PYRIDONE AND AZA-PYRIDONE COMPOUNDS AND METHODS OF USE

FIELD OF THE INVENTION

The invention relates generally to compounds for treating disorders mediated by Bruton's Tyrosine Kinase (Btk) including inflammation, immunological, and cancer, and more specifically to compounds which inhibit Btk activity. The invention also relates to methods of using the compounds for *in vitro*, *in situ*, and *in vivo* diagnosis or treatment of mammalian cells, or associated pathological conditions.

BACKGROUND OF THE INVENTION

Protein kinases, the largest family of human enzymes, encompass well over 500 proteins. Bruton's Tyrosine Kinase (Btk) is a member of the Tec family of tyrosine kinases, and is a regulator of early B-cell development as well as mature B-cell activation, signaling, and survival.

B-cell signaling through the B-cell receptor (BCR) can lead to a wide range of biological outputs, which in turn depend on the developmental stage of the B-cell. The magnitude and duration of BCR signals must be precisely regulated. Aberrant BCR-mediated signaling can cause disregulated B-cell activation and/or the formation of pathogenic auto-antibodies leading to multiple autoimmune and/or inflammatory diseases. Mutation of Btk in humans results in X-linked agammaglobulinaemia (XLA). This disease is associated with the impaired maturation of B-cells, diminished immunoglobulin production, compromised T-cell-independent immune responses and marked attenuation of the sustained calcium sign upon BCR stimulation.

Evidence for the role of Btk in allergic disorders and/or autoimmune disease and/or inflammatory disease has been established in Btk-deficient mouse models. For example, in standard murine preclinical models of systemic lupus erythematosus (SLE), Btk deficiency has been shown to result in a marked amelioration of disease progression. Moreover, Btk deficient mice can also be resistant to developing collagen-induced arthritis and can be less susceptible to Staphylococcus-induced arthritis.

A large body of evidence supports the role of B-cells and the humoral immune system in the pathogenesis of autoimmune and/or inflammatory diseases. Protein-based therapeutics (such as Rituxan) developed to deplete B-cells, represent an approach to the treatment of a number of autoimmune and/or inflammatory diseases. Because of Btk's role in B-cell

activation, inhibitors of Btk can be useful as inhibitors of B-cell mediated pathogenic activity (such as autoantibody production).

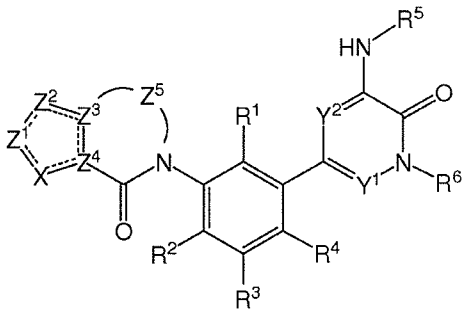
Btk is also expressed in osteoclasts, mast cells and monocytes and has been shown to be important for the function of these cells. For example, Btk deficiency in mice is associated with impaired IgE-mediated mast cell activation (marked diminution of TNF-alpha and other inflammatory cytokine release), and Btk deficiency in humans is associated with greatly reduced TNF-alpha production by activated monocytes.

Thus, inhibition of Btk activity can be useful for the treatment of allergic disorders and/or autoimmune and/or inflammatory diseases such as: SLE, rheumatoid arthritis, multiple vasculitides, idiopathic thrombocytopenic purpura (ITP), myasthenia gravis, allergic rhinitis, and asthma. In addition, Btk has been reported to play a role in apoptosis; thus, inhibition of Btk activity can be useful for cancer, as well as the treatment of B-cell lymphoma and leukemia. Moreover, given the role of Btk in osteoclast function, the inhibition of Btk activity can be useful for the treatment of bone disorders such as osteoporosis.

SUMMARY OF THE INVENTION

The invention relates generally to Formula I compounds with Bruton's Tyrosine Kinase (Btk) modulating activity.

Formula I compounds have the structures:



including stereoisomers, tautomers, or pharmaceutically acceptable salts thereof. The various substituents are defined herein below.

One aspect of the invention is a pharmaceutical composition comprised of a Formula I compound and a pharmaceutically acceptable carrier, glidant, diluent, or excipient. The pharmaceutical composition may further comprise a second therapeutic agent.

Another aspect of the invention is a process for making a pharmaceutical composition which comprises combining a Formula I compound with a pharmaceutically acceptable carrier.

The invention includes a method of treating a disease or disorder which method comprises administering a therapeutically effective amount of a Formula I compound to a patient with a disease or disorder selected from immune disorders, cancer, cardiovascular disease, viral infection, inflammation, metabolism/endocrine function disorders, neurological disorders, rheumatoid arthritis, and mediated by Bruton's tyrosine kinase.

The invention includes a kit for treating a condition mediated by Bruton's tyrosine kinase, comprising: a) a first pharmaceutical composition comprising a Formula I compound; and b) instructions for use.

The invention includes a Formula I compound for use as a medicament, and for use in treating a disease or disorder selected from immune disorders, cancer, cardiovascular disease, viral infection, inflammation, metabolism/endocrine function disorders, neurological disorders, rheumatoid arthritis, and mediated by Bruton's tyrosine kinase.

The invention includes use of a Formula I compound in the manufacture of a medicament for the treatment of immune disorders, cancer, cardiovascular disease, viral infection, inflammation, metabolism/endocrine function disorders and neurological disorders, and where the medicament mediates Bruton's tyrosine kinase.

The invention includes methods of making a Formula I compound.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows an exemplary synthetic route to prepare 6-chloro,4-amino pyridazinone compounds, including 6-chloro-4-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazin-2-ylamino)pyridazin-3(2*H*)-one **101f**, from 3-nitropyrazole-5-carboxylic acid.

Figure 2 shows an exemplary synthetic route to a tricyclic amide-phenyl boronate compounds, including 2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-*a*]indol-1(2*H*)-one **101m**, from 4,5,6,7-tetrahydro-1H-indole.

Figure 3 shows an exemplary synthetic route to tricyclic amide-phenyl bromide compounds, including 2-bromo-6-(1-oxo-3,4,5,6,7,8-hexahydrobenzothieno[2,3-*c*]pyridin-2(1*H*)-yl)benzyl acetate **104h**, from 4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxylic acid.

Figure 4 shows another exemplary synthetic route to tricyclic amide-phenyl bromide compounds, including 6,6-dimethyl-3,4,6,7-tetrahydro-5*H*-cyclopenta[4,5]thieno[2,3-*c*]pyridine-1(2*H*)-one **105i**, from 3-methylcyclopent-2-enone.

Figure 5 shows an exemplary synthetic route to tricyclic 1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrido[3,4-b]indolizin-1(2H)-one compounds as boronate

esters, including 2-(1-Oxo-3,4,6,7,8,9-hexahydropyrido[3,4-*b*]indolizin-2(1*H*)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl Acetate **118f** from 5,6,7,8-tetrahydroindolizine-2-carboxylic acid.

Figure 6 shows an exemplary synthetic route to intermediate 2-Bromo-4-fluoro-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **198d** from 1,3-dibromo-5-fluoro-2-iodobenzene.

Figure 7 shows an exemplary synthetic route to intermediate 4-Fluoro-2-(1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **198g**.

Figure 8 shows an exemplary synthetic route to intermediate 5-Fluoro-2-(1-methyl-5-(5-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **210e**.

Figure 9 shows an exemplary synthetic route to intermediate 5-[5-fluoro-2-(acetoxymethyl)-3-(1-methyl-5-{[5-(4-methylpiperazin-1-yl)pyridin-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$]trideca-1(9),2(7)-dien-6-one **212c**.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying structures and formulas. While the invention will be described in conjunction with the enumerated embodiments, it will be understood that they are not intended to limit the invention to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents which may be included within the scope of the present invention as defined by the claims. One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. The present invention is in no way limited to the methods and materials described. In the event that one or more of the incorporated literature, patents, and similar materials differs from or contradicts this application, including but not limited to defined terms, term usage, described techniques, or the like, this application controls.

DEFINITIONS

The term "alkyl" as used herein refers to a saturated linear or branched-chain monovalent hydrocarbon radical of one to twelve carbon atoms (C_1–C_{12}), wherein the alkyl radical may be optionally substituted independently with one or more substituents described

below. In another embodiment, an alkyl radical is one to eight carbon atoms (C_1–C_8), or one to six carbon atoms (C_1–C_6). Examples of alkyl groups include, but are not limited to, methyl (Me, -CH_3), ethyl (Et, -CH_2CH_3), 1-propyl (n-Pr, n-propyl, -$CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, -$CH(CH_3)_2$), 1-butyl (n-Bu, n-butyl, -$CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, -$CH_2CH(CH_3)_2$), 2-butyl (s-Bu, s-butyl, -$CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl, -$C(CH_3)_3$), 1-pentyl (n-pentyl, -$CH_2CH_2CH_2CH_2CH_3$), 2-pentyl (-$CH(CH_3)CH_2CH_2CH_3$), 3-pentyl (-$CH(CH_2CH_3)_2$), 2-methyl-2-butyl (-$C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl (-$CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl (-$CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl (-$CH_2CH(CH_3)CH_2CH_3$), 1-hexyl (-$CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl (-$CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl (-$CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl (-$C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl (-$CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl (-$CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl (-$C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl (-$CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl (-$C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl (-$CH(CH_3)C(CH_3)_3$, 1-heptyl, 1-octyl, and the like.

The term "alkylene" as used herein refers to a saturated linear or branched-chain divalent hydrocarbon radical of one to twelve carbon atoms (C_1–C_{12}), wherein the alkylene radical may be optionally substituted independently with one or more substituents described below. In another embodiment, an alkylene radical is one to eight carbon atoms (C_1–C_8), or one to six carbon atoms (C_1–C_6). Examples of alkylene groups include, but are not limited to, methylene (-CH_2-), ethylene (-CH_2CH_2-), propylene (-$CH_2CH_2CH_2$-), and the like.

The terms "carbocycle", "carbocyclyl", "carbocyclic ring" and "cycloalkyl" refer to a monovalent non-aromatic, saturated or partially unsaturated ring having 3 to 12 carbon atoms (C_3–C_{12}) as a monocyclic ring or 7 to 12 carbon atoms as a bicyclic ring. Bicyclic carbocycles having 7 to 12 atoms can be arranged, for example, as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, and bicyclic carbocycles having 9 or 10 ring atoms can be arranged as a bicyclo [5,6] or [6,6] system, or as bridged systems such as bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane and bicyclo[3.2.2]nonane. Examples of monocyclic carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, cyclohexadienyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, cyclododecyl, and the like.

"Aryl" means a monovalent aromatic hydrocarbon radical of 6-20 carbon atoms (C_6–C_{20}) derived by the removal of one hydrogen atom from a single carbon atom of a parent

aromatic ring system. Some aryl groups are represented in the exemplary structures as "Ar". Aryl includes bicyclic radicals comprising an aromatic ring fused to a saturated, partially unsaturated ring, or aromatic carbocyclic ring. Typical aryl groups include, but are not limited to, radicals derived from benzene (phenyl), substituted benzenes, naphthalene, anthracene, biphenyl, indenyl, indanyl, 1,2-dihydronaphthalene, 1,2,3,4-tetrahydronaphthyl, and the like. Aryl groups are optionally substituted independently with one or more substituents described herein.

"Arylene" means a divalent aromatic hydrocarbon radical of 6-20 carbon atoms (C_6–C_{20}) derived by the removal of two hydrogen atom from a two carbon atoms of a parent aromatic ring system. Some arylene groups are represented in the exemplary structures as "Ar". Arylene includes bicyclic radicals comprising an aromatic ring fused to a saturated, partially unsaturated ring, or aromatic carbocyclic ring. Typical arylene groups include, but are not limited to, radicals derived from benzene (phenylene), substituted benzenes, naphthalene, anthracene, biphenylene, indenylene, indanylene, 1,2-dihydronaphthalene, 1,2,3,4-tetrahydronaphthyl, and the like. Arylene groups are optionally substituted

The terms "heterocycle," "heterocyclyl" and "heterocyclic ring" are used interchangeably herein and refer to a saturated or a partially unsaturated (i.e., having one or more double and/or triple bonds within the ring) carbocyclic radical of 3 to about 20 ring atoms in which at least one ring atom is a heteroatom selected from nitrogen, oxygen, phosphorus, sulfur, and silicon, the remaining ring atoms being C, where one or more ring atoms is optionally substituted independently with one or more substituents described below. A heterocycle may be a monocycle having 3 to 7 ring members (2 to 6 carbon atoms and 1 to 4 heteroatoms selected from N, O, P, and S) or a bicycle having 7 to 10 ring members (4 to 9 carbon atoms and 1 to 6 heteroatoms selected from N, O, P, and S), for example: a bicyclo [4,5], [5,5], [5,6], or [6,6] system. Heterocycles are described in Paquette, Leo A.; "Principles of Modern Heterocyclic Chemistry" (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and J. Am. Chem. Soc. (1960) 82:5566. "Heterocyclyl" also includes radicals where heterocycle radicals are fused with a saturated, partially unsaturated ring, or aromatic carbocyclic or heterocyclic ring. Examples of heterocyclic rings include, but are not limited to, morpholin-4-yl, piperidin-1-yl, piperidonyl, oxopiperazinyl, piperazinyl, piperazin-4-yl-2-one, piperazin-4-yl-3-one, pyrrolidin-1-yl, thiomorpholin-4-yl, S-dioxothiomorpholin-4-yl, azocan-1-yl, azetidin-1-yl, octahydropyrido[1,2-a]pyrazin-2-yl,

[1,4]diazepan-1-yl, pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, homopiperazinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinylimidazolinyl, imidazolidinyl, 3-azabicyco[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, azabicyclo[2.2.2]hexanyl, 3H-indolyl quinolizinyl and N-pyridyl ureas. Spiro moieties are also included within the scope of this definition. Examples of a heterocyclic group wherein 2 ring atoms are substituted with oxo (=O) moieties are pyrimidinonyl and 1,1-dioxo-thiomorpholinyl. The heterocycle groups herein are optionally substituted independently with one or more substituents described herein.

The term "heteroaryl" refers to a monovalent aromatic radical of 5-, 6-, or 7-membered rings, and includes fused ring systems (at least one of which is aromatic) of 5-20 atoms, containing one or more heteroatoms independently selected from nitrogen, oxygen, and sulfur. Examples of heteroaryl groups are pyridinyl (including, for example, 2-hydroxypyridinyl), imidazolyl, imidazopyridinyl, pyrimidinyl (including, for example, 4-hydroxypyrimidinyl), pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxadiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, triazolyl, thiadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. Heteroaryl groups are optionally substituted independently with one or more substituents described herein.

The heterocycle or heteroaryl groups may be carbon (carbon-linked), or nitrogen (nitrogen-linked) bonded where such is possible. By way of example and not limitation, carbon bonded heterocycles or heteroaryls are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline.

By way of example and not limitation, nitrogen bonded heterocycles or heteroaryls are bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β-carboline.

The terms "treat" and "treatment" refer to therapeutic treatment, wherein the object is to slow down (lessen) an undesired physiological change or disorder, such as the development or spread of arthritis or cancer. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment. Those in need of treatment include those with the condition or disorder.

The phrase "therapeutically effective amount" means an amount of a compound of the present invention that (i) treats the particular disease, condition, or disorder, (ii) attenuates, ameliorates, or eliminates one or more symptoms of the particular disease, condition, or disorder, or (iii) prevents or delays the onset of one or more symptoms of the particular disease, condition, or disorder described herein. In the case of cancer, the therapeutically effective amount of the drug may reduce the number of cancer cells; reduce the tumor size; inhibit (i.e., slow to some extent and preferably stop) cancer cell infiltration into peripheral organs; inhibit (i.e., slow to some extent and preferably stop) tumor metastasis; inhibit, to some extent, tumor growth; and/or relieve to some extent one or more of the symptoms associated with the cancer. To the extent the drug may prevent growth and/or kill existing cancer cells, it may be cytostatic and/or cytotoxic. For cancer therapy, efficacy can be measured, for example, by assessing the time to disease progression (TTP) and/or determining the response rate (RR).

"Inflammatory disorder" as used herein can refer to any disease, disorder, or syndrome in which an excessive or unregulated inflammatory response leads to excessive inflammatory symptoms, host tissue damage, or loss of tissue function. "Inflammatory disorder" also refers to a pathological state mediated by influx of leukocytes and/or neutrophil chemotaxis.

"Inflammation" as used herein refers to a localized, protective response elicited by injury or destruction of tissues, which serves to destroy, dilute, or wall off (sequester) both the injurious agent and the injured tissue. Inflammation is notably associated with influx of leukocytes and/or neutrophil chemotaxis. Inflammation can result from infection with pathogenic organisms and viruses and from noninfectious means such as trauma or reperfusion following myocardial infarction or stroke, immune response to foreign antigen, and autoimmune responses. Accordingly, inflammatory disorders amenable to treatment with Formula I compounds encompass disorders associated with reactions of the specific defense system as well as with reactions of the nonspecific defense system.

"Specific defense system" refers to the component of the immune system that reacts to the presence of specific antigens. Examples of inflammation resulting from a response of the specific defense system include the classical response to foreign antigens, autoimmune diseases, and delayed type hypersensitivity response mediated by T-cells. Chronic inflammatory diseases, the rejection of solid transplanted tissue and organs, e.g., kidney and bone marrow transplants, and graft versus host disease (GVHD), are further examples of inflammatory reactions of the specific defense system.

The term "nonspecific defense system" as used herein refers to inflammatory disorders that are mediated by leukocytes that are incapable of immunological memory (e.g., granulocytes, and macrophages). Examples of inflammation that result, at least in part, from a reaction of the nonspecific defense system include inflammation associated with conditions such as adult (acute) respiratory distress syndrome (ARDS) or multiple organ injury syndromes; reperfusion injury; acute glomerulonephritis; reactive arthritis; dermatoses with acute inflammatory components; acute purulent meningitis or other central nervous system inflammatory disorders such as stroke; thermal injury; inflammatory bowel disease; granulocyte transfusion associated syndromes; and cytokine-induced toxicity.

"Autoimmune disease" as used herein refers to any group of disorders in which tissue injury is associated with humoral or cell-mediated responses to the body's own constituents.

"Allergic disease" as used herein refers to any symptoms, tissue damage, or loss of tissue function resulting from allergy. "Arthritic disease" as used herein refers to any disease that is characterized by inflammatory lesions of the joints attributable to a variety of etiologies. "Dermatitis" as used herein refers to any of a large family of diseases of the skin that are characterized by inflammation of the skin attributable to a variety of etiologies. "Transplant rejection" as used herein refers to any immune reaction directed against grafted tissue, such as organs or cells (e.g., bone marrow), characterized by a loss of function of the

grafted and surrounding tissues, pain, swelling, leukocytosis, and thrombocytopenia. The therapeutic methods of the present invention include methods for the treatment of disorders associated with inflammatory cell activation.

"Inflammatory cell activation" refers to the induction by a stimulus (including, but not limited to, cytokines, antigens or auto-antibodies) of a proliferative cellular response, the production of soluble mediators (including but not limited to cytokines, oxygen radicals, enzymes, prostanoids, or vasoactive amines), or cell surface expression of new or increased numbers of mediators (including, but not limited to, major histocompatability antigens or cell adhesion molecules) in inflammatory cells (including but not limited to monocytes, macrophages, T lymphocytes, B lymphocytes, granulocytes (i.e., polymorphonuclear leukocytes such as neutrophils, basophils, and eosinophils), mast cells, dendritic cells, Langerhans cells, and endothelial cells). It will be appreciated by persons skilled in the art that the activation of one or a combination of these phenotypes in these cells can contribute to the initiation, perpetuation, or exacerbation of an inflammatory disorder.

The term "NSAID" is an acronym for "non-steroidal anti-inflammatory drug" and is a therapeutic agent with analgesic, antipyretic (lowering an elevated body temperature and relieving pain without impairing consciousness) and, in higher doses, with anti-inflammatory effects (reducing inflammation). The term "non-steroidal" is used to distinguish these drugs from steroids, which (among a broad range of other effects) have a similar eicosanoid-depressing, anti-inflammatory action. As analgesics, NSAIDs are unusual in that they are non-narcotic. NSAIDs include aspirin, ibuprofen, and naproxen. NSAIDs are usually indicated for the treatment of acute or chronic conditions where pain and inflammation are present. NSAIDs are generally indicated for the symptomatic relief of the following conditions: rheumatoid arthritis, osteoarthritis, inflammatory arthropathies (e.g. ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome, acute gout, dysmenorrhoea, metastatic bone pain, headache and migraine, postoperative pain, mild-to-moderate pain due to inflammation and tissue injury, pyrexia, ileus, and renal colic. Most NSAIDs act as non-selective inhibitors of the enzyme cyclooxygenase, inhibiting both the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes. Cyclooxygenase catalyzes the formation of prostaglandins and thromboxane from arachidonic acid (itself derived from the cellular phospholipid bilayer by phospholipase A_2). Prostaglandins act (among other things) as messenger molecules in the process of inflammation. COX-2 inhibitors include celecoxib, etoricoxib, lumiracoxib, parecoxib, rofecoxib, rofecoxib, and valdecoxib.

The terms "cancer" refers to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. A "tumor" comprises one or more cancerous cells. Examples of cancer include, but are not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia or lymphoid malignancies. More particular examples of such cancers include squamous cell cancer (*e.g.*, epithelial squamous cell cancer), lung cancer including small- cell lung cancer, non-small cell lung cancer ("NSCLC"), adenocarcinoma of the lung and squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer including gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, as well as head and neck cancer.

A "chemotherapeutic agent" is a chemical compound useful in the treatment of cancer, regardless of mechanism of action. Classes of chemotherapeutic agents include, but are not limited to: alkylating agents, antimetabolites, spindle poison plant alkaloids, cytotoxic/antitumor antibiotics, topoisomerase inhibitors, antibodies, photosensitizers, and kinase inhibitors. Chemotherapeutic agents include compounds used in "targeted therapy" and conventional chemotherapy. Examples of chemotherapeutic agents include: erlotinib (TARCEVA®, Genentech/OSI Pharm.), docetaxel (TAXOTERE®, Sanofi-Aventis), 5-FU (fluorouracil, 5-fluorouracil, CAS No. 51-21-8), gemcitabine (GEMZAR®, Lilly), PD-0325901 (CAS No. 391210-10-9, Pfizer), cisplatin (cis-diamine, dichloroplatinum(II), CAS No. 15663-27-1), carboplatin (CAS No. 41575-94-4), paclitaxel (TAXOL®, Bristol-Myers Squibb Oncology, Princeton, N.J.), trastuzumab (HERCEPTIN®, Genentech), temozolomide (4-methyl-5-oxo- 2,3,4,6,8-pentazabicyclo [4.3.0] nona-2,7,9-triene- 9-carboxamide, CAS No. 85622-93-1, TEMODAR®, TEMODAL®, Schering Plough), tamoxifen ((Z)-2-[4-(1,2-diphenylbut-1-enyl)phenoxy]-*N*,*N*-dimethylethanamine, NOLVADEX®, ISTUBAL®, VALODEX®), and doxorubicin (ADRIAMYCIN®), Akti-1/2, HPPD, and rapamycin.

More examples of chemotherapeutic agents include: oxaliplatin (ELOXATIN®, Sanofi), bortezomib (VELCADE®, Millennium Pharm.), sutent (SUNITINIB®, SU11248, Pfizer), letrozole (FEMARA®, Novartis), imatinib mesylate (GLEEVEC®, Novartis), XL-518 (Mek inhibitor, Exelixis, WO 2007/044515), ARRY-886 (Mek inhibitor, AZD6244, Array BioPharma, Astra Zeneca), SF-1126 (PI3K inhibitor, Semafore Pharmaceuticals), BEZ-235 (PI3K inhibitor, Novartis), XL-147 (PI3K inhibitor, Exelixis), PTK787/ZK 222584 (Novartis), fulvestrant (FASLODEX®, AstraZeneca), leucovorin (folinic acid), rapamycin

(sirolimus, RAPAMUNE®, Wyeth), lapatinib (TYKERB®, GSK572016, Glaxo Smith Kline), lonafarnib (SARASAR™, SCH 66336, Schering Plough), sorafenib (NEXAVAR®, BAY43-9006, Bayer Labs), gefitinib (IRESSA®, AstraZeneca), irinotecan (CAMPTOSAR®, CPT-11, Pfizer), tipifarnib (ZARNESTRA™, Johnson & Johnson), ABRAXANE™ (Cremophor-free), albumin-engineered nanoparticle formulations of paclitaxel (American Pharmaceutical Partners, Schaumberg, Il), vandetanib (rINN, ZD6474, ZACTIMA®, AstraZeneca), chloranmbucil, AG1478, AG1571 (SU 5271; Sugen), temsirolimus (TORISEL®, Wyeth), pazopanib (GlaxoSmithKline), canfosfamide (TELCYTA®, Telik), thiotepa and cyclosphosphamide (CYTOXAN®, NEOSAR®); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide and trimethylomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analog topotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogs); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogs, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, chlorophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosoureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimnustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, calicheamicin gamma1I, calicheamicin omegaI1 (Angew Chem. Intl. Ed. Engl. (1994) 33:183-186); dynemicin, dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, carminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, nemorubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, porfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogs such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine;

pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfornithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, OR); razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; vinorelbine (NAVELBINE®); novantrone; teniposide; edatrexate; daunomycin; aminopterin; capecitabine (XELODA®, Roche); ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; and pharmaceutically acceptable salts, acids and derivatives of any of the above.

Also included in the definition of "chemotherapeutic agent" are: (i) anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens and selective estrogen receptor modulators (SERMs), including, for example, tamoxifen (including NOLVADEX®; tamoxifen citrate), raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and FARESTON® (toremifine citrate); (ii) aromatase inhibitors that inhibit the enzyme aromatase, which regulates estrogen production in the adrenal glands, such as, for example, 4(5)-imidazoles, aminoglutethimide, MEGASE® (megestrol acetate), AROMASIN® (exemestane; Pfizer), formestanie, fadrozole, RIVISOR® (vorozole), FEMARA® (letrozole; Novartis), and ARIMIDEX® (anastrozole; AstraZeneca); (iii) anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; as well as troxacitabine (a 1,3-dioxolane nucleoside cytosine analog); (iv) protein kinase inhibitors such as MEK inhibitors (WO 2007/044515); (v) lipid kinase inhibitors; (vi) antisense oligonucleotides, particularly those which inhibit expression of genes in signaling pathways implicated in aberrant cell proliferation, for example, PKC-alpha, Raf and H-Ras,

such as oblimersen (GENASENSE®, Genta Inc.); (vii) ribozymes such as VEGF expression inhibitors (e.g., ANGIOZYME®) and HER2 expression inhibitors; (viii) vaccines such as gene therapy vaccines, for example, ALLOVECTIN®, LEUVECTIN®, and VAXID®; PROLEUKIN® rIL-2; topoisomerase 1 inhibitors such as LURTOTECAN®; ABARELIX® rmRH; (ix) anti-angiogenic agents such as bevacizumab (AVASTIN®, Genentech); and pharmaceutically acceptable salts, acids and derivatives of any of the above.

Also included in the definition of "chemotherapeutic agent" are therapeutic antibodies such as alemtuzumab (Campath), bevacizumab (AVASTIN®, Genentech); cetuximab (ERBITUX®, Imclone); panitumumab (VECTIBIX®, Amgen), rituximab (RITUXAN®, Genentech/Biogen Idec), pertuzumab (OMNITARG™, 2C4, Genentech), trastuzumab (HERCEPTIN®, Genentech), tositumomab (Bexxar, Corixia), and the antibody drug conjugate, gemtuzumab ozogamicin (MYLOTARG®, Wyeth).

Humanized monoclonal antibodies with therapeutic potential as chemotherapeutic agents in combination with the Btk inhibitors of the invention include: alemtuzumab, apolizumab, aselizumab, atlizumab, bapineuzumab, bevacizumab, bivatuzumab mertansine, cantuzumab mertansine, cedelizumab, certolizumab pegol, cidfusituzumab, cidtuzumab, daclizumab, eculizumab, efalizumab, epratuzumab, erlizumab, felvizumab, fontolizumab, gemtuzumab ozogamicin, inotuzumab ozogamicin, ipilimumab, labetuzumab, lintuzumab, matuzumab, mepolizumab, motavizumab, motovizumab, natalizumab, nimotuzumab, nolovizumab, numavizumab, ocrelizumab, omalizumab, palivizumab, pascolizumab, pecfusituzumab, pectuzumab, pertuzumab, pexelizumab, ralivizumab, ranibizumab, reslivizumab, reslizumab, resyvizumab, rovelizumab, ruplizumab, sibrotuzumab, siplizumab, sontuzumab, tacatuzumab tetraxetan, tadocizumab, talizumab, tefibazumab, tocilizumab, toralizumab, trastuzumab, tucotuzumab celmoleukin, tucusituzumab, umavizumab, urtoxazumab, and visilizumab.

A "metabolite" is a product produced through metabolism in the body of a specified compound or salt thereof. Metabolites of a compound may be identified using routine techniques known in the art and their activities determined using tests such as those described herein. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, deamidation, esterification, deesterification, enzymatic cleavage, and the like, of the administered compound. Accordingly, the invention includes metabolites of compounds of the invention, including compounds produced by a process comprising contacting a Formula I compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof.

The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, contraindications and/or warnings concerning the use of such therapeutic products.

The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

The term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

"Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

"Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., *McGraw-Hill Dictionary of Chemical Terms* (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., New York, 1994. The compounds of the invention may contain asymmetric or chiral centers, and therefore exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of the invention, including but not limited to, diastereomers, enantiomers and atropisomers, as well as mixtures thereof such as racemic mixtures, form part of the present invention. Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L, or *R* and *S*, are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical

reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity. In one aspect, a stereoisomer of this invention can be present in predominant form, e.g. greater than 50% ee (enantiomeric excess), greater than 80% ee, greater than 90% ee, greater than 95% ee, or greater than 99% ee.

The term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible via a low energy barrier. For example, proton tautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons.

The term "diastereomer" refers to stereoisomeric molecules which are not enantiomers. Diastereomers include cis-trans isomers and conformational isomers which have the same molecular formula but which have a different geometric structure.

The phrase "pharmaceutically acceptable salt" as used herein, refers to pharmaceutically acceptable organic or inorganic salts of a compound of the invention. Exemplary salts include, but are not limited, to sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate "mesylate", ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, and pamoate (i.e., 1,1'-methylene-bis(2-hydroxy-3-naphthoate)) salts. A pharmaceutically acceptable salt may involve the inclusion of another molecule such as an acetate ion, a succinate ion or other counter ion. The counter ion may be any organic or inorganic moiety that stabilizes the charge on the parent compound. Furthermore, a pharmaceutically acceptable salt may have more than one charged atom in its structure. Instances where multiple charged atoms are part of the pharmaceutically acceptable salt can have multiple counter ions. Hence, a pharmaceutically acceptable salt can have one or more charged atoms and/or one or more counter ion.

If the compound of the invention is a base, the desired pharmaceutically acceptable salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, methanesulfonic acid, phosphoric acid and the like, or with an organic acid, such as acetic acid, trifluoroacetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, a pyranosidyl acid,

such as glucuronic acid or galacturonic acid, an alpha hydroxy acid, such as citric acid or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such as benzoic acid or cinnamic acid, a sulfonic acid, such as p-toluenesulfonic acid or ethanesulfonic acid, or the like.

If the compound of the invention is an acid, the desired pharmaceutically acceptable salt may be prepared by any suitable method, for example, treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal hydroxide or alkaline earth metal hydroxide, or the like. Illustrative examples of suitable salts include, but are not limited to, organic salts derived from amino acids, such as glycine and arginine, ammonia, primary, secondary, and tertiary amines, and cyclic amines, such as piperidine, morpholine and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum and lithium.

The phrase "pharmaceutically acceptable" indicates that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

A "solvate" refers to an association or complex of one or more solvent molecules and a compound of the invention. Examples of solvents that form solvates include, but are not limited to, water, isopropanol, ethanol, methanol, DMSO, ethylacetate, acetic acid, and ethanolamine.

The terms "compound of this invention," and "compounds of the present invention" include compounds of Formulas I and stereoisomers, tautomers, solvates, metabolites, and pharmaceutically acceptable salts and prodrugs thereof.

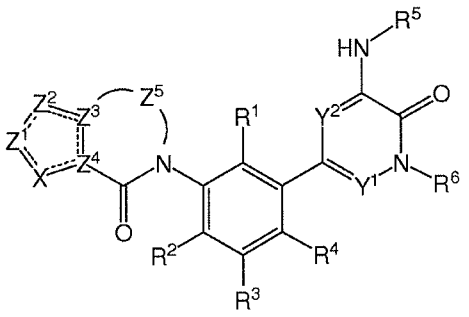
Any formula or structure given herein, including Formula I compounds, is also intended to represent hydrates, solvates, and polymorphs of such compounds, and mixtures thereof.

Any formula or structure given herein, including Formula I compounds, is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as, but not limited to 2H (deuterium, D), 3H (tritium), 11C, 13C, 14C, 15N, 18F, 31P, 32P, 35S, 36Cl, and 125I. Various isotopically labeled compounds of the present invention, for example those into which radioactive isotopes such as 3H, 13C, and 14C are incorporated.

Such isotopically labelled compounds may be useful in metabolic studies, reaction kinetic studies, detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. Deuterium labelled or substituted therapeutic compounds of the invention may have improved DMPK (drug metabolism and pharmacokinetics) properties, relating to distribution, metabolism, and excretion (ADME). Substitution with heavier isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements. An 18F labeled compound may be useful for PET or SPECT studies. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent. Further, substitution with heavier isotopes, particularly deuterium (i.e., 2H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index. It is understood that deuterium in this context is regarded as a substituent in the compound of the formula (I). The concentration of such a heavier isotope, specifically deuterium, may be defined by an isotopic enrichment factor. In the compounds of this invention any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition. Accordingly, in the compounds of this invention any atom specifically designated as a deuterium (D) is meant to represent deuterium.

PYRIDONE AND AZA-PYRIDONE COMPOUNDS

The present invention provides pyridone and aza-pyridone compounds of Formula I, including Formulas Ia-bf, and pharmaceutical formulations thereof, which are potentially useful in the treatment of diseases, conditions and/or disorders modulated by Btk kinase



I

including stereoisomers, tautomers, or pharmaceutically acceptable salts thereof, wherein:

R^1 is H, D, F, Cl, CN, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2OH$, heteroaryl selected from imidazolyl and pyrazolyl, heterocyclyl selected from oxetanyl and azetidinyl, and C_1–C_3 alkyl;

R^2, R^3 and R^4 are independently selected from H, D, F, Cl, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2OH$, and C_1–C_3 alkyl;

R^5 is optionally substituted C_6–C_{20} aryl, C_3–C_{12} carbocyclyl, C_2–C_{20} heterocyclyl, C_1–C_{20} heteroaryl, $-(C_6$–C_{20} aryl$)-(C_2$–C_{20} heterocyclyl$)$, $-(C_1$–C_{20} heteroaryl$)-(C_2$–C_{20} heterocyclyl$)$, $-(C_1$–C_{20} heteroaryl$)-(C_1$–C_6 alkyl$)$, or $-(C_1$–C_{20} heteroaryl$)$–$C(=O)-(C_2$–C_{20} heterocyclyl$)$;

R^6 is H, F, $-NH_2$, $-OH$, or optionally substituted C_1–C_3 alkyl;

X is S, S(=O), $S(=O)_2$, N, NR^6, O, or CR^7;

R^7 is independently selected from H, D, F, Cl, $-CH_3$, $-CH_2CH_3$, $-CN$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-NH_2$, $-OH$, and $-OCH_3$;

Y^1 and Y^2 are independently selected from CR^6 and N;

Z^1, Z^2, Z^3, and Z^4 are independently selected from C, CR^7, and N;

Z^5 is selected from $-C(R^3)_2-$, $-C(=O)-$, $-N(R^6)-$, $-C(R^3)_2C(R^3)_2-$, $-C(R^3)_2C(=O)-$, $-CR^3=CR^3-$, $-CR^3=N-$, $-N(R^6)C(R^3)_2-$, $-N(R^6)C(R^3)_2C(R^3)_2-$, and $-OC(R^3)_2C(R^3)_2-$;

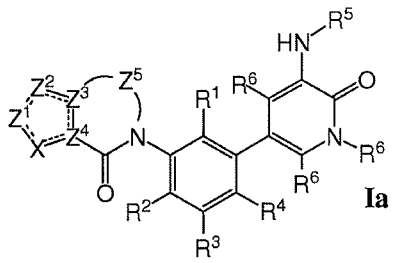
one of Z^1 and Z^2, or X and Z^1, where X is not S, S(=O), or $S(=O)_2$, forms a five-, six-, or seven-membered aryl, carbocyclyl, heterocyclyl or heteroaryl ring;

where alkyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more groups independently selected from D, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH_2OH$, $-CH_2CH_2OH$, $-C(CH_3)_2OH$, $-CH(OH)CH(CH_3)_2$, $-C(CH_3)_2CH_2OH$, $-CH_2CH_2SO_2CH_3$, $-CH_2OP(O)(OH)_2$, $-CN$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CO_2H$, $-COCH_3$, $-CO_2CH_3$, $-CO_2C(CH_3)_3$, $-COCH(OH)CH_3$, $-CONH_2$, $-CONHCH_3$, –

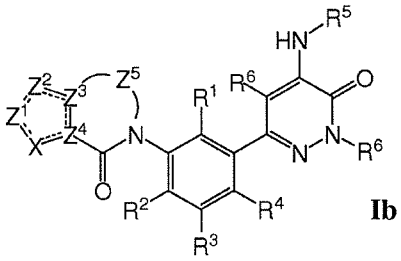
$CON(CH_3)_2$, $-C(CH_3)_2CONH_2$, $-NO_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHCOCH_3$, $-N(CH_3)COCH_3$, $-NHS(O)_2CH_3$, $-N(CH_3)C(CH_3)_2CONH_2$, $-N(CH_3)CH_2CH_2S(O)_2CH_3$, =O, $-OH$, $-OCH_3$, $-OCH_2CH_2N(CH_3)_2$, $-OP(O)(OH)_2$, $-S(O)_2N(CH_3)_2$, $-SCH_3$, $-CH_2OCH_3$, $-S(O)_2CH_3$, cyclopropyl, azetidinyl, 1-methylazetidin-3-yl)oxy, N-methyl-N-oxetan-3-ylamino, azetidin-1-ylmethyl, oxetanyl, and morpholino.

In one aspect, Formula I compounds are 3-amino-5-phenyl pyridine-2(1H)-one **Ia** where Y^1 and Y^2 are CR^6, 4-amino-6-phenyl pyridazin-3(2H)-one **Ib** where Y^1 is N and Y^2 is CR^6, and 3-amino-5-phenyl pyrazin-2(1H)-ones **Ic** where Y^1 is CR^6 and Y^2 is N.

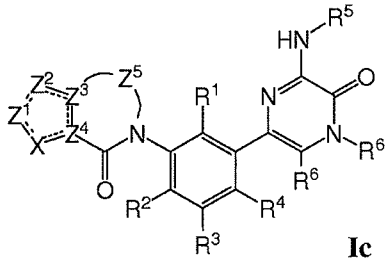
Exemplary embodiments of Formula I compounds include compounds of Formulas Ia-Ibf:



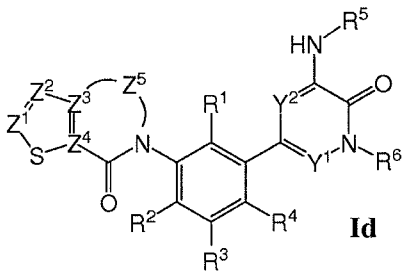
Ia



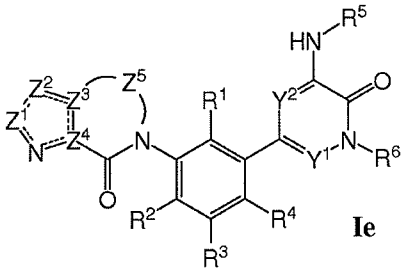
Ib



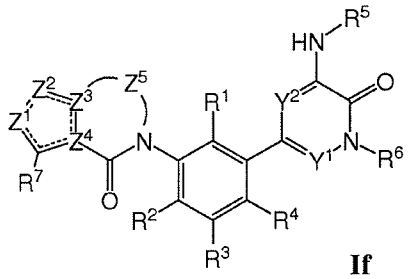
Ic



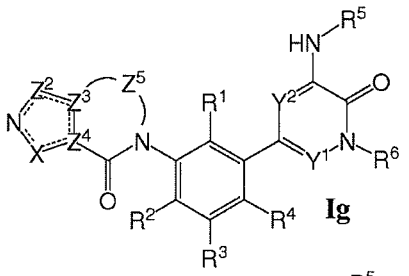
Id



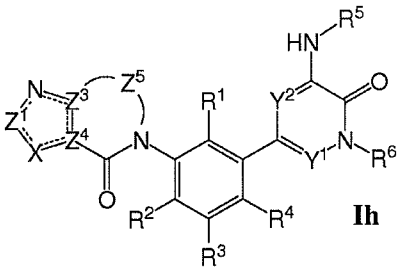
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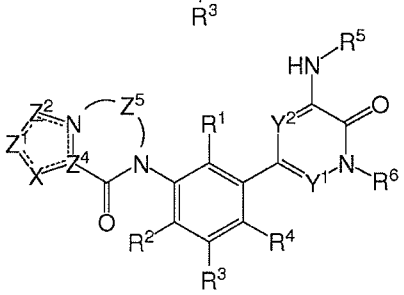
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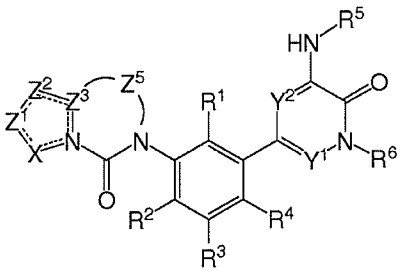
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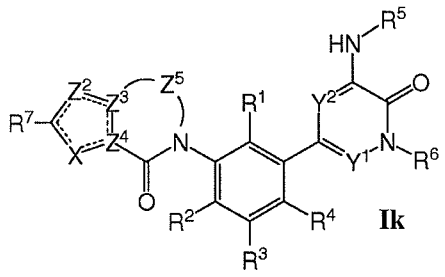
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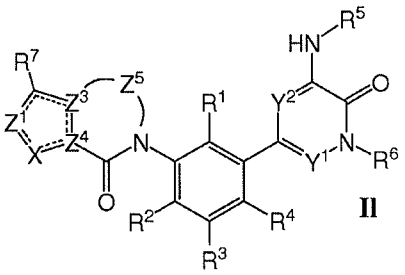
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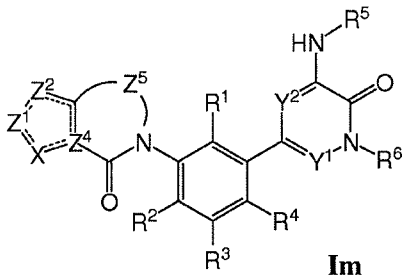
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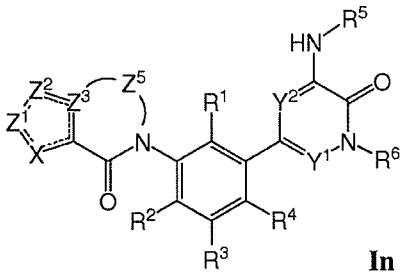
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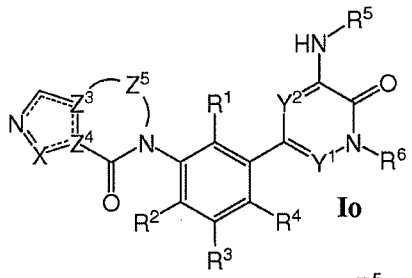
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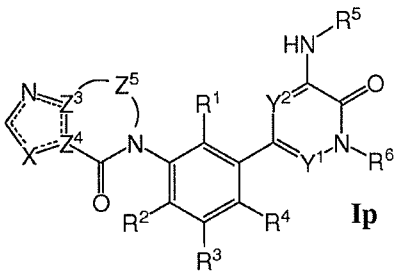
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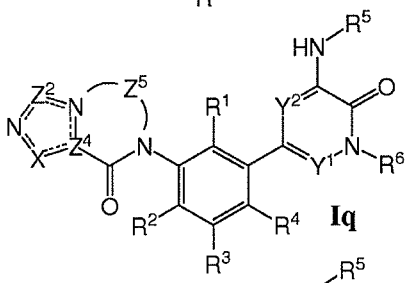
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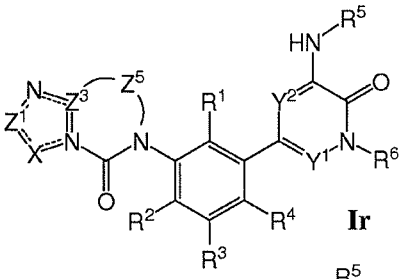
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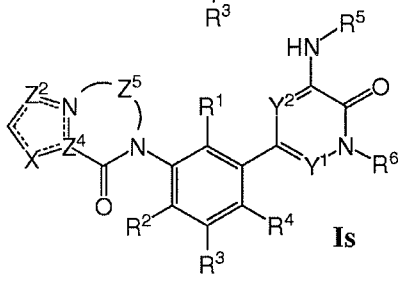
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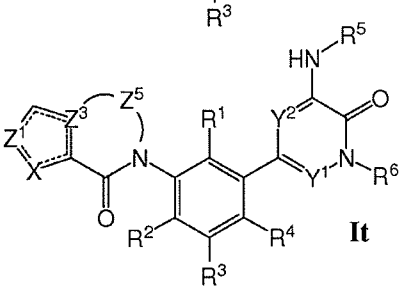
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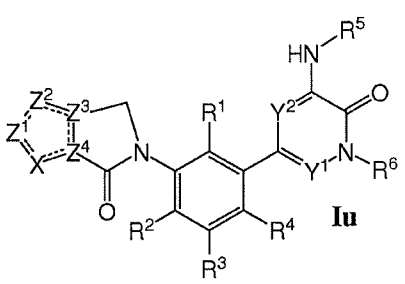
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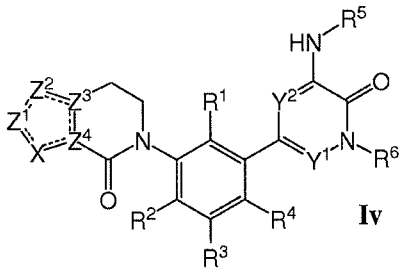
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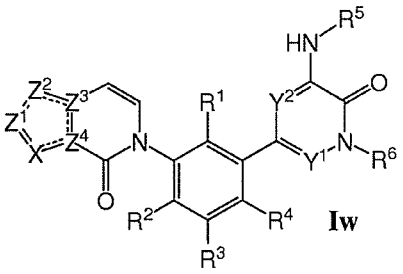
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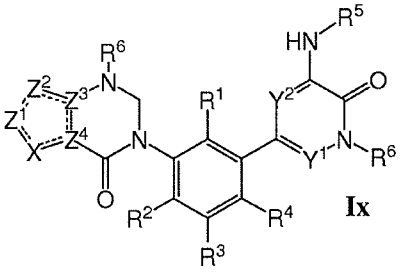
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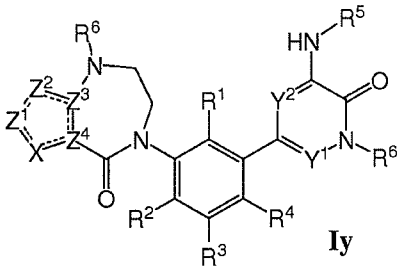
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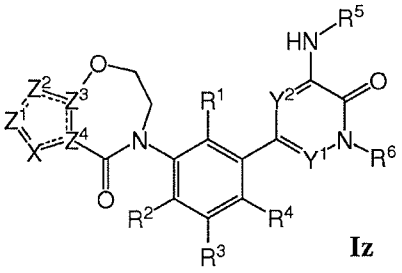
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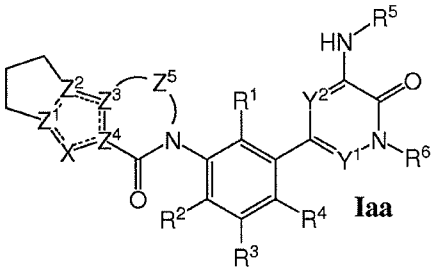
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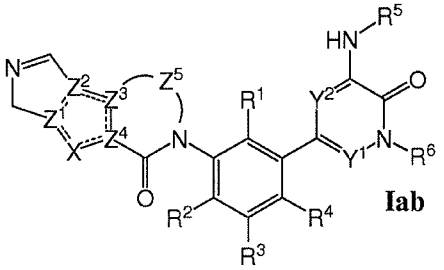
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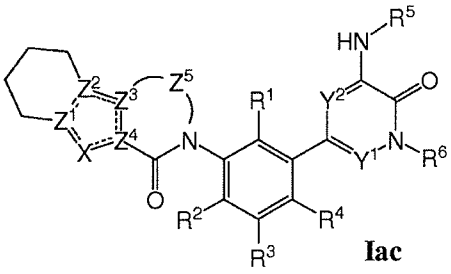
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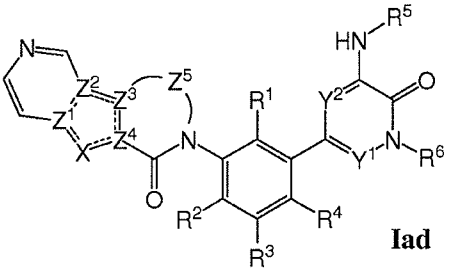
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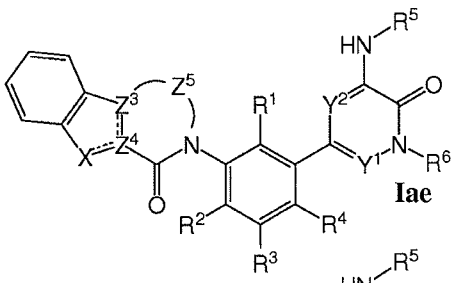
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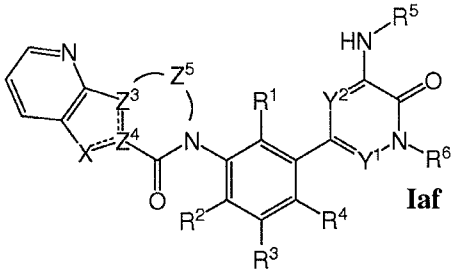
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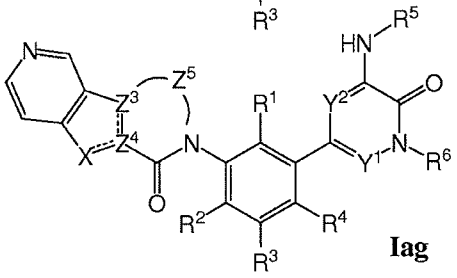
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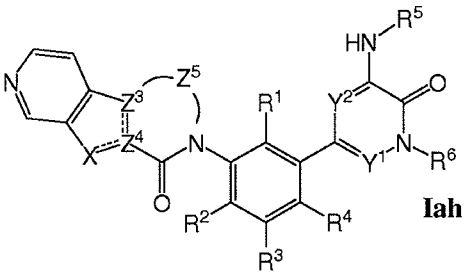
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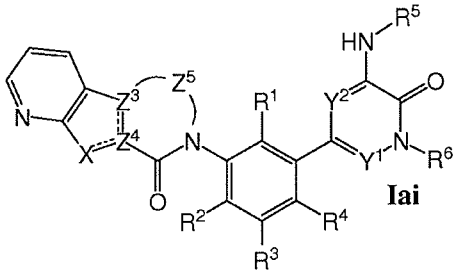
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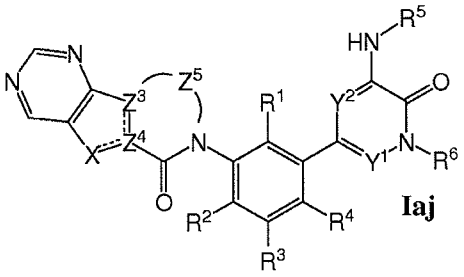
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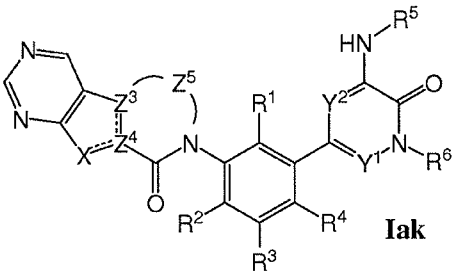
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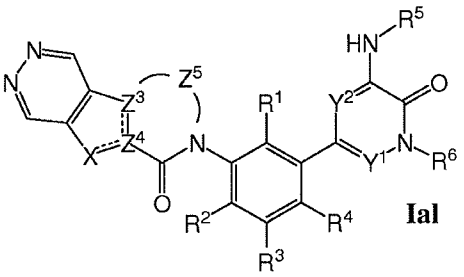
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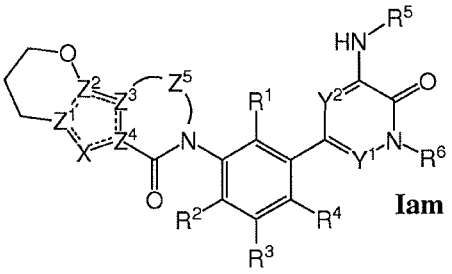
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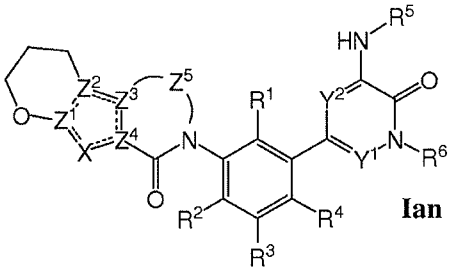
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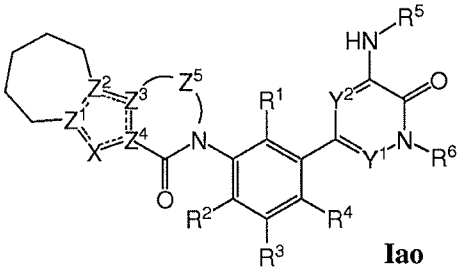
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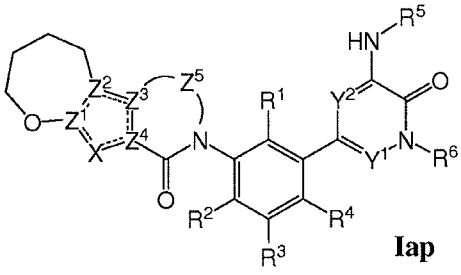
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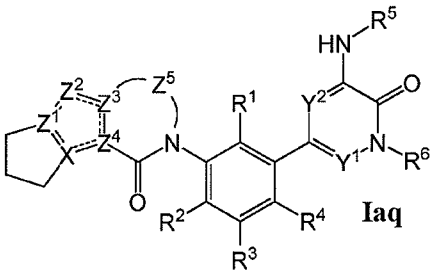
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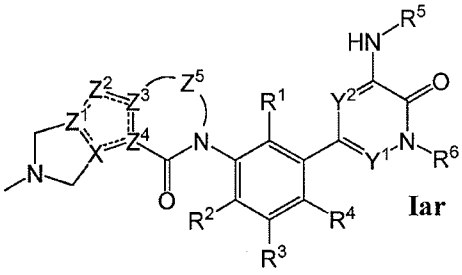
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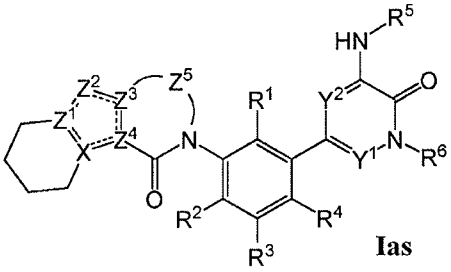
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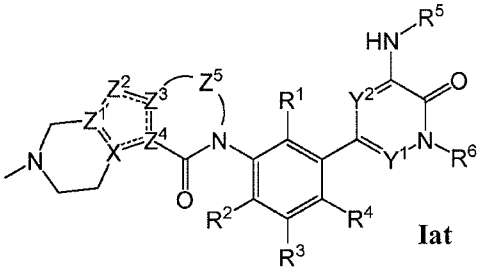
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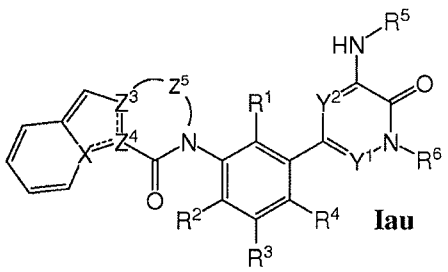
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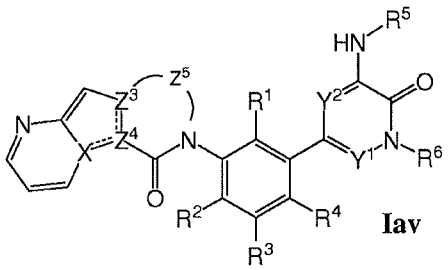
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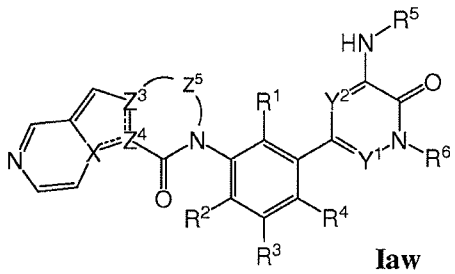
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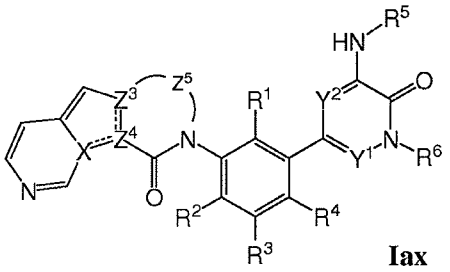
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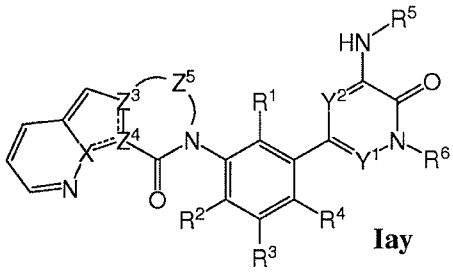
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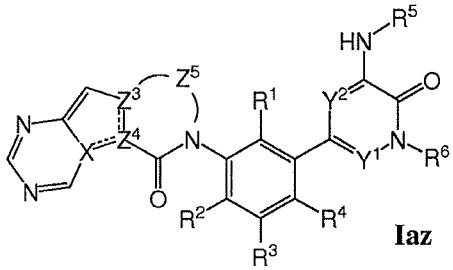
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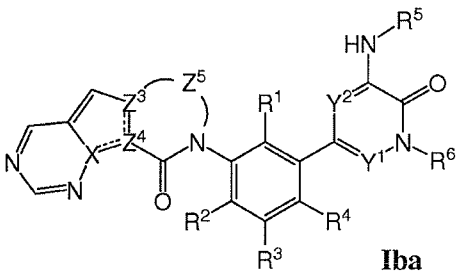
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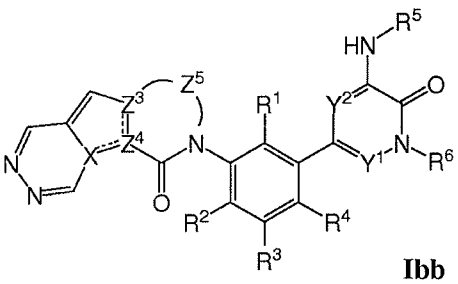
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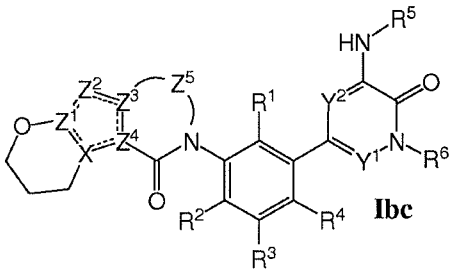
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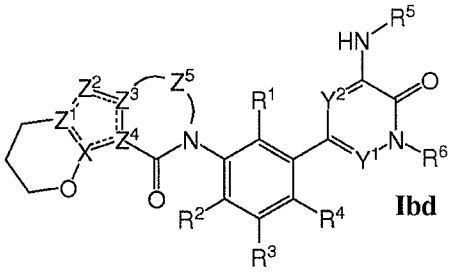
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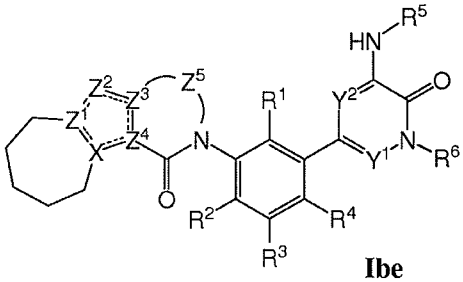
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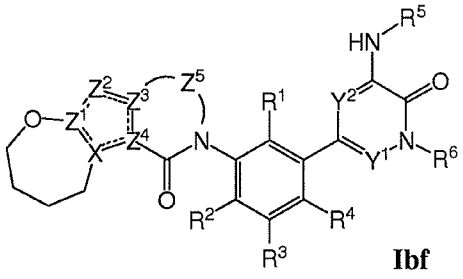
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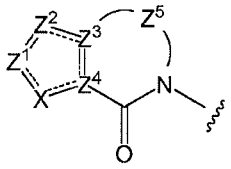


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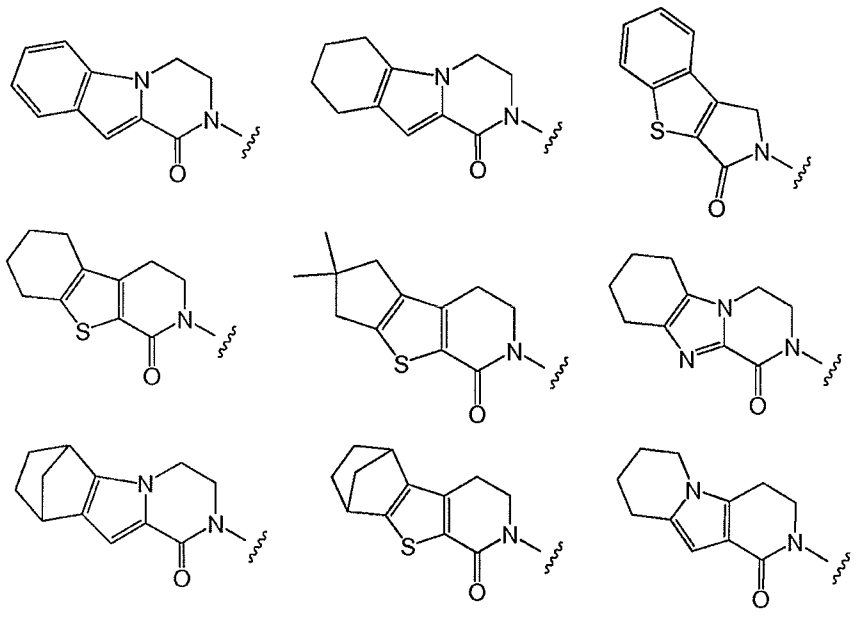


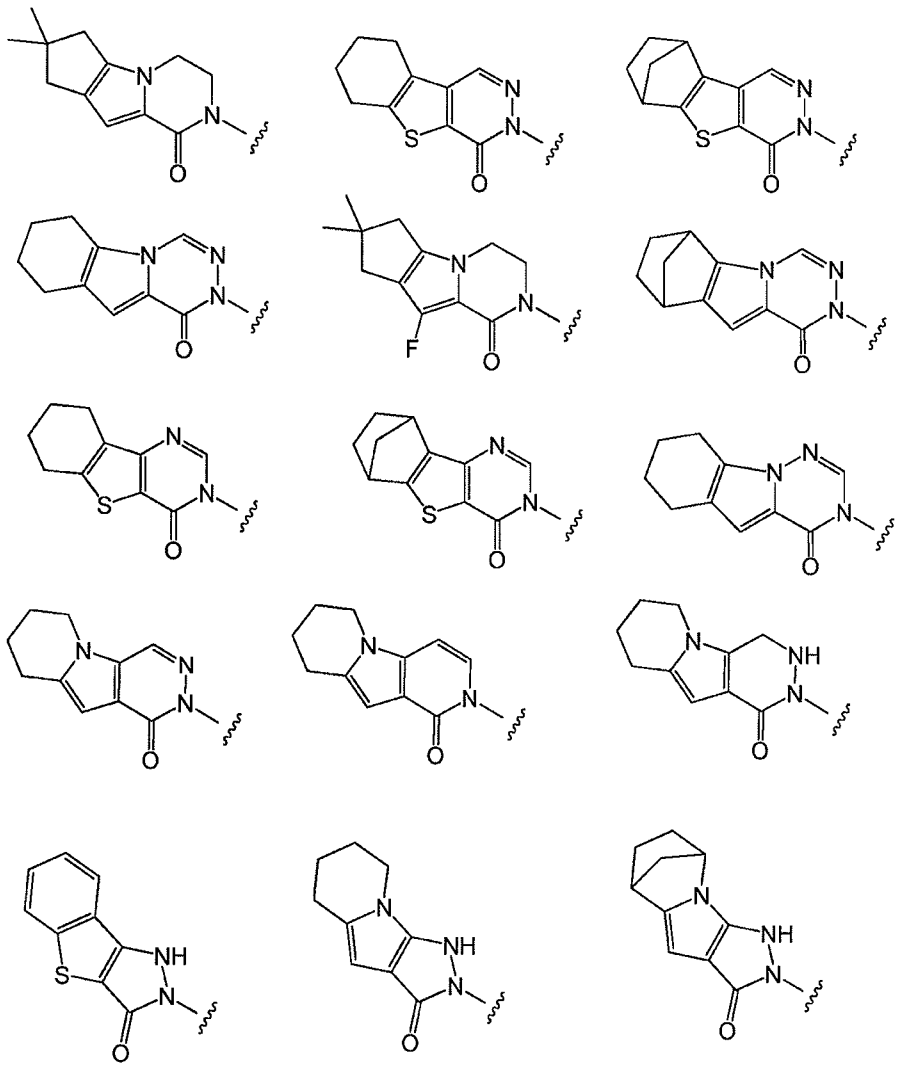
Ibf

Exemplary embodiments of Formula I compounds include where the group:



forms the structures:





where the wavy line indicates the site of attachment.

Exemplary embodiments of Formula I compounds include wherein the center phenyl ring group is substituted or not substituted such as: (i) R^1, R^2, R^3, and R^4 are each H; (ii) or one or more of R^1, R^2, R^3, and R^4 are F; (iii) R^1 is selected from F, $-CH_3$, $-CH_2F$, $-CHF_2$, and $-CF_3$; (iv) R^1 is $-CH_2OH$; (v) R^3 is F; and (vi) R^1 is $-CH_2OH$, R^2 and R^4 are each H, and R^3 is F.

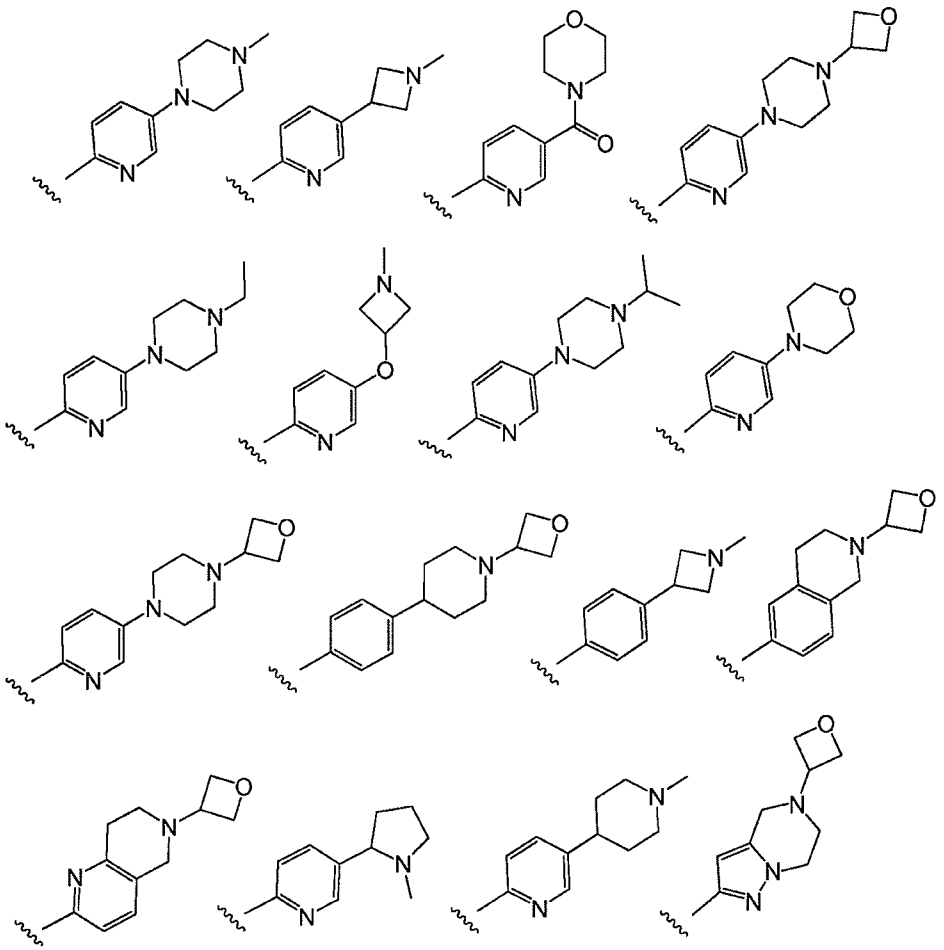
Exemplary embodiments of Formula I compounds include wherein R^5 is optionally substituted C_6–C_{20} aryl selected from phenyl and naphthyl.

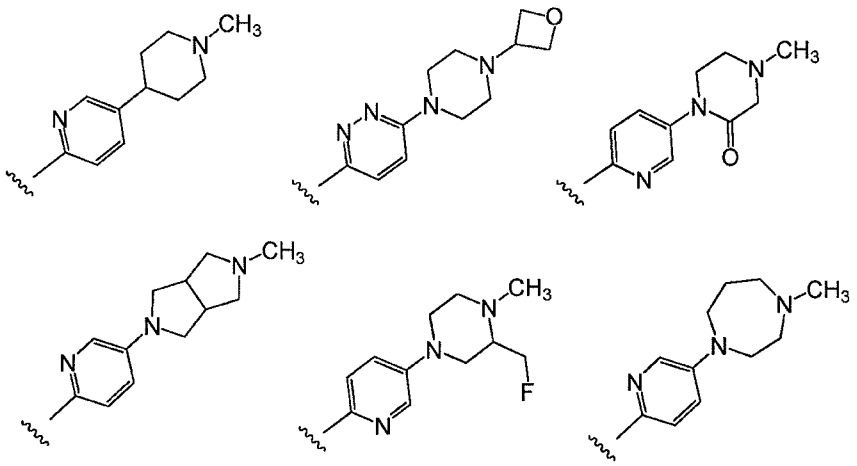
Exemplary embodiments of Formula I compounds include wherein R^5 is optionally substituted C_3–C_{12} carbocyclyl selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

Exemplary embodiments of Formula I compounds include wherein R^5 is optionally substituted C_2–C_{20} heterocyclyl selected from oxetanyl, azetidinyl, pyrrolidinyl, tetrahydrofuryl, piperidinyl, piperazinyl, morpholinyl, and tetrahydropyranyl.

Exemplary embodiments of Formula I compounds include wherein R^5 is optionally substituted C_1–C_{20} heteroaryl selected from pyrazolyl, pyridinyl, pyrimidinyl, 5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl, 5-acetyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl, 6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-2-yl, and 1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridine-2-yl.

Exemplary embodiments of Formula I compounds include wherein R^5 is selected from the structures:





where the wavy line indicates the site of attachment.

Exemplary embodiments of Formula I compounds include wherein R^6 is H.

Exemplary embodiments of Formula I compounds include wherein Y^1 is CR^6 and Y^2 is N.

Exemplary embodiments of Formula I compounds include wherein Y^1 is N and Y^2 is CR^6.

Exemplary embodiments of Formula I compounds include wherein Y^1 and Y^2 are each CR^6.

Each solid/dashed line, ----- , in the five-membered ring formed by X, Z^1, Z^2, Z^3, and Z^4 in the structures of Formula I compounds represents a single bond or a double bond, with the proviso that any two double bonds in the ring are not adjacent.

The Formula I compounds of the invention may contain asymmetric or chiral centers, and therefore exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of the invention, including but not limited to, diastereomers, enantiomers and atropisomers, as well as mixtures thereof such as racemic mixtures, form part of the present invention.

In addition, the present invention embraces all diastereomers, including cis-trans (geometric) and conformational isomers. For example, if a Formula I compound incorporates a double bond or a fused ring, the cis- and trans-forms, as well as mixtures thereof, are embraced within the scope of the invention.

In the structures shown herein, where the stereochemistry of any particular chiral atom is not specified, then all stereoisomers are contemplated and included as the compounds of the invention. Where stereochemistry is specified by a solid wedge or dashed line representing a particular configuration, then that stereoisomer is so specified and defined.

The compounds of the present invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms.

The compounds of the present invention may also exist in different tautomeric forms, and all such forms are embraced within the scope of the invention. The term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible via a low energy barrier. For example, proton tautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons.

BIOLOGICAL EVALUATION

The relative efficacies of Formula I compounds as inhibitors of an enzyme activity (or other biological activity) can be established by determining the concentrations at which each compound inhibits the activity to a predefined extent and then comparing the results. Typically, the preferred determination is the concentration that inhibits 50% of the activity in a biochemical assay, i.e., the 50% inhibitory concentration or "IC_{50}". Determination of IC_{50} values can be accomplished using conventional techniques known in the art. In general, an IC_{50} can be determined by measuring the activity of a given enzyme in the presence of a range of concentrations of the inhibitor under study. The experimentally obtained values of enzyme activity then are plotted against the inhibitor concentrations used. The concentration of the inhibitor that shows 50% enzyme activity (as compared to the activity in the absence of any inhibitor) is taken as the IC_{50} value. Analogously, other inhibitory concentrations can be defined through appropriate determinations of activity. For example, in some settings it can be desirable to establish a 90% inhibitory concentration, i.e., IC_{90}, etc.

Formula I compounds were tested by a standard biochemical Btk Kinase Assay (Example 901).

A general procedure for a standard cellular Btk Kinase Assay that can be used to test Formula I compounds is a Ramos Cell Btk Assay (Example 902).

A standard cellular B-cell proliferation assay can be used to test Formula I compounds with B-cells purified from spleen of Balb/c mice (Example 903).

A standard T cell proliferation assay can be used to test Formula I compounds with T-cells purified from spleen of Balb/c mice (Example 904).

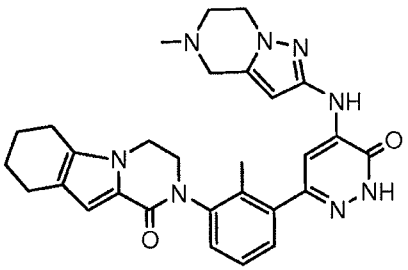
A CD86 Inhibition assay can be conducted on Formula I compounds for the inhibition of B cell activity using total mouse splenocytes purified from spleens of 8-16 week old Balb/c mice (Example 905).

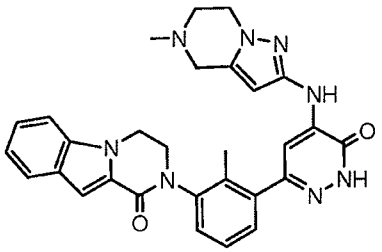
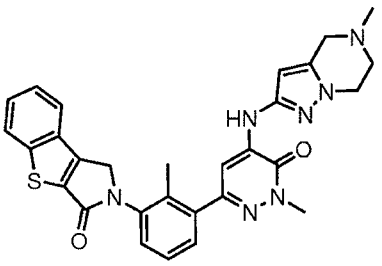
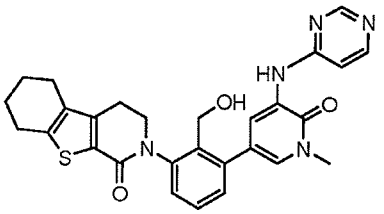
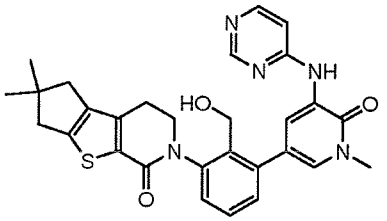
A B-ALL Cell Survival Assay can be conducted on Formula I compounds to measure the number of viable B-ALL cells in culture (Example 906).

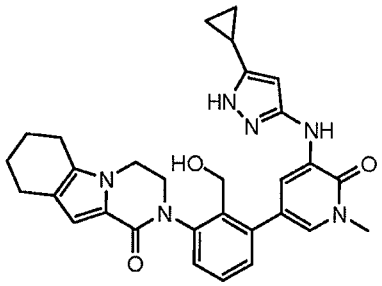
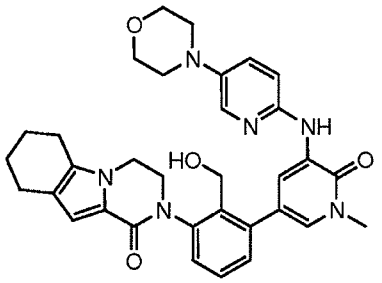
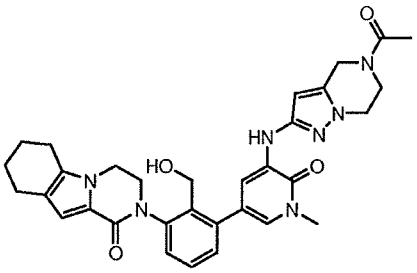
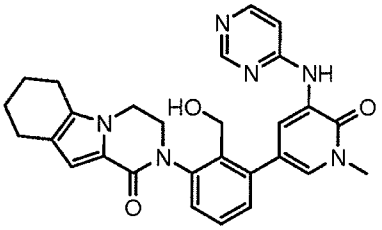
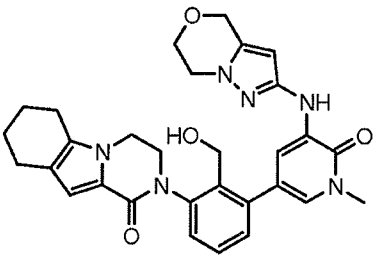
A CD69 Whole Blood Assay can be conducted on Formula I compounds to determine the ability of compounds to inhibit the production of CD69 by B lymphocytes in human whole blood activated by crosslinking surface IgM with goat F(ab')2 anti-human IgM (Example 907).

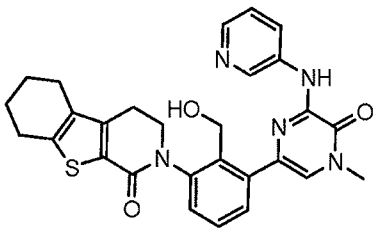
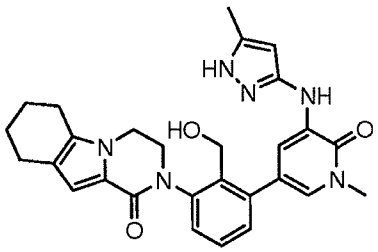
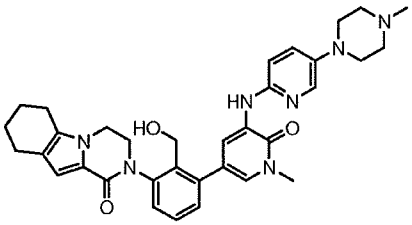
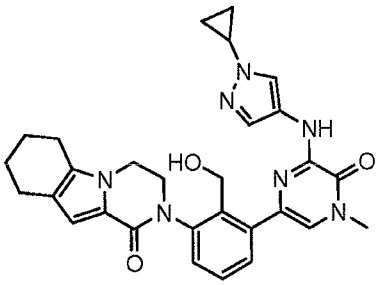
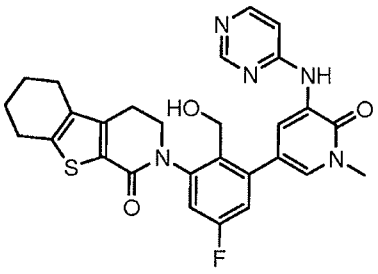
Exemplary Formula I compounds in Tables 1, 2, and 3 were made, characterized, and tested for inhibition of Btk according to the methods of this invention, and have the following structures and corresponding names (ChemDraw Ultra, Version 9.0.1, and ChemBioDraw, Version 11.0, CambridgeSoft Corp., Cambridge MA). Where more than one name is associated with a Formula I compound or intermediate, the chemical structure shall define the compound.

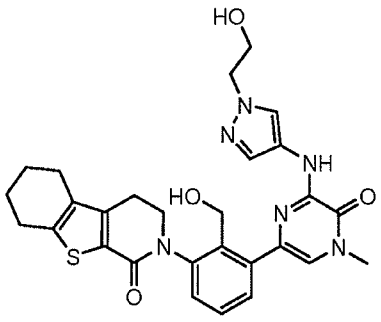
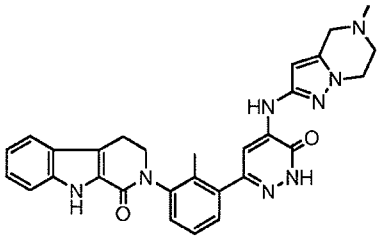
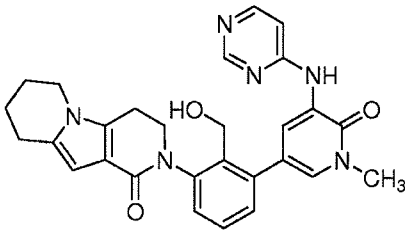
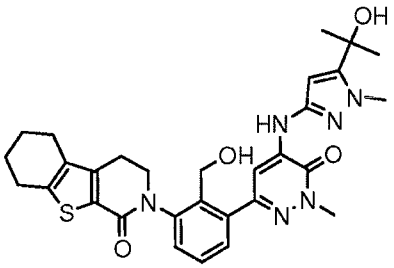
Table 1.

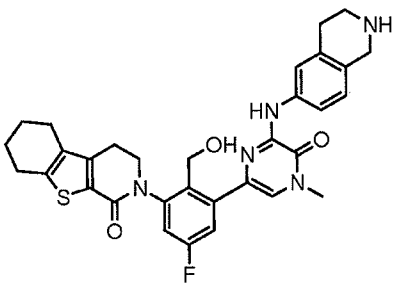
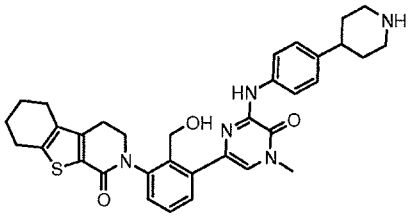
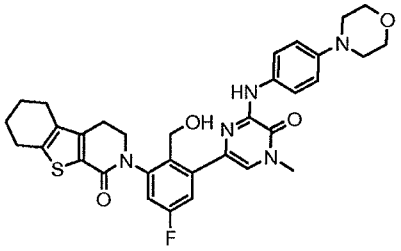
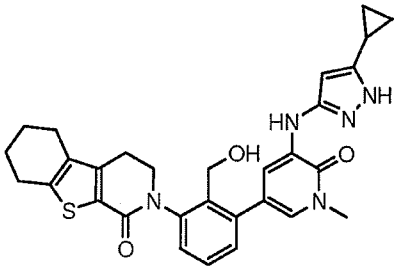
No.	Structure	Name	M+H m/z	Btk IC_{50} (μMol)
101		2-(2-methyl-3-(5-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	525.2	0.002

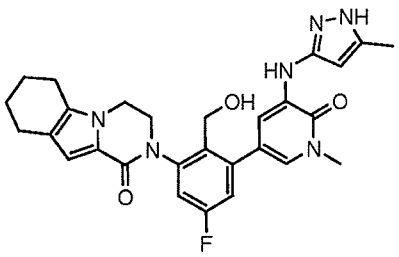
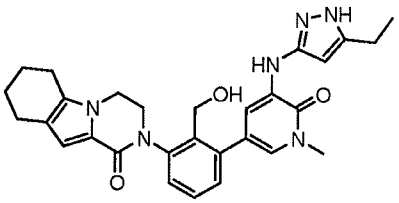
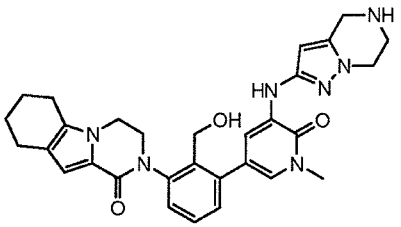
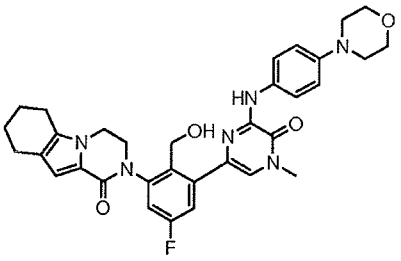
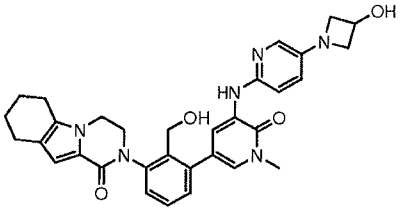
102		2-(2-methyl-3-(5-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one	521.3	0.0229
103		4-{2-Methyl-3-[1-methyl-5-({5-methyl-4H,5H,6H,7H-pyrazolo[1,5-a]pyrazin-2-yl}amino)-6-oxo-1,6-dihydropyridazin-3-yl]phenyl}-7-thia-4-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6),9,11-tetraen-5-one	538.2	3.2
104		5-[2-(Hydroxymethyl)-3-[1-methyl-6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydropyridin-3-yl]phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	514.2	0.00087
105		10-[2-(Hydroxymethyl)-3-[1-methyl-6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydropyridin-3-yl]phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.02,6]dodeca-1(8),2(6)-dien-9-one	528.2	0.010

106		2-(3-(5-(5-cyclopropyl-1H-pyrazol-3-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	525	0.0010
107		2-(2-(hydroxymethyl)-3-(1-methyl-5-(5-morpholinopyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	581	0.0101
108		2-(3-(5-(5-acetyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	582.3	0.0061
109		2-(2-(hydroxymethyl)-3-(1-methyl-6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	497.2	0.0062
110		2-(3-(5-(6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-	541.4	0.0077

		hexahydropyrazino[1,2-a]indol-1(2H)-one		
111		5-[2-(Hydroxymethyl)-3-[4-methyl-5-oxo-6-(pyridine-3-ylamino)-4,5-dihydropyrazin-2-yl]phenyl]-8-thia-5-azatricyclo[7.4.0.02,7]trideca-1(9),2(7)-dien-6-one	514.2	
112		2-(2-(hydroxymethyl)-3-(1-methyl-5-(5-methyl-1H-pyrazol-3-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	499.3	
113		2-(2-(hydroxymethyl)-3-(1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridine-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	594.3	0.005
114		2-(3-(6-(1-cyclopropyl-1H-pyrazol-4-ylamino)-4-methyl-5-oxo-4,5-dihydropyrazin-2-yl)-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	526.3	
115		5-[5-Fluoro-2-(hydroxymethyl)-3-[1-methyl-6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydropyridin-3-yl]phenyl]-8-thia-5-azatricyclo[7.4.0.02,7]trideca-1(9),2(7)-dien-	532.2	

		6-one		
116		5-[3-(6-{[1-(2-Hydroxyethyl)-1H-pyrazol-4-yl]amino}-4-methyl-5-oxo-4,5-dihydropyrazin-2-yl)-2-(hydroxymethyl)phenyl]-8-thia-5-azatricyclo[7.4.0.02,7]trideca-1(9),2(7)-dien-6-one	547.2	0.006
117		2-(2-methyl-3-(5-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-one	521.2	
118		2-(2-(hydroxymethyl)-3-(1-methyl-6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrido[3,4-b]indolizin-1(2H)-one	497.2	
119		5-[2-(hydroxymethyl)-3-(5-{[5-(2-hydroxypropan-2-yl)-1-methyl-1H-pyrazol-3-yl]amino}-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl]-8-thia-5-azatricyclo[7.4.0.02,7]trideca-1(9),2(7)-dien-6-one	575.2	0.007

120		5-[5-fluoro-2-(hydroxymethyl)-3-[4-methyl-5-oxo-6-(1,2,3,4-tetrahydroisoquinolin-6-ylamino)-4,5-dihydropyrazin-2-yl]phenyl]-8-thia-5-azatricyclo[7.4.0.02,7]trideca-1(9),2(7)-dien-6-one	586	
121		5-[2-(hydroxymethyl)-3-(4-methyl-5-oxo-6-{[4-(piperidin-4-yl)phenyl]amino}-4,5-dihydropyrazin-2-yl)phenyl]-8-thia-5-azatricyclo[7.4.0.02,7]trideca-1(9),2(7)-dien-6-one	596.3	
122		5-[5-fluoro-2-(hydroxymethyl)-3-(4-methyl-6-{[4-(morpholin-4-yl)phenyl]amino}-5-oxo-4,5-dihydropyrazin-2-yl)phenyl]-8-thia-5-azatricyclo[7.4.0.02,7]trideca-1(9),2(7)-dien-6-one	616	
123		5-(3-{5-[(5-cyclopropyl-1H-pyrazol-3-yl)amino]-1-methyl-6-oxo-1,6-dihydropyridin-3-yl}-2-(hydroxymethyl)phenyl)-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	542.1	0.003

124		5-[5-fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-[(5-methyl-1H-pyrazol-3-yl)amino]-1,2-dihydropyridin-2-one	517	
125		3-[(5-ethyl-1H-pyrazol-3-yl)amino]-5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-1,2-dihydropyridin-2-one	513.3	
126		2-(2-(Hydroxymethyl)-3-(1-methyl-6-oxo-5-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	540.3	
127		2-(5-fluoro-2-(hydroxymethyl)-3-(4-methyl-6-(4-morpholinophenylamino)-5-oxo-4,5-dihydropyrazin-2-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	599	
128		2-(3-(5-(5-(3-hydroxyazetidin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2	567.2	

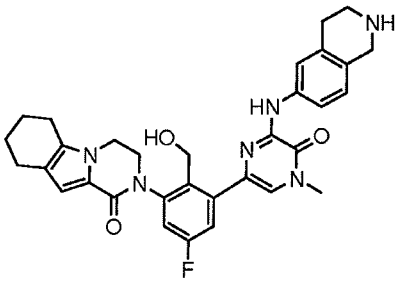
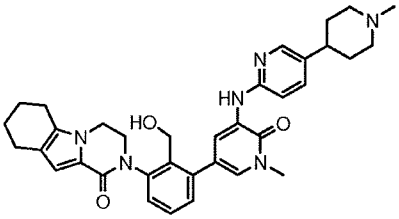
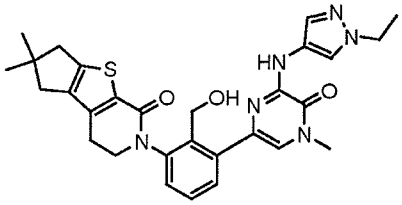
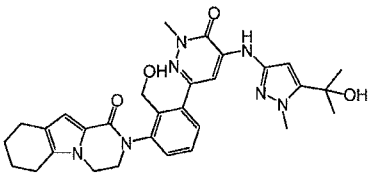
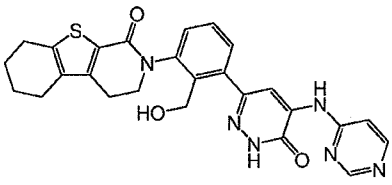
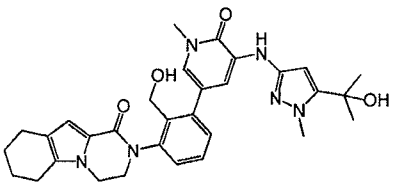
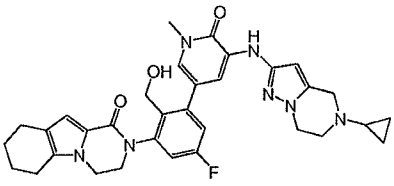
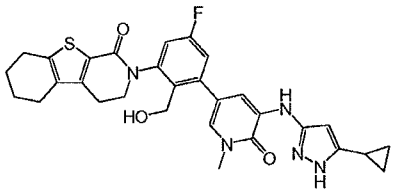
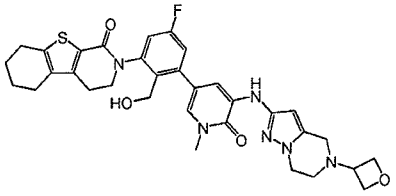
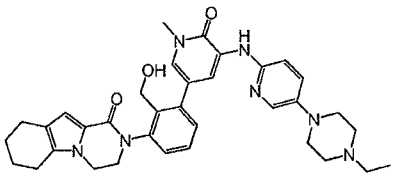
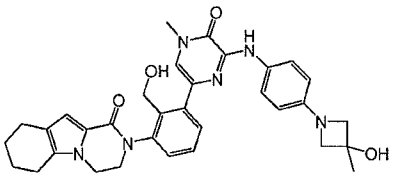
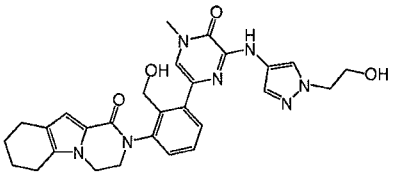
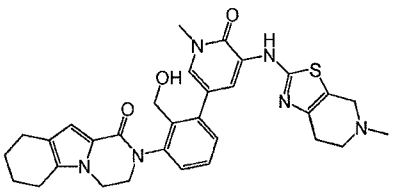
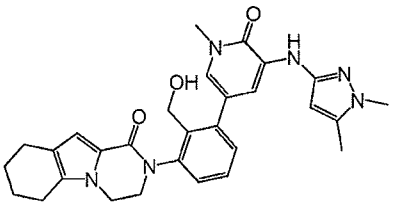
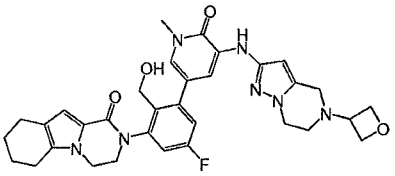
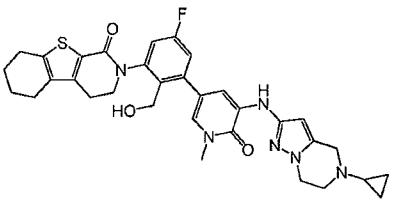
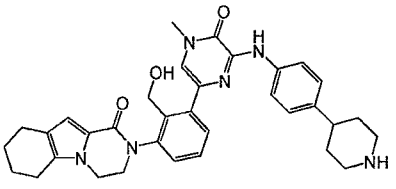
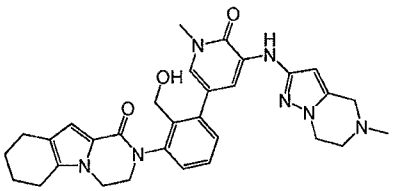
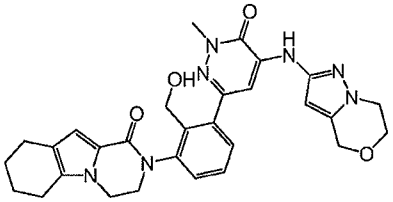
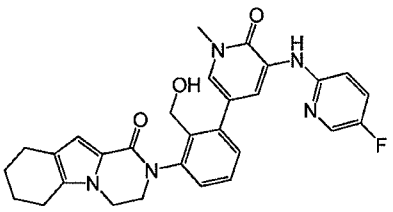
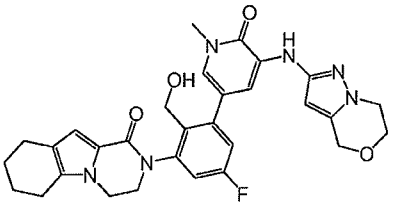
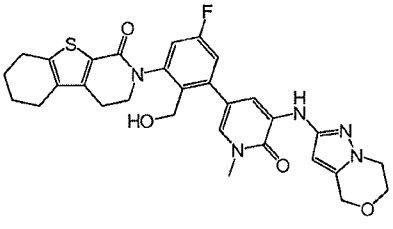
		-a]indol-1(2H)-one		
129		2-(5-fluoro-2-(hydroxymethyl)-3-(4-methyl-5-oxo-6-(1,2,3,4-tetrahydroisoquinolin-6-ylamino)-4,5-dihydropyrazin-2-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	569	
130		2-(2-(hydroxymethyl)-3-(1-methyl-5-(5-(1-methylpiperidin-4-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	593.4	
131		5-(3-(6,6-Dimethyl-3,4,6,7-tetrahydro-5*H*-cyclopenta[4,5]thieno[2,3-*c*]pyridine-1(2*H*)-yl)-2-(hydroxymethyl)phenyl)-1-methyl-3-(1-ethyl-1*H*-pyrazol-4-ylamino)pyrazin-2(1*H*)-one	545.1	0.002

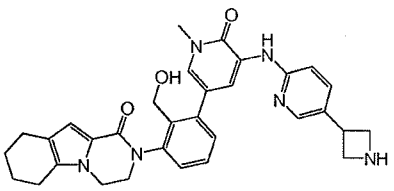
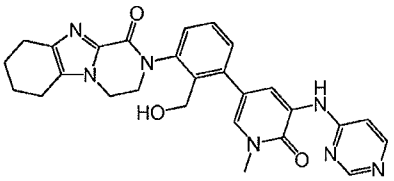
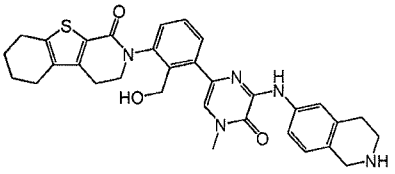
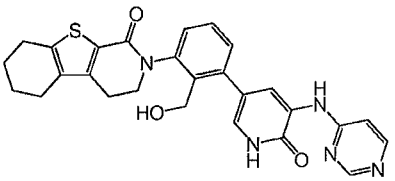
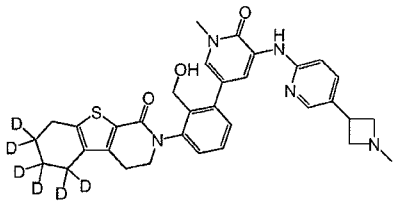
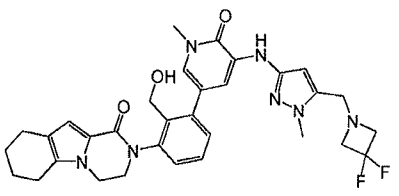
Table 2.

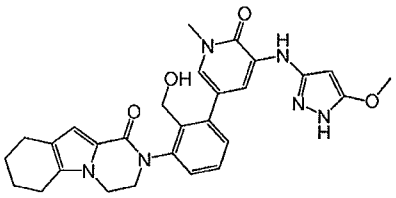
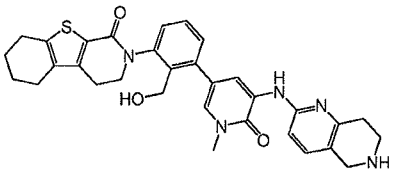
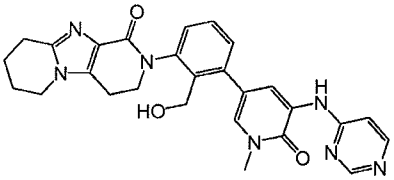
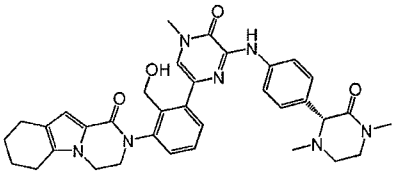
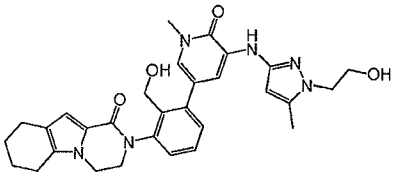
No.	Structure	Name	MH+ m/z	Btk IC_{50} (μMol)
132		2-(2-(hydroxymethyl)-3-(5-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-pyrazol-3-ylamino)-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	558.3	
133		5-[2-(hydroxymethyl)-3-[6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydropyridazin-3-yl]phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	501.1	
134		5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-3-{[5-(2-hydroxypropan-2-yl)-1-methyl-1H-pyrazol-3-yl]amino}-1-methyl-1,2-dihydropyridin-2-one	557.3	
135		3-({5-cyclopropyl-4H,5H,6H,7H-pyrazolo[1,5-a]pyrazin-2-yl}amino)-5-[5-fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-1,2-dihydropyridin-2-one	598	

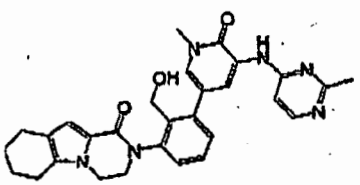
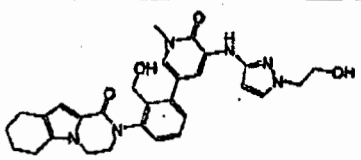
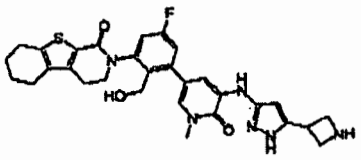
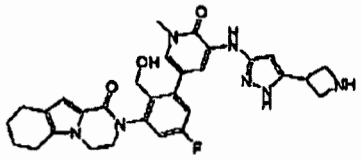
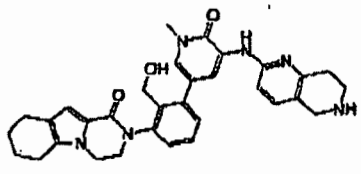
136		5-(3-{5-[(5-cyclopropyl-1H-pyrazol-3-yl)amino]-1-methyl-6-oxo-1,6-dihydropyridin-3-yl}-5-fluoro-2-(hydroxymethyl)phenyl)-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	560	
137		5-[5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[5-(oxetan-3-yl)-4H,5H,6H,7H-pyrazolo[1,5-a]pyrazin-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	631	
138		3-{[5-(4-ethylpiperazin-1-yl)pyridine-2-yl]amino}-5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-1,2-dihydropyridin-2-one	608.3	
139		3-{[4-(3-hydroxy-3-methylazetidin-1-yl)phenyl]amino}-5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-1,2-dihydropyrazin-2-one	581	
140		3-{[1-(2-hydroxyethyl)-1H-pyrazol-4-yl]amino}-5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-1,2-dihydropyrazin-2-one	529.59	

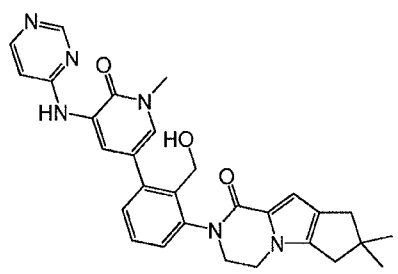
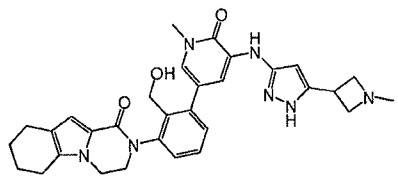
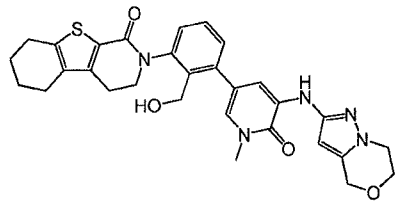
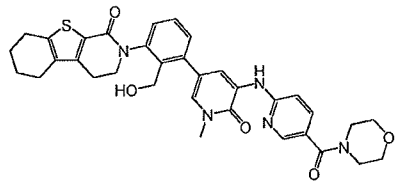
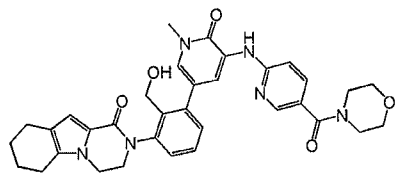
141		2-(2-(hydroxymethyl)-3-(1-methyl-5-(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	570.71	
142		3-[(1,5-dimethyl-1H-pyrazol-3-yl)amino]-5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-1,2-dihydropyridin-2-one	512.6	
143		5-[5-fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-{[5-(oxetan-3-yl)-4H,5H,6H,7H-pyrazolo[1,5-a]pyrazin-2-yl]amino}-1,2-dihydropyridin-2-one	613.68	
144		5-{3-[5-({5-cyclopropyl-4H,5H,6H,7H-pyrazolo[1,5-a]pyrazin-2-yl}amino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl]-5-fluoro-2-(hydroxymethyl)phenyl}-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	614.73	
145		5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-{[4-(piperidin-4-yl)phenyl]amino}-1,2-dihydropyrazin-2-one	579.4	

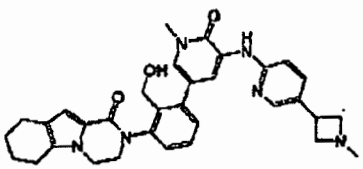
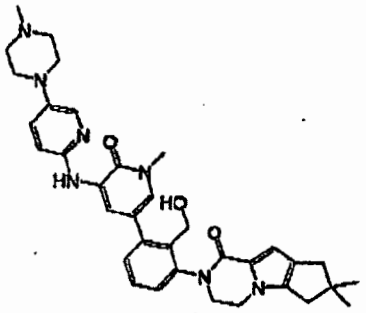
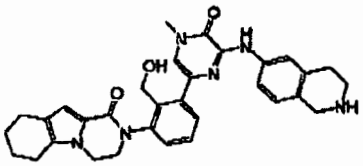
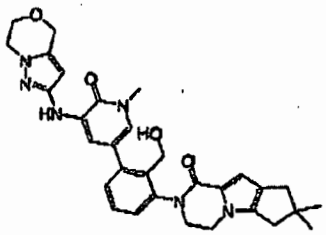
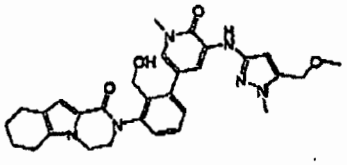
146		5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-({5-methyl-4H,5H,6H,7H-pyrazolo[1,5-a]pyrazin-2-yl}amino)-1,2-dihydropyridin-2-one	554	
147		6-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-2-methyl-4-{4H,6H,7H-pyrazolo[3,2-c][1,4]oxazin-2-ylamino}-2,3-dihydropyridazin-3-one	542	
148		3-[(5-fluoropyridin-2-yl)amino]-5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-1,2-dihydropyridin-2-one	514	
149		5-[5-fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-{4H,6H,7H-pyrazolo[3,2-c][1,4]oxazin-2-ylamino}-1,2-dihydropyridin-2-one	559	0.005
150		5-[5-fluoro-2-(hydroxymethyl)-3-(1-methyl-6-oxo-5-{4H,6H,7H-pyrazolo[3,2-c][1,4]oxazin-2-ylamino}-1,6-dihydropyridin-3-yl)phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	576	

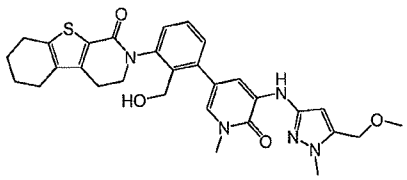
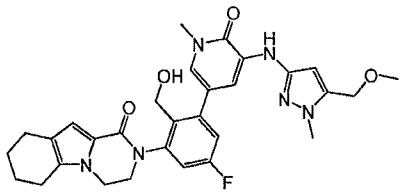
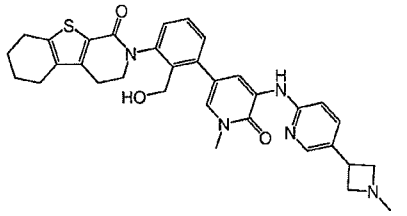
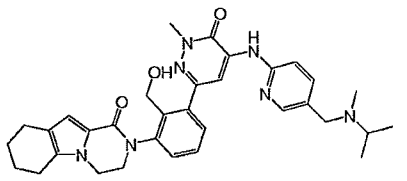
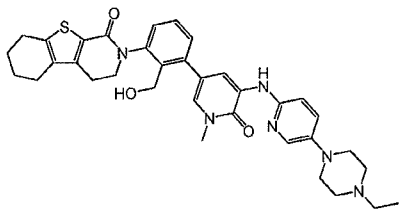
151		3-{[5-(azetidin-3-yl)pyridine-2-yl]amino}-5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-1,2-dihydropyridin-2-one	551.3	
152		11-[2-(hydroxymethyl)-3-[1-methyl-6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydropyridin-3-yl]phenyl]-1,8,11-triazatricyclo[7.4.0.0^{2,7}]trideca-2(7),8-dien-10-one	498.2	
153		5-[2-(hydroxymethyl)-3-[4-methyl-5-oxo-6-(1,2,3,4-tetrahydroisoquinolin-6-ylamino)-4,5-dihydropyrazin-2-yl]phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	568.1	
154		5-[2-(hydroxymethyl)-3-[6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydropyridin-3-yl]phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	500.1	
155		11,11,12,12,13,13-hexahydrogenio-5-[2-(hydroxymethyl)-3-(1-methyl-5-{[5-(1-methylazetidin-3-yl)pyridine-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	588.2	
156		3-({5-[(3,3-difluoroazetidin-1-yl)methyl]-1-methyl-1H-pyrazol-3-yl}amino)-5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-	604.4	

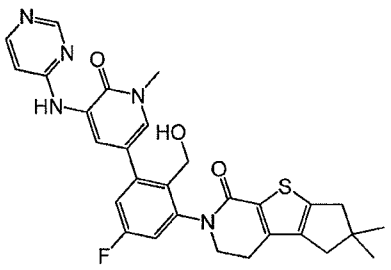
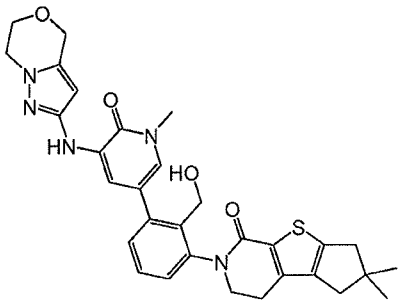
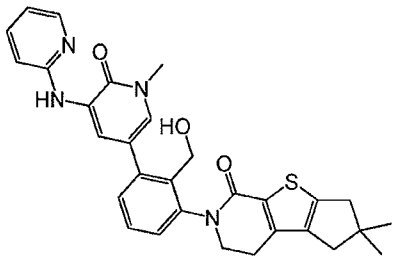
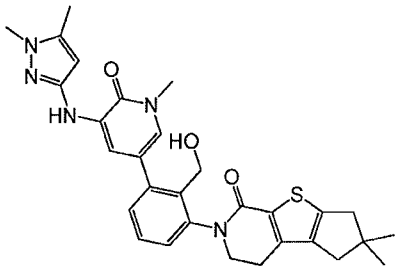
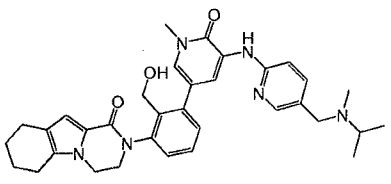
		yl}phenyl]-1-methyl-1,2-dihydropyridin-2-one		
157		5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-3-[(5-methoxy-1H-pyrazol-3-yl)amino]-1-methyl-1,2-dihydropyridin-2-one	515.4	
158		5-[2-(hydroxymethyl)-3-[1-methyl-6-oxo-5-(5,6,7,8-tetrahydro-1,6-naphthyridin-2-ylamino)-1,6-dihydropyridin-3-yl]phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	568.3	
159		5-[2-(hydroxymethyl)-3-[1-methyl-6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydropyridin-3-yl]phenyl]-1,5,8-triazatricyclo[7.4.0.0^{2,7}]trideca-2(7),8-dien-6-one	498.2	
160		3-({4-[(2R)-1,4-dimethyl-3-oxopiperazin-2-yl]phenyl}amino)-5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-1,2-dihydropyrazin-2-one	622.4	
161		3-{[1-(2-hydroxyethyl)-5-methyl-1H-pyrazol-3-yl]amino}-5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-1,2-dihydropyridin-2-one	543	

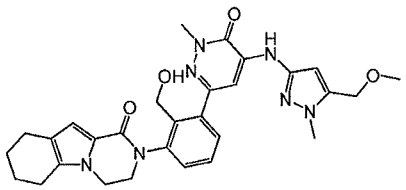
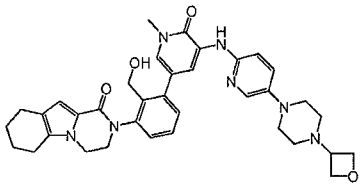
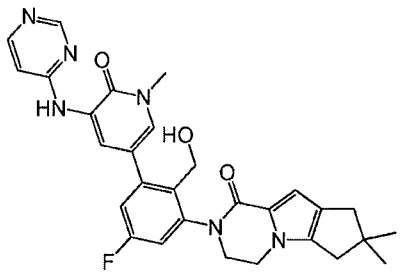
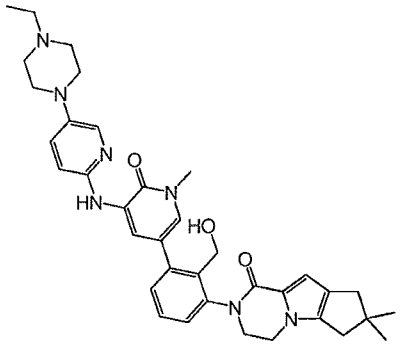
162		5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-[(2-methylpyrimidin-4-yl)amino]-1,2-dihydropyridin-2-one	511	
163		3-{[1-(2-hydroxyethyl)-1H-pyrazol-3-yl]amino}-5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-1,2-dihydropyridin-2-one	529	
164		5-[3-(5-{[5-(azetidin-3-yl)-1H-pyrazol-3-yl]amino}-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-(hydroxymethyl)phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	575	
165		3-{[5-(azetidin-3-yl)-1H-pyrazol-3-yl]amino}-5-[5-fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-1,2-dihydropyridin-2-one	558	
166		5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-(5,6,7,8-tetrahydro-1,6-naphthyridin-2-ylamino)-1,2-dihydropyridin-2-one	551.3	

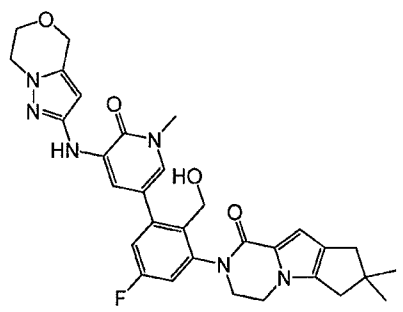
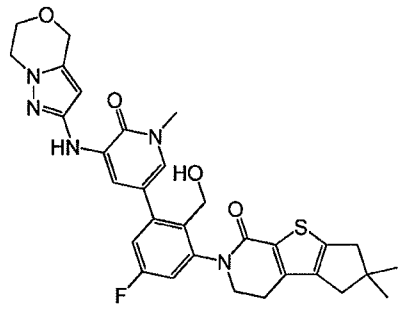
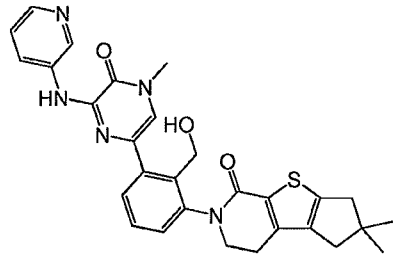
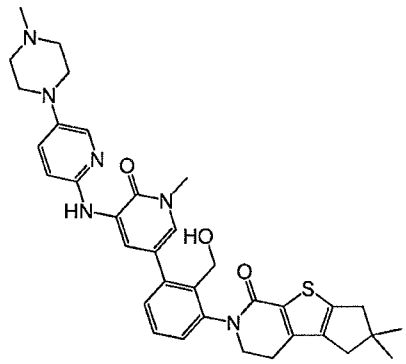
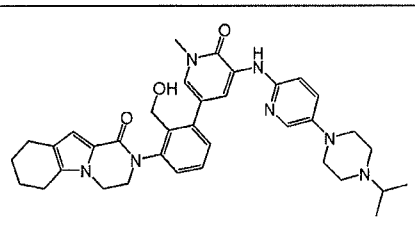
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168		5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-{[5-(1-methylazetidin-3-yl)-1H-pyrazol-3-yl]amino}-1,2-dihydropyridin-2-one	554	
169		5-[2-(hydroxymethyl)-3-(1-methyl-6-oxo-5-{4H,6H,7H-pyrazolo[3,2-c][1,4]oxazin-2-ylamino}-1,6-dihydropyridin-3-yl)phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	558	
170		5-[2-(hydroxymethyl)-3-(1-methyl-5-{[5-(morpholin-4-ylcarbonyl)pyridine-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	626	
171		5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-{[5-(morpholin-4-ylcarbonyl)pyridine-2-yl]amino}-1,2-dihydropyridin-2-one	609	

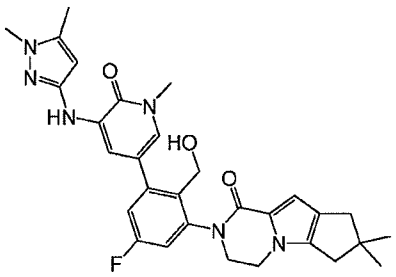
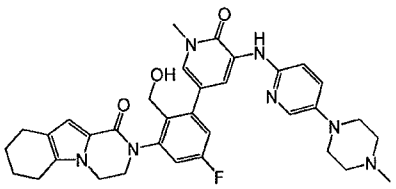
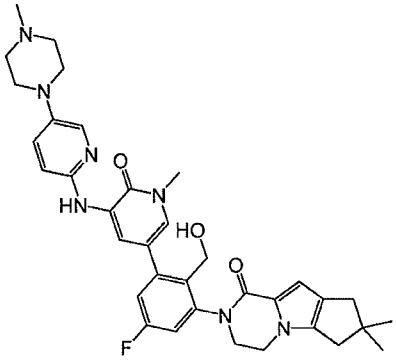
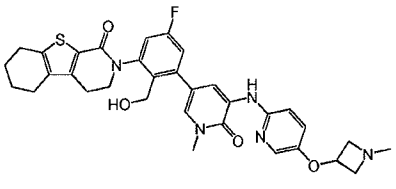
172		5-[2-(hydroxymethyl)-3-(1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-{[5-(1-methylazetidin-3-yl)pyridine-2-yl]amino}-1,2-dihydropyridin-2-one	565	
173		10-[2-(hydroxymethyl)-3-(1-methyl-5-{[5-(4-methylpiperazin-1-yl)pyridine-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one	608.4	
174		5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-(1,2,3,4-tetrahydroisoquinolin-6-ylamino)-1,2-dihydropyrazin-2-one	551.4	
175		10-[2-(hydroxymethyl)-3-(1-methyl-6-oxo-5-{4H,6H,7H-pyrazolo[3,2-c][1,4]oxazin-2-ylamino}-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one	555.3	
176		5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-3-{[5-(methoxymethyl)-1-methyl-1H-pyrazol-3-yl]amino}-1-methyl-1,2-dihydropyridin-2-one	543	

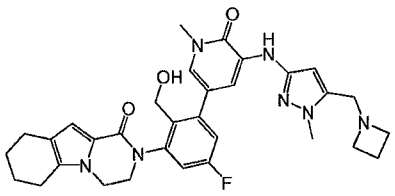
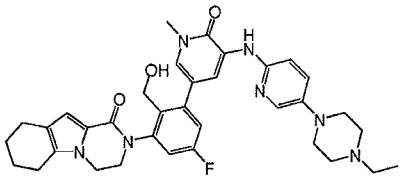
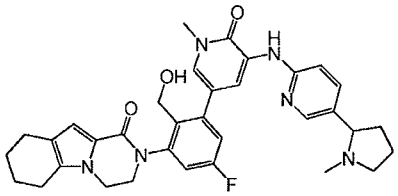
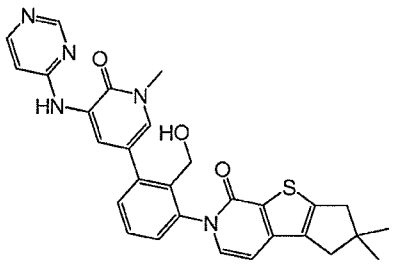
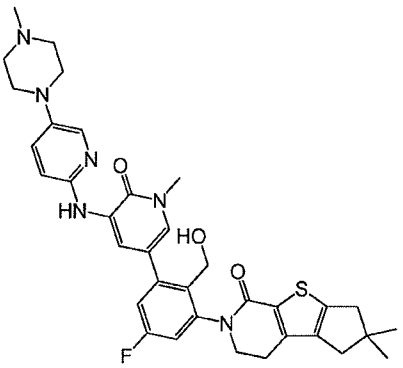
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177		5-[2-(hydroxymethyl)-3-(5-{[5-(methoxymethyl)-1-methyl-1H-pyrazol-3-yl]amino}-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	560	
178		5-[5-fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-3-{[5-(methoxymethyl)-1-methyl-1H-pyrazol-3-yl]amino}-1-methyl-1,2-dihydropyridin-2-one	561	
179		5-[2-(hydroxymethyl)-3-(1-methyl-5-{[5-(1-methylazetidin-3-yl)pyridine-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	582	
180		6-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-2-methyl-4-[(5-{[methyl(propan-2-yl)amino]methyl}pyridine-2-yl)amino]-2,3-dihydropyridazin-3-one	582.5	
181		5-[3-(5-{[5-(4-ethylpiperazin-1-yl)pyridine-2-yl]amino}-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-(hydroxymethyl)phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	625.4	

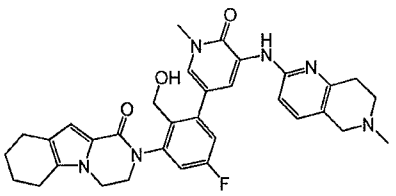
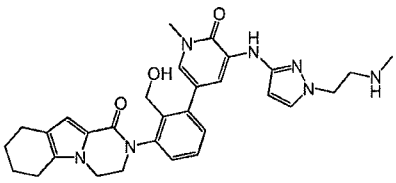
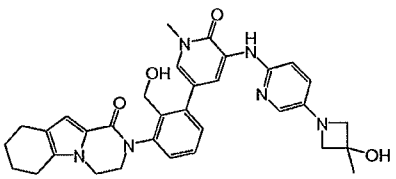
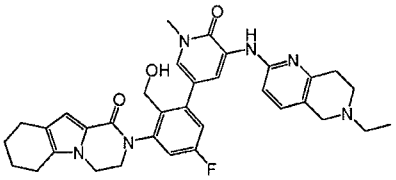
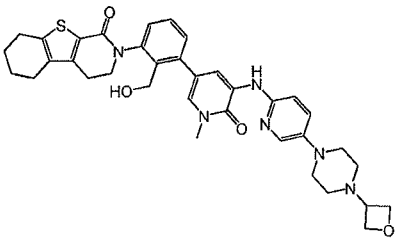
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183		10-[2-(hydroxymethyl)-3-(1-methyl-6-oxo-5-{4H,6H,7H-pyrazolo[3,2-c][1,4]oxazin-2-ylamino}-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one	572.3	
184		10-[2-(hydroxymethyl)-3-[1-methyl-6-oxo-5-(pyridine-2-ylamino)-1,6-dihydropyridin-3-yl]phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one	527.2	
185		10-(3-{5-[(1,5-dimethyl-1H-pyrazol-3-yl)amino]-1-methyl-6-oxo-1,6-dihydropyridin-3-yl}-2-(hydroxymethyl)phenyl)-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one	544.2	
186		5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-[(5-{[methyl(propan-2-yl)amino]methyl}pyridine-2-yl)amino]-1,2-dihydropyridin-2-one	581.4	

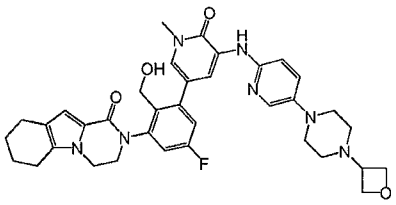
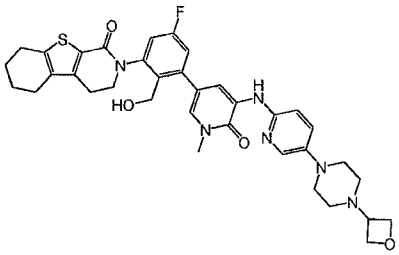
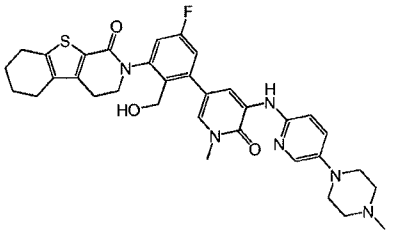
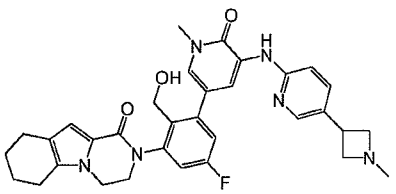
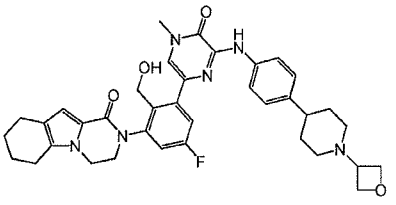
187		6-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-4-{[5-(methoxymethyl)-1-methyl-1H-pyrazol-3-yl]amino}-2-methyl-2,3-dihydropyridazin-3-one	544	
188		5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-({5-[4-(oxetan-3-yl)piperazin-1-yl]pyridine-2-yl}amino)-1,2-dihydropyridin-2-one	636	
189		10-[5-fluoro-2-(hydroxymethyl)-3-[1-methyl-6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydropyridin-3-yl]phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one	529.7	
190		10-[3-(5-{[5-(4-ethylpiperazin-1-yl)pyridine-2-yl]amino}-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-(hydroxymethyl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one	622.5	

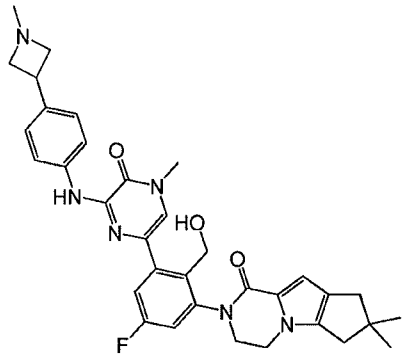
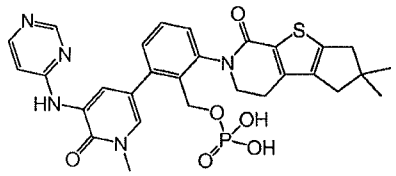
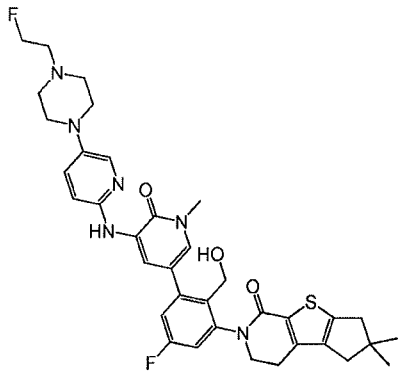
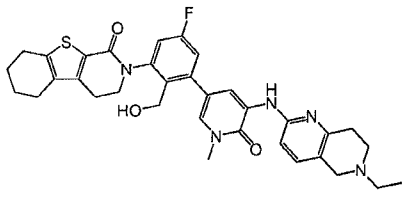
191		10-[5-fluoro-2-(hydroxymethyl)-3-(1-methyl-6-oxo-5-{4H,6H,7H-pyrazolo[3,2-c][1,4]oxazin-2-ylamino}-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one	573.4	
192		10-[5-fluoro-2-(hydroxymethyl)-3-(1-methyl-6-oxo-5-{4H,6H,7H-pyrazolo[3,2-c][1,4]oxazin-2-ylamino}-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one	590.2	
193		10-[2-(hydroxymethyl)-3-[4-methyl-5-oxo-6-(pyridine-3-ylamino)-4,5-dihydropyrazin-2-yl]phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one	528.2	
194		10-[2-(hydroxymethyl)-3-(1-methyl-5-{[5-(4-methylpiperazin-1-yl)pyridine-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one	625.3	
195		5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-({5-[4-(propan-2-yl)piperazin-1-yl]pyridine-2-yl}amino)-1,2-	622	

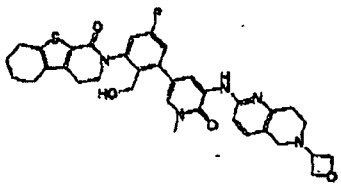
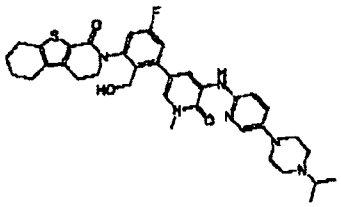
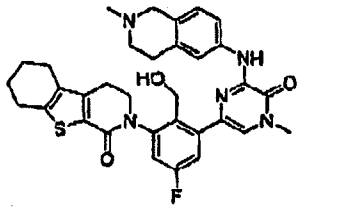
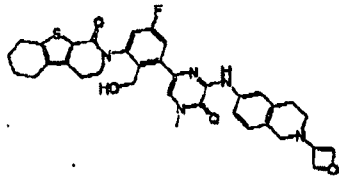
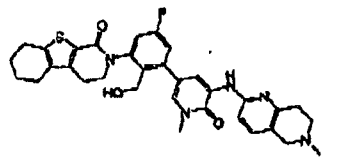
		dihydropyridin-2-one		
196		10-(3-{5-[(1,5-dimethyl-1H-pyrazol-3-yl)amino]-1-methyl-6-oxo-1,6-dihydropyridin-3-yl}-5-fluoro-2-(hydroxymethyl)phenyl)-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one	545.4	
197		2-(5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridine-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	612.5	0.002
198		10-[5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[5-(4-methylpiperazin-1-yl)pyridine-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one	626	
199		5-[5-fluoro-2-(hydroxymethyl)-3-[1-methyl-5-({5-[(1-methylazetidin-3-yl)oxy]pyridine-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	616	

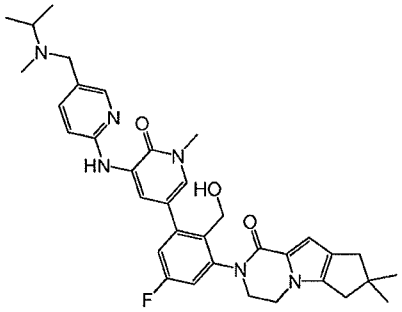
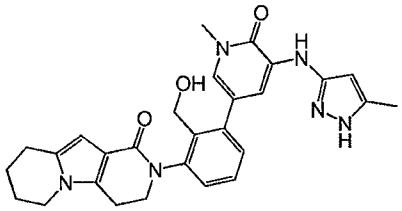
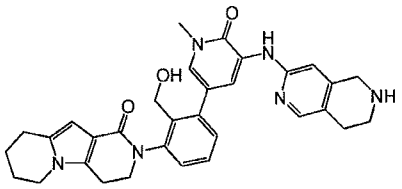
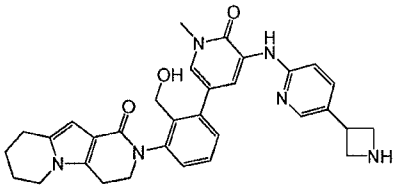
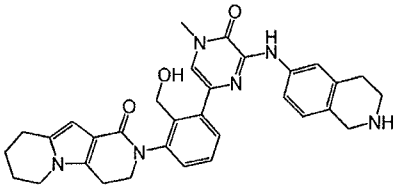
200		3-{[5-(azetidin-1-ylmethyl)-1-methyl-1H-pyrazol-3-yl]amino}-5-[5-fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-1,2-dihydropyridin-2-one	586.5	
201		3-{[5-(4-ethylpiperazin-1-yl)pyridine-2-yl]amino}-5-[5-fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-1,2-dihydropyridin-2-one	626.4	
202		5-[5-fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-{[5-(1-methylpyrrolidin-2-yl)pyridine-2-yl]amino}-1,2-dihydropyridin-2-one	597.4	
203		10-[2-(hydroxymethyl)-3-[1-methyl-6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydropyridin-3-yl]phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6),11-trien-9-one	526.2	
204		10-[5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[5-(4-methylpiperazin-1-yl)pyridine-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one	643.3	

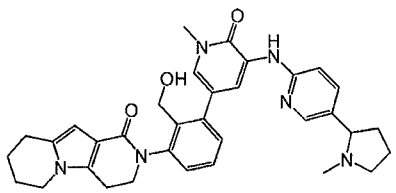
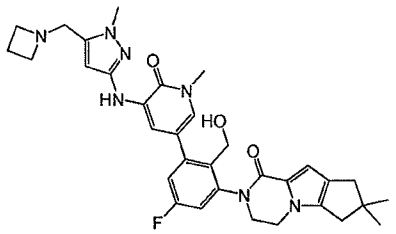
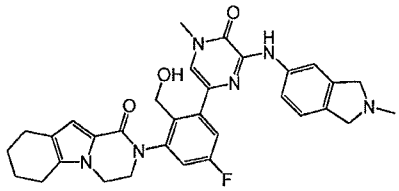
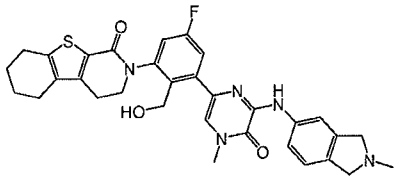
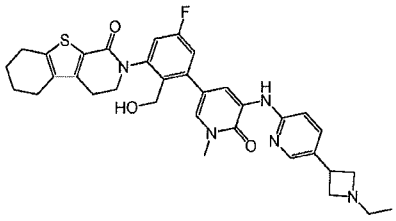
205		5-[5-fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-[(6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-2-yl)amino]-1,2-dihydropyridin-2-one	583	
206		5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-({1-[2-(methylamino)ethyl]-1H-pyrazol-3-yl}amino)-1,2-dihydropyridin-2-one	542	
207		3-{[5-(3-hydroxy-3-methylazetidin-1-yl)pyridine-2-yl]amino}-5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-1,2-dihydropyridin-2-one	581	
208		3-[(6-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-2-yl)amino]-5-[5-fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-1,2-dihydropyridin-2-one	597	
209		5-[2-(hydroxymethyl)-3-[1-methyl-5-({5-[4-(oxetan-3-yl)piperazin-1-yl]pyridine-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	653	

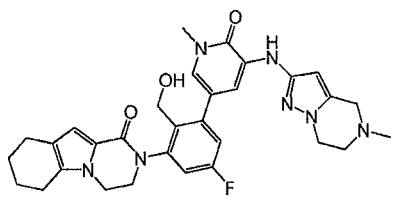
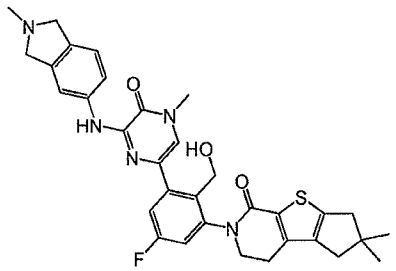
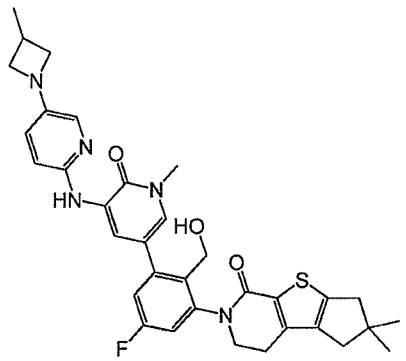
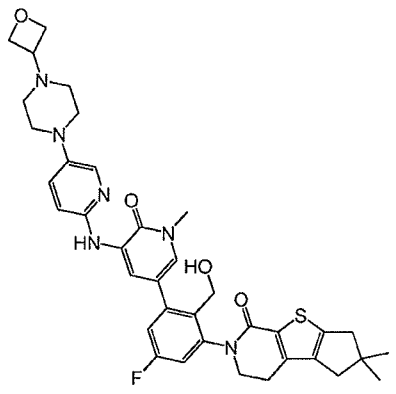
210		2-(5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(4-(oxetan-3-yl)piperazin-1-yl)pyridine-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	654	0.0039
211		5-[5-fluoro-2-(hydroxymethyl)-3-[1-methyl-5-({5-[4-(oxetan-3-yl)piperazin-1-yl]pyridine-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	671	
212		2-(5-Fluoro-2-hydroxymethyl-3-{1-methyl-5-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-3,4,5,6,7,8-hexahydro-2H-benzo[4,5]thieno[2,3-c]pyridine-1-one	629	0.0010
213		5-[5-fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-{[5-(1-methylazetidin-3-yl)pyridine-2-yl]amino}-1,2-dihydropyridin-2-one	583	
214		5-[5-fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-({4-[1-(oxetan-3-yl)piperidin-4-yl]phenyl}amino)-1,2-dihydropyrazin-2-one	653.6	

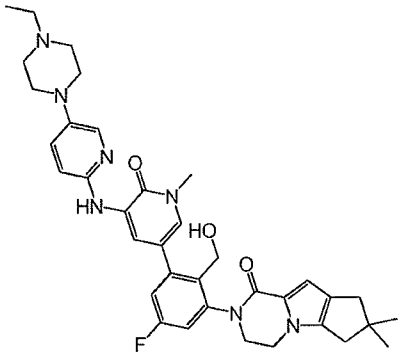
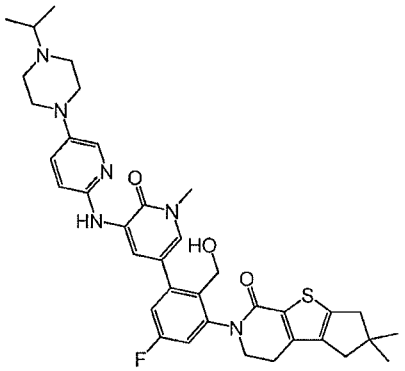
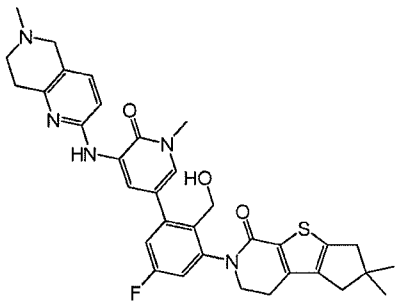
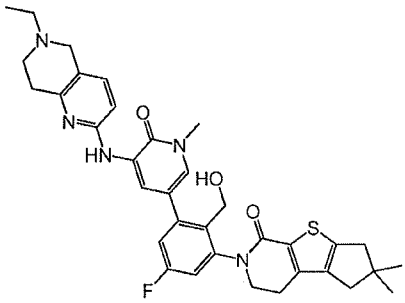
215		10-[5-fluoro-2-(hydroxymethyl)-3-(4-methyl-6-{[4-(1-methylazetidin-3-yl)phenyl]amino}-5-oxo-4,5-dihydropyrazin-2-yl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one	597.5	
216		[(2-{4,4-dimethyl-9-oxo-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-10-yl}-6-[1-methyl-6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydropyridin-3-yl]phenyl)methoxy]phosphonic acid	608.2	
217		10-{5-fluoro-3-[5-({5-[4-(2-fluoroethyl)piperazin-1-yl]pyridine-2-yl}amino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl]-2-(hydroxymethyl)phenyl}-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one	675.3	
218		5-(3-{5-[(6-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-2-yl)amino]-1-methyl-6-oxo-1,6-dihydropyridin-3-yl}-5-fluoro-2-(hydroxymethyl)phenyl)-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	614	

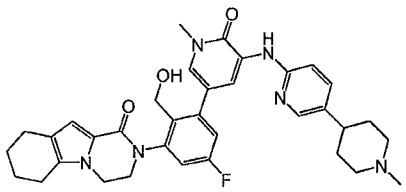
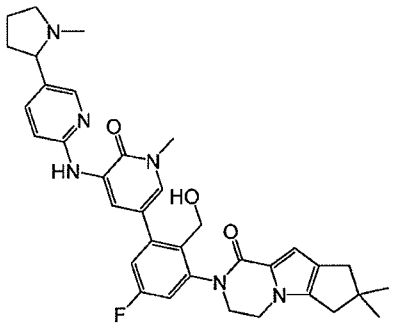
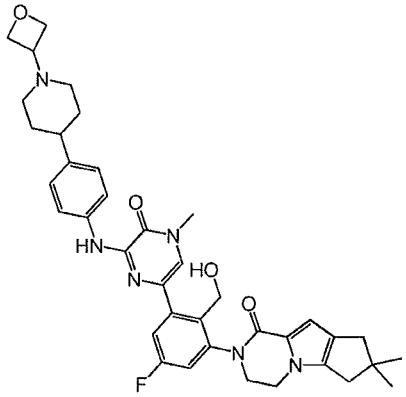
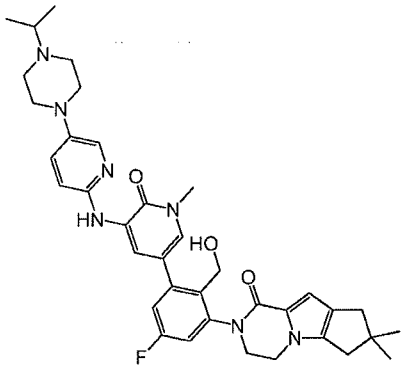
219		5-[5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[6-(oxetan-3-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	642	
220		5-[5-fluoro-2-(hydroxymethyl)-3-{1-methyl-6-oxo-5-({5-[4-(propan-2-yl)piperazin-1-yl]pyridine-2-yl}amino)-1,6-dihydropyridin-3-yl]phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	657	
221		5-[5-Fluoro-2-(hydroxymethyl)-3-{4-methyl-6-[(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)amino]-5-oxo-4,5-dihydropyrazin-2-yl}phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	600	
222		5-[5-fluoro-2-(hydroxymethyl)-3-(4-methyl-6-{[2-(oxetan-3-yl)-1,2,3,4-tetrahydroisoquinolin-6-yl]amino}-5-oxo-4,5-dihydropyrazin-2-yl)phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	642	
223		5-[5-fluoro-2-(hydroxymethyl)-3-{1-methyl-5-[(6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-2-yl)amino]-6-oxo-1,6-dihydropyridin-3-yl}phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	600	

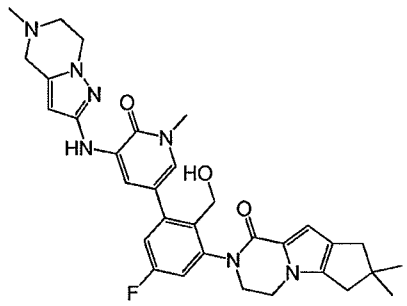
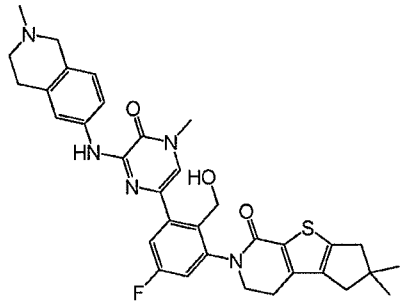
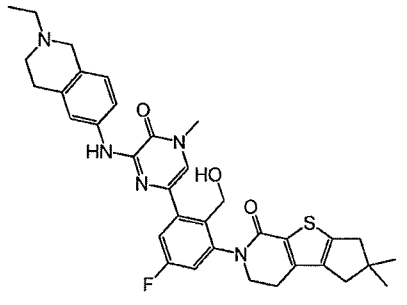
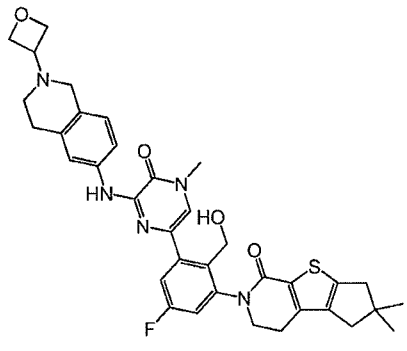
224		10-[5-fluoro-2-(hydroxymethyl)-3-{1-methyl-5-[(5-{[methyl(propan-2-yl)amino]methyl}pyridine-2-yl)amino]-6-oxo-1,6-dihydropyridin-3-yl}phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one	613.6	
225		5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrido[3,4-b]indolizin-2-yl}phenyl]-1-methyl-3-[(5-methyl-1H-pyrazol-3-yl)amino]-1,2-dihydropyridin-2-one	499.2	
226		5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrido[3,4-b]indolizin-2-yl}phenyl]-1-methyl-3-(5,6,7,8-tetrahydro-2,6-naphthyridin-3-ylamino)-1,2-dihydropyridin-2-one	551.2	
227		3-{[5-(azetidin-3-yl)pyridine-2-yl]amino}-5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrido[3,4-b]indolizin-2-yl}phenyl]-1-methyl-1,2-dihydropyridin-2-one	551.2	
228		5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrido[3,4-b]indolizin-2-yl}phenyl]-1-methyl-3-(1,2,3,4-tetrahydroisoquinolin-6-ylamino)-1,2-dihydropyrazin-2-one	551.2	

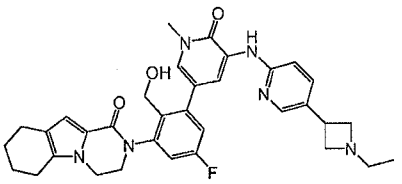
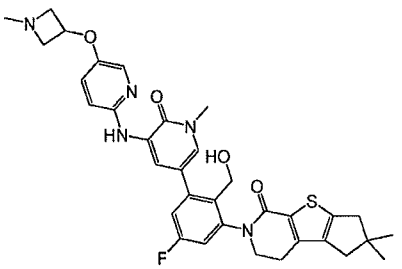
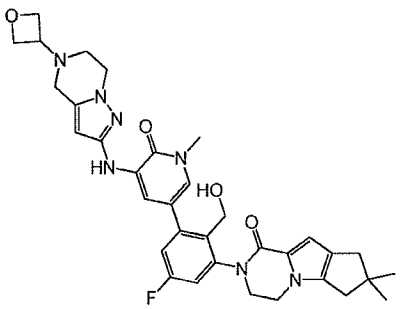
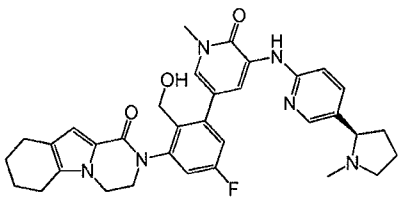
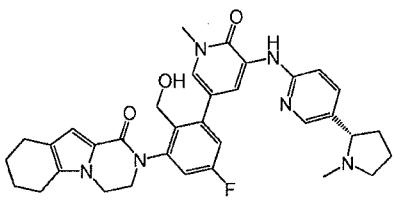
229		5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrido[3,4-b]indolizin-2-yl}phenyl]-1-methyl-3-{[5-(1-methylpyrrolidin-2-yl)pyridine-2-yl]amino}-1,2-dihydropyridin-2-one	579.2	
230		10-[3-(5-{[5-(azetidin-1-ylmethyl)-1-methyl-1H-pyrazol-3-yl]amino}-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-(hydroxymethyl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one	600.6	
231		5-[5-fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-[(2-methyl-2,3-dihydro-1H-isoindol-5-yl)amino]-1,2-dihydropyrazin-2-one	569	
232		5-[5-fluoro-2-(hydroxymethyl)-3-{4-methyl-6-[(2-methyl-2,3-dihydro-1H-isoindol-5-yl)amino]-5-oxo-4,5-dihydropyrazin-2-yl}phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	586	
233		5-[3-(5-{[5-(1-ethylazetidin-3-yl)pyridine-2-yl]amino}-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-(hydroxymethyl)phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	614	

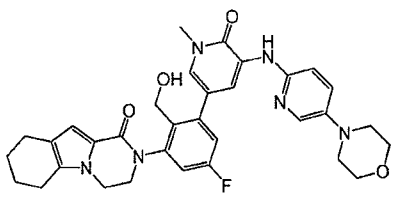
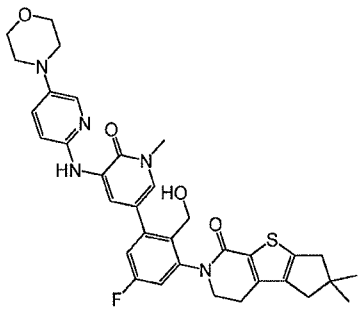
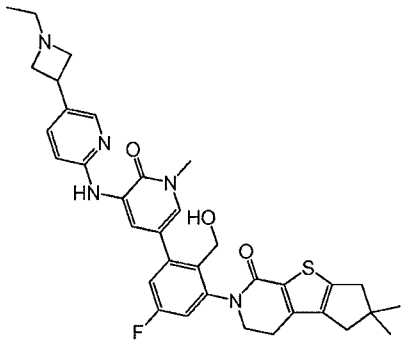
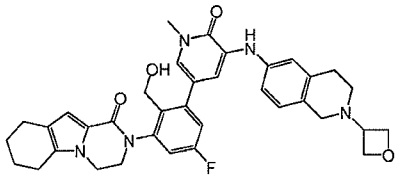
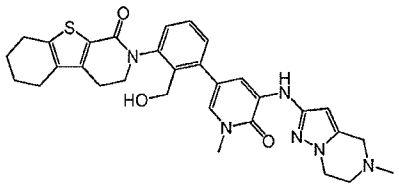
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235		10-[5-fluoro-2-(hydroxymethyl)-3-{4-methyl-6-[(2-methyl-2,3-dihydro-1H-isoindol-5-yl)amino]-5-oxo-4,5-dihydropyrazin-2-yl}phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one	600.2	
236		10-[5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[5-(3-methylazetidin-1-yl)pyridine-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one	614.3	
237		10-[5-fluoro-2-(hydroxymethyl)-3-[1-methyl-5-({5-[4-(oxetan-3-yl)piperazin-1-yl]pyridine-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one	685.4	

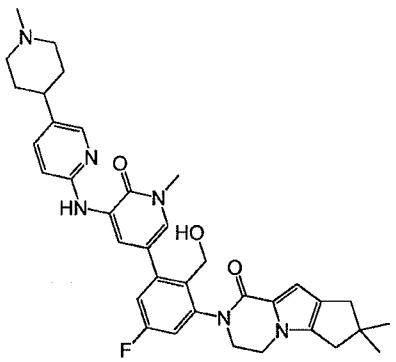
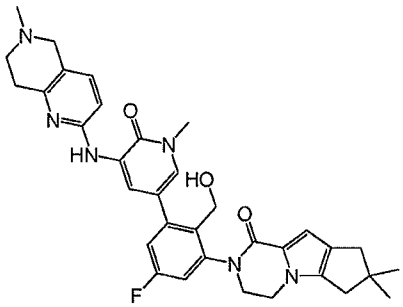
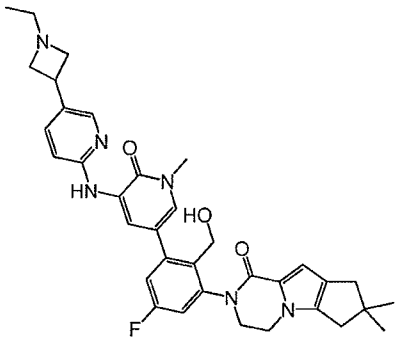
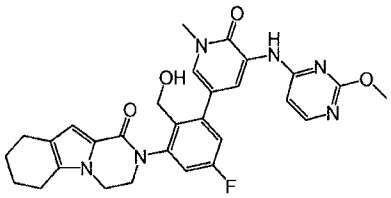
238		10-[3-(5-{[5-(4-ethylpiperazin-1-yl)pyridine-2-yl]amino}-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-(hydroxymethyl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one	640.6	
239		10-[5-fluoro-2-(hydroxymethyl)-3-[1-methyl-6-oxo-5-({5-[4-(propan-2-yl)piperazin-1-yl]pyridine-2-yl}amino)-1,6-dihydropyridin-3-yl]phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one	671.3	
240		10-[5-fluoro-2-(hydroxymethyl)-3-{1-methyl-5-[(6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-2-yl)amino]-6-oxo-1,6-dihydropyridin-3-yl}phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one	614.3	
241		10-(3-{5-[(6-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-2-yl)amino]-1-methyl-6-oxo-1,6-dihydropyridin-3-yl}-5-fluoro-2-(hydroxymethyl)phenyl)-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one	628.3	

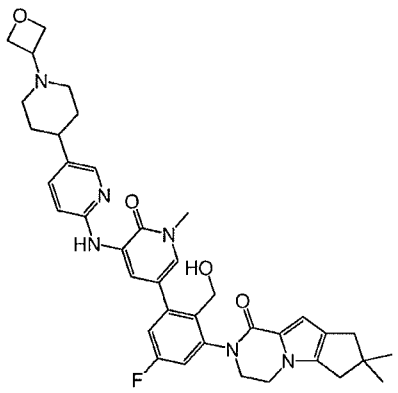
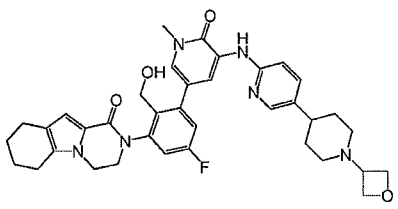
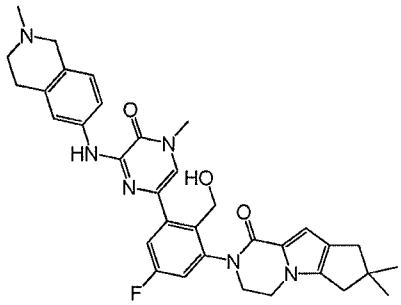
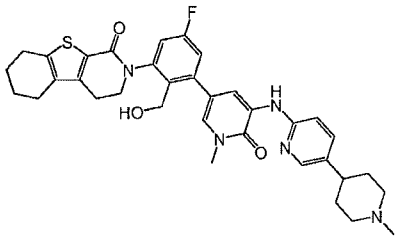
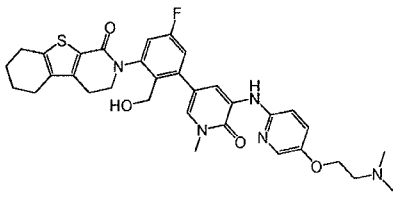
242		5-[5-fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-{[5-(1-methylpiperidin-4-yl)pyridine-2-yl]amino}-1,2-dihydropyridin-2-one	611.5	
243		10-[5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[5-(1-methylpyrrolidin-2-yl)pyridine-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one	611.5	
244		10-[5-fluoro-2-(hydroxymethyl)-3-[4-methyl-6-({4-[1-(oxetan-3-yl)piperidin-4-yl]phenyl}amino)-5-oxo-4,5-dihydropyrazin-2-yl]phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one	667.6	
245		10-[5-fluoro-2-(hydroxymethyl)-3-[1-methyl-6-oxo-5-({5-[4-(propan-2-yl)piperazin-1-yl]pyridine-2-yl}amino)-1,6-dihydropyridin-3-yl]phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one	654.6	

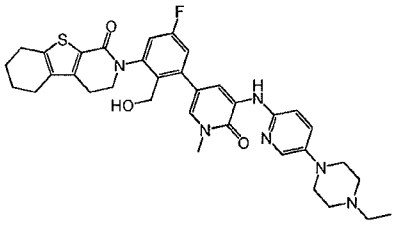
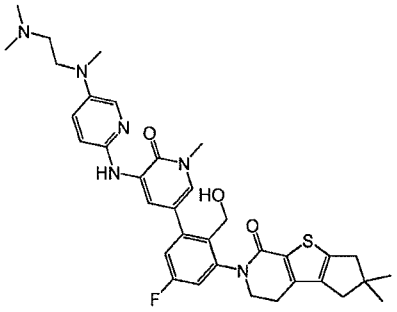
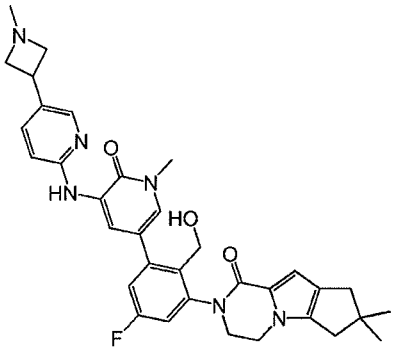
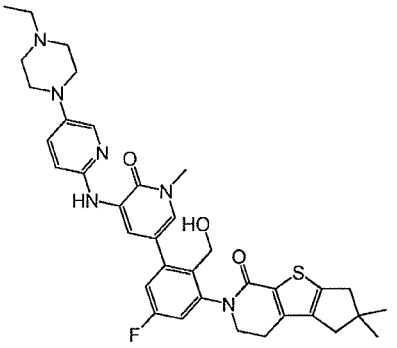
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247		10-[5-fluoro-2-(hydroxymethyl)-3-{4-methyl-6-[(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)amino]-5-oxo-4,5-dihydropyrazin-2-yl}phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one	614	
248		10-(3-{6-[(2-ethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)amino]-4-methyl-5-oxo-4,5-dihydropyrazin-2-yl}-5-fluoro-2-(hydroxymethyl)phenyl)-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one	628	
249		10-[5-fluoro-2-(hydroxymethyl)-3-(4-methyl-6-{[2-(oxetan-3-yl)-1,2,3,4-tetrahydroisoquinolin-6-yl]amino}-5-oxo-4,5-dihydropyrazin-2-yl)phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one	656	

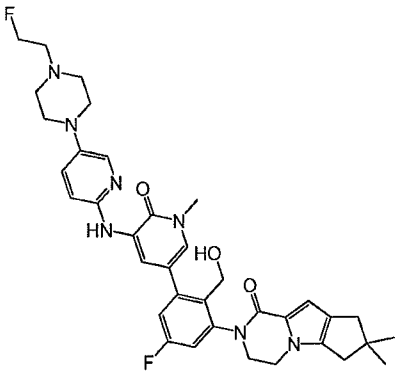
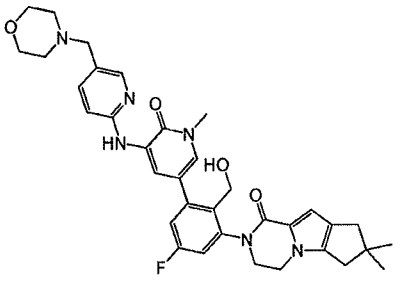
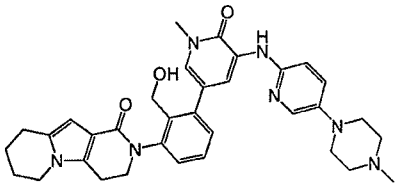
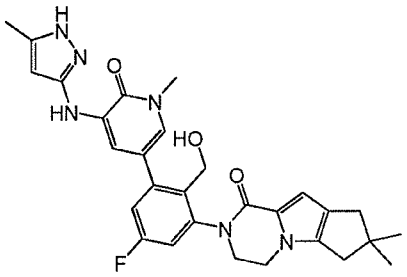
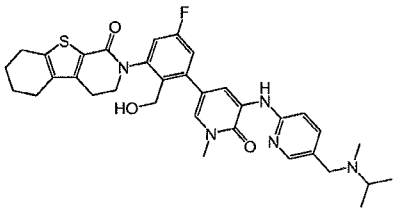
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251		10-[5-fluoro-2-(hydroxymethyl)-3-[1-methyl-5-({5-[(1-methylazetidin-3-yl)oxy]pyridine-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one	630.3	
252		10-[5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[5-(oxetan-3-yl)-4H,5H,6H,7H-pyrazolo[1,5-a]pyrazin-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one	628.5	
253		5-[5-fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-({5-[(2R)-1-methylpyrrolidin-2-yl]pyridine-2-yl}amino)-1,2-dihydropyridin-2-one	597.4	
254		5-[5-fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-({5-[(2S)-1-methylpyrrolidin-2-yl]pyridine-2-yl}amino)-1,2-dihydropyridin-2-one	597.4	

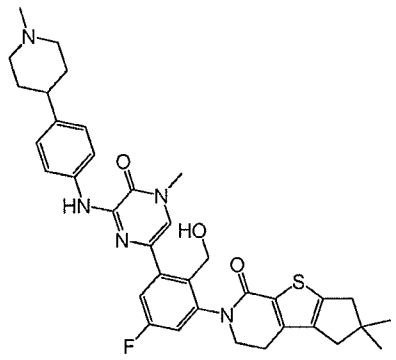
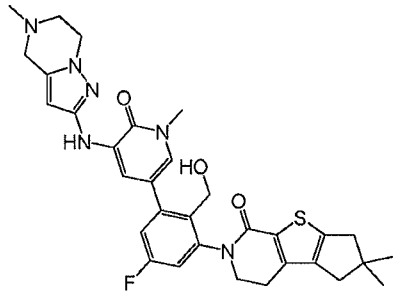
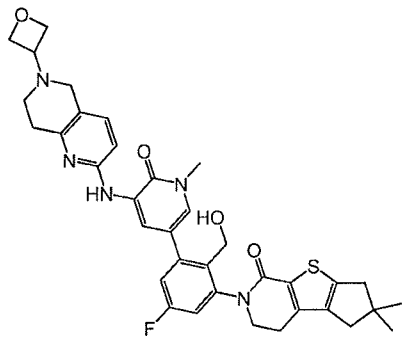
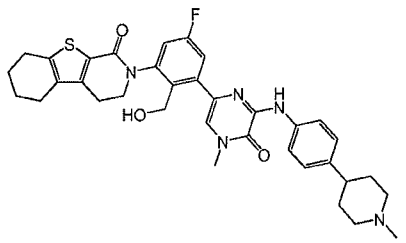
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256		10-[5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[5-(morpholin-4-yl)pyridine-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one	630	
257		10-[3-(5-{[5-(1-ethylazetidin-3-yl)pyridine-2-yl]amino}-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-(hydroxymethyl)phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one	628	
258		5-[5-fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-{[2-(oxetan-3-yl)-1,2,3,4-tetrahydroisoquinolin-6-yl]amino}-1,2-dihydropyridin-2-one	624	
259		5-[2-(hydroxymethyl)-3-[1-methyl-5-({5-methyl-4H,5H,6H,7H-pyrazolo[1,5-a]pyrazin-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	571	

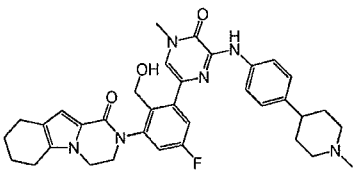
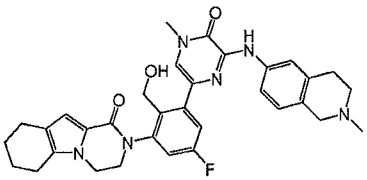
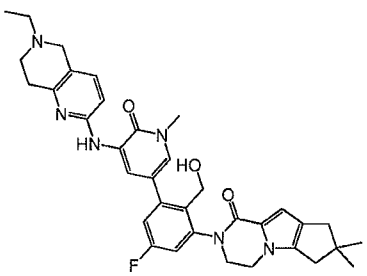
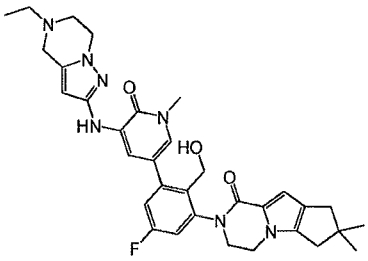
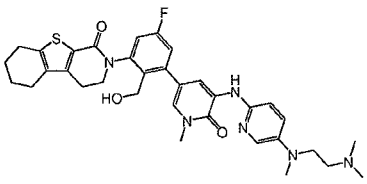
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261		10-[5-fluoro-2-(hydroxymethyl)-3-{1-methyl-5-[(6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-2-yl)amino]-6-oxo-1,6-dihydropyridin-3-yl}phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one	597.5	
262		10-[3-(5-{[5-(1-ethylazetidin-3-yl)pyridine-2-yl]amino}-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-(hydroxymethyl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one	611.5	
263		5-[5-fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-3-[(2-methoxypyrimidin-4-yl)amino]-1-methyl-1,2-dihydropyridin-2-one	545.5	

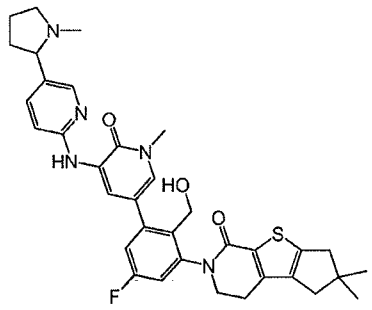
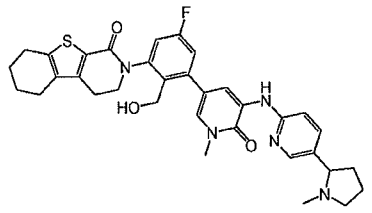
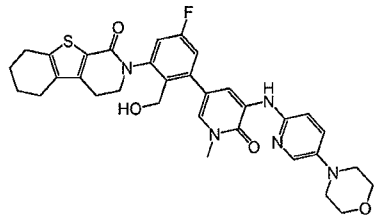
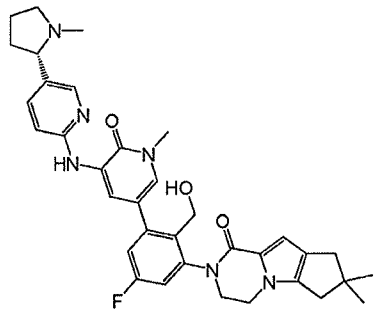
264		10-[5-fluoro-2-(hydroxymethyl)-3-[1-methyl-5-({5-[1-(oxetan-3-yl)piperidin-4-yl]pyridine-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one	667.6	
265		5-[5-fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-({5-[1-(oxetan-3-yl)piperidin-4-yl]pyridine-2-yl}amino)-1,2-dihydropyridin-2-one	653.6	0.0028
266		10-[5-fluoro-2-(hydroxymethyl)-3-{4-methyl-6-[(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)amino]-5-oxo-4,5-dihydropyrazin-2-yl}phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one	597.4	
267		5-[5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[5-(1-methylpiperidin-4-yl)pyridine-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	628	0.0038
268		5-{3-[5-({5-[2-(dimethylamino)ethoxy]pyridine-2-yl}amino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl]-5-fluoro-2-(hydroxymethyl)phenyl}-8-thia-5-	618	0.0020

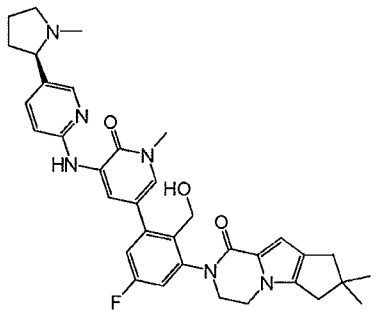
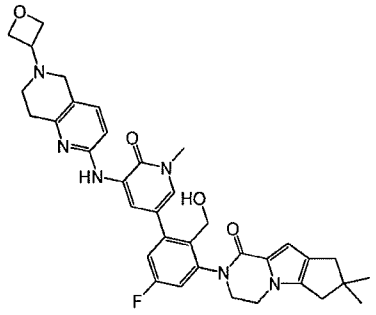
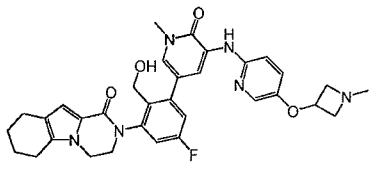
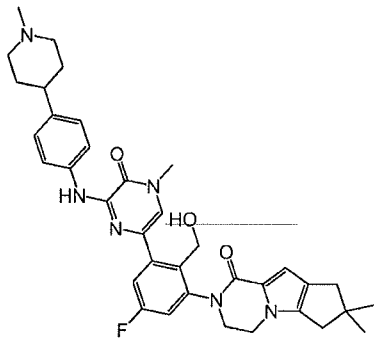
		azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one		
269		5-[3-(5-{[5-(4-ethylpiperazin-1-yl)pyridine-2-yl]amino}-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-(hydroxymethyl)phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	643.4	0.004
270		10-(3-{5-[(5-{[2-(dimethylamino)ethyl](methyl)amino}pyridine-2-yl)amino]-1-methyl-6-oxo-1,6-dihydropyridin-3-yl}-5-fluoro-2-(hydroxymethyl)phenyl)-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one	645.3	0.0040
271		10-[5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[5-(1-methylazetidin-3-yl)pyridine-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one	597.4	0.0047
272		10-[3-(5-{[5-(4-ethylpiperazin-1-yl)pyridine-2-yl]amino}-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-(hydroxymethyl)phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one	657.6	0.0064

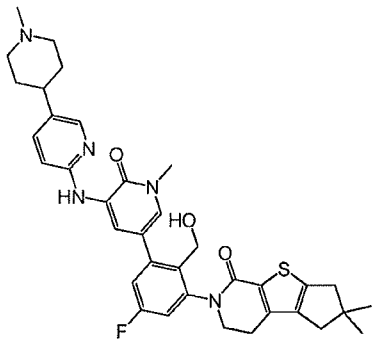
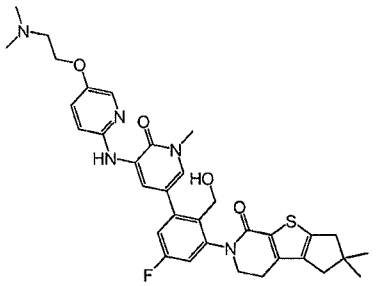
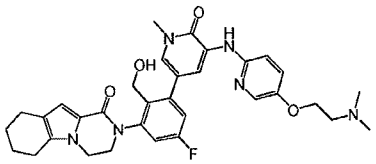
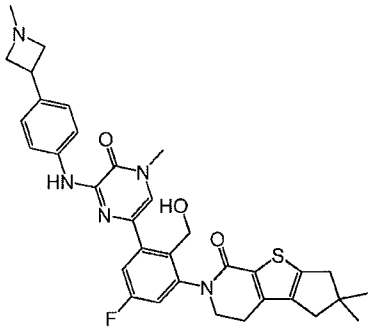
273		10-{5-fluoro-3-[5-({5-[4-(2-fluoroethyl)piperazin-1-yl]pyridine-2-yl}amino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl]-2-(hydroxymethyl)phenyl}-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one	658.5	0.00635
274		10-[5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[5-(morpholin-4-ylmethyl)pyridine-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one	627.5	0.00234
275		5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrido[3,4-b]indolizin-2-yl}phenyl]-1-methyl-3-{[5-(4-methylpiperazin-1-yl)pyridine-2-yl]amino}-1,2-dihydropyridin-2-one	594.3	0.0163
276		10-[5-fluoro-2-(hydroxymethyl)-3-{1-methyl-5-[(5-methyl-1H-pyrazol-3-yl)amino]-6-oxo-1,6-dihydropyridin-3-yl}phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one	531.4	0.0022
277		5-[5-fluoro-2-(hydroxymethyl)-3-{1-methyl-5-[(5-{[methyl(propan-2-yl)amino]methyl}pyridine-2-yl)amino]-6-oxo-1,6-dihydropyridin-3-yl}phenyl]-	616.4	0.0034

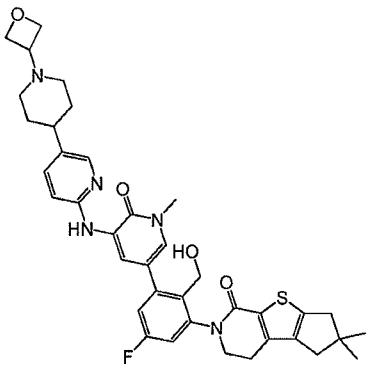
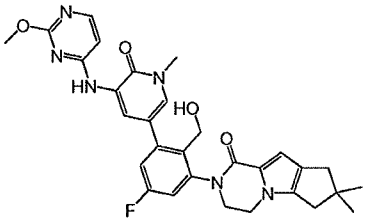
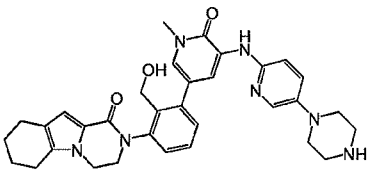
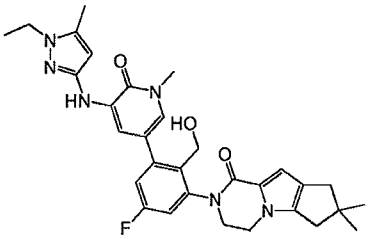
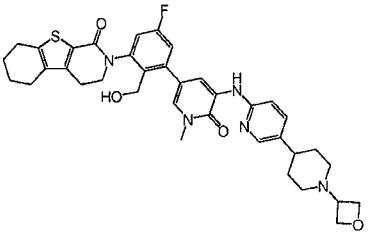
		8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one		
278		10-[5-fluoro-2-(hydroxymethyl)-3-(4-methyl-6-{[4-(1-methylpiperidin-4-yl)phenyl]amino}-5-oxo-4,5-dihydropyrazin-2-yl)phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one	642	0.0026
279		10-[5-fluoro-2-(hydroxymethyl)-3-[1-methyl-5-({5-methyl-4H,5H,6H,7H-pyrazolo[1,5-a]pyrazin-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one	603	0.0049
280		10-[5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[6-(oxetan-3-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one	656	0.0042
281		5-[5-fluoro-2-(hydroxymethyl)-3-(4-methyl-6-{[4-(1-methylpiperidin-4-yl)phenyl]amino}-5-oxo-4,5-dihydropyrazin-2-yl)phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	628	0.0052

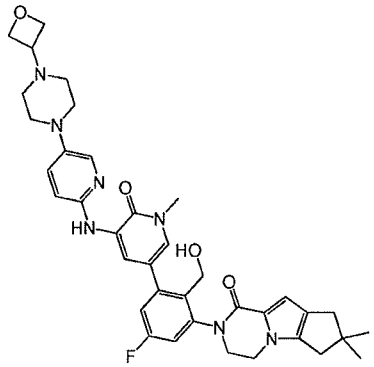
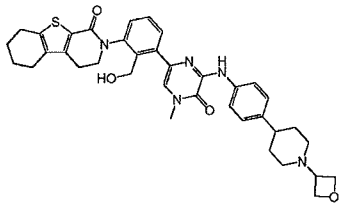
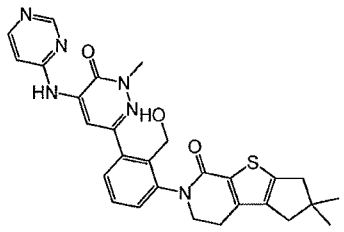
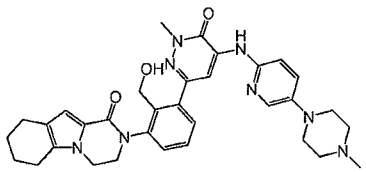
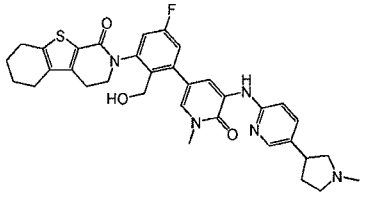
282		5-[5-fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-{[4-(1-methylpiperidin-4-yl)phenyl]amino}-1,2-dihydropyrazin-2-one	611	0.004
283		5-[5-fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-[(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)amino]-1,2-dihydropyrazin-2-one	583	0.0081
284		10-(3-{5-[(6-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-2-yl)amino]-1-methyl-6-oxo-1,6-dihydropyridin-3-yl}-5-fluoro-2-(hydroxymethyl)phenyl)-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one	611.5	0.0028
285		10-{3-[5-({5-ethyl-4H,5H,6H,7H-pyrazolo[1,5-a]pyrazin-2-yl}amino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl]-5-fluoro-2-(hydroxymethyl)phenyl}-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one	600.6	0.0036
286		5-(3-{5-[(5-{[2-(dimethylamino)ethyl](methyl)amino}pyridine-2-yl)amino]-1-methyl-6-oxo-1,6-dihydropyridin-3-yl}-5-fluoro-2-(hydroxymethyl)phenyl)-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	631.3	0.0034

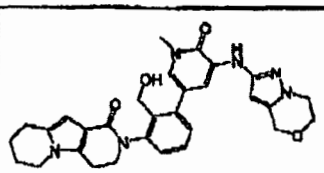
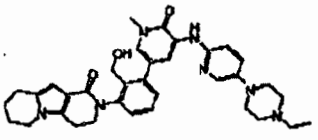
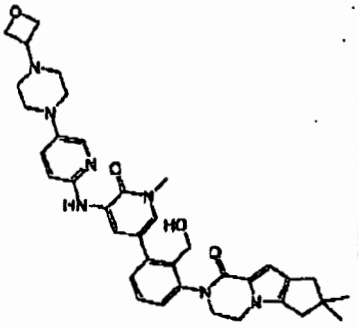
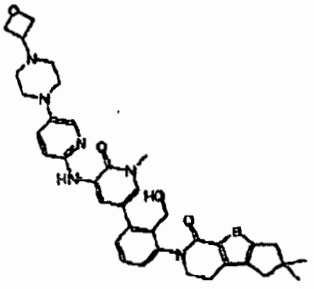
287		10-[5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[5-(1-methylpyrrolidin-2-yl)pyridine-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one	628.3	0.0014
288		5-[5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[5-(1-methylpyrrolidin-2-yl)pyridine-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	614.3	0.0021
289		5-[5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[5-(morpholin-4-yl)pyridine-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	616.3	0.0050
290		10-[5-fluoro-2-(hydroxymethyl)-3-[1-methyl-5-({5-[(2S)-1-methylpyrrolidin-2-yl]pyridine-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one	611.5	

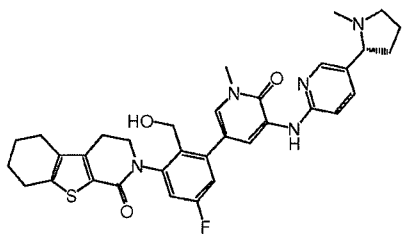
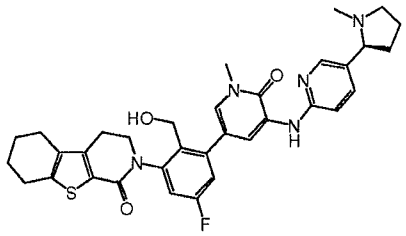
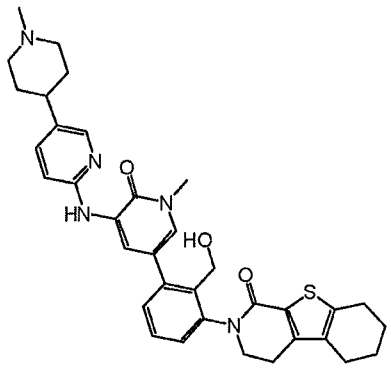
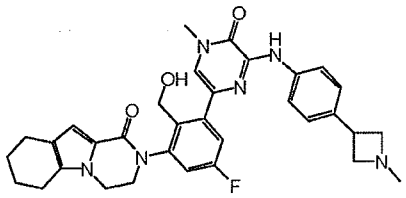
291		10-[5-fluoro-2-(hydroxymethyl)-3-[1-methyl-5-({5-[(2R)-1-methylpyrrolidin-2-yl]pyridine-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one	611.5	0.00174
292		10-[5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[6-(oxetan-3-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one	639.5	0.0116
293		5-[5-fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-({5-[(1-methylazetidin-3-yl)oxy]pyridine-2-yl}amino)-1,2-dihydropyridin-2-one	599	0.0098
294		10-[5-fluoro-2-(hydroxymethyl)-3-(4-methyl-6-{[4-(1-methylpiperidin-4-yl)phenyl]amino}-5-oxo-4,5-dihydropyrazin-2-yl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one	625	0.016

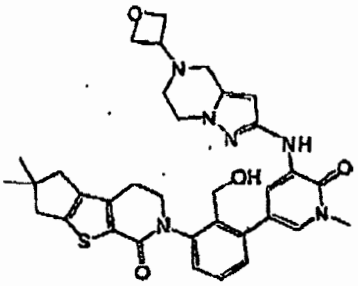
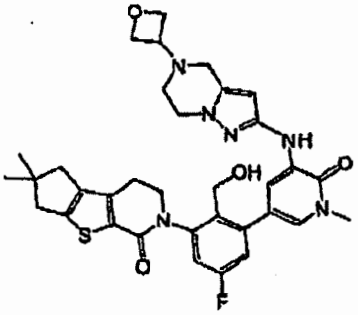
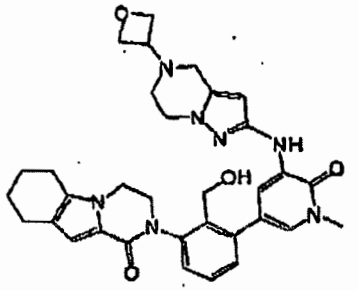
295		10-[5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[5-(1-methylpiperidin-4-yl)pyridine-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one	642	0.0022
296		10-{3-[5-({5-[2-(dimethylamino)ethoxy]pyridine-2-yl}amino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl]-5-fluoro-2-(hydroxymethyl)phenyl}-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one	632	0.0030
297		3-({5-[2-(dimethylamino)ethoxy]pyridine-2-yl}amino)-5-[5-fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-1,2-dihydropyridin-2-one	601	0.0042
298		10-[5-fluoro-2-(hydroxymethyl)-3-(4-methyl-6-{[4-(1-methylazetidin-3-yl)phenyl]amino}-5-oxo-4,5-dihydropyrazin-2-yl)phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one	614	0.0053

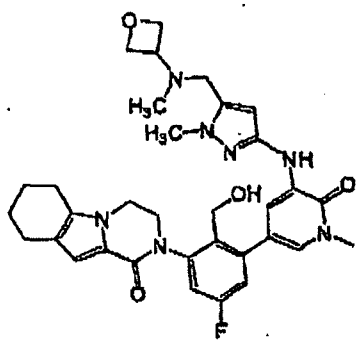
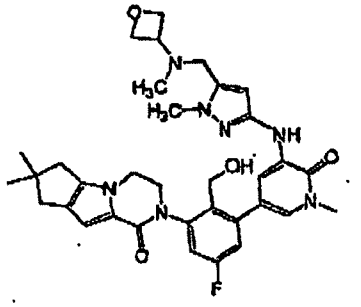
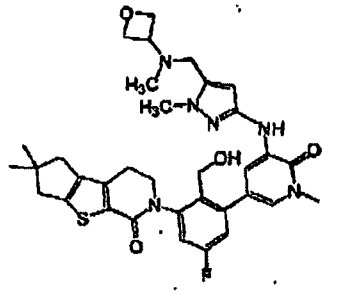
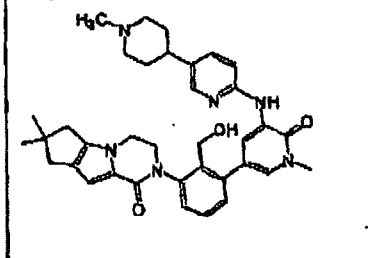
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300		10-[5-fluoro-2-(hydroxymethyl)-3-{5-[(2-methoxypyrimidin-4-yl)amino]-1-methyl-6-oxo-1,6-dihydropyridin-3-yl}phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one	559.4	0.0034
301		5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-{[5-(piperazin-1-yl)pyridine-2-yl]amino}-1,2-dihydropyridin-2-one	580.4	0.0061
302		10-(3-{5-[(1-ethyl-5-methyl-1H-pyrazol-3-yl)amino]-1-methyl-6-oxo-1,6-dihydropyridin-3-yl}-5-fluoro-2-(hydroxymethyl)phenyl)-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one	559.4	0.0099
303		5-[5-fluoro-2-(hydroxymethyl)-3-[1-methyl-5-({5-[1-(oxetan-3-yl)piperidin-4-yl]pyridine-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-	670.3	0.0049

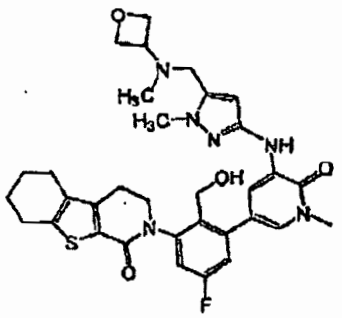
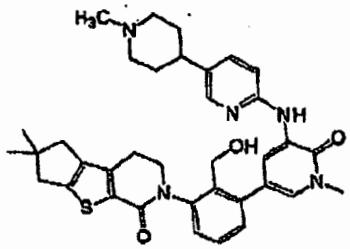
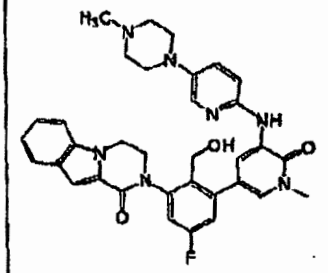
		1(9),2(7)-dien-6-one		
304		10-[5-fluoro-2-(hydroxymethyl)-3-[1-methyl-5-({5-[4-(oxetan-3-yl)piperazin-1-yl]pyridine-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one	668	0.0078
305		5-[2-(hydroxymethyl)-3-[4-methyl-6-({4-[1-(oxetan-3-yl)piperidin-4-yl]phenyl}amino)-5-oxo-4,5-dihydropyrazin-2-yl]phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	652	0.0171
306		10-[2-(hydroxymethyl)-3-[1-methyl-6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydropyridazin-3-yl]phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one	529.3	
307		6-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-2-methyl-4-{[5-(4-methylpiperazin-1-yl)pyridine-2-yl]amino}-2,3-dihydropyridazin-3-one	595.6	0.0071
308		5-[5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[5-(1-methylpyrrolidin-3-yl)pyridine-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-	614.3	0.0033

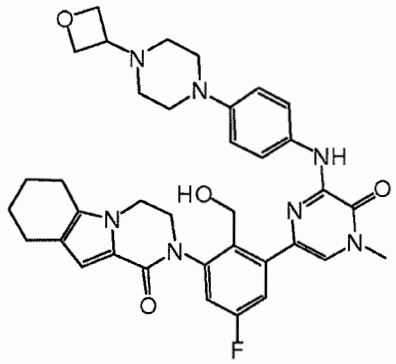
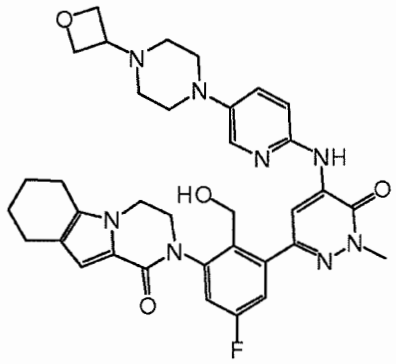
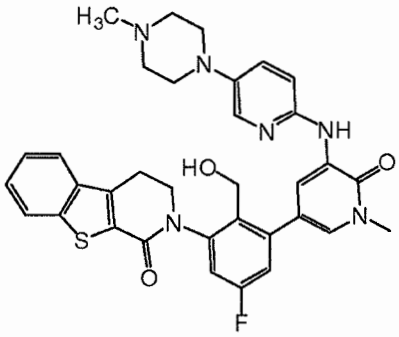
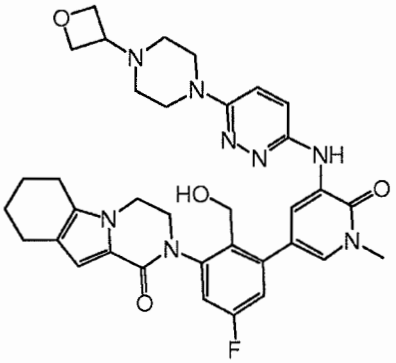
		1(9),2(7)-dien-6-one		
309		5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrido[3,4-b]indolizin-2-yl}phenyl]-1-methyl-3-{4H,6H,7H-pyrazolo[3,2-c][1,4]oxazin-2-ylamino}-1,2-dihydropyridin-2-one	541.2	0.0165
310		3-{[5-(4-ethylpiperazin-1-yl)pyridine-2-yl]amino}-5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrido[3,4-b]indolizin-2-yl}phenyl]-1-methyl-1,2-dihydropyridin-2-one	608.3	0.0166
311		10-[2-(hydroxymethyl)-3-[1-methyl-5-({5-[4-(oxetan-3-yl)piperazin-1-yl]pyridine-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one	650	0.0052
312		10-[2-(hydroxymethyl)-3-[1-methyl-5-({5-[4-(oxetan-3-yl)piperazin-1-yl]pyridine-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one	667	0.043

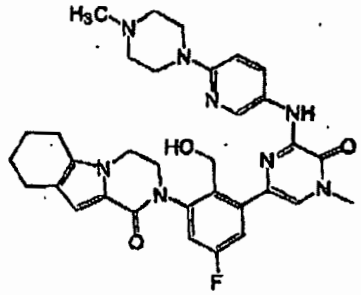
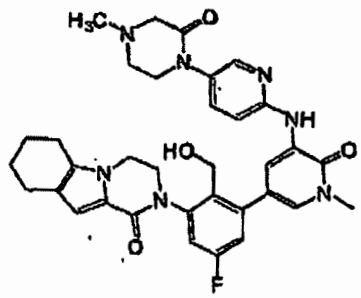
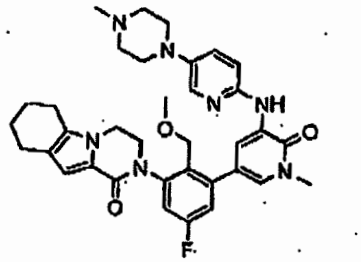
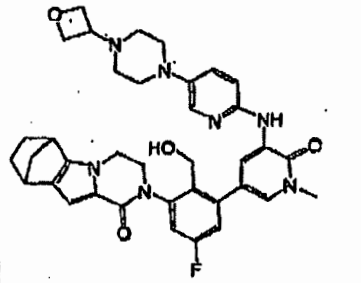
313		5-[5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[5-(2S)-(1-methylpyrrolidin-2-yl)pyridine-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	614.2	
314		5-[5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[5-(2R)-(1-methylpyrrolidin-2-yl)pyridine-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	614.2	
315		5-[2-(hydroxymethyl)-5-[1-methyl-5-({4-[1-methylpiperidin-4-yl]pyridine-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-8-thia-5-azatricyclo-[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	610	
316		5-[5-fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-[(4-(1-methylazetidin-3-yl)phenyl)amino)-1,2-dihydropyrazin-2-one	583	

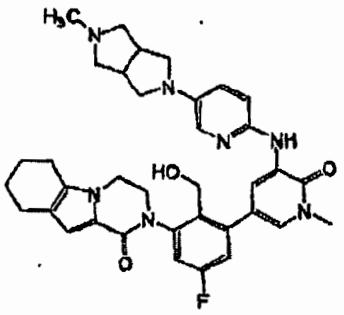
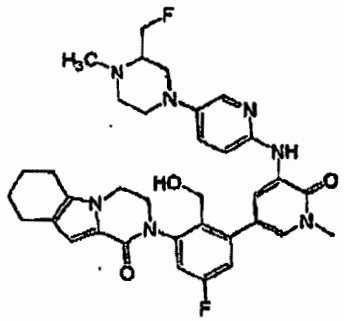
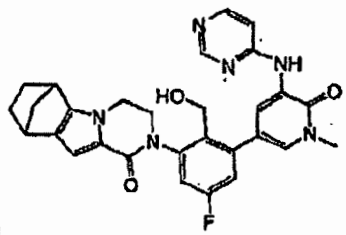
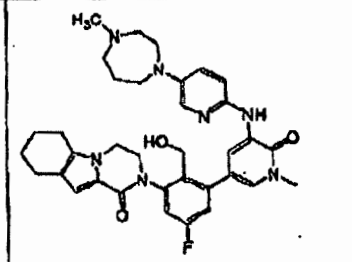
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318		10-[5-fluoro-2-(hydroxymethyl)-3-[1-methyl-5-({5-(oxetan-3-yl)-4H,5H,6H,7H-pyrazolo[1,5-a]pyrazin-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-4,4-dimethyl-7-thia-10-azatricyclo-[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one	645.3	
319		2-(2-(Hydroxymethyl)-3-(1-methyl-5-(5-(oxetan-3-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	596	

320		5-{5-fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrido[3,4-b]indolizin-2-yl}phenyl]-3-{1-methyl-5-(N-methyl, N-oxetan-3-ylaminomethyl-1H-pyrazol-3-yl)amino}-1,2-dihydropyridin-2-one	616	
321		10-[5-Fluoro-2-(Hydroxymethyl)-3-{1-methyl-5-[(1- methyl-5-{[methyl(oxetan-3-yl)amino]methyl}-1H-pyrazol-3-yl)amino]-6-oxo-1,6-dihydropyridin-3-yl}phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one	630	
322		10-[5-Fluoro-2-(hydroxymethyl)-3-{1-methyl-5-[(1-methyl-5-{[methyl(oxetan-3-yl)amino]methyl}-1H-pyrazol-3-yl)amino]-6-oxo-1,6-dihydropyridin-3-yl}phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one	647	
323		10-[2-(Hydroxymethyl)-3-(1-methyl-5-{[5-(1-methylpiperidin-4-yl)pyridin-2-yl]amino}-6-oxopyridin-3-yl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one	607	

324		5-[5-fluoro-2-(hydroxymethyl)-5-[1-methyl-5-({1-methyl-5-(N-methyl, N-oxetan-3-ylaminomethyl)-1H-pyrazol-3-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-8-thia-5-azatricyclo-[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one	633	
325		10-[2-(hydroxymethyl)-3-[1-methyl-5-({5-[1-(methylpiperidin-4-yl)pyridine-2-yl)amino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)- 4,4-dimethyl-7-thia-10-azatricyclo-[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one	624	
326		2-(5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridine-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one	608	

327		5-[5-fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-{[4-(oxetan-3-yl)piperazin-1-yl]}phenyl}amino}-1,2-dihydropyrazin-2-one	654.8	
328		5-[5-fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-2-methyl-4-{[4-(oxetan-3-yl)piperazin-1-yl]}phenyl}amino}-2,3-dihydropyrazin-3-one	655.3	
329		2-(5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridine-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4-dihydro-2H-[1]benzothiolo[2,3-c]pyridine-1-one	625	
330		5-[5-fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-({5-[4-(oxetan-3-yl)piperazin-1-yl]pyrazin-2-yl}amino)-1,2-dihydropyridin-2-one	655	

331		5-[5-fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-{[4-methylpiperazin-1-yl]phenyl]amino}-1,2-dihydropyrazin-2-one	613	
332		2-(5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(4-methyl-2-oxopiperazin-1-yl)pyridine-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	626	
333		2-(5-fluoro-2-(methoxymethyl)-3-(1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridine-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)- 3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	626	
334		2-(5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(4-(oxetan-3-yl)-piperazin-1-yl)pyridine-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydro-6,9-methanopyrazino[1,2-a]indol-1(2H)-one	666	

335		2-(5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	638.3	
336		2-(5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(4-methyl-3-fluoromethyl-piperazin-1-yl)pyridine-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)- 3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	644	
337		2-(5-fluoro-2-(hydroxymethyl)-3-(1-methyl-6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydro-6,9-methanopyrazino[1,2-a]indol-1(2H)-one	527	
338		2-(5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(4-methyl-1,4-diazepan-1-ylpyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	626	

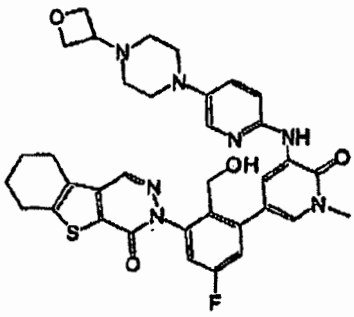
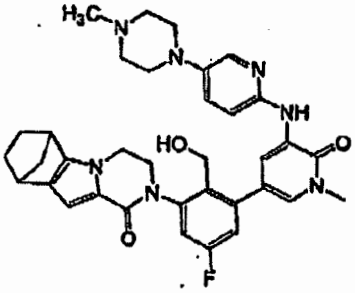
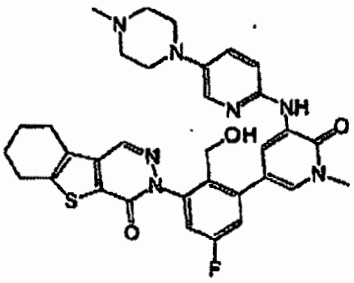
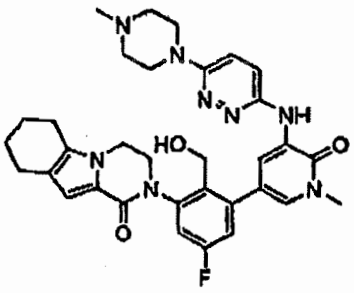
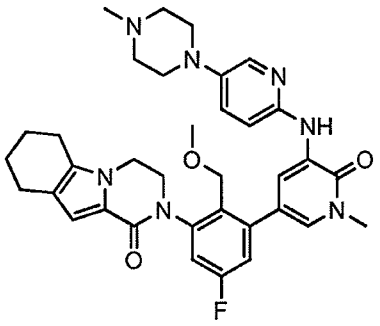
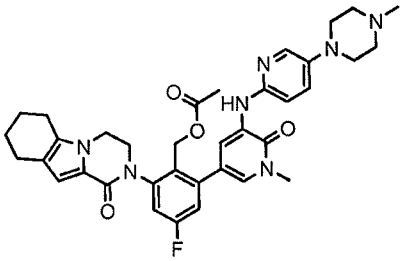
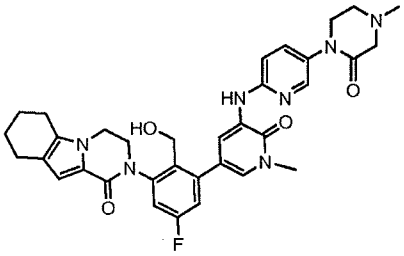
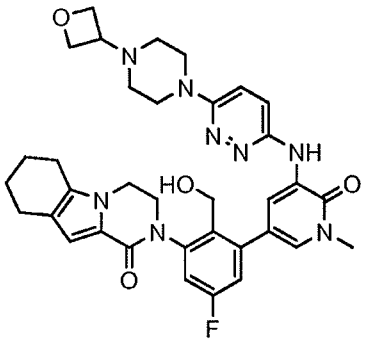
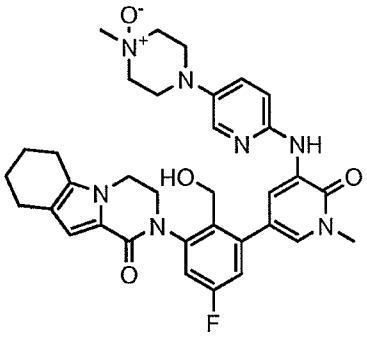
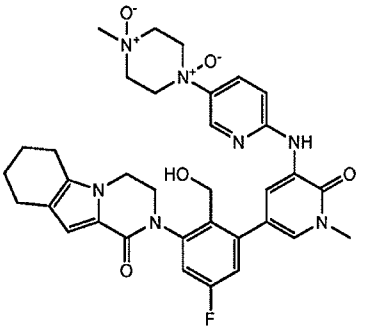
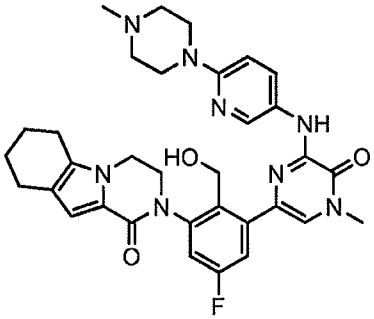
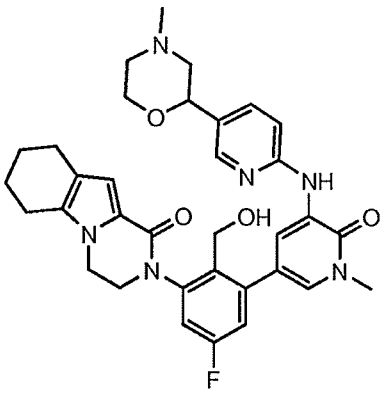
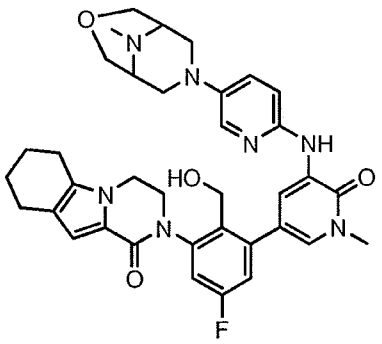
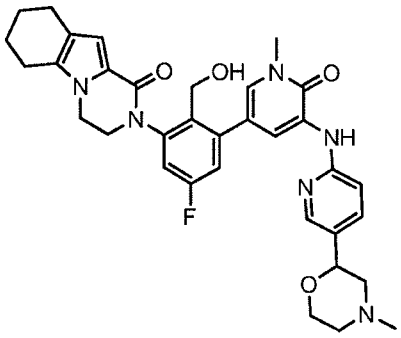
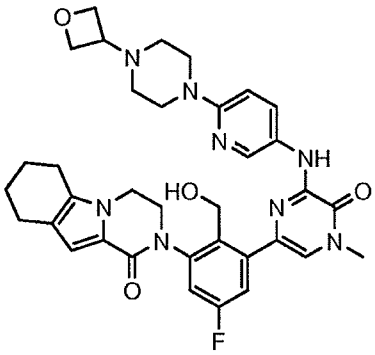
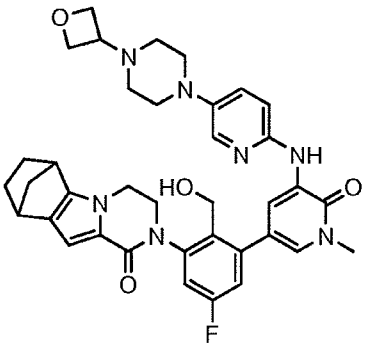
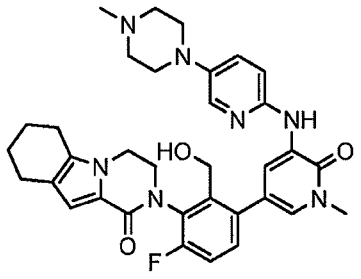
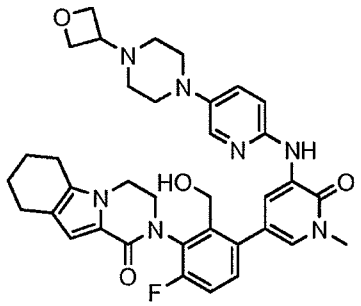
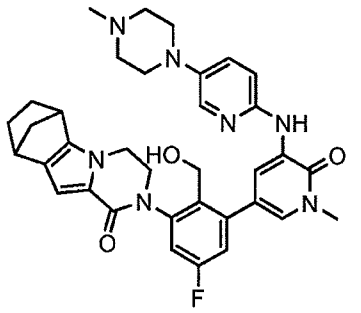
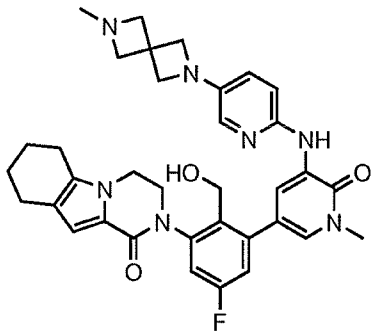
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340		2-(5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(4-methylpiperazin-1-ylpyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydro-6,9-methanopyrazino[1,2-a]indol-1(2H)-one	624	
341		5-[5-fluoro-2-(hydroxymethyl)-3-[1-methyl-5-({5-[4-methylpiperazin-1-yl]pyridine-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-8-thia-4,5-diazatricyclo[7.4.0.0^{2,7}]-trideca-1(9),2(7),3(4)-trien-6-one	628	
342		2-(5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(6-(4-methylpiperazin-1-yl)pyridazin-3-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	613	

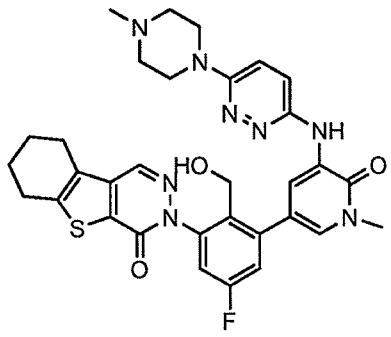
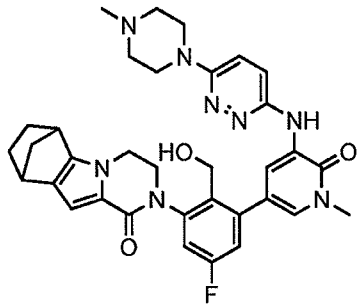
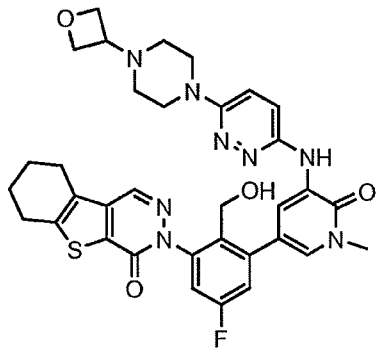
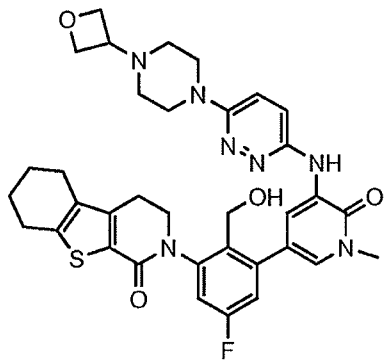
Table 3.

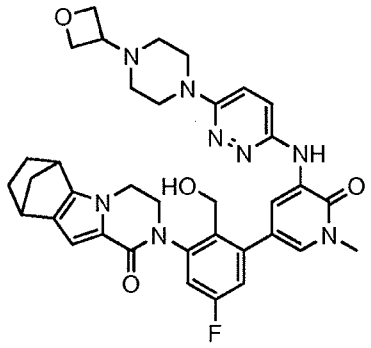
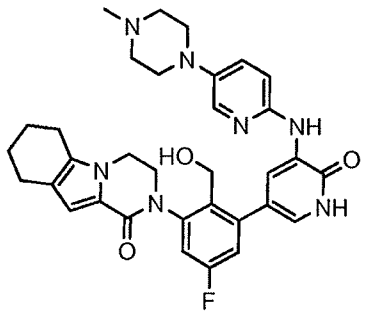
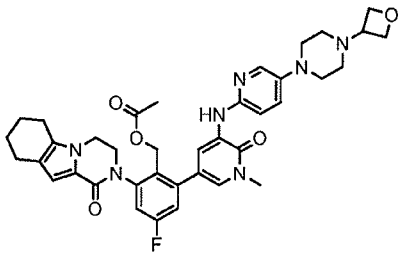
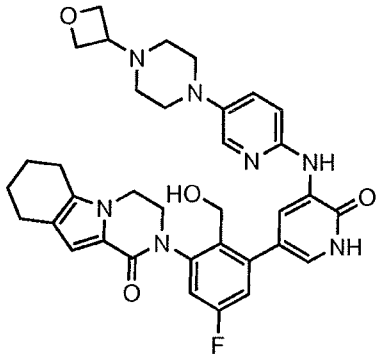
No.	Structure	Name	MH+ m/z
343		2-(5-fluoro-2-(methoxymethyl)-3-(1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	626.3
344		4-fluoro-2-(1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate	654.3
345		2-(5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(4-methyl-2-oxopiperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	626.3
346		2-(5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(6-(4-(oxetan-3-yl)piperazin-1-yl)pyridazin-3-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	655.3

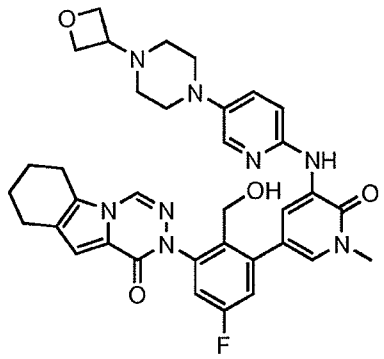
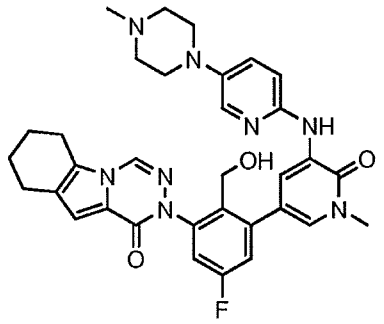
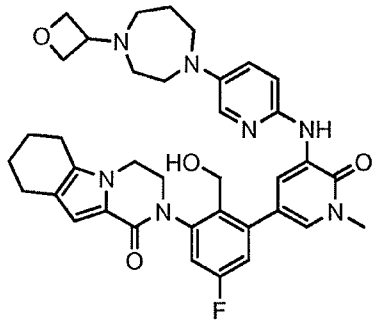
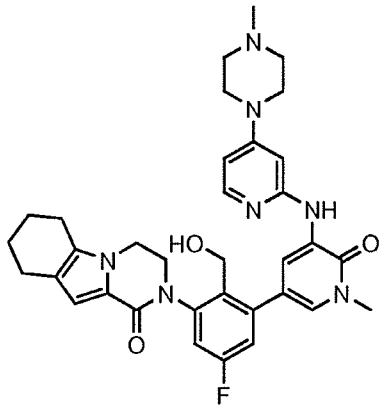
347		4-(6-(5-(5-fluoro-2-(hydroxymethyl)-3-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)phenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)pyridin-3-yl)-1-methylpiperazine 1-oxide	628.3
348		1-(6-(5-(5-fluoro-2-(hydroxymethyl)-3-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)phenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)pyridin-3-yl)-4-methylpiperazine 1,4-dioxide	644.3
349		2-(5-fluoro-2-(hydroxymethyl)-3-(4-methyl-6-(6-(4-methylpiperazin-1-yl)pyridin-3-ylamino)-5-oxo-4,5-dihydropyrazin-2-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	613.3
350		2-(5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(4-methylmorpholin-2-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	613.3

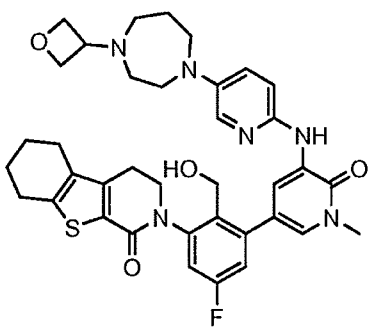
351		2-(5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(9-methyl-3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	654.3
352		2-(5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(4-methylmorpholin-2-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	613.3
353		2-(5-fluoro-2-(hydroxymethyl)-3-(4-methyl-6-(6-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-3-ylamino)-5-oxo-4,5-dihydropyrazin-2-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	655.3
354		2-(5-fluoro-2-(hydroxymethyl)-3-(1-methyl-6-oxo-5-(3-(4-(oxetan-3-yl)piperazin-1-yl)pyrid-6-ylamino)-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydro-6,9-methanopyrazino[1,2-a]indol-1(2H)-one	666.3

355		2-(6-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	612.3
356		2-(6-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	654.3
357		2-(5-fluoro-2-(hydroxymethyl)-3-(1-methyl-6-oxo-5-(3-(4-methylpiperazin-1-yl)pyrid-6-ylamino)-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydro-6,9-methanopyrazino[1,2-a]indol-1(2H)-one	624.3
358		2-(5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	624.3

359		3-(5-Fluoro-2-hydroxymethyl-3-{1-methyl-5-[6-(4-methyl-piperazin-1-yl)-pyridazin-3-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-6,7,8,9-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyridazin-4-one	629.2
360		2-(5-fluoro-2-(hydroxymethyl)-3-(1-methyl-6-oxo-5-(3-(4-methylpiperazin-1-yl)pyridazin-6-ylamino)-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydro-6,9-methanopyrazino[1,2-a]indol-1(2H)-one	625.3
361		3-(5-Fluoro-2-hydroxymethyl-3-{1-methyl-5-[6-(4-oxetan-3-yl-piperazin-1-yl)-pyridazin-3-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-6,7,8,9-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyridazin-4-one	671.2
362		2-(5-Fluoro-2-hydroxymethyl-3-{1-methyl-5-[6-(4-oxetan-3-yl-piperazin-1-yl)-pyridazin-3-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-3,4,5,6,7,8-hexahydro-2H-benzo[4,5]thieno[2,3-c]pyridin-1-one	672.3

363		2-(5-fluoro-2-(hydroxymethyl)-3-(1-methyl-6-oxo-5-(3-(4-(oxetan-3-yl)piperazin-1-yl)pyridazin-6-ylamino)-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydro-6,9-methanopyrazino[1,2-a]indol-1(2H)-one	667.3
364		2-(5-fluoro-2-(hydroxymethyl)-3-(5-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	598.3
365		4-fluoro-2-(1-methyl-5-(5-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate	696.3
366		2-(5-fluoro-2-(hydroxymethyl)-3-(5-(5-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	640.3

367		2-(5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-6,7,8,9-tetrahydro-[1,2,4]triazino[4,5-a]indol-1(2H)-one	653.3
368		2-(5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-6,7,8,9-tetrahydro-[1,2,4]triazino[4,5-a]indol-1(2H)-one	611.3
369		2-(5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(4-(oxetan-3-yl)-1,4-diazepan-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	668.3
370		2-(5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(4-(4-methylpiperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	612.3

371		2-(5-Fluoro-2-hydroxymethyl-3-{1-methyl-5-[5-(4-oxetan-3-yl-[1,4]diazepan-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-3,4,5,6,7,8-hexahydro-2H-benzo[4,5]thieno[2,3-c]pyridin-1-one	685.3

ADMINISTRATION OF FORMULA I COMPOUNDS

The compounds of the invention may be administered by any route appropriate to the condition to be treated. Suitable routes include oral, parenteral (including subcutaneous, intramuscular, intravenous, intraarterial, intradermal, intrathecal and epidural), transdermal, rectal, nasal, topical (including buccal and sublingual), vaginal, intraperitoneal, intrapulmonary and intranasal. For local immunosuppressive treatment, the compounds may be administered by intralesional administration, including perfusing or otherwise contacting the graft with the inhibitor before transplantation. It will be appreciated that the preferred route may vary with for example the condition of the recipient. Where the compound is administered orally, it may be formulated as a pill, capsule, tablet, etc. with a pharmaceutically acceptable carrier or excipient. Where the compound is administered parenterally, it may be formulated with a pharmaceutically acceptable parenteral vehicle and in a unit dosage injectable form, as detailed below.

A dose to treat human patients may range from about 10 mg to about 1000 mg of Formula I compound. A typical dose may be about 100 mg to about 300 mg of the compound. A dose may be administered once a day (QID), twice per day (BID), or more frequently, depending on the pharmacokinetic and pharmacodynamic properties, including absorption, distribution, metabolism, and excretion of the particular compound. In addition, toxicity factors may influence the dosage and administration regimen. When administered orally, the pill, capsule, or tablet may be ingested daily or less frequently for a specified period of time. The regimen may be repeated for a number of cycles of therapy.

METHODS OF TREATMENT WITH FORMULA I COMPOUNDS

Formula I compounds of the present invention are useful for treating a human or animal patient suffering from a disease or disorder arising from abnormal cell growth, function or behavior associated with Btk kinase such as an immune disorder, cardiovascular disease, viral infection, inflammation, a metabolism/endocrine disorder or a neurological disorder, may thus be treated by a method comprising the administration thereto of a compound of the present invention as defined above. A human or animal patient suffering from cancer may also be treated by a method comprising the administration thereto of a compound of the present invention as defined above. The condition of the patient may thereby be improved or ameliorated.

Formula I compounds may be useful for *in vitro*, *in situ*, and *in vivo* diagnosis or treatment of mammalian cells, organisms, or associated pathological conditions, such as systemic and local inflammation, immune-inflammatory diseases such as rheumatoid arthritis, immune suppression, organ transplant rejection, allergies, ulcerative colitis, Crohn's disease, dermatitis, asthma, systemic lupus erythematosus, Sjögren's Syndrome, multiple sclerosis, scleroderma/systemic sclerosis, idiopathic thrombocytopenic purpura (ITP), anti-neutrophil cytoplasmic antibodies (ANCA) vasculitis, chronic obstructive pulmonary disease (COPD), psoriasis, and for general joint protective effects.

Methods of the invention also include treating such diseases as arthritic diseases, such as rheumatoid arthritis, monoarticular arthritis, osteoarthritis, gouty arthritis, spondylitis; Behcet disease; sepsis, septic shock, endotoxic shock, gram negative sepsis, gram positive sepsis, and toxic shock syndrome; multiple organ injury syndrome secondary to septicemia, trauma, or hemorrhage; ophthalmic disorders such as allergic conjunctivitis, vernal conjunctivitis, uveitis, and thyroid-associated ophthalmopathy; eosinophilic granuloma; pulmonary or respiratory disorders such as asthma, chronic bronchitis, allergic rhinitis, ARDS, chronic pulmonary inflammatory disease (e.g., chronic obstructive pulmonary disease), silicosis, pulmonary sarcoidosis, pleurisy, alveolitis, vasculitis, emphysema, pneumonia, bronchiectasis, and pulmonary oxygen toxicity; reperfusion injury of the myocardium, brain, or extremities; fibrosis such as cystic fibrosis; keloid formation or scar tissue formation; atherosclerosis; autoimmune diseases, such as systemic lupus erythematosus (SLE), autoimmune thyroiditis, multiple sclerosis, some forms of diabetes, and Reynaud's syndrome; and transplant rejection disorders such as GVHD and allograft rejection; chronic glomerulonephritis; inflammatory bowel diseases such as chronic inflammatory bowel disease (CIBD), Crohn's disease, ulcerative colitis, and necrotizing enterocolitis; inflammatory dermatoses such as contact dermatitis, atopic dermatitis, psoriasis, or urticaria; fever and myalgias due to infection; central or peripheral nervous system inflammatory disorders such as meningitis, encephalitis, and brain or spinal cord injury due to minor trauma; Sjogren's syndrome; diseases involving leukocyte diapedesis; alcoholic hepatitis; bacterial pneumonia; antigen-antibody complex mediated diseases; hypovolemic shock; Type I diabetes mellitus; acute and delayed hypersensitivity; disease states due to leukocyte dyscrasia and metastasis; thermal injury; granulocyte transfusion-associated syndromes; and cytokine-induced toxicity.

The methods of the invention can have utility in treating subjects who are or can be subject to reperfusion injury, i.e., injury resulting from situations in which a tissue or organ

experiences a period of ischemia followed by reperfusion. The term "ischemia" refers to localized tissue anemia due to obstruction of the inflow of arterial blood. Transient ischemia followed by reperfusion characteristically results in neutrophil activation and transmigration through the endothelium of the blood vessels in the affected area. Accumulation of activated neutrophils in turn results in generation of reactive oxygen metabolites, which damage components of the involved tissue or organ. This phenomenon of "reperfusion injury" is commonly associated with conditions such as vascular stroke (including global and focal ischemia), hemorrhagic shock, myocardial ischemia or infarction, organ transplantation, and cerebral vasospasm. To illustrate, reperfusion injury occurs at the termination of cardiac bypass procedures or during cardiac arrest when the heart, once prevented from receiving blood, begins to reperfuse. It is expected that inhibition of Btk activity may result in reduced amounts of reperfusion injury in such situations.

PHARMACEUTICAL FORMULATIONS

In order to use a compound of this invention for the therapeutic treatment of mammals including humans, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition. According to this aspect of the invention there is provided a pharmaceutical composition comprising a compound of this invention in association with a pharmaceutically acceptable diluent or carrier.

A typical formulation is prepared by mixing a compound of the present invention and a carrier, diluent or excipient. Suitable carriers, diluents and excipients are well known to those skilled in the art and include materials such as carbohydrates, waxes, water soluble and/or swellable polymers, hydrophilic or hydrophobic materials, gelatin, oils, solvents, water and the like. The particular carrier, diluent or excipient used will depend upon the means and purpose for which the compound of the present invention is being applied. Solvents are generally selected based on solvents recognized by persons skilled in the art as safe (GRAS) to be administered to a mammal. In general, safe solvents are non-toxic aqueous solvents such as water and other non-toxic solvents that are soluble or miscible in water. Suitable aqueous solvents include water, ethanol, propylene glycol, polyethylene glycols (e.g., PEG 400, PEG 300), etc. and mixtures thereof. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present

invention or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

The formulations may be prepared using conventional dissolution and mixing procedures. For example, the bulk drug substance (i.e., compound of the present invention or stabilized form of the compound (e.g., complex with a cyclodextrin derivative or other known complexation agent) is dissolved in a suitable solvent in the presence of one or more of the excipients described above. The compound of the present invention is typically formulated into pharmaceutical dosage forms to provide an easily controllable dosage of the drug and to enable patient compliance with the prescribed regimen.

The pharmaceutical composition (or formulation) for application may be packaged in a variety of ways depending upon the method used for administering the drug. Generally, an article for distribution includes a container having deposited therein the pharmaceutical formulation in an appropriate form. Suitable containers are well known to those skilled in the art and include materials such as bottles (plastic and glass), sachets, ampoules, plastic bags, metal cylinders, and the like. The container may also include a tamper-proof assemblage to prevent indiscreet access to the contents of the package. In addition, the container has deposited thereon a label that describes the contents of the container. The label may also include appropriate warnings.

Pharmaceutical formulations of the compounds of the present invention may be prepared for various routes and types of administration. For example, a compound of Formula I having the desired degree of purity may optionally be mixed with pharmaceutically acceptable diluents, carriers, excipients or stabilizers (Remington's Pharmaceutical Sciences (1980) 16th edition, Osol, A. Ed.), in the form of a lyophilized formulation, milled powder, or an aqueous solution. Formulation may be conducted by mixing at ambient temperature at the appropriate pH, and at the desired degree of purity, with physiologically acceptable carriers, i.e., carriers that are non-toxic to recipients at the dosages and concentrations employed. The pH of the formulation depends mainly on the particular use and the concentration of compound, but may range from about 3 to about 8. Formulation in an acetate buffer at pH 5 is a suitable embodiment.

The compound ordinarily can be stored as a solid composition, a lyophilized formulation or as an aqueous solution.

The pharmaceutical compositions of the invention will be formulated, dosed and administered in a fashion, i.e., amounts, concentrations, schedules, course, vehicles and route of administration, consistent with good medical practice. Factors for consideration in this

context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The "therapeutically effective amount" of the compound to be administered will be governed by such considerations, and is the minimum amount necessary to ameliorate, or treat the hyperproliferative disorder.

As a general proposition, the initial pharmaceutically effective amount of the inhibitor administered parenterally per dose will be in the range of about 0.01-100 mg/kg, namely about 0.1 to 20 mg/kg of patient body weight per day, with the typical initial range of compound used being 0.3 to 15 mg/kg/day.

Acceptable diluents, carriers, excipients and stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as TWEEN™, PLURONICS™ or polyethylene glycol (PEG). The active pharmaceutical ingredients may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980).

Sustained-release preparations of compounds of Formula I may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing a compound of Formula I, which matrices are in the form of shaped articles, e.g., films, or microcapsules. Examples of sustained-release matrices

include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinyl alcohol)), polylactides (US 3773919), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate) and poly-D-(-)-3-hydroxybutyric acid.

The formulations include those suitable for the administration routes detailed herein. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in *Remington's Pharmaceutical Sciences* (Mack Publishing Co., Easton, PA). Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations of a compound of Formula I suitable for oral administration may be prepared as discrete units such as pills, capsules, cachets or tablets each containing a predetermined amount of a compound of Formula I. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets may optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient therefrom. Tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, e.g., gelatin capsules, syrups or elixirs may be prepared for oral use. Formulations of compounds of Formula I intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as starch, gelatin or acacia; and lubricating agents, such as magnesium

stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

For treatment of the eye or other external tissues, e.g., mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include a polyhydric alcohol, i.e., an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulfoxide and related analogs. The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the invention include Tween® 60, Span® 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

Aqueous suspensions of Formula I compounds contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, croscarmellose, povidone, methylcellulose, hydroxypropyl methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene

oxide with a long chain aliphatic alcohol (e.g., heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan monooleate). The aqueous suspension may also contain one or more preservatives such as ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

The pharmaceutical compositions of compounds of Formula I may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butanediol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion may contain from about 3 to 500 μg of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such formulations in a concentration of about 0.5 to 20% w/w, for example about 0.5 to 10% w/w, for example about 1.5% w/w.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 microns (including particle sizes in a range between 0.1 and 500 microns in increments microns such as 0.5, 1, 30 microns, 35 microns, etc.), which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol or dry powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as compounds heretofore used in the treatment or prophylaxis disorders as described below.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

The formulations may be packaged in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water, for injection immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

The invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefore. Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid

or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered parenterally, orally or by any other desired route.

COMBINATION THERAPY

The compounds of Formula I may be employed alone or in combination with other therapeutic agents for the treatment of a disease or disorder described herein, such as inflammation or a hyperproliferative disorder (e.g., cancer). In certain embodiments, a compound of Formula I is combined in a pharmaceutical combination formulation, or dosing regimen as combination therapy, with a second therapeutic compound that has anti-inflammatory or anti-hyperproliferative properties or that is useful for treating an inflammation, immune-response disorder, or hyperproliferative disorder (e.g., cancer). The second therapeutic agent may be an NSAID anti-inflammatory agent. The second therapeutic agent may be a chemotherapeutic agent. The second compound of the pharmaceutical combination formulation or dosing regimen preferably has complementary activities to the compound of Formula I such that they do not adversely affect each other. Such compounds are suitably present in combination in amounts that are effective for the purpose intended. In one embodiment, a composition of this invention comprises a compound of Formula I, or a stereoisomer, tautomer, solvate, metabolite, or pharmaceutically acceptable salt or prodrug thereof, in combination with a therapeutic agent such as an NSAID.

The combination therapy may be administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations. The combined administration includes coadministration, using separate formulations or a single pharmaceutical formulation, and consecutive administration in either order, wherein preferably there is a time period while both (or all) active agents simultaneously exert their biological activities.

Suitable dosages for any of the above coadministered agents are those presently used and may be lowered due to the combined action (synergy) of the newly identified agent and other therapeutic agents or treatments.

The combination therapy may provide "synergy" and prove "synergistic", i.e., the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the compounds separately. A synergistic effect may be attained when the active ingredients are: (1) co-formulated and administered or delivered simultaneously in a combined, unit dosage formulation; (2) delivered by alternation or in

parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect may be attained when the compounds are administered or delivered sequentially, e.g., by different injections in separate syringes, separate pills or capsules, or separate infusions. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, i.e., serially, whereas in combination therapy, effective dosages of two or more active ingredients are administered together.

In a particular embodiment of therapy, a compound of Formula I, or a stereoisomer, tautomer, solvate, metabolite, or pharmaceutically acceptable salt or prodrug thereof, may be combined with other therapeutic, hormonal or antibody agents such as those described herein, as well as combined with surgical therapy and radiotherapy. Combination therapies according to the present invention thus comprise the administration of at least one compound of Formula I, or a stereoisomer, tautomer, solvate, metabolite, or pharmaceutically acceptable salt or prodrug thereof, and the use of at least one other cancer treatment method. The amounts of the compound(s) of Formula I and the other pharmaceutically active therapeutic agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

METABOLITES OF COMPOUNDS OF FORMULA I

Also falling within the scope of this invention are the *in vivo* metabolic products of Formula I described herein. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, deamidation, esterification, deesterification, enzymatic cleavage, and the like, of the administered compound. Accordingly, the invention includes metabolites of compounds of Formula I, including compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof.

Metabolite products typically are identified by preparing a radiolabelled (e.g., ^{14}C or ^{3}H) isotope of a compound of the invention, administering it parenterally in a detectable dose (e.g., greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, e.g., by MS, LC/MS or NMR analysis. In

general, analysis of metabolites is done in the same way as conventional drug metabolism studies well known to those skilled in the art. The metabolite products, so long as they are not otherwise found *in vivo*, are useful in diagnostic assays for therapeutic dosing of the compounds of the invention.

ARTICLES OF MANUFACTURE

In another embodiment of the invention, an article of manufacture, or "kit", containing materials useful for the treatment of the diseases and disorders described above is provided. In one embodiment, the kit comprises a container comprising a compound of Formula I, or a stereoisomer, tautomer, solvate, metabolite, or pharmaceutically acceptable salt or prodrug thereof. The kit may further comprise a label or package insert on or associated with the container. The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, contraindications and/or warnings concerning the use of such therapeutic products. Suitable containers include, for example, bottles, vials, syringes, blister pack, etc. The container may be formed from a variety of materials such as glass or plastic. The container may hold a compound of Formula I or a formulation thereof which is effective for treating the condition and may have a sterile access port (for example, the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At least one active agent in the composition is a compound of Formula I. The label or package insert indicates that the composition is used for treating the condition of choice, such as cancer. In addition, the label or package insert may indicate that the patient to be treated is one having a disorder such as a hyperproliferative disorder, neurodegeneration, cardiac hypertrophy, pain, migraine or a neurotraumatic disease or event. In one embodiment, the label or package inserts indicates that the composition comprising a compound of Formula I can be used to treat a disorder resulting from abnormal cell growth. The label or package insert may also indicate that the composition can be used to treat other disorders. Alternatively, or additionally, the article of manufacture may further comprise a second container comprising a pharmaceutically acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

The kit may further comprise directions for the administration of the compound of Formula I and, if present, the second pharmaceutical formulation. For example, if the kit

comprises a first composition comprising a compound of Formula I and a second pharmaceutical formulation, the kit may further comprise directions for the simultaneous, sequential or separate administration of the first and second pharmaceutical compositions to a patient in need thereof.

In another embodiment, the kits are suitable for the delivery of solid oral forms of a compound of Formula I, such as tablets or capsules. Such a kit preferably includes a number of unit dosages. Such kits can include a card having the dosages oriented in the order of their intended use. An example of such a kit is a "blister pack". Blister packs are well known in the packaging industry and are widely used for packaging pharmaceutical unit dosage forms. If desired, a memory aid can be provided, for example in the form of numbers, letters, or other markings or with a calendar insert, designating the days in the treatment schedule in which the dosages can be administered.

According to one embodiment, a kit may comprise (a) a first container with a compound of Formula I contained therein; and optionally (b) a second container with a second pharmaceutical formulation contained therein, wherein the second pharmaceutical formulation comprises a second compound with anti-hyperproliferative activity. Alternatively, or additionally, the kit may further comprise a third container comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

In certain other embodiments wherein the kit comprises a composition of Formula I and a second therapeutic agent, the kit may comprise a container for containing the separate compositions such as a divided bottle or a divided foil packet, however, the separate compositions may also be contained within a single, undivided container. Typically, the kit comprises directions for the administration of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing physician.

PREPARATION OF FORMULA I COMPOUNDS

Compounds of Formula I may be synthesized by synthetic routes that include processes analogous to those well-known in the chemical arts, particularly in light of the

description contained herein, and those for other heterocycles described in: Comprehensive Heterocyclic Chemistry II, Editors Katritzky and Rees, Elsevier, 1997, e.g. Volume 3; Liebigs Annalen der Chemie, (9):1910-16, (1985); Helvetica Chimica Acta, 41:1052-60, (1958); Arzneimittel-Forschung, 40(12):1328-31, (1990), each of which are expressly incorporated by reference. Starting materials are generally available from commercial sources such as Aldrich Chemicals (Milwaukee, WI) or are readily prepared using methods well known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, *Reagents for Organic Synthesis*, v. 1-23, Wiley, N.Y. (1967-2006 ed.), or *Beilsteins Handbuch der organischen Chemie*, 4, Aufl. ed. Springer-Verlag, Berlin, including supplements (also available via the Beilstein online database).

Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing Formula I compounds and necessary reagents and intermediates are known in the art and include, for example, those described in R. Larock, Comprehensive Organic Transformations, VCH Publishers (1989); T. W. Greene and P. G .M. Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley and Sons (1999); and L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995) and subsequent editions thereof.

Compounds of Formula I may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds, or 10 to 100 compounds. Libraries of compounds of Formula I may be prepared by a combinatorial 'split and mix' approach or by multiple parallel syntheses using either solution phase or solid phase chemistry, by procedures known to those skilled in the art. Thus according to a further aspect of the invention there is provided a compound library comprising at least 2 compounds, or pharmaceutically acceptable salts thereof.

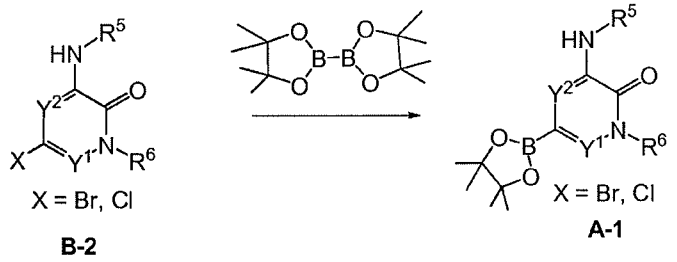
The Figures and Examples provide exemplary methods for preparing Formula I compounds. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the Formula I compounds. Although specific starting materials and reagents are depicted and discussed in the Figures and Examples, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the exemplary compounds prepared by the described methods can be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art.

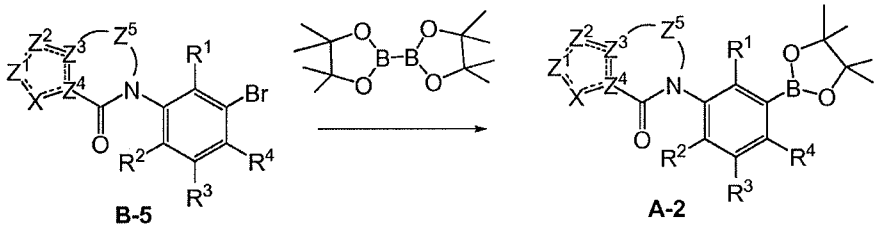
In preparing compounds of Formulas I, protection of remote functionality (e.g., primary or secondary amine) of intermediates may be necessary. The need for such

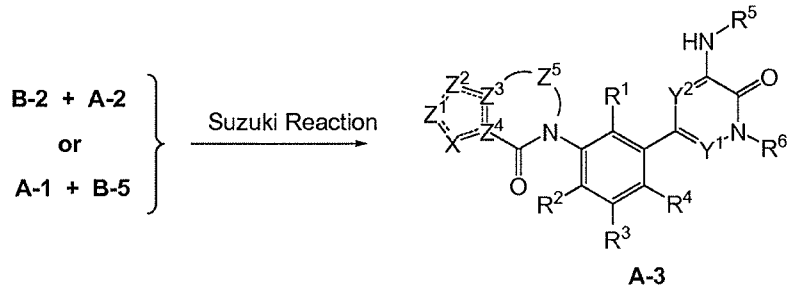
protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. Suitable amino-protecting groups include acetyl, trifluoroacetyl, t-butoxycarbonyl (BOC), benzyloxycarbonyl (CBz) and 9-fluorenylmethyleneoxycarbonyl (Fmoc). The need for such protection is readily determined by one skilled in the art. For a general description of protecting groups and their use, see T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.

General Preparative Procedures

General Procedure A Suzuki Coupling







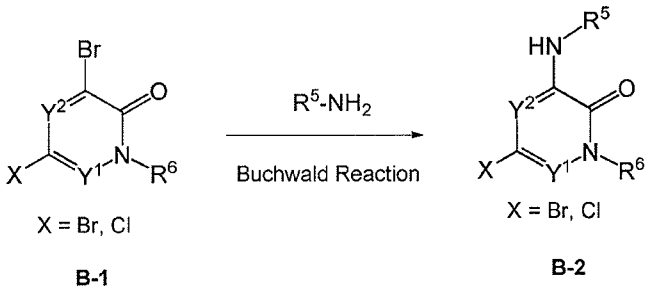
The Suzuki-type coupling reaction is useful to form carbon-carbon bonds to attach the rings of Formula I compounds and intermediates such as **A-3** (Suzuki (1991) Pure Appl. Chem. 63:419-422; Miyaura and Suzuki (1979) Chem. Reviews 95(7):2457-2483; Suzuki (1999) J. Organometal. Chem. 576:147-168). Suzuki coupling is a palladium mediated cross coupling reaction of an arylhalide, such as **B-2** or **B-5**, with a boronic acid such as **A-1** or **A-2**. For example, **B-2** may be combined with about 1.5 equivalents of 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane), and dissolved in about 3 equivalents of sodium carbonate as a 1 molar solution in water and an equal volume of acetonitrile. A catalytic

amount, or more, of a low valent palladium reagent, such as bis(triphenylphosphine)palladium(II) dichloride, is added. In some cases potassium acetate is used in place of sodium carbonate to adjust the pH of the aqueous layer. The reaction is then heated to about 140-150 °C under pressure in a microwave reactor such as the Biotage Optimizer (Biotage, Inc.) for 10 to 30 minutes. The contents are extracted with ethyl acetate, or another organic solvent. After evaporation of the organic layer the boron ester **A-1** may be purified on silica or by reverse phase HPLC. Substituents Y^1, Y^2, R^5 and R^6 are as defined, or protected forms or precursors thereof. Likewise, bromide intermediate **B-5** can be boronylated to give **A-2**. Substituents Y^1, Y^2, R^1, R^2, R^3, R^4, Z^1, Z^2, Z^3, Z^4, and X are as defined, or protected forms or precursors thereof.

Suzuki coupling of **B-2** and **A-2**, or of **A-1** and **B-5**, gives Formula I compound or intermediate **A-3**. Boronic ester (or acid) (1.5 eq) **A-1** or **A-2**, and a palladium catalyst such as bis(triphenylphosphine)palladium(II) chloride (0.05 eq) is added to a mixture of halo intermediate (1 eq) **B-2** or **B-5** in acetonitrile and 1 M of sodium carbonate aqueous solution (equal volume as acetonitrile). The reaction mixture is heated to about 150 °C in a microwave for about 15 min. LC/MS indicates when the reaction is complete. Water is added to the mixture, and the precipitated product is filtered and purified by HPLC to yield the product **A-3**. Substituents $R^{1'}$, $R^{2'}$, $R^{4'}$ may be R^1, R^2, R^4 as defined, or protected forms or precursors thereof.

A variety of palladium catalysts can be used during the Suzuki coupling step. Various low valent, Pd(II) and Pd(0) catalysts may be used in the Suzuki coupling reaction, including $PdCl2(PPh_3)_2$, $Pd(t\text{-}Bu)_3$, $PdCl_2$ dppf CH_2Cl_2, $Pd(PPh_3)_4$, $Pd(OAc)/PPh_3$, $Cl_2Pd[(Pet_3)]_2$, $Pd(DIPHOS)_2$, $Cl_2Pd(Bipy)$, $[PdCl(Ph_2PCH_2PPh_2)]_2$, $Cl_2Pd[P(o\text{-}tol)_3]_2$, $Pd_2(dba)_3/P(o\text{-}tol)_3$, $Pd_2(dba)/P(furyl)_3$, $Cl_2Pd[P(furyl)_3]_2$, $Cl_2Pd(PMePh_2)_2$, $Cl_2Pd[P(4\text{-}F\text{-}Ph)_3]_2$, $Cl_2Pd[P(C_6F_6)_3]_2$, $Cl_2Pd[P(2\text{-}COOH\text{-}Ph)(Ph)_2]_2$, $Cl_2Pd[P(4\text{-}COOH\text{-}Ph)(Ph)_2]_2$, and encapsulated catalysts Pd EnCat™ 30, Pd EnCat™ TPP30, and Pd(II)EnCat™ BINAP30 (US 2004/0254066).

General Procedure B Buchwald reaction



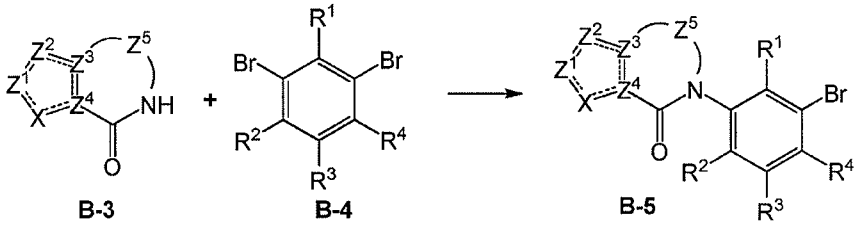
X = Br, Cl

B-1

X = Br, Cl

B-2

The Buchwald reaction is useful to aminate 6-bromo intermediates **B-1** (Wolf and Buchwald (2004) Org. Synth Coll. Vol. 10:423; Paul et al (1994) Jour. Amer. Chem. Soc. 116:5969-5970). To a solution of halo intermediate **B-1** in DMF is added the appropriate amine R^5-NH_2 (200 mol %), Cs_2CO_3 (50 mol%), $Pd_2(dba)_3$ (5 mol%), and XANTPHOS (10 mol%). The reaction is heated to about 110 °C under pressure in a Biotage optimizer microwave reactor for about 30 min. The resulting solution is concentrated *in vacuo* to give **B-2**. Other palladium catalysts and phosphine ligands may be useful.



N-Aryl amide intermediates **B-5** can also be prepared under Buchwald conditions with cyclic amide intermediates **B-3** and aryl bromides **B-4**.

Figure 1 shows an exemplary synthetic route to prepare 6-chloro,4-amino pyridazinone compounds, including 6-chloro-4-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazin-2-ylamino)pyridazin-3(2*H*)-one **101f**, from 3-nitropyrazole-5-carboxylic acid.

Figure 2 shows an exemplary synthetic route to a tricyclic amide-phenyl boronate compounds, including 2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-*a*]indol-1(2*H*)-one **101m**, from 4,5,6,7-tetrahydro-1H-indole.

Figure 3 shows an exemplary synthetic route to tricyclic amide-phenyl bromide compounds, including 2-bromo-6-(1-oxo-3,4,5,6,7,8-hexahydrobenzothieno[2,3-*c*]pyridin-2(1*H*)-yl)benzyl acetate **104h**, from 4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxylic acid.

Figure 4 shows another exemplary synthetic route to tricyclic amide-phenyl bromide compounds, including 6,6-dimethyl-3,4,6,7-tetrahydro-5*H*-cyclopenta[4,5]thieno[2,3-*c*]pyridine-1(2*H*)-one **105i**, from 3-methylcyclopent-2-enone.

Figure 5 shows an exemplary synthetic route to tricyclic 1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrido[3,4-b]indolizin-1(2H)-one compounds as boronate esters, including 2-(1-oxo-3,4,6,7,8,9-hexahydropyrido[3,4-*b*]indolizin-2(1*H*)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **118f** from 5,6,7,8-tetrahydroindolizine-2-carboxylic acid.

Figure 6 shows an exemplary synthetic route to intermediate 2-Bromo-4-fluoro-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **198d** from 1,3-dibromo-5-fluoro-2-iodobenzene.

Figure 7 shows an exemplary synthetic route to intermediate 4-Fluoro-2-(1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **198g**.

Figure 8 shows an exemplary synthetic route to intermediate 5-Fluoro-2-(1-methyl-5-(5-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **210e**.

Figure 9 shows an exemplary synthetic route to intermediate 5-[5-fluoro-2-(acetoxymethyl)-3-(1-methyl-5-{[5-(4-methylpiperazin-1-yl)pyridin-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$]trideca-1(9),2(7)-dien-6-one **212c**.

METHODS OF SEPARATION

In the methods of preparing Formula I compounds, it may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, for example: reverse-phase and normal phase; size exclusion; ion exchange; high, medium and low pressure liquid chromatography methods and apparatus; small scale analytical; simulated moving bed (SMB) and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography.

Another class of separation methods involves treatment of a mixture with a reagent selected to bind to or render otherwise separable a desired product, unreacted starting material, reaction by product, or the like. Such reagents include adsorbents or absorbents such as activated carbon, molecular sieves, ion exchange media, or the like. Alternatively, the reagents can be acids in the case of a basic material, bases in the case of an acidic material, binding reagents such as antibodies, binding proteins, selective chelators such as crown ethers, liquid/liquid ion extraction reagents (LIX), or the like. Selection of appropriate methods of separation depends on the nature of the materials involved, such as, boiling point and molecular weight in distillation and sublimation, presence or absence of polar functional

groups in chromatography, stability of materials in acidic and basic media in multiphase extraction, and the like.

Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereoisomers to the corresponding pure enantiomers. Also, some of the compounds of the present invention may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of a chiral HPLC column.

A single stereoisomer, e.g., an enantiomer, substantially free of its stereoisomer may be obtained by resolution of the racemic mixture using a method such as formation of diastereomers using optically active resolving agents (Eliel, E. and Wilen, S. "Stereochemistry of Organic Compounds," John Wiley & Sons, Inc., New York, 1994; Lochmuller, C. H., (1975) J. Chromatogr., 113(3):283-302). Racemic mixtures of chiral compounds of the invention can be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure stereoisomers, and (3) separation of the substantially pure or enriched stereoisomers directly under chiral conditions. See: "Drug Stereochemistry, Analytical Methods and Pharmacology," Irving W. Wainer, Ed., Marcel Dekker, Inc., New York (1993).

Under method (1), diastereomeric salts can be formed by reaction of enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine, α-methyl-β-phenylethylamine (amphetamine), and the like with asymmetric compounds bearing acidic functionality, such as carboxylic acid and sulfonic acid. The diastereomeric salts may be induced to separate by fractional crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid can result in formation of the diastereomeric salts.

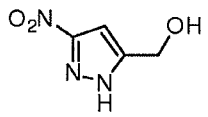
Alternatively, by method (2), the substrate to be resolved is reacted with one enantiomer of a chiral compound to form a diastereomeric pair (E. and Wilen, S.

"Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., 1994, p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the pure or enriched enantiomer. A method of determining optical purity involves making chiral esters, such as a menthyl ester, e.g., (-) menthyl chloroformate in the presence of base, or Mosher ester, α-methoxy-α-(trifluoromethyl)phenyl acetate (Jacob III. J. Org. Chem. (1982) 47:4165), of the racemic mixture, and analyzing the ^{1}H NMR spectrum for the presence of the two atropisomeric enantiomers or diastereomers. Stable diastereomers of atropisomeric compounds can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (WO 96/15111). By method (3), a racemic mixture of two enantiomers can be separated by chromatography using a chiral stationary phase ("Chiral Liquid Chromatography" (1989) W. J. Lough, Ed., Chapman and Hall, New York; Okamoto, J. Chromatogr., (1990) 513:375-378). Enriched or purified enantiomers can be distinguished by methods used to distinguish other chiral molecules with asymmetric carbon atoms, such as optical rotation and circular dichroism.

EXAMPLES

Example 101 2-(2-methyl-3-(5-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one **101**

Example 101a (3-Nitro-1*H*-pyrazol-5-yl)methanol **101a**

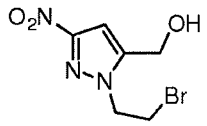


101a

A 3-L three-neck round-bottomed flask equipped with a mechanical stirrer, addition funnel and nitrogen inlet was purged with nitrogen and charged with 3-nitropyrazole-5-carboxylic acid (28.0 g, 178 mmol) and THF (420 mL) and cooled to –5 °C using an ice/acetone bath. Borane-THF complex solution (1.0 M, 535 mL, 535 mmol) was added at a rate that maintained the internal reaction temperature below 5 °C. After the addition was complete the cooling bath was removed and the reaction was stirred at room temperature for 18 h. After this time the reaction was cooled to –5 °C using an ice/acetone bath, water (70 mL) and 4N hydrochloric acid (70 mL) was added and the reaction was stirred at reflux for 1

h in order to destroy the borane complex with pyrazole. The reaction was cooled to room temperature and concentrated under reduced pressure to a volume of approximately 30 mL. Ethyl acetate (175 mL) was added and the mixture stirred for 15 min. The aqueous layer was separated and extracted with ethyl acetate (4 × 200 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate (2 × 50 mL), brine (50 mL) and dried over sodium sulfate, the drying agent was removed by filtration, and the filtrate concentrated under reduced pressure to afford **101a** in a 94% yield (24.0 g) as a light yellow solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.90 (br s, 1H), 6.87 (s, 1H), 5.58 (t, 1H, J = 5.4 Hz), 4.53 (d, 2H, J = 5.1 Hz); MS (ESI+) m/z 144.0 (M+H)

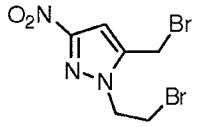
Example 101b (1-(2-Bromoethyl)-3-nitro-1*H*-pyrazol-5-yl)methanol **101b**



101b

A 1-L three-necked round-bottomed flask equipped with a mechanical stirrer and thermoregulator was purged with nitrogen and charged with (3-nitro-1*H*-pyrazol-5-yl)methanol **101a** (25.0 g, 175 mmol), DMF (250 mL), and cesium carbonate (70.0 g, 215 mmol) was heated at 104 °C for 5 min. The reaction mixture was then cooled to 0 °C using an ice/acetone bath and dibromoethane (329 g, 1.75 mol) was added portionwise (no exotherm). The reaction was stirred at 0 °C for 1 then at room temperature for 4 h. After this time a solution of KH_2PO4 (40 g) in water (400 mL) was added slowly. The reaction mixture stirred at room temperature for 30 min. Ethyl acetate (450 mL) was added and the aqueous layer was separated and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with water (200 mL), brine (200 mL), dried over sodium sulfate, and the drying agent was removed by filtration. The filtrate was concentrated under reduced pressure to afford an 86% yield (37.5 g) of crude **101b** as an orange oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (s, 1H), 4.82 (d, 2H, J = 5.4 Hz), 4.66 (t, 2H, J = 6.3 Hz), 3.83 (t, 2H, J = 6.3 Hz); MS (ESI+) m/z 249.9 (M+H).

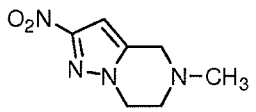
Example 101c 1-(2-Bromoethyl)-5-(bromomethyl)-3-nitro-1*H*-pyrazole **101c**



101c

A 500-mL three-necked round-bottomed flask equipped with a magnetic stirrer, nitrogen inlet and reflux condenser was purged with nitrogen and charged with (1-(2-bromoethyl)-3-nitro-1*H*-pyrazol-5-yl)methanol **101b** (37.0 g, 148 mmol) and chloroform (160 mL). The reaction was cooled to –5 °C using an ice/acetone bath and phosphorous tribromide (40.0 g, 148 mmol) was added portionwise. The cooling bath was removed and the reaction stirred at reflux for 2 h. After this time, the reaction was cooled to –5 °C and saturated aqueous sodium bicarbonate (250 mL) was added until a pH of 8.5 was reached. The mixture was extracted with ethyl acetate (3 × 150 mL) and the combined organic layers were washed with saturated aqueous sodium carbonate (2 × 50 mL), brine (75 mL), dried over sodium sulfate and the drying agent was removed by filtration. The filtrate was concentrated under reduced pressure to afford a yellow residue that was dissolved with gentle heating in methylene chloride (60 mL). Hexanes (approximately 20 mL) was added and the solution became cloudy. The mixture was heated until a solid precipitate formed, methylene chloride (9 mL) was added and the solution became clear. The solution was left to cool to room temperature and after 4 h the resulting crystals were collected by vacuum filtration. The filter cake was washed with a ice cold 1:2 mixture of methylene chloride:hexanes (2 × 20 mL) to afford 1-(2-bromoethyl)-5-(bromomethyl)-3-nitro-1*H*-pyrazole (19.7 g). The combined filtrates were evaporated and the procedure was performed again to afford an additional 9.70 g of 1-(2-bromoethyl)-5-(bromo-methyl)-3-nitro-1H-pyrazole. The solids were combined and dried under high vacuum for 18 h to afford a 57% yield (26.0 g) of **101c** as white crystals: mp 95–97 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (s, 1H), 4.63 (t, 2H, J = 6.0 Hz), 4.54 (s, 2H), 3.86 (t, 2H, J = 6.0 Hz).

Example 101d 5-Methyl-2-nitro-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine **101d**

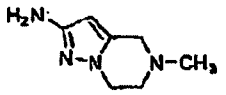


101d

A 1-L single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was charged with THF (350 mL), **101c** (10.0 g, 32.2 mmol), 2M methylamine solution in THF (113 mL, 225 mmol) and stirred at room temperature for 72 h. After this time the reaction was concentrated to dryness under reduced pressure, and the resulting solid was stirred with a mixture of ethyl acetate (75 mL) and 10% aqueous potassium carbonate

(75 mL). The aqueous layer was separated and extracted with ethyl acetate (2 × 75 mL). The combined organic extracts were washed with 10% aqueous potassium carbonate (75 mL), followed by brine (50 mL) and dried over sodium sulfate. The drying agent was removed by filtration, and the filtrate concentrated under reduced pressure to afford **101d** in 97% yield (5.70 g) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.62 (s, 1H), 4.28 (t, 2H, J = 5.4 Hz), 3.67 (s, 2H), 2.95 (t, 2H, J = 5.4 Hz), 2.52 (s, 3H); MS (ESI+) *m/z* 183.0 (M+H)

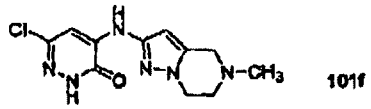
Example 101e 5-Methyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazin-2-amine **101e**



101e

A 500-mL Parr reactor bottle was purged with nitrogen and charged with 10% palladium on carbon (50% wet, 800 mg dry weight) and a solution of 5-methyl-2-nitro-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine **101d** (4.00 g, 2.20 mmol) in ethanol (160 mL). The bottle was attached to Parr hydrogenator, evacuated, charged with hydrogen gas to a pressure of 45 psi and shaken for 2 h. After this time, the hydrogen was evacuated, and nitrogen was charged into the bottle. Celite 521 (1.0 g) was added, and the mixture was filtered through a pad of Celite 521. The filter cake was washed with ethanol (2 × 75 mL), and the combined filtrates were concentrated to dryness under reduced pressure to afford a 99% yield of **101e** (3.31 g) as an orange solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.34 (s, 1H), 3.98 (t, 2H, J = 5.4 Hz), 3.52 (s, 3H), 2.84 (t, 2H, J = 5.7 Hz), 2.45 (s, 3H); MS (ESI+) *m/z* 153.1 (M+H)

Example 101f 6-Chloro-4-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazin-2-ylamino)pyridazin-3(2*H*)-one **101f**

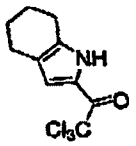


101f

A 50-mL single-neck round-bottomed flask equipped with a magnetic stirrer, reflux condenser and nitrogen inlet was charged with 1,4-dioxane (5.0 mL), **101e** (152 mg, 1.00 mmol), 4-bromo-6-chloropyridazin-3(2H)-one (209 mg, 1.00 mmol) and a 1 M THF solution of LiHMDS (5.0 mL, 5.00 mmol). After bubbling nitrogen through the resulting solution for 30 min, Xantphos (49 mg, 0.05 mmol) and tris(dibenzylideneacetone) dipalladium(0) (59 mg,

0.085 mmol) were added, and the reaction mixture was heated at reflux for 3 h. After this time, the reaction was cooled to room temperature, and water (10 mL) was added. The pH was adjusted to 6.5 with 2 N hydrochloric acid. The resulting precipitate was collected by vacuum filtration, washed with water (2 × 25 mL), absorbed on silica gel and purified by flash chromatography to afford a 74% yield (210 mg) of **101f** as a light brown solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.94 (s, 1H), 9.55 (s, 1H), 7.68 (s, 1H), 5.96 (s, 1H), 4.04 (t, 1H, J = 5.7 Hz), 3.53 (s, 2H), 2.82 (t, 2H, J = 5.7 Hz), 2.36 (s, 3H); MS (ESI+) m/z 281.1 (M+H)

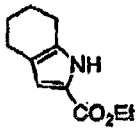
Example 101g 2,2,2-Trichloro-1-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)ethanone **101g**



101g

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer, condenser and nitrogen inlet was purged with nitrogen and charged with 4,5,6,7-tetrahydro-1H-indole (3.00 g, 24.8 mmol), trichloroacetyl chloride (13.5 g, 74.4 mmol) and 1,2-dichloroethane (50 mL). The solution was stirred at 85 °C for 2 h. After that time, the reaction mixture was concentrated under reduced pressure to afford a 100% yield (6.50 g) of **101g** as a black semi-solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.94 (s, 1H), 7.05 (s, 1H), 2.62 (t, 2H, J = 6.0 Hz), 2.47 (t, 2H, J = 6.0 Hz), 1.80 (m, 2H), 1.65 (m, 2H); MS (ESI+) m/z 266.0 (M+H)

Example 101h Ethyl 4,5,6,7-Tetrahydro-1*H*-indole-2-carboxylate **101h**

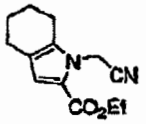


101h

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was purged with nitrogen and charged with **101g** (6.50 g, 24.8 mmol), sodium ethoxide (17.0 mg, 0.25 mmol) and ethanol (40 mL). The solution was stirred at room temperature for 1 h. After that time, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography to afford a 100% yield (4.80 g) of **101h** as a brown solid: mp 70–72 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.08 (s, 1H), 6.75

(s, 1H), 4.25 (q, 2H, J = 7.2 Hz), 2.65 (t, 2H, J = 6.0 Hz), 2.56 (t, 2H, J = 6.0 Hz), 1.85 (m, 4H), 1.28 (t, 3H, J = 7.2 Hz); MS (ESI+) m/z 194.1 (M+H)

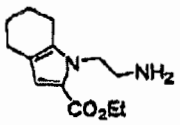
Example 101i Ethyl 1-(Cyanomethyl)-4,5,6,7-tetrahydro-1*H*-indole-2-carboxylate **101i**



101i

A 125-mL single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was purged with nitrogen and charged with **101h** (5.76 g, 29.8 mmol) and DMF (50 mL). The solution was cooled to 0 °C using an ice bath. NaH (60% dispersion in mineral oil, 1.43 g, 35.8 mmol) was added. The resulting mixture was stirred at room temperature for 1 h. After that time, bromoacetonitrile (1.43 g, 35.8 mmol) was added. The mixture was stirred at room temperature for 14 h. After that time, the reaction mixture was concentrated under reduced pressure and the residue was partitioned between ethyl acetate (150 mL) and water (450 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 150 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography to afford a 55% yield (3.80 g) of ethyl 1-(cyanomethyl)-4,5,6,7-tetrahydro-1*H*-indole-2-carboxylate **101i** as a yellow semi-solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.66 (s, 1H), 5.29 (s, 2H), 4.28 (q, 2H, J = 7.2 Hz), 2.62 (t, 2H, J = 6.3 Hz), 2.49 (t, 2H, J = 6.3 Hz), 1.92 (m, 2H), 1.75 (m, 2H), 1.33 (t, 3H, J = 7.2 Hz); MS (ESI+) m/z 233.1 (M+H)

Example 101j Ethyl 1-(2-Aminoethyl)-4,5,6,7-tetrahydro-1*H*-indole-2-carboxylate **101j**

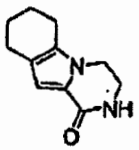


101j

A 200-mL Parr reactor bottle was purged with nitrogen and charged with 10% palladium on carbon (50% wet, 1.28 g dry weight), ethyl 1-(cyanomethyl)-4,5,6,7-tetrahydro-1*H*-indole-2-carboxylate **101i** (3.00 g, 12.9 mmol), 12% hydrochloric acid (6.5 mL, 25 mmol), ethyl acetate (60 mL) and ethanol (40 mL). The bottle was attached to a Parr hydrogenator, evacuated, charged with hydrogen gas to a pressure of 50 psi and shaken for 6

h. After this time, the hydrogen was evacuated, and nitrogen was charged into the bottle. Celite 521 (4.0 g) was added, and the mixture was filtered through a pad of Celite 521. The filter cake was washed with ethanol (2 × 20 mL), and the combined filtrates were concentrated to dryness under reduced pressure. The residue was partitioned between ethyl acetate (150 mL) and 10% aqueous potassium carbonate (100 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 75 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was triturated with ethanol (5 mL) to afford a 71% yield (1.71 g) of ethyl 1-(2-aminoethyl)-4,5,6,7-tetrahydro-1*H*-indole-2-carboxylate **101j** as a white solid: mp 102–104 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.61 (s, 1H), 6.22 (br, 2H), 4.15 (m, 4H), 2.77 (m, 2H), 2.59 (t, 2H, J = 6.5 Hz), 2.42 (t, 2H, J = 6.5 Hz), 1.70 (m, 2H), 1.62 (m, 2H), 1.23 (t, 3H, J = 7.0 Hz); MS (APCI+) m/z 237.2 (M+H)

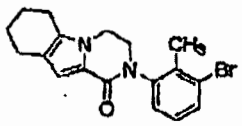
Example 101k Ethyl 1-(2-Aminoethyl)-4,5,6,7-tetrahydro-1*H*-indole-2-carboxylate **101k**



101k

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was purged with nitrogen and charged with ethyl 1-(2-aminoethyl)-4,5,6,7-tetrahydro-1*H*-indole-2-carboxylate **101j** (1.80 g, 7.63 mmol), sodium ethoxide (1.55 g, 22.8 mmol) and ethanol (50 mL). The mixture was stirred at 55 °C for 5 h. After that time, the reaction mixture was concentrated under reduced pressure and the residue was partitioned between ethyl acetate (200 mL) and water (100 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography to afford a 42% yield (605 mg) of ethyl 1-(2-aminoethyl)-4,5,6,7-tetrahydro-1*H*-indole-2-carboxylate **101k** as a white solid: mp 207–209 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.41 (s, 1H), 6.36 (s, 1H), 3.84 (t, 2H, J = 6.0 Hz), 3.42 (m, 2H), 2.51 (t, 2H, J = 6.0 Hz), 2.42 (t, 2H, J = 6.0 Hz), 1.76 (m, 2H), 1.65 (m, 2H); (APCI+) m/z 191.3 (M+H)

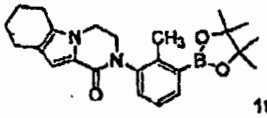
Example 101l 2-(3-Bromo-2-methylphenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-*a*]indol-1(2*H*)-one **101l**



1011

A 50-mL three-neck round-bottomed flask equipped with a reflux condenser, magnetic stirrer and nitrogen inlet was charged with ethyl 1-(2-aminoethyl)-4,5,6,7-tetrahydro-1*H*-indole-2-carboxylate **101k** (560 m g, 2.95 mmol), 2,6-dibromotoluene (1.47 g, cesium carbonate (1.92 g, 5.90 mmol), *N,N'*-dimethylethylenediamine (260 mg, 2.95 mmol) and 1,4-dioxane (25 mL). After bubbling nitrogen through the resulting suspension for 30 min, copper *N,N'*-dimethylethylenediamine (260 mg, 2.95 mmol) was added, and the reaction mixture was heated at 105 °C (oil bath temperature) for 14 h. After this time, the mixture was cooled to room temperature and filtered. The filtrate was diluted with ethyl acetate (100 mL) and water (20 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography to afford a 57% yield (600 mg) of 2-(3-bromo-2-methylphenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-*a*]indol-1(2*H*)-one **1011** as a white solid: mp 163–165 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.57 (dd, 1H, J = 8.0, 0.5 Hz), 7.32 (d, 1H, J = 7.5 Hz), 7.21 (t, 1H, J = 8.0 Hz), 6.50 (s, 1H), 4.11 (m, 3H), 3.75 (m, 1H), 2.59 (m, 2H), 2.45 (m, 2H), 2.21 (s, 3H), 1.78 (m, 2H), 1.68 (m, 2H); (APCI+) *m/z* 358.6 (M+H)

Example 101m 2-(2-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-*a*]indol-1(2*H*)-one **101m**



101m

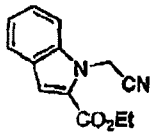
A 50-mL three-neck round-bottomed flask equipped with a reflux condenser, magnetic stirrer and nitrogen inlet was charged with of 2-(3-bromo-2-methylphenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-*a*]indol-1(2*H*)-one **1011** (600 mg, 1.67 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane (1.70 g, 6.70 mmol), potassium acetate (656 mg, 6.68 mmol), and 1,4-dioxane (25 mL). After bubbling nitrogen through the resulting suspension for 30 min, XPhos (159 mg, 0.334 mmol) and tris(dibenzylideneacetone)dipalladium(0) (153 mg, 0.167 mmol) were added, and the reaction mixture was heated at 105 °C (oil bath temperature) for 14 h. After this time, the mixture was

cooled to room temperature and filtered. The filtrate was diluted with ethyl acetate (75 mL) and water (20 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3×25 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography to afford a 109 % crude yield (740 mg) of 2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-*a*]indol-1(2*H*)-one **101m** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (dd, 1H, J = 6.6, 2.1 Hz), 7.26 (m, 2H), 6.80 (s, 1H), 4.10 (m, 3H), 3.75 (m, 1H), 2.54 (m, 4H), 2.45 (s, 3H), 1.87 (m, 2H), 1.75 (m, 2H), 1.25 (s, 12H); MS (APCI+) *m/z* 407.7 (M+H)

A 100-mL three-neck round-bottomed flask equipped with a reflux condenser, magnetic stirrer and nitrogen inlet was charged with 2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-*a*]indol-1(2*H*)-one **101m** (740 mg, 1.67 mmol), 6-chloro-4-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazin-2-ylamino)pyridazin-3(2*H*)-one **101f** (422 mg, 1.34 mmol), sodium carbonate (568 mg, 5.36 mmol), DMF (5 mL), water (5 mL) and 1,4-dioxane (20 mL). After bubbling nitrogen through the resulting suspension for 30 min, tetrakis(triphenylphosphine)palladium(0) (155 mg, 0.134 mmol) was added, and the reaction mixture was heated at 100 °C for 15 h. After this time, the mixture was cooled to room temperature and diluted with ethyl acetate (100 mL) and water (30 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3×25 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to afford a 17% yield (120 mg) of **101** as an off-white solid: mp 195–197 °C ; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.95 (s, 1H), 9.19 (s, 1H), 7.75 (s, 1H), 7.34 (m, 2H), 7.29 (m, 1H), 6.50 (s, 1H), 5.96 (s, 1H), 4.14 (m, 1H), 4.08 (m, 2 H), 3.95 (m, 2H), 3.77 (m, 1H), 3.51 (s, 2H), 2.78 (t, 2H, J = 6.0 Hz), 2.60 (m, 2H), 2.46 (t, 2H, J = 6.0 Hz), 2.35 (s, 3H), 2.07 (s, 3H), 1.78 (m, 2H), 1.68 (m, 2H); MS (ESI+) *m/z* 521 (M+H)

Example 102 2-(2-methyl-3-(5-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **102**

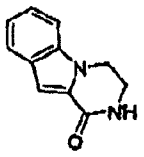
Example 102a Ethyl 1-(Cyanomethyl)-1*H*-indole-2-carboxylate **102a**



102a

A 250-mL single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was purged with nitrogen and charged with ethyl indole-2-carboxylate (10.0 g, 52.9 mmol) and DMF (100 mL). The solution was cooled to 0 °C using an ice bath. NaH (60% dispersion in mineral oil, 2.54 g, 63.5 mmol) was added. The resulting mixture was stirred at room temperature for 1 h. After that time, bromoacetonitrile (7.62 g, 63.5 mmol) was added. The mixture was stirred at room temperature for 14 h. After that time, the reaction mixture was concentrated under reduced pressure and the residue was partitioned between ethyl acetate (300 mL) and water (900 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 300 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography to afford a 66% yield (8.00 g) of **102a** as an off-white solid: mp 65–67 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, 1H, J = 8.1), 7.44 (m, 3H), 7.25 (m, 1H), 5.62 (s, 2H), 4.42 (q, 2H, J = 7.2 Hz), 1.43 (t, 3H, J = 7.2 Hz); MS (ESI+) *m/z* 229.1 (M+H).

Example 102b 3,4-Dihydropyrazino[1,2-*a*]indol-1(2*H*)-one **102b**

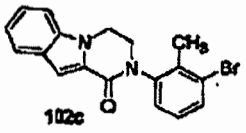


102b

A 500-mL Parr reactor bottle was purged with nitrogen and charged with 10% palladium on carbon (50% wet, 3.47 g dry weight), **102a** (8.00 g, 35.0 mmol), 12% hydrochloric acid (17.5 mL, 70 mmol), ethyl acetate (150 mL) and ethanol (100 mL). The bottle was attached to a Parr hydrogenator, evacuated, charged with hydrogen gas to a pressure of 50 psi and shaken for 6 h. After this time, the hydrogen was evacuated, and nitrogen was charged into the bottle. Celite 521 (10.0 g) was added, and the mixture was filtered through a pad of Celite 521. The filter cake was washed with ethanol (2 × 50 mL), and the combined filtrates were concentrated to dryness under reduced pressure. The residue

was partitioned between ethyl acetate (400 mL) and 10% aqueous potassium carbonate (300 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 200 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was triturated with ethanol (5 mL) to afford a 70% yield (4.57 g) of **102b** as an off-white solid: mp 228–230 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, 1H, J = 8.1 Hz), 7.34 (m, 3H), 7.18 (m, 1H), 6.75 (br s, 1H), 4.29 (t, 2H, J = 5.4 Hz), 3.84 (m, 2H); MS (ESI+) *m/z* 187.1 (M+H).

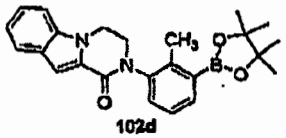
Example 102c 2-(3-Bromo-2-methylphenyl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one **102c**



102c

A 100-mL three-neck round-bottomed flask equipped with a reflux condenser, magnetic stirrer and nitrogen inlet was charged with **102b** (1.00 g, 5.37 mmol), (2.69 g, 10.7 mmol), cesium carbonate (3.49 g, 10.7 mmol), *N,N'*-dimethylethylenediamine (473 mg, 5.37 mmol) and 1,4-dioxane (45 mL). After bubbling nitrogen through the resulting suspension for 30 min, copper iodide (510 mg, 2.69 mmol) was added, and the reaction mixture was heated at 105 °C (oil bath temperature) for 14 h. After this time, the mixture was cooled to room temperature and filtered. The filtrate was diluted with ethyl acetate (200 mL) and water (40 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography to afford a 62% yield (1.18 g) of **102c** as an off-white solid: mp 178–180 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (dt, 1H, J = 8.2, 1.0 Hz), 7.58 (dd, 1H, J = 7.8, 1.2 Hz), 7.37 (m, 3H), 7.19 (m, 3H), 4.45 (m, 2H), 4.21 (m, 1H), 3.95 (m, 1H), 2.38 (s, 3H); MS (ESI+) *m/z* 355.0 (M+H).

Example 102d 2-(2-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one **102d**



102d

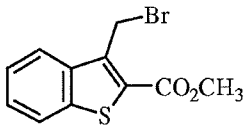
A 100-mL three-neck round-bottomed flask equipped with a reflux condenser, magnetic stirrer and nitrogen inlet was charged with **102c** (1.18 g, 3.32 mmol),

4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (929 mg, 3.65 mmol), potassium acetate (491 mg, 4.98 mmol) and 1,4-dioxane (25 mL). After bubbling nitrogen through the resulting suspension for 30 min, XPhos (317 mg, 0.664 mmol) and tris(dibenzylideneacetone)-dipalladium(0) (561 mg, 0.332 mmol) were added, and the reaction mixture was heated at 105 °C (oil bath temperature) for 14 h. After this time, the mixture was cooled to room temperature and filtered. The filtrate was diluted with ethyl acetate (150 mL) and water (40 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chroma-tography to afford a 57% yield (760 mg) of **102d** as an off-white solid: mp 193–195 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (dd, 1H, J = 7.0, 1.7 Hz), 7.74 (d, 1H, J = 8.2 Hz), 7.37 (m, 3H), 7.28 (m, 2H), 7.19 (m, 1H), 4.45 (m, 2H), 4.22 (m, 1H), 3.94 (m, 1H), 2.50 (s, 3H), 1.35 (s, 12H); MS (ESI+) *m/z* 403.2 (M+H).

A 25-mL three-neck round-bottomed flask equipped with a reflux condenser, magnetic stirrer and nitrogen inlet was charged with **102d** (760 mg, 1.89 mmol), **101f** (379 mg, 1.35 mmol), sodium carbonate (430 mg, 4.05 mmol), DMF (5 mL), water (2.5 mL) and 1,4-dioxane (8 mL). After bubbling nitrogen through the resulting suspension for 30 min, tetrakis(triphenylphosphine)palladium(0) (437 mg, 0.378 mmol) was added, and the reaction mixture was heated at reflux for 14 h. After this time, the mixture was cooled to room temperature and diluted with ethyl acetate (100 mL) and water (30 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 25 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica to afford a 26% yield (183 mg) of **102** as an off-white solid: mp 188–190 °C (dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.99 (s, 1H), 9.23 (s, 1H), 7.79 (s, 1H), 7.71 (d, 1H, J = 8.1 Hz), 7.61 (d, 1H, J = 7.9 Hz), 7.38 (m, 4H), 7.14 (m, 2H), 5.97 (s, 1H), 4.63 (m, 1H), 4.49 (m, 1H), 4.27 (m, 1H), 4.12 (m, 3H), 3.51 (s, 2H), 2.79 (t, 2H, J = 5.1 Hz), 2.35 (s, 3H), 2.18 (s, 3H); MS (ESI+) *m/z* 521.2 (M+H).

Example 103 4-{2-Methyl-3-[1-methyl-5-({5-methyl-4H,5H,6H,7H-pyrazolo[1,5-a]pyrazin-2-yl}amino)-6-oxo-1,6-dihydropyridazin-3-yl]phenyl}-7-thia-4-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6),9,11-tetraen-5-one **103**

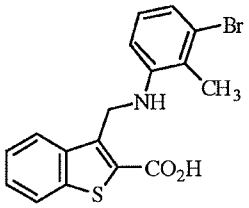
Example 103a Methyl 3-(Bromomethyl)benzo[*b*]thiophene-2-carboxylate **103a**



103a

A 250-mL single-neck round-bottomed flask equipped with a magnetic stirrer, nitrogen inlet and reflux condenser was purged with nitrogen and charged with methyl 3-methylbenzo[*b*]thiophene-2-carboxylate (2.00 g, 9.70 mmol) and benzene (20 mL). *N*-bromosuccinimide (1.72 g, 9.70 mmol) and 2,2'-azobisisobutyronitrile (160 mg, 1.00 mmol) were added, and the mixture was refluxed for 2 h. After this time, the mixture was cooled to room temperature and filtered. The filter cake was rinsed with carbon tetrachloride (20 mL) and the filtrate was concentrated under reduced pressure. The resulting residue was purified by column chromatography to afford **103a** in 82% yield (2.27 g) as a white solid: mp 101–102 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (m, 1H), 7.86 (m, 1H), 7.51 (m, 2H), 5.22 (s, 2H), 3.97 (s, 3H).

Example 103b 3-((3-Bromo-2-methylphenylamino)methyl)benzo[*b*]thiophene-2-carboxylic Acid **103b**

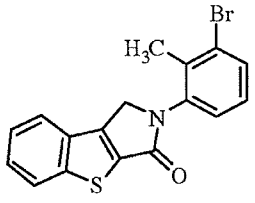


103b

A 250-mL single-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was purged with nitrogen and charged with **103a** (2.26 g, 7.92 mmol), 3-bromo-2-methylaniline (1.77 g, 9.51 mmol) and acetonitrile (50 mL). Cesium carbonate (7.75 g, 23.8 mmol) was added, and the mixture was stirred at 50 °C for 14 h. After this time, the reaction mixture was concentrated under reduced pressure and the resulting residue was dissolved in THF (15 mL), methanol (15 mL) and water (15 mL) and treated with lithium hydroxide monohydrate (1.30 g, 31.0 mmol). After stirring at room temperature for 14 h, the solvent was removed under reduced pressure and the resulting residue was acidified with 2 M hydrochloric acid to pH 5. The resulting mixture was extracted with ethyl acetate (3 × 30 mL), and the organic extracts were combined and dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography to afford **103b** in 59% yield (1.70 g) as a white solid: mp 120–121 °C; ^{1}H

NMR (500 MHz, DMSO-d_6) δ 8.30 (d, 1H, J = 12.5 Hz), 7.98 (d, 1H, J = 12.5 Hz), 7.46 (m, 2H), 6.77 (m, 3H), 4.97 (s, 2H), 2.15 (s, 3H); MS (ESI+) m/z 378.9 (M+H).

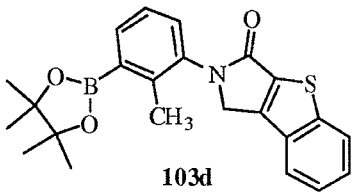
Example 103c 2-((3-Bromo-2-methylphenyl)-1*H*benzothieno[2,3-*c*]pyrrol-3(2*H*)-one **103c**



103c

A 250-mL single-neck round-bottomed flask equipped with a magnetic stirrer was purged with nitrogen and charged with **103b** (1.70 g, 4.51 mmol), triethylamine (914 mg, 9.00 mmol) and anhydrous DMF (25 mL). Benzotriazol-1-yl-oxy-*tris*(dimethylamino)-phosphonium hexafluorophosphate (BOP, 2.60 g, 5.90 mmol) was added, and the reaction was stirred at room temperature for 14 h. After this time, the reaction was diluted with water (20 mL), and the resulting suspension was filtered. The filter cake was dissolved in methylene chloride (40 mL), and the solution was washed with saturated aqueous sodium bicarbonate (10 mL), water (10 mL), and dried over sodium sulfate. The drying agent was removed by filtration, and the solvent was evaporated under reduced pressure. The resulting residue was purified by flash chromatography to afford a 78% yield of **103c** (1.26 g) as a white semi-solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (m, 1H), 7.80 (m, 1H), 7.60 (d, 1H, J = 8.0 Hz), 7.49 (m, 2H), 7.28 (d, 1H, J = 8.0 Hz), 7.16 (t, 1H, J = 8.0 Hz), 4.85 (s, 2H), 2.37 (s, 3H).

Example 103d 2-(2-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-benzothieno[2,3-*c*]pyrrol-3(2*H*)-one **103d**

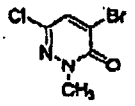


103d

A 250-mL single-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was purged with nitrogen and charged with **103c** (1.26 g, 3.51 mmol), 4,4,4',4',-5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane (2.23 g, 8.80 mmol), potassium acetate (1.00 g, 10.20 mmol) and 1,4-dioxane (30 mL). A stream of nitrogen was passed through the resulting suspension for 30 min. [1,1'-Bis(diphenylphosphino)ferrocene]-

dichloropalladium(II) (260 mg, 0.355 mmol) was added, and the reaction was stirred at reflux for 3 h. After this time, the mixture was cooled to ambient temperature, partitioned between water (25 mL) and ethyl acetate (50 mL) and filtered through a plug of Celite 521. The organic phase was separated, dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography to afford quantitative yield (1.84 g) of **103d** as a yellow semi-solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (m, 1H), 7.80 (m, 2H), 7.47 (m, 2H), 7.35 (d, 1H, J = 7.5 Hz), 7.28 (d, 1H, J = 7.5 Hz), 4.86 (s, 2H), 2.48 (s, 3H), 1.35 (s, 12H).

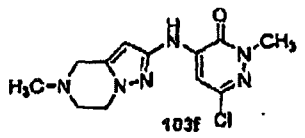
Example 103e 4-Bromo-6-chloro-2-methylpyridazin-3(2*H*)-one **103e**



103e

A 250-mL single-necked round bottomed flask equipped with a magnetic stirrer was purged with nitrogen and charged with 4-bromo-6-chloropyridazin-3(2H)-one (1.00 g, 4.77 mmol) and DMF (15 mL). Sodium hydride (60% by weight in oil, 229 mg, 5.73 mmol) was added in one portion. After stirring at room temperature for 10 minutes, iodomethane (1.02 g, 7.16 mmol) was added and the reaction stirred at room temperature for 1.5 h. The reaction was then quenched with aqueous saturated sodium bicarbonate (10 mL) and the resulting solution poured into water (150 mL). The mixture was then extracted with ethyl acetate (250 mL). The organic layer was dried over sodium sulfate. The drying agent was then removed by filtration, and the filtrate was concentrated under reduced pressure to residue. Purification by column chromatography afforded **103e** in a 68% yield (722 mg) as a white solid: mp 107–108 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (s, 1H), 3.81 (s, 3H).

Example 103f 6-Chloro-2-methyl-4-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazin-2-ylamino)pyridazin-3(2*H*)-one **103f**



103f

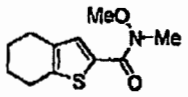
A 250-mL three-neck round-bottomed flask equipped with a reflux condenser, magnetic stirrer and nitrogen inlet was charged with 4-bromo-6-chloro-2-methylpyridazin-3(2*H*)-one **103e** (1.90 g, 8.53 mmol), **101e** (1.18 g, 7.75 mmol) and 1,4-dioxane (40 mL). The flask was purged with nitrogen and cooled to 0 °C. A 1 M solution of lithium

hexamethyldisilazide in THF (39 mL, 39.0 mmol) was added. After bubbling nitrogen through the resulting suspension for 30 min, Xantphos (381 mg, 0.659 mmol) and tris(dibenzylideneacetone)-dipalladium(0) (355 mg, 0.388 mmol) were added, and the reaction mixture was heated at reflux for 2 h. After this time, the mixture was cooled to room temperature and diluted with water (10 mL). The pH of the solution was adjusted to 7.6 with 2 N hydrochloric acid. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 40 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica to afford a 76% yield (1.74 g) of **103f** as an off-white solid: mp 184–186 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.62 (s, 1H), 7.72 (s, 1H), 6.00 (s, 1H), 4.04 (t, 2H, J = 5.1 Hz), 3.65 (s, 3H), 3.53 (s, 2H), 2.82 (t, 2H, J = 5.1 Hz), 2.37 (s, 3H); MS (ESI+) m/z 295.1 (M+H).

A 150-mL single-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was purged with nitrogen and charged with **103d** (580 mg, 1.43 mmol), **103f** (300 mg, 1.00 mmol), sodium carbonate (320 mg, 3.00 mmol), 1,4-dioxane (8 mL), DMF (5 mL) and water (2.5 mL). This mixture was degassed with nitrogen for 30 min. Tetrakis(triphenylphosphine)palladium (120 mg, 0.103 mmol) was added. After heating at reflux for 14 h, the reaction mixture was cooled to room temperature and partitioned between water (40 mL) and methylene chloride (100 mL). The layers were separated, and the aqueous phase was extracted with methylene chloride (2 × 50 mL). The organic extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography to afford **103** in 44% yield (240 mg) as an off-white solid: mp 175–176 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.28 (s, 1H), 8.20 (m, 1H), 8.04 (s, 1H), 7.81 (s, 1H), 7.56 (m, 3H), 7.40 (m, 2H), 5.99 (s, 1H), 5.12 (s, 1H), 3.97 (t, 2H, J = 5.5 Hz), 3.76 (s, 3H), 3.51 (s, 2H), 2.79 (t, 2H, J = 8.5 Hz), 2.35 (s, 3H), 2.17 (s, 3H); MS (ESI+) m/z 538.2 (M+H).

Example 104 5-[2-(Hydroxymethyl)-3-[1-methyl-6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydropyridin-3-yl]phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one **104**

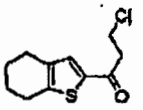
Example 104a *N*-Methoxy-*N*-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-2-carboxamide **104a**



104a

A 250-mL single-neck round-bottomed flask equipped with a magnetic stirrer was purged with nitrogen, charged with 4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxylic acid (3.00 g, 16.5 mmol), methylene chloride (80 mL), and DMF (60 mg, 0.825 mmol) and cooled to 0 °C. To the resulting solution, oxalyl chloride (2.31 g, 18.2 mmol) was added dropwise. After this addition was complete, the reaction was warmed to room temperature and stirred for 2 h. After this time, the reaction was concentrated to dryness under reduced pressure. The resulting white solid was dissolved in methylene chloride (80 mL) and the solution cooled to 0 °C. Triethylamine (5.00 g, 49.5 mmol) and N,O-dimethylhydroxylamine (1.61 g, 16.5 mmol) were then added. After the addition was complete, the cooling bath was removed, and the reaction mixture was stirred at room temperature for 16 h. After this time, the reaction mixture was partitioned between water (100 mL) and ethyl acetate (200 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate (100 mL). The combined organic extracts were washed with water (100 mL), followed by brine (100 mL) and dried over sodium sulfate. The drying agent was removed by filtration, and the solvent was evaporated under reduced pressure. The resulting residue was purified by flash chromatography to afford an 88% yield of **104a** (3.29 g) as a white solid: mp 36–37 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (s, 1H), 3.76 (s, 3H), 3.34 (s, 3H), 2.78 (t, 2H, J = 6.0 Hz), 2.62 (t, 2H, J = 6.0 Hz), 1.82 (m, 4H); MS (APCI+) *m/z* 226.3 (M+H)

Example 104b 3-Chloro-1-(4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)propan-1-one **104b**

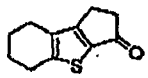


104b

A 100-mL single-necked round-bottomed flask equipped with a magnetic stirrer was purged with nitrogen and charged with **104a** (2.70 g, 12.0 mmol) and anhydrous THF (45 mL), and the solution was cooled to -10 °C with acetone/ice bath. A 1.0 M solution of vinylmagnesium bromide in THF (13.2 mL, 13.2 mmol) was added dropwise, and the resulting reaction mixture was stirred at 0 °C for 4 h. After this time, the reaction mixture was partitioned between ethyl acetate (100 mL) and 2 M aqueous hydrochloric acid (40 mL).

The layers were separated, and the aqueous phase was extracted with ethyl acetate (40 mL). The combined organic extracts were washed with water (100 mL), followed by brine (100 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was dissolved in methylene chloride (30 mL), and a 2 M solution of hydrogen chloride in diethyl ether (15 mL) was added. After stirring at room temperature for 1 h, the solvents were removed under reduced pressure. Purification of the resulting residue by column chromatography afforded a 29% yield (804 mg) of **104b** as an off-white solid: mp 57–58 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (s, 1H), 3.89 (t, 2H, J = 7.0 Hz), 3.30 (t, 2H, J = 7.0 Hz), 2.81 (t, 2H, J = 6.0 Hz), 2.64 (t, 2H, J = 6.0 Hz), 1.83 (m, 4H); MS (ECI+) *m/z* 229.1 (M+H)

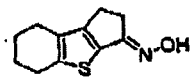
Example 104c 5,6,7,8-Tetrahydro-1*H*-benzo[*b*]cyclopenta[*d*]thiophen-3(2*H*)-one **104c**



104c

A 50-mL single-necked round-bottomed flask equipped with a magnetic stirrer was charged with **104b** (800 mg, 3.51 mmol) and 98% sulfuric acid (8 mL). After stirring at 95 °C for 16 h, the reaction mixture was poured into ice (50 g), and the resulting suspension was extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography to afford **104c** in 47% yield (320 mg) as an off-white solid: mp 75–76 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.89 (m, 2H), 2.87–2.83 (m, 4H), 2.56 (t, 2H, J = 6.5 Hz), 1.84 (m, 4H)

Example 104d 5,6,7,8-Tetrahydro-1*H*-benzo[*b*]cyclopenta[*d*]thiophen-3(2*H*)-one oxime **104d**

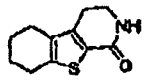


104d

A 100-mL single-neck round-bottomed flask equipped with a mechanical stirrer and nitrogen inlet was charged with hydroxylamine hydrochloride (573 mg, 8.25 mmol) and methanol (10 mL). The mixture was cooled to 0 °C using an ice bath. Sodium acetate (677 mg, 8.25 mmol) was added. The mixture was stirred at 0 °C for 30 min. After this time, **104c** (319 mg, 1.65 mmol) was added, and the reaction was stirred at room temperature for 16 h.

After this time, the mixture was concentrated, and the resulting residue was triturated with water (10 mL). The resulting solid was collected and dried in a vacuum oven at 45 °C to afford an 84% yield (287 mg) of **104d** as an off-white solid: mp 173–174 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.38 (s, 1H), 2.97 (m, 2H), 2.77–2.73 (m, 4H), 2.47 (m, 2H), 1.75 (m, 4H); MS (APCI+) *m/z* 208.3 (M+H)

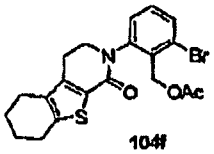
Example 104e 3,4,5,6,7,8-Hexahydrobenzothieno[2,3-*c*]pyridin-1(2*H*)-one **104e**



104e

A 50-mL single-neck round-bottomed flask equipped with a reflux condenser, magnetic stirrer and nitrogen inlet was charged with **104d** (285 mg, 1.38 mmol) and polyphosphoric acid (15 g). After stirring at 80 °C for 16 h, the reaction mixture was cooled to room temperature, and water (30 mL) was added. The resulting mixture was stirred for 30 min and filtered. The filter cake was washed with water (20 mL) and dried in a vacuum oven at 45 °C to afford a 75% yield (215 mg) of **104e** as an off-white solid: mp 203 °C dec; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.62 (s, 1H), 3.59 (t, 2H, J = 7.0 Hz), 2.81 (t, 2H, J = 6.0 Hz), 2.72 (t, 2H, J = 7.0 Hz), 2.48 (t, 2H, J = 6.0 Hz), 1.84 (m, 4H). MS (APCI+) *m/z* 208.3 (M+H)

Example 104f 2-Bromo-6-(1-oxo-3,4,5,6,7,8-hexahydrobenzothieno[2,3-*c*]pyridin-2(1*H*)-yl)benzyl acetate **104f**



104f

A 100-mL three-neck round-bottomed flask equipped with a reflux condenser, magnetic stirrer and nitrogen inlet was charged with **104e** (214 mg, 1.04 mmol), 2,6-dibromobenzyl acetate **104g** (519 mg, 2.08 mmol), cesium carbonate (678 mg, 2.08 mmol), *N,N'*-dimethylethylenediamine (92 mg, 1.04 mmol) and 1,4-dioxane (10 mL). After bubbling nitrogen through the resulting suspension for 30 min, copper iodide (99 mg, 0.520 mmol) was added, and the reaction mixture was heated at 100 °C (oil bath temperature) for 16 h. After this time, the mixture was cooled to room temperature and filtered. The filtrate was diluted

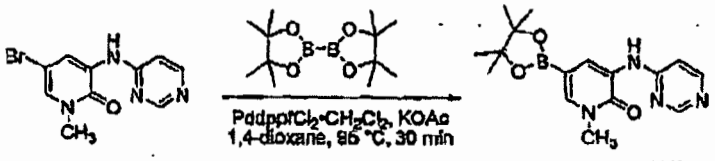
with ethyl acetate (100 mL) and water (50 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography to afford a 30% yield (138 mg) of 2-Bromo-6-(1-oxo-3,4,5,6,7,8-hexahydrobenzothieno[2,3-*c*]pyridin-2(1*H*)-yl)benzyl acetate **104f** as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (dd, 1H, J = 7.0, 1.5 Hz), 7.30–7.24 (m, 2H), 5.23 (m, 2H), 4.06 (m, 1H), 3.77 (m, 1H), 2.98 (m, 1H), 2.83–2.77 (m, 3H), 2.50 (m, 2H), 2.04 (s, 3H), 1.85 (m, 4H)

Example 104g 2,6-dibromobenzyl acetate **104g**

A 250-mL single-neck round-bottomed flask equipped with a magnetic stirrer, reflux condenser and nitrogen inlet was purged with nitrogen and charged with 2,6-dibromotoluene (2.50 g, 10.0 mmol), *N*-bromosuccinimide (1.78 g, 10.0 mmol) and carbon tetrachloride (40 mL). The solution was heated to 80 °C (oil bath temperature), and 2,2'-azobisisobutyronitrile (164 mg, 1.00 mmol) was added. The resulting mixture was refluxed for 14 h. After that time, the mixture was cooled to room temperature and filtered. The filter cake was washed with carbon tetrachloride (2 × 20 mL). The filtrate was diluted with ethyl acetate (200 mL) and washed with water (40 mL), saturated aqueous sodium bicarbonate (40 mL) and brine (40 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to afford a quantative yield (3.28 g) of 1,3-dibromo-2-(bromomethyl)benzene as a yellow solid: mp 77–78 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, 2H, J = 8.1 Hz), 7.07 (t, 1H, J = 8.1 Hz), 4.83 (s, 2H)

A 250-mL single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was purged with nitrogen and charged with 1,3-dibromo-2-(bromomethyl)benzene (3.28 g, 10.0 mmol), potassium acetate (3.93 g, 40.0 mmol) and DMF (100 mL). The solution was stirred at room temperature for 14 h. After that time, the reaction mixture was diluted with water (900 mL) and extracted with ethyl acetate (3 × 200 mL). The combined organic layers were washed with brine (100 mL), dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography to afford an 88% yield (2.70 g) of 2,6-dibromobenzyl acetate **104g** as an off-white solid: mp 62–65 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, 2H, J = 8.0 Hz), 7.07 (t, 1H, J = 7.9 Hz), 5.42 (s, 2H), 2.11 (s, 3H); MS (ESI+)

Example 104h 1-methyl-3-(pyrimidin-4-ylamino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one **104h**



109b 104h

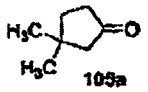
A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and thermoregulator was purged with nitrogen and charged with 5-bromo-1-methyl-3-(pyrimidin-4-ylamino)pyridin-2(1H)-one **109b** (300 mg, 1.07 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (534 mg, 2.14 mmol), potassium acetate (210 mg, 2.14 mmol) and 1,4-dioxane (10 mL). A stream of nitrogen was passed through the resulting suspension for 30 min. [1,1'-Bis(diphenylphosphino)ferrocene]dichloro-palladium(II), complex with dichloromethane ($PddppfCl_2 \cdot CH_2Cl_2$, 39 mg, 0.054 mmol) was then added, and the reaction was stirred at 95 °C for 30 min. After this time, the mixture was cooled to ambient temperature, partitioned between water (40 mL) and ethyl acetate (60 mL) and filtered through a plug of Celite 521. The organic phase was separated, dried over sodium sulfate, filtered and concentrated under reduced pressure to afford crude **104h** as a black oil which was used directly in the next step without further purification. MS (ESI+) *m/z* 329.1 (M+H)

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was purged with nitrogen and charged with **104f** (136 mg, 0.313 mmol), crude **104h** (1.07 mmol, presumed quantitative yield), sodium carbonate (100 mg, 0.940 mmol), 1,4-dioxane (5 mL) and water (1 mL). This mixture was degassed with nitrogen for 30 min. Tetrakis(triphenyl-phosphine)palladium mixture (636 mg, 0.031 mmol) was added. After heating at 100 °C for 3 h, the reaction was cooled to room temperature and partitioned between water (40 mL) and methylene chloride (100 mL). The layers were separated, and the aqueous phase was extracted with methylene chloride (2 × 50 mL). The organic extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was dissolved in methanol (5 mL), and potassium carbonate (500 mg, 3.62 mmol) was added. After stirring at room temperature for 2 h, the reaction mixture was partitioned between water (20 mL) and methylene chloride (20 mL). The layers were separated, and the aqueous phase was extracted with methylene chloride (2 × 20 mL). The organic extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography to afford **104** in 26% yield (42 mg) as a white solid: mp >250 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.17 (s,

1H), 8.71 (d, 1H, J = 2.5 Hz), 8.64 (s, 1H), 8.29 (d, 1H, J = 6.0 Hz), 7.52 (d, 1H, J = 2.5 Hz), 7.45 (t, 1H, J = 7.5 Hz), 7.36–7.30 (m, 3H), 4.84 (t, 1H, J = 3.5 Hz), 4.36 (m, 2H), 4.03 (m, 1H), 3.87 (m, 1H), 3.60 (s, 3H), 2.96 (m, 1H), 2.85 (m, 1H), 2.77 (m, 2H), 2.58–2.46 (m, 2H), 1.79 (m, 4H); MS (APCI+) *m/z* 514.2 (M+H)

Example 105 10-[2-(Hydroxymethyl)-3-[1-methyl-6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydropyridin-3-yl]phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one **105**

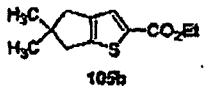
Example 105a 3,3-Dimethylcyclopentanone **105a**



105a

A 1-L three-neck round-bottomed flask equipped with a magnetic stirrer, addition funnel and nitrogen inlet was purged with nitrogen and charged with ether (200 mL) and copper (I) iodide (54.46 g, 0.286 mol). The mixture was cooled to 0 °C, methyllithium (1.6 M in ether, 357.5 mL, 0.572 mol) was added dropwise to the reaction mixture over 1.5 h and stirred at 0 °C for additional 2 h. After this time a solution of 3-methylcyclo-pent-2-enone (25 g, 0.260 mol) in ether (150 mL) was added dropwise over 1.5 h. The reaction mixture was then stirred at 0 °C for 2 h and poured into sodium sulfate deca-hydrate (300 g). The resulting mixture was stirred for 30 min. After this time the mixture was filtered and washed with ether (1000 mL). The filtrate was concentrated and distilled under reduced pressure to afford a 70% yield (20.5 g) of 3,3-dimethylcyclo-pentanone **105a** as a colorless liquid: bp 50–55 °C (at 10 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 (t, 2H, J = 7.8 Hz), 2.05 (s, 2H), 1.79 (t, 2H, J = 7.8 Hz); MS (ESI+) *m/z* 113.3 (M+H)

Example 105b Ethyl 5,5-Dimethyl-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-2-carboxylate **105b**

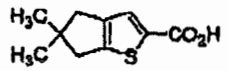


105b

A 500-mL three-neck round-bottomed flask equipped with a magnetic stirrer, reflux condenser, addition funnel and nitrogen inlet was purged with nitrogen and charged with DMF (9.49 g, 0.100 mol) and methylene chloride (100 mL). The reaction mixture was cooled to 0 °C and phosphorus oxychloride (14.1 g, 0.920 mol) was added dropwise to the reaction over 30 min. Once this addition was complete, the reaction was warmed to room temperature and stirred for 1 h. After this time a solution of **105a** (11.2 g, 0.100 mol) in

methylene chloride (100 mL) was added dropwise over 1 h. The reaction was then stirred at reflux for 18 h. The reaction mixture was cooled to room temperature and poured into a mixture of crushed ice (400 mL) and sodium acetate (100 g, 1.22 mol). The resulting mixture was stirred for 45 min. After this time the aqueous layer was separated and extracted with methylene chloride (2 × 500 mL). The combined organic layers were then washed with water (2 × 200 mL), followed by brine (200 mL) and dried over sodium sulfate. The drying agent was then removed by filtration, and the filtrate was concentrated to afford crude product 2-chloro-4,4-dimethylcyclopent-1-enecarbaldehyde which was placed in a 500-mL three-neck round bottomed flask equipped with a mechanical stirrer, reflux condenser and nitrogen inlet. Methylene chloride (200 mL), ethyl 2-mercaptoacetate (11.0 g, 0.092 mol) and triethylamine (30 g, 0.207 mol) were then added. The reaction mixture was then stirred at reflux for 6 h. After this time the reaction was cooled to room temperature and concentrated to a thick orange residue. Ethanol (200 mL) and triethylamine (30.0 g, 0.207 mol) were added and the reaction was heated at reflux for 12 h. The reaction was then cooled to room temperature and concentrated under reduced pressure and the resulting residue was diluted with ether (600 mL). The resulting mixture was washed with 1 M hydrochloric acid (150 mL), brine (100 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography to afford **105b** in 34% yield (7.70 g) as a colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (s, 1H), 4.33 (q, 2H, J = 7.2 Hz), 2.72 (s, 2H), 2.56 (s, 2H), 1.38 (t, 3H, J = 1.8 Hz), 1.17 (s, 6H); MS (ESI+) *m/z* 225.1

Example 105c 5,5-Dimethyl-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-2-carboxylic acid **105c**

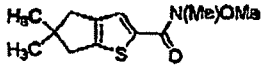


105c

In a 250-mL single-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser, **105b** (4.00 g, 17.8 mmol) was dissolved in ethanol (50 mL). THF (50 mL), water (50 mL) and lithium hydroxide (854 mg, 35.6 mmol) were added, and the mixture was stirred at 60 °C for 4 h. After this time the reaction was cooled to room temperature and acidified with 2M hydrochloric acid to pH 1.5, and then extracted with ethyl acetate (2 × 200 mL). The organic layers were combined, washed with water (2 × 100 mL), followed by brine (100 ml) and dried over sodium sulfate. The drying agent was then separated by filtration. After evaporating the resulting filtrate, **105c** was obtained in 91% yield (3.2 g) as a white

solid: mp 170–172 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.77 (s, 1H), 7.46 (s, 1H), 2.71 (s, 2H), 2.53 (s, 2H), 1.20 (s, 6H); MS (ESI–) *m/z* 195.0

Example 105d 5,5-Dimethyl-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-2-carboxylic acid **105d**

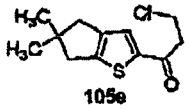


105d

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer, reflux condenser and a bubbler placed on the condenser was charged with **105c** (2.30 g, 11.6 mmol), toluene (25 mL), thionyl chloride (4.09 g, 34.9 mmol) and DMF (1 drop). The mixture was heated at reflux for 1 h and then evaporated under reduced pressure on a rotary evaporator at 45 °C. The resulting acid chloride was diluted with methylene chloride (20 mL).

In a separate 250-mL three-neck round-bottomed flask equipped with a magnetic stirrer *N,O*-dimethylhydroxylamine hydrochloride (2.26 g, 23.2 mmol) and *N,N*-diisopropylethylamine (2.97 g, 23.0 mmol) were dissolved in anhydrous methylene chloride (20 mL) under nitrogen, and the solution was cooled to 0 °C in an ice/water bath. The solution of the acid chloride was added, and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was extracted with water (100 mL), 10% aqueous citric acid (50 mL) and a 1:1 mixture of saturated aqueous sodium bicarbonate and water (100 mL). The organic layer was dried over sodium sulfate and evaporated under reduced pressure on a rotary evaporator to afford a 93% yield (2.60 g) of **105d** as a light yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (s, 1H), 3.77 (s, 3H), 3.35 (s, 3H), 2.74 (s, 2H), 2.58 (s, 2H), 1.23 (s, 6H)

Example 105e 3-Chloro-1-(5,5-dimethyl-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-2-yl)propan-1-one **105e**

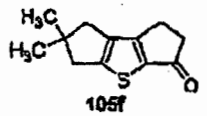


105e

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer was purged with nitrogen and charged with **105d** (2.41 g, 10.0 mmol) and anhydrous THF (20 mL). The solution was cooled to -70 °C, and 1 M vinylmagnesium bromide in THF (11 mL, 11.0 mmol) was added with the reaction temperature maintained below -60 °C. The reaction mixture was stirred at -13 to -7 °C for 2 h and then warmed to room temperature over 30 min.

The reaction was again cooled to -70 °C, and a 2 M solution of hydrogen chloride in ether (22.5 ml, 45 mmol) was added. The reaction was then stored in a freezer at -10 °C overnight. After this time the mixture was evaporated under reduced pressure on a rotary evaporator, and the resulting residue partitioned between water (100 mL) and ether (100 mL). The ether extract was dried over sodium sulfate and evaporated under reduced pressure on a rotary evaporator to afford crude **105e** (2.86 g, 118%) as a brown oil with approximately 75% purity (by NMR): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (s, 1H), 3.89 (t, 2H, J = 6.9 Hz), 3.30 (t, 2H, J =6.9 Hz), 2.75 (s, 2H), 2.59 (s, 2H), 1.24 (s, 6H)

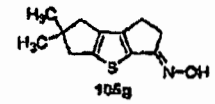
Example 105f 6,6-Dimethyl-1,2,6,7-tetrahydrodicyclopenta[*b*,*d*]thiophen-3(5*H*)-one **105f**



105f

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer was charged with crude **105e** (2.86 g, 10.0 mmol presuming quantitative yield) and 98% sulfuric acid. The reaction mixture was heated in a 90 °C oil bath overnight. The reaction mixture was placed into an ice/acetone bath, and a cold (5 °C) solution of dipotassium hydrogen phosphate (105 g, 0.603 mol) in water (300 mL) was added in one portion. The resulting mixture was shaken with ethyl acetate (300 mL) and filtered. The filter cake was washed with ethyl acetate (100 mL). The ethyl acetate layer of the filtrate was separated, dried over sodium sulfate and evaporated under reduced pressure on a rotary evaporator. the resulting residue was purified by flash column chromatography (silica, 80:20 hexanes/ethyl acetate) to afford **105f** in 37% yield over two steps (683 mg) as an amorphous brown solid: mp 60–62 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.92–2.87 (m, 4H), 2.79 (s, 2H), 2.53 (s, 2H), 1.26 (s, 6H); MS (ESI+) *m/z* 207.0 (M+H)

Example 105g 6,6-Dimethyl-1,2,6,7-tetrahydrodicyclopenta[*b*,*d*]thiophen-3(5*H*)-one **105g**

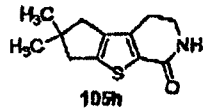


105g

A 250-mL single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was charged with hydroxylamine hydrochloride (688 mg, 9.90 mmol), sodium acetate (812 mg, 9.90 mmol) and methanol (10 mL), and the mixture at room temperature for

30 min. After this time, a solution of **105f** (680 mg, 3.30 mmol) was added dropwise at room temperature, and the reaction was stirred at room temperature for 14 h under nitrogen atmosphere. Since the reaction was not complete, hydroxylamine hydrochloride (1.15 g, 16.5 mmol) and sodium acetate (1.35 g, 16.5 mmol) were added, and the stirring was continued at room temperature for 58 h. After this time, the mixture was diluted with methylene chloride (150 mL) and water (100 mL), and the layers were separated. The organic layer was washed with brine (50 mL) and dried over sodium sulfate. The drying agent was removed by filtration and the filtrate was concentrated to afford crude **105g** in quantitative yield (730 mg) as a yellow semi-solid which was used in the next step without purification: mp 122–124 °C; ^{1}H NMR for major isomer (500 MHz, $CDCl_3$) δ 3.13–3.11 (m, 2H), 2.85–2.83 (m, 2H), 2.77 (s, 2H), 2.49 (s, 2H), 1.24 (s, 6H); MS (ESI+) *m/z* 222.0 (M+H)

Example 105h 6,6-Dimethyl-3,4,6,7-tetrahydro-5*H*-cyclopenta[4,5]thieno[2,3-*c*]pyridine-1(2*H*)-one **105h**



105h

A 100-mL three-neck round-bottomed flask equipped with a reflux condenser, mechanical stirrer and nitrogen inlet was charged with **105g** (700 mg, 3.16 mmol) and polyphosphoric acid (25 g). The reaction mixture was stirred at 80 °C for 13 h under nitrogen atmosphere. After this time, the mixture was cooled to 0 °C and water (50 mL) was added dropwise carefully maintaining the internal temperature between 10–45 °C. The mixture was diluted with 90:10 methylene chloride/methanol (100 mL) and the layers were separated. The aqueous layer was extracted with 90:10 methylene chloride/methanol (50 mL), and the combined organic layers were washed with saturated aqueous sodium bicarbonate (50 mL), brine (150 mL) and dried over sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography (silica, 95:5 methylene chloride/methanol) to afford 6,6-dimethyl-3,4,6,7-tetrahydro-5*H*-cyclopenta[4,5]thieno[2,3-*c*]pyridine-1(2*H*)-one **105h** in 90% yield (630 mg) as an amorphous off-white solid: mp 205–207 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.51 (s, 1H), 3.60–3.56 (m, 2H), 2.76–2.73 (m, 4H), 2.49 (s, 2H), 1.26 (s, 6H); MS (ESI+) *m/z* 222.0 (M+H)

Example 105i (2-Bromo-6-{4,4-dimethyl-9-oxo-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-10-yl}phenyl)methyl Acetate **105i**

A 250-mL single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was charged with **105h** (624 mg, 2.82 mmol), 2,6-dibromobenzyl acetate **104g** (1.73 g, 5.65 mmol), cesium carbonate (1.84 g, 5.65 mmol), *N,N'*-dimethylethylenediamine (249 mg, 2.82 mmol) and 1,4-dioxane (15 mL). After bubbling nitrogen through the resulting suspension for 30 min, copper iodide (269 mg, 1.41 mmol) was added. A reflux condenser was attached to the flask, and the reaction mixture was heated at 90 °C for 14 h. After this time, the mixture was cooled to room temperature and filtered. The filtrate was diluted with ethyl acetate (100 mL) and water (50 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (2×30 mL), and the combined organic layers were washed with brine (100 mL) and dried over sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography (silica, 70:30 hexanes/ethyl acetate) to afford **105i** in 52% yield (660 mg) as a white solid: mp 126–128 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (dd, J = 7.5, 1.5 Hz, 1H), 7.29–7.24 (m, 2H), 5.24 (s, 2H), 4.05–3.99 (m, 1H), 3.78–3.74 (m, 1H), 3.06–2.99 (m, 1H), 2.84–2.80 (m, 1H), 2.77 (s, 2H), 2.52 (s, 2H), 2.05 (s, 3H), 1.27 (s, 6H); MS (ESI+) *m/z* 448.0 (M+H)

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was charged with **105i** (250 mg, 0.558 mmol), crude 1-methyl-3-(pyrimidin-4-ylamino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one **104h** prepared above, 400 mg, 0.951 mmol, presuming quantitative yield in the previous step), sodium carbonate (177 mg, 1.67 mmol), DMF (2 mL), water (2 mL) and 1,4-dioxane (10 mL). After bubbling nitrogen through the resulting suspension for 30 min, tetrakis(triphenylphosphine)palladium(0) (129 mg, 0.112 mmol) was added. A reflux condenser was attached to the flask, and the reaction mixture was heated at 100 °C for 12 h. After this time, the mixture was diluted with 90:10 methylene chloride/methanol (100 mL) and water (75 mL), and the layers were separated. The aqueous layer was extracted with 90:10 methylene chloride/methanol (2 × 50 mL), and the combined organic layers were washed with brine (100 mL) and dried over sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was dissolved in THF (5 mL), water (5 mL) and methanol (5 mL). Lithium hydroxide monohydrate (117 mg, 2.79 mmol) was added, and the mixture was stirred at room temperature for 2 h. After this time, the mixture was diluted with 90:10 methylene chloride/methanol (100 mL) and water (50 mL), and the layers were separated. The aqueous layer was extracted with 90:10 methylene chloride/methanol (2×75 mL), and the combined

organic layers were washed with brine (100 mL) and dried over sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography (silica, 90:10 methylene chloride/methanol) and preparative HPLC (70:30 water/acetonitrile) to afford **105** in 14% yield (42 mg) as an amorphous off- white solid: mp 252–254 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.18 (s, 1H), 8.71 (s, 1H), 8.64 (s, 1H), 8.30 (d, J = 6.0 Hz, 1H), 7.53 (s, 1H), 7.47 (t, J = 7.5 Hz, 1H), 7.37–7.31 (m, 3H), 4.86–4.85 (m, 1H), 4.40–4.32 (m, 2H), 4.05–4.00 (m, 1H), 3.88–3.84 (m, 1H), 3.60 (s, 3H), 3.05–2.99 (m, 1H), 2.91–2.88 (m, 1H), 2.75 (s, 2H), 2.57–2.53 (m, 2H), 1.23 (s, 6H); MS (ESI+) *m/z* 528.2 (M+H)

Example 106 2-(3-(5-(5-cyclopropyl-1*H*-pyrazol-3-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **106**

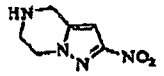
Example **106** was prepared using the same procedure as example **136e** and Example **136** except using **113a** and **136d** to yield 20 mg of **106** as a white solid. MS (ESI+) *m/z* 525 (M + H).

Example 107 2-(2-(hydroxymethyl)-3-(1-methyl-5-(5-morpholinopyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **107**

Example **107** was prepared using the same procedure as example **301** using **255c** and **114a** as starting material to yield 122 mg of **107** as a white solid. MS (ESI+) *m/z* 581 (M+H).

Example 108 2-(3-(5-(5-acetyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **108**

Example 108a 2-nitro-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine **108a**

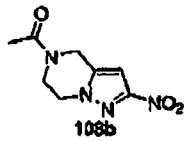


108a

A sealed tube equipped with a magnetic stirrer was charged with 1-(2-bromoethyl)-5-(bromomethyl)-3-nitro-1*H*-pyrazole **101c** (4 g, 12.9 mmol) 0.5M ammonia solution in dioxane (200 mL). The resulting mixture was carefully heated to 50 °C overnight. After this time, the reaction mixture was concentrated under reduced pressure, and to the residue was added H_2O (50 mL) and EtOAc (50 mL). The aqueous layer was separated and extracted with

EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (100 mL) and dried over sodium sulfate. The resulting solution was concentrated under reduced pressure to afford a 100% yield (2.1 g) of crude 2-nitro-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine **108a**.

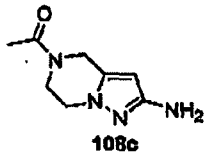
Example 108b 1-(2-nitro-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)ethanone **108b**



108b

A 200 mL round bottom flask was charged with 2-nitro-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine **108a** (2.1g, 12.9 mmol), triethylamine (5.5 mL, 38.7 mmol), acetyl chloride (1.1 mL, 15.5 mmol) and CH_2Cl_2 (100 mL). The mixture stirred at room temperature over night. After this time, the reaction mixture was concentrated under reduced pressure, and to the residue was added H_2O (50 mL) and EtOAc (50 mL). The aqueous layer was separated and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (100 mL). The combined aqueous extracts were back extracted with 9:1 CH_2Cl_2:MeOH (2 x 50 mL). The combined organics were dried over sodium sulfate. The resulting residue was purified by column chromatography eluting with a gradient of CH_2Cl_2 – 9:1 CH_2Cl_2: MeOH to afford a 84% yield (2.3 g) of 1-(2-nitro-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)ethanone **108b**.

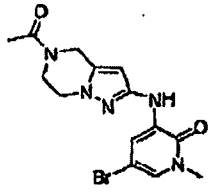
Example 108c 1-(2-amino-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)ethanone **108c**



108c

A 500-mL Parr hydrogenation bottle was charged with 1-(2-nitro-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)ethanone **108b** (2.3 g, 10.9 mmol), 10% palladium on carbon (50% wet, 570 mg dry weight) and ethanol (100 mL). The bottle was evacuated, charged with hydrogen gas to a pressure of 50 psi and shaken for 2 h on a Parr hydrogenation apparatus. The catalyst was removed by filtration through a pad of Celite 521 washing with 1:1 CH_2Cl_2:MeOH (500mL). The resulting solution was concentrated under reduced pressure to afford a 95% yield (1.9 g) of crude 1-(2-amino-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)ethanone **108c**.

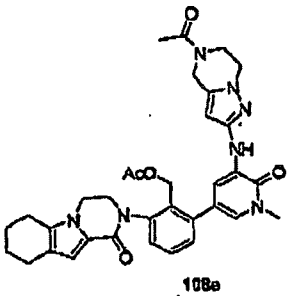
Example 108d 3-(5-acetyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-5-bromo-1-methylpyridin-2(1H)-one **108d**



108d

A sealed tube was equipped with a magnetic stirrer and charged with 1-(2-amino-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)ethanone **108c** (860 mg, 4.8 mmol), 3,5-dibromo-1-methylpyridin-2(1H)-one (1.8 g, 6.7 mmol), and cesium carbonate (3.4 g, 10.5 mmol) in 1,4-dioxane (67 mL). After bubbling nitrogen through the solution for 30 min, Xantphos (330 mg, 0.6 mmol) and tris(dibenzylideneacetone) dipalladium(0) (300 mg, 0.3 mmol) were added, and the reaction mixture was heated to 100 °C for 16 h. After this time, H_2O (50 mL) and EtOAc (50 mL) were added. The aqueous layer was separated and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (100 mL) and dried over sodium sulfate. The resulting residue was purified by column chromatography eluting with a gradient of CH_2Cl_2 – 60:35:5 CH_2Cl_2:Et_2O:MeOH to afford a 41% yield (720 mg) of 3-(5-acetyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-5-bromo-1-methylpyridin-2(1H)-one **108d**.

Example 108e 2-(5-(5-acetyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **108e**



108e

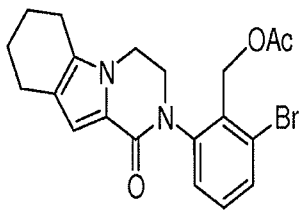
A microwave tube equipped with a magnetic stirrer was charged with 3-(5-acetyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-5-bromo-1-methylpyridin-2(1H)-one **108d** (120 mg, 0.3 mmol), 2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-

(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **114a** (200 mg, 0.4 mmol), DME (4 mL) and 1M aqueous sodium carbonate (1 mL). After bubbling nitrogen for 15 min, $Pd(PPh_3)_4$ (19 mg, 0.02 mmol) was added. The mixture was heated in a microwave to 130 °C for 15 min. After this time, ethyl acetate (5 mL) and water (5 mL) were added. The separated aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organics were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography eluting with a gradient of CH_2Cl_2 – 60:35:5 CH_2Cl_2:Et_2O:MeOH to afford a 33% yield (69 mg) of 2-(5-(5-acetyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **108e**.

A 25 mL round bottom flask with a magnetic stirrer was charged with 2-(5-(5-acetyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **108e** (69 mg, 0.11 mmol), lithium hydroxide (8 mg, 0.3 mmol), THF (1 mL), *i*-PrOH (1 mL) and water (2 mL). The mixture stirred at rt for 2 h. After this time, EtOAc (3 mL) and water (3 mL) were added. The separated aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organics were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography eluting with a gradient of CH_2Cl_2 – 75:18:7 CH_2Cl_2:Et_2O:MeOH to afford a 63% yield (40 mg) of 2-(3-(5-(5-acetyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **108**. MS (ESI+) *m/z* 582.3 (M + H).

Example 109 2-(2-(hydroxymethyl)-3-(1-methyl-6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **109**

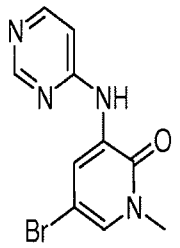
Example 109a 2-bromo-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **109a**



A 100-mL three-neck round-bottomed flask equipped with a reflux condenser, magnetic stirrer and nitrogen inlet was charged with 3,4,6,7,8,9-hexahydropyrazino[1,2-

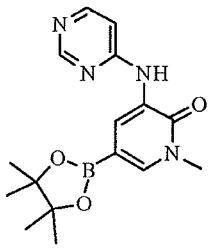
a]indol-1(2H)-one **101k** (720 mg, 3.78 mmol), 2,6-dibromobenzyl acetate **104g** (2.33 g, 7.57 mmol), cesium carbonate (2.47 g, 7.57 mmol), *N,N'*-dimethylethylenediamine (333 mg, 3.78 mmol) and 1,4-dioxane (31 mL). After bubbling nitrogen through the resulting suspension for 30 min, copper iodide (360 mg, 1.89 mmol) was added, and the reaction mixture was heated at 105 °C (oil bath temperature) for 3 days. After this time, the mixture was cooled to room temperature and filtered. The filtrate was diluted with ethyl acetate (200 mL) and water (40 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography to afford a 31% yield (490 mg) of 2-bromo-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **109a**.

Example 109b 5-bromo-1-methyl-3-(pyrimidin-4-ylamino)pyridin-2(1H)-one **109b**



A solution of pyrimidin-4-amine (2.0 g, 21 mmol), 3,5-dibromo-1-methylpyridin-2(1H)-one (6.2 g, 23.1 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.96g, 1.1 mmol), Xantphos (1.03 g, 1.79 mmol), and cesium carbonate (7.5 g, 23 mmol) in dioxane (25 mL) was heated in a sealed tube at 130 °C for 18 hours. The mixture was diluted with CH_2Cl_2 (100 mL) and filtered through a plug of celite. The solution was concentrated in vacuo on the rotary evaporator. The material was then dissolved in minimal CH_2Cl_2 (5 mL) and was triturated with Et_2O (80 mL). The product was then filtered and washed with Et_2O (100 mL) to afford 2.9 g (49 %) of **109b**.

Example 109c 1-Methyl-3-(pyrimidin-4-ylamino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one **109c**



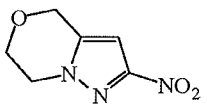
109c

A solution of 5-bromo-1-methyl-3-(pyrimidin-4-ylamino)pyridin-2(1H)-one **109b** (600 mg, 2.13 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (596 mg, 2.35 mmol), [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (174 mg, 0.213 mmol), potassium acetate (628 mg, 6.40 mmol) in dioxane (4.5 mL) was sealed in a microwave tube and heated to 130 °C for 10 minutes. The solution was filtered through a plug of celite and concentrated. The crude 1-methyl-3-(pyrimidin-4-ylamino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one **109c** was carried on to the next step without purification.

A solution of **109c** (crude, 2.13 mmol), **109a** (300 mg, 0.719 mmol), tetrakis(triphenylphosphine)palladium(0) (83 mg, 0.0719 mmol), and sodium carbonate (229 mg, 2.16 mmol) in dioxane (4.5 mL) and water (2.3 mL) was sealed in a microwave tube and heated to 130 °C for 10 minutes. The organics layer was separated from the aqueous and filtered through a plug of celite. The material was then adsorbed to celite and was purified via silica chromatography using 0-100% ethyl acetate in hexanes followed by a switch to 0-15% methanol in dichloromethane to afford 105 mg (27%) of **109**.

Example 110 2-(3-(5-(6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **110**

Example 110a 2-Nitro-6,7-dihydro-4*H*-pyrazolo[5,1-c][1,4]oxazine **110a**

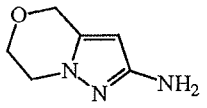


110a

A 250-mL single-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was charged with **101c** (3.00 g, 9.59 mmol) and 4M aqueous hydrobromic acid (120 mL), and the resulting mixture was heated at reflux for 24 h. After this time, the reaction mixture was concentrated under reduced pressure to approximately 6 mL volume,

and the residue was stirred in 2M aqueous sodium hydroxide (40 mL) for 2 h. After this time methylene chloride was added (40 mL) and the mixture was stirred for 15 min. The aqueous layer was separated and extracted with methylene chloride (2 × 50 mL). The combined organic extracts were washed with brine (100 mL) and dried over sodium sulfate. The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to afford a 62% yield (1.01 g) of **110a** as a white solid: mp 110–112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 6.68 (s, 1H), 4.87 (s, 2H), 4.28 (t, 2H, J = 5.4 Hz), 4.20 (t, 2H, J = 5.1 Hz); MS (ESI+) *m/z* 170.0 (M+H).

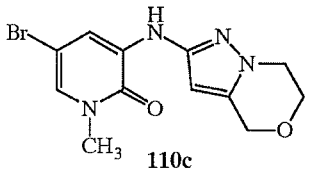
Example 110b 6,7-Dihydro-4*H*-pyrazolo[5,1-c][1,4]oxazin-2-amine **110b**



110b

A 500-mL Parr hydrogenation bottle was purged with nitrogen and charged with **110a** (1.01 g, 5.92 mmol), 10% palladium on carbon (50% wet, 125 mg dry weight) and ethanol (50 mL). The bottle was evacuated, charged with hydrogen gas to a pressure of 25 psi and shaken for 2 h on a Parr hydrogenation apparatus. The hydrogen was then evacuated and nitrogen charged to the bottle. The catalyst was removed by filtration through a pad of Celite 521 and the filtrate concentrated under reduced pressure. The resulting residue was purified by column chromatography using 400 cc of silica gel and eluting with 3% methanol in methylene chloride. The fractions containing **110b** were collected to afford, after concentrating under reduced pressure, a 73% yield (601 mg) of **110b** as a yellow solid: mp 74–76°C ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.37 (s, 1H), 4.72 (s, 2H), 4.07 (t, 2H, J = 5.1 Hz), 3.98 (t, 2H, J = 5.1 Hz), 3.57 (br s, 2H); MS (ESI+) *m/z* 140.4 (M+H).

Example 110c 5-Bromo-3-(6,7-dihydro-4*H*-pyrazolo[5,1-c][1,4]oxazin-2-ylamino)-1-methylpyridin-2(1*H*)-one **110c**

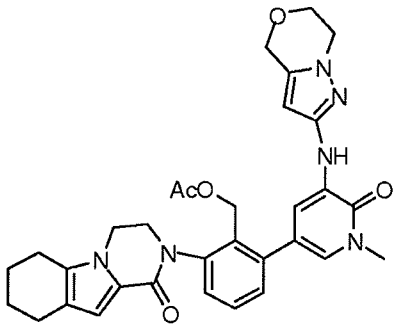


110c

A 50-mL three-neck round-bottomed flask equipped with a magnetic stirrer, reflux condenser and nitrogen inlet was charged with 1,4-dioxane (20 mL), **110b** (600 mg, 4.31 mmol), 3,5-dibromo-1-methyl pyridine –2(1H)-one (1.44 g, 5.40 mmol) and cesium carbonate (3.08 g, 9.48 mmol). After bubbling nitrogen through the resulting solution for 30

min, Xantphos (300 mg, 0.52 mmol) and tris(dibenzylideneacetone)-dipalladium(0) (320 mg, 0.35 mmol) were added, and the reaction mixture was heated at reflux for 2 h. After this time the reaction was cooled to room temperature, partitioned between ethyl acetate (75 mL) and water (75 mL) and filtered. The aqueous layer was separated and extracted with ethyl acetate (2 x 25 mL). The organic layers were combined and washed with brine (50 mL) and dried over sodium sulfate. The drying agent was removed by filtration and the filtrate concentrated under reduced pressure. The resulting residue was purified by column chromatography using 500 cc of silica gel and eluting with 1% methanol in methylene chloride. The fractions containing **110c** were collected to afford, after concentrating under reduced pressure, a 31% yield (433 mg) of **110c** as a green solid: mp 195–197 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 7.92 (d, 1H, J = 2.4 Hz), 7.44 (s, 1H), 6.90 (d, 1H, J = 2.4 Hz), 5.65 (s, 1H), 4.80 (s, 2H), 4.13 (s, 2H), 3.61 (s, 5H); MS (ESI+) *m/z* 324.9 (M+H).

Example 110d 2-(5-(6,7-Dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **110d**



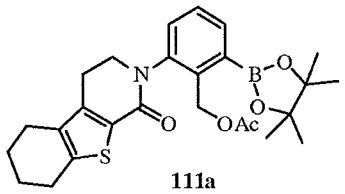
110d

A microwave tube equipped with a magnetic stirrer was charged with 5-bromo-3-(6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-2-ylamino)-1-methylpyridin-2(1H)-one **110c** (130 mg, 0.4 mmol), 2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **114a** (220 mg, 0.5 mmol), DME (4 mL) and 1M aqueous sodium carbonate (1.2 mL). After bubbling N2 for 15 min, $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) was added. The mixture was heated in microwave to 130 °C for 20 min. After this time, EtOAc (5 mL) and water (5 mL) were added. The separated aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organics were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography eluting with a gradient of CH_2Cl_2 – 60:35:5 CH_2Cl_2:Et_2O:MeOH to afford a 89% yield (210 mg) of **110d**.

A 25 mL round bottom flask with a magnetic stirrer was charged with **110d** (210 mg, 0.4 mmol), lithium hydroxide (45 mg, 1.1 mmol), THF (3.6 mL), *i*-PrOH (3.6 mL) and water (7.2 mL). The mixture stirred at rt for 3 h. After this time, EtOAc (10 mL) and water (10 mL) were added. The separated aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organics were washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography eluting with a gradient of CH_2Cl_2 – 60:35:5 CH_2Cl_2:Et_2O:MeOH to afford a 57% yield (110 mg) of **110**. MS (ESI+) *m/z* 541.3 (M + H).

Example 111 5-[2-(Hydroxymethyl)-3-[4-methyl-5-oxo-6-(pyridine-3-ylamino)-4,5-dihydropyrazin-2-yl]phenyl]-8-thia-5-azatricyclo[7.4.0.02,7]trideca-1(9),2(7)-dien-6-one **111**

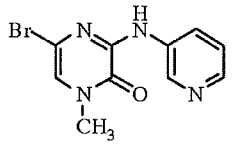
Example 111a 2-(1-Oxo-3,4,5,6,7,8-hexahydrobenzothieno[2,3-*c*]pyridin-2(1*H*)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl Acetate **111a**



111a

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was purged with nitrogen and charged with **104f** (1.18 g, 2.72 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane (2.04 g, 8.16 mmol), potassium acetate (800 mg, 8.16 mmol) and 1,4-dioxane (20 mL). A stream of nitrogen was passed through the resulting suspension for 30 min. [1,1'-Bis(diphenylphosphino)ferrocene]-dichloropalladium(II) (398 mg, 0.544 mmol) was then added, and the reaction was stirred at 90 °C for 8 h. After this time, the mixture was cooled to ambient temperature, partitioned between water (25 mL) and ethyl acetate (50 mL) and filtered through a plug of Celite 521. The organic phase was separated, dried over sodium sulfate, filtered and concentrated under reduced pressure. the resulting residue was purified by flash chromatography to afford a 77% yield (1.01 g) of **111a** as a brown solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, 1H, *J* = 7.0 Hz), 7.41 (t, 1H, *J* = 7.0 Hz), 7.37 (d, 1H, *J* = 7.0 Hz), 5.49 (d, 1H, *J* = 11.5 Hz), 5.23 (d, 1H, *J* = 11.5 Hz), 4.01 (m, 1H), 3.76 (m, 1H), 2.96 (m, 1H), 2.81–2.75 (m, 3H), 2.50 (m, 2H), 1.99 (s, 3H), 1.86 (m, 4H), 1.33 (s, 12H); MS (ESI+) *m/z* 482.2 (M+H).

Example 111b 5-Bromo-1-methyl-3-(pyridin-3-ylamino)pyrazin-2(1*H*)-one **111b**



111b

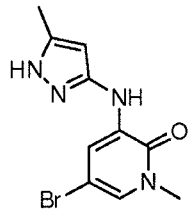
A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer, reflux condenser and nitrogen inlet was charged with THF (15 mL), 3,5-dibromo-1-methyl pyrazin–2(1H)-one (1.00 g, 3.73 mmol), 3-aminopyridine (351 mg, 3.73 mmol) and sodium *tert*-butoxide (789 mg, 8.21 mmol). After bubbling nitrogen through the resulting solution for 30 min, di-μ-bromobis(tri-t-butylphosphino)dipalladium(I) (29 mg, 0.037 mmol) was added, and the reaction mixture was stirred at room temperature for 2.5 h. After this time the reaction was partitioned between ethyl acetate (50 mL) and water (50 mL) and filtered. The aqueous layer was separated and extracted with ethyl acetate (2 × 25 mL). The organic layers were combined, washed with brine (50 mL) and dried over sodium sulfate. The drying agent was removed by filtration and the filtrate concentrated under reduced pressure. The resulting residue was purified by column chromatography to afford a 35% yield (370 mg) of **111b** as a brown solid: mp >250 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.75 (s, 1H), 9.08 (d, 1H, J = 2.5 Hz), 8.32 (m, 1H), 8.24 (dd, 1H, J = 5.0, 1.5 Hz), 7.40 (s, 1H), 7.36 (dd, 1H, J = 8.5, 4.5 Hz), 3.45 (s, 3H); MS (APCI+) *m/z* 281.0 (M+H).

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was purged with nitrogen and charged with **111a** (134 mg, 0.279 mmol), **111b** (71 mg, 0.253 mmol), sodium carbonate (80 mg, 0.759 mmol), 1,4-dioxane (5 mL) and water (1 mL). This mixture was degassed with nitrogen for 30 min. Tetrakis(triphenylphosphine)palladium (29 mg, 0.025 mmol) was added. After heating at 100 °C for 3 h, the reaction mixture was cooled to room temperature and partitioned between water (40 mL) and methylene chloride (100 mL). The layers were separated, and the aqueous phase was extracted with methylene chloride (2 × 50 mL). The organic extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was dissolved in methanol (5 mL), and potassium carbonate (500 mg, 3.62 mmol) was added. After stirring at room temperature for 2 h, the reaction mixture was partitioned between water (20 mL) and methylene chloride (20 mL). The layers were separated, and the aqueous phase was extracted with methylene chloride (2 × 20 mL). The organic extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography to afford **111** in 38% yield (49 mg) as a white solid: mp 164–165 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.54 (s, 1H), 9.14 (d, 1H, J = 2.5

Hz), 8.42 (m, 1H), 8.18 (dd, 1H, J = 4.5, 1.5 Hz), 7.54 (d, 1H, J = 8.0 Hz), 7.49–7.46 (m, 2H), 7.34 (d, 1H, J = 8.0 Hz), 7.30 (dd, 1H, J = 8.0, 4.5 Hz), 4.81 (m, 1H), 4.49 (dd, 1H, J = 11.0, 3.5 Hz), 4.43 (dd, 1H, J = 11.0, 6.5 Hz), 4.02 (m, 1H), 3.86 (m, 1H), 3.56 (s, 3H), 2.95 (m, 1H), 2.86 (m, 1H), 2.77 (m, 2H), 2.58–2.46 (m, 2H), 1.79 (m, 4H); MS (APCI+) *m/z* 514.2 (M+H).

Example 112 2-(2-(hydroxymethyl)-3-(1-methyl-5-(5-methyl-1H-pyrazol-3-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **112**

Example 112a 5-Bromo-1-methyl-3-(5-methyl-1H-pyrazol-3-ylamino)pyridin-2(1H)-one **112a**



112a

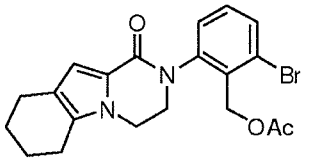
A 250ml sealed tube with a magnetic stirrer was charged with 5-methyl-1H-pyrazol-3-amine (0.91g, 9.36mmol), 3,5-dibromo-1-methyl-1H-pyridin-2-one (2.1g, 7.87mmol), cesium carbonate (7.6g, 23.56mmol) and 1,4-dioxane (78 mL). After degassing for 10 minutes, tris(dibenzylideneacetone)dipalladium(0) (0.72g, 0.8mmol) and Xantphos (0.91g, 1.57mmol) were added. The reaction mixture was heated at 115 °C for 48 hours. Then the mixture was cooled to room temperature and partitioned between dichloro-methane (50 mL) and water (30 mL). The organic phase was separated, and the aqueous layer was extracted with dichloromethane (3 X 30 mL). The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica, 9:1 methylene chloride/ methanol) to give 85% yield (1.88 g) of **112a** as a solid: MS (ESI+) *m/z* 285.0 (M+H).

A 10 mL microwave vial with a magnetic stirrer was charged with 2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **114a** (181 mg, 0.39 mmol), **112a** (85 mg, 0.3 mmol), 1M sodium carbonate solution (1.2 mL, 1.2 mmol) and 1,2-dimethoxyethane (3 mL). After bubbling nitrogen through the resulting suspension for 10 min, tetrakis(triphenylphosphine)-palladium(0) (18 mg, 0.015 mmol) was added. The reaction mixture was heated at 130 °C for 10 minutes in a microwave reactor. Then ethyl acetate (10 mL) and water (5 mL) were added,

and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 10 mL), and the combined organic layers were washed with brine and dried over sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography (silica, 60:35:5 methylene chloride/diethyl ether/methanol) to give 100 mg mixture of **112b** and **112** as a yellow residue. The residue was dissolved in a mixture of THF (1 mL), water (0.5 mL) and isopropanol (1 mL). Lithium hydroxide monohydrate (31 mg, 0.74 mmol) was added, and the mixture was stirred at room temperature for 2 h. After this time, the mixture was diluted with 90:10 methylene chloride/methanol (10 mL) and water (5 mL), and the layers were separated. The aqueous layer was extracted with 90:10 methylene chloride/methanol (2 × 10 mL), and the combined organic layers were washed with brine and dried over sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography (silica, 60:35:5 methylene chloride/ether/methanol) to afford a 18% yield (two steps, 28 mg) of 2-(2-(hydroxymethyl)-3-(1-methyl-5-(5-methyl-1H-pyrazol-3-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **112** as a white solid: MS (ESI+) *m/z* 499.3 (M+H).

Example 113 2-(2-(hydroxymethyl)-3-(1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridine-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **113**

Example 113a Acetic Acid 2-Bromo-6-(1-oxo-3,4,6,7,8,9-hexahydro-1H-pyrazino[1,2-a]indol-2-yl)-benzyl Ester **113a**

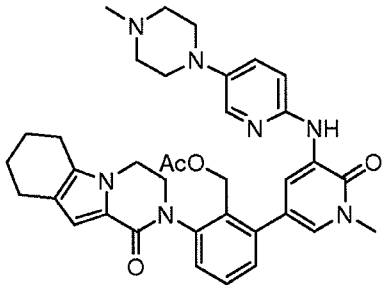


113a

A 350-mL sealed tube equipped with a magnetic stirring bar was charged with 3,4,6,7,8,9-hexahydro-2H-pyrazino[1,2-a]indol-1-one **101k** (5.0 g, 0.026 mol), 2,6-dibromobenzyl acetate **104g** (16.2 g, 0.052 mol) *N,N'*-dimethylethylenediamine (2.6 mL, 0.026 mol), Cs_2CO_3 (17.0 g, 0.052 mol), and 1,4-dioxane (80 mL). After a stream of nitrogen was passed through the resulting suspension for 30 min., CuI (2.5 g, 0.013 mol) was added and the resulting reaction mixture was stirred at 95 °C for 16 h. Then the mixture was cooled to room temperature, partitioned between EtOAc (50 mL) and water (50 mL), and the organic

phase was extracted with EtOAc (30 mL x 3). The combined organic phases were washed with water (20 mL x 2) and brine (20 mL x 1), dried (Na_2SO_4), and concentrated. The crude product was purified by flash chromatography (dichloromethane:MeOH, 97:3) to give 35% yield (4.5 g) of **113a** as white solids.

Example 113b Acetic Acid 2-{1-Methyl-5-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-6-(1-oxo-3,4,6,7,8,9-hexahydro-1H-pyrazino[1,2-a]indol-2-yl)-benzyl Ester **113b**



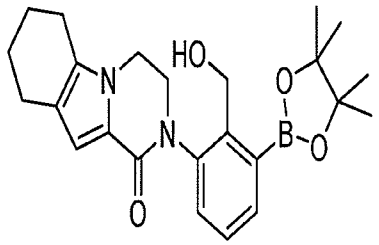
113b

In a 10-mL glass vessel equipped with a magnetic stirring bar were placed 1-methyl-3-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyridin-2-one **197f** (210 mg, 0.49 mmol), **113a** (250 mg, 0.60 mmol), $Pd(PPh_3)_4$ (50 mg, 0.043 mmol) in 2 N Na_2CO_3 (2 mL) and 1,2-dimethoxyethane (5 mL). The vessel was sealed with a septum and placed into the microwave cavity. After the reaction mixture was stirred at 125 °C for 7 min., it was purified by flash chromatography (dichloromethane:methanol, 85:15) to give 34% (105 mg) of acetic acid 2-{1-methyl-5-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-6-(1-oxo-3,4,6,7,8,9-hexahydro-1H-pyrazino[1,2-a]indol-2-yl)-benzyl ester **113b** as solids.

A 100-mL, single-necked, round-bottomed flask equipped with a magnetic stirring bar was charged with **113b** (105 mg, 0.17 mmol), $LiOH•H_2O$ (35 mg, 0.83 mmol), THF (2 mL), isopropanol(2 mL), and water (1 mL). After the reaction mixture was stirred at room temperature for 3 h, it was partitioned between dichloromethane (5 mL) and water (5 mL), and the organic phase was extracted with dichloromethane (5 mL x 3). The combined organic phases were washed with water (5 mL x 2) and brine (5 mL x 1), dried (Na_2SO_4), and concentrated. The crude product was re-dissolved in dichloromethane (3 mL). To this solution was added hexane (10 mL) and the resulting precipitates were filtered to give 80% yield (79 mg) of 2-(2-hydroxymethyl-3-{1-methyl-5-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-3,4,6,7,8,9-hexahydro-2H-pyrazino[1,2-a]indol-1-one **113**; MS(ESI^+) *m/z* 594.3 (M+H).

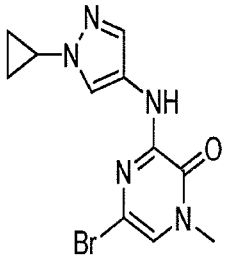
Example 114 2-(3-(6-(1-cyclopropyl-1H-pyrazol-4-ylamino)-4-methyl-5-oxo-4,5-dihydropyrazin-2-yl)-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **114**

Example 114a 2-(2-(Acetoxymethyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **114a**



To a round-bottomed flask equipped with a stirring bar, 2-(3-bromo-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **113a** (1.96 g, 4.70 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.79 g, 7.05 mmol), $Cl_2Pd(dppf)_2 \cdot CH_2Cl_2$ (306.9 mg, 0.376 mmol), KOAc (4.77 g, 18.79 mmol), and dioxane (33.6 mL) were added. The mixture was heated at 95 °C overnight. The resulting mixture was filtered through Celite, washed with ethyl acetate (200 mL). The organic phase was washed with water (50 mL), dried over $MgSO_4$, and and the solvent removed *in vacuo* to yield the crude product **114a**, which was directly used as starting material other syntheses.

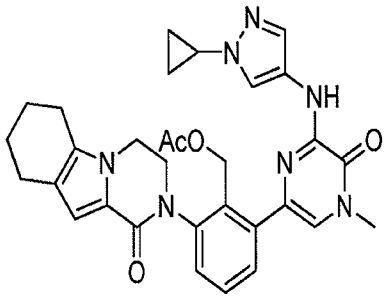
Example 114b 5-Bromo-3-(1-cyclopropyl-1H-pyrazol-4-ylamino)-1-methylpyrazin-2(1H)-one **114b**



To a seal tube equipped with a stirring bar, 1-cyclopropyl-1H-pyrazol-4-amine (600 mg, 4.87 mmol), 3,5-dibromo-1-methylpyrazin-2(1H)-one (1.96 g, 7.31 mmol), $Pd_2(dba)_3$ (223.1 mg, 0.244 mmol), XantPhos (225.5 mg, 0.390 mmol), Cs_2CO_3 (5.25 g, 16.08 mmol) and dioxane (12 mL) were added. The tube was sealed and heated at 100 °C overnight. CH_2Cl_2 (200 mL) was added to the resulting mixture, and the CH_2Cl_2 solution was washed with water (30 mL X 3). The precipitate in the aqueous phase was filtered as pure product **114b**. The organic phase was dried over $MgSO_4$, filtered and solvent removed *in vacuo*. CH_2Cl_2 / ether (1:2, 3 mL) were added to the residue and the mixture was sonicated. The

precipitate was filtered, combined with the filtered solids from the aqueous phase, and dried. 5-Bromo-3-(1-cyclopropyl-1H-pyrazol-4-ylamino)-1-methylpyrazin-2(1H)-one **114b** was obtained as a yellow solid.

Example 114c 2-(6-(1-Cyclopropyl-1H-pyrazol-4-ylamino)-4-methyl-5-oxo-4,5-dihydropyrazin-2-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl) benzyl Acetate **114c**

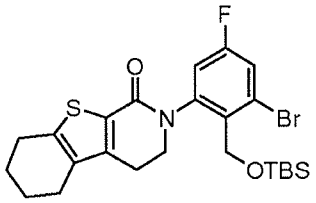


To a microwave tube equipped with a stirring bar, **114b** (200 mg, 0.645 mmol), **114a** (0.903 mmol), $Pd(PPh_3)_4$, Na_2CO_3 aqueous solution (1.0 N, 2.13 mL, 2.13 mmol), DME (2.0 mL) were added. The mixture was reacted in microwave at 135 °C for 15 min. DCM (200 mL) was added and the resulting mixture was washed with water (30 mL X 3), brine (30 mL X 1), dried over $MgSO_4$, filtered, and removed solvent *in vacuo*. Silica gel column chromatography (MeOH: DCM = 5: 95) gave 2-(6-(1-cyclopropyl-1H-pyrazol-4-ylamino)-4-methyl-5-oxo-4,5-dihydropyrazin-2-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **114c**, it was directly used in the next step.

To a round-bottomed flask equipped with a stirring bar, **114c** THF (1.25 mL), *i*-PrOH (1.25 mL), H_2O (1.25 mL), LiOH H_2O (135 mg) were added. The resulting mixture was stirred at RT for 1 hr. Removed all the solvent *in vacuo* and silica gel column chromatography (MeOH: DCM = 10: 90) gave 38.6 mg 2-(3-(6-(1-cyclopropyl-1H-pyrazol-4-ylamino)-4-methyl-5-oxo-4,5-dihydropyrazin-2-yl)-2-(hydroxymethyl)-phenyl)-3,4,6,7,8,9-hexahydro-pyrazino[1,2-a]indol-1(2H)-one **114** as a yellow solid. MS (ESI+) *m/z* 526.3 (M + H).

Example 115 5-[5-Fluoro-2-(hydroxymethyl)-3-[1-methyl-6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydropyridin-3-yl]phenyl]-8-thia-5-azatricyclo[7.4.0.02,7]trideca-1(9),2(7)-dien-6-one **115**

Example 115b *tert*-Butyl(2-bromo-4-fluoro-6-(1-oxo-3,4,5,6,7,8-hexahydrobenzothieno[2,3-*c*]pyridin-2(1*H*)-yl) benzyloxy)dimethylsilane **115b**



115b

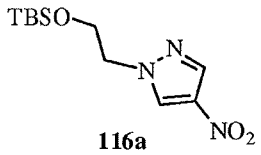
A sealed tube with a magnetic stirrer was charged with **104e** (1.11g, 5.37 mmol), **115a** (4.24g, 10.7 mmol), cesium carbonate (3.49g, 10.7mmol), *N,N'*-dimethylethylenediamine (0.47g, 5.37mmol) and 1,4-dioxane (45mL). After degassed for 10 minutes, copper iodide (0.51g, 2.68mmol) was added, and the reaction mixture was heated at 105 °C for 2days. Another portion of *N,N'*-dimethylethylenediamine (0.47g, 5.37mmol) and copper iodide (0.51g, 2.68mmol) was added, and the reaction mixture was heated at 105 °C for another 5 hours. After this time, the mixture was cooled to room temperature and filtered. The filtrate was diluted with ethyl acetate (50 mL) and water (40 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (silica, Ethyl Acetate/ Hexanes) to afford a 40% yield (1.14g) of compound **115b** as a yellow solid: MS (ESI+) *m/z* 524.1(M+H).

A 10 mL microwave vial with a magnetic stirrer was charged with **115b** (157 mg, 0.3 mmol), 1-methyl-3-(pyrimidin-4-ylamino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one **109c** (148 mg, 0.45 mmol), 1M sodium carbonate solution (1.2 mL, 1.2 mmol) and 1,2-Dimethoxyethane (3 mL). After bubbling nitrogen through the resulting suspension for 10 min, tetrakis(triphenylphosphine)palladium(0) (18 mg, 0.015 mmol) was added. The reaction mixture was heated at 130 °C for 15 minutes in the microwave reactor. The reaction was repeated at the same scale, and the reaction mixture was combined. Ethyl Acetate (20 mL) and water (10 mL) were added, and the layers were separated. The aqueous layer was extracted with Ethyl acetate (2 × 10 mL), and the combined organic layers were washed with brine and dried over sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography (silica, 60:35:5 methylene chloride/ether/methanol) to give 400mg mixture of compounds **115c** and **115** as a yellow residue.The above residue was dissolved in methanol (5 mL). 10-Camphorsulfonic acid (350 mg, 1.5 mmol) was added, and the mixture was stirred at room temperature for 1 h. After this time, the mixture was basified with saturated sodium bicarbonate. The aqueous layer was extracted with methylene chloride (2 × 10 mL), and the combined organic layers were washed with brine and dried over sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated under

reduced pressure, and the resulting residue was purified by flash column chromatography (NH-silica, Ethyl acetate/Hexanes) to afford a 33% yield (88 mg) of compound **115** as a pale yellow solid: MS (ESI+) *m/z* 532.2 (M+H)

Example 116 5-[3-(6-{[1-(2-Hydroxyethyl)-1H-pyrazol-4-yl]amino}-4-methyl-5-oxo-4,5-dihydropyrazin-2-yl)-2-(hydroxymethyl)phenyl]-8-thia-5-azatricyclo[7.4.0.02,7]trideca-1(9),2(7)-dien-6-one **116**

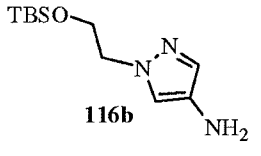
Example 116a 1-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-4-nitro-1*H*-pyrazole **116a**



116a

A 100-mL single-neck round-bottomed flask equipped with a reflux condenser and magnetic stirrer was purged with nitrogen and charged with 4-nitro-1*H*-pyrazole (500 mg, 4.42 mmol), (2-bromoethoxy)(tert-butyl)dimethylsilane (2.12 g, 8.85 mmol), cesium carbonate (5.76 g, 17.7 mmol) and anhydrous DMF (5 mL). After heating at 70 °C for 1 h, the mixture was cooled to room temperature and diluted with methylene chloride (50 mL) and water (30 mL). The organic layer was separated, and the aqueous layer was extracted with methylene chloride (2 × 30 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography to afford a 92% yield (1.11 g) of **116a** as a white solid: mp 63–64 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 1H), 8.08 (s, 1H), 4.24 (t, 2H, J = 4.5 Hz), 3.95 (t, 2H, J = 4.5 Hz), 0.84 (s, 9H), -0.04 (s, 6H).

Example 116b 1-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-1*H*-pyrazol-4-amine **116b**

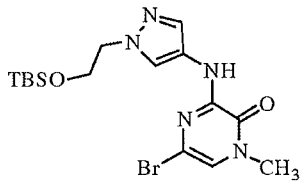


116b

A 250-mL Parr reactor bottle was purged with nitrogen and charged with 10% palladium on carbon (50% wet, 150 mg dry weight) and a solution of **116a** (1.11 g, 4.10 mmol) in ethanol (20 mL). The bottle was attached to a Parr hydrogenator, evacuated, charged with hydrogen gas to a pressure of 50 psi and shaken for 3 h. After this time, the hydrogen was evacuated, and nitrogen was charged into the bottle. Celite 521 (1.00 g) was added, and the mixture was filtered through a pad of Celite 521. The filter cake was washed

with ethanol (2 x 25 mL), and the combined filtrates were concentrated to dryness under reduced pressure to afford a 100% yield of **116b** (985 mg) as an orange oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (s, 1H), 7.11 (s, 1H), 4.09 (t, 2H, *J* = 5.5 Hz), 3.89 (t, 2H, *J* = 5.5 Hz), 3.25 (br s, 2H), 0.86 (s, 9H), -0.32 (s, 6H). MS (ESI+) *m/z* 242.2 (M+H).

Example 116c 5-Bromo-3-(1-(2-(*tert*-butyldimethylsilyloxy)ethyl)-1*H*-pyrazol-4-ylamino)-1-methylpyrazin-2(1*H*)-one **116c**



116c

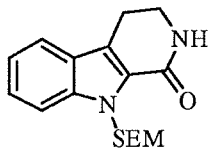
A 100-mL three-neck round-bottomed flask equipped with a reflux condenser, magnetic stirrer and nitrogen inlet was charged with **116b** (400 mg, 1.66 mmol), 3,5-dibromo-1-methyl pyrazin–2(1H)-one (443 mg, 1.66 mmol), cesium carbonate (1.19 g, 3.65 mmol), and 1,4-dioxane (20 mL). After bubbling nitrogen through the resulting suspension for 30 min, Xantphos (144 mg, 0.249 mmol) and tris(dibenzylideneacetone)-dipalladium(0) (152 mg, 0.166 mmol) were added, and the reaction mixture was heated at reflux for 4 h. After this time, the mixture was cooled to room temperature and filtered, and the filter cake was washed with methylene chloride (2 x 20 mL). The filtrates were combined and concentrated under reduced pressure, and the resulting residue was purified by column chromatography to afford a 51% yield (353 mg) of **116c** as a yellow solid: mp 172–173 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (s, 1H), 8.06 (s, 1H), 7.65 (s, 1H), 6.70 (s, 1H), 4.28 (t, 2H, *J* = 5.0 Hz), 3.97 (t, 2H, *J* = 5.5 Hz), 3.51 (s, 3H), 0.85 (s, 9H), -0.79 (s, 6H); MS (APCI+) *m/z* 428.3 (M+H).

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was purged with nitrogen and charged with **116c** (150 mg, 0.312 mmol), **111a** (133 mg, 0.312 mmol), sodium carbonate (99 mg, 0.936 mmol), 1,4-dioxane (5 mL) and water (1 mL). This mixture was degassed with nitrogen for 30 min. Tetrakis-(triphenylphosphine)palladium (36 mg, 0.031 mmol) was added. After heating at 100 °C for 3 h, the reaction mixture was cooled to room temperature and partitioned between water (40 mL) and methylene chloride (100 mL). The layers were separated, and the aqueous phase was extracted with methylene chloride (2 x 50 mL). The organic extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was dissolved in methanol (5 mL), and potassium carbonate (500 mg, 3.62 mmol) was added.

After stirring at room temperature for 2 h, the reaction mixture was partitioned between water (20 mL) and methylene chloride (20 mL). The layers were separated, and the aqueous phase was extracted with methylene chloride (2 × 20 mL). The organic extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was redissolved in THF (5 mL), and tetrabutylammonium fluoride trihydrate (500 mg, 1.58 mmol) was added. After stirring at room temperature for 3 h, the solvent was removed under reduced pressure, and the resulting residue was washed with water (10 mL). The resulting solid was purified by flash chromatography to afford **116** in 27% yield (47 mg) as an off-white solid: mp 171–172 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.56 (s, 1H), 8.16 (s, 1H), 7.75 (s, 1H), 7.58 (d, 1H, J = 8.0 Hz), 7.44 (t, 1H, J = 8.0 Hz), 7.33–7.32 (m, 2H), 4.86 (m, 1H), 4.81 (t, 1H, J = 5.5 Hz), 4.51 (dd, 1H, J = 11.0, 6.5 Hz), 4.44 (dd, 1H, J = 11.0, 6.5 Hz), 4.06 (t, 2H, J = 5.5 Hz), 4.02 (m, 1H), 3.68 (t, 2H, J = 5.5 Hz), 3.88 (m, 1H), 3.68 (q, 2H, J = 5.5 Hz), 3.52 (s, 3H), 2.98 (m, 1H), 2.86 (m, 1H), 2.77 (m, 2H), 2.58–2.46 (m, 2H), 1.79 (m, 4H); MS (APCI+) *m/z* 547.2 (M+H)

Example 117 2-(2-methyl-3-(5-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-one **117**

Example 117a 9-((2-(Trimethylsilyl)ethoxy)methyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-one **117a**

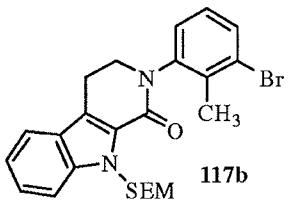


117a

A 25-mL single-neck round-bottomed flask equipped with a magnetic stirrer was purged with nitrogen and charged with anhydrous DMF (4 mL) and a 60% dispersion of sodium hydride in mineral oil (181 mg, 4.52 mmol) and the reaction mixture was cooled to 0 °C. 1,2,3,4-tetrahydro-1-oxo-beta-carboline (841 mg, 4.52 mmol) was added, and the reaction was stirred at 0 °C for 15 min. After this time, 2-(trimethylsilyl)ethoxymethyl chloride (829 mg, 4.97 mmol) was added, and the reaction was stirred at 0 °C for 1 h. The reaction mixture was then partitioned between water (10 mL) and ethyl acetate (20 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate (2 × 10 mL). The organic extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography to afford **117a** in 57%

yield (818 mg) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, 1H, J = 8.0 Hz), 7.65 (d, 1H, J = 8.0 Hz), 7.46 (t, 1H, J = 8.0 Hz), 7.27 (t, 1H, J = 8.0 Hz), 6.14 (s, 2H), 5.72 (br s, 1H), 3.75 (t, 2H, J = 7.0 Hz), 3.66 (t, 2H, J = 8.0 Hz), 3.14 (t, 2H, J = 7.0 Hz), 0.96 (t, 2H, J = 8.0 Hz), -0.25 (s, 9H).

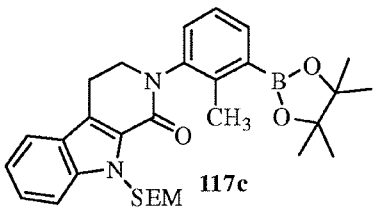
Example 117b 2-(3-Bromo-2-methylphenyl)-9-((2-(trimethylsilyl)ethoxy)methyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-one **117b**



117b

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was charged with **117a** (400 mg, 1.27 mmol), 2,6-dibromotoluene (633 mg, 2.53 mmol), cesium carbonate (828 mg, 2.54 mmol), N-methylethylenediamine (112 mg, 1.27 mmol) and 1,4-dioxane (20 mL). After bubbling nitrogen through the resulting suspension for 30 min, copper iodide (121 mg, 2.54 mmol) was added. A reflux condenser was attached to the flask, and the reaction mixture was heated at 100 °C for 16 h. After this time, the mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash column to afford **117b** in 41% yield (251 mg) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, 1H, J = 8.0 Hz), 7.68 (d, 1H, J = 8.0 Hz), 7.63 (d, 1H, J = 8.0 Hz), 7.47 (t, 1H, J = 8.0 Hz), 7.32–7.28 (m, 2H), 7.21 (t, 1H, J = 8.0 Hz), 6.13 (s, 2H), 4.15 (m, 1H), 3.93 (m, 1H), 3.69 (m, 2H), 3.29 (m, 2H), 2.45 (s, 3H), 0.95 (t, 2H, J = 8.0 Hz), -0.07 (s, 9H).

Example 117c 2-(2-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-9-((2-(trimethylsilyl)ethoxy)methyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-one **117c**



117c

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer, reflux condenser and nitrogen inlet was charged with **117b** (250 mg, 0.515 mmol), 4,4,4',4',-5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane (157 mg, 0.619 mmol), potassium acetate

(152 mg, 1.55 mmol) and 1,4-dioxane (5 mL). After bubbling nitrogen through the resulting suspension for 30 min, [1,1-Bis(diphenylphosphino)ferrocene]-dichloro-palladium(II)/CH_2Cl_2 (38 mg, 0.052 mmol) was added, and the reaction mixture was heated at 95 °C for 5 h. After this time, the mixture was diluted with ethyl acetate (20 mL) and water (20 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (50 mL), and the combined organic layers were washed with brine (50 mL) and dried over sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography to afford **117c** in 97% yield (242 mg) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, 1H, *J* = 8.0 Hz), 7.72 (d, 1H, *J* = 8.0 Hz), 7.68 (d, 1H, *J* = 8.0 Hz), 7.46 (t, 1H, *J* = 8.0 Hz), 7.39–7.28 (m, 2H), 7.21 (t, 1H, *J* = 8.0 Hz), 6.19 (d, 1H, *J* = 10.5 Hz), 6.15 (d, 1H, *J* = 10.5 Hz), 4.16 (m, 1H), 3.97 (m, 1H), 3.68 (m, 2H), 3.29 (m, 2H), 2.45 (s, 3H), 0.95 (t, 2H, *J* = 8.0 Hz), 1.34 (s, 12H), -0.07 (s, 9H).

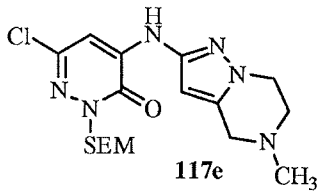
Example 117d 4-Bromo-6-chloro-2-((2-(trimethylsilyl)ethoxy)methyl)pyridazin-3(2*H*)-one **117d**



117d

A 500-mL single-neck round-bottomed flask equipped with a magnetic stirrer was purged with nitrogen and charged with anhydrous DMF (150 mL) and 4-bromo-6-chloro-pyridazin-3(2H)-one (10.0 g, 47.8 mmol). The reaction mixture was cooled to 0 °C and sodium hydride was added. The reaction was stirred at 0 °C for 20 min. After this time, 2-(Trimethylsilyl)ethoxymethyl chloride (11.9 g, 71.6 mmol) was added and the cooling bath was removed, and the reaction was stirred at room temperature for 3 h. The reaction was then quenched with saturated aqueous sodium bicarbonate (30 mL). The mixture was extracted with ethyl acetate (2 × 300 mL). The extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography to afford **117d** in a 56% yield (9.00 g) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1H), 5.42 (s, 2H), 3.79 (t, 2H, *J* = 5.4 Hz), 0.96 (t, 2H, *J* = 5.4 Hz), 0.01 (s, 9H).

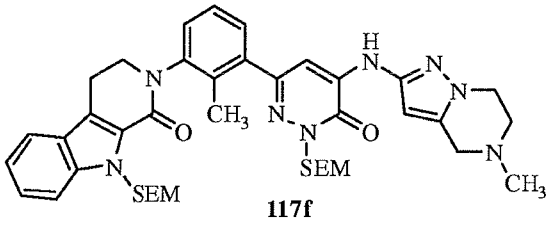
Example 117e 6-Chloro-4-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazin-2-ylamino)-2-((2-(trimethylsilyl)ethoxy)methyl)pyridazin-3(2*H*)-one **117e**



117e

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was charged with **117d**(1.12 g, 3.29 mmol), **103e** (500 mg, 3.29 mmol), cesium carbonate (3.22 g, 9.87 mmol) and 1,4-dioxane (25 mL). After bubbling nitrogen through the resulting solution for 30 min, Xantphos (286 mg, 0.494 mmol) and tris(dibenzylideneacetone)dipalladium(0) (301 mg, 0.329 mmol) were added and the reaction mixture was heated at reflux for 3 h. After this time, the reaction mixture was cooled to room temperature and partitioned between water (30 mL) and methylene chloride (60 mL). The layers were separated, and the aqueous phase was extracted with methylene chloride (60 mL). The organic extracts were combined, dried over sodium sulfate and filtered, and the solvent was removed from the filtrate under reduced pressure. The resulting residue was purified by column chromatography to afford a 72% yield (977 mg) of **117e** as a yellow solid: mp 68–69 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.56 (s, 1H), 5.70 (s, 1H), 5.47 (s, 2H), 4.16 (t, 2H, J = 5.5 Hz), 3.73 (m, 2H), 3.63 (s, 2H), 2.94 (t, 2H, J = 5.5 Hz), 2.51 (s, 3H), 0.98 (m, 2H), 0.12 (s, 9H); MS (ESI+) m/z 411.2 (M+H).

Example 117f 2-(2-Methyl-3-(5-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazin-2-ylamino)-6-oxo-1-((2-(trimethylsilyl)ethoxy)methyl)-1,6-dihydropyridazin-3-yl)phenyl)-9-((2-(trimethylsilyl)ethoxy)methyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-one **117f**



117f

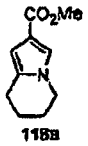
A 50-mL single-neck round-bottomed flask equipped with a magnetic stirrer, reflux condenser and nitrogen inlet was charged with 1,4-dioxane (5 mL), water (1 mL) and sodium carbonate (143 mg, 1.35 mmol). After bubbling nitrogen through the resulting mixture for 30 min, **117c** (240 mg, 0.451 mmol), **117e** (185 mg, 0.451 mmol) and tetrakis(triphenylphosphine)palladium(0) (52 mg, 0.045 mmol) were added, and the reaction mixture was heated at 100 °C for 3 h. After this time, the reaction was cooled to room

temperature and partitioned between water (25 mL) and methylene chloride (50 mL). The organic layer was separated, washed with brine (75 mL) and dried over sodium sulfate. The drying agent was removed by filtration, and the filtrate was concentrated under reduced pressure to a dark oil, which was purified by flash chromatography to afford an 89% yield (315 mg) of 117f as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.66 (d, 1H, J = 8.0 Hz), 7.45 (m, 3H), 7.39 (t, 1H, J = 8.0 Hz), 7.34 (d, 1H, J = 8.0 Hz), 7.24 (t, 2H, J = 8.0 Hz), 6.12 (d, 1H, J = 10.5 Hz), 6.05 (d, 1H, J = 10.5 Hz), 5.69 (s, 1H), 5.63 (d, 1H, J = 10.5 Hz), 5.52 (d, 1H, J = 10.5 Hz), 4.09 (m, 2H), 3.88 (m, 2H), 3.75 (m, 2H), 3.68 (s, 3H), 3.59 (m, 2H), 3.26–3.17 (m, 4H), 2.61 (m, 2H), 2.29 (s, 3H), 0.98 (t, 2H, J = 8.0 Hz), 0.85 (t, 2H, J = 8.0 Hz), -0.01 (s, 9H), -0.07 (s, 9H); MS (ESI+) *m/z* 781.4 (M+H).

A 50-mL single-neck round-bottomed flask equipped with a magnetic stirrer was purged with nitrogen and charged with 117f (315 mg, 0.404 mmol), anisole (438 mg, 4.04 mmol), methylene chloride (3 mL) and trifluoroacetic acid (3 mL). After stirring at room temperature for 2 h, the reaction mixture was concentrated, and the resulting residue was partitioned between 1 M aqueous potassium dihydrogen phosphate (10 mL) and methylene chloride (20 mL). The layers were separated, and the aqueous phase was extracted with methylene chloride (2 × 10 mL). The organic extracts were combined and dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography to afford 117 in 23% yield (49 mg) as a white solid: mp 254 °C dec; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.97 (s, 1H), 11.74 (s, 1H), 9.21 (s, 1H), 7.79 (s, 1H), 7.65 (d, 1H, J = 8.0 Hz), 7.44–7.37 (m, 3H), 7.34 (d, 1H, J = 8.0 Hz), 7.26 (t, 1H, J = 8.0 Hz), 7.08 (t, 1H, J = 8.0 Hz), 5.75 (s, 1H), 4.17 (m, 1H), 3.97 (t, 2H, J = 5.0 Hz), 3.84 (m, 1H), 3.51 (s, 2H), 3.17 (m, 2H), 2.79 (t, 2H, J = 5.0 Hz), 2.35 (s, 3H), 2.18 (s, 3H); MS (ESI+) *m/z* 521.2 (M+H)

Example 118 2-(2-(hydroxymethyl)-3-(1-methyl-6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrido[3,4-b]indolizin-1(2H)-one 118

Example 118a Methyl 5,6,7,8-Tetrahydroindolizine-2-carboxylate 118a

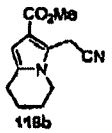


118a

A 500-mL round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was purged with nitrogen and charged with 5,6,7,8-tetrahydroindolizine-2-carboxylic acid

(30.4 g, 184 mmol), DMF (1.00 g, 13.6 mmol) and methylene chloride (300 mL). The solution was cooled to 0 °C using an ice bath. Oxalyl chloride (28.0 g, 221 mmol) was added dropwise, and the reaction mixture was warmed to room temperature over 30 min and stirred for 5 h. After this time, the resulting solution was concentrated to afford a brown solid. This solid was dissolved in anhydrous methanol (400 mL), and the solution was cooled to 0 °C. Triethylamine (57 g, 552 mmol) was added to the reaction mixture, and it was stirred for a further 2 h at room temperature. After this time, the reaction mixture was concentrated to dryness under reduced pressure. The residue was diluted with methylene chloride (300 mL) and washed with water (200 mL) and saturated aqueous sodium bicarbonate (200 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was titrated with hexane (200 mL) to afford **118a** in 58% yield (19.1 g) as a white solid: mp 72–74 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.13 (s, 1H), 6.23 (s, 1H), 3.93 (t, 2H, J = 6.0 Hz), 3.77 (s, 3H), 2.75 (t, 2H, J = 6.0 Hz), 1.93 (m, 2H), 1.80 (m, 2H); (APCI+) m/z 180.1 (M+H)

Example 118b Methyl 3-(Cyanomethyl)-5,6,7,8-tetrahydroindolizine-2-carboxylate **118b**

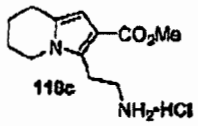


118b

A 500-mL three-neck round-bottomed flask equipped with an addition funnel, thermometer and charged with **118a** (6.70 g, 37.4 mmol), Iodoacetonitrile (12.5 g, 74.9 mmol), iron (II) sulfate heptahydrate (5.20 g, 18.7 mmol) and dimethyl sulfoxide (250 mL). Hydrogen peroxide (35%, 18.2 g, 187 mmol) was added dropwise to the mixture in 1 h through a syringe pump at room temperature using a water bath. Iron (II) sulfate heptahydrate (2 to 3 equivalent) was added to the reaction mixture in portions to keep the temperature between 25 °C to 35 °C, until the color of the reaction mixture is deep red. If TLC show the reaction not completed, then more hydrogen peroxide (2-3 equivalent) and more iron (II) sulfate heptahydrate (1-2 equivalent) were added in the same manner until the reaction is completed. After that time, the reaction mixture was partitioned between saturated sodium bicarbonate solution (200 mL) and ethyl acetate (400 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with saturated Sodium thiosulfate solution (50 mL),

dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography to afford a 78% yield (6.40 g) of **118b** as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.23 (s, 1H), 4.23 (s, 2H), 3.94 (t, 2H, J = 6.5 Hz), 3.81 (s, 3H), 2.74 (t, 2H, J = 6.5 Hz), 2.00 (m, 2H), 1.83 (m, 2H); (APCI+) *m/z* 219.3 (M+H)

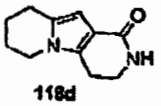
Example 118c Methyl 3-(2-Aminoethyl)-5,6,7,8-tetrahydroindolizine-2-carboxylate Hydrogen Chloride Salt **118c**



118c

Intermediate **118b** was hydrogenated with platinum oxide catalyst under 50 psi of hydrogen in ethanol and ethyl acetate in the presence of hydrogen chloride overnight at room temperature to give **118c** (380 mg, 1.74 mmol) which was used in directly in the next step.

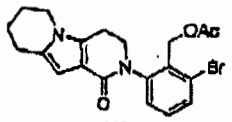
Example 118d 3,4,6,7,8,9-Hexahydropyrido[3,4-*b*]indolizin-1(2*H*)-one **118d**



118d

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was purged with nitrogen and charged with methyl 3-(2-aminoethyl)-5,6,7,8-tetrahydroindolizine-2-carboxylate hydrogen chloride salt **118c** (estimated 1.74 mmol, presuming quantitative yield), sodium ethoxide (354 mg, 5.22 mmol) and ethanol (20 mL). The mixture was stirred at 55 °C for 5 h. After that time, the reaction mixture was concentrated under reduced pressure and the residue was partitioned between ethyl acetate (200 mL) and water (100 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography to afford a 67% yield (220 mg) of **118d** as a white solid: mp 195–197 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.76 (s, 1H), 5.89 (s, 1H), 3.78 (t, 2H, J = 6.5 Hz), 3.35 (m, 2H), 2.66 (m, 4H), 1.87 (m, 2H), 1.72 (m, 2H); (APCI+) *m/z* 191.3 (M+H)

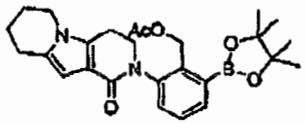
Example 118e 2-Bromo-6-(1-oxo-3,4,6,7,8,9-hexahydropyrido[3,4-*b*]indolizin-2(1*H*)-yl)benzyl Acetate **118e**



118e

A 250-mL three-neck round-bottomed flask equipped with a reflux condenser, magnetic stirrer was purged with nitrogen and charged with **118d** (1.50 g, 7.89 mmol), 2,6-dibromobenzyl acetate **104g** (4.80 g, 15.7 mmol), cesium carbonate (5.11 g, 15.7 mmol), *N,N'*-dimethylethylenediamine (695 mg, 7.89 mmol), and 1,4-dioxane (100 mL). After bubbling nitrogen through the resulting suspension for 20 min, copper iodide (752 mg, 3.95 mmol) was added, and the reaction mixture was heated at 95 °C (oil bath temperature) for 12 h. And then *N,N'*-dimethylethylenediamine (695 mg, 7.89 mmol) and copper iodide (752 mg, 3.95 mmol) were added and heated at 95 °C for another 12 h, repeated this until most of **118d** was converted to **118e**, about 48 h. After this time, the mixture was cooled to room temperature and filtered. The filtrate was diluted with ethyl acetate (300 mL) and water (100 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography to afford a 27% yield (905 mg) of **118e** as an off-white solid: mp 176–178 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.64 (dd, 1H, J = 7.5, 1.8 Hz), 7.37 (m, 2H), 5.99 (s, 1H), 5.00 (d, 2H, J = 6.0Hz), 4.00 (m, 1H), 3.85 (m, 2H), 3.62 (m, 1H), 2.93 (t, 2H, J = 6.1Hz), 2.67 (t, 2H, J = 6.1Hz), 2.00 (d, 3H, J = 6.0 Hz), 1.90 (m, 2H), 1.75 (m, 2H); MS (ESI+) *m/z* 417.0 (M+H)

Example 118f 2-(1-Oxo-3,4,6,7,8,9-hexahydropyrido[3,4-*b*]indolizin-2(1*H*)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl Acetate **118f**



118f

A 100-mL three-neck round-bottomed flask equipped with a reflux condenser, magnetic stirrer and nitrogen inlet was charged with **118e** (1.20 g, 2.88 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (2.20 g, 8.65 mmol), potassium acetate (1.13 g, 11.5 mmol) and 1,4-dioxane (50 mL). After bubbling nitrogen through the resulting suspension for 20 min, [1,1-Bis(diphenylphosphino)ferrocene]dichloro-palladium(II) (210 mg, 0.288 mmol) was added, and the reaction mixture was heated at 95 °C

for 8 h. After this time, the mixture was cooled to room temperature and filtered. The filter cake was washed with ethyl acetate (40 mL). The filtrate was diluted with ethyl acetate (150 mL) and water (40 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to afford a 100% yield (1.35 g) of crude **118f** as a yellow oil.

A 100-mL three-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was charged with **118f** (400 mg, 0.862 mmol), 5-bromo-1-methyl-3-(pyrimidin-4-ylamino)pyridin-2(1H)-one **109b** (241 mg, 0.862 mmol), sodium carbonate (365 mg, 3.45 mmol), water (4 mL) and 1,4-dioxane (20 mL). After bubbling nitrogen through the resulting suspension for 20 min, tetrakis(triphenylphosphine)-palladium(0) (100 mg, 0.086 mmol) was added, and the reaction mixture was heated at 100 °C for 2 h. After this time, the reaction mixture was cooled to room temperature and filtered, and the filter cake was washed with a 1:10 mixture of methanol and methylene chloride (30 mL). The filtrate was concentrated under reduced pressure to afford a brown residue. Another 50-mL single-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was charged with residue obtained above, THF (5 mL), ethanol (5 mL), water (5 mL) and lithium hydroxide (83.0 mg, 3.45 mmol). The mixture was stirred at 50 °C for 2 h. After this time, the reaction mixture was concentrated under reduced pressure. The resulting residue was purified by flash chromatography to afford a 23% (106 mg) yield of **118** as an off-white solid: mp 173–175 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.16 (s, 1H), 8.72 (s, 1H), 8.64 (s, 1H), 8.29 (d, 1H, J = 6.0 Hz), 7.55 (s, 1H), 7.45 (t, 1H, J = 7.5 Hz), 7.29 (m, 3H), 6.00 (s, 1H), 4.75 (t, 1H, J = 5.0 Hz), 4.31 (d, 2H, J = 5.0 Hz), 4.00 (m, 1H), 3.96 (m, 1H), 3.81 (m, 2H), 3.60 (s, 3H), 3.00 (m, 1H), 2.91 (m, 1H), 2.71 (t, 2H, J = 5.5 Hz), 1.92 (m, 2H), 1.75 (m, 2H); MS (ESI+) *m/z* 497.2 (M+H)

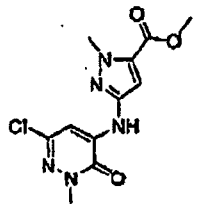
Example 119 5-[2-(Hydroxymethyl)-3-(5-{[5-(2-hydroxypropan-2-yl)-1-methyl-1H-pyrazol-3-yl]amino}-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl]-8-thia-5-azatricyclo[7.4.0.0 ^{2,7}]trideca-1(9),2(7)-dien-6-one **119**

Example 119a Methyl 3-Amino-1-methyl-1H-pyrazole-5-carboxylate **119a**

In a 250 mL Parr hydrogenation flask was placed methyl 1-methyl-3-nitro-1H-pyrazole-5-carboxylate, (530mg, 2.9mmol) dissolved in ethyl acetate (15mL) and ethanol (15mL), to which was added 10% Pd/C (Degussa type) (100mg). The mixture was placed on the Parr apparatus and pressurized with hydrogen to 50 PSI and shaken for 2.5 hrs. The reaction was filtered through a pad of celite which was washed with ethyl acetate. The

solvent was removed under vacuum to give **119a** as a white solid (450mg, 2.9mmol, quantitative yield).

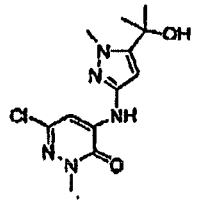
Example 119b Methyl 3-(6-Chloro-2-methyl-3-oxo-2,3-dihydropyridazin-4-ylamino)-1-methyl-1H-pyrazole-5-carboxylate **119b**



119b

In a 3-neck RBF was placed **119a** (500mg, 3.2mmol), 4-bromo-6-chloro-2-methylpyridazin-3(2H)-one (725mg, 3.2mmol), cesium carbonate (2.3g, 7.0mmol), and Xantphos (160mg, 8.5mol%). The flask was evacuated and filled with nitrogen 3X. Dioxane (20ml) was added and the mixture degassed for 25min with bubbling nitrogen. Tris(dibenzylideneacetone)dipalladium(0) (150mg, 5mol%) was then added and the reaction heated to 100°C for 6hrs. The reaction was cooled and diluted with EtOAc (125mL) and saturated aqueous NaHCO3 (50mL), the layers were separated and extracted EtOAc (2x100mL). The organics were washed with brine 3X, dried over Na2SO4, filtered, and concentrated under reduced pressure. The residue was purified by chromatography: ISCO 40g silica, EtOAc/hexanes, to give **119b**.

Example 119c 6-Chloro-4-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-pyrazol-3-ylamino)-2-methylpyridazin-3(2H)-one **119c**

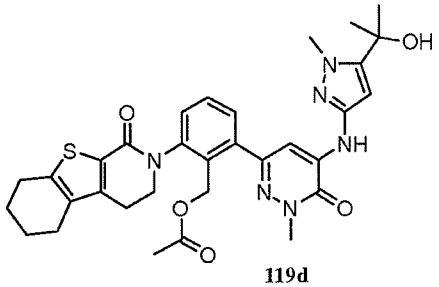


119c

In a 100mL round bottom flask containing **119b** (500mg, 1.7mmol) under nitrogen was added anh. THF (20mL) and anh.toluene (5mL) and the mixture stirred and cooled to -20 to -30°C. 3.0M methylmagnesium bromide in diethylether (1.6mL, 4.75mmol) was then slowly added. After the addition the reaction was allowed to slowly warm to room temp. and

stir for about 3hrs after which the reaction was quenched with 1N HCl. Concentrated to remove THF, diluted with ethyl acetate and water then adjusted the pH to ~6-7 with 1M NaOH. Separated and extracted 2X with ethyl acetate washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by chromatography: ISCO 24g silica, ethyl acetate /hexanes, to give **119c**.

Example 119d 2-(5-(5-(2-Hydroxypropan-2-yl)-1-methyl-1H-pyrazol-3-ylamino)-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **119d**



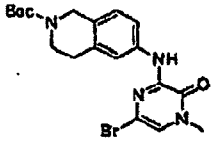
119d

In a microwave vial was placed **119c** (150mg, 0.50mmol) and **111a** (240mg, 0.50mmol) and DME (4mL) was added followed by 1N Na_2CO_3 (1.1mL). After degassing with bubbling argon for 5min, tetrakis(triphenylphosphine)palladium(0) (29mg, 5mol%) was added and the mixture was heated in a microwave reactor at 130°C for 15min. An additional 40mg **111a** was added and the mixture heated an additional 10min. The reaction was diluted with ethyl acetate and water, the ethyl acetate layer separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by chromatography: ISCO 12g silica, eluting with methanol and CH_2Cl_2, to give **119d** (170mg, 56% yield).

To a vial containing **119d** (170mg, 0.28mmol) dissolved in THF (1.5mL) and I-propanol (1.5ml) was added 1N LiOH/water (1.4mL, 1.4mmol) and the mixture stirred overnight after with the reaction was judged complete by LC-MS. The mixture was concentrated then diluted with ethyl acetate and water and 1N HCl and 1N NaOH were added to adjust the pH to 7. The ethyl acetate layer was separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was triturated with ethyl acetate and the solids collected by filtration to give **119** (98mg, 61% yield). MS (ESI+) *m/z* 575.2 (M + H).

Example 120 5-[5-Fluoro-2-(hydroxymethyl)-3-[4-methyl-5-oxo-6-(1,2,3,4-tetrahydroisoquinolin-6-ylamino)pyrazin-2-yl]phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one 120

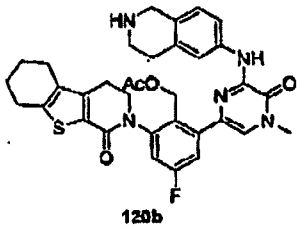
Example 120a *tert*-Butyl 6-(6-bromo-4-methyl-3-oxo-3,4-dihydropyrazin-2-ylamino)-3,4-dihydroisoquinoline-2(1H)-carboxylate 120a



120a

A mixture of tert-butyl 6-amino-3,4-dihydroisoquinoline-2(1H)-carboxylate (3 g, 12mmol), 3,5-dibromo-1-methylpyrazin-2(1H)-one (2.68 g, 10mmol), and triethylamine (1.5 g, 15mmol) in IPA (50 mL) was heated at 70°C for 15 h. The mixture was cooled to room temperature. The resulting yellow solids were collected by filtration and dried in vacuum to afford **120a** as a yellow solid (2.83 g, 65%).MS: $[M+H]^+$ 435.

Example 120b 4-Fluoro-2-[4-methyl-5-oxo-6-(1,2,3,4-tetrahydroisoquinolin-6-ylamino)pyrazin-2-yl]-6-{6-oxo-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-5-yl}phenyl}methyl acetate 120b



120b

Following Example 150b, 482 mg of 218b and 435 mg of 120a were reacted to give 362 mg (51%) of 120b as a yellow solid MS: $[M+H]^+$ 711.

Following Example 149, 200 mg of 120b was converted to 120 as a white solid (78 mg, 42%). ^{1}H NMR (500 MHz, MeOD) δ 7.72 (s, 1H), 7.58 (d, J=8.0, 1H), 7.39 (m, 2H), 7.21 (ss, J=9.5, 1H), 7.10 (d, J=8.5, 1H), 4.62 (d, J=12, 1H), 4.50 (d, J=12, 1H), 4.11 (m, 3H), 3.98 (m, 1H), 3.64 (s, 3H), 3.28(s, 2H), 2.95 (m, 4H), 2.85 (s, 2H), 2.60 (m, 2H), 1.9 (m, 4H).

Example 121 5-[2-(Hydroxymethyl)-3-(4-methyl-5-oxo-6-([4-(piperidin-4-yl)phenyl]-amino}-4,5-dihydropyrazin-2-yl)phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one 121

Example 121a *tert*-Butyl 4-(4-(6-bromo-4-methyl-3-oxo-3,4-dihydropyrazin-2-ylamino)phenyl)-piperidine-1-carboxylate **121a**

Compound **121a** was synthesized using the same procedure as example **112a**, except using tert-butyl 4-(4-aminophenyl)piperidine-1-carboxylate (0.83g, 3.0 mmol), 3,5-dibromo-1-methylpyrazin-2(1H)-one (0.88 g, 3.3mmol), cesium carbonate (1.27 g, 3.9 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.275 g, 0.3mmol), Xantphos (0.26 g, 0.45mmol) and 1,4-dioxane (30 mL). The reaction mixture was heated at 100 °C overnight. Work-up and purified by flash column chromatography (silica, ethyl acetate/ hexanes) to give a 80% yield (1.1 g) of **121a** as a solid: MS (ESI+) *m/z* 465.0 (M+H).

Example 121b 5-[2-(Acetoxymethyl)-3-(4-methyl-5-oxo-6-{[4-(piperidin-4-yl)phenyl]-amino}-4,5-dihydropyrazin-2-yl)phenyl]-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$]trideca-1(9),2(7)-dien-6-one **121b**

A 10 mL microwave vial with a magnetic stirrer was charged with **111a** (173 mg, 0.36 mmol), **121a** (139 mg, 0.3 mmol), 1M sodium carbonate solution (1.2 mL, 1.2 mmol) and 1,2-dimethoxyethane (3 mL). After bubbling nitrogen through the resulting suspension for 10 min, tetrakis(triphenylphosphine)-palladium(0) (18 mg, 0.015 mmol) was added. The reaction mixture was heated at 130 °C for 15 minutes in the microwave reactor. After this time, ethyl acetate (15 mL) and water (10 mL) were added, and the layers were separated. The aqueous layer was extracted with Ethyl acetate (2 × 20 mL), and the combined organic layers were washed with brine and dried over sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography (silica, ethyl acetate/hexanes) to afford compound **121b** as yellow oil (240 mg).

Compound **121b** was dissolved in methylene chloride (10 mL). Trifluoroacetic acid (0.3 mL, 3.9 mmol) was added, and the mixture was stirred at room temperature for 4 h. After this time, the mixture was basified by saturated sodium bicarbonate, and the aqueous layer was extracted with methylene chloride (2 × 15 mL). The combined organic layers were washed with brine and dried over sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated, and the resulting residue **121c** was dissolved in a mixture of THF (1.5 mL), water (0.8 mL) and isopropanol (1.5 mL). Lithium hydroxide monohydrate (56 mg, 1.32 mmol) was added, and the mixture was stirred at room temperature for 3 h. After this time, the mixture was diluted with 90:10 methylene chloride/methanol (10 mL) and water (5 mL), and the layers were separated. The aqueous layer was extracted with 90:10 methylene chloride/methanol (2 × 10 mL), and the combined organic layers were washed

with brine and dried over sodium sulfate. The drying agent was removed by filtration. The filtrate was purified by flash column chromatography (silica, methylene chloride/ methanol) to afford a 35% yield (3 steps, 63 mg) of compound **121** as a light pink solid: MS (ESI+) *m/z* 596.3 (M+H).

Example 122 5-[5-Fluoro-2-(hydroxymethyl)-3-(4-methyl-6-{[4-(morpholin-4-yl)phenyl]amino}-5-oxo-4,5-dihydropyrazin-2-yl)phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one **122**

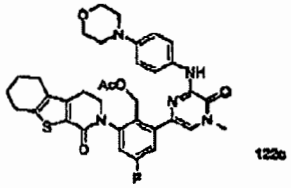
Example 122a 5-Bromo-1-methyl-3-(4-morpholinophenylamino) pyrazin-2(1H)-one (3-3) **122a**

A microwave vial equipped with a magnetic stirrer was charged with 3,5-dibromo-1-methylpyrazin-2(1H)-one (1.97 g, 7.4 mmol), 4-morpholinobenzenamine (1.97 g, 11.1 mmol), and isopropanol (25 mL). The system was evacuated and then refilled with N_2. It was heated at 90°C for 16 h. Then, the mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with 5:1 petroleum ether/ethyl acetate to afford **122a** (2.3 g, 85%). LCMS: $[M+H]^+$ 365.

Example 122b 4-Methyl-6-(4-morpholinophenylamino)-5-oxo-4,5-dihydropyrazin-2-ylboronic Acid **122b**

A microwave vial equipped with a magnetic stirrer was charged with **122a** (764mg, 2.1 mmol), $(PinB)_2$ (2.75 g, 10 mmol), $Pd(dppf)Cl_2$ (0.1g, 0.13 mmol), KOAc (0.6 g, 6 mmol), and DMF (5 mL). The system was evacuated and then refilled with N_2. The reaction mixture was then heated at 105°C for 1 h, then cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure to give the crude **122b**, which was used without further purification. LCMS: $[M+H]^+$ 331.

Example 122c [4-Fluoro-2-(4-methyl-6-{[4-(morpholin-4-yl)phenyl]amino}-5-oxopyrazin-2-yl)-6-{6-oxo-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-5-yl}phenyl]methyl Acetate **122c**



122c

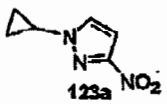
A 25 mL vial was charged with (2-bromo-4-fluoro-6-{6-oxo-8-thia-5-azatricyclo-[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-5-yl}phenyl)methyl acetate **212a** (300 mg, 0.67 mmol),

122b (440 mg, 1.33 mmol) suspended in 1,2-dimethoxyethane (15 mL) and water (1 mL). The resulting orange solution was heated for 30 minutes in a Biotage microwave reactor held at a constant temperature of 130°C. After reaction the residue was purified by reverse phase Combi-flash eluting with 0.3% NH_4HCO_3 in 1:6 water/CH_3CN to **122c** as a brown solid (200 mg, 46%). MS: $(M+H)^+$ 658.

To a solution of **122c** (220 mg, 0.33 mmol) in propan-2-ol (7 mL), tetrahydrofuran (7 mL), and water (2 mL) was added LiOH (804 mg, 33 mmol). The mixture was stirred at 30°C for 2 h. It was then evaporated under reduced pressure and the residue was purified by prep-HPLC to afford **122** as a yellow solid (82 mg, 40%). MS: $(M+H)^+$ 616. ^1H NMR (500 MHz, MeOD) δ 1.89 (s, 5 H), 2.55-2.63 (m, 2 H), 2.94 (s, 2 H), 3.11-3.13 (t, 5 H), 3.64 (s, 3 H), 3.82-3.84 (t, 4 H), 3.93-3.98 (m, 1 H), 4.07-4.14 (m, 1 H), 4.43-4.53 (m, 2 H), 6.97-6.99 (d, 2 H), 7.18-7.20 (d, 1 H), 7.29 (s, 1H), 7.36-7.38 (d, 1H), 7.62-7.64 (d, 2H).

Example 123 5-(3-{5-[(5-cyclopropyl-1H-pyrazol-3-yl)amino]-1-methyl-6-oxo-1,6-dihydropyridin-3-yl}-2-(hydroxymethyl)phenyl)-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one **123**

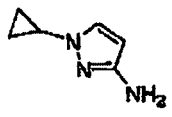
Example 123a 1-Cyclopropyl-3-nitro-1*H*-pyrazole **123a**



123a

A 250-mL three-neck round-bottomed flask equipped with a reflux condenser and magnetic stirrer was purged with nitrogen and charged with 3-nitro-(1H)pyrazole (1.30 g, 11.5 mmol), cyclopropylboronic acid (1.98 g, 23.0 mmol), sodium carbonate (3.66 g, 34.5 mmol), 2,2'-bipyridyl (3.58 g, 23.0 mmol), dichloroethane (60 mL) and copper(II) acetate (2.08 g, 11.5 mmol). The reaction mixture was heated at 70 °C (oil bath temperature) for 3 h. After this time, another portion of cyclopropyl boronic acid (1.98 g, 23.0 mmol) was added, and the mixture was heated for 3 h. After this time, the mixture was cooled to room temperature and filtered. The filtrate was diluted with ethyl acetate (350 mL) and water (40 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 150 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (silica, 0% to 100% ethyl acetate/hexanes) to afford an 85% yield (1.49 g) of **123a** as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, 1H, J = 2.4 Hz), 6.87 (d, 1H, J = 2.5 Hz), 3.71 (m, 1H), 1.25 (m, 2H), 1.12 (m, 2H); MS (APCI+) *m/z* 154.1 (M+H).

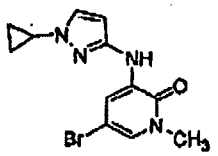
Example 123b 1-Cyclopropyl-1*H*-pyrazol-3-amine **123b**



123b

A 250-mL Parr reactor bottle was purged with nitrogen and charged with 10% palladium on carbon (50% wet, 137 mg dry weight) and a solution of **123a** (600 mg, 3.92 mmol) in ethanol (70 mL). The bottle was attached to a Parr hydrogenator, evacuated, charged with hydrogen gas to a pressure of 50 psi and shaken for 3 h. After this time, the hydrogen was evacuated, and nitrogen was charged into the bottle. Celite 521 (1.00 g) was added, and the mixture was filtered through a pad of Celite 521. The filter cake was washed with ethanol (2 × 25 mL), and the combined filtrates were concentrated to dryness under reduced pressure to afford a 93% yield of **123b** (450 mg) as a purple oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (d, 1H, J = 2.4 Hz), 5.55 (d, 1H, J = 2.4 Hz), 3.43 (m, 1H), 2.92 (br s, 2H), 1.01 (m, 2H), 0.93 (m, 2H); MS (ESI+) *m/z* 124.1 (M+H).

Example 123c 5-Bromo-3-(1-cyclopropyl-1*H*-pyrazol-3-ylamino)-1-methylpyridin-2(1*H*)-one **123c**



123c

A 250-mL three-neck round-bottomed flask equipped with a reflux condenser, magnetic stirrer and nitrogen inlet was charged with **123b** (444 mg, 3.61 mmol), 2,5-dibromo-1-methylpyrazin-6-one (1.06 g, 3.97 mmol), cesium carbonate (3.52 g, 10.8 mmol), and 1,4-dioxane (45 mL). After bubbling nitrogen through the resulting suspension for 30 min, Xantphos (177 mg, 0.306 mmol) and tris(dibenzylideneacetone)-dipalladium(0) (165 mg, 0.180 mmol) were added, and the reaction mixture was heated at reflux for 3 h. After this time, the mixture was cooled to room temperature and diluted with ethyl acetate (150 mL) and water (30 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 150 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was triturated with methanol (20 mL) to afford a 63% yield (700 mg) of **123c** as an off-white solid: mp 161–163 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.42 (s, 1H), 8.00 (d, 1H, J = 2.5 Hz), 7.57 (d, 1H, J = 2.4 Hz), 7.38 (d,

1H, J = 2.5 Hz), 6.05 (d, 1H, J = 2.4 Hz), 3.61 (m, 1H), 3.49 (s, 1H), 0.95 (m, 4H); MS (ESI+) *m/z* 309.0 (M+H).

A 150-mL single-neck round-bottomed flask equipped with a reflux condenser, magnetic stirrer and nitrogen inlet was charged with **123c** (247 mg, 0.800 mmol), **111a** (770 mg, 1.60 mmol), sodium carbonate (254 mg, 2.40 mmol), DMF (5 mL), water (2.5 mL) and 1,4-dioxane (8 mL). After bubbling nitrogen through the resulting suspension for 30 min, tetrakis(triphenylphosphine)palladium(0) (93 mg, 0.080 mmol) was added, and the reaction mixture was heated at reflux for 14 h. After this time, the mixture was cooled to room temperature and diluted with ethyl acetate (150 mL) and water (30 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 150 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was dissolved in a mixture of THF (8 mL), methanol (4 mL) and water (4 mL). To the resulting solution was added lithium hydroxide monohydrate (167 mg, 3.40 mmol). The mixture was stirred for 2 h at room temperature and then concentrated in vacuo. The residue was partitioned between ethyl acetate (150 mL) and water (30 mL). The organic layer was separated, and the aqueous layer was extracted with a 20% (v/v) solution of methanol in methylene chloride (3 × 150 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (silica, 0% to 10% methanol/methylene chloride) to afford a 19% yield (84 mg) of **123** as an off-white solid: mp 200–201 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.75 (s, 1H), 7.98 (s, 1H), 7.92 (s, 1H), 7.418 (t, 1H, J = 8.0 Hz), 7.31 (d, 1H, J = 7.5 Hz), 7.27 (d, 1H, J = 7.5 Hz), 7.21 (s, 1H), 5.78 (s, 1H), 4.79 (m, 1H), 4.36 (m, 2H), 4.12 (m, 1H), 3.80 (m, 1H), 3.56 (s, 3H), 2.95 (m, 1H), 2.80 (m, 1H), 2.78 (s, 2H), 1.80 (m, 5H), 0.87 (m, 2H), 0.62 (m, 2H); MS (ESI+) *m/z* 542.1 (M+H).

Example 124 5-[5-fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-[(5-methyl-1H-pyrazol-3-yl)amino]-1,2-dihydropyridin-2-one **124**

Example 124a 1-Methyl-3-(5-methyl-1H-pyrazol-3-ylamino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one **124a**

A microwave vial equipped with a magnetic stirrer was charged with 5-bromo-1-methyl-3-(5-methyl-1H-pyrazol-3-ylamino)pyridine-2(1H)-one **112a** (2.3 g, 8.3 mmol), $(PinB)_2$ (11 g, 41 mmol), $Pd(dppf)Cl_2$ (0.4g, 0.5 mmol), KOAc (2.4 g, 25 mmol), and 1,4-dioxane (150 mL). The system was evacuated and then refilled with N_2. The reaction mixture was heated at 100°C for 0.5 h under microwave irradiation. Then, the mixture was cooled to

room temperature and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography eluting with 5:1 petroleum ether/ethyl acetate to afford **124a** (0.57 g, 21%). LCMS: $[M+H]^+$ 331.

Example 124b 4-Fluoro-2-(1-methyl-5-(5-methyl-1H-pyrazol-3-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-benzyl acetate **124b**

A mixture of **124a** (330 mg, 1 mmol), 2-bromo-4-fluoro-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **197d** (434 mg, 1 mmol), $PdCl_2$(dppf) (82 mg, 0.1mmol), 2.0M Na_2CO_3 (2.0 equiv) in DME (10 mL) was heated at 120°C under microwave irradiation for 0.5 h. The solvent was evaporated in *vacuo*. The residue was purified on reverse phase Combi-flash to give the title compound (160 mg, 29%). LCMS: $[M+H]^+$ 559

A mixture of **124b** (150 mg, 0.27 mmol) and LiOH (324 mg, 14 mmol) in isopropanol/THF (1:1, 10 mL) and water (3 mL) was stirred at 30°C for 2 h. The mixture was evaporated in *vacuo* and the residue was extracted with ethyl acetate (10 mL X 2). The combined ethyl acetate extract was concentrated under reduced pressure and the residue was purified with prep-HPLC to give **124** (60 mg, 43%). LCMS: $[M+H]^+$ 517. ^1H NMR (500 MHz, DMSO) δ 11.74 (s, 1H), 8.00 (m, 2H), 7.30 (m, 2H), 7.16 (dd, J = 9.5, 1H), 6.52 (s, 1H), 5.87 (s, 1H), 4.87 (m, 1H), 4.33 (m, 2H), 4.12 (m, 3H), 3.87 (m, 1H), 3.56 (s, 3H), 2.59 (m, 2H), 2.47 (m, 2H), 2.45 (s, 3H), 1.70 (m, 4H).

Example 125 3-[(5-ethyl-1H-pyrazol-3-yl)amino]-5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-1,2-dihydropyridin-2-one **125**

Experiment 125a 5-Bromo-3-(5-ethyl-1H-pyrazol-3-ylamino)-1-methylpyridin-2(1H)-one 125a

A 350-mL sealed tube equipped with a magnetic stirring bar was charged with 3,5-dibromo-1-methyl-1H-pyridin-2-one (3.2 g, 0.012 mol), 5-ethyl-1H-pyrazol-3-amine (2.0 g, 0.018 mol), $Pd_2(dba)_3$ (0.55 g, 0.60 mmol), 9,9-dimethyl-4,5-bis(diphenyl-phosphino)xanthene (0.49 g, 0.00084 mol), Cs_2CO_3 (7.8 g, 0.024 mol), and 1,4-dioxane (80 mL). After the reaction mixture was stirred at 105°C for 16 h, it was cooled to room temperature, partitioned between dichloromethane (50 mL) and water (30 mL), and the organic phases were extracted with dichloromethane (30 mL x 3). The combined organic phases were washed with water (30 mL x 2) and brine (20 mL x 1), dried (Na_2SO_4), and filtered through a pad of Celite, and the resulting filtrated was concentrated. To the crude

product were added dichloromethane (20 mL) and ether (100 mL). The mixture was sonicated for 10 min., and the resulting precipitates were filtered to give 42% yield (1.5 g) of 5-bromo-3-(5-ethyl-1H-pyrazol-3-ylamino)-1-methylpyridin-2(1H)-one (125a) as a solid.

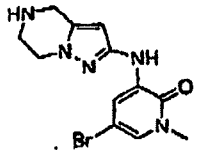
Example 125b 2-(5-(5-Ethyl-1H-pyrazol-3-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **125b**

In a 10-mL glass vessel equipped with a magnetic stirring bar were placed **125a** (116 mg, 0.39 mmol), 2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **114a** (200 mg, 0.43 mmol), $Pd(PPh_3)_4$ (30 mg, 0.0.26 mmol) in 2 N Na_2CO_3 (2 mL) and 1,2-dimethoxyethane (5 mL). The vessel was sealed with a septum and placed into the microwave cavity. After the reaction mixture was stirred at 125 °C for 7 min., it was purified by flash chromatography (dichloromethane:methanol, 85:15) to give 23% (50 mg) of **125b** as a solid.

A 25-mL, single-necked, round-bottomed flask equipped with a magnetic stirring bar was charged with **125b** (50 mg, 0.090 mmol), $LiOH \cdot H_2O$ (20 mg, 0.83 mmol), THF (2 mL), isopropanol (2 mL), and water (2 mL). After the reaction mixture was stirred at room temperature for 3 h, it was partitioned between dichloromethane (5 mL) and water (5 mL), and the organic phase was extracted with dichloromethane (5 mL x 3). The combined organic phases were washed with water (5 mL x 2) and brine (5 mL x 1), dried (Na_2SO_4), and concentrated. The crude product was re-dissolved in dichloromethane (3 mL). To this solution was added hexane (10 mL) and the resulting precipitates were filtered to give 50% yield (23 mg) of 2-(3-(5-(5-ethyl-1H-pyrazol-3-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **125** MS(ESI$^+$) *m/z* 513.3 (M+H).

Example 126 2-(2-(Hydroxymethyl)-3-(1-methyl-6-oxo-5-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **126**

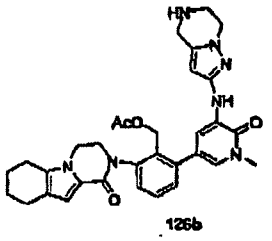
Experiment 126a 5-Bromo-1-methyl-3-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)pyridin-2(1H)-one **126a**



126a

A 50 mL round bottom flask with a magnetic stirrer and reflux condenser was charged with 3-(5-acetyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-5-bromo-1-methylpyridin-2(1H)-one **108d** (250 mg, 0.7 mmol), aqueous NaOH (5N, 6 mL), ethanol (6 mL). The mixture stirred at reflux for 30 min. After this time, ethyl acetate (5 mL) and water (5 mL) were added. The separated aqueous layer was extracted with ethyl acetate (2 x 5 mL). The combined organics were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to afford a 91% yield (200 mg) of crude 5-bromo-1-methyl-3-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)pyridin-2(1H)-one (**126a**).

Example 126b **2-(1-Methyl-6-oxo-5-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate 126b**



126b

A microwave tube equipped with a magnetic stirrer was charged with **126a** (210 mg, 0.65 mmol), 2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **114a** (330 mg, 0.7 mmol), DME (6 mL) and 1M aqueous sodium carbonate (1.9 mL). After bubbling N2 for 15 min, $Pd(PPh_3)_4$ (38 mg, 0.03 mmol) was added. The mixture was heated in microwave to 135 °C for 15 min. After this time, ethyl acetate (10 mL) and water (10 mL) were added. The separated aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organics were washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography eluting with a gradient of CH_2Cl_2 – 9:1 CH_2Cl_2:MeOH to afford a 36% yield (140 mg) of **126b**.

A 25 mL round bottom flask with a magnetic stirrer was charged with **126b** (140 mg, 0.24 mmol), lithium hydroxide (50 mg, 1.2 mmol), THF (1.2 mL), *i*-propanol (1.2 mL) and water (2.4 mL). The mixture stirred at rt for 1 h. After this time ethyl acetate (5 mL) and water (5 mL) were added. The separated aqueous layer was extracted with ethyl acetate (2 x 5 mL). The combined organics were washed with brine (10 mL), dried over sodium sulfate,

filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography eluting with a gradient of CH_2Cl_2–60:35:5 CH_2Cl_2:Et_2O:MeOH to afford a 33% yield (42 mg) of **126**. MS (ESI+) *m/z* 540.3 (M + H).

Example 127 2-(5-fluoro-2-(hydroxymethyl)-3-(4-methyl-6-(4-morpholinophenylamino)-5-oxo-4,5-dihydropyrazin-2-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **127**

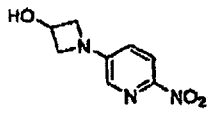
Example 127a 4-Fluoro-2-(4-methyl-6-(4-morpholinophenylamino)-5-oxo-4,5-dihydropyrazin-2-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **127a**

A mixture of 4-methyl-6-(4-morpholinophenylamino)-5-oxo-4,5-dihydropyrazin-2-yl boronic acid **122b** (330 mg, 1 mmol), 2-bromo-4-fluoro-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **197d** (434 mg, 1 mmol), $PdCl_2$(dppf) (82 mg, 0.1 mmol), 2.0M Na_2CO_3 (1 mL, 2.0 equiv) in DME (10 mL) was heated at 130°C under microwave irradiation for 0.5 h. The solvent was evaporated in *vacuo* and the residue was purified on reverse phase Combi-flash to give **127a** (200 mg, 45%). LCMS: $[M+H]^+$ 641.

A mixture of **127a** (200 mg, 0.31 mmol) and LiOH (372 mg, 16 mmol) in ^{i}PrOH/THF (1:1, 10 mL) and H_2O (3 mL) was stirred at 30°C for 2 h. The mixture was then evaporated in *vacuo* and the residue was extracted with ethyl acetate (10 mL X 2). The combined extract was concentrated under reduced pressure and the residue was purified with prep-HPLC to give **127** (58 mg, 33%). LCMS: $[M+H]^+$ 599 ^{1}H NMR (500 MHz, DMSO) δ 9.13 (s, 1H), 7.81 (m, 2H), 7.43 (s, 1H), 7.34 (m, 2H), 6.89 (m, 2H), 6.52 (s, 1H), 4.85 (s, 1H), 4.14 (m, 1H), 3.72 (m, 3H), 3.56 (m, 3H), 3.07 (m, 4H), 2.63 (m, 3H), 2.47 (m, 2H), 1.75 (m, 4H).

Example 128 2-(3-(5-(5-(3-hydroxyazetidin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **128**

Example 128a 1-(6-Nitropyridin-3-yl)azetidin-3-ol **128a**

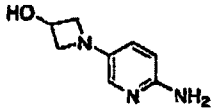


128a

A 50 mL round bottom flask with a magnetic stirrer and reflux condenser was charged with 3-hydroxyazetidine·HCl (2 g, 18.4 mmol), 5-bromo-2-nitropyridine (2.1 g, 10.2 mmol), diisopropylethylamine (5.4 mL, 30.7 mmol), tetrabutylammonium iodide (5.7 g, 15.4 mmol) and N,N-dimethylacetamide (10 mL). The mixture stirred at 120 °C for 16 h. After this time

the mixture was cooled and ethyl acetate (25 mL) and water (25 mL) were added. The separated aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organics were washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography eluting with a gradient of 4:1 hexanes: ethyl acetate o – 100 ethyl acetate to afford a 52% yield (1.9 g) of **128a**.

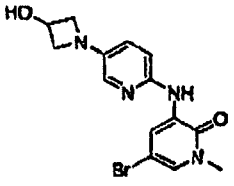
Example 128b 1-(6-Aminopyridin-3-yl)azetidin-3-ol **128b**



128b

A 500-mL Parr hydrogenation bottle was charged with **128a** (1.9 g, 9.6 mmol), 10% palladium on carbon (50% wet, 570 mg dry weight) and ethanol (100 mL). The bottle was evacuated, charged with hydrogen gas to a pressure of 50 psi and shaken for 24 h on a Parr hydrogenation apparatus. The catalyst was removed by filtration through a pad of Celite 521 washing with 1:1 CH_2Cl_2:MeOH (500mL). The resulting residue was purified by column chromatography eluting with a gradient of 100% DCM – 100% 3:1 DCM:MeOH to afford a 70% yield (1.1 g) of **128b**.

Example 128c 5-Bromo-3-(5-(3-hydroxyazetidin-1-yl)pyridin-2-ylamino)-1-methylpyridin-2(1H)-one **128c**

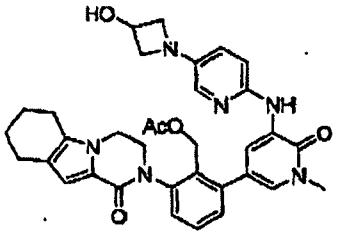


128c

A sealed tube was equipped with a magnetic stirrer and charged with **128b** (375 mg, 2.3 mmol), 3,5-dibromo-1-methylpyridin-2(1H)-one (848 g, 3.2 mmol) and cesium carbonate (1.7 g, 5 mmol) in 1,4-dioxane (24 mL). After bubbling nitrogen through the solution for 30 min, Xantphos (160 mg, 0.3 mmol) and tris(dibenzylideneacetone) dipalladium(0) (150 mg, 0.2 mmol) were added, and the reaction mixture was heated to 100 °C for 5 days. After this time, H_2O (20 mL) and EtOAc (20 mL) were added. The aqueous layer was separated and extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were washed with brine (50 mL) and dried over sodium sulfate. The

resulting residue was purified by column chromatography eluting with a gradient of CH_2Cl_2 – 9:1 CH_2Cl_2:MeOH to afford a 39% yield (430 mg) of **128c**.

Example 128d 2-(5-(5-(3-Hydroxyazetidin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **128d**



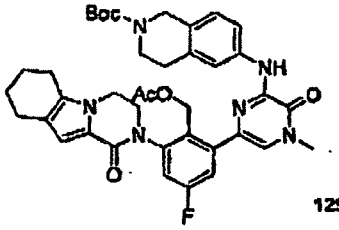
128d

A microwave tube equipped with a magnetic stirrer was charged with **128c** (220 mg, 0.6 mmol), 2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **114a** (350 mg, 0.8 mmol), DME (7 mL) and 1M aqueous sodium carbonate (1.9 mL). After bubbling N2 for 15 min, $Pd(PPh_3)_4$ (36 mg, 0.03 mmol) was added. The mixture was heated in microwave to 135 °C for 15 min. After this time, ethyl acetate (10 mL) and water (10 mL) were added. The separated aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organics were washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography eluting with a gradient of CH_2Cl_2 – 60:35:5 CH_2Cl_2:diethyl ether:MeOH to afford a 30% yield (110 mg) of **128d**.

A 25 mL round bottom flask with a magnetic stirrer was charged with **128d** (110 mg, 0.2 mmol), lithium hydroxide (38 mg, 0.9 mmol), THF (0.9 mL), *i*-propanol (0.9 mL) and water (1.8 mL). The mixture stirred at room temperature (rt) for 1 hr. After this time, ethyl acetate (5 mL) and water (5 mL) were added. The separated aqueous layer was extracted with ethyl acetate (2 x 5 mL). The combined organics were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography eluting with a gradient of CH_2Cl_2 – 60:35:5 CH_2Cl_2:diethyl ether:MeOH to afford a 12% yield (12 mg) of **128**. MS (ESI+) *m/z* 567.2 (M + H).

Example 129 2-(5-fluoro-2-(hydroxymethyl)-3-(4-methyl-5-oxo-6-(1,2,3,4-tetrahydroisoquinolin-6-ylamino)-4,5-dihydropyrazin-2-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **129**

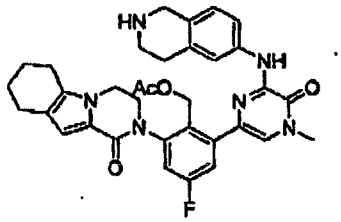
Example 129a *tert*-Butyl-6-(6-(2-(acetoxymethyl)-5-fluoro-3-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)phenyl)-4-methyl-3-oxo-3,4-dihydropyrazin-2-ylamino)-3,4-dihydroisoquinoline-2(1H)-carboxylate **129a**



129a

A mixture of 482 mg of 4-fluoro-2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6 -(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **210d** and 435 mg of tert-butyl-6-(6-bromo-4-methyl-3-oxo-3,4-dihydropyrazin-2-ylamino)-3,4-dihydro-isoquinoline-2(1H)-carboxylate **120a**, $PdCl_2(dppf)$ (1110 mg, 0.015 mmol), 2 M Na_2CO_3 solution (3 mL) in DME (16 mL) was heated at 120°C under microwave irradiation for 0.5 h. The solvent was evaporated in *vacuo* and the residue was purified on reverse phase Combi-flash to give **129a** as a yellow solid (362 mg, 51%). MS: $[M+H]^+$ 711.

Example 129b 4-Fluoro-2-(4-methyl-5-oxo-6-(1,2,3,4-tetrahydroisoquinolin-6-ylamino)-4,5-dihydropyrazin-2-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **129b**



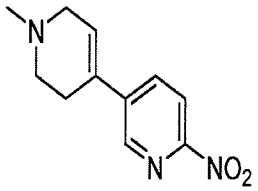
129b

To the solution of **129a** (360 mg 0.51 mmol) in DCM (30 mL) was added 3M HCl in dioxane (8mL) at room temperature. The mixture was stirred at room temperature for 5 h. After the reaction was completed, the solvent was removed at reduced pressure to afford **129b** as a yellow solid (310 mg, 99%).

Following Example 149, 250 mg of **129b** was converted to **129** as a white solid (98 mg, 42%). ^{1}H NMR (500 MHz, MeOD) δ 7.62 (s, 1H), 7.55 (dd, J=7.0, 1H), 7.41 (dd, J=9.5, 1H), 7.38 (s, 1H), 7.20 (dd, J=9.5, 1H), 7.04 (d, J=8.5, 1H), 6.71 (s, 1H), 4.59 (d, J=12, 1H), 4.8 (d, J=11.5, 1H), 4.20 (m, 3H), 4.00 (m, 3H), 3.64 (s, 3H), 3.13 (m, 2H), 2.86 (m, 2H), 2.64 (m, 2H), 2.54 (m, 2H), 1.88 (m, 2H), 1.78 (m, 2H).

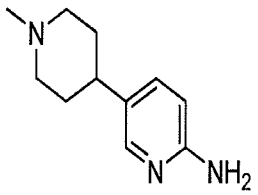
Example 130 2-(2-(hydroxymethyl)-3-(1-methyl-5-(5-(1-methylpiperidin-4-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **130**

Example 130a 5-(1-Methyl-1,2,3,6-tetrahydropyridin-4-yl)-2-nitropyridine **130a**



To a round-bottomed flask equipped with a stirring bar, 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine (1.50 g, 6.72 mmol), 5-bromo-2-nitropyridine (1.64 g, 8.07 mmol), $Pd(PPh_3)_4$ (388 mg, 0.336 mmol), Na_2CO_3 aqueous solution (1.0 N, 20.2 mL, 20.2 mmol), dioxane (60.6 mL) were added. The reaction mixture was heated at 100 °C for 10 hrs. CH_2Cl_2 (200 mL) was added to the resulting mixture was washed with water (30 mL X 3). CH_2Cl_2 (200 mL) was added and the resulting mixture was washed with water (30 mL X 3), brine (30 mL X 1), dried over $MgSO_4$, filtered, and removed solvent *in vacuo*. Silica gel column chromatography (MeOH: DCM = 5: 95) gave 5-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-2-nitropyridine (**130a**) as a yellow solid.

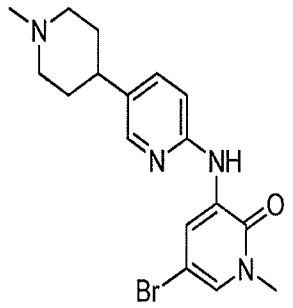
Example 130b 5-(1-Methylpiperidin-4-yl)pyridin-2-amine **130b**



In a hydrogenation bottle, **130a** (1.25 g, 5.73 mmol), EtOH (100 mL), 10 % Pd / C (304 mmol, 0.286 mmol) were added. The mixture was hydrogenated at 55 psi for 2 hrs, filtered through celite, and washed with MeOH (20 mL). The solvent was removed *in vacuo*

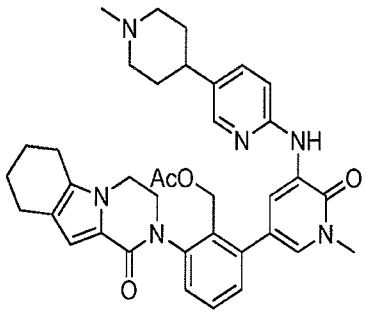
and off-white solids were obtained as 5-(1-methylpiperidin-4-yl)pyridin-2-amine **130b** (1.13 g, 100 %).

Example 130c 5-Bromo-1-methyl-3-(5-(1-methylpiperidin-4-yl)pyridin-2-ylamino)pyridin-2(1H)-one **130c**



To a round-bottomed flask equipped with a stirring bar, **130b** (1.08 g, 5.65 mmol), 3,5-dibromo-1-methylpyridin-2(1H)-one (2.26 g, 8.47 mmol), $Pd_2(dba)_3$ (517 mg, 0.565 mmol), XantPhos (523 mg, 0.903 mmol), Cs_2CO_3 (6.07 g, 18.6 mmol) and dioxane (28.3 mL) were added. The reaction mixture was heated at 100 °C overnight. CH_2Cl_2 (200 mL) was added to the resulting mixture was washed with water (30 mL X 3). CH_2Cl_2 (200 mL) was added and the resulting mixture was washed with water (30 mL X 3), brine (30 mL X 1), dried over $MgSO_4$, filtered, and removed solvent *in vacuo*. CH_2Cl_2/ ether (1:2, 5 mL) were added followed by sonication, the precipitation was filtered and dried. Compound **130c** was obtained as a green solid, 784 mg (37 %).

Example 130d 2-(1-Methyl-5-(5-(1-methylpiperidin-4-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **130d**



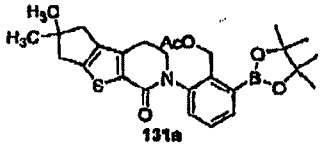
To a microwave tube equipped with a stirring bar, **130c** (250 mg, 0.663 mmol), 2-(2-(hydroxymethyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **114a** (338 mg, 0.729 mmol), $Pd(PPh_3)_4$ (38.3 mg, 0.033 mmol), Na_2CO_3 aqueous solution (1.0 N, 2.19 mL, 2.19 mmol), DME (2 mL) were

added. The mixture was reacted in microwave at 135 °C for 15 min. CH_2Cl_2 (200 mL) was added and the resulting mixture was washed with water (30 mL X 3), brine (30 mL X 1), dried over $MgSO_4$, filtered, and removed solvent *in vacuo*. Silica gel column chromatography (MeOH: DCM = 5: 95) gave **130d**.

To a round-bottomed flask equipped with a stirring bar, **130d** THF (1.25 mL), *i*-PrOH (1.25 mL), H_2O (1.25 mL), LiOH H_2O (135 mg) were added. The resulting mixture was stirred at RT for 1 hr. The solvent was removed *in vacuo* and the resulting residue was added to CH_2Cl_2 (200 mL), the solution was washed with water (30 mL X 3), brine (30 mL X 1), dried over $MgSO_4$, filtered, and removed solvent *in vacuo*. Silica gel column chromatography (MeOH: CH_2Cl_2 = 10: 90) gave **130** as an off-white solid, 39 mg. MS (ESI+) *m/z* 593.4 (M + H).

Example 131 5-(3-(6,6-Dimethyl-3,4,6,7-tetrahydro-5*H*-cyclopenta[4,5]thieno[2,3-*c*]pyridine-1(2*H*)-yl)-2-(hydroxymethyl)phenyl)-1-methyl-3-(1-ethyl-1*H*-pyrazol-4-ylamino) pyrazin-2(1*H*)-one **131**

Example 131a 2-(6,6-Dimethyl-3,4,6,7-tetrahydro-5*H*-cyclopenta[4,5]thieno[2,3-*c*]pyridine-1(2*H*)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl Acetate **131a**

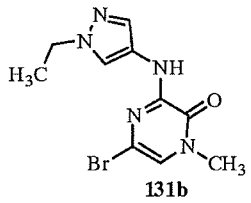


131a

A 250-mL single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was charged with **105i** (411 mg, 0.917 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane (698 mg, 2.75 mmol), potassium acetate (360 mg, 3.66 mmol) and 1,4-dioxane (15 mL). After bubbling nitrogen through the resulting suspension for 30 min, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (35 mg, 0.047 mmol) was added. A reflux condenser was attached to the flask, and the reaction mixture was heated at 90 °C for 14 h. After this time, more $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (70 mg, 0.094 mmol) was added, and the reaction was stirred for 4 h at 90 °C. After this time, the mixture was diluted with ethyl acetate (100 mL) and water (75 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (50 mL), and the combined organic layers were washed with brine (50 mL) and dried over sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash column

chromatography (silica, 70:30 hexanes/ethyl acetate) to afford **131a** in 82% yield (373 mg) as an amorphous off-white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (dd, J = 7.5, 1.5 Hz, 1H), 7.41 (t, J = 7.5 Hz, 1H), 7.35 (dd, J = 7.0, 1.5 Hz, 1H), 5.51 (d, J = 11.5 Hz, 1H), 5.26 (d, J = 11.5 Hz, 1H), 4.03–3.98 (m, 1H), 3.77–3.72 (m, 1H), 3.05–2.98 (m, 1H), 2.82–2.76 (m, 1H), 2.76 (s, 2H), 2.52 (s, 2H), 1.99 (s, 3H), 1.33 (s, 12H), 1.27 (s, 3H), 1.26 (s, 3H); MS (ESI+) *m/z* 496.2 (M+H).

Example 131b 5-Bromo-3-(1-ethyl-1*H*-pyrazol-4-ylamino)-1-methylpyrazin-2(1*H*)-one **131b**



131b

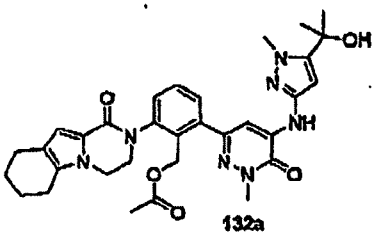
Following Example 111b, reaction of 1-ethyl-1*H*-pyrazol-4-amine (500 mg, 4.50 mmol) and 3,5-dibromo-1-methyl pyrazin–2(1H)-one (1.33 g, 4.95 mmol) afforded a 75% yield (1.01 g) of **131b** as an off-white solid: mp 237–239 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.02 (s, 1H), 7.73 (s, 1H), 7.20 (s, 1H), 4.11 (q, 2H, J = 7.5 Hz), 3.41 (s, 3H), 1.34 (t, 3H, J = 7.3 Hz); MS (ESI+) *m/z* 298.0 (M+H).

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was charged with **131b** (200 mg, 0.670 mmol), boronate **131a** (365 mg, 0.737 mmol), sodium carbonate (184 mg, 1.73 mmol), DMF (2 mL), water (2 mL) and 1,4-dioxane (10 mL). After bubbling nitrogen through the resulting suspension for 30 min, tetrakis(triphenylphosphine)palladium(0) (134 mg, 0.116 mmol) was added. A reflux condenser was attached to the flask, and the reaction mixture was heated at 100 °C for 14 h. After this time, the mixture was diluted with 90:10 methylene chloride/methanol (100 mL) and water (75 mL), and the layers were separated. The aqueous layer was extracted with 90:10 methylene chloride/methanol (2 × 50 mL), and the combined organic layers were washed with brine (100 mL) and dried over sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was dissolved in a mixture of THF (5 mL), water (5 mL) and methanol (5 mL). Lithium hydroxide monohydrate (121 mg, 2.89 mmol) was added, and the mixture was stirred at room temperature for 2 h. After this time, the mixture was diluted with 90:10 methylene chloride/methanol (100 mL) and water (50 mL), and the layers were separated. The aqueous

layer was extracted with 90:10 methylene chloride/methanol (2 × 75 mL), and the combined organic layers were washed with brine (100 mL) and dried over sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography (silica, 90:10 methylene chloride/methanol) to afford **131** in 26% yield (96 mg) as an amorphous yellow solid: mp 138–140 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.56 (s, 1H), 8.16 (s, 1H), 7.73 (s, 1H), 7.56 (dd, J = 7.5, 1.0 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 7.34 (dd, J = 7.5, 1.0 Hz, 1H), 7.31 (s, 1H), 4.85–4.82 (m, 1H), 4.56–4.53 (m, 1H), 4.47–4.44 (m, 1H), 4.08–4.02 (m, 3H), 3.90–3.86 (m, 1H), 3.52 (s, 3H), 3.03–3.00 (m, 1H), 2.92–2.87 (m, 1H), 2.75 (s, 2H), 2.54 (d, J = 5.0 Hz, 2H), 1.32 (t, J = 7.5 Hz, 3H), 1.23 (s, 6H); MS (ESI+) *m/z* 545.1 (M+H).

Example 132 2-(2-(hydroxymethyl)-3-(5-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-pyrazol-3-ylamino)-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **132**

Example 132a 2-(2-(Acetydroxymethyl)-3-(5-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-pyrazol-3-ylamino)-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **132a**



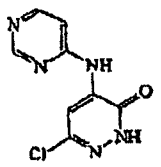
132a

Following Example **119d**, **119e** (150mg, 0.50mmol), **113a** (257mg, 0.55mmol), 1N Na_2CO_3 (1.1mL) and tetrakis(tripheny-phosphine)-palladium(0) (29mg, 5mol%) were reacted to give **132a** (160mg, 53% yield).

Following Example 132, **132a** (160mg, 0.27mmol), 1N LiOH (1.3mL), THF (2mL) and isopropanol (2mL) were reacted to give **132** (118mg, 78% yield) as a white solid. MS (ESI+) *m/z* 558.3 (M + H).

Example 133 2-(2-(Hydroxymethyl)-3-(6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydropyridazin-3-yl)phenyl)-3,4,5,6,7,8-hexahydrobenzothieno[2,3-*c*]pyridin-1(2*H*)-one **133**

Example 133a 6-Chloro-4-(pyrimidin-4-ylamino)pyridazin-3(2*H*)-one **133a**



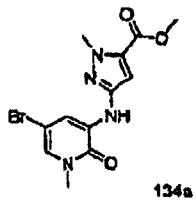
133a

A 1-L three-neck round-bottomed flask equipped with a mechanical stirrer, nitrogen inlet and reflux condenser was charged with 4-bromo-6-chloropyridazin-3(2*H*)-one (7.30 g, 35.0 mmol), 2-aminopyrimidine (3.33 g, 35.0 mmol), cesium carbonate (25.0 g, 76.8 mmol) and 1,4-dioxane (345 mL). After bubbling nitrogen through the resulting solution for 30 minutes, Xantphos (1.71 g, 2.96 mmol) and tris(dibenzylideneacetone)di-palladium(0) (1.60 g, 1.74 mmol) were added and the reaction mixture was heated at reflux for 3 h. After this time the reaction was cooled to room temperature and filtered. The filter cake was washed with methylene chloride (3 × 50 mL) and water (3 × 20 mL) and dried in a vacuum oven overnight at 45 °C to afford **133a** (5.54 g, 71%) as a tan solid: mp >300 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.28 (br s, 1H), 9.90 (br s, 1H), 8.91 (s, 1H), 8.51 (d, 1H, J = 6.0 Hz), 8.39 (s, 1H), 7.53 (dd, 1H, J = 1.5, 6.0 Hz); MS (ESI+) *m/z* 224.1 (M+H).

Following Example 119d, **133a** (145 mg, 0.650 mmol) and **111a** (313 mg, 0.650 mmol) afforded a 18% yield (60 mg) of **133** as a pink solid: mp 150–151 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.30 (s, 1H), 9.81 (s, 1H), 8.79 (s, 1H), 8.66 (s, 1H), 8.47 (s, 1H), 7.48 (m, 2H), 7.43 (m, 2H), 4.66 (m, 1H), 4.44 (m, 1H), 4.38 (m, 1H), 4.04 (m, 1H), 3.85 (m, 1H), 2.94 (m, 1H), 2.87 (m, 1H), 2.77 (m, 2H), 2.53 (m, 1H), 1.79 (m, 4H); MS (ESI+) *m/z* 501.1 (M+H).

Example 134 2-(2-(Hydroxymethyl)-3-(5-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-pyrazol-3-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **134**

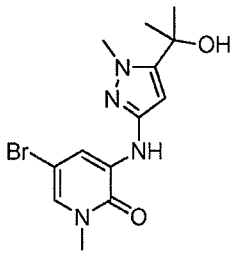
Example 134a Methyl 3-(5-Bromo-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)-1-methyl-1H-pyrazole-5-carboxylate **134a**



134a

Following Example 119a, 3,5-dibromo-1-methylpyridin-2(1H)-one (2.0g, 7.5mmol) was converted to **134a**.

Example 134b 5-Bromo-3-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-pyrazol-3-ylamino)-1-methylpyridin-2(1H)-one **134b**



12

Following Example 119b, **132a** (330mg, 0.97mmol) and 3.0M in ether MeMgBr (5.8mmol, 1.9mL) in THF (10mL) were reacted to give **134b** (270mg, 82% yield).

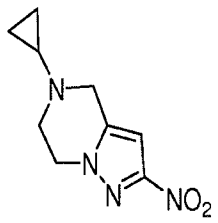
Example 134c 2-(5-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-pyrazol-3-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **134c**

Following Example 119, **113b** (120mg, 0.35mmol), **113a** (180mg, 0.39mmol), 1N Na_2CO_3 (0.8mL) and Palladium tetrakis (20mg, 5mol%) were reacted to give **134c** (85mg, 40% yield).

Following Example 119, **134c** (80mg, 0.13mmol), 1N LiOH (0.7mL), THF (1.5mL) and isopropanol (1.5mL) were reacted. The product was purified via column chromatography, silica, MeOH/CH2Cl2 then triturated with EtOAc to give **134** (18mg, 25% yield). MS (ESI+) *m/z* 557.3 (M + H).

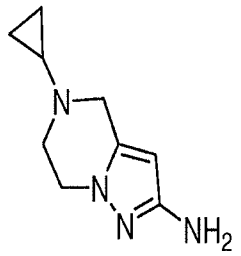
Example 135 2-(3-(5-(5-cyclopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **135**

Example 135a 5-Cyclopropyl-2-nitro-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine **135a**



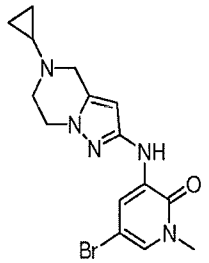
A mixture of 1-(2-bromoethyl)-5-(bromomethyl)-3-nitro-1H-pyrazole **101c** (4 g, 12.9 mmol) and cyclopropanamine (7.35 g, 129 mmol) in THF (40 mL) was stirred at 30°C overnight. After the completion of the reaction, the mixture was filtered off and the solid was washed with THF (100 mL). The filtrate was concentrated under reduced pressure to give **135a** (2.68 g, 99%). MS: $[M+H]^+$ 209.

Example 135b 5-Cyclopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-amine **135b**



A mixture of 5-cyclopropyl-2-nitro-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine **135a** (2.68 g, 12.9 mmol), Fe (3.6 g, 64.4 mmol) and NH_4Cl (4.1 g, 77.4 mmol) in ethanol (30 mL) and water (5 mL) was heated at reflux for 2 h. After the completion of the reaction, the mixture was filtered off. And the solid was washed with ethanol (150 mL). The filtrate was evaporated in *vacuo* and the residue was extracted with methanol /methylene chloride (1/7). The combined extracts were dried over Na_2SO_4 and evaporated. The residue was purified on reverse phase Combi-flash to give **135b** (1.8 g, 75%). MS: $[M+H]^+$ 179.

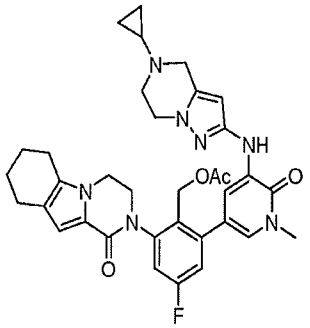
Example 135c 5-Bromo-3-(5-cyclopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-1-methylpyridin-2(1H)-one **135c**



A mixture of 5-cyclopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-amine **135b** (1.39 g, 7.8 mmol), XantPhos (450 mg, 0.78 mmol), Pd_2dba_3 (476 mg, 0.52 mmol), 3,5-dibromo-1-methylpyridin-2(1H)-one (1.72 g, 6.5 mmol) and Cs_2CO_3 (6.3 mg. 19.5 mmol) in 1,4-dioxane (30 mL) was heated at reflux for 1 h. After the completion of the reaction the mixture was filtered off and the solid was washed with methanol (60 mL). The filtrate was

evaporated in *vacuo* and the residue was purified on reverse phase Combi-flash to give **135c** (0.84 g, 30%). MS: $[M+H]^+$ 364.

Example 135d 2-(5-(5-Cyclopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-fluoro-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **135d**

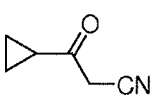


A mixture of 4-fluoro-2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **210d** (105 mg, 0.26 mmol), **135c** (100 mg, 0.28 mmol), $PdCl_2$(dppf) (29 mg, 0.039 mmol), K_3PO_4 (100 mg), and NaOAc (50 mg) in MeCN (10 mL) and water (3 mL) was heated at 110°C for 2 h. The solvent was evaporated in *vacuo*. The residue was purified on reverse phase Combi-flash to give **135d** (100 mg, 60%). MS: $[M+H]^+$ 640.

A mixture of **135d** (100 mg, 0.16 mmol) and LiOH hydrate (100 mg. 2.3 mmol) in isopropanol (10 mL) and water (3 mL) was stirred at 30°C for 2 h. The mixture was evaporated in *vacuo* and the residue was extracted with ethyl acetate (10 mL × 2). The combined extracts were concentrated under reduced pressure and the residue was purified with prep-HPLC to give **135** (40 mg, 42%). MS: $[M+H]^+$ 598. ^{1}H NMR (500 MHz, MeOD) δ 7.89 (s, 1H), 7.26 (s, 1H), 7.20 (d, J = 9.0, 2H), 6.72 (s, 1H), 5.88 (s, 1H), 4.52-4.44 (m, 2H), 4.22-4.18 (m, 3H), 4.03-3.97 (m, 3H), 3.81 (s, 2H), 3.69 (s, 3H), 3.15-3.13 (m, 2H), 2.67-2.61 (m, 2H), 2.57-2.51 (m, 2H), 1.96-1.87 (m, 3H), 1.81-1.75 (m, 2H), 0.62-0.58 (m, 2H), 0.53-0.49 (m, 2H).

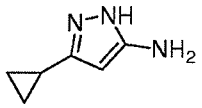
Example 136 5-(3-{5-[(5-Cyclopropyl-1H-pyrazol-3-yl)amino]-1-methyl-6-oxo-1,6-dihydropyridin-3-yl}-5-fluoro-2-(hydroxymethyl)phenyl)-8-thia-5-azatricyclo-[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one **136**

Example 136a 3-Cyclopropyl-3-oxopropanenitrile **136a**



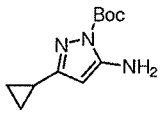
To a solution of CH_3CN (0.34 mL, 6.58 mmol) in THF (3 mL) at -78°C under N_2 protection was added LDA (3.3 mL, 6.58 mmol) dropwise. The reaction mixture was stirred at -78°C for 3 h. Then ethyl cyclopropanecarboxylate (0.5 g, 4.38 mmol) in THF (2 mL) was added and the mixture was allowed to warm to room temperature in a period of 1 h. Water (2 mL) was added and the solvents were removed under reduced pressure. CH_2Cl_2 (2 mL) was added and the pH of the mixture was adjusted to 5 with 2N HCl. It was then extacted with CH_2Cl_2 (5 mL × 2), dried over Na_2SO_4, and concentracted to afford **136a** as a yellow oil, which was used in the next step without further purification.

Example 136b 3-Cyclopropyl-1H-pyrazol-5-amine **136b**



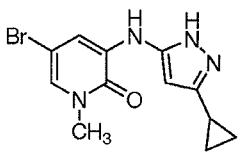
To a solution of **136a** (477 mg, 4.38 mmol) in MeOH (5 mL) was added $N_2H_4.H_2O$ (80%) (5 mL). The reaction mixture was heated at 75°C for 15 h. MeOH was removed under reduced pressure. The residue was extracted with CH_2Cl_2 (2 X 8 mL), dried over Na_2SO_4, and concentrated. The residue was purified by flash column eluting with 100:1 CH_2Cl_2/ MeOH to afford **136b** as a yellow oil (37%, for two steps). LCMS: $(M+H)^+$ 124.

Example 136c *tert*-Butyl 5-Amino-3-cyclopropyl-1H-pyrazole-1-carboxylate **136c**



To a mixture of **136b** (0.25 g, 2 mmol) and K_2CO_3 (0.828 g, 6 mmol) in THF (5 mL) was added $(Boc)_2O$ (0.436g, 2 mmol) in THF (5 mL). The reaction mixture was stirred at room temperature for 15 h. It was then filtered and concentrated. The residue was purified by flash column eluting with 6:1 petroleum ether/ethyl acetate to afford **136c** as a white solid (240 mg, 54%). LCMS: $(M\text{-}Boc)^+$ 124.

Example 136d 5-Bromo-3-(3-cyclopropyl-1H-pyrazol-5-ylamino)-1-methylpyridin-2(1H)-one **136d**



A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was charged with 1,4-dioxane (15 mL), **136c** (455 mg, 1.95 mmol) , 3,5-

dibromo-1-methylpyridin-2(1H)-one (0.40 g, 1.5 mmol) and cesium carbonate (1.22 g, 3.75 mmol). After bubbling nitrogen through the resulting mixture for 30 minutes, XantPhos (87 mg, 0.15 mmol) and tris(dibenzylideneacetone)dipalladium(0) (70 mg, 0.075 mmol) were added, and the reaction mixture was heated at reflux for 15 h. After this time the reaction was cooled to room temperature, partitioned between ethyl acetate (30 mL) and water (30 mL) and filtered. The aqueous layer was separated and extracted with ethyl acetate 2 X 50 mL). The organic layers were combined, washed with brine (50 mL) and dried over Na_2SO_4. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified on flash column eluting with 50:1 CH_2Cl_2/MeOH to afford **136d** as a yellow solid (320 mg, 50%). LCMS: $(M+H)^+$ 309. ^1H NMR (500 MHz, DMSO) δ 11.85 (s, 1H), 8.23 (s, 1H), 8.02 (d, J = 2.5, 1H), 7.35 (d, J = 2.5, 1H), 5.77 (d, J = 2, 1H), 3.46 (s, 3H), 1.83 (m, 1H), 0.90 (m, 2H), 0.64 (m, 2H)

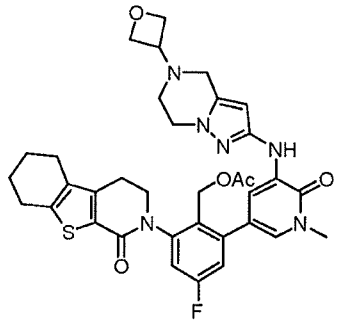
Example 136e (2-{5-[(5-Cyclopropyl-1H-pyrazol-3-yl)amino]-1-methyl-6-oxopyridin-3-yl}-4-fluoro-6-{6-oxo-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$]trideca-1(9),2(7)-dien-5-yl}phenyl)methyl acetate **136e**

A 25 mL sealed vial was charged with (4-fluoro-6-{6-oxo-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$]trideca-1(9),2(7)-dien-5-yl}-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-methyl acetate **212b** (580 mg, 1.16 mmol), **136d** (300 mg, 0.97 mmol), CH_3COONa (160 mg, 1.94 mmol), K_3PO_4 (410 mg, 1.94 mmol), $PdCl_2$(dppf) (100 mg, 0.12 mmol), CH_3CN (12 mL), and H_2O (1 mL). The mixture was heated at 110 °C for 2 hours. The reaction mixture was evaporated and the residue was purified by flash column eluting with 50:1 methylene chloride/methanol containing 0.5% triethylamine to give **136e** as a black solid (300 mg, 52%).

To a solution of **136e** (300 mg, 0.50 mmol) in propan-2-ol (3 mL), tetrahydrofuran (3 mL), and water (3 mL) was added LiOH (1.0 g, 25 mmol). The mixture was stirred at 30°C for 2 h. Then, 20 mL H_2O was added and extracted with EA (30 mL × 3). The combined organic layer was dried with Na_2SO_4 and concentrated to give yellow solid, which was further purified by prep-HPLC to give **136** as a white solid (200 mg, 70%). LCMS: $(M+H)^+$ 560 ^1H NMR (500 MHz, DMSO) δ 7.78 (s, 1H), 7.25 (d, J = 2.5, 1H), 7.21 (m, 2H), 5.79 (s, 1H), 4.48 (m, 2H), 4.15 (m, 1H), 4.00 (m, 1H), 3.69 (s, 3H), 3.07 (m, 1H), 2.95 (m, 1H), 2.85 (m, 2H), 2.61 (m, 2H), 1.89 (m, 5H), 0.96 (m, 2H), 0.73 (m, 2H).

Example 137 5-[5-Fluoro-2-(hydroxymethyl)-3-[1-methyl-5-(5-(oxetan-3-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-6-oxopyridin-3-yl]phenyl]-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$]trideca-1(9),2(7)-dien-6-one **137**

Example 137a 5-[5-Fluoro-3-[1-methyl-5-(5-(oxetan-3-yl)-4,5,6,7-tetrahydropyrazolo-[1,5-a]pyrazin-2-ylamino)-6-oxopyridin-3-yl] benzyl acetate]-8-thia-5-azatricyclo-[7.4.0.$0^{2,7}$]trideca-1(9),2(7)-dien-6-one **137a**



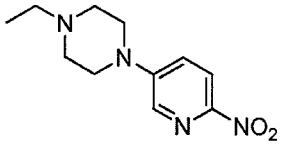
137a

A 25 mL sealed tube was charged with (4-fluoro-2-{6-oxo-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$]trideca-1(9),2(7)-dien-5-yl}-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl acetate **212b** (990 mg, 2 mmol), 5-bromo-1-methyl-3-(5-(oxetan-3-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)pyridin-2(1H)-one **252a** (500 mg, 1.3 mmol), CH_3COONa (220 mg, 2.6 mmol), K_3PO_4 (700 mg, 2.6 mmol), and $PdCl_2(dppf)$ (110 mg, 0.13 mmol) suspended in CH_3CN (25 mL) and H_2O (1 mL). The mixture was stirred at 110℃ for 2 hours. The solvent was then evaporated and the residue was purified by silical-gel column eluting with 20:1 CH_2Cl_2/methanol to give **137a** as a brown solid (300 mg, 35%). MS: $(M+H)^+$ 673.

To a solution of **137a** (270 mg, 0.4 mmol) in propan-2-ol (8 mL), tetrahydrofuran (8 mL), and water (1.5 mL) was added LiOH (964 mg, 40 mmol). The mixture was stirred at 30℃ for 2 h. It was then evaporated under reduced pressure and the residue was purified by prep-HPLC to afford **137** as a yellow solid (84 mg, 33%). MS: $(M+H)^+$ 631. 1H NMR (500 MHz, MeOD) δ 1.87 (s, 4 H), 2.52-2.56 (d, 2 H), 2.83-2.90 (d, 5 H), 3.01 (s, 1 H), 3.56-3.74 (t, 6 H), 3.96-4.01 (t, 4 H), 4.44-4.48 (t, 2 H), 4.63 (s, 2 H), 4.74 (s, 2 H), 5.87 (s, 1 H), 7.16-7.18 (d, 2 H), 7.25 (s, 1 H), 7.89 (s, 1 H).

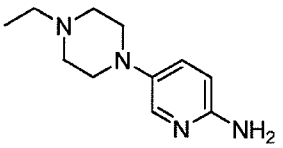
Example 138 2-(3-(5-(5-(4-Ethylpiperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **138**

Example 138a 1-Ethyl-4-(6-nitropyridin-3-yl)piperazine **138a**



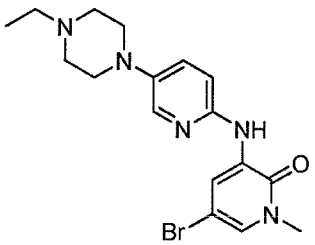
To a sealed tube equipped with a stirring bar, 5-bromo-2-nitropyridine (3.00 g, 14.78 mmol), 1-ethylpiperazine (5.06 g, 44.34 mmol), tetrabutylammonium iodide (273 mmol, 0.739 mmol), K_2CO_3 (6.128 g, 44.34 mmol), and DMSO (30 mL) were added. The tube was sealed and heated at 90 °C overnight. Water (200 mL) was added and the precipitation was filtered to afford **138a** as a yellow solid, 1.24 g.

Example 138b 5-(4-Ethylpiperazin-1-yl)pyridin-2-amine **138b**



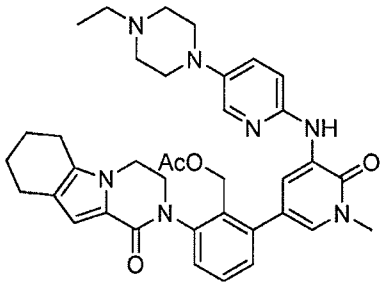
In a hydrogenation bottle, **138a** (2.59 g, 10.96 mmol) , EtOH (100 mL), 10 % Pd / C (580 mg, 0.55 mmol) were added. The mixture was hydrogenated at 55 psi for 2 hrs, and then filtered through celite and washed with MeOH (20 mL). The solvent was removed *in vacuo* and pink solids were obtained as **138b** (2.51 g, 82 %).

Example 138c 5-Bromo-3-(5-(4-Ethylpiperazin-1-yl)pyridin-2-ylamino)-1-methylpyridin-2(1H)-one **138c**



To a round-bottomed flask equipped with a stirring bar, **138b** (2.52 g, 12.22 mmol), 3,5-dibromo-1-methylpyridin-2(1H)-one (4.89 g, 18.32 mmol), $Pd_2(dba)_3$ (1.12 g, 1.22 mmol), XantPhos (1.13 mg, 1.96 mmol), Cs_2CO_3 (13.14 g, 40.33 mmol) and dioxane (50 mL) were added. The reaction mixture was heated at 100 °C overnight. CH_2Cl_2 (200 mL) was added to the resulting mixture was washed with water (30 mL X 3). CH_2Cl_2 (200 mL) was added and the resulting mixture was washed with water (30 mL X 3), brine (30 mL X 1), dried over $MgSO_4$, filtered, and removed solvent *in vacuo*. CH_2Cl_2 / ether (1:2, 5 mL) was added followed by sonication, the precipitation was filtered as **138c**, a yellow solid, 2.718 g (57 %).

Example 138d 2-(5-(5-(4-Ethylpiperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **138d**



To a microwave tube equipped with a stirring bar, **138c** (250 mg, 0.637 mmol), 2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **114a** (325.5 mg, 0.701 mmol), $Pd(PPh_3)_4$ (36.8 mg, 0.0319 mmol), Na_2CO_3 aqueous solution (1.0 N, 2.10 mL, 2.10 mmol), DME (2.0 mL) were added. The mixture was reacted in microwave at 135 °C for 15 min. CH_2Cl_2 (200 mL) was added and the resulting mixture was washed with water (30 mL X 3), brine (30 mL X 1), dried over $MgSO_4$, filtered, and removed solvent *in vacuo*. Silica gel column chromatography (MeOH: CH_2Cl_2 = 5: 95) gave 2-(5-(5-(4-ethylpiperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **138d**.

To a round-bottomed flask equipped with a stirring bar, **138d**, THF (5.0 mL), *i*-PrOH (5.0 mL), H_2O (5.0 mL), LiOH H_2O (200 mg) were added. The resulting mixture was stirred at RT for 2 hrs. Removed all the solvent *in vacuo* and the resulting residue was added to CH_2Cl_2 (200 mL), the solution was washed with water (30 mL X 3), brine (30 mL X 1), dried over $MgSO_4$, filtered, and removed solvent *in vacuo*. Silica gel column chromatography (MeOH: CH_2Cl_2 = 10: 90) gave **138** as a gray solid, 60 mg. MS (ESI+) *m/z* 608.3 (M + H).

Example 139 3-{[4-(3-Hydroxy-3-methylazetidin-1-yl)phenyl]amino}-5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-1,2-dihydropyrazin-2-one **139**

Following Example 301, 1-(4-aminophenyl)-3-methylazetidin-3-ol was converted to 99 mg of **139** as a white solid. MS (ESI+) *m/z* 581 (M + H).

Example 140 2-(3-(6-(1-(2-Hydroxyethyl)-1H-pyrazol-4-ylamino)-4-methyl-5-oxo-4,5-dihydropyrazin-2-yl)-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **140**

Example 140a 5-Bromo-3-(1-(2-hydroxyethyl)-1H-pyrazol-4-ylamino)-1-methylpyrazin-2(1H)-one **140a**

A flask equipped with a magnetic stirrer was charged with 1-(2-(tert-butyldimethylsilyloxy)ethyl)-1H-pyrazol-4-amine **116b** (1. 7 g, 7.1 mmol), 3,5-dibromo-1-methylpyrazin-2(1H)-one (1.25 g, 4.7 mmol), and IPA (25 mL). The system was evacuated and then refilled with N_2. The reaction mixture was heated at 90°C for 6 h. Then, the mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with petroleum ether/ethyl acetate to afford **140a** (1.7 g, 78%). LCMS: $[M+H]^+$ 314.

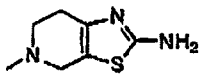
Example 140b 2-(6-(1-(2-Hydroxyethyl)-1H-pyrazol-4-ylamino)-4-methyl-5-oxo-4,5-dihydropyrazin-2-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **140b**

A mixture of **140a** (595 mg, 1.9 mmol), 2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **114a** (882 mg, 1.9 mmol), CH_3COONa (309 mg, 3.8 mmol), $PdCl_2(dppf)$ (153 mg, 0.19 mmol) and K_3PO_4 (1 g, 3.8 mmol) suspended in CH_3CN (30 mL) and H_2O (2 mL) was heated at 110 °C for 15 h under argon atmosphere. After reaction CH_3CN was evaporated and the residue was purified by reverse phase Combi-flash eluting with 0.3% NH_4HCO_3 in 1:4 water/CH_3CN to give **140b** as a brown solid (477 mg, 44%). LCMS: $[M+H]^+$ 572.

A mixture of **140b** (410 mg, 0.72 mmol) and LiOH (372 mg, 16 mmol) in ^{i}PrOH/THF (1:1, 10 mL) and H_2O (3 mL) was stirred at 30 °C for 2 h. The mixture was evaporated in *vacuo* and the residue was extracted with EtOAc (10 mL X 2). The combined extract was concentrated under reduced pressure and the residue was purified on pre-HPLC to give **140** (200 mg, 54%).LCMS: $[M+H]^+$ 530 ^{1}H NMR (500 MHz, CDCl3) δ 7.71 (s, 1H), 7.68 (s, 1H), 7.49 (s, 1H), 7.36 (m, 2H), 7.27 (m, 1H), 6.92 (s, 1H), 6.78 (s, 1H), 5.29 (s, 1H), 4.43 (d, J = 12, 1H), 4.21 (m, 4H), 4.04 (m, 2H), 4.01 (m, 3H), 3.63 (s, 3H), 2.55 (dt, J = 14.5, 4H), 1.78 (m, 4H).

Example 141 2-(2-(Hydroxymethyl)-3-(1-methyl-5-(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **141**

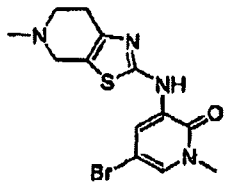
Example 141a 5-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-amine **141a**



141a

A solution of 1-methyl-4-piperidone (11.3 g, 100mmol) in 2-propanol (80 mL) was heated to 50°C. To the solution was sequentially added a solution of cyanamide (4.2 g, 100mmol) in 2-propanol (25 mL) and sulfur powder (3.2 g). After a catalytic amount of pyrrolidine (1.3 mL) was added thereto, the resultant mixture was stirred at or above 50°C for 2 hours. The reaction mixture was allowed to cool to room temperature, followed by stirring for overnight. The resultant mixture was cooled to or below 10 °C in an ice-water bath, and was stirred for 1 hour at the same temperature. The precipitated crystals were collected by filtration, and washed with 2-propanol (20 mL). The wet crystals were dried under reduced pressure, to give **141a** (10 g, 60%). LCMS: $[M+H]^+$ 170 ^{1}H NMR (500 MHz, DMSO) δ 6.70 (s, 2H), 3.31 (s, 2H), 2.61 (t, J = 5.5, 2H), 2.45 (m,, 2H), 2.33 (s,3H).

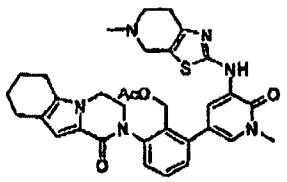
Example 141b 5-Bromo-1-methyl-3-(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-ylamino)pyridin-2(1H)-one **141b**



141b

Following Example 110c, 3 g of **141a** and 4 g of 3,5-dibromo-1-methylpyridin-2(1H)-one were reacted to give **141b** as a yellow solid (2.8 g, 52%). LCMS: $[M+H]^+$ 357

Example 141c 2-(1-Methyl-5-(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **141c**



141c

Following Example 147b, 232 mg of **114a** and 178 mg of **141b** were reacted to give **141c** as a yellow solid (240 mg, 80%). LCMS: $[M+H]^+$ 613

Following Example 148, 240 mg of **141c** was converted to **141** as a white solid (112 mg, 50%). LCMS: $[M+H]^+$ 514.

Example 142 2-(3-(5-(1,5-Dimethyl-1H-pyrazol-3-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **142**

Example 142a 5-Bromo-3-(1,5-dimethyl-1H-pyrazol-3-ylamino)-1-methylpyridin-2(1H)-one **142a**

A solution of 5-bromo-1-methyl-3-(5-methyl-1H-pyrazol-3-ylamino)pyridin-2(1H)-one **112a** (2.8g, 9.9 mmol) in anhydrous DMF (10 mL) was treated with 60% dispersion of NaH in mineral oil (0.5 g, 13 mmol) while stirring under nitrogen. After effervescence the reaction was stirred for an additional 30 minutes. At this time the reaction was treated with MeI (0.98 g, 7 mmol) and continued to *stir* under nitrogen for 2 hours. Water (50 mL) was added slowly and the mixture was filtered and then concentrated. The residue was purified by flash column chromatography eluting with petroleum ether/ethyl acetate to afford **142a** (0.7 g, 24%), which was used directly without further purification. LCMS: (M+H)+ 297.

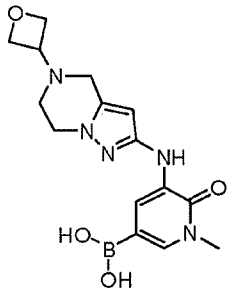
Example 142b 2-(5-(1,5-Dimethyl-1H-pyrazol-3-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **142b**

A mixture of **142a** (510 mg, 1.7 mmol), 2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **114a** (882 mg, 1.9 mmol), CH_3COONa (309 mg, 3.8 mmol), $PdCl_2$(dppf) (153 mg, 0.19 mmol), and K_2PO_4 (1 g, 3.8 mmol) suspended in CH_3CN (30 mL) and H_2O (2 mL) was heated at 110°C for 15 h under argon atmosphere. It was then evaporated and the residue was purified by reverse phase Combi-flash eluting with 0.3% NH_4HCO_3 1:4 water/CH_3CN to give **142b** as a brown solid (200 mg, 21%). LCMS: $[M+H]^+$ 555.

A mixture of **142b** (210 mg, 0.38 mmol) and LiOH (372 mg, 16 mmol) in ^iPrOH/THF (1:1, 10 mL) and water (3 mL) was stirred at 30 °C for 2 h. The mixture was evaporated in *vacuo*, and the residue was extracted with EtOAc (10 mL X 2). The combined extract was concentrated under reduced pressure and the residue was purified on prep-HPLC to give **142** (95 mg, 50%). LCMS: $[M+H]^+$ 530. ^1H NMR (500 MHz, CDCl3) δ 7.88 (s, 1H), 7.43 (m, 2H), 7.38 (s, 1H), 7.30 (m, 1H), 7.21 (m, 1H), 6.84 (s, 1H), 5.71 (s, 1H), 4.58 (d, J = 11.5, 1H), 4.38 (d, J = 11.5,, 1H), 4.13 (m, 3H), 3.94 (m, 1H), 3.67 (s, 3H), 3.64 (s, 3H), 2.57 (m, 4H), 2.21 (s, 3H), 1.78 (m, 4H).

Example 143 2-(5-Fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(oxetan-3-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **143**

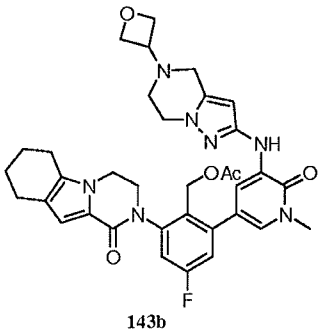
Example 143a 1-Methyl-5-(5-(oxetan-3-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-ylboronic cid **143a**



143a

To a solution of 5-bromo-1-methyl-3-(5-(oxetan-3-yl)-4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrazin-2-ylamino)pyridin-2(1H)-one **252a** (1g, 2.64 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (2 g, 7.92 mmol) in dioxane (40 mL) was added $PdCl_2$(dppf) (215 mg, 0.26 mmol) and CH_3COOK (776 mg, 7.92 mmol). The mixture was stirred at 100°C for 6 h under argon atmosphere. After reaction the mixture was filtered and evaporated in *vacuo*. The residue was purified by reverse phase combiflash eluting with 0.3% NH_4HCO_3 in 1:3 water/CH_3CN to give **143a** as a white solid (300 mg, 33%). MS: $(M+H)^+$ 346.

Example 143b 4-Fluoro-2-(1-methyl-5-(5-(oxetan-3-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **143b**



143b

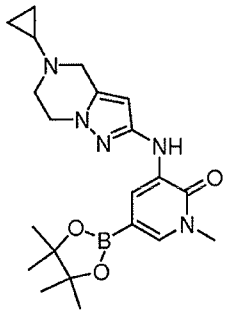
A 25 mL vial was charged with **143a** (238 mg, 0.7 mmol), 2-bromo-4-fluoro-6-(1-oxo-3,4,6,7,8,9-hexahydro-pyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **197d** (300 mg, 0.7 mmol), Na_2CO_3 (147 mg, 1.4 mmol), $PdCl_2$(dppf) (56 mg, 0.07 mmol) suspended in DME

(15 mL), and H_2O (1 mL). The resulting orange mixture was heated for 30 minutes in a Biotage microwave reactor at 130°C. After reaction the residue was purified by reverse phase Combi-flash eluting with 0.3% NH_4HCO_3 in 1:7 water/CH_3CN to give **143b** as a brown solid (150 mg, 33%). MS: $(M+H)^+$ 656.

To a solution of 4-fluoro-2-(1-methyl-5-(5-(oxetan-3-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydro-pyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **143b** (120 mg, 0.18 mmol) in propan-2-ol (5 mL), tetrahydrofuran (5 mL) and water (1.5 mL) was added LiOH (440 mg, 18 mmol). The mixture was stirred at 30°C for 2 h. The reaction mixture was then evaporated and the residue was purified by prep-HPLC to afford **143** as a yellow solid (50 mg, 45%). MS: $(M+H)^+$ 614. ^1H NMR (500 MHz, MeOD) δ 1.79 (s, 2 H), 1.90 (s, 2 H), 2.54-2.56 (t, J=6.5 Hz, 2 H), 2.63-2.67 (m, 2 H), 2.86-2.88 (t, J=6 Hz, 2 H), 3.59 (s, 2 H), 3.70 (s, 3 H), 3.76-3.79 (m, 1 H), 4.00-4.07 (m, 3 H), 4.21 (s, 3 H), 4.48-4.53 (m, 2 H), 4.64-4.67 (t, J=6.5 Hz, 2 H), 4.75-4.78 (t, J=7 Hz, 2 H), 5.90 (s, 1H), 6.72 (s, 1 H), 7.20-7.27 (m, 3H), 7.91-7.92 (d, 1H).

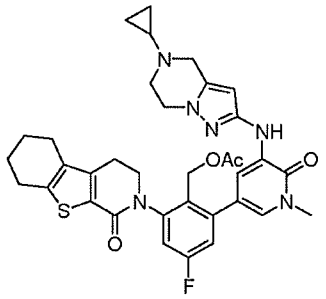
Example 144 5-[5-Fluoro-2-(hydroxymethyl)-3-[1-methyl-5-(5-cyclopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-6-oxopyridin-3-yl]phenyl]-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$]trideca-1(9),2(7)-dien-6-one **144**

Example 144a 3-(5-Cyclopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one **144a**



A mixture of 5-bromo-3-(5-cyclopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]-pyrazin-2-ylamino)-1-methylpyridin-2(1H)-one **135c** (0.9 g, 2.48 mmol), bis(pinacolato)diboron (1.26 g, 4.96 mmol), $PdCl_2$(dppf) (272 mg, 0.37 mmol) and KOAc (486 mg, 4.96 mmol) in 1,4-dioxane (40 mL) was heated at reflux for 15 h. After the completion of the reaction, the mixture was filtered off, and washed with ethyl acetate (100 mL). The filtrate was evaporated in *vacuo* and the residue was purified on silica gel column to give **144a** (407 mg, 40%). MS: $[M+H]^+$ 412.

Example 144b 5-[5-Fluoro-3-[1-methyl-5-(5-cyclopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-6-oxopyridin-3-yl]benzylacetate]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one **144b**

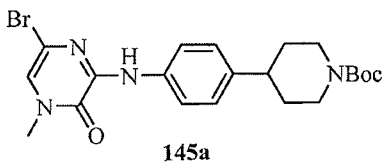


A mixture of **144a** (300 mg, 0.73 mmol), (2-bromo-4-fluoro-6-{6-oxo-8-thia-5-azatricyclo-[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-5-yl}phenyl)methyl acetate (**212a**) (297 mg, 0.66 mmol), $PdCl_2$(dppf) (73 mg, 0.1 mmol), and 2M Na_2CO_3 solution (2 mL) in DME (8 mL) was heated at 120°C under microwave irradiation for 0.5 h. The solvent was evaporated in *vacuo* and the residue was purified on reverse phase Combi-flash to give **144b** (173 mg, 40%). MS: $[M+H]^+$ 657.

A mixture of **144b** (170 mg, 0.26 mmol) and LiOH hydrate (104 mg, 2.6 mmol) in ^{i}PrOH (15 mL) and H_2O (3 mL) was stirred at 30°C for 2 h. The mixture was evaporated in *vacuo* and the residue was extracted with EtOAc (20 mL × 2). The combined extracts were concentrated under reduced pressure. The residue was purified on prep-HPLC to give **144** (50 mg, 31%). MS: $[M+H]^+$ 615. ^{1}H NMR (500 MHz, MEOD) δ 7.89 (d, J = 2.0, 1H), 7.26 (d, J = 2.0, 1H), 7.22-7.18 (m, 2H), 5.89 (s, 1H), 4.52-4.46 (m, 2H), 4.17-4.11 (m, 1H), 4.02-3.97 (m, 3H), 3.82 (s, 2H), 3.69 (s, 3H), 3.16-3.14 (m, 2H), 3.10-3.03 (m, 1H), 2.96-2.90 (m, 1H), 2.87-2.85 (m, 2H), 2.65-2.53 (m, 2H), 1.97-1.85 (m, 5H), 0.62-0.58 (m, 2H), 0.53-0.50 (m, 2H)

Example 145 2-(2-(Hydroxymethyl)-3-(4-methyl-5-oxo-6-(4-(piperidin-4-yl)phenyl-amino)-4,5-dihydropyrazin-2-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **145**

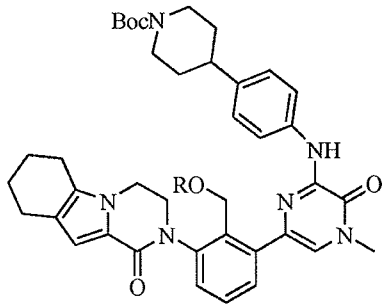
Example 145a tert-Butyl 4-(4-(6-bromo-4-methyl-3-oxo-3,4-dihydropyrazin-2-ylamino)phenyl)-piperidine-1-carboxylate **145a**



145a

Compound **145a** was synthesized using the same procedure as Example 112a, except using tert-butyl 4-(4-aminophenyl)piperidine-1-carboxylate (0.83g, 3.0 mmol), 3,5-dibromo-1-methylpyrazin-2(1H)-one (0.88 g, 3.3mmol), cesium carbonate (1.27 g, 3.9 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.275 g, 0.3mmol), Xantphos (0.26 g, 0.45mmol) and 1,4-dioxane (30 mL). The reaction mixture was heated at 100 °C overnight. Work-up and purified by flash column chromatography (silica, ethyl acetate/ hexanes) to give a 80% yield (1.1 g) of tert-butyl 4-(4-(6-bromo-4-methyl-3-oxo-3,4-dihydropyrazin-2-ylamino)phenyl)-piperidine-1-carboxylate **145a** as a solid: MS (ESI+) *m/z* 465.0 (M+H).

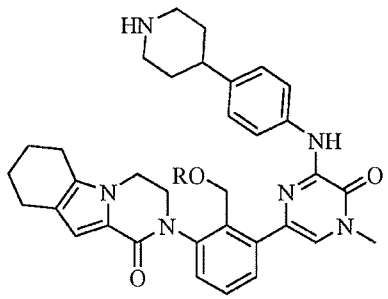
Example 145b



145b (R=Ac/H)

The compound mixture **145b** was synthesized using the same procedure as Example 121b, except using 2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **114a** (162 mg, 0.35 mmol), tert-butyl 4-(4-(6-bromo-4-methyl-3-oxo-3,4-dihydropyrazin-2-ylamino)phenyl)-piperidine-1-carboxylate **145a** (135 mg, 0.3 mmol), 1M sodium carbonate solution (1.2 mL, 1.2 mmol), tetrakis(triphenylphosphine)palladium(0) (18 mg, 0.015 mmol) and 1,2-dimethoxyethane (3 mL). Work-up and flash column chromatography (silica, ethyl acetate/hexanes) afford **145b** (120 mg) as yellow oil.

Example 145c



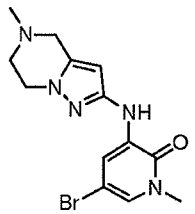
145c (R=Ac/H)

The compound mixture was synthesized using the same procedure as Example 121c, except using **145b** (120 mg), Trifluoroacetic acid (0.5 mL, 6.5 mmol) in methylene chloride (7 mL). Workup and concentrated to dryness to gave compound **145c** as yellow oil, which was used without purification in the next step.

Compound **145** was synthesized using the same procedure as for Example 121, except using a mixture of THF (1 mL), water (0.5 mL) and isopropanol (1 mL), compound **145c** and lithium hydroxide monohydrate (50 mg, 1.30 mmol). Work-up and flash column chromatography (silica, methylene chloride/ 20% TEA in methanol) give a yellow solid (68mg), which was flushed out from a basic aluminum column (ethyl acetate) again to afford a 15% yield (3 steps, 25 mg) of **145** as a white solid: MS (ESI+) *m/z* 579.4 (M+H)..

Example 146 2-(2-(Hydroxymethyl)-3-(1-methyl-5-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **146**

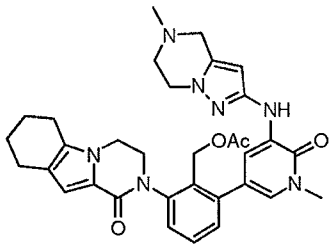
Example 146a 5-Bromo-1-methyl-3-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)pyridin-2(1H)-one **146a**



146a

A suspension of 5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-amine **101e** (1 g, 6.6 mmol), 3,5-dibromo-1-methylpyridin-2(1H)-one (1.7 g, 6.6 mmol), XantPhos (380 mg, 0.66 mmol), $Pd_2(dba)_3$ (602 mg, 0.66 mmol) and Cs_2CO_3 (4 g, 13.2 mmol) in dioxane (30 mL) was heated in a sealed tube at 120°C for 2 h under nitrogen. After reaction the solvent was filtered and the filtrate was evaporated in *vacuo* to give a yellow solid. The yellow solid was washed with EtOAc (10 mL × 3) to give **146a** as a yellow solid (1 g, 45%), which was used without further purification.MS: $(M+H)^+$ 338.

Example 146b 2-(1-Methyl-5-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **146b**



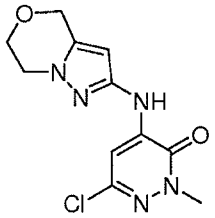
146b

A 25 mL vial was charged with 5-bromo-1-methyl-3-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)pyridin-2(1H)-one **145a** (500 mg, 1.48 mmol), 2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **114a** (664 mg, 1.48 mmol), CH_3COONa (243 mg, 2.96 mmol), $PdCl_2(dppf)$ (121 mg, 0.148 mmol), and K_3PO_4 (790 mg, 2.96 mmol) suspended in CH_3CN (50 mL) and H_2O (3 mL). It was then heated at 110°C for 12 h under argon atmosphere. After reaction the mixture was evaporated and the residue was purified by reverse phase Combi-flash eluting with 0.3% NH_4HCO_3 in 1:5 water/CH_3CN to give **146b** as a brown solid (200 mg, 23%). MS: $(M+H)^+$ 596.

To a solution of 2-(1-methyl-5-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexa-hydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **146b** (180 mg, 0.3 mmol) in propan-2-ol (9 mL), tetrahydrofuran (9 mL), and water (3 mL) was added LiOH (726 mg, 30 mmol). The mixture was stirred at 30°C for 2 h. After reaction the mixture was evaporated and the residue was purified by prep-HPLC to afford **146** as a white solid (67 mg, 41%).MS: $(M+H)^+$ 554. ^1H NMR (500 MHz, MeOD) δ 1.80 (s, 2 H), 1.90 (s, 2 H), 2.49 (s, 3 H), 2.54-2.57 (t, 2 H), 2.63-2.67 (m, 2 H), 2.93-2.96 (t, J=5.5 Hz, 2 H), 3.64 (s, 2 H), 3.70 (s, 3 H), 4.02-4.06 (m, 3 H), 4.18-4.23 (m, 3 H), 4.49-4.57 (m, 2 H), 5.89 (s, 1 H), 6.72 (s, 1H), 7.23 (s, 1 H), 7.36-7.38 (d, 1H), 7.41-7.42 (d, 1H), 7.49-7.52 (t, 1H), 7.1 (s, 1H).

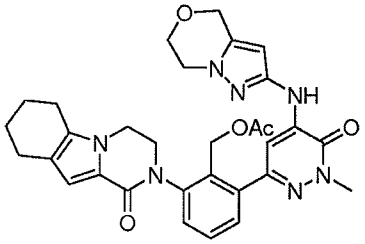
Example 147 2-(3-(5-(6,7-Dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **147**

Example 147a 6-Chloro-4-(6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-2-ylamino)-2-methylpyridazin-3(2H)-one **147a**



A mixture of 6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-2-amine **110b** (0.8 g, 5.76 mmol), xantophos (360 mg, 0.623 mmol), Pd_2dba_3 (384 mg, 0.42 mmol), 4-bromo-6-chloro-2-methylpyridazin-3(2H)-one **103e** (1.28 g, 5.76 mmol) and Cs_2CO_3 (5.05 g. 17.3 mmol) in 1,4-dioxane (40 mL) was heated at reflux for 2 h. After the completion of the reaction, the mixture was filtered off, and washed with MeOH (60 mL). The filtrate was evaporated in *vacuo*. The residue was purified on reverse phase Combi-flash to give **147a** (1.3 g, 81%). MS: $[M+H]^+$ 282.

Example 147b 2-(5-(6,7-Dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **147b**



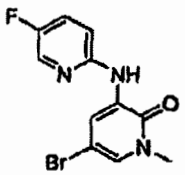
A mixture of 6-chloro-4-(6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-2-ylamino)-2-methylpyridazin-3(2H)-one **147a** (400 mg, 1.42 mmol), 2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-benzyl acetate **114a** (660 mg, 1.42 mmol), $PdCl_2$(dppf) (155 mg, 0.21 mmol), K_3PO_4 (150 mg), and NaOAc (50 mg) in MeCN (20 mL) and H_2O (4 mL) was heated at 110°C in sealed tube for 2 h. The solvent was evaporated in *vacuo* and the residue was purified on reverse phase Combi-flash to give **147b** (273 mg, 33%). MS: $[M+H]^+$ 584.

A mixture of 2-(5-(6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **147b** (410 mg, 0.7 mmol) and LiOH hydrate (590 mg, 14 mmol) in ^{i}PrOH (20 mL) and H_2O (4 mL) was stirred at 30°C for 2 h. The mixture was evaporated in *vacuo* and the residue was extracted with ethyl acetate (20 mL × 2). The combined extracts were concentrated under reduced pressure. The residue was purified on prep-HPLC to give

147 (120 mg, 32%). MS: $[M+H]^+$ 542. ^1H NMR (500 MHz, DMSO) δ 9.30 (s, 1H), 7.90 (s, 1H), 7.49-7.46 (m, 1H), 7.41-7.37 (m, 2H), 6.51 (s, 1H), 6.04 (s, 1H), 4.74 (s, 2H), 4.62-4.60 (m, 1H), 4.48-4.45 (m, 1H), 4.39-4.35 (m, 1H), 4.18-4.06 (m, 3H), 4.04-3.95 (m, 4H), 3.90-3.85 (m, 1H), 3.75 (s, 3H), 2.60-2.56 (m, 2H), 2.51-2.45 (m, 2H), 1.82-1.74 (m, 2H), 1.73-1.64 (m, 2H).

Example 148 2-(3-(5-(5-Fluoropyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **148**

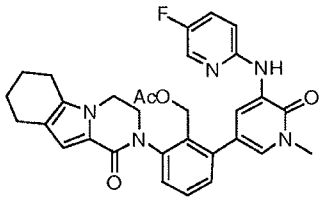
Example 148a 5-Bromo-3-(5-fluoropyridin-2-ylamino)-1-methylpyridin-2(1H)-one **148a**



148a

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was charged with 1,4-dioxane (50 mL), 5-fluoropyridin-2-amine (0.67 g, 6 mmol), 3,5-dibromo-1-methylpyridin-2(1H)-one (1.34 g, 5 mmol) and cesium carbonate (4.89 g, 15 mmol). After bubbling nitrogen through the resulting solution for 30 minutes, XantPhos (576 mg, 1 mmol) and tris(dibenzylideneacetone)dipalladium(0) (460 mg, 0.5 mmol) were added, and the reaction mixture was heated at reflux for 15 h. After this time the reaction was cooled to room temperature, partitioned between ethyl acetate (100 mL) and water (100 mL) and filtered. The aqueous layer was separated and extracted with ethyl acetate (50 mL × 2). The organic layers were combined and washed with brine (50 mL) and dried over sodium sulfate. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was washed with acetonitrile (30 mL) and filtered to afford 148a (900 mg, 61%). MS: $[M+H]^+$ 298.

Example 148b 2-(5-(5-Fluoropyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **148b**



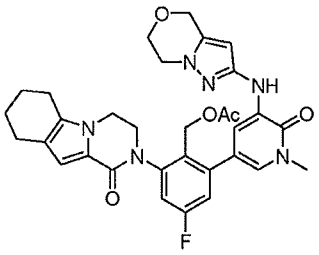
148b

A sealed tube was charged with the mixture of 2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **114a** (232 mg, 0.5 mmol), **148a** (148 mg, 0.50 mmol), $Pd(dppf)Cl_2$ (25 mg, 0.03 mmol), $K_3PO_4.3H_2O$(266 mg, 1.0 mmol), and NaOAc (82 mg, 1.0 mmol) in CH_3CN (18 mL). The system was evacuated and refilled with N_2. The reaction mixture was heated at 110 °C for 2 h. It was then cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography eluting with 30:1 DCM/MeOH to afford **148b** as a yellow solid (200 mg, 72%). MS: $[M+H]^+$ 556.

At room temperature, to the solution of **148b** (200 mg, 0.36 mmol) in THF/iPA/H_2O (6 mL/6 mL/2 mL) was added LiOH (87 mg, 3.6 mmol) while stirring. This mixture was stirred for 0.5 h. Then, 20 mL H_2O was added and extracted with ethyl acetate (30 mL X 3). The combined organic layer was dried with Na_2SO_4 and concentrated to get a yellow solid, which was further purified by prep-HPLC to afford **148** as a white solid (110 mg, 59%). LCMS: $[M+H]^+$ 514. ^1H NMR (500 MHz, DMSO) δ 8.77 (s, 1H), 8.62 (d, J = 2.0, 1H), 8.16 (d, J = 2.5, 1H), 7.59 (m,, 1H), 7.47 (t, J = 7.5,1H), 7.39-7.14 (m, 2H), 7.34 (m, 2H), 6.52 (s, 1H), 4.85 (s, 1H), 4.35 (d, J = 4.0, 2H), 4.17 (m, 2 H), 4.10 (m, 1H), 3.90 (m, 1H), 3.61 (s, 3H), 2.60 (m, 2H), 2.48 (m, 2H), 1.80 (t, J=5.5, 2H), 1.70 (m, 2H).

Example 149 2-(3-(5-(6,7-Dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **149**

Example 149a 2-(5-(6,7-Dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-fluoro-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **149a**

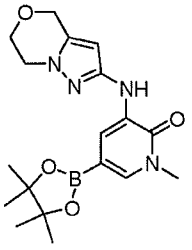


A mixture of 2-(acetoxymethyl)-5-fluoro-3-(1-oxo-3,4,6,7,8,9-hexahydro-pyrazino[1,2-a]indol-2(1H)-yl)phenylboronic acid **210d** (150 mg, 0.38 mmol), 5-bromo-3-(6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-2-ylamino)-1-methylpyridin-2(1H)-one **110c** (122 mg, 0.38 mmol), $PdCl_2$(dppf) (41 mg, 0.056 mmol), K_3PO_4 (100 mg), and NaOAc (50 mg) in MeCN (10 mL) and H_2O (3 mL) was heated at 110°C in a sealed tube for 2 h. The solvent was evaporated in *vacuo* and the residue was purified on reverse phase Combi-flash to give **149a** (120 mg, 53%). MS: $[M+H]^+$ 601.

A mixture of **149a** (120 mg, 0.2 mmol) and LiOH hydrate (84 mg, 2 mmol) in ^{i}PrOH (10 mL) and H_2O (3 mL) was stirred at 30°C for 2 h. The mixture was evaporated in *vacuo* and the residue was extracted with ethyl acetate (10 mL × 2). The combined extracts were concentrated under reduced pressure and the residue was purified on prep-HPLC to give **149** (60 mg, 54%). MS: $[M+H]^+$ 559. ^{1}H NMR (500 MHz, MeOD) δ 7.82 (s, 1H), 7.16 (s, 1H), 7.10 (d, J = 9.0, 2H), 6.62 (s, 1H), 5.77 (s, 1H), 4.67 (s, 2H), 4.43-4.35 (m, 2H), 4.11-4.07 (m, 3H), 4.00-3.99 (m, 2H), 3.93-3.90 (m, 3H), 3.60 (s, 3H), 2.55-2.52 (m, 2H), 2.46-2.43 (m, 2H), 1.82-1.78 (m, 2H), 1.71-1.67 (m, 2H).

Example 150 5-[5-Fluoro-2-(hydroxymethyl)-3-(1-methyl-6-oxo-5-{4H,6H,7H-pyrazolo[3,2-c][1,4]oxazin-2-ylamino}pyridin-3-yl)phenyl]-8-thia-5-azatricyclo-[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one **150**

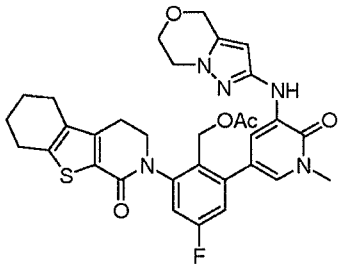
Example 150a 3-(6,7-Dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-2-ylamino)-1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one **150a**



A mixture of 5-bromo-3-(6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-2-ylamino)-1-methylpyridin-2(1H)-one **110c** (1.3 g, 4.0 mmol), bis(pinacolato)diboron (2.03 g, 8 mmol), $PdCl_2$(dppf) (439 mg, 0.6 mmol) and KOAc (784 mg, 8.0 mmol) in 1,4-dioxane (60 mL) was

heated at reflux for 15 h. After the completion of the reaction, the mixture was filtered off and washed with EtOAc (100 mL). The filtrate was evaporated in *vacuo* and the residue was purified on silica gel column to give **150a** (446 mg, 30%). MS: $[M+H]^+$ 373.

Example 150b [4-Fluoro-2-(1-methyl-6-oxo-5-{4H,6H,7H-pyrazolo[3,2-c][1,4]oxazin-2-ylamino}pyridin-3-yl)-6-{6-oxo-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-5-yl}phenyl]methyl Acetate **150b**



A mixture of **150a** (260 mg, 0.70 mmol), (2-bromo-4-fluoro-6-{6-oxo-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-5-yl}phenyl)methyl acetate **218a** (225 mg, 0.50 mmol), $PdCl_2$(dppf) (55 mg, 0.075 mmol), 2 M Na_2CO_3 solution (1.5 mL) in DME (8 mL) was heated at 120°C under microwave irradiation for 0.5 h. The solvent was evaporated in *vacuo* and the residue was purified on reverse phase Combi-flash to give **150b** (154 mg, 50%). MS: $[M+H]^+$ 618.

A mixture of **150b** (150 mg, 0.24 mmol) and LiOH hydrate (96 mg, 2.4 mmol) in ^{i}PrOH (15 mL) and H_2O (3 mL) was stirred at 30°C for 2 h. The mixture was evaporated in *vacuo* and the residue was extracted with ethyl acetate (20 mL × 2). The combined extracts were concentrated under reduced pressure. The residue was purified on prep-HPLC to give **150** (70 mg, 51%). MS: $[M+H]^+$ 576. ^{1}H NMR (500 MHz, DMSO) δ 8.22 (s, 1H), 8.00 (s, 1H), 7.32-7.29 (m, 2H), 7.17-7.15 (m, 1H), 5.93 (s, 1H), 4.86-4.85 (m, 1H), 4.71 (s, 2H), 4.36-4.28 (m, 2H), 4.10-3.84 (m, 7H), 3.57 (s, 3H), 3.02-2.92 (m, 1H), 2.90-2.76 (m, 3H), 1.86-1.74 (m, 4H).

Example 151 2-(3-(5-(5-(Azetidin-3-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **151**

Example 151a 2-(5-(5-(Azetidin-3-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **151a**

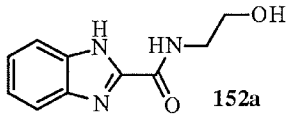
In a 44-mL sealed tube equipped with a magnetic stirring bar were placed 3-(5-(azetidin-3-yl)pyridin-2-ylamino)-5-bromo-1-methylpyridin-2(1H)-one **155n** (60 mg, 0.18

mmol), 2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **114a** (110 mg, 0.23 mmol), $Pd(PPh_3)_4$ (21 mg, 0.0.18 mmol) in 2 N Na_2CO_3 (3 mL), DME (2 mL), and dioxane (3 mL). After the reaction mixture was stirred at 100 °C for 14 h., it was partitioned between dichloromethane (5 mL) and water (5 mL), and the organic phase was extracted with dichloromethane (5 mL x 3). The combined organic phases were washed with water (5 mL x 2) and brine (5 mL x 1), dried (Na_2SO_4), and concentrated. The crude product was purified by flash chromatography (dichloromethane:MeOH, 85:15) to give 40% (40 mg) of 2-(5-(5-(azetidin-3-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **151a** as a solid.

A 25-mL, single-necked, round-bottomed flask equipped with a magnetic stirring bar was charged with **151a** (40 mg, 0.068 mmol), $LiOH•H_2O$ (20 mg, 0.48 mmol), THF (2 mL), *i*-PrOH (2 mL), and water (2 mL). After the reaction mixture was stirred at room temperature for 3 h, it was partitioned between dichloromethane (5 mL) and water (5 mL), and the organic phase was extracted with dichloromethane (5 mL x 3). The combined organic phases were washed with water (5 mL x 2) and brine (5 mL x 1), dried (Na_2SO_4), and concentrated. The crude product was re-dissolved in dichloromethane (3 mL). To this solution was added hexane (10 mL) and the resulting precipitates were filtered to give 88% yield (33 mg) of **151**; MS(ESI^+) *m/z* 551.3 (M+H).

Example 152 2-(2-(Hydroxymethyl)-3-(1-methyl-6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-*a*]benzoimidazole-1-one **152**

Example 152a *N*-(2-Hydroxyethyl)-1*H*-benzo[*d*]imidazole-2-carboxamide **152a**

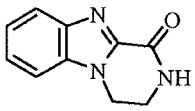


152a

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was purged with nitrogen and charged with 1*H*-benzo[*d*]imidazole-2-carboxylic acid (1.50 g, 9.26 mmol) and thionyl chloride (10 mL). After heating at reflux for 16 h, the suspension was cooled to room temperature and filtered. The filter cake was washed with toluene (10 mL) and dried under vacuum at room temperature for 5 h. The resulting solid was charged into a 100-mL single-neck round-bottomed flask equipped with a magnetic

stirrer and reflux condenser, followed by chloroform (10 mL) and 2-hydroxyethylamine (559 mg, 9.17 mmol). After stirring at reflux for 16 h, the reaction mixture was concentrated under reduced pressure, and the resulting residue was triturated with water (20 mL) and dried in a vacuum oven at 45 °C to afford a 73% yield (1.41 g) of **152a** as a white solid: mp 194–195 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.13 (s, 1H), 8.74 (s, 1H), 7.71–7.29 (m, 4H), 4.80 (s, 1H), 3.55 (dd, 2H, J = 10.5, 5.5 Hz), 3.38 (dd, 2H, J = 10.5, 5.5 Hz); MS (APCI+) m/z 206.6 (M+H).

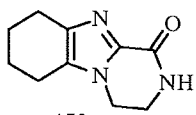
Example 152b 3,4-Dihydropyrazino[1,2-*a*]benzoimidazole-1-one **152b**



152b

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was purged with nitrogen and charged with **152a** (1.41 g, 6.84 mmol) and DMF (10 mL), and the reaction mixture was cooled to 0 °C. A solution of thionyl chloride (896 mg, 7.53 mmol) in DMF (5 mL) was added dropwise. The reaction was heated at 150 °C for 2 h. After this time, the solvent was removed under reduced pressure. The resulting residue was partitioned between water (20 mL) and methylene chloride (20 mL). The layers were separated, and the aqueous phase was extracted with methylene chloride (2 × 20 mL). The organic extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography to afford a 52% yield (672 mg) of **152b** as a brown solid: mp >250 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.53 (s, 1H), 7.76 (d, 1H, J = 9.0 Hz), 7.66 (d, 1H, J = 9.0 Hz), 7.40 (t, 1H, J = 9.0 Hz), 7.31 (t, 1H, J = 9.0 Hz), 4.41 (t, 2H, J = 6.0 Hz), 3.71 (m, 2H); MS (APCI+) m/z 188.4 (M+H).

Example 152c 3,4,6,7,8,9-Hexahydropyrazino[1,2-*a*]benzoimidazole-1-one **152c**

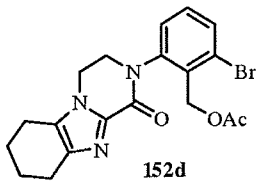


152c

A 250-mL stainless steel pressure reactor was charged with 10% palladium on carbon (50% wet, 150 mg dry weight) and a solution of **152b** (670 mg, 3.58 mmol) in acetic acid (25 mL). The reactor was evacuated, charged with hydrogen gas to a pressure of 350 psi and stirred at 95 °C for 16 h. After this time, the hydrogen was evacuated, and nitrogen was

charged into the reactor. Celite 521 (1.00 g) was added, and the mixture was filtered through a pad of Celite 521. The filter cake was washed with ethanol (2 × 25 mL), and the combined filtrates were concentrated to dryness under reduced pressure. To the resulting residue was added water (10 mL), and followed by potassium carbonate to adjust pH to 9. The mixture was extracted with methylene chloride (4 × 20 mL), and the organic extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure to afford a 71% yield **152c** (487 mg) as a white solid: mp >250 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.86 (s, 1H), 3.98 (t, 2H, J = 6.5 Hz), 3.51 (m, 2H), 2.50 (m, 4H), 1.75 (m, 4H); MS (APCI+) *m/z* 192.6 (M+H).

Example 152d 2-Bromo-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-*a*]benzoimidazole-2-yl)benzyl Acetate **152d**



152d

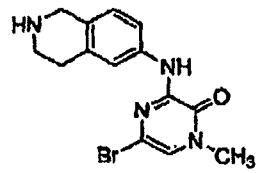
A 100-mL three-neck round-bottomed flask equipped with a reflux condenser, magnetic stirrer and nitrogen inlet was charged with **152c** (485 mg, 2.54 mmol), **104g** (1.56 g, 5.08 mmol), cesium carbonate (1.66 g, 5.08 mmol), *N,N'*-dimethylethylene-diamine (447 mg, 5.08 mmol) and 1,4-dioxane (20 mL). After bubbling nitrogen through the resulting suspension for 30 min, copper iodide (484 mg, 2.54 mmol) was added, and the reaction mixture was heated at 100 °C (oil bath temperature) for 16 h. After this time, the mixture was cooled to room temperature and filtered. The filtrate was diluted with ethyl acetate (100 mL) and water (50 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography to afford a yellow oil, which was dissolved in methylene chloride (5 mL). Acetyl chloride (506 mg, 2.54 mmol) and triethylamine (1.28 g, 12.7 mmol) were added, and the reaction mixture was stirred at room temperature for 2 h. After this time, the reaction mixture was diluted with methylene chloride (50 mL) and saturated aqueous sodium bicarbonate (20 mL). The organic layer was separated, and the aqueous layer was extracted with methylene chloride (3 × 50 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to afford a 13% yield (140 mg) of **152d** as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, 1H, J = 8.0 Hz), 7.27 (t, 1H, J = 8.0 Hz),

7.18 (d, 1H, J = 8.0 Hz), 5.26 (d, 1H, J = 12.0 Hz), 5.14 (d, 1H, J = 12.0 Hz), 4.32 (m, 1H), 4.24 (m, 1H), 4.14 (m, 1H), 3.87 (m, 1H), 2.75 (m, 2H), 2.56 (m, 2H), 2.07 (s, 3H), 1.83 (m, 4H); MS (APCI+) *m/z* 418.8 (M+H).

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was purged with nitrogen and charged with **152d** (140 mg, 0.335 mmol), **104h** (140 mg, 0.426 mmol), sodium carbonate (106 mg, 1.00 mmol), 1,4-dioxane (5 mL) and water (1 mL). This mixture was degassed with nitrogen for 30 min. Tetrakis(triphenylphosphine)palladium (39 mg, 0.033 mmol) was added. After heating at 100 °C for 5 h, the reaction mixture was cooled to room temperature and partitioned between water (40 mL) and methylene chloride (100 mL). The layers were separated, and the aqueous phase was extracted with methylene chloride (2 × 50 mL). The organic extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was dissolved in methanol (5 mL), and potassium carbonate (500 mg, 3.62 mmol) was added. After stirring at room temperature for 2 h, the reaction mixture was partitioned between water (20 mL) and methylene chloride (20 mL). The layers were separated, and the aqueous phase was extracted with methylene chloride (2 × 20 mL). The organic extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography to afford **152** in 9% yield (15 mg) as a yellow solid: mp 205–206 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.18 (s, 1H), 8.70 (d, 1H, J = 2.5 Hz), 8.64 (m, 1H), 8.30 (d, 1H, J = 6.0 Hz), 7.51–7.47 (m, 2H), 7.39 (d, 1H, J = 8.0 Hz), 7.35 (d, 1H, J = 8.0 Hz), 7.31 (d, 1H, J = 6.0 Hz), 4.92 (t, 1H, J = 4.5 Hz), 4.36 (m, 2H), 4.27 (m, 2H), 4.19 (m, 1H), 3.97 (m, 1H), 3.61 (s, 3H), 2.63 (m, 2H), 2.52 (m, 2H), 1.87 (m, 4H); MS (ESI+) *m/z* 498.2 (M+H).

Example 153 2-(2-(Hydroxymethyl)-3-(4-methyl-5-oxo-6-(1,2,3,4-tetrahydroisoquinolin-6-ylamino)-4,5-dihydropyrazin-2-yl)phenyl)-3,4,5,6,7,8-hexahydrobenzothieno[2,3-*c*]pyridin-1(2*H*)-one **153**

Example 153a 5-Bromo-1-methyl-3-(1,2,3,4-tetrahydroisoquinolin-6-ylamino)pyrazin-2(1*H*)-one **153a**



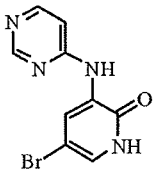
153a

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was purged with nitrogen and charged with **120a** (1.14 g, 2.62 mmol), methylene chloride (10 mL) and trifluoroacetic acid (10 mL). The solution was stirred for 2 h at room temperature. After this time, the solution was concentrated under reduced pressure. The residue was partitioned between methylene chloride (100 mL) and 1 M aqueous dibasic potassium phosphate (30 mL). The aqueous layer was extracted with a 20% (v/v) solution of methanol in methylene chloride (3 × 100 mL). The organic extracts were combined, washed with brine (20 mL) and dried over sodium sulfate. The drying agent was removed by filtration, and the filtrate was concentrated under reduced pressure to afford a 68% yield (600 mg) of **153a** as an off-white solid: mp 170–171 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.30 (s, 1H), 7.62 (m, 2H), 7.31 (s, 1H), 6.97 (d, 1H, J = 7.8 Hz), 4.10 (br s, 1H), 3.83 (s, 2H), 3.43 (s, 3H), 2.96 (t, 2H, J = 5.7 Hz), 2.68 (t, 2H, J = 5.7 Hz); MS (ESI+) m/z 334.0 (M+H).

A 50-mL three-neck round-bottomed flask equipped with a reflux condenser, magnetic stirrer and nitrogen inlet was charged with **153a** (168 mg, 0.500 mmol), **111a** (289 mg, 0.600 mmol), sodium carbonate (159 mg, 1.50 mmol), DMF (5 mL), water (2.5 mL) and 1,4-dioxane (8 mL). After bubbling nitrogen through the resulting suspension for 30 min, tetrakis(triphenylphosphine)palladium(0) (58 mg, 0.050 mmol) was added, and the reaction mixture was heated at reflux for 14 h. After this time, the mixture was cooled to room temperature, and methanol (2 mL), water (2 mL) and lithium hydroxide monohydrate (42 mg, 1.00 mmol) were added. The mixture was stirred for 4 h at room temperature and then concentrated in vacuo. The residue was partitioned between ethyl acetate (150 mL) and water (30 mL). The organic layer was separated, and the aqueous layer was extracted with a 20% (v/v) solution of methanol in methylene chloride (3 × 150 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (silica, 0% to 10% methanol/methylene chloride) to afford a 4% yield (12 mg) of **153** as an off-white solid: 209–210 °C dec; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.04 (s, 1H), 7.74 (s, 1H), 7.61 (d, 1H, J = 7.4 Hz), 7.53 (d, 1H, J = 8.0 Hz), 7.46 (t, 1H, J = 8.0 Hz), 7.40 (s, 1H), 7.32 (d, 1H, J = 7.4 Hz), 6.90 (d, 1H, J = 8.3 Hz), 4.77 (m, 1H), 4.53 (m, 1H), 4.43 (m, 1H), 4.02 (m, 1H), 3.87 (m, 1H), 3.77 (s, 2H), 3.58 (s, 3H), 2.91 (m, 4H), 2.79 (s, 2H), 2.63 (m, 2H), 1.78 (m, 4H); MS (ESI+) m/z 568.1 (M+H).

Example 154 2-(2-(Hydroxymethyl)-3-(6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydropyridin-3-yl)phenyl)-3,4,5,6,7,8-hexahydrobenzothieno[2,3-*c*]pyridin-1(2*H*)-one **154**

Example 154a 5-Bromo-3-(pyrimidin-4-ylamino)pyridin-2(1*H*)-one **154a**



154a

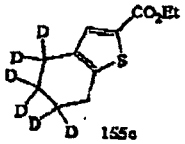
A 250-mL three-neck round-bottomed flask equipped with a reflux condenser, magnetic stirrer and nitrogen inlet was charged with 2-aminopyrimidine (376 mg, 3.95 mmol), 3,5-dibromo pyridin-2(1H)-one (1.00 g, 3.95 mmol), 1 M THF solution of lithium hexamethyldisilazide (20 mL, 20.0 mmol), and 1,4-dioxane (25 mL). After bubbling nitrogen through the resulting suspension for 30 min, Xantphos (194 mg, 0.211 mmol) and tris(dibenzylideneacetone)dipalladium(0) (165 mg, 0.197 mmol) were added, and the reaction mixture was heated at reflux for 3 h. After this time, the mixture was cooled to room temperature and diluted with ethyl acetate (150 mL) and water (30 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 150 mL). The combined organic extracts were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography followed by trituration with ethyl acetate (20 mL) to afford a 24% yield (250 mg) of **154a** as an off-white solid: mp 150–151 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.03 (s, 1H), 9.27 (s, 1H), 8.54 (s, 1H), 8.20 (d, 1H, J = 6.0 Hz), 7.85 (s, 1H), 6.64 (d, 1H, J = 6.0 Hz); MS (ESI+) m/z 268.2 (M+H).

A 50-mL three-neck round-bottomed flask equipped with a reflux condenser, magnetic stirrer and nitrogen inlet was charged with **154a** (175 mg, 0.655 mmol), **111a** (315 mg, 0.655 mmol), sodium carbonate (208 mg, 2.00 mmol), DMF (2.5 mL), water (1.2 mL) and 1,4-dioxane (4 mL). After bubbling nitrogen through the resulting suspension for 30 min, tetrakis(triphenylphosphine)palladium(0) (76 mg, 0.065 mmol) was added, and the reaction mixture was heated at reflux for 14 h. After this time, the mixture was cooled to room temperature, and methanol (2 mL), water (2 mL) and lithium hydroxide monohydrate (82 mg, 1.95 mmol) were added. The mixture was stirred for 2 h at room temperature and then concentrated in vacuo. The residue was partitioned between ethyl acetate (150 mL) and water (30 mL). The organic layer was separated, and the aqueous layer was extracted with a 20% (v/v) solution of methanol in methylene chloride (3 × 150 mL). The combined organic extracts were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (silica, 0% to 10% methanol/methylene chloride) to afford a 5% yield (15 mg) of **154** as an off-white solid: mp 200–201 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.99 (s, 1H), 9.34 (s, 1H), 8.57 (s, 1H), 8.21 (d, 1H, J = 6.0 Hz), 8.00 (s, 1H),

7.62 (s, 1H), 7.44 (t, 1H, J = 7.5 Hz), 7.35 (d, 1H, J = 7.0 Hz), 6.70 (d, 1H, J = 5.5 Hz), 5.05 (br s, 1H), 4.28 (t, 1H, J = 11.0 Hz), 4.18 (d, 1H, J = 10.0 Hz), 3.96 (m, 1H), 3.90 (m, 1H), 2.94 (m, 1H), 2.84 (m, 1H), 2.77 (m, 2H), 1.76 (m, 4H); MS (ESI+) *m/z* 500.1 (M+H).

Example 155 5,5,6,6,7,7-Hexadeutero-2-(2-(hydroxymethyl)-3-(1-methyl-5-(5-(1-methylazetidin-3-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,5,6,7,8-hexahydrobenzothieno[2,3-*c*]pyridin-1(2*H*)-one **155**

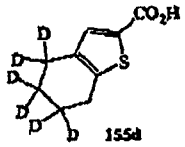
Example 155c Ethyl 4,4,5,5,6,6-Hexadeutero-4,5,6,7-tetrahydrobenzo[*b*]thiophene-2-carboxylate **155c**



155c

Intermediate **155a** (1.53 g) was reacted with ethyl 2-mercaptoacetate (1.57 g) using the same general procedure as described in Example 105b. Intermediate **155c** was obtained as a clear oil in 51% yield (1.46 g): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (s, 1H), 4.31 (q, 2H, J = 7.5 Hz), 2.77 (s, 2H), 1.35 (t, 3H, J = 7.5 Hz); MS (ESI+) *m/z* 217 (M+H).

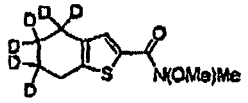
Example 155d 4,4,5,5,6,6-Hexadeutero-4,5,6,7-tetrahydrobenzo[*b*]thiophene-2-carboxylic Acid **155d**



155d

Intermediate **155d** (1.34 g) was saponified using the same general procedure as described in Example 105c. Intermediate **155d** was obtained as a white solid in 94% yield (1.10 g): mp 192–193 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.75 (br s, 1H), 7.40 (s, 1H), 2.73 (s, 2H).

Example 155e 4,4,5,5,6,6-Hexadeutero-*N*-methoxy-*N*-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-2-carboxamide **155e**

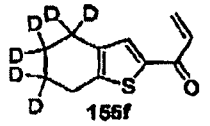


155e

A 250-mL single-neck round-bottomed flask equipped with a magnetic stirrer was purged with nitrogen, charged with **155d** (5.67 g, 30.1 mmol), methylene chloride (100 mL),

and DMF (110 mg, 1.50 mmol) and cooled to 0 °C. To the resulting solution, oxalyl chloride (4.21 g, 33.1 mmol) was added dropwise. After this addition was complete, the reaction was warmed to room temperature and stirred for 3 h. After this time, the reaction was concentrated to dryness under reduced pressure. The residue was dissolved in methylene chloride (100 mL), and the resulting solution was cooled to 0 °C. Triethylamine (9.15 g, 90.3 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (3.23 g, 33.1 mmol) were added. After the addition was complete, the cooling bath was removed, and the reaction mixture was stirred at room temperature for 14 h. After this time, the reaction mixture was partitioned between water (100 mL) and ethyl acetate (200 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate (100 mL). The combined organic extracts were washed with water (100 mL), followed by brine (100 mL) and dried over sodium sulfate. The drying agent was removed by filtration, and the solvent was evaporated under reduced pressure. The resulting residue was purified by flash chromatography (silica, 0% to 100% ethyl acetate/hexanes) to afford a 90% yield of **155e** (6.29 g) as a white solid: mp 47–48 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (s, 1H), 3.76 (s, 3H), 3.31 (s, 3H), 2.77 (s, 2H); MS (ESI+) *m/z* 232.1 (M+H).

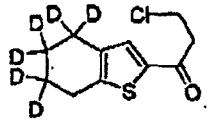
Example 155f 1-(4,4,5,5,6,6-Hexadeutero-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)prop-2-en-1-one **155f**



155f

A 250-mL single-necked round-bottomed flask equipped with a magnetic stirrer was purged with nitrogen and charged with **155e** (6.29 g, 27.2 mmol) and anhydrous THF (60 mL), and the resulting solution was cooled to -25 °C with acetone/ice bath. A 1.0 M solution of vinylmagnesium bromide in THF (32.3 mL, 32.6 mmol) was added dropwise, and the resulting reaction mixture was stirred at 0 °C for 1 h. After this time, the reaction mixture was partitioned between ethyl acetate (250 mL) and 2 M hydrochloric acid (50 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate (40 mL). The combined organic extracts were washed with water (100 mL), followed by brine (100 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to afford a crude quantitative yield of **155f** (5.39 g) as a semi-solid. The material was used in the next step without further purification.

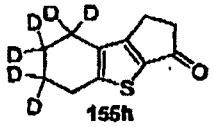
Example 155g 3-Chloro-1-(4,4,5,5,6,6-hexadeutero-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)propan-1-one **155g**



155g

A 250-mL single-necked round-bottomed flask equipped with a magnetic stirrer was purged with nitrogen and charged with **155f** (5.39 g, 27.2 mmol), methylene chloride (60 mL), and the resulting solution was cooled to 0 °C. A 2 M solution of hydrogen chloride in diethyl ether (34 mL) was added. After stirring at room temperature for 3 h, the solvents were removed under reduced pressure. Purification of the resulting residue by column chromatography (silica, 0% to 50% ethyl acetate/hexanes) afforded a quantitative yield (6.38 g) of **155g** as an off-white solid: mp 51–53 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (s, 1H), 3.89 (t, 2H, J = 7.0 Hz), 3.30 (t, 2H, J = 7.0 Hz), 2.79 (s, 2H); MS (ESI+) *m/z* 235.1 (M+H).

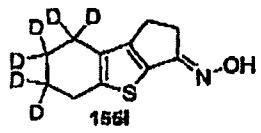
Example 155h 6,6,7,7,8,8-Hexadeutero-5,6,7,8-tetrahydro-1*H*-benzo[*b*]cyclopenta[*d*]thiophen-3(2*H*)-one **155h**



155h

A 250-mL single-necked round-bottomed flask equipped with a magnetic stirrer was charged with **155g** (6.38 g, 27.2 mmol) and 98% sulfuric acid (50 mL). After stirring at 95 °C for 14 h, the reaction mixture was poured into ice (50 g), and the resulting suspension was extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (silica, 0% to 50% ethyl acetate/hexanes) to afford **155h** in a 56% yield (3.03 g) as an off-white solid: mp 43–44 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.91 (m, 6H).

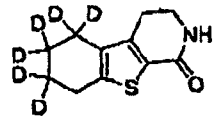
Example 155i 6,6,7,7,8,8-Hexadeutero-5,6,7,8-tetrahydro-1*H*-benzo[*b*]cyclopenta[*d*]thiophen-3(2*H*)-one Oxime **155i**



155i

A 250-mL single-neck round-bottomed flask equipped with a mechanical stirrer and nitrogen inlet was charged with hydroxylamine hydrochloride (1.59 g, 22.9 mmol) and methanol (40 mL). The mixture was cooled to 0 °C using an ice bath. Sodium acetate trihydrate (3.19 g, 22.9 mmol) was added. The mixture was stirred at 0 °C for 30 min. After this time, **155h** (3.03 g, 15.3 mmol) was added, and the reaction was stirred at room temperature for 14 h. After this time, the mixture was concentrated, redissolved in methylene chloride (200 mL) with water (30 mL). The organic layer was separated, and the aqueous layer was extracted with methylene chloride (3 × 150 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to afford a 84% yield (2.72 g) of **155i** as an off-white solid: mp 174–176 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.12 (m, 2H), 2.82 (m, 4H); MS (ESI+) *m/z* 214.1 (M+H).

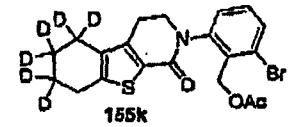
Example 155j 5,5,6,6,7,7-Hexadeutero-3,4,5,6,7,8-hexahydrobenzothieno[2,3-*c*]pyridin-1(2*H*)-one **155j**



155j

A 50-mL single-neck round-bottomed flask equipped with a reflux condenser, magnetic stirrer and nitrogen inlet was charged with **155i** (2.72 g, 12.8 mmol) and polyphosphoric acid (150 g). After stirring at 80 °C for 14 h, the reaction mixture was cooled to room temperature, and water (300 mL) was added. The resulting mixture was stirred for 30 min and filtered. The filter cake was washed with water (20 mL) and dried in a vacuum oven at 45 °C to afford a 74% yield (2.00 g) of **155j** as an off-white solid: mp 204–205 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.58 (s, 1H), 3.58 (m, 2H), 2.79 (s, 2H), 2.71 (t, 2H, J = 7.0 Hz); MS (ESI+) *m/z* 214.1 (M+H).

Example 155k 2-Bromo-6-(5,5,6,6,7,7-hexadeutero-1-oxo-3,4,5,6,7,8-hexahydrobenzothieno[2,3-*c*]pyridin-2(1*H*)-yl)benzyl Acetate **155k**

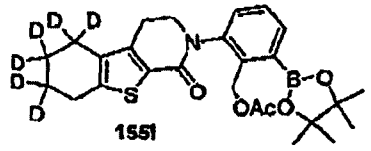


155k

A 250-mL three-neck round-bottomed flask equipped with a reflux condenser, magnetic stirrer and nitrogen inlet was charged with **155j** (1.00 g, 4.69 mmol), **104g** (2.89 g, 9.38 mmol), cesium carbonate (4.59 g, 14.1 mmol), *N,N'*-dimethylethylene-diamine (412 mg,

4.69 mmol) and 1,4-dioxane (35 mL). After bubbling nitrogen through the resulting suspension for 30 min, copper iodide (447 mg, 2.35 mmol) was added, and the reaction mixture was heated at 80 °C (oil bath temperature) for 20 h. After this time, the mixture was cooled to room temperature and filtered. The filtrate was diluted with ethyl acetate (150 mL) and water (30 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (silica, 0% to 40% ethyl acetate/ hexanes) to afford a 35% yield (715 mg) of **155k** as an off-white solid: mp 74–75 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (m, 1H), 7.31 (m, 2H), 5.15 (d, 1H, J = 12.0 Hz), 5.04 (d, 1H, J = 12.0 Hz), 3.99 (m, 1H), 3.65 (m, 1H), 2.81 (m, 1H), 2.74 (s, 2H), 2.06 (s, 3H); MS (ESI+) *m/z* 440.1 (M+H).

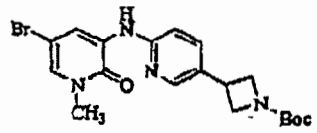
Example 155l 2-(5,5,6,6,7,7-Hexadeutero-1-oxo-3,4,5,6,7,8-hexahydrobenzothieno[2,3-c]pyridin-2(1*H*)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl Acetate **155l**



155l

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was purged with nitrogen and charged with **155k** (710 mg, 1.61 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (819 mg, 3.22 mmol), potassium acetate (474 mg, 4.83 mmol) and 1,4-dioxane (12 mL). After bubbling nitrogen through the resulting suspension for 30 min, [1,1'-bis(diphenylphosphino)-ferrocene] dichloropalladium(II) (118 mg, 0.161 mmol) was added, and the reaction mixture was heated at reflux for 2 h. After this time, the mixture was cooled to room temperature and diluted with ethyl acetate (150 mL) and water (30 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 150 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to afford a crude **155l** (785 mg) in a quantitative yield. The material was used in the next step without further purification.

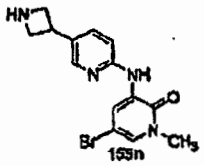
Example 155m *tert*-Butyl 3-(6-(6-Bromoo-2-methyl-3-oxo-2,3-dihydropyrin-4-ylamino)pyridin-3-yl)azetidine-1-carboxylate **155m**



155m

A 250-mL single-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was charged with *tert*-butyl 3-(6-aminopyridin-3-yl)azetidine-1-carboxylate (333 mg, 1.33 mmol), 3,5-dibromo-1-methylpyridin-2(1H)-one (350 mg, 1.33 mmol), cesium carbonate (870 mg, 2.70 mmol) and 1,4-dioxane (10 mL). After bubbling nitrogen through the resulting solution for 30 min, Xantphos (66 mg, 0.114 mmol) and tris(dibenzylideneacetone)dipalladium(0) (61 mg, 0.066 mmol) were added and the reaction mixture was heated at 105 °C for 3 h. After this time, the mixture was cooled to room temperature and filtered. The filter cake was washed with methylene chloride (2 × 10 mL), and the combined filtrates were concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica to afford a 79% yield (460 mg) of **155m** as a green solid: mp 134–136 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.75 (s, 1H), 8.65 (s, 1H), 8.19 (s, 1H), 7.66 (dd, 1H, J = 8.5, 2.0 Hz), 7.51 (s, 1H), 7.35 (d, 1H, J = 8.5 Hz), 4.21 (t, 2H, J = 8.0 Hz), 3.81 (m, 2H), 3.51 (s, 3H), 1.40 (s, 9H); MS (ESI+) *m/z* 436.1 (M+H).

Example 155n 3-(5-(Azetidin-3-yl)pyridin-2-ylamino)-5-bromo-1-methylpyridin-2(1*H*)-one **155n**

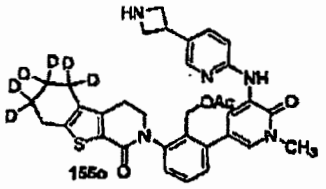


155n

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was purged with nitrogen and charged with **155m** (1.20 g, 2.76 mmol), methylene chloride (10 mL) and trifluoroacetic acid (10 mL). The solution was stirred for 2 h at room temperature. After this time, the solution was concentrated under reduced pressure. The residue was partitioned between methylene chloride (100 mL) and 1 M aqueous dibasic potassium phosphate (30 mL). The aqueous layer was extracted with a 20% (v/v) solution of methanol in methylene chloride (3 × 100 mL). The organic extracts were combined, washed with brine (20 mL) and dried over sodium sulfate. The drying agent was removed by filtration, and the filtrate was concentrated under reduced pressure to afford a quantitative

yield (920 mg) of **155n** as an off-white solid: mp 123–124 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.72 (s, 1H), 8.65 (d, 1H, J = 2.3 Hz), 8.19 (d, 1H, J = 2.1 Hz), 7.71 (dd, 1H, J = 8.6, 2.2 Hz), 7.51 (d, 1H, J = 2.3 Hz), 7.33 (d, 1H, J = 8.2 Hz), 3.74 (m, 3H), 3.58 (m, 2H), 3.52 (s, 3H); MS (ESI+) *m/z* 335.1 (M+H).

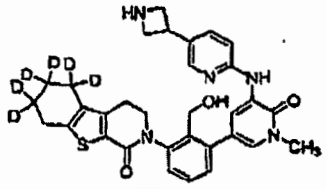
Example 155o 2-(5-(5-(Azetidin-3-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-6-(5,5,6,6,7,7-hexadeutero-1-oxo-3,4,5,6,7,8-hexahydrobenzothieno[2,3-*c*]pyridin-2(1*H*)-yl)benzyl Acetate **155o**



155o

A 100-mL three-neck round-bottomed flask equipped with a reflux condenser, magnetic stirrer and nitrogen inlet was charged with crude **155l** (785 mg, presumed 1.61 mmol), **155n** (450 mg, 1.34 mmol), sodium carbonate (426 mg, 4.02 mmol), DMF (10 mL), water (5 mL) and 1,4-dioxane (16 mL). After bubbling nitrogen through the resulting suspension for 30 min, tetrakis(triphenylphosphine)palladium(0) (155 mg, 0.134 mmol) was added, and the reaction mixture was heated at reflux for 14 h. The residue was partitioned between ethyl acetate (150 mL) and water (30 mL). The organic layer was separated, and the aqueous layer was extracted with a 20% (v/v) solution of methanol in methylene chloride (3 × 150 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to afford crude **155o**. The material was used in the next step without further purification.

Example 155p 2-(3-(5-(5-(Azetidin-3-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-(hydroxymethyl)phenyl)-5,5,6,6,7,7-hexadeutero-3,4,5,6,7,8-hexahydrobenzothieno[2,3-*c*]pyridin-1(2*H*)-one **155p**



155p

A 100-mL single-neck round-bottomed flask equipped with a was charged with crude **155o** from the previous step, THF (8 mL), methanol (4 mL), water (4 mL) and lithium

hydroxide monohydrate (420 mg, 10.0 mmol) were added. The mixture was stirred for 4 h at room temperature and then concentrated in vacuo. The residue was partitioned between ethyl acetate (150 mL) and water (30 mL). The organic layer was separated, and the aqueous layer was extracted with a 20% (v/v) solution of methanol in methylene chloride (3 × 150 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (silica, 0% to 10% methanol/methylene chloride) to afford a 15% yield (140 mg) of **155p** as an off-white solid: mp 140–142 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.65 (d, 1H, J = 2.0 Hz), 8.53 (s, 1H), 8.10 (d, 1H, J = 2.4 Hz), 7.67 (m, 1H), 7.45 (t, 1H, J = 8.0 Hz), 7.31 (m, 4H), 4.81 (t, 1H, J = 5.0 Hz), 4.35 (m, 2H), 4.04 (m, 1H), 3.88 (m, 1H), 3.71 (m, 3H), 3.59 (s, 3H), 3.55 (m, 2H), 2.96 (m, 1H), 2.86 (m, 1H), 2.77 (s, 2H); MS (ESI+) *m/z* 574.3 (M+H).

A 150-mL single-neck round-bottomed flask equipped with a magnetic stirrer was purged with nitrogen, charged with **155p** (140 mg, 0.244 mmol), 37% solution of formaldehyde in water (26 mg, 0.317 mmol) and methanol (10 mL). A suspension of sodium cyanoborohydride (48 mg, 0.732 mmol) and zinc chloride (50 mg, 0.366 mmol) in methanol (4 mL) was added, and the reaction was stirred at room temperature for 16 h. After this time, the reaction mixture was concentrated in vacuo. The residue was partitioned between ethyl acetate (150 mL) and water (30 mL). The organic layer was separated, and the aqueous layer was extracted with a 20% (v/v) solution of methanol in methylene chloride (3 × 150 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (silica, 0% to 10% methanol/methylene chloride) to afford a 45% yield (65 mg) of **155** as a white solid: mp 190–192 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.65 (d, 1H, J = 2.5 Hz), 8.58 (s, 1H), 8.15 (d, 1H, J = 2.5 Hz), 7.67 (dd, 1H, J = 8.5, 2.5 Hz), 7.46 (t, 1H, J = 8.0 Hz), 7.33 (m, 4H), 4.81 (t, 1H, J = 4.0 Hz), 4.35 (m, 2H), 4.02 (m, 1H), 3.85 (m, 3H), 3.64 (m, 1H), 3.59 (s, 3H), 3.42 (m, 2H), 2.98 (m, 1H), 2.87 (m, 1H), 2.76 (s, 2H), 2.47 (s, 3H); MS (ESI+) *m/z* 588.2 (M+H).

Example 156 2-(3-(5-(5-((3,3-Difluoroazetidin-1-yl)methyl)-1-methyl-1H-pyrazol-3-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **156**

Example 156a Methyl 5-Nitro-1*H*-pyrazole-3-carboxylate **156a**

A 50-mL single-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was purged with nitrogen and charged with 5-nitro-1H-pyrazole-3-carboxylic acid (0.86 g, 5.5 mmol) and anhydrous methanol (10 mL), and the reaction

mixture was cooled to 0 °C in an ice/water cooling bath. To the resulting solution thionyl chloride (1.7 g, 14.4 mmol) was added dropwise. After the addition was complete, the bath was removed, and the reaction was heated at reflux for 3 h. After this time, the reaction was concentrated to dryness under reduced pressure to afford a quantitative yield of **156a** (0.94 g) as a white solid: MS (ESI-) *m/z* 170 (M-H).

Example 156b Methyl 1-Methyl-3-nitro-1*H*-pyrazole-5-carboxylate **156b**

A 50-mL single-neck round-bottomed flask equipped with a magnetic stirrer was purged with nitrogen and charged with methyl 5-nitro-1*H*-pyrazole-3-carboxylate **(156a)** (0.94 g, 5.5 mmol), anhydrous *N,N*-dimethylformamide (11 mL), methyl iodide (0.85g, 6mmol) and potassium carbonate (0.83g, 6.1 mmol). The reaction was stirred at room temperature for 16 h. After this time the reaction was diluted with water (40 mL) and extracted with methylene chloride (3 × 25 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was subjected to flash chromatography (silica, ethyl acetate/hexanes) to afford methyl 1-methyl-3-nitro-1*H*-pyrazole-5-carboxylate **156b** in 66% yield (0.67 g) as a white solid: MS (ESI+) *m/z* 186.0 (M+H). Also isolated was the regioisomer methyl 1-methyl-5-nitro-1*H*-pyrazole-3-carboxylate in 15% yield (0.15 g) as a white solid: MS (ESI-) *m/z* 186.0 (M+H).

Example 156c (1-Methyl-3-nitro-1*H*-pyrazol-5-yl)methanol **156c**

A 100-mL three-neck round-bottomed flask equipped with a magnetic stirrer, addition funnel and nitrogen inlet was purged with nitrogen and charged with **156b** (0.67 g, 3.6 mmol), THF (20 mL) and cooled to 0 °C using an ice bath. 2 M lithium borohydride solution (3.6 mL, 7.2 mmol) was added dropwise at a rate that maintained the internal reaction temperature below 5 °C. After the addition was complete, the cooling bath was removed and the reaction was stirred at room temperature for 3 h. The reaction was cooled to 0 °C using an ice bath, and saturated aqueous sodium bicarbonate (30 mL) was added dropwise. The layers were separated, and aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (silica, ethyl acetate/hexanes) to afford a quant. yield (0.56 g) of (1-methyl-3-nitro-1*H*-pyrazol-5-yl)methanol (**156c**) as an off-white solid: MS (ESI+) *m/z* 158.1 (M+H).

Example 156d 5-(Bromomethyl)-1-methyl-3-nitro-1*H*-pyrazole **156d**

A 25-mL round-bottomed flask equipped with a magnetic stirrer and reflux condenser was purged with nitrogen and charged with **156c** (0.56 g, 3.6 mmol) and chloroform (10 mL). The reaction was cooled to 0 °C using an ice bath and phosphorous tribromide (0.98 g, 3.6

mmol) was added dropwise. The cooling bath was removed and the reaction stirred at reflux for 3 h. After this time, the reaction was cooled to 0 °C and diluted with methylene chloride (25 mL). Saturated aqueous sodium bicarbonate was added until a pH of 8.5 was reached. The layers were separated, and the aqueous layer was extracted with methylene chloride (3 × 25 mL). The combined organic layers were washed with brine (30 mL), dried over sodium sulfate and concentrated under reduced pressure to afford a quantitative yield (0.79 g) of **156d** as an off-white solid: MS (ESI+) *m/z* 222.1 (M+H).

Example 156e 5-((3,3-Difluoroazetidin-1-yl)methyl)-1-methyl-3-nitro-1H-pyrazole **156e**

A sealed tube with a magnetic stirrer was charged with DMF (5 mL), 5-(Bromomethyl)-1-methyl-3-nitro-1*H*-pyrazole **156d** (0.39 g, 1.78 mmol), 3,3-difluoroazetidine hydrochloride (276 mg, 2.13 mmol) and DIPEA (0.8 mL, 4.45 mmol). The reaction mixture was heated at 65 °C for 3-5 h. After this time the reaction was concentrated to dryness under reduced pressure, and the resulting residue was diluted with a mixture of Ethyl Acetate (15 mL) and water (15 mL). The aqueous layer was separated and extracted with Ethyl Acetate (2 × 15 mL). The combined organic extracts were dried over sodium sulfate and concentrated under reduced pressure to afford a quantitative yield of **156e** as yellow oil, which was used without further purification for the next step. MS (ESI+) *m/z* 233.0 (M+H).

Example 156f 5-((3,3-Difluoroazetidin-1-yl)methyl)-1-methyl-1H-pyrazol-3-amine **156f**

A Parr reactor bottle was purged with nitrogen and charged with 10% palladium on carbon (30% wet, 150 mg dry weight) and a solution of **156e** (1.78 mmol) in ethanol (25 mL). The bottle was attached to a Parr hydrogenator, evacuated, charged with hydrogen gas to a pressure of 40 psi and shaken for 2 h. After this time, the hydrogen was evacuated, and the reaction mixture was filtered through a pad of Celite 521. The filter cake was washed with ethanol (2 × 25 mL), and the combined filtrates were concentrated to dryness under reduced pressure to afford a quantitative yield of **156f** (360mg) as yellow oil: MS (ESI+) *m/z* 203.1 (M+H).

Example 156g 5-Bromo-3-(5-((3,3-difluoroazetidin-1-yl)methyl)-1-methyl-1H-pyrazol-3-ylamino)-1-methylpyridin-2(1H)-one **156g**

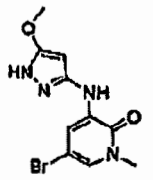
Intermediate **156g** was synthesized using the same procedure as Example 112a, except using **156f** (360mg, 1.78 mmol), 3,5-dibromo-1-methyl-1H-pyridin-2-one (0.43 g, 1.6 mmol), cesium carbonate (1.56 g, 4.8 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.15

g, 0.16mmol), Xantphos (0.18 g, 0.32mmol) and 1,4-dioxane (18 mL). The reaction mixture was heated at 115 °C for 24 hours. Work-up and flash column chromatography (silica, 60:35:5 methylene chloride/diethyl ether/methanol) give 38% yield (0.23 g) of **156g** as a green solid: MS (ESI+) *m/z* 390.1 (M+H).

Following Example 121c, except using 2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **114a** (165 mg, 0.35 mmol), **156g** (115 mg, 0.3 mmol), 1M sodium carbonate solution (1.2 mL, 1.2 mmol), tetrakis(triphenylphosphine)palladium(0) (18 mg, 0.015 mmol) and 1,2-Dimethoxyethane (3 mL). Work-up and flash column chromatography (silica, 60:35:5 methylene chloride/diethyl ether/methanol) afford **156h** (a mixture of compound **156** and its acetate) as yellow oil (190 mg). The mixture (0.3mmol) was deprotected using a mixture of THF (2 mL), water (1 mL) and isopropanol (2 mL), and Lithium hydroxide monohydrate (80 mg, 1.90 mmol). Work-up and flash column chromatography (silica, 60:35:5 methylene chloride/diethyl ether/methanol) afford a 12% yield (2 steps, 22 mg) of **156** as a white solid: MS (ESI+) *m/z* 604.4 (M+H).

Example 157 2-(2-(Hydroxymethyl)-3-(5-(5-methoxy-1H-pyrazol-3-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **157**

Example 157a 5-Bromo-3-(5-methoxy-1H-pyrazol-3-ylamino)-1-methylpyridin-2(1H)-one **157a**

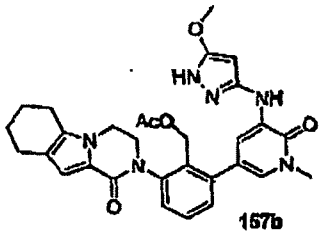


157a

A sealed tube was equipped with a magnetic stirrer and charged with 5-methoxy-1H-pyrazol-3-amine (1.9 g, 17 mmol), 3,5-dibromo-1-methylpyridin-2(1H)-one (4.9 g, 18 mmol) and cesium carbonate (12 g, 37 mmol) in 1,4-dioxane (160 mL). After bubbling nitrogen through the solution for 30 min, Xantphos (1.1 g, 2 mmol) and tris(dibenzylideneacetone) dipalladium(0) (1.1 g, 1.2 mmol) were added, and the reaction mixture was heated to 100 °C for 16 hours. After this time, H_2O (50 mL) and EtOAc (50 mL) were added. The aqueous layer was separated and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (100 mL) and dried over sodium sulfate. The resulting solution was

concentrated under reduced pressure to near dryness and the desired product fell out of solution. Filtering and washing with Et_2O (10 mL) afforded 12% yield (590 mg) of crude **157a**.

Example 157b 2-(5-(5-Methoxy-1H-pyrazol-3-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **157b**



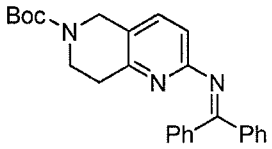
157b

A microwave tube equipped with a magnetic stirrer was charged with **157a** (94 mg, 0.3 mmol), 2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **114a** (180 mg, 0.4 mmol), DME (4 mL) and 1M aqueous sodium carbonate (0.9 mL). After bubbling N_2 for 15 min, $Pd(PPh_3)_4$ (18 mg, 0.02 mmol) was added. The mixture was heated in microwave to 130 °C for 25 min. After this time, EtOAc (5 mL) and water (5 mL) were added. The separated aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organics were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography eluting with a gradient of CH_2Cl_2 – 60:35:5 CH_2Cl_2:Et_2O:MeOH to afford a 19% yield (33 mg) of **157b**.

A 25 mL round bottom flask with a magnetic stirrer was charged with **157b** (33 mg, 0.06 mmol), lithium hydroxide (10 mg, 1.2 mmol), THF (0.3 mL), *i*-PrOH (0.3 mL) and water (0.6 mL). The mixture stirred at rt for 1 h. After this time, EtOAc (5 mL) and water (5 mL) were added. The separated aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organics were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography eluting with a gradient of CH_2Cl_2 – 60:35:5 CH_2Cl_2:Et_2O:MeOH to afford a 76% yield (23 mg) of **157**. MS (ESI+) *m/z* 515.4 (M + H).

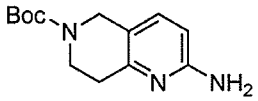
Example 158 5-[2-(Hydroxymethyl)-3-[1-methyl-6-oxo-5-(5,6,7,8-tetrahydro-1,6-naphthyridin-2-ylamino)-1,6-dihydropyridin-3-yl]phenyl]-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$]trideca-1(9),2(7)-dien-6-one **158**

Example 158a tert-Butyl 2-(Diphenylmethyleneamino)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate **158a**



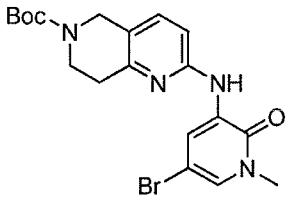
To a round-bottomed flask equipped with a stirring bar, tert-butyl 2-chloro-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (1.09 g, 4.05 mmol), diphenyl-methanimine 26 (2.20 g, 12.14 mmol), Pd(OAc)2 (181.6 mg, 0.809 mmol), BINAP (503.8 mg, 0.809 mmol), Cs_2CO_3 (6.59 g, 20.23 mmol) and toluene (16 mL) were added. The reaction mixture was heated at 110 °C for 2 days. The reaction mixture was filtered and removed solvent *in vacuo*. The residue **158a** was directly used in the next step.

Example 158b tert-Butyl 2-Amino-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate **158b**



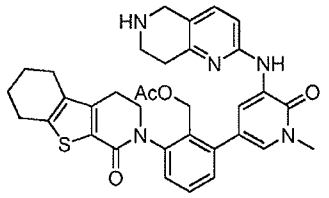
Intermediate **158a** was added to a round-bottomed flask. MeOH (50 mL) and NH_2OH HCl (1.76 g, 25.3 mmol) was added. The resulting mixture was stirred at RT for 5 hrs. The solvents were removed in vacuo and silica gel column (MeOH: DCM = 10: 90) gave **158b** as dark oil, 851 mg (84 %, 2 steps).

Example 158c tert-Butyl 2-(5-Bromo-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate **158c**



To a round-bottomed flask equipped with a stirring bar, **158b** (851 mg, 3.41 mmol), 3,5-dibromo-1-methylpyridin-2(1H)-one (1.37 g, 5.12 mmol), $Pd_2(dba)_3$ (312.5 mg, 0.341 mmol), XantPhos (316 mg, 0.546 mmol), Cs_2CO_3 (3.67 g, 11.3 mmol) and dioxane (17 mL) were added. The reaction mixture was heated at 100 °C overnight. DCM (200 mL) was added to the resulting mixture was washed with water (30 mL X 3). DCM (200 mL) was added and the resulting mixture was washed with water (30 mL X 3), brine (30 mL X 1), dried over $MgSO_4$, filtered, and removed solvent *in vacuo*. DCM / ether (1 : 2, 5 mL) was added followed by sonication, the precipitation was filtered as **158c**, green solids, 865 mg (58 %).

Example 158d 5-[2-(Acetoxymethyl)-3-[1-methyl-6-oxo-5-(5,6,7,8-tetrahydro-1,6-naphthyridin-2-ylamino)-1,6-dihydropyridin-3-yl]phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one **158d**

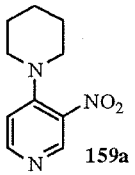


To a microwave tube equipped with a stirring bar, **158c** (300 mg, 0.689 mmol), boronic ester **111a** (365 mg, 0.758 mmol), $Pd(PPh_3)_4$ (39.8 mg, 0.034 mmol), Na_2CO_3 aqueous solution (1.0 N, 2.27 mL. 2.27 mmol), 1,2-dimethoxyethane (3.0 mL) were added. The mixture was reacted in microwave at 130 °C for 10 min. methylene chloride (200 mL) was added and the resulting mixture was washed with water (30 mL X 3), brine (30 mL X 1), dried over $MgSO_4$, filtered, and removed solvent *in vacuo*. Silica gel column chromatography (MeOH: methylene chloride = 5: 95) gave **158d.**

To a round-bottomed flask equipped with a stirring bar, **158d**, THF (5 mL), *i*-propanol (5 mL), water (5 mL), LiOH monohydrate (278 mg) were added. The resulting mixture was stirred at room temperature for 1 hr. The solvent was removed *in vacuo* and the resulting residue was added to methylene chloride (200 mL), the solution was washed with water (30 mL X 3), brine (30 mL X 1), dried over $MgSO_4$, filtered, and removed solvent *in vacuo*. Silica gel column chromatography (methanol: methylene chloride = 10: 90) gave **158** as a yellow solid (145 mg). MS (ESI+) *m/z* 568.3 (M + H).

Example 159 2-(2-(Hydroxymethyl)-3-(1-methyl-6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrido[3,4-*b*]imidazo[4,5-*c*]pyridine-1-one **159**

Example 159a 3-Nitro-4-(piperidin-1-yl)pyridine **159a**

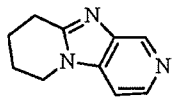


159a

A 500-mL single-neck round-bottomed flask equipped with a reflux condenser and magnetic stirrer was purged with nitrogen and charged with 3-nitro-4-chloro-pyridine (10.0 g, 63.3 mmol), piperidine (16.2 g, 190 mmol) and ethanol (200 mL). After heating at 70 °C for 2

h, the solvent was removed under reduced pressure, and the residue was partitioned between ethyl acetate (200 mL) and 10% aqueous potassium carbonate (100 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography to afford a 100% yield (15.2 g) of **159a** as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.31 (d, 1H, J = 6.0 Hz), 6.86 (d, 1H, J = 6.0 Hz), 3.22 (t, 4H, J = 4.5 Hz), 1.72 (m, 6H); MS (APCI+) *m/z* 208.4 (M+H).

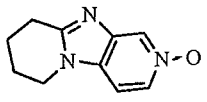
Example 159b 6,7,8,9-Tetrahydropyrido[3,4-*b*]imidazo[4,5-*c*]pyridine **159b**



159b

A 500-mL single-neck round-bottomed flask equipped with a reflux condenser and magnetic stirrer was purged with nitrogen and charged with **159a** (6.00 g, 29.0 mmol) and triethyl phosphite (200 mL). After heating at 110 °C for 24 h, the triethyl phosphite was removed under reduced pressure, and the residue was partitioned between methylene chloride (200 mL) and water (100 mL). The organic layer was separated, and the aqueous layer was extracted with methylene chloride (2 × 100 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography to afford a 53% yield (2.66 g) of **159b** as a yellow solid: mp 94–95 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.37 (d, 1H, J = 6.0 Hz), 7.22 (d, 1H, J = 6.0 Hz), 4.09 (t, 2H, J = 6.0 Hz), 3.11 (t, 2H, J = 6.0 Hz), 2.15 (m, 2H), 2.05 (m, 2H); MS (APCI+) *m/z* 174.1 (M+H).

Example 159c 6,7,8,9-Tetrahydropyrido[3,4-*b*]imidazo[4,5-*c*]pyridine 2-Oxide **159c**

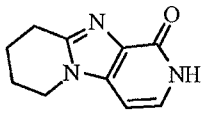


159c

A 100-mL single-neck round-bottomed flask equipped with a reflux condenser and magnetic stirrer was charged with **159b** (2.50 g, 14.4 mmol) and methylene chloride (50 mL), and the reaction mixture was cooled to 0 °C. 3-chloroperbenzoic acid (4.99 g, 28.9 mmol)

was added, and the mixture was stirred at room temperature for 1.5 h. After this time, the solvent was removed under reduced pressure, and the residue was purified by column chromatography to afford an 83% yield (2.26 g) of **159c** as a yellow solid: mp 178–179 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.15 (d, 1H, J = 6.0 Hz), 7.19 (d, 1H, J = 6.0 Hz), 4.12 (t, 2H, J = 6.0 Hz), 3.12 (t, 2H, J = 6.0 Hz), 2.18 (m, 2H), 2.05 (m, 2H); MS (APCI+) *m/z* 190.4 (M+H).

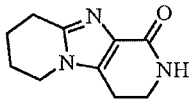
Example 159d 6,7,8,9-Tetrahydropyrido[3,4-*b*]imidazo[4,5-*c*]pyridine-1-one **159d,**



159d

A 250-mL single-neck round-bottomed flask equipped with a reflux condenser and magnetic stirrer was purged with nitrogen and charged with **159c** (2.26 g, 12.0 mmol) and acetic anhydride (90 mL). After heating at 140 °C for 1.5 h, the solvent was removed under reduced pressure, and the residue was purified by column chromatography to afford a 62% yield (1.40 g) of **159d** as a yellow solid: mp >250 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.3 (s, 1H), 7.24 (d, 1H, J = 7.0 Hz), 6.39 (d, 1H, J = 6.0 Hz), 4.07 (t, 2H, J = 6.0 Hz), 3.11 (t, 2H, J = 6.0 Hz), 2.13 (m, 2H), 2.02 (m, 2H); MS (APCI+) *m/z* 190.7 (M+H).

Example 159e 3,4,6,7,8,9-hexahydropyrido[3,4-*b*]imidazo[4,5-*c*]pyridine-1-one **159e**

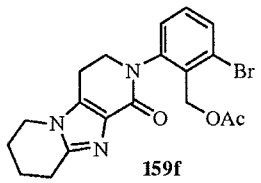


159e

A 250-mL stainless steel pressure reactor was charged with 10% palladium on carbon (50% wet, 250 mg dry weight) and a solution of **159d** (1.07 g, 5.66 mmol) in acetic acid (50 mL). The reactor was evacuated, charged with hydrogen gas to a pressure of 350 psi and stirred at 85 °C for 48 h. After this time, the hydrogen was evacuated, and nitrogen was charged into the reactor. Celite 521 (1.00 g) was added, and the mixture was filtered through a pad of Celite 521. The filter cake was washed with ethanol (2 × 25 mL), and the combined filtrates were concentrated to dryness under reduced pressure. To the resulting residue was added water (10 mL), followed by potassium carbonate to adjust pH to 9. The mixture was extracted with methylene chloride (4 × 20 mL), and the organic extracts were combined,

dried over sodium sulfate, filtered and concentrated under reduced pressure to afford a 69% yield of **159e** (749 mg) as a white solid: mp >250 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.28 (s, 1H), 3.85 (t, 2H, J = 6.0 Hz), 3.62 (m, 2H), 2.92 (t, 2H, J = 6.0 Hz), 2.81 (t, 2H, J = 6.0 Hz), 2.03 (m, 2H), 1.94 (m, 2H); MS (APCI+) *m/z* 192.7 (M+H).

Example 159f 2-Bromo-6-(1-oxo-3,4,6,7,8,9-hexahydropyrido[3,4-*b*]imidazo[4,5-*c*]pyridine-2-yl)benzyl Acetate **159f**



159f

A 100-mL three-neck round-bottomed flask equipped with a reflux condenser, magnetic stirrer and nitrogen inlet was charged with **159e** (745 mg, 3.90 mmol), **104g** (2.40 g, 7.80 mmol), cesium carbonate (2.54 g, 7.80 mmol), copper iodide (743 mg, 3.90 mmol), and 1-methyl-2-pyrrolidinone (7 mL). After heating at 120 °C (oil bath temperature) for 16 h, the mixture was cooled to room temperature and partitioned between methylene chloride (100 mL) and water (50 mL). The organic layer was separated, and the aqueous layer was extracted with methylene chloride (3 × 50 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography to afford a yellow oil, which was dissolved in methylene chloride (5 mL). Acetyl chloride (306 mg, 3.90 mmol) and triethylamine (1.97 g, 19.5 mmol) was added, and the reaction mixture was stirred at room temperature for 2 h. After this time, the reaction mixture was diluted with methylene chloride (50 mL) and saturated aqueous sodium bicarbonate (20 mL). The organic layer was separated, and the aqueous layer was extracted with methylene chloride (3 × 50 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to afford a 6% yield (100 mg) of **159f** as a pink oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, 1H, J = 8.0 Hz), 7.34 (t, 1H, J = 8.0 Hz), 7.16 (d, 1H, J = 8.0 Hz), 5.18 (m, 2H), 4.18 (m, 1H), 4.04 (m, 1H), 3.87 (m, 1H), 3.79 (m, 1H), 3.16 (m, 1H), 3.05 (m, 1H), 2.95 (m, 2H), 2.09–1.99 (m, 7H); MS (APCI+) *m/z* 418.9 (M+H).

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was purged with nitrogen and charged with **159f** (100 mg, 0.239 mmol), **104h** (350 mg, 1.07 mmol), sodium carbonate (183 mg, 1.72 mmol), 1,4-dioxane (8 mL) and water (2 mL). This mixture was degassed with nitrogen for 30 min. Tetrakis(tri-

phenylphosphine)palladium (66 mg, 0.057 mmol) was added. After heating at 100 °C for 5 h, the reaction mixture was cooled to room temperature and partitioned between water (40 mL) and methylene chloride (100 mL). The layers were separated, and the aqueous phase was extracted with methylene chloride (2 × 50 mL). The organic extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was dissolved in methanol (5 mL), and potassium carbonate (500 mg, 3.62 mmol) was added. After stirring at room temperature for 2 h, the reaction mixture was partitioned between water (20 mL) and methylene chloride (20 mL). The layers were separated, and the aqueous phase was extracted with methylene chloride (2 × 20 mL). The organic extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography to afford **159** in 10% yield (12 mg) as a light brown solid: mp >250 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.16 (s, 1H), 8.71 (d, 1H, J = 2.0 Hz), 8.64 (s, 1H), 8.29 (dd, 1H, J = 6.0, 1.5 Hz), 7.53 (s, 1H), 7.45 (td, 1H, J = 6.0, 1.5 Hz), 7.31 (m, 3H), 4.75 (m, 1H), 4.32 (m, 2H), 4.02 (m, 2H), 3.88 (m, 2H), 3.60 (s, 3H), 3.05 (m, 1H), 2.96 (m, 1H), 2.76 (t, 2H, J = 5.5 Hz), 1.95 (m, 2H), 1.86 (m, 2H); MS (ESI+) *m/z* 498.2 (M+H).

Example 160 3-({4-[(2*R*)-1,4-Dimethyl-3-oxopiperazin-2-yl]phenyl}amino)-5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-1,2-dihydropyrazin-2-one **160**

Following Example 121b, 2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **114a** (167 mg, 0.36 mmol), 5-bromo-3-(4-(1,4-dimethyl-3-oxopiperazin-2-yl)phenylamino)-1-methylpyrazin-2(1H)-one **160a** (WO 2009/039397; 122 mg, 0.3 mmol), 1M sodium carbonate solution (0.9 mL, 0.9 mmol), tetrakis(triphenylphosphine)-palladium(0) (18 mg, 0.015 mmol) and 1,2-dimethoxyethane (3 mL). Work-up and flash column chromatography (silica, 60:35:5 methylene chloride/diethyl ether/methanol) afford a mixture of 2-(5-(4-(1,4-dimethyl-3-oxopiperazin-2-yl)phenylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **160b** and **160** as yellow oil. The mixture (0.3mmol) was deprotected using a mixture of THF (1 mL), water (0.5 mL) and isopropanol (1 mL), and Lithium hydroxide monohydrate (80 mg, 1.90 mmol). Work-up and flash column chromatography (silica, 60:35:5 methylene chloride/diethylether/methanol) afford a 37% yield of compound **160** (2 steps, 70 mg) as a white solid: MS (ESI+) *m/z* 622.4 (M+H).

Example 161 2-(3-(5-(1-(2-Hydroxyethyl)-5-methyl-1H-pyrazol-3-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **161**

Example 161a 5-Bromo-3-(1-(2-(tert-butyldimethylsilyloxy)ethyl)-5-methyl-1H-pyrazol-3-ylamino)-1-methylpyridin-2(1H)-one **161a**

A solution of 5-bromo-1-methyl-3-(5-methyl-1H-pyrazol-3-ylamino)pyridin-2(1H)-one **112a** (1.08g, 3.8 mmol) in anhydrous DMF (10 mL) was treated with 60% dispersion of NaH in mineral oil (0.17 g, 4.3 mmol) while stirring under nitrogen. After effervescence the reaction was stirred for an additional 30 min. At this time the reaction was treated with (2-bromoethoxy)(*tert*-butyl)dimethylsilane (15-1) (0.908 g, 3.8mmol) and continued to stir under nitrogen for 10 hours. After reaction water (50 mL) was added slowly and the mixture was filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography eluting with petroleum ether/ethyl acetate to afford **161a** (1g, 35%), which was used directly without further purification. LCMS: (M+H)+ 443.

Example 161b 2-(5-(1-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-5-methyl-1H-pyrazol-3-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydro-pyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **161b**

A mixture of **161a** (750mg, 1.7 mmol), 2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **114a** (882 mg, 1.9 mmol), CH_3COONa (309 mg, 3.8 mmol), $PdCl_2(dppf)$ (153 mg, 0.19 mmol) and K_3PO_4 (1 g, 3.8 mmol) suspended in CH_3CN (30 mL) and H_2O (2 mL) was heated at 110°C for 12 h under argon atmosphere. After reaction the mixture was evaporated and the residue was purified by reverse phase Combi-flash eluting with 0.3% NH_4HCO_3 in 1:4 water/CH_3CN to give **161b** as a brown solid (210 mg, 18%). LCMS: $[M+H]^+$ 699.

Example 161c 2-(3-(5-(1-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-5-methyl-1H-pyrazol-3-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **161c**

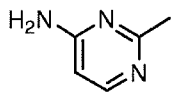
A mixture of **161b** (210 mg, 0.4 mmol) and LiOH (372 mg, 16 mmol) in isopropanol/THF (1:1, 10 mL) and water (3 mL) was stirred at 30 °C for 2 h. The mixture was evaporated in *vacuo* and the residue was extracted with ethyl acetate (2 X 10 mL). The combined extract was concentrated under reduced pressure and the residue was purified on prep-HPLC to **161c**. LCMS: $[M+H]^+$ 657

A solution of **161c**, camphorsulfonic acid (330 mg, 1.5 mmol) in methanol (30 mL) was stirred at room temperature for 3 h. After reaction methanol was evaporated and the

residue was purified by prep-HPLC to afford **161** as a brown solid (63 mg, 29%, two steps). LCMS: $[M+H]^+$ 543. ^1H NMR (500 MHz, DMSO) δ 7.96 (m, 1H), 7.45 (m, 1H), 7.33 (m, 2H), 7.24 (m, 1H), 6.51 (s, 1H), 5.87 (s, 1H), 4.86 (m, 1H), 4.77 (m, 1H), 4.36 (m, 2H), 4.15 (m, 3H), 3.90 (m, 3H), 3.64 (m, 2H), 3.57 (s, 3H), 2.51 (m, 2H), 2.46 (m, 2H), 2.19 (s, 3H),1.79 (m, 4H).

Example 162 2-(2-(Hydroxymethyl)-3-(1-methyl-5-(2-methylpyrimidin-4-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **162**

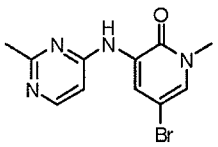
Example 162a 2-Methylpyrimidin-4-amine **162a**



162a

In a pressure-resistant vessel made of stainless steel having an inner volume of 500 mL was charged with 3-methoxypropanenitrile (10 g, 120 mmol), 1.1.1-trimethoxy-ethane (39 g, 324mmol) and 40.0 g (560 mmol, 24% by weight ammonia-methanol solution). The mixture was stirred at 130°C for 8 hours. After completion of the reaction, it was filtered and concentrated to give a yellow solid. The solid was washed with ethyl acetate (50 mL), dried in *vacuo* to afford **162a** (7.8 g, 60%). LCMS: $[M+H]^+$ 110

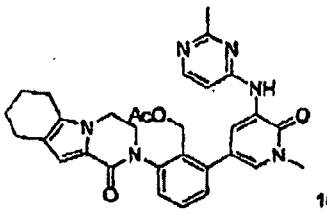
Example 162b 5-Bromo-1-methyl-3-(2-methylpyrimidin-4-ylamino)pyridin-2(1H)-one **162b**



162b

Following Example 148a, 2.0 g of **162a** and 4.0 g of 3,5-dibromo-1-methyl-pyridin-2(1H)-one were reacted to give **162b** as a yellow solid (2.3 g, 50%). LCMS: $[M+H]^+$ 357 ^1H NMR (500 MHz, DMSO) δ 9.20 (s, 1H), 8.78 (s, 1H), 8.26 (d, J=4.5, 1H), 7.68 (s, 1H), 7.18 (d, J=4.5, 1H), 3.59 (s, 3H), 2.52 (s, 3H).

Example 162c 2-(1-Methyl-5-(2-methylpyrimidin-4-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **162c**



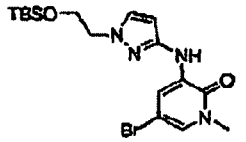
162c

Following Example 148b, 464 mg of 2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **114a** and 443 mg of **162b** were reacted to give **162c** as a yellow solid (386 mg, 70%). LCMS: $[M+H]^+$ 553

Following Example 148 160 mg of **162c** was hydrolyzed to give **162** as a white solid (90 mg, 60%). LCMS: $[M+H]^+$ 511. ^1H NMR (500 MHz, DMSO) δ 9.04 (s, 1H), 8.87 (s, 1H), 8.21 (s, 1H), 7.55 (s, 1H), 7.48 (s, 1H), 7.36 (t,J=6.5, 1H),7.12 (s, 1H), 6.52 (s, H), 4.85 (s, 1H), 4.40 (s, 1H),4.17-4.10 (m, 3 H), 3.92 (m, 1H), 3.61(s, 3H), 2.60 (m, 2H), 2.47 (m,2H), 2.42 (S, 3H), 1.80 (m, 2H), 1.69 (m, 2H).

Example 163 2-(3-(5-(1-(2-Hydroxyethyl)-1H-pyrazol-3-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **163**

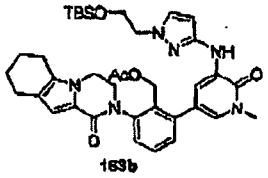
Example 163a 5-Bromo-3-(1-(2-(*tert*-butyldimethylsilyloxy)ethyl)-1H-pyrazol-3-ylamino)-1-methylpyridin-2(1H)-one **163a**



163a

A mixture of 1-(2-(*tert*-butyldimethylsilyloxy)ethyl)-1H-pyrazol-3-amine **116b** (1.2 g, 5 mmol), 3,5-dibromo-1-methylpyridin-2(1H)-one (1.3 g, 5 mmol), XantPhos (300 mg, 0.5 mmol), $Pd_2(dba)_3$ (460 mg, 0.5 mmol) and Cs_2CO_3 (4 g, 2.5 mmol) in dioxane (30 mL) was heated in a sealed tube at 120 °C for 2 h under nitrogen. After reaction the mixture was filtered and the filtrated was evaporated in *vacuo* to give a yellow solid, which was then washed with ethyl acetate (6 mL × 3) to give **163a** as a yellow solid (0.80 g, 38%) and used without further purification. MS: $(M+H)^+$ 427.

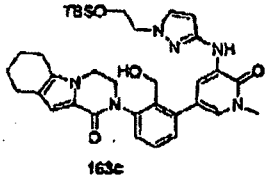
Example 163b 2-(5-(1-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-1H-pyrazol-3-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate 163b



163b

A mixture of 163a (800 mg, 1.88 mmol), 2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate 114a (1.3 g, 2.82 mmol), sodium acetate (308 mg, 3.76 mmol), $PdCl_2(dppf)$ (153 mg, 0.188 mmol) and K_3PO_4 (1 g, 3.76 mmol) suspended in CH_3CN (50 mL) and water (3 mL) was heated at 110 °C for 12 h under argon atmosphere. The mixture was then evaporated and the residue was purified by reverse phase Combi-flash eluting with 0.3% NH_4HCO_3 in 1:5 water/CH_3CN to give 163b as a brown solid (350 mg, 29%). MS: $(M+H)^+$ 685

Example 163c 2-(3-(5-(1-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-1H-pyrazol-3-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-163c



163c

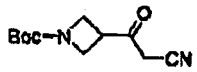
To a solution of 163b (460 mg, 0.67 mmol) in propan-2-ol (15 mL), tetrahydrofuran (15 mL), and water (5 mL) was added LiOH monohyydrate(1.6 g, 67 mmol). The mixture was stirred at 30 °C for 2 h. It was then evaporated and the residue was purified by reverse phase Combi-flash eluting with 0.3% NH_4HCO_3 in 1:4 water/CH_3CN to give 163c as a brown solid (300 mg, 70%). MS: $(M+H)^+$ 643

A solution of 163c (300 mg, 0.50 mmol), camphorsulfonic acid (330 mg, 1.5 mmol) in methanol (30 mL) was stirred at room temperature for 3 h. It was then evaporated and the residue was purified by prep-HPLC to afford 163 as a brown solid (140 mg, 57%). MS: $(M+H)^+$ 529. ^1H NMR (500 MHz, MeOD) δ 1.79 (s, 2 H), 1.89 (s, 2 H), 2.54-2.56 (t, J=5.5

Hz, 2 H), 2.62-2.66 (m, 2 H), 3.70 (s, 3 H), 3.84-3.86 (t, J=5.5 Hz, 2 H), 4.01-4.02 (m, 1 H), 4.09-4.11 (t, J=5.5 Hz, 2 H), 4.17-4.22 (m, 3 H), 4.49-4.57 (m, 2 H), 6.05-6.06 (d, 1 H), 6.71 (s, 1 H), 7.22-7.23 (d, 1 H), 7.35-7.37 (d, 1H), 7.40-7.42 (d, 1 H), 7.48-7.51 (m, 2H), 7.94-7.95 (d, 1H).

Example 164 5-[3-(5-{[5-(Azetidin-3-yl)-1H-pyrazol-3-yl]amino}-1-methyl-6-oxopyridin-3-yl)-5-fluoro-2-(hydroxymethyl)phenyl]-8-thia-5-azatricyclo-[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one 164

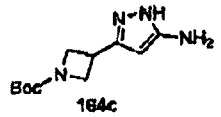
Example 164b *tert*-Butyl 3-(2-Cyanoacetyl)azetidine-1-carboxylate 164b



164b

Following Example 136a, 1-*tert*-butyl 3-ethyl azetidine-1,3-dicarboxylate 164a was converted to 164b as a yellow oil (crude). LCMS: (M+H)$^+$ 424. ^{1}H NMR (500 MHz, DMSO) δ 12.1 (dd, J = 2, 1H), 8.38 (s, 1H), 8.04 (d, J = 2.5, 1H), 7.36 (s, J = 2.5, 1H), 6.06 (d, J = 2.5, 1H), 4.18 (s, 2H), 3.80 (m, 1H), 3.49 (s, 3H), 1.39 (s, 9H).

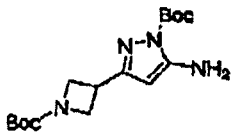
Example 164c *tert*-Butyl 3-(5-Amino-1H-pyrazol-3-yl)azetidine-1-carboxylate 164c



164c

Following Example 136b, 164b was converted to 164c which was used directly in the next step without further purification.

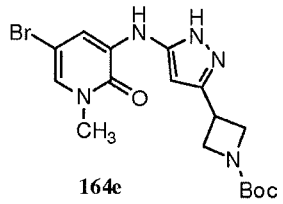
Example 164d *tert*-Butyl 5-Amino-3-(1-(*tert*-butoxycarbonyl)azetidin-3-yl)-1H-pyrazole-1-carboxylate 164d



164d

Following Example 136c, 164c was converted to 164d in 26% yield.

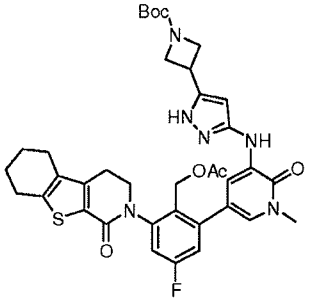
Example 164e *tert*-Butyl 3-(5-(5-Bromo-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)-1H-pyrazol-3-yl)azetidine-1-carboxylate 164e



164c

Following Example 136d, **164d** was converted to **164e** in 50% yield.

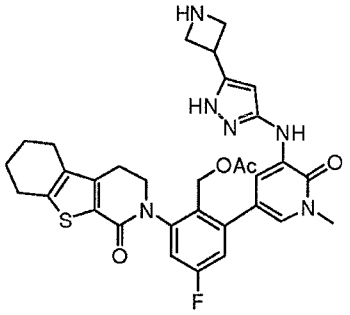
Example 164e [2-(5-{[5-(Azetidin-3-yl)-1H-pyrazol-3-yl]*tert*-butoxycarbonylamino}-1-methyl-6-oxopyridin-3-yl)-4-fluoro-6-{6-oxo-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-5-yl}phenyl]methyl Acetate **164e**



164e

Following Example 136e, **164d** and (4-fluoro-2-{6-oxo-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-5-yl}-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl acetate **112b** were reacted to give **164e** in 39% of yield.

Example 164f [2-(5-{[5-(Azetidin-3-yl)-1H-pyrazol-3-yl]amino}-1-methyl-6-oxopyridin-3-yl)-4-fluoro-6-{6-oxo-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-5-yl}phenyl]methyl Acetate **164f**



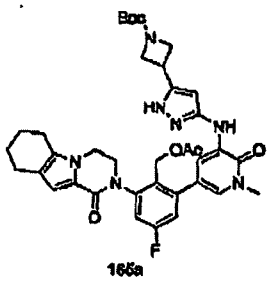
164f

To a solution of **164e** (300 mg, 0.42 mmol) in dioxane (2 mL) at room temperature was added HCl/dioxane (4M, 6 mL) dropwise. The reaction mixture was stirred for 1 h. After the reaction was finished, it was concentrated to afford **164f** (crude product) as a black solid, which was used in the next step without purification. LCMS: $(M+H)^+$ 617

Following Example 136, **164f** was converted to **164** in 20% yield. LCMS: $(M+H)^+$ 575. ^1H NMR (500 MHz, DMSO) δ 7.78 (s, 1H), 7.28 (d, J = 1.5, 1H), 7.223(s, 1H), 7.21 (s, 1H), 6.21 (s, 1H), 4.50 (m, 2H), 4.14 (m, 1H), 4.00 (m, 3H), 3.90 (m, 2H), 3.71 (s, 3H), 3.09 (m, 1H), 2.96 (m, 1H), 2.86 (m, 2H), 2.60 (m, 2H), 1.88 (m, 4H).

Example 165 2-(3-(5-(5-(Azetidin-3-yl)-1H-pyrazol-3-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **165**

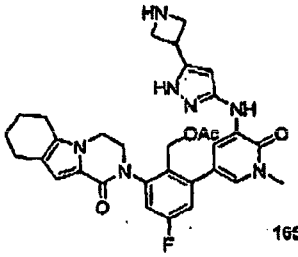
Example 165a *tert*-Butyl 3-(3-(5-(2-(Acetoxymethyl)-5-fluoro-3-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)phenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)-1H-pyrazol-5-yl)azetidine-1-carboxylate **165a**



165a

Following Example 164f, **164e** and 4-fluoro-2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **210d** were reacted to give **165a** in 20% yield. LCMS: $(M+H)^+$ 700

Example 165b 2-(5-(5-(Azetidin-3-yl)-1H-pyrazol-3-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-fluoro-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **165b**



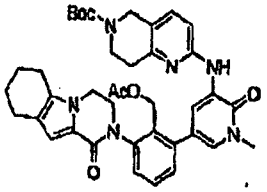
165b

Following Example 164g, **165a** was converted to crude **165b** which was used directly in the next step without further purification. LCMS: $(M+H)^+$ 600

Following Example 164, 165b was converted to 165 in 40% (two steps). LCMS: $(M+H)^+$ 558. ^1H NMR (500 MHz, DMSO) δ 7.78 (s, 1H), 7.28 (d, J = 1.5, 1H), 7.22(s, 1H), 7.21 (s, 1H), 6.21 (s, 1H), 4.50 (m, 2H), 4.14 (m, 1H), 4.00 (m, 3H), 3.90 (m, 2H), 3.71 (s, 3H), 3.09 (m, 1H), 2.96 (m, 1H), 2.86 (m, 2H), 2.60 (m, 2H), 1.88 (m, 4H).

Example 166 2-(2-(Hydroxymethyl)-3-(1-methyl-6-oxo-5-(5,6,7,8-tetrahydro-1,6-naphthyridin-2-ylamino)-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one 166

Example 166a *tert*-Butyl 2-(5-(2-(Acetoxymethyl)-3-(1-oxo-3,4,6,7,8,9-hexahydro-pyrazino[1,2-a]indol-2(1H)-yl)phenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate 166a

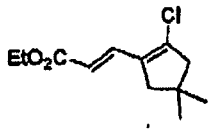


To a microwave tube equipped with a stirring bar, *tert*-butyl 2-(5-bromo-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate 158c (300 mg, mmol), 2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate 114a (352 mg, 0.758 mmol), $Pd(PPh_3)_4$ (39.8 mg, 0.035 mmol), Na_2CO_3 aqueous solution (1.0 N, 2.27 mL, 2.27 mmol), and 1,2-dimethoxyethane(3.5 mL) were added. The mixture was reacted in microwave at 130 °C for 10 min. methylene chloride (200 mL) was added and the resulting mixture was washed with water (30 mL X 3), brine (30 mL X 1), dried over $MgSO_4$, filtered, and removed solvent *in vacuo*. Silica gel column chromatography (methanol: methylene chloride = 5: 95) gave 166a.

To a round-bottomed flask equipped with a stirring bar, 166a and methylene chloride (10 mL) were added. The solution was cooled to 0 °C in an ice-water bath. TFA (1 mL) was added and the resulting solution was stirred overnight. All the volatiles were removed *in vacuo*, and to the bottle THF (10 mL), *i*-PrOH (10 mL), H_2O (10 mL), LiOH H_2O (1.00 g) were added. The resulting mixture was stirred at RT for 1 hr. All the solvent were removed *in vacuo* and the resulting residue was added to methylene chloride (200 mL), the solution was washed with water (X 30 mL), brine (30 mL), dried over $MgSO_4$, filtered, and removed solvent *in vacuo*. Silica gel column chromatography (methanol: methylene chloride = 10: 90) gave 166 as a light brown solid, 53 mg. MS (ESI+) *m/z* 551.3 (M + H).

Example 167 10-[2-(Hydroxymethyl)-3-[1-methyl-6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydropyridin-3-yl]phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-9-one 167

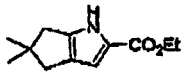
Example 167a (E)-Ethyl 3-(2-Chloro-4,4-dimethylcyclopent-1-enyl)acrylate 167a



167a

The following two procedures were adapted from *Organic Preparations and Procedures Int.*, 29(4):471-498. A 500-mL single neck round bottomed flask equipped with a magnetic stirrer and nitrogen inlet was charged with 2-chloro-4,4-dimethylcyclopent-1-enecarbaldehyde (38 g, 240 mmol) in benzene (240 mL). To the solution was added ethoxycarbonylmethylene triphenylphosphorane (84 g, 240 mmol). The mixture was stirred for 14 h. After that time, the solvent was evaporated and the residue was triturated with hexanes (2 L) to extract the product away from the PPh_3 by-products. The organic layer was dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography using a 100% hexane – 1:1 hexane/ethyl acetate gradient to afford a 37% yield (20 g) of 167a.

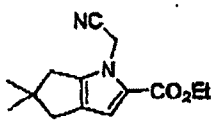
Example 167b Ethyl 5,5-Dimethyl-1,4,5,6-tetrahydrocyclopenta[b]pyrrole-2-carboxylate 167b



167b

A 250-mL single neck round bottomed flask equipped with a magnetic stirrer and nitrogen inlet was charged with 167a (17 g, 74 mmol) in DMSO (100 mL). To the solution was added sodium azide (9.6 g, 150 mmol). The mixture was then heated to 75 °C and stirred for 8 h. After cooling to rt, H_2O (100 mL) and CH_2Cl_2 (200 mL) were added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography using a 100% hexane – 1:1 hexane/ethyl acetate gradient to afford a 37% yield (5.7 g) of 167b.

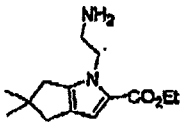
Example 167c Ethyl 1-(Cyanomethyl)-5,5-dimethyl-1,4,5,6-tetrahydrocyclopenta[b]pyrrole-2-carboxylate **167c**



167c

A 250-mL single neck round bottomed flask equipped with a magnetic stirrer and nitrogen inlet was charged with **167b** (6.2 g, 30 mmol) in DMF (57 mL). To the solution was added NaH (80% dispersion in mineral oil, 1.26 g, 42.1 mmol). The resulting mixture was stirred at rt for 90 min. After that time, bromoacetonitrile (2.94 mL, 42 mmol) was added. The mixture was stirred for 14 h. After that time, water (100 mL) and ethyl acetate (200 mL) were added and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 X 50 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography to afford a 95% yield (7 g) of **167c**.

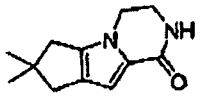
Example 167d Ethyl 1-(2-Aminoethyl)-5,5-dimethyl-1,4,5,6-tetrahydrocyclopenta[b]pyrrole-2-carboxylate hydrochloride **167d**



167d

A 500-mL Parr reactor bottle was purged with nitrogen and charged with 10% palladium on carbon (50% wet, 2.0 g dry weight), **167c** (4.5 g, 18 mmol), 12% hydrochloric acid (9.2 mL, 37 mmol), ethyl acetate (80 mL) and ethanol (52 mL). The bottle was attached to a Parr hydrogenator, evacuated, charged with hydrogen gas to a pressure of 50 psi and shaken for 6 h. After this time, the hydrogen was evacuated, and nitrogen was charged into the bottle. Celite 521 (10.0 g) was added, and the mixture was filtered through a pad of Celite 521. The filter cake was washed with ethanol (2 × 50 mL), and the combined filtrates were concentrated to dryness under reduced pressure. The crude residue **167d** was carried onto the next step without further purification.

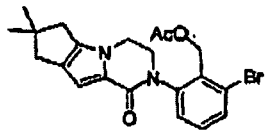
Example 167e 4,4-Dimethyl-1,10-diazatricyclo[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-9-one **167e**



167e

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was purged with nitrogen and charged with crude **167d** (~18 mmol), sodium ethoxide (6.2 g, 92 mmol) and ethanol (120 mL). The mixture was stirred at 55 °C over night. After that time, the reaction mixture was concentrated under reduced pressure and the residue was partitioned between ethyl acetate (200 mL) and water (100 mL). The solution was filtered. The solid was washed with ethyl acetate (15 mL) to give 850 mg of **167e**. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to near dryness. The solution was filtered and the solid (1.44 g) was washed with ethyl acetate (15 mL). The combined solids were dried under vacuum a afford 61% yield (2.3 g) of **167e**.

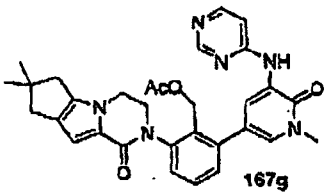
Example 167f 2-Bromo-6-(9-oxo-4,4-dimethyl-1,10-diazatricyclo[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-10-yl)benzyl Acetate **167f**



167f

A microwave tube equipped with a magnetic stirrer was charged with **167e** (301 mg, 1.47 mmol), 2,6-dibromobenzyl acetate **104g** (1.1 g, 3.0 mmol), CuI (140 mg, 0.7 mmol) Cs_2CO_3 (961 mg, 3.0 mmol), N',N',N',N'-tetramethylethylenediamine (0.22 mL, 1.5 mmol) and 1,2-dimethoxyethane(4.1 mL). The mixture was heated in microwave to 150 °C for 3 h. After this time, the mixture was filtered and the resulting solid was washed with 9:1 CH_2Cl_2 / MeOH (50 mL). The combined organics were washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography eluting with a gradient of hexanes– ethyl acetate to afford a 32% yield (200 mg) of **167f**.

Example 167g 10-[2-(Acetoxymethyl)-3-[1-methyl-6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydropyridin-3-yl]phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-9-one **167g**



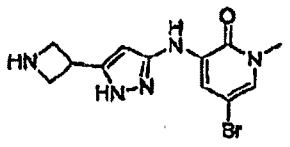
167g

A microwave tube equipped with a magnetic stirrer was charged with 1-methyl-3-(pyrimidin-4-ylamino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one **109e** (210 mg, 0.64 mmol), **167f** (140 mg, 0.3 mmol), 1,2-dimethoxyethane(4 mL) and 1M aqueous sodium carbonate (1 mL). After bubbling N_2 for 15 min, $Pd(PPh_3)_4$ (18 mg, 0.02 mmol) was added. The mixture was heated in microwave to 130 °C for 25 min. After this time, ethyl acetate (5 mL) and water (5 mL) were added. The separated aqueous layer was extracted with ethyl acetate (2 x 5 mL). The combined organics were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography eluting with a gradient of CH_2Cl_2 – 60:35:5 CH_2Cl_2:diethyl ether:methanol to afford a 53% yield (93 mg) of **167g**.

A 25 mL round bottom flask with a magnetic stirrer was charged with **167g** (93 mg, 0.17 mmol), lithium hydroxide (35 mg, 0.8 mmol), THF (0.8 mL), isopropanol(0.8 mL) and water (1.7 mL). The mixture stirred at rt for 1 h. After this time, ethyl acetate (5 mL) and water (5 mL) were added. The separated aqueous layer was extracted with ethyl acetate (2 x 5 mL). The combined organics were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography eluting with a gradient of CH_2Cl_2 – 60:35:5 CH_2Cl_2:diethyl ether:methanol to afford a 76% yield (23 mg) of **167**. MS (ESI+) *m/z* 511.8 (M + H).

Example 168 2-(2-(Hydroxymethyl)-3-(1-methyl-5-(5-(1-methylazetidin-3-yl)-1H-pyrazol-3-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **168**

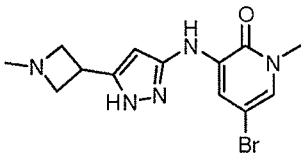
Example 168a 3-(5-(Azetidin-3-yl)-1H-pyrazol-3-ylamino)-5-bromo-1-methylpyridin-2(1H)-one **168a**



168a

To solution of tert-butyl 3-(3-(5-bromo-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)-1H-pyrazol-5-yl)azetidine-1-carboxylate **164e** (1 g, 2.36 mmol) in dioxane (10 ml) at room temperature, was added HCl/dioxane (4M, 20 mL) dropwise. Then the reaction mixture was stirred for 1 h at room temperature. After the reaction was finished, it was concentrated to afford **168a** as a yellow solid, which was used in the next step without purification. LCMS: $(M+H)^+$ 325

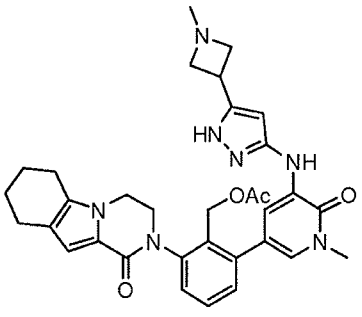
Example 168b 5-Bromo-1-methyl-3-(5-(1-methylazetidin-3-yl)-1H-pyrazol-3-ylamino)pyridine-2(1H)-one **168b**



168b

To a solution of 3-(5-(azetidin-3-yl)-1H-pyrazol-3-ylamino)-5-bromo-1-methylpyridin-2(1H)-one **168a** (crude, 2.36 mmol) in methanol (30 mL) and acetic acid (5 mL) at 0 °C, was added CH_2O (30% wt in H_2O) (12 g, 120 mmol), followed by the addition of $NaBH_4$ (1.8 g, 47.2 mmol) in small portions over the period of 1 h at 0°C. After the reaction was finished, the mixture was adjusted to pH>7 with 2N aq. NaOH. It was then extracted with methylene chloride (60 mL × 3), dried over Na_2SO_4 and, concentrated to give a yellow solid, which was further purified on flash column eluting with 50:1 methylene chloride/methanol containing 0.5% triethylamine to afford **168b** as a yellow solid (50%, two steps).

Example 168c 2-(1-Methyl-5-(5-(1-methylazetidin-3-yl)-1H-pyrazol-3-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **168c**



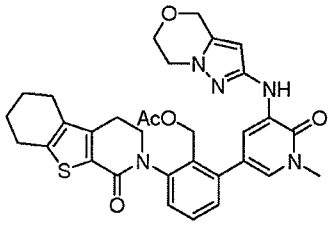
168c

Following Example 136e, **168b** and 2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **114a** were reacted to give **168c** in 20% yield.

Following Example 136, **168c** was converted to **168** in 54% yield. LCMS: $(M+H)^+$ 554. ^1H NMR (500 MHz, DMSO) δ 8.05 (s, 1H), 8.01 (s, 1H), 7.45 (t, J = 8, 1H), 7.31 (m, 2H), 7.24 (d, J = 2.5, 1H), 6.50 (s, 1H), 6.02 (s, 1H), 4.37 (m, 2H), 4.14 (m, 3H), 3.88 (m, 1H), 3.57 (s, 3H), 3.53 (m, 2H), 3.50 (m, 2H), 3.03 (m, 2H), 2.61 (m, 2H), 2.47 (m, 3H), 2.23 (s, 3H), 1.78 (m, 2H), 1.69 (m, 2H).

Example 169 5-[2-(Hydroxymethyl)-3-[1-methyl-6-oxo-5-({4H,6H,7H-pyrazolo[3,2-c][1,4]oxazin-2-yl}amino)-1,6-dihydropyridin-3-yl]phenyl]-8-thia-5-azatricyclo-[7.4.0.$0^{2,7}$]trideca-1(9),2(7)-dien-6-one **169**

Example 169a {2-[1-Ethyl-6-oxo-5-({4H,6H,7H-pyrazolo[3,2-c][1,4]oxazin-2-yl}amino)1,6-dihydropyridin-3-yl]-6-{6-oxo-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$]trideca-1(9),2(7)-dien-5-yl}phenyl}methyl Acetate **169a**

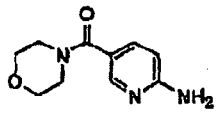


A mixture of 5-bromo-3-(6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-2-ylamino)-1-methylpyridin-2(1H)-one **110c** (500 mg, 1.54 mmol), (2-{6-oxo-8-thia-5-azatricyclo-[7.4.0.$0^{2,7}$]trideca-1(9),2(7)-dien-5-yl}-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl acetate **111a** (750 mg, 1.56 mmol), $PdCl_2$(dppf) (170 mg, 0.23 mmol), K_3PO_4 (150 mg), and sodium acetate (60 mg) in MeCN (25 mL) and water (5 mL) was heated at reflux for 2 h. The solvent was evaporated in *vacuo* and the residue was purified on reverse phase Combi-flash to give **169a** (369 mg, 40%). MS: $[M+H]^+$600.

A mixture of **169a** (440 mg, 0.73 mmol) and LiOH hydrate (308 mg, 7.3 mmol) in isopropanol(20 mL) and H_2O (4 mL) was stirred at 30℃ for 2 h. The mixture was evaporated in *vacuo* and the residue was extracted with ethyl acetate (20 mL × 2). The combined extracts were concentrated under reduced pressure. And the residue was purified on pre-HPLC to give **169** (104 mg, 26%). MS: $[M+H]^+$ 558. ^1H NMR (500 MHz, CDCl3) δ 7.93 (s, 1H), 7.46-7.39 (m, 3H), 7.31-7.24 (m, 3H), 5.73 (s, 1H), 4.78 (s, 2H), 4.61 (d, J = 11.5, 1H), 4.42-4.20 (m, 2H), 4.14-3.98 (m, 4H), 3.90-3.82 (m, 1H), 3.69 (s, 3H), 3.04-2.80 (m, 4H), 2.60-2.46 (m, 2H), 1.94-1.82 (m, 4H).

Example 170 5-[2-(Hydroxymethyl)-3-[1-methyl-5-({5-[(morpholin-4-yl)carbonyl]pyridine-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one 170

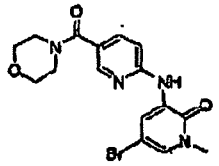
Example 170a (6-Aminopyridin-3-yl)(morpholino)methanone 170a



170a

To a solution of morpholine (9.00 g, 103 mmol) in EtOH (400 mL) was added EDCI (10.0 g, 52.2 mmol), HOBt (7.00 g 51.8 mmol), and 6-aminonicotinic acid (6.00 g, 43.4 mmol). After stirring for 18 h, the resulting suspension was filtered. The solid was triturated with a mixture of MeOH (100 mL) and methylene chloride (100 mL) to afford 170a as a white solid (2.7 g, 30%). LCMS: (M+H)$^+$ 208

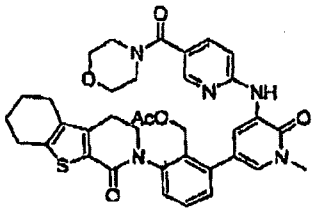
Example 170b 5-Bromo-1-methyl-3-(5-(morpholine-4-carbonyl)pyridin-2-ylamino)pyridine-2(1H)-one 170b



170b

Following Example 136a, 170a and 3,5-dibromo-1-methylpyridin-2(1H)-one were reacted to give 170b in 21% yield. LCMS: (M+H)$^+$ 394. ^{1}H NMR (500 MHz, MeOD) δ 8.84 (d, J=2.5, 1H), 8.42 (d, J=2, 1H), 7.72 (m, 1H), 7.42 (d, J=2, 1H), 7.11 (d, J=8.5, 1H), 3.72 (m, 8H), 3.63 (s, 3H).

Example 170c {2-[1-Methyl-5-({5-[(morpholin-4- yl)carbonyl]pyridin-2-yl}amino)-6-oxo-1,6- dihydropyridin-3-yl]-6-{6-oxo-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-5- yl}phenyl}methyl Acetate 170c



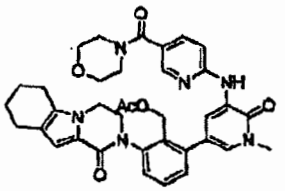
170c

Following Example 136e, 170b and (2-(6-oxo-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-5-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl acetate 111a were reacted to give 170c in 65% yield. LCMS: $(M+H)^+$ 668

Following Example 148, 170c was converted to 170 in 71% yield. LCMS: $(M+H)^+$ 626. ^{1}H NMR (500 MHz, DMSO) δ 8.95 (s, 1H), 8.72 (d, J=2, 1H), 8.25 (d, J=2, 1H), 7.64 (dd, J=8.5, 1H), 7.45 (m, 2H), 7.35 (m, 3H), 4.85 (t, J=4, 1H), 4.35 (m, 2H), 4.03 (m, 1H), 3.88 (m, 1H), 3.59 (m, 7H), 3.49 (m, 4H), 2.98 (m, 1H), 2.85 (m, 1H), 2.77 (m, 2H), 2.54 (m, 2H), 1.79 (m, 4H).

Example 171 2-(2-(Hydroxymethyl)-3-(1-methyl-5-(5-(morpholine-4-carbonyl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one 171

Example 171a 2-(1-Methyl-5-(5-(morpholine-4-carbonyl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate 171a



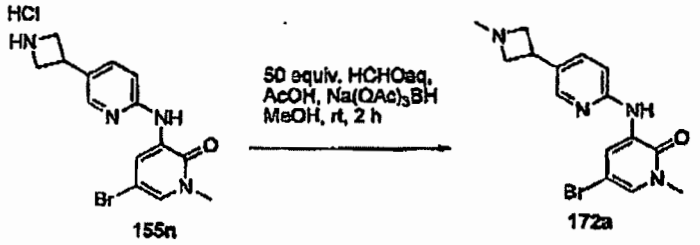
171a

Following Example 136d, 5-bromo-1-methyl-3-(5-(morpholine-4-carbonyl)pyridin-2-ylamino)pyridin-2(1H)-one 170a and 2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate 114a were reacted to give 171a in 27% yield. LCMS: $(M+H)^+$ 651

Following Example 170, 171a was converted to 171 in 60% yield. LCMS: $(M+H)^+$ 609. ^{1}H NMR (500 MHz, DMSO) δ 8.85 (d, J=2, 1H), 8.32 (d, J=1.5, 1H), 7.71 (dd, J=8.5, 1H), 7.53 (m, 1H), 7.43 (m, 3H), 7.35 (m, 3H), 7.11 (d, J=8, 1H), 6.72 (s, 1H), 4.56 (m, 2H), 4.21 (s, 3H), 4.03 (m, 1H), 3.71 (m, 11H), 2.65 (m, 2H), 2.55 (m, 2H), 1.89 (m, 2H), 1.80 (m, 1H).

Example 172 2-(2-(Hydroxymethyl)-3-(1-methyl-5-(5-(1-methylazetidin-3-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one 172

Example 172a 5-Bromo-1-methyl-3-(5-(1-methylazetidin-3-yl)pyridin-2-ylamino)pyridine-2(1H)-one 172a



155n 172a

A mixture of 3-(5-(azetidin-3-yl)pyridin-2-ylamino)-5-bromo-1-methylpyridin-2(1H)-one **155n** (469 mg, 1.4 mmol), 37% aqueous formaldehyde solution (4 g, 50 mmol), $NaBH_3CN$ (261 mg, 4.2 mmol), and 1M zinc chloride in 1,2-diethoxyethane (4 mL, 4.2 mmol) and methanol (40 mL) was stirred for 2 hours at room temperature. The mixture was added to water (20 mL) and extracted with methylene chloride (50 mL × 3). The organic layers were concentrated under reduced pressure. The residue was purified by column chromatography eluting with 10:1 methylene chloride/methanol to give **172a** as a yellow solid (0.3 g, 83%). MS: $[M+H]^+$ 348.

Example 172b 2-(1-Methyl-5-(5-(1-methylazetidin-3-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **172b**

A sealed tube was charged with the mixture of **172a** (167 mg, 0.48 mmol), 2-(2-(hydroxymethyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **114a** (231 mg, 0.48 mmol), $Pd(dppf)Cl_2$ (39 mg, 0.048 mmol), and Na_2CO_3 (101 mg, 0.96 mmol) in N,N-dimethylformamide (18 mL). The system was evacuated and then refilled with N_2. And the reaction mixture was heated at 150°C under microwave irradiation for 1 h. Then, the mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and the resulting residue was purified by column chromatography eluting with 15:1 methylene chloride/methanol to give **172b** as a brown solid (140 mg, 50%). MS: $[M+H]^+$ 606.

To a solution of **172b** (150 mg, 0.25mol) in THF/isopropyl acetate/H_2O (6 mL/6 mL/2 mL) was added LiOH (346 mg, 14 mmol) while stirring at room temperature. This mixture was stirred for 2 h. Then, 20 mL of water was added and the mixture was extracted with ethyl acetate (60 mL × 3). The combined organic layer was dried with Na_2SO_4 and concentrated to give a yellow solid, which was further purified by prep-HPLC to afford **172** as a white solid (50 mg, 35%). MS: $[M+H]^+$ 565. ^1H NMR (500 MHz, DMSO) δ 8.66 (s, 1H), 8.54 (s, 1H), 8.10 (s, 1H), 7.65 (d, J = 8, 1H), 7.46 (m, 1H), 7.31 (m, 4H), 6.51 (s, 1H), 4.84

(s, 1H), 4.33 (m, 2H), 4.13 (m, 3H), 3.85 (m, 1H), 3.59 (s, 3H), 3.53 (m, 2H), 3.35 (m, 1H), 3.02 (m, 2H), 2.60 (m, 2H), 2.46 (m, 2H), 2.23 (s, 3H),1.77 (m, 4H).

Example 173 10-[2-(hydroxymethyl)-3-(1-methyl-5-{[5-(4-methylpiperazin-1-yl)pyridin-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-9-one **173**

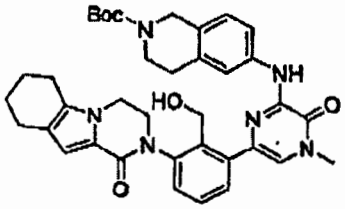
Example 173a 10-[2-(Acetoxymethyl)-3-(1-methyl-5-{[5-(4-methylpiperazin-1-yl)pyridin-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-9-one **173a**

In a 10-mL glass vessel equipped with a magnetic stirring bar were placed 1-methyl-3-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyridin-2-one **197e** (210 mg, 0.49 mmol), 10-[2-(acetoxymethyl)-3-bromophenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0 ^{2,6}]dodeca-2(6),7-dien-9-one **167f** (143 mg, 0.33 mmol), $Pd(PPh_3)_4$ (30 mg, 0.0.26 mmol) in 2 N Na_2CO_3 (2 mL) and 1,2-dimethoxyethane (5 mL). The vessel was sealed with a septum and placed into the microwave cavity. After the reaction mixture was stirred at 125 °C for 7 min., it was purified by flash chromatography (dichloromethane:methanol, 85:15) to give 26% (50 mg) of **173a** as a solid.

A 100-mL, single-necked, round-bottomed flask equipped with a magnetic stirring bar was charged with **173a** (50 mg, 0.077 mmol), $LiOH•H_2O$ (20 mg, 0.83 mmol), THF (2 mL), isopropanol (2 mL), and water (2 mL). After the reaction mixture was stirred at room temperature for 3 h, it was partitioned between dichloromethane (5 mL) and water (5 mL), and the organic phase was extracted with dichloromethane (3 X 5 mL). The combined organic phases were washed with water (5 mL x 2) and brine (5 mL x 1), dried (Na_2SO_4), and concentrated. The crude product was re-dissolved in dichloromethane (3 mL). To this solution was added hexane (10 mL) and the resulting precipitates were filtered to give 75% yield (35 mg) of **173**. MS(ESI^+) *m/z* 608.4 (M+H).

Example 174 2-(2-(hydroxymethyl)-3-(4-methyl-5-oxo-6-(1,2,3,4-tetrahydroisoquinolin-6-ylamino)-4,5-dihydropyrazin-2-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **174**

Example 174a tert-Butyl 6-(6-(2-(Acetoxymethyl)-3-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)phenyl)-4-methyl-3-oxo-3,4-dihydropyrazin-2-ylamino)-3,4-dihydroisoquinoline-2(1H)-carboxylate **174a**

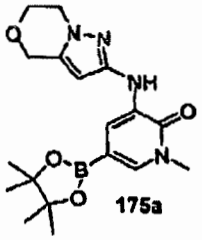


To a microwave tube equipped with a stirring bar, tert-butyl 6-(6-bromo-4-methyl-3-oxo-3,4-dihydropyrazin-2-ylamino)-3,4-dihydroisoquinoline-2(1H)-carboxylate **120a** (300 mg, 0.689 mmol), **114a** (352 mg, 0.758 mmol), $Pd(PPh_3)_4$ (39.8 mg, 0.0345 mmol), Na_2CO_3 aqueous solution (1.0 N, 2.27 mL, 2.27 mmol), 1,2-dimethoxyethane (3.5 mL) were added. The mixture was reacted in microwave at 130 °C for 10 min. methylene chloride (200 mL) was added and the resulting mixture was washed with water (30 mL X 3), brine (30 mL X 1), dried over $MgSO_4$, filtered, and removed solvent *in vacuo*. Silica gel column chromatography (methanol: methylene chloride = 5: 95) gave **174a**.

To a round-bottomed flask equipped with a stirring bar, **174a** and methylene chloride (50 mL) were added. The solution was cooled to 0 °C in an ice-water bath. TFA (1 mL) was added and the resulting solution was stirred overnight. Removed all the volatiles *in vacuo*, and to the bottle THF (10 mL), isopropanol (10 mL), water (10 mL), LiOH monohydrate (1.00 g) were added. The resulting mixture was stirred at RT for 1 hr. Tthe solvent was removed *in vacuo* and the resulting residue was added to methylene chloride (200 mL), the solution was washed with water (3 30 mL), brine (30 mL), dried over $MgSO_4$, filtered, and removed solvent *in vacuo*. Silica gel column chromatography (methanol: methylene chloride = 10: 90) gave **174** as a yellow solid, 28 mg. MS (ESI+) *m/z* 551.4 (M + H).

Example 175 10-[2-(Hydroxymethyl)-3-(1-methyl-6-oxo-5-{4H,6H,7H-pyrazolo[3,2-c][1,4]oxazin-2-ylamino}-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-9-one **175**

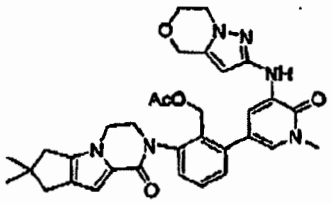
Example 175a 3-(6,7-Dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-2-ylamino)-1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one **175a**



175a

A sealed tube equipped with a magnetic stirrer was charged with 5-bromo-3-(6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-2-ylamino)-1-methylpyridin-2(1H)-one (110c) (250 mg, 0.77 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (290 mg, 1.2 mmol), potassium acetate (230 mg, 2.3 mmol) and 1,4-dioxane (5.5 mL). After bubbling nitrogen through the resulting suspension for 30 min, [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with CH_2Cl_2 (Pd Cl_2dppf:CH_2Cl_2 (1:1), 63 mg, 0.08 mmol) was then added, and the reaction was stirred at 105 °C for 90 min. After this time, the mixture was cooled to ambient temperature, partition between water (20 mL) and ethyl acetate (20 mL). The separated aqueous layer was extracted with yl acetate (2 X 10 mL). The combined organics were washed with brine (30 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting crude 175a was used in the next step without further purification.

Example 175b 10-[2-(Acetoxymethyl)-3-(1-methyl-6-oxo-5-{4H,6H,7H-pyrazolo[3,2-c][1,4]oxazin-2-ylamino}-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-9-one 175b



175b

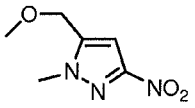
A microwave tube equipped with a magnetic stirrer was charged with 175a (120 mg, 0.31 mmol), 167f (130 mg, 0.3 mmol), 1,2-dimethoxyethane (4 mL) and 1M aqueous sodium carbonate (1 mL). After bubbling N_2 for 15 min, $Pd(PPh_3)_4$ (18 mg, 0.02 mmol) was added. The mixture was heated in microwave to 130 °C for 10 min. After this time, l acetate (5 mL) and water (5 mL) were added. The separated aqueous layer was extracted with l acetate (2 x 5 mL). The combined organics were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography eluting with a gradient of CH_2Cl_2 – 60:35:5 CH_2Cl_2:diethyl ether:methanol to afford a 74% yield (140 mg) of 175b

A 25 mL round bottom flask with a magnetic stirrer was charged with 175b (140 mg, 0.23 mmol), lithium hydroxide (49 mg, 1.2 mmol), THF (1.2 mL), *i*-PrOH (1.2 mL) and water (2.4 mL). The mixture stirred at rt for 90 min. After this time, ethyl acetate (5 mL)

and water (5 mL) were added. The separated aqueous layer was extracted with ethyl acetate (2 X 5 mL). The combined organics were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography eluting with a gradient of CH_2Cl_2 – 60:35:5 CH_2Cl_2:diethyl ether:methanol to afford a 79% yield (100 mg) of **175**. MS (ESI+) *m/z* 555.3 (M + H).

Example 176 2-(2-(Hydroxymethyl)-3-(5-(5-(methoxymethyl)-1-methyl-1H-pyrazol-3-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **176**

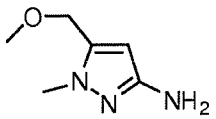
Example 176a 5-(Methoxymethyl)-1-methyl-3-nitro-1H-pyrazole **176a**



176a

A 250-mL single-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was charged with CH_3OH (50 mL), 5-(bromomethyl)-1-methyl-3-nitro-1H-pyrazole **156d** (8.8 g, 40 mmol) and CH_3ONa (4.3 g, 80 mmol). The reaction mixture was heated at reflux for 2 h. After this time the reaction was cooled to room temperature and concentrated. The residue was partitioned between ethyl acetate (60 mL) and water (60 mL). The aqueous layer was separated and extracted with ethyl acetate (50 mL ×2). The organic layers were combined, washed with brine (50 mL), and dried over sodium sulfate. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure to afford **176a** as a yellow oil (6.1 g, 90%). LCMS: $[M+H]^+$ 172.

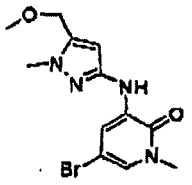
Example 176b 5-(Methoxymethyl)-1-methyl-1H-pyrazol-3-amine **176b**



176b

A 250-mL single-neck round-bottomed flask equipped with a magnetic stirrer was charged with **176a** (4 g, 23 mmol), Pd/C (1g) and C_2H_5OH (100 mL). The mixture was hydrogenated at room temperature for 15 h. It was then filtered and the filtrate was concentrated under reduced pressure to afford **176b** as a yellow oil (3.3 g, 99%), which was used in the next step without further purification. MS: $[M+H]^+$ 142.

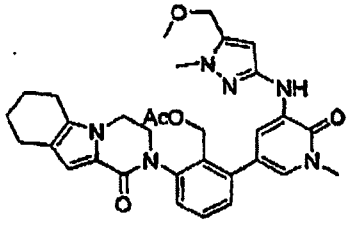
Example 176c 5-Bromo-3-(5-(methoxymethyl)-1-methyl-1H-pyrazol-3-ylamino)-1-methylpyridin-2(1H)-one **176c**



176c

Following Example 148a, 1.7 g of **176b** and 3.2 g of 3,5-dibromo-1-methylpyridin-2(1H)-one were reacted to give **176c** as a yellow solid (2.8 g, 70%). MS: $[M+H]^+$ 327. ^1H NMR (500 MHz, CDCl3) δ 7.86 (d, J = 2.5, 1H), 7.38 (s, 1H), 6.88 (d, J=2.5, 1H), 5.86 (s, 1H), 4.41 (s, 2H), 3.82 (s, 3H), 3.58 (s, 3H), 3.36 (s, 3H).

Example 176d 2-(5-(5-(Methoxymethyl)-1-methyl-1H-pyrazol-3-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **176d**



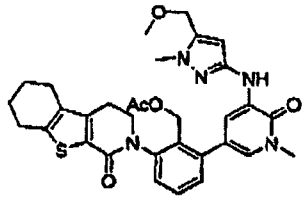
176d

Following Example 148b, 557 mg of 2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **114a** and 327 mg of 5-bromo-3-(5-(methoxymethyl)-1-methyl-1H-pyrazol-3-ylamino)-1-methylpyridin-2(1H)-one **176c** were reacted to give **176d** as a yellow solid (420 mg, 72%). LCMS: $[M+H]^+$ 585

Following Example 148, 240 mg of **176d** was converted to **176** as a white solid (133 mg, 60%). LCMS: $[M+H]^+$ 542. ^1H NMR (500 MHz, CDCl3) δ 7.91 (d, J=2, 1H), 7.43 (m, 3H), 7.30 (d, J = 2, 1H), 7.23 (s, 1H), 6.85 (s,1H), 5.96 (s, 1H), 4.60 (d, J=6, 1H), 4.40 (m, 3H), 4.16 (m, 3H), 3.94 (m, 1H), 3.76 (s, 3 H), 3.69 (s, 3H), 3.34 (s, 3H), 2.60 (m, 4H), 1.89 (m, 2H), 1.78 (m, 2H).

Example 177 5-[2-(Hydroxymethyl)-3-(5-{[5-(methoxymethyl)-1-methyl-1H-pyrazol-3-yl]amino}-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$]trideca-1(9),2(7)-dien-6-one **177**

Example 177a [2-(5-{[5-(Methoxymethyl)-1-methyl-1H-pyrazol-3-yl]amino}-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-6-{6-oxo-8-thia-5-azatricyclo[7.4.0.0^{2,7}]-trideca-1(9),2(7)-dien-5-yl}phenyl]methyl Acetate 177a



177a

Following Example 176d, 327 mg of 5-bromo-3-(5-(methoxymethyl)-1-methyl-1H-pyrazol-3-ylamino)-1-methylpyridin-2(1H)-one 176b and 481 mg of 111a were reacted to give 177a as a yellow solid (420 mg, 70%). LCMS: $[M+H]^+$ 602

Following Example 176, 240 mg of 177a was converted to 177 as a white solid (112 mg, 50%). LCMS: $[M+H]^+$ 560. ^1H NMR (500 MHz, CDCl3) δ 7.90 (s, 1H), 7.44-7.38 (m, 3H), 7.30-7.24 (m, 2H), 5.94 (s, 1H), 4.62 (d, J=11.5, 1H), 4.37 (m, 3H), 4.26 (d, J=10.5, 1H), 4.05 (m, 1H), 3.87 (m, 1H), 3.75 (s, 3H), 3.68 (s, 3 H), 3.34 (s, 3H), 2.85 (m, 4H), 2.54 (s, 2H), 1.89 (s, 5H).

Example 178 2-(5-fluoro-2-(hydroxymethyl)-3-(5-(5-(methoxymethyl)-1-methyl-1H-pyrazol-3-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one 178

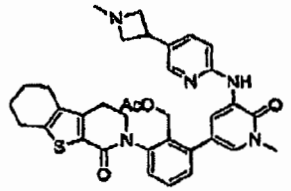
Example 178a 4-Fluoro-2-(5-(5-(methoxymethyl)-1-methyl-1H-pyrazol-3-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate 178a

A sealed tube was charged with the mixture of 4-fluoro-2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate 210d (230 mg, 0.48 mmol), 5-bromo-3-(5-(methoxymethyl)-1-methyl-1H-pyrazol-3-ylamino)-1-methylpyridin-2(1H)-one 176c (156 mg, 0.48 mmol), $Pd(dppf)Cl_2$ (39 mg, 0.048 mmol), Na_2CO_3 (101 mg, 0.96 mmol) in DMF (18 mL). The system was evacuated and then refilled with N_2. And the reaction mixture was heated at 110°C for 2h. Then, the mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and the resulting residue was purified by column chromatography eluting with 15:1 methylene chloride/methanol to give 178a as a brown solid (160 mg, 53%). MS: $[M+H]^+$ 603.

To a solution of 178a (160 mg, 0.27mol) in THF/iPA/H_2O (6 mL/6 mL/2 mL) was added LiOH (346 mg, 14 mmol) while stirring at room temperature. This mixture was stirred for 2 h. Then, 20 mL water was added and the mixture was extracted with ethyl acetate (60 mL ×3). The combined organic layer was dried with Na_2SO_4 and concentrated to give a yellow solid, which was further purified by prep-HPLC to afford 178 as a white solid (60 mg, 40%). LCMS: $[M+H]^+$ 561. ^1H NMR (500 MHz, DMSO) δ 8.16 (s, 1H), 7.99 (m, 1H), 7.32 (m, 2H), 7.18 (m, 1H), 6.52 (s, 1H), 6.11 (s, 1H), 4.89 (m, 1H), 4.38 (m, 2H), 4.31 (m, 2H), 4.17 (m, 3H), 3.90 (m, 1H), 3.64 (s, 3H), 3.57 (s, 3H), 3.26 (s, 3H), 2.63 (m, 2H), 2.51 (m, 2H), 1.70 (m, 4H).

Example 179 5-[2-(Hydroxymethyl)-3-(1-methyl-5-{[5-(1-methylazetidin-3-yl)pyridin-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$]-trideca-1(9),2(7)-dien-6-one 179

Example 179a [2-(1-Methyl-5-{[5-(1-methylazetidin-3-yl)pyridin-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)-6-{6-oxo-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$]trideca-1(9),2(7)- dien-5-yl}phenyl]methyl Acetate 179a



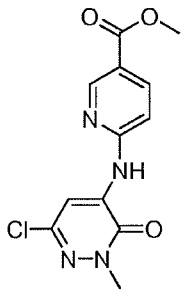
179a

Following Example 176d, 5-bromo-1-methyl-3-(5-(1-methylazetidin-3-yl)pyridin-2-ylamino)pyridin-2(1H)-one 172a and (2-{6-oxo-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$]trideca-1(9),2(7)-dien-5-yl}-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl acetate 111a were reacted to give 179a in 55% yield. LCMS: $(M+H)^+$ 624

Following Example 176, 179a was converted to 179 in 42% yield. LCMS: $(M+H)^+$ 582. ^1H NMR (500 MHz, MEOD) δ 8.73 (s, 1H), 8.17 (s, 1H), 7.74 (m, 1H), 7.51 (m, 1H), 7.40 (m, 3H), 7.10 (d, J=3.5, 1H), 4.55 (m, 2H), 4.31 (m, 2H), 4.13 (m, 1H), 4.06 (s, 3H), 3.99 (m, 1H), 3.71 (s, 3H), 3.05 (m, 1H), 2.94 (m, 6H), 2.59 (m, 2H), 1.89 (m, 4H).

Example 180 6-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-2-methyl-4-[(5-{[methyl(propan-2-yl)amino]methyl}pyridine-2-yl)amino]-2,3-dihydropyridazin-3-one 180

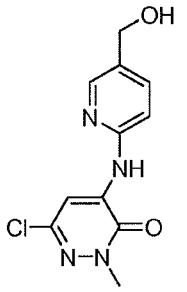
Example180a Methyl 6-(6-Chloro-2-methyl-3-oxo-2,3-dihydropyridazin-4-ylamino)nicotinate 180a



180a

Following Example 186b, 4-bromo-6-chloro-2-methylpyridazin-3(2H)-one **103e** (4.0g, 17.9mmol), **186a** (2.7g, 17.9mmol), cesium carbonate (12.8g, 39.4mmol), and Xantphos (880mg, 8.5mol%), dioxane (120ml) and tris(dibenzylideneacetone)dipalladium(0) (820mg, 5mol%) were reacted to give **180a** (3.0g, 57% yield).

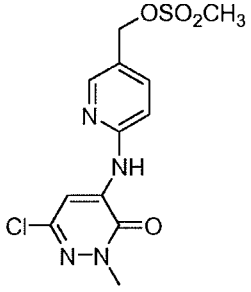
Example 180b 6-Chloro-4-(5-(hydroxymethyl)pyridin-2-ylamino)-2-methylpyridazin-3(2H)-one **180b**



180b

Following Example 186c, **180a** (3.0g, 10.2mmol), methylene chloride (100mL) and 1.0M DIBAL-H in methylene chloride (30.5mL, 30.5mmol) were reacted to give **180b** (2.3g, 86% yield).

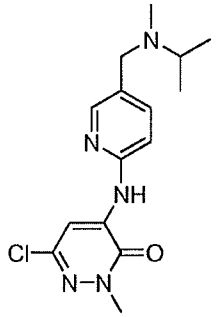
Example 180c (6-(6-chloro-2-methyl-3-oxo-2,3-dihydropyridazin-4-ylamino)pyridin-3-yl)methyl methanesulfonate **180c**



180c

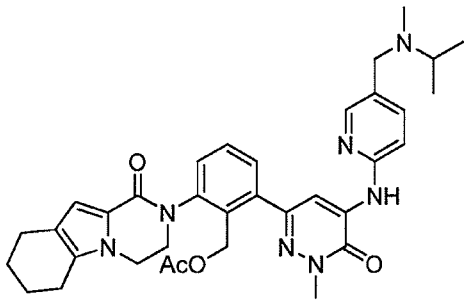
Intermediate **180b** was treated with methanesulfonyl chloride and diisopropylethylamine in methylene chloride at 0 °C to give **180c**.

Example 180d 6-Chloro-4-(5-((isopropyl(methyl)amino)methyl)pyridin-2-ylamino)-2-methylpyridazin-3(2H)-one **180d**



Following Example 186c, **180c** and methylisopropylamine were reacted to give **180d**.

Example 180e 2-(5-(5-((isopropyl(methyl)amino)methyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **180e**



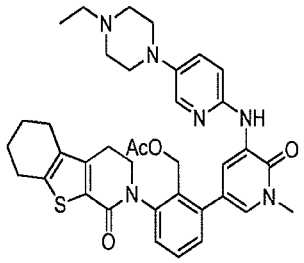
180e

Following Example 179a, **180d** (125mg, 0.39mmol), **114a** (215mg, 0.47mmol), 1N Na_2CO_3 (0.86mL) and tetrakis(trihenyl-phosphine)palladium(0) (23mg, 5mol%) were reacted to give **180e** (150mg, 61% yield).

Following Example 179, **180e** (150mg, 0.24mmol), 1N LiOH (1.2mL), THF (2mL) and isopropanol (2mL) were reacted and the mixture was purified via column chromatography, silica, methanol/methylene chloride to give **180** (105mg, 75% yield). MS (ESI+) *m/z* 582.5 (M + H).

Example 181 5-[3-(5-{[5-(4-Ethylpiperazin-1-yl)pyridine-2-yl]amino}-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-(hydroxymethyl)phenyl]-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$]trideca-1(9),2(7)-dien-6-one **181**

Example 181a 5-[3-(5-{[5-(4-Ethylpiperazin-1-yl)pyridine-2-yl]amino}-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-(acetoxymethyl)phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one **181a**

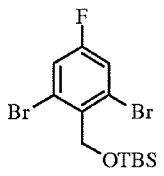


To a microwave tube equipped with a stirring bar, 5-bromo-3-(5-(4-ethyl-piperazin-1-yl)pyridin-2-ylamino)-1-methylpyridin-2(1H)-one **138c** (250 mg, 0.637 mmol), boronic ester **111a** (308 mg, 0.701 mmol), $Pd(PPh_3)_4$ (36.8 mg, 0.0319 mmol), Na_2CO_3 aqueous solution (1.0 N, 2.10 mL, 2.10 mmol), 1,2-dimethoxyethane (3.0 mL) were added. The mixture was reacted in microwave at 130 °C for 10 min. methylene chloride (200 mL) was added and the resulting mixture was washed with water (3 X 30 mL), brine (30 mL X 1), dried over $MgSO_4$, filtered, and removed solvent *in vacuo*. Silica gel column chromatography (methanol: methylene chloride = 5: 95) gave **181a**.

To a round-bottomed flask equipped with a stirring bar, **181a**, THF (5 mL), isopropanol (5 mL), water (5 mL), LiOH monohydrate (300 mg) were added. The resulting mixture was stirred at RT for 1 hr. Removed all the solvent *in vacuo* and the resulting residue was added to methylene chloride (200 mL), the solution was washed with water (30 mL X 3), brine (30 mL X 1), dried over $MgSO_4$, filtered, and removed solvent *in vacuo*. Silica gel column chromatography (methanol: methylene chloride = 10: 90) gave **181** as a brick red solid, 101 mg, MS (ESI+) *m/z* 625.4 (M + H).

Example 182 5-(3-(6,6-Dimethyl-3,4,6,7-tetrahydro-5*H*-cyclopenta[4,5]thieno[2,3-*c*]pyridine-1(2*H*)-yl)-5-fluoro-2-(hydroxymethyl)phenyl)-1-methyl-3-(pyrimidin-4-ylamino)pyridin-2(1*H*)-one **182**

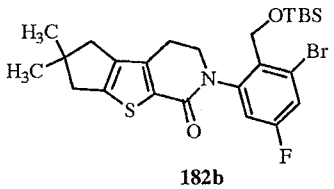
Example 182a *tert*-Butyl(2,6-dibromo-4-fluorobenzyloxy)dimethylsilane **182a**



182a

A 250-mL single-neck round-bottomed flask equipped with a magnetic stirrer was purged with nitrogen and charged with **197b** (5.00 g, 17.6 mmol), imidazole (6.00 g, 88.0 mmol) and methylene chloride (125 mL). *tert*-butyldimethylsilyl chloride (7.96 g, 52.8 mmol) was added, and the reaction mixture was stirred at room temperature for 16 h. After this time, the reaction was diluted with water (100 mL) and methylene chloride (100 mL). The layers were separated, and the aqueous phase was extracted with methylene chloride (100 mL). The organic extracts were combined and dried over sodium sulfate. The drying agent was removed by filtration, and the solvent was evaporated under reduced pressure. The resulting residue was purified by flash chromatography to afford a 96% yield (6.75 g) of **182a** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, 2H, J = 8.0 Hz), 4.93 (s, 2H), 0.93 (s, 9H), 0.15 (s, 6H).

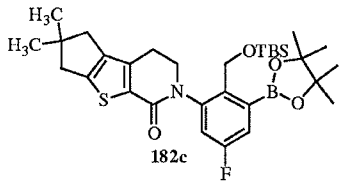
Example 182b 2-(3-Bromo-2-((*tert*-butyldimethylsilyloxy)methyl)-5-fluorophenyl)- 6-(6,6-dimethyl-3,4,6,7-tetrahydro-5*H*-cyclopenta[4,5]thieno [2,3-*c*]pyridin-1(2*H*)-one **182b**



182b

A 250-mL single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was charged with **105h** (400 mg, 1.81 mmol), **182a** (1.44 g, 3.62 mmol), cesium carbonate (1.18 g, 3.62 mmol), *N,N'*-dimethylethylenediamine (159 mg, 1.81 mmol) and 1,4-dioxane (15 mL). After bubbling nitrogen through the resulting suspension for 30 min, copper iodide (174 mg, 0.905 mmol) was added. A reflux condenser was attached to the flask, and the reaction mixture was heated at 100 °C for 16 h. After this time, the mixture was cooled to room temperature and filtered. The filtrate was diluted with ethyl acetate (100 mL) and water (50 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 30 mL), and the combined organic layers were washed with brine (100 mL) and dried over sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography to afford **182b** in 57% yield (554 mg) as a white solid: mp 38–39 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (dd, 1H, J = 8.0, 2.5 Hz), 7.00 (dd, 1H, J = 8.0, 2.5 Hz), 4.74 (s, 2H), 3.93 (m, 2H), 2.98 (m, 1H), 2.80 (m, 1H), 2.77 (s, 2H), 2.52 (s, 2H), 1.28 (s, 3H), 1.27 (s, 3H), 0.89 (s, 9H), 0.11 (s, 6H).

Example 182c 2-((*tert*-Butyldimethylsilyloxy)methyl)-5-fluorophenyl- 6-(6,6-dimethyl-3,4,6,7-tetrahydro-5*H*-cyclopenta[4,5]thieno[2,3-*c*]pyridin-1(2*H*)-yl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl-one **182c**



182c

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was charged with **182b** (554 mg, 1.03 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane (785 mg, 3.09 mmol), potassium acetate (404 mg, 4.12 mmol) and 1,4-dioxane (8 mL). After bubbling nitrogen through the resulting suspension for 30 min, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (75 mg, 0.103 mmol) was added. A reflux condenser was attached to the flask, and the reaction mixture was heated at reflux for 8 h. After this time, the mixture was diluted with ethyl acetate (100 mL) and water (75 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 X 50 mL), and the combined organic layers were washed with brine (100 mL) and dried over sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography to afford **182c** in 91% yield (600 mg) as a white solid: mp 41–42 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (dd, 1H, J = 8.0, 2.5 Hz), 7.02 (dd, 1H, J = 8.0, 2.5 Hz), 5.14 (d, 1H, J = 10.5 Hz), 5.70 (d, 1H, J = 10.5 Hz), 3.93 (m, 2H), 2.98 (m, 1H), 2.80 (m, 1H), 2.77 (s, 2H), 2.52 (s, 2H), 1.34 (s, 3H), 1.33 (s, 3H), 1.26 (s, 12H), 0.84 (s, 9H), 0.04 (s, 6H).

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was purged with nitrogen and charged with **182c** (300 mg, 0.513 mmol), **109b** (111 mg, 0.394 mmol), sodium carbonate (125 mg, 1.18 mmol), 1,4-dioxane (8 mL) and water (2 mL). This mixture was degassed with nitrogen for 30 min. Tetrakis-(triphenylphosphine)palladium(0) (46 mg, 0.039 mmol) was added. After heating at reflux for 2 h, the reaction mixture was cooled to room temperature and partitioned between water (40 mL) and methylene chloride (100 mL). The layers were separated, and the aqueous phase was extracted with methylene chloride (2 x 50 mL). The organic extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was dissolved in THF (3 mL), and tetrabutyl-ammonium fluoride trihydrate (372 mg, 1.18 mmol) was added. After stirring at room temperature for 2 h, the reaction

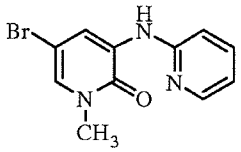
mixture was partitioned between water (20 mL) and methylene chloride (20 mL). The layers were separated, and the aqueous phase was extracted with methylene chloride (2 × 20 mL). The organic extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography to afford **182** in 41% yield (88 mg) as an off-white solid: mp >250 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.22 (s, 1H), 8.72 (d, 1H, J = 2.0 Hz), 8.65 (s, 1H), 8.29 (d, 1H, J = 6.0 Hz), 7.57 (d, 1H, J = 2.0 Hz), 7.34 (dd, 1H, J = 8.5, 3.0 Hz), 7.31 (d, 1H, J = 6.0 Hz), 7.29 (dd, 1H, J = 8.5, 3.0 Hz), 4.87 (m, 1H), 4.31 (m, 2H), 4.04 (m, 1H), 3.84 (m, 1H), 3.60 (s, 3H), 3.03 (m, 1H), 2.89 (m, 1H), 2.75 (s, 2H), 2.53 (m, 2H), 1.23 (s, 6H); MS (ESI+) *m/z* 546.2 (M+H).

Example 183 5-(3-(6,6-Dimethyl-3,4,6,7-tetrahydro-5*H*-cyclopenta[4,5]thieno[2,3-*c*]pyridine-1(2*H*)-yl)-2-(hydroxymethyl)phenyl)-1-methyl-3-(6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazin-3-ylamino)pyridin-2(1*H*)-one **183**

Following Example 184, reaction of **131a** (300 mg, 0.606 mmol) with **110c** (151 mg, 0.466 mmol) gave a 51% yield (129 mg) of **183** as an off-white solid: mp 167–168 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.18 (s, 1H), 7.95 (d, 1H, J = 2.0 Hz), 7.44 (t, 1H, J = 8.0 Hz), 7.33 (dd, 1H, J = 8.0, 1.0 Hz), 7.29 (dd, 1H, J = 8.0, 1.0 Hz), 7.23 (d, 1H, J = 2.0 Hz), 5.92 (s, 1H), 4.81 (m, 1H), 4.71 (s, 2H), 4.36 (m, 2H), 4.01 (m, 3H), 3.94 (m, 2H), 3.85 (m, 1H), 3.57 (s, 3H), 3.02 (m, 1H), 2.86 (m, 1H), 2.75 (m, 2H), 2.53 (m, 2H), 1.23 (s, 6H); MS (ESI+) *m/z* 572.3 (M+H).

Example 184 5-(3-(6,6-Dimethyl-3,4,6,7-tetrahydro-5*H*-cyclopenta[4,5]thieno[2,3-*c*]pyridine-1(2*H*)-yl)-2-(hydroxymethyl)phenyl)-1-methyl-3-(pyridin-2-ylamino)pyridin-2(1*H*)-one **184**

Example 184a 5-Bromo-1-methyl-3-(pyridin-2-ylamino)pyridin-2(1*H*)-one **184a**



184a

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer, nitrogen inlet and reflux condenser was charged with 3,5-dibromo-1-methylpyridin-2(1H)-one (936 mg, 3.51 mmol), 2-aminopyridine (300 mg, 3.19 mmol), cesium carbonate (3.11 g, 9.57 mmol) and 1,4-dioxane (20 mL). After bubbling nitrogen through the resulting solution for 20 minutes, Xantphos (184 mg, 0.319 mmol) and

tris(dibenzylideneacetone)dipalladium(0) (146 mg, 0.160 mmol) were added, and the reaction mixture was heated at 100 °C for 3 h. After this time, the reaction was cooled to room temperature, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography to afford a 42% yield (376 mg) of **184a** as an off-white solid: mp 153–154 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.75 (s, 1H), 8.69 (d, 1H, J = 2.4 Hz), 8.26 (dd, 1H, J = 5.4, 1.5 Hz), 7.61 (m, 1H), 7.54 (d, 1H, J = 2.4 Hz), 7.33 (d, 1H, J = 5.4 Hz), 6.86 (m, 1H), 3.45 (s, 3H).

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was purged with nitrogen and charged with **131a** (300 mg, 0.606 mmol), **184a** (131 mg, 0.466 mmol), sodium carbonate (148 mg, 1.40 mmol), 1,4-dioxane (8 mL) and water (2 mL). This mixture was degassed with nitrogen for 30 min. Tetrakis(triphenylphosphine)palladium (54 mg, 0.047 mmol) was added. After heating at 100 °C for 3 h, the reaction mixture was cooled to room temperature and partitioned between water (40 mL) and methylene chloride (100 mL). The layers were separated, and the aqueous phase was extracted with methylene chloride (2 × 50 mL). The organic extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was dissolved in methanol (5 mL), and potassium carbonate (500 mg, 3.62 mmol) was added. After stirring at room temperature for 2 h, the reaction mixture was partitioned between water (20 mL) and methylene chloride (20 mL). The layers were separated, and the aqueous phase was extracted with methylene chloride (2 × 20 mL). The organic extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography to afford **184** in 49% yield (118 mg) as a white solid: mp 150–151 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.66 (d, 1H, J = 2.0 Hz), 8.57 (m, 1H), 8.16 (dd, 1H, J = 5.0, 1.0 Hz), 7.57 (m, 1H), 7.45 (t, 1H, J = 8.0 Hz), 7.38 (d, 1H, J = 2.0 Hz), 7.36–7.31 (m, 2H), 7.28 (d, 1H, J = 8.0 Hz), 6.78 (dd, 1H, J = 11.0, 5.0 Hz), 4.82 (m, 1H), 4.35 (m, 2H), 4.02 (m, 1H), 3.86 (m, 1H), 3.59 (s, 3H), 3.01 (m, 1H), 2.87 (m, 1H), 2.75 (s, 2H), 2.53 (m, 2H), 1.23 (s, 6H); MS (ESI+) *m/z* 527.2 (M+H).

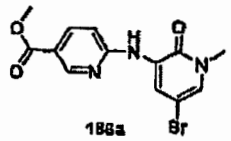
Example 185 5-(3-(6,6-Dimethyl-3,4,6,7-tetrahydro-5*H*-cyclopenta[4,5]thieno[2,3-*c*]pyridine-1(2*H*)-yl)-2-(hydroxymethyl)phenyl)-1-methyl-3-(1,5-dimethyl-1*H*-pyrazol-4-ylamino)pyridin-2(1*H*)-one **185**

Using the same general procedure as described for the preparation of **184**, reaction of **131a** (300 mg, 0.606 mmol) with **142a** (138 mg, 0.466 mmol) gave a 41% yield (104 mg) of **185** as a yellow solid: mp 164–165 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.93–7.92 (m, 2H),

7.44 (t, 1H, J = 7.5 Hz), 7.33 (dd, 1H, J = 7.5, 1.0 Hz), 7.29 (dd, 1H, J = 7.5, 1.0 Hz), 7.21 (d, 1H, J = 2.0 Hz), 5.88 (s, 1H), 4.83 (m, 1H), 4.36 (m, 2H), 4.02 (m, 1H), 3.87 (m, 1H), 3.57 (s, 3H), 3.56 (s, 3H), 3.03 (m, 1H), 2.86 (m, 1H), 2.75 (m, 2H), 2.53 (m, 2H), 2.17 (s, 3H), 1.23 (s, 6H); MS (ESI+) *m/z* 544.2 (M+H).

Example 186 2-(2-(Hydroxymethyl)-3-(5-(5-((isopropyl(methyl)amino)methyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **186**

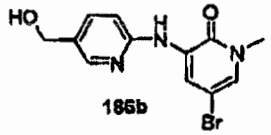
Example 186a Methyl 6-(5-Bromo-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)nicotinate **186a**



186a

In a 300mL sealed tube was placed 3,5-dibromo-1-methylpyridin-2(1H)-one (4.0g, 15.0mmol), methyl 6-aminonicotinate (2.3g, 15.0mmol), cesium carbonate (10.7g, 33mmol), and Xantphos (740mg, 8.5mol%). The flask was evacuated and filled with nitrogen 3X. Dioxane (100ml) was added and the mixture degassed for 25min with bubbling nitrogen. Tris(dibenzylideneacetone)dipalladium(0) (690mg, 5mol%) was then added, the vessel sealed and the reaction heated to 120 °C overnight. The reaction was cooled and diluted with Ethyl acetate (500mL) and saturated aqueous $NaHCO_3$ (150mL), the layers were separated and extracted ethyl acetate 2X. The organics were washed with brine 3X, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by chromatography: ISCO 80g silica, ethyl acetate/hexanes, to give **186a**.

Example 186b 5-bromo-3-(5-(hydroxymethyl)pyridin-2-ylamino)-1-methylpyridin-2(1H)-one **186b**

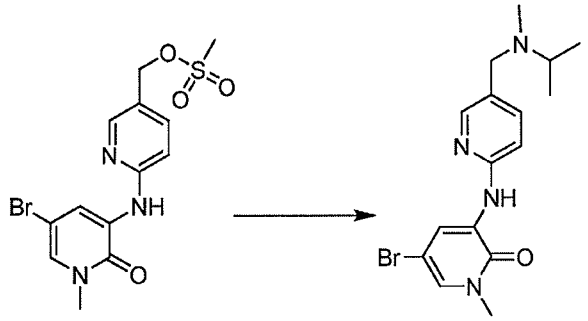


186b

In a flask under N_2, **186a** (500mg, 1.5mmol) was suspended in methylene chloride and cooled to -78°C in a dry ice/acetone bath. 1.0M DIBAL-H in methylene chloride (4.4mL, 4.4mmol) was slowly added via syringe. After the addition was complete the reaction was allowed to warm to -20°C at which time the dry ice/acetone bath was exchanged for a ice/water bath and the reaction stirred an additional 0.5 hr at which time it was slowly

quenched with 1N HCl (~5mL). The reaction was then diluted with ethyl acetate and allowed to stir and warm to room temp over ~1hr. The pH was adjusted to ~7 with 1N NaOH and 50mL of saturated aqueous Rochelle's salt was added and the mixture heated and stirred at 40°C for 1hr during which time the mixture cleared. The layers were separated, the organics washed with brine, dried over Na_2SO_4, filtered and concentrated to give **186b** as a white solid (420mg, 90% yield).

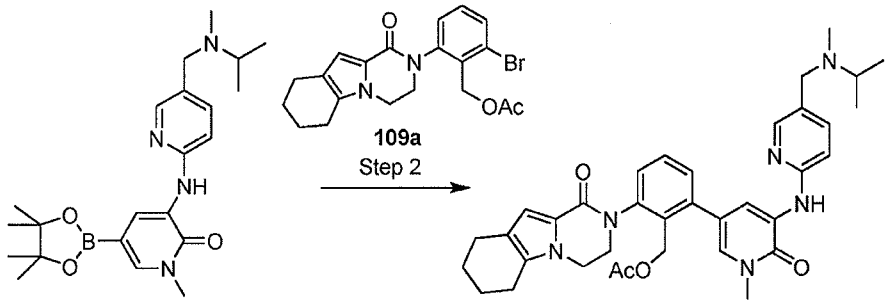
Example 186d 5-Bromo-3-(5-((isopropyl(methyl)amino)methyl)pyridin-2-ylamino)-1-methylpyridin-2(1H)-one **186d**



186c **186d**

In a flask under N_2, **186b** (350mg, 1.13mmol) was suspended in methylene chloride (20mL) then di-isopropylethylamine (0.89mL, 5.09mmol) was added and the reaction cooled to 0°C in an ice/water bath. Methanesulfonyl chloride (518mg, 0.35mL, 4.52mmol) was added and the reaction allowed to warm to room temp and stir for ~1hr. The reaction was diluted with methylene chloride and saturated aqueous sodium bicarbonate was added. The layers were separated and the organics again washed with bicarb then dried over anh. magnesium sulfate, filtered and concentrated to give the mesylate **186c** which was used directly to produce **186d** by dissolving **186c** in DMF (10mL) and transfering the solution to a pressure flask whereupon N-methylpropan-2-amine (1.2mL, 830mg, 11.3mmol) was added, the flask sealed, and heated to 80°C overnight. The reaction was allowed to cool then diluted with ethyl acetate and water and the layers separated. The organics were washed with brine 4X, dried over Na_2SO_4, filtered and concentrated to give **186d**.

Example 186f 2-(5-(5-((Isopropyl(methyl)amino)methyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **186f**



186e 186f

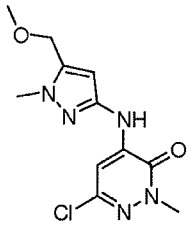
Step1: In a pressure flask was placed **186d** (205mg, 0.56mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (213mg, 0.84mmol), potassium acetate (220mg, 2.24mmol) and 1,1'-bis(diphenylphosphino)ferrocene-palladium (II) dichloride dichloromethane complex (817mg, 0.1mol%). The flask was evacuated and filled with N_2 3X, dioxane (5mL) was added, the vessel sealed and heated to 90°C for ~3hrs. The reaction was allowed to cool then diluted with ethyl acetate, and filtered through a pad of celite and concentrated under reduced pressure to give **186e** which was used directly in the next step.

Step 2: **186e** was dissolved in DME (5mL) and transferred to a pressure flask containing **109a** (187mg, 0.45mmol), 1N Na_2CO_3 (1.2ml) and tetrakis(tripheny-phosphine)palladium(0) (32mg, 5mol%). The flask was sealed and heated to 100°C overnight. The reaction was then diluted with ethyl acetate and water, separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by chromatography: ISCO 12g silica, eluting with methanol and CH_2Cl_2, to give **186f** (110mg, 32% yield over 2 steps).

Following Example 119, **186f** (110mg, 0.18mmol), 1N LiOH (0.88mL), THF (2mL) and isopropanol (2mL) were reacted and purified via column chromatography, ISCO 12g silica, methanol / methylene chloride to give **186** (80mg, 77% yield). MS (ESI+) *m/z* 581.4 (M + H).

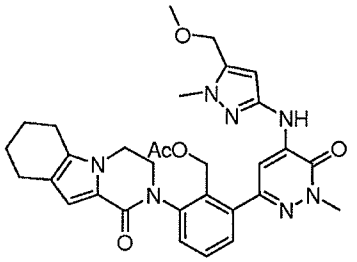
Example 187 2-(2-(Hydroxymethyl)-3-(5-(5-(methoxymethyl)-1-methyl-1H-pyrazol-3-ylamino)-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **187**

Example 187a 6-Chloro-4-(5-(methoxymethyl)-1-methyl-1H-pyrazol-3-ylamino)-2-methylpyridazin-3(2H)-one **187a**



A mixture of 5-(methoxymethyl)-1-methyl-1H-pyrazol-3-amine **176b** (600 mg, 4.26 mmol), XantPhos (300 mg, 0.51 mmol), Pd_2dba_3 (310 mg, 0.34 mmol), 4-bromo-6-chloro-2-methylpyridazin-3(2H)-one (**103e**) (1.22 g, 5.53 mmol) and Cs_2CO_3 (4.2 g. 12.8 mmol) in 1,4-dioxane (40 mL) was heated at reflux for 2 h. After the completion of the reaction, the mixture was filtered off and washed with methanol (100 mL). The filtrate was evaporated in *vacuo* and the residue was purified on reverse phase Combi-flash to give **187a** (1.13 g, 94%). MS: $[M+H]^+$ 284.

Example 187b 2-(5-(5-(Methoxymethyl)-1-methyl-1H-pyrazol-3-ylamino)-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **187b**



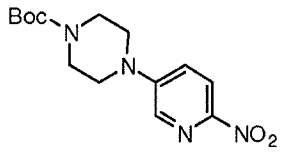
A mixture of 6-chloro-4-(5-(methoxymethyl)-1-methyl-1H-pyrazol-3-ylamino)-2-methylpyridazin-3(2H)-one **187a** (300 mg, 1.06 mmol), 2-(acetoxy-methyl)-3-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)phenylboronic acid **114a** (500 mg, 1.3 mmol), $PdCl_2$(dppf) (116 mg, 0.16 mmol), K_3PO_4 (100 mg), and NaOAc (50 mg) in MeCN (15 mL) and water (3 mL) was heated at reflux for 2 h. The solvent was evaporated in *vacuo* and the residue was purified on reverse phase Combi-flash to **187b** (310 mg, 50%). MS: $[M+H]^+$ 586.

A mixture of **187b** (310 mg, 0.53 mmol) and LiOH hydrate (222 mg, 5.3 mmol) in isopropanol (20 mL) and water (4 mL) was stirred at 30°C for 2 h. The mixture was evaporated in *vacuo* and the residue was extracted with ethyl acetate (20 mL × 2). The combined extracts were concentrated under reduced pressure. The residue was purified on prep-HPLC to give **187** (103 mg, 36%). MS: $[M+H]^+$ 544. ^1H NMR (500 MHz, DMSO) δ 9.25 (s, 1H), 7.89 (s, 1H), 7.50-7.47 (m, 1H), 7.42-7.38 (m, 2H), 6.51 (s, 1H), 6.22 (s, 1H),

4.63-4.60 (m, 1H), 4.48-4.45 (m, 1H), 4.40-4.35 (m, 3H), 4.20-4.05 (m, 3H), 3.90-3.86 (m, 1H), 3.75 (s, 3H), 3.67 (s, 3H), 3.26 (s, 3H), 2.65-2.54 (m, 2H), 2.48-2.42 (m, 2H), 1.84-1.74 (m, 2H), 1.74-1.64 (m, 2H).

Example 188 2-(2-(Hydroxymethyl)-3-(1-methyl-5-(5-(4-(oxetan-3-yl)piperazin-1-yl)pyridine-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **188**

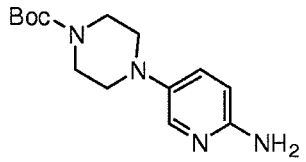
Example 188a *tert*-Butyl 4-(6-Nitropyridin-3-yl)piperazine-1-carboxylate **188a**



188a

Into a solution of 5-bromo-2-nitropyridine (30 g, 148 mmol) in DMSO (1 L) were added K_2CO_3 (40 g, 296 mmol) and *tert*-butyl piperazine-1-carboxylate (28g, 148 mmol). The mixture was stirred at 65 degree for overnight. After cooling down, it was poured into water (2 L). The solid precipitated was collected and dried under vacuum. It was then further purified by flash column eluting with 20:1 petroleum ether/ethyl acetate and then with methylene chloride to give **188a** as a yellow solid (17 g, 37%). MS: $[M+H]^+$ 309.

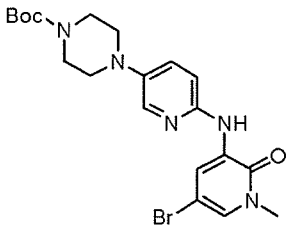
Example 188b *tert*-Butyl 4-(6-Aminopyridin-3-yl)piperazine-1-carboxylate **188b**



188b

A 500-mL bottle was purged with nitrogen and charged with **188a** (3.1 g, 10 mmol), 10% palladium on carbon (50% wet, 1.0 g) and ethanol (100 mL). It was evacuated, charged with hydrogen gas, and stirred for 16 h at room temperature. The hydrogen was then evacuated and nitrogen was charged into the bottle. The catalyst was removed by filtration through a pad of Celite and the filtrate concentrated under reduced pressure to afford **188b** (2.7 g, 97%). MS: $[M+H]^+$ 279

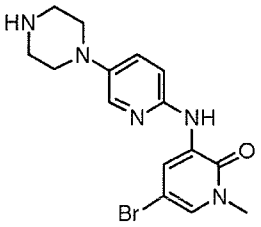
Example 188c *tert*-Butyl 4-(6-(5-bromo-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)pyridine-3-yl)piperazine-1-carboxylate **188c**



188c

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was charged with 1,4-dioxane (50 mL), **188b** (1.3 g, 4.7 mmol), 3,5-dibromo-1-methylpyridin-2(1H)-one (1.24 g, 4.7 mmol), and cesium carbonate (3.8 g, 12 mmol). After bubbling nitrogen through the resulting mixture for 30 minutes, XantPhos (272 mg, 0.47 mmol) and tris(dibenzylideneacetone)dipalladium(0) (430 mg, 0.47 mmol) were added, and the reaction mixture was heated at reflux for 3 h. After this time the reaction was cooled to room temperature, partitioned between ethyl acetate (100 mL) and water (100 mL), and filtered. The aqueous layer was separated and extracted with ethyl acetate (50 mL × 2). The organic layers were combined, washed with brine (50 mL), and dried over sodium sulfate. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified on flash column eluting with 50:1 methylene chloride/methanol to afford **188c** (1.3 g, 59%). MS: $[M+H]^+$ 464.

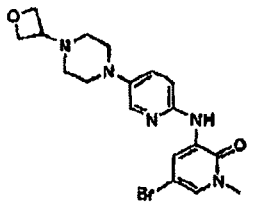
Example 188d 5-Bromo-1-methyl-3-(5-(piperazin-1-yl)pyridin-2-ylamino)pyridin-2(1H)-one **188d**



188d

A mixture of **188c** (3.6 g, 7.8 mmol) and 4.0 M HCl/dioxane (10 mL) was stirred for 5 h at room temperature. It was then concentrated at reduced pressure. The residue was basified with aqueous 1.0M NaOH and extracted with methylene chloride. The combined organic layers were washed with water and concentrated under reduced pressure to give **188d** (2.46 g, 87%). MS: $[M+H]^+$ 364.

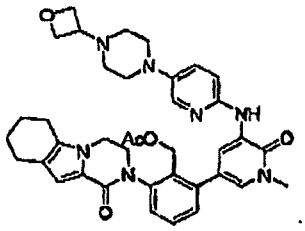
Example 188e 5-Bromo-1-methyl-3-(5-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-2-ylamino)pyridin-2(1H)-one **188e**



188e

A mixture of **188d** (2.75 g, 7.5 mmol), oxetan-3-one (1.6 g, 22.7 mmol), $NaBH_3CN$ (4.75 g, 22.5 mmol), and zinc chloride (3 g, 22.7 mmol) in methanol (125 mL) was stirred for 5 hours at 50 degree. The mixture was added to water and extracted with methylene chloride for three times. The organic layers were concentrated under reduced pressure. The residue was purified by column chromatography eluting with 25:1 methylene chloride/methanol to give **188e** (1.92 g, 61%). MS: $[M+H]^+$ 420. ^1H NMR (500 MHz, DMSO) δ 8.58 (d, J = 2.5, 1H), 8.55 (s, 1H), 7.94 (d, J = 3, 1H), 7.54 (d, J = 2.5, 1H), 7.39 (dd, J = 3, 1H), 7.25 (d, J = 4, 1H), 4.56 (t, J = 6.5, 2H), 4.46 (t, J = 6.5, 2H), 3.50 (s, 3H), 3.43 (m, 1 H), 3.01 (m, 4H), 2.40 (m, 4H).

Example 188f 2-(1-Methyl-5-(5-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **188f**



188f

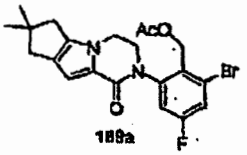
Following Example 148b, 464 mg of 2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **114a** and 420 mg of **188e** were reacted to give **188f** as a yellow solid (360 mg, 54%). LCMS: $[M+H]^+$ 678

Following Example 148, 270 mg of **188f** was converted to **188** as a white solid (144 mg, 54%). LCMS: $[M+H]^+$ 635. ^1H NMR (500 MHz, CDCl3) δ: 8.55 (d, J=2.5, 1H), 7.89 (d, J=3, 1H), 7.80 (s,1H), 7.47-7.41 (m, 3H), 7.26-7.21 (m,2H), 6.85 (s, 1H), 6.83 (d, J=8.5, 1H), 4.72-4.65 (m, 3H), 4.59 (d,J=10.5, 1H), 4.43-4.36 (m, 2H), 4.20-4.13 (m, 3 H), 3.93-3.89 (m,

1H), 3.59-3.57 (m, 1H), 3.15 (s, 3H), 3.05 (m, 1H), 2.6-2.51 (m, 7H), 1.89 (s, 2H), 1.78 (S, 2H).

Example 189 10-[5-Fluoro-2-(hydroxymethyl)-3-[1-methyl-6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydropyridin-3-yl]phenyl]-4,4-dimethyl-1,10-diazatricyclo-[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-9-one 189

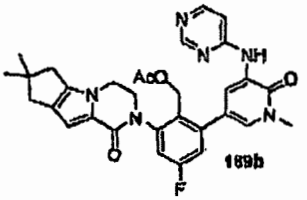
Example 189a 2-Bromo-4-fluoro-6-(9-oxo-4,4-dimethyl-1,10diazatricyclo[6.4.0.$0^{2,6}$]-dodeca-2(6),7-dien-10-yl)benzyl Acetate 189a



189a

A sealed tube was equipped with a magnetic stirrer and charged with 167e (740 mg, 3.6 mmol), 2,6-dibromo-4-fluorobenzyl acetate 197c (2.4 g, 7.2 mmol) and cesium carbonate (2.6 g, 7.9 mmol) in 1,4-dioxane (36 mL). After bubbling nitrogen through the solution for 30 min, Xantphos (250 mg, 0.43 mmol) and tris(dibenzylideneacetone) dipalladium(0) (260 mg, 0.29 mmol) were added, and the reaction mixture was heated to 100 °C for 16 h. After this time, H_2O (50 mL) and ethyl acetate (50 mL) were added. The aqueous layer was separated and extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with brine (100 mL) and dried over sodium sulfate. The resulting residue was purified by column chromatography eluting with a gradient of 100% hexanes – 100% Ethyl acetate to afford a 56% yield (910 mg) of 189a.

Example 189b 10-[5-Fluoro-2-(acetoxymethyl)-3-[1-methyl-6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydropyridin-3-yl]phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-9-one 189b



189b

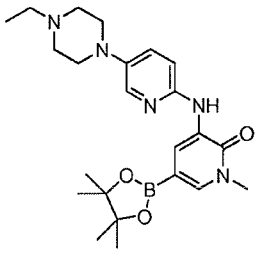
A microwave tube equipped with a magnetic stirrer was charged with 1-methyl-3-(pyrimidin-4-ylamino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one 109c (170 mg, 0.5 mmol), 189a (150 mg, 0.33 mmol), 1,2-dimethoxyethane (4 mL) and 1M aqueous sodium carbonate (1 mL). After bubbling N_2 for 15 min, $Pd(PPh_3)_4$ (19 mg, 0.02

mmol) was added. The mixture was heated in microwave to 130 °C for 10 min. After this time, Ethyl acetate (5 mL) and water (5 mL) were added. The separated aqueous layer was extracted with ethyl acetate (2 x 5 mL). The combined organics were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography eluting with a gradient of CH_2Cl_2 – 60:35:5 methylene chloride:diethyl ether:methanol to afford a 37% yield (71 mg) of **189b**.

A 25 mL round bottom flask with a magnetic stirrer was charged with **189b** (71 mg, 0.12 mmol), lithium hydroxide (26 mg, 0.6 mmol), THF (0.6 mL), isopropanol (0.6 mL) and water (1.2 mL). The mixture stirred at rt for 1 h. After this time, ethyl acetate (5 mL) and water (5 mL) were added. The separated aqueous layer was extracted with ethyl acetate (2 X 5 mL). The combined organics were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography eluting with a gradient of C methylene chloride – 60:35:5 CH_2Cl_2:diethyl ether:methanol to afford a 58% yield (38 mg) of **189**. MS (ESI+) *m/z* 529.7 (M + H).

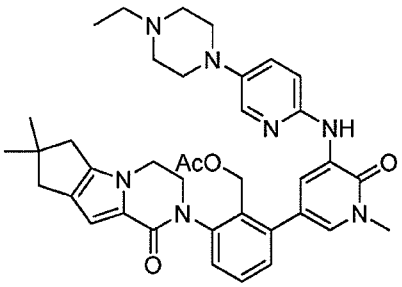
Example 190 10-[3-(5-{[5-(4-Ethylpiperazin-1-yl)pyridine-2-yl]amino}-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-(hydroxymethyl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-9-one **190**

Example 190a 3-(5-(4-Ethylpiperazin-1-yl)pyridin-2-ylamino)-1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one **190a**



To a round-bottomed flask equipped with a stirring bar, 5-bromo-3-(5-(4-ethylpiperazin-1-yl)pyridin-2-ylamino)-1-methylpyridin-2(1H)-one **138c** (305.6 mg, 0.696 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (185.4 ,g, 0.730 mmol), $Pd_2(dba)_3$ (63.7 mg, 0.070 mmol), X-Phos (66.3 mg, 0.139 mmol), KOAc (102.4 mg, 1.043 mmol), and dioxane (5 mL) were added. The mixture was heated at 90 °C for 4 hrs. The resulting mixture was filtered through celite, washed with ethyl acetate (200 mL). The organic phase was washed with water (50 mL), dried over $MgSO_4$, and removed solvent *in vacuo* to yield the crude product **190a** which was used directly in the next step.

Example 190b 10-[3-(5-{[5-(4-Ethylpiperazin-1-yl)pyridine-2-yl]amino}-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-(acetoxymethyl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-9-one **190b**

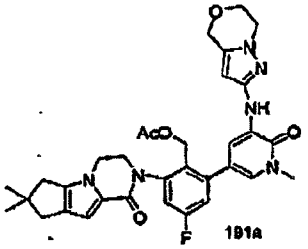


To a microwave tube equipped with a stirring bar, bromide **167f** (150 mg, 0.348 mmol), **190a** (306 mg, 0.696 mmol), $Pd(PPh_3)_4$ (40.2 mg, 0.0348 mmol), Na_2CO_3 aqueous solution (1.0 N, 1.15 mL, 1.15 mmol), DME (4 mL) were added. The mixture was reacted in microwave at 130 °C for 10 min. methylene chloride (200 mL) was added and the resulting mixture was washed with water (3 X 30 mL), brine (30 mL X 1), dried over $MgSO_4$, filtered, and removed solvent *in vacuo*. Silica gel column chromatography (methanol: methylene chloride = 5: 95) gave **190b**.

To a round-bottomed flask equipped with a stirring bar, **190b**, THF (3 mL), isopropanol (3 mL), water (3 mL), LiOH monohydrate (200 mg) were added. The resulting mixture was stirred at RT for 1 hr. Removed all the solvent *in vacuo* and the resulting residue was added to methylene chloride (200 mL), the solution was washed with water (3 X 30 mL), brine (30 mL), dried over $MgSO_4$, filtered, and removed solvent *in vacuo*. Silica gel column chromatography (MeOH: methylene chloride = 10: 90) gave **190** as a yellow solid, 16 mg. MS (ESI+) *m/z* 622.5 (M + H).

Example 191 10-[3-(5-{[5-(4-Ethylpiperazin-1-yl)pyridine-2-yl]amino}-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-(hydroxymethyl)phenyl]-4,4-dimethyl-1,10-diazatricyclo-[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-9-one **191**

Example 191a 10-[3-(5-{[5-(4-Ethylpiperazin-1-yl)pyridine-2-yl]amino}-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-(hydroxymethyl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one 191a



191a

A microwave tube equipped with a magnetic stirrer was charged with 3-(6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-2-ylamino)-1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one **150a** (200 mg, 0.5 mmol), **189a** (150 mg, 0.34 mmol), 1,2-dimethoxyethane (4 mL) and 1M aqueous sodium carbonate (1 mL). After bubbling N_2 for 15 min, $Pd(PPh_3)_4$ (19 mg, 0.02 mmol) was added. The mixture was heated in microwave to 130 °C for 10 min. After this time, ethyl acetate (5 mL) and water (5 mL) were added. The separated aqueous layer was extracted with ethyl acetate (2 x 5 mL). The combined organics were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography eluting with a gradient of methylene chloride – 60:35:5 CH_2Cl_2:diethyl ether:methanol to afford a 59% yield (125 mg) of **191a**.

A 25 mL round bottom flask with a magnetic stirrer was charged with **191a** (130 mg, 0.2 mmol), lithium hydroxide (43 mg, 1.0 mmol), THF (1 mL), isopropanol (1 mL) and water (2 mL). The mixture stirred at rt for 30 min. After this time, ethyl acetate (5 mL) and water (5 mL) were added. The separated aqueous layer was extracted with ethyl acetate (2 x 5 mL). The combined organics were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography eluting with a gradient of methylene chloride – 60:35:5 CH_2Cl_2:diethyl ether:methanol to afford a 59% yield (68 mg) of **191**. MS (ESI+) *m/z* 573.4 (M + H).

Example 192 6-(3-(5-(6,7-Dihydro-4*H*-pyrazolo[5,1-c][1,4]oxazin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-(hydroxymethyl)phenyl)-2,3-(5,5-dimethyl-5,6-dihydro-4*H*-cyclopenta)-5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one 192

A 100-mL three-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was charged with **182c** (300 mg, 0.513 mmol), **110c** (167 mg, 0.513 mmol), sodium carbonate (218 mg, 2.05 mmol), water (6 mL) and 1,4-dioxane (30 mL). After bubbling nitrogen through the resulting suspension for 20 min, tetrakis(triphenyl-phosphine)-palladium(0) (60.0 mg, 0.051 mmol) was added, and the reaction mixture was heated at 100°C for 4 h. After this time, the reaction mixture was cooled to room temperature and filtered, and the filter cake was washed with a 1:10 mixture of methanol and methylene chloride (30 mL). The filtrate was concentrated under reduced pressure to afford a brown residue. Another 50-mL single-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was charged with the residue thus obtained, tetrabutylammonium fluoride (1.0 M in THF, 2 mL, 2.00 mmol) and THF (6 mL). The mixture was stirred at room temperature for 1.5 h. After this time, the reaction mixture was concentrated under reduced pressure. The resulting residue was purified by flash chromatography to afford a 36% (110 mg) yield of **192** as an off-white solid: mp 170–172 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.99 (d, 1H, J = 2.0 Hz), 7.32 (dd, 1H, J = 9.0, 3.0 Hz), 7.28 (d, 1H, J = 2.0 Hz), 7.15 (dd, 1H, J = 9.0, 3.0 Hz), 5.93 (s, 1H), 4.86 (t, 1H, J = 5.0 Hz)

Example 193 5-(2-(Hydroxymethyl)-3-(6,6-dimethyl-3,4,6,7-tetrahydro-5*H*-cyclopenta[4,5]thieno[2,3-*c*]pyridine-1(2*H*)-yl))-1-methyl-3-(pyridin-3-ylamino)pyrazin-2(1*H*)-one **193**

Following Example 204, reaction of **111b** (132 mg, 0.466 mmol) with **131a** (300 mg, 0.606 mmol) afforded a 31% yield (75 mg) of **193** as an off-white solid: mp 135–136 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.53 (s, 1H), 9.15 (d, 1H, J = 1.9 Hz), 8.42 (m, 1H), 8.17 (dd, 1H, J = 4.5, 1.4 Hz), 7.54 (dd, 1H, J = 7.4, 1.0 Hz), 7.47 (m, 2H), 7.34 (dd, 1H, J = 8.0, 1.5 Hz), 7.30 (m, 1H), 4.82 (m, 1H), 4.46 (m, 2H), 4.01 (m, 1H), 3.86 (m, 1H), 3.56 (s, 3H), 3.02 (m, 1H), 2.88 (m, 1H), 2.75 (s, 2H), 2.54 (d, 2H, J = 6.0 Hz), 1.23 (s, 6H); MS (ESI+) *m/z* 528.2 (M+H).

Example 194 5-(2-(Hydroxymethyl)-3-(6,6-dimethyl-3,4,6,7-tetrahydro-5*H*-cyclopenta[4,5]thieno[2,3-*c*]pyridine-1(2*H*)-yl)-1-methyl-3-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)pyridin-2(1*H*)-one **194**

Following Example 204, reaction of **197e** (176 mg, 0.466 mmol) with **131a** (300 mg, 0.606 mmol) afforded a brown residue. A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer was charged with the above crude residue, THF (8 mL), methanol (4 mL), water (4 mL) and lithium hydroxide monohydrate (196 mg, 4.66 mmol).

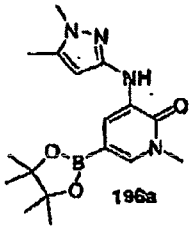
The mixture was stirred for 2 h at room temperature and then concentrated in vacuo. The residue was partitioned between a 20% (v/v) solution of methanol in methylene chloride (150 mL) and water (30 mL). The organic layer was separated, and the aqueous layer was extracted with a 20% (v/v) solution of methanol in methylene chloride (3 × 30 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (silica, 0% to 10% methanol/methylene chloride) to afford a 33% yield (95 mg) of **194** as an off-white solid: mp 142–143 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.54 (d, 1H, J = 2.5 Hz), 8.33 (s, 1H), 7.85 (d, 1H, J = 3.0 Hz), 7.45 (t, 1H, J = 7.4 Hz), 7.35 (m, 2H), 7.32 (m, 2H), 7.20 (d, 1H, J = 9.3 Hz), 4.84 (m, 1H), 4.32 (m, 2H), 4.03 (m, 1H), 3.85 (m, 1H), 3.58 (s, 3H), 3.03 (m, 5H), 2.87 (m, 1H), 2.75 (s, 2H), 2.53 (m, 2H), 2.43 (m, 4H), 2.20 (s, 3H), 1.23 (s, 6H); MS (ESI+) *m/z* 625.3 (M+H).

Example 195 5-[2-(Hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino-[1,2-a]indol-2-yl}phenyl]-1-methyl-3-({5-[4-(propan-2-yl)piperazin-1-yl]pyridine-2-yl}amino)-1,2-dihydropyridin-2-one **195**

Following Example 138, 5-bromo-1-methyl-3-(5-(4-(1-methylethyl)piperazin-1-yl)pyridin-2-ylamino)pyridin-2(1H)-one **220a** was converted to 75 mg of **195** as a white solid. MS (ESI+) *m/z* 622 (M + H).

Example 196 10-(3-{5-[(1,5-Dimethyl-1H-pyrazol-3-yl)amino]-1-methyl-6-oxo-1,6-dihydropyridin-3-yl}-5-fluoro-2-(hydroxymethyl)phenyl)-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one **196**

Example 196a 3-(1,5-Dimethyl-1H-pyrazol-3-ylamino)-1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one **196a**

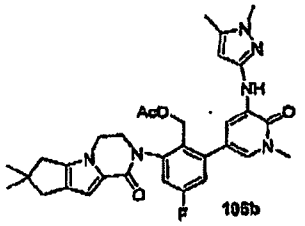


196a

A sealed tube equipped with a magnetic stirrer was charged with 5-bromo-3-(1,5-dimethyl-1H-pyrazol-3-ylamino)-1-methylpyridin-2(1H)-one **142a** (380 mg, 1.4 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (690 mg, 2.7 mmol), potassium

acetate (401 mg, 4.1 mmol) and 1,4-dioxane (34 mL). After bubbling nitrogen through the resulting suspension for 30 min, [1,1'-bis(diphenylphosphino)ferrocene]dichloro-palladium(II) complex with methylene chloride (Pd Cl_2dppf:CH_2Cl_2 (1:1), 110 mg, 0.14 mmol) was then added, and the reaction was stirred at 105 °C for 16 h. After this time, the mixture was cooled to ambient temperature, partition between water (20 mL) and ethyl acetate (20 mL). The separated aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organics were washed with brine (30 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting crude **196a** was used in the next step without further purification.

Example 196b 10-(3-{5-[(1,5-Dimethyl-1H-pyrazol-3-yl)amino]-1-methyl-6-oxo-1,6-dihydropyridin-3-yl}-5-fluoro-2-(acetoxymethyl)phenyl)-4,4-dimethyl-1,10-diazatricyclo[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-9-one **196b**



196b

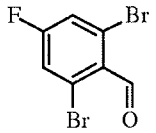
A microwave tube equipped with a magnetic stirrer was charged with **196a** (450 mg, 1.3 mmol), **189a** (240 mg, 0.5 mmol), DME (4 mL) and 1M aqueous sodium carbonate (1.5 mL). After bubbling N2 for 15 min, $Pd(PPh_3)_4$ (31 mg, 0.03 mmol) was added. The mixture was heated in microwave to 130 °C for 10 min. After this time, EtOAc (5 mL) and water (5 mL) were added. The separated aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organics were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography eluting with a gradient of methylene chloride – 60:35:5 methylene chloride:diethyl ether:methanol to afford a 83% yield (260 mg) of **196b**.

A 25 mL round bottom flask with a magnetic stirrer was charged with **196b** (260 mg, 0.5 mmol), lithium hydroxide (94 mg, 2.2 mmol), THF (2 mL), isopropanol(2 mL) and water (5 mL). The mixture stirred at rt for 30 min. After this time, ethyl acetate (5 mL) and water (5 mL) were added. The separated aqueous layer was extracted with ethyl acetate (2 x 5 mL). The combined organics were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column

chromatography using the Biotage KPNH 12+M column eluting with a gradient of hexanes – ethyl acetate to afford a 46% yield (110 mg) of **196**. MS (ESI+) *m/z* 545.4 (M + H).

Example 197 2-(5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **197**

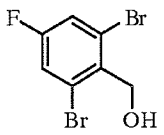
Example 197a 2,6-Dibromo-4-fluorobenzaldehyde **197a**



197a

A solution of 1,3-dibromo-5-fluoro-2-iodobenzene (50 g, 132 mmol) in anhydrous toluene (300 mL) cooled to –35 °C was added the solution of isopropylmagnesium chloride (84 mL, 171 mmol, 2.0 M in diethyl ether) over a period of 30 minutes while maintaining the internal temperature below -25°C. A clear brown solution was obtained. Stirring was continued for 1.5 h. Then anhydrous DMF (34 mL, 436 mmol) was added over a period of 30 minutes. The temperature of the reaction mixture increased to -19°C. The reaction mixture was warmed to 10°C (room temper-ature) over 1h and stirred at this temperature for 1.5 h. The reaction was quenched with saturated aqueous NH_4Cl (100 mL), filtered and evaporated under reduced pressure. The residue was purified by silica-gel column chromatography (eluting with petroleum ether/ethyl acetate: from 50:1 to 20:1) to give **197a** (20 g, yield 54%) as a yellow solid.

Example 197b 2,6-Dibromo-4-fluorophenyl)methanol **197b**

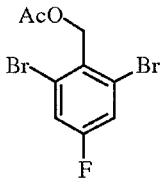


197b

A solution of **197a** (20 g, 71 mmol) in ethanol (500 mL) was added $NaBH_4$ (10 g, 284 mmol). The mixture was stirred at room temperature (10°C) for 4 h. TLC showed the start material disappeared. The reaction was quenched with HCl solution (150 mL, 1 M). Most of ethanol was evaporated at reduced pressure. The residue was extracted by ethyl acetate (3 × 500 mL). The organic layers was combined and dried with anhydrous Na_2SO_4, evaporated *in vacuo.* The residue was purified by silica-gel column chromatography (eluting

with petroleum ether/ethyl acetate: from 50:1 to 20:1) to give **197b** (15 g, yield 75%) as a white solid.

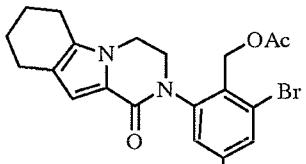
Example 197c 2,6-Dibromo-4-fluorobenzyl acetate **197c**



197c

A 500-mL single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was charged with **197b** (23.0 g, 81.0 mmol), triethylamine (25.0 g, 247 mmol) in anhydrous methylene chloride (100 mL). Acetic anhydride (10.0 g, 98.0 mmol) was added and this mixture was stirred at room temperature for 16 h. After this time, the mixture was diluted with methylene chloride (100 mL) and washed with saturated aqueous sodium bicarbonate (100 mL). The layers were separated and the aqueous layer was extracted with methylene chloride (2 x 20 mL). The organic extracts were combined and dried over sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography (silica, 0% to 50% ethyl acetate/hexanes) to afford **197c** in 87% yield (23.0 g) as a white solid.

Example 197d 2-Bromo-4-fluoro-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **197d**

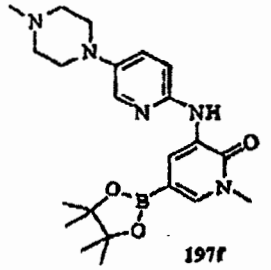


197d

A 250-mL single-neck round-bottomed flask equipped with a magnetic stirrer was charged with ethyl 1-(2-aminoethyl)-4,5,6,7-tetrahydro-1*H*-indole-2-carboxylate **101k** (3.8 g, 20 mmol), **197c** (20 g, 60 mmol), Xantphos (1.2g, 2 mmol), tris(dibenzylideneacetone)dipalladium(0) (1.8g, 2 mmol), Cs_2CO_3 (16 g, 50 mmol), and 1,4-dioxane (120 mL). The system was evacuated and then refilled with N_2. A reflux condenser was attached to the flask, and the reaction mixture was heated at 100 °C for 16 h. It was then cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography eluting with

5:1 petroleum ether/ethyl acetate to afford 197d in 60% yield (5.2 g) as a white solid. MS: $[M+H]^+$ 435. ^1H NMR (500 MHz, DMSO) δ 7.70 (dd, J = 3, 1H), 7.48 (dd, J = 3, 1H), 6.52 (s, 1H), 5.01 (m, 2H), 4.18 (m, 2H), 4.02 (m, 1H), 3.73 (m, 1H), 2.60 (m, 2H), 2.45 (m, 2H), 1.98 (s, 3H), 1.77 (m, 2 H), 1.68 (m, 2H)

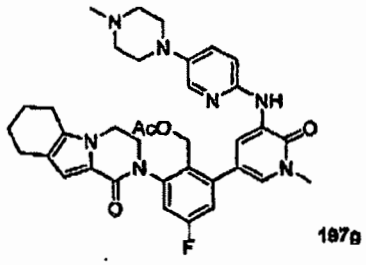
Example 197f 1-Methyl-3-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyridin-2-one 197f



197f

A 1-L single-neck round-bottomed flask equipped with a magnetic stirrer and thermoregulator was purged with nitrogen and charged with 197e, prepared according to US 2009/0318448, (10.0 g, 0.027 mol), bis(pinacolato)diboron (8.06 g, 0.032 mol), potassium acetate (10.4 g, 0.11 mol) and 1,4-dioxane (200 mL). After a stream of nitrogen was passed through the resulting suspension for 30 min., $Pd(dppf)Cl_2$ CH_2Cl_2 (582 mg, 0.795 mmol) was added. The resulting reaction mixture was stirred at reflux for 3 h. Then, it was cooled to room temperature, partitioned between water (400 mL) and ethyl acetate (600 mL) and filtered through a pad of Celite. The organic phase was extracted, dried over sodium sulfate, filtered and concentrated. The residue was triturated with a mixture of diethyl ether (50 mL) and hexanes (250 mL), and the suspension was filtered. The filter cake was dried under vacuum at room temperature to afford a 27 % yield (3.04 g) of 197f as a brown solid.

Example 197g 4-Fluoro-2-(1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate 197g



197g

In a 10-mL glass vessel equipped with a magnetic stirring bar were placed **197f** (244 mg, 0.58 mmol), **197d** (200 mg, 0.46 mmol), $Pd(PPh_3)_4$ (33 mg, 0.030 mmol) in 2 N Na_2CO_3 (1 mL) and DME (2 mL). The vessel was sealed with a septum and placed into the microwave cavity. After the reaction mixture was stirred at 125 °C for 7 min., it was purified by flash chromatography (dichloromethane:methanol, 85:15) to give 30% (90 mg) of **197g** as a solid.

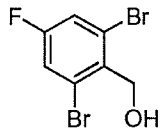
A 100-mL, single-necked, round-bottomed flask equipped with a magnetic stirring bar was charged with **197g** (90 mg, 0.14 mmol), LiOH hydrate (60 mg, 1.4 mmol), THF (2 mL), *i*-PrOH (2 mL), and water (2 mL). After the reaction mixture was stirred at room temperature for 3 h, it was partitioned between dichloromethane (5 mL) and water (5 mL), and the organic phase was extracted with dichloromethane (5 mL x 3). The combined organic phases were washed with water (5 mL x 2) and brine (5 mL x 1), dried (Na_2SO_4), and concentrated. The crude product was re-dissolved in dichloromethane (3 mL). To this solution was added hexane (10 mL) and the resulting precipitates were filtered to give 81% yield (69 mg) of **197**. MS (ESI+) *m/z* 612.5 (M+H)

Example 198 10-[5-Fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[5-(4-methylpiperazin-1-yl)pyridine-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-9-one **198**

Example 198a 2,6-Dibromo-4-fluorobenzaldehyde **198a**

A solution of 1,3-dibromo-5-fluoro-2-iodobenzene (50 g, 132 mmol) in anhydrous toluene (300 mL) cooled to –35° was added the solution of isopropylmagnesium chloride (84 mL, 171 mmol, 2.0 M in Et_2O) over a period of 30 minute while maintaining the internal temperature below -25 ° (Figure 6). A clear brown solution was obtained. Stirring was continued for 1.5 h. Then anhydrous DMF (34 mL, 436 mmol) was added over a period of 30 minutes. The temperature of the reaction mixture increased to -19 °. The reaction mixture was warmed to 10 ° (room temperature) over 1h and stirred at this temperature for 1.5 h. The reaction was quenched with saturated aqueous NH_4Cl (100 mL), filtered and evaporated under reduced pressure. The residue was purified by silica-gel column chromatography (eluting with petroleum ether/ethyl acetate: from 50:1 to 20:1) to give **198a** (20 g, yield 54%) as a yellow solid.

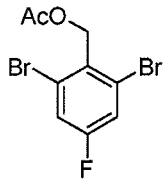
Example 198b 2,6-Dibromo-4-fluorophenyl)methanol **198b**



198b

A solution of **198a** (20 g, 71 mmol) in EtOH (500 mL) was added $NaBH_4$ (10 g, 284 mmol). The mixture was stirred at room temperature (10 ℃) for 4 h. TLC showed the start material disappeared. The reaction was qunched with HCl solution (150 mL, 1 M). Most of EtOH was evaporated at reduced pressure. The residue was extracted by ethyl acetate (3 × 500 mL). The organic layers was combined and dried with anhy. Na_2SO_4, evaporated *in vacuo*. The residue was purified by silica-gel column chromatography (eluting with petroleum ether/ethyl acetate: from 50:1 to 20:1) to give **198b** (15 g, yield 75%) as a white solid.

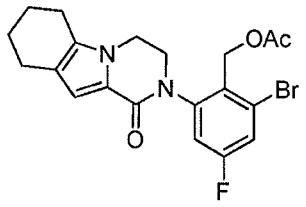
Example 198c 2,6-Dibromo-4-fluorobenzyl acetate **198c**



198c

A 500-mL single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was charged with **198b** (23.0 g, 81.0 mmol), triethylamine (25.0 g, 247 mmol) in anhydrous methylene chloride (100 mL). Acetic anhydride (10.0 g, 98.0 mmol) was added and this mixture was stirred at room temperature for 16 h. After this time, the mixture was diluted with methylene chloride (100 mL) and washed with saturated aqueous sodium bicarbonate (100 mL). The layers were separated and the aqueous layer was extracted with methylene chloride (2 x 20 mL). The organic extracts were combined and dried over sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography (silica, 0% to 50% ethyl acetate/hexanes) to afford **198c** in 87% yield (23.0 g) as a white solid.

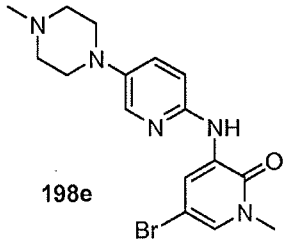
Example 198d 2-Bromo-4-fluoro-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **198d**



198d

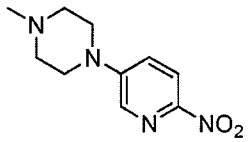
A 250-mL single-neck round-bottomed flask equipped with a magnetic stirrer was charged with ethyl 1-(2-aminoethyl)-4,5,6,7-tetrahydro-1*H*-indole-2-carboxylate **101k** (3.8 g, 20 mmol), **198c** (20 g, 60 mmol), Xantphos (1.2g, 2 mmol), tris(dibenzylideneacetone)dipalladium(0) (1.8g, 2 mmol), Cs_2CO_3 (16 g, 50 mmol), and 1,4-dioxane (120 mL). The system was evacuated and then refilled with N_2. A reflux condenser was attached to the flask, and the reaction mixture was heated at 100 °C for 16 h. It was then cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography eluting with 5:1 PE/EA to afford **198d** in 60% yield (5.2 g) as a white solid. MS: $[M+H]^+$ 435. ^1H NMR (500 MHz, DMSO) δ 7.70 (dd, J = 3, 1H), 7.48 (dd, J = 3, 1H), 6.52 (s, 1H), 5.01 (m, 2H), 4.18 (m, 2H), 4.02 (m, 1H), 3.73 (m, 1H), 2.60 (m, 2H), 2.45 (m, 2H), 1.98 (s, 3H), 1.77 (m, 2 H), 1.68 (m, 2H)

Example 198e 5-bromo-1-methyl-3-[5-(4-methylpiperazin-1-yl)-pyridin-2-ylamino]-1H-pyridin-2-one **198e**



198e

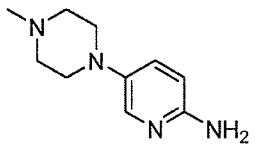
Step 1: 1-methyl-4-(6-nitropyridin-3-yl)piperazine



According to US 2009/0318448, into a solution of 5-bromo-2-nitropyridine (2.0 g, 9.85 mmol) in DMSO (10 mL) was added K2C03 (2.72 g, 19.7 mmol) and 1-methylpiperazine (1.64 mL, 14. 8 mmol), and tetrabutylammonium iodide (36 mg). The mixture was stirred at 120 degree C for overnight. It was allowed to cool down and acidified with 1N HCl. The mixture was extracted with DCM. The aqueous layer was basified with saturated Na2CO3, and further extracted with DCM. The combined organic layers were dried

over Na2SO4 and concentrated to give a brown solid, which was washed with small amount of water. The solid was dried under vacuum to give 2.16 g of 1-methyl-4-(6-nitropyridin-3-yl)piperazine (99% yield) as a yellow powder. LCMS: $(M+H)^+$ 223

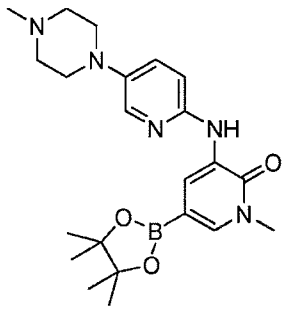
Step 2: 5-(4-methylpiperazin-1-yl)pyridin-2-amine



The suspension of 1-methyl-4-(6-nitropyridin-3-yl)piperazine (5 g, 22.5 mmol), NH4Cl (12 g, 225 mmol), and Fe (5 g, 5 mmol) was stirred in EtOH/H2O (1:1) (100 mL) at 80 ^{0}C for 3 h. TLC showed starting material 1-methyl-4-(6-nitropyridin-3-yl)piperazine disappeared. After filtration on a pad of Celite, the solvent was removed under vacuum. EA and brine were added into the mixture and the organic layer was separated, dried over Na2SO4 and concentrated at reduced pressure to give 2.5 g of 5-(4-methylpiperazin-1-yl)pyridin-2-amine (yield 60%). LCMS: $(M+H)^+$ 193

Step 3: 5-(4-methylpiperazin-1-yl)pyridin-2-amine (1 g, 10.5 mmol), 3,5-dibromo-1-methylpyridin-2(1H)-one (1.87 g, 7 mmol), and Cs2CO3 (5 g, 21 mmol) were added to dioxane (30 mL) in a sealed tube. After bubbling nitrogen through the resulting solution for 15 minutes, Xantphos (405 mg, 0.7 mmol) and tris(dibenzylideneacetone)dipalladium(0) (320 mg, 0.35 mmol) were added, and the reaction mixture was stirred at 100 °C for 0.5h. After filtration, the solid was washed by warm EA, and the filtrate was concentrated to afford the crude product as a black solid. The crude product was the re-crystallized from MeOH to give 1.26g (64%) of **198e**. LCMS: $(M+H)^+$ 380. ^{1}H NMR (500 MHz, DMSO) δ 8.57 (d, J = 2.5, 1H), 8.54 (s, 1H), 7.93 (d, J = 3, 1H), 7.44 (d, J = 2.5, 1H), 7.38 (dd, J = 3.5, 2H), 7.24 (d, J = 4.5, 1H), 3.50 (s, 3H), 3.07 (m, 4H), 2.44 (m, 4H), 2.21 (s, 3H).

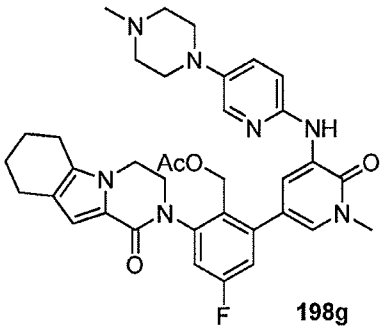
Example 198f 1-Methyl-3-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyridin-2-one **198f**



198f

A 1-L single-neck round-bottomed flask equipped with a magnetic stirrer and thermoregulator was purged with nitrogen and charged with **198e** (10.0 g, 0.027 mol), bis(pinacolato)diboron (8.06 g, 0.032 mol), potassium acetate (10.4 g, 0.11 mol) and 1,4-dioxane (200 mL). After a stream of nitrogen was passed through the resulting suspension for 30 min., $Pd(dppf)Cl_2$ CH_2Cl_2 (582 mg, 0.795 mmol) was added. The resulting reaction mixture was stirred at reflux for 3 h. Then, it was cooled to room temperature, partitioned between water (400 mL) and ethyl acetate (600 mL) and filtered through a pad of Celite. The organic phase was extracted, dried over sodium sulfate, filtered and concentrated. The residue was triturated with a mixture of diethyl ether (50 mL) and hexanes (250 mL), and the suspension was filtered. The filter cake was dried under vacuum at room temperature to afford a 27 % yield (3.04 g) of **198f** as brown solids.

Example 198g 4-Fluoro-2-(1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **198g**



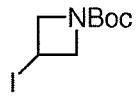
198g

In a 10-mL glass vessel equipped with a magnetic stirring bar were placed **198f** (244 mg, 0.58 mmol), **198d** (200 mg, 0.46 mmol), $Pd(PPh_3)_4$ (33 mg, 0.030 mmol) in 2 N Na_2CO_3 (1 mL) and DME (2 mL). The vessel was sealed with a septum and placed into the microwave cavity. After the reaction mixture was stirred at 125 °C for 7 min., it was purified by flash chromatography (dichloromethane:MeOH, 85:15) to give 30% (90 mg) of **198g** as solids.

Following Example 148, **198g** was converted to 75 mg of **198** as a white solid. MS (ESI+) *m/z* 626.6 (M + H).

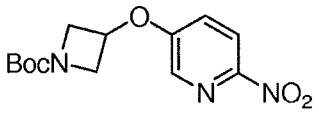
Example 199 5-[5-Fluoro-2-(hydroxymethyl)-3-[1-methyl-5-({5- [(1-methylazetidin-3-yl)oxy]pyridin-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$]trideca-1(9),2(7)-dien-6- one **199**

Example 199a *tert*-Butyl 3-Iodoazetidine-1-carboxylate **199a**



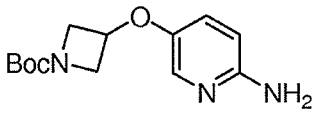
A solution of *tert*-butyl 3-hydroxyazetidine-1-carboxylate (25-3) (3.5 g, 0.02 mol) in toluene (200 mL) was treated with imidazole (4.08 g, 0.06 mol), PPh_3 (0.6 g, 0.04 mol), and I_2 (7.62 g, 0.03 mol). The mixture was heated at 100°C for 1 h and cooled down to room temperature. It was then poured into saturated $NaHCO_3$ solution (30 mL). Excess PPh_3 was destroyed by addition of iodine until I_2 coloration persisted in organic layer. The mixture was washed with 5% Na_2SO_3 solution, dried over Na_2SO_4, and evaporated in *vacuo*. The residue was purified on silical gel column to give **199a** (5.31 g, 93%). MS: $[M+H]^+$ 284.

Example 199b *tert*-Butyl 3-(6-Nitropyridin-3-yloxy)azetidine-1-carboxylate **199b**



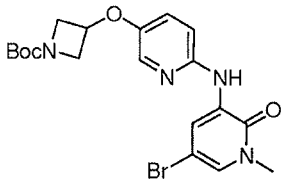
A mixture of **199a** (2.24 g, 7.9 mmol), 6-nitropyridin-3-ol (1 g, 7.2 mmol) and Cs_2CO_3 (2.6 g, 7.9 mmol) in DMF (8 mL) was heated at 125°C in a sealed tube for overnight. The mixture was filtered off and washed with ethyl acetate (20 mL × 2). The filtrate was evaporated in *vacuo* and the residue was purified on reverse phase Combi-flash to give **199b** (1.25 g, 59%). MS: $[M+H]^+$ 296.

Example 199c *tert*-Butyl 3-(6-Aminopyridin-3-yloxy)azetidine-1-carboxylate **199c**



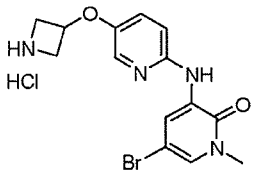
A 100-mL Parr hydrogenation bottle was purged with nitrogen and charged with **199b** (1.07 g, 3.6 mmol), 10% palladium on carbon (50% wet, 0.3 g) and methanol (60 mL). The bottle was evacuated, charged with hydrogen gas to a pressure of 25 psi, and shaken for 2 h on a Parr hydrogenation apparatus. The hydrogen was then evacuated and nitrogen charged to the bottle. The catalyst was removed by filtration through a pad of Celite and the filtrate was concentrated under reduced pressure to afford **199c** (0.95 g, 99%). MS: $[M+H]^+$ 266.

Example 199d *tert*-Butyl 3-(6-(5-Bromo-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)pyridin-3-yloxy)azetidine-1-carboxylate **199d**



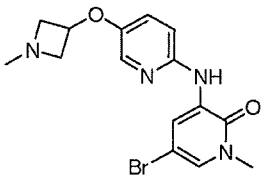
A mixture of **199c** (950 mg, 3.6 mmol), XantPhos (125 mg, 0.29 mmol), Pd_2dba_3 (260 mg, 0.29 mmol), 3,5-dibromo-1-methylpyridin-2(1H)-one (1.03 g, 3.9 mmol) and Cs_2CO_3 (1.8 g. 7.2 mmol) in 1,4-dioxane (20 mL) was heated at reflux for 2 h. After the completion of the reaction, the mixture was filtered off and washed with methanol (100 mL). The filtrate was evaporated in *vacuo*. The residue was purified on reverse phase Combi-flash to give **199d** (1.46 g, 91%). MS: $[M+H]^+$ 451.

Example 199e 3-(5-(Azetidin-3-yloxy)pyridin-2-ylamino)-5-bromo-1-methylpyridin-2(1H)-one hydrochloride **199e**



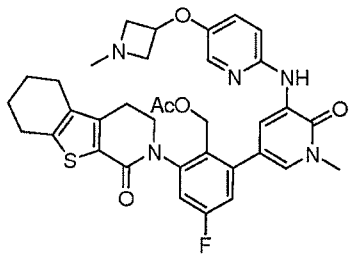
A mixture of **199d** (1.46 g, 3.2 mmol) and HCl/1,4-dioxane (3.2 mL, 12.8 mmol, 4 M) in methanol (20 mL) was heated at 80 °C for 1 h. The mixture was concentrated under reduced pressure to give **199e** (1.24 g, 99%). MS: $[M+H]^+$ 351.

Example 199f 5-Bromo-1-methyl-3-(5-(1-methylazetidin-3-yloxy)pyridin-2-ylamino)-pyridine-2(1H)-one **199f**



A mixture of **199e** (1.24 g, 3.2 mmol), HCHO solution (15 mL, 37% in water), acetic acid (1 mL) and $NaBH(OAc)_3$ (1.36 g, 6.4 mmol) in methanol (10 mL) was stirred at room temperature for 4 h. The solvent was evaporated in *vacuo* and the residue was extracted with ethyl acetate (20 mL × 3). The combined extracts were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified on reverse phase Combi-flash to give **199f** (940 mg, 80%). MS: $[M+H]^+$ 365.

Example 199g {4-Fluoro-2-[1-methyl-5-({5-[(1-methylazetidin-3-yl)oxy]pyridin-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]-6-{6-oxo-8-thia-5azatricyclo[7.4.0.$0^{2,7}$]-trideca-1(9),2(7)-dien-5-yl}phenyl}methyl Acetate **199g**



A mixture of **199f** (434 mg, 1.2 mmol), (4-fluoro-2-{6-oxo-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-5-yl}-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl acetate **212b** (600 mg, 1.2 mmol), $PdCl_2$(dppf) (134 mg, 0.18 mmol), K_3PO_4 (150 mg), and NaOAc (100 mg) in MeCN (8 mL) and water (2 mL) was heated at 110°C in a sealed tube for 2 h. The solvent was evaporated in *vacuo*. The residue was purified on reverse phase Combi-flash to give **199g** (320 mg, 41%). MS: $[M+H]^+$ 658.

A mixture of **199g** (320 mg, 0.49 mmol) and LiOH hydrate (409 mg, 9.8 mmol) in isopropanol (20 mL) and water (3 mL) was stirred at 30 °C for 2 h. The mixture was evaporated in *vacuo* and the residue was extracted with ethyl acetate (20 mL × 2). The combined extracts were concentrated under reduced pressure. The residue was purified on prep-HPLC to give **199** (30mg, 10%). MS: $[M+H]^+$ 616. ^{1}H NMR (500 MHz, CDCl3) δ 8.52 (d, J = 2.0, 1H), 7.82 (s, 1H), 7.75 (d, J = 2.5, 1H), 7.48 (d, J = 2.0, 1H), 7.16-7.14 (m, 1H), 7.11-7.09 (m, 1H), 6.98-6.96 (m, 1H), 6.79 (d, J = 9.0, 1H), 4.76-7.72 (m, 1H), 4.56 (d, J = 11.5, 1H), 4.32-4.25 (m, 1H), 4.19-4.07 (m, 2H), 3.97-3.80 (m, 3H), 3.69 (s, 3H), 3.23-3.15 (m, 2H), 3.00-2.81 (m, 4H), 2.59-2.50 (m, 2H), 2.47 (s, 2H), 1.93-1.83 (m, 4H).

Example 200 2-(3-(5-(5-(Azetidin-1-ylmethyl)-1-methyl-1H-pyrazol-3-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **200**

Example 200a 5-(Azetidin-1-ylmethyl)-1-methyl-3-nitro-1H-pyrazole **200a**

Following Example 156e, 5-(bromomethyl)-1-methyl-3-nitro-1H-pyrazole **156d** (1.76 g, 8 mmol), azetidine (550 mg, 9.6 mmol), di-isopropylethylamine (1.75 mL, 10 mmol) and methylene chloride (40 mL) were stirred at room temperature for 3-5 h. Work-up and concentrated under reduced pressure to afford 5-(azetidin-1-ylmethyl)-1-methyl-3-nitro-1H-pyrazole **200a** (quant.) as yellow oil, which was used without further purification for the next step. MS (ESI+) *m/z* 197.1 (M+H).

Example 200b 5-(Azetidin-1-ylmethyl)-1-methyl-1H-pyrazol-3-amine **200b**

Following Example 156f, 10% palladium on carbon (30% wet, 480 mg dry weight) and a solution of **200a** (1.6g, 8 mmol) in ethanol (50 mL) were reacted. The reaction mixture was filtered through a pad of Celite 521. The filter cake was washed with ethanol (2 X 30 mL), and the combined filtrates were concentrated to dryness under reduced pressure to afford 5-(azetidin-1-ylmethyl)-1-methyl-1H-pyrazol-3-amine **200b** (quantitative) as yellow oil. MS (ESI+) *m/z* 167.1 (M+H).

Example 200c 3-(5-(Azetidin-1-ylmethyl)-1-methyl-1H-pyrazol-3-ylamino)-5-bromo-1-methylpyridin-2(1H)-one **200c**

Following Example 156g, **200b** (350mg, 2 mmol), 3,5-dibromo-1-methyl-1H-pyridin-2-one(0.54 g, 2 mmol), cesium carbonate (1.3 g, 4 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.18 g, 0.2 mmol), Xantphos (0.23 g, 0.4 mmol) and 1,4-dioxane (20 mL) were heated at 100 °C for 8 hours. Work-up and flash column chromatography (silica, 3:1 methylene chloride /methanol) give a 98% yield (0.69 g) of 3-(5-(azetidin-1-ylmethyl)-1-methyl-1H-pyrazol-3-ylamino)-5-bromo-1-methylpyridin-2(1H)-one **200c** as a yellow solid. MS (ESI+) *m/z* 354.1 (M+H).

Example 200d 2-(5-(5-(Azetidin-1-ylmethyl)-1-methyl-1H-pyrazol-3-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-fluoro-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **200d**

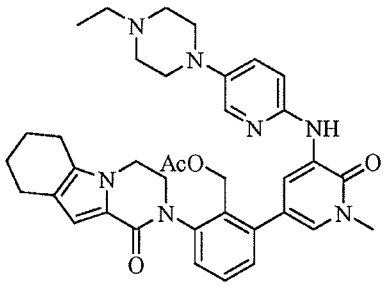
Following Example 121b, 4-fluoro-2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **210d** (202 mg, 0.42 mmol), 3-(5-(azetidin-1-ylmethyl)-1-methyl-1H-pyrazol-3-ylamino)-5-bromo-1-methylpyridin-2(1H)-one **200c** (105 mg, 0.3 mmol), 1M sodium carbonate solution (1.2 mL,

1.2 mmol), tetrakis(triphenylphosphine)palladium(0) (18 mg, 0.015 mmol) and 1,2-Dimethoxyethane (3 mL) were heated at 130 °C for 10 minutes in the microwave reactor. Work-up and the resulting residue was purified by flash column chromatography (silica, 3:1 methylene chloride /methanol) to give 180 mg compound **200d** (quant., contain 3% **200**) as a yellow residue: MS (ESI+) *m/z* 628.1 (M+H).

Intermediate **200d** (0.3mmol) was deprotected using Example 121, using THF (1 mL), water (0.5 mL), isopropanol (1 mL) and lithium hydroxide monohydrate (80 mg, 1.93 mmol). Work-up and the resulting residue was purified by flash column chromatography (NH-silica, ethyl acetate/hexanes) to afford a 25% yield (two steps, 45 mg) of **200** as a light pink solid: MS (ESI+) *m/z* 586.6 (M+H).

Example 201 2-(5-(5-(4-Ethylpiperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Alcohol **201**

Example 201b 2-(5-(5-(4-Ethylpiperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **201b**



201b

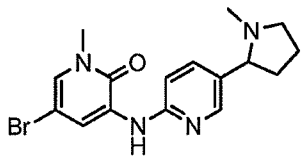
A 44-mL sealed tube equipped with a magnetic stirrer was charged with **138e** (190 mg, 0.49 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane (200 mg, 0.79 mmol), potassium acetate (190 mg, 2.0 mmol) and 1,4-dioxane (5 mL). After the mixture was degassed for 30 minutes, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (40 mg, 0.049 mmol) was added. The resulting reaction mixture was stirred at 105 °C for 6 h. Then, it was cooled to room temperature and filtered through a pad of Celite. The filtrate was concentrated, and the crude boronolate product was redissolved in DME (2 mL) and transferred into a 10-mL microwave reaction vessel. To this solution was added 2-bromo-4-fluoro-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **197d** (171 mg, 0.39 mmol), $Pd(PPh_3)_4$ (30 mg, 0.025 mmol), and 2 N Na_2CO_3 (2 mL). Then, the reaction mixture was

degassed for 5 minutes and placed into the microwave cavity. After the reaction mixture was stirred at 125 °C for 7 min., it was purified by flash chromatography (dichloromethane:MeOH, 85:15) to give 46% (120 mg) of **201b** as solids.

A 100-mL, single-necked, round-bottomed flask equipped with a magnetic stirring bar was charged with 2-(5-(5-(4-ethylpiperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **201b** (120 mg, 0.18 mmol), $LiOH•H_2O$ (80 mg, 1.8 mmol), THF (2 mL), isopropanol(2 mL), and water (2 mL). After the reaction mixture was stirred at room temperature for 3 h, it was partitioned between dichloromethane (5 mL) and water (5 mL), and the organic phase was extracted with dichloromethane (3 X 5 mL). The combined organic phases were washed with water 2 X 5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. The crude product was re-dissolved in dichloromethane (3 mL). To this solution was added hexane (10 mL) and the resulting precipitates were filtered to give 40% yield (45 mg) of **201**; MS(ESI^+) *m/z* 626.4 (M+H).

Example 202 5-[5-fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-{[5-(1-methylpyrrolidin-2-yl)pyridine-2-yl]amino}-1,2-dihydropyridin-2-one **202**

Example 202a 5-Bromo-1-methyl-3-(5-(1-methylpyrrolidin-2-yl)pyridin-2-ylamino)pyridin-2(1H)-one **202a**



202a

Following Example 142a, 5-(1-methylpyrrolidin-2-yl)pyridin-2-amine (500mg, 2 mmol), 3,5-dibromo-1-methylpyridin-2(1H)-one (0.54 g, 2 mmol), cesium carbonate (1.9 g, 6 mmol), tris(dibenzylidene-acetone)dipalladium(0) (0.18 g, 0.2 mmol), Xantphos (0.23 g, 0.4 mmol) and 1,4-dioxane (20 mL) were heated at 100 °C for 8 hours. Work-up and flash column chromatography (silica, 9:1 methylene chloride /methanol) give a 82% yield (0.6 g) of 5-bromo-1-methyl-3-(5-(1-methylpyrrolidin-2-yl)pyridin-2-ylamino)pyridin-2(1H)-one **202a** as a green solid: MS (ESI+) *m/z* 365.0 (M+H).

Following Example 121b, 4-fluoro-2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **210d** (338 mg, 0.7 mmol), **202a** (181 mg, 0.5 mmol), 1M sodium carbonate solution (2 mL, 2 mmol), tetrakis(triphenylphosphine)palladium(0) (29 mg, 0.025 mmol) and 1,2-dimethoxyethane (5

mL) were reacted. Work-up and flash column chromatography (silica, 3:1 methylene chloride /methanol) give a mixture (200 mg) of 4-fluoro-2-(1-methyl-5-(5-(1-methylpyrrolidin-2-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate and **202** as a yellow residue.

The above residue was deprotected following Example 121, except using a mixture of THF (1 mL), water (0.5 mL), isopropanol (1 mL) and lthium hydroxide monohydrate (55 mg, 1.2 mmol). Work-up and flash column chromatography (NH-silica, ethyl acetate/hexanes) give a 32% yield (60 mg) of **202** as a yellow solid: MS (ESI+) *m/z* 597.4 (M+H).

Example 203 5-(3-(6,6-Dimethyl-5,7-dihydro-5*H*-cyclopenta[4,5]thieno[2,3-*c*]pyridine-1(2*H*)-yl)-2-(hydroxymethyl)phenyl)-1-methyl-3-(pyrimidin-4-ylamino)pyridin-2(1*H*)-one **203**

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was charged with **105i** (226 mg, 0.506 mmol), **109c** (200 mg, 0.610 mmol), sodium carbonate (160 mg, 1.51 mmol), water (2 mL) and 1,4-dioxane (8 mL). After bubbling nitrogen through the resulting suspension for 30 min, tetrakis(triphenyl-phosphine)palladium(0) (60 mg, 0.052 mmol) was added. A reflux condenser was attached to the flask, and the reaction mixture was heated at 100 °C for 2 h. After this time, the mixture was diluted with 90:10 methylene chloride/methanol (100 mL) and water (75 mL), and the layers were separated. The aqueous layer was extracted with 90:10 methylene chloride/methanol (2 × 50 mL), and the combined organic layers were washed with brine (100 mL) and dried over sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was dissolved in a mixture of THF (3 mL), water (3 mL) and methanol (3 mL). Lithium hydroxide monohydrate (61 mg, 1.45 mmol) was added, and the reaction was stirred at room temperature for 2 h. After this time, the mixture was diluted with 90:10 methylene chloride/methanol (100 mL) and water (50 mL), and the layers were separated. The aqueous layer was extracted with 90:10 methylene chloride/ methanol (2 × 75 mL), and the combined organic layers were washed with brine (100 mL) and dried over sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography (silica, 0% to 10% methanol/methylene chloride) followed by trituration with methanol (10 mL) to afford **203** in 37% yield (57 mg) as an amorphous white solid: mp 170–171 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.18 (s, 1H), 8.74 (d, 1H, J = 3.5 Hz), 8.65 (s, 1H), 8.29 (d, 1H, J = 10.0 Hz), 7.93 (d, 1H, J = 10.0 Hz), 7.57 (d, 1H, J = 3.5 Hz), 7.43 (t, 1H, J = 13.0 Hz), 7.32 (m, 2H),

7.24 (d, 1H, J = 13.0 Hz), 7.19 (d, 1H, J = 13.0 Hz), 4.83 (m, 1H), 4.38 (d, 2H, J = 6.5 Hz), 3.60 (s, 3H), 2.90 (s, 2H), 2.74 (s, 2H), 1.28 (s, 6H); MS (ESI+) *m/z* 526.2 (M+H).

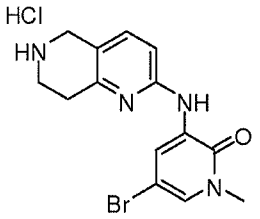
Example 204 5-(5-Fluoro-2-(hydroxymethyl)-3-(6,6-dimethyl-3,4,6,7-tetrahydro-5*H*-cyclopenta[4,5]thieno[2,3-*c*]pyridine-1(2*H*)-yl)-1-methyl-3-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)pyridin-2(1*H*) **204**

A 100-mL three-neck round-bottomed flask equipped with a reflux condenser, magnetic stirrer and nitrogen inlet was charged with **197e** (170 mg, 0.450 mmol), **182c** (300 mg, 0.513 mmol), sodium carbonate (143 mg, 1.35 mmol), water (2 mL) and 1,4-dioxane (8 mL). After bubbling nitrogen through the resulting suspension for 30 min, tetrakis(triphenylphosphine)palladium(0) (52 mg, 0.045 mmol) was added, and the reaction mixture was heated at reflux for 2 h. After that time, the mixture was cooled to room temperature and diluted with methylene chloride (100 mL) and water (30 mL). The organic layer was separated, and the aqueous layer was extracted with methylene chloride (3 × 30 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to afford brown residue.

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer was purged with nitrogen and charged with the above crude residue, THF (10 mL) and a 1 M solution of tetrabutylammonium fluoride in THF (4.50 mmol, 4.5 mL). The resulting mixture was stirred at room temperature for 1 h. After this time, the mixture was diluted with methylene chloride (100 mL) and washed with water (30 mL). The organic layer was separated, and the aqueous layer was extracted with methylene chloride (3 × 30 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (silica, 0% to 10% methanol/methylene chloride) to afford a 53% yield (154 mg) of **204** as an off-white solid: mp 143–145 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.54 (d, 1H, J = 2.5 Hz), 8.35 (s, 1H), 7.86 (d, 1H, J = 3.0 Hz), 7.34 (m, 3H), 7.21 (d, 1H, J = 8.9 Hz), 7.17 (dd, 1H, J = 9.3, 3.0 Hz), 4.85 (m, 1H), 4.32 (m, 2H), 4.04 (m, 1H), 3.85 (m, 1H), 3.58 (s, 3H), 3.03 (m, 5H), 2.87 (m, 1H), 2.75 (s, 2H), 2.53 (m, 2H), 2.43 (m, 4H), 2.20 (s, 3H), 1.23 (s, 6H); MS (ESI+) *m/z* 643.3 (M+H).

Example 205 2-(5-Fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **205**

Example 205a 5-Bromo-1-methyl-3-(5,6,7,8-tetrahydro-1,6-naphthyridin-2-ylamino)pyridin- 2(1H)-one **205a**



tert-Butyl 2-(5-bromo-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)-7,8-dihydro-1,6- naphthyridine-6(5H)-carboxylate **158c** (3.2 g, 7.4 mmol) was suspended in methylene chloride (20 mL), saturated hydrogen chloride in dioxane (20 mL) was added dropwise. The reaction mixture was stirred for 20 minutes and concentrated under reduced pressure to give **205a**, which was used without further purification in the next step. LC/MS: m/z 336 $(M+H)^+$

Example 205b 5-Bromo-1-methyl-3-(6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-2-ylamino)pyridin-2(1H)-one **205b**

A mixture of **205a** (2.75 g, 7.5 mmol), formaldehyde (37 percent in water, 30 ml, 375 mmol), $NaBH(OAc)_3$ (4.75 g, 22.5 mmol) and acetic acid (25 ml, 150 mmol) in methanol (125 ml) was stirred for 4 hours at room temperature. The mixture was then brought to basic condition with saturated NaOH solution and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography eluting with 4:1 ethyle acetate/methanol to give **205b** (2.0 g, 77%). LC/MS: m/z 349 $(M+H)^+$

Example 205c 4-Fluoro-2-(1-methyl-5-(6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **205c**

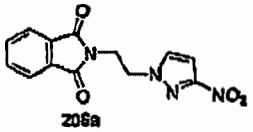
A 15 mL microwave reaction vial with a magnetic atirrer was charged with **205b** (0.35 g, 1 mmol), 4-fluoro-2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **210d** (0.48 g, 1 mmol), potassium phosphate (0.54 g, 2 mmol), sodium acetate (0.17 g, 2 mmol), acetonitrile (10 mL), water (1 mL), and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane (0.08 g, 0.1 mmol). The mixture was heated at 110 ^{0}C for 2 hours under argon atmosphere. After this time, the mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by column-chromatography eluting with 40:1 DMC/methanol to give **205c** (0.22 g, 36%). LC/MS: m/z 625 $(M+H)^+$

A 25 mL round bottomed flask with a magnetic stirrer was charged with compound 4-fluoro-2-(1-methyl-5-(6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-2-ylamino)-6-oxo-1,6-

A 25 mL round bottomed flask with a magnetic stirrer was charged with compound 4-fluoro-2-(1-methyl-5-(6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **205c** (0.2 g, 0.32 mmol), LiOH (2 g, 48 mmol), THF(5 mL), isopropanol (5 mL) and water (2 mL). The reaction mixture was stirred at room temperature for 30 minutes and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by prep-HPLC to give **205** (100 mg, 53%). LC/MS: m/z 583 $(M+H)^+$. ^{1}H NMR (500 MHz, DMSO) δ 8.79 (d, J = 2, 1H), 8.45 (s, 1H), 7.44 (d, J = 2, 1H), 7.31 (m, 2H), 7.20 (m, 1H), 7.08 (d, J = 9, 1H), 6.52 (s, 1H), 4.89 (m, 1H), 4.34 (m, 2H), 4.17 (m, 3H), 3.89 (m, 1H), 3.59 (s, 3H), 3.38 (m, 2H), 2.75 (m, 2H), 2.62 (m, 4H), 2.51 (m, 2H), 2.33 (s, 3H), 1.70 (m, 4H).

Example 206 2-(2-(Hydroxymethyl)-3-(1-methyl-5-(1-(2-(methylamino)ethyl)-1H-pyrazol-3-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **206**

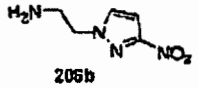
Example 206a 2-(2-(3-Nitro-1H-pyrazol-1-yl)ethyl)isoindoline-1,3-dione **206a**



206a

A solution of 4-nitro-1H-pyrazole (10 g, 88.5 mmol) in anhydrous DMF (250 mL) was treated with 60% dispersion of NaH in mineral oil (4.6 g, 115 mmol) while stirring under nitrogen. After effervescence the reaction was stirred for an additional 30 minutes. At this time the reaction was treated with 2-(2-bromoethyl)isoindoline-1,3-dione (18-2) (25 g, 97.3 mmol) and continued to stir under nitrogen for 3 hours. Water (50 mL) was then added slowly and the mixture was filtered to give **206a** as a white solid (20 g, 80%), which was used directly without further purification. LCMS: (M+H)+ 287.

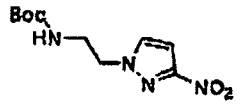
Example 206b 2-(3-Nitro-1H-pyrazol-1-yl)ethanamine **206b**



206b

A solution of **206a** (2.0 g, 7.0 mmol) in ethanol (30 mL) was added hydrazine hydrate (1 mL, 21 mmol) and the mixture was stirred at room temperature for 3 hours. The mixture was evaporated and the residue was purified by silica-gel eluting with 10:1 methylene chloride/methanol to give **206b** as a white solid (0.8 g, 80%). MS: $(M+H)^+$ 157.

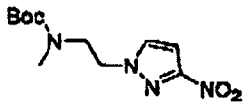
Example 206c *tert*-Butyl 2-(3-Nitro-1H-pyrazol-1-yl)ethylcarbamate **206c**



206c

To a solution of 206b (18 g, 115 mmol) in methylene chloride (400 mL) was added $(Boc)_2O$ (50 g, 230 mmol) and triethylamine (35 g, 346 mmol). The mixture was stirred at room temperature for 5 hours. It was then evaporated and purified by silical-gel column eluting with 1:1 petroleum ether/ethyl acetate to give 206c as a white solid (24 g, 80%). MS: $(M+H)^+$ 257.

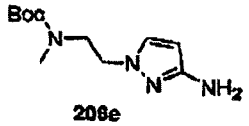
Example 206d *tert*-Butyl Methyl(2-(3-nitro-1H-pyrazol-1-yl)ethyl)carbamate 206d



206d

To a solution of 206c (5 g, 19.5 mmol) in THF (40 mL) was added NaH (938 mg, 23.4 mmol). The reaction mixture was stirred at room temperature for 30 minutes. Iodomethane (1.7 mL, 25.4 mmol) was added and the mixture was stirred for additional 15 hours. It was then evaporated and purified by silical-gel column eluting with 2:1 petroleum ether/ethyl acetate to give 206d as a white solid (4.5 g, 85%). MS: $(M+H)^+$ 271.

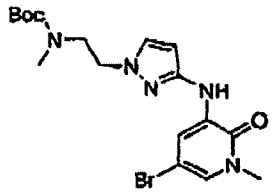
Example 206e *tert*-Butyl 2-(3-Amino-1H-pyrazol-1-yl)ethyl(methyl)carbamate 206e



206e

To a solution of 206d (4.5 g, 1.7 mmol) in ethanol (40 mL) was added Fe (4.7 g, 8.5 mmol) and NH_4Cl (900 mg, 17 mmol). The reaction mixture was stirred at room temperature for 4 hours. It was then evaporated and purified by silical-gel column eluting with 2:1 petroleum ether/ethyl acetate to give 206e as a brown solid (3.2 g, 80%). MS: $(M+H)^+$ 241.

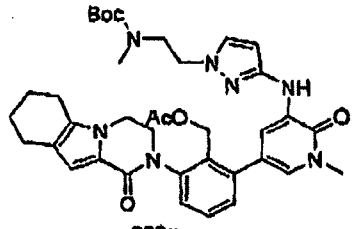
Example 206f *tert*-Butyl 2-(3-(5-Bromo-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)-1H-pyrazol-1-yl)ethyl(methyl)carbamate 206f



206f

A mixture of (206e (2 g, 8.3 mmol), 3,5-dibromo-1-methylpyridin-2(1H)-one (2.2 g, 8.3 mmol), XantPhos (482 mg, 0.83 mmol), $Pd_2(dba)_3$ (762 mg, 0.83 mmol) and Cs_2CO_3 (6.8 g, 21 mmol) in dioxane (80 mL) was heated at 100°C for 15 h under nitrogen. It was then filtered, evaporated in *vacuo*, and purified by silical-gel column eluting with 1:2 petroleum ether/ethyl acetate to give **206f** as a yellow solid (2.7 g, 77%). MS: $(M+H)^+$ 426.

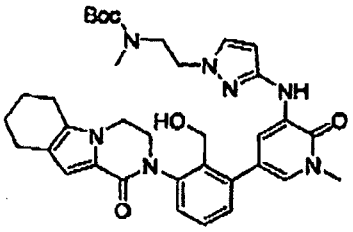
Example 206g 2-(5-(1-(2-(*tert*-Butoxycarbonyl(methyl)amino)ethyl)-1H-pyrazol-3-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydro-pyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate 206g



206g

A mixture of **206f** (800 mg, 1.9 mmol), 2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate (**114a**) (873 mg, 1.9 mmol), CH_3COONa (309 mg, 3.8 mmol), $PdCl_2(dppf)$ (153 mg, 0.19 mmol) and K_3PO_4 (1 g, 3.8 mmol) suspended in CH_3CN (30 mL) and H_2O (2 mL) was heated at 110°C for 15 h under argon atmosphere. It was then evaporated and the residue was purified by reverse phase Combi-flash eluting with 0.3% NH_4HCO_3 in1:4 water/CH_3CN to give **206g** as a brown solid (800 mg, 63%). MS: $(M+H)^+$ 684

Example 206h *tert*-Butyl 2-(3-(5-(2-(Hydroxymethyl)-3-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)phenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)-1H-pyrazol-1-yl)ethyl(methyl)carbamate 206h



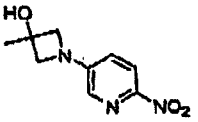
206h

To a solution of **206g** (750 mg, 1.1 mmol) in propan-2-ol (15 mL), tetrahydrofuran (15 mL), and water (5 mL) was added LiOH (2.6 g, 110 mmol). The mixture was stirred at 30°C for 2 h. It was then evaporated and the residue was purified by reverse phase Combi-flash eluting with 0.3% NH_4HCO_3 in 1:3 water/CH_3CN to give **206h** as a brown solid (500 mg, 71%). MS: $(M+H)^+$ 642

A solution of **206h** (500 mg, 0.78 mmol) in HCl/ethyl acetate (5 mL) was stirred at room temperature for 2 h. It was then evaporated and the residue was purified by prep-HPLC to afford **206** as a brown solid (134 mg, 35%).MS: $(M+H)^+$ 542. ^1H NMR (500 MHz, MeOD) δ 1.79 (s, 2 H), 1.89 (s, 2 H), 2.35 (s, 3 H), 2.54-2.56 (t, J=6 Hz, 2 H), 2.63-2.67 (m, 2 H), 2.97-2.99 (t, J=6 Hz, 2 H), 3.71 (s, 3 H), 4.00-4.03 (m, 1 H), 4.14-4.23 (m, 5 H), 4.50-4.60 (m, 2 H), 6.06-6.07 (d, 1 H), 6.71 (s, 1 H), 7.23-7.24 (d, 1 H), 7.37-7.43 (m, 2H), 7.49-7.52 (m, 2 H), 8.01-8.02 (d, 1H).

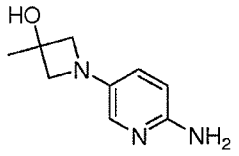
Example 207 2-(3-(5-(5-(3-Hydroxy-3-methylazetidin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **207**

Example 207a 3-Methyl-1-(6-nitropyridin-3-yl)azetidin-3-ol **207a**



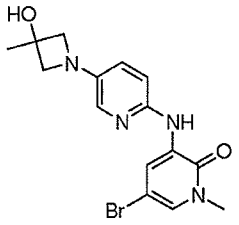
A mixture of 5-bromo-2-nitropyridine (3.28 g, 16.3 mmol), XantPhos (1.13 g, 1.96 mmol), Pd_2dba_3 (1.19 g, 1.30 mmol), 3-methylazetidin-3-ol hydrochloride (2 g, 16.3 mmol) and Cs_2CO_3 (15.9 g, 48.9 mmol) in 1,4-dioxane (70 mL) was heated at reflux for 2 h. After the completion of the reaction, the mixture was filtered off, and washed with MeOH (100 mL). The filtrate was evaporated in *vacuo* and the residue was purified on reverse phase Combi-flash to give **207a** (2.5 g, 71%). MS: $[M+H]^+$ 210.

Example 207b 1-(6-Aminopyridin-3-yl)-3-methylazetidin-3-ol **207b**



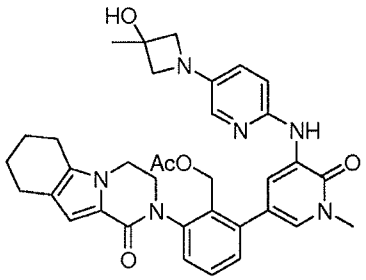
A 100-mL Parr hydrogenation bottle was purged with nitrogen and charged with **207a** (2.3 g, 11 mmol), 10% palladium on carbon (50% wet, 1.0 g) and methanol (100 mL). The bottle was evacuated, charged with hydrogen gas to a pressure of 25 psi and shaken for 2 h on a Parr hydrogenation apparatus. The hydrogen was then evacuated and nitrogen charged to the bottle. The catalyst was removed by filtration through a pad of Celite and the filtrate was concentrated under reduced pressure to afford **207b** (1.85 g, 92%). MS: $[M+H]^+$ 180.

Example 207c 5-Bromo-3-(5-(3-hydroxy-3-methylazetidin-1-yl)pyridin-2-ylamino)-1-methylpyridin-2(1H)-one **207c**



A mixture of **207b** (1.84 g, 10.3 mmol), XantPhos (714 mg, 1.24 mmol), Pd_2dba_3 (755 mg, 0.82 mmol), 3,5-dibromo-1-methylpyridin-2(1H)-one (3.27 g, 12.3 mmol) and Cs_2CO_3 (10 g. 30.9 mmol) in 1,4-dioxane (50 mL) was heated at reflux for 2 h. After the completion of the reaction, the mixture was filtered off, and washed with MeOH (100 mL). The filtrate was evaporated in *vacuo* and the residue was purified on reverse phase Combi-flash to give **207c** (2.11 g, 54%). MS: $[M+H]^+$ 365.

Example 207d 2-(5-(5-(3-Hydroxy-3-methylazetidin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **207d**



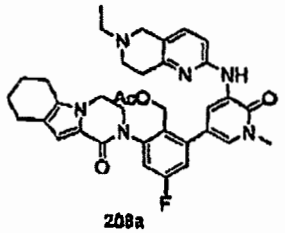
A mixture of **207c** (364 mg, 1.0 mmol), 2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **114a** (510

A mixture of **207c** (364 mg, 1.0 mmol), 2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **114a** (510 mg, 1.1 mmol), $PdCl_2(dppf)$ (110 mg, 0.15 mmol), K_3PO_4 (100 mg), and NaOAc (50 mg) in MeCN (20 mL) and water (4 mL) was heated at reflux for 2 h. The solvent was evaporated in *vacuo* and the residue was purified on reverse phase Combi-flash to give **207d** (267 mg, 43%). MS: $[M+H]^+$ 623.

A mixture of **207d** (350 mg, 0.56 mmol) and LiOH hydrate (236 mg, 5.6 mmol) in ^{i}PrOH (20 mL) and water (4 mL) was stirred at 30°C for 2 h. The mixture was evaporated in *vacuo* and the residue was extracted with ethyl acetate (20 mL × 2). The combined extracts were concentrated under reduced pressure. And the residue was purified on prep-HPLC to give **207** (130 mg, 40%). MS: $[M+H]^+$581. ^{1}H NMR (500 MHz, DMSO) δ 8.48 (*s*, 1H), 8.25 (s, 1H), 7.48-7.44 (m, 2H), 7.34-7.28 (m, 3H), 7.17 (d, J = 8.5, 1H), 6.89-6.87 (m, 1H), 6.51 (s, 1H), 5.47 (s, 1H), 4.84-4.83 (m, 1H), 4.33 (d, J = 4.5, 2H), 4.18-4.06 (m, 3 H), 3.90-3.86 (m, 1H), 3.70 (d, J = 7.5, 2H), 3.58 (s, 3H), 3.53-3.52 (m, 2H), 2.64-2.54 (m, 2H), 2.47-2.45 (m, 2H), 1.82-1.75 (m, 2H), 1.73-1.65 (m, 2H), 1.43 (s, 3H).

Example 208 2-(3-(5-(6-Ethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **208**

Example 208a 2-(5-(6-Ethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-fluoro-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **208a**



208a

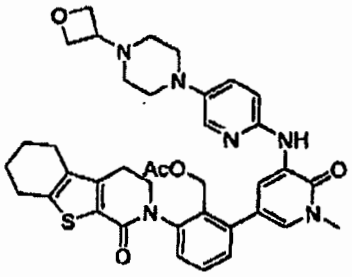
Following Example 136e, 5-bromo-3-(6-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-2-ylamino)-1-methylpyridin-2(1H)-one and 4-fluoro-2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **210d** was converted to **208a** in 42% yield. LCMS: $(M+H)^+$ 639

Following Example 136, **208a** was converted to **208** in 40% yield. LCMS: $(M+H)^+$ 597. ^{1}H NMR (500 MHz, DMSO) δ 8.80 (d, J=2, 1H), 8.45 (s, 1H), 7.45 (d, J=2, 1H), 7.31

(m, 2H), 7.20 (dd, J=10, 1H), 7.07 (d, J=9, 1H), 6.53 (s, 1H), 4.36 (s, 2H), 4.14 (m, 3H), 3.90 (m, 1H), 3.60 (s, 3H), 2.74 (m, 2H), 2.68 (m, 2H), 2.59 (m, 2H), 2.47 (m, 3H), 1.79 (m, 2H), 1.69 (m, 2H), 1.08 (t, J=7.5, 3H).

Example 209 5-[2-(Hydroxymethyl)-3-[1-methyl-5-({5-[4-(oxetan-3- yl)piperazin-1-yl]pyridine-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6- one **209**

Example 209a {2-[1-Methyl-5-({5-[4-(oxetan-3-yl)piperazin-1-yl]pyridin-2-yl}amino)-6-oxopyridin-3-yl]-6-{6-oxo-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-5-yl}phenyl}methyl Acetate **209a**



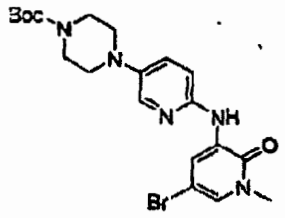
209a

Following Example 148c, 481 mg of **111a** and 420 mg of 5-bromo-1-methyl-3-(5-(4-(oxetan-3-yl)piperazin-1-yl)pyridine-2-ylamino)pyridin-2(1H)-one **188e** were reacted to give **209a** as a yellow solid (347 mg, 50%). MS: $[M+H]^+$ 695

Following Example 148, 230 mg of **209a** was converted to **209** as a white solid (108 mg, 50%). MS: $[M+H]^+$ 653. ^{1}H NMR (500 MHz, DMSO) δ 8.56 (d, J=2.5, 1H), 8.37 (s, 1H), 7.86 (d, J=3.0, 1H), 7.45 (d, J=7.5, 1H), 7.36-7.30 (m, 4H), 7.23 (d, J=9.0, 1H), 4.82 (s, 1H), 4.55 (t, J=6.5, 2H), 4.45 (t, J=6.0, 2H), 4.35 (s, 2H), 4.02(m, 1H), 3.82 (m, 1H), 3.58 (s, 3H), 3.42 (m, 2H), 3.06 (t, J=4.5, 4H), 2.92-2.80 (m, 2H), 2.78 (s, 2H), 2.53 (m, 1H), 2.38 (s, 4H), 1.80 (s, 4H).

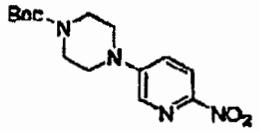
Example 210 2-(5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **210**

Example 210a 5-Bromo-1-methyl-3-[5-(4-*tert*-butoxycarbonylpiperazin-1-yl)-pyridin-2-ylamine **210a**



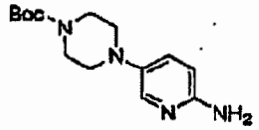
210a

Step 1: *tert*-Butyl 4-(6-Nitropyridin-3-yl)piperazine-1-carboxylate

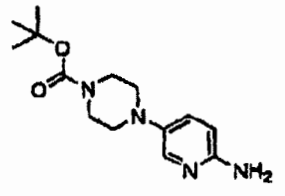


To solution of 5-bromo-2-nitropyridine (30 g, 148 mmol) in DMSO (1 L) were added K_2CO_3 (40 g, 296 mmol) and tert-butyl piperazine-1-carboxylate (28g, 148 mmol). The mixture was stirred at 65°C overnight. After cooling down, it was poured into water (2 L). The solid precipitated was collected and dried under vacuum. It was then purified by flash column eluting with PE:EA (20:1) and then DCM to give 17 gm of *tert*-butyl 4-(6-nitropyridin-3-yl)piperazine-1-carboxylate as a yellow solid (37% yield). MS: $[M+H]^+$ 309

Step 2: *tert*-Butyl 4-(6-Aminopyridin-3-yl)piperazine-1-carboxylate

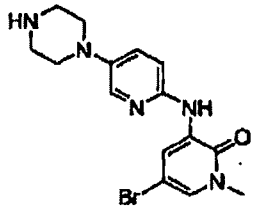


A 500-mL bottle was purged with nitrogen and charged with *tert*-butyl 4-(6-nitropyridin-3-yl)piperazine-1-carboxylate (3.1 g, 10 mmol), 10% palladium on carbon (50% wet, 1 g) and ethanol (100 mL). The bottle was evacuated, charged with hydrogen gas, and stirred for 16 h at room temperature. The hydrogen was then evacuated and nitrogen charged into the bottle. The catalyst was removed by filtration through a pad of Celite and the filtrate concentrated under reduced pressure to afford *tert*-butyl 4-(6-aminopyridin-3-yl)piperazine-1-carboxylate (2.7 g, 97%). MS: $[M+H]^+$ 279



Step 3: A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was charged with 1,4-dioxane (50 mL), *tert*-butyl 4-(6-aminopyridin-3-yl)piperazine-1-carboxylate, prepared according to US 7456168, (1.3 g, 4.7 mmol), 3,5-dibromo-1-methylpyridin-2(1H)-one (1.24 g, 4.7 mmol) and cesium carbonate (3.8 g, 12 mmol). After bubbling nitrogen through the resulting solution for 30 min, Xantphos (272 mg, 0.47 mmol) and tris(dibenzylideneacetone)dipalladium(0) (430 mg, 0.47 mmol) were added, and the reaction mixture was heated at reflux for 3 h. After this time the reaction was cooled to room temperature, partitioned between ethyl acetate (100 mL) and water (100 mL) and filtered. The aqueous layer was separated and extracted with ethyl acetate (2 × 50 mL). The organic layers were combined and washed with brine (50 mL) and dried over sodium sulfate. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified on flash column eluting with DCM:MeOH (50:1) to afford **210a** (1.3 g, 59%). MS: $[M+H]^+$ 464.

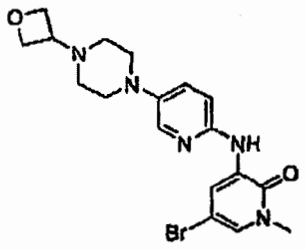
Example 210b 5-Bromo-1-methyl-3-[5-(piperazin-1-yl)-pyridin-2-ylamino]-1H-pyridin-2-one **210b**



210b

Compound **210a** (3.6 g, 7.8 mmol) was suspended in 4.0 M HCl/dioxane (10 mL). The reaction mixture was stirred for 5h at room temperature and concentrated at reduced pressure. The desired product was basified with aqueous 1. 0 M NaOH and was extracted with methylene chloride. The combined organic layers were washed with H2O and concentrated under reduced pressure to give 2.46g of **210b** with an 87% yield. MS: $[M+H]^+$ 364.

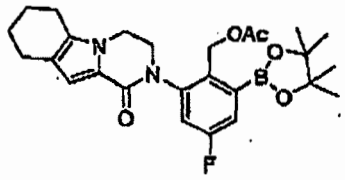
Example 210c 5-Bromo-1-methyl-3-[5-(4-(oxetan-3-yl)piperazin-1-yl)-pyridin-2-ylamino]-1H-pyridin-2-one **210c**



210c

A mixture of 210b (2.75 g, 7.5 mmol), oxetan-3-one (1.6 g, 22.7 mmol), $NaBH_3CN$ (4.75 g, 22.5 mmol) and zinc chloride (3 g, 22.7 mmol) in methanol (125 mL) was stirred for 5 hours at 50 degree. The mixture was added to water and extracted with methylene chloride three times. The organic layers were concentrated under reduced pressure. The residue was purified by column-chromatography eluting with methylene chloride: methanol = 25:1 to give 210c (1.92 g, 61%). MS: $[M+H]^+$ 420. ^1H NMR (500 MHz, DMSO) δ 8.58 (d, J = 2.5, 1H), 8.55 (s, 1H), 7.94 (d, J = 3, 1H), 7.54 (d, J = 2.5, 1H), 7.39 (dd, J = 3, 1H), 7.25 (d, J = 4, 1H), 4.56 (t, J = 6.5, 2H), 4.46 (t, J = 6.5, 2H), 3.50 (s, 3H), 3.43 (m, 1 H), 3.01 (m, 4H), 2.40 (m, 4H).

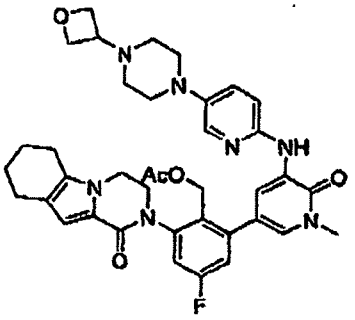
Example 210d 2-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-4-fluoro-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate 210d



210d

A 250-mL single-neck round-bottomed flask equipped with a magnetic stirrer was charged with 197d (3.8 g, 8.65 mmol), bis(pinacolato)diboron (11 g, 43.25 mmol), $Pd(dppf)Cl_2$ (0.4g, 0.5 mmol), KOAc (2.5 g, 26 mmol), and 1,4-dioxane (150 mL). The system was evacuated and then refilled with N_2. A reflux condenser was attached to the flask, and the reaction mixture was heated at 100 °C for 15 h. It was then cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography eluting with 5:1 petroleum ether/ethyl acetate to afford 210d in 77% yield (3.2 g) as a yellow solid. MS: $[M+H]^+$ 483.

Example 210e 5-Fluoro-2-(1-methyl-5-(5-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **210e**



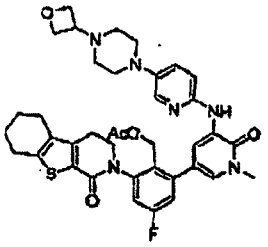
210e

A sealed tube was charged with the mixture of **210d** (337 mg, 0.7 mmol), **210c** (294 mg, 0.7 mmol), $Pd(dppf)Cl_2$ (33 mg, 0.04 mmol), $K_3PO_4.3H_2O$(372 mg, 1.4 mmol), and NaOAc (115 mg, 1.4 mmol) in 20 mL CH_3CN. The system was evacuated and refilled with N_2. The reaction mixture was heated at 110 °C for 2h. It was then cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography eluting with 30:1 DCM/MeOH to afford **210e** in 54% yield (263 mg) as a yellow solid. MS: $[M+H]^+$ 696.

At room temperature, to the solution of **210e** (250 mg, 0.36mol) in THF/iso-propanol/water (6 mL/6 mL/2 mL) was added LiOH (87 mg, 3.6 mmol) while stirring. This mixture was stirred for 0.5 h. Then, 20 mL of water was added and extracted with ethyl acetate (30 mL X 3). The combined organic layer was dried with Na_2SO_4 and concentrated to get a yellow solid which was further purified by prep-HPLC to afford **210** as a white solid (134 mg, 57% yield). LCMS: $[M+H]^+$ 654. ^1H NMR (500 MHz, MEOD) δ 8.53 (d, J = 2.5, 1H), 7.93 (d, J = 3, 1H), 7.42 (dd, J = 3, 1H), 7.34 (d, J = 2.5, 1H), 7.23 (s, 1H), 7.21 (s, 1H), 7.03 (d, J = 4.5, 1H), 6.72 (s, 1H), 4.73 (t, J = 2, 2H), 4.64 (t, J = 1.5, 2H), 4.51 (m, 2 H), 4.21 (s, 3H), 4.03 (m, 1H), 3.71 (s, 3H), 3.57 (m, 1H), 3.17 (t, J = 4.5, 4H), 2.65 (m, 2H), 2.55 (m, 6H), 1.90 (m, 2H), 1.79 (m, 2H)

Example 211 5-[5-Fluoro-2-(hydroxymethyl)-3-[1-methyl-5-({5-[4-(oxetan-3-yl)piperazin-1-yl]pyridin-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$]trideca-1(9),2(7)-dien-6-one **211**

Example 211a {4-Fluoro-2-[1-methyl-5-({5-[4-(oxetan-3-yl)piperazin-1-yl]pyridin-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]-6-{6-oxo-8-thia-5-azatricyclo[7.4.0.0^{2,7}]-trideca-1(9),2(7)-dien-5-yl}phenyl}methyl Acetate 211a



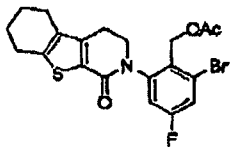
211a

Following Example 148h, 400 mg of (4-fluoro-2-{6-oxo-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-5-yl}-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl acetate 212b and 336 mg of 5-bromo-1-methyl-3-(5-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-2-ylamino)pyridine-2(1H)-one 210c were reacted to give 211a as a yellow solid (319 mg, 56%). LCMS: $(M+H)^+$ 713

Following Example 148, 270 mg of 211a was converted to 211 as a white solid (120 mg, 48%). LCMS: $[M+H]^+$ 671. ^{1}H NMR (500 MHz, DMSO) δ 8.56 (s, 1H), 8.39 (s, 1H), 7.87 (s,1H), 7.38-7.16 (m, 5H), 4.8 (s,1H), 4.56 (t, J=6.5 2H), 4.46 (t, J=6.5, 2H), 4.33 (s, 1H), 4.05 (m,1H), 3.87 (m, 1H), 3.58(s, 3 H), 3.43 (t, J=6, 2H), 3.06 (m, 4H), 2.88-2.78 (m, 4H), 2.38 (t, J=5, 1H), 1.79(m, 4H).

Example 212 5-[5-Fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[5-(4-methylpiperazin-1-yl)pyridine-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6- one 212

Example 212a 2-Bromo-4-fluoro-6-(1-oxo-3,4,5,6,7,8-hexahydrobenzothieno[2,3-*c*]pyridin-2(1*H*)-yl)benzyl Acetate 212a

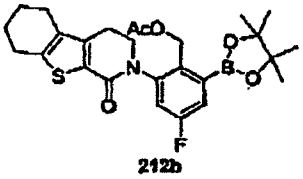


212a

A solution of 104e (3 g, 14.5 mmol), 2,6-dibromo-4-fluorobenzyl acetate 197e (14 g, 43.5 mmol), Xantphos (839 mg, 1.45 mmol), $Pd_2(dba)_3$ (1.33 g, 1.45 mmol) and Cs_2CO_3 (9.4 g, 29 mmol) in dioxane (200 mL) was heated at 100 °C for 15 h under nitrogen. After

filtration, the filtrate was evaporated in *vacuo* and purified by flash column eluting with ethyl acetate/petroleum ether (1:1) to give **212a** (5 g, yield 77 %) as a yellow solid. LCMS: $(M+H)^+$ 452. ^1H NMR (500 MHz, DMSO) δ 7.71 (dd, J = 2.5, 1H), 7.51 (dd, J = 3, 1H), 5.04 (m, 1H), 4.10 (m, 1H), 3.68 (m, 1H), 2.86 (m, 2H), 2.77 (m, 2H), 2.55 (m, 3H), 1.98 (s, 3H), 1.78 (m, 4H)

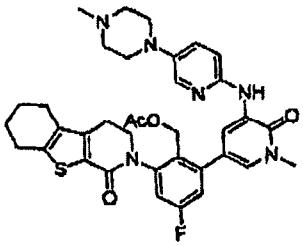
Example 212b 2-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-4-fluoro-6-(1-oxo-3,4,5,6,7,8-hexahydrobenzothieno[2,3-*c*]pyridin-2(1*H*)-yl)benzyl Acetate **212b**



212b

A solution of **212a** (3 g, 6.65 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bis(1,3,2-dioxa-borolane) (10 g, 40 mmol) in dioxane (160 mL) was added $PdCl_2$(dppf) (543 mg, 0.66 mmol) and CH_3COOK (3.9 g, 40 mmol). The mixture was stirred at 100° for 15 h under argon atmosphere. The mixture was filtered and evaporated in *vacuo* and purified by flash column eluting with ethyl acetate/petroleum ether (1:2) to give **212b** (2.5 g, yield 76 %) as a yellow solid. LCMS: $(M+H)^+$ 500

Example 212c [4-Fluoro-2-(1-methyl-5-{[5-(4-methylpiperazin-1-yl)pyridin-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)-6-{6-oxo-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$]-trideca-1(9),2(7)-dien-5-yl}phenyl]methyl Acetate **212c**



212c

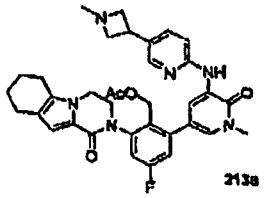
A 25 mL sealed tube was charged with **212b** (990 mg, 2 mmol), 5-bromo-1-methyl-3-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)pyridine-2(1H)-one **198e** (500 mg, 1.3 mmol), CH_3COONa (220 mg, 2.6 mmol), K_3PO_4 (700 mg, 2.6 mmol), and $PdCl_2$(dppf) (110 mg, 0.13 mmol) suspended in CH_3CN (25 mL) and water (1 mL). The mixture was heated at 110 °C for 2 hours. It was evaporated and the residue was purified by silical-gel column eluting with

20:1 methylene chloride/methanol to give **212c** as a brown solid (500 mg, 56%). LCMS: $[M+H]^+$ 670

To a solution of **212c** (500 mg, 0.75 mmol) in propan-2-ol (8 mL), tetrahydrofuran (8 mL), and water (1.5 mL) was added LiOH (964 mg, 40 mmol). The mixture was stirred at 30°C for 2 h. Then, 20 mL H_2O was added and the mixture was extracted with ethyl acetate (3 X 30 mL). The combined organic layer was dried with Na_2SO_4 and concentrated to give a yellow solid, which was further purified by prep-HPLC to give **212** as a white solid (200 mg, 48%). LCMS: $[M+H]^+$ 629. ^1H NMR (500 MHz, DMSO-d_6) δ 8.56 (d, J = 2, 1H), 8.37 (s, 1H), 7.85 (d, J = 2.5, 1H), 7.34 (m, 3H), 7.19 (m, 2H), 4.86 (s, 1H), 4.32 (s, 2H), 4.05 (m, 1H), 3.87 (m, 1H), 3.57 (s, 3H), 3.02 (m, 4H), 2.96 (m, 1H), 2.87 (m, 1H), 2.77 (m, 2H), 2.54 (m, 1H), 2.43 (m, 4H), 2.19 (s, 3H), 1.79 (m, 4H).

Example 213 2-(5-Fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(1-methylazetidin-3-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **213**

Example 213a 4-Fluoro-2-(1-methyl-5-(5-(1-methylazetidin-3-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **213a**



213a

Following Example 148b, 482 mg of 4-fluoro-2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **210d** and 350 mg 5-bromo-1-methyl-3-(5-(1-methylazetidin-3-yl)pyridin-2-ylamino)pyridin-2(1H)-one **172a**, were reacted to give **213a** as a yellow solid (324 mg, 52%). MS: $[M+H]^+$ 625

Following the procedures as described for **148** and starting with 220 mg of **213a**, compound **213** was obtained as a white solid (82 mg, 40%). MS: $[M+H]^+$ 583. ^1H NMR (500 MHz, CDCl3) δ 8.64 (d, J=2.0, 1H), 8.13 (d, J=2.5, 1H), 7.89 (s, 1H), 7.58 (m, 1H), 7.50 (d, J=2.5, 1H), 7.16 (dd, J=9.0, 1H), 6.96 (dd, J=8.5, 1H), 6.86 (s, 1H), 6.83 (d, J=8.5, 1H), 4.55 (d, J=11.5, 1H), 4.40(s, 1H), 4.30 (s, 1H), 4.16 (m, 2H), 3.91 (m, 1H), 3.72 (m,5H), 3.60 (m, 1H), 3.14 (t, J=7.0, 2H), 2.59 (m, 4H), 2.38 (s, 3H), 1.90-1.79 (m,5H).

Example 214 2-(5-Fluoro-2-(hydroxymethyl)-3-(4-methyl-6-(4-(1-(oxetan-3-yl)piperidin-4-yl)phenylamino)-5-oxo-4,5-dihydropyrazin-2-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **214**

Example 214a 5-Bromo-1-methyl-3-(4-(piperidin-4-yl)phenylamino)pyrazin-2(1H)-one **214a**

Compound **214a** was synthesized using the same procedure as for **121c**, except using tert-butyl 4-(4-(6-bromo-4-methyl-3-oxo-3,4-dihydropyrazin-2-ylamino)phenyl)-piperidine-1-carboxylate (**121a**) (0.53g, 1.08 mmol), trifluoroacetic acid (0.9 mL, 10.8 mmol) and methylene chloride (20 mL). Work-up and concentration afforded a quantitative yield of **214a** (390 mg) as yellow oil, which was used without purification in the next step.

Example 214b 5-Bromo-1-methyl-3-(4-(1-(oxetan-3-yl)piperidin-4-yl)phenylamino)-pyrazin-2(1H)-one **214b**

A 100-mL sealed tube with a magnetic stirrer was purged with nitrogen and charged with **214a** (390 mg, 1.08 mmol), oxetan-3-one (800 mg, 11 mmol) and methanol (10 mL). A suspension of sodium cyanoborohydride (208 mg, 3.3 mmol) and zinc chloride (225 mg, 1.65 mmol) in methanol (10 mL) was added, and the reaction was heated at 48 °C for 12 hours. After this time, the reaction mixture was concentrated, and the residue was partitioned between ethyl acetate (50 mL) and 10% aqueous potassium carbonate (10 mL). The aqueous layer was extracted with ethyl acetate (3×30 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by column chromatography (silica, 60:35:5 methylene chloride/diethyl ethyl/methanol) to afford a 60% yield (270 mg) of 5-bromo-1-methyl-3-(4-(1-(oxetan-3-yl)piperidin-4-yl)phenylamino)pyrazin-2(1H)-one (**214b**) as a yellow solid: MS (ESI+) *m/z* 421.2 (M+H).

Example 214c 4-Fluoro-2-(4-methyl-6-(4-(1-(oxetan-3-yl)piperidin-4-yl)phenylamino)-5-oxo-4,5-dihydropyrazin-2-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **214c**

Following Example 121b, 4-fluoro-2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **210d** (217 mg, 0.45 mmol), **214b** (158 mg, 0.375 mmol), 1M sodium carbonate solution (1.5 mL, 1.5 mmol), tetrakis(triphenylphosphine)palladium(0) (22 mg, 0.019 mmol) and 1,2-dimethoxyethane (3.5 mL) were heated at 130 °C for 15 minutes in the microwave reactor. Work-up and flash column chromatography (silica, 60:35:5 methylene chloride/diethyl

ether/methanol) give a 62% yield (160 mg) of **214c** as brown oil: MS (ESI+) *m/z* 696.1 (M+H).

Compound **214** was synthesized using the same procedure as for **121**, except using a mixture of THF (1 mL), water (0.5 mL) and isopropanol (1 mL), **214c** (160 mg, 0.23mmol) and lithium hydroxide monohydrate (80 mg, 2 mmol). Work-up and flash column chromatography (NH-silica, ethyl acetate /Hexanes) give a 34% yield (52 mg) of **214** as a yellow solid: MS (ESI+) *m/z* 653.6 (M+H).

Example 215 10-[5-Fluoro-2-(hydroxymethyl)-3-(4-methyl-6-{[4-(1-methylazetidin-3-yl)phenyl]amino}-5-oxo-4,5-dihydropyrazin-2-yl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-9-one **215**

Example 215a 10-[5-Fluoro-2-(acetoxymethyl)-3-(4-methyl-6-{[4-(1-methylazetidin-3-yl)phenyl]amino}-5-oxo-4,5-dihydropyrazin-2-yl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-9-one **215a**

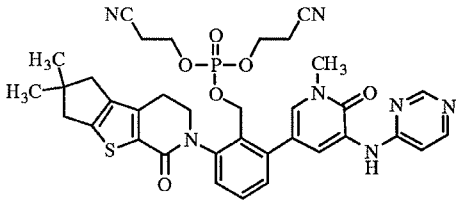
A 44-mL sealed tube equipped with a magnetic stirrer was charged with **298c** (160 mg, 0.48 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (180 mg, 0.71 mmol), potassium acetate (188 mg, 1.9 mmol) and 1,4-dioxane (5 mL). After the mixture was degassed for 30 minutes, Pd(dppf)Cl_2 •CH_2Cl_2 (39 mg, 0.048 mmol) was added. The resulting reaction mixture was stirred at 105 °C for 4 h. Then, it was cooled to room temperature and filtered through a pad of Celite. The filtrate was concentrated, and the crude mixture was redissolved in 1,2-dimethoxyethane (2 mL) and transferred into a 10-mL microwave reaction vessel. To this solution was added 10-[2-(acetoxy-methyl)-3-bromo-5-fluorophenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-9-one **189a** (172 mg, 0.38 mmol), Pd(PPh_3)$_4$ (30 mg, 0.024 mmol), and 2 N Na_2CO_3 (2 mL). Then, the reaction mixture was degassed for 5 minutes and placed into the microwave cavity. After the reaction mixture was stirred at 125 °C for 10 min., it was purified by flash chromatography (dichloromethane:methanol, 3:1) to give 20% (49 mg) of **215a**.

A 25-mL, single-necked, round-bottomed flask equipped with a magnetic stirring bar was charged with **215a** (49 mg, 0.077 mmol), LiOH•H_2O (16 mg, 0.38 mmol), THF (2 mL), isopropanol (2 mL), and water (2 mL). After the reaction mixture was stirred at room temperature for 3 h, it was partitioned between dichloromethane (5 mL) and water (5 mL), and the organic phase was extracted with dichloromethane (3 X 5 mL). The combined organic phases were washed with water (2 X 5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. The crude product was re-dissolved in dichloromethane (3 mL). To this

solution was added hexane (10 mL) and the resulting precipitate was filtered to give 74% yield (34 mg) of **215**. MS(ESI$^+$) *m/z* 597.5 (M+H).

Example 216 Di-sodium 2-(1-Methyl-6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydro-pyridin-3-yl)-6-(6,6-Dimethyl-3,4,6,7-tetrahydro-5*H*-cyclopenta[4,5]thieno[2,3-*c*]pyridine-1(2*H*)-yl)benzyl Phosphate **216**

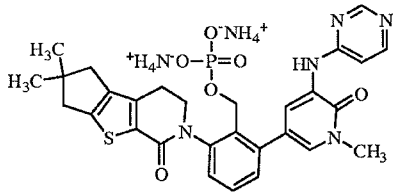
Example 216a *Bis*(2-cyanoethyl) 2-(1-Methyl-6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydropyridin-3-yl)-6-(6,6-Dimethyl-3,4,6,7-tetrahydro-5*H*-cyclopenta[4,5]thieno-[2,3-*c*]pyridine-1(2*H*)-yl)benzyl Phosphate **216a**



216a

A 250-mL single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was charged with **105** (850 mg, 1.61 mmol), 1*H*-tetrazole (451 mg, 6.44 mmol) and methylene chloride (20 mL). A solution of bis(2-cyanoethyl)-N.N- diisopropyl phosphoramidite (1.31 g, 4.83 mmol) in methylene chloride (5 mL) was added at room temperature, and the reaction mixture was stirred for 3 h under nitrogen atmosphere. After this time, the reaction mixture was cooled to 0 °C and a 5.5 M solution of *tert*-butyl hydroperoxide in decane (2.00 mL, 11.0 mmol) was added dropwise, and the reaction mixture was stirred at 0 °C for 3 h under nitrogen atmosphere. After this time, the mixture was concentrated under reduced pressure to a volume of 5 mL, and the resulting suspension was loaded on a silica gel column and eluted with 90:10 methylene chloride/methanol to afford **216a** in 39% yield (450 mg) as a white semi-solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (d, *J*= 0.5 Hz, 1H), 8.73 (d, *J* = 2.0 Hz, 1H), 8.36 (d, *J* = 5.5 Hz, 1H), 8.17 (s, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.38–7.35 (m, 2H), 7.09 (d, *J* = 2.0 Hz, 1H), 6.76 (dd, *J* = 6.0, 1.5 Hz, 1H), 5.21–5.14 (m, 2H), 4.15–4.04 (m, 5H), 3.86–3.83 (m, 1H), 3.72 (s, 3H), 3.21–3.18 (m, 1H), 2.90–2.82 (m, 1H), 2.79 (d, *J* = 3.5 Hz, 2H), 2.63–2.48 (m, 6H), 1.28 (s, 3H), 1.27 (s, 3H); MS (ESI+) *m/z* 714.2 (M+H).

Example 216b Di-ammonium 2-(1-Methyl-6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydro-pyridin-3-yl)-6-(6,6-Dimethyl-3,4,6,7-tetrahydro-5*H*-cyclopenta[4,5]thieno[2,3-*c*]pyridine-1(2*H*)-yl)benzyl Phosphate **216b**



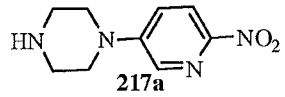
216b

A 250-mL single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was charged with **216a** (450 mg, 0.631 mmol) and acetonitrile (8 mL), and the mixture was cooled to 0 °C. Triethylamine (4 mL) was added followed bis trimethyl-silyl trifluoroacetamide (4 mL), and the mixture was stirred at room temperature for 40 h. After this time, the mixture was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography (silica, 40:20:40 chloroform/ methanol/ammonia) to afford **216b** in 52% yield (210 mg) as an amorphous yellow solid: mp 260–262°C d; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.12 (s, 1H), 8.66 (s, 1H), 8.62 (d, J = 2.0 Hz, 1H), 8.27 (d, J = 4.0 Hz, 1H), 7.54 (s, 1H), 7.43 (t, J = 7.5 Hz, 1H), 7.32–7.27 (m, 3H), 7.15 (br s, 2H), 4.69 (d, J = 9.0 Hz, 1H), 4.46 (d, J = 7.0 Hz, 1H), 3.87–3.83 (m, 3H), 3.57 (s, 3H), 3.36–3.17 (br s, 8H), 2.77–2.63 (m, 3H), 1.23 (s, 3H), 1.21 (s, 3H); MS (ESI+) *m/z* 608.2 (M+H for $C_{29}H_{30}N_5O_6PS$).

A 200-mL single-neck round-bottomed flask equipped with a magnetic stirrer was charged with **216b** (210 mg, 0.327 mmol), methanol (10 mL) and water (5 mL). A 0.1 M solution of sodium hydroxide in water (6.50 mL, 0.65 mmol) was added at room temperature, and the mixture was stirred for 30 min. After this time, the mixture was concentrated under reduced pressure and dried under vacuum at 45 °C for 14 h to afford **216** in 92% yield (197 mg) as an amorphous yellow solid: mp 256–258 °C dec; ^{1}H NMR (500 MHz, DMSO-d_6/D_2O (15:1)) δ 8.65 (s, 1H), 8.63 (d, J = 1.5 Hz, 1H), 8.28 (d, J = 6.0 Hz, 1H), 8.09 (d, J = 1.5 Hz, 1H), 7.47 (t, J = 7.5 Hz, 1H), 7.38 (d, J = 7.5 Hz, 1H), 7.24 (d, J = 7.5 Hz, 1H), 7.16 (d, J = 6.0 Hz, 1H), 4.72 (d, J = 9.5 Hz, 1H), 4.45 (d, J = 8.0 Hz, 1H), 4.23–4.21 (m, 1H), 3.83–3.78 (m, 1H), 3.71 (s, 3H), 3.48–3.41 (m, 1H), 2.78–2.73 (m, 3H), 2.59–2.49 (m, 2H), 1.23 (s, 3H), 1.22 (s, 3H); MS (ESI+) *m/z* 608.2 (M+H for $C_{29}H_{30}N_5O_6PS$).

Example 217 5-(5-Fluoro-2-(hydroxymethyl)-3-(6,6-Dimethyl-3,4,6,7-tetrahydro-5*H*-cyclopenta[4,5]thieno[2,3-*c*]pyridine-1(2*H*)-yl)-3-(5-(4-(2-fluoroethyl)piperazin-1-yl)pyridin-2-ylamino)-1-methylpyridin-2(1*H*)-one **217**

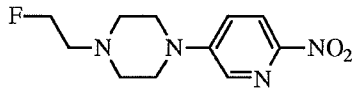
Example 217a 1-(6-Nitropyridin-3-yl)piperazine **217a**



217a

A 250-mL three-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was charged with 2-nitro-5-bromopyridine (5.00 g, 24.6 mmol), piperazine (5.66 g, 65.7 mmol) and acetonitrile (70 mL). The reaction mixture was heated at reflux for 20 h. After this time, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was diluted with ethyl acetate (200 mL) and washed with saturated aqueous sodium bicarbonate (100 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was titrated with hexane/ethyl acetate (1:1, 30 mL) to afford **217a** in 41% yield (2.10 g) as a yellow solid: mp 113–115 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.23 (d, 1H, J = 3.5 Hz), 8.13 (d, 1H, J = 9.0 Hz), 7.44 (dd, 1H, J = 9.0, 3.5 Hz), 3.41 (t, 4H, J = 5.0 Hz), 2.82 (t, 4H, J = 5.0 Hz), 1.90 (s, 1H); MS (ESI+) m/z 209.1 (M+H).

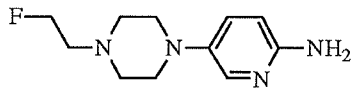
Example 217b 1-(2-Fluoroethyl)-4-(6-nitropyridin-3-yl)piperazine **217b**



217b

A 250-mL single-neck round-bottomed flask equipped with a magnetic stirrer, reflux condenser, and nitrogen inlet was charged with **217a** (598 mg, 2.87 mmol), 1-bromo-2-fluoroethane (1.09 g, 8.61 mmol), potassium carbonate (1.19 g, 8.61 mmol), THF (10 mL) and DMF (10 mL). The reaction mixture was heated at 85 °C for 14 h under nitrogen atmosphere. After this time, the mixture was diluted with 90:10 methylene chloride/methanol (100 mL) and water (75 mL), and the layers were separated. The aqueous layer was extracted with 90:10 methylene chloride/methanol (50mL), and the combined organic layers were washed with brine (100 mL) and dried over sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography (silica, 95:5 methylene chloride/methanol) to afford **217b** in 63% yield (460 mg) as a yellow semi-solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, J = 9.0 Hz, 1H), 8.14 (d, J = 3.0 Hz, 1H), 7.21 (dd, J = 9.0, 2.0 Hz, 1H), 4.67 (t, J = 5.0 Hz, 1H), 4.57 (t, J = 5.0 Hz, 1H), 3.49 (t, J = 5.0 Hz, 4H), 2.81 (t, J = 5.0 Hz, 1H), 2.75 (t, J = 5.0 Hz, 1H), 2.73 (t, J = 5.5 Hz, 4H); MS (ESI+) m/z 255.1 (M+H).

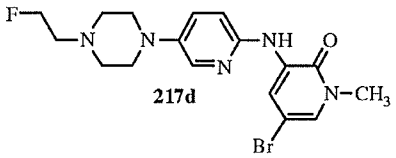
Example 217c 5-(4-(2-Fluoroethyl)piperazin-1-yl)pyridin-2-amine **217c**



217c

A 250-mL Parr reactor bottle was purged with nitrogen and charged with 10% palladium on carbon (50% wet, 75 mg dry weight) and a solution of **217b** (455 mg, 1.79 mmol) in ethanol (20 mL). The bottle was attached to a Parr hydrogenator, evacuated, charged with hydrogen gas to a pressure of 50 psi and shaken for 3 h. After this time, the hydrogen was evacuated, and nitrogen was charged into the bottle. Celite 521 (3.50 g) was added, and the mixture was filtered through a pad of Celite 521. The filter cake was washed with ethanol (2 × 50 mL), and the combined filtrates were concentrated to dryness under reduced pressure to afford a quantitative yield of **217c** (425 mg) as a yellow semi-solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 3.0 Hz, 1H), 7.20 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.51 (d, *J* = 8.5 Hz, 1H), 4.66 (t, *J* = 5.0 Hz, 1H), 4.56 (t, *J* = 5.0 Hz, 1H), 4.35–4.15 (br s, 2H), 3.08 (t, *J* = 5.0 Hz, 4H), 2.79 (t, *J* = 5.0 Hz, 1H), 2.74 (t, *J* = 4.5 Hz, 1H), 2.71 (t, *J* = 5.0 Hz, 4H); MS (ESI+) *m/z* 225.1 (M+H).

Example 217d 5-Bromo-3-(5-(4-(2-fluoroethyl)piperazin-1-yl)pyridin-2-ylamino)-1-methylpyridin-2(1*H*)-one **217d**



217d

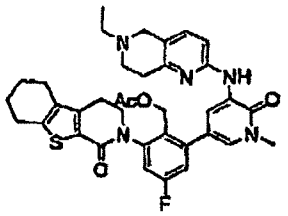
A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was charged with **217c** (402 mg, 1.79 mmol), 3,5-dibromo-1-methyl-pyridin-2(1H)-one (478 mg, 1.79 mmol), cesium carbonate (1.75 g, 5.37 mmol) and 1,4-dioxane (15 mL). After bubbling nitrogen through the resulting suspension for 30 min, Xantphos (93 mg, 0.161 mmol) and tris(dibenzylideneacetone)dipalladium(0) (82 mg, 0.090 mmol) were added. A reflux condenser was attached to the flask, and the reaction mixture was heated at 100 °C for 3 h. After this time, the mixture was cooled to room temperature and diluted with 90:10 methylene chloride/methanol (100 mL) and water (75 mL), and the layers were separated. The aqueous layer was extracted with 90:10 methylene chloride/methanol (2 × 50 mL), and the combined organic layers were washed with brine and dried over sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography (silica, 95:5 methylene chloride/methanol) to afford **217d** in 62% yield (459 mg) as an amorphous yellow

solid: mp 141–143 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (d, *J* = 2.0 Hz, 1H), 7.99 (d, *J* = 3.0 Hz, 1H), 7.74 (s, 1H), 7.24 (d, *J* = 3.0 Hz, 1H), 6.93 (d, *J* = 2.0 Hz, 1H), 6.76 (d, *J* = 9.0 Hz, 1H), 4.67 (t, *J* = 5.0 Hz, 1H), 4.57 (t, *J* = 5.0 Hz, 1H), 3.59 (s, 3H), 3.16 (t, *J* = 5.0 Hz, 4H), 2.80 (t, *J* = 5.0 Hz, 1H), 2.75 (t, *J* = 5.0 Hz, 1H), 2.73 (t, *J* = 5.5 Hz, 4H); MS (ESI+) *m/z* 410.1 (M+H)

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was charged with **217d** (177 mg, 0.431 mmol), **182c** (315 mg, 0.539 mmol), sodium carbonate (100 mg, 0.862 mmol), water (2 mL) and 1,4-dioxane (10 mL). After bubbling nitrogen through the resulting suspension for 30 min, tetrakis(triphenylphosphine)palladium(0) (100 mg, 0.086 mmol) was added. A reflux condenser was attached to the flask, and the reaction mixture was heated at 90 °C for 1 h. After this time, the mixture was diluted with 90:10 methylene chloride/methanol (100 mL) and water (75 mL), and the layers were separated. The aqueous layer was extracted with 90:10 methylene chloride/methanol (2 × 50 mL), and the combined organic layers were washed with brine (100 mL) and dried over sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was dissolved in a mixture of THF. A 1.0 M solution of tetra-butyl-ammonium fluoride in THF (1.10 mL, 1.10 mmol) was added, and the mixture was stirred at room temperature for 3 h. After this time, the mixture was diluted with 90:10 methylene chloride/methanol (75 mL) and water (50 mL), and the layers were separated. The aqueous layer was extracted with 90:10 methylene chloride/methanol (2 × 50 mL), and the combined organic layers were washed with brine (100 mL) and dried over sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography (silica, 95:5 methylene chloride/methanol) to afford **217** in 25% yield (73 mg) as an amorphous yellow solid: mp 158–160 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.55 (d, *J* = 2.0 Hz, 1H), 8.35 (s, 1H), 7.86 (d, *J* = 3.0 Hz, 1H), 7.37–7.31 (m, 3H), 7.22 (d, *J* = 9.0 Hz, 1H), 7.17 (dd, *J* = 9.5, 3.0 Hz, 1H), 4.85 (t, *J* = 4.0 Hz, 1H), 4.61 (t, *J* = 5.0 Hz, 1H), 4.51 (t, *J* = 5.0 Hz, 1H), 4.35–4.30 (m, 2H), 4.08–4.02 (m, 1H), 3.87–3.82 (m, 1H), 3.58 (s, 3H), 3.05–2.99 (m, 5H), 2.91–2.87 (m, 1H), 2.75 (s, 2H), 2.68 (t, *J* = 5.0 Hz, 1H), 2.62 (t, *J* = 4.5 Hz, 1H), 2.57–2.53 (m, 4H), 2.52 (d, *J* = 4.5 Hz, 2H), 1.23 (s, 6H); MS (ESI+) *m/z* 675.3 (M+H).

Example 218 5-(3-{5-[(6-ethyl-5,6,7,8-tetrahydro-1,6- naphthyridin-2-yl)amino]-1-methyl-6-oxo-1,6-dihydropyridin-3-yl}-5-fluoro-2-(hydroxymethyl)phenyl)-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one 218.

Example 218a (2-{5-[(6-Ethyl-5,6,7,8-tetrahydro-1,6- naphthyridin-2-yl)amino]-1-methyl-6-oxo-1,6-dihydropyridin-3-yl}-4-fluoro-6-{6-oxo-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-5-yl}phenyl)methyl Acetate 218a



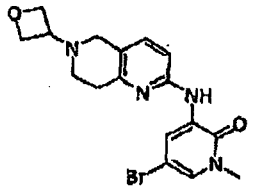
218a

A 25 mL sealed tube was charged with (2-{6-oxo-8-thia-5-azatricyclo[7.4.0.0^{2,7}]-trideca-1(9),2(7)-dien-5-yl}-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-methyl acetate (212b) (893 mg, 1.8 mmol), 5-bromo-3-(6-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-2-ylamino)-1-methylpyridin-2(1H)-one (500 mg, 1.4 mmol), CH_3COONa (226 mg, 2.75 mmol), K_3PO_4 (733 mg, 2.75 mmol), $PdCl_2$(dppf) (112 mg, 0.14 mmol) suspended in CH_3CN (25 mL) and H_2O (1 mL). The mixture was stirred at 110°C for 2 hours. After reaction the solvent was evaporated and the residue was purified by silical-gel column eluting with 20:1 methylene chloride/methanol to give 218a as a brown solid (400 mg, 44%). MS: $(M+H)^+$ 656.

To a solution of 218a (350 mg, 0.53 mmol) in propan-2-ol (10 mL), tetrahydrofuran (10 mL), and water (2 mL) was added LiOH (1.28 g, 53 mmol). The mixture was stirred at 30°C for 2 h. After reaction the mixture was evaporated and the residue was purified by prep-HPLC to afford 218 as a yellow solid (124 mg, 38%). MS: $(M+H)^+$ 614. ^{1}H NMR (500 MHz, DMSO) δ 1.06-1.09 (t, J=7.5Hz, 3 H), 1.80 (s, 4 H), 2.55-2.58 (m, 2 H), 2.67-2.68 (d, 2 H), 2.74-2.79 (d, 4 H), 2.85-2.98 (m, 2 H), 3.43 (s, 2 H), 3.60 (s, 3 H), 3.87-3.89 (m, 1 H), 4.05-4.07 (m, 1 H), 4.37-4.38 (d, 2 H), 4.87-4.89 (t, J=4.5Hz, 1 H), 7.07-7.09 (d, 1 H), 7.19-7.21 (m, 1 H), 7.29-7.34 (m, 2 H), 7.45-7.46 (d, 1 H), 8.46 (s, 1 H), 8.79-8.80 (d, 1 H).

Example 219 5-[5-Fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[6- (oxetan-3-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one 219

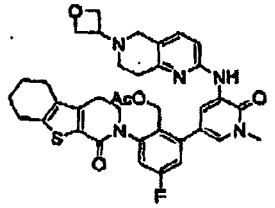
Example 219a 5-Bromo-1-methyl-3-(6-(oxetan-3-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2-ylamino)pyridin-2(1H)-one 219a



219a

A mixture of 5-bromo-1-methyl-3-(5,6,7,8-tetrahydro-1,6-naphthyridin-2-ylamino)pyridine-2(1H)-one hydrochloride **205a** (800 mg, 2.16 mmol), oxetan-3-one (778 mg, 10.8 mmol), $NaBH_3CN$ (681 mg, 10.8 mmol), and zinc chloride (1.47 g, 10.8 mmol) in methanol (30 mL) was stirred for 4 hours at 50°C. The mixture was added to H_2O (30 mL) and extracted with DCM (50 mL ×3). The organic layers were concentrated under reduced pressure. The residue was purified by column chromatography eluting with 10:1 ethyl acetate/methanol to give **219a** as a yellow solid (750 mg, 89%). MS: $[M+H]^+$ 391.

Example 219b [4-Fluoro-2-(1-methyl-5-{[6-(oxetan-3-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)-6-{6-oxo-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$]trideca-1(9),2(7)-dien-5-yl}phenyl]methyl Acetate **219b**



219b

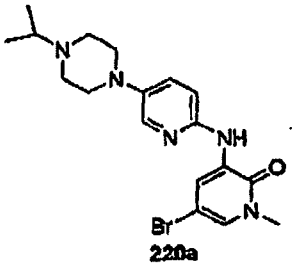
A 25 mL sealed tube was charged with (2-{6-oxo-8-thia-5-azatricyclo-[7.4.0.$0^{2,7}$]trideca-1(9),2(7)-dien-5-yl}-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl acetate **212b** (512 mg, 1.0 mmol), **219a** (400 mg, 1.0 mmol), CH_3COONa (168 mg, 2.0 mmol), K_3PO_4 (546 mg, 2.0 mmol), and $PdCl_2(dppf)$ (84 mg, 0.1 mmol) suspended in CH_3CN (25 mL) and H_2O (1 mL). The mixture was stirred in at 110°C for 2 hours. After reaction the mixture was evaporated and the residue was purified by column chromatography eluting with 10:1 methylene chloride/methanol to give **219b** as a brown solid (450 mg, 64%). MS: $(M+H)^+$ 684.

A solution of **219b** (400 mg, 0.58 mmol) in propan-2-ol (12 mL), tetrahydrofuran (12 mL), and water (2 mL) was added LiOH (1.4 g, 58 mmol). The mixture was stirred at 30°C for 2 h. After reaction the mixture was evaporated and the residue was purified by prep-

HPLC to afford 219 as a yellow solid (213 mg, 57%). MS: $(M+H)^+$ 642. ^1H NMR (500 MHz, DMSO) δ 1.80 (s, 4 H), 2.55-2.58 (m, 3 H), 2.77-2.79 (d, 4 H), 2.85-2.89 (m, 1 H), 2.96-2.98 (m, 1 H), 3.36 (s, 2 H), 3.60-3.61 (d, 4 H), 3.87-3.89 (m, 1 H), 4.05-4.07 (m, 1 H), 4.37-4.38 (d, 2 H), 4.50-4.52 (t, J=5Hz, 2 H), 4.59-4.62 (t, J=6.5Hz, 2 H), 4.87-4.90 (t, J=4Hz, 2 H), 7.08-7.10 (d, 1 H), 7.19-7.21 (m, 1 H), 7.29-7.34 (m, 2 H), 7.45-7.46 (d, 1 H), 8.46 (s, 1 H), 8.79-8.80 (d, 1 H).

Example 220 5-[5-Fluoro-2-(hydroxymethyl)-3-[1-methyl-6-oxo-5-({5-[4-(propan-2-yl)piperazin-1-yl]pyridin-2-yl}amino)-1,6-dihydropyridin-3-yl]phenyl]-8-thia-5-azatricyclo[7.4.0.02,7]trideca-1(9),2(7)-dien-6- one 220

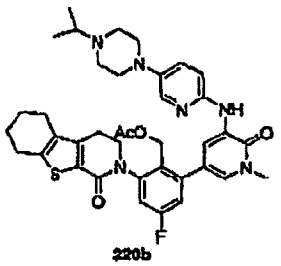
Example 220a 5-Bromo-3-(5-(4-isopropylpiperazin-1-yl)pyridin-2-ylamino)-1-methylpyridin-2(1H)-one 220a



220a

A mixture of 5-bromo-1-methyl-3-(5-(piperazin-1-yl)pyridin-2-ylamino)pyridin-2(1H)-one 188d (1.2 g, 3.3 mmol), and acetone (1.0 g, 16.5 mmol) in methanol/acetic acid (30 mL/3 mL) was stirred for 5 minutes at room temperature, followed by the addition of $NaBH(OAc)_3$ (3.5 g, 16.5 mmol). The mixture was stirred at 50°C for 2 h. It was cooled to room temperature and H_2O (50 mL) was added. The mixture was extracted with DCM (50 mL) three times. The organic layers were concentrated under reduced pressure and the residue was purified by column chromatography eluting with 25:1 DCM/methanol to give 220a (2.97 g, 81%). MS: $[M+H]^+$ 406. ^1H NMR (500 MHz, DMSO) δ 8.58 (d, J = 3.0, 1H), 8.53 (s, 1H), 7.92 (d, J = 3.0, 1H), 7.44 (d, J = 2.5, 1H), 7.37 (d, J = 2.5, 1H), 7.25 (d, J = 8, 1H), 3.51 (s, 3H), 3.06 (t, J = 4.5, 4H), 2.69 (s, 1H), 2.57-2.50 (m, 4H), 1.00 (d, J=7, 6H).

Example 220b {4-Fluoro-2-[1-methyl-6-oxo-5-({5-[4-(propan-2- yl)piperazin-1-yl]pyridin-2-yl}amino)-1,6-dihydropyridin-3-yl]-6-{6-oxo-8-thia-5-azatricyclo-[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-5- yl}phenyl}methyl Acetate 220b



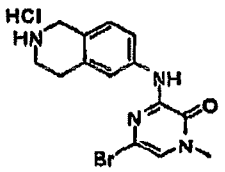
220b

Following the procedures as described for **148b** and starting with 400 mg of (4-fluoro-2-{6-oxo-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-5-yl}-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl acetate **212b** and 340 mg 5-bromo-3-(5-(4-isopropylpiperazin-1-yl)pyridin-2-ylamino)-1-methylpyridin-2(1H)-one **220a**, compound **220b** was obtained as a yellow solid (446 mg, 82%).MS: $[M+H]^+$ 699

Following the procedures as described for **148** and starting with 200 mg of **220b**, compound **220** was obtained as a white solid (70 mg, 37%). MS: $[M+H]^+$ 657. ^{1}H NMR (500 MHz, DMSO) δ 8.56 (d, J=2.5, 1H), 8.37 (s, 1H), 7.85 (d, J=2.5,1H), 7.34 (m, 3H), 7.23 (m, 2H), 4.68 (s, 1H), 4.32(s, 2H), 4.06 (s, 1H), 3.85 (s,1H), 3.58 (s, 3H), 3.02(s, 4H), 2.78 (m, 4H), 2.55 (m, 7H), 1.80 (d, J=3.5, 4H), 1.00 (d, J=7, 6H).

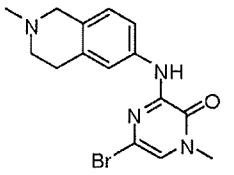
Example 221 5-[5-Fluoro-2-(hydroxymethyl)-3-{4-methyl-6-[(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)amino]-5-oxo-4,5-dihydropyrazin-2-yl}phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one **221**

Example 221a 5-Bromo-1-methyl-3-(1,2,3,4-tetrahydroisoquinolin-6-ylamino)pyrazin-2(1H)-one **221a**



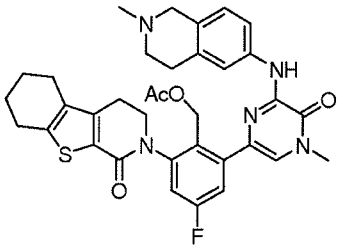
To a solution of tert-butyl 6-(6-bromo-4-methyl-3-oxo-3,4-dihydropyrazin-2-ylamino)-3,4- dihydroisoquinoline-2(1H)-carboxylate **120a** (3.6 g, 8.3 mmol) in dioxane (10 mL) was added saturated hydrogen chloride solution in dioxane (20 mL) dropwise. The reaction mixture was stirred for 20 minutes and concentrated under reduced pressure to give **221a**, which was used without further purification in the next step. LC/MS: m/z 336 $(M+H)^+$

Example 221b 5-Bromo-1-methyl-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-ylamino)pyrazin- 2(1H)-one **221b**



A mixture of **221a** (2.75 g, 7.5 mmol), formaldehyde (37% in H_2O, 30 mL, 375 mmol), $NaBH(OAc)_3$ (4.75 g, 22.5 mmol), and AcOH (25 ml, 150 mmol) in methanol (125 ml) was stirred for 4 hours at room temperature. The mixture was then brought to basic condition with saturated NaOH solution and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography eluting with 4:1 ethyl acetate/methanol to give **221b**. (0.9 g, 34.4%) LC/MS: m/z 350 $(M+H)^+$

Example 221c (4-Fluoro-2-{4-methyl-6-[(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)amino]-5-oxo-4,5-dihydropyrazin-2-yl}-6-{6-oxo-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$]-trideca-1(9), 2(7)-dien-5- yl}phenyl)methyl Acetate **221c**



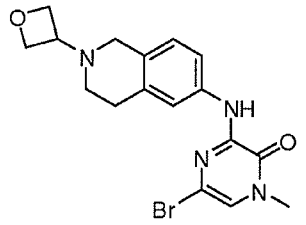
A 15 mL microwave vial with a magnetic atirrer was charged with 5-bromo- 1-methyl-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-ylamino)pyrazin-2(1H)-one (0.42 g, 1.2 mmol), **212b** (0.6 g, 1.2 mmol), potassium phosphate (0.64 g, 2.4 mmol), sodium acetate (0.2 g, 2.4 mmol), acetonitrile (10 mL), water (1 mL), and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane (0.1 g, 0.12 mmol). The reaction mixture was heated at 110^0C for 2 hours under argon atmosphere. After this time, the mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography eluting with 40:1 DMC/methanol to give **221c** (0.667g, 86.6%). LC/MS: m/z 642 $(M+H)^+$

A 25 mL round bottomed flask with a magnetic stirrer was charged with **221c** (0.647 g, 1.0 mmol), LiOH (2.1 g, 50 mmol), THF(10 mL), isopropanol (10 mL) and water (5 mL). The reaction mixture was stirred at room temperature for 30 minutes and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by prep-HPLC to give **221**. LC/MS: m/z 600 $(M+H)^+$. ^{1}H NMR (500 MHz, DMSO) δ 9.13 (s, 1H), 7.80 (s, 1H), 7.62 (d, J = 8.5, 1H), 7.51 (s, 1H), 7.39 (d, J = 10, 1H), 7.30 (d, J = 6.5,, 1H), 6.97 (d, J = 8.5,

1H), 4.86 (m, 1H), 44.51 (m, 3H), 4.41 (m, 1H), 4.05 (m, 1H), 3.87 (m, 1H), 3.55 (m, 6H), 2.77 (m, 3H), 2.55 (m, 3H), 2.31 (m, 3H), 1.80 (m, 4H).

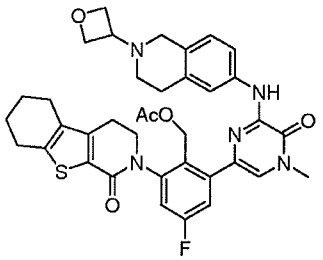
Example 222 5-[5-Fluoro-2-(hydroxymethyl)-3-(4-methyl-6-{[2- (oxetan-3-yl)-1,2,3,4-tetrahydroisoquinolin-6-yl]amino}-5-oxo-4,5-dihydropyrazin-2-yl)phenyl]-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$]trideca-1(9),2(7)-dien-6-one **222**

Example 222a 5-Bromo-1-methyl-3-(2-(oxetan-3-yl)-1,2,3,4-tetrahydroisoquinolin-6-ylamino) pyrazin-2(1H)-one **222a**



A mixture of 5-bromo-1-methyl-3-(1,2,3,4-tetrahydroisoquinolin-6-ylamino)pyrazin-2(1H)-one **221a** (2.75 g, 7.5 mmol), oxetan-3-one (2.5 g, 37.5 mmol), $NaBH_3CN$ (4.75 g, 22.5 mmol) and zinc chloride (5 g, 37.5 mmol) in methanol (125 ml) was stirred for 4 hours at room temperature. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography eluting with 20:1 DCM/methanol to **222a** (0.76 g, 25.9%). LC/MS: m/z 392 $(M+H)^+$

Example 222b [4-Fluoro-2-(4-methyl-6-{[2-(oxetan-3-yl)-1,2,3,4-tetrahydroisoquinolin-6-yl]amino}-5-oxo-4,5-dihydropyrazin-2-yl)-6-{6-oxo-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$]trideca-1(9),2(7)-dien-5- yl}phenyl]methyl Acetate **222b**



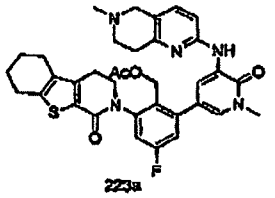
A 250 mL round bottomed flask with a magnetic atirrer was charged with **222a** (0.31 g, 0.8 mmol), (4-fluoro-2-{6-oxo-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$]-trideca-1(9),2(7)-dien-5-yl}-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-methyl acetate **212b** (0.4 g, 0.8 mmol), potassium phosphate (0.43 g, 1.6 mmol), sodium acetate (0.13 g, 1.6 mmol), acetonitrile (30 mL), water (2 mL), and 1,1'-bis(diphenyl-phosphino)ferrocene-palladium(II)dichloride dichloromethane (0.07 g, 0.08 mmol). The reaction mixture was refluxed for overnight under argon atmosphere. After this time, the mixture was cooled to

room temperature and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography eluting with 40:1 methylene chloride/methanol to give **222b** (0.491 g, 89.3%). LC/MS: m/z 684$(M+H)^+$

A 25 mL round bottomed flask with a magnetic stirrer was charged with **222b** (0.471 g, 0.69 mmol), LiOH (1.45 g, 34.5 mmol), THF(10 mL), isopropanol (10 mL) and water (5 mL). The reaction mixture was stirred at room temperature for 30 minutes and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by prep-HPLC to give **222** as a white solid (20 mg, 11%). LC/MS: m/z 642 $(M+H)^+$. ^{1}H NMR (500 MHz, DMSO) δ 9.14 (s, 1H), 7.82 (s, 1H), 7.63 (d, J = 8.5, 1H), 7.51 (s, 1H), 7.39 (d, J = 10, 1H), 7.30 (d, J = 6.5, 1H), 6.97 (d, J = 8.5, 1H), 4.86 (m, 1H), 4.84 (m, 2H), 4.51 (m, 3H), 4.41 (m, 1H), 4.05 (m, 1H), 3.87 (m, 1H), 3.55 (m, 5H), 2.88 (m, 1H), 2.77 (m, 1H), 2.53 (m, 4H), 1.80 (m, 4H), 1.23 (m, 2H).

Example 223 5-[5-Fluoro-2-(hydroxymethyl)-3-{1-methyl-5-[(6- methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-2-yl)amino]-6-oxo-1,6-dihydropyridin-3-yl}phenyl]-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$]trideca-1(9),2(7)- dien-6-one **223**

Example 223a (4-Fluoro-2-{1-methyl-5-[(6-methyl-5,6,7,8- tetrahydro-1,6-naphthyridin-2-yl)amino]-6-oxo-1,6-dihydropyridin-3-yl}-6-{6-oxo-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$] trideca-1(9),2(7)-dien-5- yl}phenyl)methyl Acetate **223a**



223a

Following the procedures as described for **136a** and starting with 5-bromo-1-methyl-3-(6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-2-ylamino)pyridine-2(1H)-one **205b** and (4-fluoro-2-{6-oxo-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$]trideca-1(9),2(7)-dien-5-yl}-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl acetate **212b**, compound **223a** was obtained in 50% yield.

Following the procedures as described for compound **136f** and starting with **223a**, compound **223** was obtained in 33% yield. LCMS: $(M+H)^+$ 600. ^{1}H NMR (500 MHz, MEOD) δ 8.87 (d, J=2, 1H), 7.40 (d, J=2.5, 1H), 7.35 (d, J=8, 1H), 7.23 (s, 1H), 7.21 (s, 1H), 6.88 (d, J=8, 1H), 4.56 (m, 2H), 4.16 (m, 1H), 4.01 (m, 1H), 3.72 (s, 3H), 3.57 (s, 2H), 3.05 (m, 1H), 2.95 (m, 3H), 2.84 (m, 4H), 2.59 (m, 2H), 2.49 (s, 3H), 1.90 (m, 4H).

Example 224 10-[5-Fluoro-2-(hydroxymethyl)-3-{1-methyl-5-[(5-{[methyl(propan-2-yl)amino]methyl}pyridine-2-yl)amino]-6-oxo-1,6-dihydropyridin-3-yl}phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one **224**

Example 224a 10-[5-Fluoro-2-(acetoxymethyl)-3-{1-methyl-5-[(5-{[methyl(propan-2-yl)amino]methyl}pyridine-2-yl)amino]-6-oxo-1,6-dihydropyridin-3-yl}phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one **224a**

Following Example 186f, **186e** (365mg, 0.64mmol) and **189** (230mg, 0.51mmol) were reacted to give **224a** (80mg, 20% yield).

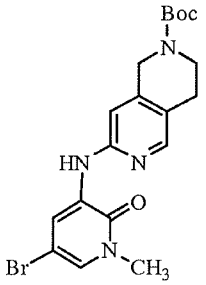
Following Example 186, **224a** (80mg, 0.12mmol), 1N LiOH (0.61mL), THF (2mL) and isopropanol (2mL) were reacted and triturated with EtOAc to give **224** (57mg, 76% yield). MS (ESI+) *m/z* 613.6 (M + H).

Example 225 2-(2-(Hydroxymethyl)-3-(1-methyl-5-(5-methyl-1*H*-pyrazol-3-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrido[3,4-*b*]indolizin-1(2*H*)-one **225**

Using the same general procedure as described for **118**, reaction of **112a** (200 mg, 0.706 mmol) and **118f** (330 mg, 0.710 mmol) afforded a 17% yield (60 mg) of **225** as a green-yellow solid: mp 199–200 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.69 (s, 1H), 7.99 (s, 1H), 7.93 (s, 1H), 7.41 (t, 1H, J = 8.0 Hz), 7.25 (d, 3H, J = 8.5 Hz), 6.00 (s, 1H), 5.86 (s, 1H), 4.69 (br s, 1H), 4.31 (m, 2H), 3.97 (m, 1H), 3.91 (m, 1H), 3.79 (m, 2H), 3.56 (s, 3H), 3.01 (m, 1H), 2.90 (m, 1H), 2.70 (m, 2H), 2.15 (s, 3H), 1.90 (m, 2H), 1.74 (m, 2H); MS (ESI+) *m/z* 499.2 (M+H).

Example 226 2-(2-(Hydroxymethyl)-3-(1-methyl-6-oxo-5-(5,6,7,8-tetrahydro-2,6-naphthyridin-3-ylamino)-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrido[3,4-*b*]indolizin-1(2*H*)-one **226**

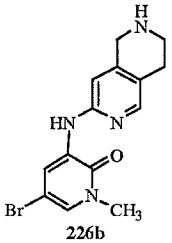
Example 226a *tert*-Butyl 7-(5-Bromo-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)-3,4-dihydro-2,6-naphthyridine-2(1*H*)-carboxylate **226a**



226a

A 100-mL three-neck round-bottomed flask equipped with a magnetic stirrer, nitrogen inlet and reflux condenser was charged with 3,5-dibromo-1-methylpyridin-2(1H)-one (536 mg, 2.01 mmol), *tert*-butyl 7-amino-3,4-dihydro-2,6-naphthyridine-2(1*H*)-carboxylate (500 mg, 2.01 mmol), cesium carbonate (1.44 g, 4.40 mmol) and 1,4-dioxane (30 mL). After bubbling nitrogen through the resulting mixture for 20 minutes, Xantphos (98.4 mg, 0.170 mmol) and tris(dibenzylideneacetone)dipalladium(0) (91.6 mg, 0.100 mmol) were added, and the reaction mixture was heated at 100°C for 6 h. After this time, the reaction was cooled to room temperature, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography to afford a 96% yield (840 mg) of **226a** as a yellow solid: mp 126–128 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (d, 1H, *J* = 2.5 Hz), 8.10 (s, 1H), 7.79 (s, 1H), 6.95 (d, 1H, *J* = 2.5 Hz), 6.55 (s, 1H), 4.53 (s, 2H), 3.64 (t, 2H, *J* = 5.0 Hz), 3.59 (s, 3H), 2.77 (t, 2H, *J* = 5.0 Hz), 1.49 (s, 9H); MS (ESI+) *m/z* 435.0 (M+H).

Example 226b 5-Bromo-1-methyl-3-(5,6,7,8-tetrahydro-2,6-naphthyridin-3-ylamino)pyridin-2(1*H*)-one **226b**



226b

A 50-mL single-neck round-bottomed flask equipped with a magnetic stirrer was purged with nitrogen and charged with **226a** (840 mg, 1.94 mmol) and methylene chloride (12 mL). Trifluoroacetic acid (6 mL) was added. The reaction was stirred at room temperature for 2 h. After this time, the reaction mixture was evaporated under reduced pressure. The residue **226b** was directly used in the following step.

A 100-mL three-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was charged with 1/2 of the amount of crude **226b** prepared above (0.898 mmol presumed), **118f** (416 mg, 0.898 mmol), sodium carbonate (381 mg, 3.59 mmol), water (4 mL) and 1,4-dioxane (20 mL). After bubbling nitrogen through the resulting suspension for 20 min, tetrakis(triphenylphosphine)-palladium(0) (104 mg, 0.090 mmol) was added, and the reaction mixture was heated at 100 °C for 4 h. After this time, the reaction mixture was cooled to room temperature and filtered, and the filter cake was washed with a 1:10 mixture of methanol and methylene chloride (30 mL). The filtrate was concentrated under reduced pressure to afford a brown residue. Another 50-mL single-neck round-bottomed flask

equipped with a magnetic stirrer and reflux condenser was charged with residue obtained above, THF (10 mL), ethanol (10 mL), water (10 mL) and lithium hydroxide (86.0 mg, 3.59 mmol). The mixture was stirred at 50 °C for 2 h. After this time, the reaction mixture was concentrated under reduced pressure. The resulting residue was purified by flash chromatography to afford a 7.7% (38 mg) yield of **226** as an off-white solid: mp 197–199 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.53 (d, 1H, J = 2.0 Hz), 8.23 (s, 1H), 7.90 (s, 1H), 7.43 (t, 1H, J = 7.5 Hz), 7.35 (d, 1H, J = 2.0 Hz), 7.28 (s, 1H), 7.27 (s, 1H), 6.93 (s, 1H), 6.00 (s, 1H), 4.72 (t, 1H, J = 5.0 Hz), 4.32 (d, 2H, J = 5.0 Hz), 3.96 (m, 1H), 3.90 (m, 1H), 3.82 (m, 2H), 3.75 (s, 2H), 3.58 (s, 3H), 3.00 (m, 1H), 2.94 (m, 1H), 2.90 (t, 2H, J = 5.0 Hz), 2.70 (m, 2H), 2.56 (m, 2H), 1.92 (m, 2H), 1.76 (m, 2H); MS (ESI+) *m/z* 551.2 (M+H).

Example 227 2-(3-(5-(5-(Azetidin-3-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrido[3,4-*b*]indolizin-1(2*H*)-one **227**

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was charged with **155n** (312 mg, 0.931 mmol), **118f** (472 mg, 1.12 mmol), sodium carbonate (296 mg, 2.79 mmol), DMF (2 mL), water (2 mL) and 1,4-dioxane (10 mL). After bubbling nitrogen through the resulting suspension for 30 min, tetrakis-(triphenylphosphine)palladium(0) (215 mg, 0.186 mmol) was added. A reflux condenser was attached to the flask, and the reaction mixture was heated at 100 °C for 14 h. After this time, the mixture was diluted with 90:10 methylene chloride/methanol (100 mL) and water (75 mL), and the layers were separated. The aqueous layer was extracted with 90:10 methylene chloride/methanol (2 × 50 mL), and the combined organic layers were washed with brine (100 mL) and dried over sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was dissolved in a mixture of THF (5 mL), water (5 mL) and methanol (5 mL). Lithium hydroxide monohydrate (195 mg, 4.66 mmol) was added, and the mixture was stirred at room temperature for 3 h. After this time, the mixture was diluted with 90:10 methylene chloride/methanol (100 mL) and water (50 mL), and the layers were separated. The aqueous layer was extracted with 90:10 methylene chloride /methanol (2 X 75 mL), and the combined organic layers were washed with brine (100 mL) and dried over sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography (silica, 90:10 methylene chloride/methanol) to afford **227** in 7% yield (36 mg) as an amorphous off-white solid: mp

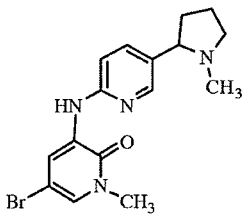
227–229 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.66 (d, J = 1.5 Hz, 1H), 8.53 (s, 1H), 8.11 (s, 1H), 7.68 (d, J = 7.0 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.39 (s, 1H), 7.29 (m, 3H), 6.01 (s, 1H), 4.72 (t, J = 4.5 Hz, 1H), 4.33 (s, 2H), 3.99–3.88 (m, 3H), 3.84–3.75 (m, 2H), 3.59 (m, 3H), 3.51 (m, 5H), 3.02–2.91 (m, 2H), 2.72 (t, J = 5.5 Hz, 2H), 1.92 (t, J = 5.0 Hz, 2H), 1.77–1.73 (m, 2H); MS (ESI+) m/z 551.2 (M+H).

Example 228 2-(2-(Hydroxymethyl)-3-(4-methyl-5-oxo-6-(1,2,3,4-tetrahydroisoquinolin-7-ylamino)-4,5-dihydropyrazin-2-yl)phenyl)-3,4,6,7,8,9-hexahydropyrido[3,4-*b*]indolizin-1(2*H*)-one **228**

Using the same general procedure as described for the preparation of **226**, reaction of **153a** (400 mg, 1.19 mmol) with **118f** (718 mg, 1.55 mmol) followed by hydrolysis gave a 12% yield (88 mg) of **228** as a white solid: mp 218–220 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.03 (s, 1H), 7.73 (s, 1H), 7.63 (dd, 1H, J = 7.5, 2.0 Hz), 7.52 (dd, 1H, J = 7.5, 2.0 Hz), 7.43 (t, 2H, J = 8.0 Hz), 7.25 (dd, 1H, J = 7.5, 1.0 Hz), 6.90 (d, 1H, J = 8.0 Hz), 6.00 (s, 1H), 4.71 (dd, 1H, J = 7.0, 3.5 Hz), 4.46 (m, 2H), 3.94 (m, 2H), 3.82 (m, 2H), 3.77 (s, 2H), 3.54 (s, 3H), 3.00 (m, 1H), 2.93 (m, 1H), 2.90 (t, 2H, J = 5.0 Hz), 2.70 (t, 2H, J = 6.0 Hz), 2.62 (t, 2H, J = 6.0 Hz), 2.45 (m,1H), 1.92 (m, 2H), 1.76 (m, 2H); MS (ESI+) m/z 551.2 (M+H).

Example 229 2-(2-(Hydroxymethyl)-3-(1-methyl-5-(5-(1-methylpyrrolidin-2-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrido[3,4-*b*]indolizin-1(2*H*)-one **229**

Example 229a 5-Bromo-1-methyl-3-(5-(1-methylpyrrolidin-2-yl)pyridin-2-ylamino)pyridin-2(1*H*)-one **229a**



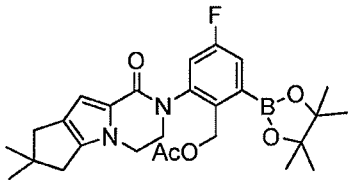
229a

Using the same general procedure as described for the preparation of **226b**, reaction of 3,5-dibromo-1-methylpyridin-2(1H)-one (1.51 g, 5.65 mmol) with 5-(1-methylpyrrolidin-2-yl)-2-amino pyridine (1.00 g, 5.65 mmol) gave an 81% yield (1.65 g) of **229a** as a yellow solid: mp 143–145 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.73 (s, 1H), 8.68 (d, 1H, J = 2.4 Hz), 8.15 (d, 1H, J = 2.1 Hz), 7.55 (dd, 1H, J = 8.9, 2.1 Hz), 7.52 (s, 1H), 7.30 (d, 1H, J = 8.9 Hz), 3.52 (s, 3H), 3.13 (t, 1H, J = 7.5 Hz), 2.99 (t, 1H, J = 7.5 Hz), 2.19 (m, 1H), 2.10 (m, 1H), 2.05 (s, 3H), 1.79 (m, 2H), 1.71 (m, 1H); MS (ESI+) m/z 363.3 (M+H).

Using the same general procedure as described for the preparation of **226**, reaction of **229a** (500 mg, 1.38 mmol) with **118f** (705 mg, 1.52 mmol) followed by a hydrolysis gave a 27% yield (215 mg) of **229** as a white solid: mp 146–148 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.67 (dd, 1H, J = 2.0 Hz), 8.52 (s, 1H), 8.05 (s, 1H), 7.53 (dd, 1H, J = 8.5, 2.5 Hz), 7.44 (t, 1H, J = 8.0 Hz), 7.39 (d, 1H, J = 2.5 Hz), 7.29-7.24 (m, 3H), 6.00 (s, 1H), 4.72 (t, 1H, J = 5.0 Hz), 4.32 (d, 2H, J = 5.0 Hz), 3.99 (m, 1H), 3.90 (m, 1H), 3.81 (m, 2H), 3.58 (s, 3H), 3.11 (t, 1H, J = 8.0 Hz), 3.00 (m, 1H), 2.93 (m, 2H), 2.71 (t, 2H, J = 6.0 Hz), 2.17 (q, 1H, J = 9.0 Hz), 2.06 (m, 1H), 2.03 (s, 3H), 1.92 (t, 2H, J = 6.0 Hz), 1.83-1.72 (m, 4H), 1.59 (m, 1H); MS (ESI+) m/z 579.2 (M+H).

Example 230 10-[3-(5-{[5-(Azetidin-1-ylmethyl)-1-methyl-1H-pyrazol-3-yl]amino}-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-(hydroxymethyl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one **230**

Example 230a 2-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-4-fluoro-6-(9-oxo-4,4-dimethyl-1,10diazatricyclo[6.4.0.0^{2,6}]-dodeca-2(6),7-dien-10-yl)benzyl Acetate **230a**



230a

Following Example 211d, 2-Bromo-4-fluoro-6-(9-oxo-4,4-dimethyl-1,10diazatricyclo[6.4.0.0^{2,6}]-dodeca-2(6),7-dien-10-yl)benzyl Acetate **189a** (450 mg, 1.0 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (635 mg, 2.5 mmol), potassium acetate (393 mg, 4.0 mmol), bis(diphenylphosphino)-ferrocene]dichloropalladium(II) complex with CH_2Cl_2 (Pd Cl_2dppf:CH_2Cl_2 (1:1), 66 mg, 0.08 mmol) and 1,4-dioxane (20 mL) were heated at 100 °C for 5 h. The reaction mixture was cooled to room temperature and filtered through a pad of Celite 521. The filter cake was washed with Ethyl Acetate (2 × 25 mL), and the combined filtrates were concentrated to dryness under reduced pressure to afford compound **230a** (quantitative yield) as black oil, which was used directly for the next step. MS (ESI+) m/z 497.3 (M+H).

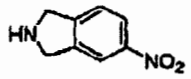
Example 230b 10-[3-(5-{[5-(Azetidin-1-ylmethyl)-1-methyl-1H-pyrazol-3-yl]amino}-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-(acetoxymethyl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one **230b**

Example 230b was synthesized using the same procedure as 121b, except using compound 230a (223 mg, 0.45 mmol), 3-(5-(azetidin-1-ylmethyl)-1-methyl-1H-pyrazol-3-ylamino)-5-bromo-1-methylpyridin-2(1H)-one (200c) (160 mg, 0.45 mmol), 1M sodium carbonate solution (1.5 mL, 1.5 mmol), tetrakis(triphenylphosphine)palladium(0) (26 mg, 0.022 mmol) and 1,2-dimethoxyethane (4.5 mL). The reaction mixture was heated at 130 °C for 15 minutes in the microwave reactor. Work-up and flash column chromatography (silica, 9:1 methylene chloride/methanol) give a 43% yield (120 mg) of compound 230b as brown oil: MS (ESI+) *m/z* 643.1 (M+H).

Following the same procedure as 121, except using a mixture of THF (1 mL), water (0.5 mL) and isopropanol (1 mL), compound 230b (120 mg, 0.2mmol) and lithium hydroxide monohydrate (50 mg, 1.2 mmol) were reacted. Work-up and flash column chromatography (NH-silica, ethyl acetate /hexanes) give a 30% yield (36 mg) of compound 230 as a light green solid: MS (ESI+) *m/z* 600.6 (M+H).

Example 231 2-(5-fluoro-2-(hydroxymethyl)-3-(4-methyl-6-(2-methylisoindolin-5-ylamino)-5-oxo-4,5-dihydropyrazin-2-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one 231

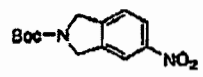
Example 231a 5-Nitroisoindoline 231a



231a

To the suspension of isoindoline (2 g, 16.8 mmol) in 98% H_2SO_4 (10 mL) was added dropwise the mixture of concentrated nitric acid (2 mL) and 98% sulfuric acid (2 mL) at 0°C. The mixture was stirred at 0°C for 45 minutes. The resulting yellow solution was then poured into ice water. The white solid precipitate was collected by filtration. The solid was washed with water (20 mL × 2) and dried in vacuum to afford 231a as a white solid (700 mg, 51%). MS: [M+H]+ 165.

Example 231b *tert*-Butyl 5-Nitroisoindoline-2-carboxylate 231b

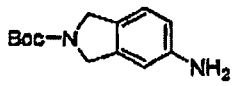


231b

The mixture of 5-nitroisoindoline (600 mg, 3.66 mmol) and $(Boc)_2O$ (1.6 g, 7.31 mmol) in THF (30 mL) was stirred at room temperature for 2h. The resulting red solution was then concentrated under reduced pressure and the residue was purified by flash column

chromatography eluting with 5:1 petroleum ether/ethyl acetate to afford **231b** as a yellow solid (750 mg, 80%). MS: $[M+H]^+$ 209.

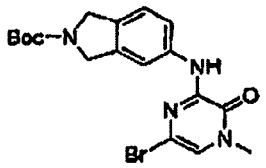
Example 231c *tert*-Butyl 5-Aminoisoindoline-2-carboxylate **231c**



231c

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer was charged with *tert*-butyl 5-nitroisoindoline-2-carboxylate (650 mg, 2.5 mmol) and C_2H_5OH (50 mL). This solution was hydrogenated with Pd/C (160mg) at room temperature for 15 h. It was then filtered and the filtrate was concentrated under reduced pressure to afford **231c** as a yellow oil (585 mg, 99%), which was used in the next step without further purification. MS: $[M+H]^+$ 179.

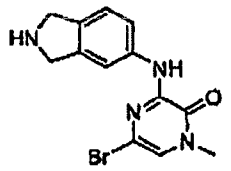
Example 231d *tert*-Butyl 5-(6-Bromo-4-methyl-3-oxo-3,4-dihydropyrazin-2-ylamino)isoindoline-2-carboxylate **231d**



231d

Following the procedures as described for **129a** and starting with 600 mg of *tert*-butyl 5-aminoisoindoline-2-carboxylate (**231c**) and 685 mg of 3,5-dibromo-1-methylpyrazin-2(1H)-one, **231d** was obtained as a yellow solid (732 mg, 68%). MS: $[M+H]^+$ 421.

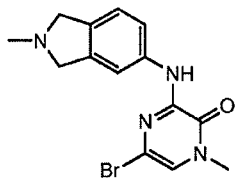
Example 231e 5-Bromo-3-(isoindolin-5-ylamino)-1-methylpyrazin-2(1H)-one **231e**



231e

Following the procedures as described for **129b** and starting with 460 mg of *tert*-butyl 5-(6-bromo-4-methyl-3-oxo-3,4-dihydropyrazin-2-ylamino)isoindoline-2-carboxylate, **231e** was obtained as a yellow solid (352 mg, 99%). MS: $[M+H]^+$ 321

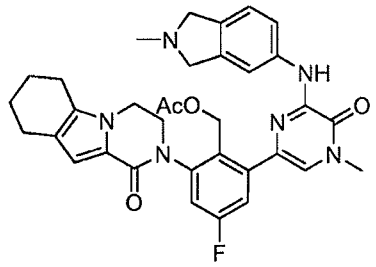
Example 231f 5-Bromo-1-methyl-3-(2-methylisoindolin-5-ylamino)pyrazin-2(1H)-one **231f**



231f

Following the procedures as described for **220a** and starting with 336 mg of 5-bromo-3-(isoindolin-5-ylamino)-1-methylpyrazin-2(1H)-one, compound **231f** was obtained as a yellow solid (237 mg, 75%). MS: $[M+H]^+$ 337. ^{1}H NMR (500 MHz, CDCl3) δ 8.31 (s, 1H), 7.67 (s, 1H), 7.52 (t, J=7.0, 1H), 7.18 (d, J=8.0, 1H), 6.74 (s, 1H), 3.94(s, 2H), 3.89 (s, 2H), 3.52 (s, 3H), 2.60 (s, 3H).

Example 231g 4-Fluoro-2-(4-methyl-6-(2-methylisoindolin-5-ylamino)-5-oxo-4,5-dihydropyrazin-2-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **231g**



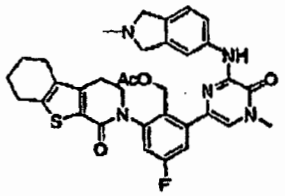
231g

Following the procedures as described for compound **148h** and starting with 400 mg of 4-fluoro-2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **210d** and 278 mg of 5-bromo-1-methyl-3-(2-methylisoindolin-5-ylamino)pyrazin-2(1H)-one **231f**, compound **231g** was obtained as a yellow solid (258 mg, 51%). MS: $[M+H]^+$ 611.

Following Example 148, **231g** was converted to **231** as a white solid (116 mg, 50%). ^{1}H NMR (500 MHz, DMSO) δ 9.23 (s, 1H), 7.90 (s, 1H), 7.73 (d, J=8, 1H), 7.51 (s, 1H), 7.37 (dd, J=10.0, 1H), 7.31 (dd, J=10.0, 1H), 7.13 (d, J=8.0, 1H), 6.53(s, 1H), 4.88 (s, 1H), 4.50 (d, J=8.0, 1H), 4.50 (d, J=11.5, 1H), 4.40 (m, 1H), 4.13 (m, 3H), 3.89 (m, 1H), 3.78 (m, 4H), 3.52 (s, 3H), 2.59 (m, 2H), 2.48 (m, 5H), 1.79 (s, 2H), 1.70 (s, 2H).

Example 232 5-[5-fluoro-2-(hydroxymethyl)-3-{4-methyl-6-[(2- methyl-2,3-dihydro-1H-isoindol-5-yl)amino]-5-oxo-4,5-dihydropyrazin-2-yl}phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one **232**

Example 232a (4-Fluoro-2-{4-methyl-6-[(2-methyl-2,3-dihydro-1H- isoindol-5-yl)amino]-5-oxo-4,5-dihydropyrazin-2-yl}-6-{6-oxo-8-thia-5azatricyclo[7.4.0.0^{2,7}]-trideca-1(9),2(7)-dien-5- yl}phenyl)methyl Acetate 232a



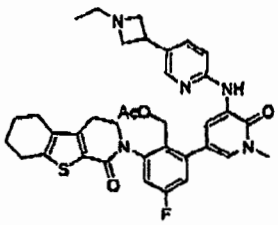
232a

Following the procedures as described for 148h and starting with 499 mg of (4-fluoro-2-{6-oxo-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-5-yl}-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl acetate 212b and 335 mg of 5-bromo-1-methyl-3-(2-methylisoindolin-5-ylamino)pyrazin-2(1H)-one, compound 232a was obtained as a yellow solid (320 mg, 51%).MS: $[M+H]^+$ 628.

Following the procedures as described for 148 and starting with 300 mg of 232a, compound 232 was obtained as a white solid (117 mg, 42%). ^{1}H NMR (500 MHz, DMSO) δ 9.23 (s, 1H), 7.90 (s, 1H), 7.72 (s, 1H), 7.51 (d, J=8.0, 1H), 7.36 (s, 1H), 7.31 (s, 1H), 7.13 (s, 1H), 4.85 (s, 1H), 4.50 (s, 1H), 4.40(m, 1H), 4.05 (s, 1H), 3.87 (s, 1H), 3.78 (d, J=6.5, 4H), 3.56 (s, 3H), 3.33 (s, 3H), 2.97 (s, 1H), 2.87 (s,1H), 2.79 (s, 2H), 2.50 (m, 3H), 1.80 (s, 4H).

Example 233 5-[3-(5-{[5-(1-Ethylazetidin-3-yl)pyridin-2- yl]amino}-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-(hydroxymethyl)phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6- one 233

Example 233a [2-(5-{[5-(1-Ethylazetidin-3-yl)pyridin-2- yl]amino}-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-fluoro-6-{6-oxo-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-5- yl}phenyl]methyl Acetate 233a



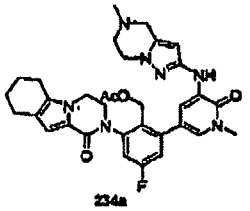
Following the procedures as described for 136e and starting with 5-bromo-3-(5-(1-ethylazetidin-3-yl)pyridin-2-ylamino)-1-methylpyridin-2(1H)-one (250a) and (4-fluoro-2-{6-oxo-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-5-yl}-6-(4,4,5,5-tetramethyl-1,3,2-

dioxaborolan-2-yl)phenyl)methyl acetate **212b**, compound **233a** was obtained in 67% yield. LCMS: $(M+H)^+$ 597

Following the procedures as described for **136** and starting with**233a**, compound **233** was obtained in 58% yield. LCMS: $(M+H)^+$ 614. ^1H NMR (500 MHz, DMSO) δ 8.66 (d, J=2, 1H), 8.56 (s, 1H), 8.11 (d, J=2, 1H), 7.65 (dd, J=9, 1H), 7.41 (d, J=2, 1H), 7.33 (dd, J=9.5, 1H), 7.28 (d, J=8, 1H), 7.18 (dd, J=9, 1H), 4.86 (t, J=4, 1H), 4.32 (d, J=4.5, 2H), 4.05 (m, 1H), 3.86 (m, 1H), 3.59 (s, 3H), 3.49 (m, 3H), 2.97 (m, 3H), 2.86 (m, 1H), 2.78 (m, 2H), 2.56 (m, 1H), 2.40 (m, 2H), 1.79 (m, 4H), 0.87 (t, J=7, 3H).

Example 234 2-(5-Fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **234**

Example 234a {4-Fluoro-2-[1-methyl-5-({5-methyl-4H,5H,6H,7H-pyrazolo[1,5-a]pyrazin-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]-6-{1-oxo-1H,2H,3H,4H,-6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl}methyl Acetate **234a**



234a

A 25 mL sealed tube was charged with 4-fluoro-2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate (**210d**) (500 mg, 1.0 mmol), 5-bromo-1-methyl-3-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)pyridin-2(1H)-one (**146a**) (350 mg, 1.0 mmol), CH_3COONa (170 mg, 2.0 mmol), K_3PO_4 (552 mg, 2.0 mmol), $PdCl_2(dppf)$ (85 mg, 0.1 mmol) suspended in CH_3CN (25 mL) and H_2O (1 mL). The mixture was heated at 110°C for 2 hours. It was then evaporated and the residue was purified by silical-gel column eluting with 20:1 methylene chloride/methanol to give **234a** as a brown solid (400 mg, 63%). MS: $(M+H)^+$ 614.

A solution of **234a** (400 mg, 0.65 mmol) in propan-2-ol (10 mL), tetrahydrofuran (10 mL) and water (2 mL) was added LiOH (1.57 g, 65 mmol). The mixture was stirred at 30°C for 2 h. It was then evaporated and the residue was purified by prep-HPLC to afford **234** as a yellow solid (119 mg, 32%). MS: $(M+H)^+$ 572. ^1H NMR (500 MHz, MEOD) δ 1.78-1.80 (t, 2

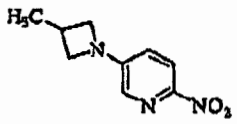
H), 1.89-1.90 (d, 2 H), 2.49 (s, 3 H), 2.54-2.56 (t, J=6 Hz, 2 H), 2.64-2.66 (m, 2 H), 2.94-2.96 (t, 2 H), 3.64 (s, 2 H), 3.67 (s, 3 H), 4.04-4.06 (m, 3 H), 4.20 (s, 3 H), 4.46-4.51 (m, 2 H), 5.89 (s, 1 H), 6.72 (s, 1 H), 7.20-7.22 (d, 2 H), 7.26-7.27 (d, 1 H), 7.91 (s, 1 H).

Example 235 5-(5-Fluoro-2-(hydroxymethyl)-3-(6,6-dimethyl-3,4,6,7-tetrahydro-5*H*-cyclopenta[4,5]thieno[2,3-*c*]pyridine-1(2*H*)-yl)phenyl)-1-methyl-3-(2-methylisoindolin-5-ylamino)pyrazin-2(1*H*)-one **235**

A 100-mL three-neck round-bottomed flask equipped with a reflux condenser, magnetic stirrer and nitrogen inlet was charged with **231e** (150 mg, 0.447 mmol), **131a** (340 mg, 0.581 mmol), sodium carbonate (142 mg, 1.34 mmol), water (2 mL) and 1,4-dioxane (8 mL). After bubbling nitrogen through the resulting suspension for 30 min, tetrakis-(triphenylphosphine)palladium(0) (52 mg, 0.045 mmol) was added, and the reaction mixture was heated at reflux for 2 h. After that time, the mixture was cooled to room temperature and diluted with methylene chloride (100 mL) and water (30 mL). The organic layer was separated, and the aqueous layer was extracted with methylene chloride (3 × 30 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to afford a brown residue. A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer was purged with nitrogen and charged with the crude residue, THF (10 mL) and a 1 M solution of tetrabutylammonium fluoride in THF (4.50 mmol, 4.5 mL). The resulting mixture was stirred at room temperature for 2 h. After this time, the mixture was diluted with methylene chloride (100 mL) and washed with water (30 mL). The organic layer was separated, and the aqueous layer was extracted with methylene chloride (3 × 30 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (silica, 0% to 10% methanol/methylene chloride) to afford a 44% yield (120 mg) of **235** as an off-white solid: mp 218–220 °C (dec); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.21 (s, 1H), 7.89 (d, 1H, J = 1.0 Hz), 7.70 (dd, 1H, J = 8.1, 2.0 Hz), 7.50 (s, 1H), 7.34 (dd, 1H, J = 9.9, 3.0 Hz), 7.30 (dd, 1H, J = 9.1, 2.5 Hz), 7.13 (d, 1H, J = 8.0 Hz), 4.82 (m, 1H), 4.50 (m, 1H), 4.04 (m, 1H), 4.04 (m, 1H), 3.84 (m, 1H), 3.75 (m, 4H), 3.54 (s, 3H), 3.02 (m, 1H), 2.89 (m, 1H), 2.75 (s, 2H), 2.53 (d, 2H, J = 6.5 Hz), 2.46 (s, 3H), 1.23 (s, 6H); MS (ESI+) *m/z* 600.2 (M+H).

Example 236 5-(5-Fluoro-2-(hydroxymethyl)-3-(6,6-dimethyl-3,4,6,7-tetrahydro-5*H*-cyclopenta[4,5]thieno[2,3-*c*]pyridine-1(2*H*)-yl)-3-(5-(3-methylazetidin-1-yl)pyridin-2-ylamino)-1-methylpyridin-2(1*H*)-one **236**

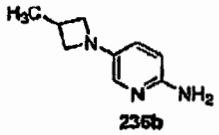
Example 236a 5-(3-Methylazetidin-1-yl)-2-nitropyridine **236a**



236a

A 500-mL single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was charged with 3-methylazetidinium benzenesulfonate (4.02 g, 17.5 mmol), 2-nitro-5-bromo pyridine (3.56 g, 17.5 mmol), cesium carbonate (28.5 g, 87.7 mmol) and 1,4-dioxane (50 mL). After bubbling nitrogen through the resulting suspension for 30 min, Xantphos (862 mg, 1.50 mmol) and tris(dibenzylidene-acetone)dipalladium(0) (800 mg, 0.900 mmol) were added. A reflux condenser was attached to the flask, and the reaction mixture was heated at reflux for 3 h. After this time, the mixture was cooled to room temperature and diluted with 90:10 methylene chloride/methanol (100 mL) and water (75 mL), and the layers were separated. The aqueous layer was extracted with 90:10 methylene chloride/methanol (2 × 50 mL), and the combined organic extracts were washed with brine and dried over sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography (silica, 0% to 80% ethyl acetate/hexanes) to afford 236a in 69% yield (2.35 g) as an amorphous yellow solid: mp 141–143 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, 1H, J = 9.0 Hz), 7.60 (d, 1H, J = 2.5 Hz), 6.66 (dd, 1H, J = 9.0, 2.5 Hz), 4.23 (t, 2H, J = 8.5 Hz), 3.68 (m, 2H), 2.99 (m, 1H), 1.36 (d, 3H, J = 7.0 Hz; MS (ESI+) *m/z* 194.0 (M+H)

Example 236b 5-(3-Methylazetidin-1-yl)pyridin-2-amine 236b

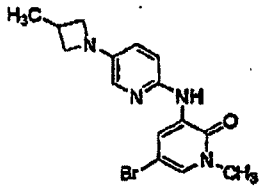


236b

A 250-mL Parr reactor bottle was purged with nitrogen and charged with 10% palladium on carbon (50% wet, 800 mg dry weight) and a solution of 236a (2.58 g, 13.4 mmol) in a mixture of ethanol (25 mL) and ethyl acetate (25 mL). The bottle was attached to a Parr hydrogenator, evacuated, charged with hydrogen gas to a pressure of 50 psi and shaken for 3 h. After this time, the hydrogen was evacuated, and nitrogen was charged into the bottle. Celite 521 (3.50 g) was added, and the mixture was filtered through a pad of Celite 521. The filter cake was washed with ethanol (2 × 50 mL), and the combined filtrates were concentrated to dryness under reduced pressure to afford a quantitative yield of 236b (2.21 g)

as a purple oil: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.19 (d, 1H, J = 3.0 Hz), 6.66 (dd, 1H, J = 9.0, 3.0 Hz), 6.36 (d, 1H, J = 8.5 Hz), 5.13 (br s, 2H), 3.81 (t, 2H, J = 7.5 Hz), 3.21 (t, 2H, J = 6.5 Hz), 2.70 (m, 1H), 1.18 (d, 3H, J = 7.0 Hz); MS (ESI+) *m/z* 164.1 (M+H).

Example 236c 5-Bromo-1-methyl-3-(5-(3-methylazetidin-1-yl)pyridin-2-ylamino)pyridin-2(1*H*)-one 236c



236c

Using the same procedure as described for the preparation of 121a, a reaction of 236b (1.04 g, 6.40 mmol) with 3,5-dibromo-1-methylpyridin-2(1H)-one (1.90 g, 7.12 mmol) afforded a 44% yield (980 mg) of 236c as a brown solid: mp 135–136 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.49 (d, 1H, J = 5.5 Hz), 8.42 (s, 1H), 7.50 (d, 1H, J = 4.5 Hz), 7.41 (d, 1H, J = 7.0 Hz), 7.20 (d, 1H, J = 14.5 Hz), 6.85 (dd, 1H, J = 14.5, 5.0 Hz), 3.91 (m, 2H), 3.49 (s, 3H), 3.34 (m, 2H), 2.75 (m, 1H), 1.21 (d, 3H, J = 11.5 Hz; MS (ESI+) *m/z* 350.2 (M+H).

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was charged with 236c (140 mg, 0.400 mmol), 182c (304 mg, 0.520 mmol), sodium carbonate (130 mg, 1.23 mmol), water (2 mL) and 1,4-dioxane (10 mL). After bubbling nitrogen through the resulting suspension for 30 min, tetrakis(triphenylphosphine)palladium(0) (50 mg, 0.043 mmol) was added. A reflux condenser was attached to the flask, and the reaction mixture was heated at reflux for 2 h. After this time, the mixture was diluted with 90:10 methylene chloride/methanol (100 mL) and water (75 mL), and the layers were separated. The aqueous layer was extracted with 90:10 methylene chloride/methanol (2 X 50 mL), and the combined organic layers were washed with brine (100 mL) and dried over sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was dissolved in THF. A 1 M solution of tetrabutylammonium fluoride in THF (1.20 mL, 1.20 mmol) was added, and the mixture was stirred at room temperature for 14 h. After this time, the mixture was diluted with 90:10 methylene chloride/methanol (75 mL) and water (50 mL), and the layers were separated. The aqueous layer was extracted with 90:10 methylene chloride/methanol (2 X 50 mL), and the combined organic extracts were washed with brine

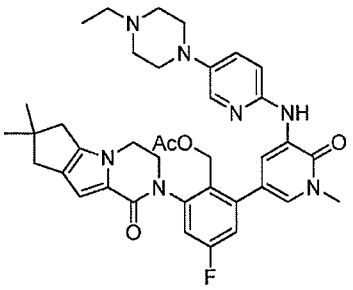
(100 mL) and dried over sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography (silica, 0% to 10% methylene chloride/methanol) to afford **236** in 14% yield (35 mg) as an amorphous brown solid: mp 170–171 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.45 (d, 1H, J = 2.5 Hz), 8.22 (s, 1H), 7.31 (m, 2H), 7.15 (m, 2H), 6.83 (dd, 1H, J = 9.0, 3.0 Hz), 4.83 (t, 1H, J = 4.5 Hz), 4.32 (m, 2H), 4.05 (m, 1H), 3.88 (m, 3H), 3.02 (m, 1H), 2.89 (m, 1H), 2.75 (s, 3H), 2.54 (m, 4H); MS (ESI+) *m/z* 614.3 (M+H).

Example 237 6-(3-(5-(4-(Oxetan-3-yl)piperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-(hydroxymethyl)phenyl)-2,3-(5,5-dimethyl-5,6-dihydro-4*H*-cyclopenta)-5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one **237**

A 100-mL three-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was charged with **210c** (160 mg, 0.382 mmol), **182c** (300 mg, 0.512 mmol), sodium carbonate (162 mg, 1.53 mmol), water (6 mL) and 1,4-dioxane (30 mL). After bubbling nitrogen through the resulting suspension for 20 min, tetrakis(triphenyl-phosphine)-palladium(0) (44.0 mg, 0.038 mmol) was added, and the reaction mixture was heated at 100 °C for 4 h. After this time, the reaction mixture was cooled to room temperature and filtered, and the filter cake was washed with a 1:10 mixture of methanol and methylene chloride (30 mL). The filtrate was concentrated under reduced pressure to afford a brown residue. Another 50-mL single-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was charged with the residue obtained above, tetrabutylammonium fluoride (1.0 M in THF, 1.54 mL, 1.54 mmol) and THF (10 mL). The mixture was stirred at room temperature for 1.5 h. After this time, the reaction mixture was concentrated under reduced pressure. The resulting residue was purified by flash chromatography to afford a 24% (86 mg) yield of **237** as a yellow solid: mp 175–177 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.55 (d, 1H, J = 2.0 Hz), 8.36 (s, 1H), 7.86 (d, 1H, J = 3.0 Hz), 7.35 (m, 3H), 7.22 (d, 1H, J = 9.0 Hz), 7.16 (dd, 1H, J = 9.0, 3.0 Hz), 4.85 (t, 1H, J = 5.0 Hz), 4.55 (t, 2H, J = 6.5 Hz), 4.45 (t, 2H, J = 6.0 Hz), 4.32 (m, 2H), 4.04 (m, 1H), 3.86 (m, 1H), 3.58 (s, 3H), 3.44 (m, 1H), 3.06 (t, 4H, J = 4.5 Hz), 3.03 (m, 1H), 2.89 (m, 1H), 2.75 (s, 2H), 2.52 (m, 2H), 2.38 (t, 4H, J = 4.5 Hz); MS (ESI+) *m/z* 685.4 (M+H).

Example 238 10-[3-(5-{[5-(4-Ethylpiperazin-1-yl)pyridine-2-yl]amino}-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-(hydroxymethyl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one **238**

Example 238a 10-[3-(5-{[5-(4-Ethylpiperazin-1-yl)pyridine-2-yl]amino}-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-(acetoxymethyl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-9-one **238a**



To a microwave tube equipped with a stirring bar, **189a** (381.9 mg, 0.850 mmol), 3-(5-(4-ethylpiperazin-1-yl)pyridin-2-ylamino)-1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one (**201a**) (560 mg, 1.275 mmol), $Pd(PPh_3)_4$ (49.1 mg, 0.043 mmol), Na_2CO_3 aqueous solution (1.0 N, 2.81 mL, 2.81 mmol), 1,2-dimethoxy-ethane (4 mL) were added. The mixture was reacted in microwave at 130 °C for 10 min. methylene chloride (200 mL) was added and the resulting mixture was washed with water (30 mL X 3), brine (30 mL X 1), dried over $MgSO_4$, filtered, and removed solvent *in vacuo*. Silica gel column chromatography (methanol: methylene chloride = 5: 95) gave **238a.**

To a round-bottomed flask equipped with a stirring bar, **238a**, THF (5 mL), *i*-PrOH (5 mL), H_2O (5 mL), LiOH H_2O (200 mg) were added. The resulting mixture was stirred at RT for 1 hr. The solvent was removed *in vacuo* and the resulting residue was added to methylene chloride (200 mL), the solution was washed with water (30 mL X 3), brine (30 mL X 1), dried over $MgSO_4$, filtered, and removed solvent *in vacuo*. Silica gel column chromatography (MeOH:methylene chloride / 10:90) gave **238** 53 as a pink solid, 143 mg. MS (ESI+) *m/z* 640.6 (M + H).

Example 239 5-(5-Fluoro-2-(hydroxymethyl)-3-(6,6-dimethyl-3,4,6,7-tetrahydro-5*H*-cyclopenta[4,5]thieno[2,3-*c*]pyridine-1(2*H*)-yl)-3-(5-(4-isopropylpiperazin-1-yl)pyridin-2-ylamino)-1-methylpyridin-2(1*H*)-one **239**

Using the same procedure as described for **236**, a reaction of **220a** (165 mg, 0.410 mmol) with **182c** (312 mg, 0.533 mmol) afforded a 21% yield (57 mg) of **239** as an off-white solid: mp 191–192 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.54 (d, 1H, J = 2.0 Hz), 8.34 (s, 1H), 7.85 (d, 1H, J = 3.0 Hz), 7.33 (m, 3H), 7.20 (d, 1H, J = 9.0 Hz), 7.15 (dd, 1H, J = 9.0, 3.0 Hz), 4.84 (t, 1H, J = 4.0 Hz), 4.32 (m, 2H), 4.04 (m, 1H), 3.84 (m, 1H), 3.57 (s, 3H), 3.02

(m, 5H), 2.87 (m, 1H), 2.75 (br s, 2H), 2.63 (m, 1H), 2.55 (m, 6H), 1.22 (s, 6H), 0.98 (d, 6H, J = 3.0 Hz); MS (ESI+) m/z 671.3 (M+H).

Example 240 5-(3-(6,6-Dimethyl-3,4,6,7-tetrahydro-5*H*-cyclopenta[4,5]thieno[2,3-*c*]pyridine-1(2*H*)-yl)-5-fluoro-2-(hydroxymethyl)phenyl)-1-methyl-3-(6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-2-ylamino)pyridin-2(1*H*)-one **240**

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was purged with nitrogen and charged with **182c** (300 mg, 0.513 mmol), **205b** (138 mg, 0.394 mmol), sodium carbonate (125 mg, 1.18 mmol), 1,4-dioxane (8 mL) and water (2 mL). This mixture was degassed with nitrogen for 30 min. Tetrakis(triphenylphosphine)palladium (46 mg, 0.039 mmol) was added. After heating at reflux for 2 h, the reaction mixture was cooled to room temperature and partitioned between water (40 mL) and methylene chloride (100 mL). The layers were separated, and the aqueous phase was extracted with methylene chloride (2 × 50 mL). The organic extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was dissolved in THF (3 mL), and tetrabuty-ammnium fluoride trihydrate (372 mg, 1.18 mmol) was added. After stirring at room temperature for 2 h, the reaction mixture was partitioned between water (20 mL) and methylene chloride (20 mL). The layers were separated, and the aqueous phase was extracted with methylene chloride (2 X 20 mL). The organic extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography to afford **240** in 22% yield (53 mg) as a yellow solid: mp 142–143 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.77 (d, 1H, J = 2.0 Hz), 8.43 (s, 1H), 7.44 (d, 1H, J = 2.0 Hz), 7.31 (dd, 1H, J = 9.5, 2.5 Hz), 7.27 (d, 1H, J = 8.0 Hz), 7.19 (dd, 1H, J = 9.5, 2.5 Hz), 7.06 (d, 1H, J = 8.0 Hz), 4.86 (m, 1H), 4.38 (m, 2H), 4.04 (m, 1H), 3.84 (m, 1H), 3.59 (s, 3H), 3.38 (s, 2H), 3.03 (m, 1H), 2.89 (m, 1H), 2.75 (s, 4H), 2.62 (m, 2H), 2.53 (m, 2H), 2.34 (s, 3H), 1.23 (s, 6H); MS (ESI+) m/z 614.3 (M+H).

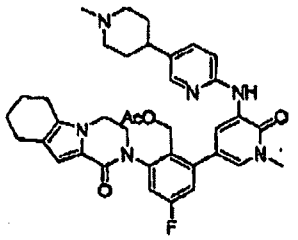
Example 241 5-(3-(6,6-Dimethyl-3,4,6,7-tetrahydro-5*H*-cyclopenta[4,5]thieno[2,3-*c*]pyridine-1(2*H*)-yl)-5-fluoro-2-(hydroxymethyl)phenyl)-1-methyl-3-(6-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-2-ylamino)pyridin-2(1*H*)-one **241**

Using the same general procedure as described for the preparation of **240**, reaction of 5-bromo-3-(6-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-2-ylamino)-1-methylpyridin-2(1H)-one (143 mg, 0.394 mmol) with **182c** (300 mg, 0.513 mmol) gave a 28% yield (70 mg) of **241** as a yellow solid: mp 134–135 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.78 (d, 1H, J = 2.0

Hz), 8.43 (s, 1H), 7.44 (d, 1H, J = 2.0 Hz), 7.31 (dd, 1H, J = 9.5, 2.5 Hz), 7.28 (d, 1H, J = 8.0 Hz), 7.18 (dd, 1H, J = 9.5, 2.5 Hz), 7.06 (d, 1H, J = 8.0 Hz), 4.86 (m, 1H), 4.38 (m, 2H), 4.04 (m, 1H), 3.84 (m, 1H), 3.59 (s, 3H), 3.43 (s, 2H), 3.03 (m, 1H), 2.89 (m, 1H), 2.75 (s, 4H), 2.62 (m, 2H), 2.53 (m, 2H), 2.50 (m, 2H), 1.23 (s, 6H), 1.08 (t, 3H, J = 7.0 Hz); MS (ESI+) *m/z* 628 (M+H).

Example 242 5-[5-Fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-{[5-(1-methylpiperidin-4-yl)pyridine-2-yl]amino}-1,2-dihydropyridin-2-one **242**

Example 242a 4-Fluoro-2-(1-methyl-5-(5-(1-methylpiperidin-4-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **242a**



To a microwave tube equipped with a stirring bar, 5-bromo-1-methyl-3-(5-(1-methylpiperidin-4-yl)pyridin-2-ylamino)pyridin-2(1H)-one (**130e**) (240 mg, 0.636 mmol), 4-fluoro-2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **210d** (336 mg, 0.763 mmol), $Pd(PPh_3)_4$ (37 mg, 0.0318 mmol), Na_2CO_3 aqueous solution (1.0 N, 2.1 mL, 2.1 mmol), 1,2-dimethoxyethane (4.2 mL) were added. The mixture was reacted in microwave at 130 °C for 10 min. methylene chloride (200 mL) was added and the resulting mixture was washed with water (3 X 30 mL), brine (30 mL), dried over $MgSO_4$, filtered, and removed solvent *in vacuo*. Silica gel column chromatography (methanol:methylene chloride = 5: 95) gave **242a**.

To a round-bottomed flask equipped with a stirring bar, **242a**, THF (5 mL), *i*-PrOH (5 mL), H_2O (5 mL), LiOH H_2O (300 mg) were added. The resulting mixture was stirred at RT for 1 hr. Removed all the solvent *in vacuo* and the resulting residue was added to methylene chloride (200 mL), the solution was washed with water (30 mL X 3), brine (30 mL X 1), dried over $MgSO_4$, filtered, and removed solvent *in vacuo*. Silica gel column chromatography (MeOH: methylene chloride = 10: 90) gave**242** as a brown solid, 56 mg. MS (ESI+) *m/z* 611.5 (M + H).

Example 243 10-[5-Fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[5-(1-methylpyrrolidin-2-yl)pyridine-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one **243**

Example 243a 10-[5-Fluoro-2-(acetoxymethyl)-3-(1-methyl-5-{[5-(1-methylpyrrolidin-2-yl)pyridine-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one **243a**

Example **243a** was synthesized using the same procedure as **121b**, except using compound **230a** (446 mg, 0.9 mmol), 5-bromo-1-methyl-3-(5-(1-methylpyrrolidin-2-yl)pyridin-2-ylamino)pyridin-2(1H)-one (**229a**) (281 mg, 0.8 mmol), 1M sodium carbonate solution (2.7 mL, 2.7 mmol), tetrakis(triphenylphosphine)-palladium(0) (47 mg, 0.040 mmol) and 1,2-dimethoxyethane (6.5 mL).The reaction mixture was heated at 130 °C for 15 minutes in the microwave reactor. Work-up and flash column chromato-graphy (silica, 9:1 methylene chloride/methanol) give a 67% yield (350 mg) of **243a** as brown oil: MS (ESI+) *m/z* 653.1 (M+H).

Following Example 121, except using a mixture of THF (2 mL), water (1 mL) and isopropanol (2 mL), compound **243a** (350 mg, 0.54 mmol) and lithium hydroxide monohydrate (150 mg, 3.5 mmol). Work-up and flash column chromatography (NH-silica, ethyl acetate /hexanes) give a 29% yield (95 mg) of compound **243** as a pale yellow solid: MS (ESI+) *m/z* 611.5 (M+H).

Example 244 10-[5-Fluoro-2-(hydroxymethyl)-3-[4-methyl-6-({4-[1-(oxetan-3-yl)piperidin-4-yl]phenyl}amino)-5-oxo-4,5-dihydropyrazin-2-yl]phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one **244**

Example 244a 10-[5-Fluoro-2-(acetoxymethyl)-3-[4-methyl-6-({4-[1-(oxetan-3-yl)piperidin-4-yl]phenyl}amino)-5-oxo-4,5-dihydropyrazin-2-yl]phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one **244a**

Following Example 121b, except using compound **230a** (188 mg, 0.38 mmol), 5-bromo-1-methyl-3-(4-(1-(oxetan-3-yl)piperidin-4-yl)phenylamino)pyrazin-2(1H)-one **214b** (160 mg, 0.38 mmol), 1M sodium carbonate solution (1.5 mL, 1.5 mmol), tetrakis(triphenylphosphine)palladium(0) (22 mg, 0.019 mmol) and 1,2-dimethoxyethane (5 mL).The reaction mixture was heated at 130 °C for 15 minutes in the microwave reactor. Work-up and flash column chromatography (silica, 60:35:5 methylene chloride/diethyl ether/methanol) give a mixture (270 mg) of compound **244a** and **244** as yellow oil.

The mixture from **244a** (270mg) was deprotected using the same procedure as **121**, except using a mixture of THF (2 mL), water (1 mL) and isopropanol (2 mL) and Lithium

hydroxide monohydrate (85 mg, 2 mmol). Work-up and flash column chromatography (NH-silica, ethyl acetate /hexanes) give a 63% yield (167 mg) of compound **244** as a pale yellow solid: MS (ESI+) *m/z* 667.6 (M+H).

Example 245 10-[5-Fluoro-2-(hydroxymethyl)-3-[1-methyl-6-oxo-5-({5-[4-(propan-2-yl)piperazin-1-yl]-pyridin-2-yl}amino)-1,6-dihydropyridin-3-yl]phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one **245**

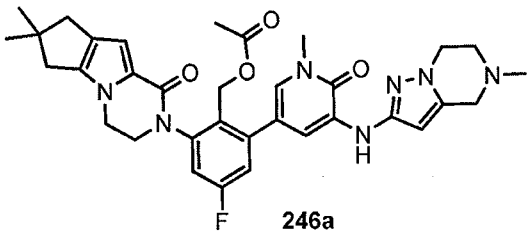
Example 245a 10-[5-Fluoro-2-(acetoxymethyl)-3-[1-methyl-6-oxo-5-({5-[4-(propan-2-yl)piperazin-1-yl]-pyridin-2-yl}amino)-1,6-dihydropyridin-3-yl]phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one **245a**

A 44-mL sealed tube equipped with a magnetic stirrer was charged with **220a** (400 mg, 1.0 mmol), **7** (508 mg, 2.0 mmol), potassium acetate (392 mg, 4.0 mmol) and 1,4-dioxane (10 mL). After the mixture was degassed for 30 minutes, Pd(dppf)Cl_2 •CH_2Cl_2 (82 mg, 0.10 mmol) was added. The resulting reaction mixture was stirred at 105 °C for 6 h. Then, it was cooled to room temperature and filtered through a pad of Celite. The filtrate was concentrated, and the crude mixture was redissolved in DME (2 mL) and transferred into a 10-mL microwave reaction vessel. To this solution was added 10-[2-(acetoxymethyl)-3-bromo-5-fluorophenyl]-4,4-dimethyl-1,10-diazatricyclo-[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one (**189a**) (270 mg, 0.60 mmol), Pd(PPh_3)$_4$ (50 mg, 0.050 mmol), and 2 N Na_2CO_3 (2 mL). Then, the reaction mixture was degassed for 5 minutes and placed into the microwave cavity. After the reaction mixture was stirred at 125 °C for 7 min., it was purified by flash chromatography (dichloromethane:methanol, 85:15) to give 49% (150 mg) of **245a**.

A 100-mL, single-necked, round-bottomed flask equipped with a magnetic stirring bar was charged with **245a** (150 mg, 0.22 mmol), LiOH•H_2O (100 mg, 2.2 mmol), THF (2 mL), isopropanol (2 mL), and water (2 mL). After the reaction mixture was stirred at room temperature for 3 h, it was partitioned between dichloromethane (5 mL) and water (5 mL), and the organic phase was extracted with dichloromethane (5 mL x 3). The combined organic phases were washed with water (5 mL x 2) and brine (5 mL x 1), dried (Na_2SO_4), and concentrated. The crude product was re-dissolved in dichloromethane (3 mL). To this solution was added hexane (10 mL) and the resulting precipitates were filtered to give 49% yield (70 mg) of **245.** MS(ESI$^+$) *m/z* 654.6 (M+H).

Example 246 10-[5-Fluoro-2-(hydroxymethyl)-3-[1-methyl-5-({5-methyl-4H,5H,6H,7H-pyrazolo[1,5-a]pyrazin-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one **246**

Example 246a 10-[5-Fluoro-2-(acetoxymethyl)-3-[1-methyl-5-({5-methyl-4H,5H,6H,7H-pyrazolo[1,5-a]pyrazin-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-9-one **246a**



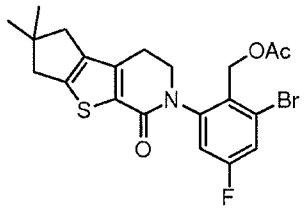
246a

A microwave tube equipped with a magnetic stirrer was charged with 5-bromo-1-methyl-3-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)pyridin-2(1H)-one **146a** (210 mg, 0.6 mmol), **230a** (460 mg, 0.9 mmol), 1,2-dimethoxyethane (8 mL) and 1M aqueous sodium carbonate (2 mL). After bubbling N_2 for 15 min, $Pd(PPh_3)_4$ (36 mg, 0.03 mmol) was added. The mixture was heated in microwave to 135 °C for 15 min. After this time, ethyl acetate (5 mL) and water (5 mL) were added. The separated aqueous layer was extracted with ethyl acetate (2 X 5 mL). The combined organics were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography eluting with a gradient of methylene chloride – 60:35:5 methylene chloride/diethyl ether/methanol to afford a 37% yield (140 mg) of **246a.**

A 25 mL round bottom flask with a magnetic stirrer was charged with **246a** (140 mg, 0.2 mmol), lithium hydroxide (200 mg, 4.8 mmol), THF (3 mL), isopropanol (3 mL) and water (2 mL). The mixture stirred at rt for 1 h. After this time, ethyl acetate (5 mL) and water (5 mL) were added. The separated aqueous layer was extracted with ethyl acetate (2 x 5 mL). The combined organics were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography using the Biotage KPNH 12+M column eluting with a gradient of hexanes - ethyl acetate to afford a 86% yield (120 mg) of **246**. MS (ESI+) *m/z* 586.6 (M + H).

Example 247 10-[5-Fluoro-2-(hydroxymethyl)-3-{4-methyl-6-[(2- methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)amino]-5-oxo-4,5-dihydropyrazin-2-yl}phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.$0^{2,6}$]dodeca-1(8),2(6)-dien-9-one **247**

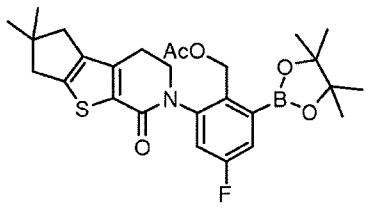
Example 247a (2-Bromo-6-{4,4-dimethyl-9-oxo-7-thia-10-azatricyclo[6.4.0.$0^{2,6}$]dodeca-1(8),2(6)-dien-10-yl}-4-fluorophenyl)methyl Acetate **247a**



247a

A mixture of 4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one (**105h**) (2 g, 9.05 mmol), 2,6-dibromo-4-fluorobenzyl acetate (**197c**)(8.8 g, 27.15 mmol), XantPhos (524 mg, 0.9 mmol), $Pd_2(dba)_3$ (828 mg, 0.9 mmol) and Cs_2CO_3 (5.9 g, 18 mmol) in dioxane (200 mL) was heated at 100°C for 15 h under nitrogen. The reaction mixture was filtered and the filtrated was evaporated in *vacuo*. The residue was purified by silical-gel column eluting with 1:1 ethyl acetate/petroleum ether to give **247a** as a yellow solid (3 g, 71%). MS: $(M+H)^+$ 466.

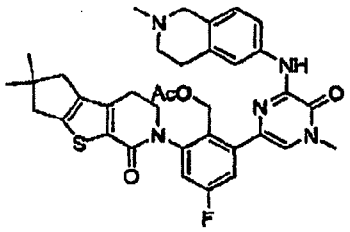
Example 247b (2-{4,4-Dimethyl-9-oxo-7-thia-10- azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-10-yl}-4-fluoro-6-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl Acetate **247b**



247b

A solution of **247a** (3 g, 6.45 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (9.8 g, 38.7 mmol) in dioxane (160 mL) was added $PdCl_2$(dppf) (525 mg, 0.65 mmol) and CH_3COOK (3.8 g, 38.7 mmol). The mixture was stirred at 100°C for 15 h under argon atmosphere. After reaction the mixture was filtered and evaporated in *vacuo* and the residue was purified by silical-gel column eluting with 1:2 ethyl acetate/petroleum ether to give **247b** as a yellow solid (2.5 g, 76%). MS: $(M+H)^+$ 514.

Example 247c (2-{4,4-Dimethyl-9-oxo-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-10-yl}-4-fluoro-6-{4-methyl-6-[(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)amino]-5-oxo-4,5-dihydropyrazin-2-yl}phenyl)methyl Acetate **247c**



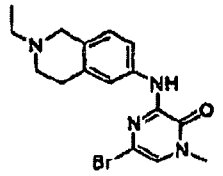
247c

A 25 mL sealed tube was charged with 247b (590 mg, 1.15 mmol), 5-bromo-1-methyl-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-ylamino)pyrazin-2(1H)-one 221b (400 mg, 1.15 mmol), CH_3COONa (189 mg, 2.3 mmol), K_3PO_4 (611 mg, 2.3 mmol), $PdCl_2$(dppf) (94 mg, 0.11 mmol) suspended in CH_3CN (25 mL) and water (1 mL). The mixture was heated at 110°C for 2 hours. The mixture was evaporated and the residue was purified by silical-gel column eluting with 20:1 methylene chloride/methanol to give 247c as a brown solid (400 mg, 53%). MS: $(M+H)^+$ 656.

A solution of 247c (400 mg, 0.61 mmol) in propan-2-ol (8 mL), tetrahydrofuran (8 mL) and water (1.5 mL) was added LiOH (1.46 g, 61 mmol). The mixture was stirred at 30°C for 2 h. It was then evaporated and the residue was purified by prep-HPLC to afford 247 as a yellow solid (124 mg, 33%). MS: $(M+H)^+$ 614. ^1H NMR (500 MHz, MeOD) δ 1.29 (s, 6 H), 2.46 (s, 3 H), 2.59-2.60 (d, 2 H), 2.74-2.76 (t, 2 H), 2.81 (s, 2 H), 2.93-2.98 (m, 3 H), 3.07-3.09 (m, 1 H), 3.59 (s, 2 H), 3.64 (s, 3 H), 3.95-3.97 (m, 1 H), 4.01-4.12 (m, 1 H), 4.48-4.51 (d, 1 H), 4.58-4.61 (d, 1 H), 7.03-7.05 (d, 1 H), 7.18-7.21 (m, 1 H), 7.38-7.41 (m, 2 H), 7.52-7.54 (d, 1 H), 7.64 (s, 1 H).

Example 248 10-(3-{6-[(2-Ethyl-1,2,3,4-tetrahydroisoquinolin-6- yl)amino]-4-methyl-5-oxo-4,5-dihydropyrazin-2-yl}-5-fluoro-2-(hydroxymethyl)phenyl)-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one 248

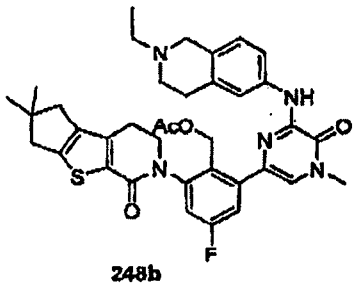
Example 248a 5-Bromo-3-(2-ethyl-1,2,3,4-tetrahydroisoquinolin-6-ylamino)-1-methylpyrazin-2(1H)-one 248a



248a

Following the procedures as described for 220a and starting with 385 mg of 5-bromo-1-methyl-3-(1,2,3,4-tetrahydroisoquinolin-6-ylamino)pyrazin-2(1H)-one (221a), 248a was obtained as yellow solid (292 mg, 70%). MS: $[M+H]^+$ 364.

Example 248b 2-{4,4-Dimethyl-9-oxo-7-thia-10-azatricyclo[6.4.0.$0^{2,6}$]dodeca-1(8),2(6)-dien-10-yl}-6-{6-[(2-ethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)amino]-4-methyl-5-oxo-4,5-dihydropyrazin-2-yl}-4-fluorophenyl)methyl Acetate 248b



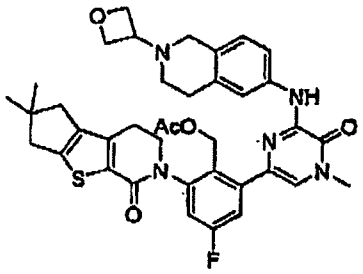
248b

Following the procedures as described for 129a and starting with 400 mg of (2-{4,4-dimethyl-9-oxo-7-thia-10-azatricyclo[6.4.0.$0^{2,6}$]dodeca-1(8),2(6)-dien-10-yl}-4-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl acetate (247b) and 283 mg of 5-bromo-3-(2-ethyl-1,2,3,4-tetrahydroisoquinolin-6-ylamino)-1-methyl-pyrazin-2(1H)-one , 248b was obtained as a yellow solid (260 mg, 50%).

Following the procedures as described for 148 and starting with 230 mg of 248b, 127 mg of 248 was obtained as a white solid (59%). ^{1}H NMR (500 MHz, DMSO) δ 9.15 (s, 1H), 7.81 (s, 1H), 7.63 (dd, J=8, 1H), 7.52 (s, 1H), 7.39 (dd, J=9.5, 1H), 7.31 (d, J=9.5, 1H), 6.97 (d, J=8.0, 1H), 4.88 (s, 1H), 4.50 (s, 1H), 4.45 (s, 1H), 4.04(m, 1H), 3.84 (m, 1H), 3.54 (s, 3H), 3.47 (s, 2H), 3.03 (m, 1H), 2.91(m, 1H), 2.76(s, 3H), 2.62-2.45(m, 6H), 1.23(s, 6H), 1.08(t, J=7.5, 3H).

Example 249 10-[5-Fluoro-2-(hydroxymethyl)-3-(4-methyl-6-{[2-(oxetan-3-yl)-1,2,3,4-tetrahydroisoquinolin-6-yl]amino}-5-oxo-4,5-dihydropyrazin-2-yl)phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.$0^{2,6}$]dodeca-1(8),2(6)-dien-9-one 249

Example 249a (2-{4,4-Dimethyl-9-oxo-7-thia-10-azatricyclo[6.4.0.$0^{2,6}$]dodeca-1(8),2(6)-dien-10-yl}-4-fluoro-6-(4-methyl-6-{[2-(oxetan-3-yl)-1,2,3,4-tetrahydroisoquinolin-6-yl]amino}-5-oxo- 4,5-dihydropyrazin-2-yl)phenyl)methyl Acetate 249a



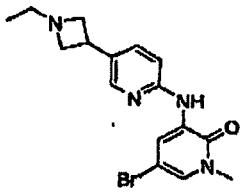
249a

Following the procedures as described for **148b** and starting with **247b** and 305 mg of **222a**, 277 mg of **249a** was obtained as a yellow solid (51%). MS: $[M+H]^+$ 698.

Following the procedures as described for compound **148** and starting with 250 mg of **249a**, 117 mg of **249** was obtained as a white solid (50%). ^{1}H NMR (500 MHz, DMSO) δ 9.17 (s, 1H), 7.85 (d, J=1.5, 1H), 7.65 (dd, J=8, 1H), 7.52 (s, 1H), 7.39 (dd, J=9.5, 1H), 7.31 (d, J=9.5, 1H), 6.97 (d, J=8.0, 1H), 4.80 (s, 1H), 4.61 (m, 2H), 4.52 (m, 1H), 4.43(m, 1H), 4.04 (m, 1H), 3.85 (m, 1H), 3.56 (m, 4H), 3.34 (s, 2H), 3.01-2.57 (m, 6H), 2.53 (m, 5H), 1.23 (s, 6H).

Example 250 2-(3-(5-(5-(1-Ethylazetidin-3-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **250**

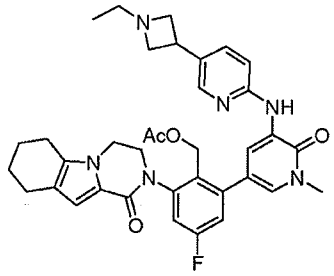
Example 250a 5-Bromo-3-(5-(1-ethylazetidin-3-yl)pyridin-2-ylamino)-1-methylpyridin-2(1H)-one **250a**



To a solution of 3-(5-(azetidin-3-yl)pyridin-2-ylamino)-5-bromo-1-methylpyridin-2(1H)-one **155n** (crude, 4.6 mmol) in methanol (50 mL) and acetic acid (5 mL) at 0 °C, was added CH_3CHO (40% wt in H_2O) (10 g, 92 mmol) followed by the addition of $NaBH(CH_3O)_3$ (20 g, 92 mmol) in small portions over a period of 1 h. After the reaction was finished, the mixture was adjusted to pH>7 with 2N NaOH. Then the mixture was extracted with DCM (80 mL × 3), dried over Na_2SO_4 and concentrated to get a yellow solid, which was purified on flash column eluting with 50:1 DCM/MeOH containing 0.5% Et_3N to afford **250a** as a yellow solid (43%, two steps). LCMS: $(M+H)^+$ 364. ^{1}H NMR (500 MHz, DMSO) δ 8.72

(s, 1H), 8.66 (d, J=3, 1H), 8.21 (d, J=3, 1H), 7.68 (dd, J=9, 1H), 7.52 (d, J=2.5, 1H), 7.32 (d, J=9, 1H), 3.54 (m, 6H), 2.99 (m, 2H), 2.42 (m, 2H), 0.89 (t, J=7, 3H).

Example 250b 2-(5-(5-(1-Ethylazetidin-3-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-fluoro-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **250b**

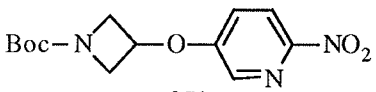


Following Example 136e, starting with **250a** and 4-fluoro-2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **210d**, a 65% yield of **250b** was obtained. LCMS: $(M+H)^+$ 639

Following Example 135, starting with **250b**, a 63% yield of **250** was obtained. LCMS: $(M+H)^+$ 597. ^{1}H NMR (500 MHz, DMSO) δ 8.66 (d, J=2, 1H), 8.56 (s, 1H), 8.11 (d, J=1.5, 1H), 7.66 (dd, J=8.5, 1H), 7.42 (d, J=2.5, 1H), 7.33 (dd, J=9.5, 1H), 7.28 (d, J=8.5, 1H), 7.19 (dd, J=9, 1H), 6.53 (s, 1H), 4.87 (t, J=4, 1H), 4.31 (d, J=4.5, 2H), 4.15 (m, 3H), 3.89 (m, 1H), 3.59 (s, 3H), 3.47 (m, 3H), 2.97 (m, 2H), 2.62 (m, 3H), 2.40 (m, 3H), 1.79 (m, 2H), 1.69 (m, 2H), 0.88 (t, J=7, 3H).

Example 251 5-(5-Fluoro-2-(hydroxymethyl)-3-(6,6-dimethyl-3,4,6,7-tetrahydro-5*H*-cyclopenta[4,5]thieno[2,3-*c*]pyridine-1(2*H*)-yl)-3-(5-(1-methylazetidin-3-yloxy))-1-methylpyridin-2(1*H*)-one **251**

Example 251a *tert*-Butyl 3-(6-Nitropyridin-3-yloxy)azetidine-1-carboxylate **251a**

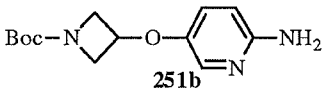


251a

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was charged with 2-nitro-5-hydroxypyridine (2.00 g, 14.3 mmol), *tert*-butyl 3-iodoazetidine-1-carboxylate (6.06 g, 21.5 mmol), sodium hydride (800 mg, 20.2 mmol) and DMF (30 mL). The reaction mixture was heated at 110 °C for 24 h. After this time, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was diluted with ethyl acetate (200 mL) and washed with saturated aqueous

sodium bicarbonate (100 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography to afford **251a** in 95% yield (4.00 g) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, 1H, *J* = 9.0 Hz), 8.14 (d, 1H, *J* = 3.0 Hz), 7.26 (dd, 1H, *J* = 9.0, 3.0 Hz), 5.04 (m, 1H), 4.39 (m, 2H), 4.06 (m, 2H), 1.44 (s, 9H); MS (ESI+) *m/z* 196.1 (M-Boc+H).

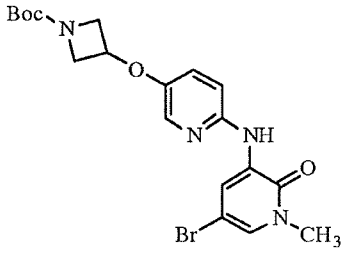
Example 251b *tert*-Butyl 3-(6-Aminopyridin-3-yloxy)azetidine-1-carboxylate **251b**



251b

A 250-mL Parr reactor bottle was purged with nitrogen and charged with platinum oxide (200 mg), **251a** (2.00 g, 6.78 mmol), ethyl acetate (30 mL) and ethanol (30 mL). The bottle was attached to a Parr hydrogenator, evacuated, charged with hydrogen gas to a pressure of 50 psi and shaken for 20 h. After this time, the hydrogen was evacuated, and nitrogen was charged into the bottle. Celite 521 (10.0 g) was added, and the mixture was filtered through a pad of Celite 521. The filter cake was washed with methanol (2 × 50 mL), and the combined filtrates were concentrated to dryness under reduced pressure to afford a 100% yield (2.01 g) of **251b** as a white solid: mp 83–84 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.53 (d, 1H, *J* = 3.0 Hz), 7.04 (dd, 1H, *J* = 9.0, 3.0 Hz), 6.41 (d, 1H, *J* = 9.0 Hz), 5.32 (br s, 2H), 4.21 (t, 2H, *J* = 6.5 Hz), 3.75 (t, 2H, *J* = 6.5 Hz), 3.25 (m, 1H), 1.37 (s, 9H); MS (ESI+) *m/z* 266.2 (M+H).

Example 251c *tert*-Butyl 3-(6-(5-Bromo-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)pyridin-3-yloxy)azetidine-1-carboxylate **251c**

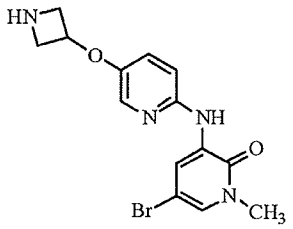


251c

Using the same procedure as described for the preparation of **250a**, reaction of **251b** (1.01 g, 3.80 mmol) with 3,5-dibromo-1-methylpyridin-2(1H)-one (1.01 g, 3.80 mmol) afforded an 81% yield (1.40 mg) of **251c** as a brown solid: mp 120–121 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.70 (s, 1H), 8.57 (d, 1H, *J* = 2.5 Hz), 7.86 (d, 1H, *J* = 3.0 Hz), 7.48 (d,

1H, *J* = 2.5 Hz), 7.35 (d, 1H, *J* = 9.0 Hz), 7.28 (m, 1H), 4.95 (m, 1H), 4.3 (m, 2H), 3.80 (m, 2H), 3.50 (s, 3H), 1.38 (s, 9H); MS (ESI+) *m/z* 452.3 (M+H).

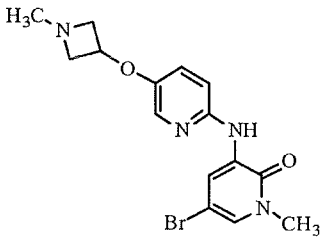
Example 251d 3-(5-(Azetidin-3-yloxy)pyridin-2-ylamino)-5-bromo-1-methylpyridin-2(1*H*)-one **251d**



251d

A 250-mL single-neck round-bottomed flask equipped with a magnetic stirrer was charged with **251c** (1.14 g, 3.10 mmol), methylene chloride (10 mL) and trifluoroacetic acid (5 mL). The reaction mixture was stirred at room temperature for 2 h. After this time, the mixture was concentrated under reduced pressure. The resulting residue was diluted with methylene chloride (100 mL) and washed with saturated aqueous sodium bicarbonate (50 mL). The aqueous layer was extracted with methylene chloride (2 × 50 mL) and the combined organic extracts were dried over sodium sulfate, filtered and concentrated to afford a 92% yield (1.10 g) of **251d** as a colorless oil. This compound was used directly for the next step without any purification: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.65 (s, 1H), 8.55 (d, 1H, *J* = 2.5 Hz), 7.82 (d, 1H, *J* = 3.0 Hz), 7.48 (d, 1H, *J* = 2.5 Hz), 7.30 (d, 1H, *J* = 9.0 Hz), 7.21 (m, 1H), 4.95 (t, 1H, *J* = 6.0 Hz), 3.76 (m, 1H), 3.48 (m, 5H); MS (ESI+) *m/z* 353.0 (M+H).

Example 251e 5-Bromo-1-methyl-3-(5-(1-methylazetidin-3-yloxy)pyridin-2-ylamino)pyridin-2(1*H*)-one **251e**



251e

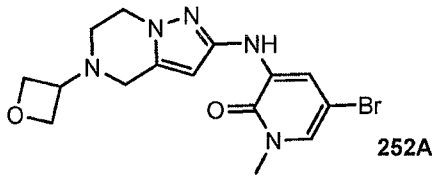
A 250-mL single-neck round-bottomed flask equipped with a magnetic stirrer was purged with nitrogen and charged with **251d** (1.10 g, 2.95 mmol), 37% solution of formaldehyde in water (111 mg, 3.70 mmol) and methanol (15 mL). A suspension of sodium cyanoborohydride (540 mg, 8.60 mmol) and zinc chloride (600 mg, 4.40 mmol) in methanol (10 mL) was added, and the reaction was stirred at room temperature for 4 h. After this time,

the reaction mixture was concentrated, and the residue was partitioned between 90:10 methylene chloride/methanol (250 mL) and 10% aqueous potassium carbonate (100 mL). The aqueous layer was extracted with 90:10 methylene chloride/ methanol (3×150 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (silica, 0% to 50% methanol/methylene chloride) to afford a 80% yield (830 mg) of **251e** as an brown solid: mp 100–101 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.66 (s, 1H), 8.55 (d, 1H, J = 2.5 Hz), 7.86 (d, 1H, J = 3.0 Hz), 7.47 (d, 1h, J = 2.5 Hz), 7.31 (d, 1H, J = 9.0 Hz), 7.24 (dd, 1H, J = 9.5, 3.5 Hz), 4.76 (m, 1H), 3.77 (t, 2H, J = 7.5 Hz), 3.50 (s, 3H), 3.03 (t, 2H, J = 7.5 Hz), 2.26 (s, 3H); MS (ESI+) *m/z* 366.0 (M+H).

Using the same procedure as described for the preparation of **239**, a reaction of **251e** (145 mg, 0.400 mmol) with **182c** (304 mg, 0.520 mmol) afforded a 15% yield (37 mg) of **251** as a off-white solid: mp 160–161 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.53 (d, 1H, J = 2.5 Hz), 8.49 (s, 1H), 7.77 (d, 1H, J = 2.5 Hz), 7.36 (d, 1H, J = 2.0 Hz), 7.32 (dd, 1H, J = 9.0, 2.5 Hz), 7.27 (d, 1H, J = 9.0 Hz), 7.22 (dd, 1H, J = 9.0, 2.5 Hz), 7.16 (dd, 1H, J = 9.0, 2.5 Hz), 4.84 (t, 1H, J = 4.0 Hz), 4.69 (m, 1H), 4.30 (m, 2H), 3.84 (m, 1H), 3.69 (m, 2H), 3.58 (s, 3H), 3.02 (m, 1H), 2.92 (m, 3H), 2.75 (m, 2H), 2.54 (m, 2H), 2.27 (s, 3H); MS (ESI+) *m/z* 630.3 (M+H).

Example 252 10-[5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[5-(oxetan-3-yl)-4H,5H,6H,7H-pyrazolo[1,5-a]pyrazin-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one **252**

Example 252a 5-bromo-1-methyl-3-(5-(oxetan-3-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)pyridin-2(1H)-one **252a**



252A

Following Example 214b, 5-bromo-1-methyl-3-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)pyridin-2(1H)-one **126a** (250 mg, 0.78 mmol), oxetan-3-one (600 mg, 8.3 mmol) were dissolved in methanol (8 mL). Sodium cyanoborohydride (148 mg, 3 mmol) and zinc chloride (165 mg, 1.5 mmol) in methanol (8 mL) was added, and the reaction was heated at 48 °C for 12 hours. Work-up and flash column chromatography (silica, 60:35:5 methylene chloride/diethyl ether/methanol) afford a 34% yield (100 mg) of **252a** as a light green solid: MS (ESI+) *m/z* 382.1 (M+H).

Following Example 121b, except using **230a** (135 mg, 0.26 mmol), **252a** (100 mg, 0.26 mmol), 1M sodium carbonate solution (1 mL, 1 mmol), tetrakis(tripheny-phosphine)palladium(0) (15 mg, 0.013 mmol) and 1,2-dimethoxyethane (2.5 mL). The reaction mixture was heated at 130 °C for 15 minutes in the microwave reactor. Work-up and flash column chromatography (silica, 60:35:5 methylene chloride/diethyl ether/methanol) give a mixture (80 mg) of **252b** and **252** as yellow oil. This mixture (80 mg) was deprotected using the same procedure 121, except using a mixture of THF (1 mL), water (0.5 mL) and isopropanol (1 mL) and Lithium hydroxide monohydrate (25 mg, 0.6 mmol). Work-up and flash column chromatography (NH-silica, Ethly Acetate /Hexanes) give a 40% yield (30 mg) of **252** as a white solid: MS (ESI+) *m/z* 628.5 (M+H).

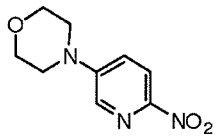
Example 253 5-[5-Fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-({5-[(2R)-1-methylpyrrolidin-2-yl]pyridine-2-yl}amino)-1,2-dihydropyridin-2-one **253**

Example 254 5-[5-Fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-({5-[(2S)-1-methylpyrrolidin-2-yl]pyridine-2-yl}amino)-1,2-dihydropyridin-2-one **254**

Examples **253** and **254** are enantiomers of racemate **202**. The racemic mixture **202** was subjected to chiral separation on a Chiralpak AD, 4.6x50mm, 3μm column (mobile phase 55% isopropanol (w/0.1% triethylamine)/45%CO_2, flow rate 5mL/min) at 40 °C to give individual enantiomers, with **254** eluting first, followed by **253** last. Examples **253** MS (ESI+) *m/z* 597.4 (M+H). Examples **254** MS (ESI+) *m/z* 597.4 (M+H).

Example 255 5-[5-Fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-{[5-(morpholin-4-yl)pyridin-2-yl]amino}-1,2-dihydropyridin-2-one **255**

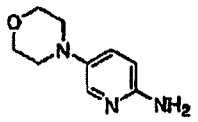
Example 255a 4-(6-Nitropyridin-3-yl)morpholine **255a**



255a

Following the procedures as described for **188a** and starting with 2 g of 5-bromo-2-nitropyridine and 968 mg morpholine, **255a** was obtained as a yellow solid (1 g, 50%). MS: $[M+H]^+$ 210. ^1H NMR (500 MHz, CDCl3) δ 8.18 (d, J = 9.0, 1H), 8.15 (d, J = 3.0, 1H), 7.22 (dd, J = 3.0, 1H), 3.90 (t, J=5.0, 4H), 3.42 (t, J=5.0, 4H).

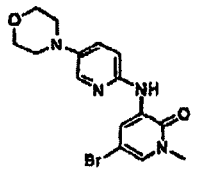
Example 255b 5-Morpholinopyridin-2-amine **255b**



255b

Following the procedures as described for **188b** and starting with 1 g of 4-(6-nitropyridin-3-yl)morpholine, **255b** was obtained as a yellow solid (840 mg, 98%). MS: $[M+H]^+$ 210

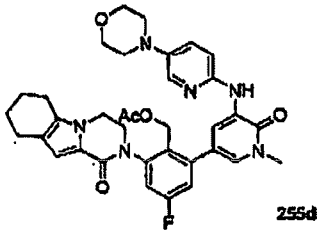
Example 255c 5-Bromo-1-methyl-3-(5-morpholinopyridin-2-ylamino)pyridin-2(1H)-one **255c**



255c

Following the procedures as described for **188c** and starting with 3,5-dibromo-1-methylpyridin-2(1H)-one (1.15g, 4.3 mmol) and 5-morpholinopyridin-2-amine (770 mg, 4.3 mmol), **255c** was obtained as a yellow solid (986 mg, 63%). MS: $[M+H]^+$ 365

Example 255d 4-Fluoro-2-(1-methyl-5-(5-morpholinopyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **255d**



255d

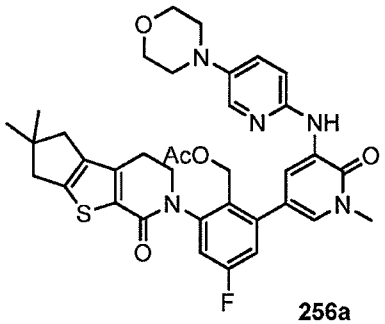
Following the procedures as described for **148c** and starting with 400 mg of 4-fluoro-2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **210d** and 302 mg of 5-bromo-1-methyl-3-(5-morpholinopyridin-2-ylamino)pyridin-2(1H)-one, **255d** was obtained as a yellow solid (281 mg, 53%). MS: $[M+H]^+$ 641

Following the procedures as described for **148** and starting with 270 mg of 4-fluoro-2-(1-methyl-5-(5-morpholinopyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate, **255** was obtained as a

white solid (103 mg, 41%). MS: $[M+H]^+$ 599. ^1H NMR (500 MHz, DMSO) δ 8.56 (d, J=2.0, 1H), 8.38 (s, 1H), 7.87 (d, J=3.0,1H), 7.36-7.32 (m, 3H), 7.25 (d, J=9.5, ,2H), 7.19 (d, J=9.0, 1H), 6.52 (s, 1H), 4.87 (s, 1H), 4.32 (d,J=4, 2H), 4.15 (m, 3H), 3.82(m, 1 H), 3.72 (t, J=4.0, 1H), 3.50 (s, 3H), 3.02 (t, J=4.5, 3H), 2.61 (m, 2H), 2.47(m, 2H), 1.80(s, 2H), 1.68(S, 2H).

Example 256 10-[5-Fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[5- (morpholin-4-yl)pyridine-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.$0^{2,6}$]dodeca-1(8),2(6)-dien-9-one **256**

Example 256a (2-{4,4-Dimethyl-9-oxo-7-thia-10-azatricyclo[6.4.0.$0^{2,6}$]dodeca-1(8),2(6)-dien-10-yl}-4-fluoro-6-(1-methyl-5-{[5-(morpholin-4-yl)pyridin-2-yl]amino}-6-oxo-1,6-dihydropyridin-3- yl)phenyl)methyl Acetate **256a**



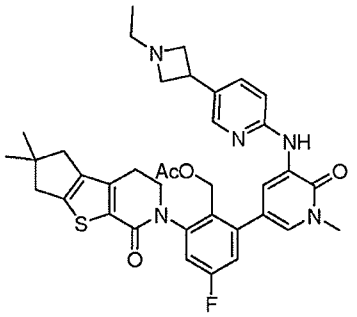
256a

Following Example 148b, starting with 400 mg of (2-{4,4-dimethyl-9-oxo-7-thia-10-azatricyclo[6.4.0.$0^{2,6}$]dodeca-1(8),2(6)-dien-10-yl}-4-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl acetate **247b** and 284 mg 5-bromo-1-methyl-3-(5-morpholinopyridin-2-ylamino)pyridin-2(1H)-one **255c**, 277 mg of **256a** was obtained as a yellow solid (53%). MS: $[M+H]^+$ 672

Following Example 148, starting with 270 mg of **256a**, 103 mg of **256** was obtained as a white solid (41%). MS: $[M+H]^+$ 630. ^1H NMR (500 MHz, DMSO) δ 8.56 (d, J=2.0, 1H), 8.38 (s, 1H), 7.88 (d, J=3.0,1H), 7.36-7.32 (m, 3H), 7.25 (d, J=9.5, ,2H), 7.19 (d, J=9.0, 1H), 4.85 (s, 1H), 4.32 (d,J=4, 2H), 4.07 (m, 3H), 3.86(m, 1 H), 3.72 (t, J=4.0, 1H), 3.50 (s, 3H), 3.02 (t, J=4.5, 3H), 2.89 (m, 1H), 2.76 (s, 2H), 2.53 (m, 2H), 1.23 (s, 6H).

Example 257 10-[3-(5-{[5-(1-Ethylazetidin-3-yl)pyridin-2- yl]amino}-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-(hydroxymethyl)phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.$0^{2,6}$]dodeca-1(8),2(6)- dien-9-one **257**

Example 257a (2-{4,4-Dimethyl-9-oxo-7-thia-10-azatricyclo[6.4.0.$0^{2,6}$]dodeca-1(8),2(6)-dien-10-yl}-6-(5-{[5-(1-ethylazetidin-3-yl)pyridin-2-yl]amino}-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4- fluorophenyl)methyl Acetate **257a**

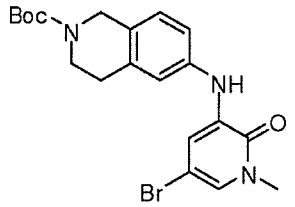


Following Example 136a, starting with 5-bromo-3-(5-(1-ethylazetidin-3-yl)pyridin-2-ylamino)-1-methylpyridin-2(1H)-one **250a** and (2-{4,4-dimethyl-9-oxo-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-10-yl}-4-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl acetate **247b**, compound **257a** was obtained in 37% yield.

Following Example 136, starting with **257a**, compound **257** was obtained in 46% yield. LCMS: $(M+H)^+$ 628. ^{1}H NMR (500 MHz, DMSO) δ 8.66 (d, J=2, 1H), 8.55 (s, 1H), 8.12 (d, J=2.5, 1H), 7.65 (dd, J=8.5, 1H), 7.42 (d, J=2, 1H), 7.33 (dd, J=9.5, 1H), 7.28 (d, J=9, 1H), 7.19 (dd, J=9, 1H), 4.86 (t, J=4, 1H), 4.33 (m, 2H), 4.05 (m, 1H), 3.86 (m, 1H), 3.59 (s, 3H), 3.49 (m, 3H), 3.04 (m, 1H), 2.97 (m, 2H), 2.89 (m, 1H), 2.76 (s, 2H), 2.55 (m, 2H), 2.40 (m, 2H), 1.79 (m, 4H), 1.23 (s, 6H), 0.88 (t, J=7, 3H).

Example 258 2-(5-Fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(2-(oxetan-3-yl)-1,2,3,4-tetrahydroisoquinolin-6-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **258**

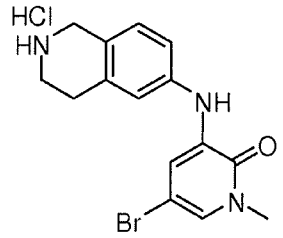
Example 258a *tert*-Butyl 6-(5-Bromo-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)-3,4- dihydroisoquinoline-2(1H)-carboxylate **258a**



A 100 mL round bottomed flask was charged with tert-butyl 6-amino-3,4-dihydroisoquinoline-2(1H)-carboxylate (2 g, 8 mmol), 3,5-dibromo-1-methylpyridin-2(1H)-one (1.8 g, 6.7 mmol), cesium carbonate (4.4 g, 13.4 mmol), XantPhos (0.41 g, 0.7 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.64 g, 0.7 mmol) and 1,4-dioxane (50 mL).The reaction mixture was refluxed under argon atmosphere for 2 h. After this time, the mixture was cooled to room temperature and filtered. The filtrate was concentrated under

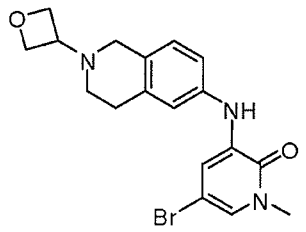
reduced pressure. The residue was purified by column chromatography eluting with 25:1 dichloromethane/methanol to give **258a** (2.18 g, 63%). LC/MS: m/z 435 $(M+H)^+$

Example 258b 5-Bromo-1-methyl-3-(1,2,3,4-tetrahydroisoquinolin-6-ylamino)pyridine-2(1H)-one **258b**



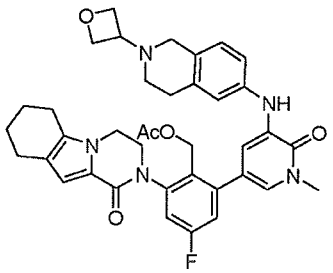
Compound **258a** (2.18 g, 5 mmol) was suspended in dioxane (10 mL). Saturated hydrogen chloride in dioxane (20 mL) was added dropwise. The reaction mixture was stirred for 20 minutes and concentrated under reduced pressure to afford **258b**, which was used without further purification in the next step. LC/MS: m/z 335 $(M+H)^+$

Example 258c 5-Bromo-1-methyl-3-(2-(oxetan-3-yl)-1,2,3,4-tetrahydroisoquinolin-6-ylamino) pyridin-2(1H)-one **258c**



A mixture of **258b** (1.7 g, 5 mmol), oxetan-3-one (1.8 g, 25 mmol), $NaBH_3CN$ (1 g, 15 mmol) and zinc chloride (3.4 g, 25 mmol) in methanol (50 mL) was stirred for 4 hours at room temperature. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography eluting with 25:1 dichloromethane/methanol to give **258c** (1.8 g, 92%). LC/MS: m/z 391 $(M+H)^+$

Example 258d 4-Fluoro-2-(1-methyl-5-(2-(oxetan-3-yl)-1,2,3,4-tetrahydroisoquinolin-6-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **258d**

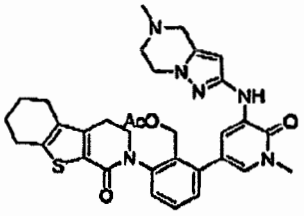


A 15 mL microwave reaction vial with a magnetic stirrer was charged with **258c** (0.39 g, 1 mmol), 4-fluoro-2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **210d** (0.48 g, 1 mmol), potassium phosphate (0.54 g, 2 mmol), sodium acetate (0.17 g, 2 mmol), acetonitrile (10 mL), water (1 mL), and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane (0.08 g, 0.1 mmol). The reaction mixture was heated at 110 ^{0}C for 2 hours under argon atmosphere. After this time, the mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography eluting with 40:1 dichloromethane /methanol to give **258d** (0.3 g, 50%). *LC/MS*: m/z 666 $(M+H)^{+}$

A 25 mL round bottomed flask with a magnetic stirrer was charged with **258d** (0.6 g, 0.9 mmol), LiOH (2 g, 48 mmol), THF(5 mL), isopropanol (5 mL) and water (2 mL). The reaction mixture was stirred at room temperature for 30 minutes and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by prep-HPLC to give **258**. LC/MS: m/z 624 $(M+H)^{+}$. ^{1}H NMR (500 MHz, DMSO) δ 7.62 (s, 1H), 7.82 (s, 1H), 7.34 (m, 3H), 7.20 (m, 1H), 7.09 (m, 2H), 6.94 (m, 1H), 4.86 (m, 1H), 4.96 (m, 1H), 4.60 (m, 2H), 4.51 (m, 2H), 4.31 (m, 2H), 4.14 (m, 3H), 3.87 (m, 1H), 3.58 (m, 4H), 3.33 (m, 3H), 2.75 (m, 2H), 2.60 (m, 3H), 2.50 (m, 3H), 1.78 (m, 4H).

Example 259 5-[2-(Hydroxymethyl)-3-[1-methyl-5-({5-methyl- 4H,5H,6H,7H-pyrazolo[1,5-a]pyrazin-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one **259**

Example 259a {2-[1-Methyl-5-({5-methyl-4H,5H,6H,7H-pyrazolo[1,5- a]pyrazin-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]-6-{6-oxo-8-thia-5 azatricyclo[7.4.0.0^{2,7}]-trideca-1(9),2(7)-dien-5- yl}phenyl}methyl Acetate **259a**



259a

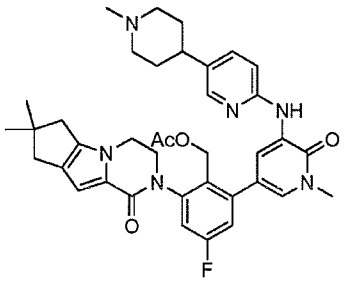
A 25 mL sealed tube was charged with (2-{6-oxo-8-thia-5-azatricyclo[7.4.0.0^{2,7}]-trideca-1(9),2(7)-dien-5-yl}-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-methyl acetate **111a** (571 mg, 1.2 mmol), 5-bromo-1-methyl-3-(5-methyl-4,5,6,7-

tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)pyridin-2(1H)-one **146a** (400 mg, 1.2 mmol), CH_3COONa (195 mg, 2.4 mmol), K_3PO_4 (631 mg, 2.4 mmol), $PdCl_2(dppf)$ (97 mg, 0.12 mmol) suspended in CH_3CN (25 mL) and H_2O (1 mL). The mixture was heated at 110°C for 2 hours. It was then evaporated and the residue was purified by column chromatography eluting with 20:1 methylene chloride/methanol to give **259a** as a brown solid (500 mg, 69%). MS: $(M+H)^+$ 613.

A solution of **259a** (500 mg, 0.82 mmol) in propan-2-ol (10 mL), tetrahydrofuran (10 mL) and water (2 mL) was added LiOH (1.96 g, 82 mmol). The mixture was stirred at 30°C for 2 h. It was then evaporated and the residue was purified by prep-HPLC to afford **259** as a yellow solid (159 mg, 34%). MS: $(M+H)^+$ 571. ^1H NMR (500 MHz, DMSO) δ 1.79 (s, 4 H), 2.35 (s, 2 H), 2.53-2.55 (m, 1 H), 2.76-2.79 (m, 4 H), 2.84-2.88 (m, 1 H), 2.96-2.98 (m, 1 H), 3.48 (s, 2 H), 3.57 (s, 3 H), 3.87-3.93 (m, 3 H), 3.99-4.03 (m, 1 H), 4.35 (s, 2 H), 4.81 (s, 1 H), 5.88 (s, 1 H), 7.23-7.24 (d, 2 H), 7.29-7.34 (m, 2 H), 7.43-7.46 (d, 1 H), 7.97-7.98 (d, 1 H), 8.10 (s, 1 H).

Example 260 10-[5-Fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[5-(1-methylpiperidin-4-yl)pyridine-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-9-one **260**

Example 260a 10-[5-Fluoro-2-(acetoxymethyl)-3-(1-methyl-5-{[5-(1-methylpiperidin-4-yl)pyridine-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-9-one **260a**



To a microwave tube equipped with a stirring bar, 5-bromo-1-methyl-3-(5-(1-methylpiperidin-4-yl)pyridin-2-ylamino)pyridin-2(1H)-one **130c** (162 mg, 0.429 mmol), boronic ester **212b** (347 mg, 0.700 mmol), $Pd(PPh_3)_4$ (24.8 mg, 0.022 mmol), Na_2CO_3 aqueous solution (1.0 N, 1.42 mL, 1.42 mmol), 1,2-dimethoxyethane (4.0 mL) were added. The mixture was reacted in microwave at 130°C for 15 min. Dichloromethane (200 mL) was added and the resulting mixture was washed with water (3 X 30 mL), brine (30 mL X 1), dried over $MgSO_4$, filtered, and removed solvent *in vacuo*. Silica gel column chromatography (methanol:dichloromethane = 5: 95) gave **260a**.

To a round-bottomed flask equipped with a stirring bar, **260a**, THF (5 mL), *i*-PrOH (5 mL), H_2O (5 mL), LiOH H_2O (300 mg) were added. The resulting mixture was stirred at RT for 1 hr. Removed all the solvent *in vacuo* and the resulting residue was added to dichloromethane (200 mL), the solution was washed with water (3 X 30 mL), brine (30 mL), dried over $MgSO_4$, filtered, and removed solvent *in vacuo*. Silica gel column chromatography (MeOH: dichloromethane = 10: 90) gave alcohol **260** as yellow solids, 48 mg. MS (ESI+) *m/z* 625.5 (M + H).

Example 261 10-[5-Fluoro-2-(hydroxymethyl)-3-{1-methyl-5-[(6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-2-yl)amino]-6-oxo-1,6-dihydropyridin-3-yl}phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-9-one **261**

Example 261a 10-[5-Fluoro-2-(acetoxymethyl)-3-{1-methyl-5-[(6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-2-yl)amino]-6-oxo-1,6-dihydropyridin-3-yl}phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-9-one **261a**

In a 10-mL microwave reaction vessel equipped with a magnetic stirring bar were placed 5-bromo-1-methyl-3-(6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-2-ylamino)pyridin-2(1H)-one **205b** (150 mg, 0.43 mmol), 10-[2-(acetoxymethyl)-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-fluorophenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-9-one **230a** (248 mg, 0.50 mmol), $Pd(PPh_3)_4$ (30 mg, 0.026 mmol) in 2 N Na_2CO_3 (2 mL) and 1,2-dimethoxyethane (2 mL). After the reaction mixture was stirred at 125°C for 10 minutes, it was purified by flash chromatography (dichloromethane:methanol, 3:1) to give 36% (100 mg) of **261a** as a solid.

A 25-mL, single-necked, round-bottomed flask equipped with a magnetic stirring bar was charged with **261a** (100 mg, 0.16 mmol), LiOH•H_2O (200 mg, 4.8 mmol), THF (2 mL), isopropanol (2 mL), and water (2 mL). After the reaction mixture was stirred at room temperature for 2 h, it was partitioned between dichloromethane (5 mL) and water (5 mL), and the organic phase was extracted with dichloromethane (5 mL x 3). The combined organic phases were washed with water (2 X 5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. The crude product was re-dissolved in dichloromethane (3 mL). To this solution was added hexane (10 mL) and the resulting precipitate was filtered to give 36% yield (34 mg) of **261.** MS(ESI^+) *m/z* 597.5 (M+H).

Example 262 10-[3-(5-{[5-(1-Ethylazetidin-3-yl)pyridine-2-yl]amino}-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-(hydroxymethyl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-9-one **262**

Examples 262a and 262b Following Example 271a, **262b** was produced using **250a** (305mg, 0.84mmol) in Step 1 and using **189a** (302mg, 0.67mmol) in Step 2 in Example 271b. The product was purified via column chromatography: ISCO 12g silica , 0-10% MeOH, to give desired product **262b** (105mg, 19% yield).

Following Example 119, **262a** (105mg, 0.36mmol), 1N LiOH (0.8mL), THF (2mL) and isopropanol (2mL) were reacted to give **262** (85mg, 87% yield). MS (ESI+) *m/z* 611.5 (M + H).

Example 263 2-(5-Fluoro-2-(hydroxymethyl)-3-(5-(2-methoxypyrimidin-4-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **263**

Example 263a 5-Bromo-3-(2-methoxypyrimidin-4-ylamino)-1-methylpyridin-2(1H)-one **263a**

Following Example 112a, 2-methoxypyrimidin-4-amine (0.625g, 5 mmol), 3,5-dibromo-1-methyl-1H-pyridin-2-one (1.34 g, 5 mmol), cesium carbonate (4.88 g, 15 mmol), tris(dibenzylideneacetone)-dipalladium(0) (0.465 g, 0.5 mmol), Xantphos (0.58 g, 1 mmol) and 1,4-dioxane (50 mL) were heated at 100 °C for 24 hours. The mixture was cooled to room temperature, and filtered through a pad of Celite 521. The filter cake was washed with 9:1 methylene chloride/ methanol (2 X 25 mL), and the combined filtrates were concentrated to dryness. The residue was dissolve in methylene chloride, diethyl ethyl was added, and the resulting precipitate was filtered to give a quantitative yield (1.57 g) of **263a** as a green solid: MS (ESI+) *m/z* 313.1 (M+H).

Example 263b 4-Fluoro-2-(5-(2-methoxypyrimidin-4-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **263b**

Following Example 121b, **263a** (158 mg, 0.5 mmol), 4-fluoro-2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **210d** (242 mg, 0.5 mmol), 1M sodium carbonate solution (2 mL, 2 mmol), tetrakis(triphenylphosphine)palladium(0) (29 mg, 0.025 mmol) and 1,2-dimethoxyethane (5 mL) were heated at 130 °C for 15 minutes in the microwave reactor. Work-up and flash column chromatography (silica, 60:35:5 methylene chloride/diethyl ether/methanol) gave a 98% yield (290 mg) of **263b** as yellow oil: MS (ESI+) *m/z* 587.6 (M+H).

Following Example 121, a mixture of THF (2 mL), water (1 mL) and isopropanol (2 mL), **263b** (290 mg, 0.5 mmol) and lithium hydroxide monohydrate (105mg, 2.5 mmol) were

reacted. Work-up and flash column chromatography (NH-silica, ethyl acetate /hexanes) gave a 26% yield (70 mg) of **263** as a solid: MS (ESI+) *m/z* 545.1 (M+H).

Example 264 10-[5-Fluoro-2-(hydroxymethyl)-3-[1-methyl-5-({5-[1-(oxetan-3-yl)piperidin-4-yl]pyridine-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-9-one **264**

Example 264a *tert*-Butyl 4-(6-(5-Bromo-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)pyridin-3-yl)piperidine-1-carboxylate **264a**

Following Example 112a, *tert*-butyl 4-(6-aminopyridin-3-yl)piperidine-1-carboxylate (1.9 g, 5.5 mmol), 3,5-dibromo-1-methylpyridin-2(1H)-one (1.47 g, 5.5 mmol), cesium carbonate (5.36 g, 16.5 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.53 g, 0.55 mmol), Xantphos (0.63 g, 1.1 mmol) and 1,4-dioxane (50 mL) were heated at 100 °C for 8 hours. Work-up and concentrated to dryness. Wash the resulting solid with diethyl ether, filtered and give 56% yield (1.4 g) of **264a** as a grey solid: MS (ESI+) *m/z* 465.2 (M+H).

Example 264b 5-Bromo-1-methyl-3-(5-(piperidin-4-yl)pyridin-2-ylamino)pyridin-2(1H)-one **264b**

Following Example 121c, **264a** (0.58g, 1.25 mmol), trifluoroacetic acid (0.96 mL, 12.5mmol) and methylene chloride (20 mL) were reacted. Work-up and concentrated to afford a quantitative yield of **264b** (454 mg) as yellow oil, which was used without purification in the next step. MS (ESI+) *m/z* 365.2 (M+H).

Example 264c 5-Bromo-1-methyl-3-(5-(1-(oxetan-3-yl)piperidin-4-yl)pyridin-2-ylamino)pyridin-2(1H)-one **264c**

Following Example 214b, **264b** (450 mg, 1.25 mmol), oxetan-3-one (800 mg, 11.1 mmol) in methanol (10 mL) were mixed. Sodium cyanoborohydride (236 mg, 3.75 mmol) and zinc chloride (256 mg, 1.88 mmol) in methanol (10 mL) was added, and the reaction was heated at 48 °C for 12 hours. Work-up and flash column chromatography (silica, 60:35:5 methylene chloride/diethyl ether/methanol) afford a 30% yield (160 mg) of **264c** as a light green solid: MS (ESI+) *m/z* 421.1 (M+H).

Following Example 121b, **264c** (160 mg, 0.38 mmol), **230a** (188 mg, 0.38 mmol), 1M sodium carbonate solution (1.5 mL, 1.5 mmol), tetrakis(triphenylphosphine)-palladium(0) (22 mg, 0.019 mmol) and 1,2-dimethoxyethane (3.5 mL) were heated at 130 °C for 15 minutes in the microwave reactor. Work-up and flash column chromatography (silica, 9:1 methylene chloride/ methanol) gave a mixture (110 mg) of compound **264c** and **264** as yellow oil. The mixture (110 mg) was deprotected using the same procedure as for **121**, except using a mixture of THF (1 mL), water (0.5 mL) and isopropanol (1 mL), and lithium hydroxide

monohydrate (50mg, 1.2 mmol). Work-up and flash column chromatography (NH-silica, ethyl acetate /hexanes) give a 56% yield (60 mg) of compound 264 as a yellow solid: MS (ESI+) *m/z* 667.6 (M+H).

Example 265 2-(5-Fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(1-(oxetan-3-yl)piperidin-4-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one 265

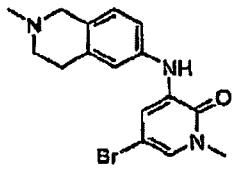
Example 265a 4-Fluoro-2-(1-methyl-5-(5-(1-(oxetan-3-yl)piperidin-4-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate 265a

Following Example 121b, 264c (210 mg, 0.5 mmol), 4-fluoro-2-(1-oxo-3,4,6,7,8,9-hexahydro-pyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate 210d (242 mg, 0.5 mmol), 1M sodium carbonate solution (2 mL, 2 mmol), tetrakis(triphenylphosphine)palladium(0) (29 mg, 0.025 mmol) and 1,2-dimethoxyethane (5 mL) were heated at 130 °C for 15 minutes in the microwave reactor. Work-up and flash column chromatography (silica, 9:1 methylene chloride/ methanol) gave a 69% yield (240 mg) of 265a as brown oil: MS (ESI+) *m/z* 695.5 (M+H).

Following Example 121, a mixture of THF (2 mL), water (1 mL) and isopropanol (2 mL), 265a (240 mg, 0.35 mmol) and lithium hydroxide monohydrate (100mg, 2.5 mmol) were reacted. Work-up and flash column chromatography (NH-silica, ethyl acetate /hexanes) give a 30% yield (70 mg) of 265 as a yellow solid: MS (ESI+) *m/z* 653.6 (M+H).

Example 266 10-[5-Fluoro-2-(hydroxymethyl)-3-{4-methyl-6-[(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)amino]-5-oxo-4,5-dihydropyrazin-2-yl}phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one 266

Example 266a 5-Bromo-1-methyl-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-ylamino)pyridin-2(1H)-one 266a.

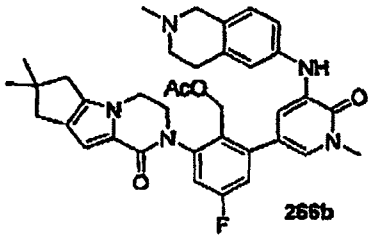


266a

A 100 mL round bottom flask with a magnetic stirrer was charged with 258b (350 mg, 0.8 mmol), formaldehyde (37% aqueous soln, 4.1 mmol), $NaBH_3CN$ (150 mg, 2.4 mmol),

$ZnCl_2$ (170 mg, 1.2 mmol) in methanol (46 mL). The mixture was stirred for 16 h at room temperature. After this time, the mixture was concentrated under reduced pressure and 10% aqueous K_2CO_3 (25 mL). The desired product crashed out of this mixture and was filtered. Upon washing with diethyl ether (20 mL) afforded a 85% yield (240 mg) of 266a.

Example 266b 10-[5-Fluoro-2-(acetoxymethyl)-3-{4-methyl-6-[(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)amino]-5-oxo-4,5-dihydropyrazin-2-yl}phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-9-one 266b



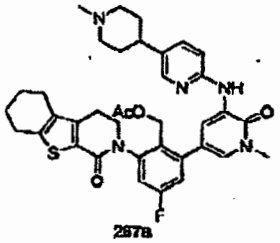
266b

A microwave tube equipped with a magnetic stirrer was charged with 266a (240 mg, 0.7 mmol), 210d (460 mg, 0.9 mmol), 1,2-dimethoxyethane (8 mL) and 1M aqueous sodium carbonate (2 mL). After bubbling N_2 for 15 min, $Pd(PPh_3)_4$ (40 mg, 0.03 mmol) was added. The mixture was heated in microwave to 120 °C for 10 min. After this time, ethyl acetate (5 mL) and water (5 mL) were added. The separated aqueous layer was extracted with ethyl acetate (2 X 5 mL). The combined organics were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography eluting with a gradient of methylene chloride – 9:1 methylene chloride:methanol to afford a 27% yield (120 mg) of 266b.

A 25 mL round bottom flask with a magnetic stirrer was charged with 266b (120 mg, 0.2 mmol), lithium hydroxide (40 mg, 0.9 mmol), THF (1 mL), isopropanol (1 mL) and water (2 mL). The mixture stirred at rt for 30 min. After this time, ethyl acetate (5 mL) and water (5 mL) were added. The separated aqueous layer was extracted with ethyl acetate (2 x 5 mL). The combined organics were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography using the Biotage KPNH 12+M column eluting with a gradient of hexanes - ethyl acetate to afford a 45% yield (50 mg) of 266. MS (ESI+) *m/z* 597.4 (M + H).

Example 267: 5-[5-Fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[5-(1-methylpiperidin-4-yl)pyridin-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$]trideca-1(9),2(7)-dien-6- one 267

Example 267a [4-Fluoro-2-(1-methyl-5-{[5-(1-methylpiperidin-4- yl)pyridin-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)-6-{6-oxo-8-thia-5-azatricyclo[7.4.0.0^{2,7}]-trideca-1(9),2(7)-dien-5-yl}phenyl]methyl Acetate 267a



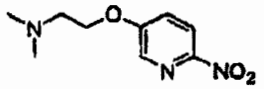
267a

A sealed tube was charged with the mixture of 5-bromo-1-methyl-3-(5-(1-methylpiperidin-4-yl)pyridin-2-ylamino)pyridin-2(1H)-one **130e** (400 mg, 1.0 mmol), (4-fluoro-2-{6-oxo-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-5-yl}-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl acetate **247b** (534 mg, 1.0 mmol), $Pd(dppf)Cl_2$ (87 mg, 0.1 mmol), $K_3PO_4.3H_2O$(569 mg, 2.0 mmol), and NaOAc (175 mg, 2.0 mmol) in CH_3CN (20 mL). The system was evacuated and then refilled with N_2. And the reaction mixture was heated at 110 °C for 2 h. Then, the mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and the resulting residue was purified by column chromatography eluting with 10:1 methylene chloride/methanol to give **267a** as a brown solid (350 mg, 49%). MS: $[M+H]^+$ 670.

A solution of **267a** (100 mg, 0.15 mmol) in propan-2-ol (5 mL), tetrahydrofuran (5 mL) and water (1 mL) was added LiOH (358 mg, 15 mmol). The mixture was stirred at 30°C for 2 h. It was then evaporated and the residue was purified by prep-HPLC to afford **267** as a yellow solid (18 mg, 19%). MS: $(M+H)^+$ 628. ^1H NMR (500 MHz, MEOD) δ 1.83-1.96 (m, 8 H), 2.53-2.66 (m, 8 H), 2.85 (t, 2 H), 2.92-2.97 (m, 1 H), 3.04-3.07 (m, 1 H), 3.23-3.26 (d, 2 H), 3.98-4.01 (m, 1 H), 4.12-4.15 (m, 1 H), 4.48-4.55 (m, 2 H), 7.05 (d, 1 H), 7.20-7.23 (m, 2 H), 7.39 (d, 1 H), 7.55-7.57 (m, 1 H), 8.12 (s, 1 H), 8.65 (s, 1 H).

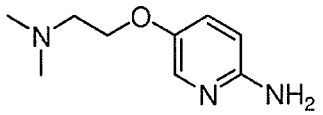
Example 268 5-{3-[5-({5-[2-(Dimethylamino)ethoxy]pyridin-2- yl}amino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl]-5-fluoro-2-(hydroxymethyl)phenyl}-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one 268

Example 268a N,N-Dimethyl-2-(6-nitropyridin-3-yloxy)ethanamine 268a



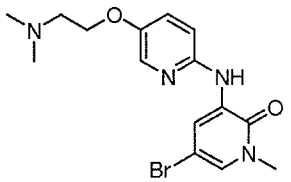
A mixture of 6-nitropyridin-3-ol (0.5 g, 3.57 mmol), 2-chloro-N,N-dimethyl-ethanamine hydrochloride (0.61 g, 4.29 mmol) and Cs_2CO_3 (2.56 g, 7.85 mmol) in DMF (7 mL) was stirred at 120°C in a sealed tube for 15 hr. The mixture was filtered and the filtrate was worked up with ethyl acetate and water. The aqueous phase was extracted with ethyl acetate. The combined extracts were dried over sodium sulfate and concen-trated under reduced pressure. The residue was purified on flash column to give **268a** (0.46 g, 61%). MS: $[M+H]^+$ 212.

Example 268b 5-(2-(Dimethylamino)ethoxy)pyridin-2-amine **268b**



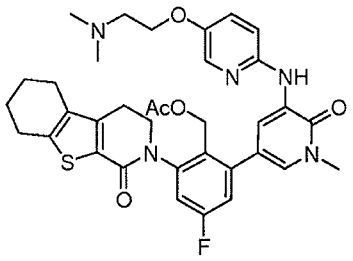
A 100-mL Parr hydrogenation bottle was purged with nitrogen and charged with **268a** (0.92 g, 4.36 mmol), 10% palladium on carbon (50% wet, 0.2 g) and methanol (30 mL). The bottle was evacuated, charged with hydrogen gas to a pressure of 25 psi and shaken for 2 h on a Parr hydrogenation apparatus. The hydrogen was then evacuated and nitrogen charged to the bottle. The catalyst was removed by filtration through a pad of Celite and the filtrate was concentrated under reduced pressure to afford **268b** (0.66 g, 83%). MS: $[M+H]^+$ 182.

Example 268c 5-Bromo-3-(5-(2-(dimethylamino)ethoxy)pyridin-2-ylamino)-1-methy-lpyridin-2(1H)-one **268c**



A mixture of **268b** (570 mg, 3.15 mmol), XantPhos (109 mg, 0.19 mmol), Pd_2dba_3 (230 mg, 0.25 mmol), 3,5-dibromo-1-methylpyridin-2(1H)-one (918 mg, 3.46 mmol) and Cs_2CO_3 (2.05 g. 6.3 mmol) in 1,4-dioxane (20 mL) was heated at reflux for 2 h. After the completion of the reaction, the mixture was filtered off and washed with methanol (100 mL). The filtrate was evaporated in *vacuo*. The residue was purified on reverse phase Combi-flash to give **268c** (922 mg, 80%). MS: $[M+H]^+$ 367.

Example 268d {2-[5-({5-[2-(Dimethylamino)ethoxy]pyridin-2- yl}amino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl]-4-fluoro-6-{6-oxo-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$]trideca-1(9),2(7)-dien-5- yl}phenyl}methyl Acetate **268d**

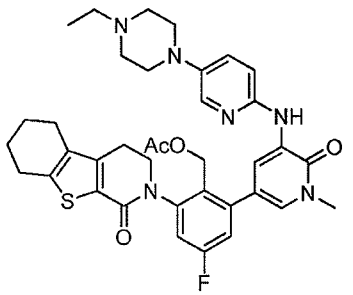


A mixture of **268c** (360 mg, 0.99 mmol), (4-fluoro-2-{6-oxo-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-5-yl}-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl acetate **212b** (494 mg, 0.99 mmol), $PdCl_2(dppf)$ (86 mg, 0.12 mmol), K_3PO_4 (150 mg), and NaOAc (50 mg) in MeCN (6mL) and water (2 mL) was heated at 110℃ in a sealed tube for 2 h. The solvent was evaporated in *vacuo*. The residue was purified on reverse phase Combi-flash to give **268d** (367 mg, 60%). MS: $[M+H]^+$ 660.

A mixture of **268d** (700 mg, 1.06 mmol) and LiOH hydrate (446 mg, 10.6 mmol) in isopropanol (15 mL) and water (5 mL) was stirred at 30℃ for 2 h. The mixture was evaporated in *vacuo* and the residue was extracted with ethyl acetate (2 X 20 mL). The combined extracts were concentrated under reduced pressure. The residue was purified on prep-HPLC to give **268** (94 mg, 14%). MS: $[M+H]^+$ 618. ^1H NMR (500 MHz, CDCl3) δ 8.54 (d, J = 2.0, 1H), 7.95 (d, J = 3.0, 1H), 7.80 (s, 1H), 7.48 (d, J = 2.5, 1H), 7.23-7.21 (m, 1H), 7.16-7.14 (m, 1H), 6.98-6.96 (m, 1H), 6.81 (d, J = 9.0, 1H), 4.57 (d, J = 11.5, 1H), 4.30 (t, J = 10.5, 1H), 4.20-4.02 (m, 4H), 3.87-3.80 (m, 1H), 3.69 (s, 3H), 3.00-2.84 (m, 4H), 2.75-2.73 (m, 2H), 2.59-2.48 (m, 2H), 2.37 (s, 6H), 1.94-1.83 (m, 4H).

Example 269 5-[3-(5-{[5-(4-Ethylpiperazin-1-yl)pyridine-2-yl]amino}-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-(hydroxymethyl)phenyl]-8-thia-5-azatricyclo-[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one **269**

Example 269a 5-[3-(5-{[5-(4-Ethylpiperazin-1-yl)pyridine-2-yl]amino}-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-(hydroxymethyl)phenyl]-8-thia-5-azatricyclo-[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one **269a**

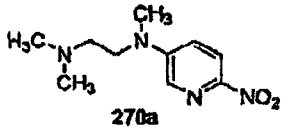


To a microwave tube equipped with a stirring bar, 5-bromo-3-(5-(4-ethyl-piperazin-1-yl)pyridin-2-ylamino)-1-methylpyridin-2(1H)-one **138c** (300 mg, 0.765 mmol), boronic ester **212b** (420.1 mg, 0.841 mmol), $Pd(PPh_3)_4$ (44.2 mg, 0.038 mmol), Na_2CO_3 aqueous solution (1.0 N, 2.52 mL, 2.52 mmol), 1,2-dimethoxyethane (4.0 mL) were added. The mixture was reacted in microwave at 130 °C for 15 min. Methylene chloride (200 mL) was added and the resulting mixture was washed with water (3 X 30 mL), brine (30 mL), dried over $MgSO_4$, filtered, and removed solvent *in vacuo*. Silica gel column chromatography (methanol: methylene chloride = 5: 95) gave acetate **269a**.

To a round-bottomed flask equipped with a stirring bar, **269a**, THF (5 mL), isopropanol (5 mL), water (5 mL), LiOH H_2O (300 mg) were added. The resulting mixture was stirred at RT for 1 hr. The solvent was removed *in vacuo* and the resulting residue was added to methylene chloride (200 mL), the solution was washed with water (3 X 30 mL), brine (30 mL), dried over $MgSO_4$, filtered, and removed solvent *in vacuo*. Silica gel column chromatography (methanol: methylene chloride = 10: 90) gave **269** as a light brown solid, 158 mg. MS (ESI+) *m/z* 643.4 (M + H).

Example 270 3-(5-((2-(Dimethylamino)ethyl)(methyl)amino)pyridin-2-ylamino)-5-(5-fluoro-2-(hydroxymethyl)-3-(6,6-dimethyl-3,4,6,7-tetrahydro-5*H*-cyclopenta-[4,5]thieno[2,3-*c*]pyridine-1(2*H*)-yl)phenyl)-1-methylpyridin-2(1*H*)-one **270**

Example 270a N^1,N^1,N^2-Trimethyl-N^2-(6-nitropyridin-3-yl)ethane-1,2-diamine **270a**

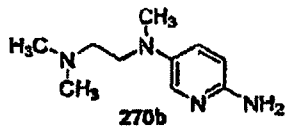


270a

A 100-mL round-bottomed flask equipped with a magnetic stirrer was charged with 1e (3.00 g, 14.8 mmol), N^1,N^1,N^2-trimethylethane-1,2-diamine (2.26 g, 22.2 mmol) and *N,N*-dimethylacetamide (10 mL). *N,N*-di-isopropylethylamine (3.69 g, 28.6 mmol) and tetrabutylammonium iodide (8.18 g, 22.8 mmol) were added, and the reaction mixture was stirred at 90 °C for 14 h. After this time, the reaction was cooled to room temperature and poured into water (20 mL). The resulting mixture was extracted with ethyl acetate (100 mL). The organic layer was separated and dried over sodium sulfate. The drying agent was removed by filtration, and the filtrate was concentrated under reduced pressure. Purification of the resulting residue by column chromatography afforded **270a** in 75% yield (2.50 g) as a

yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, 1H, J = 9.1 Hz), 7.98 (d, 1H, J = 3.2 Hz), 7.00 (dd, 1H, J = 9.1, 3.2 Hz), 3.58 (t, 1H, J = 6.9 Hz), 3.14 (s, 3H), 2.52 (t, 2H, J = 7.1 Hz), 2.29 (s, 6H); MS (ESI+) *m/z* 225.1 (M+H).

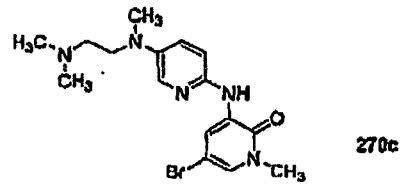
Example 270b N^5-(2-(Dimethylamino)ethyl)-N^5-methylpyridine-2,5-diamine **270b**



270b

A 250-mL Parr reactor bottle was purged with nitrogen and charged with 10% palladium on carbon (50% wet, 1.00 g dry weight) and a solution of 270a (2.20 g, 9.80 mmol) in ethanol (150 mL). The bottle was attached to a Parr hydrogenator, evacuated, charged with hydrogen gas to a pressure of 50 psi and shaken for 3 h. After this time, the hydrogen was evacuated, and nitrogen was charged into the bottle. Celite 521 (1.00 g) was added, and the mixture was filtered through a pad of Celite 521. The filter cake was washed with ethanol (2 X 25 mL), and the combined filtrates were concentrated to dryness under reduced pressure to afford a quantitative yield of 270b (1.91 g) as a purple oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, 1H, J = 2.9 Hz), 7.05 (dd, 1H, J = 8.5, 2.9 Hz), 6.48 (dd, 1H, J = 8.9, 0.5 Hz), 4.04 (br s, 2H), 3.28 (t, 2H, J = 7.1 Hz), 2.84 (s, 3H), 2.43 (t, 2H, J = 7.4 Hz), 2.26 (s, 6H); MS (ESI+) *m/z* 195.2 (M+H).

Example 270c 5-Bromo-3-(5-((2-(dimethylamino)ethyl)(methyl)amino)pyridin-2-ylamino)-1-methylpyridin-2(1*H*)-one **270c**

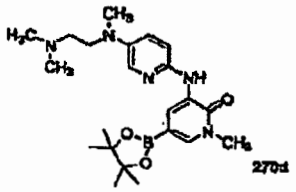


270c

A 100-mL two-neck round-bottomed flask equipped with a reflux condenser, magnetic stirrer and nitrogen inlet was charged with 270b (1.00 g, 5.20 mmol), 3,5-dibromo-1-methylpyridin-2(1H)-one (1.53 g, 5.72 mmol), cesium carbonate (5.09 g, 15.6 mmol), and 1,4-dioxane (52 mL). After bubbling nitrogen through the resulting suspension for 30 min, Xantphos (257 mg, 0.442 mmol) and tris(dibenzylidene-acetone)dipalladium(0) (239 mg, 0.260 mmol) were added, and the reaction mixture was heated at reflux for 3 h. After this time, the mixture was cooled to room temperature and diluted with ethyl acetate (150 mL)

and water (30 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 X 150 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was triturated with methanol (20 mL) to afford a 63% yield (700 mg) of 270c as an off-white solid: mp 161–163 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.50 (d, 1H, J = 2.3 Hz), 8.39 (s, 1H), 7.75 (d, 1H, J = 2.4 Hz), 7.40 (d, 1H, J = 2.4 Hz), 7.17 (m, 2H), 3.50 (s, 3H), 3.56 (t, 2H, J = 6.9 Hz), 2.86 (s, 3H), 2.35 (t, 2H, J = 7.1 Hz), 2.16 (s, 6H); MS (ESI+) m/z 380.1 (M+H).

Example 270d 3-(5-((2-(Dimethylamino)ethyl)(methyl)amino)pyridin-2-ylamino)-1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one 270d



270d

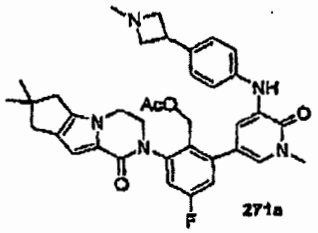
A 100-mL single-neck round-bottomed flask equipped with a reflux condenser, magnetic stirrer and nitrogen inlet was charged with 270c (500 mg, 1.32 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (668 mg, 2.63 mmol), potassium acetate (389 mg, 3.96 mmol), and 1,4-dioxane (10 mL). After bubbling nitrogen through the resulting suspension for 30 min, [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) (97 mg, 0.132 mmol) was added, and the reaction mixture was heated at reflux for 1 h. After this time, the mixture was cooled to room temperature and diluted with ethyl acetate (150 mL) and water (30 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 X 150 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to afford 270d in a crude quantitative yield. The residue was used without further purification.

A 50-mL three-neck round-bottomed flask equipped with a reflux condenser, magnetic stirrer and nitrogen inlet was charged with 247a (420 mg, 0.901 mmol), 270d (290 mg, 0.690 mmol), sodium carbonate (220 mg, 2.07 mmol), water (2 mL) and 1,4-dioxane (8 mL). After bubbling nitrogen through the resulting suspension for 30 min, tetrakis(triphenylphosphine)palladium(0) (80 mg, 0.069 mmol) was added, and the reaction mixture was heated at reflux for 2 h. After this time, the mixture was cooled to room temperature and diluted with ethyl acetate (150 mL) and water (30 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 150 mL). The

combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was dissolved in a mixture of THF (10 mL), methanol (10 mL) and water (10 mL). Lithium hydroxide monohydrate (420 mg, 10.0 mmol) was added to the resulting solution. The mixture was stirred for 2 h at room temperature and then concentrated in vacuo. The residue was partitioned between ethyl acetate (150 mL) and water (30 mL). The organic layer was separated, and the aqueous layer was extracted with a 20% (v/v) solution of methanol in methylene chloride (3 × 150 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (silica, 0% to 20% methanol/methylene chloride) to afford a 14% yield (53 mg) of 270 as an off-white solid: mp 106–107 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.45 (d, 1H, J = 2.5 Hz), 8.20 (s, 1H), 7.69 (d, 1H, J = 2.5 Hz), 7.32 (m, 2H), 7.17 (m, 3H), 4.84 (t, 1H, J = 4.0 Hz), 4.33 (m, 2H), 4.04 (m, 1H), 3.84 (m, 1H), 3.58 (s, 3H), 3.03 (m, 1H), 2.89 (m, 1H), 2.75 (s, 2H), 2.53 (d, 2H, J = 8.9 Hz), 2.32 (t, 2H, J = 7.2 Hz), 2.14 (s, 6H), 1.23 (s, 6H); MS (ESI+) *m/z* 645.3 (M+H).

Example 271 10-[5-Fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[5-(1-methylazetidin-3-yl)pyridine-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one 271

Example 271a 10-[5-Fluoro-2-(acetoxymethyl)-3-(1-methyl-5-{[5-(1-methylazetidin-3-yl)pyridine-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one 271a



271a

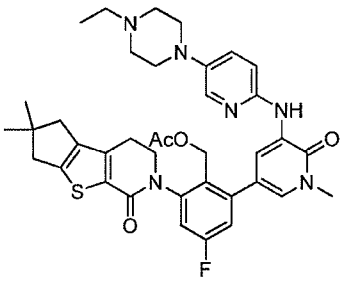
A microwave tube equipped with a magnetic stirrer was charged with 5-bromo-1-methyl-3-(5-(1-methylazetidin-3-yl)pyridin-2-ylamino)pyridin-2(1H)-one (172a) (216 mg, 0.6 mmol), 230a (390 mg, 0.8 mmol), 1,2-dimethoxyethane (8 mL) and 1M aqueous sodium carbonate (2 mL). After bubbling N_2 for 15 min, $Pd(PPh_3)_4$ (36 mg, 0.03 mmol) was added. The mixture was heated in microwave to 130 °C for 15 min. After this time, ethyl acetate (5 mL) and water (5 mL) were added. The separated aqueous layer was extracted with ethyl acetate (2 x 5 mL). The combined organics were washed with brine (10 mL), dried over

sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography eluting with a gradient of methylene chloride – 9:1 methylene chloride:methanol to afford a 30% yield (120 mg) of **271a.**

A 25 mL round bottom flask with a magnetic stirrer was charged with **271a** (110 mg, 0.2 mmol), lithium hydroxide (40 mg, 0.9 mmol), THF (1 mL), isopropanol (1 mL) and water (2 mL). The mixture stirred at rt for 30 min. After this time, ethyl acetate (5 mL) and water (5 mL) were added. The separated aqueous layer was extracted with ethyl acetate (2 x 5 mL). The combined organics were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography using the Biotage KPNH 12+M column eluting with a gradient of hexanes - ethyl acetate to afford an 88% yield (94 mg) of **271**. MS (ESI+) *m/z* 597.4 (M + H).

Example 272 10-[3-(5-{[5-(4-Ethylpiperazin-1-yl)pyridine-2-yl]amino}-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-(hydroxymethyl)phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.$0^{2,6}$]dodeca-1(8),2(6)-dien-9-one **272**

Example 272a 10-[3-(5-{[5-(4-Ethylpiperazin-1-yl)pyridine-2-yl]amino}-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-(acetoxymethyl)phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.$0^{2,6}$]dodeca-1(8),2(6)-dien-9-one **272a**



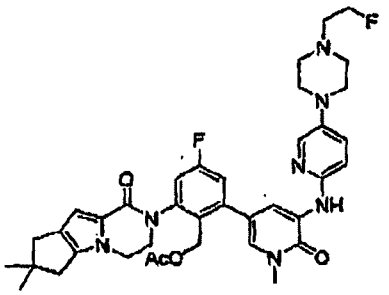
To a microwave tube equipped with a stirring bar, **182b** (270 mg, 0.579 mmol), 3-(5-(4-ethylpiperazin-1-yl)pyridin-2-ylamino)-1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one **201a** (382 mg, 0.868 mmol), $Pd(PPh_3)_4$ (34 mg, 0.029 mmol), Na_2CO_3 aqueous solution (1.0 N, 1.91 mL, 1.91 mmol), 1,2-dimethoxyethane (4.0 mL) were added. The mixture was reacted in microwave at 130 °C for 15 min. Methylene chloride (200 mL) was added and the resulting mixture was washed with water (30 mL X 3), brine (30 mL X 1), dried over $MgSO_4$, filtered, and removed solvent *in vacuo*. Silica gel column chromatography (methanol: methylene chloride = 5: 95) gave **272a**.

To a round-bottomed flask equipped with a stirring bar, **272a**, THF (5 mL), isopropanol (5 mL), water (5 mL), LiOH H_2O (300 mg) were added. The resulting mixture was stirred at RT for 1 hr. The solvent was removed *in vacuo* and the resulting residue was

added to methylene chloride (200 mL), the solution was washed with water (30 mL X 3), brine (30 mL X 1), dried over $MgSO_4$, filtered, and removed solvent *in vacuo*. Silica gel column chromatography (methanol: methylene chloride = 10: 90) gave 272 as yellow solids, 143 mg. MS (ESI+) *m/z* 657.6 (M + H).

Example 273 10-{5-Fluoro-3-[5-({5-[4-(2-fluoroethyl)piperazin-1-yl]pyridine-2-yl}amino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl]-2-(hydroxymethyl)phenyl}-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one 273

Example 273b 10-{5-Fluoro-3-[5-({5-[4-(2-fluoroethyl)piperazin-1-yl]pyridine-2-yl}amino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl]-2-(acetoxymethyl)phenyl}-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one 273b



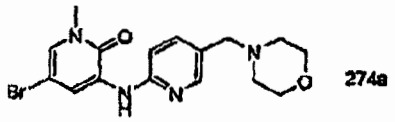
273b

Following Example 186f, 273a (which was prepared *in situ* from 217d using conditions analogous to those used to prepare 270d) (200mg, 0.49mmol) and 189a (176mg, 0.39mmol) were reacted to give 273b (115mg, 33% yield).

Following Example 186, 273b (115mg, 0.16mmol), 1N LiOH (0.82mL), THF (3mL) and isopropanol (3mL) were reacted and purified via HPLC (acetonitrile/water/TFA). To the residue was added ethyl acetate and saturated aqueous sodium bicarbonate and the mixture stirred for ~15min. The layers layers were separated and the organics were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to give 273 (23mg, 22% yield). MS (ESI+) *m/z* 658.5 (M + H).

Example 274 10-[5-Fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[5-(morpholin-4-ylmethyl)pyridine-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one 274

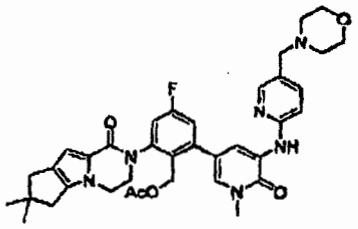
Example 274a 5-Bromo-1-methyl-3-(5-(morpholinomethyl)pyridin-2-ylamino)pyridin-2(1H)-one 274a



274a

Following Example 186d, compound 274a was prepared.

Example 274c 10-[5-Fluoro-2-(acetoxymethyl)-3-(1-methyl-5-{[5-(morpholin-4-ylmethyl)pyridine-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one 274c



274c

Following Examples 186e and 186f, 274a (300mg, 0.79mmol) in Step 1 to afford 274b *in situ* and then reacting with 189a (284mg, 0.63mmol) in Step 2 gave 274c (250mg, 46% yield).

Following Example 119, 274c (250mg, 0.36mmol), 1N LiOH (1.5mL), THF (3mL) and isopropanol (3mL) were reacted, purified via column chromatography: ISCO 12g silica, 0-10% methanol, then triturated with methylene chloride/diethylether to give 274 (89mg, 39% yield). MS (ESI+) *m/z* 627.5 (M + H).

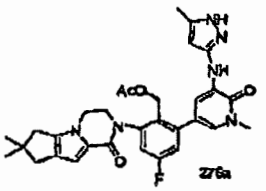
Example 275 2-(2-(Hydroxymethyl)-3-(1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrido[3,4-*b*]indolizin-1(2*H*)-one 275

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was charged with 197e (210 mg, 0.560 mmol), 118f (330 mg, 0.710 mmol), sodium carbonate (175 mg, 1.70 mmol), water (2 mL) and 1,4-dioxane (8 mL). After bubbling nitrogen through the resulting suspension for 30 min, tetrakis(triphenylphosphine)palladium(0) (64 mg, 0.055 mmol) was added. A reflux condenser was attached to the flask, and the reaction mixture was heated at 100 °C for 2 h. After this time, the mixture was diluted with 90:10 methylene chloride/methanol (100 mL) and water (75 mL), and the layers were separated. The aqueous layer was extracted with 90:10 methylene chloride/methanol (2 × 50 mL), and the combined organic extracts were washed with brine

(100 mL) and dried over sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was dissolved in a mixture of THF (3 mL), water (3 mL) and methanol (3 mL). Lithium hydroxide monohydrate (100 mg, 2.40 mmol) was added, and the reaction was stirred at room temperature for 2 h. After this time, the mixture was diluted with 90:10 methylene chloride/methanol (100 mL) and water (50 mL), and the layers were separated. The aqueous layer was extracted with 90:10 methylene chloride/methanol (2 X 75 mL), and the combined organic extracts were dried over sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography (silica, 0% to 10% methanol/methylene chloride) to afford **275** in 8% yield (35 mg) as an amorphous off-white solid: mp 180–181 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.54 (d, 1H, J = 2.5 Hz), 8.31 (s, 1H), 7.84 (d, 1H, J = 2.5 Hz), 7.42 (t, 1H, J = 8.0 Hz), 7.35 (m, 1H), 7.26 (d, 2H, J = 8.0 Hz), 7.19 (d, 1H, J = 9.0 Hz), 6.00 (s, 1H), 4.69 (t, 1H, J = 5.0 Hz), 4.31 (d, 2H, J = 4.5 Hz), 3.99 (m, 1H), 3.95 (m, 1H), 3.88 (m, 2H), 3.57 (s, 3H), 3.05 (m, 5H), 2.90 (m, 1H), 2.70 (t, 2H, J = 6.0 Hz), 2.42 (m, 5H), 2.19 (s, 3H), 1.91 (m, 2H), 2.73 (m, 2H); MS (ESI+) *m/z* 594.3 (M+H).

Example 276 10-[5-Fluoro-2-(hydroxymethyl)-3-{1-methyl-5-[(5-methyl-1H-pyrazol-3-yl)amino]-6-oxo-1,6-dihydropyridin-3-yl}phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one **276**

Example 276a 10-[5-Fluoro-2-(hydroxymethyl)-3-{1-methyl-5-[(5-methyl-1H-pyrazol-3-yl)amino]-6-oxo-1,6-dihydropyridin-3-yl}phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one **276a**



276a

A microwave tube equipped with a magnetic stirrer was charged with 5-bromo-1-methyl-3-(5-methyl-1H-pyrazol-3-ylamino)pyridin-2(1H)-one **112a** (150 mg, 0.5 mmol), **230a** (350 mg, 0.7 mmol), 1,2-dimethoxyethane (6.4 mL) and 1M aqueous sodium carbonate (1.6 mL). After bubbling N_2 for 15 min, $Pd(PPh_3)_4$ (31 mg, 0.03 mmol) was added. The mixture was heated in microwave to 130 °C for 15 min. After this time, ethyl acetate (5 mL) and water (5 mL) were added. The separated aqueous layer was extracted with ethyl acetate

(2 x 5 mL). The combined organics were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography eluting with a gradient of methylene chloride – 60:35:5 methylene chloride:diethyl ether:methanol to afford a 16% yield (50 mg) of **276a.**

A 25 mL round bottom flask with a magnetic stirrer was charged with **276a** (50 mg, 0.1 mmol), lithium hydroxide (18 mg, 0.4 mmol), THF (0.4 mL), isopropanol (0.4 mL) and water (1 mL). The mixture stirred at rt for 30 min. After this time, ethyl acetate (5 mL) and water (5 mL) were added. The separated aqueous layer was extracted with ethyl acetate (2 x 5 mL). The combined organics were washed with brine (10 mL), dried over sodium sulfate and filtered. The mixture was concentrated under reduced pressure to near dryness when the desired product crashed out and was filtered. Upon washing with diethyl ether (10 mL) afforded an 87% yield (40 mg) of **276.** MS (ESI+) *m/z* 531.4 (M + H).

Example 277 5-[5-Fluoro-2-(hydroxymethyl)-3-{1-methyl-5-[(5-{[methyl(propan-2-yl)amino]methyl}pyridine-2-yl)amino]-6-oxo-1,6-dihydropyridin-3-yl}phenyl]-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$]trideca-1(9),2(7)-dien-6-one **277**

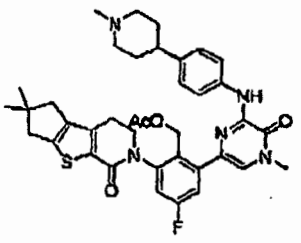
Example 277a 5-[5-Fluoro-2-(acetoxymethyl)-3-{1-methyl-5-[(5-{[methyl(propan-2-yl)amino]methyl}pyridine-2-yl)amino]-6-oxo-1,6-dihydropyridin-3-yl}phenyl]-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$]trideca-1(9),2(7)-dien-6-one **277a**

Following Example 186, **186e** (270mg, 0.74mmol) produced *in situ* was reacted with **212a** (267mg, 0.59mmol) in Step 2. Purified by column chromatography: ISCO 12g silica, 50-100% ethyl acetate/hexanes then 0-15% MeOH/CH2Cl2 to give **277a** (270mg, 55% yield).

Following Example 119, **277a** (270mg, 0.41mmol), 1N LiOH (2.0mL), THF (4mL) and isopropanol (4mL) were reacted, and triturated with ether to give **277** (185mg, 73% yield). MS (ESI+) *m/z* 616.4 (M + H).

Example 278 10-[5-Fluoro-2-(hydroxymethyl)-3-(4-methyl-6-{[4- (1-methylpiperidin-4-yl)phenyl]amino}-5-oxo-4,5-dihydropyrazin-2-yl)phenyl]-4,4-dimethyl-7-thia-10- azatricyclo[6.4.0.$0^{2,6}$]dodeca-1(8),2(6)-dien-9- one **278**

Example 278a 10-[5-Fluoro)-3-(4-methyl-6-{[4- (1-methylpiperidin-4-yl)phenyl]amino}-5-oxo-4,5-dihydropyrazin-2-yl)benzyl acetate]-4,4-dimethyl-7-thia-10-azatricyclo-[6.4.0.$0^{2,6}$]dodeca-1(8),2(6)-dien-9- one **278a**



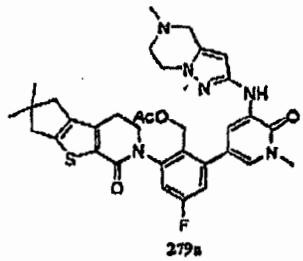
278a

Following Example 136d, 282c and (2-{4,4-dimethyl-9-oxo-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-10-yl}-4-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl acetate 247b were reacted to give 278a in 62% yield. LCMS: $(M+H)^+$ 684

Following Example 136, 278a was converted to 278 in 39% yield. LCMS: $(M+H)^+$ 642. ^{1}H NMR (500 MHz, DMSO) δ 9.22 (s, 1H), 7.90 (s, 1H), 7.87 (s, 1H), 7.48 (s, 1H), 7.36 (dd, J=9.5, 1H), 7.31 (dd, J=9, 1H), 7.16 (s, 1H), 7.14 (s, 1H), 4.46 (m, 2H), 4.05 (m, 2H), 3.85 (m, 2H), 3.54 (s, 3H), 3.01 (m, 1H), 2.92 (m, 3H), 2.75 (s, 2H), 2.53 (m, 2H), 2.44 (m, 1H), 2.27 (s, 3H), 2.13 (m, 2H), 1.70 (m, 4H), 1.22 (s, 6H).

Example 279 10-[5-Fluoro-2-(hydroxymethyl)-3-[1-methyl-5-({5- methyl-4H,5H,6H,7H-pyrazolo[1,5-a]pyrazin-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one 279

Example 279a (2-{4,4-Dimethyl-9-oxo-7-thia-10-azatricyclo[6.4.0.0^{2,6}dodeca-1(8),2(6)-dien-10-yl}-4-fluoro-6-[1-methyl-5-({5-methyl-4H,5H,6H,7H-pyrazolo[1,5-a]pyrazin-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl)methyl Acetate 279a



279a

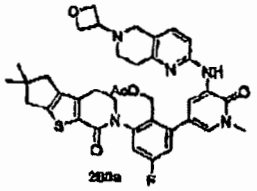
A 25 mL sealed tube was charged with 5-bromo-1-methyl-3-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)pyridin-2(1H)-one 146a (340 mg, 1.0 mmol), (2-{4,4-dimethyl-9-oxo-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-10-yl}-4-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl acetate 247b (480 mg,

1.0 mmol), CH_3COONa (168 mg, 2.0 mmol), K_3PO_4 (546 mg, 2.0 mmol), $PdCl_2(dppf)$ (84 mg, 0.1 mmol) suspended in CH_3CN (25 mL) and water (1 mL). The mixture was heated at 110 °C for 2 hours, evaporated, and the residue was purified by column chromatography eluting with 15:1 methylene chloride/methanol to give **279a** as a brown solid (300 mg, 46%). MS: $(M+H)^+$ 645.

To a solution of **279a** (300 mg, 0.46 mmol) in propan-2-ol (10 mL), tetrahydrofuran (10 mL) and water (2 mL) was added LiOH (1.1 g, 57 mmol). The mixture was stirred at 30 °C for 2 h. It was then evaporated and the residue was purified by prep-HPLC to afford **279** as a white solid (99 mg, 35%). MS: $(M+H)^+$ 603. ^1H NMR (500 MHz, MEOD) δ 1.29 (d, 6 H), 2.49 (s, 3 H), 2.59 (d, 2 H), 2.81 (s, 2 H), 2.94-2.97 (m, 3 H), 3.07-3.14 (m, 1 H), 3.64 (s, 2 H), 3.70 (s, 3 H), 3.97-3.99 (m, 1 H), 4.05-4.07 (t, 2 H), 4.12-4.15 (m, 1 H), 4.47-4.54 (m, 2 H), 5.89 (s, 1 H), 7.19-7.22 (m, 2 H), 7.26 (d, 1 H), 7.91 (s, 1 H).

Example 280 10-[5-Fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[6-(oxetan-3-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one **280**

Example 280a (2-{4,4-Dimethyl-9-oxo-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-10-yl}-4-fluoro-6-(1-methyl-5-{[6-(oxetan-3-yl)-5,6,7,8-tetrahydro-1,6-naph-thyridin-2-yl]amino)-6- oxo-1,6-dihydropyridin-3-yl)phenyl)methyl Acetate **280a**

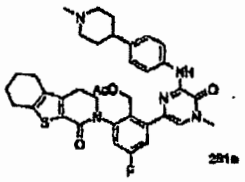


A 25 mL sealed tube was charged with 5-bromo-1-methyl-3-(6-(oxetan-3-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2-ylamino)pyridin-2(1H)-one **219a** (400 mg, 1.0 mmol), (2-{4,4-dimethyl-9-oxo-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-10-yl}-4-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl acetate **247b** (493 mg, 1.0 mmol), CH_3COONa (168 mg, 2.0 mmol), K_3PO_4 (546 mg, 2.0 mmol), $PdCl_2(dppf)$ (84 mg, 0.1 mmol) suspended in CH_3CN (25 mL) and H_2O (1 mL). The mixture was heated at 110 °C for 2 hours. It was then evaporated and the residue was purified by column chromatography eluting with 20:1 methylene chloride/methanol (20:1) to give **280a** as a brown solid (400 mg, 56%). MS: $(M+H)^+$ 698.

To a solution of **280a** (400 mg, 0.57 mmol) in propan-2-ol (10 mL), tetrahydrofuran (10 mL) and water (2 mL) was added LiOH (1.4 g, 57 mmol). The mixture was stirred at 30 °C for 2 h. It was then evaporated and the residue was purified by prep-HPLC to afford **280** as a white solid (52 mg, 14%). MS: $(M+H)^+$ 656. ^1H NMR (500 MHz, MEOD) δ 1.29 (d, 6 H), 2.56-2.63 (q, 2 H), 2.70-2.72 (t, 2 H), 2.81 (s, 2 H), 2.93-2.99 (m, 3 H), 3.08-3.12 (m, 1 H), 3.47 (s, 2 H), 3.72-3.74 (m, 4 H), 3.96-4.01 (m, 1 H), 4.13-4.18 (m, 1 H), 4.51-4.60 (q, 2 H), 4.68-4.71 (t, 2 H), 4.76-4.79 (t, 2 H), 6.89 (d, 1 H), 7.21-7.23 (d, 2 H), 7.34 (d, 1 H), 7.40 (s, 1 H), 8.78 (s, 1 H).

Example 281 5-[5-Fluoro-2-(hydroxymethyl)-3-(4-methyl-6-{[4-(1-methylpiperidin-4-yl)phenyl]amino}-5-oxo-4,5-dihydropyrazin-2-yl)phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one **281**

Example 281a [4-Fluoro-2-(4-methyl-6-{[4-(1-methylpiperidin-4-yl)phenyl]amino}-5-oxo-4,5-dihydropyrazin-2-yl)-6-(6-oxo-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-5-yl}phenyl]methyl acetate **281a**

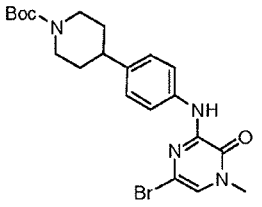


Following Example 136d, **282c**)and (4-fluoro-2-{6-oxo-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-5-yl}-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl acetate **212b** were reacted to give **281a** in 73% yield. LCMS: $(M+H)^+$ 670

Following Example 136, **281a** was converted to **281** in 70% yield. LCMS: $(M+H)^+$ 628. ^1H NMR (500 MHz, DMSO) δ 9.21 (s, 1H), 7.87 (s, 1H), 7.85 (s, 1H), 7.47 (s, 1H), 7.35 (dd, J=10, 1H), 7.30 (dd, J=9, 1H), 7.16 (s, 1H), 7.14 (s, 1H), 4.84 (m, 1H), 4.48 (m, 1H), 4.40 (m, 1H), 3.86 (m, 1H), 3.53 (s, 3H), 2.96 (m, 1H), 2.87 (m, 4H), 2.78 (m, 2H), 2.42 (m, 2H), 2.19 (s, 3H), 1.96 (m, 2H), 1.80 (m, 4H), 1.62 (m, 5H).

Example 282 2-(5-Fluoro-2-(hydroxymethyl)-3-(4-methyl-6-(4-(1-methylpiperidin-4-yl)phenylamino)-5-oxo-4,5-dihydropyrazin-2-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **282**

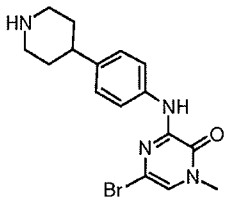
Example 282a *tert*-Butyl 4-(4-(6-Bromo-4-methyl-3-oxo-3,4-dihydropyrazin-2-ylamino)phenyl)piperidine-1-carboxylate **282a**



282a

A mixture of *tert*-butyl 4-(4-aminophenyl)piperidine-1-carboxylate (2.5 g, 9.06 mmol) and 3,5-dibromo-1-methylpyrazin-2(1H)-one (2.2 g, 8.23 mmol) in isopropanol (30 mL) was heated at 85 ℃ for 15 h. After the reaction was finished, it was filtered and the solid was washed with isopropanol to afford **282a** as a white solid (2.9 g, 80%).LCMS: $(M+H)^+$ 463

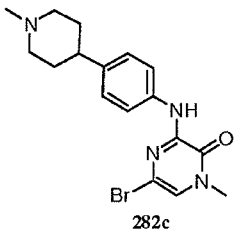
Example 282b 5-Bromo-1-methyl-3-(4-(piperidin-4-yl)phenylamino)pyrazin-2(1H)-one **282b**



282b

Following Example 247a, **282a** was converted to **282b** in 99% yield.

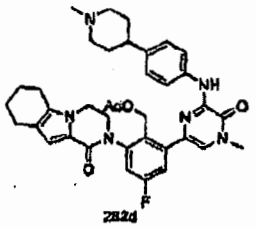
Example 282c 5-Bromo-1-methyl-3-(4-(1-methylpiperidin-4-yl)phenylamino)pyrazin-2(1H)-one **282c**



282c

Following Example 247b, **282b** was converted to **282c** in 65% yield.

Example 282d 4-Fluoro-2-(4-methyl-6-(4-(1-methylpiperidin-4-yl)phenylamino)-5-oxo-4,5-dihydropyrazin-2-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **282d**

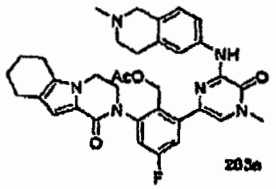


Following Example 247c, **282c** and 4-fluoro-2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **210d** were reacted to give **282d** in 41% yield.

Following Example 136, **282d** was converted to **282** in 36% yield. LCMS: $(M+H)^+$ 611. ^{1}H NMR (500 MHz, DMSO) δ 9.22 (s, 1H), 7.90 (s, 1H), 7.88 (s, 1H), 7.49 (s, 1H), 7.36 (dd, J=9.5, 1H), 7.30 (dd, J=9.5, 1H), 7.17 (s, 1H), 7.15 (s, 1H), 6.54 (s, 1H), 4.47 (m, 2H), 4.15 (m, 3H), 3.88 (m, 2H), 2.91 (m, 2H), 2.59 (m, 2H), 3.05 (m, 1H), 2.46 (m, 3H), 2.25 (s, 3H), 2.07 (m, 2H), 1.80 (m, 2H), 1.70 (m, 6H).

Example 283 2-(5-Fluoro-2-(hydroxymethyl)-3-(4-methyl-6-(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-ylamino)-5-oxo-4,5-dihydropyrazin-2-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **283**

Example 283a 4-Fluoro-2-(4-methyl-6-(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-ylamino)-5-oxo-4,5-dihydropyrazin-2-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **283a**



Following Example 148b, 290 mg of 4-fluoro-2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **210d** and 209 mg 5-bromo-1-methyl-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-ylamino)pyrazin-2(1H)-one **221b** were reacted to give **283a** as a yellow solid (217 mg, 58%). MS: $[M+H]^+$ 699

Following Example 148, **283a** was converted to **283** as a white solid (84 mg, 43%). ^{1}H NMR (500 MHz, DMSO) δ 9.15 (s, 1H), 7.82 (s, 1H), 7.65 (d, J=8, 1H), 7.52 (s, 1H), 7.39 (dd, J=10, 1H), 7.31 (dd, J=10, 1H), 6.96 (d, J=8.0, 1H), 6.53(s, 1H), 4.87 (s, 1H), 4.49

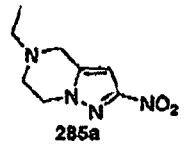
(m, 1H), 4.42 (m, 1H), 4.13(m, 3H), 3.88 (m, 1H), 3.54 (s, 3H), 3.41 (s, 2H), 3.30 (s, 1H), 2.76 (d, J=5.5, 6H), 2.58 (m, 5H), 23.2 (s, 3H), 1.79 (s, 2H), 1.70 (s, 2H).

Example 284 10-(3-{5-[(6-Ethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-2-yl)amino]-1-methyl-6-oxo-1,6-dihydropyridin-3-yl}-5-fluoro-2-(hydroxymethyl)phenyl)-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one 284

In a 48-mL sealed tube equipped with a magnetic stirring bar were placed 5-bromo-1-methyl-3-(6-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-2-ylamino)pyridin-2(1H)-one (143 mg, 0.4 mmol), 10-[2-(acetoxymethyl)-3-(4,4,5,5-tetramethyl[1,3,2]-dioxaborolan-2-yl)-5-fluorophenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]-dodeca-2(6),7-dien-9-one 230a (496 mg, 1.0 mmol), $Pd(PPh_3)_4$ (23 mg, 0.020 mmol) in 2 N Na_2CO_3 (4 mL) and DME (4 mL). After the reaction mixture was stirred at 100°C for 1 h, it was purified by flash chromatography (dichloromethane:methanol, 3:1) to give 7 % (18 mg) of 284 MS(ESI$^+$) *m/z* 611.5 (M+H).

Example 285 10-{3-[5-({5-Ethyl-4H,5H,6H,7H-pyrazolo[1,5-a]pyrazin-2-yl}amino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl]-5-fluoro-2-(hydroxymethyl)phenyl}-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one 285

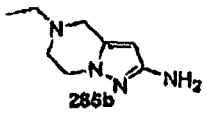
Example 285a 5-Ethyl-2-nitro-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine 285a



285a

A sealed tube equipped with a magnetic stirrer was charged with 1-(2-bromoethyl)-5-(bromomethyl)-3-nitro-1*H*-pyrazole 101c (2.8 g, 9 mmol) 2M ethylamine solution in THF (27 mL). The resulting mixture was heated to 35 °C overnight. After this time, the reaction mixture was concentrated under reduced pressure, and to the residue was added water (50 mL) and ethyl acetate (50 mL). The aqueous layer was separated and extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with brine (100 mL) and dried over sodium sulfate. The resulting solution was concentrated under reduced pressure to afford a 100% yield (1.8 g) of crude 285a.

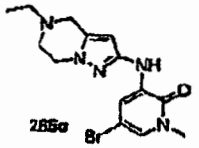
Example 285b 5-Ethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-amine 285b



285b

A 500-mL Parr hydrogenation bottle was charged with **285a** (1.8 g, 9 mmol), 10% palladium on carbon (50% wet, 500 mg dry weight) and ethanol (100 mL). The bottle was evacuated, charged with hydrogen gas to a pressure of 50 psi and shaken for 1 h on a Parr hydrogenation apparatus. The catalyst was removed by filtration through a pad of Celite 521 washing with 1:1 methylene chloride:methanol (500mL). The resulting solution was concentrated under reduced pressure to afford a 71% yield (1.7 g) of crude **285b**.

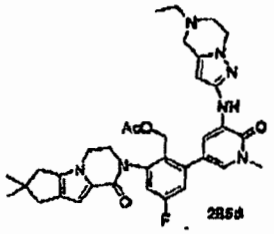
Example 285c 5-Bromo-3-(5-ethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-1-methylpyridin-2(1H)-one **285c**



285c

A sealed tube was equipped with a magnetic stirrer and charged with **285b** (1.1 g, 6.4 mmol), 3,5-dibromo-1-methylpyridin-2(1H)-one **5** (1.7 g, 6.4 mmol) and cesium carbonate (4.6 g, 14 mmol) in 1,4-dioxane (64 mL). After bubbling nitrogen through the solution for 30 min, Xantphos (440 mg, 0.8 mmol) and tris(dibenzylideneacetone) dipalladium(0) (400 mg, 0.5 mmol) were added, and the reaction mixture was heated to 100 °C for 16 h. After this time, water (50 mL) and ethyl acetate (50 mL) were added. The aqueous layer was separated and extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with brine (100 mL) and dried over sodium sulfate. The resulting residue was purified by column chromatography eluting with a gradient of methylene chloride – 60:35:5 methylene chloride:diethyl ether:methanol to afford a 28% yield (620 mg) of **285e**.

Example 285d 10-{3-[5-({5-Ethyl-4H,5H,6H,7H-pyrazolo[1,5-a]pyrazin-2-yl}amino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl]-5-fluoro-2-(acetoxymethyl)phenyl}-4,4-dimethyl-1,10-diazatricyclo[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-9-one **285d**



285d

A microwave tube equipped with a magnetic stirrer was charged with **285c** (190 mg, 0.5 mmol), **230a** (350 mg, 0.7 mmol), 1,2-dimethoxyethane (6.4 mL) and 1M aqueous

sodium carbonate (1.6 mL). After bubbling N_2 for 15 min, $Pd(PPh_3)_4$ (31 mg, 0.03 mmol) was added. The mixture was heated in microwave to 130 °C for 15 min. After this time, ethyl acetate (5 mL) and water (5 mL) were added. The separated aqueous layer was extracted with ethyl acetate (2 X 5 mL). The combined organics were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography eluting with a gradient of methylene chloride – 60:35:5 methylene chloride:diethyl ether:methanol to afford a 35% yield (120 mg) of **285d**.

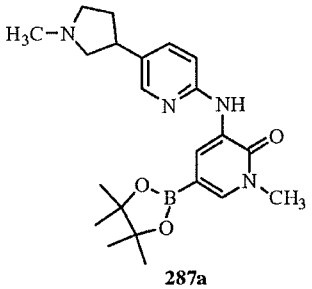
A 25 mL round bottom flask with a magnetic stirrer was charged with **285d** (120 mg, 0.2 mmol), lithium hydroxide (40 mg, 1 mmol), THF (1 mL), isopropanol (1 mL) and water (2 mL). The mixture stirred at rt for 30 min. After this time, ethyl acetate (5 mL) and water (5 mL) were added. The separated aqueous layer was extracted with ethyl acetate (2 X 5 mL). The combined organics were washed with brine (10 mL), dried over sodium sulfate and filtered. The mixture was concentrated under reduced pressure to near dryness when the desired product crashed out and was filtered. Washing with diethyl ether (10 mL) afforded an 78% yield (90 mg) of **285**. MS (ESI+) *m/z* 600.6 (M + H).

Example 286 2-(3-(5-(5-((2-(Dimethylamino)ethyl)(methyl)amino)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-(hydroxymethyl)phenyl)-3,4,5,6,7,8-hexahydrobenzothieno[2,3-*c*]pyridin-1(2*H*)-one **286**

Following Example 270, reaction of **212a** (550 mg, 1.20 mmol) and **270d** (428 mg, 1.00 mmol) afforded a 8% yield (49 mg) of **286** as an off-white solid: mp 122–123 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.45 (d, 1H, J = 2.0 Hz), 8.20 (s, 1H), 7.69 (d, 1H, J = 2.4 Hz), 7.31 (m, 2H), 7.17 (m, 3H), 4.83 (t, 1H, J = 4.6 Hz), 4.32 (d, 2H, J = 4.3 Hz), 4.06 (m, 1H), 3.87 (m, 1H), 3.58 (s, 3H), 2.96 (m, 1H), 2.86 (m, 1H), 2.83 (s, 3H), 2.78 (m, 2H), 2.54 (m, 1H), 2.32 (t, 2H, J = 7.0 Hz), 2.14 (s, 6H), 1.80 (m, 4H); MS (ESI+) *m/z* 631.3 (M+H).

Example 287 5-(5-Fluoro-2-(hydroxymethyl)-3-(6,6-dimethyl-3,4,6,7-tetrahydro-5*H*-cyclopenta[4,5]thieno[2,3-*c*]pyridine-1(2*H*)-yl)phenyl)-1-methyl-3-(5-(1-methylpyrrolidin-3-yl)pyridin-2-ylamino)pyridin-2(1*H*)-one **287**

Example 287a 1-Methyl-3-(5-(1-methylpyrrolidin-3-yl)pyridin-2-ylamino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one **287a**



287a

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was charged with **202a** (481 mg, 1.33 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (675 mg, 2.66 mmol), potassium acetate (392 mg, 3.99 mmol) and 1,4-dioxane (12 mL). After bubbling nitrogen through the resulting suspension for 30 min, $Pd(dppf)Cl_2$ (97.0 mg, 0.133 mmol) was added. A reflux condenser was attached to the flask, and the reaction mixture was heated at 100 °C for 3 h. After this time, the mixture was diluted with ethyl acetate (100 mL) and water (75 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 50 mL), and the combined organic layers were washed with brine (100 mL) and dried over sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated under reduced pressure to afford crude **287a** in quantitative yield (548 mg) as a brown semi-solid. The crude mixture was used in the next reaction without further purification: MS (ESI+) *m/z* 411.2 (M+H).

A 250-mL single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was charged with crude **287a** (274 mg, 0.668 mmol, presuming quantitative yield), **247a** (420 mg, 0.865 mmol), sodium carbonate (207 mg, 1.99 mmol), water (2 mL) and 1,4-dioxane (10 mL). After bubbling nitrogen through the resulting suspension for 30 min, tetrakis(triphenylphosphine)palladium(0) (151 mg, 0.133 mmol) was added. A reflux condenser was attached to the flask, and the reaction mixture was heated at 90 °C for 1 h. After this time, the mixture was diluted with 90:10 methylene chloride/methanol (100 mL) and water (75 mL), and the layers were separated. The aqueous layer was extracted with 90:10 methylene chloride/methanol (2 × 50 mL), and the combined organic layers were washed with brine (100 mL) and dried over sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was dissolved in THF (5 mL), water (5 mL) and methanol (5 mL). Lithium hydroxide monohydrate (47 mg, 1.12 mmol) was added, and the mixture was stirred at room temperature for 2 h. After this time, the mixture was diluted with 90:10 methylene chloride/methanol (100 mL) and water (50 mL), and the layers were separated. The aqueous

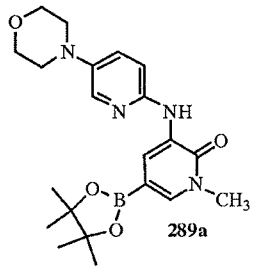
layer was extracted with 90:10 methylene chloride/methanol (2 X 75 mL), and the combined organic layers were washed with brine (100 mL) and dried over sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography (silica, 80:20 methylene chloride/ methanol) to afford **287** in 27% yield (110 mg) as an amorphous off-white solid: mp 181–183 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.64 (d, J = 2.0 Hz, 1H), 8.49 (s, 1H), 8.07 (d, J = 2.5 Hz, 1H), 7.54 (dd, J = 8.5, 2.5 Hz, 1H), 7.40 (d, J = 2.0 Hz, 1H), 7.34 (dd, J = 9.0, 2.5 Hz, 1H), 7.25 (d, J = 8.5 Hz, 1H), 7.19 (dd, J = 9.5, 2.5 Hz, 1H), 4.86 (t, J = 4.0 Hz, 1H), 4.34–4.32 (m, 2H), 4.10–4.03 (m, 1H), 3.87–3.83 (m, 1H), 3.59 (s, 3H), 3.25–3.20 (m, 1H), 3.05–2.99 (m, 1H), 2.91–2.87 (m, 1H), 2.81–2.77 (m, 1H), 2.75 (s, 2H), 2.60–2.58 (m, 2H), 2.55–2.50 (m, 2H), 2.49–2.32 (m, 1H), 2.27 (s, 3H), 2.22–2.17 (m, 1H), 1.71–1.67 (m, 1H), 1.23 (s, 6H); MS (ESI+) *m/z* 628.3 (M+H).

Example 288 2-(5-Fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(1-methylpyrrolidin-2-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,5,6,7,8-hexahydrobenzothieno[2,3-*c*]pyridin-1(2*H*)-one **288**

Following Example 286, reaction of **212a** (450 mg, 1.04 mmol) and **287b** (328 mg, 0.810 mmol) afforded a 26% yield (130 mg) of **288** as an off-white solid: mp 164–166 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.67 (d, 1H, J = 2.0 Hz), 8.55 (s, 1H), 8.06 (d, 1H, J = 2.4 Hz), 7.53 (dd, 1H, J = 8.5, 2.4 Hz), 7.41 (d, 1H, J = 2.4 Hz), 7.32 (dd, 1H, J = 9.1, 2.1 Hz), 7.26 (d, 1H, J = 9.0 Hz), 7.19 (dd, 1H, J = 9.0, 2.0 Hz), 4.85 (t, 1H, J = 4.2 Hz), 4.32 (m, 2H), 4.04 (m, 1H), 3.87 (m, 1H), 3.59 (s, 3H), 3.13 (m, 1H), 2.95 (m, 2H), 2.84 (m, 1H), 2.78 (m, 2H), 2.54 (m, 1H), 2.18 (q, 1H, J = 4.0 Hz), 2.04 (m, 4H), 1.80 (m, 6H), 1.58 (m,1H); MS (ESI+) *m/z* 614.3 (M+H).

Example 289 2-(5-Fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-morpholinopyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,5,6,7,8-hexahydrobenzothieno[2,3-*c*]pyridin-1(2*H*)-one **289**

Example 289a 1-Methyl-3-(5-morpholinopyridin-2-ylamino)-5-(4,4,5,5-tetramethyl1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one **289a**



289a

A 250-mL single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was charged with **255c** (610 mg, 1.70 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (850 mg, 3.40 mmol), potassium acetate (492 mg, 5.00 mmol) and 1,4-dioxane (20 mL). After bubbling nitrogen through the resulting suspension for 30 min, $Pd(dppf)Cl_2/CH_2Cl_2$ (122 mg, 0.200 mmol) was added. A reflux condenser was attached to the flask, and the reaction mixture was heated at 90 °C for 2 h. After this time, the mixture was diluted with ethyl acetate (100 mL) and water (75 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (50 mL), and the combined organic extracts were washed with brine (50 mL) and dried over sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by trituration with hexanes/ethyl acetate (80:20, 25 mL) to afford **289a** in quantitative yield (688 mg) as a brown solid: mp 100–101 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.45 (d, 1H, J = 1.5 Hz), 8.21 (s, 1H), 7.91 (s, 1H), 7.89 (d, 1H, J = 3.0 Hz), 7.66 (d, 1H, J = 6.5 Hz), 7.14 (d, 1H, J = 9.0 Hz), 3.73 (t, 4H, J = 4.5 Hz), 3.55 (s, 3H), 3.05 (t, 4H, J = 4.5 Hz), 1.29 (s, 12H); MS (ESI+) m/z 413.0 (M+H)

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was purged with nitrogen and charged with **289a** (485 mg, 0.415 mmol), **247a** (488 mg, 1.10 mmol), sodium carbonate (264 mg, 2.50 mmol), 1,4-dioxane (8 mL) and water (2 mL). This mixture was degassed with nitrogen for 30 min. Tetrakis(triphenylphosphine)palladium (96 mg, 0.083 mmol) was added. After heating at 100 °C for 2 h, the reaction mixture was cooled to room temperature and partitioned between water (40 mL) and methylene chloride (100 mL). The layers were separated, and the aqueous phase was extracted with methylene chloride (2 X 50 mL). The organic extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was dissolved in methanol (5 mL), and potassium carbonate (745 mg, 5.40 mmol) was added. After stirring at room temperature for 1 h, the reaction mixture was partitioned between water (20 mL) and methylene chloride (20 mL). The layers were separated, and the aqueous phase was extracted with methylene chloride (2 × 20 mL). The organic extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica, 0% to 15% methanol/methylene chloride) to afford **289** in 51% yield (130 mg) as a yellow solid: mp 220–221 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.55 (d, 1H, J = 2.0 Hz), 8.37 (s, 1H), 7.87 (d, 1H, J = 3.0 Hz), 7.34 (m, 3H), 7.23 (d, 1H, J = 9.0 Hz), 7.16 (dd, 1H, J = 9.5,

3.0 Hz), 4.83 (t, 1H, J = 4.0 Hz), 4.32 (m, 2H), 4.05 (m, 1H), 3.86 (m, 1H), 3.71 (t, 4H, J = 4.5 Hz), 3.58 (s, 3H), 3.01 (t, 4H, J = 4.5 Hz), 2.98 (m, 1H), 2.87 (m, 1H), 2.77 (m, 2H), 2.54 (m, 1H), 1.79 (m, 4H); MS (ESI+) *m/z* 616.2 (M+H).

Example 290 10-[5-Fluoro-2-(hydroxymethyl)-3-[1-methyl-5-({5-[(2S)-1-methylpyrrolidin-2-yl]pyridine-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one **290**

Example 291 10-[5-Fluoro-2-(hydroxymethyl)-3-[1-methyl-5-({5-[(2R)-1-methylpyrrolidin-2-yl]pyridine-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one **291**

Compounds **290** and **291** are enantiomers of racemate **243**. The racemic mixture **243** was subjected to chiral separation on a Chiralpak AD, 4.6x50mm, 3μm column (mobile phase 45% isopropanol (w/0.1%triethylamine)/55%CO_2, flow rate 5mL/min) at 40°C to give individual enantiomers, with **290** eluting first: MS (ESI+) *m/z* 611.5 (M+H) and Example **291** eluting last: MS (ESI+) *m/z* 611.5 (M+H).

Example 292 10-[5-Fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[6-(oxetan-3-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one **292**

Example 292a 10-[5-Fluoro-2-(acetoxymethyl)-3-(1-methyl-5-{[6-(oxetan-3-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one **292a**

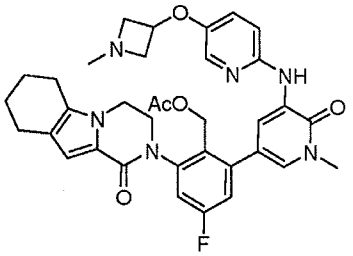
In a 10-mL microwave reaction vessel equipped with a magnetic stirring bar were placed 5-bromo-1-methyl-3-(6-(oxetan-3-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2-ylamino)pyridin-2(1H)-one **219a** (250 mg, 0.64 mmol), 10-[2-(acetoxymethyl)-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-fluorophenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one **230a** (635 mg, 1.3 mmol), $Pd(PPh_3)_4$ (37 mg, 0.03 mmol) in 2 N Na_2CO_3 (2 mL) and 1,2-dimethoxyethane (2 mL). After the reaction mixture was stirred at 125 °C for 10 minutes, it was purified by flash chromatography (dichloromethane:methanol, 3:1) to give 12% (50 mg) of **292a** as a solid.

A 25-mL, single-necked, round-bottomed flask equipped with a magnetic stirring bar was charged with **292a** (50 mg, 0.078 mmol), $LiOH•H_2O$ (50 mg, 1.2 mmol), THF (2 mL), *i*-PrOH (2 mL), and water (2 mL). After the reaction mixture was stirred at room temperature for 2 h, it was partitioned between dichloromethane (5 mL) and water (5 mL), and the organic phase was extracted with dichloromethane (5 mL x 3). The combined organic phases were

washed with water (5 mL x 2) and brine (5 mL x 1), dried (Na_2SO_4), and concentrated. The crude product was re-dissolved in dichloromethane (3 mL). To this solution was added hexane (10 mL) and the resulting precipitates were filtered to give 12% yield (6 mg) of **292** MS(ESI$^+$) *m/z* 639.5 (M+H).

Example 293 2-(5-Fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(1-methylazetidin-3-yloxy)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **293**

Example 293a 4-Fluoro-2-(1-methyl-5-(5-(1-methylazetidin-3-yloxy)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **293a**

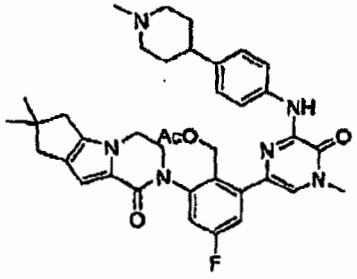


A mixture of 5-bromo-1-methyl-3-(5-(1-methylazetidin-3-yloxy)pyridin-2-ylamino)pyridine-2(1H)-one **199f** (200 mg, 0.55 mmol), 4-fluoro-2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **210d** (270 mg, 0.56 mmol), $PdCl_2$(dppf) (40 mg, 0.055 mmol), K_3PO_4 (150 mg), NaOAc (50 mg) in MeCN (8mL) and water (2 mL) was heated at 110°C in a sealed tube for 2 h. The solvent was evaporated in *vacuo*. The residue was purified on reverse phase Combi-flash to give **293a** (307 mg, 70%). MS: $[M+H]^+$ 641.

A mixture of **293a** (287 mg, 0.45 mmol) and LiOH hydrate (188 mg, 4.5 mmol) in isopropanol (25 mL) and water (5 mL) was stirred at 30°C for 2 h. The mixture was evaporated in *vacuo* and the residue was extracted with ethyl acetate (20 mL × 2). The combined extracts were concentrated under reduced pressure. And the residue was purified on prep-HPLC to give **293** (60 mg, 25%). MS: $[M+H]^+$ 599. ^{1}H NMR (500 MHz, CDCl3) δ 8.51 (s, 1H), 7.81 (s, 1H), 7.74 (s, 1H),7.48 (s, 1H), 7.16-7.14 (m, 1H), 7.11-7.09 (m, 1H), 6.95-6.93 (m, 1H), 6.86 (s, 1H), 6.79 (d, J = 9.0, 1H), 4.76-4.72 (m, 1H), 4.53 (d, J = 8.5, 1H), 4.34-4.25 (m, 2H), 4.20-4.13 (m, 3H), 3.95-3.84 (m, 3H), 3.69 (s, 3H), 3.24-3.13 (m, 2H), 2.64-2.52 (m, 4H), 2.46 (s, 3H), 1.93-1.84 (m, 2H), 1.81-1.75 (m, 2H).

Example 294 10-[5-Fluoro-2-(hydroxymethyl)-3-(4-methyl-6-{[4-(1-methylpiperidin-4-yl)phenyl]amino}-5-oxo-4,5-dihydropyrazin-2-yl)phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one 294

Example 294a (2-{4,4-Dimethyl-9-oxo-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-10-yl}-4-fluoro-6-(4-methyl-6-{[4-(1-methylpiperidin-4-yl)phenyl]amino}-5-oxo-4,5-dihydropyrazin-2-yl)phenyl)methyl Acetate 294a



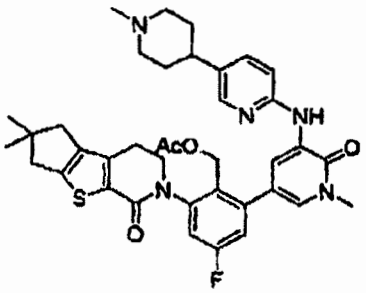
294a

Following Example 150b, 282c and (2-{4,4-dimethyl-9-oxo-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-10-yl}-4-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl acetate 230a were reacted to give 294a in 81% yield. LCMS: $(M+H)^+$ 667

Following Example 150, 294a was converted to 294 in 47% yield. LCMS: $(M+H)^+$ 625. ^{1}H NMR (500 MHz, DMSO) δ 9.20 (s, 1H), 7.89 (s, 1H), 7.87 (s, 1H), 7.48 (s, 1H), 7.36 (dd, J=10, 1H), 7.31 (dd, J=9.5, 1H), 7.17 (s, 1H), 7.15 (s, 1H), 6.52 (s, 1H), 4.85 (m, 1H), 4.49 (m, 1H), 4.40 (m, 1H), 4.20 (m, 2H), 4.12 (m, 1H), 3.87 (m, 1H), 3.54 (s, 3H), 2.84 (d, J=10.5, 1H), 2.57 (s, 2H), 2.42 (s, 2H), 2.38 (m, 1H), 2.18 (s, 3H), 1.93 (t, J=9, 2H), 1.66 (m, 4H), 1.22 (s, 6H).

Example 295 10-[5-Fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[5-(1-methylpiperidin-4-yl)pyridin-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one 295

Example 295a (2-{4,4-Dimethyl-9-oxo-7-thia-10-azatricyclo[6.4.0.0^{2,5}]dodeca-1(8), 2(6)-dien-10-yl}-4-fluoro-6-(1-methyl-5-{[5-(1-methylpiperidin-4-yl)pyridin-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl)methyl Acetate 295a



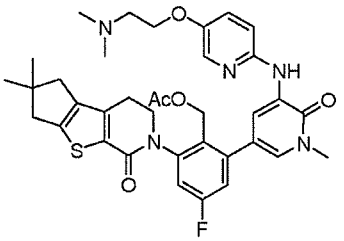
295a

A sealed tube was charged with the mixture of 5-bromo-1-methyl-3-(5-(1-methylpiperidin-4-yl)pyridin-2-ylamino)pyridin-2(1H)-one **282c** (350mg, 0.93 mmol), (2-{4,4-dimethyl-9-oxo-7-thia-10-azatricyclo[6.4.0.$0^{2,6}$]dodeca-1(8), 2(6)-dien-10-yl}-4-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl acetate **247b** (448mg, 0.93 mmol), $Pd(dppf)Cl_2$ (76 mg, 0.09 mmol), $K_3PO_4.3H_2O$(495 mg, 1.86 mmol), and NaOAc (153 mg, 1.86 mmol) in CH_3CN (20 mL). The system was evacuated and then refilled with N_2. And the reaction mixture was heated at 110°C for 2 h. The mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography eluting with 15:1 methylene chloride/methanol to give **295a** as a brown solid (300 mg, 47%). MS: $[M+H]^+$ 684

A solution of **295a** (250 mg, 0.37 mmol) in propan-2-ol (8 mL), tetrahydrofuran (8 mL) and water (1 mL) was added LiOH (878 mg, 37 mmol) was stirred at 30°C for 2 h. It was then evaporated and the residue was purified by prep-HPLC to afford **295** as a yellow solid (76 mg, 32%). MS: $(M+H)^+$ 642. ^1H NMR (500 MHz, MEOD) δ 1.29 (d, 6 H), 1.94-2.02 (m, 2 H), 2.18 (d, 2 H), 2.56-2.64 (m, 2 H), 2.81(s, 2 H), 2.94-3.03 (m, 5 H), 3.08-3.19 (m, 3 H), 3.66(d, 1 H), 3.74 (s, 3 H), 3.92-3.97(m, 1 H), 4.14-4.19 (m, 1 H), 4.50 (s, 1 H), 7.21-7.28 (m, 2 H), 7.84 (s, 1 H), 7.95(d, 1 H), 8.13 (s, 1 H).

Example 296 10-{3-[5-({5-[2-(Dimethylamino)ethoxy]pyridin-2- yl}amino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl]-5-fluoro-2-(hydroxymethyl)phenyl}-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.$0^{2,6}$]dodeca-1(8),2(6)- dien-9-one **296**

Example 296a (2-{4,4-Dimethyl-9-oxo-7-thia-10-azatricyclo[6.4.0.$0^{2,6}$]dodeca-1(8),2(6)-dien-10-yl}-6-[5-({5-[2-(dimethylamino)ethoxy]pyridin-2-yl}amino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl]-4-fluorophenyl)methyl Acetate **296'**

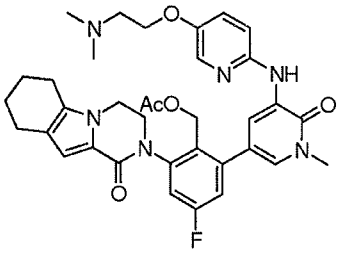


A mixture of 5-bromo-3-(5-(2-(dimethylamino)ethoxy)pyridin-2-ylamino)-1-methylpyridin-2(1H)-one **268c** (244 mg, 0.67 mmol), (2-{4,4-dimethyl-9-oxo-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-10-yl}-4-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl acetate **247b** (342 mg, 0.67 mmol), $PdCl_2(dppf)$ (59 mg, 0.08 mmol), K_3PO_4 (150 mg), and NaOAc (50 mg) in MeCN (6mL) and water (2 mL) was heated at 110°C in a sealed tube for 2 h. The solvent was evaporated in *vacuo* and the residue was purified on reverse phase Combi-flash to give **296a** (287 mg, 60%). MS: $[M+H]^+$ 674.

A mixture of **296a** (186 mg, 0.28 mmol) and LiOH hydrate (116 mg, 2.8 mmol) in isopropanol (25 mL) and water (5 mL) was stirred at 30°C for 2 h. The mixture was evaporated in *vacuo* and the residue was extracted with ethyl acetate (20 mL × 2). The combined extracts were concentrated under reduced pressure and the residue was purified on prep-HPLC to give **296** (126 mg, 71%). MS: $[M+H]^+$ 632.

Example 297 2-(3-(5-(5-(2-(Dimethylamino)ethoxy)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **297**

Example 297a 2-(5-(5-(2-(Dimethylamino)ethoxy)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-fluoro-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **297a**



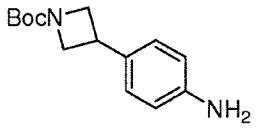
A mixture of 5-bromo-3-(5-(2-(dimethylamino)ethoxy)pyridin-2-ylamino)-1-methylpyridin-2(1H)-one **268c** (205 mg, 0.56 mmol), 4-fluoro-2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **210d** (270 mg, 0.56 mmol), $PdCl_2(dppf)$ (51 mg, 0.07 mmol), K_3PO_4 (100 mg), and NaOAc (40 mg) in MeCN (6mL) and water (2 mL) was heated at 110 °C in a sealed

tube for 2 h. The solvent was evaporated in *vacuo*. The residue was purified on reverse phase Combi-flash to give **297a** (206 mg, 50%). MS: $[M+H]^+$ 643.

A mixture of **297a** (186 mg, 0.29 mmol) and LiOH hydrate (122 mg, 2.9 mmol) in isopropanol (15 mL) and water (3 mL) was stirred at 30°C for 2 h. The mixture was evaporated in *vacuo* and the residue was extracted with ethyl acetate (20 mL × 2). The combined extracts were concentrated under reduced pressure and the residue was purified on prep-HPLC to give **297** (84mg, 48%). MS: $[M+H]^+$ 601. ^{1}H NMR (500 MHz, CDCl3) δ8.53 (d, J = 2.5, 1H), 7.94 (d, J = 3.0, 1H), 7.80 (s, 1H), 7.47 (d, J = 2.0, 1H), 7.23-7.21 (m, 1H), 7.16-7.14 (m, 1H), 6.95-6.93 (m, 1H), 6.86 (s, 1H), 6.81 (d, J = 9.0, 1H), 4.55 (d, J = 10.5, 1H), 4.40-4.26 (m, 2H), 4.22-4.15 (m, 3H), 4.15-4.04 (m, 2H), 3.94-3.86 (m, 1H), 3.69 (s, 3H), 2.75-2.73 (m, 2H), 2.62-2.54 (m, 4H), 2.37 (s, 6H), 1.92-1.86 (m, 2H), 1.82-1.76 (m, 2H).

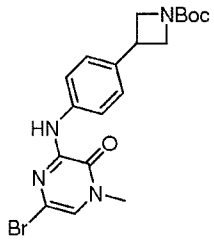
Example 298 10-[5-fluoro-2-(hydroxymethyl)-3-(4-methyl-6-{[4-(1-methylazetidin-3-yl)phenyl]amino}-5-oxopyrazin-2-yl)phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one **298**

Example 298a *tert*-Butyl 3-(4-Aminophenyl)azetidine-1-carboxylate **298a**



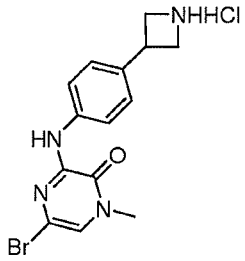
A mixture of *tert*-butyl 3-iodoazetidine-1-carboxylate (1 g, 3.53 mmol), 4-aminophenylboronic acid (630 mg, 4.59 mmol), NiI_2 (66 mg, 0.212 mmol), NaHMDS (1.94 g, 10.6 mmol), (1R,2S)-2-aminocyclohexanol (24 mg, 0.212 mmol) in isopropanol (8 mL) was stirred at 150°C in microwave for 2 h. It was then evaporated and the residue was dissolved with water and ethyl acetate. The water phase was separated and extracted with ethyl acetate. The combined extracts were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified with column chromatography to give **298a** (360 mg, 40%). MS: $[M+H]^+$ 249.

Example 298b *tert*-Butyl 3-(4-(6-Bromo-4-methyl-3-oxo-3,4-dihydropyrazin-2-ylamino)phenyl)azetidine-1-carboxylate **298b**



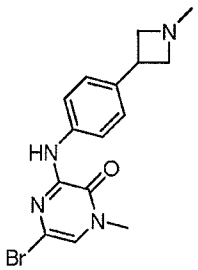
A mixture of **298a** (500 mg, 2.02 mmol), 3,5-dibromo-1-methylpyrazin-2(1H)-one (536 mg, 2.02 mmol) and triethylamine (0.6 mL, 4.04 mmol) in isopropanol (10 mL) was heated at reflux for 4 days. The solvent was evaporated in *vacuo* and the residue was purified on reverse phase Combi-flash to afford **298b** (690 mg, 66%). MS: $[M+H]^+$ 435.

Example 298c 3-(4-(Azetidin-3-yl)phenylamino)-5-bromo-1-methylpyrazin-2(1H)-one Hydrochloride **298c**



A mixture of **298b** (690 mg, 1.6 mmol) and HCl/1,4-dioxane (8M, 8 mL) in methanol (30 mL) was stirred at room temperature overnight. The mixture was evaporated in *vacuo* and the residue was purified on reverse phase Combi-flash to give **298c** (100 mg, 17%). MS: $[M+H]^+$ 335.

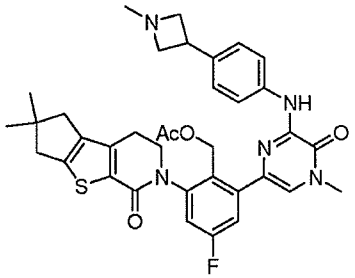
Example 298d 5-Bromo-1-methyl-3-(4-(1-methylazetidin-3-yl)phenylamino)pyrazin-2(1H)-one **298d**



A mixture of **298c** (100 mg, 0.24 mmol), $NaBH(OAc)_3$ (100 mg, 0.48 mmol), HCHO (10 mL) and acetic acid (1 mL) in methanol (15 mL) was stirred at room temperature for 4 h. The solvent was evaporated in *vacuo* and the residue was neutralized with $NaHCO_3$ solution until pH 8 was reached. The mixture was extracted with ethyl acetate. The combined extracts

were dried over sodium sulfate and concentrated under reduced pressure to give **298d** (100 mg), which was used for the next step without further purification. MS: $[M+H]^+$ 349.

Example 298e (2-{4,4-Dimethyl-9-oxo-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-10-yl}-4-fluoro-6-(4-methyl-6-{[4-(1-methylazetidin-3-yl)phenyl]amino}-5-oxo-4,5-dihydropyrazin-2- yl)phenyl)methyl Acetate **298e**



To a sealed tube was charged a mixture of (2-{4,4-Dimethyl-9-oxo-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-10-yl}-4-fluoro-6-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl Acetate **247b** (100 mg, 0.19 mmol), 5-bromo-1-methyl-3-(4-(1-methylazetidin-3-yl)phenylamino)pyrazin-2(1H)-one **298d** (68 mg, 0.19 mmol), $PdCl_2$(dppf) (14 mg, 0.019 mmol), K_3PO_4 (60 mg), and NaOAc (30 mg) in MeCN (5 mL) and water (1 mL). It was heated at 110°C for 2 h. The solvent was evaporated in *vacuo* and the residue was purified on reverse phase Combi-flash to give **298e** (100 mg, 82%). MS: $[M+H]^+$ 656.

A mixture of **298e** (100 mg, 0.16 mmol) and LiOH hydrate (66 mg, 1.6 mmol) in isopropanol (10 mL) and water (2 mL) was stirred at 30 °C for 2 h. The mixture was evaporated in *vacuo* and the residue was extracted with ethyl acetate (2 X 20 mL). The combined extracts were concentrated under reduced pressure. And the residue was purified on pre-HPLC to give **298** (60 mg, 63%). MS: $[M+H]^+$ 614. ^{1}H NMR (500 MHz, CDCl3) δ 8.29 (s, 1H), 7.72 (d, J = 7.5, 2H), 7.55 (s, 1H), 7.45-7.43 (m, 1H), 7.30 (s, 1H), 7.01-6.99 (m, 1H), 4.56 (d, J = 11.5, 1H), 4.41-4.30 (m, 2H), 4.10-4.05 (m, 1H), 3.90-3.85 (m, 1H), 3.82-3.72 (m, 2H), 3.64 (s, 3H), 3.22-3.10 (m, 2H), 3.04-2.97 (m, 1H), 2.93-2.88 (m, 1H), 2.79 (s, 2H), 2.57-2.50 (m, 2H), 2.39 (s, 3H), 1.27 (s, 6H).

Example 299 10-[5-Fluoro-2-(hydroxymethyl)-3-[1-methyl-5-({5-[1-(oxetan-3-yl)piperidin-4-yl]pyridine-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one **299**

Following Example 121b, compound **247b** (256 mg, 0.5 mmol), 5-bromo-1-methyl-3-(5-(1-(oxetan-3-yl)piperidin-4-yl)pyridin-2-ylamino)pyridin-2(1H)-one **264e** (210 mg, 0.5 mmol), 1M sodium carbonate solution (2 mL, 2 mmol), tetrakis(triphenylphosphine)palladium(0) (29 mg, 0.025 mmol) and 1,2-dimethoxyethane (5 mL) were reacted. The reaction mixture was heated at 130 °C for 15 minutes in the microwave reactor. Work-up and flash column chromatography (silica, 9:1 methylene chloride/methanol) give a mixture of compound **299a** and **299** as yellow oil.

The above residue (0.5 mmol) was deprotected using the same procedure as **121**, except using a mixture of THF (2 mL), water (1 mL) and isopropanol (2 mL and lithium hydroxide monohydrate (105 mg, 2.5 mmol). Work-up and flash column chromatography (NH-silica, ethyl acetate /hexanes) give a 12% yield (40 mg) of **299** as a pale yellow solid: MS (ESI+) *m/z* 684.5 (M+H).

Example 300 10-[5-Fluoro-2-(hydroxymethyl)-3-[1-methyl-5-({5-[1-(oxetan-3-yl)piperidin-4-yl]pyridine-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one **300**

Example 300a 5-Bromo-3-(2-methoxypyrimidin-4-ylamino)-1-methylpyridin-2(1H)-one **300a**

Following Example 121a, 2-methoxypyrimidin-4-amine (0.625g, 5 mmol), 3,5-dibromo-1-methyl-1H-pyridin-2-one (1.34 g, 5 mmol), cesium carbonate (4.88 g, 15 mmol), tris(dibenzylideneacetone)-dipalladium(0) (0.465 g, 0.5 mmol), Xantphos (0.58 g, 1 mmol) and 1,4-dioxane (50 mL) were reacted. The reaction mixture was heated at 100 °C for 24 hours, then cool to room temperature, and filtered through a pad of Celite 521. The filter cake was washed with 9:1 methylene chloride/ methanol (2 X 25 mL), and the combined filtrates were concentrated to dryness. The residue was dissolve in methylene chloride, diethyl ethyl was added, and the resulting precipitate was filtered to give a quantitative yield (1.57 g) of **300a** as a green solid: MS (ESI+) *m/z* 313.1 (M+H).

Example 300b 10-[5-Fluoro-2-(acetoxymethyl)-3-[1-methyl-5-({5-[1-(oxetan-3-yl)piperidin-4-yl]pyridine-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one **300b**

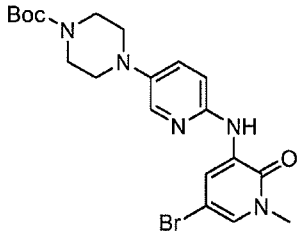
Following Example 121b, **300a** (242 mg, 0.5 mmol), **230a** (210 mg, 0.5 mmol), 1M sodium carbonate solution (2 mL, 2 mmol), tetrakis(triphenylphosphine)palladium(0) (29 mg, 0.025 mmol) and 1,2-dimethoxyethane (5 mL).The reaction mixture was heated at 130°C for 15 minutes in the microwave reactor. Work-up and flash column chromatography (silica,

60:35:5 methylene chloride/diethyl ether/methanol) give a 67% yield (200 mg) of **300b** as a yellow solid: MS (ESI+) *m/z* 602.4 (M+H).

Following Example 121, a mixture of THF (2 mL), water (1 mL) and isopropanol (2 mL), **300b** (200 mg, 0.33 mmol) and lithium hydroxide monohydrate (105mg, 2.5 mmol). Work-up and flash column chromatography (NH-silica, Ethyl Acetate /Hexanes) give a 29% yield (55 mg) of compound **300** as a white solid: MS (ESI+) *m/z* 559.4 (M+H).

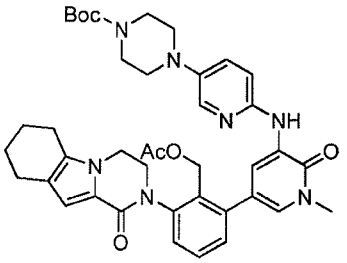
Example 301 2-(2-(Hydroxymethyl)-3-(1-methyl-6-oxo-5-(5-(piperazin-1-yl)pyridin-2-ylamino)-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **301**

Example 301a *tert*-Butyl 4-(6-(5-Bromo-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)pyridin-3-yl)piperazine-1-carboxylate **301a**



To a round-bottomed flask equipped with a stirring bar, *tert*-butyl 4-(6-aminopyridin-3-yl)piperazine-1-carboxylate (2.00 g, 7.18 mmol), 3,5-dibromo-1-methylpyridin-2(1H)-one (2.87 g, 10.77 mmol), $Pd_2(dba)_3$ (657 mg, 0.718 mmol), XantPhos (665 mg, 1.15 mmol), Cs_2CO_3 (7.72 g, 23.7 mmol) and dioxane (40 mL) were added. The reaction mixture was heated at 100 °C for 40 hrs. Ethyl acetate (200 mL) was added and the resulting mixture was washed with water (30 mL X 3), brine (30 mL X 1), dried over $MgSO_4$, filtered, and removed solvent *in vacuo*. Methylene chloride / ether (1:2, 5 mL) was added followed by sonication, the precipitate was filtered as **301a**, yellow solids, 1.946 g (58 %).

Example 301b *tert*-Butyl 4-(6-(5-(2-(Acetoxymethyl)-3-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)phenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)pyridin-3-yl)piperazine-1-carboxylate **301b**

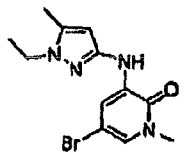


To a microwave tube equipped with a stirring bar, **301a** (500 mg, 1.077 mmol), 2-(2-(hydroxymethyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **114a** (546 mg, 1.292 mmol), $Pd(PPh_3)_4$ (62 mg, 0.054 mmol), Na_2CO_3 aqueous solution (1.0 N, 3.55 mL, 3.55 mmol), 1,2-dimethoxyethane (4.3 mL) were added. The mixture was reacted in microwave at 130°C for 10 min. Methylene chloride (200 mL) was added and the resulting mixture was washed with water (3 X 30 mL), brine (30 mL), dried over $MgSO_4$, filtered, and removed solvent *in vacuo*. Silica gel column chromatography (methanol: methylene chloride = 5: 95) gave **301b**.

To a round-bottomed flask equipped with a stirring bar, **301b**, methylene chloride (10 mL) was added. The solution was cooled to 0 °C in an ice-water bath. TFA (1 mL) was added and the resulting solution was stirred overnight. Removed all the volatiles *in vacuo*, and to the bottle THF (5 mL), isopropanol (5 mL), H_2O (5 mL), LiOH monohydrate (300 mg) were added. The resulting mixture was stirred at RT for 1 hr. Removed all the solvent *in vacuo* and the resulting residue was added to methylene chloride (200 mL), the solution was washed with water (3 X 30 mL), brine (30 mL), dried over $MgSO_4$, filtered, and removed solvent *in vacuo*. Silica gel column (methanol: methylene chloride = 10: 90) followed by prep-HPLC gave **301** as a yellow solid, 9 mg. MS (ESI+) *m/z* 580.4 (M + H).

Example 302 10-(3-{5-[(1-Ethyl-5-methyl-1H-pyrazol-3-yl)amino]-1-methyl-6-oxo-1,6-dihydropyridin-3-yl}-5-fluoro-2-(hydroxymethyl)phenyl)-4,4-dimethyl-1,10-diazatricyclo[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-9-one **302**

Example 302a 5-Bromo-3-(1-ethyl-5-methyl-1H-pyrazol-3-ylamino)-1-methylpyridin-2(1H)-one **302a**

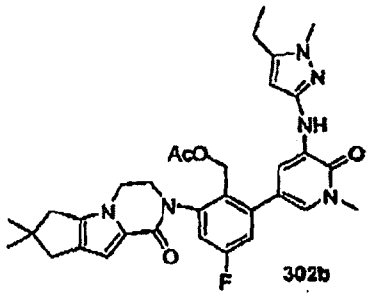


302a

A sealed tube was equipped with a magnetic stirrer and charged with 1-ethyl-5-methyl-1H-pyrazol-3-amine (870 mg, 7 mmol), 3,5-dibromo-1-methylpyridin-2(1H)-one (1.9 g, 7 mmol) and cesium carbonate (5 g, 15 mmol) in 1,4-dioxane (69 mL). After bubbling nitrogen through the solution for 30 min, Xantphos (480 mg, 0.8 mmol) and tris(dibenzylideneacetone) dipalladium(0) (450 mg, 0.5 mmol) were added, and the reaction mixture was heated to 100°C for 16 h. After this time, water (50 mL) and ethyl acetate (50 mL) were added. The aqueous layer was separated and extracted with ethyl acetate (2 X 50

mL). The combined organic extracts were washed with brine (100 mL) and dried over sodium sulfate. The mixture was concentrated under reduced pressure to near dryness when the desired product crashed out and was filtered. Washing with diethyl ether (10 mL) afforded a 40% yield (870 mg) of **302a**.

Example 302b 10-(3-{5-[(1-Ethyl-5-methyl-1H-pyrazol-3-yl)amino]-1-methyl-6-oxo-1,6-dihydropyridin-3-yl}-5-fluoro-2-(acetoxymethyl)phenyl)-4,4-dimethyl-1,10-diazatricyclo[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-9-one **302b**



302b

A microwave tube equipped with a magnetic stirrer was charged with **302a** (170 mg, 0.5 mmol), **230a** (350 mg, 0.7 mmol), 1,2-dimethoxyethane (4 mL) and 1M aqueous sodium carbonate (1.6 mL). After bubbling N_2 for 15 min, $Pd(PPh_3)_4$ (31 mg, 0.03 mmol) was added. The mixture was heated in microwave to 130°C for 15 min. After this time, ethyl acetate (5 mL) and water (5 mL) were added. The separated aqueous layer was extracted with ethyl acetate (2 x 5 mL). The combined organics were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography eluting with a gradient of methylene chloride – 60:35:5 methylene chloride:diethyl ether: methanol to afford a 60% yield (190 mg) of **302b**.

A 25 mL round bottom flask with a magnetic stirrer was charged with **302b** (190 mg, 0.3 mmol), lithium hydroxide (70 mg, 1.6 mmol), THF (1.6 mL), isopropanol (1.6 mL) and water (3.2 mL). The mixture stirred at room temperature for 2 h. After this time, ethyl acetate (5 mL) and water (5 mL) were added. The separated aqueous layer was extracted with ethyl acetate (2 X 5 mL). The combined organics were washed with brine (10 mL), dried over sodium sulfate and filtered. The mixture was concentrated under reduced pressure to near dryness when the desired product crashed out and was filtered. Upon washing with diethyl ether (10 mL) afforded a 51% yield (90 mg) of **302**. MS (ESI+) *m/z* 559.4 (M + H).

Example 303 5-[5-Fluoro-2-(hydroxymethyl)-3-[1-methyl-5-({5-[1-(oxetan-3-yl)piperidin-4-yl]pyridine-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6-one **303**

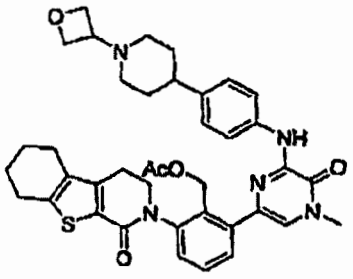
Following Example 299, compound **212b** was converted to **303**. MS (ESI+) *m/z* 670.3 (M + H).

Example 304 10-[5-Fluoro-2-(hydroxymethyl)-3-[1-methyl-5-({5-[4-(oxetan-3-yl)piperazin-1-yl]pyridine-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-9-one **304**.

To a solution of (2-{4,4-dimethyl-9-oxo-1,10-diazatricyclo[6.4.0.0^{2,6}]dodeca-2(6),7-dien-10-yl}-4-fluoro-6-[1-methyl-5-({5-[4-(oxetan-3-yl)piperazin-1-yl]pyridin-2-yl}amino)-6-oxo-1,6- dihydropyridin-3-yl]phenyl)methyl acetate **304a** (200 mg, 0.28 mmol) in THF/iPA/H_2O (6 mL/6 mL/2 mL) at room temperature was added LiOH (70 mg, 2.9 mmol) while stirring. This mixture was stirred for 0.5 h. Then, 20 mL H_2O was added and the mixture was extracted with ethyl acetate (30 mL X 3). The combined organic layers were dried with Na_2SO_4 and concentrated to give a yellow solid which was further purified by prep-HPLC to afford **304** as a white solid (100 mg, 53%). LCMS: $[M+H]^+$ 668. ^{1}H NMR (500 MHz, DMSO): δ 1.23 (s, 6H), 2.37-2.39 (m, 5H), 2.53-2.57 (m, 2H), 3.07 (s, 4H), 3.43-3.45 (m, 2H), 3.60 (s, 3H), 3.85-3.87 (m, 1H), 4.16-1.19 (m, 3H), 4.32 (d, *J*=6.0 Hz, 2H), 4.45-4.50 (m, 2H), 4.54-4.58 (m, 2H), 4.86 (s, 1H), 6.47-6.51 (m, 1H), 7.18-7.25 (m, 2H), 7.34-7.39 (m, 3H), 7.83-7.86 (m, 1H), 8.35-8.37 (m, 1H), 8.53-8.56 (m, 1H).

Example 305 5-[2-(Hydroxymethyl)-3-[4-methyl-6-({4-[1-(oxetan-3-yl)piperidin-4-yl]phenyl}amino)-5-oxo-4,5-dihydropyrazin-2-yl]phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-6- one **305**

Example 305a {2-[4-Methyl-6-({4-[1-(oxetan-3-yl)piperidin-4-yl]phenyl}amino)-5-oxo-4,5-dihydropyrazin-2-yl]-6-{6-oxo-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-5-yl}phenyl}methyl Acetate **305a**



305a

Following Example 136e, 5-bromo-1-methyl-3-(4-(1-(oxetan-3-yl)piperidin-4-yl)phenylamino)pyrazin-2(1H)-one **214b** and (2-{6-oxo-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-5-yl}-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl acetate **111a** afforded **305a** in 68% yield. LCMS: $(M+H)^+$ 694

Following Example 136, **305a** was converted to **305** in 51% yield. LCMS: $(M+H)^+$ 652. ^{1}H NMR (500 MHz, DMSO) δ 9.18 (s, 1H), 7.88 (s, 1H), 7.86 (s, 1H), 7.52 (d, J=7.5, 1H), 7.46 (t, J=7.5, 1H), 7.38 (s, 1H), 7.17 (s, 1H), 7.32 (d, J=7.5, 1H), 7.15 (d, J= 8.5, 2H), 4.78 (m, 1H), 4.52 (m, 3H), 4.43 (m, 3H), 4.01 (m, 1H), 3.87 (m, 1H), 3.54 (s, 3H), 3.37 (m, 1H), 2.96 (m, 1H), 2.86 (m, 1H), 2.78 (m, 4H), 2.43 (m, 2H), 1.82 (s, 6H), 1.72 (m, 2H), 1.60 (m, 2H).

Example 306 10-[2-(Hydroxymethyl)-3-[1-methyl-6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydropyridazin-3-yl]phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one **306**

Example 306b 10-[2-(Acetoxymethyl)-3-[1-methyl-6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydropyridazin-3-yl]phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.$0^{2,6}$]dodeca-1(8),2(6)-dien-9-one **306b**

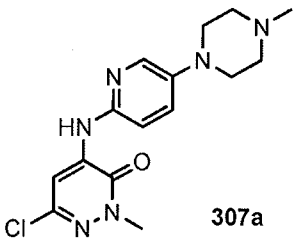
Step1: In a pressure flask was placed 5-chloro-1-methyl-3-(pyrimidin-4-ylamino)pyridazin-2(1H)-one (300mg, 1.26mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (577mg, 2.27mmol), potassium acetate (247mg, 2.32mmol), X-Phos (2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl) (120mg, 20mol%), and Tris(dibenzylideneacetone)dipalladium(0) (115mg, 10mol%) The flask was evacuated and filled with N_2 3X, dioxane (12mL) was added, the vessel sealed and heated to 90°C for 2hrs. The reaction was allowed to cool then diluted with ethyl acetate, and filtered through a pad of celite and concentrated under reduced pressure to give **306a** which was used directly in the next step.

Step 2: **306a** was dissolved in dioxane (7mL) and transferred to a pressure flask containing **189a** (448mg, 1.0mmol), 10% K_2CO_3/water (2.5ml) and bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (45mg, 5mol%). The flask was sealed and heated to 100°C overnight. The reaction was then diluted with ethyl acetate and water, separated, washed with brine 3X, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by chromatography: ISCO 24g silica, eluting with 50-100% ethyl acetate/hexanes, to give **306b** (250mg, 35% yield over 2 steps).

Following Example 119, **306b** (250mg, 0.44mmol), 1N LiOH (2.2mL), THF (4.5mL) and isopropanol (4.5mL) were reacted. The product was triturated with ether and dried under vacuum to give **306** (185mg, 80% yield) as an off-white solid. MS (ESI+) *m/z* 529.3 (M + H).

Example 307 2-(2-(Hydroxymethyl)-3-(1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **307**.

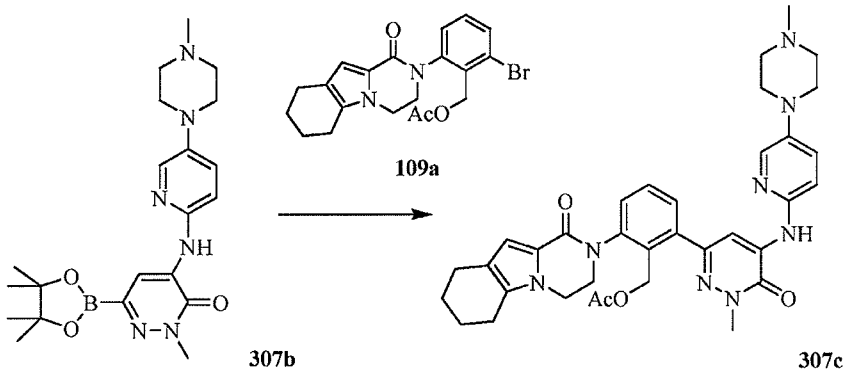
Example 307a 6-Chloro-2-methyl-4-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)pyridazin-3(2H)-one **307a**



307a

Following Example 119b, 4-bromo-6-chloro-2-methylpyridazin-3(2H)-one (1.5g, 6.7mmol), 5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamine (1.3g, 6.7mmol), cesium carbonate (4.8g, 39.4mmol), and Xantphos (330mg, 8.5mol%), dioxane (50ml) and tris(dibenzylideneacetone)dipalladium(0) (307mg, 5 mol%) were reacted. Purified via column chromatography: ISCO 40g silica, 50-100% ethyl acetate/hexanes then 0-10% methanol to give **307a** (1.2g, 53%) as a light tan solid.

Example 307c 2-(2-(Acetoxymethyl)-3-(1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **307c**



Following Example 306b, **307a** (422mg, 1.26mmol) was converted to the boron intermediate **307b**, which was coupled under Suzuki conditions with **109a** (420mg, 1.0mmol). The crude product was purified via column chromatography: ISCO 24g silica , 50-100% ethyl acetate/hexanes then 0-10% MeOH, to give **307c** (285mg, 36% yield).

Following Example 119, **307c** (285mg, 0.45mmol), 1N LiOH (2.2mL), THF (5mL) and isopropanol (5mL) were reacted, triturated with ethyl acetate and dried under vacuum to give **307** (115mg, 43% yield) as slightly yellow solid. MS (ESI+) *m/z* 595.6 (M + H).

Example 308 5-[5-Fluoro-2-(Hydroxymethyl)-3-(1-methyl-5-{[5-(1-methylpyrrolidin-3-yl)pyridine-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-8-thia-5-azatricyclo-[7.4.0.$0^{2,7}$]trideca-1(9),2(7)-dien-6-one **308**

Following Example 270, reaction of boronate **212b** with bromide **202a** yielded **308**. MS (ESI+) *m/z* 614.3 (M + H).

Example 309 5-[2-(Hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrido[3,4-b]indolizin-2-yl}phenyl]-1-methyl-3-{4H,6H,7H-pyrazolo[3,2-c][1,4]oxazin-2-ylamino}-1,2-dihydropyridin-2-one **309**

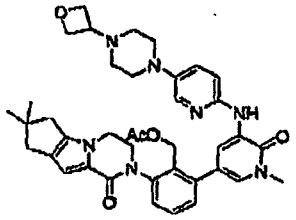
Following Example 270, reaction of boronate **113a** with bromide **110c** yielded **309**. MS (ESI+) *m/z* 541.2 (M + H).

Example 310 3-{[5-(4-Ethylpiperazin-1-yl)pyridine-2-yl]amino}-5-[2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrido[3,4-b]indolizin-2-yl}phenyl]-1-methyl-1,2-dihydropyridin-2-one **310**

Following Example 270, reaction of boronate **113a** with bromide **138c** yielded **310**. MS (ESI+) *m/z* 608.3 (M + H).

Example 311 10-[2-(Hydroxymethyl)-3-[1-methyl-5-({5-[4-(oxetan-3-yl)piperazin-1-yl]pyridine-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-9-one **311**

Example 311a (2-{4,4-Dimethyl-9-oxo-1,10- diazatricyclo[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-10- yl}-6-[1-methyl-5-({5-[4-(oxetan-3-yl)piperazin-1-yl]pyridin-2-yl}amino)-6-oxo-1,6-dihydropyridin-3- yl]phenyl)methyl Acetate **311a**



311a

A sealed tube was charged with the mixture of (2-{4,4-dimethyl-9-oxo-1,10-diazatricyclo[6.4.0.02,6]dodeca-2(6),7-dien-10-yl}-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl acetate (335 mg, 0.7 mmol), 5-bromo-1-methyl-3-(5-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-2-ylamino)pyridin-2(1H)-one **188e** (294 mg, 0.7 mmol), $Pd(dppf)Cl_2$ (33 mg, 0.04 mmol), $K_3PO_4.3H_2O$(372 mg, 1.4 mmol), and NaOAc (115 mg, 1.4 mmol) in CH_3CN (20 mL). The system was evacuated and refilled with N_2. The reaction mixture was heated at 110 °C for 2 h. It was then cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography eluting with 30:1 methylene chloride/methanol to afford **311a** as a yellow solid (208 mg, 43%). MS: $[M+H]^+$ 692.

At room temperature, to the solution of **311a** (200 mg, 0.29mol) in THF/isopropanol/water (6 mL/6 mL/2 mL) was added LiOH (70 mg, 2.9 mmol) while stirring. This mixture was stirred for 0.5 h. Then, 20 mL water was added and the mixture was extracted with ethyl acetate (3 X 30 mL). The combined organic layer was dried with Na_2SO_4 and concentrated to give a yellow solid which was further purified by prep-HPLC to afford **311** as a white solid (100 mg, 53%). LCMS: $[M+H]^+$ 650. ^1H NMR (500 MHz,

DMSO) δ 1.22 (s, 6 H), 2.37-2.42(m, 6 H), 2.56 (d, *J*=11.0 Hz, 1H), 3.06 (d, *J*=4.5 Hz,, 4 H), 3.41-3.44 (m, 2 H), 3.59 (s, 3 H), 3.85-3.90 (m, 1 H),4.08-4.21 (m, 3 H), 4.35 (d, *J*=4.5 Hz, 2 H), 4.45-4.47 (m, 2H), 4.54-4.57 (m, 2H), 4.84-4.86 (m, 1 H), 6.45 (s, 1H), 7.22 (d, *J*=9.0 Hz, 1H), 7.31-7.47 (m, 4H), 7.86 (d, *J*=3.0Hz, 1H), 8.37 (s, 1H), 8.56 (d, *J*=2.0 Hz, 1H).

Example 312 10-[2-(Hydroxymethyl)-3-[1-methyl-5-({5-[4-(oxetan-3- yl)piperazin-1-yl]pyridine-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.$0^{2,6}$]dodeca-1(8),2(6)-dien-9- one **312**

Example 312a (2-{4,4-Dimethyl-9-oxo-7-thia-10-azatricyclo[6.4.0.$0^{2,6}$]dodeca-1(8),2(6)-dien-10-yl}-6-[1-methyl-5-({5-[4-(oxetan-3-yl)piperazin-1-yl]pyridin-2-yl}amino)-6-oxo-1,6-dihydropyridin-3- yl]phenyl)methyl Acetate **312a**

Following Example 136e, 5-bromo-1-methyl-3-(5-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-2-ylamino)pyridin-2(1H)-one (24-7) and (2-{4,4-dimethyl-9-oxo-7-thia-10-azatricyclo[6.4.0.$0^{2,6}$]dodeca-1(8),2(6)-dien-10-yl}-6-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl acetate **131a** was converted to **312a** in 63% yield. LCMS: $(M+H)^+$ 709

Following Example 136, **312a** was converted to **312** in 60% yield. LCMS: $(M+H)^+$ 667. ^{1}H NMR (500 MHz, MEOD) δ 8.52 (s, 1H), 7.93 (m, 1H), 7.50 (m, 1H), 7.42 (m, 3H), 7.30 (s, 1H), 7.05 (m, 1H), 4.73 (t, J=6.5, 2H), 4.64 (t, J=6, 2H), 4.56 (m, 2H), 4.14 (m, 1H), 3.98 (m, 1H), 3.71 (s, 3H), 3.67 (m, 1H), 3.16 (m, 4H), 3.11 (m, 1H), 2.96 (m, 1H), 2.81 (s, 2H), 2.60 (m, 2H), 2.53 (s, 4H), 1.29 (d, J=3, 6H).

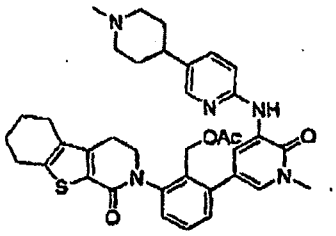
Example 313 5-[5-Fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[5-(2*S*)-(1-methylpyrrolidin-2-yl)pyridine-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$]trideca-1(9),2(7)-dien-6-one **313**

Example 314 5-[5-Fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[5-(2*R*)-(1-methylpyrrolidin-2-yl)pyridine-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$]trideca-1(9),2(7)-dien-6-one **314**

Compounds **313** and **314** are enantiomers of racemate **288.** The racemic mixture **288** was subjected to chiral separation on a Chiralpak AD, 4.6x50mm, 3μm column (mobile phase 55% isopropanol (w/0.1%triethylamine)/45%CO_2, flow rate 5mL/min) at 40 °C to give individual enantiomers, with **313** eluting first, and **314** eluting last.

Example 315 5-[2-(Hydroxymethyl)-3-(1-methyl-5-{[5-(1- methylpiperidin-4-yl)pyridine-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$]trideca-1(9),2(7)-dien-6- one **315**

Example 315a [2-(1-Methyl-5-{[5-(1-methylpiperidin-4-yl)pyridin-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)-6-{6-oxo-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$]trideca-1(9),2(7)-dien-5-yl}phenyl]methyl Acetate 315a



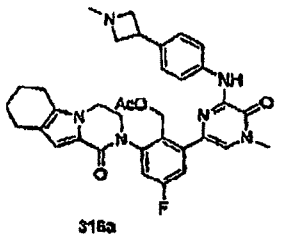
315a

A sealed tube was charged with the mixture of 5-bromo-1-methyl-3-(5-(1-methylpiperidin-4-yl)pyridin-2-ylamino)pyridin-2(1H)-one 130c (400mg, 1.06 mmol), (2-{6-oxo-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$]trideca-1(9),2(7)-dien-5-yl}-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl acetate 111a (512mg, 1.06 mmol), $Pd(dppf)Cl_2$ (87 mg, 0.1 mmol), $K_3PO_4.3H_2O$(566 mg, 2.12 mmol), and NaOAc (174 mg, 2.12 mmol) in CH_3CN (25 mL). The system was evacuated and then refilled with N_2. The reaction mixture was heated at 110°C for 2h. Then, the mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography eluting with 10:1 methylene chloride/methanol to give 315a as a brown solid (300 mg, 43%). MS: $[M+H]^+$ 652

A solution of 315a (250 mg, 0.38 mmol) in propan-2-ol (10 mL), tetrahydrofuran (10 mL) and water (1.5 mL) was added LiOH (922 mg, 38 mmol). The mixture was stirred at 30 °C for 2 h. It was then evaporated and the residue was purified by reverse phase Combi-flash eluting with 0.3% NH_4HCO_3 in 1:4 water/CH_3CN to give 315 as a white solid (37 mg, 16%). MS: $(M+H)^+$ 610. ^1H NMR (500 MHz, MeOD) δ 1.74-1.84 (m, 4 H), 1.87-1.95 (m, 4 H), 2.13-2.18 (t, J=11.5, 2 H), 2.32 (s, 3 H), 2.52-2.61(m, 3 H), 2.85-2.87 (t, J=4.5, 2 H), 2.92-3.06 (m, 4 H), 3.71(s, 3 H), 3.99-4.03 (m, 1 H), 4.12-4.17 (m, 1 H), 4.52-4.59 (m, 2 H), 7.03 (d, 1 H), 7.34 (d, 1 H), 7.39 (d, 1 H), 7.42 (d, 1 H), 7.51 (d, 1 H), 7.56 (d, 1 H), 8.08 (s, 1 H), 8.62 (s, 1 H).

Example 316 5-[5-Fluoro-2-(hydroxymethyl)-3-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]-1-methyl-3-[(4-(1-methylazetidin-3-yl)phenyl)amino)-1,2-dihydropyrazin-2-one 316

Example 316a 4-Fluoro-2-(4-methyl-6-(4-(1-methylazetidin-3-yl)phenylamino)-5-oxo-4,5-dihydropyrazin-2-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate 316a



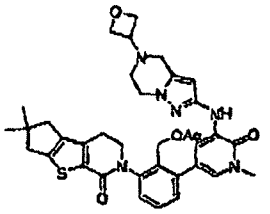
316a

A sealed tube was charged with the mixture of 5-bromo-1-methyl-3-(4-(1-methylazetidin-3-yl)phenylamino)pyrazin-2(1H)-one **298e** (200mg, 0.58 mmol), 4-fluoro-2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **210d** (280mg, 0.58 mmol), $Pd(dppf)Cl_2$ (40 mg, 0.06 mmol), $K_3PO_4.3H_2O$(300 mg, 1.16 mmol), and NaOAc (100 mg, 1.16 mmol) in CH_3CN (20 mL). The system was evacuated and then refilled with N_2. And the reaction mixture was heated at 110°C for 3 h. Then, the mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography eluting with 15:1 methylene chloride/methanol to give **216a** as a brown solid (150 mg, 42%). MS: $[M+H]^+$ 625

A solution of **316a** (130 mg, 0.21 mmol) in propan-2-ol (7 mL), tetrahydrofuran (7 mL), and water (1 mL) was added LiOH (500 mg, 21 mmol). The mixture was stirred at 30°C for 2 h. It was evaporated and the residue was purified by prep-HPLC to afford **316** as a white solid (14 mg, 12%). MS: $(M+H)^+$ 583. ^1H NMR (500 MHz, MEOD) δ 1.77-1.81 (m, 2 H), 1.89-1.95 (m, 2 H), 2.46 (s, 3 H), 2.55 (t, J=6, 2 H), 2.60-2.68 (m, 2 H), 3.64 (s, 3 H), 3.73-3.77 (m, 1 H), 3.85(s, 2 H), 4.16-4.27 (m, 1 H), 4.46-4.59 (m, 2 H), 6.72 (s, 1 H), 7.19-7.21 (d, 1 H), 7.8-7.30 (d, 2 H), 7.31-7.41 (dd, 2 H), 7.78 (d, 2 H).

Example 317 10-[2-(Hydroxymethyl)-3-(1-methyl-5-{[5-(oxetan-3-yl)-4H,5H,6H,7H-pyrazolo[1,5-a]pyrazin-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.$0^{2,6}$]dodeca-1(8),2(6)- dien-9-one 317

Example 317a (2-(4,4-Dimethyl-9-oxo-7-thia-10-azatricyclo[6.4.0.$0^{2,6}$]dodeca-1(8),2(6)-dien-10-yl)-6-(1-methyl-5-{[5-(oxetan-3-yl)-4H,5H,6H,7H-pyrazolo[1,5-a]pyrazin-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl)methyl Acetate 317a



317a

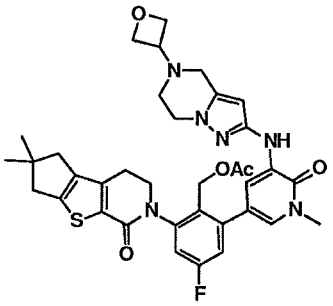
A sealed tube was charged with the mixture of 5-bromo-1-methyl-3-(5-(oxetan-3-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)pyridin-2(1H)-one **252a** (275 mg, 0.7 mmol), (2-{4,4-dimethyl-9-oxo-7-thia-10-azatricyclo[6.4.0.$0^{2,6}$]dodeca-1(8),2(6)-dien-10-yl}-4-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl acetate **131a** (356 mg, 0.7 mmol), $Pd(dppf)Cl_2$ (59 mg, 0.07 mmol), $K_3PO_4.3H_2O$(317 mg, 1.4 mmol), and NaOAc (118 mg, 1.4 mmol) in CH_3CN (20 mL). The system was evacuated and refilled with N_2. The reaction mixture was heated at 110°C for 2h. It was then cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography eluting with 30:1 methylene chloride/methanol to afford **317a** as a yellow solid (300 mg, 61%). MS: $[M+H]^+$ 669.

At room temperature, to the solution of **317a** (300 mg, 0.5 mol) in THF/isopropanol/water (6 mL/6 mL/2 mL) was added LiOH (70 mg, 2.9 mmol) while stirring. This mixture was stirred for 0.5 h. Then, 20 mL H_2O was added and the mixture was extracted with ethyl acetate (3 X 30 mL). The combined organic layer was dried with Na_2SO_4 and concentrated to get a yellow solid, which was further purified by prep-HPLC to afford **317** as a white solid (93 mg, 28%). MS: $[M+H]^+$ 627. ^1H NMR (500 MHz, DMSO) δ 1.24 (s, 6 H), 2.65 (s, 1 H), 2.75 (d, *J*=8.5 Hz, 4 H), 2.88-2.91 (m, 1 H), 3.00-3.03 (m, 1 H), 3.50 (s, 2 H), 3.57 (s, 3 H), 3.67 (t, *J*=6.0 Hz, 1 H), 3.84-3.89 (m, 1 H), 3.93 (t, *J*=6.0 Hz, 2 H), 4.00-4.05 (m, 1 H), 4.34-4.36 (m, 2 H), 4.49 (t, *J*=6.0 Hz, 2 H), 4.59 (t, *J*=7.0 Hz, 2 H), 4.83 (d, *J*=5.0 Hz, 1 H), 5.91 (s, 1 H), 7.24 (d, *J*=2.0 Hz, 1 H), 7.24-7.35 (m, 2 H), 7.45 (t, *J*=7.0 Hz, 1 H), 7.98 (d, *J*=2.0 Hz, 1 H), 8.13 (s, 1 H).

Example 318 10-[5-Fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[5-(oxetan-3-yl)-4H,5H,6H,7H-pyrazolo[1,5-a]pyrazin-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.$0^{2,6}$]dodeca-1(8),2(6)-dien-9-one **318**

Example 318a (2-{4,4-Dimethyl-9-oxo-7-thia-10-azatricyclo[6.4.0.$0^{2,6}$]dodeca-1(8),2(6)-dien-10-yl}-4-fluoro-6-(1-methyl-5-{[5-(oxetan-3-yl)-

4H,5H,6H,7H-pyrazolo[1,5-a]pyrazin-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl)methyl Acetate **318a**



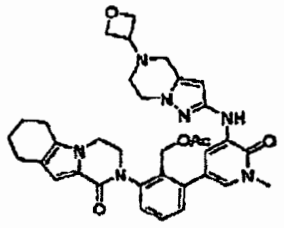
318a

A sealed tube was charged with the mixture of (2-{4,4-dimethyl-9-oxo-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-10-yl}-4-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl acetate **247b** (300 mg, 0.584 mmol), 5-bromo-1-methyl-3-(5-(oxetan-3-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)pyridin-2(1H)-one **252a** (222 mg, 0.584 mmol), Pd(dppf)Cl_2 (48 mg, 0.0584 mmol), $K_3PO_4.3H_2O$(311 mg, 1.168 mmol), and NaOAc (96 mg, 1.168 mmol) in CH_3CN (20mL). The system was evacuated and then refilled with N_2. And the reaction mixture was heated at 110°C for 2h. Then, the mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography eluting with 30:1 methylene chloride/ methanol to afford **318a** as a yellow solid (304 mg, 74%). MS: $[M+H]^+$ 687.

To a solution of **318a** (300 mg, 0.44mol) in THF/isopropanol/water (6mL/6mL/2mL) was added LiOH (100 mg, 4.16 mmol) at room temperature. The mixture was stirred for 0.5 h. Then, 20mL H_2O was added and the mixture was extracted with ethyl acetate (30mL × 3). The combined organic layer was dried with Na_2SO_4 and concentrated to give a yellow solid, which was further purified by prep-HPLC to afford **318** as a white solid (68.7 mg, 52.3%). ^1H NMR (500 MHz, DMSO) δ 8.17(s, 1H), 7.98 (d, J=6Hz, 1H), 7.30 (t, 2H), 7.17 (t, 1H), 5.91 (s, 1H), 4.88 (t, 1H), 4.58 (t, 2H), 4.48 (t, 2H), 4.32 (d, 1H), 4.05 (t, 1H), 4.02 (m, 3H), 3.94 (m, 2H), 3.92 (s, 1H), 3.83 (s, 1H), 3.30 (s, 1H), 3.02 (m, 1H), 2.88 (s, 4H), 2.73 (s, 2H), 1.20 (s, 6H)

Example 319 2-(2-(Hydroxymethyl)-3-(1-methyl-5-(5-(oxetan-3-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **319**

Example 319a [2-(1-Methyl-5-{[5-(oxetan-3-yl)-4H,5H,6H,7H-pyrazolo[1,5-a]pyrazin-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)-6-{1-oxo-1H,2H,3H,4H,6H,7H,8H,9H-pyrazino[1,2-a]indol-2-yl}phenyl]methyl Acetate 319a



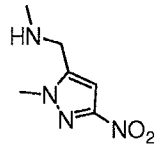
319a

A sealed tube was charged with the mixture of 5-bromo-1-methyl-3-(5-(oxetan-3-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)pyridin-2(1H)-one 252a (265 mg, 0.7 mmol),2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate 114a (320 mg, 0.7 mmol), $Pd(dppf)Cl_2$ (56 mg, 0.07 mmol), $K_3PO_4.3H_2O$(367 mg, 1.4 mmol), and NaOAc (113 mg, 1.4 mmol) in CH_3CN (20 mL). The system was evacuated and refilled with N_2. The reaction mixture was heated at 110°C for 2h. It was then cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography eluting with 30:1 methylene chloride/ methanol to afford 319a as a yellow solid (200 mg, 38%). MS: $[M+H]^+$ 638.

At room temperature, to the solution of 319a (150 mg, 0.24mol) in THF/isopropanol/water (6 mL/6 mL/2 mL) was added LiOH (70 mg, 2.9 mmol) while stirring. This mixture was stirred for 0.5 h. Then, 20 mL water was added and the mixture was extracted with ethyl acetate (3 X 30 mL). The combined organic layer was dried with Na_2SO_4 and concentrated to give a yellow solid, which was further purified by prep-HPLC to afford 319 as a white solid (50 mg, 28%). MS: $[M+H]^+$ 596. ^1H NMR (500 MHz, DMSO) δ 1.23 (t, *J*=7.0 Hz, 2 H), 1.70-2.08 (m, 5 H), 2.74-2.76 (m, 2 H), 3.50 (s, 2 H), 3.57 (s, 3 H), 3.67 (s, 1 H), 3.91-3.94(m, 3 H), 4.03-4.16 (m, 4 H), 4.35 (s, 2 H), 4.48-4.50 (m, 2 H), 4.58-4.60 (m, 2 H), 4.61 (s, 1 H), 5.91 (s, 1 H), 6.51 (s, 1 H), 7.23 (s, 1 H), 7.30-7.34 (m, 2 H), 7.44-7.47 (m, 1 H), 7.98 (d, *J*=2.0 Hz, 1 H) , 8.12 (s, 1 H).

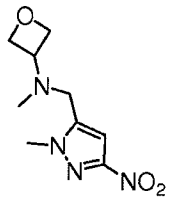
Example 320 2-(5-Fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one 320

Example 320a N-Methyl(1-methyl-3-nitro-1H-pyrazol-5-yl)methanamine **320a**



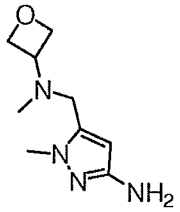
To a stirred solution of $MeNH_2$ (30% wt in H_2O) (2.5 g, 20 mmol) in acetone (10 mL) at 0℃ (ice bath) was added K_2CO_3 (415 mg, 3 mmol), followed by the dropwise addition of a solution of 5-(bromomethyl)-1-methyl-3-nitro-1H-pyrazole (220 mg, 1 mmol) in acetone (5 mL). The reaction mixture was then warmed to room temperature and stirred for 3 h. The solvent was removed and the residue was extracted with methylene chloride (15 mL × 3), dried over Na_2SO_4 and concentrated to afford **320a** as a yellow oil (170 mg, 99%), which was used in the next step without additional purification. LCMS: $(M+H)^+$ 171

Example 320b N-Methyl-N-((1-methyl-3-nitro-1H-pyrazol-5-yl)methyl)oxetan-3-amine **320b**



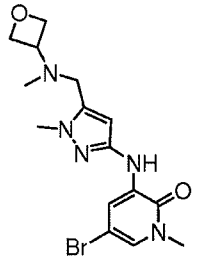
To a mixture of **320a** (170 mg, 1 mmol) in methanol (4 mL), $ZnCl_2$ (1 mmol/L in diethyl ether) (2 mL, 2 mmol) and oxetan-3-one (150 mg, 2 mmol) were added at room temperature under nitrogen protection, followed by the addition of $NaBH_3CN$ (130 mg, 2 mmol). The reaction mixture was warmed to 50°C and stirred for 3 h. The mixture was then cooled to room temperature and the solvent was removed. The residue was purified on flash column eluting with 50:1 methylene chloride/methanol to afford **320b** as a yellow solid (180 mg, 80%, two steps). LCMS: $(M+H)^+$ 227. ^1H NMR (500 MHz, DMSO) δ 6.99 (s, 1H), 4.52 (t, J=6.5, 2H), 4.42 (t, J=6, 2H), 3.98 (s, 3H), 3.63 (m, 1H), 3.50 (s, 2H), 2.03 (s, 3H).

Example 320c 1-Methyl-5-((methyl(oxetan-3-yl)amino)methyl)-1H-pyrazol-3-amine **320c**



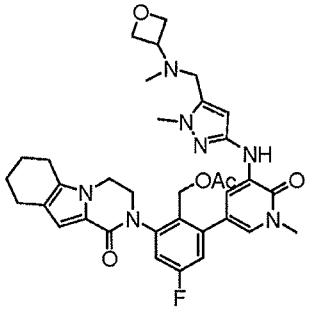
To a solution of **320b** (1.8 g, 7.96 mmol) in ethanol (20 mL) and water (20 mL), NH_4Cl (3.3 g, 63.6 mmol) and iron powder (1.80 g, 31.8 mmol) were added. The reaction mixture was heated at 70 °C for 2 h. After that, the mixture was cooled to room temperature and filtered. The filtrate was evaporated and the residue was extracted with methylene chloride (30 mL × 3), dried Na_2SO_4, and concentrated to afford the crude product, which was purified on flash column eluting with 50:1 methylene chloride/methanol containing 0.5% triethylamine to afford **320c** as a yellow oil (1.3 g, 83%). LCMS: $(M+H)^+$ 197

Example 320d 5-Bromo-1-methyl-3-(1-methyl-5-((methyl(oxetan-3-yl)amino)methyl)-1H-pyrazol-3-ylamino)pyridin-2(1H)-one **320d**



Following Example 136d, **320c** and 3,5-dibromo-1-methylpyridin-2(1H)-one were reacted to give **320d** in 63% yield. LCMS: $(M+H)^+$ 383. ^1H NMR (500 MHz, DMSO) δ 8.35 (s, 1H), 7.99 (d, J=2.5, 1H), 7.36 (d, J=2.5, 1H), 5.99 (s, 1H), 4.50 (t, J=7, 2H), 4.40 (t, J=6.5, 2H), 3.77 (s, 3H), 3.57 (m, 1H), 3.49 (s, 3H), 3.35 (s, 2H), 2.01 (s, 3H).

Example 320e 4-Fluoro-2-(1-methyl-5-(1-methyl-5-((methyl(oxetan-3-yl)amino)methyl)-1H-pyrazol-3-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **320e**



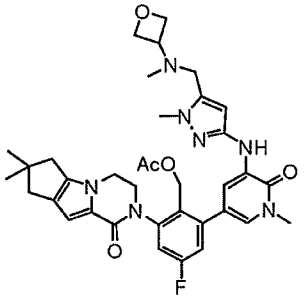
Following Example 136e, **210d** was converted to **320e** in 71% yield.

Following Example 136, **320e** was converted to **320** in 66% yield. LCMS: $(M+H)^+$ 616. ^1H NMR (500 MHz, DMSO) δ 8.07 (s, 1H), 7.97 (s, 1H), 7.30 (m, 2H), 7.17 (d, J=9.5, 1H), 6.53 (s, 1H), 6.02 (s, 1H), 4.88 (m, 1H), 4.50 (t, J=6.5, 2H), 4.40 (t, J=5.5, 2H), 4.32 (s,

2H), 4.14 (m, 3H), 3.89 (m, 1H), 3.70 (s, 3H), 3.57 (m, 4H), 2.59 (m, 2H), 2.47 (m, 2H), 2.00 (s, 3H), 1.80 (m, 2H), 1.70 (m, 2H).

Example 321 10-[5-Fluoro-2-(Hydroxymethyl)-3-{1-methyl-5-[(1- methyl-5-{[methyl(oxetan-3-yl)amino]methyl}-1H-pyrazol-3-yl)amino]-6-oxo-1,6-dihydropyridin-3-yl}phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-9-one **321**

Example 321a (2-{4,4-Dimethyl-9-oxo-1,10-diazatricyclo[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-10- yl}-4-fluoro-6-{1-methyl-5-[(1-methyl-5-{[methyl(oxetan-3-yl)amino]methyl}-1H-pyrazol-3-yl)amino]-6-oxo-1,6-dihydropyridin-3-yl}phenyl)methyl **321a**

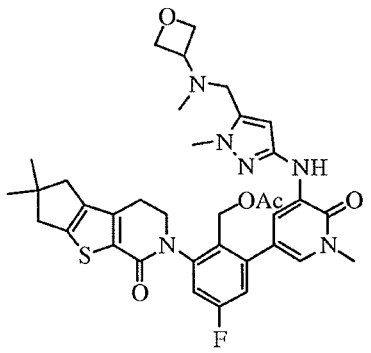


Following Example 136e, 5-bromo-1-methyl-3-(1-methyl-5-((methyl(oxetan-3-yl)amino)methyl)-1H-pyrazol-3-ylamino)pyridin-2(1H)-one **320d** and **230a** were reacted to give **321a** in 65% yield. LCMS: $(M+H)^+$ 672

Following Example 136, **321a** was converted to **321** in 59% yield. LCMS: $(M+H)^+$ 630. ^{1}H NMR (500 MHz, DMSO) δ 8.07 (s, 1H), 7.97 (d, J=2.5, 1H), 7.33 (d, J=2.5, 1H), 7.31 (d, J=3, 1H), 7.29 (d, J=2, 1H), 7.17 (dd, J=9.5, 1H), 6.51 (s, 1H), 6.02 (s, 1H), 4.89 (t, J=4.5, 1H), 4.50 (t, J=6.5, 2H), 4.40 (t, J=6, 2H), 4.33 (d, J=4.5, 2H), 4.21 (m, 2H), 4.13 (m, 1H), 3.88 (m, 1H), 3.70 (s, 3H), 3.57 (m, 4H), 2.57 (s, 2H), 2.42 (s, 2H), 2.00 (s, 3H), 1.22 (s, 6H).

Example 322 10-[5-Fluoro-2-(hydroxymethyl)-3-{1-methyl-5-[(1- methyl-5-{[methyl(oxetan-3-yl)amino]methyl}-1H-pyrazol-3-yl)amino]-6-oxo-1,6-dihydropyridin-3-yl}phenyl]-4,4-dimethyl-7-thia-10- azatricyclo[6.4.0.$0^{2,6}$]dodeca-1(8),2(6)-dien-9- one **322**

Example 322a (2-{4,4-Dimethyl-9-oxo-7-thia-10-azatricyclo[6.4.0.$0^{2,6}$]dodeca-1(8),2(6)-dien-10-yl}-4-fluoro-6-{1-methyl-5-[(1-methyl-5-{[methyl(oxetan-3-yl)amino]methyl}-1H-pyrazol-3-yl)amino]-6-oxo-1,6-dihydropyridin-3-yl}phenyl)methyl acetate **322a**



322a

A sealed tube was charged with the mixture of 5-bromo-1-methyl-3-(1-methyl-5-((methyl(oxetan-3-yl)amino)methyl)-1H-pyrazol-3-ylamino)pyridin-2(1H)-one **320d** (250 mg, 0.65 mmol), (2-{4,4-dimethyl-9-oxo-7-thia-10-azatricyclo[6.4.0.$0^{2,6}$]dodeca-1(8),2(6)-dien-10-yl}-4-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl acetate **247b** (334 mg, 0.65 mmol), $Pd(dppf)Cl_2$ (55 mg, 0.07 mmol), $K_3PO_4.3H_2O$(345 mg, 1.3 mmol), and NaOAc (105 mg, 1.3 mmol) in CH_3CN (20 mL). The system was evacuated and refilled with N_2. The reaction mixture was heated at 110°C for 2h. It was then cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography eluting with 30:1 methylene chloride/methanol to afford **322a** as a yellow solid (300 mg, 56%). MS: $[M+H]^+$ 689.

At room temperature, to a solution of **322a** (250 mg, 0.35 mol) in THF/isopropanol/water (6 mL/6 mL/2 mL) was added LiOH (70 mg, 2.9 mmol) while stirring. This mixture was stirred for 0.5 h. Then, 20 mL water was added and the mixture was extracted with ethyl acetate (30 mL X 3). The combined organic layer was dried with Na_2SO_4 and concentrated to yield a yellow solid, which was further purified by prep-HPLC to afford **322** as a white solid (94 mg, 36%). MS: $[M+H]^+$ 647. ^1H NMR (500 MHz, DMSO) δ 1.23 (s, 6 H), 2.01 (s, 3 H), 2.50-2.52 (m, 2 H), 2.76 (s, 2 H), 2.88-2.91 (m, 1 H), 3.04 (s, 1 H), 3.55-3.57 (m, 4 H), 3.70 (s, 3 H), 3.86 (t, *J*=6.0 Hz,1 H), 4.06 (d, *J*=5.5 Hz, 1 H), 4.33-4.41 (m, 4 H), 4.50 (t, *J*=6.5 Hz, 2 H), 4.88 (t, *J*=5.0 Hz, 1 H), 6.02 (s, 1 H), 7.16-7.18 (m, 1 H), 7.29-7.34 (m, 2 H), 7.97 (d, *J*=2.5 Hz, 1 H), 8.07 (s, 1 H).

Example 323 10-[2-(Hydroxymethyl)-3-(1-methyl-5-{[5-(1-methylpiperidin-4-yl)pyridin-2-yl]amino}-6-oxopyridin-3-yl)phenyl]-4,4-dimethyl-1,10-diaza-tricyclo[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-9-one **323**

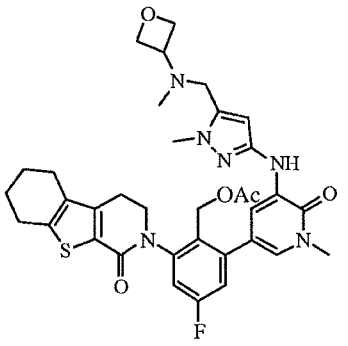
Example 323a (2-{4,4-Dimethyl-9-oxo-1,10-diazatricyclo[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-10-yl}-6-(1-methyl-5-{[5-(1-methylpiperidin-4-yl)pyridin-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl)methyl Acetate 323a

A 25 mL sealed tube was charged with 5-bromo-1-methyl-3-(5-(1-methylpiperidin-4-yl)pyridin-2-ylamino)pyridin-2(1H)-one 282c (376 mg, 1.0 mmol), (2-{4,4-dimethyl-9-oxo-1,10-diazatricyclo[6.4.0.$0^{2,6}$]dodeca-2(6),7-dien-10-yl}-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl acetate (478 mg, 1.0 mmol), CH_3COONa (168 mg, 2.0 mmol), K_3PO_4 (546 mg, 2.0 mmol), $PdCl_2$(dppf) (84 mg, 0.1 mmol) suspended in CH_3CN (25 mL) and H_2O (1 mL). The mixture was heated at 110°C for 2 hours. It was then evaporated and the residue was purified by column chromatography eluting with 15:1 methylene chloride/methanol to give 323a as a brown solid (278 mg, 43%). MS: $(M+H)^+$ 649.

A solution of 323a (200 mg, 0.3 mmol) in propan-2-ol (10 mL), tetrahydrofuran (10 mL) and water (2 mL) was added LiOH (1.1 g, 57 mmol). The mixture was stirred at 30°C for 2 h. It was then evaporated and the residue was purified by prep-HPLC to afford 323 as a white solid (41 mg, 22%). MS: $(M+H)^+$ 607. ^1H NMR (500 MHz, DMSO) δ 8.65 (s, 1H), 8.50 (s, 1H), 8.05 (s, 1H), 7.51 (m, 2H), 7.46 (m, 3H), 7.31 (d, J = 8.5, 1H), 6.50 (s, 1H), 4.83 (m, 1H), 4.39 (m, 2H), 4.13 (m, 1H), 3.85 (m, 1H), 3.59 (s, 3H), 3.03 (m, 1H), 2.91 (m, 3H), 2.84 (m, 2H), 2.64 (m, 1H), 2.46 (m, 1H), 2.17 (s, 3H), 1.80 (m, 2H), 1.60 (m, 4H),1.22 (s, 6H).

Example 324 5-[5-Fluoro-2-(hydroxymethyl)-3-{1-methyl-5-[(1- methyl-5-{[methyl(oxetan-3-yl)amino]methyl}-1H-pyrazol-3-yl)amino]-6-oxo-1,6-dihydropyridin-3-yl}phenyl]-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$]trideca-1(9),2(7)-dien-6-one 324

Example 324a (4-Fluoro-2-{1-methyl-5-[(1-methyl-5-{[methyl(oxetan-3-yl)amino]methyl}-1H-pyrazol-3-yl)amino]-6-oxo-1,6-dihydropyridin-3-yl}-6-{6-oxo-8-thia-5-azatricyclo[7.4.0.$0^{2,7}$]trideca-1(9),2(7)- dien-5-yl}phenyl)methyl Acetate 324a



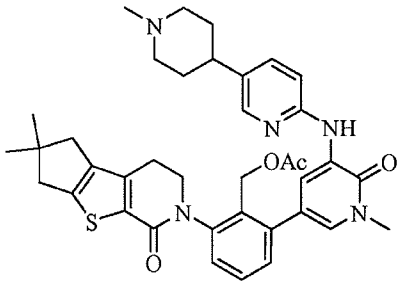
324a

A sealed tube was charged with the mixture of 5-bromo-1-methyl-3-(1-methyl-5-((methyl(oxetan-3-yl)amino)methyl)-1H-pyrazol-3-ylamino)pyridin-2(1H)-one **320d** (150 mg, 0.39 mmol), (4-fluoro-2-{6-oxo-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-dien-5-yl}-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl acetate **247b** (195 mg, 0.39 mmol), $Pd(dppf)Cl_2$ (33 mg, 0.04 mmol), $K_3PO_4.3H_2O$(207 mg, 0.78 mmol), and NaOAc (63 mg, 0.78 mmol) in CH_3CN (20 mL). The system was evacuated and refilled with N_2. The reaction mixture was heated at 110 °C for 2h. It was then cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography eluting with 30:1 methylene chloride/methanol to afford **324a** as a yellow solid (150 mg, 56%). MS: $[M+H]^+$ 675.

At room temperature, to a solution of **324a** (150 mg, 0.22mol) in THF/isopropanol/water (6 mL/6 mL/2 mL) was added LiOH (70 mg, 2.9 mmol) while stirring. This mixture was stirred for 0.5 h. Then, 20 mL H_2O was added and extracted with ethyl acetate (3 X 30 mL). The combined organic layer was dried with Na_2SO_4 and concentrated to get a yellow solid, which was further purified by prep-HPLC to afford **324** as a white solid (43 mg, 31%). MS: $[M+H]^+$ 633. ^1H NMR (500 MHz, DMSO) δ 1.75-1.80 (m, 4 H), 2.00 (s, 4 H), 2.85 (s, 4 H), 2.36 (s, 1 H), 2.64 (s, 1 H), 2.78 (s, 2 H), 2.83-2.89 (m, 1 H), 2.94-3.01 (m, 1 H), 3.58 (s, 3 H), 3.69 (s, 3 H), 3.86-3.89 (m, 1 H), 4.02-4.07 (m, 1 H), 4.32 (d, *J*=3.0 Hz, 2 H), 4.39 (t, *J*=6.5 Hz, 2H), 4.49 (t, *J*=6.5 Hz, 2 H), 4.85 (d, *J*=4.5 Hz, 1 H), 6.01 (s, 1 H), 7.15-7.18 (m, 1 H), 7.28-7.32 (m, 2 H), 7.96 (d, *J*=2.0 Hz, 1 H), 8.06 (s, 1 H).

Example 325 10-[2-(Hydroxymethyl)-3-(1-methyl-5-{[5-(1-methylpiperidin-4-yl)pyridine-2-yl]amino}-6-oxopyridin-3-yl)phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-9-one **325**

Example 325a (2-{4,4-Dimethyl-9-oxo-7-thia-10-azatricyclo[6.4.0.0^{2,6}]dodeca-1(8),2(6)-dien-10-yl}-6-(1-methyl-5-{[5-(1-methylpiperidin-4-yl)pyridin-2-yl]amino}-6-oxopyridin-3-yl)phenyl)methyl Acetate **325a**



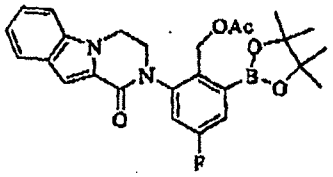
325a

A 25 mL sealed tube is charged with 5-bromo-1-methyl-3-(5-(1-methylpiperidin-4-yl)pyridine-2-ylamino)pyridin-2(1H)-one **282c** (376 mg, 1.0 mmol), (2-{4,4-dimethyl-9-oxo-7-thia-10-azatricyclo[6.4.0.0^{2,6}}]dodeca-1(8),2(6)-dien-10-yl}-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl acetate **131a** (495 mg, 1.0 mmol), CH_3COONa (168 mg, 2.0 mmol), K_3PO_4 (546 mg, 2.0 mmol), $PdCl_2(dppf)$ (84 mg, 0.1 mmol) suspended in CH_3CN (25 mL) and water (1 mL). The mixture was heated at 110°C for 2 hours. It was then evaporated and the residue was purified by column chromatography eluting with 50:1 methylene chloride/methanol to give **325a** as a brown solid (278mg, 42%). MS: $(M+H)^+$ 666.

A solution of **325a** (200 mg, 0.3 mmol) in isopropanol (10 mL), and tetrahydrofuran (10 mL) and water (2 mL) was added LiOH (1.1 g, 57 mmol). The mixture was stirred at 30°C for 2 h. It was then evaporated and the residue was purified by prep-HPLC to afford **325** as a white solid (54mg, 29%). MS: $(M+H)^+$ 624. ^1H NMR (500 MHz, DMSO) δ 8.66 (s, 1H), 8.50 (s, 1H), 8.10 (s, 1H), 7.51 (m, 2H), 7.46 (m, 3H), 7.31 (d, J = 8.5, 1H), 4.83 (m, 1H), 4.39 (m, 2H), 4.13 (m, 1H), 3.85 (m, 1H), 3.59 (s, 3H), 3.03 (m, 1H), 2.91 (m, 3H), 2.84 (m, 2H), 2.64 (m, 1H), 2.46 (m, 1H), 2.23 (s, 3H), 1.80 (m, 2H), 1.66 (m, 4H),1.20 (s, 6H).

Example 326 2-(5-Fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one **326**

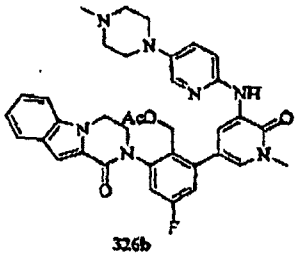
Example 326a 4-Fluoro-2-(1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl Acetate **326a**



326a

Following Examples 102c and 102d, **326a** was prepared.

Example 326b 4-fluoro-2-(1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **326b**



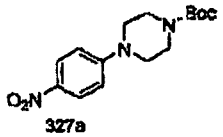
326b

Following Example 148h, 478 mg of **326a** and 378 mg 5-bromo-1-methyl-3-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)pyridin-2(1H)-one **197d** were reacted to give **326b** was obtained as a yellow solid (324 mg, 50%). MS: $[M+H]^+$ 650

Following Example 148, 260 mg of **326b** was converted to **326** as a white solid (100 mg, 41%). MS: $[M+H]^+$ 607. ^1H NMR (500 MHz, DMSO) δ 8.58 (d, J=2.0, 1H), 8.39 (s, 1H), 7.87 (d, J=3.0, 1H), 7.73 (d, J=8.0, 1H), 7.63 (d, J=8.0, 1H), 7.46 (dd, J=9.0, 1H), 7.36(m, 3H), 7.23 (m, 2H), 7.17 (m, 2H), 4.99 (d, J=4.5, 1H), 4.65(m, 1H), 4.50 (m, 1H), 4.38 (s, 2H), 4.29 (m, 1H), 4.10 (m,1H), 3.59 (s, 3H), 3.04 (t, J=4.0, 4H), 4.36 (t, J=4.0, 4H), 2.20 (s, 3H).

Example 327 2-(5-Fluoro-2-(hydroxymethyl)-3-(4-methyl-6-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenylamino)-5-oxo-4,5-dihydropyrazin-2-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **327**

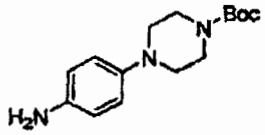
Example 327a *tert*-Butyl 4-(4-Nitrophenyl)piperazine-1-carboxylate **327a**



327a

Following Example 188a, 1-fluoro-4-nitrobenzene (2.8 g, 20 mmol) and N-Boc-piperazine (11 g, 60 mmol) were reacted to give 327a as a yellow solid (3 g, 51%). MS: $[M+H]^+$ 308.

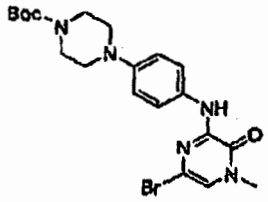
Example 327b *tert*-Butyl 4-(4-Aminophenyl)piperazine-1-carboxylate 327b



327b

Following Example 188b, 327a was reduced to 327b as a yellow solid (1.35 g, 99%). MS: $[M+H]^+$ 278.

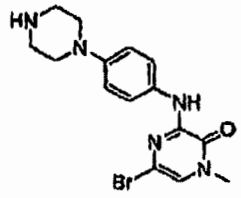
Example 327c *tert*-Butyl 4-(4-(6-Bromo-4-methyl-3-oxo-3,4-dihydropyrazin-2-ylamino)phenyl)piperazine-1-carboxylate 327c



327c

Following Example 188c, 327b (2.6 g, 9.4 mmol) and 3,5-dibromo-1-methylpyrazin-2(1H)-one (2.5 g, 9.4mmol) were reacted to give 327c as a yellow solid (2.96 g, 68%). MS: $[M+H]^+$ 464.

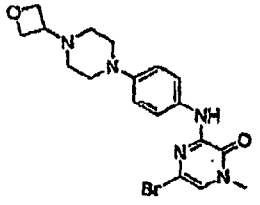
Example 327d 5-Bromo-1-methyl-3-(4-(piperazin-1-yl)phenylamino)pyrazin-2(1H)-one 327d



327d

Following Example 188d, 327c was deprotected to give 327d as a yellow solid (1.57 g, 99%). MS: $[M+H]^+$ 364.

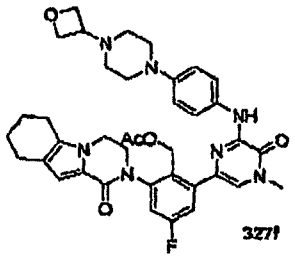
Example 327e 5-Bromo-1-methyl-3-(4-(4-(oxetan-3-yl)piperazin-1yl)phenyl-amino)pyrazin-2(1H)-one 327e



327e

Following Example 188e, 1.2 g (3 mmol) of 327d was converted to 327e as a yellow solid (943 mg, 75%). MS: $[M+H]^+$ 420.

Example 327f 4-Fluoro-2-(4-methyl-6-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenylamino)-5-oxo-4,5-dihydropyrazin-2-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate 327f



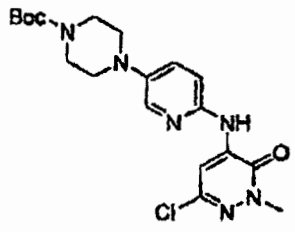
327f

Following Example 148b, 300 mg of 4-fluoro-2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate 210d and 287 mg of 327e were reacted to give 327f as a yellow solid (220 mg, 51%). LCMS: $[M+H]^+$ 696

Following Example 148, 220 mg of 327f was converted to 327 as a white solid (87 mg, 42%). ^{1}H NMR (500 MHz, DMSO) δ 9.11 (s, 1H), 7.81 (d, J=8.5, 1H), 7.43 (s, 1H), 7.35 (t, J= 7.0, 1H), 7.29 (d, J=9.0, 1H), 6.88 (d, J=8.5, 2H), 6.53 (s, 1H), 4.86 (s, 1H), 4.56 (t, J=6.5, 2H), 4.67 (d, t=5.5, 3H), 4.42(m, 1H), 4.11 (m, 3H), 3.89 (m, 1H), 3.53 (s, 3H), 3.43 (s, 1H), 3.10 (t, J=4.5, 4H), 2.62 (m, 2H), 2.46 (m, 2H), 2.39 (t, J=4.5, 4H), 1.79 (s, 2H), 1.70 (s, 2H).

Example 328 2-(5-Fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one 328

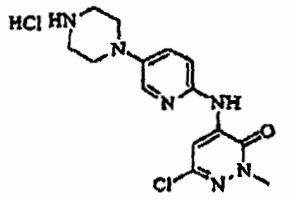
Example 328a 4-(6-(6-Chloro-2-methyl-3-oxo-2,3-dihydropyridazin-4-yl-amino)pyridin-3-yl)piperazine-1-carboxylate 328a



328a

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was charged with 1,4-dioxane (50 mL), tert-butyl 4-(6-aminopyridin-3-yl)piperazine-1-carboxylate **188b** (2.0 g, 7.2 mmol), 4-bromo-6-chloro-2-methyl-pyridin-3(2H)-one (1.6 g, 7.2 mmol) and cesium carbonate (4.7 g, 14.4 mmol). After bubbling nitrogen through the resulting mixture for 30 minutes, XantPhos (500 mg, 0.9 mmol) and tris(dibenzylideneacetone)dipalladium(0) (450 mg, 0.45 mmol) was added, and the reaction mixture was heated at reflux for 3 h. After this time the reaction was cooled to room temperature, partitioned between ethyl acetate (100 mL) and water (100 mL), and filtered. The aqueous layer was separated and extracted with ethyl acetate (50 mL × 2). The organic layers were combined, washed with brine (50 mL), and dried over sodium sulfate. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified on flash column eluting with petroleum ether/ethyl acetate to afford **328a** (1.4 g, 43%). MS: $[M+H]^+$ 421

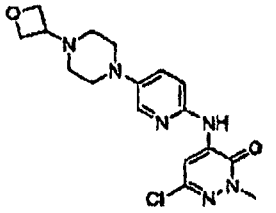
Example 328b 6-Chloro-2-methyl-4-(5-(piperazin-1-yl)pyridin-2-ylamino)pyridazin-3(2H)-one Hydrochloride **328b**



328b

Intermediate **328a** (1.4 g, 3.3 mmol) was suspended in 4.0 M HCl/dioxane (10 mL). The reaction mixture was stirred at room temperature for 2 h and concentrated under reduced pressure to give **328b** (1.1 g, 96%). MS: $[M+H]^+$ 321.

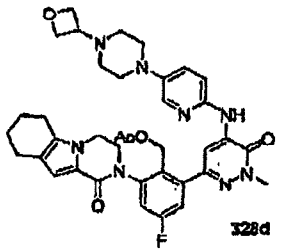
Example 328c 6-Chloro-2-methyl-4-(5-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-2-ylamino)pyridazin-3(2H)-one **328c**



328c

A mixture of **328b** (1.2 g, 3.5 mmol), oxetan-3-one (0.5 g, 7.0 mmol), $NaBH_3CN$ (0.44 g, 7.0 mmol) and zinc chloride (0.93 g, 7.0 mmol) in methanol (125 ml) was stirred at 50 degree for 3.5 hours. The mixture was added to water and extracted with methylene chloride. The organic layers were combined and concentrated under reduced pressure. The residue was purified by column chromatography eluting with 25:1 methylene chloride/methanol to give **328c** (0.63 g, 50%). MS: $[M+H]^+$ 377.

Example 328d 4-Fluoro-2-(1-methyl-5-(5-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridazin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **328d**



328d

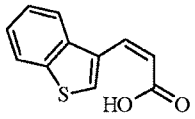
A sealed tube was charged with the mixture of 4-fluoro-2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **210d** (420 mg, 0.9 mmol), **328c** (300 mg, 0.78 mmol), $Pd(dppf)Cl_2$ (66 mg, 0.078 mmol), $K_3PO_4.3H_2O$(360 mg, 1.56 mmol), and NaOAc (130 mg, 1.56 mmol) in CH_3CN(20ml). The system was evacuated and then refilled with N_2. And the reaction mixture was heated at 110°C for 2h. Then, the mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography eluting with 30:1 methylene chloride/methanol to afford **328d** as a yellow solid (400 mg, 72%). MS: $[M+H]^+$ 696.

To the solution of **328d** (350 mg, 0.5 mol) in THF/iPA/H_2O (6ml/6ml/2ml) was added LiOH (600 mg, 25 mmol) while stirring at room temperature. And this mixture was stirred for 0.5 h. Then, 20 mL water was added and resulting mixture was extracted with ethyl

acetate (30mL x 3). The combined organic layer was dried with Na_2SO_4 and concentrated to give a yellow solid, which was further purified by prep-HPLC to afford **328** as a white solid (100 mg, 27%). ^{1}H NMR (500 MHz, DMSO) δ 9.25 (s, 1 H), 8.41 (s, 1 H), 7.97 (d, *J*=3.5 Hz, 1 H), 7.39-7.45 (m, 3 H) , 7.25-7.28 (m, 1 H), 6.52(s, 2 H), 4.66(t, *J*=5.0 Hz, 2 H), 4.55 (t, *J*=6.5 Hz, 2 H), 4.41-4.46 (m, 3 H), 4.31-4.34 (m, 1 H), 4.11-4.18 (m, 3 H), 3.85-3.87 (m, 1 H), 3.77 (s, 3 H), 3.43 (t, *J*=6.5 Hz, 1 H), 3.12 (t, *J*=5.0 Hz, 4 H), 2.54-2.63 (m, 2 H), 2.46 (t, *J*=6.0 Hz, 2 H), 2.39 (t, *J*=5.0 Hz, 4 H), 1.79 (t, *J*=5.5 Hz, 2 H),1.69 (s, 2 H).

Example 329 5-[5-Fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[5-(4-methylpiperazin-1-yl)pyridin-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7),10,12- tetraen-6-one **329**

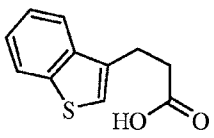
Example 329a (2Z)-3-(1-Benzothiophen-3-yl)prop-2-enoic Acid **329a**



329a

A suspension of benzo[b]thiophene-3-carbaldehyde (4.9 g, 30 mol), malonic acid (6.6 g, 60 mmol) and piperidine (1 mL) in 100 mL anhydrous pyridine was heated at 110°C for overnight. The reaction mixture was cooled to room temperature and the solvent was removed in *vacuo*. The residue was taken up in 100 mL of water and 1 N hydrochloric acid was added to adjust the pH of this solution to ca. 3. The resulting suspension was filtered and the yellow solid was collected, washed with water (3 x 30 mL) dried in *vacuo* to give **329a** as a yellow solid (5.5 g, 89%). MS: $[M+H]^+$ 205.

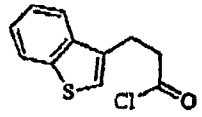
Example 329b 3-(1-Benzothiophen-3-yl)propanoic Acid **329b**



329b

A suspension of **329a** (5.5 g, 27 mmol) and 10% Pd/C (600 mg) in 1:1 methanol/ethyl acetate (100 mL) was hydrogenated in a Parr apparatus at 50 psi for overnight. The mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to give crude **329b** as a brown solid (5.0 g, 90%), which was used without further purification for the next step. MS: $[M+H]^+$ 207. ^{1}H NMR (500 MHz, CDCl3) δ 2.81-2.84 (t, J=8.5, 2H), 3.18-3.21 (m, 2H), 7.16 (s, 1H), 7.34-7.41 (m, 2H), 7.74-7.76(d, 1H), 7.85-7.87 (d, 1H).

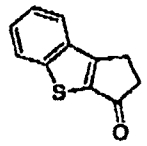
Example 329c 3-(1-Benzothiophen-3-yl)propanoyl Chloride 329c



329c

Intermediate 329b (5.0 g, 24 mmol) in sulfurous dichloride (15 mL) was heated at 100 °C for 4 hours. The mixture was cooled to room temperature and the solvent was evaporated *in vacuo*. 30 mL methylene chloride was added to the residue and the resulting mixture was evaporated under reduced pressure to give 329c as a brown solid (5.3 g, 97%), which was used without further purification for the next step. MS: $[M+H]^+$ 225.

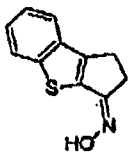
Example 329d 7-Thiatricyclo[6.4.0.$0^{2,6}$]dodeca-1(8),2(6),9,11- tetraen-5-one 329d



329d

To 329c (5.0 g, 22.3 mmol) in methylene chloride (50 mL) was added anhydrous aluminum trichloride (5.9 g, 44.6 mmol). The mixture was stirred at room temperature for overnight. The reaction solution was evaporated in *vacuo* and the residue was purified by column chromatography eluting with 20:1 methylene chloride/methanol to give 329d as a yellow solid (2.3 g, 55%). MS: $[M+H]^+$ 189. ^1H NMR (500 MHz, CDCl3) δ 3.05-3.07 (m, 2H), 3.21-3.23 (m, 2H), 7.45-7.52 (m, 2H), 7.88-7.91 (m, 2H).

Example 329e N-[(5Z)-7-Thiatricyclo[6.4.0.$0^{2,6}$]dodeca- 1(8),2(6),9,11-tetraen-5-ylidene]hydroxylamine 329e

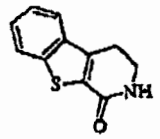


329e

To a solution of $NH_2OH.HCl$ (18.4 g, 266 mmol) in MeOH (600 mL) at 0°C was slowly added CH_3COONa (21.8 g, 266 mmol). After stirring at 0°C for 30 min, 329d (10 g, 53 mmol) was added. The reaction solution was allowed to warm to room temperature and stirred for overnight. It was then evaporated *in vacuo*. 100 mL of water was added to the

residue and the resulting mixture was extracted with ethyl acetate (500 mL × 3). The organic layers were combined, washed with brine (50 mL), and dried over sodium sulfate. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure to give **329e** as a yellow solid (10 g, 92%). MS: $[M+H]^+$ 203.

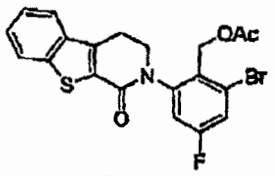
Example 329f 8-Thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7),10,12-tetraen-6-one **329f**



329f

A solution of **329e** (5 g, 25 mmol) in PPA (80 mL) was stirred at 150°C in an oil bath for overnight. The reaction was cooled to room temperature and diluted with 150 mL of water/ice. The solid was collected by filtration, washed with 3 X 50 mL of water and dried in a vacuum oven under reduced pressure to afford the crude product, which was further purified by column chromatography eluting with 1:1 ethyl acetate/petroleum ether to give **329f** as a yellow solid (3 g, 60%).MS: $[M+H]^+$ 204

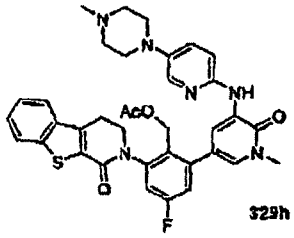
Example 329g (2-Bromo-4-fluoro-6-{6-oxo-8-thia-5-azatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7),10,12- tetraen-5-yl}phenyl)methyl Acetate **329g**



329g

A mixture of **329f** (700 mg, 3.4 mmol), **197c** (3.35g, 10.2 mmol), XantPhos (200 mg, 0.34 mmol), $Pd_2(dba)_3$ (316 mg, 0.34 mmol) and Cs_2CO_3 (2.25 g, 6.8 mmol) in dioxane (50 mL) was heated at 100°C for 15 h under argon atmosphere. It was then filtered and evaporated in *vacuo*. The residue was purified by column chromatography eluting with 1:3 ethyl acetate/petroleum ether to give **329g** as a white solid (500 mg, 33%). MS: $[M+H]^+$ 448.

Example 329h [4-Fluoro-2-(1-methyl-5-{[5-(4-methylpiperazin-1- yl)pyridin-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)-6-{6-oxo-8-thia-5azatricyclo[7.4.0.0^{2,7}]-trideca-1(9),2(7),10,12- tetraen-5-yl}phenyl]methyl **329h**



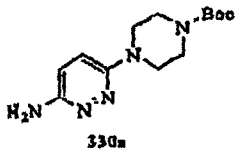
329h

A sealed tube was charged with the mixture of 329g (300 mg, 0.66 mmol), 1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-ylboronic acid 197f (690 mg, 1.32 mmol), $Pd(dppf)Cl_2$ (54 mg, 0.066 mmol), and Na_2CO_3 (141 mg, 1.32 mmol) in DMF (22 mL). The system was evacuated and then refilled with N_2. And the reaction mixture was heated at 130°C in microwave for 1 h. Then, the mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and the resulting residue was purified by column chromatography eluting with 15:1 methylene chloride/methanol to give 329h as a brown solid (300 mg, 67%). MS: $[M+H]^+$ 667.

At room temperature, to a solution of 329h (250 mg, 0.38mol) in THF/isopropanol/water (10 mL/10 mL/2 mL) was added LiOH (90 mg, 38 mmol) while stirring. This mixture was stirred for 2 h. Then, 20 mL water was added and resulting mixture was extracted with ethyl acetate (30 mL X 3). The combined organic layer was dried with Na_2SO_4 and concentrated to give a yellow solid, which was further purified by prep-HPLC to afford 329 as a brown solid (37 mg, 16%). MS: $[M+H]^+$ 625. ^1H NMR (500 MHz, MEOD) δ 1.31 (s, 3H), 2.39 (s, 4H), 2.65-2.69 (m, 4H), 3.30-3.33 (m, 2H), 3.68 (s, 3H), 4.11-4.16 (m, 1H), 4.24-4.30 (m, 1H), 4.50-4.56 (m, 2H), 6.99 (d, 1H), 7.20 (d, 1H), 7.22 (d, 1 H), 7.30 (s, 1H), 7.36-7.38 (m, 1H), 7.47-7.54 (m, 2H), 7.89-7.95 (m, 2H), 7.97 (d, 1H), 8.53 (s, 1H).

Example 330 2-(5-Fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(6-(4-(oxetan-3-yl)piperazin-1-yl)pyridazin-3-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one 330

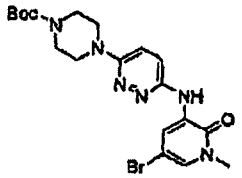
Example 330a *tert*-Butyl 4-(6-Aminopyridazin-3-yl)piperazine-1-carboxylate 330a



330a

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer was charged with 6-chloropyridazin-3-amine (2.58 g, 20 mmol) and N-Boc-piperazine (22.3 g, 120 mmol). The reaction mixture was heated at 140°C and stirred for 2 h. It was then cooled to room temperature and the resulting solid was washed with ethyl acetate (100mL), and the resulting residue was purified by flash column chromatography eluting with 30:1 methylene chloride/methanol to afford **330a** as a yellow solid (3.5 g, 60%). MS: $[M+H]^+$ 280.

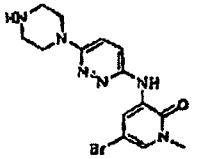
Example 330b *tert*-Butyl 4-(6-(5-Bromo-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)pyridazin-3-yl)piperazine-1-carboxylate **330b**



330b

Following Example 188c, 3,5-dibromo-1-methylpyridin-2(1H)-one (536 mg, 2.0 mmol) and **330a** (558 mg, 2.0 mmol) were reacted to give **330b** as a yellow solid (560 mg, 60%). MS: $[M+H]^+$ 467

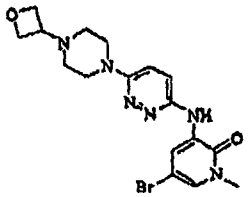
Example 330c 5-Bromo-1-methyl-3-(6-(piperazin-1-yl)pyridazin-3-ylamino)pyridin-2(1H)-one **330c**



330c

Following Example 188d, 560 mg (1.2 mmol) of **330b** was deprotected to give **330c** as a yellow solid (440 mg, 99%). MS: $[M+H]^+$ 367

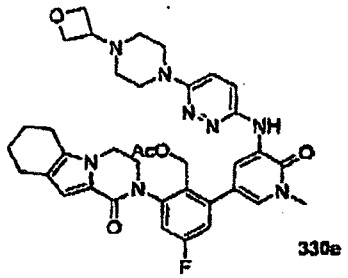
Example 330d 5-Bromo-1-methyl-3-(6-(4-(oxetan-3-yl)piperazin-1-yl)pyridazin-3-ylamino)pyridin-2(1H)-one **330d**



330d

Following Example 210a, 400 mg (1.1 mmol) of **330c** was converted to **330d** as a yellow solid (312 mg, 68%). MS: $[M+H]^+$ 421

Example 330e 4-Fluoro-2-(1-methyl-5-(6-(4-(oxetan-3-yl)piperazin-1-yl)pyridazin-3-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **330e**



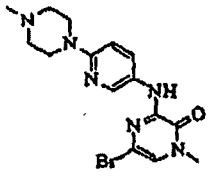
330e

Following Example 210a, 207 mg of 4-fluoro-2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **210d** (0.43 mmol) and 180 mg of **330d** (0.43 mmol) were reacted to give **330e** as a yellow solid (156 mg, 51%). MS: $[M+H]^+$ 697.

Following Example 210, **330e** (150 mg 0.22 mmol) was hydrolyzed to give **330** as a yellow solid (60 mg, 42%). LCMS: $[M+H]^+$ 655. ^1H NMR (500 MHz, CDCl3) δ 8.67 (d, J=2.5, 1H), 7.77 (s, 1H), 7.48 (d, J=2.0, 1H), 7.12 (dd, J= 8.5, 1H), 6.98 (m, 3H), 6.86(s, 1H), 4.69 (m, 4H), 4.51(d, J=11, 1H), 4.20 (m, 5H), 3.86 (m, 1H), 3.71 (s, 3H), 3.56 (m, 5H), 2.60 (m, 4H), 2.47 (m, 4H), 1.90 (s, 2H), 1.80 (s, 2H).

Example 331 2-(5-Fluoro-2-(hydroxymethyl)-3-(4-methyl-6-(6-(4-methyl piperazin-1-yl)pyridine-3-ylamino)-5-oxo-4,5-dihydropyrazin-2-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H) **331**

Example 331a 5-Bromo-1-methyl-3-(6-(4-methylpiperazin-1-yl)pyridine-3-ylamino) pyrazin-2(1H)-one **331a**

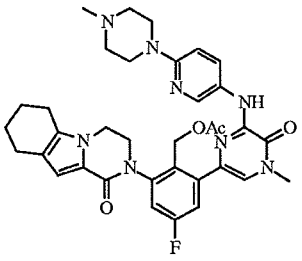


331a

A mixture of 6-(4-methylpiperazin-1-yl)pyridin-3-amine (1 g, 5.2 mmol) prepared according to US 2009/0318448, 3,5-dibromo-1-methylpyrazin-2(1H)-one (1.7 g, 6.2 mmol),

and isopropanol (20 mL) was stirred at reflux for 16 h. After the reaction was completed, the solvent was removed to give **331a** as a brown solid (500 mg, 30%). MS: $[M+H]^+$ 379.

Example 331b 4-Fluoro-2-(4-methyl-6-(6-(4-methylpiperazin-1-yl)pyridin-3-ylamino)-5-oxo-4,5-dihydropyrazin-2-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **331b**



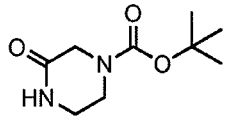
331b

A sealed tube was charged with the mixture of **331a** (400 mg, 1 mmol), 4-fluoro-2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **210d** (578 mg, 1.2 mmol), $Pd(dppf)Cl_2$ (82 mg, 0.1 mmol), $K_3PO_4.3H_2O$(760 mg, 2 mmol), and NaOAc (164 mg, 2 mmol) in CH_3CN (10 mL). The system was evacuated and then refilled with N_2 and the reaction mixture was heated at 110°C for 2 h. The mixture was then cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography eluting with 50:1 methylene chloride/methanol to afford **331b** as a yellow solid (100 mg, 14%). MS: $[M+H]^+$ 655.

To the solution of **331b** (100 mg, 0.15mmol) in THF/isopropanol/water (2 mL/2 mL/1 mL) was added LiOH (15 mg, 0.75 mmol). The reaction mixture was stirred at 30 °C for 1 h. Then, 20 mL water was added and the mixture was extracted with ethyl acetate (90 mL × 3). The combined organic layer was dried with Na_2SO_4 and concentrated to give yellow solid, which was purified by prep-HPLC to give **331** as a yellow solid (42 mg, 45%). MS: $[M+H]^+$ 613. ^1H NMR (500 MHz, DMSO) δ 9.26 (s, 1H), 8.67 (d, J = 2.5, 1H), 8.35 (q, J = 2.5, 1H), 7.44 (s, 1H), 7.32 (m, 2H), 6.82-6.80 (d, J = 9, 1H), 6.52 (s, 1H), 4.46-4.36 (m, 2H), 4.16-4.09 (m, 3H), 3.88-3.87 (m, 1H), 3.52 (s, 3H), 3.40-3.34 (m, 5H), 2.60-2.57 (m, 2H), 2.51-2.45 (m, 2H), 2.39-2.37 (m, 4H), 2.20 (s, 3H), 1.79-1.69 (m, 4H).

Example 332 2-(5-Fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(4-methyl-2-oxopiperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **332**

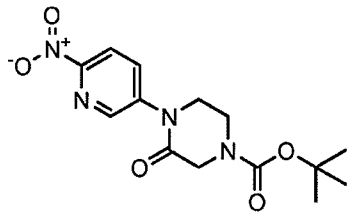
Example 332a *tert*-Butyl 3-Oxopiperazine-1-carboxylate **332a**



332a

To a dry 100 mL one necked round bottom flask equipped with a stirring bar was added piperazin-2-one (5.0 g, 50 mmol), anhydrous dichloromethane (60 mL), and Et_3N (3.2 mL, 22.5 mmol) and the reaction mixture was stirred for 1 h at room temperature. The organic layer was concentrated under reduced pressure to afford **332a** (10 g, 99%).

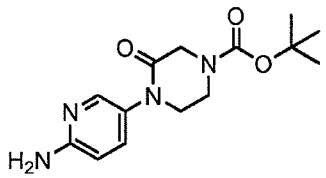
Example 332b *tert*-Butyl 4-(6-Nitropyridin-3-yl)-3-oxopiperazine-1-carboxylate **332b**



332b

A microwave vial was charged with **332a** (1.5 g, 7.5 mmol) in 30 mL of anhydrous 1,4-dioxane, 5-bromo-2-nitropyridine (1.27 g, 6.25 mmol), diacetoxypalladium (71.8 mg, 0.32 mmol), Xantphos (278 mg, 0.48 mmol), and Cs_2CO_3 (2.04 g, 6.25 mmol). After three cycles of vacuum/argon flash, it was heated at 120 °C under microwave irradiation for 1.5 h. The reaction mixture was filtered and the filtrate was evaporated in vacuum. The residue was purified by silica gel-column chromatography eluting with 3:1 petroleum ether/ethyl acetate to afford **332b** as a yellow solid (1.1 g, 54%). MS: $[M+H]^+$ 323. ^1H NMR (500 MHz, $CDCl_3$) δ 8.68 (d, J = 2.5 Hz, 1H), 8.31 (d, J = 9 Hz, 1H), 8.15 (m, 1H), 4.33 (s, 2H), 3.91 (m, 4H).

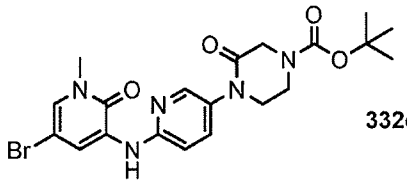
Example 332c *tert*-Butyl 4-(6-Aminopyridin-3-yl)-3-oxopiperazine-1-carboxylate **332c**



332c

To a solution of **332b** (1.1 g, 3.4 mmol) in methanol (20 mL) was added Pd/C (10%) (250 mg). After three cycles of vacuum/H_2 flash, the mixture was stirred under H_2 at room temperature for 10 h. The mixture was filtered and the filtrate was evaporated in *vacuo* to afford **332c** (946 mg, 95%), which was used for the next step without further purification. MS: $[M+H]^+$ 293.

Example 332d *tert*-Butyl 4-(6-(5-Bromo-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino) pyridin-3-yl)-3-oxopiperazine-1-carboxylate **332d**



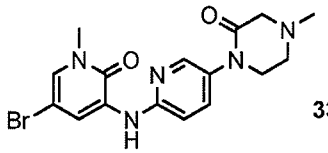
332d

A reaction vessel was charged with **332c** (946 mg, 3.2 mmol) in 40 mL of anhydrous 1,4-dioxane, 3,5-dibromo-1-methylpyridin-2(1H)-one (1.11 g, 4.2 mmol), tris(dibenzylideneacetone)dipalladium(0) (146 mg, 0.16 mmol), Xantphos (185 mg, 0.32 mmol), and Cs_2CO_3 (2.6 g, 8.0 mmol). After three cycles of vacuum/Argon flash, it was stirred at 110 °C for 4 h. The reaction mixture was filtered and the filtrate was evaporated in vacuum. The crude was purified by silica-gel column chromatography eluting with 50:1 methylene chloride/methanol to afford **332d** as a yellow solid (706 mg, 46%). MS: $[M+H]^+$ 479.

Example 332e 1-(6-(5-Bromo-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)pyridin-3-yl) piperazin-2-one **332e**

A 50-mL round-bottomed flask equipped with a magnetic stirrer and reflux condenser was charged with HCl in 1,4-dioxane (20 mL) and **332d** (706 mg, 1.47mmol). The mixture was stirred for at 65°C for 6 h. It was then concentrated under reduced pressure to afford **332e** as a yellow solid (500 mg, 90%). MS: $[M+H]^+$ 379.

Example 332f 1-(6-(5-Bromo-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)pyridin-3-yl)-4- methylpiperazin-2-one **332f**



332f

To a solution of 1-(6-(5-bromo-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino) pyridin-3-yl)piperazin-2-one (**332e**) (500 mg, 1.32 mmol) in methanol (20 mL) was added $Na(OAc)_3BH$ (2.0 g , 13.2 mmol), formaldehyde (30% aq., 8 mL), and acetic acid (2.7 mL, 45 mmol). The mixture was stirred for 4 h. The pH of the reaction mixture was adjust to 11~13 by adding NaOH (1M). It was then extracted with methylene chloride three times. The combined organic exact was dried over anhydrous Na_2SO_4, filtered, and evaporated in *vacuo*. The residue was purified by silica-gel column eluting with 50:1 methylene chloride/methanol to afford **332f** as a gray solid (312 mg, 60%). MS: $[M+H]^+$ 393. ^1H NMR (500 MHz, $CDCl_3$) δ 8.61 (d, J = 2.5 Hz, 1H), 8.17 (d, J = 2.5 Hz, 1H), 7.88 (s, 1H), 7.45 (dd, J = 9 Hz, 1H),

6.92 (d, J = 2.5 Hz, 1H), 6.74 (d, J = 9 Hz, 1H), 3.64 (m, 2H), 3.53 (s, 3H), 3.22 (s, 2H), 2.74 (m, 2H), 2.35 (s, 3H).

Example 332g 4-Fluoro-2-(1-methyl-5-(5-(4-methyl-2-oxopiperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl acetate **332g**

A reaction vessel was charged with the mixture of 1-(6-(5-bromo-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)pyridin-3-yl)-4-methylpiperazin-2-one (**332f**) (0.3 g, 0.76 mmol),4-fluoro-2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **210d** (0.37 g, 0.76 mmol), $PdCl_2$(dppf) (65 mg, 0.076 mmol), K_3PO_4 (325 mg, 1.53 mmol), and NaOAc (125 mg, 1.53 mmol) in MeCN (15 mL) and water (1 mL). It was then bubbled with argon for 15 min and heated at 110°C for 3 h. After evaporation of solvent in *vacuo*, the residue was purified on silica-gel column eluting with 50:1 methylene chloride/methanol to afford **332g** (0.4 g, 63%). MS: $[M+H]^+$ 668.

A mixture of **332g** (350 mg, 0.52 mmol) and LiOH hydrate (1.1 g, 26 mmol) in isopropanol (3 mL), THF (3 mL) and water (3 mL) was stirred at 30°C for 1 h. The mixture was evaporated in *vacuo*, and the residue was extracted with methylene chloride (30 mL × 3). The combined extracts were concentrated under reduced pressure and the residue was purified on silica gel column eluting with 50:1 methylene chloride/methanol to afford **332** as a yellow solid (120 mg, 32%). MS: $[M+H]^+$ 626. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (d, J = 2 Hz, 1H), 8.17 (d, J = 2.5 Hz, 1H), 7.58 (dd, J = 8.5 Hz, 1H), 7.42 (d, J = 2.5 Hz, 1H), 7.23 (s, 1H), 7.21 (s, 1H), 7.12 (d, J = 9 Hz, 1H), 6.73 (s, 1H), 4.53 (m, 2H), 4.22 (s, 2H), 4.03 (m, 1H), 3.73 (s, 4H), 3.27 (s, 2H), 2.87 (m, 2H), 2.65 (m, 1H), 2.55 (m, 2H), 2.43 (s, 3H), 1.89 (m, 2H), 1.79 (m, 2H).

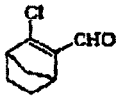
Example 333 2-(5-Fluoro-2-(methoxymethyl)-3-(1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **333**

To a solution of 2-(5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **197** (200 mg, 0.33 mmol) and K_2CO_3(135 mg, 0.99 mmol) in DMF(30 mL) was added the solution of iodomethane (70 mg, 0.50 mmol) in DMF(5 mL) at room temperature. The reaction mixture was stirred for 1 h. It was then filtered and the residue was purified by prep-HPLC to afford **333** as a yellow solid (165 mg, 80%). MS: $[M+H]^+$ 626. ^{1}H NMR (500 MHz, DMSO) δ 8.59 (d, J=2.0, 1H), 8.49 (s, 1H),

7.97 (d, J=2.0, 1H), 7.44 (s, 1H), 7.39 (s, 1H), 7.32 (m, 2H), 7.17 (m, 1H),6.52 (s, 1H), 4.31 (s, 2H), 4.14 (m, 3H), 3.88 (s, 1H), 3.56 (s, 3H), 3.54 (s, 4H), 3.44 (s, 4H), 3.12 (s, 6H), 2.58 (m, 2H), 2.46 (s,2H), 1.79 (s, 2H), 1.68 (s, 2H).

Example 334 {4-Fluoro-2-[1-methyl-5-({5-[4-(oxetan-3- yl)piperazin-1-yl]pyridin-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]-6-{7-oxo-3,6-diazatetracyclo[9.2.1.$0^{2,10}$.$0^{3,8}$]tetradeca-2(10),8-dien-6-yl}phenyl}methyl Acetate 334

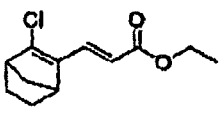
Example 334a 3-Chlorobicyclo[2.2.1]hept-2-ene-2-carbaldehyde 334a



334a

A 250-mL three-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was purged with nitrogen and charged with anhydrous 1,2-dichloroethane (24 mL) and anhydrous DMF (9.12 g, 125 mmol). The reaction mixture was cooled to 0°C, and phosphorus oxychloride (15.3 g, 100 mmol) was added over a period of 5 minutes, while maintaining the reaction temperature between 0 and 10°C. The cooling bath was removed, and the reaction was stirred at room temperature for 30 minutes. A solution of bicyclo[2.2.1]heptan-2-one (5.50 g, 50.0 mmol) in 1,2-dichloroethane (10 mL) was added and the resulting mixture was heated at 80°C for overnight. After this time, the reaction was poured into a solution of potassium monohydrogenphosphate (43.5 g, 250 mmol) in water (200 mL) and stirred for 15 minutes. The organic layer was separated and concentrated under reduced pressure. The residue was dissolved in methylene chloride (300 mL) and washed with water (2 x 50 mL). The methylene chloride layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure.The residue was purified by column chromatography eluting with 1:100 ethyl acetate/petroleum ether to give 334a as a yellow oil (2.2 g, 28%). MS: $[M+H]^+$ 157. ^{1}H NMR (500 MHz, CDCl3) δ 9.80 (s, 1H), 3.42 (s, 1H), 3.07 (d, J= 1.7 Hz, 1H,), 1.95-1.77 (m, 2H), 1.67 (t, J = 8.9Hz, 1H), 1.41-1.17 (m, 3H).

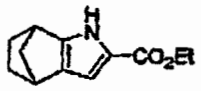
Example 334b (E)-Ethyl 3-(3-Chlorobicyclo[2.2.1]hept-2-en-2-yl)acrylate 334b



334b

To a solution of 334a (9.0 g, 57.7 mmol) in methylene chloride (250 mL) was added ethyl 2-(triphenyl- λ^5-phosphanylidene)acetate (20 g, 57.7 mmol). The mixture was stirred at room temperature for overnight. After reaction the reaction solution was evaporated in *vacuo*. The residue was purified by column chromatography eluting with 1:100 ethyl acetate/petroleum ether to give 334b as a yellow oil (6.0 g, 46%). MS: $[M+H]^+$ 227.

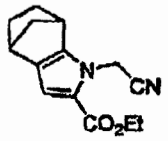
Example 334c Ethyl 3-Azatricyclo[5.2.1.$0^{2,6}$]deca-2(6),4- diene-4-carboxylate 334c



334c

To a solution of 334b (5.0 g, 22 mmol) in DMSO (30 mL) was added NaN_3 (2.2 g, 33 mmol) and the mixture was heated at 105°C for 6 hours. Water (13 mL) was added to reaction the mixture after cooling down to room temperature, and resulting mixture was extracted with methylene chloride (50 mL × 3). The organic phase was dried (Na_2SO_4) and evaporated to dryness. The residue was purified by column chromatography eluting with 20:1 methylene chloride/methanol to give 334c as a brown solid (2.7 g, 60%). MS: $[M+H]^+$ 206. ^1H NMR (500 MHz, CDCl3) δ 11.51 (s, 1H), 6.45 (dd, 1H), 4.14-4.19 (m, 2H,), 3.25 (d, 2H,), 1.79-1.82 (m, 2H), 1.73 (d, 1H), 1.22-1.25 (t, J=6.5, 3H), 0.89-0.91 (m, 2H).

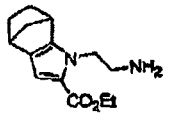
Example 334d Ethyl 3-(Cyanomethyl)-3-azatricyclo[5.2.1.$0^{2,6}$]deca-2(6),4-diene-4- carboxylate 334d



334d

To a solution of 334c (3.0 g, 14.6 mmol) in anhydrous DMF (30 mL) was added NaH (880 mg, 22 mmol). The mixture was stirred at room temperature for 30 minutes. 2-Bromoacetonitrile (3.5 g, 29.3 mmol) was added and the resulting mixture was heated at 65°C for 1 hour. It was then cooled to room temperature and stirred for overnight. After reaction water (30 mL) was added and the reaction mixture was extracted with ethyl acetate (3 X 200 mL). The organic phase was evaporated to dryness. The residue was purified by column chromatography eluting with 20:1 methylene chloride/methanol to give 334d as a brown solid (2.6 g, 72%). MS: $[M+H]^+$ 245.

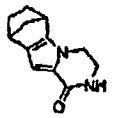
Example 334e Ethyl 3-(2-Aminoethyl)-3-azatricyclo[5.2.1.$0^{2,6}$]deca-2(6),4-diene-4- carboxylate 334e



334e

A suspension of 334d (4.0 g, 16 mmol) and Raney Ni (400 mg) in methanol (60 mL) was hydrogenated in a Parr apparatus at 50 psi for overnight. The mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography eluting with 20:1 methylene chloride/methanol to give 334e as a yellow solid (2 g, 50%). MS: $[M+H]^+$ 249.

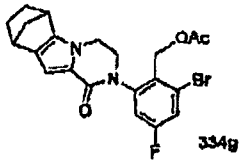
Example 334f 3,6-Diazatetracyclo[9.2.1.$0^{2,10}$.$0^{3,8}$]tetradeca- 2(10),8-dien-7-one 334f



334f

To a solution of ethyl 3-(2-aminoethyl)-3-azatricyclo[5.2.1.$0^{2,6}$]deca-2(6),4-diene-4-carboxylate (334e) (1.8 g, 7.2 mmol) in ethanol (40 mL) was added sodium meth-oxide (2.5 g, 36 mmol). The mixture was heated at 65°C for 12 hours. It was then cooled to room temperature. The solvent was evaporated to dryness. The residue was purified by column chromatography eluting with 20:1 methylene chloride/methanol to give 334f as a brown solid (800 mg, 53%). MS: $[M+H]^+$ 203.

Example 334g (2-Bromo-4-fluoro-6-{7-oxo-3,6-diazatetracyclo[9.2.1.$0^{2,10}$.$0^{3,8}$]tetradeca- 2(10),8-dien-6-yl}phenyl)methyl Acetate 334g

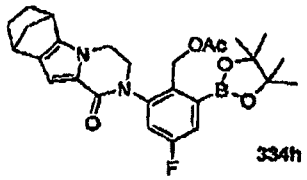


334g

Into a sealed tube was charged with 334f (800 mg, 4 mmol) and 197e (3.8 g, 12 mmol) in dioxane (25 mL), and cesium carbonate (2.6 g, 8 mmol). After bubbling nitrogen through the resulting solution for 30 min, XantPhos (230 mg, 0.4 mmol) and tris(dibenzylideneacetone)-dipalladium(0) (362 mg, 0.4 mmol) were added, and the reaction

mixture was heated at 100°C for 4 h. After this time the reaction was cooled to room temperature, and partitioned between ethyl acetate (100 mL) and water (100 mL). The aqueous layer was separated and extracted with ethyl acetate (50 mL × 3). The organic layers were combined, washed with brine (20 mL × 3), and dried over sodium sulfate. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography eluting with 1:5 ethyl acetate/petroleum ether to give **334g** as a brown solid (1.3 g, 72%). MS: $[M+H]^+$ 447.

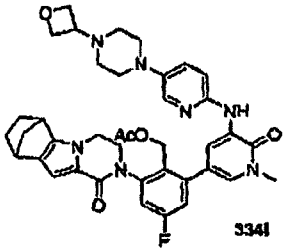
Example 334h (4-Fluoro-2-{7-oxo-3,6-diazatetracyclo[9.2.1.$0^{2,10}$.$0^{3,8}$]tetradeca- 2(10),8-dien-6-yl}-6-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl Acetate **334h**



334h

To a solution of **334g** (450 mg, 1.0 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (770 mg, 3.0 mmol) in dioxane (40 mL) was added $PdCl_2$(dppf) (82 mg, 0.1 mmol) and CH_3COOK (593 mg, 6 mmol). The mixture was stirred at 100°C for 12 h under argon atmosphere. After reaction the mixture was filtered and evaporated in *vacuo*. The residue was purified by column chromatography eluting with 1:4 ethyl acetate/petroleum ether to give **334h** as a brown solid (400 mg, 80%). MS: $[M+H]^+$ 495.

Example 334i {4-Fluoro-2-[1-methyl-5-({5-[4-(oxetan-3- yl)piperazin-1-yl]pyridin-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]-6-{7-oxo-3,6-diazatetracyclo[9.2.1.$0^{2,10}$.$0^{3,8}$]tetradeca-2(10),8-dien-6-yl}phenyl}methyl Acetate **334i**



334i

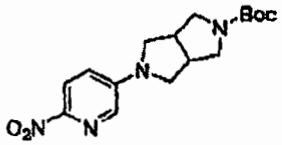
A sealed tube was charged with **334h** (300 mg, 0.6mmol), **188e** (254 mg, 0.6 mmol), Na_2CO_3 (129 mg, 1.2 mmol), $PdCl_2$(dppf) (50 mg, 0.06 mmol) suspended in DMF (20 mL), and H_2O (1 mL). The mixtue was stirred at 80 °C for 5 hours. After reaction the mixture was

partitioned between ethyl acetate and water. The organic phase was washed with water (2X), dried over sodium sulfate and concentrated. The residue was purified by reverse phase Combi-flash eluting with 0.3% NH_4HCO_3 in 1:5 water/CH_3CN to give 334i as a brown solid (300 mg, 70%). MS: $(M+H)^+$ 708.

At room temperature, to the solution of 334i (280 mg, 0.4mol) in THF/isopropanol/water (10 mL/10mL/2 mL) was added LiOH (950 mg, 40 mmol) while stirring. This mixture was stirred for 2 h. Then, 20 mL water was added and resulting mixture was extracted with ethyl acetate (3 X 30 mL). The combined organic layer was dried with Na_2SO_4 and concentrated to give a yellow solid, which was further purified by reverse phase Combi-flash eluting with 0.3% NH_4HCO_3 in 1:4 water/CH_3CN to give 334 as a white solid (160 mg, 67%). MS: $[M+H]^+$ 666. ^1H NMR (500 MHz, MEOD) δ 8.53 (s, 1H), 7.93 (d, 1H), 7.43 (d, 1H), 7.34 (s, 1H), 7.20-7.22 (m, 2H), 7.04 (d, 1H), 6.67 (s 1H), 4.72-4.75 (t, J=6.5, 1H), 4.63-4.66 (t, J = 6, 2H), 4.47-4.56 (M, 2H), 4.21-4.39 (m, 3 H), 3.98-4.06 (m, 1H), 3.71 (s, 3H), 3.56-3.60 (m, 1H), 3.48 (s, 1H), 3.17-3.19 (t, J=4.5, 4H), 2.71 (s, 1H), 2.53-2.55 (t, J=5, 4H), 1.88-1.95 (m, 3H), 1.67-1.69 (m, 1H), 1.04-1.17 (m, 2H).

Example 335 2-(5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one 335

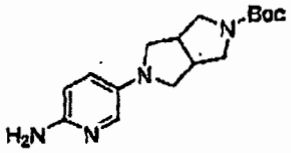
Example 335a *tert*-Butyl 5-(6-Nitropyridin-3-yl)-hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate 335a



335a

Following Example 188a, reaction of 404 mg of *tert*-butyl hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (2 mmol) and 566 mg 5-fluoro-2-nitropyridine (1.1 mmol) gave 335a as a yellow solid (234 mg, 35%). MS: $[M+H]^+$ 335. ^1H NMR (500 MHz, DMSO) δ 8.18 (d, J=9.0, 1H), 7.87 (d, J=3.5, 1H), 7.06 (dd, J=9.0, 1H), 3.66 (s, 2H), 3.55 (s, 2H), 3.36 (s, 2H), 3.18 (s, 2H), 3.05 (s, 2H), 1.39 (s, 9H).

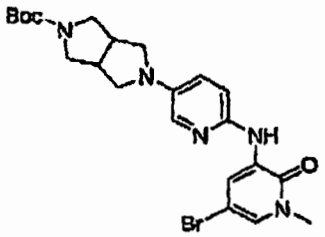
Example 335b *tert*-Butyl 5-(6-Aminopyridin-3-yl)-hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate 335b



335b

Following Example 188b, 234 mg of 335a (0.7 mmol) was reduced to give 335b as a yellow solid (213 mg, 99%). MS: $[M+H]^+$ 305

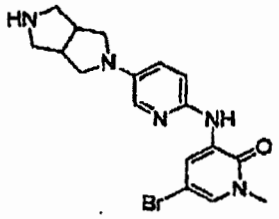
Example 335c *tert*-Butyl 5-(6-(5-Bromo-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)pyridine-3-yl)-hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate 335c



335c

Following Example 188c, 3,5-dibromo-1-methylpyridin-2(1H)-one (212 mg, 0.79 mmol) and 335b (200 mg, 0.66mmol) were reacted to give 335c as a yellow solid (194 mg, 60%). MS: $[M+H]^+$ 492

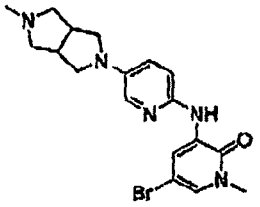
Example 335d 5-Bromo-3-(5-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridin-2-ylamino-1-methylpyridin-2(1H)-one 335d



335d

Following Example 188d, 194 mg (0.4 mmol) of 335c was deprotected to give 335d as a yellow solid (154 mg, 99%). MS: $[M+H]^+$ 392

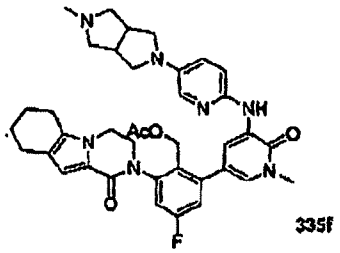
Example 335e 5-Bromo-1-methyl-3-(5-(5-methyl-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridin-2-ylamino)pyridin-2(1H)-one 335e



335e

Following Example 188e, 154 mg (0.4 mmol) of 335d was methylated to give 335e as a yellow solid (119 mg, 75%). MS: $[M+H]^+$ 404.

Example 335f 4-Fluoro-2-(1-methyl-5-(5-(5-methyl-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate 335f



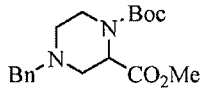
335f

Following Examples 148h, 142 mg of 4-fluoro-2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate 210d (0.29 mmol) and 119 mg of 335e (0.29 mmol) were reacted to give 335f as a yellow solid (100 mg, 51%). LCMS: $[M+H]^+$ 680

Following Example 148, 100 mg of 335f (0.15 mmol), 335 was obtained as a white solid (39 mg, 42%). ^1H NMR (500 MHz, CDCl3) δ 8.45 (d, J=2.0, 1H), 7.70 (d, J=2.5, 1H), 7.67 (s, 1H), 7.42 (d, J= 2.5, 1H), 7.17 (m, 1H), 7.04(dd, J=9.0, 1H), 6.95 (dd, J=6.0, 1H), 6.86(s, 1H), 6.79(d, J=9.0, 1H), 4.54 (d, J=11.0, 1H), 4.31 (m, 1H), 4.16 (m, 3H), 3.91(m, 1H), 3.70 (s, 3H), 3.27 (s, 2H), 3.18 (s, 2H), 2.99 (s, 2H), 2.83 (s, 2H), 2.59 (m, 4H), 2.46 (m, 2H), 2.38 (s, 3H), 1.90 (s, 2H), 1.80 (s, 2H).

Example 336 2-(5-Fluoro-3-(5-(5-(3-(fluoromethyl)-4-methylpiperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one 336

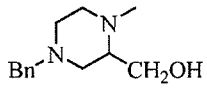
Example 336a 1-*tert*-Butyl 2-Methyl 4-benzylpiperazine-1,2-dicarboxylate 336a



336a

To a dry 100 mL round bottom flask equipped with a stirring bar under N_2 was added 1-*tert*-butyl 2-methyl piperazine-1,2-dicarboxylate (5 g, 20.5 mmol), anhydrous acetonitrile (60 mL), benzyl bromide (2.7 mL, 22.5 mmol), and triethylamine (8.5 mL, 61.5 mmol). The reaction mixture was heated at 71°C for 45 minutes and concentrated under reduced pressure. It was then diluted with methylene chloride and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude compound was purified by flash column chromato-graphy eluting with 8:1 petroleum either/ethyl acetate to afford **336a** (4.5 g, 66%). MS: $[M+H]^+$ 335. ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (m, 5H), 4.60 (m, 1H), 3.78 (m, 4H), 3.57 (m, 1H), 3.43 (m, 1H), 3.28 (m, 2H), 2.77 (m, 1H), 2.19 (m, 1H), 2.11 (m, 1H), 1.47 (s, 5H), 1.42 (s, 4H).

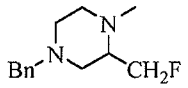
Example 336b (4-Benzyl-1-methylpiperazin-2-yl)methanol **336b**



336b

To a solution of **336a** (1 g, 2.99 mmol) in 100 mL of anhydrous tetrahydrofuran was slowly added lithium aluminum hydride (342 mg, 8.98 mmol) at 0°C and the mixture was stirred for 30 min. Then, it was refluxed for 3 h and the reaction mixture was poured onto ice portion-wise. The resulting mixture was filtered and the filtrate was evaporated *in vacuo*. After addition of 100 mL brine to the residue, it was extracted with methylene chloride (100 mL x 3). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated to afford **336b** as yellow oil (0.60 g, 91%). MS: $[M+H]^+$ 221.

Example 336c 4-Benzyl-2-(fluoromethyl)-1-methylpiperazine **336c**

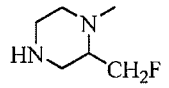


336c

To an ice-cooled solution of diethylaminosulfur trifluoride (10.8 mL, 81.8 mmol) in methylene chloride under N_2 was added **336b** (9.0 g, 40.9 mmol) in methylene chloride dropwise. The yellow solution was stirred at 0 °C for 1 h and then room temperature for 15 h. The reaction mixture was then diluted with $NaHCO_3$, and the organic layer was separated and dried over Na_2SO_4. The crude product was purified on silica gel column chromatography eluting with 50:1 methylene chloride/methanol to afford **336c** as a yellow oil (3.0 g, 33%).

MS: $[M+H]^+$ 223. ^1H NMR (500 MHz, DMSO) δ 7.28 (m, 5H), 4.50 (m, 0.5H), 4.43 (m, 1H), 4.35 (m, 0.5H), 3.45 (s, 2H), 2.67 (m, 2H), 2.60 (m, 1H), 2.29 (m, 1H), 2.24 (s, 3H), 2.20 (m, 1H), 2.11 (m, 1H), 1.94 (m, 1H).

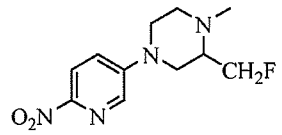
Example 336d 2-(Fluoromethyl)-1-methylpiperazine **336d**



336d

A 250-mL single-neck round-bottomed flask equipped with a magnetic stirrer was charged with **336c** (3.0 g, 13.5 mmol), methanol (80 mL), and Pd/C (10%) (300 mg). The reaction mixture was stirred at 25°C under H_2 for 15 h. After the reaction was finished, it was filtered and concentrated to afford **336d** as a yellow oil (1.6 g, 90%).

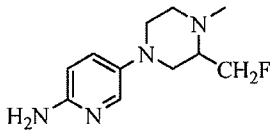
Example 336e 2-(Fluoromethyl)-1-methyl-4-(6-nitropyridin-3-yl)piperazine **336e**



336e

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was charged with 1,4-dioxane (50 mL), **336d** (1.6 g, 12.1 mmol), 5-bromo-2-nitropyridine (3.7 g, 18.2 mmol), and cesium carbonate (9.9 g, 30.2 mmol). After bubbling nitrogen through the resulting solution for 30 min, Xantphos (700 mg, 0.12 mmol) and tris(dibenzylideneacetone)-dipalladium(0) (550 mg, 0.06 mmol) were added. After three cycles of vacuum/argon flash, the reaction mixture was heated at reflux for 15 h. After this time the reaction was cooled to room temperature, filtered, and concentrated to afford a black solid as a crude product, which was further purified by column chromatography eluting with 100:1 methylene chloride /methanol to afford **336e** as a yellow solid (2.6 g, 76%). MS: $[M+H]^+$ 255. ^1H NMR (500 MHz, MeOD) δ 8.20 (m, 2H), 7.52 (dd, J=9, 1H), 4.72 (m, 0.5H), 4.64 (m, 1H), 4.56 (m, 0.5H), 4.01 (m, 1H), 3.94 (m, 1H), 3.19 (m, 1H), 3.06 (m, 1H), 3.00 (m, 1H), 2.50 (m, 2H), 2.46 (s, 3H).

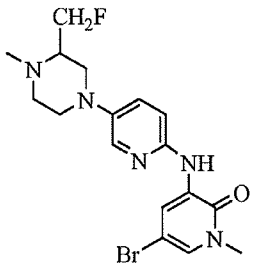
Example 336f 5-(3-(Fluoromethyl)-4-methylpiperazin-1-yl)pyridin-2-amine **336f**



336f

A 250-mL single-neck round-bottomed flask equipped with a magnetic stirrer was charged with **336e** (2.6 g, 10.2 mmol), methanol (50 mL), and Pd/C (10%) (260 mg). The reaction mixture was stirred under H_2 for 15 h. After the reaction was finished, it was filtered and concentrated to afford **336f** as a black oil, which was used in the next step without further purification. MS: $[M+H]^+$ 225.

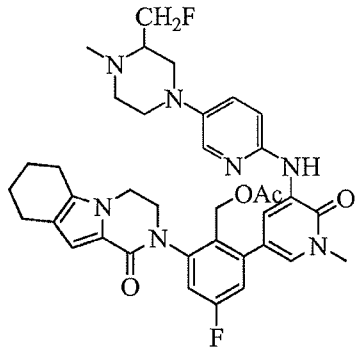
Example 336g 5-Bromo-3-(5-(3-(fluoromethyl)-4-methylpiperazin-1-yl)pyridin-2-ylamino)-1-methylpyridin-2(1H)-one **336g**



336g

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was charged with 1,4-dioxane (60 mL), **336f** (crude, 14.1 mmol), 3,5-dibromo-1-methylpyridin-2(1H)-one (4.5 g, 16.9 mmol), and cesium carbonate (11.5 g, 35.2 mmol). After bubbling nitrogen through the resulting solution for 30 min, Xantphos (820 mg, 1.41 mmol) and tris(dibenzylideneacetone)dipalladium(0) (645 mg, 0.7 mmol) were added. After three cycles of vacuum/argon flash, the reaction mixture was heated at reflux for 15 h. The reaction was cooled to room temperature, filtered and concentrated to afford a black solid, which was purified by column chromatography eluting with methylene chloride/ methanol (from 100:1 to 50:1) to afford **336g** as a yellow solid (3.1 g, 50%). MS: $[M+H]^+$ 410.

Example 336h 4-Fluoro-2-(5-(5-(3-(fluoromethyl)-4-methylpiperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **336h**



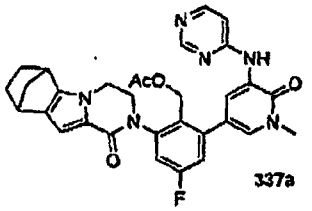
336h

A reaction vessel was charged with a mixture of **336g** (1 g, 2.4 mmol), 4-fluoro-2-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate **210d** (1.3 g, 2.68 mmol), $PdCl_2$(dppf) (190 mg, 0.24 mmol), K_3PO_4 (1 g, 4.8 mmol), and NaOAc (390 mg, 4.8 mmol) in MeCN (15 mL) and water (1.5 mL). It was bubbled with nitrogen for 30 min and then heated at 110°C for 3 h. The solvent was evaporated in vacuum and the residue was purified on silica gel column chromatography eluting with 5:1 methylene chloride /methanol to afford **336h** (0.80 g, 45%). MS: $[M+H]^+$ 686.

A mixture of **336h** (750 mg, 1.09 mmol) and LiOH hydrate (2.3 g, 55 mmol) in isopropanol (10 mL), THF (10 mL), and water (10 mL) was stirred at 30°C for 1 h. The mixture was evaporated in *vacuo*, and the residue was extracted with methylene chloride (30 mL x 3). The combined extracts were concentrated under reduced pressure and the residue was purified on silica gel column eluting with 50:1 methylene chloride /methanol to afford **336** as a yellow solid (700 mg, 93%). MS: $[M+H]^+$ 644. ^1H NMR (500 MHz, MeOD) δ 8.54 (d, J = 2 Hz, 1H), 7.92 (d, J = 1.5 Hz, 1H), 7.42 (m, 1H), 7.33 (m, 1H), 7.22 (s, 1H), 7.20 (s, 1H), 7.02 (m, 1H), 6.72 (s, 1H), 4.46-4.69 (m, 4H), 4.20 (s, 3H), 4.02 (m, 1H), 3.70 (s, 3H), 3.49 (d, J = 11.5 Hz, 1H), 3.42 (d, J = 11.5 Hz, 1H), 2.94 (m, 1H), 2.85 (m, 1H), 2.71 (m, 1H), 2.64 (m, 2H), 2.56 (m, 4H), 2.44 (s, 3H), 1.88 (m, 2H), 1.79, (m, 2H).

Example 337 6-[5-Fluoro-2-(hydroxymethyl)-3-{1-methyl-6-oxo-5- [(pyrimidin-4-yl)amino]-1,6-dihydropyridin-3-yl}phenyl]-3,6-diazatetracyclo[9.2.1.$0^{2,10}$.$0^{3,8}$]tetradeca-2(10),8-dien-7-one **337**

Example 337a (4-Fluoro-2-{1-methyl-6-oxo-5-[(pyrimidin-4- yl)amino]-1,6-dihydro-pyridin-3-yl}-6-{7-oxo-3,6-diazatetracyclo[9.2.1.$0^{2,10}$.$0^{3,8}$]tetradeca-2(10),8-dien-6-yl}phenyl)methyl Acetate **337a**



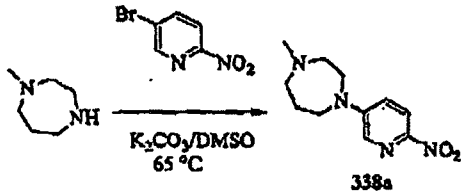
337a

A sealed tube was charged with(2-bromo-4-fluoro-6-{7-oxo-3,6-diazatetracyclo-[9.2.1.$0^{2,10}$.$0^{3,8}$]tetradeca-2(10),8-dien-6-yl}phenyl)methyl acetate 334g (400 mg, 0.9 mmol), 1-methyl-3-(pyrimidin-4-ylamino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one 109c (294 mg, 0.9 mmol), Na_2CO_3 (190 mg, 1.8 mmol), and $PdCl_2$(dppf) (73 mg, 0.09 mmol) suspended in DMF (20 mL) and water (1 mL). The mixture was stirred at 60°C for 6 hours. It was then partitioned between water and ethyl acetate. The organic phase was washed with water and evaporated to dryness. The residue was purified by column chromatography eluting with 15:1 methylene chloride/methanol to give 337a as a brown solid (300 mg, 58%). MS: $[M+H]^+$ 569.

At room temperature, to the solution of337a (270 mg, 0.47mol) in THF/isopropanol/water (10 mL/10mL/2 mL) was added LiOH (1.1 g, 47 mmol) while stirring. This mixture was stirred for 2 h. Then, 20 mL water was added and the resulting mixture was extracted with ethyl acetate (30 mL X 3). The combined organic layer was dried with Na_2SO_4 and concentrated to get a yellow solid, which was further purified by reverse phase Combi-flash eluting with 0.3% NH_4HCO_3 in 1:5 water/CH_3CN to give 337 as a white solid (138 mg, 48%). MS: $[M+H]^+$ 527. ^1H NMR (500 MHz, MEOD) δ 8.87 (s, 1H), 8.67 (s, 1H), 8.29 (d, 1H), 7.55 (s, 1H), 7.22-7.24 (m, 2H), 7.10 (d, 1H), 6.68 (d, 1H), 4.48-4.55 (m, 2H), 4.18-4.40 (m, 3H), 3.98-4.06 (m, 1H), 3.72 (s, 3 H), 3.45-3.48 (m, 1H), 1.88-1.98 (m, 3H), 1.67-1.69 (m, 1H), 1.30 (m, 1H), 1.12-1.17 (m, 1H), 1.02-1.07 (m, 1H).

Example 338 2-(5-Fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(4-methyl-1,4-diazepan-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one 338

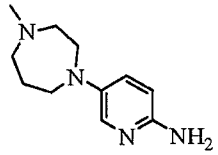
Example 338a 1-Methyl-4-(6-nitropyridin-3-yl)-1,4-diazepane 338a



338a

To a solution of 1-methyl-1,4-diazepane (1 g, 8.8 mmol) in DMSO (20 mL) were added K_2CO_3 (2.4 g, 18 mmol) and 5-bromo-2-nitropyridine (51-7) (1.78g, 8.8 mmol). The mixture was stirred at 65°C for overnight. It was allowed to cool to room temperature and poured into water. The resulting solid was collected and dried under vacuum. The solid was further purified by flash column eluting with 3:1 petroleum ether/ethyl acetate and then methylene chloride to give **338a** as a yellow solid (800 mg, 69%). MS: $[M+H]^+$ 236.

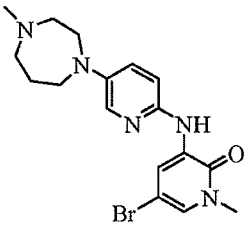
Example 338b 1-Methyl-4-(6-nitropyridin-3-yl)-1,4-diazepane **338b**



338b

A 500-mL bottle was purged with nitrogen and charged with **338a** (0.8 g, 3.4 mmol), 10% palladium on carbon (50% wet, 100 mg) and methanol (100 mL). The bottle was evacuated, charged with hydrogen gas, and stirred at room temperature for 16 h. The hydrogen was then evacuated and nitrogen charged to the bottle. The catalyst was removed by filtration through a pad of Celite and the filtrate was concentrated under reduced pressure to afford **338b** (0.6 g, crude). MS: $[M+H]^+$ 207.

Example 338c 5-Bromo-1-methyl-3-(5-(4-methyl-1,4-diazepan-1-yl)pyridin-2-ylamino)pyridine-2(1H)-one **338c**

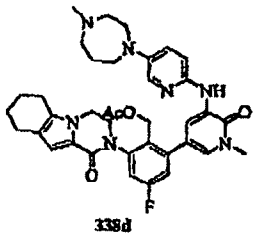


338c

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer and reflux condenser was charged with **338b** (968mg, 4.7 mmol), 3,5-dibromo-1-methylpyridin-2(1H)-one (1.24 g, 4.7 mmol) and cesium carbonate (3.8 g, 12 mmol). After bubbling nitrogen through the resulting solution for 30 minutes, XantPhos (272 mg, 0.47 mmol) and tris(dibenzylideneacetone)dipalladium(0) (430 mg, 0.47 mmol) were added. The reaction mixture was heated at reflux for 3 h. After this time the reaction was cooled to room temperature, partitioned between ethyl acetate (100 mL) and water (100 mL), and filtered. The aqueous layer was separated and extracted with ethyl acetate (2 x 50 mL). The organic layers were combined, washed with brine (50 mL), and dried over sodium sulfate. The

drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified on flash column eluting with petroleum ether/ethyl acetate to afford 338c (918 mg, 50%). MS: $[M+H]^+$ 392.

Example 338d 4-Fluoro-2-(1-methyl-5-(5-(4-methyl-1,4-diazepan-1-yl)pyridine-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate 338d



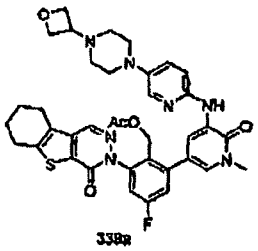
338d

A sealed tube was charged with the mixture of 338c (274 mg, 0.7 mmol), 210d (337 mg, 0.7 mmol), $Pd(dppf)Cl_2$ (33 mg, 0.04 mmol), $K_3PO_4.3H_2O$(372 mg, 1.4 mmol), and NaOAc (115 mg, 1.4 mmol) in CH_3CN(20ml). The system was evacuated and then refilled with N_2. And the reaction mixture was heated at 110°C under microwave irradiation for 3 h. The mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography eluting with 30:1 methylene chloride/methanol to afford 338d as a yellow solid (120 mg, 43%). MS: $[M+H]^+$ 668.

A solution of 338d (120 mg, 0.18 mmol) in propan-2-ol (10 mL), tetrahydrofuran (10 mL) and water (2 mL) was added LiOH (1.1 g, 57 mmol). The mixture was stirred at 30°C for 2 h. It was then evaporated and the residue was purified by prep-HPLC to afford 338 as a white solid (60 mg, 54%). MS: $(M+H)^+$ 626. ^1H NMR (500 MHz, MeOD) δ 8.18 (s, 1H), 7.62 (s, 1H), 7.16 (s, 1H), 7.06 (m, 3H), 6.88 (d, J = 11.5, 2H), 6.59 (s, 1H), 4.38 (m, 2H), 4.07 (m 3H), 3.87 (m, 1H), 3.57 (s, 3H), 3.42 (m, 2H), 3.31 (m, 2H), 3.20 (s, 3H), 2.60 (m, 2H), 2.50 (m, 4H), 2.42 (m, 2H), 1.75 (m, 6H).

Example 339 5-[5-fluoro-2-(hydroxymethyl)-3-[1-methyl-5-({5-[4-(oxetan-3-yl)piperazin-1-yl]pyridine-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-8-thia-4,5-diazatricyclo[7.4.0.0^{2,7}]-trideca-1(9),2(7),3(4)-trien-6-one 339

Example 339a [4-Fluoro-2-(1-methyl-5-{[5-(4-(oxetan-3-yl)piperazin-1-yl)pyridine-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)-6-(6-oxo-8-thia-4,5-diazatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7),3- trien-5-yl)phenyl]methyl Acetate 339a



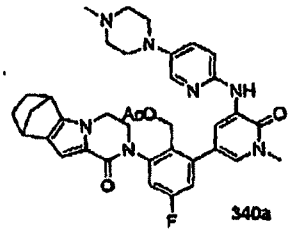
339a

Following Example 210a, 150 mg (0.30 mmol) of (4-fluoro-2-{6-oxo-8-thia-4,5-diazatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7),3- trine-5-yl}-6-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl acetate **341b** was converted to **339a** as a yellow solid (129 mg, 60%). MS: $[M+H]^+$ 712

Following Example 148, 120 mg of **339a** (0.17 mmol) was converted to **339** as a white solid (56 mg, 50%). MS: $[M+H]^+$ 670. ^{1}H NMR (500 MHz, DMSO) δ 8.56 (d, J = 3.0 Hz, 1H), 8.48 (s, 1H), 8.41 (s, 1H), 7.88 (d, J = 3.0 Hz, 1H), 7.37 (m, 4H), 7.23 (d, J = 9.5 Hz, 1H), 4.60 (t, J = 10.0 Hz, 1H), 4.56(t, J = 13.0 Hz, 2H), 4.46(t, J = 12.0 Hz, 2H), 4.28(s, 2H), 3.58 (s, 3H), 3.43 (m, 1H), 3.07 (t, J = 9.0 Hz, 4H) 2.93 (s, 2H), 2.85 (s, 2H), 2.38 (t, J = 9.0 Hz, 4H), 1.87 (m, 4H).

Example 340 2-(5-Fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(4-methylpiperazin-1-ylpyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)- 3,4,6,7,8,9-hexahydro-6,9-methanopyrazino[1,2-a]indol-1(2H)-one **340**

Example 340a {4-Fluoro-2-[1-methyl-5-({5-[4-methylpiperazin-1-yl]pyridin-2yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]-6-{7-oxo-3,6-diazatetracyclo[9.2.1.0^{2,10}.0^{3,8}]tetradeca-2(10),8-dien-6-yl}phenyl}methyl Acetate **340a**



340a

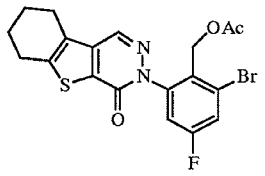
A microwave vial equipped with a magnetic stirrer was charged with (2-bromo-4-fluoro-6-{7-oxo-3,6-diazatetracyclo[9.2.1.0^{2,10}.0^{3,8}]tetradeca-2(10),8-dien-6-yl}phenyl)methyl acetate **334g** (293 mg, 0.65 mmol), 1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridine-2-ylamino)-6-oxo-1,6-dihydropyridin-3-ylboronic acid **197f** (450 mg, 1.3 mmol), $PdCl_2$(dppf) (54 mg, 0.065 mmol), 2.0 M Na_2CO_3 (2.0 equiv), and 1,2-dimethoxyethane (18

mL). After three cycles of vacuum/argon flash, the mixture was heated at 130°C under microwave irradiation for 0.5 h. It was then filtered and the filtrate was evaporated in *vacuo*. The residue was purified on flash column chromatography eluting with 10:1 dichloromethane/methanol to afford **340a** as a brown solid (130 mg, 33%). LCMS: $[M+H]^+$ 666

A mixture of **340a** (130 mg, 0.20 mmol) and LiOH (470 mg, 20.0 mmol) in isopropanol/THF (1:1, 10 mL) and water (3 mL) was stirred at 30°C for 2 h. The mixture was evaporated in *vacuo* and the residue was extracted with ethyl acetate (30 mL X 2). The combined ethyl acetate extract was concentrated under reduced pressure and the residue was purified with prep-HPLC to afford **340** (50 mg, 41%). LCMS: $[M+H]^+$ 624. ^1H NMR (500 MHz, MEOD) δ 8.54 (s, 1H), 7.93 (s, 1H), 7.41-7.43 (m, 1H), 7.34 (s, 1H), 7.20-7.22 (m, 2H), 7.02-7.04 (d, J = 9.0 Hz, 1H), 6.67-6.68 (d, J = 3.0 Hz, 1H), 4.46-4.55 (m, 2H), 4.18-4.38 (m, 3H), 3.98-4.06 (m, 1H), 3.71 (s, 3H), 3.46-3.48 (m, 1H), 3.14-3.18 (m, 4H), 2.62-2.64 (t, J = 4.5 Hz, 4H), 2.36 (s, 3H), 1.88-1.95 (m, 3H), 1.67-1.69 (m, 1H), 1.01-1.30 (m, 2H).

Example 341 5-[5-Fluoro-2-(hydroxymethyl)-3-(1-methyl-5-{[5-(4-methylpiperazin-1-yl)pyridin-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-8-thia-4,5-diazatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7),3- trien-6-one **341**

Example 341a (2-Bromo-4-fluoro-6-{6-oxo-8-thia-4,5-diazatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7),3- trien-5-yl}phenyl)methyl acetate **341a**

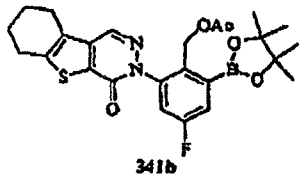


341a

A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer was charged with 8-thia-4,5-diazatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7),3-trien-6-one (1 g, 4.85 mmol), 2,6-dibromo-4-fluorobenzyl acetate **197c** (4.8 g, 14.6 mmol), copper(I) iodide (553 mg, 2.9 mmol), N^1,N^2-dimethylethane-1,2-diamine(512 mg, 5.82 mmol), Cs_2CO_3 (3.2 g, 9.7 mmol), and 1,4-dioxane (50 mL). The system was evacuated and then refilled with N_2. A reflux condenser was attached to the flask, and the reaction mixture was heated at 100°C for 16 h. It was then cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and the resulting residue was purified by flash column

chromatography eluting with 5:1 petroleum ether/ethyl acetate to afford **341a** as a yellow solid (437 mg, 20%). MS: $[M+H]^+$ 451.

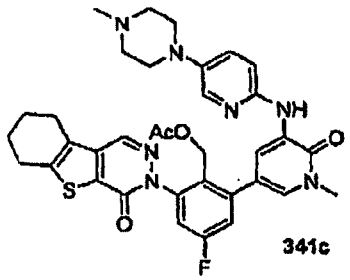
Example 341b (4-Fluoro-2-{6-oxo-8-thia-4,5-diazatricyclo[7.4.0.$0^{2,7}$]trideca-1(9),2(7),3- trine-5-yl}-6-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl acetate **341b**



341b

Following Example 210d, **341a** (400 mg 0.88 mmol) was convereted to **341b** as a yellow solid (353 mg, 80%). MS: $[M+H]^+$ 499

Example 341c [4-Fluoro-2-(1-methyl-5-{[5-(4-methylpiperazin-1- yl)pyridin-2-yl]amino}-6-oxo-1,6-dihydropyridin-3-yl)-6-{6-oxo-8-thia-4,5-diazatricyclo-[7.4.0.$0^{2,7}$]trideca-1(9),2(7),3- trien-5-yl}phenyl]methyl Acetate **341c**



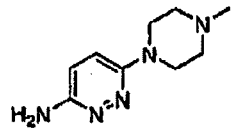
341c

Following Example 210a, 180 mg (0.36 mmol) of **341b** was converted to **341c** as a yellow solid (120 mg, 50%). MS: $[M+H]^+$ 670

Following Example 148, 120 mg of **341c** (0.18 mmol) was converted to **341** as a white solid (46 mg, 41%). MS: $[M+H]^+$ 628. ^{1}H NMR (500 MHz, CDCl3) δ 8.58 (d, J=2.5, 1H), 8.26 (s, 1H), 7.95 (d, J=3.0, 1H), 7.77 (s, 1H), 7.45 (d, J=2.0, 1H), 7.31 (m, 1H), 7.25(m, 1H), 7.11 (dd, J=8.0, 1H), 6.82 (d, J=9.0, 1H), 4.31 (s, 1H), 4.01(s, 1H), 3.71 (s, 3H), 3.15 (t, J=4.5, 4H), 2.99 (t, J=5.0, 2H), 2.87 (t, J=5.5, 2H), 2.60 (t, J=5.0, 4H), 2.37 (s, 3H), 1.99 (s, 4H).

Example 342 2-(5-Fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(6-(4-methylpiperazin-1-yl)pyridazin-3-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one **342**

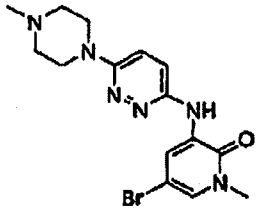
Example 342a 6-(4-Methylpiperazin-1-yl)pyridazin-3-amine **342a**



342a

A sealed tube equipped with a magnetic stirrer was charged with 6-chloro-pyridazin-3-amine (1.3 g, 10 mmol) and 1-methylpiperazine (15 mL). The reaction mixture was heated at 170°C for 3 h. It was then cooled to room temperature and concentrated under reduced pressure. The resulting residue was washed with CH_3CN (20 mL) to afford **342a** as a yellow solid (1.5 g, 78%). MS: $[M+H]^+$ 194. ^1H NMR (500 MHz, DMSO) δ 7.12 (d, J = 9.0 Hz, 1H), 6.74 (d, J = 9.0 Hz, 1H), 5.72 (s, 2H), 3.27 (t, J = 4.5 Hz, 4H), 2.40 (t, J = 4.5 Hz, 4H), 2.20 (s, 3H).

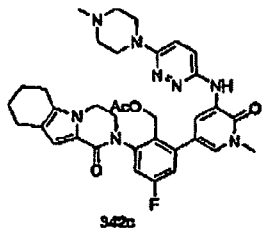
Example 342b 5-Bromo-1-methyl-3-(6-(4-methylpiperazin-1-yl)pyridazin-3-ylamino)-pyridin-2(1H)-one **342b**



342b

Following Example 188c, **342a** (580 mg, 3.0 mmol) was converted to **342b** as a yellow solid (920 mg, 80%). MS: $[M+H]^+$ 381

Example 342c 4-Fluoro-2-(1-methyl-5-(6-(4-methylpiperazin-1-yl)pyridazin-3-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)-6-(1-oxo-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-2(1H)-yl)benzyl Acetate **342c**



342c

Following Example 188f, 482 mg of **342b** (1.0 mmol) and 379 mg of 5-bromo-1-methyl-3-(6-(4-methylpiperazin-1-yl)pyridazin-3-ylamino)pyridin-2(1H)-one (1.0 mmol) were reacted to give **342c** as a yellow solid (261 mg, 40%). MS: $[M+H]^+$ 655.

Following Example 188, **342c** (150 mg 0.23 mmol) was converted to **342** as a white solid (73 mg, 52%). LCMS: $[M+H]^+$ 613. ^1H NMR (500 MHz, $CDCl_3$) δ 8.68 (d, J = 2.5 Hz, 1H), 7.76 (s, 1H), 7.46 (d, J = 2.0 Hz, 1H), 7.12 (dd, J = 9.0 Hz, 1H), 7.0 (m, 2H), 6.90 (dd, J = 9.0 Hz, 1H), 6.86 (s, 1H), 4.50 (dd, J = 11.0 Hz, 1H), 4.27 (m, 2H), 4.16 (m, 3H), 3.88 (m, 1H), 3.71 (s, 3H), 3.54 (m, 4H), 2.58 (m, 7H), 2.35 (s, 3H), 1.90 (m, 2H), 1.71 (m, 2H).

Example 901 Biochemical Btk Assay

A generalized procedure for a standard biochemical Btk Kinase Assay that can be used to test Formula I compounds is as follows. A master mix minus Btk enzyme is prepared containing 1X Cell Signaling kinase buffer (25 mM Tris-HCl, pH 7.5, 5 mM beta-glycerophosphate, 2 mM dithiothreitol, 0.1 mM Na_3VO_4, 10 mM $MgCl_2$), 0.5 μM Promega PTK Biotinylated peptide substrate 2, and 0.01% BSA. A master mix plus Btk enzyme is prepared containing 1X Cell Signaling kinase buffer, 0.5 μM PTK Biotinylated peptide substrate 2, 0.01% BSA, and 100 ng/well (0.06 mU/well) Btk enzyme. Btk enzyme is prepared as follows: full length human wildtype Btk (accession number NM-000061) with a C-terminal V5 and 6x His tag was subcloned into pFastBac vector for making baculovirus carrying this epitope-tagged Btk. Generation of baculovirus is done based on Invitrogen's instructions detailed in its published protocol "Bac-to-Bac Baculovirus Expression Systems" (Cat. Nos. 10359-016 and 10608-016). Passage 3 virus is used to infect Sf9 cells to overexpress the recombinant Btk protein. The Btk protein is then purified to homogeneity using Ni-NTA column. The purity of the final protein preparation is greater than 95% based on the sensitive Sypro-Ruby staining. A solution of 200 μM ATP is prepared in water and adjusted to pH7.4 with 1N NaOH. A quantity of 1.25 μL of compounds in 5%DMSO is transferred to a 96-well ½ area Costar polystyrene plate. Compounds are tested singly and with an 11-point dose-responsive curve (starting concentration is 10 μM; 1:2 dilution). A quantity of 18.75 μL of master mix minus enzyme (as a negative control) and master mix plus enzyme is transferred to appropriate wells in 96-well ½ area costar polystyrene plate. 5 μL of 200 μM ATP is added to that mixture in the 96-well ½ area Costar polystyrene plate for final ATP concentration of 40 μM. The reaction is allowed to incubate for 1 hour at room temperature. The reaction is stopped with Perkin Elmer 1X detection buffer containing 30 mM EDTA, 20 nM SA-APC, and 1 nM PT66 Ab. The plate is read using time-resolved fluorescence with a Perkin Elmer Envision using excitation filter 330 nm, emission filter 665 nm, and 2nd emission filter 615 nm. IC_{50} values are subsequently calculated. Alternatively, the Lanthascreen assay can be used to evaluate Btk activity through quantification of its

phosphorylated peptide product. The FRET (Fluorescence Resonance Energy Transfer) that occurs between the fluorescein on the peptide product and the terbium on the detection antibody decreases with the addition of inhibitors of Btk that reduce the phosphorylation of the peptide. In a final reaction volume of 25 uL, Btk (h) (0.1 ng/25 ul reaction) is incubated with 50 mM Hepes pH 7.5, 10 mM MgCl2, 2 mM $MnCl_2$, 2 mM DTT, 0.2 mM NaVO4, 0.01% BSA, and 0.4 uM fluorescein poly-GAT. The reaction is initiated by the addition of ATP to 25 uM (Km of ATP). After incubation for 60 minutes at room temperature, the reaction is stopped by the addition of a final concentration of 2 nM Tb-PY20 detection antibody in 60 mM EDTA for 30 minutes at room temperature. Detection is determined on a Perkin Elmer Envision with 340 nM excitation and emission at 495 nm and 520 nm. Exemplary Btk inhibition IC50 values are in Tables 1, 2, and 3.

Example 902 Ramos Cell Btk Assay

Another generalized procedure for a standard cellular Btk Kinase Assay that can be used to test Formula I compounds is as follows. Ramos cells are incubated at a density of $0.5x10^7$ cells/ml in the presence of test compound for 1 hr at 37 °C. Cells are then stimulated by incubating with 10 μg/ml anti-human IgM $F(ab)_2$ for 5 minutes at 37 °C. Cells are pelleted, lysed, and a protein assay is performed on the cleared lysate. Equal protein amounts of each sample are subject to SDS-PAGE and western blotting with either anti-phosphoBtk(Tyr223) antibody (Cell Signaling Technology #3531; Epitomics, cat. #2207-1) or phosphoBtk(Tyr551) antibody (BD Transduction Labs #558034) to assess Btk autophosphorylation or an anti-Btk antibody (BD Transduction Labs #611116) to control for total amounts of Btk in each lysate.

Example 903 B-Cell Proliferation Assay

A generalized procedure for a standard cellular B-cell proliferation assay that can be used to test Formula I compounds is as follows. B-cells are purified from spleens of 8-16 week old Balb/c mice using a B-cell isolation kit (Miltenyi Biotech, Cat # 130-090-862). Testing compounds are diluted in 0.25% DMSO and incubated with 2.5×10^5 purified mouse splenic B-cells for 30 min prior to addition of 10μg/ml of an anti-mouse IgM antibody (Southern Biotechnology Associates Cat # 1022-01) in a final volume of 100 μl. Following 24 hr incubation, 1 μCi ^{3}H-thymidine is added and plates are incubated an additional 36 hr prior to harvest using the manufacturer's protocol for SPA[^{3}H] thymidine uptake assay

system (Amersham Biosciences # RPNQ 0130). SPA-bead based fluorescence is counted in a microbeta counter (Wallace Triplex 1450, Perkin Elmer).

Example 904 T Cell Proliferation Assay

A generalized procedure for a standard T cell proliferation assay that can be used to test Formula I compounds is as follows. T cells are purified from spleens of 8-16 week old Balb/c mice using a Pan T cell isolation kit (Miltenyi Biotech, Cat # 130-090-861). Testing compounds are diluted in 0.25% DMSO and incubated with 2.5 x 10^5 purified mouse splenic T cells in a final volume of 100 µl in flat clear bottom plates precoated for 90 min at 37°C with 10 µg/ml each of anti-CD3 (BD # 553057) and anti-CD28 (BD # 553294) antibodies. Following 24 hr incubation, 1 µCi ^{3}H-thymidine is added and plates incubated an additional 36 hr prior to harvest using the manufacturer's protocol for SPA[^{3}H] thymidine uptake assay system (Amersham Biosciences # RPNQ 0130). SPA-bead based fluorescence was counted in a microbeta counter (Wallace Triplex 1450, Perkin Elmer).

Example 905 CD86 Inhibition Assay

A generalized procedure for a standard assay for the inhibition of B cell activity that can be used to test Formula I compounds is as follows. Total mouse splenocytes are purified from spleens of 8-16 week old Balb/c mice by red blood cell lysis (BD Pharmingen #555899). Testing compounds are diluted to 0.5% DMSO and incubated with 1.25 x 10^6 splenocytes in a final volume of 200 µl in flat clear bottom plates (Falcon 353072) for 60 min at 37°C. Cells are then stimulated with the addition of 15 µg/ml IgM (Jackson ImmunoResearch 115-006-020), and incubated for 24 hr at 37°C, 5% CO_2. Following the 24 hr incubation, cells are transferred to conical bottom clear 96-well plates and pelleted by centrifugation at 1200 x g x 5 min. Cells are preblocked by CD16/CD32 (BD Pharmingen #553142), followed by triple staining with CD19-FITC (BD Pharmingen #553785), CD86-PE (BD Pharmingen #553692), and 7AAD (BD Pharmingen #51-68981E). Cells are sorted on a BD FACSCalibur and gated on the $CD19^+/7AAD^-$ population. The levels of CD86 surface expression on the gated population is measured versus test compound concentration. Exemplary results are in Table 4.

Table 4.	
Compound	CD86 inhibition EC_{50} (μM)
105	0.064
110	0.022
113	0.021
114	0.188
115	0.078
197	0.022
210	0.010
211	0.009
212	0.009
273	0.003
277	0.028
284	0.006
285	0.011
286	0.004
289	0.010
290	0.010
296	0.001
299	0.009
300	0.009
308	0.063
311	0.030
313	0.006
318	0.018

319	0.016
321	0.044

Example 906 B-ALL Cell Survival Assay

The following is a procedure for a standard B-ALL (acute lymphoblastic leukemia) cell survival study using an XTT readout to measure the number of viable cells. This assay can be used to test Formula I compounds for their ability to inhibit the survival of B-ALL cells in culture. One human B-cell acute lymphoblastic leukemia line that can be used is SUP-B15, a human Pre-B-cell ALL line that is available from the ATCC.

SUP-B15 pre-B-ALL cells are plated in multiple 96-well microtiter plates in 100 µl of Iscove's media + 20% FBS at a concentration of 5 x 10^5 cells/ml. Test compounds are then added with a final conc. of 0.4% DMSO. Cells are incubated at 37°C with 5% CO_2 for up to 3 days. After 3 days cells are split 1:3 into fresh 96-well plates containing the test compound and allowed to grow up to an additional 3 days. After each 24h period, 50 ul of an XTT solution is added to one of the replicate 96-well plates and absorbance readings are taken at 2, 4 and 20 hours following manufacturer's directions. The reading taken with an OD for DMSO only treated cells within the linear range of the assay (0.5- 1.5) is then taken and the percentage of viable cells in the compound treated wells are measured versus the DMSO only treated cells.

Example 907 CD69 Whole Blood Assay

Human blood is obtained from healthy volunteers, with the following restrictions: 1 week drug-free, non-smokers. Blood (approximately 20 mls to test 8 compounds) is collected by venipuncture into Vacutainer® (Becton, Dickinson and Co.) tubes with sodium heparin.

Solutions of Formula I compounds at 10 mM in DMSO are diluted 1:10 in 100% DMSO, then are diluted by three-fold serial dilutions in 100% DMSO for a ten point dose-response curve. The compounds are further diluted 1:10 in PBS and then an aliquot of 5.5 µl of each compound is added in duplicate to a 2 ml 96-well plate; 5.5 µl of 10% DMSO in PBS is added as control and no-stimulus wells. Human whole blood – HWB (100 µl) is added to each well. After mixing the plates are incubated at 37 °C, 5% CO_2, 100% humidity for 30 minutes. Goat F(ab')2 anti-human IgM (10 µl of a 500 µg/ml solution, 50 µg/ml final) is added to each well (except the no-stimulus wells) with mixing and the plates are incubated

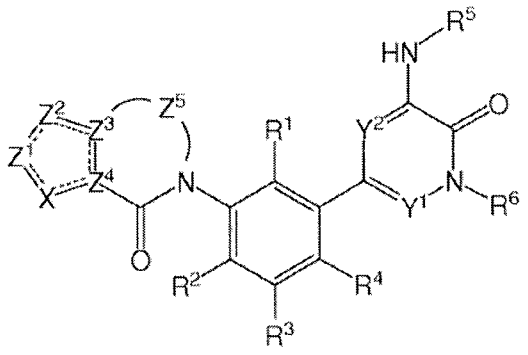
for an additional 20 hours. At the end of the 20 hour incubation, samples are incubated with fluorescent labeled antibodies for 30 minutes, at 37 °C, 5% CO_2, 100% humidity. Include induced control, unstained and single stains for compensation adjustments and initial voltage settings. Samples are then lysed with PharM Lyse™ (BD Biosciences Pharmingen) according to the manufacturer's instructions. Samples are then transferred to a 96 well plate suitable to be run on the BD Biosciences HTS 96 well system on the LSRII machine. Data acquired and Mean Fluorescence Intensity values were obtained using BD Biosciences DIVA Software. Results are initially analyzed by FACS analysis software (Flow Jo). The IC50 for test compounds is defined as the concentration which decreases by 50% the percent positive of CD69 cells that are also CD20 positive stimulated by anti-IgM (average of 8 control wells, after subtraction of the average of 8 wells for the no-stimulus background). The IC50 values are calculated by Prism version 5, using a nonlinear regression curve fit.

Exemplary IC50 values of selected compounds from Tables 1, 2, and 3 in the CD69 Whole Blood Assay include:

Compound No.	IC50 (micromolar)
105	0.088
197	0.023
304	0.035
311	0.044
339	0.053
341	0.024
322	0.053
323	0.024

We Claim:

1. A compound selected from Formula I:



I

or stereoisomers, tautomers, or pharmaceutically acceptable salts thereof, wherein:

R^1 is H, D, F, Cl, CN, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2OH$, heteroaryl selected from imidazolyl and pyrazolyl, heterocyclyl selected from oxetanyl and azetidinyl, and C_1–C_3 alkyl;

R^2, R^3 and R^4 are independently selected from H, D, F, Cl, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2OH$, and C_1–C_3 alkyl;

R^5 is optionally substituted C_6–C_{20} aryl, C_3–C_{12} carbocyclyl, C_2–C_{20} heterocyclyl, C_1–C_{20} heteroaryl, $-(C_6$–C_{20} aryl)–(C_2–C_{20} heterocyclyl), $-(C_1$–C_{20} heteroaryl)–(C_2–C_{20} heterocyclyl), $-(C_1$–C_{20} heteroaryl)–(C_1–C_6 alkyl), or $-(C_1$–C_{20} heteroaryl)–C(=O)–(C_2–C_{20} heterocyclyl);

R^6 is H, F, $-NH_2$, $-OH$, or optionally substituted C_1–C_3 alkyl;

X is S, S(=O), $S(=O)_2$, N, NR^6, O, or CR^7;

R^7 is independently selected from H, D, F, Cl, $-CH_3$, $-CH_2CH_3$, $-CN$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-NH_2$, $-OH$, and $-OCH_3$;

Y^1 and Y^2 are independently selected from CR^6 and N;

Z^1, Z^2, Z^3, and Z^4 are independently selected from C, CR^7, and N;

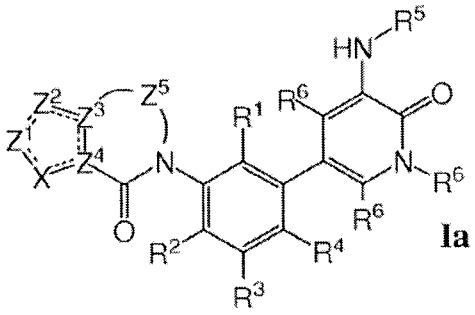
Z^5 is $-CR^3=N-$;

one of Z^1 and Z^2, or X and Z^1, where X is not S, S(=O), or $S(=O)_2$, forms a five-, six-, or seven-membered aryl, carbocyclyl, heterocyclyl or heteroaryl ring;

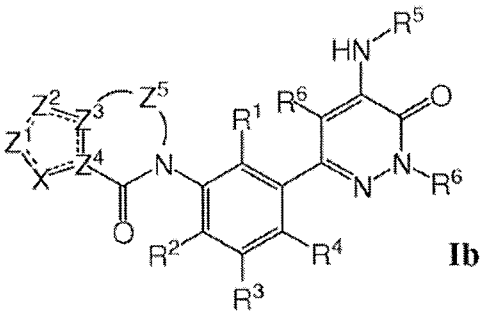
where alkyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more groups independently selected from D, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH_2OH$, $-CH_2CH_2OH$, $-C(CH_3)_2OH$, $-CH(OH)CH(CH_3)_2$, $-C(CH_3)_2CH_2OH$, $-CH_2CH_2SO_2CH_3$, $-CH_2OP(O)(OH)_2$, $-CN$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CO_2H$, $-COCH_3$, $-CO_2CH_3$, $-CO_2C(CH_3)_3$, $-COCH(OH)CH_3$, $-CONH_2$, $-CONHCH_3$, $-CON(CH_3)_2$,

$-C(CH_3)_2CONH_2$, $-NO_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHCOCH_3$, $-N(CH_3)COCH_3$, $-NHS(O)_2CH_3$, $-N(CH_3)C(CH_3)_2CONH_2$, $-N(CH_3)CH_2CH_2S(O)_2CH_3$, =O, $-OH$, $-OCH_3$, $-OCH_2CH_2N(CH_3)_2$, $-OP(O)(OH)_2$, $-S(O)_2N(CH_3)_2$, $-SCH_3$, $-CH_2OCH_3$, $-S(O)_2CH_3$, cyclopropyl, azetidinyl, 1-methylazetidin-3-yl)oxy, N-methyl-N-oxetan-3-ylamino, azetidin-1-ylmethyl, oxetanyl, and morpholino.

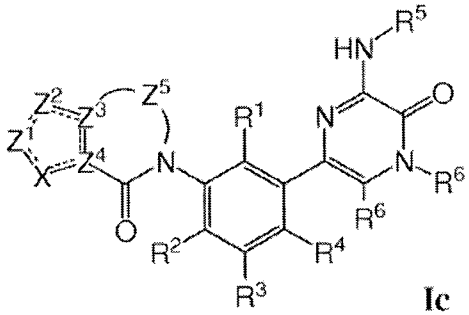
2. The compound of claim 1 selected from Formulas Ia-c:



Ia

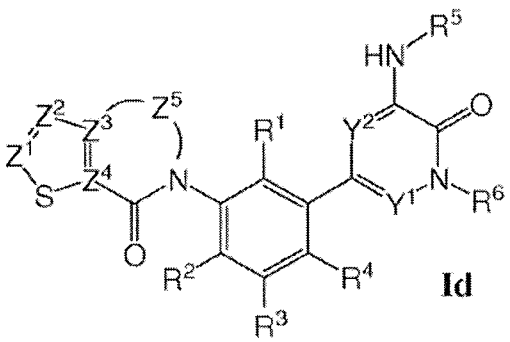


Ib

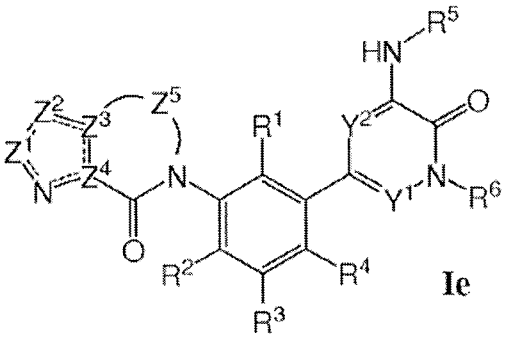


Ic

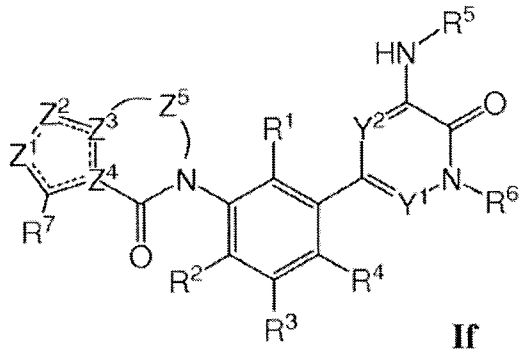
3. The compound of claim 1 selected from Formulas Id-f:



Id

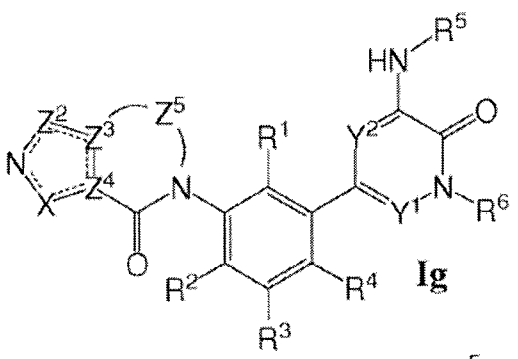


Ie

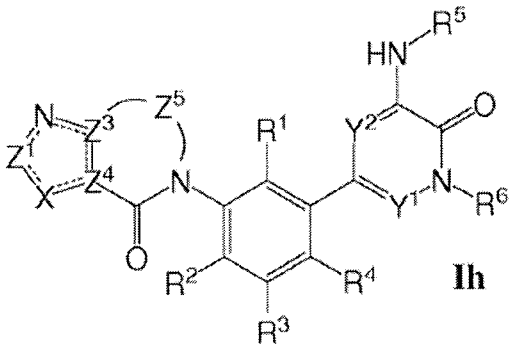


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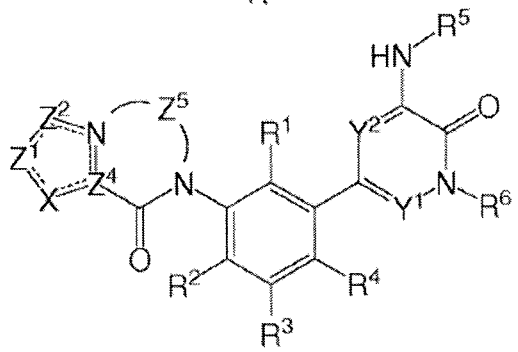
4. The compound of claim 1 selected from Formulas Ig-n:



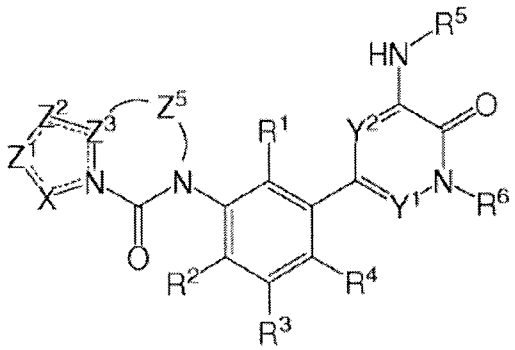
Ig



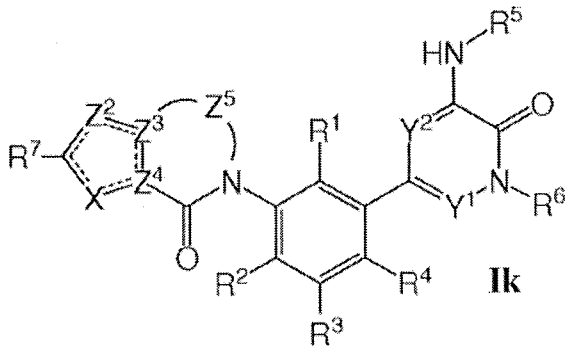
Ih



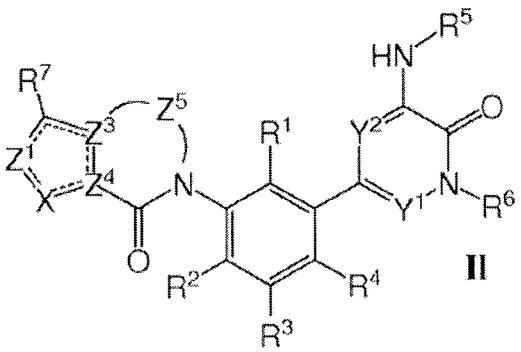
Ii



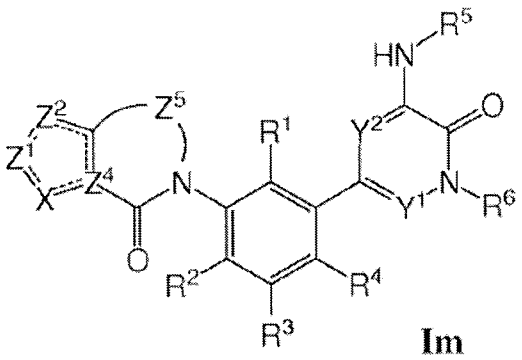
Ij



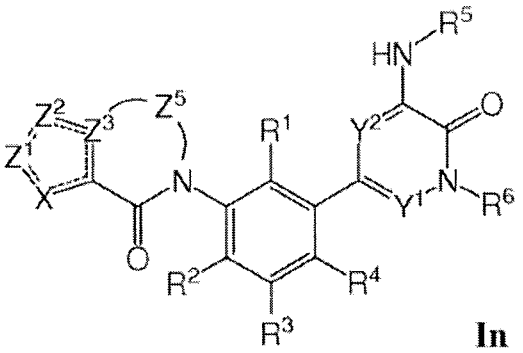
Ik



Il

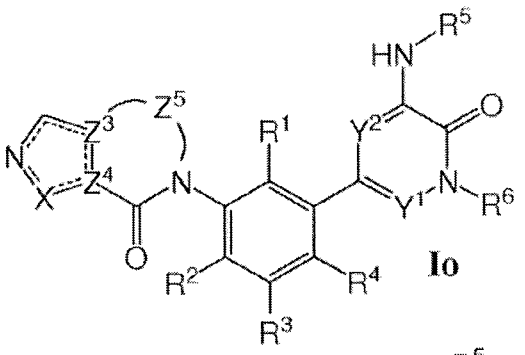


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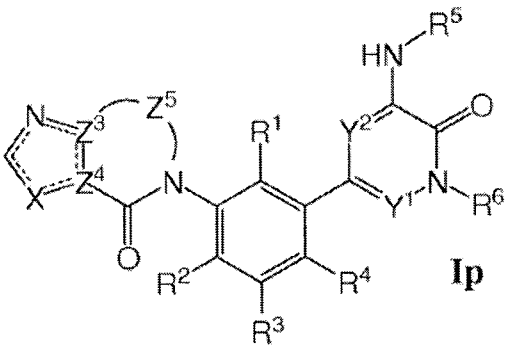


In

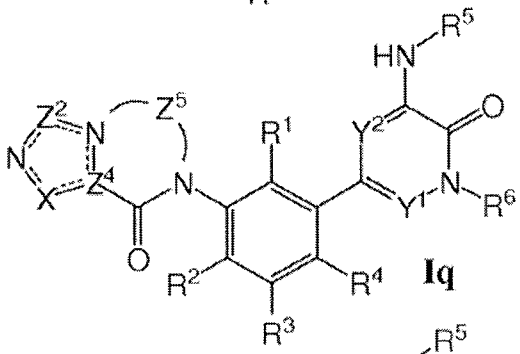
5. The compound of claim 1 selected from Formulas Io-t:



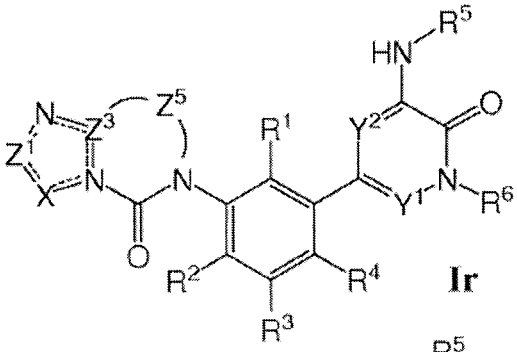
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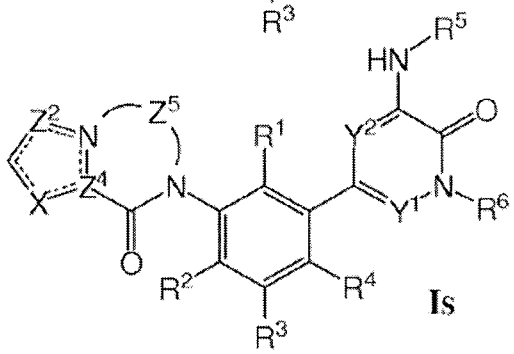
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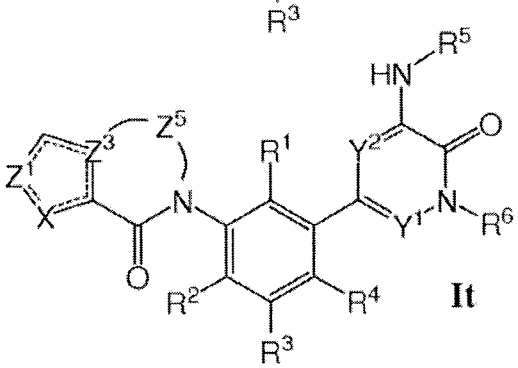
Iq



Ir

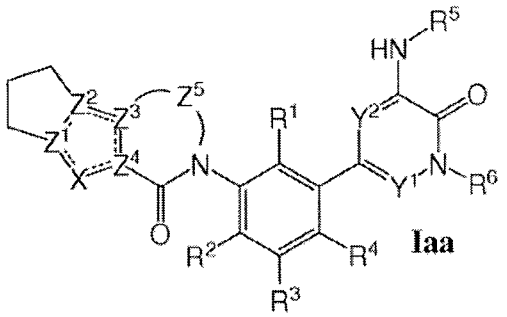


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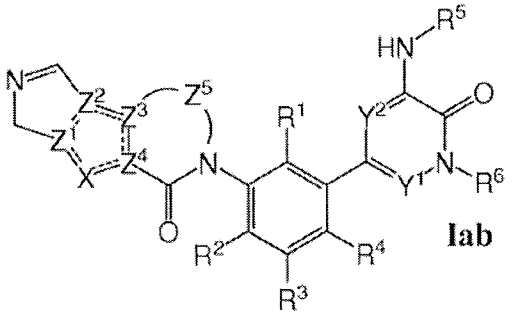


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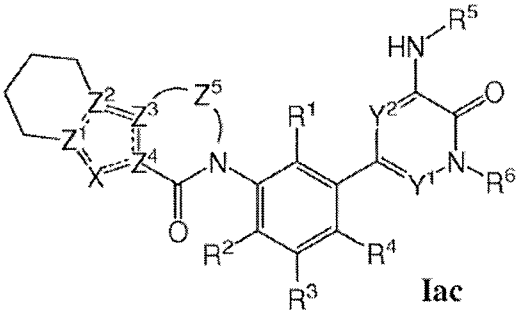
6. The compound of claim 1 where Z^1 and Z^2 forms a five-, six-, or seven- membered aryl, carbocyclyl, heterocyclyl or heteroaryl ring, and selected from Formulas Iaa-ap:



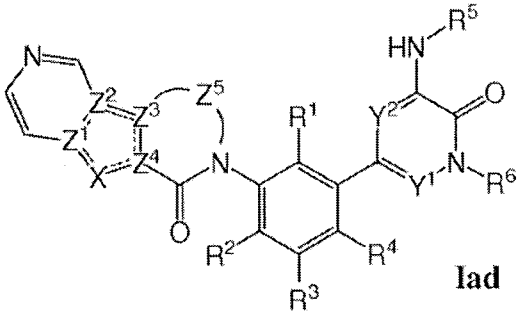
Iaa



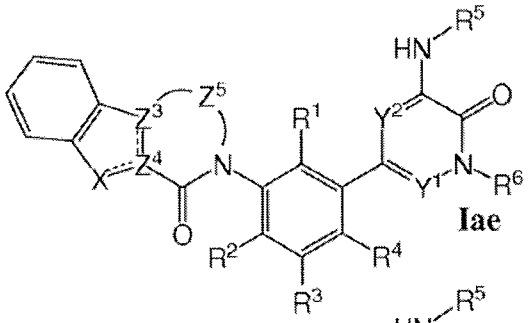
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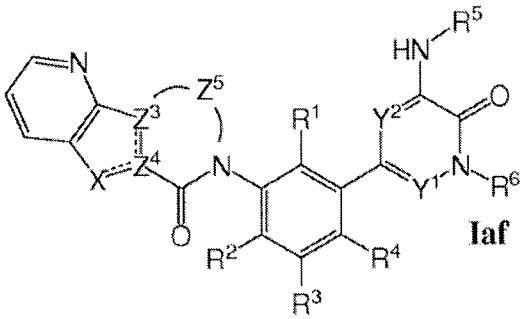
Iac



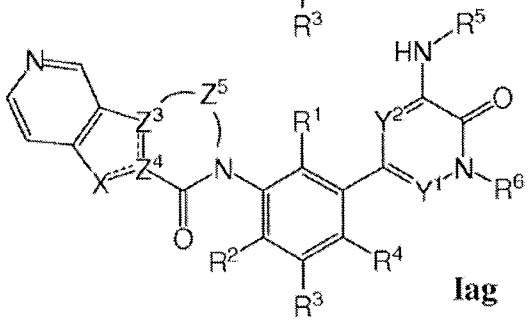
Iad



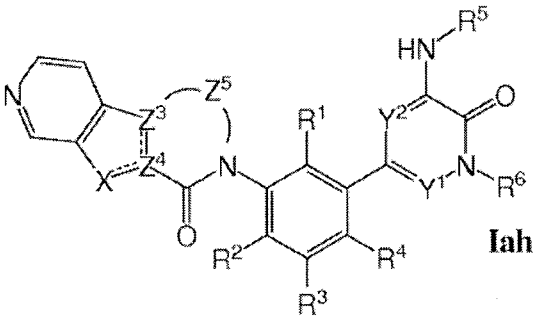
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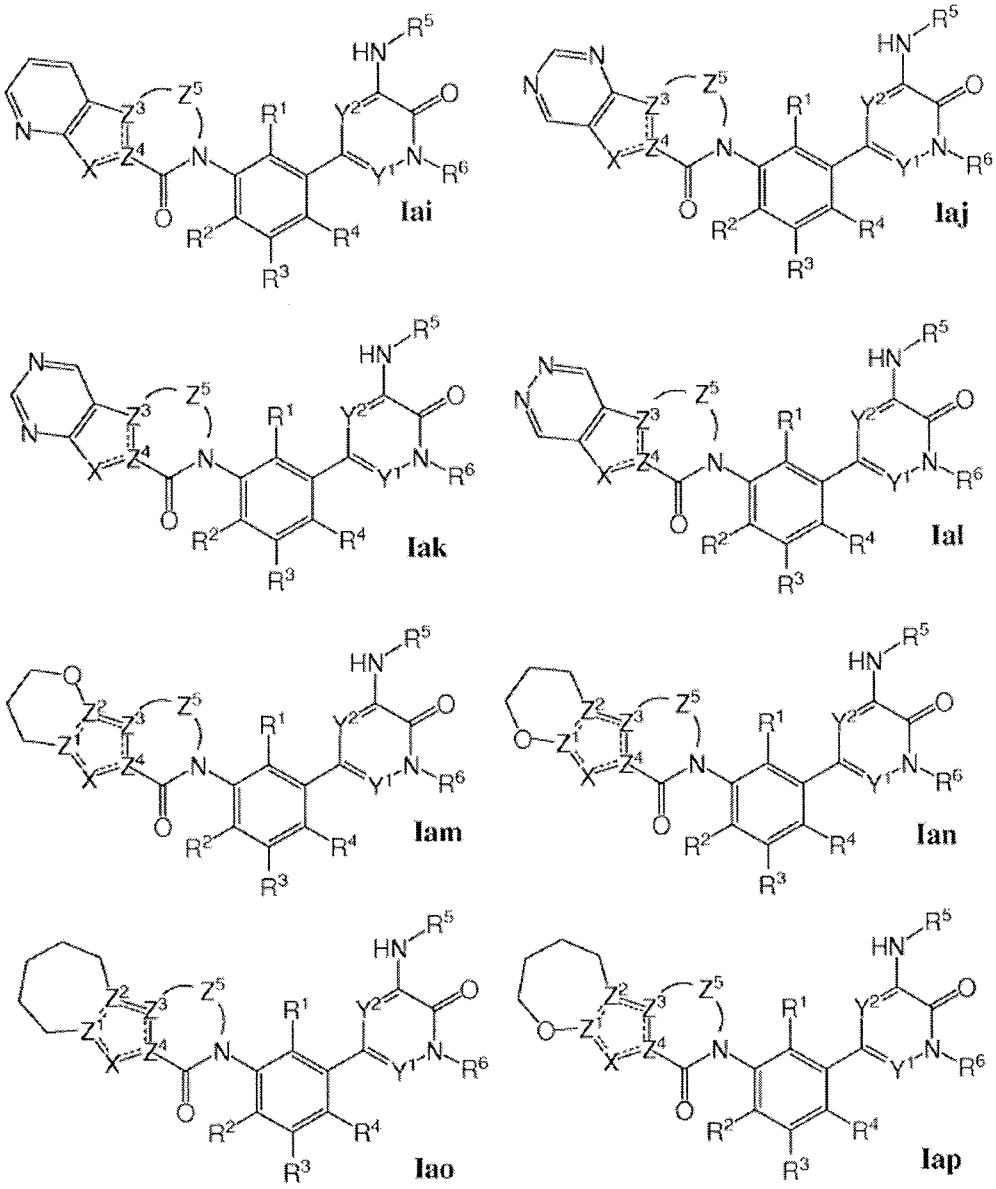
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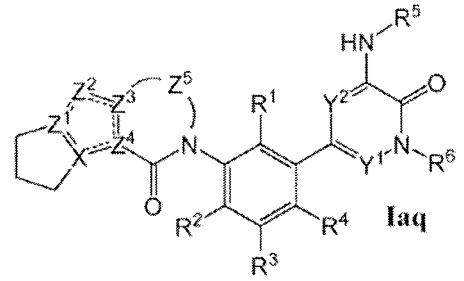
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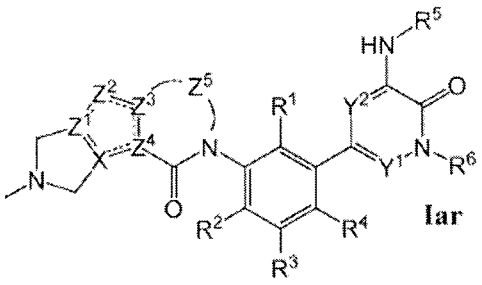
Iah



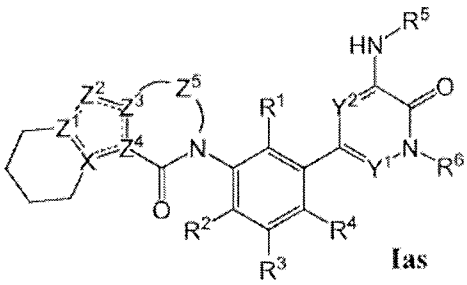
7. The compound of claim 1 where X and Z^1, and X is not S, forms a five-, six-, or seven-membered aryl, carbocyclyl, heterocyclyl or heteroaryl ring, and selected from Formulas Iaq-bf:



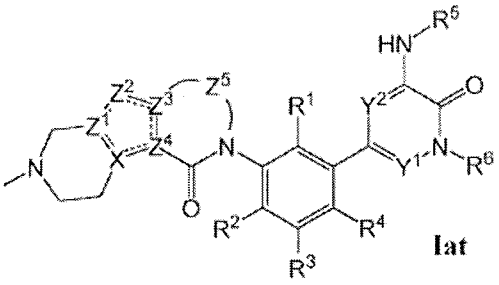
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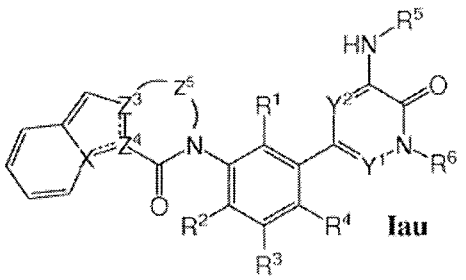
Iar



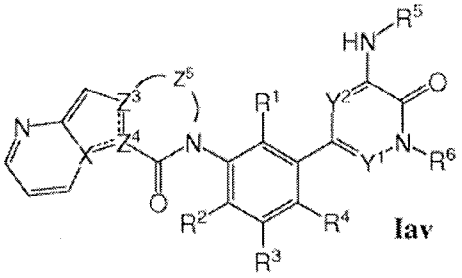
Ias



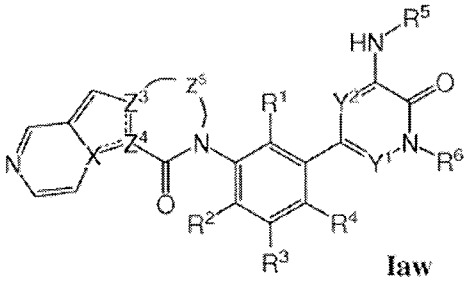
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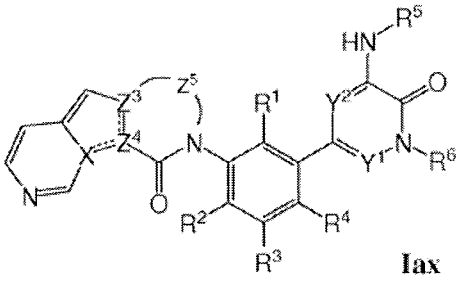
Iau



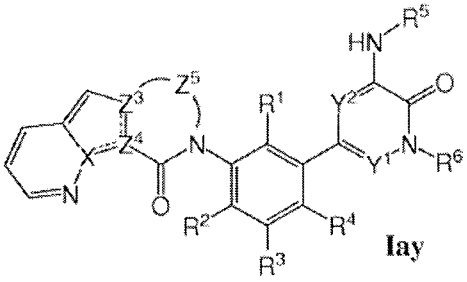
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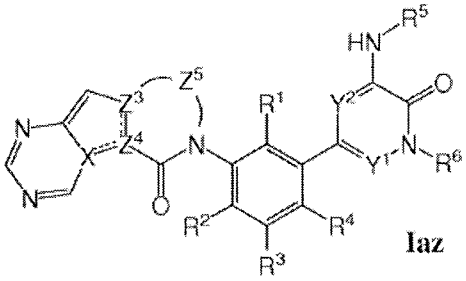
Iaw



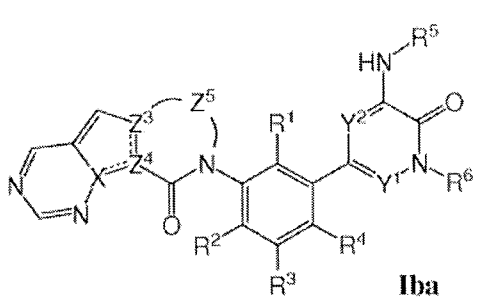
Iax



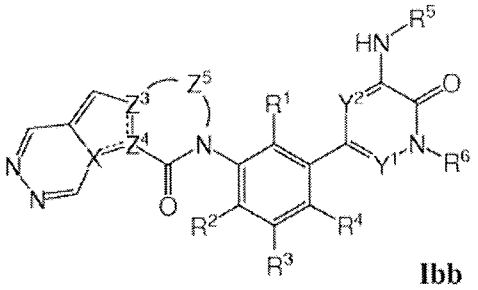
Iay



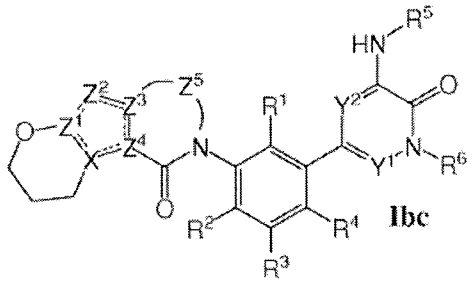
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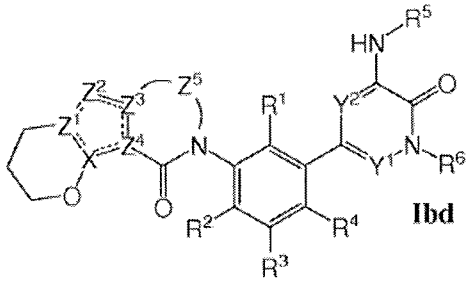
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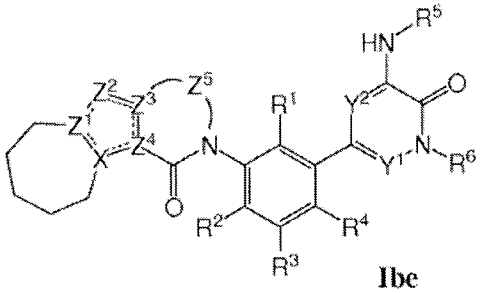
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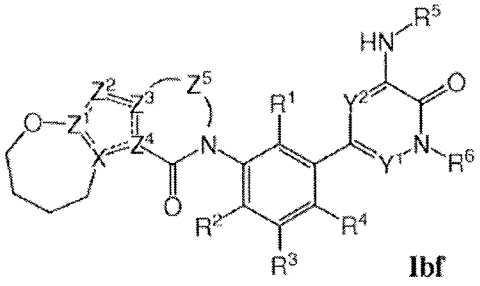
Ibc



Ibd

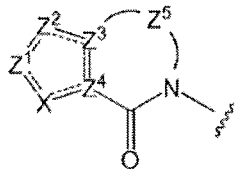


Ibe

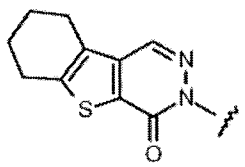


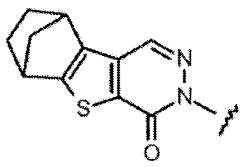
Ibf

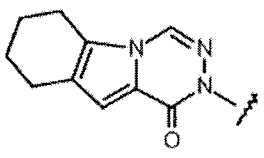
8. The compound of claim 1 where the group:

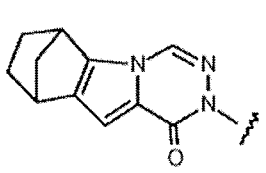
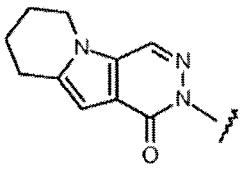


forms the structures:







where the wavy line indicates the site of attachment.

9. The compound of claim 1 to 7 wherein R^1, R^2, R^3, and R^4 are each H.

10. The compound of claim 1 wherein R^1 is selected from F, $-CH_3$, $-CH_2F$, $-CHF_2$, and $-CF_3$.

11. The compound of claim 1 wherein R^1 is $-CH_2OH$.

12. The compound of claim 1 wherein R^3 is F.

13. The compound of claim 1 wherein R^1 is $-CH_2OH$, R^2 and R^4 are each H, and R^3 is F.

14. The compound of claim 1 wherein R^5 is optionally substituted C_6-C_{20} aryl selected from phenyl and naphthyl.

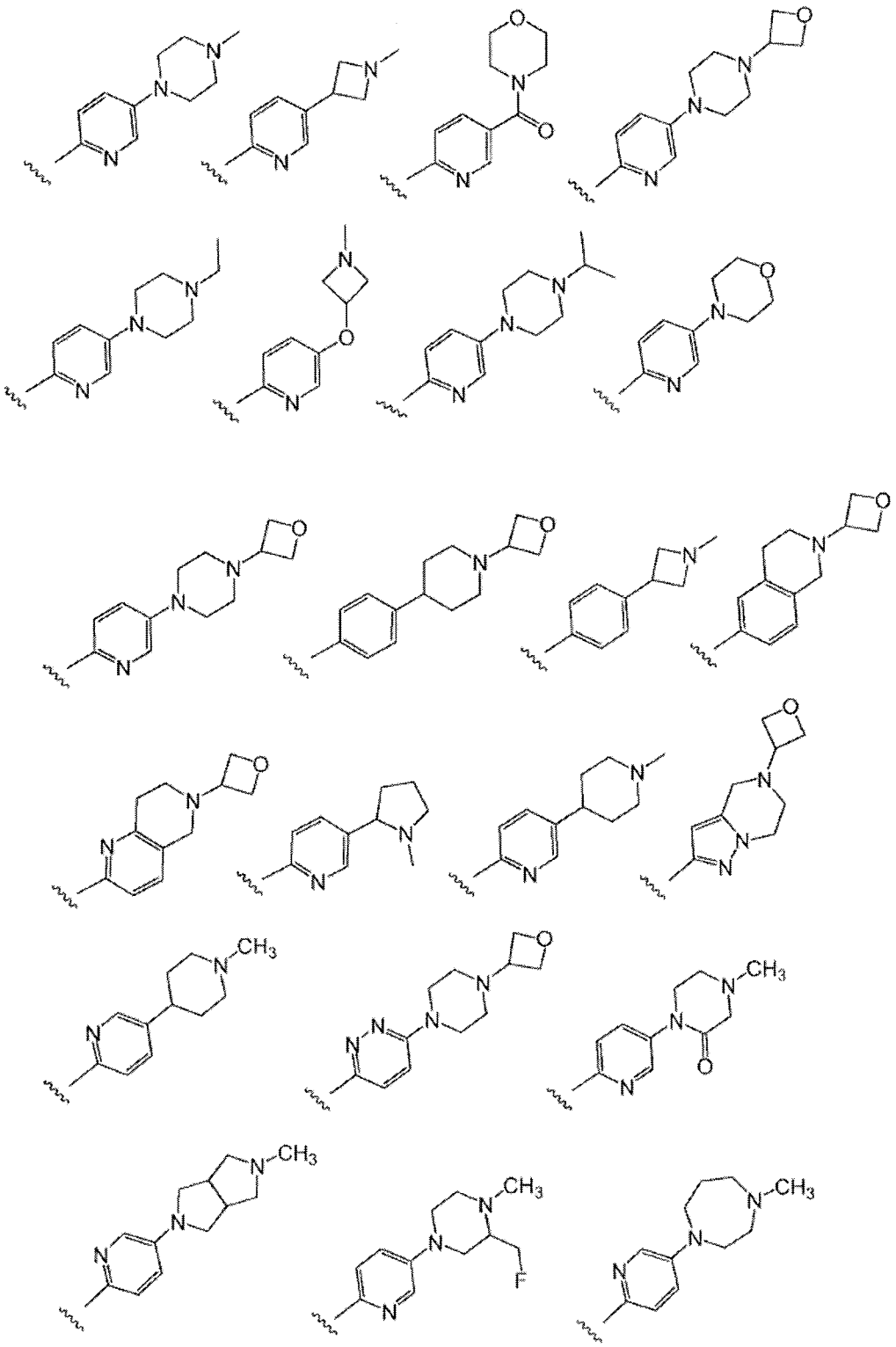
15. The compound of claim 1 wherein R^5 is optionally substituted C_3-C_{12} carbocyclyl selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

16. The compound of claim 1 wherein R^5 is optionally substituted C_2-C_{20} heterocyclyl selected from oxetanyl, azetidinyl, pyrrolidinyl, tetrahydrofuryl, piperidinyl, piperazinyl, morpholinyl, and tetrahydropyranyl.

17. The compound of claim 1 wherein R^5 is optionally substituted C_1–C_{20} heteroaryl selected from pyrazolyl, pyridinyl, pyrimidinyl, 5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl, 5-acetyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl, 6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-2-yl, and 1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridin-2-yl.

18. The compound of claim 17 wherein R^5 is substituted with one or more groups selected from F, Cl, $-CH_3$, cyclopropyl, azetidinyl, oxetanyl, and morpholino.

19. The compound of claim 1 wherein R^5 is selected from the structures:



where the wavy line indicates the site of attachment.

20. The compound of claim 1 wherein R^6 is H.

21. The compound of claim 1 wherein X is S.

22. The compound of claim 1 wherein X is N.

23. The compound of claim 1 wherein X is CR^7.

24. The compound of claim 1 wherein Y^1 is CR^6 and Y^2 is N.

25. The compound of claim 1 wherein Y^1 is N and Y^2 is CR^6.

26. The compound of claim 1 wherein Y^1 and Y^2 are each CR^6.

27. The compound of claim 1 selected from:

5-[5-fluoro-2-(hydroxymethyl)-3-[1-methyl-5-({5-[4-(oxetan-3-yl)piperazin-1-yl]pyridine-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-8-thia-4,5-diazatricyclo[7.4.0.0^{2,7}]-trideca-1(9),2(7),3(4)-trien-6-one,

5-[5-fluoro-2-(hydroxymethyl)-3-[1-methyl-5-({5-[4-methylpiperazin-1-yl]pyridine-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-8-thia-4,5-diazatricyclo[7.4.0.0^{2,7}]-trideca-1(9),2(7),3(4)-trien-6-one,

3-(5-Fluoro-2-hydroxymethyl-3-{1-methyl-5-[6-(4-methyl-piperazin-1-yl)-pyridazin-3-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-6,7,8,9-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyridazin-4-one,

3-(5-Fluoro-2-hydroxymethyl-3-{1-methyl-5-[6-(4-oxetan-3-yl-piperazin-1-yl)-pyridazin-3-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-6,7,8,9-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyridazin-4-one,

2-(5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-6,7,8,9-tetrahydro-[1,2,4]triazino[4,5-a]indol-1(2H)-one, and

2-(5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-6,7,8,9-tetrahydro-[1,2,4]triazino[4,5-a]indol-1(2H)-one.

28. A pharamceutical composition comprised of a compound of claim 1 and a pharmaceutically acceptable carrier, glidant, diluent, or excipient.

29. The pharmaceutical composition of claim 28, further comprising a second therapeutic agent.

30. A process for making a pharmaceutical composition which comprises combining a compound of claim 1 with a pharmaceutically acceptable carrier.