolidine-1-carboxamide	465

Exam. No.	Structure	Compound name	LC MS
16A-vii		1-((1R,2S)-2-(hydroxymethyl)cyclopentyl)-3-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)urea	479
16A-viii		(R)-2-(hydroxymethyl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)pyrrolidine-1-carboxamide	465
16A-ix		(R)-3-hydroxy-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)pyrrolidine-1-carboxamide	451
16A-x		(S)-1-(2-(methoxymethyl)pyrrolidin-1-yl)-3-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)urea	494
16A-xi		2-((4-amino-2-fluorophenyl)thio)-N-(5-methyl-1H-pyrazol-3-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	356
16A-xii		2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoacetic acid	410

Exam. No.	Structure	Compound name	LC MS
16A-xiii		(R)-2-(3-hydroxypyrrolidin-1-yl)-N-(4-(((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-oxoacetamide	479

The following compounds were prepared using a procedure similar to that described in Example 16.

Exam. No.	Structure	Compound name	LC MS (M+H) ⁺ or (M-H) where indicated
16-i		(S)-2-(2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(((4-((5-(trifluoromethyl)-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	533
16-ii		(R)-2-(3-hydroxypiperidin-1-yl)-N-(4-(((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	479
16-iii		(S)-2-(3-hydroxypiperidin-1-yl)-N-(4-(((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	479

Exam. No.	Structure	Compound name	LC MS (M+H) ⁺ or (M-H) where indicated
16-iv		N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-(piperidin-1-yl)acetamide	461 (M-H)
16-v		2-(2-(hydroxymethyl)piperidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	491 (M-H)
16-vi		(S)-2-((R)-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)propanamide	491 (M-H)
16-vii		(R)-2-((R)-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)propanamide	491 (M-H)

Exam. No.	Structure	Compound name	LC MS (M+H) ⁺ or (M-H) where indicated
16-viii		2-((4-(cyclopropanecarboxamido)phenyl)thio)-4-((5-methyl-1H-pyrazol-3-yl)amino)-N-(3-(piperidin-1-yl)propyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	574
16-ix		N-(4-((6-(hydroxymethyl)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide	436

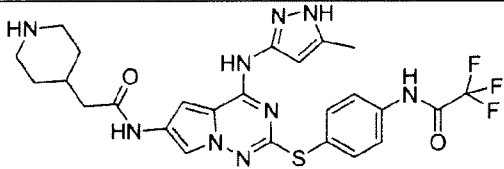
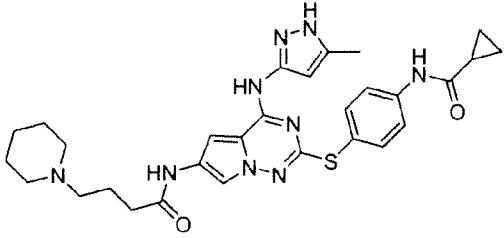
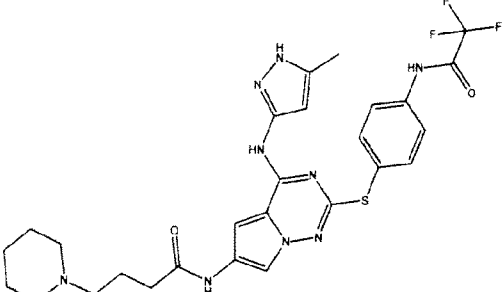
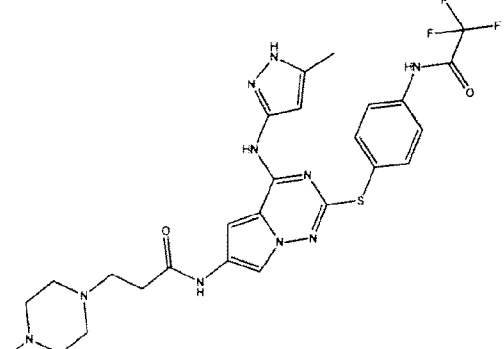
Example 017

Preparation of N-(4-((6-(3-(Piperidin-1-yl)propanamido)-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-yl)sulfanyl)phenyl)cyclopropanecarboxamide

[00503] **Example 017A:** To a suspension of N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)-6-nitropyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)cyclopropanecarboxamide from Step 6 of Example 002 (375 mg, 0.83 mmol) in anhydrous THF was added Raney-Ni slurry (ca. 1 mL). The mixture was vigorously stirred under an atmosphere of H₂ at rt overnight. Raney-Ni was separated by filtration, and the filtrate was concentrated to a residue (350 mg). To a solution of this residue in THF (4 mL) were added triethylamine (120 μ L, 0.64 mmol), DMAP (26 mg, 0.24 mmol), and 3-(piperidin-1-yl)propanoic acid (37 mg, 0.24 mmol). After stirring for 5 min, EDCI (82 mg, 0.43 mmol) was added. The resulting mixture was stirred at rt for 16 h, then the mixture was processed by conventional methods to give N-(4-((6-(3-(piperidin-1-yl)propanamido)-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-yl)sulfanyl)phenyl)cyclopropanecarboxamide (63 mg, 54% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.60 (s, 1H), 10.56 (s, 1H),

10.46 (s, 1H), 9.23 (s, 1H), 7.86 (s, 1H), 7.75-7.73 (d, 2H), 7.55-7.53 (d, 2H), 7.10 (s, 1H), 5.55 (s, 1H), 3.46 (m, 2H), 3.43 (m, 2H), 3.38 (m, 2H), 3.36 (m, 2H), 2.02 (s, 2H), 1.84-1.81 (t, 3H), 1.69-1.63 (m, 3H), 1.40 (m, 1H), 0.80 (d, 4H); LCMS (ESI) m/z 560 $[M+H]^+$.

The following compounds were prepared using a procedure similar to that described in Example 17.

Exam. No.	Structure	Compound name	LC MS (M+H) ⁺
17-i		2,2,2-trifluoro-N-(4-(((4-((5-methyl-1H-pyrazol-3-yl)amino)-6-(2-(piperidin-4-yl)acetamido)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	574
17-ii		N-(4-(((4-((5-methyl-1H-pyrazol-3-yl)amino)-6-(4-(piperidin-1-yl)butanamido)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide	574
17-iii		N-(4-((5-methyl-1H-pyrazol-3-yl)amino)-2-(((4-(2,2,2-trifluoroacetamido)phenyl)thio)pyrrolo[2,1-f][1,2,4]triazin-6-yl)-4-(piperidin-1-yl)butanamide	603
17-iv		N-(4-((5-methyl-1H-pyrazol-3-yl)amino)-2-(((4-(2,2,2-trifluoroacetamido)phenyl)thio)pyrrolo[2,1-f][1,2,4]triazin-6-yl)-3-(4-methylpiperazin-1-yl)propanamide	601

Exam. No.	Structure	Compound name	LC MS (M+H) ⁺
17-v		N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)-6-(3-(piperidin-1-yl)propanamido)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-3-(trifluoromethyl)benzamide	662
17-vi		3-fluoro-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)-6-(3-(piperidin-1-yl)propanamido)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)benzamide	614
17-vii		(S)-tert-butyl 2-(2-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-6-yl)amino)-2-oxoethyl)pyrrolidine-1-carboxylate	632
17-viii		N-(4-((6-(4-(dimethylamino)butanamido)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide	534

Exam. No.	Structure	Compound name	LC MS (M+H) ⁺
17-ix		(R)-N-(4-((6-(2-aminopropanamido)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide	492
17-x		(S)-N-(4-((6-(2-aminopropanamido)-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide	492
17-xi		N-(4-((6-(3-(diethylamino)propanamido)-4-((3-methyl-1H-pyrazol-5-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)cyclopropanecarboxamide	548

Example 018

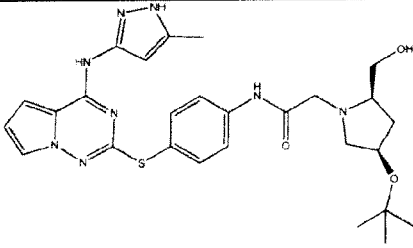
Preparation of 2-((2S,4R)-4-tert-Butoxy-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00504] **Example 018A:** To (2S,4R)-4-tert-butoxypyrrolidine-2-carboxylic acid (200 mg, 1.068 mmol) in THF (5 mL) was added 1M lithium aluminum hydride in ether (2.13 mL, 2.13 mmol) and the mixture was stirred at ambient temperature for 12 h, at which time formation of the product was confirmed by LCMS. The reaction was quenched by addition of water (0.083 mL), 10% NaOH (0.083 mL) and then additional water (0.243 mL) followed by stirring for 15 min. The mixture was filtered

through Celite and the filtrate was concentrated under reduced pressure to afford crude (2S,4R)-4-tert-butoxypyrrolidin-2-yl)methanol, which was used in next step without further purification.

[00505] Example 018B: To a solution of 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 016B (50 mg, 0.12 mmol) in DMF (3 mL) were added ((2S,4R)-4-tert-butoxypyrrolidin-2-yl)methanol (41.58 mg, 0.24 mmol), N,N-diisopropylethylamine (41.8 μ L, 0.24 mmol), and potassium iodide (19.9 mg, 0.125 mmol). The mixture was heated at 50 °C for 12 h, at which time formation of product was confirmed by LCMS. The mixture was purified by preparative HPLC (Phenomenex phenylhexyl reverse phase column) eluting with a gradient of solvent B (0.05% HOAc/CH₃CN) in solvent A (0.05% HOAc/H₂O) to afford 2-((2S,4R)-4-tert-butoxy-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (28.4 mg, 43 %) as its acetate salt. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.05 (brs, 1H), 10.70 (s, 1H), 9.85 (s, 1H), 7.90-7.50 (m, 5H), 7.20 (s, 1H), 6.55 (s, 1H), 5.60 (s, 1H), 4.70 (brs, 1H), 4.20 (m, 1H), 3.80-3.10 (m, 6H), 2.90 (s, 1H), 2.30 (m, 1H), 2.10 (s, 3H), 1.90 (s, 3H), 1.70 (m, 1H), 1.20 (s, 9H); LCMS (ESI) *m/z* 551 (M+H)⁺.

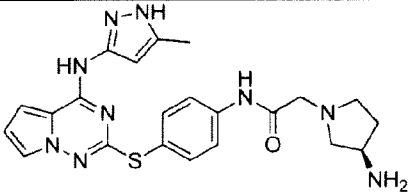
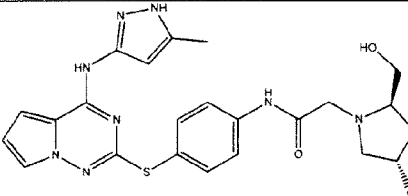
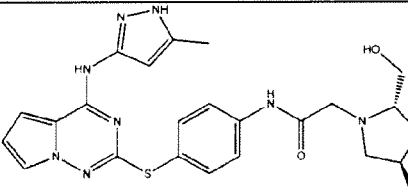
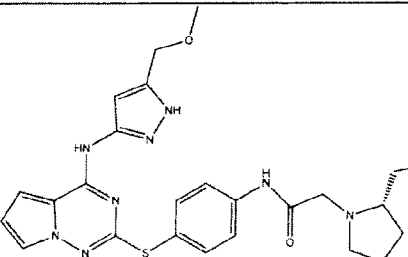
The following compounds were prepared using a procedure similar to that described in Example 18. In some cases, borane in THF was used in place of lithium aluminum hydride of example 18A.

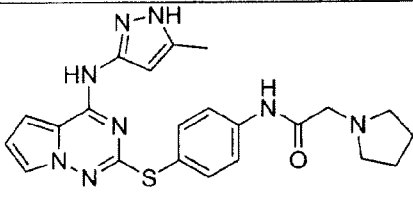
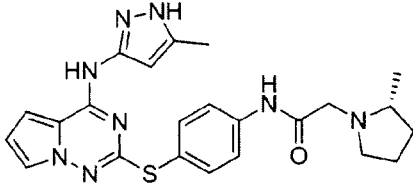
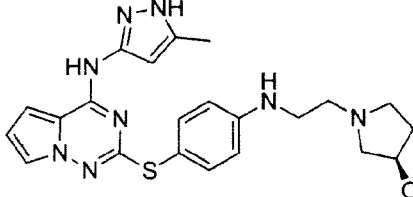
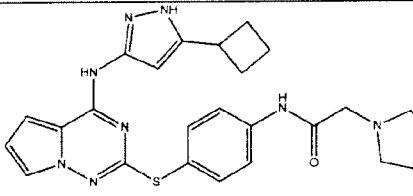
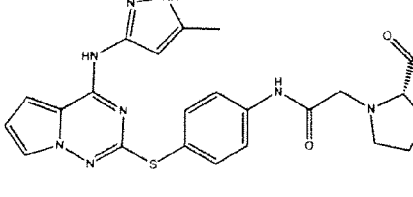
Example No.	Structure	Compound name	LC MS (M+H) ⁺ unless otherwise indicated
18-i		2-((2R,4R)-4-(tert-butoxy)-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	551

Example No.	Structure	Compound name	LC MS (M+H) ⁺ unless otherwise indicated
18-ii		2-((1S,3aS,7aR)-1-(hydroxymethyl)hexahydro-1H-isindol-2(3H)-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	533
18-iii		(R)-2-(2-(2-hydroxyethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	493
18-iv		2-((3R,4R)-3-(hydroxymethyl)-4-isopropylpyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	519 (M-H)
18-v		2-((2S,4R)-4-(tert-butoxy)-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methoxymethyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	581

The following compounds were prepared using a procedure similar to that described in Example 18B. In certain cases, where the coupling partner contained a Boc-protected amino group an additional deprotection step was required. In certain cases, an additional reduction step was required.

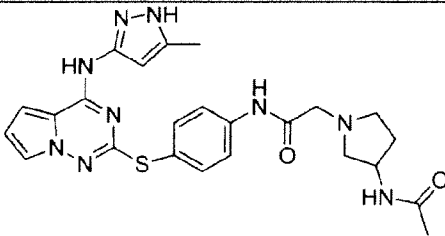
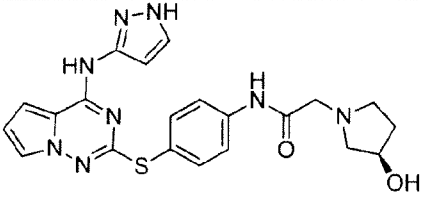
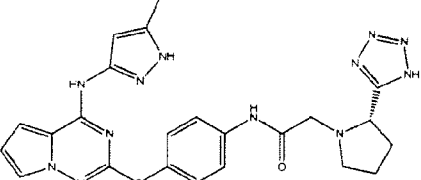
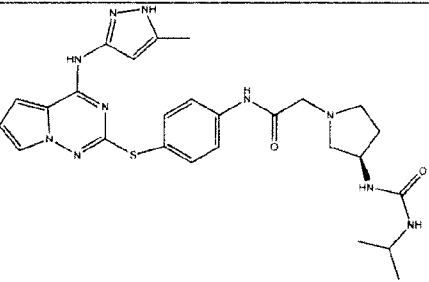
Exam. No.	Structure	Compound name	LC MS (M+H) ⁺ except as otherwise indicated
18B-i		(S)-1-(2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)pyrrolidine-2-carboxamide	492
18B-ii		2-(3-hydroxyazetidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	451
18B-iii		(S)-2-(2-(hydroxymethyl)-2-methylpyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	493
18B-iv		(S)-tert-butyl 3-(hydroxymethyl)-4-(2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)piperazine-1-carboxylate	594

Exam. No.	Structure	Compound name	LC MS (M+H) ⁺ except as otherwise indicated
18B-v		(R)-2-(3-aminopyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	462 (M-H)
18B-vi		2-((2R,4S)-4-hydroxy-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	493 (M-H)
18B-vii		2-((2S,4R)-4-amino-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	545
18B-viii		(S)-2-(2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-(methoxymethyl)-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	509

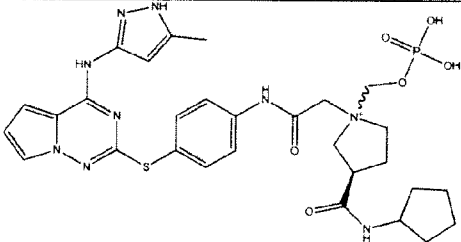
Exam. No.	Structure	Compound name	LC MS (M+H) ⁺ except as otherwise indicated
18B-ix		N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-(pyrrolidin-1-yl)acetamide	449
18B-x		(R)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-(2-methylpyrrolidin-1-yl)acetamide	463
18B-xi		(R)-1-(2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)ethyl)pyrrolidin-3-ol	451
18B-xii		(R)-N-(4-((4-((5-cyclobutyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-(3-hydroxypyrrolidin-1-yl)acetamide	505
18B-xiii		(S)-1-(2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)pyrrolidine-2-carboxylic acid	493

Exam. No.	Structure	Compound name	LC MS (M+H) ⁺ except as otherwise indicated
18B-xiv		2-((2S,4R)-4-(tert-butoxy)-2-(2-hydroxypropan-2-yl)pyrrolidin-1-yl)-N-(4-((4-((5-cyclopropyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	605
18B-xv		2-((2S,4R)-4-(tert-butoxy)-2-(2-hydroxypropan-2-yl)pyrrolidin-1-yl)-N-(4-((4-((5-cyclobutyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	617 (M-H)
18B-xvi		2-((2S,4R)-4-(tert-butoxy)-2-(2-hydroxypropan-2-yl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	579
18B-xvii		2-((3R,4R)-3-(hydroxymethyl)-4-(trifluoromethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	547

Exam. No.	Structure	Compound name	LC MS (M+H) ⁺ except as otherwise indicated
		mide	
18B-xviii		(S)-4,4-difluoro-1-(2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)pyrrolidine-2-carboxylic acid	529
18B-xix		(2S,4R)-4-(tert-butoxy)-1-(2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)pyrrolidine-2-carboxylic acid	565
18B-xx		(R)-N-(4-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-(3-(methylsulfonamido)pyrrolidin-1-yl)acetamide	542
18B-xxi		(R)-2-(2-(methoxymethyl)pyrrolidin-1-yl)-N-(4-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	493

Exam. No.	Structure	Compound name	LC MS (M+H) ⁺ except as otherwise indicated
18B-xxii		(R)-2-(3-acetamidopyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	506
18B-xxiii		(R)-N-(4-((4-((1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-(3-hydroxypyrrolidin-1-yl)acetamide	451
18B-xxiv		(S)-2-(2-(1H-tetrazol-5-yl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	517
18B-xxv		(R)-2-(3-(3-isopropylureido)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	549

Exam. No.	Structure	Compound name	LC MS (M+H) ⁺ except as otherwise indicated
18B-xxvi		(R)-isopropyl 1-(2-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethylpyrrolidin-3-ylcarbamate	550
18B-xxvii		(R)-N-(1-(2-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethylpyrrolidin-3-yl)pivalamide	548
18B-xxviii		(R)-3-(3-hydroxypyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)propanamide	479
18B-xxix		(R)-2-((1-(2-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethylpyrrolidin-3-yl)oxy)ethyl dihydrogen phosphate	589

Exam. No.	Structure	Compound name	LC MS (M+H) ⁺ except as otherwise indicated
18B-xxx		(3R)-3-(cyclopentylcarbamoyl)-1-(2-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)-1-((phosphonoxy)methyl)pyrrolidin-1-ium	670

Example 019

Preparation of N-(4-(4-(5-Methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-((R)-3-hydroxypyrrolidin-1-yl)acetamide

[00506] To a solution of (R)-pyrrolidin-3-ol (87 mg, 1.00 mmol) in DMF (2 ml) under N₂ were added K₂CO₃ (173 mg, 1.25 mmol), KI (42 mg, 0.25 mmol) and N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-chloroacetamide (104 mg, 0.25 mmol). The mixture was stirred overnight at 40 °C, then water (10 mL) was added, and the mixture was extracted with EtOAc (3 x 15mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4] triazin-2-ylthio)phenyl)-2-((R)-3-hydroxypyrrolidin-1-yl)acetamide as a solid (102 mg, 22% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.05 (s, 1H), 10.62 (s, 1H), 9.96 (s, 1H), 7.78 (d, 2H), 7.58 (m, 3H), 7.21 (s, 1H), 6.63 (s, 1H), 4.82 (m, 1H), 3.32 (m, 2H), 3.27 (s, 2H), 2.79 (m, 2H), 2.49 (m, 1H), 2.03 (s, 3H) 1.62 (m, 4H), 1.08 (m, 3H; MS (ESI) m/z 465 (M+H)⁺.

Example 020

Preparation of (S)-2-(4,4-Difluoro-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

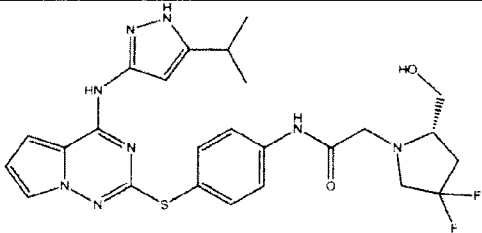
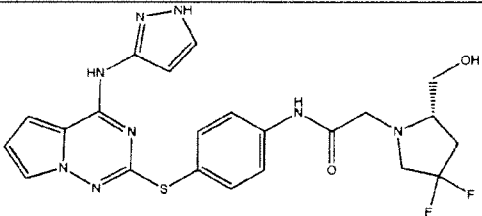
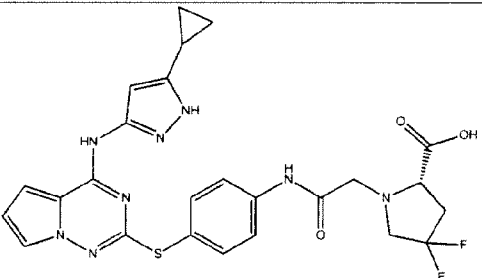
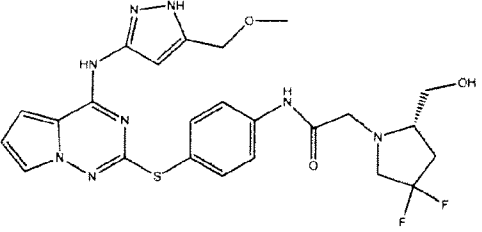
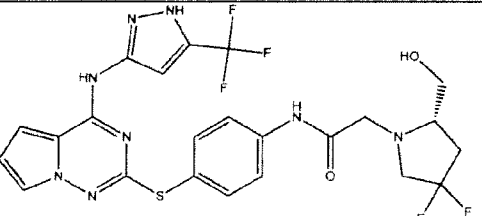
[00507] Example 020A Step 1: Preparation of (S)-(4,4-difluoropyrrolidin-2-yl)methanol: To a solution of (S)-1-(tert-butoxycarbonyl)-4,4-difluoropyrrolidine-2-carboxylic acid (200 mg, 0.796 mmol) in THF (4 mL) was added 1M BH₃ in THF (1.59 mL, 1.59 mmol) and the solution was heated under reflux for 5 h. The mixture was treated with acetic acid (0.3 mL). Ethyl acetate was added, and the organic layer was washed with brine, dried over MgSO₄, filtered and concentrated to dryness to afford (S)-tert-butyl 4,4-difluoro-2-(hydroxymethyl)pyrrolidine-1-carboxylate (160 mg, 80%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 4.95 (brs, 1H), 4.00-3.65 (m, 2H), 3.60-3.40 (m, 1H), 2.40 (s, 3H).

Example 020A, Step 2: (S)-tert-butyl 4,4-difluoro-2-(hydroxymethyl)pyrrolidine-1-carboxylate was treated with 4N HCl in 1,4-dioxane and the mixture was stirred at ambient temperature for 4 h. The mixture was concentrated under reduced pressure. The crude (S)-(4,4-difluoropyrrolidin-2-yl)methanol was used for the next step without further purification.

[00509] Example 020B: (S)-2-(4,4-difluoro-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was prepared as a white solid (35.71 mg, 57%) using a procedure analogous to that described in Example 018B, substituting (S)-(4,4-difluoropyrrolidin-2-yl)methanol for the ((2S,4R)-4-tert-butoxypyrrolidin-2-yl)methanol used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.05 (s, 1H), 10.65 (s, 1H), 10.05 (s, 1H), 7.75 (d, 2H), 7.65-7.60 (m, 3H), 7.20 (s, 1H), 6.55 (s, 1H), 5.60 (s, 1H), 4.95 (s, 1H), 3.65 (d, 1H), 3.55-3.25 (m, 4H), 3.05 (m, 2H), 2.40-2.10 (m, 3H), 2.05 (s, 3H); LCMS (ESI) *m/z* 515 (M+H)⁺.

The following compounds were prepared using a procedure similar to that described in Example 20.

Example No.	Structure	Compound name	LC MS (M+H) ⁺

Example No.	Structure	Compound name	LC MS (M+H) ⁺
20-i		(S)-2-(4,4-difluoro-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(((5-isopropyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	543
20-ii		(S)-N-(4-(((4-((1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-(4,4-difluoro-2-(hydroxymethyl)pyrrolidin-1-yl)acetamide	501
20-iii		(S)-1-(2-(((4-((5-cyclopropyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)-4,4-difluoropyrrolidine-2-carboxylic acid	553
20-iv		(S)-2-(4,4-difluoro-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(((4-((5-(methoxymethyl)-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	545
20-v		(S)-2-(4,4-difluoro-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(((4-((5-(trifluoromethyl)-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	569

Example No.	Structure	Compound name	LC MS (M+H) ⁺
		yl)thio)phenyl)acetamide	

Example 021

Preparation of N-(4-((6-(2-Diethylamino)acetamido)-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-yl)sulfanyl)phenyl)cyclopropanecarboxamide

[00510] N-(4-((6-(2-diethylaminol)acetamido)-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-yl)sulfanyl)phenyl)cyclopropanecarboxamide was synthesized as a yellow solid (20 mg, 31% yield) using a procedure analogous to that described in Example 002 Step 7, substituting diethylamine (50 μ L, 0.48 mmol) for the piperidine used in Example 002. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.07 (s, 1H), 10.57 (s, 1H), 10.44 (s, 1H), 10.06 (s, 1H), 7.85 (s, 1H), 7.73 (d, 2H), 7.53 (d, 2H), 7.25 (s, 1H), 5.55 (s, 1H), 2.67 (t, 4H), 2.02 (s, 3H), 1.82 (t, 1H), 1.04 (t, 6H), 0.82 (d, 4H); LCMS (ESI) *m/z* 534 (M+H)⁺.

Example 022

Preparation of 2-((2S,4R)-4-Fluoro-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00511] **Example 022A: ((2S,4R)-4-fluoropyrrolidin-2-yl)methanol** was prepared using a procedure analogous to that described in Example 020A, substituting (2S,4R)-1-(tert-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid for the (S)-1-(tert-butoxycarbonyl)-4,4-difluoropyrrolidine-2-carboxylic acid used in Example 020A.

[00512] **Example 022B: 2-((2S,4R)-4-Fluoro-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide** (11 mg, 18 %) was synthesized as a white solid using a procedure analogous to that described in Example 018B, substituting ((2S,4R)-4-fluoropyrrolidin-2-yl)methanol for the ((2S,4R)-4-tert-butoxypyrrolidin-2-yl)methanol used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.05 (s, 1H), 10.65 (s, 1H), 10.05 (s, 1H), 7.80 (d, 2H), 7.60 (m, 3H), 7.20 (s, 1H), 6.55 (s, 1H),

5.60 (s, 1H), 5.40-5.05 (m, 1H), 4.80 (s, 1H), 3.70-3.25 (m, 4H), 3.10 (m, 1H), 3.80 (m, 1H), 2.10-1.80 (m, 5H); LCMS (ESI) m/z 497 (M+H)⁺.

Example 023

Preparation of 2-((1S,2S,5R)-2-(Hydroxymethyl)-3-azabicyclo[3.1.0]hexan-3-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00513] **Example 023A:** (1S,2S,5R)-3-azabicyclo[3.1.0]hexan-2-ylmethanol was prepared using a procedure analogous to that described in Example 018A, substituting (1S,2S,5R)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid for the (S)-1-(tert-butoxycarbonyl)-4,4-difluoropyrrolidine-2-carboxylic acid used in Example 018A.

[00514] **Example 023B:** 2-((1S,2S,5R)-2-(hydroxymethyl)-3-azabicyclo[3.1.0]hexan-3-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was synthesized as a white solid (21.02 mg, 35 %) using a procedure analogous to that described in Example 018B, substituting (1S,2S,5R)-3-azabicyclo[3.1.0]hexan-2-ylmethanol for the ((2S,4R)-4-tert-butoxypyrrolidin-2-yl)methanol used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.05 (s, 1H), 10.70 (s, 1H), 9.70 (s, 1H), 7.80 (d, 2H), 7.65 (m, 3H), 7.20 (s, 1H), 6.60 (s, 1H), 5.60 (s, 1H), 4.70 (s, 1H), 4.75-2.60 (m, 7H), 2.05 (s, 3H), 1.60-1.30 (m, 2H), 0.80 (m, 1H), 0.30 (m, 1H); LCMS (ESI) m/z 491 (M+H)⁺.

Example 024

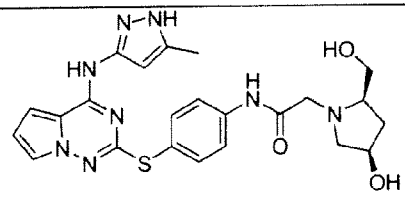
Preparation of 2-((2R,4R)-2-(Hydroxymethyl)-4-methoxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

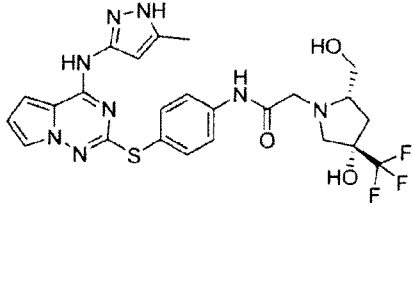
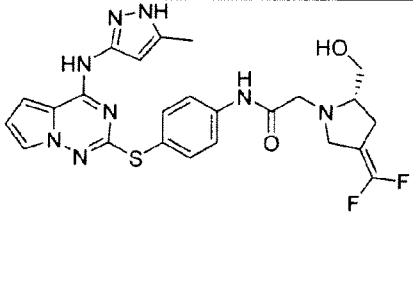
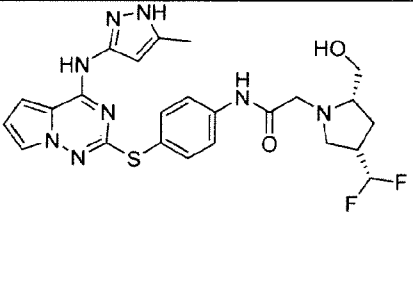
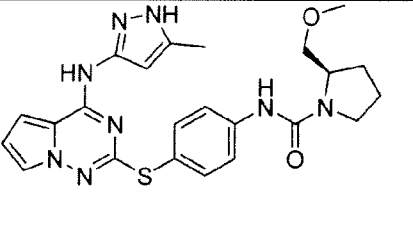
[00515] **Example 024A Step 1:** To a solution of methyl (2R,4R)-1-tert-butyloxycarbonyl-4-methoxypyrrolidine-2-carboxylate (290 mg, 1.118 mmol) in THF (4 mL) was added lithium borohydride (48.7 mg, 2.23 mmol) and the resulting mixture was heated under reflux for 3 h. The reaction was quenched with acetic acid before EtOAc was added. The solution was washed with brine and concentrated to dryness to afford (2R,4R)-tert-butyl 2-(hydroxymethyl)-4-methoxypyrrolidine-1-carboxylate, which was used in the next step without further purification.

[00516] **Example 024A Step 2:** (2R,4R)-tert-Butyl 2-(hydroxymethyl)-4-methoxypyrrolidine-1-carboxylate was taken up in 4N HCl in 1,4-dioxane and the mixture was stirred at ambient temperature for 4 h. The mixture was concentrated to dryness under reduced pressure. The crude ((2R,4R)-4-methoxypyrrolidin-2-yl)methanol was used for the next step without further purification.

[00517] **Example 024B:** 2-((2R,4R)-2-(hydroxymethyl)-4-methoxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was synthesized as a white solid (32.85 mg, 53 %) using a procedure analogous to that described in Example 018B, substituting ((2R,4R)-4-methoxypyrrolidin-2-yl)methanol for the ((2S,4R)-4-tert-butoxypyrrolidin-2-yl)methanol used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.05 (s, 1H), 10.65 (s, 1H), 10.00 (d, 1H), 7.80 (d, 2H), 7.60 (m, 3H), 7.20 (s, 1H), 6.55 (s, 1H), 4.75 (s, 1H), 3.85-3.05 (m, 9H), 2.95-2.55 (m, 2H), 2.15-1.60 (m, 5H); LCMS (ESI) *m/z* 509 (M+H)⁺.

[00518] The following compounds were prepared using a procedure similar to that described in Example 24, optionally with lithium aluminum hydride in place of lithium borohydride used in Example 24A Step 1. In certain cases, where the pyrrolidine coupling partner was protected as a benzyl carbamate, Pd/C and H₂ were used in the deprotection step (Example 24A Step2):

Exam. No.	Structure	Compound name	LC MS(M+H) ⁺ except where otherwise indicated
24-i		2-((2R,4R)-4-hydroxy-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-ylthio)phenyl)acetamide	493 (M-H)

24-ii		2-((2S,4S)-4-hydroxy-2-(hydroxymethyl)-4-(trifluoromethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	563
24-iii		(S)-2-(4-(difluoromethylene)-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	527
24-iv		2-((2S,4S)-4-(difluoromethyl)-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	529
24-v		(R)-2-(methoxymethyl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)pyrrolidine-1-carboxamide	479

Example 025

Preparation of (S)-N-(4-(4-(5-Cyclopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(4,4-difluoro-2-(hydroxymethyl)pyrrolidin-1-yl)acetamide

[00519] (S)-N-(4-(4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(4,4-difluoro-2-(hydroxymethyl)pyrrolidin-1-yl)acetamide (29.93 mg, 49 %) was synthesized as a white solid using a procedure analogous to that described in Example 018B, substituting (S)-(4,4-difluoropyrrolidin-2-yl)methanol for the ((2S,4R)-4-tert-butoxypyrrolidin-2-yl)methanol used in Example 018B, and 2-chloro-N-(4-(4-(5-cyclopropyl-1H-pyrazol-3-

ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 013A for the 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.10 (brs, 1H), 10.70 (s, 1H), 10.00 (s, 1H), 7.90-7.50 (m, 5H), 7.20 (s, 1H), 6.55 (s, 1H), 5.60 (s, 1H), 4.90 (s, 1H), 3.80-3.00 (m, 6H), 2.50-2.10 (m, 2H), 1.70 (m, 1H), 0.90 (m, 2H), 0.5 (m, 2H); LCMS (ESI) *m/z* 541 (M+H)⁺.

Example 026

Preparation of (S)-N-(4-(4-(5-Ethyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(2-(hydroxymethyl)pyrrolidin-1-yl)acetamide

[00520] **Example 026A:** 2-Chloro-N-(5-ethyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine was prepared using a procedure analogous to that described in Example 041A, substituting 5-ethyl-1H-pyrazol-3-amine for the 5-cyclobutyl-1H-pyrazol-3-amine used in Example 041A.

[00521] **Example 026B:** 2-(4-Aminophenylthio)-N-(5-ethyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine was synthesized using a procedure analogous to that described in Example 16A, substituting 2-chloro-N-(5-ethyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine for the 2-chloro-N-(5-methyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine used in Example 016A.

[00522] **Example 026C:** 2-Bromo-N-(4-(4-(5-ethyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was synthesized using a procedure analogous to that described in Example 016B, substituting 2-(4-aminophenylthio)-N-(5-ethyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine from Example 026B for the 2-(4-aminophenylthio)-N-(5-methyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine used in Example 016B, and substituting bromoacetic anhydride for the chloroacetyl chloride used in Example 016B.

[00523] **Example 026D:** To potassium iodide (56.2 mg, 0.34 mmol) in acetonitrile (3 mL) under argon was added 2-bromo-N-(4-(4-(5-ethyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (160 mg, 0.34 mmol) and the mixture was stirred for 5 min. To the mixture were added L-prolinol (66.2 μL,

0.68 mmol) and diisopropylethylamine (0.15 mL, 0.85 mmol) and the mixture was stirred at rt overnight. The mixture was then partitioned between EtOAc (30 mL) and water (10 mL), and the separated organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (Phenomenex phenylhexyl reverse phase column) eluting with a gradient of solvent B (0.05% HOAc/CH₃CN) in solvent A (0.05% HOAc/H₂O) and the isolated product was triturated with acetonitrile (30mL) to afford (S)-N-(4-(4-(5-ethyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(2-(hydroxymethyl)pyrrolidin-1-yl)acetamide (20 mg, 0.041 mmol, 12%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.1 (s, 1H), 10.66 (s, 1H), 10.01 (s, 1H), 7.79 (d, 2H), 7.56-7.59 (m, 3H), 7.24 (d, 1H), 6.60 (d, 1H), 5.71 (s, 1H), 4.75 (s, 1H), 3.62 (d, 1H), 3.09-3.21 (t, 3H), 2.75 (s, 1H), 2.39-2.46 (m, 2H), 1.63-1.99 (m, 6H), 1.09 (t, 3H); LCMS (ESI) *m/z* 493 (M + H)⁺.

Example 027

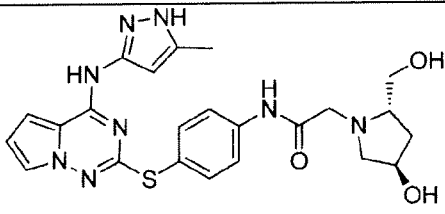
Preparation of 2-((2S,4S)-4-Hydroxy-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00524] **Example 027A:** To methyl (2S,4S)-1-tert-butoxycarbonyl-4-hydroxypyrrolidine-2-carboxylate (1.5 g, 6.11 mmol) in THF (10 mL) was added lithium borohydride (270 mg, 12.2 mmol) and the mixture was heated at 60 °C overnight. The mixture was partitioned between EtOAc and 2 N HCl and the EtOAc layer was collected, dried over sodium sulfate and concentrated to dryness to afford (2S,4S)-tert-butyl 4-hydroxy-2-(hydroxymethyl)pyrrolidine-1-carboxylate (1.2 g, 90 %). ¹H NMR (300 MHz, CDCl₃) δ 1.9 (m, 1H), 2.3 (m, 1H), 3.4-3.6(m, 3H), 3.9-4.1 (m, 2H), 4.3 (bs, 1H), 5.0-5.4 (bs, 2H).

[00525] **Example 027B:** To (2S,4S)-tert-butyl 4-hydroxy-2-(hydroxymethyl)pyrrolidine-1-carboxylate (148 mg, 0.68 mmol) was added 4N HCl/dioxane (2 mL) and the mixture was allowed to stand at rt for 2 h. The solution was evaporated to dryness followed by the addition of water (3 mL). This solution was frozen and lyophilized, and the resulting oil was dissolved in DMF (3 mL). To 1 mL of the DMF solution were added additional DMF (1 mL), diisopropylethylamine (0.115 mL, 0.66 mmol), potassium iodide (55 mg, 0.33 mmol) and 2-chloro-N-(4-(4-

(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 016B (85 mg, 0.2 mmol). The solution was stirred at rt overnight, then MeOH (2 mL) was added and the solution was evaporated to dryness. The residue was purified by preparative thin layer chromatography (89/10/1; DCM/MeOH/TEA). The obtained solid was partitioned between EtOAc and aqueous ammonium chloride. The EtOAc layer was dried with sodium sulfate and concentrated under reduced pressure to give 2-((2S,4S)-4-hydroxy-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (20 mg, 18%). ¹H NMR (300 MHz, CD₃OD) δ 1.70-1.77 (m, 1H), 2.35-2.45 (m, 1H), 2.81 (m, 1H), 3.0 (m, 1H), 3.21 (m, 1H), 3.63-3.84 (m, 3H), 4.34 (s, 1H), 5.77 (s, 1H), 6.61 (m, 1H), 6.94 (d, 1H), 7.47 (m, 1H), 7.62 (d, 2H), 7.78 (d, 2H); LCMS (ESI) *m/z* 495 (M + H)⁺.

The following compound was prepared in a similar manner.

Exam. No.	Structure	Compound name	LC MS (M+H) ⁺
27-i		2-((2S,4R)-4-hydroxy-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	495

Example 028

Preparation of 2-((2S,4S)-4-Ethoxy-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00526] **Example 028A:** To methyl (2S,4S)-1-(tert-butoxycarbonyl)-4-hydroxypyrrolidine-2-carboxylate (500 mg, 2.0 mmol) in THF (5 mL) was added lithium borohydride (90 mg, 4.0 mmol) and the mixture was heated at 80 °C for 5 h. The mixture was partitioned between EtOAc and 2 N HCl and the EtOAc layer was dried with sodium sulfate, filtered, and concentrated to dryness. The residue was

dissolved in pyridine (5 mL), then triphenylmethyl chloride (612 mg, 2.2 mmol) was added, and the mixture was stirred at rt for 4 days. The solution was concentrated, then toluene (10 mL) was added and evaporated. The residue was purified by silica gel chromatography (10-80 % hexanes/EtOAc) to afford (2S,4S)-tert-butyl 4-hydroxy-2-(trityloxymethyl)pyrrolidine-1-carboxylate (570 mg, 61%). LCMS (ESI) m/z 482 ($M + Na$)⁺.

[00527] Example 028B: To (2S,4S)-tert-butyl 4-hydroxy-2-(trityloxymethyl)pyrrolidine-1-carboxylate (107 mg, 0.23 mmol) and ethyl iodide (0.053 mL, 0.65 mmol) in DMF (2 mL) was added 60% sodium hydride/mineral oil (10 mg, 0.46 mmol) and the mixture was stirred at rt for 1 h. MeOH (1 mL) was added, then the mixture was partitioned between water and EtOAc. The EtOAc layer was dried over sodium sulfate, filtered, and concentrated to dryness. The residue was purified by preparative thin layer chromatography (20% EtOAc:hexanes) to give (2S,4S)-tert-butyl 4-ethoxy-2-(trityloxymethyl)pyrrolidine-1-carboxylate (118 mg, quantitative). LCMS (ESI) m/z 510 ($M + Na$)⁺.

[00528] Example 028C: To MeOH (4 mL) was added acetyl chloride (0.4 mL) and the mixture was stirred for 5 min. The resulting solution was then added to (2S,4S)-tert-butyl 4-ethoxy-2-(trityloxymethyl)pyrrolidine-1-carboxylate (118 mg, 0.24 mmol) and the mixture was heated at 50 °C for 1 min. Dioxane (1 mL) was then added and the solution was heated at 50 °C for 20 min, then the solution was then concentrated to dryness. To the residue were added a solution of diisopropylethylamine (0.115 mL, 0.66 mmol) in DMF (3 mL), potassium iodide (55 mg, 0.33 mmol) and 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (91 mg, 0.22 mmol). The solution was heated at 50 °C for 6 h, then tris(2-aminoethyl)amine (0.12 mL) was added followed by heating at 50 °C for 30 min. The solution was then concentrated and the residue was purified by preparative thin layer chromatography (10% DCM/MeOH) followed by preparative HPLC (Varian diphenyl reverse phase column) eluting with a gradient of solvent B (0.05% HOAc/CH₃CN) in solvent A (0.05% HOAc/H₂O) to give 2-((2S,4S)-4-ethoxy-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide as its acetate salt

(12 mg, 10 %). ¹H NMR (300 MHz, CD₃OD) δ 1.21 (t, 3H), 1.80 (m, 1H), 1.98 (s, 3H), 2.14 (s, 3H), 2.31 (m, 1H), 2.68(dd, 1H), 2.85 (m, 1H), 3.2-3.38 (m, 2H), 3.4-3.7 (m, 5H), 4.08 (m, 1H), 5.76 (s, 1H), 6.60 (m, 1H), 6.95 (d, 1H), 7.47 (m, 1H), 7.62 (d, 2H), 7.78 (d, 2H) LCMS (ESI) *m/z* 523 (M + H)⁺.

Example 029

Preparation of (R)-tert-Butyl 1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidin-3-ylcarbamate

[00529] (R)-tert-butyl 1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidin-3-ylcarbamate was prepared using a procedure analogous to that described in Example 018B, substituting (R)-tert-butyl pyrrolidin-3-ylcarbamate for the ((2S,4R)-4-tert-butoxypyrrolidin-2-yl)methanol used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.06 (s, 1H), 10.63 (s, 1H), 9.95 (s, 1H), 7.80 (d, 2H), 7.59 (s, 1H), 7.58 (d, 2H), 7.22 (s, 1H), 7.16 (d, 1H), 6.58 (m, 1H), 5.64 (s, 1H), 4.02 (m, 1H), 3.26 (s, 2H), 2.77 (m, 2H), 2.12-1.99 (m, 2H), 2.03 (s, 3H), 1.62 (m, 1H), 1.40 (s, 9H); LCMS (ESI) *m/z* 564 (M + H)⁺.

Example 030

Preparation of 2-((2S,4S)-2-(Hydroxymethyl)-4-methoxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00530] **Example 030A:** To (2S,4S)-tert-butyl 4-hydroxy-2-(trityloxymethyl)pyrrolidine-1-carboxylate from Example 028A (120 mg, 0.26 mmol) and iodomethane (0.033 mL, 0.52 mmol) in DMF (2 mL) was added 60% sodium hydride/mineral oil (10 mg, 0.26 mmol) and the mixture was stirred at rt for 1 h. The solution was concentrated and the residue was purified by preparative thin layer chromatography (20% EtOAc:hexanes) to give (2S,4S)-tert-butyl 4-methoxy-2-(trityloxymethyl)pyrrolidine-1-carboxylate (53 mg, 43%). LCMS (ESI) *m/z* 496 (M + Na)⁺

[00531] **Example 030B:** To (2S,4S)-tert-butyl 4-methoxy-2-(trityloxymethyl)pyrrolidine-1-carboxylate (53 mg, 0.11 mmol) in EtOAc (2 mL) was added 4 N HCl/dioxane (1 mL) and the solution was heated at 40 °C for 3 h. The

solution was concentrated to dryness, hexanes (5 mL) were added, and the supernatant solution was decanted. To the remaining solid in DMF (2 mL) were added diisopropylethylamine (0.078 mL, 0.44 mmol), potassium iodide (37 mg, 0.22 mmol) and 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (37 mg, 0.09 mmol) and the mixture was heated at 45 °C overnight. Acetic acid (0.15 mL) and DMSO (1 mL) were added and the mixture was purified by preparative HPLC (Varian diphenyl reverse phase column) eluting with a gradient of solvent B (0.05% HOAc/CH₃CN) in solvent A (0.05% HOAc/H₂O) to give 2-((2S,4S)-2-(hydroxymethyl)-4-methoxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (13 mg, 29 %). ¹H NMR (300 MHz, CD₃OD) δ 1.82 (m, 1H), 2.14 (s, 3H), 2.31 (m, 1H), 2.64 (dd, 1H), 2.82 (m, 1H), 3.2-3.38 (m, 5H), 3.5-3.7 (m, 3H), 3.98 (m, 1H), 5.76 (s, 1H), 6.61 (m, 1H), 6.95 (d, 1H), 7.47 (m, 1H), 7.62 (d, 2H), 7.78 (d, 2H) LCMS (ESI) *m/z* 509 (M + H)⁺.

Example 031

Preparation of 2-((2S,4R)-4-(Benzyloxy)-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00532] **Example 031A:** ((2S,4R)-4-(benzyloxy)pyrrolidin-2-yl)methanol was prepared using a procedure analogous to that described in the synthesis of Example 020A, substituting 3(2S,4R)-4-(benzyloxy)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid for the (S)-1-(tert-butoxycarbonyl)-4,4-difluoropyrrolidine-2-carboxylic acid used in Example 020A.

[00533] **Example 031B:** 2-((2S,4R)-4-(Benzyloxy)-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (7.02 mg, 10 %) was prepared as a white solid using a procedure analogous to that described in Example 018B, substituting ((2S,4R)-4-(benzyloxy)pyrrolidin-2-yl)methanol hydrochloride for the ((2S,4R)-4-tert-butoxypyrrolidin-2-yl)methanol used in Example 018B. The crude product was purified by silica gel chromatography eluting with MeOH/EtOAc. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.05 (s, 1H), 10.60 (s, 1H), 10.00 (s, 1H), 7.83 (d, 2H), 7.60 (m, 3H), 7.25 (m, 6H), 6.55 (s, 1H), 5.60 (s, 1H), 4.80 (brs, 1H), 4.45 (s, 2H), 4.10 (s,

1H), 3.60-3.20 (m, 3H), 3.05-2.60 (m, 3H), 2.05 (s, 3H), 1.95-1.85 (m, 2H); LCMS (ESI) m/z 585 (M+H)⁺.

Example 032

Preparation of (R)-N-(4-(4-(5-Cyclopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-hydroxypyrrolidin-1-yl)acetamide

[00534] (R)-N-(4-(4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-hydroxypyrrolidin-1-yl)acetamide (16.3 mg, 29 %) was synthesized as a white solid using a procedure analogous to that described in Example 018B, substituting (R)-pyrrolidin-3-ol for the ((2S,4R)-4-tert-butoxypyrrolidin-2-yl)methanol used in Example 018B, and 2-chloro-N-(4-(4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 013A for the 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.05 (s, 1H), 10.65 (s, 1H), 9.85 (s, 1H), 7.80 (d, 2H), 7.55 (m, 3H), 7.20 (s, 1H), 6.55 (s, 1H), 5.75 (s, 1H), 4.80 (brs, 1H), 4.20 (s, 1H), 3.20 (s, 2H), 2.75 (m, 3H), 2.10-1.50 (m, 4H), 0.80 (m, 2H), 0.50 (m, 2H); LCMS (ESI) m/z 491 (M+H)⁺.

Example 033

Preparation of (R)-2-(3-Hydroxypyrrolidin-1-yl)-N-(4-(4-(5-(trifluoromethyl)-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00535] **Example 033A:** A mixture of 4,4,4-trifluoro-3-oxobutanenitrile (450 mg, 3.28 mmol), hydrazine monohydrate (307 μL, 9.8 mmol), and AcOH (19 mL, 0.33 mmol) in EtOH (5 mL) was stirred and heated at reflux in a pressure tube for 3 h. The mixture was then allowed to cool to ambient temperature and the mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 0-60% EtOAc/hexanes to give 5-(trifluoromethyl)-1H-pyrazol-3-amine as an off-white solid (105 mg, 21% yield). ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.79 (m, 1H), 5.89 (s, 1H), 3.75 (t, 2H).

[00536] **Example 033B:** 2-(4-Aminophenylthio)-N-(5-trifluoromethyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine was prepared using procedures analogous to those described in Examples 026A through Example 026B, substituting 5-

(trifluoromethyl)-1H-pyrazol-3-amine from Example 033A for the 5-ethyl-1H-pyrazol-3-amine used in Example 026A.

[00537] Example 033C: 2-Chloro-N-(4-(4-(5-(trifluoromethyl)-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was prepared using a procedure analogous to that described in Example 016B substituting 2-(4-aminophenylthio)-N-(5-trifluoromethyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine from Example 033B for the 2-(4-aminophenylthio)-N-(5-methyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine used in Example 016B.

[00538] Example 033D: (R)-2-(3-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-(trifluoromethyl)-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was prepared using a procedure analogous to that described in Example 018B, substituting 3,3-difluoropyrrolidine hydrochloride for the ((2S,4R)-4-tert-butoxypyrrolidin-2-yl)methanol used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.50 (brs, 1H), 9.90 (s, 1H), 7.79 (d, 2H), 7.65 (s, 1H), 7.56 (d, 2H), 7.09 (s, 1H), 6.65 (m, 1H), 6.30 (s, 1H), 4.83 (s, 1H), 4.23 (s, 1H), 3.29 (s, 2H), 3.27-2.90 (m, 2H), 2.81 (m, 2H), 2.08 (m, 1H), 1.65 (s, 1H); LCMS (ESI) *m/z* 519 (M + H)⁺.

Example 034

Preparation of 2-((2S,4R)-4-tert-Butoxy-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-isopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

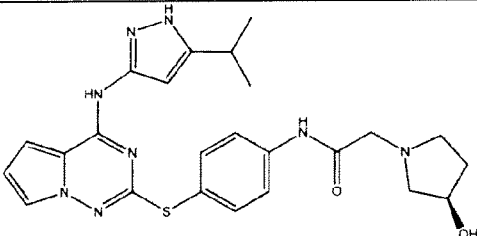
[00539] Example 034^a: 2-(4-Aminophenylthio)-N-(5-isopropyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine was prepared using procedures analogous to those described in Examples 026A through Example 026B, substituting 5-(isopropyl)-1H-pyrazol-3-amine for the 5-ethyl-1H-pyrazol-3-amine used in Example 026A.

[00540] Example 034B: 2-Chloro-N-(4-(4-(5-isopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was synthesized using a procedure analogous to that described in Example 016B substituting 2-(4-aminophenylthio)-N-(5-isopropyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-

amine from Example 034A for the 2-(4-aminophenylthio)-N-(5-methyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine used in Example 016B.

[00541] Example 34C: To potassium iodide (56.2 mg, 0.34 mmol) in DMF (3 mL) under Ar was added 2-chloro-N-(4-(4-(5-isopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (160 mg, 0.34 mmol) and the mixture was stirred for 5 min. Then ((2S,4R)-4-tert-butoxypyrrolidin-2-yl)methanol from Example 018A (66.2 μ L, 0.68 mmol) and diisopropylethylamine (0.15 mL, 0.85 mmol) were added and the mixture was stirred at 40 °C for 2 h. The mixture was partitioned between EtOAc (30 mL) and water (10 mL), and the separated EtOAc layer was dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 1% to 10% MeOH/DCM. The appropriate fractions were combined and concentrated, and the residue was triturated with anhydrous diethyl ether to afford 2-((2S,4R)-4-tert-butoxy-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-isopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (28 mg, 0.048 mmol, 19%). ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.1 (s, 1H), 10.65 (s, 1H), 9.93 (s, 1H), 7.77 (d, 2H), 7.60 (t, 3H), 7.25 (s, 1H), 6.59 (s, 1H), 5.83 (s, 1H), 4.68 (br s, 1H), 4.19 (br s, 1H), 3.34 (d, 1H), 3.15-3.23 (m, 3H), 2.77-2.87 (m, 3H), 2.36 (t, 1H), 1.89 (br s, 1H), 1.69 (br s, 1H), 1.08-1.23 (m, 15H); LCMS (ESI) m/z 579 ($\text{M} + \text{H}$) $^+$.

The following compound was prepared in a similar manner:

Exam. No.	Structure	Compound name	LC MS ($\text{M} + \text{H}$) $^+$
34-i		(R)-2-(3-hydroxypyrrolidin-1-yl)-N-(4-((4-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	493

Example 035

Preparation of N-(4-(4-(5-Cyclopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-((2S,4R)-4-fluoro-2-(hydroxymethyl)pyrrolidin-1-yl)acetamide

[00542] N-(4-(4-(5-cyclopropyl-1H-pyrazol-3-ylamino) pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-((2S,4R)-4-fluoro-2-(hydroxymethyl) pyrrolidin-1-yl) acetamide was prepared as a white solid (16.31 mg, 27 %) using a procedure analogous to that described in Example 018B, substituting ((2S,4R)-4-fluoropyrrolidin-2-yl)methanol hydrochloride for the ((2S,4R)-4-tert-butoxypyrrolidin-2-yl)methanol used in Example 018B, and 2-chloro-N-(4-(4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 013A for the 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.10 (s, 1H), 10.60 (s, 1H), 10.05 (s, 1H), 7.75 (d, 2H), 7.55 (m, 3H), 7.20 (s, 1H), 6.55 (s, 1H), 5.75 (s, 1H), 5.20 (d, 1H), 4.85 (brs, 1H), 4.45 (s, 2H), 4.10 (s, 1H), 3.60-3.20 (m, 3H), 3.05-2.60 (m, 3H), 2.05 (s, 3H), 1.95-1.85 (m, 2H); LCMS (ESI) *m/z* 523 (M+H)⁺.

Example 036

Preparation of N-(4-(4-(5-Cyclopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-((2S,4R)-4-hydroxy-2-(hydroxymethyl)pyrrolidin-1-yl)acetamide

[00543] **Example 036A:** (3R,5S)-5-(hydroxymethyl)pyrrolidin-3-ol was prepared using a procedure analogous to that described Example 024A, substituting methyl (2R,4R)-1-tert-butyloxycarbonyl-4-hydroxypyrrolidine-2-carboxylate for the methyl (2R,4R)-1-tert-butyloxycarbonyl-4-methoxypyrrolidine-2-carboxylate used in Example 024A.

[00544] **Example 036B:** N-(4-(4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-((2S,4R)-4-hydroxy-2-(hydroxymethyl)pyrrolidin-1-yl)acetamide was synthesized as a white solid (13.29 mg, 22 %) using a procedure analogous to that described in Example 013B, substituting (3R,5S)-5-(hydroxymethyl)pyrrolidin-3-ol from Example 036A for the (2S,4R)-4-tert-butoxypyrrolidin-2-yl)methanol used in Example 013B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.05 (s, 1H), 10.70 (s, 1H), 10.00 (s, 1H), 7.80 (d, 2H), 7.60 (m, 3H), 7.20 (s,

1H), 6.55 (s, 1H), 5.70 (s, 1H), 4.80 (m, 2H), 4.20 (s, 1H), 3.60 (d, 1H), 3.45-3.20 (m, 4H), 3.00 (s, 1H), 2.35 (s, 1H), 1.80 (m, 3H), 0.80 (m, 2H), 0.50 (m, 2H); LCMS (ESI) m/z 521 (M+H)⁺.

Example 037

Preparation of 2-(2-Hydroxymethyl-4-methoxy-pyrrolidin-1-yl)-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide

[00545] **Example 037A Step 1:** To (2S,4R)-tert-butyl 4-hydroxy-2-(hydroxymethyl)pyrrolidine-1-carboxylate (200 mg, 0.920 mmol) in pyridine (3 mL) was added trityl chloride (282.12mg, 1.012 mmol) and the mixture was heated at 80°C for 12 h.. The mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography to give (2S,4R)-tert-butyl 4-hydroxy-2-(trityloxymethyl)pyrrolidine-1-carboxylate (260 mg, 61 %) as a solid.

[00546] **Example 037A Step 2:** To (2S,4R)-tert-butyl 4-hydroxy-2-(trityloxymethyl)pyrrolidine-1-carboxylate (260 mg, 0.5657 mmol) in DMF (3 mL) was added 60% sodium hydride (27.1 mg, 0.679 mmol) and the mixture was stirred for 10 min, then methyl iodide (0.070 mL, 1.13 mmol) was added and the mixture was stirred for 1 h. The mixture was worked-up using EtOAc to give a solution that was concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford (2S,4R)-tert-butyl 4-methoxy-2-(trityloxymethyl)pyrrolidine-1-carboxylate (230 mg, 86%).

[00547] **Example 037A Step 3:** (2S,4R)-tert-butyl 4-methoxy-2-(trityloxymethyl)pyrrolidine-1-carboxylate was taken up in 4N HCl/dioxane and the mixture was stirred at ambient temperature for 4 h. The mixture was concentrated and the residue was dried under reduced pressure. The crude ((2S,4R)-4-methoxypyrrolidin-2-yl)methanol was used for the next step without further purification.

[00548] **Example 037B:** 2-(2-Hydroxymethyl-4-methoxy-pyrrolidin-1-yl)-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide was synthesized as a white solid (20.76 mg, 34 %) using a procedure

analogous to that described in Example 018B, substituting ((2S,4R)- (4-methoxy-pyrrolidin-2-yl)-methanol Hydrochloride from Example 037A for the ((2S,4R)-4-tert-butoxypyrrolidin-2-yl)methanol used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.05 (s, 1H), 10.65 (s, 1H), 10.00 (s, 1H), 7.80 (d, 2H), 7.55 (m, 3H), 7.20 (s, 1H), 6.55 (s, 1H), 5.60 (s, 1H), 4.70 (s, 1H), 3.90 (s, 1H), 3.60 (d, 1H), 3.30 (m, 4H), 3.25 (m, 1H), 3.20 (s, 3H), 2.90 (s, 1H), 2.05 (s, 3H), 2.80 (m, 2H); LCMS (ESI) *m/z* 509 (M+H)⁺.

Example 038

2-(2-Hydroxymethyl-4-methoxy-pyrrolidin-1-yl)-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide

[00549] N-{4-[4-(5-Cyclopropyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-2-(2-hydroxymethyl-4-methoxy-pyrrolidin-1-yl)-acetamide was synthesized as a white solid (21.18 mg, 35 %) using a procedure analogous to that described in Example 018B, substituting ((2S,4R)- (4-methoxy-pyrrolidin-2-yl)-methanol Hydrochloride from Example 037A for the ((2S,4R)-4-tert-butoxypyrrolidin-2-yl)methanol used in Example 018B, and substituting 2-chloro-N-(4-(4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 013A for the 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.00 (s, 1H), 10.80 (s, 1H), 10.05 (s, 1H), 7.80-7.40 (m, 5H), 7.20 (s, 1H), 6.55 (s, 1H), 5.80 (s, 1H), 4.10 (d, 1H), 4.30-4.05 (m, 3H), 3.80 (m, 2H), 3.20 (s, 3H), 2.20 (d, 1H), 1.90 (m, 1H), 1.70 (m, 1H), 1.20 (m, 3H), 0.80 (m, 2H), 0.50 (m, 2H); LCMS (ESI) *m/z* 535 (M+H)⁺.

Example 039

Preparation of (S)-2-(3-(Hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00550] **Example 039A:** (S)-Pyrrolidin-3-ylmethanol was prepared using a procedure analogous to that described in Example 024A, substituting methyl (S)-1-tert-butyloxycarbonylpyrrolidine-3-carboxylate for the methyl (2R,4R)-1-tert-butyloxycarbonyl-4-methoxypyrrolidine-2-carboxylate used in Example 024A.

[00551] **Example 039B:** (S)-2-(3-(Hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)

acetamide was synthesized as a white solid (20.55 mg, 35.7 %) using a procedure analogous to that described in Example 018B, substituting (S)-pyrrolidin-3-ylmethanol Hydrochloride for the ((2S,4R)-4-tert-butoxypyrrolidin-2-yl)methanol used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.10 (br s, 1H), 10.70 (s, 1H), 10.00 (s, 1H), 7.85 (d, 2H), 7.60 (m, 3H), 7.20 (s, 1H), 6.55 (s, 1H), 5.65 (s, 1H), 4.60 (br s, 1H), 3.50-3.10 (m, 3H), 2.80-2.15 (m, 5H), 2.00 (s, 3H), 1.85 (m, 2H), 1.45 (m, 1H); LCMS (ESI) *m/z* 479 (M+H)⁺.

Example 040

Preparation of (S)-N-(4-(4-(5-Cyclopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(hydroxymethyl)pyrrolidin-1-yl)acetamide

[00552] (S)-N-(4-(4-(5-Cyclopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(hydroxymethyl)pyrrolidin-1-yl)acetamide was synthesized as a white solid (14.19 mg, 24.6 %) using a procedure analogous to that described in Example 018B, substituting (S)-pyrrolidin-3-ylmethanol hydrochloride for the ((2S,4R)-4-tert-butoxypyrrolidin-2-yl)methanol used in Example 018B, and substituting 2-chloro-N-(4-(4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 013A for the 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.10 (br s, 1H), 10.65 (s, 1H), 9.85 (s, 1H), 7.80 (d, 2H), 7.60 (m, 3H), 7.20 (s, 1H), 6.55 (s, 1H), 5.70 (s, 1H), 4.60 (br s, 1H), 3.60-3.10 (m, 2H), 2.80-2.20 (m, 5H), 1.98 (s, 3H), 1.65 (m, 1H), 1.45 (m, 1H), 0.85 (m, 2H), 0.50 (m, 2H); LCMS (ESI) *m/z* 505 (M+H)⁺.

Example 041

Preparation of (S)-N-(4-(4-(5-Cyclobutyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(4,4-difluoro-2-(hydroxymethyl)pyrrolidin-1-yl)acetamide

[00553] **Example 041A:** To potassium iodide (932 mg, 5.6 mmol) in DMF (5 mL) was added 2,4-dichloropyrrolo[1,2-f][1,2,4]triazine (Mastalerz, et al. US20070004731 A1) (1.06 g, 5.6 mmol). The mixture was stirred for 5 min, then 5-cyclobutyl-1H-pyrazol-3-amine (938 mg, 6.7 mmol) and diisopropylethylamine (0.98 mL, 5.6 mmol) were added and the mixture was stirred at rt for 2 h. Water was then added and

precipitate was collected by filtration to afford 2-chloro-N-(5-cyclobutyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine (1.78 g, quantitative). LCMS (ESI) m/z 289 ($M + H$)⁺.

[00554] Example 041B: A reaction vessel containing a suspension of potassium carbonate (1.0 g, 7.28 mmol) in DMF (5 mL) was evacuated and flushed with Ar. 4-Aminobenzenethiol (639 mg, 5.1 mmol) was added and the reaction vessel was again evacuated and flushed with argon. A solution of 2-chloro-N-(5-cyclobutyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine (1.05 g, 3.64 mmol) in DMF (5 mL) was then added and the vial was again evacuated and flushed with argon. The solution was then heated to 120 °C overnight. Water was added and the precipitated solid was collected by filtration then triturated with 2:1 ether/acetonitrile (9 mL) to afford 2-(4-aminophenylthio)-N-(5-cyclobutyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine (710 mg, 52%). LCMS (ESI) m/z 378 ($M + H$)⁺.

[00555] Example 041C: To 2-(4-aminophenylthio)-N-(5-cyclobutyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine (250 mg, 0.66 mmol) in THF (5 mL) at 0 °C was added dropwise a solution of chloroacetyl chloride (0.11 mL, 1.39 mmol) in THF (5 mL). The solution was stirred at 0 °C for 30 min, then allowed to warm to rt for 1 h. A 10% sodium hydroxide solution (5 mL) was then added and the mixture was stirred for 5 min. The mixture was subjected to extractive workup using EtOAc, and the organic fraction was dried (sodium sulfate) and concentrated to afford 2-chloro-N-(4-(4-(5-cyclobutyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (295 mg, 98%). LCMS (ESI) m/z 454 ($M + H$)⁺.

[00556] Example 041D: To (S)-(4,4-difluoropyrrolidin-2-yl)methanol hydrochloride from Example 020A (23 mg, 0.13 mmol), diisopropylethylamine (0.058 mL, 0.33 mmol), and potassium iodide (18 mg, 0.11 mmol) in DMF (2 mL) was added 2-chloro-N-(4-(4-(5-cyclobutyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (50 mg, 0.11 mmol) and the mixture was heated at 45 °C for 5 h. Acetic acid (0.1 mL) and DMSO (3 mL) were added and the mixture was purified by preparative HPLC (Varian diphenyl reverse phase column) eluting with a gradient of solvent B (0.05% HOAc/CH₃CN) in solvent A (0.05%

HOAc/H₂O). The collected fractions were concentrated, and then treated with DCM (20 mL), thiophenol resin (300 mg, 1.3 mmol/g), triethylamine (0.05 mL) and MP-carbonate resin (100 mg, 3 mmol/g) overnight. The mixture was filtered and the filtrate was washed with aqueous ammonium chloride and concentrated to afford (S)-N-(4-(4-(5-cyclobutyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(4,4-difluoro-2-(hydroxymethyl)pyrrolidin-1-yl)acetamide (33 mg, 54 %). ¹H NMR (300 MHz, CD₃OD) δ 1.20 (m, 2H), 1.7-2.4 (m, 8H), 2.87 (m, 1H), 2.96 (m, 1H), 3.3-3.7 (m, 4H), 5.90 (s, 1H), 6.52 (m, 1H), 6.85 (d, 1H), 7.38 (m, 1H), 7.51 (d, 2H), 7.66 (d, 2H); LCMS (ESI) *m/z* 555 (M + H)⁺.

Example 042

Preparation of (R)-N-(2-Fluoro-4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-hydroxypyrrolidin-1-yl)acetamide

[00557] **Example 042A:** To 4-bromo-2-fluoroaniline (200 mg, 1.05 mmol) in toluene (3 mL) were added cesium carbonate (513 mg, 1.57 mmol), palladium(tetrakis(triphenylphosphine)) (60 mg, 0.05 mmol), and triisopropylsilylthiol (0.25 mL, 1.15 mmol). The reaction vessel was evacuated and flushed with argon and then heated in a microwave reactor at 120 °C for 2.5 h. The solution was filtered and concentrated. To the residue in DMF (3 mL) were added cesium fluoride (470 mg, 3.15 mmol), cesium carbonate (340 mg, 1.05 mmol), and a solution of 2-chloro-N-(5-methyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine (155 mg, 0.63 mmol) in DMF (2 mL). The reaction vessel was evacuated and flushed with argon and the mixture was stirred overnight at 120 °C. The mixture was partitioned between EtOAc and water, and the residue from concentration of the organic phase was purified by preparative thin layer chromatography to give impure 2-(4-amino-3-fluorophenylthio)-N-(5-methyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine, which was used in the next step without further purification. LCMS (ESI) *m/z* 356 (M + H)⁺.

[00558] **Example 042B:** To impure 2-(4-amino-3-fluorophenylthio)-N-(5-methyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine (ca. 0.3 mmol) in THF (3 mL) was added chloroacetyl chloride (0.53 mL, 0.66 mmol) and the mixture was stirred at rt for 30 min. The mixture was partitioned between 1 N NaOH and EtOAc, and the

organic layer was dried over sodium sulfate, filtered, and concentrated to give impure 2-chloro-N-(2-fluoro-4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide, which was used directly in the next step. LCMS (ESI) m/z 432 (M + H)⁺.

[00559] Example 042C: To 2-chloro-N-(2-fluoro-4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 042B (ca. 0.05 mmol) in DMF (1 mL) were added diisopropylethyl amine (0.02 mL), potassium iodide (20 mg), and (R)-pyrrolidin-3-ol (0.02 mL) and the mixture was heated at 50 °C for 2 h and then kept at ca. 4 °C for 3 days. The mixture was purified by preparative HPLC (Varian diphenyl reverse phase column) eluting with a gradient of solvent B (0.05% HOAc/CH₃CN) in solvent A (0.05% HOAc/H₂O) to give (R)-N-(2-fluoro-4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-hydroxypyrrolidin-1-yl)acetamide as its diacetate salt (5.96 mg, 21%). ¹H NMR (300 MHz, CD₃OD) δ 1.9 (m, 1H), 1.97 (s, 6H), 2.16 (s, 3H), 2.24 (m, 1H), 2.8-2.95 (m, 2H), 3.05 (m, 1H), 3.15 (m, 1H), 3.65 (s, 2H), 4.45 (m, 1H), 5.87 (s, 1H), 6.59 (m, 1H), 6.98 (m, 1H), 7.4-7.55 (m, 3H), 8.25 (t, 1H); LCMS (ESI) m/z 483 (M + H)⁺.

Example 043

Preparation of (S)-2-(4,4-Difluoro-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(2-fluoro-4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00560] (S)-2-(4,4-difluoro-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(2-fluoro-4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was synthesized as its diacetate salt (7.5 mg, 25%) using a procedure analogous to that described in Example 042C, substituting ((2S,4R)-4-fluoropyrrolidin-2-yl)methanol from Example 022A for the (R)-pyrrolidin-3-ol used in Example 042C. ¹H NMR (300 MHz, CD₃OD) δ 2.03 (m, 6H), 2.18 (s, 3H), 2.27-2.5 (m, 2H), 3.04 (m, 1H), 3.18 (m, 1H), 3.5-3.8 (m, 5H), 5.87 (s, 1H), 6.61 (m, 1H), 6.91 (m, 1H), 7.4-7.55 (m, 3H), 8.3 (t, 1H); LCMS (ESI) m/z 533 (M + H)⁺.

Example 044

Preparation of 2-((2S,4S)-4-Fluoro-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00561] **Example 044A:** ((2S,4S)-4-fluoropyrrolidin-2-yl)methanol was prepared using a procedure analogous to that described Example 020A, substituting (2S,4S)-1-(tert-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid for the (S)-1-(tert-butoxycarbonyl)-4,4-difluoropyrrolidine-2-carboxylic acid used in Example 020A.

[00562] **Example 044B:** 2-((2S,4S)-4-Fluoro-2-(hydroxymethyl) pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was synthesized as a white solid (12.5 mg, 21 %) using a procedure analogous to that described in Example 018B, substituting ((2S,4S)-4-fluoropyrrolidin-2-yl)methanol hydrochloride for the ((2S,4R)-4-tert-butoxypyrrolidin-2-yl)methanol used in Example 018B. The reaction mixture was purified by silica gel chromatography eluting with DCM/MeOH. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.10 (brs, 1H), 10.65 (s, 1H), 10.10 (s, 1H), 7.85-7.55 (m, 5H), 7.20 (s, 1H), 6.55 (s, 1H), 5.65 (s, 1H), 5.35-5.05 (d, 1H), 4.80 (s, 1H), 3.80-3.10 (m, 4H), 2.80 (m, 3H), 2.40-2.15 (m, 1H), 2.05 (s, 3H), 1.85 (s, 1H); LCMS (ESI) *m/z* 497 (M+H)⁺.

Example 045

Preparation of N-((R)-1-((4-(4-(5-Methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylcarbonyl)methyl)pyrrolidin-3-yl)isobutyramide

[00563] The intermediate compound N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-((R)-3-aminopyrrolidin-1-yl)acetamide was prepared using a procedure analogous to that described in Example 018B, substituting R-3-aminopyrrolidine for the ((2S,4R)-4-tert-butoxypyrrolidin-2-yl)methanol used in Example 018B. To N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-((R)-3-aminopyrrolidin-1-yl)acetamide (50 mg, 0.11 mmol) in anhydrous THF was added dropwise a solution of isobutyryl chloride in THF. The mixture was stirred for 2 h at rt, then water was added and the mixture was extracted with EtOAc. The organic layer was separated, dried and concentrated under reduced pressure. The residue was purified by silica gel

chromatography eluting with 20:1 to 10:1 DCM/MeOH to give N-((R)-1-((4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylcarbamoyl)methyl)pyrrolidin-3-yl)isobutyramide (41 mg, 39% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.82 (s, 1H), 10.64 (d, 1H), 10.35 (t, 1H), 8.15 (d, 1H), 7.71 (d, 2H), 7.63 (d, 2H), 7.57 (s, 1H), 6.58 (d, 1H), 5.68 (t, 1H), 4.31 (d, 2H), 3.30-3.42 (m, 1H), 2.05 (s, 2H), 1.88-1.94 (m, 1H), 1.01 (d, 6H); LCMS (ESI) *m/z* 534 (M+H)⁺.

Example 046

Preparation of 2-(3,3-Difluoropyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00564] 2-(3,3-difluoropyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was prepared using a procedure analogous to that described in Example 018B, substituting 3,3-difluoropyrrolidine hydrochloride for the ((2S,4R)-4-tert-butoxypyrrolidin-2-yl)methanol used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.05 (s, 1H), 10.61 (s, 1H), 10.11 (s, 1H), 7.76 (d, 2H), 7.58 (s, 1H), 7.57 (d, 2H), 7.22 (s, 1H), 6.58 (m, 1H), 5.64 (s, 1H), 3.62 (m, 1H), 3.39 (m, 2H), 3.16 (m, 1H), 3.13 (m, 2H), 2.90 (s, 2H), 2.32 (m, 2H), 2.03 (s, 3H); LCMS (ESI) *m/z* 483 (M-H)⁺.

Example 047

Preparation of 2-((2S,4R)-4-(Difluoromethyl)-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00565] **Example 047A:** Methyl (S)-1-tert-butyloxycarbonyl-4-(difluoromethylene)pyrrolidine-2-carboxylate (synthesized using a procedure analogous to that described in Qiu, X.-L. et al., J. Org. Chem. 2002, 67, 7162-7164) (300 mg, 1.08 mmol) in EtOH (5 mL) was stirred under a hydrogen atmosphere in the presence of 10% Pd/C (50 mg) for several days. The mixture was filtered through Celite and concentrated under reduced pressure to give methyl (2S,4R)-1-tert-butyloxycarbonyl-4-(difluoromethyl)pyrrolidine-2-carboxylate, together with its 4-epimer.

[00566] Example 047B Step 1: Preparation of ((2S,4R)-4-

(difluoromethyl)pyrrolidin-2-yl)methanol: To a stirring solution of impure methyl (2S,4R)-1-tert-butyloxycarbonyl-4-(difluoromethyl)pyrrolidine-2-carboxylate from Example 047A (330 mg, 1.08 mmol) in THF (5 mL) at rt was added LiBH₄ (50 mg, 2.3 mmol). The mixture was stirred at rt overnight, and then heated at 60 °C for 90 min. The mixture was partitioned between EtOAc (15 mL) and saturated aq NaHCO₃ (10 mL), and the organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 10-40% EtOAc/hexanes to give (2S,4R)-tert-butyl 4-(difluoromethyl)-2-(hydroxymethyl)pyrrolidine-1-carboxylate as the minor isomer (50 mg, 18 % yield). LCMS (ESI) *m/z* 252 (M + H)⁺.

[00567] Example 047B Step 2: 2S,4R)-tert-butyl 4-(difluoromethyl)-2-

(hydroxymethyl)pyrrolidine-1-carboxylate (50 mg, 0.20 mmol) was dissolved in EtOAc (1.0 mL) and treated with 4N HCl/1,4-dioxane (0.5 mL) and the mixture was kept at rt overnight. The mixture was concentrated under reduced pressure to give ((2S,4R)-4-(difluoromethyl)pyrrolidin-2-yl)methanol as its hydrochloride salt (38 mg, 100%).

[00568] Example 047C: 2-((2S,4R)-4-(difluoromethyl)-2-

(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was prepared using a procedure analogous to that described in Example 018B, substituting ((2S,4R)-4-(difluoromethyl)pyrrolidin-2-yl)methanol hydrochloride from Example 047B for the ((2S,4R)-4-tert-butoxypyrrolidin-2-yl)methanol used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.06 (s, 1H), 10.63 (s, 1H), 9.99 (s, 1H), 7.77 (d, 2H), 7.60 (s, 1H), 7.60 (d, 2H), 7.25 (s, 1H), 6.59 (d, 1H), 6.09 (td, 1H), 5.63 (s, 1H), 4.73 (s, 1H), 3.64 (d, 1H), 3.43 (d, 2H), 3.18 (m, 4H), 2.47-2.92 (m, 3H), 2.03 (s, 3H), 1.84 (m, 2H), 1.17 (m, 3H). LCMS (ESI) *m/z* 527 (M + H)⁺.

Example 048

Preparation of tert-Butyl 3-fluoro-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxylate

[00569] **Example 048A** To a stirring mixture of tert-butyl 2-fluoroacrylate (350 mg, 2.4 mmol) and N-(methoxymethyl)-N-(trimethylsilylmethyl) benzylamine (735 μ L, 2.9 mmol) in DCM (5 mL) at 0 °C was added trifluoroacetic acid (27 μ L, 0.24 mmol). The mixture was stirred at rt overnight and then partitioned between diethyl ether (25 mL) and saturated aq NaHCO₃ (10 mL). The organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue (300 mg) in MeOH (5 mL) was stirred under a hydrogen atmosphere in the presence of 10% Pd/C (50 mg) at rt overnight. The mixture was then filtered through Celite and the filtrate was concentrated under reduced pressure to give tert-butyl 3-fluoropyrrolidine-3-carboxylate as a colorless oil. LCMS (ESI) *m/z* 190 (M + H)⁺.

[00570] **Example 048B:** tert-butyl 3-fluoro-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxylate was prepared using a procedure analogous to that described in Example 018B, substituting tert-butyl 3-fluoropyrrolidine-3-carboxylate from Example 048A for the ((2S,4R)-4-tert-butoxypyrrolidin-2-yl)methanol used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.07 (s, 1H), 10.63 (s, 1H), 10.10 (s, 1H), 7.77 (d, 2H), 7.59 (s, 1H), 7.58 (d, 2H), 7.23 (s, 1H), 6.58 (d, 1H), 5.63 (s, 1H), 4.03 (m, 1H), 3.38 (m, 2H), 3.14 (m, 1H), 3.04 (m, 2H), 2.73 (m, 1H), 2.45- 2.05 (m, 2H), 2.03 (s, 3H), 1.48 (s, 9H); LCMS (ESI) *m/z* 565 (M-H)⁻.

Example 049

Preparation of (R)-2-(3-(Hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00571] **Example 049A:** (R)-pyrrolidin-3-ylmethanol was prepared using a procedure analogous to that described in Example 024A, substituting methyl (R)-1-(tert-butyloxycarbonyl)pyrrolidine-3-carboxylate for the methyl (2R,4R)-1-tert-butyloxycarbonyl-4-methoxypyrrolidine-2-carboxylate used in Example 024A.

[00572] **Example 049B:** (R)-2-(3-(Hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was synthesized as a white solid (7 mg, 12 %) using a procedure analogous to that described in Example 018B, substituting (R)-pyrrolidin-3-ylmethanol hydrochloride for the ((2S,4R)-4-tert-butoxypyrrolidin-2-yl)methanol used in Example 018B. ¹H

NMR (300 MHz, DMSO- d_6) δ 12.10 (brs, 1H), 10.70 (s, 1H), 10.00 (s, 1H), 7.80 (d, 2H), 7.60 (m, 3H), 7.20 (s, 1H), 5.60 (s, 1H), 4.65 (brs, 1H), 3.55-3.10 (m, 4H), 3.80-2.15 (m, 5H), 2.00 (s, 3H), 1.80 (m, 1H), 1.40 (m, 1H); LCMS (ESI) m/z 479 (M+H)⁺.

Example 050

Preparation of (R)-N-(4-(4-(5-Cyclopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(hydroxymethyl)pyrrolidin-1-yl)acetamide

[00573] (R)-N-(4-(4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(hydroxymethyl)pyrrolidin-1-yl)acetamide was synthesized as a white solid (17.99 mg, 31 % using a procedure analogous to that described in Example 013B, substituting (R)-pyrrolidin-3-ylmethanol hydrochloride for the (S)-pyrrolidin-(2-yl)methanol used in Example 013B. Purification was accomplished by silica gel chromatography eluting with DCM/MeOH. ¹H NMR (300 MHz, DMSO- d_6) δ 12.10 (br s, 1H), 10.65 (s, 1H), 10.05 (s, 1H), 7.80 (d, 2H), 7.60 (s, 3H), 7.20 (s, 1H), 6.55 (s, 1H), 5.70 (s, 1H), 4.60 (br s, 1H), 3.60-2.20 (m, 7H), 1.80-1.30 (m, 4H), 1.10 (m, 1H), 0.80 (m, 2H), 0.50 (s, 2H); LCMS (ESI) m/z 505 (M+H)⁺.

Example 051

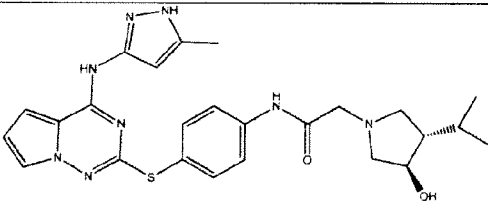
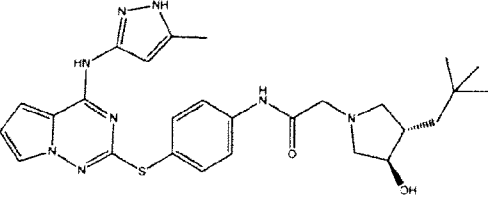
Preparation of 2-(trans-3-tert-Butoxy-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00574] **Example 051A:** To benzyl 2,5-dihydro-1H-pyrrole-1-carboxylate (1 g, 4.9 mmol) in DCM (10 mL) at 0 °C was added 3-chloroperbenzoic acid (1.43 g, 6.4 mmol). The solution was allowed to warm to rt and stir for 5 h. Aq sodium thiosulfate and 1N NaOH were added and the mixture was extracted with DCM. The organic layer was dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography eluting with 0-70% ethylacetate in hexanes to afford benzyl 6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate as an oil (560 mg, 52%); LCMS (ESI) m/z 220 (M + H)⁺.

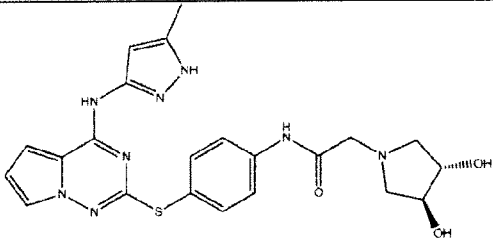
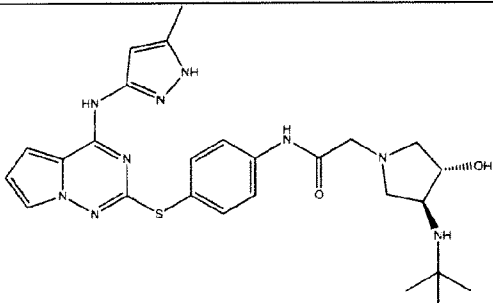
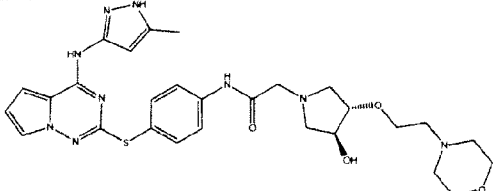
[00575] **Example 051B:** To benzyl 6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate (980 mg, 4.47 mmol) in DCM (5 mL) were added tert-butanol (5 mL) and tris(perfluorophenyl)borane (50 mg, 0.1 mmol), and the mixture was heated at 80 °C overnight. The mixture was purified by silica gel chromatography eluting with 0-10%

DCM/MeOH to give the intermediate *trans*-benzyl 3-tert-butoxy-4-hydroxypyrrolidine-1-carboxylate as an oil, which was dissolved in MeOH (20 mL). Palladium hydroxide (100 mg) was added and the mixture was stirred under a hydrogen atmosphere for 3 h. The mixture was filtered and the filtrate was concentrated to afford *trans*-4-tert-butoxypyrrolidin-3-ol (404 mg, 56%). LCMS (ESI) m/z 160 ($M + H$)⁺.

[00576] Example 051C: To *trans*-4-tert-butoxypyrrolidin-3-ol (404 mg, 2.54 mmol) in DMF (6 mL) were added diisopropylethylamine (0.66 mL, 3.81 mmol), potassium iodide (100 mg, 0.6 mmol), and 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (841 mg, 2.03 mmol). The mixture was heated at 50 °C for 2 h, then the mixture was concentrated and the residue was purified by silica gel chromatography eluting with 0-8 % DCM/MeOH containing 0.1% TEA to afford 2-((trans-3-tert-butoxy-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (315 mg, 23%). ¹H NMR (300 MHz, CD₃OD) δ 1.25 (s, 9H), 2.03 (s, 3H), 2.51 (dd, 1H), 2.69 (d, 1H), 2.95 (dd, 1H), 3.20 (m, 1H), 3.34 (s, 2H), 4.06 (m, 1H), 5.75 (s, 1H), 6.61 (s, 1H), 6.95 (d, 1H), 7.47 (s, 1H), 7.62 (d, 2H), 7.79 (d, 2H); LCMS (ESI) m/z 537 ($M + H$)⁺.

Exam. No.	Structure	Compound name	LC MS (M+H) ⁺
51-i		2-((3R,4S)-3-hydroxy-4-isopropylpyrrolidin-1-yl)-N-(4-((4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[2,1-f][1,2,4]triazin-2-ylthio)phenyl)acetamide	507
51-ii		2-((3R,4S)-3-hydroxy-4-neopentylpyrrolidin-1-yl)-N-(4-((4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[2,1-f][1,2,4]triazin-2-ylthio)phenyl)acetamide	535

Exam. No.	Structure	Compound name	LC MS (M+H)
		de	
51-iii		N-((3R,4R)-4-hydroxy-1-(2-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)pyrrolidin-3-yl)-N-methylisobutyramide	564
51-iv		N-((3R,4R)-4-hydroxy-1-(2-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)pyrrolidin-3-yl)isobutyramide	550
51-v		2-((3S,4R)-3-(tert-butyl)-4-hydroxypyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	521
51-vi		2-((3S,4S)-3-hydroxy-4-(4-(trifluoromethyl)phenyl)amino)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	624
51-vii		2-((3S,4S)-3-hydroxy-4-(3-(trifluoromethyl)phenyl)amino)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	624

Exam. No.	Structure	Compound name	LC MS (M+H) ⁺
		f[1,2,4]triazin-2-yl)thio)phenyl)acetamide	
51-viii		2-((3S,4S)-3,4-dihydroxypyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	481
51-ix		2-((3S,4S)-3-(tert-butylamino)-4-hydroxypyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	536
51-x		2-((3S,4S)-3-hydroxy-4-(2-morpholinoethoxy)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	594

Example 052

Preparation of (R)-N-(4-(4-(5-(Difluoromethyl)-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-hydroxypyrrolidin-1-yl)acetamide

[00577] **Example 052A:** To a refluxing suspension of sodium hydride in THF under Ar was added dropwise an acetonitrile solution of methyl difluoroacetate over 40 min. The mixture was heated at 80 °C overnight then concentrated under reduced pressure. The residue was dissolved in water and acidified to pH 1.0 with 3N hydrochloric acid.

The acidified solution was extracted with ether, and the ether layer was dried over MgSO_4 , filtered, and concentrated under reduced pressure to afford crude 4,4-difluoro-3-oxobutanenitrile (4.13 g, 34.7 mmol).

[00578] **Example 052B:** To 4,4-difluoro-3-oxobutanenitrile from the previous step (3.7 g, 31.07 mmol) suspended in ethanol (100 mL) at rt under Ar was added dropwise hydrazine hydrate (1.99 mL, 62.15 mmol) and the mixture was heated at reflux overnight. The mixture was allowed to cool to rt and then was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 12% to 85% EtOAc/hexanes to afford 5-(difluoromethyl)-1H-pyrazol-3-amine (867 mg, 21% over 2 steps). ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 11.85 (s, 1H), 6.68 (t, 1H), 5.42 (s, 1H), 5.18 (br s, 2H); LCMS (ESI) m/z 134 ($\text{M} + \text{H}$) $^+$.

[00579] **Example 052C:** 2-Chloro-N-(5-difluoromethyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine (370 mg, 1.3 mmol, 24%) was synthesized using a procedure analogous to that described in Example 041A, substituting 5-(difluoromethyl)-1H-pyrazol-3-amine from Example 052B for the 5-cylobutyl-1H-pyrazol-3-amine used in Example 041A. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 13.52 (s, 1H), 11.3 (s, 1H), 7.80 (br,s, 1H), 7.3-7.45 (m, 1H), 7.05-7.25 (m, 2H), 6.75 (br,s,1H); LCMS (ESI) m/z 285 ($\text{M} + \text{H}$) $^+$.

[00580] **Example 052D:** 2-(4-Aminophenylthio)-N-(5-difluoromethyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine (100 mg, 0.27 mmol, 24%) was synthesized using a procedure analogous to that described in Example 016A, substituting 2-chloro-N-(5-difluoromethyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine from the previous step for the 2-chloro-N-(5-methyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine used in Example 016A. LCMS (ESI) m/z 374 ($\text{M} + \text{H}$) $^+$.

[00581] **Example 052E:** 2-Chloro-N-(4-(4-(5-difluoromethyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (82.1 mg, 0.18 mmol, 87%) was synthesized using a procedure analogous to that described in Example 016B, substituting 2-(4-aminophenylthio)-N-(5-difluoromethyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine from previous step for the 2-(4-

aminophenylthio)-N-(5-methyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine used in Example 016B. LCMS (ESI) m/z 450 ($M + H$)⁺.

[00582] Example 052F: (R)-N-(4-(4-(5-(difluoromethyl)-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-hydroxypyrrolidin-1-yl)acetamide (20.1 mg, 44%) was synthesized using a procedure analogous to that described in Example 018B, substituting 2-chloro-N-(4-(4-(5-difluoromethyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from previous step for the 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide used in Example 018B, and substituting (R)-pyrrolidin-3-ol for the ((2S,4R)-4-tert-butoxypyrrolidin-2-yl)methanol used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.1 (s, 1H), 10.95 (s, 1H), 9.92 (s, 1H), 7.79 (d, 2H), 7.65 (t, 3H), 7.18 (s, 1H), 6.85 (s, 1H), 6.67 (br s, 1H), 6.27 (br s, 1H), 4.85 (d, 1H), 4.25 (br s, 1H), 3.28 (s, 2H), 2.77-2.84 (m, 3H), 1.99-2.1 (m, 2H), 1.64 (br s, 1H); LCMS (ESI) m/z 501 ($M + H$)⁺.

Example 053

Preparation of (S)-2-(4,4-Difluoro-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-(difluoromethyl)-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00583] (S)-2-(4,4-difluoro-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-(difluoromethyl)-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (20.1 mg, 0.04 mmol, 44%) was synthesized using a procedure analogous to that described in Example 018B, substituting 2-chloro-N-(4-(4-(5-difluoromethyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 052E for the 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide used in Example 018B, and (S)-(4,4-difluoropyrrolidin-2-yl)methanol from Example 020A for the ((2S,4R)-4-tert-butoxypyrrolidin-2-yl)methanol used in Example 018B. (8.0 mg, 0.014 mmol, 16%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.25 (s, 1H), 10.97 (s, 1H), 10.03 (s, 1H), 7.74 (d, 2H), 7.58-7.64 (t, 3H), 7.04-7.18 (d, 1H), 6.85 (s, 1H), 6.64 (br s, 1H), 6.27 (br s, 1H), 4.88 (s, 1H), 3.70 (d, 1H), 3.49 (br s, 3H), 3.05-3.11 (m, 2H), 2.20-2.42 (m, 2H), 1.24 (br s, 1H); LCMS (ESI) m/z 551 ($M + H$)⁺.

Example 054**Preparation of 2-(trans-3-(4-Fluorophenoxy)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide**

[00584] **Example 054A:** To benzyl 6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate from Example 051A (1.5 g, 6.84 mmol) in DMF (10 mL) were added 4-fluorophenol (1.91 g, 17.1 mmol) and cesium carbonate (6.67 g, 20.5 mmol) and the mixture was heated at 100 °C for 0.5 h and then at 110 °C for 1 h. The mixture was partitioned between ethyl acetate and water, and then the organic layer was washed with saturated sodium chloride, dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography eluting with 0-10% DCM/MeOH to afford trans-benzyl 3-(4-fluorophenoxy)-4-hydroxypyrrolidine-1-carboxylate (750 mg, 33%). LCMS (ESI) m/z 354 ($M + Na$)⁺.

[00585] **Example 054B:** To 3-(4-fluorophenoxy)-4-hydroxypyrrolidine-1-carboxylate (750 mg, 2.26 mmol) in MeOH (10 mL) was added palladium hydroxide (75 mg). The mixture was stirred under a hydrogen atmosphere for 1.5 h, then additional palladium hydroxide (75 mg) was added and stirring was continued under hydrogen for 1 h. The mixture was filtered and the filtrate was concentrated. To the residue were added diisopropylethylamine (0.75 mL, 4.32 mmol), potassium iodide (100 mg, 0.6 mmol), and 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (890 mg, 2.15 mmol). The mixture was heated at 50 °C for 1 h, then at 70 °C for 2 h. The mixture was concentrated and the residue was purified by silica gel chromatography eluting with 0-8 % DCM/MeOH containing 0.1% TEA to afford 2-(trans-3-(4-fluorophenoxy)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (650 mg, 50%). ¹H NMR (300 MHz, CD₃OD) δ 2.16 (s, 3H), 2.7-2.9 (m, 2H), 3.06 (dd, 1H), 3.3-3.5 (m, 3H), 4.28 (s, 1H), 4.62 (s, 1H), 5.75 (s, 1H), 6.60 (s, 1H), 6.9-7.1 (m, 5H), 7.46 (s, 1H), 7.62 (d, 2H), 7.79 (d, 2H); LCMS (ESI) m/z 575 ($M + H$)⁺.

Example 055**Preparation of 2-(3-Fluoro-3-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide**

[00586] **Example 055A Step 1:** To a stirring solution of tert-butyl 1-benzyl-3-fluoropyrrolidine-3-carboxylate from Step 1 of Example 48A (150 mg, 0.54 mmol) in THF (5 mL) at rt was added LiBH₄ (50 mg, 2.3 mmol). The mixture was stirred at rt overnight, and then was heated at 60 °C for 90 min. The mixture was partitioned between EtOAc (15 mL) and saturated aq NaHCO₃ (10 mL), and the organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc to give (1-benzyl-3-fluoropyrrolidin-3-yl)methanol (90 mg, 80% yield). LCMS (ESI) *m/z* 210 (M + H)⁺.

[00587] **Example 055B:** (1-benzyl-3-fluoropyrrolidin-3-yl)methanol (90 mg) was dissolved in MeOH (3 mL) and 10% Pd/C (25 mg) was added under an argon atmosphere. The mixture was stirred under a hydrogen atmosphere at rt overnight. The mixture was then filtered through Celite and the filtrate was concentrated under reduced pressure to give (3-fluoropyrrolidin-3-yl)methanol as a colorless oil (50 mg, 99% yield). LCMS (ESI) *m/z* 190 (M + H)⁺.

[00588] **Example 055C:** 2-(3-fluoro-3-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was prepared using a procedure analogous to that described in Example 018B, substituting (3-fluoropyrrolidin-3-yl)methanol from Example 055B for the pyrrolidine derivative used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.07 (s, 1H), 10.63 (s, 1H), 10.04 (s, 1H), 7.78 (d, 2H), 7.59 (s, 1H), 7.58 (d, 2H), 7.23 (s, 1H), 6.58 (m, 1H), 5.63 (s, 1H), 4.03 (m, 1H), 3.55 (m, 2H), 2.85 (m, 2H), 2.66 (m, 1H), 2.03 (s, 3H), 1.96 (m, 2H); LCMS (ESI) *m/z* 497 (M + H)⁺.

Example 056

Preparation of 2-(*trans*-3-Fluoro-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00589] **Example 056A:** To benzyl 2,5-dihydro-1H-pyrrole-1-carboxylate (1.5 g, 7.38 mmol) in THF (15 mL) was added 2.5% osmium tetroxide/water (0.2 mL). The solution was stirred for 1.5 h at rt, then additional 2.5% osmium tetroxide/water (0.1 mL) was added and the solution was stirred overnight at rt. The mixture was purified

by silica gel chromatography eluting with 0-13% DCM/ MeOH to afford *cis*-benzyl 3,4-dihydroxypyrrolidine-1-carboxylate as an oil (434 mg, 24%); LCMS (ESI) m/z 260 ($M + Na$)⁺.

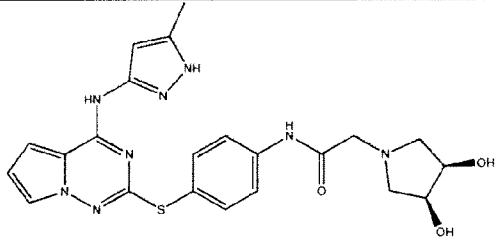
[00590] **Example 056B:** To *cis*-benzyl 3,4-dihydroxypyrrolidine-1-carboxylate (383 mg, 1.61 mmol) in pyridine (10 mL) at 0 °C was added benzoyl chloride (0.187 mL, 1.61 mmol) and the mixture was allowed to warm to rt overnight. The solution was concentrated and the residue was purified by silica gel chromatography eluting with 0-13% DCM/methanol to afford impure *cis*-benzyl 3-(benzoyloxy)-4-hydroxypyrrolidine-1-carboxylate (483 mg). LCMS (ESI) m/z 364 ($M + Na$)⁺.

[00591] **Example 056C:** To impure *cis*-benzyl 3-(benzoyloxy)-4-hydroxypyrrolidine-1-carboxylate (120 mg, 0.35 mmol) from Example 056B in DCM (3 mL) was added Dcoxo-Fluor (130 mg, 0.7 mmol). The mixture was stirred for 2 h at rt and then purified by preparative thin layer chromatography eluting with 20% EtOAc in hexanes to afford *trans*-benzyl 3-(benzoyloxy)-4-fluoropyrrolidine-1-carboxylate (43 mg, 35%); LCMS (ESI) m/z 366 ($M + Na$)⁺.

[00592] **Example 056D:** To *trans*-Benzyl 3-(benzoyloxy)-4-fluoropyrrolidine-1-carboxylate (43 mg, 0.125 mmol) in MeOH (10 mL) was added sodium methoxide (20 mg) and the mixture was stirred at rt for 45 min. Palladium hydroxide (30 mg) was then added and stirring was continued under a nitrogen atmosphere for 30 min, then the solution was filtered and the filtrate was concentrated to dryness. To the residue in DMF (2 mL) were added diisopropylethylamine (0.5 mL, 0.25 mmol), potassium iodide (20 mg, 0.12 mmol), and 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (26 mg, 0.06 mmol), and the mixture was heated at 50 °C for 2 h. Acetic acid (0.1 mL) and DMSO (2 mL) were added and mixture was purified by preparative HPLC (Varian diphenyl reverse phase column) eluting with a gradient of solvent B (0.05% HOAc/CH₃CN) in solvent A (0.05% HOAc/H₂O) to afford 2-(*trans*-3-fluoro-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide as its acetate salt ¹H NMR (300 MHz, CD₃OD) δ 2.0 (s, 3H), 2.13 (s, 3H), 2.75 (dd, 1H), 2.86-3.03 (m, 2H), 3.18 (m, 1H), 3.46 (s, 2H), 4.32

(m, 1H), 4.9 (m, 1H), 5.76 (s, 1H), 6.60 (m, 1H), 6.95 (m, 1H), 7.46 (m, 1H), 7.62 (d, 2H), 7.76 (d, 2H); LCMS (ESI) m/z 483 (M + H)⁺.

The following compound was prepared in a similar manner.

Exam. No.	Structure	Compound name	LC MS (M+H) ⁺
56A-i		2-((3S,4R)-3,4-dihydroxypyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	481

Example 057

Preparation of 2-(*trans*-3-(2-Ethoxyethoxy)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00593] **Example 057A:** To benzyl 6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate from Example 051A (118 mg, 0.538 mmol) in 2-ethoxyethanol (0.5 mL) and DCM (3 mL) was added tris(perfluorophenyl)borane (15 mg) and the mixture was heated at 100 °C for 4 h. The mixture was filtered through silica gel eluting with DCM. The eluate was concentrated under reduced pressure to afford *trans*-benzyl 3-(2-ethoxyethoxy)-4-hydroxypyrrolidine-1-carboxylate (35 mg, 20%) which was used in the next step without further purification; LCMS (ESI) m/z 332 (M + Na)⁺.

[00594] **Example 057B:** To *trans*-benzyl 3-(2-ethoxyethoxy)-4-hydroxypyrrolidine-1-carboxylate (35 mg, 0.2 mmol) in MeOH (10 mL) was added palladium hydroxide (40 mg) and the mixture was stirred under a hydrogen atmosphere for 30 min. The solution was then filtered and the filtrate was concentrated. To the residue in DMF (2 mL) were added diisopropylethylamine (0.7 mL, 0.4 mmol), potassium iodide (50 mg, 0.3 mmol) and 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (50 mg, 0.12 mmol) and the mixture was heated at 50 °C for 3 h. Acetic acid (0.15 mL) and DMSO (2 mL) were added and the mixture was purified by preparative HPLC (Varian diphenyl reverse phase column) eluting with a gradient of solvent B (0.05% HOAc/CH₃CN) in

solvent A (0.05% HOAc/H₂O) to afford 2-(*trans*-3-(2-ethoxyethoxy)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide as its acetate salt (35 mg, 49%). ¹H NMR (300 MHz, CD₃OD) δ 1.18 (t, 3H), 2.0 (s, 3H), 2.14 (s, 3H), 2.8-2.9 (m, 2H), 3.16 (dd, 1H), 3.5-3.8 (m, 8H), 3.94 (m, 1H), 4.27 (m, 1H), 5.77 (s, 1H), 6.60 (m, 1H), 6.95 (d, 1H), 7.46 (m, 1H), 7.62 (d, 2H), 7.76 (d, 2H); LCMS (ESI) *m/z* 553 (M + H)⁺.

Example 058

Preparation of N-(4-(4-(1H-Pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-((2S,4R)-4-tert-butoxy-2-(hydroxymethyl)pyrrolidin-1-yl)acetamide

[00595] **Example 058A:** N-(4-(4-(1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-chloroacetamide was prepared using procedures analogous to those described in Examples 41A through 41C, substituting 1H-pyrazol-3-amine for the 5-cyclobutyl-1H-pyrazol-3-amine used in Example 041A.

[00596] **Example 058B:** N-(4-(4-(1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-((2S,4R)-4-tert-butoxy-2-(hydroxymethyl)pyrrolidin-1-yl)acetamide was synthesized as a white solid (23.71 mg, 35 %) using a procedure analogous to that described in Example 018B, substituting N-(4-(4-(1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-chloroacetamide from Example 58A for the 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide used in Example 018B. Purification by silica gel chromatography eluting with DCM/MeOH afforded N-(4-(4-(1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-((2S,4R)-4-tert-butoxy-2-(hydroxymethyl)pyrrolidin-1-yl)acetamide. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.40 (br s, 1H), 10.75 (s, 1H), 9.85 (s, 1H), 7.75 (d, 2H), 7.60 (m, 3H), 7.40 (s, 1H), 7.20 (s, 1H), 6.60 (s, 1H), 6.10 (s, 1H), 4.70 (s, 1H), 4.20 (s, 1H), 3.70-3.15 (m, 3H), 2.80 (s, 1H), 2.30 (s, 1H), 1.90 (s, 1H), 1.70 (s, 1H), 1.15 (s, 11H); LCMS (ESI) *m/z* 559 (M+Na)⁺.

Example 059

Preparation of (R)-2-(3-tert-Butoxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00597] **Example 059A:** To a stirring solution of (R)-(-)-CBZ-3-pyrrolidinol (250mg, 1.13mmol) in THF (5mL) was added tert-butyl 2, 2, 2-trichloroacetimidate (0.202 mL, 1.13 mmol). The solution was stirred at rt for 3 h, then additional tert-butyl 2, 2, 2-trichloroacetimidate (0.202ml, 1.13mmol) was added and the mixture was stirred for 0.5 h. Additional tert-butyl 2, 2, 2-trichloroacetimidate (0.202ml, 1.13mmol) was then added and the mixture was stirred for an additional 1 h. DCM (15 mL) was added and the mixture was filtered. The filtrate was purified by silica gel chromatography eluting with 30% EtOAc/hexanes to afford impure (R)-benzyl 3-tert-butoxypyrrolidine-1-carboxylate (500 mg); LCMS (ESI) m/z 300 ($M + Na$)⁺. To impure (R)-benzyl 3-tert-butoxypyrrolidine-1-carboxylate in 1:1 MeOH:THF (8 mL) was added palladium hydroxide (80 mg) and the mixture was stirred under a hydrogen atmosphere overnight, and then filtered. The filtrate was concentrated to afford crude (R)-3-tert-butoxypyrrolidine (110 mg, 67 %); LCMS (ESI) m/z 144 ($M + H$)⁺.

[00598] **Example 059B:** To (R)-3-tert-butoxypyrrolidine (69 mg, 0.48 mmol) in DMF (10mL) were added potassium iodide (40 mg, 0.242 mmol) and 2-chloro-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide (100mg, 0.242mmol), followed by dropwise addition of N,N-diisopropylethylamine (0.041 mL, 0.242 mmol). The solution was stirred at 50 °C overnight, then additional N,N-diisopropylethylamine (0.2 mL) and potassium iodide (50 mg) were added and stirring was continued for 1 day. The resulting mixture was purified by preparative HPLC (Varian diphenyl reverse phase column) eluting with a gradient of solvent B (0.05% HOAc/CH₃CN) in solvent A (0.05% HOAc/H₂O) to afford (R)-2-(3-tert-butoxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide as its diacetate salt (31 mg, 22%); ¹H NMR (300 MHz, CD₃OD) δ 1.23 (s, 9H), 1.89 (m, 1H), 1.98 (s, 6H), 2.14 (s, 3H), 2.26 (m, 1H), 2.9-3.0 (m, 2H), 3.1-3.3 (m, 2H), 3.69 (s, 2H), 4.45 (m, 1H), 5.79 (s, 1H), 6.61 (m, 1H), 6.94 (d, 1H), 7.47 (m, 1H), 7.62 (d, 2H), 7.76 (d, 2H); LCMS (ESI) m/z 521 ($M + H$)⁺.

Example 060

Preparation of 2-(3,3-Difluoro-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00599] Example 060A: To a solution of benzyl 6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate from Example 051A (310 mg, 1.41 mmol) and benzyl alcohol (0.22 mL, 2.12 mmol) in DCM (3 mL) was added tris(perfluorophenyl)borane (19 mg), and the mixture was heated at 100 °C for 2 h, then allowed to cool to rt. Dess-Martin periodinane (1.19 g, 2.82 mmol) was added and the mixture was stirred at rt for 1 h, then at 50 °C for 1 h. The mixture was partitioned between 1 N NaOH and DCM, and the organic layer was collected, dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography eluting with 0-60% hexanes/EtOAc to afford benzyl 3-(benzyloxy)-4-oxopyrrolidine-1-carboxylate (320 mg, 70% over 2 steps); LCMS (ESI) m/z 348 ($M + Na$)⁺.

[00600] Example 060B: To benzyl 3-(benzyloxy)-4-oxopyrrolidine-1-carboxylate (96 mg, 0.3 mmol) in DCM (3 mL) was added Deoxo-Fluor (0.16 mL, 0.89 mmol) and the solution was stirred at rt overnight. The mixture was filtered through a plug of silica gel washing with DCM, then the eluate was concentrated to afford benzyl 4-(benzyloxy)-3,3-difluoropyrrolidine-1-carboxylate (90 mg, 88%); LCMS (ESI) m/z 370 ($M + Na$)⁺.

[00601] Example 060C: To benzyl 4-(benzyloxy)-3,3-difluoropyrrolidine-1-carboxylate (90 mg, 0.26 mmol) in MeOH (10 mL) was added palladium hydroxide (50 mg) and the mixture stirred under a hydrogen atmosphere for 5 h. The mixture was filtered and the filtrate was concentrated. To the residue in DMF (2 mL) were added N,N-diisopropylethylamine (0.07 mL, 0.52 mmol), potassium iodide (50 mg, 0.3 mmol) and 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (50 mg, 0.13 mmol) and the mixture was heated at 50 °C for 2 h and then at 40 °C overnight. Acetic acid (0.15 mL) and DMSO (2 mL) were added and the mixture was purified by preparative HPLC (Varian diphenyl reverse phase column) eluting with a gradient of solvent B (0.05% HOAc/CH₃CN) in solvent A (0.05% HOAc/H₂O) to afford 2-(3,3-difluoro-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (18 mg, 28%). ¹H NMR (300 MHz, CD₃OD) δ 2.14 (s, 3H), 2.8 (m, 1H), 3.1-3.3 (m, 3H), 3.40 (s, 2H), 4.25 (m, 1H), 5.76

(s, 1H), 6.60 (m, 1H), 6.95 (d, 1H), 7.47 (m, 1H), 7.62 (d, 2H), 7.76 (d, 2H); LCMS (ESI) m/z 501 (M + H)⁺.

Example 061

Preparation of 2-((R)-3-(2-Morpholinoethoxy)pyrrolidin-1-yl)- N-(4-(4-(5-methyl- 1H-pyrazol-3-ylamino) pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00602] **Example 061A:** To SOCl₂ (10 mL) at 0 °C was added dropwise 2-morpholinoethanol (1.00 g), and the mixture was stirred at 60 °C for 12 h. The mixture was concentrated to dryness under reduced pressure. The residue was partitioned between DCM (20 mL) and 10% aq Na₂CO₃ (10 mL) then the organic layer was washed with water (10 mL), dried (Na₂SO₄), and filtered. The filtrate was concentrated under reduced pressure to afford 4-(2-chloroethyl)-morpholine (0.64 g, 56% yield). ¹H NMR (400 MHz, CDCl₃) δ 2.54 (t, 4H), 2.75 (t, 2H), 3.61 (t, 2H), 3.73 (t, 4H).

[00603] **Example 061B:** A mixture of (R)-tert-butyl 3-hydroxypyrrolidine-1-carboxylate (109 mg) and 60% NaH (23 mg) in DMF (1 mL) was stirred at 0 °C for 30 min. To the mixture was added dropwise a solution of 4-(2-chloroethyl)-morpholine (87 mg) in DMF (1 mL) and the mixture was stirred at 0 °C for 2 h and at rt overnight. Water (10 mL) and DCM (10 mL) were added at 0 °C. The organic layer was washed with water (2 X 10 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The residue (101 mg) was purified by silica gel chromatography (DCM: MeOH = 100:1~10:1, v:v) to give (R)-tert-butyl 3-(2-morpholinoethoxy)pyrrolidine-1-carboxylate as a yellow oil (70 mg, 40% yield); LCMS(ESI) m/z 301(M+H)⁺.

[00604] **Example 061C:** A mixture of (R)-tert-butyl 3-(2-morpholinoethoxy)pyrrolidine-1-carboxylate (70 mg) and 4M HCl (1 mL) in 1,4-dioxane (1 mL) was stirred at rt for 4 h, at which time analysis by LCMS indicated that the reaction was complete. To the mixture was added water (1 mL), and the solution was washed twice with diethyl ether (2 mL) and concentrated under reduced pressure to give 4-(2-((R)-pyrrolidin-3-yloxy)ethyl)morpholine hydrochloride as a pale yellow powder (51 mg, 93% yield); LCMS (ESI) m/z 201(M+H)⁺.

[00605] **Example 061D:** A mixture of 4-(2-((R)-pyrrolidin-3-yloxy)ethyl)morpholine hydrochloride from the previous step (47 mg), 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 016B (55 mg) and Na₂CO₃ (55 mg) in DMF (1 mL) was stirred at rt overnight. The mixture was filtered and the filtrate was purified by Al₂O₃ column chromatography eluting with 100:1 to 10:1 DCM/MeOH to give a yellow powder (40 mg). After purification by preparative TLC (DCM: MeOH = 7:1, v:v), 2-((R)-3-(2-morpholinoethoxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was obtained as a pale yellow powder (20 mg, 27% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.73 (m, 1H), 2.04 (m, 4H), 2.40 (m, 4H), 2.46 (m, 1H), 2.51 (m, 1H), 2.61 (m, 2H), 2.71 (m, 1H), 2.88 (m, 1H), 3.29 (m, 2H), 3.47 (m, 2H), 3.55 (m, 3H), 4.04 (m, 1H), 5.65 (s, 1H), 6.58 (m, 1H), 7.23 (m, 1H), 7.58 (m, 3H), 7.78 (d, 2H), 10.02 (s, 1H), 10.62 (s, 1H), 12.05 (s, 1H); LCMS(ESI) *m/z* 578(M+H)⁺.

Example 062

Preparation of (S)-2-(2-Methoxymethyl-pyrrolidin-1-yl)-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide

[00606] 2-(2-Methoxymethyl-pyrrolidin-1-yl)-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide was prepared as a white solid (40.11 mg, 56 %) using a procedure analogous to that described in Example 018B, substituting (S)-2-(methoxymethyl)pyrrolidine for the ((2S,4R)-4-tert-butoxypyrrolidin-2-yl)methanol used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.70 (s, 1H), 10.0 (s, 1H), 7.80 (d, 2H), 7.60 (s, 3H), 7.20 (s, 1H), 6.50 (s, 1H), 5.60 (s, 1H), 3.65 (d, 1H), 3.45-3.20 (m, 6H), 3.20 (m, 1H), 2.80 (m, 1H), 2.05 (s, 3H), 1.90 (m, 1H), 1.70 (m, 2H), 1.55 (m, 1H), 1.40 (s, 1H); LCMS (ESI) *m/z* 493 (M+H)⁺.

Example 063

Preparation of 2-((R)-3-(2-Methoxyethoxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00607] **Example 063A:** A mixture of (R)-tert-butyl 3-hydroxypyrrolidine-1-carboxylate (100 mg) and 60% NaH (26mg) in DMF (1 mL) was stirred at 0 °C for 30

min. To the mixture was added dropwise a solution of 1-chloro-2-methoxyethane (111 mg) in DMF (1 mL) and the mixture was stirred at 0 °C for 2 h, and then at rt overnight. Water (10 mL) and DCM (10 mL) were added at 0 °C. The organic layer was washed twice with water (10 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure to afford crude (R)-tert-butyl 3-(2-methoxyethoxy)pyrrolidine-1-carboxylate (85 mg) as yellow oil, which was directly used in the next step.

[00608] Example 063B: A mixture of (R)-tert-butyl 3-(2-methoxyethoxy)pyrrolidine-1-carboxylate from the previous step (85 mg) and 4M HCl (1 mL) in THF (2 mL) was stirred at rt for 4 h, at which time LCMS showed the reaction was complete. Water (1 mL) was added and the aqueous solution was washed with ethyl ether (2 X 2 mL) and concentrated under reduced pressure to give (R)-3-(2-methoxyethoxy)pyrrolidine hydrochloride as a yellow oil (50 mg), which was used directly in the next step. LCMS (ESI) *m/z* 146 (M+H)⁺.

[00609] Example 063C: A mixture of (R)-3-(2-methoxyethoxy)pyrrolidine hydrochloride from the previous step (50 mg), N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino) pyrrolo[1,2-f][1,2,4] triazin- 2-ylthio)phenyl)-2-chloroacetamide (60 mg) and Na₂CO₃ (60 mg) in DMF (1 mL) was stirred at rt overnight. The mixture was filtered and the filtrate was purified by Al₂O₃ column chromatography eluting with 100:1 to 10:1 DCM/MeOH to give a yellow powder (40 mg). After purification by preparative TLC eluting with 7:1 DCM: MeOH 2-((R)-3-(2-methoxyethoxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl- 1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was isolated as a pale yellow powder (20 mg, 26% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.72 (m, 1H), 2.04 (m, 4H), 2.49 (m, 2H), 2.59 (m, 1H), 2.71 (m, 1H), 3.25 (m, 3H), 3.27 (m, 2H), 3.49(m, 2H), 3.51 (m, 2H), 4.47 (m, 1H), 5.63 (s, 1H), 6.58 (m, 1H), 7.23 (m, 1H), 7.58 (m, 3H), 7.78 (d, 2H), 10.01 (s, 1H), 10.63 (s, 1H), 12.07 (s, 1H); LCMS (ESI) *m/z* 523(M+H)⁺.

Example 064

Preparation of 2-((2S,4R)-4-(4-Fluorophenoxy)-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00610] Example 064A Step 1 (Preparation of ((2S,4R)-4-(4-fluorophenoxy)pyrrolidin-2-yl)methanol): To a solution of (2S,4S)-tert-butyl 4-hydroxy-2-(trityloxymethyl)pyrrolidine-1-carboxylate (500 mg, 1.087 mmol) in DCM (5 mL) at 0 °C were added triethylamine (0.303 mL, 2.16 mmol) and methanesulfonyl chloride (0.10 mL, 1.3 mmol). The mixture was stirred at ambient temperature for 1 h, at which time formation of the product was determined by LCMS. The mixture was diluted with EtOAc and washed with ammonium chloride and brine, then dried over MgSO₄, filtered, and concentrated under reduced pressure to afford crude (2S,4S)-tert-butyl 4-(methanesulfonyloxy)-2-(trityloxymethyl)pyrrolidine-1-carboxylate.

[00611] Example 064A Step 2: To a solution of (2S,4S)-tert-butyl 4-(methanesulfonyloxy)-2-(trityloxymethyl)pyrrolidine-1-carboxylate from the previous step (50 mg, 0.093) in DMF (2 mL) were added potassium carbonate (38.5 mg, 0.279 mmol) and *p*-fluorophenol (31.2 mg, 0.279 mmol). The mixture was heated in a microwave reactor for 30 min at 120 °C, at which time formation of the product was determined by LCMS. The mixture was diluted with EtOAc and washed with water and brine, then concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/hexane to afford (2S,4R)-tert-butyl 4-(4-fluorophenoxy)-2-(trityloxymethyl)pyrrolidine-1-carboxylate (40 mg, 77%).

[00612] Example 064A Step 3: ((2S,4R)-4-(4-fluorophenoxy)pyrrolidin-2-yl)methanol was prepared using a procedure analogous to that described in Example 024A Step 2, substituting (2S,4R)-tert-butyl 4-(4-fluorophenoxy)-2-(trityloxymethyl)pyrrolidine-1-carboxylate from the previous step for the (2R,4R)-tert-butyl 2-(hydroxymethyl)-4-methoxypyrrolidine-1-carboxylate used in Example 024A.

[00613] Example 064B: 2-((2S,4R)-4-(4-fluorophenoxy)-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was synthesized as a

white solid (7 mg, 33 %) using a procedure analogous to that described in Example 077B, substituting ((2S,4R)-4-(4-fluorophenoxy)pyrrolidin-2-yl)methanol hydrochloride for the *trans*-4-cyclopentyl-oxy-pyrrolidin-3-ol used in Example 077B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.00 (s, 1H), 10.60 (s, 1H), 10.10 (s, 1H), 7.80 (d, 2H), 7.30-7.05 (m, 3H), 6.90 (m, 2H), 6.55 (s, 1H), 5.60 (s, 1H), 4.80 (m, 2H), 3.70-3.20 (m, 4H), 3.05 (d, 1H), 2.70 (m, 1H), 2.10-1.90 (m, 6H); LCMS (ESI) *m/z* 589 (M+H)⁺.

Example 065

Preparation of 2-[2-Hydroxymethyl-4-(2-methyl-propane-2-sulfonyl)-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfonyl]-phenyl}-acetamide

[00614] **Example 065A Step 1:** To a solution of (2S,4S)-tert-butyl 4-(methylsulfonyloxy)-2-(trityloxymethyl)pyrrolidine-1-carboxylate from Example 064A Step 1 (200 mg, 0.372 mmol) in DMF (4 mL) was added sodium 2-methylpropane-2-thiolate (150 mg, 1.33 mmol) and the mixture was heated at 40 °C for 12 h, at which time formation of the product was determined by LCMS. The reaction mixture was diluted with EtOAc, washed with water and brine, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with hexane/EtOAc to afford (2S,4R)-tert-butyl 4-(tert-butylthio)-2-(trityloxymethyl)pyrrolidine-1-carboxylate (110mg, 56%) as a solid.

[00615] **Example 065A Step 2:** To (2S,4R)-tert-butyl 4-(tert-butylthio)-2-(trityloxymethyl)pyrrolidine-1-carboxylate (50 mg, 0.094 mmol) in DCM (2 mL) was added 3-chloroperbenzoic acid (32.4 mg, 0.188 mmol) and the mixture was stirred for 1 h, at which time formation of the product was determined by LCMS. The mixture was diluted with EtOAc and washed with water and brine, then concentrated to afford crude (2S,4R)-tert-butyl 4-(tert-butylsulfonyl)-2-(trityloxymethyl)pyrrolidine-1-carboxylate, which was used directly in the next step.

[00616] **Example 065A Step 3:** [4-(2-methyl-propane-2-sulfonyl)-pyrrolidin-2-yl]-methanol was prepared using a procedure analogous to that described in Example 024A Step 2, substituting (2S,4R)-tert-butyl 4-(tert-butylsulfonyl)-2-(trityloxymethyl)pyrrolidine-1-carboxylate from Example 05A Step 2 for the

(2R,4R)-tert-butyl 2-(hydroxymethyl)-4-methoxypyrrolidine-1-carboxylate used in Example 24A.

[00617] Example 065B: 2-[2-Hydroxymethyl-4-(2-methyl-propane-2-sulfonyl)-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide) was synthesized as a white solid (22.39 mg, 62 % using a procedure analogous to that described in Example 077B, substituting ((2S,4R)-4-(tert-butylsulfonyl)pyrrolidin-2-yl)methanol hydrochloride for the 4-cyclopentyloxy-pyrrolidin-3-ol used in Example 077B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.05 (s, 1H), 10.65 (s, 1H), 10.00 (s, 1H), 7.80 (d, 2H), 7.60 (m, 3H), 7.20 (s, 1H), 6.55 (s, 1H), 5.60 (s, 1H), 4.80 (s, 1H), 4.05 (s, 1H), 3.70-3.20 (m, 4H), 3.15 (s, 1H), 2.90 (m, 2H), 2.25 (m, 1H), 2.0 (s, 3H), 1.30 (s, 9H); LCMS (ESI) *m/z* 599 (M+H)⁺.

Example 066

Preparation of 2-((2S,4R)-4-tert-Butoxy-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00618] 2-((2S,4R)-4-tert-butoxy-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was synthesized as a white solid (27.59 mg, 42 %) using a procedure analogous to that described in Example 018B, substituting 2-chloro-N-(4-(4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 13A for the 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.00 (br s, 1H), 10.60 (s, 1H), 9.90 (s, 1H), 7.75 (d, 2H), 7.60 (s, 3H), 7.20 (s, 1H), 6.55 (s, 1H), 5.75 (s, 1H), 4.70 (brs, 1H), 4.20 (m, 1H), 3.70-3.10 (m, 4H), 2.30 (s, 1H), 1.95 (s, 3H), 1.70 (m, 2H), 1.15 (s, 9H), 0.85 (m, 2H), 0.50 (s, 2H); LCMS (ESI) *m/z* 577 (M+H)⁺.

Example 067

Preparation of 2-*trans*-3-Hydroxy-4-(((R)-tetrahydrofuran-2-yl)methoxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00619] **Example 067A:** *trans*-4-(((R)-Tetrahydrofuran-2-yl)methoxy)pyrrolidin-3-ol was prepared using a procedure analogous to that described in Example 051B, substituting (R)-tetrahydrofurfuryl alcohol for the tert-butanol used in Example 051B. The product is a mixture of two diastereoisomers (2 to 1 ratio). LCMS(ESI) m/z 188 ($M + H$)⁺.

[00620] **Example 067B:** 2-*trans*-3-Hydroxy-4-(((R)-tetrahydrofuran-2-yl)methoxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was prepared using a procedure analogous to that described in Example 018B, substituting *trans*-4-(((R)-tetrahydrofuran-2-yl)methoxy)pyrrolidin-3-ol from Example 067A for the pyrrolidine derivative used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.08 (s, 1H), 10.64 (s, 1H), 10.16 (s, 1H), 8.94 (s, 1H), 7.76 (d, 2H), 7.60 (s, 1H), 7.59 (d, 2H), 7.23 (s, 1H), 6.58 (t, 1H), 5.65 (s, 1H), 5.31 (s, 1H), 4.20-3.30 (m, 9H), 2.79 (m, 2H), 2.04 (s, 3H), 1.89 (m, 4H), 1.55 (m, 1H); LCMS (ESI) m/z 565 ($M + H$)⁺.

Example 068

Preparation of 2- *trans*-[3-(4-Fluoro-phenylamino)-4-hydroxy-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide

[00621] **Example 068A:** A mixture of benzyl 6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate from Example 051A (180 mg, 0.82 mmol) and palladium hydroxide (50 mg) in MeOH (10 mL) was stirred under a hydrogen atmosphere for 45 min, then the mixture was filtered and the filtrate was concentrated under reduced pressure to afford 6-oxa-3-azabicyclo[3.1.0]hexane. 2-(6-Oxa-3-azabicyclo[3.1.0]hexan-3-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was prepared using a procedure analogous to that described in Example 018B, substituting 6-oxa-3-azabicyclo[3.1.0]hexane from above for the pyrrolidine derivative used in Example 018B to afford LCMS (ESI) m/z 463 ($M + H$)⁺.

[00622] **Example 068B:** To a solution of 2-(6-oxa-3-azabicyclo[3.1.0]hexan-3-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (40mg, 0.086 mmol) in EtOH (0.4 mL) was added 4-fluoro-

phenylamine (0.8 mL) and the mixture was heated in a sealed tube at 100 °C for 12 h, at which time formation of the product was determined by LCMS. The mixture was purified by silica gel chromatography eluting with DCM/MeOH to afford 2-*trans*-[3-(4-fluoro-phenylamino)-4-hydroxy-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide as a white solid (27.93 mg, 56 %). ¹H NMR (300 MHz, CD₃OD) δ 7.65 (d, 2H), 7.50 (d, 2H), 7.30 (s, 1H), 6.80 (m, 3H), 6.60 (m, 2H), 6.40 (s, 1H), 5.60 (s, 1H), 3.85 (s, 1H), 3.60 (s, 1H), 3.30-3.15 (m, 3H), 2.90 (m, 1H), 2.60 (m, 1H), 2.40 (m, 1H), 2.00 (s, 3H); LCMS (ESI) *m/z* 574 (M+H)⁺.

Example 069

Preparation of 2-*trans*-[3-(4-Fluoro-phenyl)-4-hydroxy-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide

[00623] **Example 069A** Step1: To THF (0.5 mL) were added 2M 4-fluorophenylmagnesium chloride in diethyl ether (0.23 mL, 0.46 mmol) and CuI (17.3 mg, 0.091 mmol) followed by dropwise addition of a solution of benzyl 6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate from Example 051A (100 mg, 0.46 mmol) in THF, and the mixture was stirred at rt for 2 h. Aq ammonium chloride was added, and the mixture was extracted with EtOAc. The organic layer was purified by chromatography to afford *trans*-phenyl 3-(4-fluorophenyl)-4-hydroxypyrrolidine-1-carboxylate.

[00624] **Example 069A** Step2: To a solution of *trans*-phenyl 3-(4-fluorophenyl)-4-hydroxypyrrolidine-1-carboxylate in MeOH (100 mg, 0.331 mmol) was added Pd(OH)₂ (30 mg) and the mixture was stirred under H₂ for 2 h, at which time completion of the reaction was confirmed by LCMS analysis. The mixture was filtered and the filtrate was concentrated to afford crude *trans*-4-(4-fluoro-phenyl)-pyrrolidin-3-ol.

[00625] **Example 069B** 2-*trans*-[3-(4-Fluoro-phenyl)-4-hydroxy-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide (29.14 mg, 40 %) was synthesized as its acetate salt using a procedure analogous to that described in Example 077C, substituting (*trans*-4-(4-

fluoro-phenyl)-pyrrolidin-3-ol for the *trans*-4-cyclopentyloxy-pyrrolidin-3-ol used in Example 077C. ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.68 (s, 1H), 10.07 (s, 1H), 7.82 (d, 2H), 7.60-7.57 (m, 3H), 7.40-7.35 (s, 3H), 6.58 (m, 1H), 5.65 (s, 1H), 4.05 (s, 1H), 3.50-3.00 (m, 5H), 2.70 (m, 2H), 2.05 (s, 3H), 1.98 (s, 3H); LCMS (ESI) *m/z* 559 (M+H)⁺.

Example 070

Preparation of N-(4-(4-(5-Methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3(R)-(3-(piperidin-1-yl)propoxy)pyrrolidin-1-yl)acetamide

[00626] **Example 070A:** To SOCl₂ (5 mL) at 0 °C was added dropwise 3-(piperidin-yl)propan-1-ol (0.50 g), and the mixture was allowed to stir at 60 °C for 12 h. The mixture was concentrated to dryness under reduced pressure, then the residue was partitioned between DCM (10 mL) and 10% aq Na₂CO₃ (10 mL). The organic layer was washed with water (10 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give 1-(3-chloropropyl)piperidine (0.41 g, 73% yield). LCMS (ESI) *m/z* 162,164(M+H)⁺.

[00627] **Example 070B:** A mixture of (R)-tert-butyl 3-hydroxypyrrolidine-1-carboxylate (100 mg) and 60% NaH (26mg) in DMF (1 mL) was stirred at 0 °C for 30 min, then a solution of 1-(3-chloropropyl)piperidine (111 mg) in DMF (1 mL) was added dropwise. The mixture was stirred at 0 °C for 2 h, and then at rt overnight. The mixture was partitioned between water (10 mL) and DCM (10 mL) at 0 °C, then the organic layer was washed with water (2 X 10 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure to afford crude (R)-tert-butyl 3-(3-(piperidin-1-yl)propoxy)pyrrolidine-1-carboxylate as a yellow oil (132 mg), which was used directly in the next step. LCMS (ESI) *m/z* 313 (M+H)⁺.

[00628] **Example 070C:** A mixture of (R)-tert-butyl 3-(3-(piperidin-1-yl)propoxy)pyrrolidine-1-carboxylate (132 mg) and 4M HCl (1 mL) in THF (2 mL) was stirred at rt for 4 h, at which time LCMS showed that the reaction was complete. Water (1 mL) was added, and the aqueous solution was washed with diethyl ether (2 X 2 mL) and concentrated under reduced pressure to give 1-(3-((R)-pyrrolidin-3-

ylthio)propyl)piperidine hydrochloride as a yellow oil (67 mg), which was used directly in the next step. LCMS (ESI) m/z 213 ($M+H$)⁺.

[00629] Example 070D: A mixture of 1-(3-((R)-pyrrolidin-3-ylthio)propyl)piperidine hydrochloride from the previous step (67 mg), 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 016B (55 mg), and Na₂CO₃ (55 mg) in DMF (1 mL) was stirred at rt overnight. The mixture was filtered and the filtrate was purified by Al₂O₃ column chromatography eluting with 100:1 to 10:1 DCM/MeOH to give a yellow powder (40 mg). Purification by preparative silica gel TLC eluting with 7:1 DCM/MeOH gave N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3(R)-(3-(piperidin-1-yl)propoxy)pyrrolidin-1-yl)acetamide as a pale yellow powder (20 mg, 24% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.49 (m, 2H), 1.70 (m, 5H), 1.89 (m, 2H), 2.04 (m, 4H), 2.64 (m, 1H), 2.73 (m, 1H), 2.80-2.98 (m, 6H), 3.20-3.40 (m, 6H), 4.04 (m, 1H), 5.63 (s, 1H), 6.58 (m, 1H), 7.23 (m, 1H), 7.58 (m, 3H), 7.78 (d, 2H), 10.16 (s, 1H), 10.66 (s, 1H), 12.14 (s, 1H); LCMS(ESI) m/z 590($M+H$)⁺.

Example 071

Preparation of 2-((*trans*-3-tert-Butoxy-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00630] 2-(*trans*-3-tert-butoxy-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was synthesized as a white solid (26.79 mg, 42 %) using a procedure analogous to that described in Example 013B, substituting *trans*-4-tert-butoxypyrrolidin-3-ol for the (S)-pyrrolidin-(2-yl)methanol used in Example 013B. ¹H NMR (300 MHz, CD₃OD) δ 7.75 (d, 2H), 7.50 (m, 2H), 7.35 (s, 1H), 6.80 (s, 1H), 6.50 (s, 1H), 5.65 (s, 1H), 3.90 (m, 2H), 3.20 (s, 2H), 3.05 (m, 1H), 2.70 (m, 1H), 2.55 (m, 1H), 2.35 (m, 1H), 1.65 (m, 1H), 0.80 (m, 2H), 0.40 (m, 2H); LCMS (ESI) m/z 563 ($M+H$)⁺.

Example 072

Preparation of 2-(*trans*-3-(2-Chlorophenoxy)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00631] To 2-(6-oxa-3-azabicyclo[3.1.0]hexan-3-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 068A (27 mg, 0.06 mmol) in DMF (1 mL) were added 2-chlorophenol (0.019 mL, 0.15 mmol) and cesium carbonate (57 mg, 0.17 mmol) and the mixture was heated at 100 °C in a microwave reactor for 20 min, then heated conventionally at 110 °C for 3 h, and then heated at 90 °C overnight. The mixture was purified by preparative HPLC (Varian diphenyl reverse phase column) eluting with a gradient of solvent B (0.05% HOAc/CH₃CN) in solvent A (0.05% HOAc/H₂O) to afford 2-(trans-3-(2-chlorophenoxy)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (3 mg, 8 %); ¹H NMR (300 MHz, CD₃OD) δ 2.13 (s, 3H), 2.8-2.9 (m, 2H), 3.14 (dd, 1H), 3.35-3.5 (m, 3H), 4.34 (m, 1H), 4.74 (m, 1H), 5.75 (s, 1H), 6.61 (m, 1H), 6.97 (m, 2H), 7.18 (d, 1H), 7.23 (t, 1H), 7.38 (dd, 1H), 7.38 (m, 1H) 7.62 (d, 2H), 7.79 (d, 2H); LCMS (ESI) m/z 591 (M + H)⁺.

Example 073

Preparation of 2-(trans-3-Hydroxy-4-(2-methylpentan-2-yloxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00632] **Example 073A:** *trans*-4-(2-Methylpentan-2-yloxy)pyrrolidin-3-ol was prepared using a procedure analogous to that described in Example 051B, substituting 2-methylpentan-2-ol for the tert-butanol used in Example 051B. LCMS(ESI) m/z 188 (M + H)⁺.

[00633] **Example 073B:** 2-(trans-3-Hydroxy-4-(2-methylpentan-2-yloxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was prepared using a procedure analogous to that described in Example 018B, substituting (3S,4S)-4-(2-methylpentan-2-yloxy)pyrrolidin-3-ol from Example 073A for the pyrrolidine derivative used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.08 (s, 1H), 10.63 (s, 1H), 9.98 (s, 1H), 7.79 (d, 2H), 7.59 (s, 1H), 7.58 (d, 2H), 7.22 (s, 1H), 6.58 (t, 1H), 5.63 (s, 1H), 5.02 (d, 1H), 3.88 (d, 2H), 3.27 (m, 2H), 3.05 (m, 1H), 2.78 (m, 1H), 2.57 (m, 1H), 2.38 (m, 1H), 2.03 (s, 3H), 1.45-1.15 (m, 6H), 1.10 (s, 6H), 0.86 (m, 3H); LCMS(ESI) m/z 565 (M + H)⁺.

Example 074**Preparation of 2-(*trans*-3-Hydroxy-4-(3-methylpentan-3-yloxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide**

[00634] **Example 074A:** *trans*-4-(3-Methylpentan-3-yloxy)pyrrolidin-3-ol was prepared using a procedure analogous to that described in Example 051B, substituting 3-methyl-3-pentanol for the tert-butanol used in Example 051B. LCMS (ESI) m/z 188 (M + H)⁺.

[00635] **Example 074B:** 2-(*trans*-3-Hydroxy-4-(3-methylpentan-3-yloxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was prepared using a procedure analogous to that described in Example 018B, substituting *trans*-4-(3-methylpentan-3-yloxy)pyrrolidin-3-ol from Example 074A for the pyrrolidine derivative used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.07 (s, 1H), 10.63 (s, 1H), 9.95 (s, 1H), 7.79 (d, 2H), 7.59 (s, 1H), 7.57 (d, 2H), 7.22 (s, 1H), 6.58 (m, 1H), 5.63 (s, 1H), 4.99 (d, 1H), 3.87 (d, 2H), 3.24 (dd, 2H), 3.06 (t, 1H), 2.75 (m, 1H), 2.59 (m, 1H), 2.36 (m, 1H), 2.03 (s, 3H), 1.42 (m, 4H), 1.05 (s, 3H), 0.81 (m, 6H); LCMS(ESI) m/z 565 (M + H)⁺.

Example 075**Preparation of 2-(3-tert-Butoxy-4-(hydroxyimino)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide**

[00636] **Example 075A:** To *trans*-benzyl 3-tert-butoxy-4-hydroxypyrrolidine-1-carboxylate prepared as an intermediate in Example 051B (543 mg, 1.85 mmol) in DCM (5 mL) was added Dess-Martin periodinane (1.18 g, 2.78 mmol) and the mixture was stirred at rt for 3 h. The mixture was partitioned between 1 N sodium hydroxide and DCM, and the separated organic layer was dried over sodium sulfate, filtered, and concentrated to yield crude benzyl 3-tert-butoxy-4-oxopyrrolidine-1-carboxylate (266 mg, 50%) which was used directly in the next step.

[00637] **Example 075B:** To benzyl 3-tert-butoxy-4-oxopyrrolidine-1-carboxylate (266 mg, 0.9 mmol) in ethanol (3 mL) was added 50% aq hydroxylamine (0.3 mL, 4.5 mmol) and the mixture was heated at 50 °C overnight. The mixture was purified by

preparative thin layer chromatography eluting with 0.1% TEA/10% MeOH in DCM; LCMS (ESI) m/z 329 ($M + Na$)⁺. To the product in MeOH (10 mL) was added palladium hydroxide (20 mg) and the mixture was stirred under a hydrogen atmosphere for 20 min and filtered. The filtrate was concentrated to afford crude 4-tert-butoxypyrrolidin-3-one oxime (55 mg, 35%) which was used directly in the next step; LCMS (ESI) m/z 173 ($M + Na$)⁺.

[00638] **Example 075C:** To 4-tert-butoxypyrrolidin-3-one oxime (55 mg, 0.31 mmol) in DMF (2 mL) were added diisopropylethylamine (0.081 mL, 0.46 mmol), potassium iodide (50 mg, 0.3 mmol), and 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (77 mg, 0.18 mmol). The mixture was heated at 50 °C for 1 h, then acetic acid (0.15 mL) and DMSO (2 mL) were added, and mixture was purified by preparative HPLC (Varian diphenyl reverse phase column) eluting with a gradient of solvent B (0.05% HOAc/CH₃CN) in solvent A (0.05% HOAc/H₂O) to afford 2-(3-tert-butoxy-4-(hydroxyimino)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (24 mg, 23%). ¹H NMR (300 MHz, CD₃OD) δ 1.30 (s, 9H), 2.13 (s, 3H), 2.85 (dd, 1H), 3.02 (dd, 1H), 3.35-3.5 (m, 3H), 3.64 (d, 1H), 4.67 (t, 1H), 5.74 (s, 1H), 6.60 (dd, 1H), 6.94 (d, 1H), 7.47 (m, 1H), 7.62 (d, 2H), 7.79 (d, 2H); LCMS (ESI) m/z 550 ($M + H$)⁺.

Example 076

Preparation of 2-((*trans*-3-tert-Butoxy-4-(2-hydroxyethoxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00639] **Example 076A:** To a stirring suspension of 60% NaH/mineral oil (25 mg, 0.625 mmol) in DMF (3 mL) at rt was added a solution of *trans*-benzyl 3-tert-butoxy-4-hydroxypyrrolidine-1-carboxylate from Example 051B (150 mg, 0.51 mmol) in DMF (1 mL). After 15 min, ethyl bromoacetate (63 μ L, 0.56 mmol) was added, and the mixture was stirred at rt for 2 h, then partitioned between EtOAc (20 mL) and water (15 mL). The organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 30% EtOAc/hexanes to give *trans*-benzyl 3-tert-butoxy-

4-(2-ethoxy-2-oxoethoxy)pyrrolidine-1-carboxylate as a colorless oil (88 mg, 45% yield). LCMS(ESI) m/z 380 ($M + H$)⁺.

[00640] Example 076B Step 1: To a stirring mixture of *trans*-benzyl 3-tert-butoxy-4-(2-ethoxy-2-oxoethoxy)pyrrolidine-1-carboxylate from Example 076A (87 mg, 0.23 mmol) in THF (1 mL) at rt was added LiBH₄ (20 mg, 0.92 mmol). After 6 h, the saturated aq NH₄Cl (1 mL) was added, and the mixture was extracted with EtOAc (20 mL). The organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 30% EtOAc/hexanes to give *trans*-benzyl 3-tert-butoxy-4-(2-hydroxyethoxy)pyrrolidine-1-carboxylate as colorless oil (55 mg).

[00641] Example 076B Step 2: To *trans*-benzyl 3-tert-butoxy-4-(2-hydroxyethoxy)pyrrolidine-1-carboxylate (55 mg) in MeOH (1 mL) under Ar was added 10% Pd/C (15 mg), and the mixture was stirred under a hydrogen atmosphere at rt for 2 h. The mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to give 2-(*trans*-4-tert-butoxypyrrolidin-3-yloxy)ethanol as a colorless oil (40 mg, 85% yield over two steps). LCMS (ESI) m/z 204 ($M + H$)⁺.

[00642] Example 076C: 2-((*trans*-3-tert-Butoxy-4-(2-hydroxyethoxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was prepared using a procedure analogous to that described in Example 018B, substituting 2-(*trans*-4-tert-butoxypyrrolidin-3-yloxy)ethanol from Example 076B for the pyrrolidine derivative used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.07 (s, 1H), 10.63 (s, 1H), 10.01 (s, 1H), 7.78 (d, 2H), 7.58 (s, 1H), 7.57 (d, 2H), 7.21 (s, 1H), 6.59 (d, 1H), 5.63 (s, 1H), 4.58 (d, 1H), 4.03 (d, 1H), 3.77 (s, 1H), 3.46 (m, 4H), 3.24 (s, 2H), 3.04 (m, 3H), 2.82 (m, 1H), 2.68 (m, 1H), 2.43 (m, 1H), 2.03 (s, 3H), 1.20 (s, 9H); LCMS (ESI) m/z 581 ($M + H$)⁺.

Example 077

Preparation of 2-(*trans*-3-Cyclopentyloxy-4-hydroxy-pyrrolidin-1-yl)-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide

[00643] **Example 077A:** To benzyl 6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate from Example 051A (100mg, 0.456 mmol) in DCM (12 mL) were added cyclopentanol (0.5 mL) and (C₆F₅)₃B (20 mg). The reaction vessel was sealed and the mixture was heated at 100 °C for 15 h, at which time formation of the product was confirmed by LCMS. The mixture was concentrated under reduced pressure and the residue was dissolved in MeOH. Pd(OH)₂ (20 mg) was added, and the mixture was stirred under H₂ for 2 h, at which time completion of the reaction was confirmed by LCMS. The mixture was filtered and the filtrate was concentrated under reduced pressure to give crude *trans*-4-cyclopentyloxy-pyrrolidin-3-ol which was used directly in the next step.

[00644] **Example 077B:** To a solution of 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 016B (50 mg, 0.121 mmol) in DMF (3 mL) were added *trans*-4-cyclopentyloxy-pyrrolidin-3-ol (41.4 mg, 0.242 mmol), diisopropylethylamine (84.3 µL, 0.484 mmol), and potassium iodide (20.1 mg, 0.125 mmol), and the mixture was heated at 50 °C for 12 h, at which time formation of product was determined by LCMS. The mixture was purified by preparative HPLC (phenomenex phenylhexyl reverse phase column) eluting with a gradient of solvent B (0.05% HOAc/CH₃CN) in solvent A (0.05% HOAc/H₂O) to afford 2-(*trans*-3-(cyclopentyloxy)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (28.4 mg, 43%) as a white solid. ¹H NMR (300 MHz, CD₃OD) δ 7.65 (d, 2H), 7.45 (d, 2H), 7.30 (s, 1H), 6.80 (s, 1H), 6.45 (s, 1H), 5.65 (s, 1H), 4.10 (s, 1H), 4.00 (s, 1H), 3.85 (s, 1H), 3.20 (m, 3H), 3.00 (m, 1H), 2.50-2.75 (m, 2H), 2.05 (s, 3H), 1.90 (s, 3H), 1.80-1.30 (m, 8H); LCMS (ESI) *m/z* 549 (M+H)⁺.

Example 078

Preparation of 2-[*trans*-3-Hydroxy-4-(1-methyl-cyclopentyloxy)-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide

[00645] **Example 078A:** *trans*-4-(1-Methyl-cyclopentyloxy)-pyrrolidin-3-ol was prepared using a procedure analogous to that described in Example 077A, substituting 1-methylcyclopentanol for the cyclopentanol used in Example 077A.

[00646] **Example 078B:** 2-[*trans*-3-Hydroxy-4-(1-methyl-cyclopentyloxy)-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide was synthesized as a white solid (10.55 mg, 15 %) using a procedure analogous to that described in Example 077B, substituting *trans*-4-(1-methyl-cyclopentyloxy)-pyrrolidin-3-ol for the *trans*-4-cyclopentyloxy-pyrrolidin-3-ol used in Example 077B. ¹H NMR (300 MHz, CD₃OD) δ 7.70 (d, 2H), 7.50 (d, 2H), 7.35 (s, 1H), 6.80 (s, 1H), 6.45 (s, 1H), 5.65 (s, 1H), 3.95 (s, 1H), 3.85 (s, 1H), 3.25 (s, 2H), 3.10 (m, 1H), 2.85 (s, 1H), 2.60 (m, 1H), 2.40 (m, 1H), 2.05 (s, 3H), 1.75-1.30 (m, 8H), 1.15 (s, 3H); LCMS (ESI) *m/z* 563 (M+H)⁺.

Example 079

Preparation of 2-[*trans*-3-(2,2-Dimethyl-propoxy)-4-hydroxy-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide

[00647] **Example 079A:** *trans*-4-(2,2-Dimethyl-propoxy)-pyrrolidin-3-ol was prepared using a procedure analogous to that described in Example 077A, substituting 2,2-dimethylpropan-1-ol for the cyclopentanol used in Example 077A.

[00648] **Example 079B:** 2-[*trans*-3-(2,2-Dimethyl-propoxy)-4-hydroxy-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide was synthesized as a white solid (27.53 mg, 41 %) using a procedure analogous to that described in Example 077B, substituting *trans*-4-(2,2-dimethyl-propoxy)-pyrrolidin-3-ol for the *trans*-4-cyclopentyloxy-pyrrolidin-3-ol used in Example 077B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.70 (s, 1H), 10.18 (s, 1H), 7.78 (d, 2H), 7.60 (d, 3H), 7.24 (s, 1H), 6.59 (s, 1H), 5.64 (s, 1H), 4.05 (m, 1H), 3.74 (m, 1H), 3.48-3.35 (s, 2H), 3.19-2.90 (m, 4H), 2.05 (s, 3H), 0.95 (s, 9H); LCMS (ESI) *m/z* 551 (M+H)⁺.

Example 080

Preparation of 2-[*trans*-3-Hydroxy-4-(tetrahydro-furan-3-yloxy)-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide

[00649] **Example 080A:** *trans*-4-(Tetrahydro-furan-3-yloxy)-pyrrolidin-3-ol was prepared using a procedure analogous to that described in Example 077A, substituting (S)-tetrahydrofuran-3-ol for the cyclopentanol used in Example 077A.

[00650] **Example 080B:** 2-[*trans*-3-Hydroxy-4-(2-methoxy-1,1-dimethyl-ethoxy)-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide was synthesized as a white solid (24.51 mg, 36 %) using a procedure analogous to that described in Example 077B, substituting *trans*-4-(tetrahydro-furan-3-yloxy)-pyrrolidin-3-ol for the *trans*-4-cyclopentyloxy-pyrrolidin-3-ol used in Example 077B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.10 (s, 1H), 10.60 (s, 1H), 10.00 (s, 1H), 7.75 (d, 2H), 7.55 (d, 3H), 7.15 (s, 1H), 6.55 (s, 1H), 5.55 (s, 1H), 5.15 (d, 1H), 4.20 (s, 1H), 3.95 (s, 1H), 3.85-3.50 (m, 5H), 3.30 (s, 2H), 3.25-3.15 (m, 2H), 3.10 (m, 1H), 2.85 (s, 1H), 2.05 (s, 3H), 1.95-1.75 (m, 2H); LCMS (ESI) *m/z* 551 (M+H)⁺.

Example 081

Preparation of 2-[*trans*-3-Hydroxy-4-(2-methoxy-1,1-dimethyl-ethoxy)-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide

[00651] **Example 081A:** *trans*-4-(2-Methoxy-1,1-dimethyl-ethoxy)-pyrrolidin-3-ol was prepared using a procedure analogous to that described in Example 077A, substituting 1-methoxy-2-methylpropan-2-ol for the cyclopentanol used in Example 077A.

[00652] **Example 081B:** 2-[*trans*-3-Hydroxy-4-(2-methoxy-1,1-dimethyl-ethoxy)-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide was synthesized as a white solid (23.54 mg, 34 %) using a procedure analogous to that described in Example 077B, substituting *trans*-4-(2-methoxy-1,1-dimethyl-ethoxy)-pyrrolidin-3-ol for the *trans*-4-cyclopentyloxy-pyrrolidin-3-ol used in Example 77B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.09 (s, 1H), 10.64 (s, 1H), 9.99 (s, 1H), 7.80 (d, 2H), 7.58 (d, 3H), 7.23 (s, 1H), 6.58 (s, 1H), 5.63 (s, 1H), 5.02 (d, 1H), 3.97 (s, 1H), 3.88 (s, 1H), 3.31 (s, 3H), 3.22 (s, 2H), 3.18 (s, 2H), 3.02 (m, 1H), 2.78 (m, 1H), 2.56 (m, 1H), 2.38 (m, 1H), 2.04 (s, 3H), 1.12 (s, 3H), 1.11 (s, 3H); LCMS (ESI) *m/z* 567 (M+H)⁺.

Example 082

Preparation of 2-[*trans*-3-Hydroxy-4-(3-methoxy-propoxy)-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide

[00653] **Example 082A:** *trans*-4-(3-Methoxy-propoxy)-pyrrolidin-3-ol was prepared using a procedure analogous to that described in Example 077A, substituting 3-methoxypropan-1-ol for the cyclopentanol used in Example 077A.

[00654] **Example 082B:** 2-[*trans*-3-Hydroxy-4-(3-methoxy-propoxy)-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide was synthesized as a white solid (23.54 mg, 35 %) using a procedure analogous to that described in Example 077B, substituting *trans*-4-(3-methoxy-propoxy)-pyrrolidin-3-ol for the *trans*-4-cyclopentyloxy-pyrrolidin-3-ol used in Example 77B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.10 (s, 1H), 10.64 (s, 1H), 10.05 (s, 1H), 7.80 (d, 2H), 7.58 (d, 3H), 7.23 (s, 1H), 6.58 (t, 1H), 5.64 (s, 1H), 5.16 (d, 1H), 4.00 (m, 1H), 3.72 (m, 1H), 3.40-3.20 (m, 9H), 3.03 (m, 1H), 2.88 (m, 1H), 2.54 (m, 2H), 2.04 (s, 3H), 1.75 (s, 2H); LCMS (ESI) *m/z* 551 (M-H)⁺.

Example 083

Preparation of 2-((2*S*,4*R*)-2-(Hydroxymethyl)-4-(1-methylcyclobutoxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00655] **Example 083A** To methyl (2*S*,4*R*)-1-benzyloxycarbonyl-4-hydroxypyrrolidine-2-carboxylate (4.9 g, 17.54 mmol) in THF (100 mL) at 0 °C under Ar was added lithium borohydride (1.53 g, 70.16 mmol). The mixture was allowed to stir at 0 °C then warm to rt and stir for 2 days. The mixture was concentrated under reduced pressure to give a residue (4.4 g) containing (2*S*,4*R*)-benzyl 4-hydroxy-2-(hydroxymethyl)pyrrolidine-1-carboxylate. LCMS (ESI) *m/z* 252 (M + H)⁺. To the residue in DMF (120 mL) under Ar were added imidazole (1.3 g, 19.3 mmol) and *t*-butyldiphenylchlorosilane (4.89 mL, 21.0 mmol) and the mixture was stirred at rt for 24 h, at which time more imidazole (1.79 g, 26.3 mmol) and *t*-butyldiphenylchlorosilane (4.48 mL, 17.5 mmol) were added, and stirring was continued at rt overnight. Additional imidazole (650 mg) and *t*-butyldiphenylchlorosilane (2.44 mL) were added. LCMS (ESI) *m/z* 252 (M + H)⁺. After a period of continued stirring, the mixture was partitioned between EtOAc (400

mL) and water (200 mL), and the separated EtOAc layer was dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 6% to 50% EtOAc/hexanes to afford (2S,4R)-benzyl 2-((tert-butyldiphenylsilyloxy)methyl)-4-hydroxypyrrolidine-1-carboxylate (2.66 g, 5.43 mmol, 31%). ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 7.54-7.58 (m, 4H), 7.35-7.45 (m, 8H), 7.13-7.25 (m, 3H), 4.92-5.06 (m, 3H), 4.35 (s, 1H), 3.95-4.04 (m, 2H), 3.69-3.73 (m, 1H), 3.41 (d, 2H), 2.14-2.18 (m, 1H), 1.99 (s, 1H), 1.05 (br, s, 9H); LCMS (ESI) m/z 490 ($\text{M} + \text{H}$) $^+$.

[00656] Example 083B: To (2S,4R)-benzyl 2-((tert-butyldiphenylsilyloxy)methyl)-4-hydroxypyrrolidine-1-carboxylate (500 mg, 1.02 mmol) and methylenecyclobutane (0.28 mL, 3.06 mmol) in DCM (9 mL) in a pressure vessel under Ar was added boron trifluoride-etherate (38.5 μL , 0.31 mmol) and the mixture was stirred at rt overnight. The mixture was partitioned between saturated aq sodium bicarbonate and EtOAc and the organic layer was dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 6% to 50% EtOAc/hexanes to afford (2S,4R)-benzyl 2-((tert-butyldiphenylsilyloxy)methyl)-4-(1-methylcyclobutoxy)pyrrolidine-1-carboxylate (60.0 mg, 0.11 mmol, 11%). LCMS (ESI) m/z 558 ($\text{M} + \text{H}$) $^+$.

[00657] Example 083C: To (2S,4R)-benzyl 2-((tert-butyldiphenylsilyloxy)methyl)-4-(1-methylcyclobutoxy)pyrrolidine-1-carboxylate (55 mg, 0.098 mmol) in THF (1.0 mL) was added tetrabutylammonium fluoride (28.55 μL , 0.098 mmol) and the mixture was stirred at rt for 2.5 days. The mixture was partitioned between EtOAc (15 mL) and water (5 mL), and the separated EtOAc layer was dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude (2S,4R)-benzyl 2-(hydroxymethyl)-4-(1-methylcyclobutoxy)pyrrolidine-1-carboxylate (42 mg, 0.13 mmol) was used directly in the next step. LCMS (ESI) m/z 320 ($\text{M} + \text{H}$) $^+$.

[00658] Example 083D: To (2S,4R)-benzyl 2-(hydroxymethyl)-4-(1-methylcyclobutoxy)pyrrolidine-1-carboxylate (42 mg, 0.13 mmol) under Ar were added 10% Pd/C (~40 mg) and MeOH (1 mL), and the mixture was stirred under an atmosphere of H_2 overnight. The mixture was filtered and the filtrate was

concentrated under reduced pressure. The crude ((2S,4R)-4-(1-methylcyclobutoxy)pyrrolidin-2-yl)methanol (33.2 mg, 0.18 mmol) was used directly in the next step. LCMS (ESI) m/z 186 (M + H)⁺.

[00659] Example 083F: 2-((2S,4R)-2-(hydroxymethyl)-4-(1-methylcyclobutoxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (8.1 mg, 16 %) was synthesized using a procedure analogous to that described in Example 018B, substituting ((2S,4R)-4-(1-methylcyclobutoxy)pyrrolidin-2-yl)methanol from the previous step for the pyrrolidine derivative used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.1 (s, 1H), 10.65 (s, 1H), 9.98 (s, 1H), 7.78 (d, 2H), 7.56-7.78 (m, 3H), 7.2 (s, 1H), 6.65 (s, 1H), 5.55 (s, 1H), 4.65 (br s, 1H), 3.98-4.05 (m, 2H), 3.50-3.60 (m, 1H), 3.17 (s, 2H), 2.80 (s, 1H), 2.42 (t, 1H), 2.02 (br s, 3H), 1.77-1.83 (m, 7H), 1.28 (br s, 4H); LCMS (ESI) m/z 561 (M-H)⁺.

Example 084

Preparation of 2-[*trans*-3-Hydroxy-4-(2-methoxyethoxy)-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide

[00660] Example 084A: *trans*-4-(2-Methoxyethoxy)-pyrrolidin-3-ol was prepared using a procedure analogous to that described in Example 077A, substituting 2-methoxyethanol for the cyclopentanol used in Example 077A.

[00661] Example 084B: 2-[*trans*-3-Hydroxy-4-(2-methoxyethoxy)-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide was synthesized as a white solid (28.4 mg, 44 %) using a procedure analogous to that described in Example 077B, substituting *trans*-4-(2-methoxyethoxy)-pyrrolidin-3-ol for the *trans*-4-cyclopentyloxy-pyrrolidin-3-ol used in Example 077B. ¹H NMR (300 MHz, CD₃OD) δ 7.65 (d, 2H), 7.40 (d, 2H), 7.25 (s, 1H), 6.75 (s, 1H), 6.40 (s, 1H), 5.60 (s, 1H), 4.10 (s, 1H), 3.70 (s, 1H), 3.60-3.15 (m, 9H), 3.10-2.80 (m, 2H), 2.70-2.40 (m, 2H), 2.05 (s, 3H); LCMS (ESI) m/z 539 (M+H)⁺.

Example 085

Preparation of 2-[*trans*-3-(1,1-Dimethyl-propoxy)-4-hydroxy-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide

[00662] **Example 085A:** *Trans*-4-(1,1-dimethyl-propoxy)-pyrrolidin-3-ol was prepared using a procedure analogous to that described in Example 077A, substituting 2-methylbutan-2-ol for the cyclopentanol used in Example 077A.

[00663] **Example 085B:** 2-[*trans*-3-(1,1-Dimethyl-propoxy)-4-hydroxy-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide was synthesized as a white solid (19.57 mg, 29 %) using a procedure analogous to that described in Example 077B, substituting *trans*-4-(1,1-dimethyl-propoxy)-pyrrolidin-3-ol for the *trans*-4-cyclopentyloxy-pyrrolidin-3-ol used in Example 077B. ¹H NMR (300 MHz, CD₃OD) δ 7.68 (d, 2H), 7.50 (d, 2H), 7.36 (m, 1H), 6.84 (d, 1H), 6.49 (m, 1H), 5.64 (s, 1H), 3.96-3.90 (m, 2H), 3.23 (s, 2H), 3.12-3.07 (m, 1H), 2.84-2.79 (m, 1H), 2.61-2.57 (m, 1H), 2.38-2.33 (m, 1H), 2.02 (s, 3H), 1.44 (q, 2H), 1.14 (s, 3H), 1.07 (s, 3H), 0.79 (t, 3H); LCMS (ESI) *m/z* 551 (M+H)⁺.

Example 086

Preparation of 2-(*trans*-3-(2,6-Dichlorophenoxy)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00664] 2-[*trans*-3-(1,1-Dimethyl-propoxy)-4-hydroxy-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide was prepared using a procedure analogous to that described in Example 072, substituting 2,6-dichlorophenol for the 2-chlorophenol used in Example 072. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.06 (s, 1H), 10.63 (s, 1H), 9.99 (s, 1H), 7.78 (d, 2H), 7.60 (s, 1H), 7.58 (d, 2H), 7.52 (d, 2H), 7.21 (s, 1H), 7.18 (m, 1H), 6.58 (m, 1H), 5.63 (s, 1H), 5.26 (d, 1H), 4.65 (s, 1H), 4.37 (s, 1H), 3.36 (m, 2H), 3.16 (m, 2H), 2.94 (m, 1H), 2.65 (m, 1H), 2.03 (s, 3H); LCMS(ESI) *m/z* 625, 627, 629 (M + H)⁺.

Example 087

Preparation of 2-(*trans*-4-tert-Butoxy-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(3-fluoro-4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00665] **Example 087A:** 2-Chloro-N-(3-fluoro-4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was prepared using a procedure analogous to that described in Examples 016A-016B, substituting 4-amino-2-fluorobenzenethiol(prepared according to Hansch, *et al. J. Org. Chem.* 1956, 21, 265-269 for the 4-aminobenzenethiol used in Example 016A. LCMS (ESI) *m/z* 432, 434 (M + H)⁺.

[00666] **Example 087B:** 2-(*trans*-3-(2,6-Dichlorophenoxy)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was prepared using a procedure analogous to that described in Example 018B, substituting 2-chloro-N-(3-fluoro-4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 087A for the 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.10 (s, 1H), 10.69 (s, 1H), 10.15 (s, 1H), 7.81 (d, 1H), 7.61 (m, 3H), 7.24 (s, 1H), 6.60 (m, 1H), 5.58 (s, 1H), 4.69 (m, 1H), 4.20 (m, 1H), 3.62 (d, 1H), 3.39 (m, 2H), 3.23 (m, 2H), 2.87 (m, 1H), 2.36 (m, 1H), 2.03 (s, 3H), 1.87 (m, 1H), 1.70 (m, 1H), 1.12 (s, 9H); LCMS(ESI) *m/z* 569 (M + H)⁺.

Example 088

Preparation of 2-[*trans*-3-Hydroxy-4-(2,2,2-trifluoro-ethoxy)-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide

[00667] **Example 088A:** To benzyl 6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate from Example 051A (50 mg, 0.228 mmol) in DMF (1 mL) were added 2,2,2-trifluoroethanol (0.3 mL) and Cs₂CO₃ (111.46 mg, 0.342 mmol). The mixture was heated in a microwave reactor at 120°C for 20 min, at which time formation of the product was determined by LCMS. The mixture was diluted with EtOAc and washed with water and brine and concentrated to dryness. To the residue in MeOH was added Pd(OH)₂ (20 mg) and the mixture was stirred under H₂ for 2 h, at which time completion of the reaction was confirmed by LCMS. The mixture was filtered through Celite and the filtrate was concentrated to afford crude *trans*-4-(2,2,2-trifluoro-ethoxy)-pyrrolidin-3-ol which was used in next step without further purification.

[00668] **Example 088B:** 2-[*trans*-3-Hydroxy-4-(2,2,2-trifluoro-ethoxy)-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide was synthesized as a white solid (19.57 mg, 29 %) using a procedure analogous to that described in Example 077B, substituting *trans*-4-(2,2,2-trifluoro-ethoxy)-pyrrolidin-3-ol for the *trans*-4-cyclopentyloxy-pyrrolidin-3-ol used in Example 077B. ¹H NMR (300 MHz, CD₃OD) δ 7.66 (d, 2H), 7.49 (d, 2H), 7.35 (d, 1H), 6.83 (d, 1H), 6.49 (m, 1H), 5.65 (s, 1H), 4.13 (m, 1H), 4.02-3.86 (m, 3H), 3.40-3.15 (m, 4H), 2.93-2.87 (m, 1H), 2.68-2.56 (m, 2H), 2.05 (s, 3H); LCMS (ESI) *m/z* 563 (M+H)⁺.

Example 089

Preparation of 2-(*trans*-3-Cyclopropylmethoxy-4-hydroxy-pyrrolidin-1-yl)-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide

[00669] **Example 089A:** *trans*-4-Cyclopropylmethoxy-pyrrolidin-3-ol was prepared using a procedure analogous to that described in Example 077A, substituting cyclopropylmethanol for the cyclopentanol used in Example 077A.

[00670] **Example 089B:** 2-(*trans*-3-Cyclopropylmethoxy-4-hydroxy-pyrrolidin-1-yl)-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide was synthesized as a white solid (24.6 mg, 38 %) using a procedure analogous to that described in Example 077B, substituting *trans*-4-cyclopropylmethoxy-pyrrolidin-3-ol for the *trans*-4-cyclopentyloxy-pyrrolidin-3-ol used in Example 077B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.90 (s, 1H), 10.46 (s, 1H), 9.83 (s, 1H), 7.60 (d, 2H), 7.41 (d, 3H), 7.05 (s, 1H), 6.40 (m, 1H), 5.46 (s, 1H), 4.94 (d, 1H), 3.83 (m, 1H), 3.59 (m, 1H), 3.12-3.02 (m, 4H), 2.88-2.82 (m, 1H), 2.73-2.68 (m, 1H), 2.40-2.35 (m, 2H), 1.90 (s, 3H), 0.86-0.78 (m, 1H), 0.31-0.26 (m, 2H), 0.01-0.03 (m, 2H); LCMS (ESI) *m/z* 535 (M+H)⁺.

Example 090

Preparation of 2-[*trans*-3-Hydroxy-4-(tetrahydro-furan-3-yloxy)-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide

[00671] **Example 090A:** *trans*-4-(Tetrahydro-furan-3-yloxy)-pyrrolidin-3-ol was prepared using a procedure analogous to that described in Example 077A, substituting (R)-tetrahydrofuran-3-ol for the cyclopentanol used in Example 077A.

[00672] **Example 090B:** 2-[*trans*-3-Hydroxy-4-(tetrahydro-furan-3-yloxy)-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide was synthesized as a white solid (29.88 mg, 45 %) using a procedure analogous to that described in Example 077B, substituting 4-(tetrahydro-furan-3-yloxy)-pyrrolidin-3-ol for the 4-cyclopentyloxy-pyrrolidin-3-ol used in Example 077B. ¹H NMR (300 MHz, CD₃OD) δ 7.75 (d, 2H), 7.58 (d, 2H), 7.44 (m, 1H), 6.91 (d, 1H), 6.57 (m, 1H), 5.73 (s, 1H), 4.31 (m, 1H), 4.16 (m, 1H), 3.92-3.71 (m, 5H), 3.37 (s, 2H), 3.20 (m, 1H), 2.98-2.93 (m, 1H), 2.72-2.68 (m, 1H), 2.59-2.55 (m, 1H), 2.08 (s, 3H), 2.01-1.96 (m, 1H); LCMS (ESI) *m/z* 551 (M+H)⁺.

Example 091

Preparation of 2-(*trans*-3-tert-Butoxy-4-hydroxypyrrolidin-1-yl)-N-(3-fluoro-4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00673] 2-(*trans*-3-tert-butoxy-4-hydroxypyrrolidin-1-yl)-N-(3-fluoro-4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was prepared using a procedure analogous to that described in Example 018B, substituting 2-chloro-N-(3-fluoro-4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 087A for the 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.10 (s, 1H), 10.69 (s, 1H), 10.15 (s, 1H), 7.81 (d, 1H), 7.61 (m, 3H), 7.24 (s, 1H), 6.60 (m, 1H), 5.58 (s, 1H), 5.01 (s, 1H), 3.75 (m, 2H), 3.50 (m, 4H), 3.20-2.80 (m, 2H), 2.78 (s, 1H), 2.55 (m, 1H), 2.40 (m, 1H), 2.02 (s, 3H), 1.12 (s, 9H); LCMS(ESI) *m/z* 555 (M + H)⁺.

Example 092

Preparation of 2-(*trans*-3-Hydroxy-4-isopropoxy-pyrrolidin-1-yl)-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide

[00674] **Example 092A:** *trans*-4-Isopropoxy-pyrrolidin-3-ol was prepared using a procedure analogous to that described in Example 077A, substituting propan-2-ol for the cyclopentanol used in Example 077A.

[00675] **Example 092B:** 2-[(*trans*-3-Hydroxy-4-isopropoxy-pyrrolidin-1-yl)-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide was synthesized as a white solid (38.98 mg, 62 %) using a procedure analogous to that described in Example 077B, substituting *trans*-4-isopropoxy-pyrrolidin-3-ol for the *trans*-4-cyclopentyloxy-pyrrolidin-3-ol used in Example 077B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.18 (s, 1H), 10.66 (s, 1H), 10.23 (s, 1H), 7.84 (d, 2H), 7.59 (m, 3H), 7.25 (s, 1H), 6.58 (m, 1H), 5.63 (s, 1H), 5.20 (d, 1H), 3.94 (m, 1H), 3.72 (m, 1H), 3.40 (s, 2H), 3.07-3.01 (m, 1H), 2.87-2.82 (m, 1H), 2.46-2.41 (m, 2H), 2.05 (s, 3H), 1.12 (t, 6H); LCMS (ESI) *m/z* 523 (M+H)⁺.

Example 093

Preparation of 2-[(*trans*-3-Hydroxy-4-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-pyrrolidin-1-yl)-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide

[00676] **Example 093A:** *trans*-4-(2,2,2-Trifluoro-1,1-dimethyl-ethoxy)-pyrrolidin-3-ol was prepared using a procedure analogous to that described in Example 088A, substituting 1,1,1-trifluoro-2-methylpropan-2-ol for 2,2,2-trifluoroethanol and substituting NMP for the DMF used in Example 088A.

[00677] **Example 093B:** 2-[(*trans*-3-Hydroxy-4-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-pyrrolidin-1-yl)-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide was synthesized as a white solid (20.11 mg, 40 %) using a procedure analogous to that described in Example 077B, substituting *trans*-4-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-pyrrolidin-3-ol for the *trans*-4-cyclopentyloxy-pyrrolidin-3-ol used in Example 077B. ¹H NMR (300 MHz, CD₃OD) δ 7.65 (d, 2H), 7.49 (d, 2H), 7.34 (m, 1H), 6.82 (d, 1H), 6.48 (m, 1H), 5.64 (s, 1H), 4.12 (m, 1H), 4.01 (m, 1H), 3.31 (s, 2H), 3.17-3.14 (m, 1H), 2.87-2.79 (m, 1H), 2.68-2.64 (m, 1H), 2.46-2.41 (m, 1H), 2.02 (s, 3H), 1.20 (s, 6H); LCMS (ESI) *m/z* 591 (M+H)⁺.

Example 094**Preparation of 2-(*trans*-3-*tert*-Butoxy-4-(2-methoxyethoxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide**

[00678] **Example 094A Step 1:** To a stirring suspension of 60% NaH/mineral oil (25 mg, 0.625 mmol) in DMF (3 mL) at rt was added a solution of *trans*-benzyl 3-*tert*-butoxy-4-hydroxypyrrolidine-1-carboxylate from Example 051A (150 mg, 0.51 mmol) in DMF (1 mL). After 15 min, 2-chloroethyl methyl ether (51 μ L, 0.56 mmol) was added, and the mixture was stirred at rt overnight. The mixture was partitioned between EtOAc (20 mL) and water (15 mL), and then the organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 0-30% EtOAc/hexanes to give *trans*-benzyl 3-*tert*-butoxy-4-(2-methoxyethoxy)pyrrolidine-1-carboxylate as a colorless oil.

[00679] **Example 094A Step 2:** To *trans*-benzyl 3-*tert*-butoxy-4-(2-methoxyethoxy)pyrrolidine-1-carboxylate (50 mg) in MeOH (1 mL) under Ar was added 10% Pd/C (15 mg), and the mixture was stirred under a hydrogen atmosphere at rt for 2 h. The mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to give *trans*-3-*tert*-butoxy-4-(2-methoxyethoxy)pyrrolidine as a colorless oil (45 mg, 41% yield over two steps). LCMS (ESI) m/z 218 (M + H)⁺.

[00680] **Example 094B:** 2-(*trans*-3-*tert*-butoxy-4-(2-methoxyethoxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was prepared using a procedure analogous to that described in Example 018B, substituting *trans*-3-*tert*-butoxy-4-(2-methoxyethoxy)pyrrolidine from Example 094A for the pyrrolidine derivative used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.07 (s, 1H), 10.63 (s, 1H), 10.01 (s, 1H), 7.77 (d, 2H), 7.59 (s, 1H), 7.57 (d, 2H), 7.22 (s, 1H), 6.58 (m, 1H), 5.63 (s, 1H), 4.04 (s, 1H), 3.78 (d, 1H), 3.53 (m, 2H), 3.44 (m, 2H), 3.24 (s, 3H), 3.02 (m, 2H), 2.03 (s, 3H), 2.80 (m, 1H), 2.67 (m, 1H), 2.39 (m, 1H), 1.10 (s, 9H); LCMS (ESI) m/z 595 (M + H)⁺.

Example 095**Preparation of N-(4-(4-(5-Methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-pivaloylpyrrolidin-1-yl)acetamide**

[00681] **Example 095A Step 1:** To a stirring solution of ethyl 1-benzylpyrrolidine-3-carboxylate in THF at -78 °C under Ar was added dropwise 1.7 M t-butyllithium (1.0 mL), and the mixture was kept at -78 °C for 30 min then allowed to warm to rt. After an additional 90 min, the mixture was treated with saturated aq NH₄Cl (5 mL) and extracted with EtOAc (50 mL). The organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 30-60% EtOA/hexanes to give N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-pivaloylpyrrolidin-1-yl)acetamide as a colorless oil (200 mg, 48% yield).

[00682] **Example 095A Step 2:** To (1-(1-Benzylpyrrolidin-3-yl)-2,2-dimethylpropan-1-one (210 mg, 0.86 mmol) in MeOH (1 mL) under Ar was added 10% Pd/C (35 mg), and the mixture was stirred under a hydrogen atmosphere at 60 °C for 2 h. The mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to give 2,2-dimethyl-1-(pyrrolidin-3-yl)propan-1-one as a colorless oil (120 mg, 90% yield). LCMS (ESI) *m/z* 156 (M + H)⁺.

[00683] **Example 095B:** N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-pivaloylpyrrolidin-1-yl)acetamide was prepared using a procedure analogous to that described in Example 018B, substituting 2,2-dimethyl-1-(pyrrolidin-3-yl)propan-1-one from Example 095A for the pyrrolidine derivative used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.08 (s, 1H), 10.63 (s, 1H), 10.08 (s, 1H), 7.81 (d, 2H), 7.59 (s, 1H), 7.57 (d, 2H), 7.22 (s, 1H), 6.58 (m, 1H), 5.63 (s, 1H), 3.65 (m, 1H), 3.30 (m, 2H), 2.91 (m, 2H), 2.56 (m, 2H), 2.02 (s, 3H), 2.00 (m, 1H), 1.78 (m, 1H), 1.08 (s, 9H); LCMS (ESI) *m/z* 533 (M + H)⁺.

Example 096

Preparation of N-(4-(4-(5-Methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(pyrrolidine-1-carbonyl)pyrrolidin-1-yl)acetamide

[00684] **Example 096A Step 1:** A mixture of ethyl 1-benzylpyrrolidine-3-carboxylate (150 mg, 0.64 mmol) and 1 mL of pyrrolidine was heated in a sealed tube

at 130 °C for 24 h. The mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography eluting with 100% EtOAc to give (1-benzylpyrrolidin-3-yl)(pyrrolidin-1-yl)methanone as a light yellow oil (65 mg, 39 % yield).

[00685] Example 096A Step 2: To (1-Benzylpyrrolidin-3-yl)(pyrrolidin-1-yl)methanone (65 mg, 0.25 mmol) in MeOH (1 mL) under Ar was added 10% Pd/C (15 mg) and the mixture was stirred under a hydrogen atmosphere at 60 °C for 2 h. The mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to give pyrrolidin-1-yl(pyrrolidin-3-yl)methanone as a colorless oil (40 mg, 95% yield). LCMS (ESI) m/z 169 (M + H)⁺.

[00686] Example 096B: N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(pyrrolidine-1-carbonyl)pyrrolidin-1-yl)acetamide was prepared using a procedure analogous to that described in Example 018B, substituting pyrrolidin-1-yl(pyrrolidin-3-yl)methanone from Example 096A for the pyrrolidine derivative used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.06 (s, 1H), 10.63 (s, 1H), 10.20 (s, 1H), 7.85 (d, 2H), 7.59 (s, 1H), 7.58 (d, 2H), 7.22 (s, 1H), 6.58 (m, 1H), 5.63 (s, 1H), 3.44 (m, 2H), 3.36 (m, 5H), 3.13 (m, 2H), 2.79 (m, 4H), 1.96 (s, 3H), 1.79 (m, 6H); MS (ESI) m/z 546 (M + H)⁺.

Example 097

Preparation of 2-(*trans*-3-Cyano-4-hydroxy-pyrrolidin-1-yl)-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide

[00687] To a solution of 2-(6-oxa-3-azabicyclo[3.1.0]hexan-3-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 068A (50 mg, 0.108 mmol) in NMP (2 mL) were added NaCN (7.93 mg, 0.162 mmol) and (C₆F₅)₃B (5 mg). The reaction vessel was sealed and the mixture was heated at 60 °C for 15 h, at which time formation of the product was detected by LCMS. The mixture was purified by preparative HPLC (Phenomenex phenylhexyl reverse phase column) eluting with a gradient of solvent B (0.05% HOAc/CH₃CN) in solvent A (0.05% HOAc/H₂O) to afford 2-(*trans*-3-cyano-4-hydroxy-pyrrolidin-1-yl)-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide as a white solid (15.94 mg, 30 %). ¹H NMR (300

MHz, CD₃OD) δ 7.64 (d, 2H), 7.49 (d, 2H), 7.36 (m, 1H), 6.83 (d, 1H), 6.50 (m, 1H), 5.66 (s, 1H), 4.47 (m, 1H), 3.65-3.18 (m, 3H), 3.00-2.88 (m, 2H), 2.79-2.66 (m, 2H), 2.13 (s, 3H); LCMS (ESI) m/z 591 (M+H)⁺.

Example 098

Preparation of (R)-N-(4-(4-(5-Methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(3-morpholinopropoxy)pyrrolidin-1-yl)acetamide

[00688] **Example 098A:** To a stirring solution of (R)-tert-butyl 3-hydroxypyrrolidine-1-carboxylate (310 mg, 1.66 mmol) in DMF (2 mL) at 0 °C was added 60% NaH (79 mg, 1.98 mmol), and the mixture was stirred at 0 °C for 10 min. Then a solution of 4-(3-chloropropyl)morpholine (298 mg, 1.82 mmol) in DMF (1 mL) was added and the mixture was stirred at rt overnight. Water (15 mL) was added and the mixture was extracted with EtOAc (15 mL x 3). The organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue (460 mg) was purified by silica gel chromatography eluting with 100:1 to 20:1 DCM/MeOH to give (R)-tert-butyl 3-(3-morpholinopropoxy)pyrrolidine-1-carboxylate as a colorless oil (260 mg, 50% yield). LCMS (ESI) m/z 315 (M + H)⁺.

[00689] **Example 098B:** To (R)-tert-butyl 3-(3-morpholinopropoxy)pyrrolidine-1-carboxylate (260 mg, 0.83 mmol) in dioxane (2 mL) was added 4M HCl/dioxane (2 mL), and the solution was stirred at rt for 4 h. Aq NaHCO₃ was added to adjust the pH to 7- 8, then the solution was concentrated under reduced pressure to give a residue containing (R)-4-(3-(pyrrolidin-3-yloxy)propyl)morpholine, which was used directly in the next step. LCMS (ESI) m/z 215 (M + H)⁺.

[00690] **Example 098C:** The residue from Example 098B containing (R)-4-(3-(pyrrolidin-3-yloxy)propyl)morpholine, 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (100 mg, 0.24 mmol), and Na₂CO₃ (102 mg, 0.96 mmol) were combined in DMF (3 mL) and the mixture was stirred at rt overnight. The mixture was subjected to Al₂O₃ chromatography eluting with 100:1 to 10:1 DCM/MeOH to give a product that was further purified by preparative TLC eluting with 10:1:0.1 DCM/MeOH/ammonia to afford (R)-N-(4-(4-

(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(3-morpholinopropoxy)pyrrolidin-1-yl)acetamide as a light yellow solid (50 mg, 35%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.09 (s, 1H), 10.65 (s, 1H), 10.08 (s, 1H), 7.79 (d, 2H), 7.55-7.59 (m, 3H), 7.22 (s, 1H), 6.57 (dd, 1H), 5.62 (s, 1H), 4.00 (m, 1H), 3.54-3.56 (m, 4H), 3.29-3.39 (m, 5H), 2.87 (dd, 1H), 2.71 (dd, 1H), 2.59 (m, 2H), 2.33-2.34 (m, 6H), 2.04 (dd, 1H), 2.03 (s, 3H), 1.64 (m, 2H); LCMS (ESI) *m/z* 592 (M + H)⁺.

Example 099

Preparation of (R)-N-(4-(4-(5-Methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolidin-1-yl)acetamide

[00691] **Example 099A:** To a stirring solution of N-methylpiperazine (5 g, 50 mmol) and 25% NaOH (10 mL) in acetone (100 mL) at 0 °C was added dropwise 1-bromo-2-chloroethane (4.15 mL, 50 mmol), and the mixture was stirred at rt for 48 h. The mixture was concentrated under reduced pressure, then water (100 mL) was added and the mixture was extracted with DCM (3 X 50 mL). The DCM layer was separated, dried (MgSO₄), filtered, and concentrated under reduced pressure to give 1-(2-chloroethyl)-4-methylpiperazine as a light yellow oil (5 g, 61%).

[00692] **Example 099B:** To a stirring solution of (R)-tert-butyl 3-hydroxypyrrolidine-1-carboxylate (330 mg, 1.76 mmol) in DMF (4 mL) at 0 °C was added 60% NaH (84 mg, 2.10 mmol), and the mixture was stirred at 0 °C for 10 min. A solution of 1-(2-chloroethyl)-4-methyl-piperazine (315 mg, 1.94 mmol) in DMF (1 mL) was added at 0 °C and the mixture was stirred at rt overnight. Water (15 mL) was added and the mixture was extracted with EtOAc (3 X 15 mL). The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 100:0 to 5:1 DCM/MeOH to give (R)-tert-butyl 3-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolidine-1-carboxylate as a light yellow oil. LCMS (ESI) *m/z* 314 (M + H)⁺.

[00693] **Example 099C:** To (R)-tert-butyl 3-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolidine-1-carboxylate (100 mg, 0.32 mmol) in dioxane (1 mL) was

added 4M HCl (1 mL), and the mixture was stirred at rt for 4 h. Aq NaHCO₃ was added to adjust the pH to 7, then the solution was concentrated under reduced pressure to give a residue containing (R)-1-methyl-4-(2-(pyrrolidin-3-yloxy)ethyl)piperazine.

[00694] Example 099D: The residue from Example 099C containing (R)-1-methyl-4-(2-(pyrrolidin-3-yloxy)ethyl)piperazine, 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (50 mg, 0.12 mmol), (R)-1-methyl-4-(2-(pyrrolidin-3-yloxy)ethyl)piperazine (500 mg) and Na₂CO₃ (51 mg, 0.48 mmol) were combined in DMF (2 mL) and the mixture was stirred at rt overnight. The mixture was purified by Al₂O₃ chromatography, eluting with 100:0 to 10:1 DCM/MeOH to give a product that was further purified by preparative TLC eluting with 10:1:0.1 DCM/MeOH/ammonia to afford (R)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolidin-1-yl)acetamide as a light yellow solid (25 mg, 35%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.09 (s, 1H), 10.64 (s, 1H), 10.05 (s, 1H), 7.79 (d, 2H), 7.55-7.58 (m, 3H), 7.22 (s, 1H), 6.58 (dd, 1H), 5.62 (s, 1H), 4.02 (m, 1H), 3.26-3.46 (m, 8H, overlapped), 2.85 (dd, 1H), 2.69 (dd, 1H), 2.57 (m, 2H), 2.45 (m, 3H), 2.33-2.35 (m, 3H), 2.14 (s, 3H), 2.04 (dd, 1H), 2.03 (s, 3H), 1.70 (m, 1H); LCMS (ESI) *m/z* 591 (M + H)⁺.

Example 100

Preparation of 2-((R)-3-(2-Hydroxyethoxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00695] Example 100A: A mixture of (R)-benzyl 3-hydroxypyrrolidine-1-carboxylate (250 mg) and 60% NaH (46 mg) in DMF (2 mL) was stirred at 0 °C for 1 h, then 2-(2-bromoethoxy)-tetrahydro-2H-pyran (236 mg) was added and the mixture was stirred at rt overnight, at which time LCMS indicated presence of the desired product (*m/z* 350 (M+H)⁺). The mixture was partitioned between DCM (10 mL) and water (10 mL), and the organic layer was washed with water (3 X 5 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with DCM to give (R)-benzyl-3-(2-(tetrahydro-2H-pyran-2-yloxy)ethoxy)pyrrolidine-1-carboxylate as a yellow oil (275 mg, 75% yield). ¹H NMR (400 MHz, CDCl₃) δ 1.50-1.66 (m, 4H), 1.73 (m, 1H), 1.82 (m, 1H),

1.97 (m, 1H), 2.07 (m, 1H), 3.47-3.71 (m, 8H), 3.98 (m, 2H), 4.64 (t, 1H), 5.15 (s, 2H), 7.28-7.42 (m, 5H).

[00696] Example 100B: A mixture of (R)-benzyl-3-(2-(tetrahydro-2H-pyran-2-yloxy)ethoxy)pyrrolidine-1-carboxylate (270 mg) and 10% Pd on carbon (50 mg) in MeOH was stirred under H₂ at rt overnight, at which time LCMS showed the presence of the desired product. The mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to give (R)-3-(2-(tetrahydro-2H-pyran-2-yloxy)ethoxy)pyrrolidine as a colorless oil (157 mg, 95% yield). LCMS (ESI) m/z 216(M+H)⁺.

[00697] Example 100C: A mixture of (R)-3-(2-(tetrahydro-2H-pyran-2-yloxy)ethoxy)pyrrolidine (160 mg) and 0.5 N HCl (1 mL) in THF (1 mL) was stirred at 0 °C for 4 h, at which time LCMS showed presence of the desired product. The pH of the mixture was adjusted to 7~8, and the mixture was concentrated under reduced pressure to give a residue containing 2-((R)-pyrrolidin-3-yloxy)ethanol. LCMS (ESI) m/z 132 (M+H)⁺.

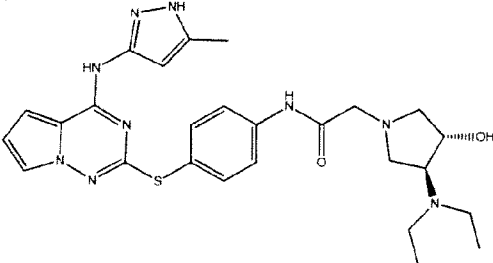
[00698] Example 100D: A mixture of the residue from Example 100C containing 2-((R)-pyrrolidin-3-yloxy)ethanol, N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4] triazin-2-ylthio) phenyl)-2-chloroacetamide (100 mg), and Na₂CO₃ (100 mg) in DMF (5 mL) was stirred at rt overnight. The mixture was filtered and the filtrate was purified by chromatography over Al₂O₃ eluting with 100:1 to 10:1 DCM/MeOH to give a yellow powder. Further purification by preparative TLC eluting with 7:1 DCM/MeOH afforded 2-((R)-3-(2-hydroxyethoxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide as a pale yellow powder (50 mg, 27% yield). ¹H NMR (400 MHz, DMSO-d₆) δ 1.74 (m, 1H), 2.04 (m, 4H), 2.61 (m, 2H), 2.70 (m, 1H), 2.89 (m, 1H), 3.29 (m, 2H), 3.40 (m, 2H), 3.50 (m, 2H), 4.07 (s, 1H), 4.60 (m, 1H), 5.64 (s, 1H), 6.58 (m, 1H), 7.23 (m, 1H), 7.58 (m, 3H), 7.80 (d, 2H), 10.01 (s, 1H), 10.63 (s, 1H), 12.07 (s, 1H); LCMS (ESI) m/z 509(M+H)⁺.

Example 101

Preparation of 2-[*trans*-3-(3-Chloro-phenylamino)-4-hydroxy-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide

[00699] To a solution of 2-(6-oxa-3-azabicyclo[3.1.0]hexan-3-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (75 mg, 0.162 mmol) from Example 068A in ethanol (0.4 mL) was added 3-chloroaniline (0.8 mL), and the mixture was heated at 100 °C for 15 h, at which time completion of the reaction was determined by LCMS. The mixture was purified by silica gel chromatography eluting with MeOH/DCM to yield 2-[*trans*-3-(3-chloro-phenylamino)-4-hydroxy-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide (32.36 mg, 34%) as a white solid. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.06 (s, 1H), 10.64 (s, 1H), 9.98 (s, 1H), 7.80 (d, 2H), 7.59 (m, 3H), 7.23 (s, 1H), 7.09 (t, 1H), 6.69- 6.54 (m, 3H), 6.20 (d, 1H), 5.66 (s, 1H), 5.30 (d, 1H), 5.65 (s, 1H), 5.30 (d, 1H), 4.12 (m, 1H), 3.61 (m, 1H), 3.40-2.95 (m, 5H), 2.54 (m, 2H), 2.05 (s, 3H); LCMS (ESI) *m/z* 590 (M)⁺.

The following compound was prepared in a similar manner.

Exam. No.	Structure	Compound name	LC MS (M+H) ⁺
101-i		2-((3S,4S)-3-(diethylamino)-4-hydroxypyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	536

Example 102

Preparation of 2-(*trans*-3-(3-Fluorophenylamino)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00700] 2-((3S,4S)-3-(3-fluorophenylamino)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was synthesized as a white solid (24.6 mg, 26 %) using a procedure analogous to that described in Example 101, substituting 3-fluoroaniline for the 3-chloroaniline used in Example 101. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.05 (s, 1H), 10.60 (s, 1H), 9.94 (s,

1H), 7.76 (d, 2H), 7.55 (m, 3H), 7.19 (s, 1H), 7.06 (q, 1H), 6.56-6.53 (m, 1H), 6.46-6.16 (m, 3H), 5.60 (s, 1H), 5.25 (d, 1H), 3.91 (m, 1H), 3.57 (m, 1H), 3.33 (s, 2H), 3.14-3.09 (m, 1H), 3.00-2.95 (m, 1H), 2.53 (m, 2H), 2.05 (s, 3H); LCMS (ESI) m/z 574 (M+H)⁺.

Example 103

Preparation of 2-(*trans*-3-*tert*-Butoxy-4-hydroxypyrrolidin-1-yl)-N-(4-(7-fluoro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00701] **Example 103A:** To a stirring solution of 2,4-dichloropyrrolo[1,2-f][1,2,4]triazine (Mastalerz, et al. US20070004731 A1) (1.0 g, 5.3 mmol) in CH₃CN at rt was added SelectFluor (N-chloromethyl-N-fluorotriethylenediammonium bis(tetrafluoroborate) (1.89 g, 5.3 mmol). The mixture was stirred at rt for 2 h, and then heated at 80 °C for 2 h. The mixture was concentrated and the residue was purified by silica gel chromatography eluting with 0-5% EtOAc in hexanes to give an impure sample of 2,4-dichloro-7-fluoropyrrolo[1,2-f][1,2,4]triazine (750 mg).

[00702] **Example 103B:** 2-Chloro-7-fluoro-N-(5-methyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine was prepared using a procedure analogous to that described in Example 041A, substituting 2,4-dichloro-7-fluoropyrrolo[1,2-f][1,2,4]triazine from Example 103A for the 2,4-dichloropyrrolo[1,2-f][1,2,4]triazine used in Example 041A and also substituting 5-methyl-1H-pyrazol-3-amine for the 5-cyclobutyl-1H-pyrazol-3-amine used in Example 041A. LCMS of the reaction mixture prior to work-up showed one major peak m/z (ESI) 267 (M+H)⁺

[00703] **Example 103C:** 2-Chloro-N-(4-(7-fluoro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was prepared using procedures analogous to those described in Examples 016A through 016B, substituting 2-chloro-7-fluoro-N-(5-methyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine from Example 103B for the 2-chloro-N-(5-methyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine used in Example 016A. MS (ESI) m/z 432,434 (M + H)⁺.

[00704] **Example 103D:** 2-(*trans*-3-*tert*-Butoxy-4-hydroxypyrrolidin-1-yl)-N-(4-(7-fluoro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-*f*][1,2,4]triazin-2-ylthio)phenyl)acetamide was prepared using a procedure analogous to that described in Example 018B, substituting 2-chloro-N-(4-(7-fluoro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-*f*][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 103C for the 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-*f*][1,2,4]triazin-2-ylthio)phenyl)acetamide used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.07 (s, 1H), 9.96 (s, 1H), 9.12 (s, 1H), 7.78 (d, 2H), 7.56 (d, 2H), 7.50 (s, 1H), 6.50 (d, 1H), 5.59 (s, 1H), 5.00 (s, 1H), 3.88 (m, 2H), 3.27 (m, 2H), 3.03 (m, 1H), 2.77 (m, 1H), 2.57 (m, 1H), 1.38 (m, 1H), 2.04 (s, 3H), 1.03 (s, 9H); MS (ESI) *m/z* 555 (M + H)⁺.

Example 104

Preparation of 2-(*trans*-3-Ethoxy-4-hydroxy-pyrrolidin-1-yl)-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-*f*][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide

[00705] **Example 104A:** *trans*-4-Ethoxy-pyrrolidin-3-ol was prepared using a procedure analogous to that described in Example 077A, substituting ethanol for the cyclopentanol used in Example 077A.

[00706] **Example 104B:** 2-(3-Ethoxy-4-hydroxy-pyrrolidin-1-yl)-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-*f*][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide was synthesized as a white solid (29.42 mg, 40 %) using a procedure analogous to that described in Example 077B, substituting 4-ethoxy-pyrrolidin-3-ol for the 4-cyclopentyloxy-pyrrolidin-3-ol used in Example 077B. ¹H NMR (300 MHz, CD₃OD) δ 7.67 (d, 2H), 7.49 (d, 2H), 7.35 (m, 1H), 6.82 (d, 1H), 6.47 (m, 1H), 5.64 (s, 1H), 4.07 (m, 1H), 3.75-3.72 (m, 1H), 3.56-3.40 (m, 2H), 3.29 (s, 2H), 3.10-3.04 (m, 1H), 2.92-2.86 (m, 1H), 2.60-2.48 (m, 2H), 2.05 (s, 3H), 1.10 (t, 3H); LCMS (ESI) *m/z* 509 (M+H)⁺.

Example 105

Preparation of 2-(3-(1-Hydroxy-2,2-dimethylpropyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-*f*][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00707] To a solution of N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-pivaloylpyrrolidin-1-yl)acetamide from Example 095 (55mg, 0.10 mmol) in 3:1 MeOH/THF was added NaBH₄ (15 mg, 0.40 mmol), and the mixture was stirred at rt overnight. The mixture was purified on reverse phase HPLC to give 2-(3-(1-hydroxy-2,2-dimethylpropyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide as an acetate salt (40 mg, 70% yield). ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.03 (s, 1H), 7.81 (d, 2H), 7.57 (d, 2H), 7.55 (s, 1H), 7.24 (s, 1H), 6.56 (m, 1H), 5.57 (s, 1H), 4.55 (brs, 1H), 3.22 (m, 2H), 3.06 (m, 1H), 2.81 (m, 2H), 2.34 (m, 3H), 2.00 (s, 3H), 1.89 (s, 1H), 0.83 (s, 9H); MS (ESI) *m/z* 535 (M + H)⁺.

Example 106

Preparation of (R)-N-(4-(4-(5-Methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(pyrrolidine-1-carbonyl)pyrrolidin-1-yl)acetamide

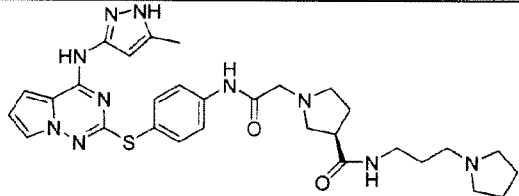
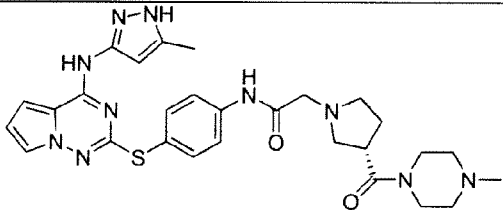
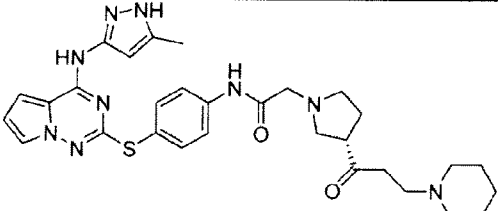
[00708] **Example 106A Step 1:** To a stirring solution of (R)-1-N-Boc beta-proline (100 mg, 0.46 mmol) in DMF (3 mL) were added pyrrolidine (50 μL, 0.70 mmol), HATU (229 mg, 0.60 mmol), and Et₃N (130 μL, 0.93 mmol), and the mixture was stirred at rt overnight. Water (10 mL) was added, and the mixture was extracted with EtOAc (20 mL). The organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 100% EtOAc to give (R)-tert-butyl 3-(pyrrolidine-1-carbonyl)pyrrolidine-1-carboxylate as colorless oil (120 mg, 96% yield).

[00709] **Example 106A Step 2:** To a stirring solution of (R)-tert-butyl 3-(pyrrolidine-1-carbonyl)pyrrolidine-1-carboxylate (120 mg, 0.44 mmol) in EtOAc (3 mL) was added 4N HCl/1,4-dioxane (1.0 mL). The resulting mixture was stirred at rt for 4 h, then concentrated under reduced pressure. Toluene (10 mL) was added and evaporated twice and the residue was dried under vacuum to give (R)-pyrrolidin-1-yl(pyrrolidin-3-yl)methanone as a light yellow oil (90 mg, 100%).

[00710] **Example 106B:** (R)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(pyrrolidine-1-carbonyl)pyrrolidin-1-yl)acetamide was prepared using a procedure analogous to that described in Example

018B, substituting (R)-pyrrolidin-1-yl(pyrrolidin-3-yl)methanone from Example 106A for the pyrrolidine derivative used in Example 018B. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.06 (s, 1H), 10.63 (s, 1H), 10.20 (s, 1H), 7.85 (d, 2H), 7.59 (s, 1H), 7.58 (d, 2H), 7.22 (s, 1H), 6.58 (m, 1H), 5.63 (s, 1H), 3.44 (m, 2H), 3.36 (m, 5H), 3.13 (m, 2H), 2.79 (m, 4H), 1.96 (s, 3H), 1.79 (m, 6H); MS (ESI) m/z 546 ($M + H$) $^+$.

[00711] The following compounds were prepared using a procedure similar to that described in Example 106.

Exam. No.	Structure	Compound name	LC MS ($M+H$) $^+$
106-i		(R)-1-(2-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)-N-(3-(pyrrolidin-1-yl)propyl)pyrrolidine-3-carboxamide	603
106-ii		(S)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)-2-(3-(4-methylpiperazine-1-carbonyl)pyrrolidin-1-yl)acetamide	575
106-iii		(S)-1-(2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)-N-(2-(piperidin-1-yl)ethyl)pyrrolidine-3-carboxamide	603

Example 107**Preparation of (R)-N-(3-Fluoro-4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(pyrrolidine-1-carbonyl)pyrrolidin-1-yl)acetamide**

[00712] (R)-N-(3-fluoro-4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(pyrrolidine-1-carbonyl)pyrrolidin-1-yl)acetamide was prepared using a procedure analogous to that described in Example 018B, substituting 2-chloro-N-(3-fluoro-4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 087A for the 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.09 (s, 1H), 10.69 (s, 1H), 10.42 (s, 1H), 7.87 (d, 1H), 7.67 (s, 1H), 7.63 (d, 2H), 7.24 (s, 1H), 6.60 (t, 1H), 5.59 (s, 1H), 3.45 (m, 3H), 3.38-3.10 (m, 5H), 2.75 (m, 4H), 2.08 (s, 3H), 1.93 (m, 3H), 1.81 (m, 2H); LCMS (ESI) *m/z* 564 (M + H)⁺.

Example 108**Preparation of N-((3S,4S)-1-((4-(4-(5-Methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylcarbonyl)methyl)-4-tert-butoxypyrrolidin-3-yl)isobutyramide**

[00713] **Example 108A:** To a stirring solution of *trans*-benzyl 3-azido-4-hydroxypyrrolidine-1-carboxylate (1.00 g) from Example 124A in DCM (5 mL) was added BF₃·Et₂O (1 drop) and the mixture was stirred at rt for 15 min. Tert-butyl-2,2,2-trichloroacetimidate (166 mg) was added and the mixture was stirred overnight at rt, at which time TLC analysis indicated incomplete reaction. Additional tert-butyl-2,2,2-trichloroacetimidate (166 mg) was added in portions. After 24 h, the mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography eluting with DCM to give *trans*-benzyl 3-tert-butoxy-4-azidopyrrolidine-1-carboxylate as a white powder (205 mg). ¹H NMR (400 MHz, CDCl₃) δ 1.24 (s, 9H), 3.31 (m, 2H), 3.72 (m, 2H), 3.89 (m, 1H), 4.05 (m, 1H), 5.15 (s, 2H), 7.28~7.43 (m, 5H); LCMS (ESI) *m/z* 319 (M+H)⁺.

[00714] **Example 108B:** A mixture of *trans*-benzyl 3-tert-butoxy-4-azidopyrrolidine-1-carboxylate (205 mg) and PPh₃ in THF was stirred at rt for 18 h, then the colorless solution was concentrated under reduced pressure. To the residue

were added MeOH (5 mL) and 0.5 N NaOH (5 mL) and the mixture was stirred at rt for 24 h. The mixture was concentrated under reduced pressure, and the residue was taken up in CHCl₃ (10 mL) and washed with brine, dried over Na₂SO₄, filtered, and concentrated. The residue was purified by silica gel chromatography to afford a white solid (34 mg). A mixture of the white solid (34 mg) and 2M NaOH (1 mL) in MeOH (2 mL) was stirred at 50 °C for 2 h, at which time LCMS showed the starting material was consumed and a new peak had formed (*m/z* 293 (M+H)). The mixture was concentrated under reduced pressure and the residue was taken up in CHCl₃ (5 mL), washed with brine, dried over Na₂SO₄, filtered, and concentrated. The residue was purified by silica gel chromatography to afford *trans*-benzyl 3-tert-butoxy-4-aminopyrrolidine-1-carboxylate as a yellow oil (13 mg, 72% yield). ¹H NMR (400 MHz, CDCl₃) δ 1.23 (s, 9H), 1.48 (br s, 2H), 3.11 (m, 1H), 3.18 (m, 1H), 3.31 (m, 1H), 3.73~3.75 (m, 3H), 5.15 (s, 2H), 7.28~7.43 (m, 5H); LCMS (ESI) *m/z* 293 (M+H)⁺.

[00715] Example 108C: To a solution of *trans*-benzyl 3-tert-butoxy-4-aminopyrrolidine-1-carboxylate (78 mg) and triethylamine (48 µL) in DCM (5 mL) at -10 °C was added isobutyryl chloride (31 µL). The mixture was stirred for 2 h, at which time TLC showed the reaction was complete. The mixture was washed with water (3 X 5 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give *trans*-benzyl 3-tert-butoxy-4-(isobutyramido)pyrrolidine-1-carboxylate as a yellow oil (92 mg, 95% yield). ¹H NMR (400 MHz, CDCl₃) δ 1.15 (d, 6H), 1.25 (s, 9H), 2.32 (m, 1H), 3.05~3.45 (m, 2H), 3.60 (m, 1H), 3.77 (m, 1H), 4.05~4.20 (m, 2H), 5.15 (s, 2H), 5.47 (m, 1H), 7.28~7.43 (m, 5H).

[00716] Example 108D: A mixture of *trans*-benzyl 3-tert-butoxy-4-(isobutyramido)pyrrolidine-1-carboxylate (87 mg) and Pd/C (10%, 20 mg) in MeOH was stirred under H₂ at rt overnight. The mixture was filtered and concentrated under reduced pressure to give a yellow oil (51 mg). To a solution of the yellow oil in DMF (1 mL) were added N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-yl thio)phenyl)-2-chloroacetamide (70 mg) and Na₂CO₃ (100 mg). The resulting mixture was stirred at rt overnight then filtered. The filtrate was concentrated under reduced pressure to give a yellow powder, which was purified by

silica gel chromatography eluting with 100:1 to 10:1 DCM/MeOH followed by preparative TLC eluting with EtOAc to give N-((3S,4S)-1-((4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylcarbamoyl)methyl)-4-tert-butoxypyrrolidin-3-yl)isobutyramide as a pale yellow powder (35 mg, 34% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.15 (d, 6H), 1.25 (s, 9H), 2.02 (m, 4H), 2.32 (m, 1H), 2.41 (m, 1H), 2.51 (m, 1H), 2.60~2.3.0 (m, 3H), 3.21 (m, 1H), 4.03 (m, 1H), 4.21 (m, 1H), 5.60 (s, 1H), 6.59 (s, 1H), 7.23 (s, 1H), 7.45~7.65 (m, 4H), 7.75~7.45 (dd, 2H), 10.12 (s, 1H), 10.67 (s, 1H), 12.11 (s, 1H); LCMS (ESI) *m/z* 606(M+H)⁺.

Example 109

Preparation of N-(*trans*-1-((4-(4-(5-Methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylcarbamoyl)methyl)-4-tert-butoxypyrrolidin-3-yl)pivalamide

[00717] **Example 109A:** To a solution of *trans*-benzyl 3-tert-butoxy-4-aminopyrrolidine-1-carboxylate (70 mg) and triethylamine (40 μL) in DCM (3 mL) at -10 °C was added pivaloyl chloride (30 μL). The mixture was stirred for 2 h, at which time TLC showed the reaction was complete. The mixture was washed with water (3 X 5 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give *trans*-benzyl 3-tert-butoxy-4-(pivalamido)pyrrolidine-1-carboxylate as a yellow oil (82 mg, 90% yield). ¹H NMR (400 MHz, CDCl₃) δ 1.19 (s, 18H), 3.05~3.45 (m, 2H), 3.60 (m, 1H), 3.77 (m, 1H), 4.05~4.20 (m, 2H), 5.15 (s, 2H), 5.47 (m, 1H), 7.28~7.43 (m, 5H).

[00718] **Example 109B:** A mixture of *trans*-benzyl 3-tert-butoxy-4-(pivalamido)pyrrolidine-1-carboxylate (82 mg) and 10% Pd/C (20 mg) in MeOH was stirred under H₂ at rt overnight. The mixture was filtered and concentrated under reduced pressure to give a yellow oil (41 mg). To a solution of the yellow oil in DMF (1 mL) were added N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-chloroacetamide (60 mg) and Na₂CO₃ (100 mg). The resulting mixture was stirred at rt overnight, then filtered. The filtrate was concentrated under reduced pressure to give a yellow powder, which was purified by silica gel chromatography eluting with 100:1 to 10:1 DCM/MeOH followed by preparative TLC eluting with EtOAc to afford N-(*trans*-1-((4-(4-(5-methyl-1H-

pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylcarbamoyl)methyl)-4-tert-butoxypyrrolidin-3-yl)pivalamide as a pale yellow powder (12 mg, 13% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.15 (s, 18H), 2.02 (m, 4H), 2.41 (m, 1H), 2.51 (m, 1H), 2.60~23.01 (m, 3H), 3.21 (m, 1H), 4.03 (m, 1H), 4.21 (m, 1H), 5.60 (s, 1H), 6.59 (s, 1H), 7.23 (s, 1H), 7.45~7.65 (m, 4H), 7.75~7.45 (dd, 2H), 10.12 (s, 1H), 10.67 (s, 1H), 12.11 (s, 1H); LCMS (ESI) *m/z* 620 (M+H)⁺.

Example 110

Preparation of 2-[*trans*-3-Hydroxy-4-(2,2,2-trifluoro-1-trifluoromethyl-ethoxy)-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide

[00719] **Example 110A:** To a solution of benzyl 6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate (50 mg, 0.228 mmol) in 1,1,1,3,3,3-hexafluoropropan-2-ol (1 mL) was added Cs₂CO₃ (111.46 mg, 0.342 mmol) and the mixture was heated in a microwave reactor at 150 °C for 20 min, at which time formation of the product was determined by LCMS. The mixture was diluted with EtOAc, washed with water and brine, and concentrated. The residue was purified by silica gel chromatography eluting with DCM/MeOH. To the isolated product in MeOH was added Pd(OH)₂ (20 mg) and the mixture was stirred under H₂ for 2 h, at which time completion of the reaction was confirmed by LCMS. The mixture was filtered through Celite and the filtrate was concentrated to give crude *trans*-4-(2,2,2-trifluoro-1-trifluoromethyl-ethoxy)-pyrrolidin-3-ol which was used in next step without further purification.

[00720] **Example 110B:** 2-[*trans*-3-Hydroxy-4-(2,2,2-trifluoro-1-trifluoromethyl-ethoxy)-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide was synthesized as a white solid (27.19 mg, 30 %) using a procedure analogous to that described in Example 077B, substituting *trans*-4-(2,2,2-trifluoro-1-trifluoromethyl-ethoxy)-pyrrolidin-3-ol for the *trans*-4-cyclopentyloxy-pyrrolidin-3-ol used in Example 077B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.07 (s, 1H), 10.63 (s, 1H), 9.99 (s, 1H), 7.76 (d, 2H), 7.58 (d, 3H), 7.23 (s, 1H), 6.58 (m, 1H), 5.60 (s, 1H), 5.36 (d, 1H), 4.22 (m, 1H), 4.13 (m, 1H), 3.33 (m, 4H), 3.10-2.99 (m, 2H), 2.77-2.73 (m, 1H), 2.04 (s, 3H); LCMS (ESI) *m/z* 631 (M+H)⁺.

Example 111**Preparation of 2-(*trans*-3-Hydroxy-4-methoxy-pyrrolidin-1-yl)-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide**

[00721] **Example 111A:** *trans*-4-Methoxy-pyrrolidin-3-ol was prepared using a procedure analogous to that described in Example 077A, substituting methanol for the cyclopentanol used in Example 077A.

[00722] **Example 111B:** 2-(*trans*-3-Hydroxy-4-methoxy-pyrrolidin-1-yl)-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide was synthesized as a white solid (45.89 mg, 64 %) using a procedure analogous to that described in Example 077B, substituting *trans*-4-methoxy-pyrrolidin-3-ol for the *trans*-4-cyclopentylloxy-pyrrolidin-3-ol used in Example 077B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.10 (s, 1H), 10.60 (s, 1H), 10.05 (s, 1H), 7.79 (d, 2H), 7.57 (d, 3H), 7.20 (s, 1H), 6.57 (s, 1H), 5.61 (s, 1H), 5.20 (brs, 1H), 4.01 (m, 1H), 3.65 (s, 1H), 3.26 (m, 5H), 3.01 (m, 1H), 2.88 (m, 1H), 2.54 (m, 2H), 2.03 (s, 3H); LCMS (ESI) *m/z* 495 (M+H)⁺.

Example 112**Preparation of 2-(*trans*-3-Hydroxy-4-(3-methoxyphenylamino)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide**

[00723] 2-(*trans*-3-hydroxy-4-(3-methoxyphenylamino)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was synthesized as a white solid (34.51 mg, 36 %) using a procedure analogous to that described in Example 101, substituting 3-methoxyaniline for the 3-chloroaniline used in Example 101. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.05 (s, 1H), 10.64 (s, 1H), 9.98 (s, 1H), 7.81 (d, 2H), 7.60 (m, 3H), 7.23 (s, 1H), 6.98 (t, 1H), 6.59-6.57 (m, 1H), 6.24 (d, 2H), 6.14 (d, 1H), 5.86 (d, 1H), 5.66 (s, 1H), 5.24 (d, 1H), 3.94 (m, 1H), 3.67 (s, 3H), 3.39 (s, 2H), 3.18-3.13 (m, 1H), 3.02-2.97 (m, 1H), 2.57 (m, 2H), 2.03 (s, 3H); LCMS (ESI) *m/z* 586 (M+H)⁺.

Example 113

Preparation of 2-(*trans*-3-(2-Fluorophenylamino)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00724] 2-(*trans*-3-(2-fluorophenylamino)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was synthesized as a white solid (25.43 mg, 27.3 %) using a procedure analogous to that described in Example 101, substituting 2-fluoroaniline for the 3-chloroaniline used in Example 101. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.06 (s, 1H), 10.64 (s, 1H), 10.02 (s, 1H), 7.82 (d, 2H), 7.60 (m, 3H), 7.23 (s, 1H), 7.06-7.03 (m, 2H), 6.98 (m, 1H), 6.55 (m, 2H), 5.60 (s, 1H), 5.45 (d, 1H), 5.25 (d, 1H), 4.05 (br s, 1H), 3.65 (br s, 1H), 3.30 (s, 2H), 3.15 (m, 1H), 3.00 (m, 1H), 2.60 (m, 2H), 2.00 (s, 3H); LCMS (ESI) *m/z* 574 (M+H)⁺.

Example 114

Preparation of 2-(*trans*-3-(3-Fluorophenoxy)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00725] **Example 114 Step 1:** To 3-fluorophenol (62 μ L, 0.69 mmol) in DMF (4 mL) was added cesium carbonate (178.3 mg, 0.547 mmol) and the mixture was stirred at rt for 5 min, then benzyl 6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate (100 mg, 0.456 mmol) from Example 051A was added, and the mixture was stirred at 90 °C overnight. The mixture was partitioned between EtOAc (15 mL) and water (5 mL), and the separated EtOAc layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The solid residue was purified by silica gel chromatography eluting with 15% to 60% EtOAc/hexanes to afford *trans*-benzyl 3-(3-fluorophenoxy)-4-hydroxypyrrolidine-1-carboxylate (90.7 mg, 0.27 mmol, 60%). LCMS (ESI) *m/z* 332 (M + H)⁺.

[00726] **Example 114 Step 2:** To *trans*-benzyl 3-(3-fluorophenoxy)-4-hydroxypyrrolidine-1-carboxylate under Ar were added 10% palladium on carbon and MeOH. The mixture was stirred at rt under H₂ for 30 min, then the mixture was filtered and the filtrate was concentrated under reduced pressure to afford *trans*-4-(3-fluorophenoxy)pyrrolidin-3-ol (51 mg, 0.25 mmol). ¹H NMR (300 MHz, DMSO-*d*₆)

δ 7.35 (q, 1H), 6.72-6.85 (m, 3H), 5.19 (s, 1H), 4.47 (s, 1H), 4.03 (s, 1H), 3.10-3.4 (m, 1H), 3.07 (t, 1H), 2.61-2.82 (dd, 2H); LCMS (ESI) m/z 198 (M + H)⁺.

[00727] **Example 114 Step 3:** 2-(*trans*-3-(3-Fluorophenoxy)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (45.1 mg, 34%) was synthesized using a procedure analogous to that described in Example 018B, substituting *trans*-4-(3-fluorophenoxy)pyrrolidin-3-ol from the previous step for the pyrrolidine derivative used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.05 (s, 1H), 10.65 (s, 1H), 10.05 (s, 1H), 7.79 (d, 2H), 7.59 (d, 3H), 7.20-7.30 (m, 2H), 6.80-6.90 (m, 3H), 6.71 (s, 1H), 5.65 (s, 1H), 5.55 (dd, 1H), 4.60 (br s, 1H), 4.15 (d, 1H), 3.05-3.25 (m, 2H), 2.89 (s, 1H), 2.73-2.80 (m, 2H), 2.55-2.60 (m, 1H), 2.03 (s, 3H); LCMS (ESI) m/z 575 (M + H)⁺.

Example 115

Preparation of (S)-N-(4-(4-(5-Methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(pyrrolidine-1-carbonyl)pyrrolidin-1-yl)acetamide

[00728] (S)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(pyrrolidine-1-carbonyl)pyrrolidin-1-yl)acetamide (35.0 mg, 54%) was synthesized using a procedure analogous to that described in Example 018B, substituting (S)-pyrrolidin-1-yl(pyrrolidin-3-yl)methanone for the pyrrolidine derivative used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.06 (s, 1H), 10.63 (s, 1H), 10.18 (s, 1H), 7.87 (d, 2H), 7.59 (d, 3H), 7.23 (br s, 1H), 6.58 (br s, 1H), 5.64 (s, 1H), 3.42-3.47 (m, 4H), 3.21 (dd, 2H), 2.64-2.89 (m, 6H), 2.03 (br s, 3H), 1.75-1.90 (m, 5H); LCMS (ESI) m/z 544 (M-H)⁻.

Example 116

Preparation of 2-(*trans*-3-(2-Fluorophenoxy)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00729] **Example 116 Step 1:** *trans*-Benzyl 3-(2-fluorophenoxy)-4-hydroxypyrrolidine-1-carboxylate (68 mg, 0.205 mmol, 45%) was synthesized using a procedure analogous to that described in Example 114 Step 1, substituting 2-

fluorophenol for the 3-fluorophenol used in Example 114 Step 1. LCMS (ESI) m/z 332 ($M + H$)⁺.

[00730] **Example 116 Step 2:** *trans*-4-(2-Fluorophenoxy)pyrrolidin-3-ol (35.5 mg, 0.18 mmol) was synthesized using a procedure analogous to that described in Example 114 Step 2, substituting *trans*-benzyl 3-(2-fluorophenoxy)-4-hydroxypyrrolidine-1-carboxylate (68 mg, 0.205 mmol) from Example 116 Step 1 for the *trans*-benzyl 3-(3-fluorophenoxy)-4-hydroxypyrrolidine-1-carboxylate used in Example 114 Step 2. LCMS (ESI) m/z 198 ($M + H$)⁺.

[00731] **Example 116 Step 3:** 2-(*trans*-3-(2-Fluorophenoxy)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (68.2 mg, 67%) was synthesized using a procedure analogous to that described in Example 018B, substituting *trans*-4-(2-fluorophenoxy)pyrrolidin-3-ol from the previous step for the pyrrolidine derivative used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.05 (s, 1H), 10.63 (s, 1H), 10.04 (s, 1H), 7.79 (d, 2H), 7.56-7.59 (m, 3H), 7.14-7.26 (m, 4H), 7.08-7.14 (m, 1H), 6.55-6.59 (m, 1H), 5.63 (br s, 1H), 5.52 (dd, 1H), 4.65 (br s, 1H), 4.17-4.22 (m, 1H), 3.05-3.25 (m, 2H), 2.5-2.89 (m, 4H), 2.02 (s, 3H); LCMS (ESI) m/z 575 ($M + H$)⁺.

Example 117

Preparation of 2-(*trans*-3-(2,4-Difluorophenoxy)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00732] **Example 117 Step 1:** *trans*-benzyl 3-(2,4-difluorophenoxy)-4-hydroxypyrrolidine-1-carboxylate (68 mg, 0.205 mmol, 45%) was synthesized using a procedure analogous to that described in Example 114 Step 1, substituting 2,4-difluorophenol for the 3-fluorophenol used in Example 114 Step 1. LCMS (ESI) m/z 350 ($M + H$)⁺.

[00733] **Example 117 Step 2:** *trans*-4-(2,4-Difluorophenoxy)pyrrolidin-3-ol (40 mg, 0.186 mmol) was synthesized using a procedure analogous to that described in Example 114 Step 2, substituting *trans*-benzyl 3-(2,4-difluorophenoxy)-4-

hydroxypyrrolidine-1-carboxylate from Example 117 Step 1 for the *trans*-benzyl 3-(3-fluorophenoxy)-4-hydroxypyrrolidine-1-carboxylate used in Example 114 Step 2.
LCMS (ESI) m/z 216 ($M + H$)⁺.

[00734] Example 117 Step 3: 2-(*trans*-3-(2,4-Difluorophenoxy)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (60 mg, 60%) was synthesized using a procedure analogous to that described in Example 018B, substituting *trans*-4-(2,4-difluorophenoxy)pyrrolidin-3-ol from the previous step for the pyrrolidine derivative used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.07 (s, 1H), 10.64 (s, 1H), 10.05 (s, 1H), 7.80 (d, 2H), 7.56-7.59 (m, 3H), 7.28-7.35 (m, 3H), 7.07-7.25 (m, 1H), 6.59 (br s, 1H), 5.64 (br s, 1H), 5.52 (d, 1H), 4.61 (br s, 1H), 4.20 (br s, 1H), 3.10-3.22 (m, 2H), 2.51-2.89 (m, 4H), 2.05 (s, 3H); LCMS (ESI) m/z 591 ($M-H$)⁻.

Example 118

Preparation of 2-(*trans*-3-(3,4-Difluorophenylamino)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00735] 2-(*trans*-3-(3,4-difluorophenylamino)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was synthesized as a white solid (8.87 mg, 11 %) using a procedure analogous to that described in Example 101, substituting 3,4-fluoroaniline for the 3-chloroaniline used in Example 101. ¹H NMR (300 MHz, CD₃OD) δ 7.78 (d, 2H), 7.61 (d, 2H), 7.46 (s, 1H), 7.04-6.93 (m, 2H), 6.62-6.57 (m, 2H), 6.46-6.42 (m, 1H), 5.76 (s, 1H), 4.06 (m, 1H), 3.70 (m, 1H), 3.49 (s, 2H), 3.39 (m, 1H), 3.06-2.99 (m, 1H), 2.85-2.77 (m, 1H), 2.56-2.51 (m, 1H), 2.15 (s, 3H); LCMS (ESI) m/z 592 ($M+H$)⁺.

Example 119

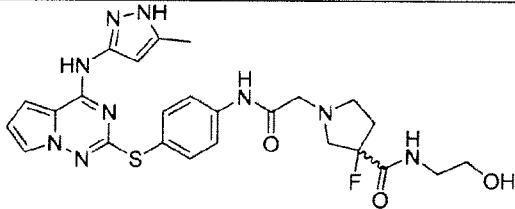
Preparation of N-Ethyl-3-fluoro-N-(2-hydroxyethyl)-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide

[00736] Example 119A: To tert-butyl 3-fluoro-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxylate from Example 048 (50 mg, 0.088 mmol) in EtOAc (0.5 mL) was added 4N HCl/1,4-dioxane (0.5 mL) and the reaction was allowed to proceed at rt overnight.

The mixture was then concentrated to dryness under reduced pressure, and the residue was titrated with CH₃CN. The solid was collected by filtration to give 3-fluoro-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxylic acid (45 mg, 95% yield). LCMS (ESI) *m/z* 511 (M + H)⁺.

[00737] Example 119B: To 3-fluoro-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxylic acid (50 mg, 0.091 mmol) in DMF (1 mL) were added 2-(ethylamino)ethanol (22 mg, 0.23 mmol), HATU (45 mg, 0.11 mmol), and Et₃N (82 μL, 0.18 mmol). The resulting mixture was stirred at rt overnight, then the mixture was purified by reverse phase HPLC to give N-ethyl-3-fluoro-N-(2-hydroxyethyl)-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide as its acetate salt (15 mg, 26% yield). ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.05 (s, 1H), 10.63 (s, 1H), 10.11 (s, 1H), 7.79 (d, 2H), 7.59 (s, 1H), 7.58 (d, 2H), 7.22 (s, 1H), 6.58 (m, 1H), 5.64 (s, 1H), 4.75 (m, 1H), 3.80-2.90 (m, 8H), 2.90-2.78 (m, 2H), 2.38-1.95 (m, 2H), 1.99 (s, 3H), 1.40-1.00 (m, 3H); LCMS (ESI) *m/z* 582 (M + H)⁺.

[00738] The following compounds were prepared using a procedure similar to that described in Example 119B.

Exam. No.	Structure	Compound name	LC MS (M+H) ⁺
119-II		3-fluoro-N-(2-hydroxyethyl)-1-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)pyrrolidine-3-carboxamide	554

Exam. No.	Structure	Compound name	LC MS (M+H) ⁺
119-III		(S)-N-(2-(dimethylamino)ethyl)-N-methyl-1-(2-((4-((4-(5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)pyrrolidine-3-carboxamide	577
119A-I		3-fluoro-1-(2-((4-((4-(5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)pyrrolidine-3-carboxylic acid	511

Example 120**Preparation of 2-(trans-3-(3,5-Difluorophenoxy)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide**

[00739] 2-(trans-3-(3,5-difluorophenoxy)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (25 mg, 37%) was synthesized using a procedure analogous to that described in Example 114, substituting 3,5-difluorophenol for the 3-fluorophenol used in Example 114. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.07 (s, 1H), 10.64 (s, 1H), 10.05 (s, 1H), 7.80 (d, 2H), 7.57-7.60 (m, 3H), 7.22-7.35 (m, 3H), 7.01-7.07 (m, 1H), 6.59 (q, 1H), 5.64 (br s, 1H), 5.52 (dd, 1H), 4.61 (br s, 1H), 4.20 (br s, 1H), 3.08-3.40 (m, 2H), 2.73-2.89 (m, 2H), 2.57-2.61 (m, 2H), 2.03 (s, 3H); LCMS (ESI) *m/z* 591 (M-H)⁺.

Example 121**Preparation of 2-(trans-3-(3,4-Difluorophenoxy)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide**

[00740] 2-(*trans*-3-(3,4-Difluorophenoxy)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-*f*][1,2,4]triazin-2-ylthio)phenyl)acetamide (78.1 mg, 53%) was synthesized using a procedure analogous to that described in Example 114, substituting 3,5-difluorophenol for 3-fluorophenol used in Example 114. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.06 (s, 1H), 10.63 (s, 1H), 10.04 (s, 1H), 7.79 (d, 2H), 7.56-7.59 (m, 3H), 7.08-7.42 (m, 3H), 6.84 (br s, 1H), 6.59 (s, 1H), 5.63 (s, 1H), 5.51 (d, 1H), 4.56 (br s, 1H), 4.15 (br s, 1H), 3.06-3.18 (m, 2H), 2.93 (s, 1H), 2.73-2.86 (m, 3H), 2.03 (s, 3H); LCMS (ESI) *m/z* 593 (M + H)⁺.

Example 122

Preparation of 2-(3-Fluoro-3-(pyrrolidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-*f*][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00741] 2-(3-Fluoro-3-(pyrrolidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-*f*][1,2,4]triazin-2-ylthio)phenyl)acetamide was prepared using a procedure analogous to that described in Example 119B, substituting pyrrolidine for the 2-(ethylamino)ethanol used in Example 119B. ¹H NMR (300 MHz, MeOD-*d*₄) δ 7.79 (d, 2H), 7.68 (s, 1H), 7.62 (d, 2H), 7.48 (s, 1H), 6.94 (d, 1H), 5.75 (s, 1H), 3.69 (m, 1H), 3.63-3.25 (m, 6H), 3.10 (m, 3H), 2.62 (m, 1H), 2.39 (m, 1H), 2.15 (s, 3H), 1.93 (m, 4H); LCMS (ESI) *m/z* 564 (M + H)⁺.

Example 123

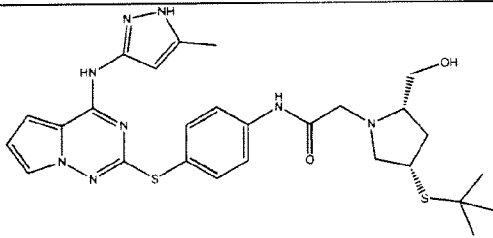
Preparation of (R)-2-(3-(*tert*-Butylthio)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-*f*][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00742] **Example 123A:** (R)-3-(*tert*-butylthio)pyrrolidine hydrochloride was synthesized using a procedure analogous to that described in Example 063B, substituting (*R*)-*tert*-butyl 3-(*tert*-butylthio)pyrrolidine-1-carboxylate from Example 154A for the (*R*)-*tert*-butyl 3-(2-methoxyethoxy)pyrrolidine-1-carboxylate used in Example 063B.

Example 123B: To a solution of N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-*f*][1,2,4]triazin-2-ylthio)phenyl)-2-chloroacetamide (50 mg, 0.12 mmol) in THF (2 mL) under N₂ at rt was added tetrabutylammonium iodide (43 mg, 0.11 mmol), and the mixture was stirred for 10 min. Then (*R*)-3-(*tert*-butylthio)pyrrolidine (38 mg, 2

eq., 0.24 mmol) and DIEA (0.5 mL) were added under N₂, and the mixture was stirred at 40 °C overnight. Water (2 mL) was added, and the mixture was extracted with EtOAc (3 x 5 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was washed with ether, dried under vacuum, then purified by preparative TLC eluting with 10:1 DCM/MeOH to afford (R)-2-(3-(tert-butylthio)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (17 mg, 25% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.07 (s, 1H), 10.62 (s, 1H), 10.04 (s, 1H), 7.80 (d, 2H), 7.58 (m, 3H), 7.22 (s, 1H), 6.58 (s, 1H), 5.64 (s, 1H), 3.34 (s, 2H), 3.18 (m, 2H), 2.78 (m, 1H), 2.62 (m, 1H), 2.44 (s, 1H), 2.33 (s, 1H), 2.04 (s, 3H), 1.66 (s, 1H), 1.30 (s, 9H); LCMS *m/z* 537 (M+H)⁺.

The following compound was prepared in a similar manner:

Exam. No.	Structure	Compound name	LC MS (M+H) ⁺
123-i		2-((2S,4S)-4-(tert-butylthio)-2-(hydroxymethyl)pyrrolidin-1-yl)-N-((4-((5-methyl-1H-pyrazol-3-ylamino)pyrrolo[2,1-f][1,2,4]triazin-2-ylthio)phenyl)acetamide	567

Example 124

Preparation of N-((S)-1-((4-(4-(5-Methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylcarbamoyl)methyl)-4,4-difluoropyrrolidin-3-yl)pivalamide

[00743] **Example 124A:** A mixture of benzyl 6-oxa-3-aza-bicyclo[3.1.0]hexane-3-carboxylate (1.80 g, 8.21 mmol), NaN₃ (1.07 g, 16.42 mmol) and NH₄Cl (0.44 g, 8.21 mmol) in 6:1 MeOH/H₂O (28 mL) was stirred at 60-65 °C overnight. The mixture was concentrated under reduced pressure at rt, and the residue was treated with 0.5 M aq NaOH and extracted with DCM (4 x 50 mL). The combined DCM extracts were washed with H₂O and brine, dried over MgSO₄, filtered, and concentrated under

reduced pressure to afford *trans*-benzyl 3-azido-4-hydroxypyrrolidine-1-carboxylate as yellow oil (1.98 g, 92% yield), which was used in the next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ 7.37-7.28 (m, 5H), 5.14 (s, 2H), 4.25 (m, 1H), 3.99-3.95 (m, 1H), 3.79-3.63 (m, 2H), 3.56-3.43 (m, 2H), 3.01 (m, 1H).

[00744] **Example 124B:** To a stirring suspension of Dess-Martin periodinane (2.91 g, 6.86 mmol) in DCM (40 mL) under N₂ was added a solution of *trans*-benzyl 3-azido-4-hydroxy pyrrolidine-1-carboxylate (1.50 g, 5.72 mmol) in DCM (20 mL) and the mixture was stirred at rt for 18 h. Water (50 mL) was added and the mixture was stirred for 2 h, then filtered. The organic phase was separated, then washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford benzyl 3-azido-4-oxopyrrolidine-1-carboxylate as a colorless oil (0.9 g, 60%). ¹H NMR (400 MHz, CDCl₃) δ 7.36-7.28 (m, 5H), 5.17 (m, 2H), 4.25 (m, 2H), 4.07-4.03 (m, 1H), 3.87-3.82 (d, 1H), 3.35-3.31 (m, 1H).

[00745] **Example 124C:** To a nitrogen purged solution of benzyl 3-azido-4-oxopyrrolidine-1-carboxylate (490 mg, 1.87 mmol) in 1,2-dichloroethane (2 mL) under N₂ at 0 °C was added dropwise a solution of (diethylamino)sulfur trifluoride (910 mg, 6.86 mmol) in 1,2-dichloroethane (0.5 mL). The mixture was heated at 60 °C overnight, and then the mixture was diluted with DCM (20 mL) and washed with saturated aq NaHCO₃, water, and brine, then dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 10:1 to 3:1 petroleum ether/EtOAc to afford benzyl 4-azido-3,3-difluoropyrrolidine-1-carboxylate (80 mg, 15%). ¹H NMR (400 MHz, CDCl₃) δ 7.38-7.28 (m, 5H), 5.17 (s, 2H), 4.12 (m, 1H), 3.88-3.76 (m, 3H), 3.61-3.53 (m, 1H).

[00746] **Example 124D:** To benzyl 4-azido-3,3-difluoropyrrolidine-1-carboxylate (400 mg, 1.42 mmol) and acetic acid (427 mg, 7.10 mmol) in a mixture of ethanol (14.2 mL) and water (2.84 mL) was added zinc dust (929 mg, 14.2 mmol) in one portion, and the mixture was stirred at 25 °C for 40 min, then filtered. The filtrate was neutralized with saturated aq NaHCO₃ and extracted with DCM (4 x 50 mL). The organic layer was concentrated under reduced pressure to afford benzyl 4-amino-3,3-

difluoro pyrrolidine-1-carboxylate as a brown oil (100 mg, 27%). LCMS (ESI) m/z 257 (M+H)⁺.

[00747] **Example 124E:** To a mixture of benzyl 4-amino-3,3-difluoropyrrolidine-1-carboxylate (80 mg, 0.19 mmol) and triethylamine (38 mg, 0.38 mmol) in DCM (2.5 mL) at 0 °C was added dropwise pivaloyl chloride (23 mg, 0.19 mmol) and the mixture was stirred at 0 °C for 16 h. The mixture was diluted with water and extracted with DCM. The organic layer was washed with brine and water, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 100:1 to 40:1 DCM/ MeOH to afford benzyl 3,3-difluoro-4-(pivalamido)pyrrolidine-1-carboxylate (50 mg, 77%). LCMS (ESI) m/z 341 (M+H)⁺.

[00748] **Example 124F:** A mixture of (*S*)-benzyl 3,3-difluoro-4-(pivalamido)pyrrolidine-1-carboxylate (50 mg, 0.15 mmol) and Pd(OH)₂ (10 mg, 0.07 mmol) in MeOH (2 mL) was stirred under H₂ at 40 °C for 30 min. The mixture was filtered and the filtrate was concentrated under reduced pressure to afford crude *N*-(4,4-difluoropyrrolidin-3-yl)pivalamide (25 mg, 81%), which was used in next step directly without further purification. LCMS (ESI) m/z 207 (M+H)⁺.

[00749] **Example 124G:** A mixture of *N*-(4-(4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrrolo[1,2-*f*][1,2,4]triazin-2-ylthio)phenyl)-2-chloroacetamide (50 mg, 0.12 mmol), *N*-((*S*)-4,4-difluoropyrrolidin-3-yl)pivalamide (25 mg, 0.12 mmol), and K₂CO₃ (33 mg, 0.24 mmol) in *N,N*-dimethylformamide (0.5 mL) was stirred at 40 °C for 16 h. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC eluting with 10:10:1 EtOAc:DCM/MeOH to afford *N*-((*S*)-1-((4-(4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrrolo[1,2-*f*][1,2,4]triazin-2-ylthio)phenylcarbamoyl)methyl)-4,4-difluoropyrrolidin-3-yl)pivalamide as a yellow solid (5 mg, 7%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.08 (s, 1H), 10.59 (s, 1H), 10.12 (s, 1H), 7.78 (d, 2H), 7.58 (m, 3H), 7.22 (s, 1H), 6.59 (s, 1H), 5.67 (s, 1H), 4.62 (m, 1H), 3.47 (m, 4H), 2.99 (m, 1H), 2.74 (m, 1H), 2.05 (m, 3H), 1.14 (s, 6H); LCMS (ESI) m/z 584 (M+H)⁺.

Example 125**Preparation of N-tert-Butyl-3-fluoro-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide**

[00750] N-tert-Butyl-3-fluoro-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide was prepared using a procedure analogous to that described in Example 119B, substituting t-butylamine for 2-(ethylamino)ethanol used in Example 119B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.07 (s, 1H), 10.63 (s, 1H), 10.25 (s, 1H), 7.78 (d, 2H), 7.60 (s, 1H), 7.43 (s, 1H), 7.23 (s, 1H), 6.58 (m, 1H), 5.65 (s, 1H), 3.34 (m, 2H), 3.13 (m, 4H), 2.80 (s, 1H), 2.37 (m, 1H), 2.16 (m, 1H), 2.04 (s, 3H), 1.30 (s, 9H); LCMS (ESI) *m/z* 566 (M + H)⁺.

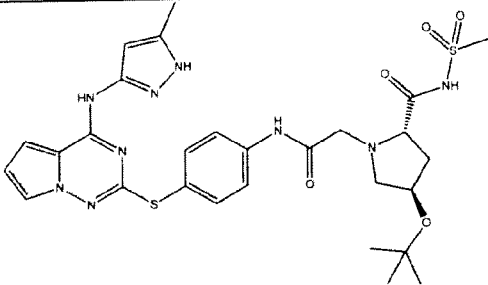
Example 126**Preparation of N,N-Dimethyl-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3(R)-carboxamide**

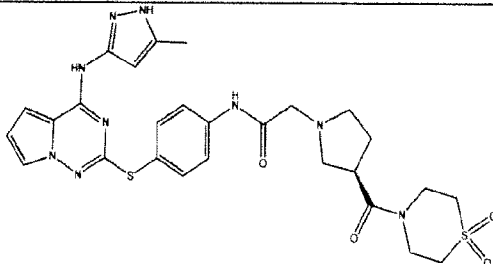
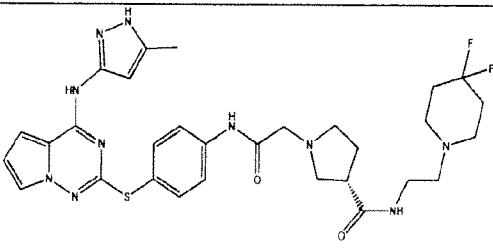
[00751] **Example 126A Step 1:** To a solution of (R)-1-(tert-butoxycarbonyl)pyrrolidine-3-carboxylic acid (125 mg, 0.58 mmol) in DMF (3 mL) was added HATU (242 mg, 0.638 mmol) and the mixture was stirred at rt for 5 min, then 2M dimethylamine/THF (0.87 mL) and DIEA (0.222 mL, 1.16 mmol) were added sequentially, and the mixture was stirred for 1 h, at which time completeness of the reaction was assessed by LCMS. The mixture was diluted with EtOAc and washed with water and brine, then dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with MeOH/DCM to afford (R)-tert-butyl 3-(dimethylcarbamoyl)pyrrolidine-1-carboxylate as a solid (127 mg, 70 %).

[00752] **Example 126A Step 2:** (R)-tert-Butyl 3-(dimethylcarbamoyl)pyrrolidine-1-carboxylate (125 mg) was dissolved in a 1:1 mixture of 4N HCl/dioxane and EtOAc and the mixture was stirred at ambient temperature for 1 h, at which time completion of the reaction was determined by LCMS. The mixture was concentrated under reduced pressure to afford (R)-N,N-dimethylpyrrolidine-3-carboxamide hydrochloride, which was used without further purification.

[00753] Example 126B: To a solution of 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 016B (50 mg, 0.121 mmol) in DMF (3 mL) were added sequentially (R)-N,N-dimethylpyrrolidine-3-carboxamide hydrochloride (60.6 mg, 0.242 mmol), diisopropylethylamine (84.3 μ L, 0.484 mmol), and potassium iodide (20.05 mg, 0.125 mmol), and the mixture was heated at 50 $^{\circ}$ C for 12 h, at which time formation of product was determined by LCMS. The mixture was purified by preparative HPLC (Phenomenex phenylhexyl reverse phase column) eluting with a gradient of solvent B (0.05% HOAc/CH₃CN) in solvent A (0.05% HOAc/H₂O) to afford N,N-dimethyl-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3(R)-carboxamide as a white solid (59.02 mg, 78 %). ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.06 (s, 1H), 10.63 (s, 1H), 10.18 (s, 1H), 7.86 (d, 2H), 7.57 (m, 3H), 7.22 (s, 1H), 6.57 (s, 1H), 5.64 (s, 1H), 3.43 (s, 2H), 3.00 (s, 3H), 2.86 (s, 3H), 2.84 (m, 1H), 2.17 (m, 3H), 2.14 (m, 1H), 2.10 (s, 3H), 1.89 (m, 1H); LCMS (ESI) *m/z* 543 (M+Na)⁺.

[00754] The following compounds were prepared in a similar manner.

Exam. No.	Structure	Compound name	LC MS (M+H) ⁺ except where otherwise indicated
126-i		(2S,4R)-4-(tert-butoxy)-1-(2-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)-N-(methylsulfonyl)pyrrolidine-2-carboxamide	642

Exam. No.	Structure	Compound name	LC MS (M+H) ⁺ except where otherwise indicated
126-ii		(R)-2-(3-(1,1-dioxidothiomorpholine-4-carbonyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	610
126-iii		(S)-N-(2-(4,4-difluoropiperidin-1-yl)ethyl)-1-(2-((4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)pyrrolidine-3-carboxamide	637 (M-H)

Example 127

Preparation of 2-((R)-3-((R)-3-Hydroxypyrrolidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00755] **Example 127A:** ((R)-3-hydroxypyrrolidin-1-yl)((R)-pyrrolidin-3-yl)methanone was prepared using a procedure analogous to that described in Example 126A, substituting (R)-pyrrolidin-3-ol for the dimethylamine used in Example 126A.

[00756] **Example 127B:** 2-((R)-3-((R)-3-hydroxypyrrolidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was synthesized as a white solid (22.59 mg, 28 %) using a procedure analogous to that described in Example 126B, substituting ((R)-3-

hydroxypyrrolidin-1-yl)((R)-pyrrolidin-3-yl)methanone hydrochloride for the (R)-N,N-dimethylpyrrolidine-3-carboxamide hydrochloride used in Example 126B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.11 (s, 1H), 10.65 (s, 1H), 10.22 (s, 1H), 7.86 (d, 2H), 7.60 (m, 3H), 7.23 (s, 1H), 6.59 (s, 1H), 5.64 (s, 1H), 5.01 (d, 1H), 4.27 (m, 2H), 3.71-3.05 (m, 6H), 2.80-2.71 (m, 4H), 2.04-1.91 (m, 7H); LCMS (ESI) *m/z* 562 (M+H)⁺.

Example 128

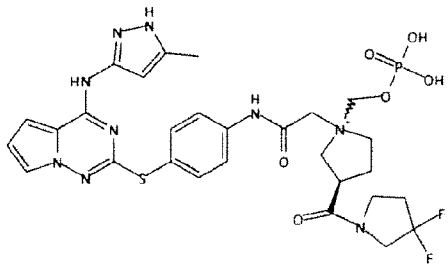
Preparation of (R)-2-(3-(3,3-Difluoropyrrolidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-*f*][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00757] **Example 128A:** (R)-(3,3-difluoropyrrolidin-1-yl)(pyrrolidin-3-yl)methanone hydrochloride was prepared using a procedure analogous to that described in Example 126A, substituting 3,3-difluoropyrrolidine for the dimethylamine used in Example 126A.

[00758] **Example 128B:** (R)-2-(3-(3,3-difluoropyrrolidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-*f*][1,2,4]triazin-2-ylthio)phenyl)acetamide was synthesized as a white solid (29.02 mg, 34 %) using a procedure analogous to that described in Example 126B, substituting (R)-(3,3-difluoropyrrolidin-1-yl)(pyrrolidin-3-yl)methanone hydrochloride for the (R)-N,N-dimethylpyrrolidine-3-carboxamide hydrochloride used in Example 126B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.05 (s, 1H), 10.63 (s, 1H), 10.13 (s, 1H), 7.84 (d, 2H), 7.58 (m, 3H), 7.25 (s, 1H), 6.59 (s, 1H), 5.64 (s, 1H), 3.77-3.24 (m, 8H), 2.81-2.70 (m, 5H), 2.09-2.03 (m, 5H); LCMS (ESI) *m/z* 582 (M+H)⁺.

[00759] The following compound was prepared in a similar manner.

Exam. No.	Structure	Compound name	LC MS (M+H) ⁺

128-i		(3R)-3-(3,3-difluoropyrrolidin-1-carbonyl)-1-(2-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)-1-((phosphonooxy)methyl)pyrrolidin-1-ium	692
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Example 129

Preparation of 2-[*trans*-3-(4-Fluoro-phenoxy)-4-hydroxy-pyrrolidin-1-yl]-N-{4-[6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide

[00760] 2-[*trans*-3-(4-Fluoro-phenoxy)-4-hydroxy-pyrrolidin-1-yl]-N-{4-[6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide was prepared as a white solid (17.11 mg, 31 %) using a procedure analogous to that described in Example 054, substituting 2-chloro-N-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 172A for the 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide used in Example 054B. The crude reaction mixture was purified by silica gel chromatography eluting with MeOH/DCM. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.03 (s, 1H), 10.48 (s, 1H), 10.03 (s, 1H), 7.77 (d, 2H), 7.64 (d, 2H), 7.47 (s, 1H), 7.16-6.97 (m, 5H), 5.60 (s, 1H), 5.47 (d, 1H), 4.54 (d, 1H), 4.15 (d, 1H), 3.32 (s, 2H), 3.21-3.04 (m, 2H), 2.79-2.75 (m, 2H), 2.20 (s, 3H), 2.10 (s, 3H); LCMS (ESI) *m/z* 589 (M+H)⁺.

Example 130

Preparation of (R)-N-(4-(6-Methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(pyrrolidine-1-carbonyl)pyrrolidin-1-yl)acetamide

[00761] **Example 130A:** (R)-Pyrrolidin-1-yl-pyrrolidin-3-yl-methanone was prepared using a procedure analogous to that described in Example 126A, substituting pyrrolidine for the dimethylamine used in Example 126A.

[00762] **Example 130B:** (R)-N-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(pyrrolidine-1-carbonyl)pyrrolidin-1-yl)acetamide was synthesized as a white solid (9.17 mg, 14 %) using a procedure analogous to that described in Example 126B, substituting pyrrolidin-1-yl-pyrrolidin-3-yl-methanone hydrochloride for the (R)-N,N-dimethylpyrrolidine-3-carboxamide hydrochloride, and 2-chloro-N-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 172A for the 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide used in Example 126B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.05 (s, 1H), 10.49 (s, 1H), 10.18 (s, 1H), 7.84 (d, 2H), 7.55 (d, 2H), 7.42 (s, 1H), 7.01 (s, 1H), 5.59 (s, 1H), 3.46-3.16 (m, 7H), 2.80-2.66 (m, 4H), 2.19 (s, 3H), 2.08 (s, 3H), 1.90-1.77 (m, 6H); LCMS (ESI) *m/z* 560 (M+H)⁺.

Example 131

Preparation of (R)-N-(4-(4-(5-Methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(piperidine-1-carbonyl)pyrrolidin-1-yl)acetamide

[00763] **Example 131A:** (*R*)-Cyclohexyl-pyrrolidin-3-yl-methanone was prepared using a procedure analogous to that described in Example 126A, substituting piperidine for the dimethylamine used in Example 126A.

[00764] **Example 131B:** (R)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(piperidine-1-carbonyl)pyrrolidin-1-yl)acetamide was synthesized as a white solid (24.56 mg, 30 %) using a procedure analogous to that described in Example 126B, substituting (*R*)-cyclohexyl-pyrrolidin-3-yl-methanone hydrochloride for the (*R*)-N,N-dimethylpyrrolidine-3-carboxamide hydrochloride used in Example 126B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.06 (s, 1H), 10.63 (s, 1H), 10.20 (s, 1H), 7.85 (d, 2H), 7.58 (m, 3H), 7.20 (s, 1H), 6.58 (s, 1H), 5.64 (s, 1H), 3.57-3.43 (m, 4H), 2.95-2.30 (m, 6H), 2.20-1.80 (m, 6H), 1.70-1.35 (m, 6H); LCMS (ESI) *m/z* 560 (M+H)⁺.

Example 132

Preparation of 2-((R)-3-((S)-3-Hydroxypyrrolidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00765] **Example 132A:** ((S)-3-hydroxypyrrolidin-1-yl)((R)-pyrrolidin-3-yl)methanone was prepared using a procedure analogous to that described in Example 126A, substituting (S)-pyrrolidin-3-ol for the dimethylamine used in Example 126A.

[00766] **Example 132B:** 2-((R)-3-((S)-3-hydroxypyrrolidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was prepared as a white solid (20.35 mg, 25%) using a procedure analogous to that described in Example 126B, substituting ((S)-3-hydroxypyrrolidin-1-yl)((R)-pyrrolidin-3-yl)methanone hydrochloride for the (R)-N,N-dimethylpyrrolidine-3-carboxamide hydrochloride used in Example 126B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.06 (s, 1H), 10.63 (s, 1H), 10.19 (s, 1H), 7.85 (d, 2H), 7.58 (m, 3H), 7.23 (s, 1H), 6.58 (m, 1H), 5.64 (s, 1H), 5.03-4.92 (m, 1H), 4.25-4.11 (m, 2H), 3.72-3.17 (m, 6H), 2.80-2.69 (m, 4H), 2.20-1.70 (m, 7H); LCMS (ESI) *m/z* 562 (M+H)⁺.

Example 133

Preparation of (R)-N-(4-(4-(5-Methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(3-(pyrrolidin-1-yl)propoxy)pyrrolidin-1-yl)acetamide

[00767] **Example 133A:** (R)-benzyl 3-(3-chloropropoxy)pyrrolidine-1-carboxylate was prepared using a procedure analogous to that described in Example 076A, substituting 1-bromo-3-chloropropane for the ethyl bromoacetate used in Example 076A.

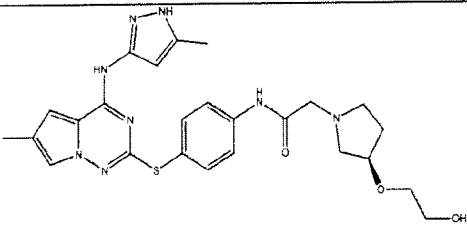
[00768] **Example 133B Step 1:** To a stirring solution of (R)-benzyl 3-(3-chloropropoxy)pyrrolidine-1-carboxylate from Example 133A (50 mg, 0.17 mmol) in CH₃CN were added N,N-diisopropylethylamine (100 μL, 0.57 mmol) and pyrrolidine (100 μL, 1.36 mmol), and the mixture was heated at 85 °C for 24 h. The mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography eluting with 10% MeOH in EtOAc with 1% Et₃N to give (R)-benzyl

3-(3-(pyrrolidin-1-yl)propoxy)pyrrolidine-1-carboxylate as a light brown oil (35 mg, 56% yield). LCMS (ESI) m/z 333 ($M + H$)⁺.

[00769] **Example 133B Step 2:** To (R)-benzyl 3-(3-(pyrrolidin-1-yl)propoxy)pyrrolidine-1-carboxylate (55 mg, 0.17 mmol) in MeOH (1 mL) under Ar was added 10% Pd/C (10 mg). The mixture was stirred under a hydrogen atmosphere at 65 °C for 2 h, and then filtered through Celite. The filtrate was concentrated under reduced pressure to give (R)-1-(3-(pyrrolidin-3-yloxy)propyl)pyrrolidine as a colorless oil (20 mg, 99% yield). LCMS (ESI) m/z 199 ($M + H$)⁺.

[00770] **Example 133C:** (R)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(3-(pyrrolidin-1-yl)propoxy)pyrrolidin-1-yl)acetamide was prepared using a procedure analogous to that described in Example 018B, substituting (R)-1-(3-(pyrrolidin-3-yloxy)propyl)pyrrolidine from Example 133B for the pyrrolidine used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.97 (s, 1H), 10.63 (s, 1H), 10.01 (s, 1H), 7.78 (br d, 2H), 7.58 (brs, 3H), 7.21 (s, 1H), 6.58 (m, 1H), 5.64 (s, 1H), 4.01 (s, 1H), 3.36 (m, 2H), 2.85 (s, 1H), 2.71 (s, 1H), 2.04 (m, 4H), 1.91 (m, 4H), 1.66 (br s, 8H); LCMS (ESI) m/z 576 ($M + H$)⁺.

The following compound was prepared following the steps in Example 133B-C:

Exam. No.	Structure	Compound name	LC MS ($M+H$) ⁺
133-i		(R)-2-(3-(2-hydroxyethoxy)pyrrolidin-1-yl)-N-(4-((6-methyl-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	523

Example 134

Preparation of (R)-1-(2-(4-(4-(5-Methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)-N-(2-morpholinoethyl)pyrrolidine-3-carboxamide

[00771] **Example 134A:** (R)-N-(2-morpholinoethyl)pyrrolidine-3-carboxamide was prepared using a procedure analogous to that described in Example 126A, substituting 2-morpholinoethanamine for the dimethylamine used in Example 126A.

[00772] **Example 134B:** (R)-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)-N-(2-morpholinoethyl)pyrrolidine-3-carboxamide was synthesized as its acetate salt (27.77 mg, 29 %) using a procedure analogous to that described in Example 126B, substituting (R)-N-(2-morpholinoethyl)pyrrolidine-3-carboxamide hydrochloride for the (R)-N,N-dimethylpyrrolidine-3-carboxamide hydrochloride used in Example 126B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.65 (s, 1H), 10.21 (s, 1H), 7.89-7.82 (m, 3H), 7.59-7.57 (m, 3H), 7.23 (s, 1H), 6.59-6.57 (m, 1H), 5.64 (s, 1H), 3.56-3.08 (m, 5H), 2.91-2.72 (m, 5H), 2.68-2.35 (m, 6H), 2.05-1.90 (m, 8H), 1.25 (m, 3H); LCMS (ESI) *m/z* 605 (M+H)⁺.

Example 135

Preparation of (R)-1-(2-(4-(4-(5-Methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)-N-(2-(pyrrolidin-1-yl)ethyl)pyrrolidine-3-carboxamide

[00773] **Example 135A:** (R)-N-(2-(pyrrolidin-1-yl)ethyl)pyrrolidine-3-carboxamide was prepared using a procedure analogous to that described in Example 126A, substituting 2-(pyrrolidin-1-yl)ethanamine for the dimethylamine used in Example 126A.

[00774] **Example 135B:** (R)-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)-N-(2-(pyrrolidin-1-yl)ethyl)pyrrolidine-3-carboxamide was synthesized as its acetate salt (30.73 mg, 33 %) using a procedure analogous to that described in Example 126B, substituting (R)-N-(2-(pyrrolidin-1-yl)ethyl)pyrrolidine-3-carboxamide hydrochloride for the (R)-N,N-dimethylpyrrolidine-3-carboxamide hydrochloride used in Example 126B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.64 (s, 1H), 10.16 (s, 1H), 7.93-7.83 (m, 3H), 7.59 (m, 3H), 7.23 (s, 1H), 6.58 (m, 1H), 5.64 (s, 1H), 3.38-3.2.50 (m, 11H), 2.10-1.80 (m, 9H), 1.66 (m, 4H); LCMS (ESI) *m/z* 589 (M+H)⁺.

Example 136**Preparation of (R)-1-(2-(4-(4-(5-Methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)-N-(3-(piperidin-1-yl)propyl)pyrrolidine-3-carboxamide**

[00775] **Example 136A:** (R)-N-(3-(piperidin-1-yl)propyl)pyrrolidine-3-carboxamide was prepared using a procedure analogous to that described in Example 126A, substituting 3-(piperidin-1-yl)propan-1-amine for the dimethylamine used in Example 126A.

[00776] **Example 136B:** (R)-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)-N-(3-(piperidin-1-yl)propyl)pyrrolidine-3-carboxamide was synthesized as its acetate salt (39.35 mg, 40.1 %) using a procedure analogous to that described in Example 126B, substituting (R)-N-(3-(piperidin-1-yl)propyl)pyrrolidine-3-carboxamide hydrochloride for the (R)-N,N-dimethylpyrrolidine-3-carboxamide hydrochloride used in Example 126B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.64 (s, 1H), 10.14 (s, 1H), 7.91-7.81 (m, 3H), 7.59-7.56 (m, 3H), 7.23 (s, 1H), 6.59-6.57 (m, 1H), 5.64 (s, 1H), 3.42-3.06 (m, 4H), 2.87-2.64 (m, 4H), 2.30-2.22 (m, 4H), 2.03-1.84 (m, 11H), 1.57-1.34 (m, 8H); LCMS (ESI) *m/z* 617 (M+H)⁺.

Example 137**Preparation of (R)-1-(2-(4-(4-(5-Methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)-N-(2-(piperidin-1-yl)ethyl)pyrrolidine-3-carboxamide**

[00777] **Example 137A:** (R)-N-(2-(piperidin-1-yl)ethyl)pyrrolidine-3-carboxamide was prepared using a procedure analogous to that described in Example 126A, substituting 2-(piperidin-1-yl)ethanamine for the dimethylamine used in Example 126A.

[00778] **Example 137B:** (R)-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)-N-(2-(piperidin-1-yl)ethyl)pyrrolidine-3-carboxamide was synthesized as its acetate salt (32.42 mg, 34 %) using a procedure analogous to that described in Example 126B, substituting (R)-N-(2-(piperidin-1-yl)ethyl)pyrrolidine-3-carboxamide hydrochloride

for the (R)-N,N-dimethylpyrrolidine-3-carboxamide hydrochloride used in Example 126B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.63 (s, 1H), 10.15 (s, 1H), 7.85-7.82 (m, 3H), 7.59-7.56 (m, 3H), 7.23 (s, 1H), 6.59-6.57 (m, 1H), 5.64 (s, 1H), 3.39-2.61 (m, 9H), 2.51-2.29 (m, 6H), 2.03-1.90 (m, 8H), 1.48-1.33 (m, 6H); LCMS (ESI) *m/z* 603 (M+H)⁺.

Example 138

Preparation of (R)-2-(3-(3-(3,3-Difluoropyrrolidin-1-yl)propoxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00779] **Example 138A:** (R)-3,3-difluoro-1-(3-(pyrrolidin-3-yloxy)propyl)pyrrolidine was prepared using a procedure analogous to that described in Example 133B, substituting 3,3-difluoropyrrolidine hydrochloride for the pyrrolidine used in Example 133B. LCMS (ESI) *m/z* 235 (M + H)⁺.

[00780] **Example 138B:** (R)-2-(3-(3-(3,3-difluoropyrrolidin-1-yl)propoxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was prepared using a procedure analogous to that described in Example 018B, substituting (R)-3,3-difluoro-1-(3-(pyrrolidin-3-yloxy)propyl)pyrrolidine from Example 138A for the pyrrolidine used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.04 (s, 1H), 10.64 (s, 1H), 10.00 (s, 1H), 7.78 (d, 2H), 7.58 (s, 1H), 7.56 (d, 2H), 7.22 (s, 1H), 6.58 (m, 1H), 5.64 (s, 1H), 4.01 (s, 1H), 3.52-3.10 (m, 4H), 3.00-2.75 (m, 2H), 2.75-2.32 (m, 8H), 2.20 (m, 2H), 2.03 (s, 3H), 1.65 (m, 3H); LCMS (ESI) *m/z* 612 (M + H)⁺.

Example 139

Preparation of (R)-1-(2-(4-(4-(5-Methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)-N-(3-morpholinopropyl)pyrrolidine-3-carboxamide

[00781] **Example 139A:** (R)-N-(3-morpholinopropyl)pyrrolidine-3-carboxamide was prepared using a procedure analogous to that described in Example 126A, substituting 3-morpholinopropan-1-amine for the dimethylamine used in Example 126A.

[00782] **Example 139B:** (R)-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)-N-(3-morpholinopropyl)pyrrolidine-3-carboxamide was synthesized as its acetate salt (40.52 mg, 41.1 %) using a procedure analogous to that described in Example 126B, substituting (R)-N-(3-morpholinopropyl)pyrrolidine-3-carboxamide hydrochloride for the (R)-N,N-dimethylpyrrolidine-3-carboxamide hydrochloride used in Example 126B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.05 (s, 1H), 10.63 (s, 1H), 10.14 (s, 1H), 7.91-7.81 (m, 3H), 7.59-7.56 (m, 3H), 7.23 (s, 1H), 6.59-6.57 (m, 1H), 5.63 (s, 1H), 3.55-2.61 (m, 13H), 2.30-2.23 (m, 6H), 2.03-1.96 (m, 8H), 1.59-1.52 (m, 2H); LCMS (ESI) *m/z* 619 (M+H)⁺.

Example 140

Preparation of (R)-N-(4-(4-(5-Methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(morpholine-4-carbonyl)pyrrolidin-1-yl)acetamide

[00783] **Example 140A:** (R)-morpholino(pyrrolidin-3-yl)methanone was prepared using a procedure analogous to that described in Example 126A, substituting morpholine for the dimethylamine used in Example 126A.

[00784] **Example 140B:** (R)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(morpholine-4-carbonyl)pyrrolidin-1-yl)acetamide was synthesized as its acetate salt (25.4 mg, 28 %) using a procedure analogous to that described in Example 126B, substituting (R)-morpholino(pyrrolidin-3-yl)methanone hydrochloride for the (R)-N,N-dimethylpyrrolidine-3-carboxamide hydrochloride used in Example 126B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.02 (s, 1H), 10.63 (s, 1H), 10.15 (s, 1H), 7.85 (brs, 2H), 7.67-7.58 (m, 3H), 6.57 (s, 1H), 5.63 (s, 1H), 3.70-3.37 (m, 11H), 3.30-2.68 (m, 5H), 2.27-2.03 (m, 8H); LCMS (ESI) *m/z* 562 (M+H)⁺.

Example 141

Preparation of (R)-N-(4-Fluorophenyl)-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide

[00785] **Example 141A:** (R)-N-(4-fluorophenyl)pyrrolidine-3-carboxamide was prepared using a procedure analogous to that described in Example 126A, substituting 4-fluoroaniline for the dimethylamine used in Example 126A.

[00786] **Example 141B:** (R)-N-(4-fluorophenyl)-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide was synthesized as a white solid (135.37 mg, 67 %) using a procedure analogous to that described in Example 126B, substituting (R)-N-(4-fluorophenyl)pyrrolidine-3-carboxamide for the (R)-N,N-dimethylpyrrolidine-3-carboxamide hydrochloride used in Example 126B. The crude reaction mixture was purified by silica gel chromatography eluting with MeOH/DCM. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.14 (s, 1H), 10.64 (s, 1H), 10.31 (d, 2H), 7.86-7.56 (m, 8H), 7.23-7.10 (m, 3H), 6.58 (s, 1H), 5.63 (s, 1H), 3.31 (s, 2H), 2.97-2.47 (m, 5H), 2.04 (s, 5H); LCMS (ESI) *m/z* 586 (M+H)⁺.

Example 142

Preparation of N-(4-(4-(5-Methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-((R)-3-(tert-butylsulfonyl)pyrrolidin-1-yl)acetamide

[00787] **Example 142A:** To a solution of (R)-tert-butyl 3-(tert-butylthio)pyrrolidine-1-carboxylate from Example 154A (248 mg, 0.95 mmol) in 1:1 MeOH/THF (4 mL) was added dropwise a solution of oxone in water (1 mL) at 0 °C. The mixture was allowed to warm to rt and stir for 1 h. The mixture was concentrated and the solid was collected by filtration washing with solvent to afford (R)-tert-butyl 3-(tert-butylsulfonyl)pyrrolidine-1-carboxylate (212 mg, 76 %). LCMS *m/z* 292 (M+H)⁺.

[00788] **Example 142B:** To a solution of (R)-tert-butyl 3-(tert-butylsulfonyl)pyrrolidine-1-carboxylate (248 mg, 0.95 mmol) in MeOH (2 mL) at 0 °C was added dropwise 4.5 M HCl/EtOAc. The mixture was allowed to warm to rt and stir for 1 h. The mixture was concentrated and dried to afford (R)-3-(tert-butylsulfinyl)pyrrolidine hydrochloride (180 mg, 80 %). LCMS *m/z* 192 (M+H)⁺. The crude product was used directly in the next step without further purification.

[00789] **Example 142C:** To a solution of N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4] triazin-2-ylthio)phenyl)-2-chloroacetamide (100 mg, 0.24 mmol) in THF (2 mL) under N₂ was added tetra-butylammonium iodide (90 mg, 0.24 mmol) at rt and the mixture was stirred for 10 min. (R)-3-(tert-

butylsulfinyl)pyrrolidine hydrochloride (54 mg, 2 eq., 0.24 mmol) and DIEA (0.5 mL) were added and the mixture was stirred at 40 °C overnight. Water (2 mL) was added and the mixture was extracted with EtOAc (3 x 5 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The solid was washed with ether and dried under vacuum, then purified by preparative TLC eluting with 10:1 DCM/MeOH to afford N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-((R)-3-(tert-butylsulfonyl)pyrrolidin-1-yl)acetamide (27 mg, 20%). ¹H NMR (400 MHz, DMSO-d₆) δ 12.21 (s, 1H), 10.61 (s, 1H), 10.11 (s, 1H), 7.80 (d, 2H), 7.58 (m, 3H), 7.22 (s, 1H), 6.58 (s, 1H), 5.63 (s, 1H), 4.11 (s, 1H), 3.38 (s, 2H), 3.02 (m, 2H), 2.78 (m, 2H), 2.20 (m, 2H), 2.00 (s, 3H); LCMS *m/z* 569 (M+H)⁺.

Example 143

(R)-2-(3-(3-(Azepan-1-yl)propoxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00790] **Example 143A:** (R)-1-(3-(pyrrolidin-3-yloxy)propyl)azepane was prepared using a procedure analogous to that described in Example 133B, substituting homopiperidine for the pyrrolidine used in Example 133B. LCMS (ESI) *m/z* 237 (M + H)⁺.

[00791] **Example 143B:** (R)-2-(3-(3-(azepan-1-yl)propoxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was prepared using a procedure analogous to that described in Example 018B, substituting (R)-1-(3-(pyrrolidin-3-yloxy)propyl)azepane from Example 143A for the pyrrolidine used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.03 (s, 1H), 10.63 (s, 1H), 10.01 (s, 1H), 7.78 (d, 2H), 7.58 (s, 1H), 7.56 (d, 2H), 7.22 (s, 1H), 6.58 (m, 1H), 5.65 (s, 1H), 4.03 (s, 1H), 3.52-3.10 (m, 4H), 3.00-2.75 (m, 6H), 2.58 (m, 2H), 2.04 (s, 3H), 1.40-1.80 (m, 8H); LCMS (ESI) *m/z* 604 (M + H)⁺.

Example 144

Preparation of (R)-2-(3-(4,4-Difluoropiperidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00792] **Example 144A:** (R)-(4,4-difluoropiperidin-1-yl)(pyrrolidin-3-yl)methanone was prepared using a procedure analogous to that described in Example 126A, substituting 4,4-difluoropiperidine for the dimethylamine used in Example 126A.

[00793] **Example 144B:** (R)-2-(3-(4,4-difluoropiperidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was synthesized as its acetate salt (51.38mg, 54 %) using a procedure analogous to that described in Example 126B, substituting (R)-(4,4-difluoropiperidin-1-yl)(pyrrolidin-3-yl)methanone hydrochloride for the (R)-N,N-dimethylpyrrolidine-3-carboxamide hydrochloride used in Example 126B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.07 (s, 1H), 10.63 (s, 1H), 10.15 (s, 1H), 7.85 (d, 2H), 7.60 (m, 3H), 7.23 (s, 1H), 6.59 (s, 1H), 5.64 (s, 1H), 3.62-3.17 (m, 6H), 2.91-2.51 (m, 5H), 2.20-2.80 (m, 10H), 1.11-1.07 (m, 2H); LCMS (ESI) *m/z* 596 (M+H)⁺.

Example 145

Preparation of (R)-N-(3-Fluorophenyl)-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide

[00794] **Example 145A:** (R)-N-(4-fluorophenyl)pyrrolidine-3-carboxamide was prepared using a procedure analogous to that described in Example 126A, substituting 3-fluoroaniline for the dimethylamine used in Example 126A.

[00795] **Example 145B:** (R)-N-(3-fluorophenyl)-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide was synthesized as a white solid (75 mg, 24 %) using a procedure analogous to that described in Example 126B, substituting (R)-N-(4-fluorophenyl)pyrrolidine-3-carboxamide hydrochloride for the (R)-N,N-dimethylpyrrolidine-3-carboxamide hydrochloride used in Example 126B. The crude reaction mixture was purified by silica gel chromatography eluting with MeOH/DCM. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.07 (s, 1H), 10.64 (s, 1H), 10.22 (s, 1H), 10.14 (s, 1H), 7.83 (d, 2H), 7.66-7.58 (m, 4H), 7.38-7.34 (m, 2H), 7.23 (s, 1H), 6.89-6.85 (m, 1H), 6.60-6.59 (m, 1H), 5.66 (s, 1H), 3.35 (s, 2H), 3.19-2.51 (m, 5H), 2.04 (s, 5H); LCMS (ESI) *m/z* 586 (M+H)⁺.

Example 146**Preparation of (R)-N-Cyclohexyl-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide**

[00796] **Example 146A:** (R)-N-cyclohexylpyrrolidine-3-carboxamide was prepared using a procedure analogous to that described in Example 126A, substituting cyclohexanamine for the dimethylamine used in Example 126A.

[00797] **Example 146B:** (R)-N-cyclohexyl-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl) pyrrolidine-3-carboxamide was synthesized as a white solid (95.91 mg, 54 %) using a procedure analogous to that described in Example 126B, substituting (R)-N-cyclohexylpyrrolidine-3-carboxamide hydrochloride for the (R)-N,N-dimethylpyrrolidine-3-carboxamide hydrochloride used in Example 126B. The crude reaction mixture was purified by silica gel chromatography eluting with MeOH/DCM. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.10 (s, 1H), 10.65 (s, 1H), 10.16 (s, 1H), 7.96-7.60 (m, 6H), 7.24 (s, 1H), 6.59 (s, 1H), 5.65 (s, 1H), 3.53-3.20 (m, 4H), 2.89-2.52 (m, 4H), 2.15-1.95 (m, 4H), 1.70-1.56 (m, 5H), 1.36-1.16 (m, 6H); LCMS (ESI) *m/z* 574 (M+H)⁺.

Example 147**Preparation of 2-(*cis*-3-(4-Fluorophenoxy)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide**

[00798] **Example 147A Step 1:** To *cis*-benzyl 3-(4-fluorophenoxy)-4-hydroxypyrrolidine-1-carboxylate from Example 054A (556 mg, 1.68 mmol), 4-nitrobenzoic acid (340 mg, 2.03 mmol), triphenylphosphine (530 mg, 2.02 mmol), and triethylamine (0.40 mL, 2.87 mmol) in tetrahydrofuran (5 mL) at 0 °C was added slowly diethyl azodicarboxylate (0.32 mL, 2.03 mmol). The ice bath was removed and the mixture was stirred at rt for 17 h under an argon atmosphere. The mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 10-100% EtOAc/hexanes to afford *cis*-benzyl 3-(4-fluorophenoxy)-4-(4-nitrobenzoyloxy) pyrrolidine-1-carboxylate as a solid (176.1 mg, 21%). LCMS (ESI) *m/z* 481 (M + H)⁺.

[00799] **Example 147A Step 2:** A mixture of *cis*-benzyl 3-(4-fluorophenoxy)-4-(4-nitrobenzoyloxy) pyrrolidine-1-carboxylate (176.1 mg, 0.367 mmol) and potassium carbonate (100mg, 0.724 mmol) in MeOH (1 mL) and water (0.1 mL) was stirred at rt for 18 h. The mixture was partitioned between EtOAc (50 mL) and saturated aq sodium chloride (50 mL), and the aqueous phase was further extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (75 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to give *cis*-benzyl 3-(4-fluorophenoxy)-4-hydroxypyrrolidine-1-carboxylate as an oil (106.8 mg, 88%). LCMS (ESI) m/z 332 ($M + H$)⁺.

[00800] **Example 147A Step 3:** A mixture of *cis*-benzyl 3-(4-fluorophenoxy)-4-hydroxypyrrolidine-1-carboxylate (106.8 mg, 0.322 mmol), 10% palladium on carbon (56 mg) and ethanol (2 mL) was stirred under an atmosphere of hydrogen gas at rt for 2 h. The mixture was filtered through Celite and concentrated under reduced pressure to give *cis*-4-(4-fluorophenoxy)pyrrolidin-3-ol as an oil (58 mg, 91%). LCMS (ESI) m/z 198 ($M + H$)⁺.

[00801] **Example 147B:** To a 1 dram vial were added *cis*-4-(4-fluorophenoxy)pyrrolidin-3-ol (58 mg, 0.294 mmol), N,N-dimethylacetamide (1 mL), 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 016B (110 mg, 0.266 mmol), diisopropylethylamine (0.20 mL, 1.21 mmol) and potassium iodide (25 mg, 0.151 mmol). The vial flushed with Ar, sealed, and stirred at 80 °C for 16 h. The mixture was partitioned between EtOAc (50 mL) and saturated aq sodium chloride (50 mL), and the aqueous phase was further extracted with EtOAc (3 x 50 mL). The combined extracts were washed with brine (3 x 50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residual oil was purified by silica gel chromatography eluting with 2-15% MeOH/DCM to afford 2-(*cis*-3-(4-fluorophenoxy)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide as a solid (103.2 mg, 68%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.06 (s, 1H), 10.63 (s, 1H), 9.98 (s, 1H), 7.81 (d, J = 8.0 Hz, 2H), 7.54-7.68 (m, 3H), 7.22 (br s, 1H), 7.08-7.13 (m, 2H), 6.96-7.00 (br s, 2H), 6.58 (m, 1H), 5.63 (s, 1H), 4.98 (d, J = 9.0 Hz, 1H), 4.68-4.72 (m,

1H), 4.31-4.35 (m, 1H), 3.20 (m, 1H), 3.01 (m, 1H), 2.78 (m, 1H), 2.68 (m, 1H), 1.93-2.03 (m, 5H); LCMS (ESI) m/z 575 (M + H)⁺.

Example 148

Preparation of (R)-2-(3-(4-Hydroxypiperidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00802] **Example 148A:** (R)-(4-Hydroxypiperidin-1-yl)(pyrrolidin-3-yl)methanone was prepared using a procedure analogous to that described in Example 126A, substituting piperidin-4-ol for the dimethylamine used in Example 126A.

[00803] **Example 148B:** (R)-2-(3-(4-Hydroxypiperidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was synthesized as its acetate salt (51.38 mg, 62 %) using a procedure analogous to that described in Example 126B, substituting (R)-(4-hydroxypiperidin-1-yl)(pyrrolidin-3-yl)methanone hydrochloride for the (R)-N,N-dimethylpyrrolidine-3-carboxamide hydrochloride used in Example 126B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.07 (s, 1H), 10.67 (s, 1H), 10.17 (s, 1H), 7.85 (d, 2H), 7.60-7.57 (m, 3H), 7.23 (s, 1H), 6.59 (s, 1H), 5.64 (s, 1H), 4.78 (brs, 1H), 4.01-2.67 (m, 14H), 2.10-1.65 (m, 10H); LCMS (ESI) m/z 598 (M+Na)⁺.

Example 149

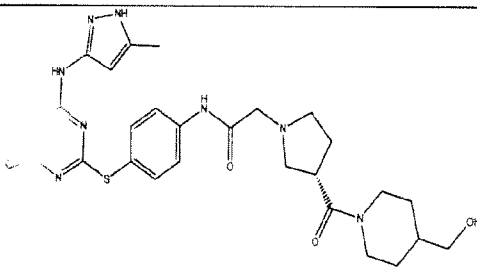
Preparation of (R)-2-(3-(4-(hydroxymethyl)piperidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00804] **Example 149A:** (R)-(4-(Hydroxymethyl)piperidin-1-yl)(pyrrolidin-3-yl)methanone was prepared using a procedure analogous to that described in Example 126A, substituting piperidin-4-ylmethanol for the dimethylamine used in Example 126A.

[00805] **Example 149B:** (R)-2-(3-(4-(Hydroxymethyl)piperidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was synthesized as its acetate salt (19 mg, 22 %) using a procedure analogous to that described in Example 126B, substituting (R)-(4-(hydroxymethyl)piperidin-1-yl)(pyrrolidin-3-yl)methanone hydrochloride for

the (R)-N,N-dimethylpyrrolidine-3-carboxamide hydrochloride used in Example 126B. ^1H NMR (300 MHz, DMSO- d_6) δ 12.07 (br s, 1H), 10.66 (s, 1H), 10.17 (s, 1H), 7.85 (d, 2H), 7.59 (m, 3H), 7.22 (s, 1H), 6.57 (s, 1H), 4.58 (m, 1H), 3.91 (m, 1H), 3.59-2.68 (m, 11H), 1.89-1.50 (m, 9H), 1.09-0.88 (m, 5H); LCMS (ESI) m/z 590 (M+H) $^+$.

The following compound was prepared in a similar manner.

Exam. No.	Structure	Compound name	LC MS (M+H) $^+$
149-i		(S)-2-(3-(4-(hydroxymethyl)piperidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide	590

Example 150

Preparation of (R)-N-Cyclopentyl-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide

[00806] **Example 150A:** (R)-N-Cyclopentylpyrrolidine-3-carboxamide was prepared using a procedure analogous to that described in Example 126A, substituting cyclopentanamine for the dimethylamine used in Example 126A.

[00807] **Example 150B:** (R)-N-Cyclopentyl-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide was synthesized as a white solid (105.4 mg, 43 %) using a procedure analogous to that described in Example 126B, substituting (R)-N-cyclopentylpyrrolidine-3-carboxamide hydrochloride for the (R)-N,N-dimethylpyrrolidine-3-carboxamide hydrochloride used in Example 126B. Crude reaction mixture was purified by silica gel chromatography eluting with MeOH/DCM. ^1H NMR (300 MHz, DMSO- d_6) δ 12.06 (s, 1H), 10.63 (s, 1H), 10.14 (s, 1H), 7.81 (d, 3H), 7.57 (m, 3H), 7.20 (m, 1H), 6.58 (m, 1H), 5.64 (s, 1H), 3.34 (s, 2H), 3.18 (d,

1H), 2.83-2.63 (m, 4H), 2.05 (s, 3H), 1.79-1.34 (m, 9H); LCMS (ESI) m/z 560 (M+H)⁺.

Example 151

Preparation of (R)-N-Cyclopropyl-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide

[00808] **Example 151A:** (R)-N-Cyclopropylpyrrolidine-3-carboxamide was prepared using a procedure analogous to that described in Example 126A, substituting cyclopropanamine for the dimethylamine used in Example 126A.

[00809] **Example 151B:** (R)-N-Cyclopropyl-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide was synthesized as a white solid (78.32 mg, 34 %) using a procedure analogous to that described in Example 126B, substituting (R)-N-cyclopropylpyrrolidine-3-carboxamide hydrochloride for (R)-N,N-dimethylpyrrolidine-3-carboxamide hydrochloride used in Example 126B. The crude reaction mixture was purified by silica gel chromatography eluting with MeOH/DCM. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.05 (s, 1H), 10.63 (s, 1H), 10.11 (s, 1H), 7.95 (d, 1H), 7.82 (s, 2H), 7.59 (m, 3H), 7.20 (s, 1H), 6.60 (s, 1H), 5.65 (s, 1H), 3.34 (s, 2H), 3.18-2.51 (m, 6H), 2.03 (s, 3H), 1.95 (m, 2H), 0.61 (m, 2H), 0.39 (m, 2H); LCMS (ESI) m/z 532 (M+H)⁺.

Example 152

Preparation of 2-(*trans*-3-Hydroxy-4-(pyridin-4-yloxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00810] **Example 152 Step 1:** *trans*-Benzyl 3-hydroxy-4-(pyridin-4-yloxy)pyrrolidine-1-carboxylate (70.0 mg, 0.22 mmol, 98%) was synthesized using a procedure analogous to that described in Example 114 Step 1, substituting 4-hydroxypyridine for the 3-fluorophenol used in Example 114 Step 1. LCMS (ESI) m/z 315 (M+H)⁺.

[00811] **Example 152 Step 2:** *trans*-4-(Pyridin-4-yloxy)pyrrolidin-3-ol (19.0 mg, 0.105 mmol) was prepared using a procedure analogous to that described in Example

114 Step 2 substituting *trans*-benzyl 3-hydroxy-4-(pyridin-4-yloxy)pyrrolidine-1-carboxylate from the previous step for the *trans*-benzyl 3-(3-fluorophenoxy)-4-hydroxypyrrolidine-1-carboxylate used in Example 114 Step 2. LCMS (ESI) m/z 181 (M+H)⁺.

[00812] **Example 152 Step 3:** 2-(*trans*-3-Hydroxy-4-(pyridin-4-yloxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was synthesized using a procedure analogous to that described in Example 018B, substituting *trans*-4-(pyridin-4-yloxy)pyrrolidin-3-ol for the pyrrolidine derivative used in Example 018B. The residue was purified by preparative HPLC (Phenomenex phenylhexyl reverse phase column) eluting with a gradient of solvent B (0.05% HOAc/CH₃CN) in solvent A (0.05% HOAc/H₂O) to afford the title compound (20.1 mg, 38%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.05 (s, 1H), 10.65 (s, 1H), 10.05 (s, 1H), 8.40 (br s, 2H), 7.80 (br s, 2H), 7.59 (br s, 3H), 7.20 (br s, 1H), 7.0 (br s, 2H), 6.60 (br s, 1H), 5.65 (br s, 1H), 4.70 (br s, 1H), 4.15 (br s, 2H), 3.10-3.20 (m, 2H), 2.80 (br s, 2H), 2.03 (s, 3H), 1.91 (s, 2H); LCMS (ESI) m/z 556 (M-H)⁻.

Example 153

Preparation of (R)-N-(4-(4-(5-Methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(3-(4-methylpiperazin-1-yl)propoxy)pyrrolidin-1-yl)acetamide

[00813] **Example 153A:** (R)-1-Methyl-4-(3-(pyrrolidin-3-yloxy)propyl)piperazine was prepared using a procedure analogous to that described in Example 133B, substituting N-methylpiperazine for the pyrrolidine used in Example 133B. LCMS (ESI) m/z 228 (M + H)⁺.

[00814] **Example 153B:** (R)-N-(4-(4-(5-Methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(3-(4-methylpiperazin-1-yl)propoxy)pyrrolidin-1-yl)acetamide was prepared using a procedure analogous to that described in Example 018B, substituting (R)-1-methyl-4-(3-(pyrrolidin-3-yloxy)propyl)piperazine from Example 153A for the pyrrolidine derivative used in Example 018B. ¹H NMR (300 MHz, MeOD-*d*₄) δ 7.77 (d, 2H), 7.61 (d, 2H), 7.47 (m, 1H), 7.35 (d, 2H), 6.95 (d, 1H), 6.61 (m, 1H), 5.11 (1H), 4.11 (m, 1H), 3.60-3.26 (m, 6H), 2.98 (m, 2H), 2.82-

2.50 (m, 4H), 2.49 (d, 1H), 2.44 (s, 3H), 2.25-2.10 (m, 1H), 2.10-1.70 (m, 3H), 1.95 (s, 3H); LCMS (ESI) m/z 605 (M + H)⁺.

Example 154

Preparation of 2-(-3-((R)-tert-Butylsulfinyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00815] **Example 154A:** To a suspension of NaH (211 mg, 5.28 mmol) in DMF (1 mL) at 0 °C was added dropwise 2-methylpropane-2-thiol (237 mg, 2.64 mmol). The mixture was allowed to warm to rt and stir for 20 min, then was added to a solution of (S)-1-(tert-butoxycarbonyl)pyrrolidin-3-yl methanesulfonate (350 mg, 1.32 mmol) in DMF (2 mL) at 0 °C. The mixture was allowed to warm to rt and stir for 8 h, then 10% aq citric acid was added. The mixture was concentrated, and the residue was purified by silica gel chromatography eluting with 5 % EtOAc/petroleum ether to afford (R)-tert-butyl 3-(tert-butylthio)pyrrolidine-1-carboxylate (300 mg, 88 %). LCMS m/z 260 (M+H)⁺.

[00816] **Example 154B:** To a solution of (R)-tert-butyl 3-(tert-butylthio)pyrrolidine-1-carboxylate (50 mg, 1.00 mmol) in DCM (1 mL) at -20 °C was added 3-chloroperbenzoic acid (190 mg, 1.10 mmol). The mixture was stirred at a temperature below -30 °C for 20 min, at which time LCMS showed the reaction was complete. Aq Na₂SO₃ was added and the mixture was concentrated. The residue was purified by silica gel chromatography eluting with 10% EtOAc/DCM to afford (R)-tert-butyl 3-(tert-butylsulfinyl)pyrrolidine-1-carboxylate.

[00817] **Example 154C:** To a solution of (R)-tert-butyl 3-(tert-butylsulfinyl)pyrrolidine-1-carboxylate (275 mg, 1.00 mmol) in MeOH (2 mL) at 0 °C was added dropwise 4.5 M HCl/ EtOAc. The mixture was allowed to warm to rt and stir for 1 h, at which time LCMS showed the reaction was complete. The mixture was concentrated and dried to afford (R)-3-(tert-butylsulfinyl)pyrrolidine hydrochloride (190 mg, 90 %).

[00818] **Example 154D:** To a solution of N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4] triazin-2-ylthio)phenyl)-2-chloroacetamide (50 mg, 0.12 mmol) in THF (2 mL) at rt under N₂ was added tetra-butyl ammonium iodide (43

mg, 0.11 mmol), and the mixture was stirred for 10 min. Then (R)-3-(tert-butylsulfinyl)pyrrolidine hydrochloride (51 mg, 0.24 mmol) and DIEA (0.5 mL) were added and the mixture was stirred at 40 °C overnight, at which time TLC showed that the starting material was consumed. Water (2 mL) was added, and the mixture was extracted with EtOAc (3 x 5 mL). The organic extracts were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The solid residue was washed with ether and dried under reduced pressure, then purified by preparative TLC eluting with 10:1 DCM/MeOH to afford 2-(-3-((R)-tert-butylsulfinyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (15 mg, 22%). ¹H NMR: ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.08 (s, 1H), 10.63 (s, 1H), 10.09 (s, 1H), 7.85 (d, 2H), 7.78 (m, 3H), 7.21 (s, 1H), 6.57 (s, 1H), 5.62 (s, 1H), 4.03 (s, 1H), 3.47 (s, 2H), 3.07 (m, 4H), 2.08 (m, 5H), 1.14 (s, 9H); LCMS *m/z* 553 (M+H)⁺.

Example 155

Preparation of 2-(*trans*-3-Hydroxy-4-(pyridin-2-yloxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00819] **Example 155 Step 1:** *trans*-Benzyl 3-hydroxy-4-(pyridin-2-yloxy)pyrrolidine-1-carboxylate (70.0 mg, 0.22 mmol, 98%) was synthesized using a procedure analogous to that described in Example 114 Step 1, substituting 4-hydroxypyridine for the 3-fluorophenol used in Example 114 Step 1. LCMS (ESI) *m/z* 315 (M+H)⁺.

[00820] **Example 155 Step 2:** *trans*-4-(Pyridin-2-yloxy)pyrrolidin-3-ol (43 mg, 0.24 mmol) was prepared using a procedure analogous to that described in Example 114 Step 2, substituting *trans*-benzyl 3-hydroxy-4-(pyridin-2-yloxy)pyrrolidine-1-carboxylate from the previous step for the *trans*-benzyl 3-(3-fluorophenoxy)-4-hydroxypyrrrolidine-1-carboxylate used in Example 114 Step 2. LCMS (ESI) *m/z* 181 (M+H)⁺.

[00821] **Example 155 Step 3:** 2-(*trans*-3-Hydroxy-4-(pyridin-2-yloxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (65.1 mg, 58%) was synthesized using a procedure

analogous to that described in Example 018B, substituting *trans*-4-(pyridin-2-yloxy)pyrrolidin-3-ol for the pyrrolidine derivative used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.06 (s, 1H), 10.63 (s, 1H), 10.04 (s, 1H), 8.17 (br s, 1H), 7.59-7.78 (m, 6H), 7.23 (s, 1H), 6.99 (d, 2H), 6.58 (br s, 1H), 5.62 (br s, 1H), 5.34 (br s, 1H), 5.08 (br s, 1H), 4.27 (s, 1H), 4.03 (s, 1H), 3.23 (br s, 1H), 3.10 (br s, 1H), 2.89 (s, 1H), 2.74 (s, 2H), 2.03 (s, 3H); LCMS (ESI) *m/z* 556 (M-H)⁺.

Example 156

Preparation of 2-((R)-3-((S)-4,4-Difluoro-2-(hydroxymethyl)pyrrolidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00822] **Example 156A:** ((S)-4,4-Difluoro-2-(hydroxymethyl)pyrrolidin-1-yl)((R)-pyrrolidin-3-yl)methanone was prepared using a procedure analogous to that described in Example 126A, substituting (S)-(4,4-difluoropyrrolidin-2-yl)methanol from Example 20A for the dimethylamine used in Example 126A.

[00823] **Example 156B:** 2-((R)-3-((S)-4,4-difluoro-2-(hydroxymethyl)pyrrolidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was synthesized as its acetate salt (27.8 mg, 31.4 %) using a procedure analogous to that described in Example 126B, substituting ((S)-4,4-difluoro-2-(hydroxymethyl)pyrrolidin-1-yl)((R)-pyrrolidin-3-yl)methanone hydrochloride for the (R)-N,N-dimethylpyrrolidine-3-carboxamide hydrochloride used in Example 126B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.68 (s, 1H), 10.14 (d, 1H), 7.83 (d, 2H), 7.58 (m, 3H), 7.22 (s, 1H), 6.58 (s, 1H), 5.64 (s, 1H), 4.23-3.85 (m, 3H), 3.52-3.17 (m, 7H), 2.84-2.60 (m, 5H), 2.20-1.80 (m, 8H); LCMS (ESI) *m/z* 612 (M+H)⁺.

Example 157

Preparation of (S)-2-(3-(3,3-Difluoropyrrolidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00824] **Example 157A:** (S)-(3,3-difluoropyrrolidin-1-yl)(pyrrolidin-3-yl)methanone was prepared using a procedure analogous to that described in Example 126A, substituting 3,3-difluoropyrrolidine for dimethylamine used in Example 126A

and substituting (R)-1-(tert-butoxycarbonyl)pyrrolidine-3-carboxylic acid for the (S)-1-(tert-butoxycarbonyl) pyrrolidine -3-carboxylic acid used in Example 126A.

[00825] Example 157B: (S)-2-(3-(3,3-difluoropyrrolidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was synthesized as a white solid (25.25 mg, 27 %) using a procedure analogous to that described in Example 126B, substituting (S)-(3,3-difluoropyrrolidin-1-yl)(pyrrolidin-3-yl)methanone hydrochloride for the (R)-N,N-dimethylpyrrolidine-3-carboxamide hydrochloride used in Example 126B. The crude reaction mixture was purified by silica gel chromatography eluting with MeOH/DCM. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.07 (s, 1H), 10.64 (s, 1H), 10.13 (s, 1H), 7.84 (d, 2H), 7.58 (m, 3H), 7.23 (s, 1H), 6.58 (s, 1H), 5.65 (s, 1H), 4.01-3.13 (m, 8H), 2.82-2.37 (m, 4H), 2.10-1.88 (m, 4H); LCMS (ESI) *m/z* 582 (M+H)⁺.

Example 158

Preparation of (S)-2-(3-(4,4-Difluoropiperidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00826] Example 158A: (S)-(4,4-difluoropiperidin-1-yl)(pyrrolidin-3-yl)methanone was prepared using a procedure analogous to that described in Example 126A, substituting 4,4-difluoropiperidine for the dimethylamine used in Example 126A and substituting (R)-1-(tert-butoxycarbonyl)pyrrolidine-3-carboxylic acid for the (S)-1-(tert-butoxycarbonyl) pyrrolidine -3-carboxylic acid used in Example 126A.

[00827] Example 158B: (S)-2-(3-(4,4-difluoropiperidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino) pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was synthesized as a white solid (110.35 mg, 41 %) using a procedure analogous to that described in Example 126B, substituting (S)-(4,4-difluoropiperidin-1-yl)(pyrrolidin-3-yl)methanone hydrochloride for the (R)-N,N-dimethylpyrrolidine-3-carboxamide hydrochloride used in Example 126B. The crude reaction mixture was purified by silica gel chromatography eluting with MeOH/DCM. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.07 (s, 1H), 10.64 (s, 1H), 10.14 (s, 1H), 7.86 (d, 2H), 7.61-7.58 (m, 3H), 7.23 (s, 1H), 6.60-6.57 (s, 1H), 5.65 (s, 1H), 3.62-3.59 (m, 4H), 3.44-2.66 (m, 7H), 2.04-1.90 (m 9H); LCMS (ESI) *m/z* 596 (M+H)⁺.

Example 159**Preparation of (S)-2-(3-(3,3-Difluoropiperidin-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide**

[00828] **Example 159A:** (S)-(3,3-Difluoropiperidin-1-yl)(pyrrolidin-3-yl)methanone was prepared using a procedure analogous to that described in Example 126A, substituting 3,3-difluoropiperidine for the dimethylamine used in Example 126A and substituting (R)-1-(tert-butoxycarbonyl)pyrrolidine-3-carboxylic acid for the (S)-1-(tert-butoxycarbonyl) pyrrolidine -3-carboxylic acid used in Example 126A.

[00829] **Example 159B:** (S)-2-(3-(3,3-Difluoropiperidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was synthesized as a white solid (84.5 mg, 32 %) using a procedure analogous to that described in Example 126B, substituting (S)-(3,3-difluoropiperidin-1-yl)(pyrrolidin-3-yl)methanone hydrochloride for the (R)-N,N-dimethylpyrrolidine-3-carboxamide hydrochloride used in Example 126B. The crude reaction mixture was purified by silica gel chromatography eluting with MeOH/DCM. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.07 (s, 1H), 10.61 (s, 1H), 10.33 (s, 1H), 7.86 (d, 2H), 7.83-7.58 (m, 3H), 7.22 (s, 1H), 6.59 (s, 1H), 5.66 (s, 1H), 3.86-3.78 (m, 2H), 3.67-3.11 (m, 7H), 2.85-2.50 (m, 2H), 2.29-1.60 (m, 9H); LCMS (ESI) *m/z* 596 (M+H)⁺.

Example 160**Preparation of (S)-N-Cyclopentyl-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide**

[00830] **Example 160A Step 1:** Into a 1 dram vial were sequentially added (S)-1-(tert-butoxycarbonyl)pyrrolidine-3-carboxylic acid (100 mg, 0.465 mmol), DCM (1 mL), 1-hydroxybenzotriazole monohydrate (80.0 mg, 0.592 mmol), ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (110 mg, 0.574 mmol), triethylamine (0.250 mL, 1.794 mmol) and cyclopentylamine (0.0550 mL, 0.557 mmol). The vial was closed and the mixture was stirred at rt for 14 h. The mixture was partitioned between DCM (5 mL) and saturated aq sodium bicarbonate (5 mL). The aqueous layer was further extracted with DCM (2 x 5 mL) and the combined

organic layers were washed with saturated aq sodium chloride (3 x 5 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residual oil was purified by silica gel chromatography eluting with 30-100% EtOAc/hexanes to afford (S)-tert-butyl 3-(cyclopentylcarbamoyl)pyrrolidine-1-carboxylate as a solid (96 mg, 73%). LCMS (ESI) m/z 305 ($M + Na$)⁺.

[00831] **Example 160A Step 2:** To a 10 mL round bottomed flask were added (S)-tert-butyl 3-(cyclopentylcarbamoyl)pyrrolidine-1-carboxylate (96 mg, 0.340 mmol), DCM (4 mL) and trifluoroacetic acid (2 mL, 26 mmol). The mixture was stirred at rt for 90 min, then concentrated under reduced pressure to give (S)-3-(cyclopentylcarbamoyl)pyrrolidinium trifluoroacetate as oil that was used directly in the next step. LCMS (ESI) m/z 183 ($M+H$)⁺.

[00832] **Example 160A Step 3:** To a 1 dram vial were added (S)-3-(cyclopentylcarbamoyl)pyrrolidinium trifluoroacetate (0.340 mmol), N,N-dimethylacetamide (2 mL), diisopropylethylamine (0.25 mL, 1.51 mmol), sodium iodide (20 mg, 0.133 mmol) and 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 016B (120 mg, 0.290 mmol). The contents were heated under Ar at 80 °C for 21 h, then the mixture was partitioned between DCM (5 mL) and saturated aq sodium bicarbonate (5 mL). The aqueous layer was further extracted with DCM (2 x 5 mL) and the combined extracts were washed with saturated aq sodium chloride (3 x 5 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residual oil was purified by preparative reverse-phase HPLC eluting with 30-100% solvent B (0.05% HOAc/CH₃CN) in solvent A (0.05% HOAc/H₂O) to afford (S)-N-cyclopentyl-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide as its acetate salt (79 mg, 44%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.00 (br s, 1H), 10.61 (s, 1H), 10.12 (s, 1H), 7.79-7.83 (m, 2H), 7.56-7.58 (m, 3H), 7.21 (br s, 1H), 6.56-6.59 (m, 1H), 5.65 (s, 1H), 3.94-4.06 (m, 1H), 3.17-3.37 (m, 4H), 2.59-2.80 (m, 5H), 2.03 (s, 3H), 1.25-1.95 (m, 13H); LCMS (ESI) m/z 560 ($M+H$)⁺.

Example 161

Preparation of (S)-2-(3-(3,3-Difluoropiperidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00833] **Example 161A:** (R)-(3,3-Difluoropiperidin-1-yl)(pyrrolidin-3-yl)methanone was prepared using a procedure analogous to that described in Example 126A, substituting 3,3-difluoropiperidine for the dimethylamine used in Example 161A.

[00834] **Example 161B:** (R)-2-(3-(3,3-Difluoropiperidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was synthesized as a white solid (22.64 mg, 24 %) using a procedure analogous to that described in Example 126B, substituting (R)-(3,3-difluoropiperidin-1-yl)(pyrrolidin-3-yl)methanone hydrochloride for the (R)-N,N-dimethylpyrrolidine-3-carboxamide hydrochloride used in Example 126B. The crude reaction mixture was purified by silica gel chromatography eluting with MeOH/DCM. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.03 (s, 1H), 10.60 (s, 1H), 10.09 (s, 1H), 7.95 (d, 2H), 7.59-7.57 (m, 3H), 7.20 (s, 1H), 6.58 (s, 1H), 5.75 (s, 1H), 3.92-3.16 (m, 7H), 2.88-2.67 (m, 4H), 2.29-1.68 (m, 9H); LCMS (ESI) *m/z* 596 (M+H)⁺.

Example 162

Preparation of (S)-N-*tert*-Butyl-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide, acetic acid salt

[00835] **Example 162 Step 1:** (*S*)-*tert*-Butyl 3-(*tert*-butylcarbamoyl)pyrrolidine-1-carboxylate was prepared using a procedure analogous to that described in Example 160 Step 1, substituting *tert*-butylamine for the cyclopentylamine used in Example 150 Step 1. the crude product was purified by silica gel chromatography eluting with of 30-100% EtOAc/hexanes to afford (*S*)-*tert*-butyl 3-(*tert*-butylcarbamoyl)pyrrolidine-1-carboxylate as a solid (88 mg, 70 %). LCMS (ESI) *m/z* 293 (M + Na)⁺.

[00836] **Example 162 Step 2:** (S)-3-(*tert*-butylcarbamoyl)pyrrolidinium trifluoroacetate was prepared using a procedure analogous to that described in Example 160 Step 2, substituting (*S*)-*tert*-butyl 3-(*tert*-butylcarbamoyl)pyrrolidine-1-

carboxylate for the (*S*)-*tert*-butyl 3-(cyclopentylcarbamoyl)pyrrolidine-1-carboxylate used in Example 160 Step 2. LCMS (ESI) m/z 171 ($M + H$)⁺.

[00837] Example 162 Step 3: (*S*)-*N-tert*-Butyl-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-*f*][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide was prepared using a procedure analogous to that described in Example 160 Step 3, substituting (*S*)-3-(*tert*-butylcarbamoyl)pyrrolidinium trifluoroacetate for the (*S*)-3-(cyclopentylcarbamoyl)pyrrolidinium trifluoroacetate used in Example 160 Step 3. Purification by preparative reverse phase HPLC eluting with 30 – 100% solvent B (0.05% HOAc/CH₃CN) in solvent A (0.05% HOAc/H₂O) afforded (*S*)-*N-tert*-butyl-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-*f*][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide as its acetate salt (88 mg, 50%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.00 (br s, 1H), 10.61 (s, 1H), 10.15 (s, 1H), 7.83 (d, *J* = 8.7 Hz, 2H), 7.57 (m, 3H), 7.21 (s, 1H), 6.56-6.59 (m, 1H), 5.65 (s, 1H), 3.17-3.37 (m, 4H), 2.59-2.76 (m, 5H), 2.04 (s, 3H), 1.85-1.95 (m, 5H), 1.25 (s, 9H); LCMS (ESI) m/z 548 ($M + H$)⁺.

Example 163

Preparation of (*S*)-*N*-(4-(4-(5-Methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-*f*][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(piperidine-1-carbonyl)pyrrolidin-1-yl)acetamide

[00838] Example 163 Step 1: (*S*)-*tert*-butyl 3-(piperidine-1-carbonyl)pyrrolidine-1-carboxylate was prepared using a procedure analogous to that described in Example 160 Step 1, substituting piperidine for the cyclopentylamine used in Example 160 Step 1. Purification by silica gel chromatography eluting with 30-100% EtOAc/hexanes afforded (*S*)-*tert*-butyl 3-(piperidine-1-carbonyl)pyrrolidine-1-carboxylate as a solid (102 mg, 78 %). LCMS (ESI) m/z 305 ($M + Na$)⁺.

[00839] Example 163 Step 2: (*S*)-3-(piperidine-1-carbonyl)pyrrolidinium trifluoroacetate was prepared using a procedure analogous to that described in Example 160 Step 2, substituting (*S*)-*tert*-butyl 3-(piperidine-1-carbonyl)pyrrolidine-1-carboxylate for the (*S*)-*tert*-butyl 3-(cyclopentylcarbamoyl)pyrrolidine-1-carboxylate used in Example 160 Step 2. LCMS (ESI) m/z 183 ($M + H$)⁺.

[00840] **Example 163 Step 3:** (*S*)-N-(4-(4-(5-Methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(piperidine-1-carbonyl)pyrrolidin-1-yl)acetamide was prepared using a procedure analogous to that described in Example 160 Step 3, substituting (*S*)-3-(piperidine-1-carbonyl)pyrrolidinium trifluoroacetate for the (*S*)-3-(cyclopentylcarbamoyl)pyrrolidinium trifluoroacetate used in Example 160 Step 3. Purification by preparative reverse-phase HPLC eluting with 30-100% solvent B = 0.05% HOAc/CH₃CN and solvent A = 0.05% HOAc/H₂O afforded (*S*)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(piperidine-1-carbonyl)pyrrolidin-1-yl)acetamide as its acetate salt (75 mg, 42%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.00 (br s, 1H), 10.62 (s, 1H), 10.16 (s, 1H), 7.86 (d, *J* = 8.7 Hz, 2H), 7.57-7.60 (m, 3H), 7.21 (m, 1H), 6.57-6.59 (m, 1H), 5.65 (s, 1H), 3.24-3.50 (m, 8H), 2.88 (m, 1H), 2.60-2.77 (m, 3H), 2.00-2.15 (m, 5H), 1.91 (s, 3H), 1.43-1.59 (m, 6H); LCMS (ESI) *m/z* 560 (M + H)⁺.

Example 164

Preparation of (*S*)-N-(4-(4-(5-Methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(morpholine-4-carbonyl)pyrrolidin-1-yl)acetamide

[00841] **Example 164 Step 1:** (*S*)-*tert*-Butyl 3-(morpholine-4-carbonyl)pyrrolidine-1-carboxylate was prepared using a procedure analogous to that described in Example 160 Step 1, substituting morpholine for the cyclopentylamine used in Example 160 Step 1. Purification by flash chromatography eluting with 50-100% EtOAc/hexanes afforded (*S*)-*tert*-butyl 3-(morpholine-4-carbonyl)pyrrolidine-1-carboxylate as a solid (96 mg, 72 %). LCMS (ESI) *m/z* 307 (M+Na)⁺.

[00842] **Example 164 Step 2:** (*S*)-3-(Morpholine-4-carbonyl)pyrrolidinium trifluoroacetate was prepared using a procedure analogous to that described in Example 160 Step 2, substituting (*S*)-*tert*-butyl 3-(morpholine-4-carbonyl)pyrrolidine-1-carboxylate for the (*S*)-*tert*-butyl 3-(cyclopentylcarbamoyl)pyrrolidine-1-carboxylate used in Example 160 Step 2. LCMS (ESI) *m/z* 185 (M + H)⁺.

[00843] **Example 164 Step 3:** (*S*)-N-(4-(4-(5-Methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(morpholine-4-

carbonyl)pyrrolidin-1-yl)acetamide was prepared using a procedure analogous to that described in Example 160 Step 3, substituting (S)-3-(morpholine-4-carbonyl)pyrrolidinium trifluoroacetate for the (S)-3-(cyclopentylcarbonyl)pyrrolidinium trifluoroacetate used in Example 160 Step 3. Purification by preparative reverse-phase HPLC eluting with 30-100% solvent B = 0.05% HOAc/CH₃CN and solvent A = 0.05% HOAc/H₂O afforded (S)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(morpholine-4-carbonyl)pyrrolidin-1-yl)acetamide as its acetate salt (114 mg, 63%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.99 (br s, 1H), 10.61 (s, 1H), 10.18 (s, 1H), 7.84 (d, *J* = 8.7 Hz, 2H), 7.57-7.60 (m, 3H), 7.22 (m, 1H), 6.57-6.59 (m, 1H), 5.65 (m, 1H), 3.19-3.58 (m, 12H), 2.97 (m, 1H), 2.66-2.82 (m, 3H), 1.92-2.20 (m, 5H), 1.91 (s, 3H); LCMS (ESI) *m/z* 562 (M + H)⁺.

Example 165

Preparation of (S)-2-(3-(4-Fluoropiperidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00844] **Example 165 Step 1:** (S)-tert-Butyl 3-(4-fluoropiperidine-1-carbonyl)pyrrolidine-1-carboxylate was prepared using a procedure analogous to that described in Example 160 Step 1, substituting 4-fluoropiperidinium hydrochloride for the cyclopentylamine used in Example 160 Step 1. Purification by flash chromatography eluting with 30-100% EtOAc/hexanes afforded (S)-tert-butyl 3-(4-fluoropiperidine-1-carbonyl)pyrrolidine-1-carboxylate as a solid (102 mg, 78 %). LCMS (ESI) *m/z* 323 (M+Na)⁺.

[00845] **Example 165 Step 2:** (S)-3-(4-Fluoropiperidine-1-carbonyl)pyrrolidinium trifluoroacetate was prepared using a procedure analogous to that described in Example 160 Step 2, substituting (S)-tert-butyl 3-(4-fluoropiperidine-1-carbonyl)pyrrolidine-1-carboxylate for the (S)-tert-butyl 3-(cyclopentylcarbonyl)pyrrolidine-1-carboxylate used in Example 160 Step 2. LCMS (ESI) *m/z* 201 (M + H)⁺.

[00846] **Example 165 Step 3:** (S)-2-(3-(4-fluoropiperidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-

ylthio)phenyl)acetamide was prepared using a procedure analogous to that described in Example 160 Step 3, substituting (S)-3-(4-fluoropiperidine-1-carbonyl)pyrrolidinium trifluoroacetate for the (S)-3-(cyclopentylcarbamoyl)pyrrolidinium trifluoroacetate used in Example 160 Step 3. Purification by preparative reverse-phase HPLC eluting with 30-100% solvent B = 0.05% HOAc/CH₃CN and solvent A = 0.05% HOAc/H₂O afforded the title compound (100 mg, 54%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.95 (br s, 1H), 10.61 (s, 1H), 10.15 (s, 1H), 7.85 (d, *J* = 8.7 Hz, 2H), 7.57-7.60 (m, 3H), 7.21 (m, 1H), 6.57-6.59 (m, 1H), 5.65 (s, 1H), 4.78-4.97 (m, 1H), 3.87-4.19 (m, 2H), 3.22-3.64 (m, 8H), 2.90 (m, 1H), 2.61-2.78 (m, 3H), 2.00-2.20 (m, 5H), 1.91 (s, 3H), 1.47-1.80 (m, 2H); LCMS (ESI) *m/z* 578 (M + H)⁺.

Example 166

Preparation of 2-(3-(3-Fluorobenzoyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00847] **Example 166A:** To 1-Boc-pyrrolidine-3-carboxylic acid (1.00 g, 4.64 mmol) in DMF (7 mL) were added sequentially DMAP (1.70 g, 13.91 mmol), N,O-dimethylhydroxylamine hydrochloride (679 mg, 6.96 mmol) and EDCI (1.11 g, 5.79 mmol). The mixture was stirred at rt overnight, then diluted with EtOAc and washed with water twice (2X), 1M citric acid solution (2X) and brine, then dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give tert-butyl 3-(methoxy(methyl)carbamoyl)pyrrolidine-1-carboxylate as a gum, which was used in the next step. LCMS (ESI) *m/z* 203 (M-tert-butyl+H)⁺.

[00848] **Example 166B:** To a stirring solution of tert-butyl 3-(methoxy(methyl)carbamoyl)pyrrolidine-1-carboxylate (150 mg, 1.58 mmol) in THF (2 mL) at 0 °C under N₂ was added 1M 3-fluorophenylmagnesium bromide/THF (1.74 mL, 1.74 mmol). The mixture was stirred at rt overnight, then purified by silica gel chromatography, eluting with 20:1 to 5:1 petroleum ether/EtOAc to give tert-butyl 3-(3-fluorobenzoyl)pyrrolidine-1-carboxylate as colorless oil (120 mg, 71%). ¹H NMR (400 MHz, CDCl₃) δ 7.75 (d, 1H), 7.65 (d, 1H), 7.49 (m, 1H), 7.31 (m, 1H), 3.95 (m, 1H), 3.45-3.78 (m, 4H), 2.19 (m, 2H), 1.47 (s, 9H); LCMS (ESI) *m/z* 279 (M - tert-butyl + H)⁺.

[00849] **Example 166C:** To a solution of tert-butyl 3-(3-fluorobenzoyl)pyrrolidine-1-carboxylate (160 mg, 0.55 mmol) in dioxane (2 mL) was added 4M HCl/dioxane (2 mL). The mixture was stirred at rt for 2 h, then aq NaHCO₃ was added to adjust the pH to 7~8, and the mixture was concentrated under reduced pressure to give a residue containing (3-fluorophenyl)(pyrrolidin-3-yl)methanone, which was used directly in the next step. LCMS (ESI) *m/z* 194 (M + H)⁺.

[00850] **Example 166D:** A mixture of the residue containing (3-fluorophenyl)(pyrrolidin-3-yl)methanone from Example 166C, 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (80 mg, 0.19 mmol), and Na₂CO₃ (81 mg, 0.76 mmol) in DMF (2 mL) was stirred at rt until the chloride starting material was consumed. The resulting mixture was purified by Al₂O₃ chromatography, eluting with 100% DCM to 90% DCM/MeOH to give a light yellow residue (100 mg). Further purification by preparative TLC afforded 2-(3-(3-fluorobenzoyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide as an off-white powder (24 mg, 22%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.08 (s, 1H), 10.65 (s, 1H), 10.08 (s, 1H), 7.77-7.88 (m, 4H), 7.53-7.63 (m, 5H), 7.23 (s, 1H), 6.59 (dd, 1H), 5.64 (s, 1H), 4.13 (m, 1H), 3.33 (dd, 2H), 2.93 (m, 2H), 2.73 (m, 2H), 2.20 (m, 1H), 2.02 (s, 3H), 2.01 (m, 1H); LCMS (ESI) *m/z* 571 (M + H)⁺.

Example 167

Preparation of 2-(3-(4-Fluorobenzoyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00851] **Example 167A:** To a stirring solution of tert-butyl 3-(methoxy(methyl)carbamoyl)pyrrolidine-1-carboxylate (250 mg, 0.97 mmol) in THF (5 mL) at 0 °C under N₂ was added 2M 4-fluorophenylmagnesium bromide/Et₂O (1.46 mL, 2.92 mmol), then the mixture was stirred at rt overnight. The reaction mixture was purified by silica gel chromatography eluting with 20:1 to 5:1 petroleum ether/EtOAc to give tert-butyl 3-(4-fluorobenzoyl)pyrrolidine-1-carboxylate as colorless oil (190 mg, 67%). ¹H NMR (400 MHz, CDCl₃) δ 8.02 (m, 2H), 7.16-7.22 (m, 2H), 3.96 (m, 1H), 3.44-3.79 (m, 4H), 2.20 (m, 2H), 1.49 (s, 9H).

[00852] **Example 167B:** To a solution of tert-butyl 3-(4-fluorobenzoyl)pyrrolidine-1-carboxylate (190 mg, 0.65 mmol) in dioxane (2 mL) was added 4 M HCl/dioxane (2

mL) and the mixture was stirred at rt for 2 h. Aq NaHCO₃ was added to adjust the pH to 7~8 and the mixture was concentrated under reduced pressure to give a residue containing (4-fluorophenyl)(pyrrolidin-3-yl)methanone. LCMS (ESI) *m/z* 194 (M + H)⁺.

[00853] Example 167C: A mixture of the residue containing (4-fluorophenyl)(pyrrolidin-3-yl)methanone from Example 167B, 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (80 mg, 0.19 mmol), and Na₂CO₃ (81 mg, 0.76 mmol) in DMF (2 mL) was stirred at rt until the chloride starting material was consumed. The reaction mixture was purified by Al₂O₃ chromatography eluting with 100% DCM to 90% DCM/MeOH to give a light yellow residue (100 mg). Further purification by preparative TLC afforded 2-(3-(4-fluorobenzoyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide as a yellow solid (57 mg, 52%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.11 (s, 1H), 10.64 (s, 1H), 10.25 (s, 1H), 8.10 (dd, 2H), 7.59 (m, 3H), 7.39 (t, 2H), 7.23 (s, 1H), 6.58 (dd, 1H), 5.64 (s, 1H), 4.14 (m, 1H), 3.40-3.47 (m, 2H), 3.00 (m, 2H), 2.78-2.84 (m, 2H), 2.23 (m, 1H), 2.03 (s, 3H), 2.00 (m, 1H); LCMS (ESI) *m/z* 571 (M + H)⁺.

Example 168

Preparation of (S)-N,N-Dimethyl-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide

[00854] Example 168A: (S)-N,N-dimethylpyrrolidine-3-carboxamide hydrochloride was prepared using a procedure analogous to that described in Example 126A, substituting (R)-1-(tert-butoxycarbonyl)pyrrolidine-3-carboxylic acid for the (S)-1-(tert-butoxycarbonyl)pyrrolidine-3-carboxylic acid used in Example 126A.

[00855] Example 168B: (S)-N,N-dimethyl-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide was synthesized as a white solid (25.37 mg, 34%) using a procedure analogous to that described in Example 126B, substituting (S)-N,N-dimethylpyrrolidine-3-carboxamide hydrochloride for the (R)-N,N-dimethylpyrrolidine-3-carboxamide hydrochloride used in Example 126B. ¹H NMR

(300 MHz, DMSO- d_6) δ 12.05 (s, 1H), 10.60 (s, 1H), 10.15 (s, 1H), 7.85 (d, 2H), 7.55 (m, 3H), 7.20 (s, 1H), 6.55 (s, 1H), 5.65 (s, 1H), 3.40-3.10 (m, 3H), 3.00 (s, 3H), 3.85 (s, 3H), 3.80 (m, 1H), 2.70 (m, 3H), 2.20 (m, 1H), 2.00 (s, 3H), 1.85 (m, 1H); LCMS (ESI) m/z 520 (M+H) $^+$.

Example 169

Preparation of (R)-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)-N-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxamide

[00856] **Example 169 Step 1:** To (R)-1-(tert-butoxycarbonyl)pyrrolidine-3-carboxylic acid (200 mg, 0.929 mmol) in DMF (5 mL) under Ar were added diisopropylethylamine (0.32 mL, 1.86 mmol) and hydroxybenzotriazole (132 mg, 0.976 mmol) and the mixture was stirred at rt for 5 min. Then EDCI (196 mg, 1.02 mmol) was added and the mixture was stirred for 20 min, then 2,2,2-trifluoroamine (132 mg, 0.976 mmol) was added and the mixture was stirred at rt over night. The mixture was partitioned between EtOAc (30 mL) and water (10 mL), and the separated EtOAc layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The solid residue was purified by silica gel chromatography eluting with 12% to 100% EtOAc/ hexanes to afford (R)-tert-butyl 3-(2,2,2-trifluoroethylcarbamoyl)pyrrolidine-1-carboxylate (170 mg, 0.57 mmol). LCMS (ESI) m/z 197 (M + H - Boc) $^+$.

[00857] **Example 169 Step 2:** To (R)-tert-butyl 3-(2,2,2-trifluoroethylcarbamoyl)pyrrolidine-1-carboxylate (170 mg, 0.57 mmol) in EtOAc was added 4N HCl/dioxane and the mixture was stirred at rt for 2 h. The mixture was concentrated under reduced pressure and the residue was triturated with EtOAc and anhydrous diethyl ether to afford (R)-N-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxamide hydrochloride (110 mg, 0.56 mmol). LCMS (ESI) m/z 197 (M + H) $^+$.

[00858] **Example 169 Step 3:** (R)-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)-N-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxamide (35.0 mg, 34%) was synthesized using a procedure analogous to that described in Example 018B, substituting (R)-N-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxamide hydrochloride for the pyrrolidine derivative

used in Example 018B. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.01 (s, 1H), 10.60 (s, 1H), 10.08 (s, 1H), 8.55 (t, 1H), 7.80 (d, 2H), 7.55-7.60 (m, 3H), 7.2 (br s, 1H), 6.55 (q, 1H), 5.65 (s, 1H), 3.8-3.99 (m, 2H), 3.60 (br s, 1H), 3.10 (br s, 1H), 2.60-3.0 (m, 5H), 2.03 (s, 3H), 1.90 (s, 2H); LCMS (ESI) m/z 572 ($\text{M} - \text{H}$) $^-$.

Example 170

Preparation of (R)-N-(2-(4,4-Difluoropiperidin-1-yl)ethyl)-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide

[00859] **Example 170 Step 1:** To DMF (5 mL) purged with Ar were added (R)-1-(tert-butoxycarbonyl)pyrrolidine-3-carboxylic acid 200 mg, 0.93 mmol), diisopropylethylamine 0.32 mL, 1.86 mmol), and HATU (371 mg, 0.98 mmol) and the mixture was stirred at rt for 20 min. Then 2-(4,4-difluoropiperidin-1-yl)ethanamine (160 mg, 0.98 mmol) was added and the mixture was stirred at rt for 1.5 h, then partitioned between EtOAc (20 mL) and water (10 mL). The separated EtOAc layer was dried over MgSO_4 , filtered, and concentrated under reduced pressure to afford (R)-tert-butyl 3-(2-(4,4-difluoropiperidin-1-yl)ethylcarbamoyl)pyrrolidine-1-carboxylate (330 mg, 0.91 mmol). LCMS (ESI) m/z 362 ($\text{M} + \text{H}$) $^+$.

[00860] **Example 170 Step 2:** (R)-N-(2-(4,4-difluoropiperidin-1-yl)ethyl)pyrrolidine-3-carboxamide (238 mg, 0.91 mmol) was prepared using a procedure analogous to that described in Example 169 Step 2, substituting (R)-tert-butyl 3-(2-(4,4-difluoropiperidin-1-yl)ethylcarbamoyl)pyrrolidine-1-carboxylate from the previous step for the (R)-tert-butyl 3-(2,2,2-trifluoroethylcarbamoyl)pyrrolidine-1-carboxylate used in Example 169 Step 2. LCMS (ESI) m/z 262 ($\text{M} + \text{H}$) $^+$.

[00861] **Example 170 Step 3:** (R)-N-(2-(4,4-Difluoropiperidin-1-yl)ethyl)-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide (21.5 mg, 22%) was synthesized using a procedure analogous to that described in Example 018B, substituting (R)-N-(2-(4,4-difluoropiperidin-1-yl)ethyl)pyrrolidine-3-carboxamide for the pyrrolidine derivative used in Example 018B. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.01 (s, 1H), 10.60 (s, 1H), 10.13 (s, 1H), 7.80 (d, 3H), 7.49-7.60 (m, 3H), 7.20 (br s,

1H), 6.50-6.60 (m, 1H), 5.65 (br s, 1H), 3.37-3.40 (m, 2H), 3.17-3.23 (m, 2H), 2.70-2.92 (m, 7H), 2.27 (br s, 2H), 2.03 (s, 3H), 1.84-2.0 (m, 8H); LCMS (ESI) m/z 574 (M + H)⁺.

Example 171

Preparation of (S)-1-(2-(4-(4-(5-Methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)-N-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxamide

[00862] **Example 171 Step 1:** (S)-tert-butyl 3-(2,2,2-trifluoroethylcarbamoyl)pyrrolidine-1-carboxylate (160 mg, 0.54 mmol) was synthesized using a procedure analogous to that described in Example 169 Step 1, substituting (S)-1-(tert-butoxycarbonyl)pyrrolidine-3-carboxylic acid for the (R)-1-(tert-butoxycarbonyl)pyrrolidine-3-carboxylic acid used in Example 169 Step 1. (LCMS (ESI) m/z 197 (M + H - Boc)⁺.

[00863] **Example 171 Step 2:** (S)-N-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxamide (120 mg, 0.61 mmol) was synthesized using a procedure analogous to that described in Example 169 Step 2, substituting (S)-tert-butyl 3-(2,2,2-trifluoroethylcarbamoyl)pyrrolidine-1-carboxylate for the (R)-tert-butyl 3-(2,2,2-trifluoroethylcarbamoyl)pyrrolidine-1-carboxylate used in Example 169 Step 2. LCMS (ESI) m/z 197 (M + H)⁺.

[00864] **Example 171 Step 3:** (S)-1-(2-(4-(4-(5-Methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)-N-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxamide (46.1 mg, 45%) was synthesized using a procedure analogous to that described in Example 018B, substituting (S)-N-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxamide for the pyrrolidine derivative used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.04 (s, 1H), 10.60 (s, 1H), 10.08 (s, 1H), 8.55 (t, 1H), 7.80 (d, 2H), 7.55-7.60 (m, 3H), 7.2 (br,s, 1H), 6.55 (q, 1H), 5.65 (s, 1H), 3.86-3.98 (m, 3H), 2.90 (br s, 1H), 2.65-2.95 (m, 6H), 2.03 (s, 3H), 1.90-1.98 (m, 1H); LCMS (ESI) m/z 574 (M + H)⁺.

Example 172

Preparation of (R)-2-(3-(3,3-Difluoropyrrolidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00865] **Example 172A:** 2-Chloro-N-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was synthesized using a procedure analogous to those described in Examples 182 C-J, substituting ethyl 4-methyl-1H-pyrrole-2-carboxylate for the methyl 4-chloro-1H-pyrrole-2-carboxylate used in Example 182C. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.01 (s, 1H), 10.55 (s, 1H), 10.45 (s, 1H), 7.72 (d, 2H), 7.58 (m, 2H), 7.42 (s, 1H), 7.00 (s, 1H), 5.59 (s, 1H), 4.28 (s, 2H), 2.19 (s, 3H), 2.02 (s, 3H); LCMS (ESI) *m/z* 428 (M+H)⁺.

[00866] **Example 172B:** (R)-2-(3-(3,3-difluoropyrrolidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was synthesized as a white solid (51.59 mg, 62 %) using a procedure analogous to that described in Example 126B, substituting (R)-(3,3-difluoropyrrolidin-1-yl)(pyrrolidin-3-yl)methanone hydrochloride from Example 128A for the (R)-N,N-dimethylpyrrolidine-3-carboxamide hydrochloride used in Example 126B, and substituting 2-chloro-N-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 172A for the 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide used in Example 126B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.00 (s, 1H), 10.45 (s, 1H), 10.10 (s, 1H), 7.80 (d, 2H), 7.55 (m, 2H), 7.40 (s, 1H), 7.00 (s, 1H), 5.60 (s, 1H), 3.95 (t, 1H), 3.75 (m, 2H), 3.55 (t, 1H), 3.45-3.10 (m, 3H), 2.85-2.65 (m, 4H), 2.40 (m, 2H), 2.20 (s, 3H), 2.15 (m, 1H), 2.05 (s, 3H), 1.90 (m, 1H); LCMS (ESI) *m/z* 596 (M+H)⁺.

Example 173

Preparation of (R)-N-Cyclopentyl-1-(2-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide

[00867] (R)-N-cyclopentyl-1-(2-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide was synthesized as a white solid (27.46 mg, 34 %) using a procedure analogous to that described in Example 126B, substituting pyrrolidine-3-carboxylic

acid cyclopentylamide hydrochloride for the (R)-N,N-dimethylpyrrolidine-3-carboxamide hydrochloride used in Example 126B, and substituting 2-chloro-N-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 172A for the 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide used in Example 126B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.00 (s, 1H), 10.45 (s, 1H), 10.10 (s, 1H), 7.80 (d, 3H), 7.55 (m, 2H), 7.40 (s, 1H), 7.00 (s, 1H), 5.60 (s, 1H), 4.00 (m, 1H), 3.40-3.15 (m, 3H), 2.90-2.60 (m, 5H), 2.20 (s, 3H), 2.05-1.90 (m, 5H), 1.85-1.25 (m, 7H); LCMS (ESI) *m/z* 574 (M+H)⁺.

Example 174

Preparation of (R)-2-(3-(3,3-Difluoropiperidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00868] (R)-2-(3-(3,3-difluoropiperidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was synthesized as a white solid (27.04 mg, 32 %) using a procedure analogous to that described in Example 126B, substituting (3,3-difluoropiperidin-1-yl)-pyrrolidin-3-yl-methanone hydrochloride for the (R)-N,N-dimethylpyrrolidine-3-carboxamide hydrochloride used in Example 126B, and substituting 2-chloro-N-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 172A for the 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide used in Example 126B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.00 (s, 1H), 10.45 (s, 1H), 10.10 (s, 1H), 7.80 (d, 2H), 7.60 (d, 2H), 7.40 (s, 1H), 7.00 (s, 1H), 5.60 (s, 1H), 3.80 (t, 2H), 3.50 (brs, 2H), 3.40-3.15 (m, 3H), 2.85-2.65 (m, 4H), 2.20 (s, 3H), 2.15-1.95 (m, 6H), 1.85 (m, 1H), 1.70-1.55 (m, 2H); LCMS (ESI) *m/z* 610 (M+H)⁺.

Example 175

Preparation of (R)-N-(2-(4,4-Difluoropiperidin-1-yl)ethyl)-1-(2-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide

[00869] **Example 175A:** (R)-N-(2-(4,4-difluoropiperidin-1-yl)ethyl)pyrrolidine-3-carboxamide hydrochloride was prepared using a procedure analogous to that

described in Example 126A, substituting 2-(4,4-difluoropiperidin-1-yl)ethanamine for the dimethylamine used in Example 126A.

[00870] **Example 175B:** (R)-N-(2-(4,4-difluoropiperidin-1-yl)ethyl)-1-(2-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide was synthesized as a white solid (28.42 mg, 31 %) using a procedure analogous to that described in Example 126B, substituting (R)-N-(2-(4,4-difluoropiperidin-1-yl)ethyl)pyrrolidine-3-carboxamide hydrochloride for the (R)-N,N-dimethylpyrrolidine-3-carboxamide hydrochloride used in Example 126B, and substituting 2-chloro-N-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 172A for the 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide used in Example 126B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.00 (s, 1H), 10.45 (s, 1H), 10.10 (s, 1H), 7.80 (d, 3H) 7.55 (d, 2H), 7.40 (s, 1H), 7.00 (s, 1H), 5.60 (s, 1H), 3.40-3.30 (m, 3H), 3.25-3.10 (m, 3H), 2.90-2.60 (m, 6H), 2.35-2.50 (m, 3H), 2.20 (s, 3H), 2.00 (s, 3H), 2.10-1.80 (m, 6H); LCMS (ESI) *m/z* 653 (M+H)⁺.

Example 176

Preparation of (R)-N-Cyclopropyl-1-(2-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide

[00871] (R)-N-cyclopropyl-1-(2-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide was synthesized as a white solid (40.24 mg, 53 %) using a procedure analogous to that described in Example 126B, substituting (R)-N-cyclopropylpyrrolidine-3-carboxamide hydrochloride for the 4-(R)-N,N-dimethylpyrrolidine-3-carboxamide hydrochloride used in Example 126B, and substituting 2-chloro-N-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 172A for the 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide used in Example 126B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.00 (s, 1H), 10.45 (s, 1H), 10.05 (s, 1H), 7.95 (d, 1H), 7.80 (d, 2H) 7.55 (d, 2H), 7.40 (s, 1H), 7.00 (s, 1H), 5.60 (s, 1H), 3.40-3.20 (m, 3H), 2.85-2.10 (m, 6H), 2.20 (s,

3H), 2.05-1.85 (m, 4H), 0.65-0.55 (m, 2H), 0.40-0.30 (m, 2H); LCMS (ESI) m/z 546 (M+H)⁺.

Example 177

Preparation of (R)-N-tert-Butyl-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide

[00872] **Example 177 Step 1:** (R)-tert-butyl 3-(tert-butylcarbamoyl)pyrrolidine-1-carboxylate (190 mg, 0.70 mmol) was synthesized using a procedure analogous to that described in Example 169 Step 1, substituting tert-butylamine for the 2,2,2-trifluoroethylamine used in Example 169 Step 1. LCMS (ESI) m/z 293 (M + Na)⁺.

[00873] **Example 177 Step 2:** (R)-N-tert-butylpyrrolidine-3-carboxamide hydrochloride (160 mg, 0.94 mmol) was synthesized using a procedure analogous to that described in Example 169 Step 2, substituting (R)-tert-butyl 3-(tert-butylcarbamoyl)pyrrolidine-1-carboxylate for the (R)-tert-butyl 3-(2,2,2-trifluoroethylcarbamoyl)pyrrolidine-1-carboxylate used in Example 169 Step 2. LCMS (ESI) m/z 171 (M + H)⁺.

[00874] **Example 177 Step 3:** (R)-N-tert-Butyl-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide (60.1 mg, 52%) was synthesized using a procedure analogous to that described in Example 018B, substituting (R)-N-tert-butylpyrrolidine-3-carboxamide for the pyrrolidine derivative used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.04 (s, 1H), 10.61 (s, 1H), 10.10 (s, 1H), 7.81 (d, 2H), 7.5-7.68 (m, 3H), 7.45 (s, 1H), 7.21 (br,s, 1H), 6.55 (t, 1H), 5.65 (s, 1H), 3.25(s, 1H), 2.60-2.90 (m, 5H), 2.04(s, 3H), 1.90-1.95 (m, 3H), 1.21 (s, 9H); LCMS (ESI) m/z 548 (M+H)⁺.

Example 178

Preparation of 2-((R)-3-(2-(Pyrrolidin-1-yl)ethoxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00875] **Example 178A:** A mixture of pyrrolidine (5 g, 70.3 mmol) and 25% aq NaOH (14.2 mL) in acetone (140 mL) was stirred at rt, then cooled to 0 °C, after which 1-bromo-2-chloroethane (10 g, 70.3 mmol) was added slowly. The mixture

was stirred at rt overnight then concentrated under reduced pressure at 20 °C. The residue was diluted with water and extracted with DCM. The organic layer was washed with 0.1 M HCl several times, then washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to afford 1-(2-chloroethyl)pyrrolidine as a yellow oil (1.65 g, 35%). ¹H NMR (400 MHz, CDCl₃) δ 3.61 (t, 2H), 2.83 (t, 2H), 2.58 (m, 4H), 1.80 (m, 4H). LCMS (ESI) *m/z* 134 (M+H)⁺.

[00876] Example 178B: To a stirring solution of (*R*)-benzyl 3-hydroxypyrrolidine-1-carboxylate (1.10 g, 5 mmol) in DMF (10 mL) at 0 °C was added 60% NaH (240 mg, 6 mmol) and the mixture was stirred at 0 °C for 10 min. A solution of 1-(2-chloroethyl) pyrrolidine from Example 178A (1.65 g, 12.3 mmol) in DMF (5 ml) was added at 0 °C and the mixture was stirred at rt overnight. Water was added, and the mixture was extracted with EtOAc. The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 100% DCM to 100:10 DCM/MeOH to afford (*R*)-benzyl 3-(2-(pyrrolidin-1-yl)ethoxy)pyrrolidine-1-carboxylate as a yellow oil (150 mg, 9%). LCMS (ESI) *m/z* 319 (M+H)⁺.

[00877] Example 178C: A mixture of (*R*)-benzyl 3-(2-(pyrrolidin-1-yl)ethoxy)pyrrolidine-1-carboxylate (120 mg, 0.38 mmol) and 10% Pd/C (20 mg) in MeOH (10 mL) was stirred under H₂ (2 atm) at rt overnight. Then the mixture was filtered and the filtrate was concentrated under reduced pressure to afford 1-(2-((*R*)-pyrrolidin-3-yloxy) ethyl)pyrrolidine as a yellow oil (75 mg), which was used directly in the next step. LCMS (ESI) *m/z* 185 (M+H)⁺.

[00878] Example 178D: A mixture of 1-(2-((*R*)-pyrrolidin-3-yloxy)ethyl)pyrrolidine (75 mg), *N*-(4-(4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrrolo[1,2-*f*][1,2,4]triazin-2-ylthio)phenyl)-2-chloroacetamide (100 mg, 0.24 mmol) and Na₂CO₃ (102 mg, 0.96 mmol) in DMF (2 mL) was stirred at rt overnight. The mixture was partitioned between water and EtOAc, and then organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC eluting with 10:1 DCM /MeOH to afford 2-((*R*)-3-(2-(pyrrolidin-1-yl) ethoxy)pyrrolidin-1-yl)-*N*-(4-(4-(5-methyl-1*H*-pyrazol-3-

ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide as a light yellow solid (15 mg, 11%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.10 (s, 1H), 10.65 (s, 1H), 10.08 (s, 1H), 7.80 (d, 2H), 7.58 (m, 3H), 6.69-6.52 (m, 1H), 5.66 (s, 1H), 4.14-4.06 (m, 1H), 3.59 (m, 3H), 3.32 (m, 3H), 3.13-2.95 (m, 5H), 2.92-2.85 (q, 1H), 2.81-2.72 (q, 1H), 2.71-2.59 (m, 2H), 2.05 (m, 4H), 1.83 (m, 4H). LCMS (ESI) *m/z* 562 (M+H)⁺.

Example 179

Preparation of (R)-N-Isopropyl-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide

[00879] **Example 179 Step 1:** (R)-tert-butyl 3-(isopropylcarbamoyl)pyrrolidine-1-carboxylate (80 mg, 0.31 mmol) was synthesized using a procedure analogous to that described in Example 169 Step 1, substituting isopropylamine for the 2,2,2-trifluoroethylamine used in Example 169 Step 1. LCMS (ESI) *m/z* 279 (M + H + Na)⁻.

[00880] **Example 179 Step 2:** (R)-N-isopropylpyrrolidine-3-carboxamide hydrochloride (60 mg, 0.38 mmol) was prepared using a procedure analogous to that described in Example 169 Step 2, substituting (R)-tert-butyl 3-(isopropylcarbamoyl)pyrrolidine-1-carboxylate from the previous step (60 mg, 0.38 mmol) for the (R)-tert-butyl 3-(2,2,2-trifluoroethylcarbamoyl)pyrrolidine-1-carboxylate used in Example 169 Step 2. LCMS (ESI) *m/z* 157 (M + H)⁺.

[00881] **Example 179 Step 3:** (R)-N-Isopropyl-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide (40.1 mg, 56%) was synthesized using a procedure analogous to that described in Example 018B, substituting (R)-N-isopropylpyrrolidine-3-carboxamide hydrochloride for the pyrrolidine derivative used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.04 (s, 1H), 10.59 (s, 1H), 10.12 (s, 1H), 7.81 (d, 2H), 7.70 (d, 1H), 7.55 (d, 3H), 7.21 (br s, 1H), 6.56 (br s, 1H), 5.60 (s, 1H), 3.37 (s, 1H), 3.23 (s, 1H), 3.18 (s, 1H), 2.60-2.86 (m, 6H), 2.27 (s, 1H), 2.03 (s, 3H), 1.02-1.35 (m, 6H); LCMS (ESI) *m/z* 534 (M + H)⁺.

Example 180

Preparation of (R)-N-Cyclobutyl-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide

[00882] **Example 180 Step 1:** (R)-tert-Butyl 3-(cyclobutylcarbamoyl)pyrrolidine-1-carboxylate (190 mg, 0.70 mmol) was synthesized using a procedure analogous to that described in Example 169 Step 1, substituting cyclobutylamine for the 2,2,2-trifluoroethylamine used in Example 169 Step 1. LCMS (ESI) m/z 291 (M + H + Na)⁺.

[00883] **Example 180 Step 2:** (R)-N-cyclobutylpyrrolidine-3-carboxamide hydrochloride (170 mg, 1.01 mmol) was prepared using a procedure analogous to that described in Example 169 Step 2, substituting (R)-tert-butyl 3-(cyclobutylcarbamoyl)pyrrolidine-1-carboxylate (190 mg, 0.70 mmol) for the (R)-tert-butyl 3-(2,2,2-trifluoroethylcarbamoyl)pyrrolidine-1-carboxylate used in Example 169 Step 2. LCMS (ESI) m/z 169 (M + H)⁺.

[00884] **Example 180 Step 3:** (R)-N-Cyclobutyl-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide (21.8 mg, 19%) was synthesized using a procedure analogous to that described in Example 018B, substituting (R)-N-cyclobutylpyrrolidine-3-carboxamide hydrochloride for the pyrrolidine derivative used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.04 (s, 1H), 10.60 (s, 1H), 10.12 (s, 1H), 8.10 (d, 1H), 7.81 (d, 2H), 7.58 (d, 3H), 7.21 (br,s, 1H), 6.57 (q, 1H), 5.65 (s, 1H), 4.10-4.30 (m, 1H), 3.25 (s, 1H), 3.19 (s, 1H), 2.60-2.86 (m, 5H), 2.1-2.15 (m, 2H), 2.03 (s, 3H), 1.80-1.95 (m, 4H), 1.55-1.65 (m, 2H); LCMS (ESI) m/z 546 (M + H)⁺.

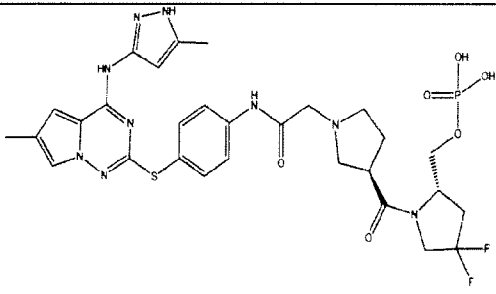
Example 181

Preparation of 2-((R)-3-((S)-4,4-difluoro-2-(hydroxymethyl)pyrrolidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00885] 2-((R)-3-((S)-4,4-difluoro-2-(hydroxymethyl)pyrrolidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was synthesized as a white solid (25 mg, 53 %) using a procedure analogous to that described in Example

126B, substituting ((S)-4,4-difluoro-2-(hydroxymethyl)pyrrolidin-1-yl)((R)-pyrrolidin-3-yl)methanone hydrochloride for the N,N-dimethylpyrrolidine-3-carboxamide hydrochloride used in Example 126B, and the 2-chloro-N-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 172A for the 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide used in Example 126B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.00 (s, 1H), 10.45 (s, 1H), 10.10 (d, 1H), 7.85 (d, 1H), 7.55 (d, 2H) 7.40 (s, 1H), 7.00 (s, 1H), 5.60 (s, 1H), 4.90 (t, 1H), 4.35-3.95 (m, 1H), 3.90-3.70 (s, 1H), 3.60-3.10 (m, 6H), 2.90-2.60 (m, 5H), 2.25 (m, 7H), 1.90-1.60 (m, 1H); LCMS (ESI) *m/z* 626 (M+H)⁺.

[00886] The following compound was prepared in a similar manner.

Exam. No.	Structure	Compound name	LC MS (M+H) ⁺
181-i		((S)-4,4-difluoro-1-((R)-1-(2-((4-((6-methyl-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)pyrrolidine-3-carbonyl)pyrrolidin-2-yl)methyl dihydrogen phosphate	706

Example 182

Preparation of (R)-1-(2-(4-(6-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)-N-cyclopropylpyrrolidine-3-carboxamide

[00887] **Example 182A:** To a stirring solution of 2,2,2-trichloro-1-(1H-pyrrol-2-yl)ethanone (12.7 g, 60 mmol) in DCM (60 mL) at 0 °C was slowly added sulfuryl chloride (9.5 g, 70 mmol) and mixture was stirred at rt overnight, then diluted with DCM (300 mL) and poured onto ice (150 g). The separated organic layer was washed with saturated aq NaHCO₃ and brine, then dried over NaSO₄, filtered and

concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 1:10 diethyl ether/hexane to give 2,2,2-trichloro-1-(4-chloro-1H-pyrrol-2-yl)ethanone as a white solid (9.1 g, 61%). ¹H NMR (300 MHz, CDCl₃) δ 9.48 (br s, 1H), 7.28 (dd, 1H), 7.12 (dd, 1H).

[00888] **Example 182B:** To a stirring solution of 2,2,2-trichloro-1-(4-chloro-1H-pyrrol-2-yl)ethanone (9.1 g, 37 mmol) in MeOH (40 mL) at rt was slowly added sodium methoxide (2.39 g, 44 mmol) and the mixture was stirred at rt for 1 h, then diluted with DCM (400 mL), washed with saturated aq NaHCO₃ and brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give methyl 4-chloro-1H-pyrrole-2-carboxylate as a white solid (5.7 g, 94%). ¹H NMR (300 MHz, CDCl₃) δ 9.31 (br s, 1H), 6.90 (dd, 1H), 6.81 (dd, 1H), 3.86 (s, 3H); LCMS (ESI) *m/z* 160 (M + H)⁺.

[00889] **Example 182C:** To a mixture of ammonium chloride (18 g, 340 mmol) and Et₂O (330 mL) at -10 °C were slowly added ammonium hydroxide (28.2 g, 806 mmol) followed by Clorox (432 mL). The mixture was stirred at -5 °C for 1 h. The separated organic layer was washed with brine then stirred with anhydrous K₂CO₃ at -78 °C for 1 h to provide ~ 0.3 M chloroamine, which was used directly in the next step.

[00890] **Example 182D:** To a solution of methyl 4-chloro-1H-pyrrole-2-carboxylate from Example 182B (5.7g, 36 mmol) in DMF (30 mL) at 0 °C was added NaH (2.03 g, 46 mmol) and the mixture was stirred for 1 h. Then ~ 0.3 M chloroamine (168 mL, 50.4 mmol) was added and the mixture was stirred at rt overnight. The mixture was diluted with EtOAc (300 mL) then washed with saturated aq NaHCO₃ and brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to provide methyl 1-amino-4-chloro-1H-pyrrole-2-carboxylate as a white solid (6.08 g, 97%). ¹H NMR (300 MHz, CDCl₃) δ 6.91 (d, 1H), 6.73 (d, 1H), 5.55 (br s, 2H), 3.83 (s, 3H); LCMS (ESI) *m/z* 175 (M + H)⁺.

[00891] **Example 182E:** To a solution of methyl 1-amino-4-chloro-1H-pyrrole-2-carboxylate (6.99 g, 40 mmol) in acetic acid (55 mL) at rt was added a solution of

potassium cyanate (6.80 g, 84 mmol) in water (20 mL) and the mixture was stirred at rt for 1 h. Water (300 mL) was added and the precipitate was collected by filtration washing with water to give methyl 4-chloro-1-ureido-1H-pyrrole-2-carboxylate as a light yellow solid (8.48 g, 98%). LCMS (ESI) m/z 218 ($M + H$)⁺.

[00892] Example 182F: To methyl 4-chloro-1-ureido-1H-pyrrole-2-carboxylate (8.48 g, 39 mmol) in EtOH (150 mL) at rt was added potassium hydroxide (4.37 g, 78 mmol), and the mixture was stirred at 60 °C overnight then allowed to cool to rt. The precipitate was collected by filtration, and then dissolved in water (200 mL). To the aqueous solution at 0 °C was added concentrated HCl, and the precipitate was collected by filtration to afford 6-chloropyrrolo[1,2-*f*][1,2,4]triazine-2,4(1H,3H)-dione as a white solid (3.2 g, 48%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.09 (br s, 1H), 11.42 (s, 1H), 7.31 (d, 1H), 6.69 (d, 1H); LCMS (ESI) m/z 184 ($M - H$)⁻.

[00893] Example 182G: To a mixture of 6-chloropyrrolo[1,2-*f*][1,2,4]triazine-2,4(1H,3H)-dione (1.00 g, 5.4 mmol) in POCl₃ (2.0 mL, 21.6 mmol) at rt was slowly added diisopropylethylamine (0.49 mL, 6.5 mmol), then the mixture was stirred at 125 °C in a sealed tube overnight. After cooling to rt, the mixture was diluted with 50 mL of toluene and the mixture was concentrated under reduced pressure. The residue was diluted with DCM (100 mL) and poured onto ice (50 g). The separated organic layer was washed with saturated aq NaHCO₃ and brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 1:5 DCM/hexane to give 2,4,6-trichloropyrrolo[1,2-*f*][1,2,4]triazine as a white solid (0.910 g, 76%). ¹H NMR (300 MHz, CDCl₃) δ 7.83 (d 1H), 7.01 (d, 1H); LCMS (ESI) m/z 223 ($M + H$)⁺.

[00894] Example 182H: 2,6-Dichloro-N-(5-methyl-1H-pyrazol-3-yl)pyrrolo[1,2-*f*][1,2,4]triazin-4-amine was prepared as a white solid (1.1 g, 95%) using a procedure analogous to that described in Example 2 Step 5, substituting 2,4,6-trichloropyrrolo[1,2-*f*][1,2,4]triazine for the 6-nitro 2,4-dichloropyrrolo[1,2-*f*][1,2,4]triazine used in Example 2 Step 5. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.37 (s, 1H), 11.13 (s, 1H), 7.97 (d, 1H), 7.38 (s, 1H), 6.53 (s, 1H), 2.27 (s, 3H); LCMS (ESI) m/z 284 ($M + H$)⁺.

[00895] **Example 182I:** 2-(4-Aminophenylthio)-6-chloro-N-(5-methyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine was prepared as a white solid (790 mg, 86%) using a procedure analogous to that described in Example 016A, substituting 2,6-dichloro-N-(5-methyl-1H-pyrazol-3-yl) pyrrolo[1,2-f][1,2,4]triazin-4-amine from Example 182H for the 2-chloro-N-(5-methyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine used in Example 016A. LCMS (ESI) m/z 372 ($M + H$)⁺.

[00896] **Example 182J:** 2-Chloro-N-(4-(6-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide was prepared as a white solid (520 mg, 97%) using a procedure analogous to that described in Example 016B, substituting 2-(4-aminophenylthio)-6-chloro-N-(5-methyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine for the 2-(4-aminophenylthio)-N-(5-methyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine used in Example 016B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.10 (s, 1H), 10.74 (s, 1H), 10.57 (s, 1H), 7.81 (s, 1H), 7.66 (dd, 4H), 7.27 (s, 1H), 5.57 (s, 1H), 4.28 (s, 2H), 2.03 (s, 3H); LCMS (ESI) m/z 449 ($M + H$)⁺.

[00897] **Example 182K:** (R)-1-(2-(4-(6-Chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)-N-cyclopropylpyrrolidine-3-carboxamide was prepared as a white solid (103 mg, 73%) using a procedure analogous to that described in Example 018B, substituting 2-Chloro-N-(4-(6-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from the previous step for the 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide used in Example 018B, and substituting (R)-N-cyclopropylpyrrolidine-3-carboxamide hydrochloride from Example 151A for the pyrrolidine derivative used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.10 (s, 1H), 10.74 (s, 1H), 10.12 (s, 1H), 7.85 (d, 1H), 7.82 (s, 1H), 7.80 (d, 2H), 7.57 (d, 2H), 7.34 (s, 1H), 5.60 (s, 1H), 3.24 (m, 2H), 2.81-2.50 (m, 6H), 2.03 (s, 3H), 1.94 (m, 2H), 0.61 (m, 2H), 0.59 (m, 2H); LCMS (ESI) m/z 566 ($M + H$)⁺.

Example 183

Preparation of (R)-N-(4-(6-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(3,3-difluoropiperidin-1-carbonyl)pyrrolidin-1-yl)acetamide

[00898] (R)-N-(4-(6-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(3,3-difluoropiperidin-1-carbonyl)pyrrolidin-1-yl)acetamide was prepared as a white solid (87 mg, 55%) using a procedure analogous to that described in Example 018B, substituting 2-chloro-N-(4-(6-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 182J for the 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide used in Example 018B, and substituting (R)-(3,3-difluoropiperidin-1-yl)(pyrrolidin-3-yl)methanone hydrochloride from Example 161A for the pyrrolidine derivative used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.10 (s, 1H), 10.73 (s, 1H), 10.10 (s, 1H), 7.86 (s, 1H), 7.82 (d, 2H), 7.58 (d, 2H), 7.27 (s, 1H), 7.34 (s, 1H), 5.60 (s, 1H), 3.82 (m, 2H), 3.53 (s, 2H), 3.42-3.21 (m, 3H), 2.73-2.67 (m, 4H), 2.11-2.06 (m, 4H), 2.03 (s, 3H), 2.00-1.51 (m, 4H); LCMS (ESI) *m/z* 630 (M + H)⁺.

Example 184

Preparation of (R)-1-(2-(4-(6-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)-N-(2-(4,4-difluoropiperidin-1-yl)ethyl)pyrrolidine-3-carboxamide

[00899] (R)-1-(2-(4-(6-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)-N-(2-(4,4-difluoropiperidin-1-yl)ethyl)pyrrolidine-3-carboxamide was prepared as a white solid (110 mg, 65%) using a procedure analogous to that described in Example 018B, substituting 2-chloro-N-(4-(6-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 182J for the 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide used in Example 018B, and substituting (R)-N-(2-(4,4-difluoropiperidin-1-yl)ethyl)pyrrolidine-3-carboxamide hydrochloride from Example 170 Step 2 for the pyrrolidine derivative used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.10 (s, 1H), 10.73 (s, 1H), 10.15 (s, 1H), 7.82 (m, 4H), 7.58 (d, 2H), 7.28 (s, 1H), 5.60 (s, 1H), 3.39-3.18 (m, 5H), 2.80-2.65 (m, 6H), 2.43-2.41 (m, 3H), 2.03 (s, 3H), 1.99-1.80 (m, 7H), 2.11-2.06 (m, 4H), 2.03 (s, 3H), 2.00-1.51 (m, 4H); LCMS (ESI) *m/z* 673 (M + H)⁺.

Example 185**Preparation of (R)-1-(2-(4-(6-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)-N,N-dimethylpyrrolidine-3-carboxamide**

[00900] (R)-1-(2-(4-(6-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)-N,N-dimethylpyrrolidine-3-carboxamide was prepared as a white solid (110 mg, 65%) using a procedure analogous to that described in Example 018B, substituting 2-chloro-N-(4-(6-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 182J for the 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide used in Example 018B, and substituting (R)-N,N-dimethylpyrrolidine-3-carboxamide hydrochloride from Example 126A for the pyrrolidine derivative used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.11 (s, 1H), 10.74 (s, 1H), 10.23 (s, 1H), 7.88 (s, 1H), 7.83 (m, 3H), 7.58 (d, 2H), 7.28 (s, 1H), 5.60 (s, 1H), 3.49-3.22 (m, 4H), 3.02 (s, 3H), 2.90 (s, 3H), 2.78 (m, 3H), 2.10 (m, 1H), 2.03 (s, 3H), 1.90 (m, 1H); LCMS (ESI) *m/z* 554 (M + H)⁺.

Example 186**Preparation of 2-((R)-3-(2-(piperidin-1-yl)ethoxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide**

[00901] **Example 186A:** To a stirring mixture of piperidine (3 g, 35.3 mmol) and 25% aq NaOH (7.1 mL) in acetone (71 mL) at 0 °C was slowly added 1-bromo-2-chloroethane (5 g, 35.3 mmol), and the mixture was stirred at rt overnight, then concentrated under reduced pressure at 20 °C. The residue was diluted with water and extracted with DCM. The organic layer was washed several times with 0.1 M HCl, then washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to afford 1-(2-chloroethyl) piperidine as a yellow oil (1.70 g, 32%). ¹H NMR (400 MHz, CDCl₃) δ 3.59-3.56 (t, 2H), 2.70-2.66 (t, 2H), 2.45-2.43 (t, 4H), 1.61-1.55 (m, 4H), 1.46-1.41 (m, 2H). LCMS (ESI) *m/z* 148 (M+H)⁺.

[00902] **Example 186B:** To a stirring solution of (R)-benzyl 3-hydroxypyrrolidine-1-carboxylate (509 mg, 2.3 mmol) in DMF (4 mL) at 0 °C was added 60% NaH (108

mg, 2.7 mmol) and the mixture was stirred at 0 °C for 10 min. A solution of 1-(2-chloroethyl)piperidine (400 mg, 2.7 mmol) in DMF (1.6 mL) was added and the mixture was stirred at rt overnight. Water was added and the mixture was extracted with EtOAc. The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 100:0 to 100:10 DCM /MeOH to afford (*R*)-benzyl 3-(2-(piperidin-1-yl)ethoxy)pyrrolidine-1-carboxylate as a yellow oil (400 mg, 45%). ¹H NMR (400 MHz, CDCl₃) δ 7.37 (m, 5H), 5.14 (s, 2H), 3.60-3.44 (m, 7H), 2.58-2.54 (m, 2H), 2.45 (m, 4H), 2.04-1.91 (m, 2H), 1.62-1.57 (m, 4H), 1.44-1.43 (m, 2H). LCMS (ESI) *m/z* 333 (M+H)⁺.

[00903] **Example 186C:** A mixture of (*R*)-benzyl 3-(2-(piperidin-1-yl)ethoxy)pyrrolidine-1-carboxylate (400 mg, 1.20 mmol) and 10% Pd/C (20 mg) in MeOH (10 mL) was stirred under H₂ (2 atm) at rt overnight. The mixture was filtered and the filtrate was concentrated under reduced pressure to afford 1-(2-((*R*)-pyrrolidin-3-yloxy)ethyl)piperidine as a yellow oil (250 mg), which was used directly in the next step. LCMS (ESI) *m/z* 199 (M+H)⁺.

[00904] **Example 186D:** A mixture of 1-(2-((*R*)-pyrrolidin-3-yloxy)ethyl)piperidine (100 mg), *N*-(4-(4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrrolo[1,2-*f*][1,2,4]triazin-2-ylthio)phenyl)-2-chloroacetamide (100 mg, 0.24 mmol) and Na₂CO₃ (102 mg, 0.96 mmol) in DMF (2 mL) was stirred at rt overnight, then the mixture was poured into water and extracted with EtOAc. The organic layer was concentrated under reduced pressure and the residue was purified by preparative TLC eluting with 10:1 DCM/MeOH to afford 2-((*R*)-3-(2-(piperidin-1-yl)ethoxy)pyrrolidin-1-yl)-*N*-(4-(4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrrolo[1,2-*f*][1,2,4]triazin-2-ylthio)phenyl)acetamide as a light yellow solid (30 mg, 12%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.08 (s, 1H), 10.64 (s, 1H), 10.03 (s, 1H), 7.80-7.78 (d, 2H), 7.58-7.55 (m, 3H), 7.22 (s, 1H), 6.58 (s, 1H), 5.64 (s, 1H), 4.05 (m, 1H), 3.29 (m, 3H), 2.85 (m, 1H), 2.71 (m, 1H), 2.60 (m, 3H), 2.06 (m, 4H), 1.73 (m, 2H), 1.51 (m, 4H), 1.37 (m, 3H), 1.25 (m, 3H); LCMS (ESI) *m/z* 576 (M+H)⁺.

Example 187

Preparation of (R)-N-(4-(6-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(3,3-difluoropyrrolidine-1-carbonyl)pyrrolidin-1-yl)acetamide

[00905] (R)-N-(4-(6-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(3,3-difluoropyrrolidine-1-carbonyl)pyrrolidin-1-yl)acetamide was prepared as a white solid (97 mg, 63%) using a procedure analogous to that described in Example 018B, substituting 2-chloro-N-(4-(6-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 182J for the 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide used in Example 018B, and substituting (R)-N-(2-(4,4-difluoropiperidin-1-yl)ethyl)pyrrolidine-3-carboxamide from Example 128A for the pyrrolidine derivative used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.11 (s, 1H), 10.74 (s, 1H), 10.23 (s, 1H), 7.96 (s, 1H), 7.84 (m, 3H), 7.58 (d, 2H), 7.28 (s, 1H), 5.61 (s, 1H), 3.96 (t, 1H), 3.76 (m, 2H), 3.69 (t, 1H), 3.58-3.37 (m, 2H), 2.89-2.68 (m, 6H), 2.47 (m, 1H), 2.18 (m, 1H), 2.03 (s, 3H), 1.92 (m, 1H); LCMS (ESI) *m/z* 616 (M + H)⁺.

Example 188

Preparation of (R)-1-(2-(4-(6-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)-N-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxamide

[00906] (R)-1-(2-(4-(6-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)-N-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxamide was prepared as a white solid (101 mg, 66%) using a procedure analogous to that described in Example 018B, substituting 2-chloro-N-(4-(6-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 182J for the 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide used in Example 018B, and substituting (R)-N-(2-(4,4-difluoropiperidin-1-yl)ethyl)pyrrolidine-3-carboxamide from Example 169 Step 2 for the pyrrolidine derivative used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.11 (s, 1H), 10.74 (s, 1H), 10.10 (s, 1H), 8.57 (s, 1H), 7.81 (m, 3H), 7.59 (d, 2H), 7.28 (s, 1H), 5.61 (s, 1H), 4.07-3.85 (m, 2H), 3.37 (t, 2H), 3.01 (m, 1H), 2.89 (m, 2H), 2.80-2.62 (m, 3H), 2.04 (s, 3H), 1.94 (m, 1H); LCMS (ESI) *m/z* 608 (M + H)⁺.

Example 189**Preparation of (R)-1-(2-(4-(6-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)-N-cyclopentylpyrrolidine-3-carboxamide**

[00907] (R)-1-(2-(4-(6-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)-N-cyclopentylpyrrolidine-3-carboxamide was prepared as a white solid (101 mg, 66%) using a procedure analogous to that described in Example 018B, substituting 2-chloro-N-(4-(6-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 182J for the 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide used in Example 018B, and substituting (R)-N-cyclopentylpyrrolidine-3-carboxamide from Example 150A for the pyrrolidine derivative used in Example 018B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.10 (s, 1H), 10.73 (s, 1H), 10.14 (s, 1H), 7.82 (m, 4H), 7.58 (d, 2H), 7.28 (s, 1H), 5.60 (s, 1H), 4.02 (m, 1H), 3.39-3.19 (m, 2H), 2.89-2.63 (m, 5H), 2.03 (s, 3H), 1.99-1.15 (m, 10H); LCMS (ESI) *m/z* 594 (M + H)⁺.

Example 190**Preparation of 2-((R)-3-(3,3-difluoro-4-hydroxypyrrolidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide**

[00908] **Example 190 Step 1:** A mixture of benzyl 4-(benzyloxy)-3,3-difluoropyrrolidine-1-carboxylate from Example 60B (482.2 mg, 1.39 mmol) and 10 % Pd/C (500 mg) in DMF (10 mL) was stirred under H₂ at rt for 4 h, then filtered through Celite washing with MeOH. The filtrate was concentrated to a volume of ca. 7 mL; LCMS (ESI) *m/z* 214 (M + H)⁺. This solution was added to a mixture of (R)-1-(*tert*-butoxycarbonyl)pyrrolidine-3-carboxylic acid (320 mg, 0.149 mmol), 1-hydroxybenzotriazole monohydrate (220.0 mg, 1.63 mmol), ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (300 mg, 1.57 mmol), and triethylamine (0.500 mL, 3.59 mmol) in DCM (3 mL), and the mixture was stirred at rt for 3 days, then partitioned between EtOAc (80 mL) and saturated aq sodium bicarbonate (80 mL). The separated aqueous layer was extracted with EtOAc (3 x 80 mL), and then the combined organic phases were washed with brine (2 x 80 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced

pressure. The residual oil was purified by silica gel chromatography eluting with 5-100 % EtOAc/hexanes to afford (*R*)-*tert*-butyl 3-(4-(benzyloxy)-3,3-difluoropyrrolidine-1-carbonyl)pyrrolidine-1-carboxylate as an oil (364.7 mg, 64 %). LCMS (ESI) m/z 433 ($M + Na$)⁺.

[00909] **Example 190 Step 2:** A mixture of (*R*)-*tert*-butyl 3-((*R/S*)-4-(benzyloxy)-3,3-difluoropyrrolidine-1-carbonyl)pyrrolidine-1-carboxylate (364.7 mg, 0.888 mmol) and 20 % palladium hydroxide on carbon (300 mg) in MeOH (5 mL) was stirred under H₂ at rt for 5 h, then filtered through Celite washing with MeOH. The filtrate was concentrated under reduced pressure to give (*R*)-*tert*-butyl 3-(3,3-difluoro-4-hydroxypyrrolidine-1-carbonyl)pyrrolidine-1-carboxylate as an oil (270.6 mg, 95%), which was used directly in the next step. LCMS (ESI) m/z 343 ($M + Na$)⁺.

[00910] **Example 190 Step 3:** To (*R*)-*tert*-butyl 3-(3,3-difluoro-4-hydroxypyrrolidine-1-carbonyl)pyrrolidine-1-carboxylate (270.6 mg, 0.845 mmol) in DCM (5 mL) was added 4 M HCl/1,4-dioxane (2.0 mL, 8.0 mmol) and the mixture was stirred at rt for 4 h. The mixture was concentrated under reduced pressure to give (*R*)-3-(3,3-difluoro-4-hydroxypyrrolidine-1-carbonyl)pyrrolidinium hydrochloride as an oil (215 mg, 100%), which was used directly in the next step. LCMS (ESI) m/z 221 ($M + H$)⁺.

[00911] **Example 190 Step 4:** To (*R*)-3-(3,3-difluoro-4-hydroxypyrrolidine-1-carbonyl)pyrrolidinium hydrochloride (53.0 mg, 0.206 mmol) in DMF (1.5 mL) were added diisopropylethylamine (0.20 mL, 1.21 mmol), sodium iodide (20 mg, 0.133 mmol) and 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 016B (70.0 mg, 0.169 mmol), and the mixture was stirred under Ar at 85 °C for 18 h. The mixture was diluted with MeOH and purified by preparative reverse-phase HPLC eluting with a gradient of 20-95% solvent B (0.05% HOAc/CH₃CN) in solvent A (0.05% HOAc/H₂O) to afford 2-((*R*)-3-(3,3-difluoro-4-hydroxypyrrolidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide as a solid acetate salt (73.1 mg, 66%). LCMS (ESI) m/z 598 ($M + H$)⁺. ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.98 (br s, 1H),

10.61 (s, 1H), 10.09 (s, 1H), 7.83 (d, $J = 8.6$ Hz, 2H), 7.56-7.59 (m, 3H), 7.21 (m, 1H), 7.58 (m, 1H), 5.65 (m, 1H), 4.30 (m, 1H), 3.53-4.05 (m, 4H), 3.04-3.52 (m, 7H), 2.60-2.84 (m, 4H), 2.03 (s, 3H), 1.90 (s, 3H).

Example 191

Preparation of 2-((*R*)-3-(3,3-difluoro-4-hydroxypyrrolidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-*f*][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00912] The acetate salt of 2-((*R*)-3-(3,3-difluoro-4-hydroxypyrrolidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-*f*][1,2,4]triazin-2-ylthio)phenyl)acetamide was prepared as a solid (75.1 mg, 68%) using a procedure analogous to that described in Example 190 Step 4, substituting 2-chloro-N-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-*f*][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 172A for the 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-*f*][1,2,4]triazin-2-ylthio)phenyl)acetamide used in Example 190 Step 4. LCMS (ESI) m/z 612 ($M + H$)⁺. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.00 (br s, 1H), 10.48 (s, 1H), 10.09 (s, 1H), 7.82 (d, $J = 8.6$ Hz, 2H), 7.56 (d, $J = 8.6$ Hz, 2H), 7.42 (s, 1H), 7.00 (s, 1H), 5.62 (s, 1H), 4.27 (m, 1H), 3.56-4.05 (m, 4H), 3.06-3.54 (m, 7H), 2.60-2.85 (m, 4H), 2.19 (s, 3H), 2.02 (s, 3H), 1.90 (s, 3H).

Example 192

Preparation of (*R*)-N-(4-(6-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-*f*][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(3,3-difluoro-4-hydroxypyrrolidine-1-carbonyl)pyrrolidin-1-yl)acetamide

[00913] (*R*)-N-(4-(6-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-*f*][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(3,3-difluoro-4-hydroxypyrrolidine-1-carbonyl)pyrrolidin-1-yl)acetamide was prepared as its acetate salt using a procedure analogous to that described in Example 190 Step 4, substituting 2-chloro-N-(4-(6-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-*f*][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 182J for the 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-*f*][1,2,4]triazin-2-ylthio)phenyl)acetamide used in Example 190 Step 4. Purification by preparative reverse-phase HPLC eluting with a gradient of 20-95% solvent B (0.05% HOAc/CH₃CN) in solvent A (0.05% HOAc/H₂O) afforded (*R*)-N-(4-(6-chloro-4-(5-methyl-1H-pyrazol-3-

ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(3,3-difluoro-4-hydroxypyrrolidine-1-carbonyl)pyrrolidin-1-yl)acetamide as a solid acetate salt (68.1 mg, 63%) LCMS (ESI) m/z 632 ($M + H$)⁺. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.08 (br s, 1H), 10.78 (br s, 1H), 10.11 (s, 1H), 7.80-7.86 (m, 3H), 7.58 (d, $J = 8.6$ Hz, 2H), 7.27 (s, 1H), 5.59 (s, 1H), 4.27 (m, 1H), 3.55-4.06 (m, 4H), 3.06-3.54 (m, 7H), 2.60-2.85 (m, 4H), 2.02 (s, 3H), 1.89 (s, 3H).

Example 193

Preparation of 2-((*R*)-3-((*R*)-4,4-difluoro-2-(hydroxymethyl)pyrrolidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide

[00914] Example 193 Step 1: A mixture of (*R*)-1-(*tert*-butoxycarbonyl)-4,4-difluoropyrrolidine-2-carboxylic acid (500.0 mg, 1.99 mmol), tetrahydrofuran (5 mL) and 1 M borane-tetrahydrofuran complex/THF (3 mL, 3 mmol) was heated under reflux for 3 h. Acetic acid (1 mL) was added, and then the mixture was partitioned between EtOAc (50 mL) and brine (50 mL). The separated organic layer was washed with brine (50 mL), dried over MgSO₄, filtered concentrated under reduced pressure. To the residual oil in DCM (5 mL) was added trifluoroacetic acid (2 mL) and the mixture was stirred at rt for 1 h. The mixture was concentrated under reduced pressure and half of the residue was dissolved in DCM, treated with 4N HCl/dioxane (20 mL), and concentrated under reduced pressure. The DCM dissolution, HCl/dioxane treatment, and concentration steps were repeated three additional times to afford (*R*)-4,4-difluoro-2-(hydroxymethyl)pyrrolidinium hydrochloride as a solid, which was used directly in the next step. LCMS (ESI) m/z 138 ($M + H$)⁺.

[00915] Example 193 Step 2: To (*R*)-1-(*tert*-butoxycarbonyl)pyrrolidine-3-carboxylic acid (62.0 mg, 0.288 mmol) in DMF (0.5 mL) were added diisopropylethylamine (0.1 mL, 0.605 mmol) and N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (110 mg, 0.289 mmol), and the mixture was stirred at rt for 5 min. Then a solution of (*R*)-4,4-difluoro-2-(hydroxymethyl)pyrrolidinium hydrochloride (84.0 mg, 0.484 mmol) and diisopropylethylamine (0.4 mL, 2.42 mmol) in DMF (0.5 mL) was added and the solution was stirred at rt for 30 min. The mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography eluting with 5-

100% EtOAc/hexanes to afford (*R*)-*tert*-butyl 3-((*R*)-4,4-difluoro-2-(hydroxymethyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carboxylate as a solid (95.5 mg, 100%). LCMS (ESI) m/z 357 ($M + Na$)⁺.

[00916] Example 193 Step 3: (*R*)-3-((*R*)-4,4-difluoro-2-(hydroxymethyl)pyrrolidine-1-carbonyl)pyrrolidinium hydrochloride was prepared as a solid (77.0 mg, 100%) using a procedure analogous to that described in Example 190 Step 3, substituting (*R*)-*tert*-butyl 3-((*R*)-4,4-difluoro-2-(hydroxymethyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carboxylate for the (*R*)-*tert*-butyl 3-(3,3-difluoro-4-hydroxypyrrolidine-1-carbonyl)pyrrolidine-1-carboxylate used in Example 190 Step 3. LCMS (ESI) m/z 235 ($M + H$)⁺.

[00917] Example 193 Step 4: 2-((*R*)-3-((*R*)-4,4-difluoro-2-(hydroxymethyl)pyrrolidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-*f*][1,2,4]triazin-2-ylthio)phenyl)acetamide was prepared as its acetate salt using a procedure analogous to that described in Example 160 Step 3, substituting (*R*)-3-((*R*)-4,4-difluoro-2-(hydroxymethyl)pyrrolidine-1-carbonyl)pyrrolidinium hydrochloride for the (*S*)-3-(cyclopentylcarbamoyl)pyrrolidinium trifluoroacetate used in Example 160 Step 3, and using a purification gradient of 20-95% solvent B (0.05% HOAc/CH₃CN) in solvent A (0.05% HOAc/H₂O) in place of the purification gradient used in Example 160 Step 3. LCMS (ESI) m/z 612 ($M + H$)⁺. ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.97 (br s, 1H), 10.61 (s, 1H), 10.17 (s, 1H), 7.79-7.83 (m, 2H), 7.57-7.60 (m, 3H), 7.21 (m, 1H), 7.58 (m, 1H), 5.67 (m, 2H), 4.90-5.18 (m, 1H), 4.26 (m, 1H), 4.06 (m, 1H), 3.86 (m, 1H), 3.38-3.66 (m, 4H), 3.23-3.36 (m, 3H), 2.60-3.20 (m, 6H), 2.00-2.20 (m, 4H), 3.79 (s, 3H).

Example 194

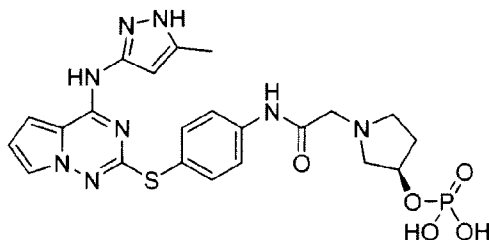
Preparation of N-(4-(6-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-*f*][1,2,4]triazin-2-ylthio)phenyl)-2-((*R*)-3-((*S*)-4,4-difluoro-2-(hydroxymethyl)pyrrolidine-1-carbonyl)pyrrolidin-1-yl)acetamide

[00918] N-(4-(6-Chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-*f*][1,2,4]triazin-2-ylthio)phenyl)-2-((*R*)-3-((*S*)-4,4-difluoro-2-(hydroxymethyl)pyrrolidine-1-carbonyl)pyrrolidin-1-yl)acetamide was synthesized as

a white solid (15 mg, 53 %) using a procedure analogous to that described in Example 126B, substituting ((S)-4,4-difluoro-2-(hydroxymethyl)pyrrolidin-1-yl)((R)-pyrrolidin-3-yl)methanone hydrochloride for the pyrrolidine-3-carboxylic acid dimethylamide used in Example 126B, and substituting 2-chloro-N-(4-(6-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 182J for the 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide used in Example 126B. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.00 (s, 1H), 10.70 (s, 1H), 10.10 (d, 1H), 7.80 (d, 3H), 7.60 (d, 2H), 7.30 (s, 1H), 5.60 (s, 1H), 4.90 (t, 1H), 4.35-4.00 (m, 2H), 3.90-3.65 (m, 1H), 3.60-3.10 (m, 6H), 2.90-2.60 (m, 5H), 2.20-2.10 (m, 1H), 2.05 (s, 1H), 1.95-1.75 (m, 1H); LCMS (ESI) *m/z* 646 (M+H)⁺.

Example 195

Preparation of (R)-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidin-3-yl dihydrogen phosphate



[00919] **Step A:** To a stirred solution of 3% tetrazole in acetonitrile (7.5 mL) was added tert-butyl (3R)-3-hydroxycyclopentylcarbamate (300 mg, 1.6 mmol) followed by dibenzyl diisopropylphosphoramidite (0.72 mL, 1.9 mmol) and the resulting mixture was stirred at rt for 2 h. After this time the mixture was cooled to 0 °C and *m*-CPBA (720 mg, 4.59 mmol) was added. The reaction mixture was stirred at this temperature for 10 min. then quenched with an aqueous solution of sodium hydrogen carbonate and extracted three times with EtOAc. The organic layers were combined, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified twice by silica gel flash chromatography eluting first with a gradient of 4% EtOAc in hexanes to 40% EtOAc in hexane and then with a gradient of 100% DCM

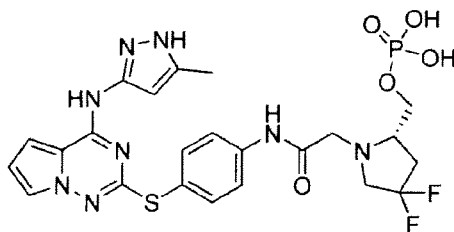
to 10% MeOH in DCM to afford (3R)-tert-butyl 3-(benzyloxy(phenethoxy)phosphoryloxy)pyrrolidine-1-carboxylate as an oil.

[00920] Step B: A mixture of (3R)-tert-butyl 3-(benzyloxy(phenethoxy)phosphoryloxy)pyrrolidine-1-carboxylate (100 mg, 0.22 mmol) in 4N HCl in 1,4-dioxane (3 mL) was heated in a Biotage microwave reactor at 120 °C for 10 min. After cooling to rt, the precipitated solid was treated with EtOAc (4 mL), filtered and washed with EtOAc. The crude residue was taken in DMF (2 mL) and treated with N,N-diisopropylethylamine (191 µL, 1.1 mmol), KI (73 mg, 0.44 mmol) and 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (87 mg, 0.210 mmol) from Example 016B. The resulting mixture was stirred at rt for 15 h, then heated at 45°C for 2 h and stirred at rt for additional 15 h. After this time the mixture was heated at 50 °C for 2 h, cooled to rt and purified by preparative HPLC eluting with a gradient of 20% to 40% solvent B (0.05% HOAc/CH₃CN) in solvent A (0.05% HOAc/H₂O) to afford (R)-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidin-3-yl dihydrogen phosphate (12 mg, 10% over 2 steps).

[00921] ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.57 (brs, 1H), 10.49 (brs, 1H), 7.78 (d, *J* = 9.0 Hz, 2H), 7.57-7.59 (m, 3H), 7.22 (brs, 1H), 6.58 (brs, 1H), 5.63 (s, 1H), 4.77 (brs, 1H), 2.96-3.19 (m, 6H), 2.01-2.20 (m, 6H); LC-MS (ESI) *m/z* 545 (M + H)⁺.

Example 196

Preparation of (S)-(4,4-difluoro-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidin-2-yl)methyl dihydrogen phosphate



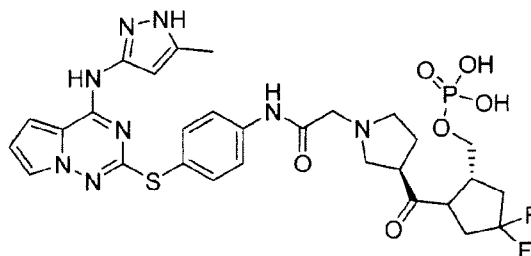
[00922] Step A: (S)-tert-butyl 2-((bis(benzyloxy)phosphoryloxy)methyl)-4,4-difluoropyrrolidine-1-carboxylate was prepared using a procedure analogous to that described in Example 195 Step A, substituting (S)-tert-butyl 4,4-difluoro-2-

(hydroxymethyl)pyrrolidine-1-carboxylate for the tert-butyl (3R)-3-hydroxycyclopentylcarbamate used in Example 195.

[00923] Step B: (S)-(4,4-difluoro-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidin-2-yl)methyl dihydrogen phosphate was prepared as a solid (21 mg, 15% over 2 steps) using a procedure analogous to that described in Example 195 Step B, substituting (S)-tert-butyl 2-((bis(benzyloxy)phosphoryloxy)methyl)-4,4-difluoropyrrolidine-1-carboxylate for the (3R)-tert-butyl 3-(benzyloxy(phenethoxy)phosphoryloxy)pyrrolidine-1-carboxylate used in Example 195 Step B. ^1H NMR (300 MHz, DMSO- d_6) δ 10.63 (s, 1H), 10.25 (s, 1H), 7.77-7.80 (d, $J = 9.0$ Hz, 2H), 7.56-7.59 (m, 3H), 7.22 (brs, 1H), 6.58 (brs, 1H), 5.64 (s, 1H), 3.94 (brs, 2H), 3.71-3.76 (m, 2H), 3.39-3.50 (m, 2H), 3.19-3.31 (m, 3H), 2.99-3.08 (m, 2H), 2.18-2.39 (m, 1H), 2.01 (m, 3H); LC-MS (ESI) m/z 545 ($M + H$) $^+$.

Example 197

Preparation of ((1R)-4,4-difluoro-2-((R)-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carbonyl)cyclopentyl)methyl dihydrogen phosphate



[00924] Step A: (3R)-tert-butyl 3-((2R)-2-((bis(benzyloxy)phosphoryloxy)methyl)-4,4-difluorocyclopentanecarbonyl)pyrrolidine-1-carboxylate was prepared (1.25 g, 78%) using a procedure analogous to that described in Example 195 Step A, substituting (3R)-tert-butyl 3-((2R)-4,4-difluoro-2-(hydroxymethyl)cyclopentanecarbonyl)pyrrolidine-1-carboxylate from Example 156A for the tert-butyl (3R)-3-hydroxycyclopentylcarbamate used in Example 195. ^1H NMR (300 MHz, CDCl $_3$) δ 7.27-7.35 (m, 10H), 4.97-5.05 (m, 4H), 4.25-4.43 (m, 2H), 3.88-3.99 (m, 1H), 3.77-3.84 (m, 2H), 3.42-3.51 (m, 3H), 3.26-3.30 (m, 1H),

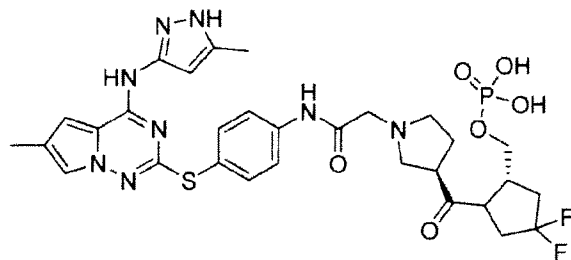
2.65-3.00 (m, 1H), 2.38-2.43 (m, 2H), 1.95-2.05 (m, 3H), 1.45 (s, 9H); LC-MS (ESI) m/z 495 $\{(M + H)^+ - \text{Boc}\}$.

[00925] Step B: To a stirred mixture of (3R)-tert-butyl 3-((2R)-2-((bis(benzyloxy)phosphoryloxy)methyl)-4,4-difluorocyclopentanecarbonyl)pyrrolidine-1-carboxylate (1.4 g, 2.35 mmol) in EtOH (10 mL) was added Pd/C (210 mg) and the resulting mixture stirred under hydrogen at rt for 2 h. After reaction completion, the mixture was filtered and concentration under reduced pressure to afford (3R)-tert-butyl 3-((2R)-4,4-difluoro-2-(phosphonooxymethyl)cyclopentanecarbonyl)pyrrolidine-1-carboxylate (850 mg), which was used in the next step without further purification. LC-MS (ESI) m/z 315 $\{(M + H)^+ - \text{Boc}\}$.

[00926] Step C: A mixture of (3R)-tert-butyl 3-((2R)-4,4-difluoro-2-(phosphonooxymethyl)cyclopentanecarbonyl)pyrrolidine-1-carboxylate (850 mg, 2.05 mmol) in EtOAc and 4N HCl in 1,4-dioxane (15 mL) was stirred at rt for 1 h. After concentration under reduced pressure the resulting crude material (66 mg, 0.21 mmol) was taken into DMF (4 mL) and treated with KI (23 mg, 0.14 mmol), N,N-diisopropylethylamine (0.15 μL , 0.84 mmol) and 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide (58 mg, 0.14 mmol) from Example 016B. The resulting mixture was heated under stirring at 40°C for 6 h, then diluted in MeOH and purified by preparative HPLC eluting with a gradient of 25% to 45% solvent B (0.05% HOAc/CH₃CN) in solvent A (0.05% HOAc/H₂O) to afford ((1R)-4,4-difluoro-2-((R)-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carbonyl)cyclopentyl)methyl dihydrogen phosphate (50 mg, 52%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.61 (s, 1H), 7.76-7.82 (m, 2H), 7.58-7.60 (m, 2H), 7.40 (brs, 1H), 6.56-6.58 (m, 1H), 5.65 (s, 1H), 4.40-4.61 (m, 1H), 4.25-4.39 (m, 1H), 3.80-4.25 (m, 4H), 3.61-3.75 (m, 2H), 3.41-3.59 (m, 1H), 3.11-3.41 (m, 2H), 2.85-3.05 (m, 1H), 2.04 (s, 3H); LC-MS (ESI) m/z 692 $\{(M + H)^+\}$.

Example 198

Preparation of ((1R)-4,4-difluoro-2-((R)-1-(2-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carbonyl)cyclopentyl)methyl dihydrogen phosphate



[00927] ((1R)-4,4-difluoro-2-((R)-1-(2-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carbonyl)cyclopentyl)methyl dihydrogen phosphate was prepared as a solid (52 mg, 53%) using a procedure analogous to that described in Example 197 Step C, substituting 2-chloro-N-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide from Example 172A for the 2-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide used in Example 197 Step C. ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.47 (s, 1H), 7.75-7.78 (m, 2H), 7.56-7.59 (m, 2H), 7.41 (s, 1H), 7.00 (s, 1H), 5.61 (s, 1H), 4.44-4.61 (m, 1H), 4.29-4.40 (m, 1H), 3.42-4.15 (m, 4H), 3.50-3.75 (m, 3H), 3.10-3.44 (m, 2H), 2.83-3.10 (m, 1H), 2.19 (s, 3H), 2.04 (s, 3H); LC-MS (ESI) *m/z* 706 [(M + H)⁺].

Example 199

Competition binding assay to determine binding constants (*K_d*) of the compounds against Aurora kinases

[00928] Competition binding assays used herein were developed, validated and performed as described in Fabian et al., *Nature Biotechnology* **2005**, 23,329-336. Kinases were produced as fusions to T7 phage (See, Fabian *et al.* or WO04/015142) or alternatively, the kinases were expressed in HEK-293 cells and subsequently tagged with DNA for PCR detection (See, WO08/005310). For the binding assays, streptavidin-coated magnetic beads were treated with biotinylated affinity ligands for 30 min at rt to generate affinity resins. The liganded beads were blocked with excess biotin and washed with blocking buffer (SeaBlock (Pierce), 1 % BSA, 0.05 % Tween 20, 1 mM DTT) to remove unbound ligand and to reduce non-specific binding. Binding reactions were assembled by combining kinase, liganded affinity beads, and test compounds in 1 x binding buffer (20 % SeaBlock, 0.17x PBS, 0.05 % Tween 20, 6 mM DTT). Test compounds were prepared as 100 x stocks in DMSO and rapidly

diluted into the aqueous environment. DMSO was added to control assays lacking a test compound. Primary screen interactions were performed in polypropylene 384-well plates in a final volume of 34 μ L, while K_d determinations were performed in polystyrene 96-well plates in a final volume of 135 μ L. The assay plates were incubated at rt with shaking for 1 h, long enough for binding reactions to reach equilibrium, and the affinity beads were washed extensively with wash buffer (1x PBS, 0.05 % Tween 20) to remove unbound protein. The beads were then resuspended in elution buffer (1x PBS, 0.05 % Tween 20, 2 μ M non-biotinylated affinity ligand) and incubated at rt with shaking for 30 min. The kinase concentration in the eluates was measured by quantitative PCR. Each kinase was tested individually against each compound. K_d s were determined using eleven serial threefold dilutions.

[00929] In one embodiment, the compounds provided herein were found to have K_d s of less than about 100 nM against Aurora kinase. In another embodiment, the compounds provided herein were found to have K_d s of less than about 50 nM against Aurora kinase. In another embodiment, the compounds provided herein were found to have K_d s of less than about 20 nM against Aurora kinase.

[00930] In one embodiment, the compounds provided herein were found to have K_d s of less than about 100 nM against Aurora A kinase. In another embodiment, the compounds provided herein were found to have K_d s of less than about 50 nM against Aurora A kinase. In another embodiment, the compounds provided herein were found to have K_d s of less than about 20 nM against Aurora A kinase. In another embodiment, the compounds provided herein were found to have K_d s of less than about 10 nM against Aurora A kinase.

[00931] In one embodiment, the compounds provided herein were found to have K_d s of less than about 100 nM against Aurora B kinase. In another embodiment, the compounds provided herein were found to have K_d s of less than about 50 nM against Aurora B kinase. In another embodiment, the compounds provided herein were found to have K_d s of less than about 20 nM against Aurora B kinase. In another embodiment, the compounds provided herein were found to have K_d s of less than about 10 nM against Aurora B kinase.

[00932] In one embodiment, the compounds provided herein were found to have K_d s of less than about 100 nM against Aurora C kinase. In another embodiment, the compounds provided herein were found to have K_d s of less than

about 50 nM against Aurora C kinase. In another embodiment, the compounds provided herein were found to have Kds of less than about 20 nM against Aurora C kinase. In another embodiment, the compounds provided herein were found to have Kds of less than about 10 nM against Aurora C kinase.

Example 200

Cell-based assay to determine Histone H3 phosphorylation

[00933] A cellular assay was performed to determine the compounds' ability to inhibit a particular function of the Aurora B kinase in human cells, in this case, to phosphorylate serine 10 of the histone H3 enzyme (HH3) during mitosis. HCT-116 cells derived from a human colorectal carcinoma cell line (ACT# CLL-247) were grown to 80-90% confluency in McCoy's 5A Complete media (*Gibco Cat#16600-108*) supplemented with 10% FBS and Penicillin (100U/mL)/Streptomycin (100ug/mL) and seeded at a concentration of 4×10^4 cells/well into pre-warmed 96-well poly-d-lysine-coated plates, and then incubated at 37°C, 5% CO₂ for 4 to 6 h. At the end of the incubation period, nocodazole was added to the wells and maintained at a final concentration of 66 ng/mL, to arrest the cells in mitosis. The cells were incubated with nocodazole overnight at 37°C, 5% CO₂ for 16 to 18 h. At the end of the incubation period, the cells were added to a 96-well propylene plate containing compounds in DMSO that were serially diluted three-fold down the row nine times for the generation of a nine-point curve. The cells were treated with compound for 2 h at 37°C, 5% CO₂. To harvest the HH3 protein, media was first aspirated from cells and the plate washed with cold PBS. The cells were lysed with cell extraction buffer (Biosource, Cat #FNN0011) supplemented with phosphatase inhibitor (Roche Cat# 1183 580 001), and the plate shaken at 5°C for 30 min followed by centrifugation at 3000xg for 20 min. The samples were then transferred to a Nunc PS 96-well plate and diluted in Standard Dilution Buffer provided in the Path Scan® Phospho Histone H3 (Ser 10) Sandwich Elisa Kit (*Cell signaling Cat# 7155*). The diluted samples were directly used following the protocol for the Path Scan® Phospho Histone H3 (Ser 10) Sandwich Elisa Kit. The phosphorylation state of HH3 was detected using an anti-phospho-Histone H3 (Ser10) antibody in a colorimetric sandwich ELISA. The reaction product was quantified by measuring the absorbance of the samples at 450 nm using a

SpectaMax Plus 384 plate reader. The concentration of a compound that inhibited the phosphorylation of HH3 by 50% was reported as the pHH3 IC₅₀ for that compound. In one embodiment, the compounds disclosed herein have been found to have pHH3 activity within the range of about 10 nM to about 200 nM. In one embodiment, the compounds disclosed herein have pHH3 IC₅₀s of less than about 350 nM. In one embodiment, the compounds disclosed herein have pHH3 IC₅₀s of less than about 200 nM. In one embodiment, the compounds disclosed herein have pHH3 IC₅₀s of less than about 100 nM. In one embodiment, the compounds disclosed herein have pHH3 IC₅₀s of less than about 50 nM. In one embodiment, the compounds disclosed herein have pHH3 IC₅₀s of less than about 30 nM.

Example 201
BrdU cellular proliferation assay

[00934] This proliferation assay is based on the detection of BrdU (bromodeoxyuridine), a synthetic thymidine analog that is incorporated into the genomic DNA of proliferating cells which is then detected with peroxidase-conjugated anti-BrdU antibody (anti-BrdU-POD). HCT-116 cells derived from a human colorectal carcinoma cell line (ATCC# CCL-247) were grown to 50-70% confluency in McCoy's 5A Complete media (*Gibco Cat#16600-108*) with 10% FBS and Penicillin (100U/mL)/Streptomycin (100ug/mL). Cells were seeded at 800 cells/well in a 96-well plate and were allowed to incubate at 37°C, 5% CO₂ overnight. On the following day, compounds in DMSO were serially diluted three-fold down the row nine times for the generation of a nine-point curve. The diluted compounds were added to the plate containing cells, and allowed to incubate for 72 h at 37°C, 5% CO₂. At the end of the incubation period, the cells were directly used following the BrdU ELISA protocol described Cell Proliferation ELISA, BrdU (colorimetric) kit (Cat # 11647229001, Roche Applied Science). The peroxidase reaction product was quantified by measuring the absorbance of the samples at 450 nm and 690 nm using a SpectaMax Plus 384 plate reader. The compounds disclosed herein have been found to have anti-proliferative activity within the range of about 10 nM to about 400 nM. In one embodiment, the compounds disclosed herein have IC₅₀s of less than about 400 nM. In one embodiment, the compounds disclosed herein have IC₅₀s of less than about 200 nM. In one embodiment, the compounds disclosed herein have IC₅₀s of less than about 200 nM. In one embodiment, the compounds disclosed herein have

IC₅₀s of less than about 100 nM. In yet another embodiment, the compounds disclosed herein have IC₅₀s of less than about 50 nM. In yet another embodiment, the compounds disclosed herein have IC₅₀s of less than about 20 nM.

The compounds provided herein were found to have activity shown in Table 2.

Table 2

Example No.	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
1-I	D	D	C	C	C
1-II	D	D	B	C	C
1-III	D	D	C	C	B
1-IV	D	D	B	C	A
1-V	D	D	C	C	B
1-VI	D	D	B	C	B
1-VII	D	D	B	C	B
1-VIII	D	D	B	C	B
1-IX	D	D	C	C	B
1-X	D	D	C	C	B
1-XI	D	D	C	C	C
1-XII	D	D	C	C	C
1-XIII	D	C	A	C	A
1-XIV	D	D	C	C	B
1-XV	D	D	C	C	B
1-XVI	D	D	C	C	B
1-XVII	D	C	C	C	A
1-XVIII	D	D	C	C	A
1-XIX	D	C	C	C	A
1-XX	D	D	C	C	B
1-XXI	D	D	C	C	ND
1-XXII	D	D	C	C	ND
1-XXIII	D	D	C	C	ND
1-XXIV	D	D	C	C	ND
1-XXV	D	D	C	C	ND
1-XXVI	D	D	C	C	ND
1-XXVII	D	D	C	C	ND
1-XXVIII	D	D	C	C	C
1-XXIX	D	D	C	C	C
2-I	D	D	B	A	C
2-II	D	D	B	A	A
2-III	D	C	C	C	A
2-IV	D	C	A	A	A
2-V	D	D	C	C	C
2-VI	D	D	C	C	B
2-VII	D	D	C	C	B
2-VIII	D	D	A	A	A
2-IX	D	D	A	A	A
2-X	D	D	A	A	A

Example No.	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
2-XI	D	C	B	A	A
2-XII	D	D	A	B	A
2-XIII	D	D	B	A	A
2-XIV	D	D	B	A	A
2-XV	D	D	A	A	ND
2- XVI	D	D	C	C	B
4-i	D	D	C	C	A
4-ii	D	D	C	C	A
4-iii	D	D	A	B	A
4-iv	D	C	B	B	A
4-v	D	D	C	C	C
4-vi	D	D	C	C	B
4-vii	D	D	C	C	C
4-viii	D	D	C	C	C
4-ix	D	D	C	C	C
4-x	D	D	C	C	C
4-xi	D	D	C	C	B
4-xii	D	D	C	C	A
4-xiii	D	D	C	C	A
4-xiv	D	D	C	C	A
4-xv	D	D	C	C	A
4-xvi	D	D	C	C	B
4-xvii	D	D	C	C	B
4-xviii	D	D	C	C	C
4-xix	D	D	C	C	A
4-xx	D	D	C	C	B
4-xxi	D	D	C	C	A
4-xxii	D	D	C	C	A
4-xxiii	D	D	C	C	B
4-xxiv	D	D	C	B	A
4-xxv	D	D	C	B	A
4-xxvi	D	D	C	C	A
4-xxvii	D	D	C	C	B
4-xxviii	D	B	A	A	A
4-xxix	D	D	C	C	B
4-xxx	D	B	B	B	A
4-xxxi	D	D	C	C	C
4-xxxii	D	D	B	C	B
4-xxxiii	D	D	C	C	C
4-xxxiv	D	D	C	C	A
4-xxxv	D	C	C	B	A
4-xxxvi	D	D	C	C	A
4-xxxvii	D	D	C	C	C
4-xxxviii	C	B	B	B	A
4-xxxix	D	C	C	C	A
4-xl	D	D	C	C	A
4-xli	D	D	C	C	A
4- xlii	D	D	B	C	C
4- xliii	D	D	C	C	C
4- xliv	D	D	C	C	B
4-xlv	D	D	C	C	C
4-xlvi	D	D	C	C	C
4-xlvii	D	D	C	C	C
4-xlviii	D	D	C	C	ND

Example No.	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
8-i	D	C	B	A	A
9-i	D	C	B	A	A
16A-i	D	D	C	C	C
16A-ii	D	D	C	C	C
16A-iii	D	D	C	C	ND
16A-iv	D	D	C	C	ND
16A-v	D	D	C	C	ND
16A-vi	D	D	C	C	ND
16A-vii	D	D	C	C	ND
16A-viii	D	D	C	C	ND
16A-ix	D	D	C	C	ND
16A-x	D	D	C	C	ND
16A-xi	D	D	B	C	ND
16A-xii	D	D	A	A	ND
16A-xiii	D	D	C	C	ND
16-i	D	D	C	C	A
16-ii	D	C	A	C	A
16-iii	D	D	B	C	A
16-iv	D	D	C	C	A
16-v	D	D	C	C	C
16-vi	D	D	C	C	B
16-vii	D	D	B	C	A
16-viii	D	D	C	C	C
16-ix	D	D	A	B	A
17-i	D	D	C	C	C
17-ii	D	D	C	B	C
17-iii	D	B	A	A	A
17-iv	D	C	A	A	A
17-v	D	C	C	C	C
17-vi	D	B	C	C	C
17-vii	D	D	C	C	C
17-viii	D	D	A	A	A
17-ix	D	D	A	A	A
17-x	D	B	B	A	A
17-xi	D	B	B	A	A
18-i	D	D	C	C	ND
18-ii	D	D	C	C	ND
18-iii	D	D	C	C	ND
18-iv	D	D	C	C	ND
18B-i	D	D	A	B	A
18B-ii	D	C	C	C	A
18B-iii	D	D	C	C	A
18B-iv	D	D	C	C	ND
18B-v	D	D	C	C	ND
18B-vi	D	D	C	C	ND
18B-vii	D	D	C	C	ND
18B-viii	D	D	C	C	ND
18B-ix	D	D	B	C	ND
18B-x	D	D	B	C	ND
18B-xi	D	D	C	C	ND
18B-xii	D	D	C	C	ND
18B-xiii	D	D	A	A	ND
18B-xiv	D	D	C	C	ND
18B-xv	D	D	C	C	ND

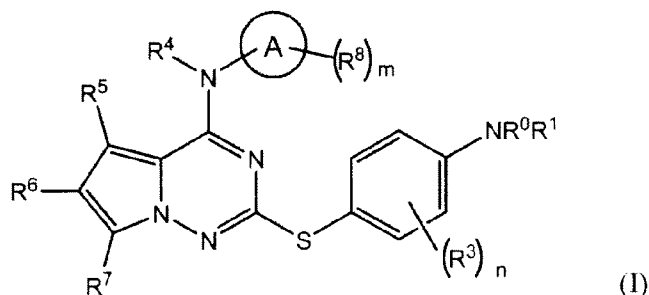
Example No.	Phos Histone H3 IC ₅₀ (nM)	BrdU ELISA HCT-116 IC ₅₀ (nM)	Aurora B Kd (nM)	Aurora A Kd (nM)	Aurora C Kd (nM)
18B-xvi	D	D	C	C	ND
18B-xvii	D	D	B	C	ND
18B-xviii	D	D	A	A	ND
18B-xix	D	D	B	C	ND
18B-xx	D	C	A	B	ND
18B-xxi	D	D	A	C	ND
18B-xxii	D	C	B	C	ND
18B-xxiii	D	D	C	C	ND
18B-xxiv	D	D	A	A	ND
18B-xxv	D	C	B	A	ND
18B-xxvi	D	D	B	C	ND
18B-xxvii	D	D	B	C	ND
18B-xxviii	D	D	C	C	ND
18B-xxix	A	A	A	A	ND
18B-xxx	ND	ND	C	B	ND
20-i	D	D	C	C	ND
20-ii	D	D	C	C	ND
20-iii	D	D	A	A	ND
24-i	D	D	C	C	ND
24-ii	D	C	C	C	ND
24-iii	D	C	A	B	ND
24-iv	D	D	A	C	ND
24-v	D	D	C	C	ND
27-i	D	D	B	C	ND
34-i	D	D	B	C	ND
51-i	D	C	A	C	ND
51-ii	D	C	B	C	ND
51-iii	D	D	B	C	ND
51-iv	D	D	A	B	ND
51-v	D	D	A	C	ND
51-vi	D	B	B	C	ND
51-vii	D	A	C	C	ND
51-viii	D	D	A	A	ND
51-ix	D	D	A	C	ND
51-x	D	D	A	C	ND
101-i	D	D	C	C	ND
106-i	D	B	A	A	ND
106-ii	D	D	B	B	ND
106-iii	D	B	B	B	ND
123-i	D	D	C	C	ND
126-i	D	D	A	B	ND
126-ii	D	D	B	C	ND
126-iii	D	B	A	B	ND
128-i	ND	ND	C	C	ND
133-i	A	A	A	B	ND
149-i	D	D	A	A	ND
181-i	D	A	A	A	ND
195	D	B	C	C	ND
196	D	B	A	A	ND
197	D	A	A	A	ND
198	D	A	A	A	ND

In Table 2, Phosphorylation Histone H3 and BrdU IC₅₀ (nM): $A \leq 50$, $50 < B \leq 150$, $150 < C \leq 300$, $D > 300$,
Aurora A, Aurora B and Aurora C Kd (nM): $A \leq 10$, $10 < B \leq 20$, $C > 20$; and
ND= no data.

[00935] Since modifications will be apparent to those of skill in the art, it is intended that the claimed subject matter be limited only by the scope of the appended claims.

What is claimed is:

1. A compound having formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

ring A is pyrazolyl;

R^0 and R^1 are selected from (i) and (ii) as follows:

- (i) R^0 and R^1 are both hydrogen provided that R^8 is cycloalkyl; and
- (ii) R^1 is hydrogen or alkyl and R^0 is $-C(O)R^2$;

R^4 is hydrogen or alkyl;

R^2 is selected from:

- (i) $-R^yNR^9R^{10}$;
- (ii) phenyl or pyrazolyl, each independently substituted with one, two or three groups selected from halo and haloalkyl; and

(iii) cyclopropyl, unsubstituted or substituted with one or two groups selected from halo and alkoxy carbonyl;

R^3 is halo or alkyl;

R^5 , R^6 and R^7 are each independently selected from hydrogen, halo, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, $-R^xNR^{11}aR^{11b}$ and $-R^xNR^{11}C(O)R^{12}$;

R^8 is alkyl, haloalkyl, hydroxyalkyl, cycloalkylalkyl, cycloalkyl or halocycloalkyl;

R^y is alkylene;

R^9 and R^{10} are selected as follows:

- (i) R^9 and R^{10} are each independently hydrogen, alkyl or cycloalkyl,

wherein alkyl and cycloalkyl are each optionally substituted with one, two or three groups independently selected from halo, alkyl, cycloalkyl, hydroxyl, haloalkyl, and alkoxy, or

(ii) R^9 and R^{10} , together with the nitrogen atom to which they are attached, form a heterocyclyl which is optionally substituted with 1 to 5 groups each independently selected from halo, cyano, alkyl, haloalkyl, alkenyl, haloalkenyl, alkynyl, haloalkynyl, $=N-OH$, $-R^xOR^{16}$, $-R^xS(O)_2R^{16}$, $-R^xC(O)R^{16}$, $-R^xNR^{17}R^{18}$, $-R^xNR^{15}C(O)R^{16}$ and $-R^xC(O)NR^{13}R^{14}$

R^{11} , R^{11a} , R^{11b} and R^{15} are each independently hydrogen or alkyl;

R^{12} is $R^xNR^{19}R^{20}$;

each R^{13} and R^{14} are independently selected from (i) and (ii) as follows:

(i) R^{13} is hydrogen or alkyl; and R^{14} is alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, or heterocyclylalkyl; R^{13} and R^{14} are each optionally substituted with 1 to 5 Q^1 , each Q^1 independently selected from halo, hydroxyl, alkoxy, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, cycloalkyl, aryl, heterocyclyl and heteroaryl; and

(ii) R^{13} and R^{14} , together with the nitrogen atom to which they are attached, form heterocyclyl or heteroaryl; optionally substituted with 1 to 5 Q^1 , each Q^1 independently selected from halo, hydroxyl, alkoxy, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, cycloalkyl, aryl, heterocyclyl and heteroaryl;

each R^x is independently alkylene or a direct bond;

each R^{15} is independently hydrogen or alkyl;

each R^{16} is independently hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroarylalkyl; wherein R^{16} is optionally substituted with 1 to 3 Q^2 , each Q^2 independently selected from alkyl, hydroxyl, alkoxy, aryloxy, halo, haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloaryl and alkoxyalkyl;

each R^{17} and R^{18} are independently selected from (i) and (ii) below:

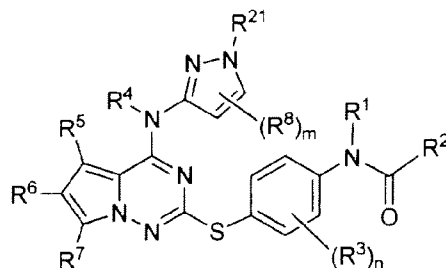
(i) R^{17} and R^{18} are each independently hydrogen, alkyl or aryl, wherein the alkyl and aryl are each optionally substituted with one to five substituents independently selected from the group consisting of halo, alkyl and $-R^xOR^{15}$; and

(ii) R^{17} and R^{18} , together with the nitrogen atom to which they are attached, form heterocyclyl or heteroaryl, where heterocyclyl and heteroaryl are each optionally substituted with one or more substituents independently selected from the group consisting of halo, alkyl, haloalkyl, hydroxyalkyl, and $-R^xOR^{15}$;

R^{19} and R^{20} are independently selected from (i) or (ii) below:

- (i) R^{19} and R^{20} are each independently hydrogen, alkyl or haloalkyl; or
- (ii) R^{19} and R^{20} , together with the nitrogen atom to which they are attached, form heterocyclyl which is optionally substituted with one or more substituents each independently selected from the group consisting of halo and alkyl;
- when Q^1 is selected from alkoxy, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, cycloalkyl, aryl, heterocyclyl and heteroaryl, each Q^1 group is independently optionally substituted with 1 to 5 groups Q^3 ;
- when Q^2 is selected from alkyl, alkoxy, aryloxy, haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloaryl and alkoxyalkyl, each Q^2 is independently optionally substituted with 1 to 5 groups Q^3 ;
- each Q^3 independently selected from alkyl, hydroxyl, alkoxy, aryloxy, halo, haloalkyl and cycloalkyl;
- each t is independently 0, 1 or 2;
- m is 0, 1 or 2; and
- n is 0-4,
- with a proviso that when R^2 is unsubstituted cyclopropyl, then R^6 is other than hydrogen.

2. The compound of claim 1 having formula (II):



II

or a pharmaceutically acceptable salt thereof, wherein

- R^1 is hydrogen or alkyl;
- R^2 is $-R^yNR^9R^{10}$;
- R^3 is halo or alkyl;
- R^4 and R^{21} are each independently hydrogen or alkyl;
- R^5 , R^6 and R^7 are each independently selected from hydrogen, halo, alkyl, $-R^xNR^{11a}R^{11b}$ and $-R^xNR^{11}C(O)R^{12}$;
- R^8 is alkyl, haloalkyl or cycloalkyl;

R^9 and R^{10} are selected from (i) and (ii) as follows:

- (i) R^9 and R^{10} are each independently hydrogen, alkyl, hydroxyalkyl, haloalkyl or cycloalkyl; and
- (ii) R^9 and R^{10} , together with the nitrogen atom to which they are attached, form a heterocyclyl which is optionally substituted with 1 to 5 groups each independently selected from halo, cyano, alkyl, haloalkyl, alkenyl, haloalkenyl, alkynyl, haloalkynyl, $=N-OH$, $-R^xOR^{16}$, $-R^xS(O)R^{16}$, $-R^xC(O)R^{16}$, $-R^xNR^{17}R^{18}$, $-R^xNR^{15}C(O)R^{16}$, and $-R^xC(O)NR^{13}R^{14}$;

R^{11} , R^{11a} , R^{11b} and R^{15} are each independently hydrogen or alkyl;

R^{12} is $R^xNR^{19}R^{20}$;

R^{13} and R^{14} are selected as follows:

- (i) R^{13} is hydrogen or alkyl; and R^{14} is alkyl, cycloalkyl, aryl, or heterocyclylalkyl; R^{13} and R^{14} are each optionally substituted with 1 to 5 Q^1 , each Q^1 independently selected from halo, hydroxyl, alkoxy, alkyl, haloalkyl, alkoxyalkyl and hydroxyalkyl;

- (ii) R^{13} and R^{14} , together with the nitrogen atom to which they are attached, form heterocyclyl or heteroaryl, optionally substituted with 1 to 5 Q^1 , each Q^1 independently selected from halo, hydroxyl, alkoxy, alkyl, haloalkyl, alkoxyalkyl and hydroxyalkyl;

each R^x is independently alkylene or a direct bond;

each R^{15} is independently hydrogen or alkyl;

each R^{16} is independently hydrogen, alkyl, alkoxy, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroarylalkyl; wherein R^{16} is optionally substituted with 1 to 3 Q^2 , each Q^2 independently selected from alkyl, hydroxyl, alkoxy, aryloxy, halo, haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloaryl and alkoxyalkyl;

each R^{17} and R^{18} are independently selected from (i) and (ii) below:

- (i) R^{17} and R^{18} are each independently hydrogen, alkyl or aryl, wherein the alkyl and aryl may each be optionally substituted with one to five substituents each independently selected from the group consisting of halo, alkyl and $-R^xOR^{15}$; and

- (ii) R^{17} and R^{18} , together with the nitrogen atom to which they are attached, form heterocyclyl or heteroaryl which is optionally substituted with one or

more substituents independently selected from the group consisting of halo, alkyl, haloalkyl, hydroxyalkyl, and $-R^xOR^{15}$;

each R^{19} and R^{20} are independently selected from (i) and (ii) below:

(i) R^{19} and R^{20} are each independently hydrogen, alkyl or haloalkyl; and

(ii) R^{19} and R^{20} , together with the nitrogen atom to which they are attached, form heterocyclyl which is optionally substituted with one or more substituents independently selected from the group consisting of halo and alkyl;

when Q^1 is selected from alkoxy, alkyl, haloalkyl, alkoxyalkyl and hydroxyalkyl, each Q^1 is independently optionally substituted with 1 to 5 groups Q^3 ;

when Q^2 is selected from alkyl, alkoxy, aryloxy, haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloaryl and alkoxyalkyl, each Q^2 is independently optionally substituted with 1 to 5 Q^3 ;

each Q^3 independently selected from alkyl, hydroxyl, alkoxy, aryloxy, halo, haloalkyl and cycloalkyl;

each t is independently 0, 1 or 2;

m is 0, 1 or 2; and

n is 0-4.

3. The compound of claim 1 or 2, wherein R^3 is fluoro or methyl.

4. The compound of any of claims 1-3, wherein R^5 and R^7 are each hydrogen and R^6 is hydrogen or $-R^xNR^{11}C(O)R^{12}$, where R^x is a direct bond, methylene or ethylene; R^{19} and R^{20} are independently selected from (i) and(ii) below:

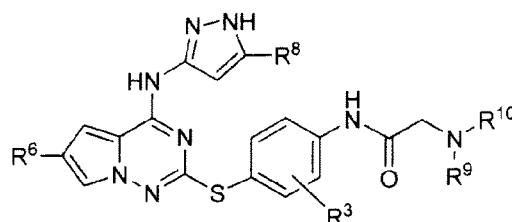
(i) R^{19} and R^{20} are each independently hydrogen, alkyl or haloalkyl; and

(ii) R^{19} and R^{20} , together with the nitrogen atom to which they are attached, form a 5- or 6- membered heterocycle which is optionally substituted with one or more substituents each independently selected from the group consisting of halo and alkyl.

5. The compound of any of claims 1-4, wherein $R^2-(CH_2)_n-NR^9R^{10}$; R^9 and R^{10} together with the nitrogen atom to which they are attached, form a 4- to 7-membered heterocyclyl which is optionally substituted with 1 to 5 groups, each independently selected from halo, cyano, alkyl, haloalkyl, alkenyl, haloalkenyl,

alkynyl, haloalkynyl, =N-OH, $-R^xOR^{16}$, $-R^xS(O)_tR^{16}$, $-R^xC(O)R^{16}$, $-R^xNR^{17}R^{18}$, $-R^xNR^{15}C(O)R^{16}$ and $-R^xC(O)NR^{13}R^{14}$ and n_1 is 1, 2 or 3.

6. The compound of claims 1 or 2 having formula (V),



or a pharmaceutically acceptable salt thereof, wherein

R^3 is halo;

R^8 is alkyl, cycloalkyl, or haloalkyl;

R^6 is hydrogen, or $-NHC(O)R^xNR^{19}R^{20}$;

R^{19} and R^{20} are independently selected from (i) and (ii) below:

(i) R^{19} and R^{20} are each independently hydrogen, alkyl or haloalkyl;

and

(ii) R^{19} and R^{20} , together with the nitrogen atom to which they are attached, form a 5- or 6- membered heterocycle which is optionally substituted with one or more substituents independently selected from the group consisting of halo and alkyl;

R^9 and R^{10} are selected as follows:

i) R^9 and R^{10} are each independently hydrogen, alkyl, hydroxyalkyl, haloalkyl or cycloalkyl; or

ii) R^9 and R^{10} , together with the nitrogen atom to which they are attached, form a 4- to 7- membered heterocycle which is optionally substituted with 1 to 5 groups, each independently selected from halo, cyano, alkyl, haloalkyl, alkenyl, haloalkenyl, alkynyl, haloalkynyl, =N-OH, $-R^xOR^{16}$, $-R^xS(O)_tR^{16}$, $-R^xC(O)R^{16}$, $-R^xNR^{17}R^{18}$, $-R^xNR^{15}C(O)R^{16}$, and $-R^xC(O)NR^{13}R^{14}$;

each R^{13} and R^{14} are independently selected from (i) and (ii) as follows:

(i) R^{13} is hydrogen or alkyl; and R^{14} is alkyl, aryl, or cycloalkyl;
 R^{13} and R^{14} are each optionally substituted with 1 to 5 Q^1 , each Q^1 independently

selected from halo, hydroxyl, alkoxy, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, cycloalkyl, aryl, heterocyclyl and heteroaryl; and

(ii) R^{13} and R^{14} , together with the nitrogen atom to which they are attached, form heterocyclyl or heteroaryl, each optionally substituted with 1 to 5 Q^1 , each Q^1 independently selected from halo, hydroxyl, alkoxy, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, cycloalkyl, aryl, heterocyclyl and heteroaryl;

each R^{15} is independently hydrogen or alkyl;

each R^{16} is independently hydrogen, alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroarylalkyl; wherein R^{16} is optionally substituted with 1 to 3 Q^2 , each Q^2 independently selected from alkyl, hydroxyl, alkoxy, aryloxy, halo, haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloaryl and alkoxyalkyl; when Q^2 is selected from alkyl, alkoxy, aryloxy, haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloaryl and alkoxyalkyl, each Q^2 is independently optionally substituted with 1 to 5 Q^3 , each Q^3 independently selected from alkyl and halo; and

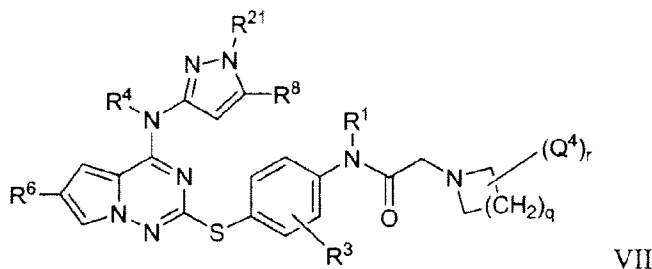
t is 0, 1 or 2.

7. The compound of claim 1, wherein R^9 and R^{10} , together with the nitrogen atom to which they are attached, form a 4- to 7- membered heterocyclyl which is optionally substituted with 1 to 3 groups selected from halo, hydroxyl, hydroxyalkyl and $-R^x C(O)NR^{13}R^{14}$, where each R^x is a independently a direct bond or alkylene and each R^{13} and R^{14} are independently selected from (i) and (ii) as follows:

(i) R^{13} is hydrogen or alkyl; and R^{14} is alkyl, aryl, cycloalkyl, arylalkyl or heterocyclylalkyl; R^{13} and R^{14} are each optionally substituted with 1 to 5 Q^1 , each Q^1 independently selected from halo, hydroxyl, alkoxy, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, cycloalkyl, aryl, heterocyclyl and heteroaryl; and

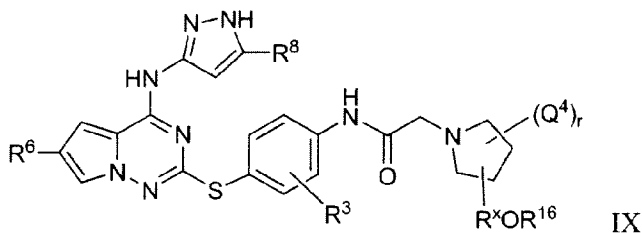
(ii) R^{13} and R^{14} , together with the nitrogen atom to which they are attached, form heterocyclyl or heteroaryl; each optionally substituted with 1 to 5 Q^1 , each Q^1 independently selected from halo, hydroxyl, alkoxy, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, cycloalkyl, aryl, heterocyclyl and heteroaryl.

8. The compound of claims 1 or 2 having formula (VII),



or a pharmaceutically acceptable salt thereof, wherein q is 1, 2 or 3; r is 0, 1, 2 or 3; each Q⁴ is independently selected from halo, cyano, alkyl, haloalkyl, alkenyl, alkynyl, haloalkenyl, haloalkynyl, =N-OH, -R^xOR¹⁶, -R^xS(O)_rR¹⁶, -R^xC(O)R¹⁶, -R^xNR¹⁷R¹⁸, -R^xNR¹⁵C(O)R¹⁶ and -R^xC(O)NR¹³R¹⁴.

9. The compound of claims 1 or 2 having formula (IX),

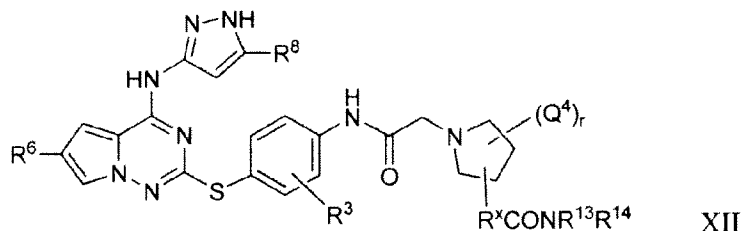


or a pharmaceutically acceptable salt thereof, wherein each Q⁴ is independently selected from halo, hydroxyl, alkoxy, and hydroxyalkyl;

R^x is a direct bond or alkylene; and

R¹⁶ is hydrogen, alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroarylalkyl; wherein R¹⁶ is optionally substituted with 1 to 3 Q², each Q² independently selected from alkyl, hydroxyl, alkoxy, aryloxy, halo, haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloaryl and alkoxyalkyl; when Q² is selected from alkyl, alkoxy, aryloxy, haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloaryl and alkoxyalkyl, each Q² is independently optionally substituted with 1 to 5 Q³, each Q³ independently selected from alkyl and halo.

10. The compound of claims 1 or 2 having formula (XII),



or a pharmaceutically acceptable salt thereof, wherein R^x is a direct bond or alkylene and R^{13} and R^{14} are selected as follows:

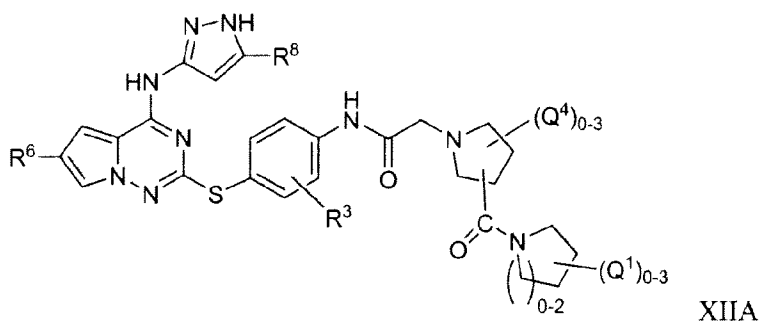
(i) R^{13} is hydrogen or alkyl; and R^{14} is alkyl, aryl, arylalkyl, cycloalkyl or heterocyclalkyl; R^{13} and R^{14} are each optionally substituted with 1 to 5 groups selected from Q^1 ;

(ii) R^{13} and R^{14} , together with the nitrogen atom to which they are attached, form heterocyclyl or heteroaryl, each optionally substituted with 1 to 5 groups selected from Q^1 ;

each Q^1 is independently selected from halo, hydroxyl, alkoxy, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, cycloalkyl, aryl, heterocyclyl and heteroaryl; and

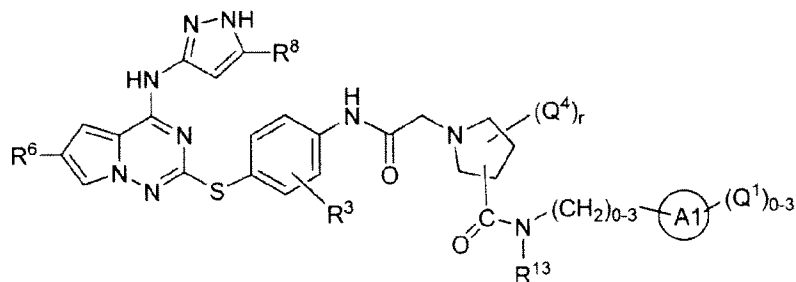
each Q^4 is independently selected from halo, hydroxyl, alkoxy and hydroxyalkyl.

11. The compound of claims 1 or 2 having formula (XIIA),



or a pharmaceutically acceptable salt thereof, where each Q^4 is independently selected from halo, hydroxyl, alkoxy and hydroxyalkyl; and each Q^1 is independently selected from halo, hydroxyl, alkoxy, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, cycloalkyl, aryl, heterocyclyl and heteroaryl.

12. The compound of claims 1 or 2 having formula (XIIC),

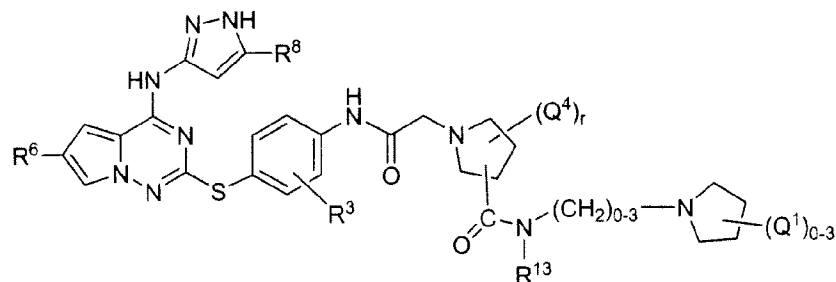


XIIC

or a pharmaceutically acceptable salt thereof, wherein A1 is aryl, cycloalkyl or heterocyclyl, each Q^4 is independently selected from halo, hydroxyl, alkoxy and hydroxyalkyl and each Q^1 is independently selected from halo, hydroxyl, alkoxy, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl and cycloalkyl.

13. The compound of claim 12, wherein A1 is selected from pyrrolidinyl, piperidinyl, morpholinyl and phenyl; and Q^1 is halo or alkyl.

14. The compound of claims 1 or 2 having formula (XIID),

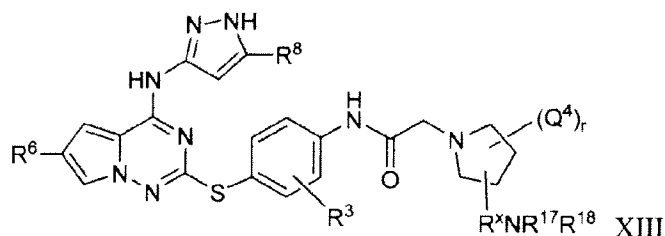


XIID

or a pharmaceutically acceptable salt thereof, wherein each Q^1 is independently selected from halo and alkyl, each Q^4 is independently selected from halo, hydroxyl, alkoxy and hydroxyalkyl and r is 0-3.

15. The compound of claim 14, wherein R^8 is alkyl or cycloalkyl; R^3 and R^6 are hydrogen; r is 0, R^{13} is hydrogen; and Q^1 is halo.

16. The compound of claims 1 or 2 having formula (XIII),



or a pharmaceutically acceptable salt thereof, where R^x is a direct bond or alkylene;

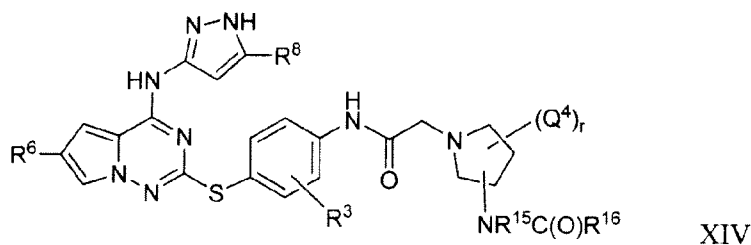
R^{17} and R^{18} are independently selected from (i) or (ii) below:

(i) R^{17} and R^{18} are each independently hydrogen or alkyl, wherein the alkyl and aryl may each be optionally substituted with one to five substituents independently selected from the group consisting of halo, alkyl and $-R^xOR^{15}$; or

(ii) R^{17} and R^{18} , together with the nitrogen atom to which they are attached, form heterocyclyl or heteroaryl each of which is optionally substituted by one or more substituents independently selected from the group consisting of halo, alkyl, haloalkyl, hydroxyalkyl, and $-R^xOR^{15}$;

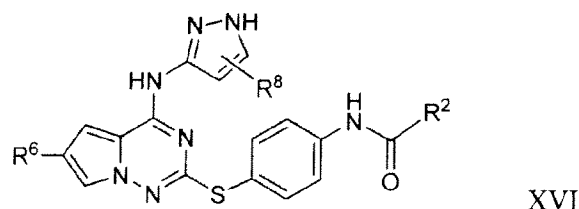
R^{15} is hydrogen or alkyl; r is 0-3, and each Q^4 is independently selected from halo, hydroxyl, alkoxy and hydroxyalkyl.

17. The compound of claims 1 or 2 having formula (XIV),



or a pharmaceutically acceptable salt thereof, wherein R^{16} is alkyl or alkoxy; R^{15} is hydrogen or alkyl; r is 0-3, and each Q^4 is independently selected from halo, hydroxyl, alkoxy and hydroxyalkyl.

18. The compound of claim 1 having formula (XVI),



or a pharmaceutically acceptable salt thereof, wherein

R^2 is selected from

i) phenyl and pyrazolyl, each substituted with one or two substituents selected from halo and haloalkyl; and

ii) cyclopropyl substituted with one or two substituents selected from halo and alkoxy carbonyl;

R^6 is selected from hydrogen and $R^xNR^{11}C(O)R^{12}$;

R^8 is alkyl or cycloalkyl;

R^{11} is hydrogen;

R^{12} is $R^xNR^{19}R^{20}$;

each R^x is independently a direct bond, methylene or ethylene; and

R^{19} and R^{20} are independently selected from (i) and (ii) below:

(i) R^{19} and R^{20} are each alkyl; and

(ii) R^{19} and R^{20} , together with the nitrogen atom to which they are attached, form heterocyclyl which is optionally substituted with an alkyl.

19. A compound selected from:

2-(cyclopropylamino)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)-6-(2-(piperidin-1-yl)acetamido)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)cyclopropanecarboxamide;

5-chloro-1-methyl-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(trifluoromethyl)benzamide;

5-chloro-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(trifluoromethyl)benzamide;

(1R,2S)-ethyl 2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)benzamido)cyclopropanecarboxylate;

N-(2,2-difluorocyclopropyl)-4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)benzamide;

N-(2-(4-(cyclopropanecarboxamido)phenylthio)-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-6-yl)-4-methylpiperazine-1-carboxamide;

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N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4] triazin-2-ylthio)phenyl)-2-(dimethylamino)acetamide;

N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4] triazin-2-ylthio)phenyl)-2-(3-hydroxypiperidin-1-yl)acetamide;

N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4] triazin-2-ylthio)phenyl)-2-(N-(2-hydroxyethyl)-N-methylamino)acetamide;

2-(4-aminophenylthio)-N-(5-cyclopropyl-1H-pyrazol-3-yl)pyrrolo[1,2-f][1,2,4]triazin-4-amine;

(S)-N-(4-(4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(2-(hydroxymethyl)pyrrolidin-1-yl)acetamide;

N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4] triazin-2-ylthio)phenyl)-2-((S)-2-(hydroxymethyl)pyrrolidin-1-yl)acetamide;

N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4] triazin-2-ylthio)phenyl)-2-(S)-3-hydroxypyrrolidin-1-yl)acetamide;

(S)-2-(2-(hydroxymethyl)azetidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

N-(4-((6-(3-(piperidin-1-yl)propanamido)-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-yl)sulfanyl)phenyl)cyclopropanecarboxamide;

2-((2S,4R)-4-tert-butoxy-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4] triazin-2-ylthio)phenyl)-2-((R)-3-hydroxypyrrolidin-1-yl)acetamide;

(S)-2-(4,4-difluoro-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

N-(4-((6-(2-diethylaminol)acetamido)-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-yl)sulfanyl)phenyl)cyclopropanecarboxamide;

2-((2S,4R)-4-fluoro-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-((1S,2S,5R)-2-(hydroxymethyl)-3-azabicyclo[3.1.0]hexan-3-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-((2R,4R)-2-(hydroxymethyl)-4-methoxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

(S)-N-(4-(4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(4,4-difluoro-2-(hydroxymethyl)pyrrolidin-1-yl)acetamide;

(S)-N-(4-(4-(5-ethyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(2-(hydroxymethyl)pyrrolidin-1-yl)acetamide;

2-((2S,4S)-4-hydroxy-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-((2S,4S)-4-ethoxy-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

(R)-tert-butyl 1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidin-3-ylcarbamate;

2-((2S,4S)-2-(hydroxymethyl)-4-methoxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-((2S,4R)-4-(benzyloxy)-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

(R)-N-(4-(4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-hydroxypyrrolidin-1-yl)acetamide;

(R)-2-(3-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-(trifluoromethyl)-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-((2S,4R)-4-tert-butoxy-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-isopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

N-(4-(4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-((2S,4R)-4-fluoro-2-(hydroxymethyl)pyrrolidin-1-yl)acetamide;

N-(4-(4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-((2S,4R)-4-hydroxy-2-(hydroxymethyl)pyrrolidin-1-yl)acetamide;

2-(2-Hydroxymethyl-4-methoxy-pyrrolidin-1-yl)-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide;

2-(2-Hydroxymethyl-4-methoxy-pyrrolidin-1-yl)-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide;

(S)-2-(3-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

(S)-N-(4-(4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(hydroxymethyl)pyrrolidin-1-yl)acetamide;

(S)-N-(4-(4-(5-cyclobutyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(4,4-difluoro-2-(hydroxymethyl)pyrrolidin-1-yl)acetamide;

(R)-N-(2-fluoro-4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-hydroxypyrrolidin-1-yl)acetamide;

(S)-2-(4,4-difluoro-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(2-fluoro-4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-((2S,4S)-4-fluoro-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

N-((R)-1-((4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)carbonyl)methyl)pyrrolidin-3-yl)isobutyramide;

2-(3,3-difluoropyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-((2S,4R)-4-(difluoromethyl)-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

tert-butyl 3-fluoro-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxylate;

(R)-2-(3-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

(R)-N-(4-(4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(hydroxymethyl)pyrrolidin-1-yl)acetamide;

2-(trans-3-tert-butoxy-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

(R)-N-(4-(4-(5-(difluoromethyl)-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-hydroxypyrrolidin-1-yl)acetamide;

(S)-2-(4,4-difluoro-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-(difluoromethyl)-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-(trans-3-(4-fluorophenoxy)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-(3-fluoro-3-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-(trans-3-fluoro-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-(*trans*-3-(2-ethoxyethoxy)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

N-(4-(4-(1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-((2S,4R)-4-tert-butoxy-2-(hydroxymethyl)pyrrolidin-1-yl)acetamide;

(R)-2-(3-tert-butoxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-(3,3-difluoro-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-((R)-3-(2-morpholinoethoxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

(S)-2-(2-Methoxymethyl-pyrrolidin-1-yl)-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide;

2-((R)-3-(2-methoxyethoxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-((2S,4R)-4-(4-fluorophenoxy)-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-[2-Hydroxymethyl-4-(2-methyl-propane-2-sulfonyl)-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide;

2-((2S,4R)-4-tert-butoxy-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(4-(4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-*trans*-3-hydroxy-4-(((R)-tetrahydrofuran-2-yl)methoxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-*trans*-[3-(4-Fluoro-phenylamino)-4-hydroxy-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide;

2-*trans*-[3-(4-Fluoro-phenyl)-4-hydroxy-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide;

(R)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(3-(piperidin-1-yl)propoxy)pyrrolidin-1-yl)acetamide;

2-((*trans*-3-tert-butoxy-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-(*trans*-3-(2-chlorophenoxy)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-(*trans*-3-hydroxy-4-(2-methylpentan-2-yloxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-(*trans*-3-hydroxy-4-(3-methylpentan-3-yloxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-(3-tert-butoxy-4-(hydroxyimino)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-((*trans*-3-tert-butoxy-4-(2-hydroxyethoxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-(*trans*-3-Cyclopentyloxy-4-hydroxy-pyrrolidin-1-yl)-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide;

2-[*trans*-3-Hydroxy-4-(1-methyl-cyclopentyloxy)-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide;

2-[*trans*-3-(2,2-Dimethyl-propoxy)-4-hydroxy-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide;

2-[*trans*-3-Hydroxy-4-(tetrahydro-furan-3-yloxy)-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide;

2-[*trans*-3-Hydroxy-4-(2-methoxy-1,1-dimethyl-ethoxy)-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide;

2-[*trans*-3-Hydroxy-4-(3-methoxy-propoxy)-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide;

2-((2*S*,4*R*)-2-(hydroxymethyl)-4-(1-methylcyclobutoxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-[*trans*-3-Hydroxy-4-(2-methoxy-ethoxy)-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide;

2-[*trans*-3-(1,1-Dimethyl-propoxy)-4-hydroxy-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide;

2-(*trans*-3-(2,6-dichlorophenoxy)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-(*trans*-4-tert-butoxy-2-(hydroxymethyl)pyrrolidin-1-yl)-N-(3-fluoro-4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-[*trans*-3-Hydroxy-4-(2,2,2-trifluoro-ethoxy)-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide;

2-(*trans*-3-Cyclopropylmethoxy-4-hydroxy-pyrrolidin-1-yl)-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide;

2-[*trans*-3-Hydroxy-4-(tetrahydro-furan-3-yloxy)-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide;

2-(*trans*-3-tert-butoxy-4-hydroxypyrrolidin-1-yl)-N-(3-fluoro-4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-(*trans*-3-Hydroxy-4-isopropoxy-pyrrolidin-1-yl)-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide;

2-[*trans*-3-Hydroxy-4-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide;

2-(*trans*-3-tert-butoxy-4-(2-methoxyethoxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-pivaloylpyrrolidin-1-yl)acetamide;

N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(pyrrolidine-1-carbonyl)pyrrolidin-1-yl)acetamide;

2-(*trans*-3-Cyano-4-hydroxy-pyrrolidin-1-yl)-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide;

(R)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(3-morpholinopropoxy)pyrrolidin-1-yl)acetamide;

(R)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolidin-1-yl)acetamide;

2-((R)-3-(2-hydroxyethoxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-[*trans*-3-(3-Chloro-phenylamino)-4-hydroxy-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide;

2-(*trans*-3-(3-fluorophenylamino)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-(*trans*-3-tert-butoxy-4-hydroxypyrrolidin-1-yl)-N-(4-(7-fluoro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-(*trans*-3-Ethoxy-4-hydroxy-pyrrolidin-1-yl)-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide;

2-(3-(1-hydroxy-2,2-dimethylpropyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

(R)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(pyrrolidine-1-carbonyl)pyrrolidin-1-yl)acetamide;

(R)-N-(3-fluoro-4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(pyrrolidine-1-carbonyl)pyrrolidin-1-yl)acetamide;

N-((3S,4S)-1-((4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylcarbamoyl)methyl)-4-tert-butoxypyrrolidin-3-yl)isobutyramide;

N-(*trans*-1-((4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylcarbamoyl)methyl)-4-tert-butoxypyrrolidin-3-yl)pivalamide;

2-[*trans*-3-Hydroxy-4-(2,2,2-trifluoro-1-trifluoromethyl-ethoxy)-pyrrolidin-1-yl]-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide;

2-(*trans*-3-Hydroxy-4-methoxy-pyrrolidin-1-yl)-N-{4-[4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide;

2-(*trans*-3-hydroxy-4-(3-methoxyphenylamino)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-(*trans*-3-(2-fluorophenylamino)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-(*trans*-3-(3-fluorophenoxy)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

(S)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(pyrrolidine-1-carbonyl)pyrrolidin-1-yl)acetamide;

2-(*trans*-3-(2-fluorophenoxy)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-(*trans*-3-(2,4-difluorophenoxy)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-(*trans*-3-(3,4-difluorophenylamino)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

N-ethyl-3-fluoro-N-(2-hydroxyethyl)-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide;

2-(*trans*-3-(3,5-difluorophenoxy)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-(*trans*-3-(3,4-difluorophenoxy)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-(3-fluoro-3-(pyrrolidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

(R)-2-(3-(tert-butylthio)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

N-(1-((4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylcarbamoyl)methyl)-4,4-difluoropyrrolidin-3-yl)pivalamide;

N-tert-butyl-3-fluoro-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide;

N,N-dimethyl-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3(R)-carboxamide;

2-((R)-3-((R)-3-hydroxypyrrolidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

(R)-2-(3-(3,3-difluoropyrrolidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-[*trans*-3-(4-fluoro-phenoxy)-4-hydroxy-pyrrolidin-1-yl]-N-{4-[6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)-pyrrolo[2,1-f][1,2,4]triazin-2-ylsulfanyl]-phenyl}-acetamide;

(R)-N-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(pyrrolidine-1-carbonyl)pyrrolidin-1-yl)acetamide;

(R)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(piperidine-1-carbonyl)pyrrolidin-1-yl)acetamide;

2-((R)-3-((S)-3-hydroxypyrrolidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

(R)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(3-(pyrrolidin-1-yl)propoxy)pyrrolidin-1-yl)acetamide;

(R)-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)-N-(2-morpholinoethyl)pyrrolidine-3-carboxamide;

(R)-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)-N-(2-(pyrrolidin-1-yl)ethyl)pyrrolidine-3-carboxamide;

(R)-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)-N-(3-(piperidin-1-yl)propyl)pyrrolidine-3-carboxamide;

(R)-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)-N-(2-(piperidin-1-yl)ethyl)pyrrolidine-3-carboxamide;

(R)-2-(3-(3-(3,3-difluoropyrrolidin-1-yl)propoxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

(R)-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)-N-(3-morpholinopropyl)pyrrolidine-3-carboxamide;

(R)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(morpholine-4-carbonyl)pyrrolidin-1-yl)acetamide;

(R)-N-(4-fluorophenyl)-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide;

N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-((R)-3-(tert-butylsulfonyl)pyrrolidin-1-yl)acetamide;

(R)-2-(3-(3-(azepan-1-yl)propoxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

(R)-2-(3-(4,4-difluoropiperidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

(R)-N-(3-fluorophenyl)-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide;

(R)-N-cyclohexyl-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide;

2-(*cis*-3-(4-fluorophenoxy)-4-hydroxypyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

(R)-2-(3-(4-hydroxypiperidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

(R)-2-(3-(4-(hydroxymethyl)piperidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

(R)-N-cyclopentyl-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide;

(R)-N-cyclopropyl-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide;

2-(*trans*-3-hydroxy-4-(pyridin-4-yloxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

(R)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(3-(4-methylpiperazin-1-yl)propoxy)pyrrolidin-1-yl)acetamide;

2-(3-((R)-tert-butylsulfinyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-(*trans*-3-hydroxy-4-(pyridin-2-yloxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-((R)-3-((S)-4,4-difluoro-2-(hydroxymethyl)pyrrolidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

(S)-2-(3-(3,3-difluoropyrrolidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

(S)-2-(3-(4,4-difluoropiperidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

(S)-2-(3-(3,3-difluoropiperidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

(S)-N-cyclopentyl-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide;

(S)-2-(3-(3,3-difluoropiperidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

(S)-N-*tert*-butyl-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide;

(S)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(piperidine-1-carbonyl)pyrrolidin-1-yl)acetamide;

(S)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(morpholine-4-carbonyl)pyrrolidin-1-yl)acetamide;

(S)-2-(3-(4-fluoropiperidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-(3-(3-fluorobenzoyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

2-(3-(4-fluorobenzoyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

(S)-N,N-dimethyl-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide;

(R)-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)-N-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxamide;

(R)-N-(2-(4,4-difluoropiperidin-1-yl)ethyl)-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide;

(S)-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)-N-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxamide;

(R)-2-(3-(3,3-difluoropyrrolidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

(R)-N-cyclopentyl-1-(2-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide;

(R)-2-(3-(3,3-difluoropiperidin-1-carbonyl)pyrrolidin-1-yl)-N-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

(R)-N-(2-(4,4-difluoropiperidin-1-yl)ethyl)-1-(2-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide;

(R)-N-cyclopropyl-1-(2-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide;

(R)-N-tert-butyl-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide;

2-((R)-3-(2-(pyrrolidin-1-yl)ethoxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

(R)-N-isopropyl-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide;

(R)-N-cyclobutyl-1-(2-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)pyrrolidine-3-carboxamide;

2-((R)-3-((S)-4,4-difluoro-2-(hydroxymethyl)pyrrolidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

(R)-1-(2-(4-(6-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)-N-cyclopropylpyrrolidine-3-carboxamide;

(R)-N-(4-(6-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(3,3-difluoropiperidine-1-carbonyl)pyrrolidin-1-yl)acetamide;

(R)-1-(2-(4-(6-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)-N-(2-(4,4-difluoropiperidin-1-yl)ethyl)pyrrolidine-3-carboxamide;

(R)-1-(2-(4-(6-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)-N,N-dimethylpyrrolidine-3-carboxamide;

2-((R)-3-(2-(piperidin-1-yl)ethoxy)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

(R)-N-(4-(6-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(3,3-difluoropyrrolidine-1-carbonyl)pyrrolidin-1-yl)acetamide;

(R)-1-(2-(4-(6-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)-N-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxamide;

(R)-1-(2-(4-(6-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenylamino)-2-oxoethyl)-N-cyclopentylpyrrolidine-3-carboxamide;

2-((R)-3-(3,3-difluoro-4-hydroxypyrrolidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

(R)-2-(3-(3,3-difluoro-4-hydroxypyrrolidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

(R)-N-(4-(6-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-(3-(3,3-difluoro-4-hydroxypyrrolidine-1-carbonyl)pyrrolidin-1-yl)acetamide;

2-((R)-3-((R)-4,4-difluoro-2-(hydroxymethyl)pyrrolidine-1-carbonyl)pyrrolidin-1-yl)-N-(4-(4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)acetamide;

N-(4-(6-chloro-4-(5-methyl-1H-pyrazol-3-ylamino)pyrrolo[1,2-f][1,2,4]triazin-2-ylthio)phenyl)-2-((R)-3-((S)-4,4-difluoro-2-(hydroxymethyl)pyrrolidine-1-carbonyl)pyrrolidin-1-yl)acetamide;

(R)-2-(3-(2-hydroxyethoxy)pyrrolidin-1-yl)-N-(4-((6-methyl-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)acetamide; and

(R)-2-((1-(2-((4-((5-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-2-yl)thio)phenyl)amino)-2-oxoethyl)pyrrolidin-3-yl)oxy)ethyl dihydrogen phosphate.

20. A pharmaceutical composition comprising a compound of any of claims 1-19 and a pharmaceutically acceptable carrier.

21. A method for treating an Aurora kinase modulated disease comprising administering a therapeutically effective amount of a compound of any of claims 1-19 to a patient.

22. The method of claim 21, wherein the disease is selected from cancer, bone disease, inflammatory disease, autoimmune disease, metabolic disease, viral diseases, fungal disease, neurological and neurodegenerative disorder, Alzheimer's disease, allergy and asthma, cardiovascular disease, and hormone related disease.

23. The method of claim 22, wherein cancer is selected from bladder, breast, colon, kidney, liver, lung, esophagus, gall bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, skin, leukemia, lymphoma, astrocytoma, neuroblastoma, glioma, schwannoma, melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoacanthoma, thyroid follicular cancer, and Kaposi's sarcoma.

24. The method of claim 21-23 further comprising administering a second pharmaceutical agent selected from anti-proliferative agent, anti-inflammatory agent, immunomodulatory agent and immunosuppressive agent.

25. The methods of claim 21, wherein the disease is rheumatoid arthritis.

26. A method for treating a cancer in a human which comprises administering a therapeutically effective amount of the compound of any of claims 1-19 to the human having the cancer.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/020836

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/53 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 7 442 700 B2 (MASTALERZ HAROLD [US] ET AL) 28 October 2008 (2008-10-28) cited in the application See all the examples	1-26
A	----- US 2006/084650 A1 (DONG QING [US] ET AL) 20 April 2006 (2006-04-20) cited in the application the whole document -----	1-26



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search

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Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Menchaca, Roberto

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2011/020836

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