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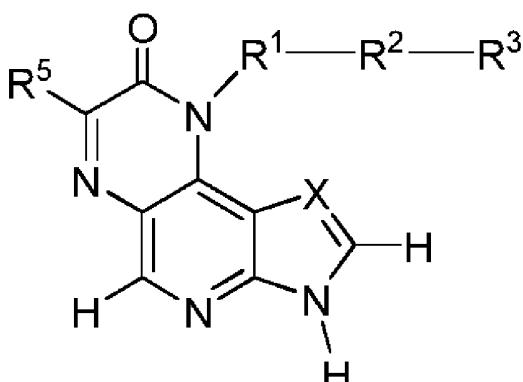
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(54) Title: TRICYCLIC PYRAZINONE COMPOUNDS, COMPOSITIONS AND METHODS OF USE THEREOF AS JANUS KINASE INHIBITORS


(I)

(57) Abstract: The invention provides novel compounds of formula I having the general formula (I) wherein X, R¹, R², R³ and R⁵ are as described herein. Accordingly, the compounds may be provided in pharmaceutically acceptable compositions and used for the treatment of immunological or hyperproliferative disorders.

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**TRICYCLIC PYRAZINONE COMPOUNDS, COMPOSITIONS AND METHODS OF USE
THEREOF AS JANUS KINASE INHIBITORS**

FIELD OF THE INVENTION

Compounds of formula I, which are inhibitors of a Janus kinase, as well as compositions containing these compounds, and methods of use including, but not limited to, *in vitro*, *in situ* and *in vivo* diagnosis or treatment of mammalian cells.

BACKGROUND OF INVENTION

Cytokine pathways mediate a broad range of biological functions, including many aspects of inflammation and immunity. Janus kinases (JAK), including JAK1, JAK2, JAK3 and TYK2 are cytoplasmic protein kinases that associate with type I and type II cytokine receptors and regulate cytokine signal transduction. Cytokine engagement with cognate receptors triggers activation of receptor associated JAKs and this leads to JAK-mediated tyrosine phosphorylation of signal transducer and activator of transcription (STAT) proteins and ultimately transcriptional activation of specific gene sets (Schindler et al., 2007, J Biol. Chem. 282: 20059-63). JAK1, JAK2 and TYK2 exhibit broad patterns of gene expression, while JAK3 expression is limited to leukocytes. Cytokine receptors are typically functional as heterodimers, and as a result, more than one type of JAK kinase is usually associated with cytokine receptor complexes. The specific JAKs associated with different cytokine receptor complexes have been determined in many cases through genetic studies and corroborated by other experimental evidence.

JAK1 was initially identified in a screen for novel kinases (Wilks A.F., 1989, Proc. Natl. Acad. Sci. U.S.A. 86:1603-1607). Genetic and biochemical studies have shown that JAK1 is functionally and physically associated with the type I interferon (e.g., IFN α), type II interferon (e.g., IFN γ), IL-2 and IL-6 cytokine receptor complexes (Kisseleva et al., 2002, gene 285:1-24; Levy et al., 2005, Nat. Rev. Mol. Cell Biol. 3:651-662; O'Shea et al., 2002, Cell, 109 (suppl.): S121-S131). JAK1 knockout mice die perinatally due to defects in LIF receptor signaling (Kisseleva et al., 2002, gene 285:1-24; O'Shea et al., 2002, Cell, 109 (suppl.): S121-S131). Characterization of tissues derived from JAK1 knockout mice demonstrated critical roles for this kinase in the IFN, IL-10, IL-2/IL-4, and IL-6 pathways. A humanized monoclonal antibody targeting the IL-6 pathway (Tocilizumab) was recently approved by the European

Commission for the treatment of moderate-to-severe rheumatoid arthritis (Scheinecker et al., 2009, Nat. Rev. Drug Discov. 8:273-274).

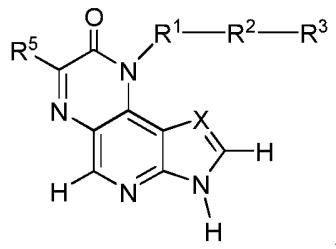
Biochemical and genetic studies have shown an association between JAK2 and single-chain (e.g., EPO), IL-3 and interferon gamma cytokine receptor families (Kisseleva et al., 2002, gene 285:1-24; Levy et al., 2005, Nat. Rev. Mol. Cell Biol. 3:651-662; O'Shea et al., 2002, Cell, 109 (suppl.): S121-S131). Consistent with this, JAK2 knockout mice die of anemia (O'Shea et al., 2002, Cell, 109 (suppl.): S121-S131). Kinase activating mutations in JAK2 (e.g., JAK2 V617F) are associated with myeloproliferative disorders (MPDs) in humans.

JAK3 associates exclusively with the gamma common cytokine receptor chain, which is present in the IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 cytokine receptor complexes. JAK3 is critical for lymphoid cell development and proliferation and mutations in JAK3 result in severe combined immunodeficiency (SCID) (O'Shea et al., 2002, Cell, 109 (suppl.): S121-S131). Based on its role in regulating lymphocytes, JAK3 and JAK3-mediated pathways have been targeted for immunosuppressive indications (e.g., transplantation rejection and rheumatoid arthritis) (Baslund et al., 2005, Arthritis & Rheumatism 52:2686-2692; Changelian et al., 2003, Science 302: 875-878).

TYK2 associates with the type I interferon (e.g., IFNalpha), IL-6, IL-10, IL-12 and IL-23 cytokine receptor complexes (Kisseleva et al., 2002, gene 285:1-24; Watford, W.T. & O'Shea, J.J., 2006, Immunity 25:695-697). Consistent with this, primary cells derived from a TYK2 deficient human are defective in type I interferon, IL-6, IL-10, IL-12 and IL-23 signaling. A fully human monoclonal antibody targeting the shared p40 subunit of the IL-12 and IL-23 cytokines (Ustekinumab) was recently approved by the European Commission for the treatment of moderate-to-severe plaque psoriasis (Krueger et al., 2007, N. Engl. J. Med. 356:580-92; Reich et al., 2009, Nat. Rev. Drug Discov. 8:355-356). In addition, an antibody targeting the IL-12 and IL-23 pathways underwent clinical trials for treating Crohn's Disease (Mannon et al., 2004, N. Engl. J. Med. 351:2069-79).

SUMMARY OF INVENTION

One aspect includes a compound of formula I:



stereoisomers, tautomers or pharmaceutically acceptable salts thereof, wherein X, R¹, R², R³ and R⁵ are defined herein.

Another aspect includes a pharmaceutical composition that includes a compound of
5 formula I and a pharmaceutically acceptable carrier, adjuvant or vehicle.

Another aspect includes a method of treating or lessening the severity of a disease or condition responsive to the inhibition of JAK1 kinase activity in a patient. The method includes administering to the patient a therapeutically effective amount of a compound of formula I.

Another aspect includes a compound of formula I, a stereoisomer, tautomer, prodrug or
10 pharmaceutically acceptable salt thereof, for use in therapy.

Another aspect includes use of a compound of Formula I, a stereoisomer, tautomer, prodrug or pharmaceutically acceptable salt thereof, in the treatment of an immunological or inflammatory disease.

Another aspect includes a compound of Formula I, a stereoisomer, tautomer, prodrug or
15 pharmaceutically acceptable salt thereof, in therapy.

Another aspect includes the use of a compound of formula I, a stereoisomer, tautomer, prodrug or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease responsive to the inhibition of JAK1 kinase activity.

Another aspect includes methods of preparing a compound of Formula I, a stereoisomer,
20 tautomer, prodrug or pharmaceutically acceptable salt thereof.

Another aspect includes a kit for treating a disease or disorder responsive to the inhibition of JAK1 kinase. The kit includes a first pharmaceutical composition comprising a compound of formula I and instructions for use

DETAILED DESCRIPTION OF THE INVENTION**DEFINITIONS**

“Acyl” means a carbonyl containing substituent represented by the formula -C(O)-R in which R is hydrogen, alkyl, a cycloalkyl, a heterocyclyl, cycloalkyl -substituted alkyl or 5 heterocyclyl-substituted alkyl wherein the alkyl, alkoxy, cycloalkyl and heterocyclyl are as defined herein. Acyl groups include alkanoyl (e.g. acetyl), aroyl (e.g. benzoyl), and heteroaroyl (e.g. pyridinoyl).

The term "alkyl" refers to a saturated linear or branched-chain monovalent hydrocarbon radical, wherein the alkyl radical may be optionally substituted independently with one or more 10 substituents described herein. In one example, the alkyl radical is one to eighteen carbon atoms (C₁-C₁₈). In other examples, the alkyl radical is C₀-C₆, C₀-C₅, C₀-C₃, C₁-C₁₂, C₁-C₁₀, C₁-C₈, C₁-C₆, C₁-C₅, C₁-C₄, or C₁-C₃. C₀ alkyl refers to a bond. Examples of alkyl groups include methyl 15 (Me, -CH₃), ethyl (Et, -CH₂CH₃), 1-propyl (n-Pr, n-propyl, -CH₂CH₂CH₃), 2-propyl (i-Pr, i-propyl, -CH(CH₃)₂), 1-butyl (n-Bu, n-butyl, -CH₂CH₂CH₂CH₃), 2-methyl-1-propyl (i-Bu, i-butyl, -CH₂CH(CH₃)₂), 2-butyl (s-Bu, s-butyl, -CH(CH₃)CH₂CH₃), 2-methyl-2-propyl (t-Bu, t-butyl, -C(CH₃)₃), 1-pentyl (n-pentyl, -CH₂CH₂CH₂CH₂CH₃), 2-pentyl (-CH(CH₃)CH₂CH₂CH₃), 3-pentyl (-CH(CH₂CH₃)₂), 2-methyl-2-butyl (-C(CH₃)₂CH₂CH₃), 3-methyl-2-butyl (-CH(CH₃)CH(CH₃)₂), 3-methyl-1-butyl (-CH₂CH₂CH(CH₃)₂), 2-methyl-1-butyl (-CH₂CH(CH₃)CH₂CH₃), 1-hexyl (-CH₂CH₂CH₂CH₂CH₂CH₃), 2-hexyl (-CH₂CH₂CH₂CH₂CH₂CH₃), 3-hexyl (-CH(CH₂CH₃)(CH₂CH₂CH₃)), 2-methyl-2-pentyl (-C(CH₃)₂CH₂CH₂CH₃), 3-methyl-2-pentyl (-CH(CH₃)CH(CH₃)CH₂CH₃), 4-methyl-2-pentyl (-CH(CH₃)CH₂CH(CH₃)₂), 3-methyl-3-pentyl (-C(CH₃)(CH₂CH₃)₂), 2-methyl-3-pentyl (-CH(CH₂CH₃)CH(CH₃)₂), 2,3-dimethyl-2-butyl (-C(CH₃)₂CH(CH₃)₂), 3,3-dimethyl-2-butyl (-CH(CH₃)C(CH₃)₃), 1-heptyl and 1-octyl.

25 The term "alkenyl" refers to linear or branched-chain monovalent hydrocarbon radical with at least one site of unsaturation, i.e., a carbon-carbon double bond, wherein the alkenyl radical may be optionally substituted independently with one or more substituents described herein, and includes radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations. In one example, the alkenyl radical is two to eighteen carbon atoms (C₂-C₁₈). In

other examples, the alkenyl radical is C₂-C₁₂, C₂-C₁₀, C₂-C₈, C₂-C₆ or C₂-C₃. Examples include, but are not limited to, ethenyl or vinyl (-CH=CH₂), prop-1-enyl (-CH=CHCH₃), prop-2-enyl (-CH₂CH=CH₂), 2-methylprop-1-enyl, but-1-enyl, but-2-enyl, but-3-enyl, buta-1,3-dienyl, 2-methylbuta-1,3-diene, hex-1-enyl, hex-2-enyl, hex-3-enyl, hex-4-enyl and hexa-1,3-dienyl.

5 The term "alkoxy" refers to a linear or branched monovalent radical represented by the formula -OR in which R is alkyl, alkenyl, alkynyl or cycloalkyl, which can be further optionally substituted as defined herein. Alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, mono-, di- and tri-fluoromethoxy and cyclopropoxy.

The term "alkynyl" refers to a linear or branched monovalent hydrocarbon radical with at least one site of unsaturation, i.e., a carbon-carbon, triple bond, wherein the alkynyl radical may be optionally substituted independently with one or more substituents described herein. In one example, the alkynyl radical is two to eighteen carbon atoms (C₂-C₁₈). In other examples, the alkynyl radical is C₂-C₁₂, C₂-C₁₀, C₂-C₈, C₂-C₆ or C₂-C₃. Examples include, but are not limited to, ethynyl (-C≡CH), prop-1-ynyl (-C≡CCH₃), prop-2-ynyl (propargyl, -CH₂C≡CH), but-1-ynyl, 15 but-2-ynyl and but-3-ynyl.

"Alkylene" refers to a saturated, branched or straight chain hydrocarbon group having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkane. In one example, the divalent alkylene group is one to eighteen carbon atoms (C₁-C₁₈). In other examples, the divalent alkylene group is C₀-C₆, 20 C₀-C₅, C₀-C₃, C₁-C₁₂, C₁-C₁₀, C₁-C₈, C₁-C₆, C₁-C₅, C₁-C₄, or C₁-C₃. The group C₀ alkylene refers to a bond. Example alkylene groups include methylene (-CH₂), 1,1-ethyl (-CH(CH₃)-), (1,2-ethyl (-CH₂CH₂)-), 1,1-propyl (-CH(CH₂CH₃)-), 2,2-propyl (-C(CH₃)₂-), 1,2-propyl (-CH(CH₃)CH₂-), 1,3-propyl (-CH₂CH₂CH₂-), 1,1-dimethyleth-1,2-yl (-C(CH₃)₂CH₂-), 1,4-butyl (-CH₂CH₂CH₂CH₂-), and the like.

25 "Alkenylene" refers to an unsaturated, branched or straight chain hydrocarbon group having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkene. In one example, the alkenylene group is two to eighteen carbon atoms (C₂-C₁₈). In other examples, the alkenylene group is C₂-C₁₂, C₂-C₁₀, C₂-C₈, C₂-C₆ or C₂-C₃. Example alkenylene groups include: 1,2-ethylene (-CH=CH-).

“Alkynylene” refers to an unsaturated, branched or straight chain hydrocarbon group having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkyne. In one example, the alkynylene radical is two to eighteen carbon atoms (C₂-C₁₈). In other examples, the alkynylene radical is C₂-C₁₂, C₂-C₁₀, C₂-C₈, C₂-C₆ or C₂-C₃. Example alkynylene radicals include: acetylene (-C≡C-), propargyl (-CH₂C≡C-), and 4-pentynyl (-CH₂CH₂CH₂C≡C-).

“Amidine” means the group -C(NH)-NHR in which R is hydrogen, alkyl, a cycloalkyl, a heterocyclyl, cycloalkyl-substituted alkyl or heterocyclyl-substituted alkyl wherein the alkyl, alkoxy, cycloalkyl and heterocyclyl are as defined herein. A particular amidine is the group -NH-C(NH)-NH₂.

“Amino” means primary (i.e., -NH₂), secondary (i.e., -NRH) and tertiary (i.e., -NRR) amines, that are optionally substituted, in which R is alkyl, alkoxy, a cycloalkyl, a heterocyclyl, cycloalkyl-substituted alkyl or heterocyclyl-substituted alkyl wherein the alkyl, alkoxy, cycloalkyl and heterocyclyl are as defined herein. Particular secondary and tertiary amines are alkylamine, dialkylamine, arylamine, diarylamine, aralkylamine and diaralkylamine wherein the alkyl is as herein defined and optionally substituted. Particular secondary and tertiary amines are methylamine, ethylamine, propylamine, isopropylamine, phenylamine, benzylamine dimethylamine, diethylamine, dipropylamine and diisopropylamine.

“Amino-protecting group” as used herein refers to a derivative of the groups commonly employed to block or protect an amino group while reactions are carried out on other functional groups on the compound. Examples of such protecting groups include carbamates, amides, alkyl and aryl groups, imines, as well as many N-heteroatom derivatives which can be removed to regenerate the desired amine group. Particular amino protecting groups are Pmb (p-Methoxybenzyl), Boc (tert-Butyloxycarbonyl), Fmoc (9-Fluorenylmethyloxycarbonyl) and Cbz (Carbobenzyloxy). Further examples of these groups are found in T. W. Greene and P. G. M. Wuts, “Protective Groups in Organic Synthesis”, 2nd ed., John Wiley & Sons, Inc., New York, NY, 1991, chapter 7; E. Haslam, “Protective Groups in Organic Chemistry”, J. G. W. McOmie, Ed., Plenum Press, New York, NY, 1973, Chapter 5, and T.W. Greene, “Protective Groups in Organic Synthesis”, John Wiley and Sons, New York, NY, 1981. The term “protected amino” refers to an amino group substituted with one of the above amino-protecting groups.

“Aryl” when used alone, or as part of another term, means a carbocyclic aromatic group, whether or not fused to one or more groups, having the number of carbon atoms designated, or if no number is designated, up to 14 carbon atoms. One example includes aryl groups having 6-14 carbon atoms. Another example includes aryl groups having 6-10 carbon atoms. Examples of 5 aryl groups include phenyl, naphthyl, biphenyl, phenanthrenyl, naphthacenyl, 1,2,3,4-tetrahydronaphthalenyl, 1H-indenyl, 2,3-dihydro-1H-indenyl, and the like (see e.g. *Lang's Handbook of Chemistry* (Dean, J. A., ed) 13th ed. Table 7-2 [1985]). A particular aryl is phenyl. Substituted phenyl or substituted aryl means a phenyl group or aryl group substituted with one, two, three, four or five, for example 1-2, 1-3 or 1-4 substituents chosen from groups specified 10 herein. In one example, optional substituents on aryl are selected from halogen (F, Cl, Br, I), hydroxy, protected hydroxy, cyano, nitro, alkyl (for example C₁-C₆ alkyl), alkoxy (for example C₁-C₆ alkoxy), benzyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, aminomethyl, protected aminomethyl, trifluoromethyl, alkylsulfonylamino, alkylsulfonylaminooalkyl, arylsulfonylamino, 15 arylsulfonylaminooalkyl, heterocyclsulfonylamino, heterocyclsulfonylaminooalkyl, heterocycl, optionally substituted phenyl, or other groups specified. One or more methyne (CH) and/or methylene (CH₂) groups in these substituents may in turn be substituted with a similar group as those denoted above. Examples of the term “substituted phenyl” include a mono- or di(halo)phenyl group such as 2-chlorophenyl, 2-bromophenyl, 4-chlorophenyl, 2,6- 20 dichlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 3-chlorophenyl, 3-bromophenyl, 4-bromophenyl, 3,4-dibromophenyl, 3-chloro-4-fluorophenyl, 2-fluorophenyl and the like; a mono- or di(hydroxy)phenyl group such as 4-hydroxyphenyl, 3-hydroxyphenyl, 2,4-dihydroxyphenyl, the protected-hydroxy derivatives thereof and the like; a nitrophenyl group such as 3- or 4-nitrophenyl; a cyanophenyl group, for example, 4-cyanophenyl; a mono- or di(lower 25 alkyl)phenyl group such as 4-methylphenyl, 2,4-dimethylphenyl, 2-methylphenyl, 4-(isopropyl)phenyl, 4-ethylphenyl, 3-(n-propyl)phenyl and the like; a mono or di(alkoxy)phenyl group, for example, 3,4-dimethoxyphenyl, 3-methoxy-4-benzyloxyphenyl, 3-ethoxyphenyl, 4-(isoproxy)phenyl, 4-(t-butoxy)phenyl, 3-ethoxy-4-methoxyphenyl and the like; 3- or 4-trifluoromethylphenyl; a mono- or dicarboxyphenyl or (protected carboxy)phenyl group such 30 4-carboxyphenyl, a mono- or di(hydroxymethyl)phenyl or (protected hydroxymethyl)phenyl such as 3-(protected hydroxymethyl)phenyl or 3,4-di(hydroxymethyl)phenyl; a mono- or

di(aminomethyl)phenyl or (protected aminomethyl)phenyl such as 2-(aminomethyl)phenyl or 2,4-(protected aminomethyl)phenyl; or a mono- or di(N-(methylsulfonylamino))phenyl such as 3-(N-methylsulfonylamino))phenyl. Also, the term "substituted phenyl" represents disubstituted phenyl groups where the substituents are different, for example, 3-methyl-4-hydroxyphenyl, 3-chloro-4-hydroxyphenyl, 2-methoxy-4-bromophenyl, 4-ethyl-2-hydroxyphenyl, 3-hydroxy-4-nitrophenyl, 2-hydroxy-4-chlorophenyl, and the like, as well as trisubstituted phenyl groups where the substituents are different, for example 3-methoxy-4-benzylxy-6-methyl sulfonylamino, 3-methoxy-4-benzylxy-6-phenyl sulfonylamino, and tetrasubstituted phenyl groups where the substituents are different such as 3-methoxy-4-benzylxy-5-methyl-6-phenyl sulfonylamino. Particular substituted phenyl groups include the 2-chlorophenyl, 2-aminophenyl, 2-bromophenyl, 3-methoxyphenyl, 3-ethoxy-phenyl, 4-benzylxyphenyl, 4-methoxyphenyl, 3-ethoxy-4-benzylxyphenyl, 3,4-diethoxyphenyl, 3-methoxy-4-benzylxyphenyl, 3-methoxy-4-(1-chloromethyl)benzylxy-6-methyl sulfonyl aminophenyl groups. Fused aryl rings may also be substituted with any, for example 1, 2 or 3, of the substituents specified herein in the same manner as substituted alkyl groups.

The terms "cancer" and "cancerous", "neoplasm", "tumor" refer 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 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, melanoma, multiple myeloma and B-cell lymphoma, brain, as well as head and neck cancer, and associated metastases.

A "chemotherapeutic agent" is an agent useful in the treatment of a given disorder, for example, cancer or inflammatory disorders. Examples of chemotherapeutic agents include

NSAIDs; hormones such as glucocorticoids; corticosteroids such as hydrocortisone, hydrocortisone acetate, cortisone acetate, tixocortol pivalate, prednisolone, methylprednisolone, prednisone, triamcinolone acetonide, triamcinolone alcohol, mometasone, amcinonide, budesonide, desonide, fluocinonide, fluocinolone acetonide, halcinonide, betamethasone, 5 betamethasone sodium phosphate, dexamethasone, dexamethasone sodium phosphate, flucortolone, hydrocortisone-17-butyrate, hydrocortisone-17-valerate, aclometasone dipropionate, betamethasone valerate, betamethasone dipropionate, prednicarbate, clobetasone-17-butyrate, clobetasol-17-propionate, flucortolone caproate, flucortolone pivalate and fluprednidene acetate; immune selective anti-inflammatory peptides (ImSAIDs) such as 10 phenylalanine-glutamine-glycine (FEG) and its D-isomeric form (feG) (IMULAN BioTherapeutics, LLC); anti-rheumatic drugs such as azathioprine, ciclosporin (cyclosporine A), D-penicillamine, gold salts, hydroxychloroquine, leflunomide, methotrexate (MTX), minocycline, sulfasalazine, cyclophosphamide, tumor necrosis factor alpha (TNF α) blockers such as etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira), certolizumab pegol 15 (Cimzia), golimumab (Simponi), Interleukin 1 (IL-1) blockers such as anakinra (Kineret), monoclonal antibodies against B cells such as rituximab (RITUXAN®), T cell costimulation blockers such as abatacept (Orencia), Interleukin 6 (IL-6) blockers such as tocilizumab (ACTEMERA®); Interleukin 13 (IL-13) blockers such as lebrikizumab; Interferon alpha (IFN) blockers such as Rontalizumab; Beta 7 integrin blockers such as rhuMAb Beta7; IgE pathway 20 blockers such as Anti-M1 prime; Secreted homotrimeric LT α 3 and membrane bound heterotrimer LT α 1/ β 2 blockers such as Anti-lymphotoxin alpha (LT α); hormone antagonists, such as tamoxifen, finasteride or LHRH antagonists; radioactive isotopes (e.g., At²¹¹, I¹³¹, I¹²⁵, Y⁹⁰, Re¹⁸⁶, Re¹⁸⁸, Sm¹⁵³, Bi²¹², P³², Pb²¹² and radioactive isotopes of Lu); miscellaneous 25 investigational agents such as thioplatin, PS-341, phenylbutyrate, ET-18-OCH₃, or farnesyl transferase inhibitors (L-739749, L-744832); polyphenols such as quercetin, resveratrol, piceatannol, epigallocatechine gallate, theaflavins, flavanols, procyanidins, betulinic acid and derivatives thereof; autophagy inhibitors such as chloroquine; alkylating agents such as thiotepa and cyclophosphamide (CYTOXAN®); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines 30 and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide and trimethylomelamine; acetogenins (especially bullatacin and

bullatacinone); delta-9-tetrahydrocannabinol (dronabinol, MARINOL®); beta-lapachone; lapachol; colchicines; betulinic acid; a camptothecin (including the synthetic analogue topotecan (HYCAMTIN®), CPT-11 (irinotecan, CAMPTOSAR®), acetylcamptothecin, scopolactin, and 9-aminocamptothecin); bryostatin; calystatin; CC-1065 (including its adozelesin, carzelesin and 5 bizelesin synthetic analogues); podophyllotoxin; podophyllinic acid; teniposide; cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, chlorophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, 10 novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosoureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimustine; antibiotics such as the enediyne antibiotics (e. g., calicheamicin, especially calicheamicin gammaI and calicheamicin omegaI (see, e.g., Nicolaou *et al.*, *Angew. Chem Int. Ed. Engl.*, 33: 183-186 (1994)); CDP323, an oral alpha-4 integrin inhibitor; dynemicin, including dynemicin A; an 15 esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, carminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin (including ADRIAMYCIN®, morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino- 20 doxorubicin, doxorubicin HCl liposome injection (DOXIL®), liposomal doxorubicin TLC D-99 (MYOCET®), pegylated liposomal doxorubicin (CAELYX®), and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, porfiromycin, puromycin, quelamycin, rodarubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; 25 anti-metabolites such as methotrexate, gemcitabine (GEMZAR®), tegafur (UFTORAL®), capecitabine (XELODA®), an epothilone, and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; 30 androgens such as calusterone, dromostanolone propionate, epitostanol, 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; 5 mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; 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 (ELDISINE®, FILDESIN®); dacarbazine; mannomustine; mitobronitol; mitolactol; 10 pipobroman; gacytosine; arabinoside (“Ara-C”); thiotepa; taxoid, *e.g.*, paclitaxel (TAXOL®), albumin-engineered nanoparticle formulation of paclitaxel (ABRAXANETM), and docetaxel (TAXOTERE®); chlorambucil; 6-thioguanine; mercaptopurine; methotrexate; platinum agents such as cisplatin, oxaliplatin (*e.g.*, ELOXATIN®), and carboplatin; vincas, which prevent tubulin polymerization from forming microtubules, including vinblastine (VELBAN®), 15 vincristine (ONCOVIN®), vindesine (ELDISINE®, FILDESIN®), and vinorelbine (NAVELBINE®); etoposide (VP-16); ifosfamide; mitoxantrone; leucovorin; novantrone; edatraxate; daunomycin; aminopterin; ibandronate; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as fenretinide, retinoic acid, including bexarotene (TARGRETIN®); bisphosphonates such as clodronate (for example, BONEFOS® or 20 OSTAC®), etidronate (DIDROCAL®), NE-58095, zoledronic acid/zoledronate (ZOMETA®), alendronate (FOSAMAX®), pamidronate (AREDIA®), tiludronate (SKELID®), or risedronate (ACTONEL®); troxacicabine (a 1,3-dioxolane nucleoside cytosine analog); antisense oligonucleotides, particularly those that inhibit expression of genes in signaling pathways implicated in aberrant cell proliferation, such as, for example, PKC-alpha, Raf, H-Ras, and 25 epidermal growth factor receptor (EGF-R); vaccines such as THERATOPE® vaccine and gene therapy vaccines, for example, ALLOVECTIN® vaccine, LEUVECTIN® vaccine, and VAXID® vaccine; topoisomerase 1 inhibitor (*e.g.*, LURTOTECAN®); rmRH (*e.g.*, ABARELIX®); BAY439006 (sorafenib; Bayer); SU-11248 (sunitinib, SUTENT®, Pfizer); perifosine, COX-2 inhibitor (*e.g.* celecoxib or etoricoxib), proteosome inhibitor (*e.g.* PS341); 30 bortezomib (VELCADE®); CCI-779; tipifarnib (R11577); orafenib, ABT510; Bcl-2 inhibitor such as oblimersen sodium (GENASENSE®); pixantrone; EGFR inhibitors (see definition

below); farnesyltransferase inhibitors such as lonafarnib (SCH 6636, SARASARTM); and pharmaceutically acceptable salts, acids or derivatives of any of the above; as well as combinations of two or more of the above such as CHOP, an abbreviation for a combined therapy of cyclophosphamide, doxorubicin, vincristine, and prednisolone; and FOLFOX, an
5 abbreviation for a treatment regimen with oxaliplatin (ELOXATINTM) combined with 5-FU and leucovorin.

Additional chemotherapeutic agents as defined herein include “anti-hormonal agents” or “endocrine therapeutics” which act to regulate, reduce, block, or inhibit the effects of hormones that can promote the growth of cancer. They may be hormones themselves, including, but not
10 limited to: anti-estrogens with mixed agonist/antagonist profile, including, tamoxifen (NOLVADEX®), 4-hydroxytamoxifen, toremifene (FARESTON®), idoxifene, droloxifene, raloxifene (EVISTA®), trioxifene, keoxifene, and selective estrogen receptor modulators (SERMs) such as SERM3; pure anti-estrogens without agonist properties, such as fulvestrant (FASLODEX®), and EM800 (such agents may block estrogen receptor (ER) dimerization,
15 inhibit DNA binding, increase ER turnover, and/or suppress ER levels); aromatase inhibitors, including steroid aromatase inhibitors such as formestane and exemestane (AROMASIN®), and nonsteroidal aromatase inhibitors such as anastrazole (ARIMIDEX®), letrozole (FEMARA®) and aminoglutethimide, and other aromatase inhibitors include vorozole (RIVISOR®), megestrol acetate (MEGASE®), fadrozole, and 4(5)-imidazoles; lutenizing
20 hormone-releasing hormone agonists, including leuprolide (LUPRON® and ELIGARD®), goserelin, buserelin, and triptorelin; sex steroids, including progestines such as megestrol acetate and medroxyprogesterone acetate, estrogens such as diethylstilbestrol and premarin, and androgens/retinoids such as fluoxymesterone, all transretinoic acid and fenretinide; onapristone; anti-progesterones; estrogen receptor down-regulators (ERDs); anti-androgens such as flutamide,
25 nilutamide and bicalutamide.

Additional chemotherapeutic agents include 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),
30 tositumomab (Bexxar, Corixia), and the antibody drug conjugate, gemtuzumab ozogamicin

(MYLOTARG®, Wyeth). Additional humanized monoclonal antibodies with therapeutic potential as agents in combination with the compounds of the invention include: apolizumab, aselizumab, atlizumab, bapineuzumab, bivatuzumab mertansine, cantuzumab mertansine, cedelizumab, certolizumab pegol, cidefusituzumab, cideftuzumab, daclizumab, eculizumab, 5 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, pexelizumab, ralivizumab, ranibizumab, reslivizumab, reslizumab, resyvizumab, rovelizumab, 10 ruplizumab, sibrotuzumab, siplizumab, sontuzumab, tacatuzumab tetraxetan, tadocizumab, talizumab, tefibazumab, tocilizumab, toralizumab, tucotuzumab celmoleukin, tucusituzumab, umavizumab, urtoxazumab, ustekinumab, visilizumab, and the anti-interleukin-12 (ABT-874/J695, Wyeth Research and Abbott Laboratories) which is a recombinant exclusively human-sequence, full-length IgG₁ λ antibody genetically modified to recognize interleukin-12 p40 15 protein.

Chemotherapeutic agents also include “EGFR inhibitors,” which refers to compounds that bind to or otherwise interact directly with EGFR and prevent or reduce its signaling activity, and is alternatively referred to as an “EGFR antagonist.” Examples of such agents include antibodies and small molecules that bind to EGFR. Examples of antibodies which bind to EGFR 20 include MAb 579 (ATCC CRL HB 8506), MAb 455 (ATCC CRL HB8507), MAb 225 (ATCC CRL 8508), MAb 528 (ATCC CRL 8509) (see, US Patent No. 4,943, 533, Mendelsohn *et al.*) and variants thereof, such as chimerized 225 (C225 or Cetuximab; ERBITUX®) and reshaped human 225 (H225) (see, WO 96/40210, Imclone Systems Inc.); IMC-11F8, a fully human, EGFR-targeted antibody (Imclone); antibodies that bind type II mutant EGFR (US Patent No. 25 5,212,290); humanized and chimeric antibodies that bind EGFR as described in US Patent No. 5,891,996; and human antibodies that bind EGFR, such as ABX-EGF or Panitumumab (see WO98/50433, Abgenix/Amgen); EMD 55900 (Stragliotto *et al.* *Eur. J. Cancer* 32A:636-640 (1996)); EMD7200 (matuzumab) a humanized EGFR antibody directed against EGFR that competes with both EGF and TGF-alpha for EGFR binding (EMD/Merck); human EGFR 30 antibody, HuMax-EGFR (GenMab); fully human antibodies known as E1.1, E2.4, E2.5, E6.2, E6.4, E2.11, E6. 3 and E7.6. 3 and described in US 6,235,883; MDX-447 (Medarex Inc); and

mAb 806 or humanized mAb 806 (Johns *et al.*, *J. Biol. Chem.* 279(29):30375-30384 (2004)). The anti-EGFR antibody may be conjugated with a cytotoxic agent, thus generating an immunoconjugate (see, *e.g.*, EP659,439A2, Merck Patent GmbH). EGFR antagonists include small molecules such as compounds described in US Patent Nos: 5,616,582, 5,457,105, 5,475,001, 5,654,307, 5,679,683, 6,084,095, 6,265,410, 6,455,534, 6,521,620, 6,596,726, 6,713,484, 5,770,599, 6,140,332, 5,866,572, 6,399,602, 6,344,459, 6,602,863, 6,391,874, 6,344,455, 5,760,041, 6,002,008, and 5,747,498, as well as the following PCT publications: WO98/14451, WO98/50038, WO99/09016, and WO99/24037. Particular small molecule EGFR antagonists include OSI-774 (CP-358774, erlotinib, TARCEVA® Genentech/OSI Pharmaceuticals); PD 183805 (CI 1033, 2-propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride, Pfizer Inc.); ZD1839, gefitinib (IRESSA®) 4-(3'-Chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline, AstraZeneca); ZM 105180 ((6-amino-4-(3-methylphenyl-amino)-quinazoline, Zeneca); BIBX-1382 (N8-(3-chloro-4-fluoro-phenyl)-N2-(1-methyl-piperidin-4-yl)-pyrimido[5,4-d]pyrimidine-2,8-diamine, Boehringer Ingelheim); PKI-166 ((R)-4-[4-[(1-phenylethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-6-yl]-phenol); (R)-6-(4-hydroxyphenyl)-4-[(1-phenylethyl)amino]-7H-pyrrolo[2,3-d]pyrimidine); CL-387785 (N-[4-[(3-bromophenyl)amino]-6-quinazolinyl]-2-butynamide); EKB-569 (N-[4-[(3-chloro-4-fluorophenyl)amino]-3-cyano-7-ethoxy-6-quinoliny]-4-(dimethylamino)-2-butenamide) (Wyeth); AG1478 (Pfizer); AG1571 (SU 5271; Pfizer); dual EGFR/HER2 tyrosine kinase inhibitors such as lapatinib (TYKERB®, GSK572016 or N-[3-chloro-4-[(3-fluorophenyl)methoxy]phenyl]-6[5[[[2methylsulfonyl)ethyl]amino]methyl]-2-furanyl]-4-quinazolinamine).

Chemotherapeutic agents also include “tyrosine kinase inhibitors” including the EGFR-targeted drugs noted in the preceding paragraph; small molecule HER2 tyrosine kinase inhibitor such as TAK165 available from Takeda; CP-724,714, an oral selective inhibitor of the ErbB2 receptor tyrosine kinase (Pfizer and OSI); dual-HER inhibitors such as EKB-569 (available from Wyeth) which preferentially binds EGFR but inhibits both HER2 and EGFR-overexpressing cells; lapatinib (GSK572016; available from Glaxo-SmithKline), an oral HER2 and EGFR tyrosine kinase inhibitor; PKI-166 (available from Novartis); pan-HER inhibitors such as canertinib (CI-1033; Pharmacia); Raf-1 inhibitors such as antisense agent ISIS-5132 available from ISIS Pharmaceuticals which inhibit Raf-1 signaling; non-HER targeted TK inhibitors such

as imatinib mesylate (GLEEVEC^J, available from Glaxo SmithKline); multi-targeted tyrosine kinase inhibitors such as sunitinib (SUTENT[®], available from Pfizer); VEGF receptor tyrosine kinase inhibitors such as vatalanib (PTK787/ZK222584, available from Novartis/Schering AG); MAPK extracellular regulated kinase I inhibitor CI-1040 (available from Pharmacia); 5 quinazolines, such as PD 153035,4-(3-chloroanilino) quinazoline; pyridopyrimidines; pyrimidopyrimidines; pyrrolopyrimidines, such as CGP 59326, CGP 60261 and CGP 62706; pyrazolopyrimidines, 4-(phenylamino)-7H-pyrrolo[2,3-d] pyrimidines; curcumin (diferuloyl methane, 4,5-bis (4-fluoroanilino)phthalimide); tyrphostines containing nitrothiophene moieties; PD-0183805 (Warner-Lamber); antisense molecules (*e.g.* those that bind to HER-encoding 10 nucleic acid); quinoxalines (US Patent No. 5,804,396); tryphostins (US Patent No. 5,804,396); ZD6474 (Astra Zeneca); PTK-787 (Novartis/Schering AG); pan-HER inhibitors such as CI-1033 (Pfizer); Affinitac (ISIS 3521; Isis/Lilly); imatinib mesylate (GLEEVEC^J); PKI 166 (Novartis); GW2016 (Glaxo SmithKline); CI-1033 (Pfizer); EKB-569 (Wyeth); Semaxinib (Pfizer); ZD6474 (AstraZeneca); PTK-787 (Novartis/Schering AG); INC-1C11 (Imclone), rapamycin (sirolimus, 15 RAPAMUNE[®]); or as described in any of the following patent publications: US Patent No. 5,804,396; WO 1999/09016 (American Cyanamid); WO 1998/43960 (American Cyanamid); WO 1997/38983 (Warner Lambert); WO 1999/06378 (Warner Lambert); WO 1999/06396 (Warner Lambert); WO 1996/30347 (Pfizer, Inc); WO 1996/33978 (Zeneca); WO 1996/3397 (Zeneca) and WO 1996/33980 (Zeneca).

20 The term "NSAID" and the terms "non-steroidal anti-inflammatory drug" refer to therapeutic agents with analgesic, antipyretic and anti-inflammatory effects. NSAIDs include non-selective inhibitors of the enzyme cyclooxygenase. Specific examples of NSAIDs include aspirin, propionic acid derivatives such as ibuprofen, fenoprofen, ketoprofen, flurbiprofen, oxaprozin and naproxen, acetic acid derivatives such as indomethacin, sulindac, etodolac, 25 diclofenac, enolic acid derivatives such as piroxicam, meloxicam, tenoxicam, droxicam, lornoxicam and isoxicam, fenamic acid derivatives such as mefenamic acid, meclofenamic acid, flufenamic acid, tolafenamic acid, and COX-2 inhibitors such as celecoxib, etoricoxib, lumiracoxib, parecoxib, rofecoxib, rofecoxib, and valdecoxib. NSAIDs can be indicated for the symptomatic relief of conditions such as rheumatoid arthritis, osteoarthritis, inflammatory 30 arthropathies, 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.

Chemotherapeutic agents also include asthma treatment agents, including inhaled corticosteroids such as fluticasone, budesonide, mometasone, flunisolide and beclomethasone; 5 leukotriene modifiers, such as montelukast, zafirlukast and zileuton; long-acting beta agonists, such as salmeterol and formoterol; combinations of the above such as combinations of fluticasone and salmeterol, and combinations of budesonide and formoterol; theophylline; short-acting beta agonists, such as albuterol, levalbuterol and pirbuterol; ipratropium; oral and intravenous corticosteroids, such as prednisone and methylprednisolone; omalizumab; 10 lebrikizumab; antihistamines; and decongestants; cromolyn; and ipratropium.

Additionally, chemotherapeutic agents include pharmaceutically acceptable salts, acids or derivatives of any of chemotherapeutic agents, described herein, as well as combinations of two or more of them.

“Cycloalkyl” refers to a non-aromatic, saturated or partially unsaturated hydrocarbon ring group wherein the cycloalkyl group may be optionally substituted independently with one or more substituents described herein. In one example, the cycloalkyl group is 3 to 12 carbon atoms (C₃-C₁₂). In other examples, cycloalkyl is C₃-C₈, C₃-C₁₀ or C₅-C₁₀. In other examples, the cycloalkyl group, as a monocycle, is C₃-C₈, C₃-C₆ or C₅-C₆. In another example, the cycloalkyl group, as a bicycle, is C₇-C₁₂. In another example, the cycloalkyl group, as a spiro system, is C₅- 15 C₁₂. Examples of monocyclic cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, perdeuteriocyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, cyclohexadienyl, cycloheptyl, 20 cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl and cyclododecyl. Exemplary arrangements of bicyclic cycloalkyls having 7 to 12 ring atoms include, but are not limited to, [4,4], [4,5], [5,5], [5,6] or [6,6] ring systems. Exemplary bridged bicyclic cycloalkyls include, but are not limited to, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane and bicyclo[3.2.2]nonane. Examples of spiro cycloalkyl include, spiro[2.2]pentane, spiro[2.3]hexane, spiro[2.4]heptane, spiro[2.5]octane and 25 spiro[4.5]decane.

“Carboxy-protecting group” as used herein refers to those groups that are stable to the conditions of subsequent reaction(s) at other positions of the molecule, which may be removed at the appropriate point without disrupting the remainder of the molecule, to give the unprotected carboxy-group. Examples of carboxy protecting groups include, ester groups and heterocyclyl groups. Ester derivatives of the carboxylic acid group may be employed to block or protect the carboxylic acid group while reactions are carried out on other functional groups on the compound. Examples of such ester groups include substituted arylalkyl, including substituted benzyls, such as 4-nitrobenzyl, 4-methoxybenzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl, pentamethylbenzyl, 3,4-methylenedioxybenzyl, benzhydryl, 4,4'-dimethoxybenzhydryl, 2,2',4,4'-tetramethoxybenzhydryl, alkyl or substituted alkyl esters such as methyl, ethyl, t-butyl allyl or t-amyl, triphenylmethyl (trityl), 4-methoxytrityl, 4,4'-dimethoxytrityl, 4,4',4"-trimethoxytrityl, 2-phenylprop-2-yl, thioesters such as t-butyl thioester, silyl esters such as trimethylsilyl, t-butyldimethylsilyl esters, phenacyl, 2,2,2-trichloroethyl, beta-(trimethylsilyl)ethyl, beta-(di(n-butyl)methylsilyl)ethyl, p-toluenesulfonylethyl, 4-nitrobenzylsulfonylethyl, allyl, cinnamyl, 1-(trimethylsilylmethyl)prop-1-en-3-yl, and like moieties. Another example of carboxy-protecting groups are heterocyclyl groups such as 1,3-oxazolinyl. Further examples of these groups are found in T. W. Greene and P. G. M. Wuts, “Protective Groups in Organic Synthesis”, 2nd ed., John Wiley & Sons, Inc., New York, N.Y., 1991, chapter 5; E. Haslam, “Protective Groups in Organic Chemistry”, J. G. W. McOmie, Ed., Plenum Press, New York, N.Y., 1973, Chapter 5, and T.W. Greene, “Protective Groups in Organic Synthesis”, John Wiley and Sons, New York, NY, 1981, Chapter 5. The term “protected carboxy” refers to a carboxy group substituted with one of the above carboxy-protecting groups.

“Guanidine” means the group -NH-C(NH)-NHR in which R is hydrogen, alkyl, alkoxy, a cycloalkyl, a heterocyclyl, cycloalkyl -substituted alkyl or heterocyclyl-substituted alkyl wherein the alkyl, alkoxy, cycloalkyl and heterocyclyl are as defined herein. A particular guanidine is the group -NH-C(NH)-NH₂.

“Hydroxy-protecting group” as used herein refers to a derivative of the hydroxy group commonly employed to block or protect the hydroxy group while reactions are carried out on other functional groups on the compound. Examples of such protecting groups include

tetrahydropyranloxy, benzoyl, acetoxy, carbamoyloxy, benzyl, and silylethers (e.g. TBS, TBDPS) groups. Further examples of these groups are found in T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", 2nd ed., John Wiley & Sons, Inc., New York, NY, 1991, chapters 2-3; E. Haslam, "Protective Groups in Organic Chemistry", J. G. W. McOmie, Ed., Plenum Press, New York, NY, 1973, Chapter 5, and T.W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, NY, 1981. The term "protected hydroxy" refers to a hydroxy group substituted with one of the above hydroxy-protecting groups.

"Heterocyclic group", "heterocyclic", "heterocycle", "heterocyclyl", or "heterocyclo" alone, and when used as a moiety in a complex group such as a heterocycloalkyl group, are used 10 interchangeably and refer to any mono-, bi-, tricyclic or spiro, saturated or unsaturated, aromatic (heteroaryl) or non-aromatic, ring system, having 3 to 20 ring atoms, where the ring atoms are carbon, and at least one atom in the ring or ring system is a heteroatom selected from nitrogen, sulfur or oxygen. In one example, heterocyclyl includes 3-12 ring atoms and includes monocycles, bicycles, tricycles and spiro ring systems, wherein the ring atoms are carbon, and at 15 least one atom in the ring or ring system is a heteroatom selected from nitrogen, sulfur or oxygen. In one example, heterocyclyl includes 1 to 4 heteroatoms. In another example, heterocyclyl includes 3- to 7-membered monocycles having one or more heteroatoms selected from nitrogen, sulfur or oxygen. In another example, heterocyclyl includes 4- to 6-membered monocycles having one or more heteroatoms selected from nitrogen, sulfur or oxygen. In 20 another example, heterocyclyl includes 3-membered monocycles. In another example, heterocyclyl includes 4-membered monocycles. In another example, heterocyclyl includes 5-6-membered monocycles. In one example, the heterocyclyl group includes 0 to 3 double bonds. Any nitrogen or sulfur heteroatom may optionally be oxidized (e.g. NO, SO, SO₂), and any nitrogen heteroatom may optionally be quaternized (e.g. [NR₄]⁺Cl⁻, [NR₄]⁺OH⁻). Example 25 heterocycles are oxiranyl, aziridinyl, thiiranyl, azetidinyl, oxetanyl, thietanyl, 1,2-dithietanyl, 1,3-dithietanyl, pyrrolidinyl, dihydro-1H-pyrrolyl, dihydrofuranyl, tetrahydrofuranyl, dihydrothienyl, tetrahydrothienyl, imidazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, dihydropyranyl, tetrahydropyranyl, hexahydrothiopyranyl, hexahdropyrimidinyl, oxazinanyl, thiazinanyl, thioxanyl, 30 homopiperazinyl, homopiperidinyl, azepanyl, oxepanyl, thiepanyl, oxazepinyl, oxazepanyl, diazepanyl, 1,4-diazepanyl, diazepinyl, thiazepinyl, thiazepanyl, tetrahydrothiopyranyl,

oxazolidinyl, thiazolidinyl, isothiazolidinyl, 1,1-dioxoisothiazolidinonyl, oxazolidinonyl, imidazolidinonyl, 4,5,6,7-tetrahydro[2H]indazolyl, tetrahydrobenzoimidazolyl, 4,5,6,7-tetrahydrobenzo[d]imidazolyl, 1,6-dihydroimidazol[4,5-d]pyrrolo[2,3-b]pyridinyl, thiazinyl, oxazinyl, thiadiazinyl, oxadiazinyl, dithiazinyl, dioxazinyl, oxathiazinyl, thiatriazinyl, 5 oxatriazinyl, dithiadiazinyl, imidazolinyl, dihydropyrimidyl, tetrahydropyrimidyl, 1-pyrrolinyl, 2-pyrrolinyl, 3-pyrrolinyl, indoliny, thiapyranyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, pyrazolidinyl, dithianyl, dithiolanyl, pyrimidinonyl, pyrimidindionyl, pyrimidin-2,4-dionyl, piperazinonyl, piperazindionyl, pyrazolidinylimidazolinyl, 3-azabicyclo[3.1.0]hexanyl, 3,6-diazabicyclo[3.1.1]heptanyl, 6-azabicyclo[3.1.1]heptanyl, 3-azabicyclo[3.1.1]heptanyl, 3-azabicyclo[4.1.0]heptanyl, azabicyclo[2.2.2]hexanyl, 2-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]octanyl, 2-azabicyclo[2.2.2]octanyl, 8-azabicyclo[2.2.2]octanyl, 7-oxabicyclo[2.2.1]heptane, azaspiro[3.5]nonanyl, azaspiro[2.5]octanyl, azaspiro[4.5]decanyl, 1-azaspiro[4.5]decan-2-only, azaspiro[5.5]undecanyl, tetrahydroindolyl, octahydroindolyl, tetrahydroisoindolyl, 15 tetrahydroindazolyl, 1,1-dioxohexahydrothiopyran. Examples of 5-membered heterocycles containing a sulfur or oxygen atom and one to three nitrogen atoms are thiazolyl, including thiazol-2-yl and thiazol-2-yl N-oxide, thiadiazolyl, including 1,3,4-thiadiazol-5-yl and 1,2,4-thiadiazol-5-yl, oxazolyl, for example oxazol-2-yl, and oxadiazolyl, such as 1,3,4-oxadiazol-5-yl, and 1,2,4-oxadiazol-5-yl. Example 5-membered ring heterocycles containing 2 to 4 nitrogen atoms include imidazolyl, such as imidazol-2-yl; triazolyl, such as 1,3,4-triazol-5-yl; 1,2,3-triazol-5-yl, 1,2,4-triazol-5-yl, and tetrazolyl, such as 1H-tetrazol-5-yl. Example benzo-fused 5-membered heterocycles are benzoxazol-2-yl, benzthiazol-2-yl and benzimidazol-2-yl. Example 20 6-membered heterocycles contain one to three nitrogen atoms and optionally a sulfur or oxygen atom, for example pyridyl, such as pyrid-2-yl, pyrid-3-yl, and pyrid-4-yl; pyrimidyl, such as pyrimid-2-yl and pyrimid-4-yl; triazinyl, such as 1,3,4-triazin-2-yl and 1,3,5-triazin-4-yl; pyridazinyl, in particular pyridazin-3-yl, and pyrazinyl. The pyridine N-oxides and pyridazine N-oxides and the pyridyl, pyrimid-2-yl, pyrimid-4-yl, pyridazinyl and the 1,3,4-triazin-2-yl groups, are other example heterocycle groups. Substituents for “optionally substituted heterocycles” include hydroxyl, alkyl, alkoxy, acyl, halogen, mercapto, oxo, carboxyl, halo- 25 substituted alkyl, amino, cyano, nitro, amidino, guanidino.

“Heteroaryl” alone and when used as a moiety in a complex group such as a heteroaralkyl group, refers to any mono-, bi-, or tricyclic ring system where at least one ring is a 5- or, 6-membered aromatic ring containing from 1 to 4 heteroatoms selected from nitrogen, oxygen, and sulfur, and in an example embodiment, at least one heteroatom is nitrogen. See, for example,

5 *Lang's Handbook of Chemistry, supra*. Included in the definition are any bicyclic groups where any of the above heteroaryl rings are fused to an aryl ring. In certain embodiments, heteroaryl includes 4-6 membered monocyclic aromatic groups where one or more ring atoms is nitrogen, sulfur or oxygen. In certain embodiments, heteroaryl includes 5-6 membered monocyclic aromatic groups where one or more ring atoms is nitrogen, sulfur or oxygen. Example heteroaryl

10 groups (whether substituted or unsubstituted) include thienyl, furyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl, tetrazolyl, thiatriazolyl, oxatriazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazinyl, tetrazinyl, tetrazolo[1,5-b]pyridazinyl, imidazol[1,2-a]pyrimidinyl and purinyl, as well as benzo-fused derivatives, for example benzoxazolyl, benzofuryl, benzothiazolyl, benzothiadiazolyl,

15 benzotriazolyl, benzoimidazolyl and indolyl. Additional examples of “heteroaryl” groups are: 1,3-thiazol-2-yl, 4-(carboxymethyl)-5-methyl-1,3-thiazol-2-yl, 4-(carboxymethyl)-5-methyl-1,3-thiazol-2-yl sodium salt, 1,2,4-thiadiazol-5-yl, 3-methyl-1,2,4-thiadiazol-5-yl, 1,3,4-triazol-5-yl, 2-methyl-1,3,4-triazol-5-yl, 2-hydroxy-1,3,4-triazol-5-yl, 2-carboxy-4-methyl-1,3,4-triazol-5-yl sodium salt, 2-carboxy-4-methyl-1,3,4-triazol-5-yl, 1,3-oxazol-2-yl, 1,3,4-oxadiazol-5-yl, 2-

20 methyl-1,3,4-oxadiazol-5-yl, 2-(hydroxymethyl)-1,3,4-oxadiazol-5-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-thiadiazol-5-yl, 2-thiol-1,3,4-thiadiazol-5-yl, 2-(methylthio)-1,3,4-thiadiazol-5-yl, 2-amino-1,3,4-thiadiazol-5-yl, 1H-tetrazol-5-yl, 1-methyl-1H-tetrazol-5-yl, 1-(1-(dimethylamino)eth-2-yl)-1H-tetrazol-5-yl, 1-(carboxymethyl)-1H-tetrazol-5-yl, 1-(carboxymethyl)-1H-tetrazol-5-yl sodium salt, 1-(methylsulfonic acid)-1H-tetrazol-5-yl, 1-(methylsulfonic acid)-1H-tetrazol-5-yl

25 sodium salt, 2-methyl-1H-tetrazol-5-yl, 1,2,3-triazol-5-yl, 1-methyl-1,2,3-triazol-5-yl, 2-methyl-1,2,3-triazol-5-yl, 4-methyl-1,2,3-triazol-5-yl, pyrid-2-yl N-oxide, 6-methoxy-2-(n-oxide)-pyridaz-3-yl, 6-hydroxypyridaz-3-yl, 1-methylpyrid-2-yl, 1-methylpyrid-4-yl, 2-hydroxypyrimid-4-yl, 1,4,5,6-tetrahydro-5,6-dioxo-4-methyl-as-triazin-3-yl, 1,4,5,6-tetrahydro-4-(formylmethyl)-5,6-dioxo-as-triazin-3-yl, 2,5-dihydro-5-oxo-6-hydroxy-astriazin-3-yl, 2,5-

30 dihydro-5-oxo-6-hydroxy-as-triazin-3-yl sodium salt, 2,5-dihydro-5-oxo-6-hydroxy-2-methyl-astriazin-3-yl sodium salt, 2,5-dihydro-5-oxo-6-hydroxy-2-methyl-as-triazin-3-yl, 2,5-dihydro-5-

oxo-6-methoxy-2-methyl-as-triazin-3-yl, 2,5-dihydro-5-oxo-as-triazin-3-yl, 2,5-dihydro-5-oxo-2-methyl-as-triazin-3-yl, 2,5-dihydro-5-oxo-2,6-dimethyl-as-triazin-3-yl, tetrazolo[1,5-b]pyridazin-6-yl and 8-aminotetrazolo[1,5-b]-pyridazin-6-yl. Heteroaryl groups are optionally substituted as described for heterocycles.

5 In particular embodiments, a heterocyclyl group is attached at a carbon atom of the heterocyclyl group. By way of example, carbon bonded heterocyclyl groups include bonding arrangements at position 2, 3, 4, 5, or 6 of a pyridine ring, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine ring, position 2, 3, 5, or 6 of a pyrazine ring, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole ring, position 10 2, 4, or 5 of an oxazole, imidazole or thiazole ring, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole ring, position 2 or 3 of an aziridine ring, position 2, 3, or 4 of an azetidine ring, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline ring or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline ring.

15 In certain embodiments, the heterocyclyl group is N-attached. By way of example, the nitrogen bonded heterocyclyl or heteroaryl group include bonding arrangements 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.

20 “Leaving group” refers to a portion of a first reactant in a chemical reaction that is displaced from the first reactant in the chemical reaction. Examples of leaving groups include, but are not limited to, hydrogen, halogen atoms, alkoxy and sulfonyloxy groups. Example sulfonyloxy groups include, but are not limited to, alkylsulfonyloxy groups (for example methyl sulfonyloxy (mesylate group) and trifluoromethylsulfonyloxy (triflate group)) and 25 arylsulfonyloxy groups (for example *p*-toluenesulfonyloxy (tosylate group) and *p*-nitrosulfonyloxy (nosylate group)).

“Optionally substituted” unless otherwise specified means that a group may be unsubstituted or substituted by one or more (e.g. 0, 1, 2, 3 or 4) of the substituents listed for that group in which said substituents may be the same or different. In an embodiment an optionally

substituted group has 1 substituent. In certain embodiments an optionally substituted group has 2 substituents. In certain embodiments an optionally substituted group has 3 substituents.

In certain embodiments, divalent groups are described generically without specific bonding configurations, for example in the group $-\text{CH}_2\text{C}(\text{O})-$. It is understood that the generic description is meant to include both bonding configurations, unless specified otherwise. For example, in the group $\text{R}^1-\text{R}^2-\text{R}^3$, if the group R^2 is described as $-\text{CH}_2\text{C}(\text{O})-$, then it is understood that this group can be bonded both as $\text{R}^1-\text{CH}_2\text{C}(\text{O})-\text{R}^3$, and as $\text{R}^1-\text{C}(\text{O})\text{CH}_2-\text{R}^3$, unless specified otherwise.

“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.

“Pharmaceutically acceptable salts” include both acid and base addition salts. “Pharmaceutically acceptable acid addition salt” refers to those salts which retain the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, carbonic acid, phosphoric acid and the like, and organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids such as formic acid, acetic acid, propionic acid, glycolic acid, gluconic acid, lactic acid, pyruvic acid, oxalic acid, malic acid, maleic acid, maloneic acid, succinic acid, fumaric acid, tartaric acid, citric acid, aspartic acid, ascorbic acid, glutamic acid, anthranilic acid, benzoic acid, cinnamic acid, mandelic acid, embonic acid, phenylacetic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, salicyclic acid and the like.

“Pharmaceutically acceptable base addition salts” include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Particularly base addition salts are the ammonium, potassium, sodium, calcium and magnesium salts. Salts derived from pharmaceutically acceptable organic nontoxic bases includes salts of primary, secondary, and tertiary amines,

substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, tromethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, 5 glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particularly organic non-toxic bases are isopropylamine, diethylamine, ethanolamine, tromethamine, dicyclohexylamine, choline, and caffeine.

A “sterile” formulation is aseptic or free from all living microorganisms and their spores.

“Stereoisomers” refers to compounds which have identical chemical constitution, but 10 differ with regard to the arrangement of the atoms or groups in space. Stereoisomers include diastereomers, enantiomers, conformers and the like.

“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.

15 “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 or biological activities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography such as HPLC.

20 “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. Many organic compounds exist in optically active forms, i.e., they 25 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 5 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.

The term "tautomer" or "tautomeric form" refers to structural isomers of different 10 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.

A "solvate" refers to an association or complex of one or more solvent molecules and a 15 compound of the present invention. Examples of solvents that form solvates include water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid, and ethanolamine. The term "hydrate" refers to the complex where the solvent molecule is water.

A "subject," "individual," or "patient" is a vertebrate. In certain embodiments, the vertebrate is a mammal. Mammals include, but are not limited to, farm animals (such as cows), 20 sport animals, pets (such as cats, dogs, and horses), primates, mice and rats. In certain embodiments, a mammal is a human.

"Therapeutically effective amount" means an amount of a compound of the present invention that (i) treats or prevents the particular disease, condition or disorder, (ii) attenuates, ameliorates or eliminates one or more symptoms of the particular disease, condition, or disorder, 25 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 in certain embodiments stop) cancer cell infiltration into peripheral organs; inhibit (i.e., slow to some extent and in certain embodiments 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, for example, be measured by assessing the time to disease progression (TTP) and/or determining the response rate (RR). In 5 the case of immunological disorders, the therapeutic effective amount is an amount sufficient to decrease or alleviate an allergic disorder, the symptoms of an autoimmune and/or inflammatory disease, or the symptoms of an acute inflammatory reaction (e.g. asthma). In some embodiments, a therapeutically effective amount is an amount of a chemical entity described herein sufficient to significantly decrease the activity or number of B-cells.

10 "Treatment" (and variations such as "treat" or "treating") refers to clinical intervention in an attempt to alter the natural course of the individual or cell being treated, and can be performed either for prophylaxis or during the course of clinical pathology. Desirable effects of treatment include preventing occurrence or recurrence of disease, alleviation of symptoms, diminishment of any direct or indirect pathological consequences of the disease, stabilized (*i.e.*, not worsening) 15 state of disease, preventing metastasis, decreasing the rate of disease progression, amelioration or palliation of the disease state, prolonging survival as compared to expected survival if not receiving treatment and remission or improved prognosis. In some embodiments, compounds of the invention are used to delay development of a disease or disorder or to slow the progression of a disease or disorder. Those in need of treatment include those already with the condition or 20 disorder as well as those prone to have the condition or disorder, (for example, through a genetic mutation) or those in which the condition or disorder is to be prevented.

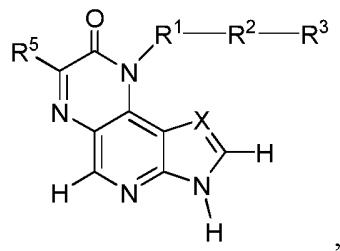
The terms "compound(s) of this invention," and "compound(s) of the present invention", unless otherwise indicated, include compounds of formula I and stereoisomers, tautomers, solvates, metabolites, salts (e.g., pharmaceutically acceptable salts), isotopes and prodrugs 25 thereof. Unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds of formula I, wherein one or more hydrogen atoms are replaced by deuterium or tritium, or one or more carbon atoms are replaced by ¹³C- or ¹⁴C-enriched carbon atom, or one or more nitrogen atoms are replaced by a ¹⁵N nitrogen atom, or one or more sulfur atoms are

replaced by a ^{33}S , ^{34}S or ^{36}S sulfur atom, or one or more oxygen atoms are replaced by a ^{17}O or ^{18}O oxygen are within the scope of this invention.

INHIBITORS OF JAK1 KINASE

In one aspect, a compound of Formula I, a stereoisomer, tautomer, prodrug and pharmaceutically acceptable salts thereof, and pharmaceutical formulations thereof, are provided that are useful in the treatment of diseases, conditions and/or disorders responsive to the inhibition of JAK1.

Another aspect of the invention provides compounds of formula I:



10

I

stereoisomers, tautomers and pharmaceutically acceptable salts thereof, wherein

X is N or CR⁴;

R¹ is absent, C₁₋₁₂ alkyl, C₁₋₁₂ alkenyl, C₁₋₁₂ alkynyl, C₃₋₁₂ cycloalkyl, C₆₋₁₄ aryl or 3-20 membered heterocyclyl, wherein R¹ is independently optionally substituted by halogen, oxo, 15 -CN, -OR^a, -SR^a, -NR^aR^b, C₁₋₃ alkylene or C₁₋₆ alkyl optionally substituted by oxo, -CN or halogen;

R² is absent, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -(C₁₋₆ alkylene)-, -(C₂₋₆ alkenylene)-, -(C₂₋₆ alkynylene)-, -(C₀₋₆ alkylene)CN, -(C₀₋₃ alkylene)NR^a(C₀₋₃ alkylene)-, -(C₀₋₃ alkylene)O(C₀₋₃ alkylene)-, -(C₀₋₃ alkylene)C(O)(C₀₋₃ alkylene)-, -(C₀₋₃ alkylene)NR^aC(O)(C₀₋₃ alkylene)-, -(C₀₋₃ alkylene)C(O)NR^a(C₀₋₃ alkylene)-, -(C₀₋₃ alkylene)C(O)O(C₀₋₃ alkylene)-, 20 -(C₀₋₃ alkylene)OC(O)(C₀₋₃ alkylene)-, -(C₀₋₃ alkylene)NR^aC(O)NR^b(C₀₋₃ alkylene)-, -(C₀₋₃ alkylene)OC(O)NR^a(C₀₋₃ alkylene)-, -(C₀₋₃ alkylene)NR^aC(O)O(C₀₋₃ alkylene)-, -(C₀₋₃ alkylene)S(O)₁₋₂(C₀₋₃ alkylene)-, -(C₀₋₃ alkylene)NR^aS(O)₁₋₂(C₀₋₃ alkylene)-, -(C₀₋₃

alkylene)S(O)₁₋₂NR^a(C₀₋₃ alkylene)– or –(C₀₋₃ alkylene)NR^aS(O)₁₋₂NR^b(C₀₋₃ alkylene)–, wherein said alkyl, alkyenyl, alkynyl, alkylene, alkenylene and alkynylene are independently optionally substituted by halogen, oxo, –CN, –OR^c, –SR^c, –NR^cR^d or C₁₋₃ alkyl optionally substituted by halogen;

5 R³ is absent, hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₆₋₁₄ aryl or 3-20 membered heterocyclyl, wherein R³ is independently optionally substituted by R⁶;

R⁴ is hydrogen, halogen or C₁₋₃ alkyl;

10 R⁵ is hydrogen, halogen, C₁₋₁₂ alkyl, C₂₋₁₂ alkenyl, C₂₋₁₂ alkynyl, –(C₀₋₃ alkylene)CN, –(C₀₋₃ alkylene)NR^aR^b, –(C₀₋₃ alkylene)OR^a, –(C₀₋₃ alkylene)SR^a, –(C₀₋₃ alkylene)C(O)R^a, –(C₀₋₃ alkylene)NR^aC(O)R^b, –(C₀₋₃ alkylene)C(O)NR^aR^b, –(C₀₋₃ alkylene)C(O)OR^a, –(C₀₋₃ alkylene)OC(O)R^a, –(C₀₋₃ alkylene)NR^aC(O)NR^aR^b, –(C₀₋₃ alkylene)OC(O)NR^aR^b, –(C₀₋₃ alkylene)NR^aC(O)OR^b, –(C₀₋₃ alkylene)S(O)₁₋₂R^a, –(C₀₋₃ alkylene)NR^aS(O)₁₋₂R^b, –(C₀₋₃ alkylene)S(O)₁₋₂NR^aR^b, –(C₀₋₃ alkylene)NR^aS(O)₁₋₂NR^aR^b, –(C₀₋₃ alkylene)C₃₋₁₂ cycloalkyl, –(C₀₋₃ alkylene)C₆₋₁₄ aryl, –(C₀₋₃ alkylene)3-12 membered heterocyclyl or –(C₀₋₃ alkylene)C(O)3-12 membered heterocyclyl, wherein said alkyl, alkenyl, alkynyl, alkylene, cycloalkyl, aryl and heterocyclyl are independently optionally substituted by halogen, oxo, –(C₀₋₃ alkylene)CN, –(C₀₋₃ alkylene)OR^c, –(C₀₋₃ alkylene)NR^cR^d, –(C₀₋₃ alkylene)C(O)R^c, –(C₀₋₃ alkylene)C(O)OR^c, –(C₀₋₃ alkylene)C(O)NR^cR^d, –(C₀₋₃ alkylene)NR^cC(O)R^d, –(C₀₋₃ alkylene)OC(O)NR^cR^d, –(C₀₋₃ alkylene)NR^cC(O)NR^cR^d, –(C₀₋₃ alkylene)NR^cC(O)OR^d, –(C₀₋₃ alkylene)S(O)₀₋₂R^c, –(C₀₋₃ alkylene)NR^cS(O)₁₋₂R^d, –(C₀₋₃ alkylene)S(O)₁₋₂NR^cR^d, –(C₀₋₃ alkylene)NR^cS(O)₁₋₂NR^cR^d or C₁₋₆ alkyl optionally substituted by oxo, –CN or halogen;

25 R⁶ is independently oxo, halogen, –CN, –C(O)R^a, –C(O)OR^a, –NR^aC(O)R^b, –C(O)NR^aR^b, –NR^aC(O)NR^aR^b, –OC(O)NR^aR^b, –NR^aC(O)OR^b, –S(O)₁₋₂R^a, –NR^aS(O)₂R^b, –S(O)₂NR^aR^b, –OR^a, –SR^a, –NR^aR^b, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, 3-7 membered heterocycl or C₆₋₁₄ aryl, and wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocycl and aryl are independently optionally substituted by halogen, oxo, –CN, –OR^c, –SR^c, –NR^cR^d or C₁₋₆ alkyl optionally substituted by oxo or halogen;

each R^a and R^b are independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, –(C₀₋₃ alkylene)C₃₋₆ cycloalkyl, –(C₀₋₃ alkylene)3-12 membered heterocycl, –(C₀₋₃ alkylene)C(O)3-12

membered heterocyclyl or $-(C_{0-3} \text{ alkylene})C_{6-14}$ aryl, wherein said alkyl, cycloalkyl, heterocyclyl and aryl are independently optionally substituted by halogen, oxo, $-CN$, $-OR^e$, $-NR^eR^f$, $-C(O)R^g$, $-C(O)OR^g$, $-C(O)NR^gR^h$, $-NR^gC(O)R^h$, $-OC(O)NR^gR^h$, $-NR^gC(O)NR^gR^h$, $-NR^gC(O)OR^h$, $-S(O)_{1-2}R^g$, $-NR^gS(O)_{1-2}R^h$, $-S(O)_{1-2}NR^gR^h$, $-NR^gS(O)_{1-2}NR^gR^h$, C_{3-6} cycloalkyl, 3-6 membered heterocyclyl, phenyl or C_{1-3} alkyl optionally substituted by oxo or halogen, or taken together with the atom to which they are attached to form a 3-6 membered heterocyclyl optionally substituted by oxo, halogen, $-C(O)C_{1-6}$ alkyl or C_{1-6} alkyl optionally substituted by oxo, halogen, OR^g or NR^gNR^h ;

each R^c and R^d are independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-(C_{0-3} \text{ alkylene})C_{3-6}$ cycloalkyl, $-(C_{0-3} \text{ alkylene})3-12$ membered heterocyclyl, $-(C_{0-3} \text{ alkylene})C(O)3-12$ membered heterocyclyl or $-(C_{0-3} \text{ alkylene})C_{6-14}$ aryl, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl and aryl are independently optionally substituted by halogen, oxo, $-CN$, $-OR^g$, $-NR^gR^h$, $-C(O)R^g$, $-C(O)OR^g$, $-C(O)NR^gR^h$, $-NR^gC(O)R^h$, $-OC(O)NR^gR^h$, $-NR^gC(O)NR^gR^h$, $-NR^gC(O)OR^h$, $-S(O)_{1-2}R^g$, $-NR^gS(O)_{1-2}R^h$, $-S(O)_{1-2}NR^gR^h$, $-NR^gS(O)_{1-2}NR^gR^h$, C_{3-6} cycloalkyl, 3-6 membered heterocyclyl, phenyl or C_{1-6} alkyl optionally substituted by oxo or halogen, or taken together with the atom to which they are attached to form a 3-6 membered heterocyclyl optionally substituted by oxo, halogen, $-C(O)C_{1-6}$ alkyl or C_{1-6} alkyl optionally substituted by oxo or halogen; and

each R^e , R^f , R^g , R^h are independently hydrogen or C_{1-6} alkyl optionally substituted by halogen or oxo.

In certain embodiments, when R^1 and R^2 are absent, one of R^3 , R^4 and R^5 is other than hydrogen.

In certain embodiments, R^1 , R^2 and R^3 are not absent at the same time.

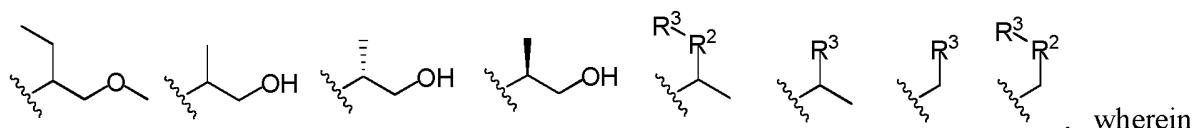
In certain embodiments, X is CR^4 , R^1 and R^2 are absent, and R^3 and R^4 are hydrogen.

25 In certain embodiments, X is CR^4 .

In certain embodiments, X is N.

In certain embodiments, R¹ is absent. In certain embodiment, R¹ is absent with the proviso that R¹, R² and R³ are not all absent at the same time.

In certain embodiment R¹ is C₁-C₆ alkyl optionally substituted by halogen, oxo, -CN, -OR^a, -SR^a, or -NR^aR^b. In one embodiment, R¹ is selected from methyl, ethyl, propyl, 5 butyl,



the wavy line represents the point of attachment in formula I.

In certain embodiments R¹ is a 3-20 membered heterocyclyl, wherein R¹ is independently optionally substituted by halogen, oxo, -CN, -OR^a, -SR^a, -NR^aR^b, C₁₋₃ alkylene or C₁₋₆ alkyl 10 optionally substituted by oxo, -CN or halogen. In certain embodiments R¹ is a 3-12 membered heterocyclyl, wherein R¹ is independently optionally substituted by halogen, oxo, -CN, -OR^a, -SR^a, -NR^aR^b, C₁₋₃ alkylene or C₁₋₆ alkyl optionally substituted by oxo, -CN or halogen. In certain embodiments R¹ is a 3-7 membered heterocyclyl, wherein R¹ is independently optionally substituted by halogen, oxo, -CN, -OR^a, -SR^a, -NR^aR^b, C₁₋₃ alkylene or C₁₋₆ alkyl optionally 15 substituted by oxo, -CN or halogen.

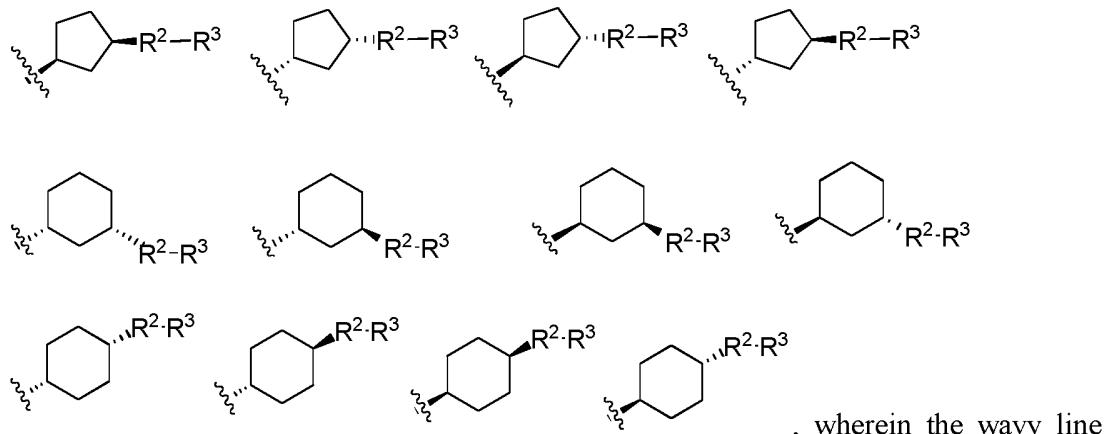
In certain embodiments R¹ is a 3-20 membered heterocyclyl, wherein R¹ is independently optionally substituted by halogen, oxo, -CN, -OR^a, -SR^a, -NR^aR^b, C₁₋₃ alkylene or C₁₋₆ alkyl 20 optionally substituted by oxo, -CN or halogen, and wherein said heterocyclyl is oxetanyl, azetidinyl, thietanyl, tetrahydrofuranyl, 2,3-dihydrofuranlyl, tetrahydrothienyl, 2,3-dihydrothienyl, pyrrolidinyl, 2,3-dihydro-1H-pyrrolyl, imidazolidinyl, 2H-pyranlyl, tetrahydropyranlyl, morpholinyl, piperazinyl, hexahydropyrimidinyl, oxazinanyl, thiazinanyl, piperidinyl, 8-azabicyclo[3.2.1]octanyl, 2-azabicyclo[2.2.2]octanyl, oxepanyl, azepanyl, 4,5,6,7-tetrahydrobenzoimidazolyl, 4,5,6,7-tetrahydro[2H]indazolyl, oxazolidinyl, thiazolidinyl, 25 isothiazolidinyl, 1,1-dioxoisothiazolidinyl, oxazolidinonyl, 3-azabicyclo[3.1.0]hexanyl or imidazolidinonyl.

In certain embodiments R¹ is a 3-7 membered heterocyclyl, wherein R¹ is independently optionally substituted by halogen, oxo, -CN, -OR^a, -SR^a, -NR^aR^b, C₁₋₃ alkylene or C₁₋₆ alkyl optionally substituted by oxo, -CN or halogen, wherein said heterocyclyl is piperidinyl.

In certain embodiments, R¹ is (R)-piperidin-3-yl, optionally substituted by halogen, oxo, -CN, -OR^a, -SR^a, -NR^aR^b, C₁₋₃ alkylene or C₁₋₆ alkyl optionally substituted by oxo, -CN or halogen. In certain embodiments, R¹ is (S)-piperidin-3-yl optionally substituted by halogen, oxo, -CN, -OR^a, -SR^a, -NR^aR^b, C₁₋₃ alkylene or C₁₋₆ alkyl optionally substituted by oxo, -CN or halogen.

In certain embodiments R¹ is piperidinyl optionally substituted by -NR^aR^b or C₁₋₆ alkyl optionally substituted by oxo, -CN or halogen.

In certain embodiments R¹ is a C₄₋₇ cycloalkyl, wherein R¹ is independently optionally substituted by halogen, oxo, -CN, -OR^a, -SR^a, -NR^aR^b, C₁₋₃ alkylene or C₁₋₆ alkyl optionally substituted by oxo, -CN or halogen. In certain embodiments, said cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. In certain embodiments, R¹ is selected from



In certain embodiments, R¹ is cyclopentyl optionally substituted by halogen, oxo, -CN, -OR^a, -SR^a, -NR^aR^b, C₁₋₃ alkylene or C₁₋₆ alkyl optionally substituted by oxo, -CN or halogen.

In certain embodiments, R¹ is cyclohexyl optionally substituted by halogen, oxo, -CN, -OR^a, -SR^a, -NR^aR^b, C₁₋₃ alkylene or C₁₋₆ alkyl optionally substituted by oxo, -CN or halogen.

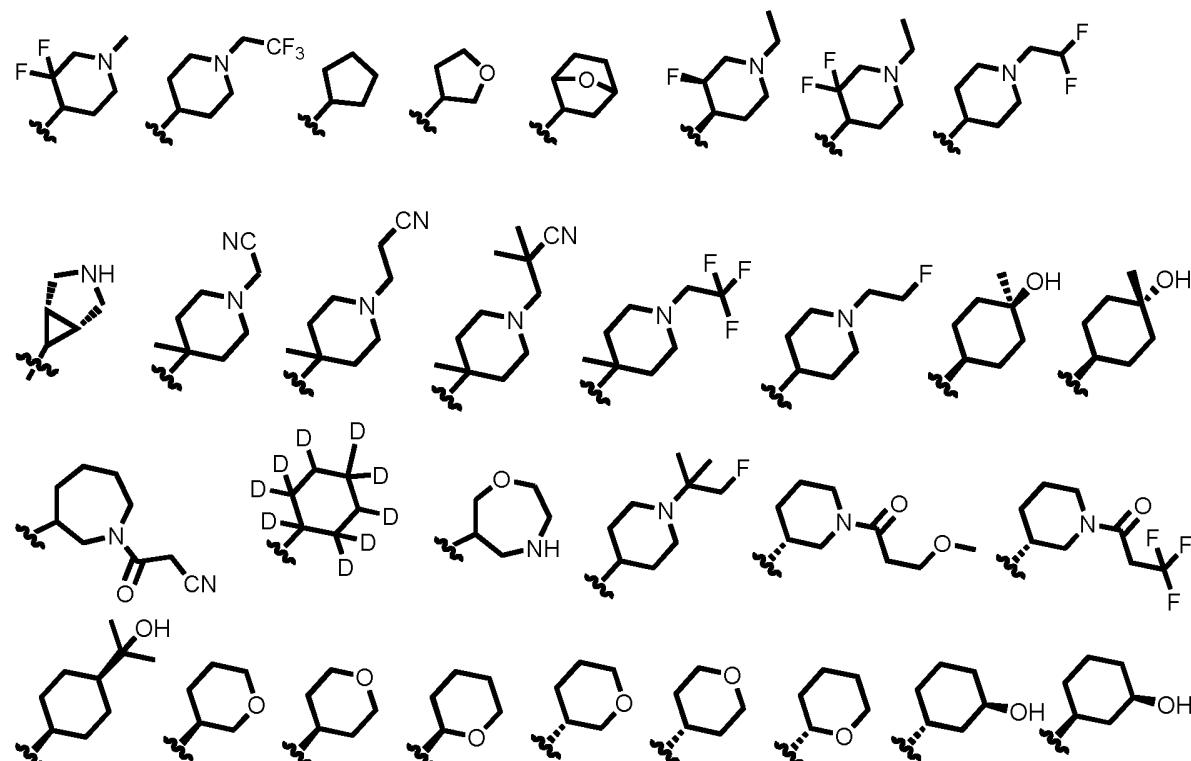
In one embodiment, R¹ is selected from cyclohexyl, 2-hydroxycyclohexyl, 3-hydroxycyclohexyl, 4-hydroxycyclohexyl, bicyclo[2.2.1]heptanyl, 2-methylcyclohexyl or 4,4-difluorocyclohexyl.

In certain embodiments, R¹ is C₆₋₁₄ aryl optionally substituted by halogen, oxo, -CN, -OR^a, -SR^a, -NR^aR^b, C₁₋₃ alkylene or C₁₋₆ alkyl optionally substituted by oxo, -CN or halogen.

5 In certain embodiments, R¹ is 4-cyanophenyl.

In certain embodiments, R¹ is selected from methyl, methylene, ethyl, propyl, butyl, phenyl, 4-cyanophenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 2-methylcyclohex-1-yl, 2-hydroxycyclohex-1-yl, 3-hydroxycyclohex-1-yl, 4-hydroxycyclohex-1-yl, bicyclo[2.2.1]heptanyl, pyrrolidinyl, piperidinyl, piperidinonyl, 2-methylpiperidin-4-yl, 3-methylpiperidin-4-yl, 4-methylpiperidin-4-yl, 2-fluoropiperidinyl, 3-fluoropiperidin-4-yl, 3,3-difluoropiperidin-4-yl, 3-methoxypiperidin-4-yl, 2,2-dimethyltetrahydropyranyl, tetrahydropyranyl, tetrahydropyran-2-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, azepanyl, octahydro-1H-indol-2-onyl, 1-azaspiro[4.5]decan-2-only, 8-azabicyclo[3.2.1]octanyl, 4,5,6,7-tetrahydrobenzoimidazoloyl, 4,5,6,7-tetrahydro-1H-indazoloyl, 1,1-dioxohexahydrothiopyranyl,

10 15 (1R,5S)-8-azabicyclo[3.2.1]octane,



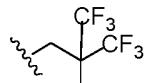
20 , and wherein the wavy line represents the point of attachment in formula I.

In certain embodiments, R¹ is selected from cyclopentyl, cyclohexyl or piperidinyl.

In certain embodiments, R² is absent. In certain embodiments, R² is absent with the proviso that R¹, R² and R³ are not all absent at the same time.

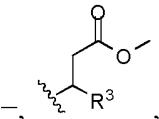
In certain embodiments, R² and R³ are absent. In certain embodiments, R² and R³ are absent with the proviso that R¹, R² and R³ are not all absent at the same time.

In certain embodiments, R² is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, wherein said alkyl, alkenyl or alkynyl are independently optionally substituted by halogen, oxo, -CN, -OR^c, -SR^c, -NR^cR^d or C₁₋₃ alkyl optionally substituted by halogen, and R³ is absent. In certain embodiments, R² is selected from -CH₂CF₃, -CH₂CH₂CF₃, -CH₂CH₂F, -C(CH₃)₂OH, -



10 CH₂C(CH₃)₂OH, -CH₂CH₂OH, -CH₂CH₂OCH₃ and , wherein the wavy line represents the point of attachment in formula I.

In certain embodiments, R² is -(C₁₋₆ alkylene)-, wherein said alkylene is optionally substituted by halogen, oxo, -CN, -OR^c, -SR^c, -NR^cR^d or C₁₋₃ alkyl optionally substituted by



halogen. In certain embodiments, R² is methylene, ethylene, -CH(CH₃)-, -C(CH₃)₂- , 15 propylene or butylene, optionally substituted by halogen, oxo, -CN, -OR^c, -NR^cR^d or C₁₋₃ alkyl, wherein the wavy line represents the point of attachment in formula I.

In certain embodiments, R² is -(C₀₋₆ alkylene)CN, wherein said alkylene is optionally substituted by halogen, oxo, -CN, -OR^c, -SR^c, -NR^cR^d or C₁₋₃ alkyl optionally substituted by halogen, and R³ is absent. In certain embodiments, R² is -CH₂CN, -CH₂CH₂CN, -CH(CH₃)CN or -CH(CH₃)CH₂CN and R³ is absent.

In certain embodiments, R² is -(C₀₋₃ alkylene)NR^a(C₀₋₃ alkylene)-, wherein said alkylene is optionally substituted by halogen, oxo, -CN, -OR^c, -SR^c, -NR^cR^d or C₁₋₃ alkyl optionally substituted by halogen. In certain embodiments, R² is -NH-, -NHCH₂- or -NHCH₂CH₂-.

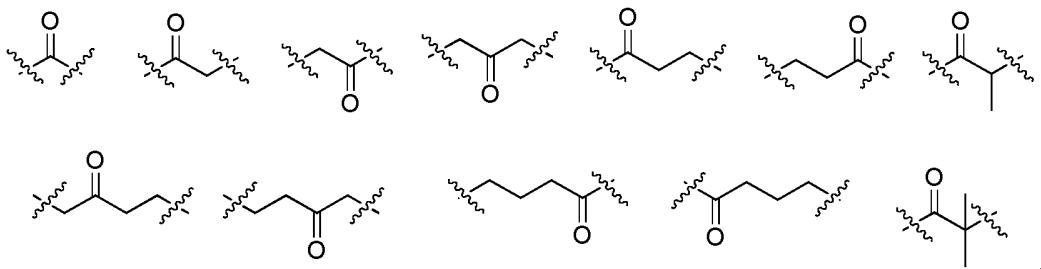
In certain embodiments, R² is -(C₀₋₃ alkylene)O(C₀₋₃ alkylene)-, wherein said alkylene is 25 optionally substituted by halogen, oxo, -CN, -OR^c, -SR^c, -NR^cR^d or C₁₋₃ alkyl optionally

substituted by halogen. In certain embodiments, R² is -CH₂O-, -CH₂C(CH₂)₂O- or -(CH₂)₂O-.

In certain embodiments, R² is -(C₀₋₃ alkylene)NR^aC(O)(C₀₋₃ alkylene)- or -(C₀₋₃ alkylene)C(O)NR^a(C₀₋₃ alkylene)-, wherein said alkylene is optionally substituted by halogen, 5 oxo, -CN, -OR^c, -SR^c, -NR^cR^d or C₁₋₃ alkyl optionally substituted by halogen. In certain embodiments, R² is -C(O)NH-, -CH₂C(O)NH- or -CH₂C(O)N(CH₃)-. In certain embodiments, R² is -NHC(O)- or -NHC(O)CH₂-.

In certain embodiments R² is -(C₀₋₃ alkylene)OC(O)NR^a(C₀₋₃ alkylene)- or -(C₀₋₃ alkylene)NR^aC(O)O(C₀₋₃ alkylene)-, wherein said alkylene is optionally substituted by halogen, 10 oxo, -CN, -OR^c, -SR^c, -NR^cR^d or C₁₋₃ alkyl optionally substituted by halogen. In certain embodiments, R² is -NHC(O)O-, -N(CH₃)C(O)O-, -NHC(O)OCH₂- or -NHC(O)OCH₂CH₂-.

In certain embodiments R² is -(C₀₋₃ alkylene)C(O)(C₀₋₃ alkylene)-, wherein said alkylene is optionally substituted by halogen, oxo, -CN, -OR^c, -SR^c, -NR^cR^d or C₁₋₃ alkyl optionally substituted by halogen. In certain embodiments, R² is selected from:

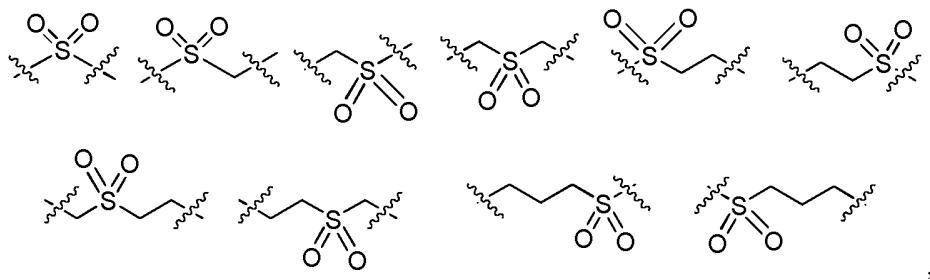


15 ,

wherein the wavy lines represent points of attachment.

In certain embodiments R² is -(C₀₋₃ alkylene)C(O)O(C₀₋₃ alkylene)- or -(C₀₋₃ alkylene)OC(O)(C₀₋₃ alkylene)-, wherein said alkylene is optionally substituted by halogen, oxo, -CN, -OR^c, -SR^c, -NR^cR^d or C₁₋₃ alkyl optionally substituted by halogen. In certain 20 embodiments, R² is selected from -C(O)O-.

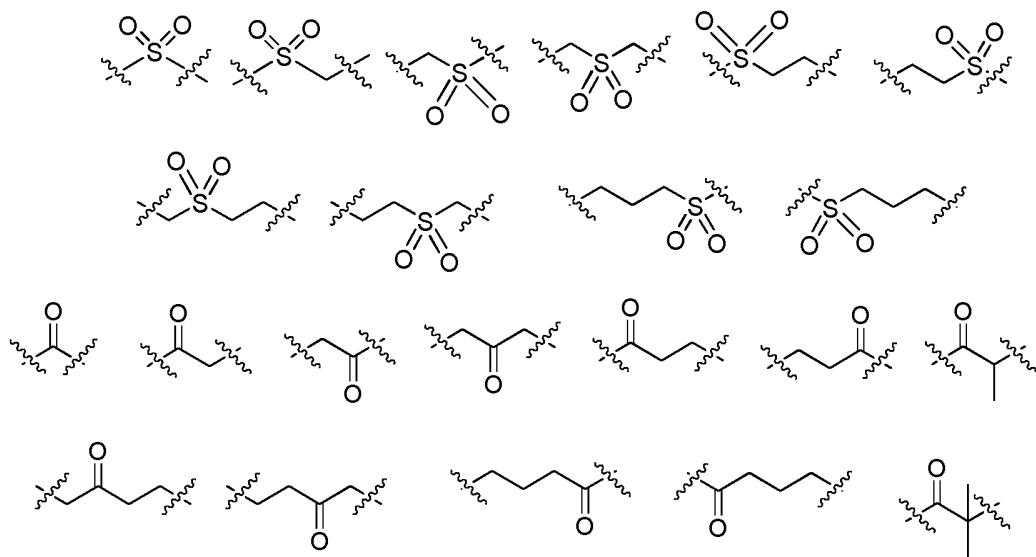
In certain embodiments R² is -(C₀₋₃ alkylene)S(O)₁₋₂(C₀₋₃ alkylene)-, wherein said alkylene is optionally substituted by halogen, oxo, -CN, -OR^c, -SR^c, -NR^cR^d or C₁₋₃ alkyl optionally substituted by halogen. In certain embodiments, R² is selected from -C(O)CH₂S(O)₂,

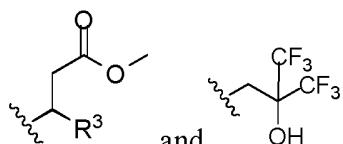


wherein the wavy lines represent points of attachment.

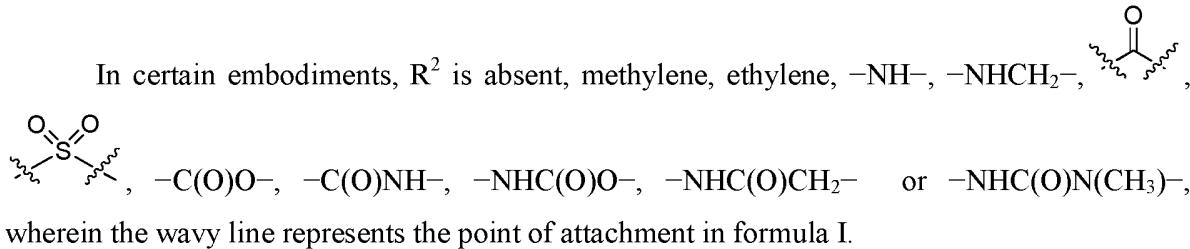
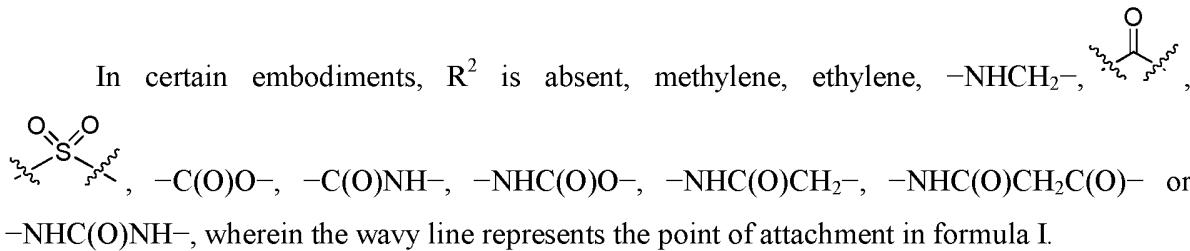
In certain embodiments, R^2 is $-(C_{0-3} \text{ alkylene})NR^aS(O)_{1-2}(C_{0-3} \text{ alkylene})-$ or $-(C_{0-3} \text{ alkylene})S(O)_{1-2}NR^a(C_{0-3} \text{ alkylene})-$, wherein said alkylene is optionally substituted by halogen, oxo, $-CN$, $-OR^c$, $-SR^c$, $-NR^cR^d$ or C_{1-3} alkyl optionally substituted by halogen. In certain 5 embodiments, R^2 is $-NHS(O)_2-$, $-N(CH_3)S(O)_2-$ or $-NHS(O)_2CH_2-$.

In certain embodiments, R^2 is selected from absent, $-NHS(O)_2-$, $-N(CH_3)S(O)_2-$, $-NHS(O)_2CH_2-$, $-C(O)CH_2S(O)_2$, $-C(O)O-$, $-NHC(O)O-$, $-N(CH_3)C(O)O-$, $-NHC(O)OCH_2-$, $-NHC(O)OCH_2CH_2-$, $-C(O)NH-$, $-CH_2C(O)NH-$, $-CH_2C(O)N(CH_3)-$, 10 $-NHC(O)-$, $-NHC(O)CH_2-$, $-CH_2O-$, $-CH_2C(CH_2)_2O-$, $-(CH_2)_2O-$, $-NH-$, $-NHCH_2-$, $-NHCH_2CH_2-$, $-CH_2CN$, $-CH_2CH_2CN$, $-CH(CH_3)CN$, $-CH(CH_3)CH_2CN$, methylene, ethylene, $-C(CH_3)_2-$, $-CH_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2F$, $-CH_2C(CH_3)_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2OCH_3$,





, wherein the wavy line represents the point of attachment in formula I.



In certain embodiments, R³ is absent.

10 In certain embodiments, R³ is hydrogen.

In certain embodiments, -R²-R³ is -CHO.

In certain embodiments, R² is absent and R³ is hydrogen.

In certain embodiments, R¹ and R² are absent.

15 In certain embodiments, R³ is absent, hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₆₋₁₄ aryl or 3-20 membered heterocyclyl, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, aryl and heterocyclyl are independently optionally substituted by R⁶.

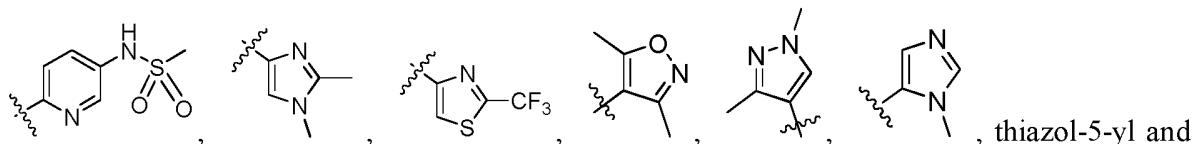
20 In certain embodiments, R³ is C₁₋₆ alkyl optionally substituted by 1 to 3 R⁶. In certain embodiments, R³ is methyl, ethyl, propyl, isopropyl, butyl, isobutyl or t-butyl optionally substituted by oxo, C₁₋₆ alkyl, halogen, -CN, -S(O)₂(C₁₋₆ alkyl), -OR^a or -NR^aR^b. In certain embodiments, R³ is selected from methyl, ethyl, n-butyl, sec-butyl, t-butyl, -CF₃, -CH₂CF₃, -CH₂CH₂F, -CH₂CH₂CF₃, -CH₂OCH₃, -CH₂CH₂OCH₃, -CH(CH₂CH₃)CH₂OCH₃,

$-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{OH}$, $-\text{CH}_2\text{C}(\text{CF}_3)_2\text{OH}$, $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{C}(\text{CH}_3)_2\text{OH}$, $-\text{CH}_2\text{CN}$, $-(\text{CH}_2)_2\text{CN}$, $-(\text{CH}_2)_3\text{CN}$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{CN}$, $-\text{C}(\text{CH}_3)_2\text{CN}$, $-\text{CH}(\text{CH}_3)\text{CN}$, $-\text{CH}_2\text{NH}_2$, $-\text{CH}(\text{CH}_3)\text{N}(\text{CH}_3)_2$ and $-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$.

In certain embodiments, R^3 is C_{3-7} cycloalkyl optionally substituted by 1 to 3 R^6 . In 5 certain embodiments, R^3 is C_{3-7} cycloalkyl optionally substituted by 1 to 3 oxo, halogen, $-\text{CN}$, $-\text{S}(\text{O})_{1-2}(\text{C}_{1-6}$ alkyl), $-\text{OR}^a$, $-\text{SR}^a$, $-\text{NR}^a\text{R}^b$ or C_{1-6} alkyl optionally substituted by oxo or halogen. In certain embodiments, R^3 is selected from cyclopropyl, 1-cyanocycloprop-1-yl, 1-trifluoromethylcycloprop-1-yl, 1-methylcycloprop-1-yl, 2-fluorocycloprop-1-yl, 2,2-dimethylcycloprop-1-yl, 2-cyanocyclopropyl, cyclobutyl, 4-carboxyclobutyl, 1-cyanocyclobut-1-10 yl, 4-aminocyclobutyl, cyclopentyl, 3-aminocyclohexyl, 4-aminocyclohexyl, 2-hydroxycyclohexyl, 3-hydroxycyclohexyl, 4-hydroxycyclohexyl and 2-hydroxycyclohexyl.

In certain embodiments, R^3 is C_{6-14} aryl optionally substituted by 1 to 3 R^6 . In certain embodiments, R^3 is C_{6-14} aryl optionally substituted by 1 to 3 C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, $-\text{CN}$, $-\text{S}(\text{O})_{1-2}(\text{C}_{1-6}$ alkyl), $-\text{OR}^a$, $-\text{SR}^a$ or $-\text{NR}^a\text{R}^b$. In certain embodiments, 15 R^3 is phenyl, 2-chloro-4-cyanophenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 3-methylsulfonylphenyl, 3-fluorophenyl or 4-methoxyphenyl.

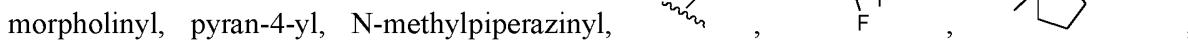
In certain embodiments, R^3 is 5-6 membered heteroaryl optionally substituted by 1 to 3 R^6 . In certain embodiments, R^3 is 5-6 membered heteroaryl optionally substituted by 1 to 3 oxo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, $-\text{CN}$, $-\text{S}(\text{O})_{1-2}(\text{C}_{1-6}$ alkyl), $-\text{OR}^a$, $-\text{SR}^a$ or 20 $-\text{NR}^a\text{R}^b$. In certain embodiments, R^3 is selected from pyridinyl, pyridin-3-yl, 6-cyanopyridinyl, 6-trifluoromethylpyridinyl, 2-cyanopyridin-4-yl, 4-cyanopyridin-2-yl, 5-cyanopyridin-2-yl, 3-fluoropyridin-5-yl, thiazol-5-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrazin-2-yl, oxazol-2-yl, oxazol-4-yl, 1-methylpyrazol-5-yl, 1-methylpyrazol-4-yl, 1-methylimidazol-2-yl



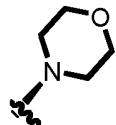
25 isothiazol-5-yl, wherein the wavy line represents the point of attachment in formula I.

In certain embodiments, R^3 is 3-12 membered heterocyclyl optionally substituted by 1 to 3 R^6 . In certain embodiments, R^3 is 4-7 membered heterocyclyl optionally substituted by 1 to 3

R^6 . In certain embodiments, R^3 is 4-7 membered heterocyclyl optionally substituted by 1 to 3 oxo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, $-CN$, $-S(O)_{1-2}R^a$, $-C(O)OR^a$, $-OR^a$, $-SR^a$ or $-NR^aR^b$, wherein said alkyl, alkenyl and alkynyl are optionally substituted by oxo, halogen, $-CN$, $-OR^c$ or $-NR^cR^d$. In certain embodiments, R^3 is selected from oxetan-3-yl, piperidin-3-yl, 5 piperidin-4-yl, N-methylpiperidin-2-yl, N-methylmorpholin-2-yl, 1-methylpyrrolidin-2-yl, pyrrolidinyl, pyrrolidinonyl, piperidinonyl, 3,3-difluoropyrrolidin-2-yl, 1-isopropylpyrrolidin-2-yl, 2-methylpyrrolidin-2-yl, 1-methylcyanopyrrolidin-2-yl, 1-cyclobutylpyrrolidin-2-yl,



10 morpholinyl, pyran-4-yl, N-methylpiperazinyl, or , , , , , and

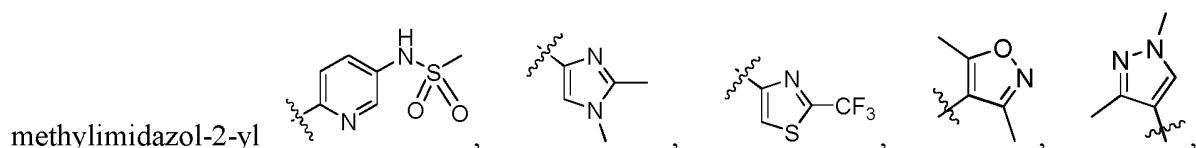


wherein the wavy line represents the point of attachment in formula I.

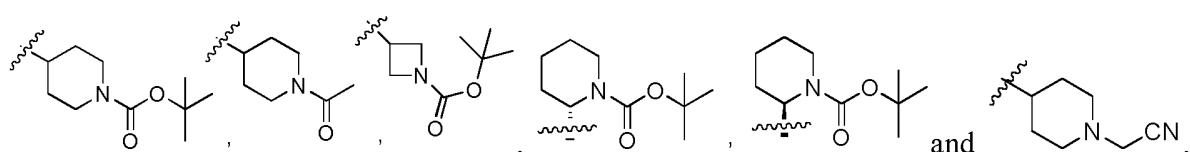
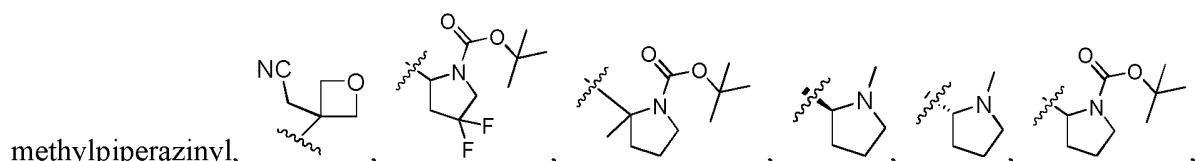
In certain embodiments, R^3 is absent, hydrogen, methyl, ethyl, trifluoromethyl, pyrrolidinyl, phenyl, pyridyl or cyclopropyl, independently optionally substituted by oxo, C_{1-6} alkyl, halogen, $-CN$, $-S(O)_2(C_{1-6}$ alkyl), $-OR^a$ or $-NR^aR^b$.

In certain embodiments, R^3 is selected from absent, hydrogen, methyl, ethyl, n-butyl, sec-butyl, t-butyl, $-CF_3$, $-CH_2CF_3$, $-CH_2CH_2F$, $-CH_2CH_2CF_3$, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, $-CH(CH_2CH_3)CH_2OCH_3$, $-CH(CH_3)CH_2CH_2OH$, $-CH_2C(CH_3)_2OH$, $-CH_2C(CF_3)_2OH$, $-CH_2CH_2OH$, $-C(CH_3)_2OH$, $-CH_2CN$, $-(CH_2)_2CN$, $-(CH_2)_3CN$, $-CH(CH_3)CH_2CN$, $-C(CH_3)_2CN$, $-CH(CH_3)CN$, $-CH_2NH_2$, $-CH(CH_3)N(CH_3)_2$, $-CH_2CH_2N(CH_3)_2$, cyclopropyl, 1-cyanocycloprop-1-yl, 1-trifluoromethylcycloprop-1-yl, 1-methylcycloprop-1-yl, 2-fluorocycloprop-1-yl, 2,2-dimethylcycloprop-1-yl, 2-cyanocyclopropyl, cyclobutyl, 4-

carboxycyclobutyl, 1-cyanocyclobut-1-yl, 4-aminocyclobutyl, cyclopentyl, 3-aminocyclohexyl, 4-aminocyclohexyl, 2-hydroxycyclohexyl, 3-hydroxycyclohexyl, 4-hydroxycyclohexyl, 2-hydroxycyclohexyl, phenyl, 2-chloro-4-cyanophenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 3-methylsulfonylphenyl, 3-fluorophenyl, 4-methoxyphenyl, pyridinyl, pyridin-3-
5 yl, 6-cyanopyridinyl, 6-trifluoromethylpyridinyl, 2-cyanopyridin-4-yl, 4-cyanopyridin-2-yl, 5-cyanopyridin-2-yl, 3-fluoropyridin-5-yl, thiazol-5-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrazin-2-yl, oxazol-2-yl, oxazol-4-yl, 1-methylpyrazol-5-yl, 1-methylpyrazol-4-yl, 1-



10 methylmorpholin-2-yl, 1-methylpyrrolidin-2-yl, pyrrolidinyl, pyrrolidinonyl, piperidinonyl, 3,3-difluoropyrrolidin-2-yl, 1-isopropylpyrrolidin-2-yl, 2-methylpyrrolidin-2-yl, 1-methylcyanopyrrolidin-2-yl, 1-cyclobutylpyrrolidin-2-yl, morpholinyl, pyran-4-yl, N-



15 wherein the wavy line represents the point of attachment in formula I.

In certain embodiments, R³ is absent, hydrogen, methyl, ethyl, -CF₃, -CH₂CF₃, -CH₂CN, -(CH₂)₂CN, -CH₂cyclopropyl, cyclopropyl, phenyl, 3-cyanophenyl, 5-cyanopyridin-2-yl or pyridin-3-yl.

20 In certain embodiments, R³ is absent, hydrogen, methyl, ethyl, t-butyl, -CF₃, -CH₂CF₃, -CH₂CN, -(CH₂)₂CN, -CH₂cyclopropyl, cyclopropyl, phenyl, 3-cyanophenyl, 5-cyanopyridin-2-yl, N-methylpyrrolidin-2-yl or pyridin-3-yl.

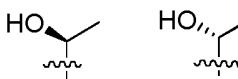
In certain embodiments, R⁴ is hydrogen, methyl or F. In certain embodiments, R⁴ is hydrogen.

In certain embodiments, R⁵ is hydrogen.

In certain embodiments, R⁵ is halogen, C₁₋₁₂ alkyl, C₂₋₁₂ alkenyl, C₂₋₁₂ alkynyl, -(C₀₋₆ alkylene)CN, -(C₀₋₃ alkylene)NR^aR^b, -(C₀₋₃ alkylene)OR^a, -(C₀₋₃ alkylene)SR^a, -(C₀₋₃ alkylene)C(O)R^a, -(C₀₋₃ alkylene)NR^aC(O)R^b, -(C₀₋₃ alkylene)C(O)NR^aR^b, -(C₀₋₃ alkylene)C(O)OR^a, -(C₀₋₃ alkylene)OC(O)R^a, -(C₀₋₃ alkylene)NR^aC(O)NR^aR^b, -(C₀₋₃ alkylene)OC(O)NR^aR^b, -(C₀₋₃ alkylene)NR^aC(O)OR^b, -(C₀₋₃ alkylene)S(O)₁₋₂R^a, -(C₀₋₃ alkylene)NR^aS(O)₁₋₂R^b, -(C₀₋₃ alkylene)S(O)₁₋₂NR^aR^b, -(C₀₋₃ alkylene)NR^aS(O)₁₋₂NR^aR^b, -(C₀₋₃ alkylene)C₃₋₆ cycloalkyl, -(C₀₋₃ alkylene)C₆₋₁₄ aryl, -(C₀₋₃ alkylene)3-12 membered heterocyclyl or -(C₀₋₃ alkylene)C(O)3-12 membered heterocyclyl, wherein said alkyl, alkenyl, alkynyl, alkylene, cycloalkyl, aryl and heterocyclyl are independently optionally substituted by halogen, oxo, -(C₀₋₃ alkylene)CN, -(C₀₋₃ alkylene)OR^c, -(C₀₋₃ alkylene)NR^cR^d, -(C₀₋₃ alkylene)C(O)R^c, -(C₀₋₃ alkylene)C(O)OR^c, -(C₀₋₃ alkylene)C(O)NR^cR^d, -(C₀₋₃ alkylene)NR^cC(O)R^d, -(C₀₋₃ alkylene)OC(O)NR^cR^d, -(C₀₋₃ alkylene)NR^cC(O)NR^cR^d, -(C₀₋₃ alkylene)NR^cC(O)OR^d, -(C₀₋₃ alkylene)S(O)₀₋₂R^c, -(C₀₋₃ alkylene)NR^cS(O)₁₋₂R^d, -(C₀₋₃ alkylene)S(O)₁₋₂NR^cR^d, -(C₀₋₃ alkylene)NR^cS(O)₁₋₂NR^cR^d or C₁₋₆ alkyl optionally substituted by oxo, -CN or halogen.

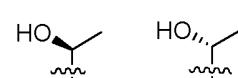
In certain embodiments, R⁵ is halogen. In certain embodiments, R⁵ is F.

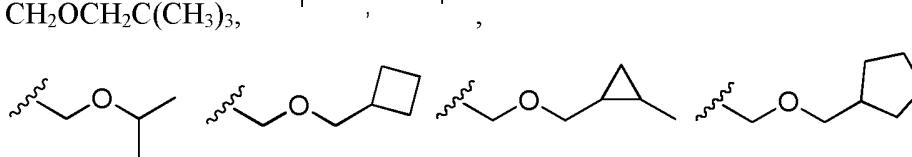
In certain embodiments, R⁵ is C₁₋₁₂ alkyl, C₂₋₁₂ alkenyl, C₂₋₁₂ alkynyl, wherein said alkyl, alkenyl and alkynyl are independently optionally substituted by halogen, oxo, -(C₀₋₃ alkylene)CN, -(C₀₋₃ alkylene)OR^c, -(C₀₋₃ alkylene)NR^cR^d, -(C₀₋₃ alkylene)C(O)R^c, -(C₀₋₃ alkylene)C(O)OR^c, -(C₀₋₃ alkylene)C(O)NR^cR^d, -(C₀₋₃ alkylene)NR^cC(O)R^d, -(C₀₋₃ alkylene)OC(O)NR^cR^d, -(C₀₋₃ alkylene)NR^cC(O)NR^cR^d, -(C₀₋₃ alkylene)NR^cC(O)OR^d, -(C₀₋₃ alkylene)S(O)₀₋₂R^c, -(C₀₋₃ alkylene)NR^cS(O)₁₋₂R^d, -(C₀₋₃ alkylene)S(O)₁₋₂NR^cR^d, -(C₀₋₃ alkylene)NR^cS(O)₁₋₂NR^cR^d or C₁₋₆ alkyl optionally substituted by oxo, -CN or halogen. In certain embodiments, R⁵ is selected from methyl, ethyl, 1-hydroxyethyl, 2-hydroxyethyl, propyl, isopropyl, butyl, 2-methylbutyl, 3,3-difluorobut-1-yl, isobutyl, -CH₂F, -CHF₂, -CF₃, -CH₂OH,

$-\text{C}(\text{CH}_3)_2\text{OH}$,  , wherein the wavy line represents the point of attachment in formula I.

In certain embodiments, R^5 is $-(\text{C}_{0-3} \text{ alkylene})\text{CN}$, wherein said alkylene is independently optionally substituted by halogen, oxo, $-(\text{C}_{0-3} \text{ alkylene})\text{CN}$, $-(\text{C}_{0-3} \text{ alkylene})\text{OR}^c$, $-(\text{C}_{0-3} \text{ alkylene})\text{NR}^c\text{R}^d$, $-(\text{C}_{0-3} \text{ alkylene})\text{C}(\text{O})\text{R}^c$, $-(\text{C}_{0-3} \text{ alkylene})\text{C}(\text{O})\text{OR}^c$, $-(\text{C}_{0-3} \text{ alkylene})\text{C}(\text{O})\text{NR}^c\text{R}^d$, $-(\text{C}_{0-3} \text{ alkylene})\text{NR}^c\text{C}(\text{O})\text{R}^d$, $-(\text{C}_{0-3} \text{ alkylene})\text{OC}(\text{O})\text{NR}^c\text{R}^d$, $-(\text{C}_{0-3} \text{ alkylene})\text{NR}^c\text{C}(\text{O})\text{NR}^c\text{R}^d$, $-(\text{C}_{0-3} \text{ alkylene})\text{NR}^c\text{C}(\text{O})\text{OR}^d$, $-(\text{C}_{0-3} \text{ alkylene})\text{S}(\text{O})_{0-2}\text{R}^c$, $-(\text{C}_{0-3} \text{ alkylene})\text{NR}^c\text{S}(\text{O})_{1-2}\text{R}^d$, $-(\text{C}_{0-3} \text{ alkylene})\text{S}(\text{O})_{1-2}\text{NR}^c\text{R}^d$, $-(\text{C}_{0-3} \text{ alkylene})\text{NR}^c\text{S}(\text{O})_{1-2}\text{NR}^c\text{R}^d$ or C_{1-6} alkyl optionally substituted by oxo, $-\text{CN}$ or halogen. In certain embodiments, R^5 is selected from $-\text{CN}$, $-\text{C}(\text{CH}_3)_2\text{CN}$.

10 In certain embodiments, R^5 is $-\text{CN}$.

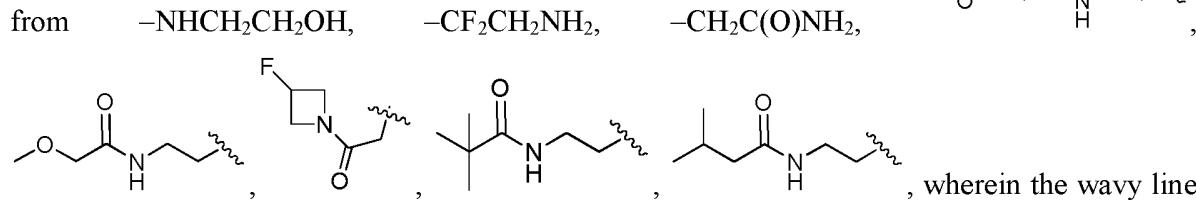
In certain embodiments, R^5 is $-(\text{C}_{0-3} \text{ alkylene})\text{OR}^a$ or $-(\text{C}_{0-3} \text{ alkylene})\text{SR}^a$, wherein said alkylene is independently optionally substituted by halogen, oxo, $-(\text{C}_{0-3} \text{ alkylene})\text{CN}$, $-(\text{C}_{0-3} \text{ alkylene})\text{OR}^c$, $-(\text{C}_{0-3} \text{ alkylene})\text{NR}^c\text{R}^d$, $-(\text{C}_{0-3} \text{ alkylene})\text{C}(\text{O})\text{R}^c$, $-(\text{C}_{0-3} \text{ alkylene})\text{C}(\text{O})\text{OR}^c$, $-(\text{C}_{0-3} \text{ alkylene})\text{C}(\text{O})\text{NR}^c\text{R}^d$, $-(\text{C}_{0-3} \text{ alkylene})\text{NR}^c\text{C}(\text{O})\text{R}^d$, $-(\text{C}_{0-3} \text{ alkylene})\text{OC}(\text{O})\text{NR}^c\text{R}^d$, $-(\text{C}_{0-3} \text{ alkylene})\text{NR}^c\text{C}(\text{O})\text{NR}^c\text{R}^d$, $-(\text{C}_{0-3} \text{ alkylene})\text{NR}^c\text{C}(\text{O})\text{OR}^d$, $-(\text{C}_{0-3} \text{ alkylene})\text{S}(\text{O})_{0-2}\text{R}^c$, $-(\text{C}_{0-3} \text{ alkylene})\text{NR}^c\text{S}(\text{O})_{1-2}\text{R}^d$, $-(\text{C}_{0-3} \text{ alkylene})\text{S}(\text{O})_{1-2}\text{NR}^c\text{R}^d$, $-(\text{C}_{0-3} \text{ alkylene})\text{NR}^c\text{S}(\text{O})_{1-2}\text{NR}^c\text{R}^d$ or C_{1-6} alkyl optionally substituted by oxo, $-\text{CN}$ or halogen. In certain embodiments, R^5 is selected from $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{C}(\text{CH}_3)_2\text{OH}$, $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{OH}$, $-\text{CH}_2\text{OCH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{OCH}_2\text{C}(\text{CH}_3)_3$, 

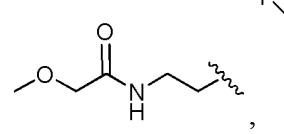
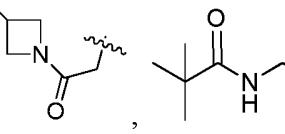
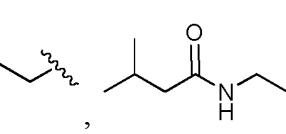
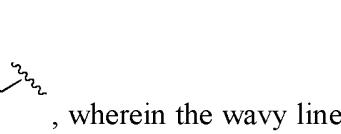
15  , wherein the wavy line represents the point of attachment in formula I.

20 In certain embodiments, R^5 is $-(\text{C}_{0-3} \text{ alkylene})\text{NR}^a\text{R}^b$, wherein said alkylene is independently optionally substituted by halogen, oxo, $-(\text{C}_{0-3} \text{ alkylene})\text{CN}$, $-(\text{C}_{0-3} \text{ alkylene})\text{OR}^c$, $-(\text{C}_{0-3} \text{ alkylene})\text{NR}^c\text{R}^d$, $-(\text{C}_{0-3} \text{ alkylene})\text{C}(\text{O})\text{R}^c$, $-(\text{C}_{0-3} \text{ alkylene})\text{C}(\text{O})\text{OR}^c$, $-(\text{C}_{0-3} \text{ alkylene})\text{C}(\text{O})\text{NR}^c\text{R}^d$, $-(\text{C}_{0-3} \text{ alkylene})\text{NR}^c\text{C}(\text{O})\text{R}^d$, $-(\text{C}_{0-3} \text{ alkylene})\text{OC}(\text{O})\text{NR}^c\text{R}^d$, $-(\text{C}_{0-3} \text{ alkylene})\text{NR}^c\text{C}(\text{O})\text{NR}^c\text{R}^d$, $-(\text{C}_{0-3} \text{ alkylene})\text{NR}^c\text{C}(\text{O})\text{OR}^d$, $-(\text{C}_{0-3} \text{ alkylene})\text{S}(\text{O})_{0-2}\text{R}^c$, $-(\text{C}_{0-3} \text{ alkylene})\text{NR}^c\text{S}(\text{O})_{1-2}\text{R}^d$, $-(\text{C}_{0-3} \text{ alkylene})\text{S}(\text{O})_{1-2}\text{NR}^c\text{R}^d$, $-(\text{C}_{0-3} \text{ alkylene})\text{NR}^c\text{S}(\text{O})_{1-2}\text{NR}^c\text{R}^d$ or C_{1-6} alkyl optionally substituted by oxo, $-\text{CN}$ or halogen. In certain embodiments, R^5 is selected from $-\text{CN}$, $-\text{C}(\text{CH}_3)_2\text{CN}$.

alkylene)NR^cC(O)NR^cR^d, -(C₀₋₃ alkylene)NR^cC(O)OR^d, -(C₀₋₃ alkylene)S(O)₀₋₂R^c, -(C₀₋₃ alkylene)NR^cS(O)₁₋₂R^d, -(C₀₋₃ alkylene)S(O)₁₋₂NR^cR^d, -(C₀₋₃ alkylene)NR^cS(O)₁₋₂NR^cR^d or C₁₋₆ alkyl optionally substituted by oxo, -CN or halogen. In certain embodiments, R⁵ is selected

from



 ,  ,  ,  , wherein the wavy line

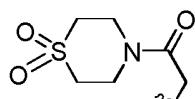
represents the point of attachment in formula I.

In certain embodiments, R⁵ is -(C₀₋₃ alkylene)C₃₋₁₂ cycloalkyl, wherein said alkylene and cycloalkyl are independently optionally substituted by halogen, oxo, -(C₀₋₃ alkylene)CN, -(C₀₋₃ alkylene)OR^c, -(C₀₋₃ alkylene)NR^cR^d, -(C₀₋₃ alkylene)C(O)R^c, -(C₀₋₃ alkylene)C(O)OR^c, -(C₀₋₃ alkylene)C(O)NR^cR^d, -(C₀₋₃ alkylene)NR^cC(O)R^d, -(C₀₋₃ alkylene)OC(O)NR^cR^d, -(C₀₋₃ alkylene)NR^cC(O)NR^cR^d, -(C₀₋₃ alkylene)NR^cC(O)OR^d, -(C₀₋₃ alkylene)S(O)₀₋₂R^c, -(C₀₋₃ alkylene)NR^cS(O)₁₋₂R^d, -(C₀₋₃ alkylene)S(O)₁₋₂NR^cR^d, -(C₀₋₃ alkylene)NR^cS(O)₁₋₂NR^cR^d or C₁₋₆ alkyl optionally substituted by oxo, -CN or halogen. In certain embodiments, R⁵ is selected from -CH₂cyclopentyl, -CH₂cyclopropyl, -CH₂CH₂cyclopropyl, cyclopropyl, 2,2-difluorocyclopropyl and cyclobutyl.

In certain embodiments, R⁵ is -(C₀₋₃ alkylene)C₃₋₇ cycloalkyl. In certain embodiments, R⁵ is cyclopropyl or cyclobutyl.

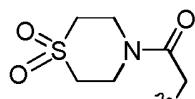
In certain embodiments, R⁵ is -(C₀₋₃ alkylene)C(O)NR^aR^b, wherein said alkylene is independently optionally substituted by halogen, oxo, -(C₀₋₃ alkylene)CN, -(C₀₋₃ alkylene)OR^c, -(C₀₋₃ alkylene)NR^cR^d, -(C₀₋₃ alkylene)C(O)R^c, -(C₀₋₃ alkylene)C(O)OR^c, -(C₀₋₃ alkylene)C(O)NR^cR^d, -(C₀₋₃ alkylene)NR^cC(O)R^d, -(C₀₋₃ alkylene)OC(O)NR^cR^d, -(C₀₋₃ alkylene)NR^cC(O)NR^cR^d, -(C₀₋₃ alkylene)NR^cC(O)OR^d, -(C₀₋₃ alkylene)S(O)₀₋₂R^c, -(C₀₋₃ alkylene)NR^cS(O)₁₋₂R^d, -(C₀₋₃ alkylene)S(O)₁₋₂NR^cR^d, -(C₀₋₃ alkylene)NR^cS(O)₁₋₂NR^cR^d or C₁₋₆ alkyl optionally substituted by oxo, -CN or halogen. In certain embodiments, R⁵ is selected from -CH₂C(O)NH₂, -CH₂C(O)NHCyclopentyl, -CH₂C(O)N(CH₃)(cyclopentyl), -CH₂C(O)NHCH₃, -

$\text{CH}(\text{CH}_3)\text{C}(\text{O})\text{NHCH}(\text{CH}_3)_2$, $-\text{CH}_2\text{C}(\text{O})(\text{pyrrolidin-1-yl})$, $-\text{CH}_2\text{C}(\text{O})(4,4\text{-difluoropiperidin-1-yl})$, $-\text{CH}_2\text{C}(\text{O})(\text{morpholinyl})$ and



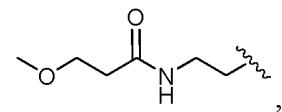
, wherein the wavy line represents the point of attachment in formula I.

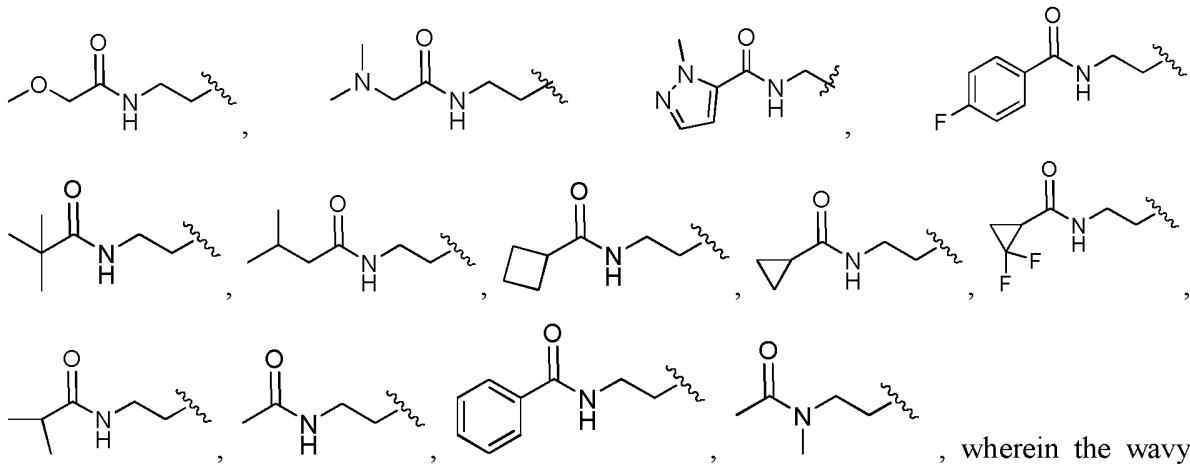
In certain embodiments, R^5 is $-(\text{C}_{0-3}\text{ alkylene})\text{C}(\text{O})\text{NR}^a\text{R}^b$, wherein said alkylene is independently optionally substituted by halogen, oxo, $-(\text{C}_{0-3}\text{ alkylene})\text{CN}$, $-(\text{C}_{0-3}\text{ alkylene})\text{OR}^c$, $-(\text{C}_{0-3}\text{ alkylene})\text{NR}^c\text{R}^d$, $-(\text{C}_{0-3}\text{ alkylene})\text{C}(\text{O})\text{R}^c$, $-(\text{C}_{0-3}\text{ alkylene})\text{C}(\text{O})\text{OR}^c$, $-(\text{C}_{0-3}\text{ alkylene})\text{C}(\text{O})\text{NR}^c\text{R}^d$, $-(\text{C}_{0-3}\text{ alkylene})\text{NR}^c\text{C}(\text{O})\text{R}^d$, $-(\text{C}_{0-3}\text{ alkylene})\text{OC}(\text{O})\text{NR}^c\text{R}^d$, $-(\text{C}_{0-3}\text{ alkylene})\text{NR}^c\text{C}(\text{O})\text{NR}^c\text{R}^d$, $-(\text{C}_{0-3}\text{ alkylene})\text{NR}^c\text{C}(\text{O})\text{OR}^d$, $-(\text{C}_{0-3}\text{ alkylene})\text{S}(\text{O})_{0-2}\text{R}^c$, $-(\text{C}_{0-3}\text{ alkylene})\text{NR}^c\text{S}(\text{O})_{1-2}\text{R}^d$, $-(\text{C}_{0-3}\text{ alkylene})\text{S}(\text{O})_{1-2}\text{NR}^c\text{R}^d$, $-(\text{C}_{0-3}\text{ alkylene})\text{NR}^c\text{S}(\text{O})_{1-2}\text{NR}^c\text{R}^d$ or C_{1-6} alkyl optionally substituted by oxo, $-\text{CN}$ or halogen. In certain embodiments, R^5 is $-\text{CH}_2\text{C}(\text{O})\text{NHCH}_3$, $-\text{CH}_2\text{C}(\text{O})\text{N}(\text{CH}_3)(\text{cyclopentyl})$, $-\text{CH}_2\text{C}(\text{O})\text{NH}(\text{cyclopentyl})$, $-\text{CH}_2\text{C}(\text{O})\text{NH}(\text{isopropyl})$, $-\text{CH}_2\text{C}(\text{O})(\text{pyrrolidin-1-yl})$, $-\text{CH}_2\text{C}(\text{O})(4,4\text{-difluoropiperidin-1-yl})$, $-\text{CH}_2\text{C}(\text{O})(\text{morpholinyl})$ or



, wherein the wavy line represents the point of attachment in formula I.

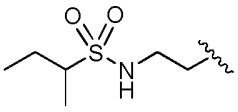
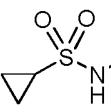
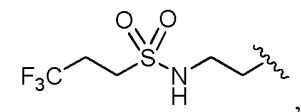
In certain embodiments, R^5 is $-(\text{C}_{0-3}\text{ alkylene})\text{NR}^a\text{C}(\text{O})\text{R}^b$, wherein said alkylene is independently optionally substituted by halogen, oxo, $-(\text{C}_{0-3}\text{ alkylene})\text{CN}$, $-(\text{C}_{0-3}\text{ alkylene})\text{OR}^c$, $-(\text{C}_{0-3}\text{ alkylene})\text{NR}^c\text{R}^d$, $-(\text{C}_{0-3}\text{ alkylene})\text{C}(\text{O})\text{R}^c$, $-(\text{C}_{0-3}\text{ alkylene})\text{C}(\text{O})\text{OR}^c$, $-(\text{C}_{0-3}\text{ alkylene})\text{C}(\text{O})\text{NR}^c\text{R}^d$, $-(\text{C}_{0-3}\text{ alkylene})\text{NR}^c\text{C}(\text{O})\text{R}^d$, $-(\text{C}_{0-3}\text{ alkylene})\text{OC}(\text{O})\text{NR}^c\text{R}^d$, $-(\text{C}_{0-3}\text{ alkylene})\text{NR}^c\text{C}(\text{O})\text{NR}^c\text{R}^d$, $-(\text{C}_{0-3}\text{ alkylene})\text{NR}^c\text{C}(\text{O})\text{OR}^d$, $-(\text{C}_{0-3}\text{ alkylene})\text{S}(\text{O})_{0-2}\text{R}^c$, $-(\text{C}_{0-3}\text{ alkylene})\text{NR}^c\text{S}(\text{O})_{1-2}\text{R}^d$, $-(\text{C}_{0-3}\text{ alkylene})\text{S}(\text{O})_{1-2}\text{NR}^c\text{R}^d$, $-(\text{C}_{0-3}\text{ alkylene})\text{NR}^c\text{S}(\text{O})_{1-2}\text{NR}^c\text{R}^d$ or C_{1-6} alkyl optionally substituted by oxo, $-\text{CN}$ or halogen. In certain embodiments, R^5 is selected from $-\text{CH}_2\text{NHC}(\text{O})\text{CH}_3$, $-\text{CH}_2\text{NHC}(\text{O})\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{NHC}(\text{O})\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{NHC}(\text{O})\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{NHC}(\text{O})\text{pyridin-3-yl}$, $-\text{CH}_2\text{NHC}(\text{O})\text{pyridin-4-yl}$,

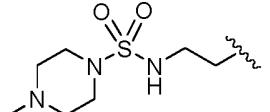




5 In certain embodiments, R^5 is $-(C_{0-3} \text{ alkylene})NR^aS(O)_{1-2}R^b$, wherein said alkylene is independently optionally substituted by halogen, oxo, $-(C_{0-3} \text{ alkylene})CN$, $-(C_{0-3} \text{ alkylene})OR^c$, $-(C_{0-3} \text{ alkylene})NR^cR^d$, $-(C_{0-3} \text{ alkylene})C(O)R^c$, $-(C_{0-3} \text{ alkylene})C(O)OR^c$, $-(C_{0-3} \text{ alkylene})C(O)NR^cR^d$, $-(C_{0-3} \text{ alkylene})NR^cC(O)R^d$, $-(C_{0-3} \text{ alkylene})OC(O)NR^cR^d$, $-(C_{0-3} \text{ alkylene})NR^cC(O)NR^cR^d$, $-(C_{0-3} \text{ alkylene})NR^cC(O)OR^d$, $-(C_{0-3} \text{ alkylene})S(O)_{0-2}R^c$, $-(C_{0-3}$

10 alkylene)NR^cS(O)_{1-2}R^d, $-(C_{0-3} \text{ alkylene})S(O)_{1-2}NR^cR^d$, $-(C_{0-3} \text{ alkylene})NR^cS(O)_{1-2}NR^cR^d$ or C_{1-6} alkyl optionally substituted by oxo, $-CN$ or halogen. In certain embodiments, R^5 is selected from $-CH_2NHS(O)_2CH_3$, $-CH_2NHS(O)_2CH_2CH_3$, $-CH_2NHS(O)_2CH_2CH(CH_3)_2$, $-CH_2NHS(O)_2CH(CH_3)_2$, $-CH_2NHS(O)_2CH_2CH_3$, $-CH_2NHS(O)_2\text{cyclopropyl}$, $-CH_2NHS(O)_2\text{cyclopentyl}$, $-CH_2N(CH_3)_2S(O)_2CH_3$, $-CH_2CH_2NHS(O)_2CH_3$,

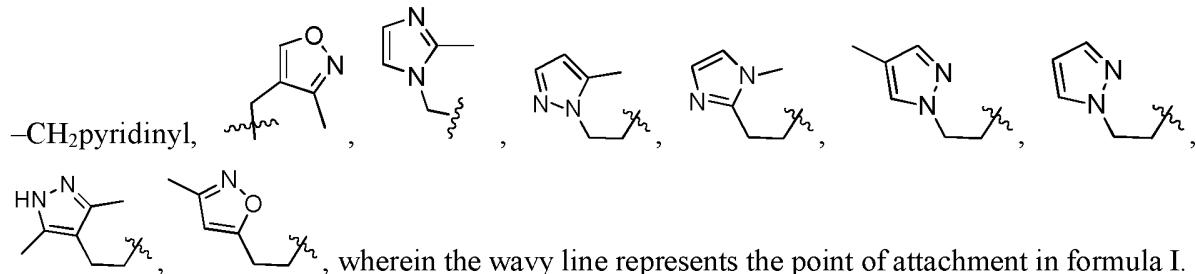
15 $CH_2CH_2NHS(O)_2CH_2CH_3$, , , 



, wherein the wavy line represents the point of attachment in formula I.

In certain embodiments, R^5 is $-(C_{0-3} \text{ alkylene})5-12 \text{ membered heteroaryl}$, wherein said alkylene and heteroaryl are independently optionally substituted by halogen, oxo, $-(C_{0-3} \text{ alkylene})CN$, $-(C_{0-3} \text{ alkylene})OR^c$, $-(C_{0-3} \text{ alkylene})NR^cR^d$, $-(C_{0-3} \text{ alkylene})C(O)R^c$, $-(C_{0-3} \text{ alkylene})C(O)OR^c$, $-(C_{0-3} \text{ alkylene})C(O)NR^cR^d$, $-(C_{0-3} \text{ alkylene})NR^cC(O)R^d$, $-(C_{0-3} \text{ alkylene})OC(O)NR^cR^d$, $-(C_{0-3} \text{ alkylene})NR^cC(O)NR^cR^d$, $-(C_{0-3} \text{ alkylene})NR^cC(O)OR^d$, $-(C_{0-3}$

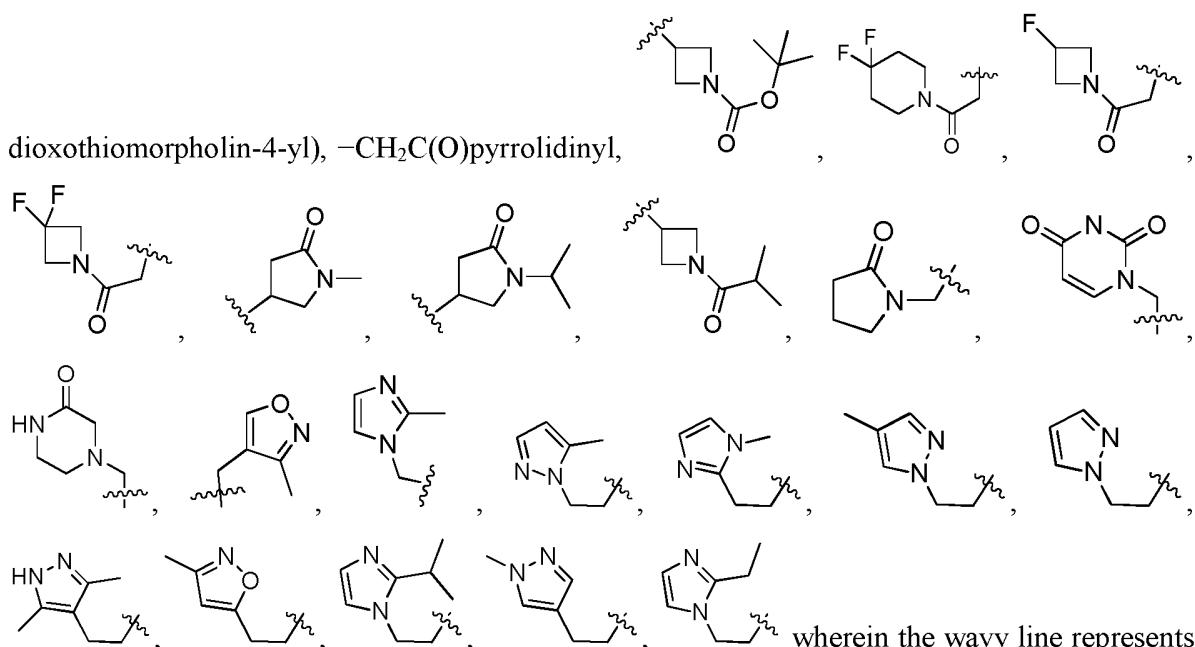
alkylene)S(O)₀₋₂R^c, -(C₀₋₃ alkylene)NR^cS(O)₁₋₂R^d, -(C₀₋₃ alkylene)S(O)₁₋₂NR^cR^d, -(C₀₋₃ alkylene)NR^cS(O)₁₋₂NR^cR^d or C₁₋₆ alkyl optionally substituted by oxo, -CN or halogen. In certain embodiments, R⁵ is selected from -CH₂CH₂triazolyl, triazolyl, pyridinyl, -CH₂pyrazolyl,



5 -CH₂pyridinyl, -CH₂triazolyl, -CH₂pyrazolyl, wherein the wavy line represents the point of attachment in formula I.

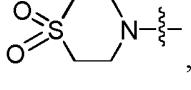
In certain embodiments, R⁵ is -(C₀₋₃ alkylene)4-6 membered heteroaryl, wherein said alkylene is independently optionally substituted by halogen, oxo, -(C₀₋₃ alkylene)CN, -(C₀₋₃ alkylene)OR^c, -(C₀₋₃ alkylene)NR^cR^d, -(C₀₋₃ alkylene)C(O)R^c, -(C₀₋₃ alkylene)C(O)OR^c, -(C₀₋₃ alkylene)C(O)NR^cR^d, -(C₀₋₃ alkylene)NR^cC(O)R^d, -(C₀₋₃ alkylene)OC(O)NR^cR^d, -(C₀₋₃ alkylene)NR^cC(O)NR^cR^d, -(C₀₋₃ alkylene)NR^cC(O)OR^d, -(C₀₋₃ alkylene)S(O)₀₋₂R^c, -(C₀₋₃ alkylene)NR^cS(O)₁₋₂R^d, -(C₀₋₃ alkylene)S(O)₁₋₂NR^cR^d, -(C₀₋₃ alkylene)NR^cS(O)₁₋₂NR^cR^d or C₁₋₆ alkyl optionally substituted by oxo, -CN or halogen. In certain embodiments, R⁵ is pyridinyl.

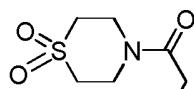
In certain embodiments, R⁵ is -(C₀₋₃ alkylene)3-12 membered heterocyclyl, wherein said alkylene and heterocyclyl are independently optionally substituted by halogen, oxo, -(C₀₋₃ alkylene)CN, -(C₀₋₃ alkylene)OR^c, -(C₀₋₃ alkylene)NR^cR^d, -(C₀₋₃ alkylene)C(O)R^c, -(C₀₋₃ alkylene)C(O)OR^c, -(C₀₋₃ alkylene)C(O)NR^cR^d, -(C₀₋₃ alkylene)NR^cC(O)R^d, -(C₀₋₃ alkylene)OC(O)NR^cR^d, -(C₀₋₃ alkylene)NR^cC(O)NR^cR^d, -(C₀₋₃ alkylene)NR^cC(O)OR^d, -(C₀₋₃ alkylene)S(O)₀₋₂R^c, -(C₀₋₃ alkylene)NR^cS(O)₁₋₂R^d, -(C₀₋₃ alkylene)S(O)₁₋₂NR^cR^d, -(C₀₋₃ alkylene)NR^cS(O)₁₋₂NR^cR^d or C₁₋₆ alkyl optionally substituted by oxo, -CN or halogen. In certain embodiments, R⁵ is selected from oxetanyl, 1,1-dioxothiomorpholinyl, -CH₂CH₂(1,1-dioxothiomorpholinyl), -CH₂CH₂triazolyl, triazolyl, -CH₂pyrazolyl, -CH₂pyridinyl, pyridinyl, pyrrolidinyl, piperidinyl, -CH₂(4-hydroxypiperidin-1-yl), morpholinyl, azetidinyl, 2-acetylpyrrolidin-3-yl, -CH₂tetrahydropyran-4-yl, tetrahydropyran-4-yl, tetrahydropyranyl, tetrahydrofuran-2-yl, -CH₂CH₂tetrahydrofuran-2-yl, -CH₂morpholinyl, 1-acetylpyrrolidin-3-yl, -C(O)morpholinyl, -CH₂C(O)morpholinyl, -CH₂C(O)(1,1-



5 the point of attachment in formula I.

In certain embodiments, R^5 is $-(\text{C}_{0-3}\text{ alkylene})4-6$ membered heterocyclyl, wherein said alkylene is independently optionally substituted by halogen, oxo, $-(\text{C}_{0-3}\text{ alkylene})\text{CN}$, $-(\text{C}_{0-3}\text{ alkylene})\text{OR}^c$, $-(\text{C}_{0-3}\text{ alkylene})\text{NR}^c\text{R}^d$, $-(\text{C}_{0-3}\text{ alkylene})\text{C}(\text{O})\text{R}^c$, $-(\text{C}_{0-3}\text{ alkylene})\text{C}(\text{O})\text{OR}^c$, $-(\text{C}_{0-3}\text{ alkylene})\text{C}(\text{O})\text{NR}^c\text{R}^d$, $-(\text{C}_{0-3}\text{ alkylene})\text{NR}^c\text{C}(\text{O})\text{R}^d$, $-(\text{C}_{0-3}\text{ alkylene})\text{OC}(\text{O})\text{NR}^c\text{R}^d$, $-(\text{C}_{0-3}\text{ alkylene})\text{NR}^c\text{C}(\text{O})\text{NR}^c\text{R}^d$, $-(\text{C}_{0-3}\text{ alkylene})\text{NR}^c\text{C}(\text{O})\text{OR}^d$, $-(\text{C}_{0-3}\text{ alkylene})\text{S}(\text{O})_{0-2}\text{R}^c$, $-(\text{C}_{0-3}\text{ alkylene})\text{NR}^c\text{S}(\text{O})_{1-2}\text{R}^d$, $-(\text{C}_{0-3}\text{ alkylene})\text{S}(\text{O})_{1-2}\text{NR}^c\text{R}^d$, $-(\text{C}_{0-3}\text{ alkylene})\text{NR}^c\text{S}(\text{O})_{1-2}\text{NR}^c\text{R}^d$ or C_{1-6} alkyl optionally substituted by oxo, $-\text{CN}$ or halogen. In certain embodiments, said heterocyclyl is oxetanyl, pyridinyl, pyrrolidinyl, pyranyl, piperidinyl, morpholinyl or

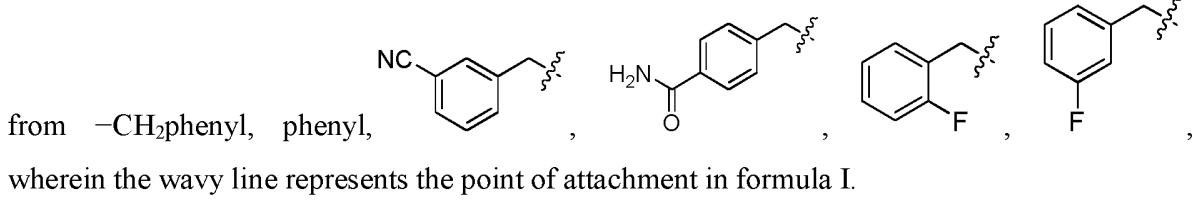
, wherein the wavy line represents the point of attachment in formula I. In
15 certain embodiments, R^5 is pyridin-3-yl, pyrrolidin-1-yl, pyran-4-yl, $-\text{CH}_2\text{C}(\text{O})(\text{pyrrolidin-1-yl})$, $-\text{CH}_2\text{C}(\text{O})(4,4\text{-difluoropiperidin-1-yl})$, $-\text{CH}_2$ (morpholinyl), $-\text{CH}_2\text{C}(\text{O})(\text{morpholinyl})$, $-\text{CH}_2(\text{pyrrolidin-2-on-1-yl})$ or



, wherein the wavy line represents the point of attachment in formula I.

In certain embodiments, R^5 is $-(C_{0-3} \text{ alkylene})S(O)_{1-2}R^a$, wherein said alkylene is independently optionally substituted by halogen, oxo, $-(C_{0-3} \text{ alkylene})CN$, $-(C_{0-3} \text{ alkylene})OR^c$, $-(C_{0-3} \text{ alkylene})NR^cR^d$, $-(C_{0-3} \text{ alkylene})C(O)R^c$, $-(C_{0-3} \text{ alkylene})C(O)OR^c$, $-(C_{0-3} \text{ alkylene})C(O)NR^cR^d$, $-(C_{0-3} \text{ alkylene})NR^cC(O)R^d$, $-(C_{0-3} \text{ alkylene})OC(O)NR^cR^d$, $-(C_{0-3} \text{ alkylene})NR^cC(O)NR^cR^d$, $-(C_{0-3} \text{ alkylene})NR^cC(O)OR^d$, $-(C_{0-3} \text{ alkylene})S(O)_{0-2}R^c$, $-(C_{0-3} \text{ alkylene})NR^cS(O)_{1-2}R^d$, $-(C_{0-3} \text{ alkylene})S(O)_{1-2}NR^cR^d$, $-(C_{0-3} \text{ alkylene})NR^cS(O)_{1-2}NR^cR^d$ or C_{1-6} alkyl optionally substituted by oxo, $-CN$ or halogen. In certain embodiments, R^5 is selected from $-CH_2S(O)_2CH_3$.

In certain embodiments, R^5 is $-(C_{0-3} \text{ alkylene})C_{6-12} \text{ aryl}$, wherein said alkylene and aryl are independently optionally substituted by halogen, oxo, $-(C_{0-3} \text{ alkylene})CN$, $-(C_{0-3} \text{ alkylene})OR^c$, $-(C_{0-3} \text{ alkylene})NR^cR^d$, $-(C_{0-3} \text{ alkylene})C(O)R^c$, $-(C_{0-3} \text{ alkylene})C(O)OR^c$, $-(C_{0-3} \text{ alkylene})C(O)NR^cR^d$, $-(C_{0-3} \text{ alkylene})NR^cC(O)R^d$, $-(C_{0-3} \text{ alkylene})OC(O)NR^cR^d$, $-(C_{0-3} \text{ alkylene})NR^cC(O)NR^cR^d$, $-(C_{0-3} \text{ alkylene})NR^cC(O)OR^d$, $-(C_{0-3} \text{ alkylene})S(O)_{0-2}R^c$, $-(C_{0-3} \text{ alkylene})NR^cS(O)_{1-2}R^d$, $-(C_{0-3} \text{ alkylene})S(O)_{1-2}NR^cR^d$, $-(C_{0-3} \text{ alkylene})NR^cS(O)_{1-2}NR^cR^d$ or C_{1-6} alkyl optionally substituted by oxo, $-CN$ or halogen. In certain embodiments, R^5 is selected

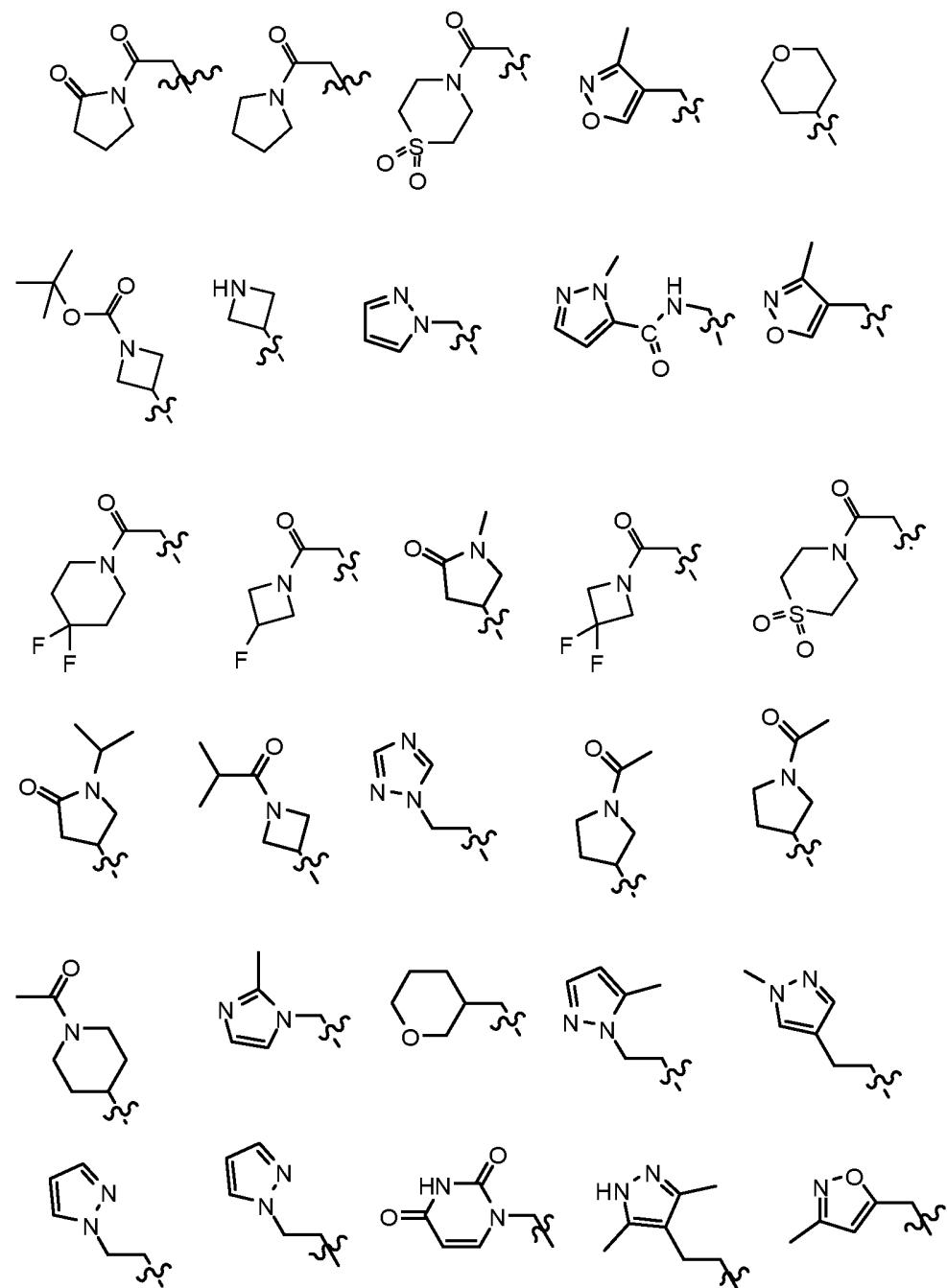


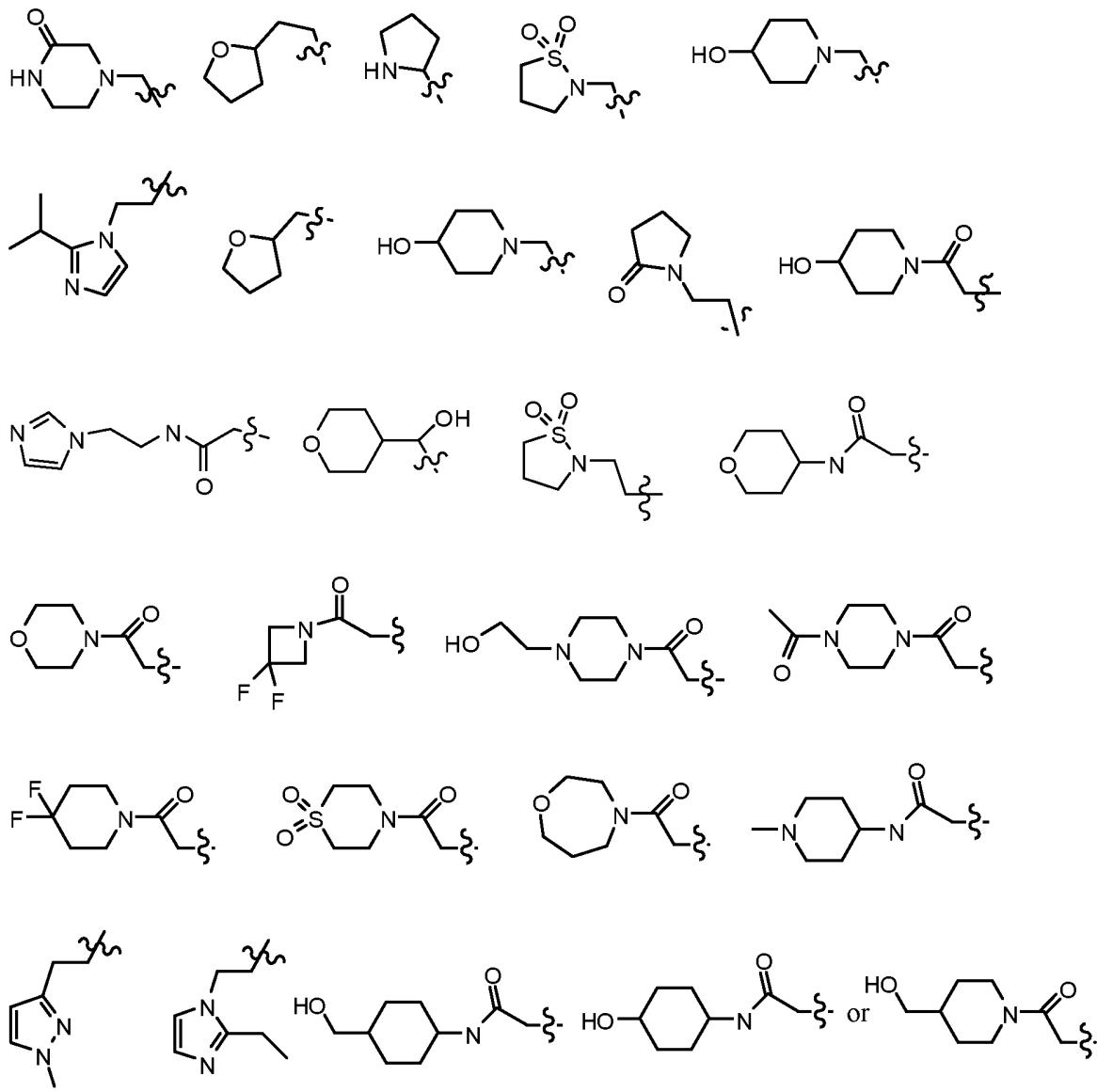
In certain embodiments, R^5 is $-(C_{0-3} \text{ alkylene})phenyl$, wherein said alkylene is optionally substituted by oxo or halogen, and said phenyl is optionally substituted by halogen, C_{1-3} alkyl, $-OR^c$ or $-NR^cR^d$.

In certain embodiments, R^5 is $-(C_{0-3} \text{ alkylene})NR^aC(O)OR^b$, wherein said alkylene is independently optionally substituted by halogen, oxo, $-(C_{0-3} \text{ alkylene})CN$, $-(C_{0-3} \text{ alkylene})OR^c$, $-(C_{0-3} \text{ alkylene})NR^cR^d$, $-(C_{0-3} \text{ alkylene})C(O)R^c$, $-(C_{0-3} \text{ alkylene})C(O)OR^c$, $-(C_{0-3} \text{ alkylene})C(O)NR^cR^d$, $-(C_{0-3} \text{ alkylene})NR^cC(O)R^d$, $-(C_{0-3} \text{ alkylene})OC(O)NR^cR^d$, $-(C_{0-3} \text{ alkylene})NR^cC(O)NR^cR^d$, $-(C_{0-3} \text{ alkylene})NR^cC(O)OR^d$, $-(C_{0-3} \text{ alkylene})S(O)_{0-2}R^c$, $-(C_{0-3} \text{ alkylene})NR^cS(O)_{1-2}R^d$, $-(C_{0-3} \text{ alkylene})S(O)_{1-2}NR^cR^d$, $-(C_{0-3} \text{ alkylene})NR^cS(O)_{1-2}NR^cR^d$ or C_{1-6} alkyl optionally substituted by oxo, $-CN$ or halogen. In certain embodiments, R^5 is selected from $-CH_2NHC(O)OCH_2CH_3$ and $-CH_2NHC(O)OCH_3$.

In certain embodiments, R⁵ is hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyano, 2-methylbutyl, N-(2-hydroxyethyl)amino, N-(2-methoxyethyl)amino, methylsulfonylaminomethyl, 2-(methylsulfonylamino)ethyl, cyclopropylmethyl, 2-[N-(2-propylsulfonyl)amino]ethyl, 2-[N-(cyclopropylsulfonyl)-amino]ethyl, 2-(cyclopropylcarbonylamino)ethyl, 2-(acetyl amino)ethyl, 2-(methoxymethylcarbonylamino)ethyl, cyclopentoxymethyl, cyclopropylmethoxymethyl, 2,2,2-trifluoroethoxymethyl, cyclohexyl, methylamino, 2-(N,N-dimethylaminocarbonyl)ethyl, 2-(N-acetyl-N-methylamino)ethyl, 2-(ethoxycarbonylamino)ethyl, 1-hydroxyethyl, N-acylaminomethyl, 2-amino-1,1-difluoroethyl, N,N-dimethylamino, hydroxymethyl, methoxy, N-methylamino, N,N-dimethylamino,N-(2,2,2-trifluoroethyl)aminomethyl, (2-carboxycyclopropyl)(hydroxy)methyl, 2-hydroxyethyl, aminocarbonylmethyl, methylaminocarbonylmethyl, ethylaminocarbonylmethyl, 1-hydroxypropyl, 1,2-dihydroxyethyl, N-(2-methylpropyl)aminocarbonylmethyl, cyclopentylaminocarbonylmethyl, 2-(methoxycarbonylamino)ethyl, 2,2,2-trifluoro-1-hydroxyethyl, tert-butylaminocarbonylmethyl, cyclobutylaminocarbonylmethyl, 2-hydroxyethoxy, isopropylaminocarbonylmethyl, N-(N'N'-dimethylaminocarbonylmethyl)aminocarbonylmethyl, 4,4-difluorocyclohexylaminocarbonylmethyl, 2,2-difluoroethylaminocarbonylmethyl, N-(2-hydroxyethyl)-N-methylaminocarbonylmethyl, cyclopentylmethyl, N-cyclopentyl-N-methylaminocarbonylmethyl, 2-amino-1,1-difluoroethyl, 3-pyridyl, morpholinomethyl, morpholinocarbonylmethyl, 2-cyano-2-methylethyl, trifluoromethyl, 1-hydroxy-1-methylethyl, 1-(N-isopropylaminocarbonyl)ethyl, 2-hydroxy-2-methylpropyl, N-(methylsulfonyl)-N-methylaminomethyl, difluoromethyl, 2-(2-butylsulfonylamino)ethyl, 2-(4-fluorophenylcarbonylamino)ethyl, 2-(cyclobutylcarbonylamino)ethyl, 2-(2-methylbutanoylamino)ethyl, 2-(benzoylamino)ethyl, 2,2-difluorocyclopropyl, 3-cyanobenzyl, 2-methylpropoxymethyl, 2-cyclopropylethyl, 3-pyridylmethyl, methylsulfonylmethyl, ethoxycarbonylaminomethyl, 3-pyridylcarbonylaminomethyl, isopropylsulfonylaminomethyl, 2-pyridylcarbonylaminomethyl, cyclopropylsulfonylaminomethyl, cyclopentylsulfonylaminomethyl, 2-methylpropanoylaminomethyl, cyclopropylcarbonylaminomethyl, 2-fluorobenzoylaminomethyl, 3-fluorobenzoylaminomethyl, 1-methylpropylsulfonylaminomethyl, 2-methylpropylsulfonylaminomethyl, methoxyacetylaminomethyl, ethylsulfonylaminomethyl, 2-(3,3,3-trifluoropropylsulfonylamino)ethyl, 2-(2,2-difluorocyclopropylcarbonylamino)ethyl, fluoromethyl, 2-

hydroxyethylamino, 2-methoxyethylamino, 1-aminoethyl, 2-(ethylsulfonylamino)ethyl, 2,2-dimethylpropoxymethyl, 1-methoxyethyl, tert-butylsulfonylaminomethyl, 2,2,2-trifluoroethylaminomethyl,





wherein the wavy line represents the point of attachment in formula I.

In certain embodiments, R^5 is methyl, ethyl, propyl, butyl, isopropyl, tert-butyl, cyclopropyl, $-NH_2$, $-NH(CH_3)$, $-N(CH_3)_2$, $-OCH_3$ or $-C(O)OEt$.

10 In certain embodiments, R^5 is hydrogen, methyl, isopropyl, cyclopropyl, $-NH_2$, $-NH(CH_3)$, $-N(CH_3)_2$, $-OCH_3$ or $-C(O)OEt$.

In certain embodiments, R^6 is independently oxo, halogen, $-CN$, $-C(O)R^a$, $-C(O)OR^a$, $-NR^aC(O)R^b$, $-C(O)NR^aR^b$, $-NR^aC(O)NR^aR^b$, $-OC(O)NR^aR^b$, $-NR^aC(O)OR^b$, $-S(O)_{1-2}R^a$,

$-NR^aS(O)_2R^b$, $-S(O)_2NR^aR^b$, $-OR^a$, $-SR^a$, $-NR^aR^b$, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, 3-7 membered heterocycl or C₆₋₁₄ aryl, and wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocycl and aryl are independently optionally substituted by halogen, oxo, -CN, -OR^c, -SR^c, -NR^cR^d or C₁₋₆ alkyl optionally substituted by oxo or halogen.

5 In certain embodiments, R⁶ is independently oxo, halogen, -CN, -C(O)(C₁₋₆ alkyl), -C(O)O(C₁₋₆ alkyl), -S(O)₂(C₁₋₆ alkyl), -NR^aS(O)₂(C₁₋₆ alkyl), -O(C₁₋₆ alkyl), C₁₋₆ alkyl, C₃₋₆ cycloalkyl or 3-7 membered heterocycl, wherein said alkyl, cycloalkyl and heterocycl are independently optionally substituted by halogen, oxo, -CN, -OR^c, -NR^cR^d or C₁₋₆ alkyl optionally substituted by halogen. In certain embodiments, R⁶ is independently oxo, F, Cl, -CN, 10 -OH, -C(O)CH₃, -CH₂CN, -CH₂CH₂CN, cyclopropyl, cyclobutyl, -CF₃, -NHS(O)₂CH₃, -S(O)₂CH₃, -C(O)OCH₃, pyrrolidinyl or pyrrolidinonyl.

In certain embodiments, R³ is optionally substituted by 1 to 3 R⁶ independently selected from oxo, halogen, -CN, -S(O)₂(C₁₋₆ alkyl), -OR^a, -NR^aR^b and C₁₋₆ alkyl, and wherein said alkyl is independently optionally substituted by halogen, oxo, -CN, -OR^c or -NR^cR^d.

15 In certain embodiments, each R^a and R^b are independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -C₃₋₆ cycloalkyl, -3-12 membered heterocycl, -C(O)3-12 membered heterocycl or -C₆₋₁₄ aryl, wherein said alkyl, cycloalkyl, heterocycl and aryl are independently optionally substituted by halogen, oxo, -CN, -OR^c, -NR^cR^f, -C(O)R^g, -C(O)OR^g, -C(O)NR^gR^h, -NR^gC(O)R^h, -OC(O)NR^gR^h, -NR^gC(O)NR^gR^h, -NR^gC(O)OR^h, 20 -S(O)₁₋₂R^g, -NR^gS(O)₁₋₂R^h, -S(O)₁₋₂NR^gR^h, -NR^gS(O)₁₋₂NR^gR^h, C₃₋₆ cycloalkyl, 3-6 membered heterocycl, phenyl or C₁₋₃ alkyl optionally substituted by oxo or halogen, or taken together with the atom to which they are attached to form a 3-6 membered heterocycl optionally substituted by oxo, halogen, -C(O)C₁₋₆ alkyl or C₁₋₆ alkyl optionally substituted by oxo, halogen, OR^g or NR^gNR^h.

25 In certain embodiments, each R^a and R^b are independently hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, 3-6 membered heterocycl, -C(O)3-6 membered heterocycl or phenyl, wherein said alkyl, cycloalkyl, heterocycl and phenyl are independently optionally substituted by halogen, oxo, -CN, -OR^e, -NR^eR^f, -C(O)R^g, -C(O)OR^g, -C(O)NR^gR^h, -NR^gC(O)R^h, -OC(O)NR^gR^h, -NR^gC(O)NR^gR^h, -NR^gC(O)OR^h, -S(O)₁₋₂R^g, -NR^gS(O)₁₋₂R^h, -S(O)₁₋₂NR^gR^h,

—NR^gS(O)₁₋₂NR^gR^h, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl or C₁₋₃ alkyl optionally substituted by oxo or halogen.

In certain embodiments, each R^a and R^b are independently hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, 5-6 membered heteroaryl or phenyl, wherein said alkyl, 5 cycloalkyl, heterocyclyl, heteroaryl and phenyl are independently optionally substituted by halogen, oxo, —CN, —OR^e, —NR^eR^f or C₁₋₃ alkyl optionally substituted by halogen.

In certain embodiments, each R^a and R^b are independently selected from hydrogen, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, sec-butyl, —CF₃, —CH₂CF₃, —CH₂F, —CHF₂, —CH₂OH, —CH₂CH₂OH, —CH₂NH₂, —CH₂CH₂NH₂, —CH₂CH₂N(CH₃)₂, —CH₂N(CH₃)₂, 10 cyclopropyl, 2,2-difluorocyclopropyl, 2-fluorocyclopropyl, 2-methylcyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, piperidinyl, morpholinyl, piperazinyl, N-methylpiperazinyl, pyrazolyl, N-methylpyrazolyl, azetidinyl, 1,1-dioxothiomorpholinyl, pyrrolidinyl, pyrrolidinonyl, pyridinyl, cyanopyridinyl, phenyl and fluorophenyl.

In certain embodiments, a R^a and a R^b are independently taken together with the atom to 15 which they are attached to form a 3-6 membered heterocyclyl optionally substituted by oxo, halogen, —C(O)C₁₋₆ alkyl or C₁₋₆ alkyl optionally substituted by oxo, halogen, OR^g or NR^gNR^h.

In certain embodiments, a R^a and a R^b are independently taken together with the atom to which they are attached to form a 3-6 membered heterocyclyl optionally substituted by oxo, halogen, —C(O)C₁₋₆ alkyl or C₁₋₆ alkyl optionally substituted by halogen. In certain 20 embodiments, said heterocyclyl is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, piperidinonyl, morpholinyl and 1,1-dioxomorpholinyl.

In certain embodiments, R^a and R^b are taken together with the atom to which they are attached to form a 4-6 membered heterocyclyl selected from azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl, optionally substituted by oxo, halogen, —C(O)C₁₋₆ alkyl or C₁₋₆ 25 alkyl.

In certain embodiments, R^a and R^b are independently hydrogen, methyl, isopropyl, cyclopropyl or cyclopentyl.

In certain embodiments, each R^c and R^d are independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -C₃₋₆ cycloalkyl, -3-12 membered heterocyclyl, -C(O)3-12 membered heterocyclyl or -C₆₋₁₄ aryl, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl and aryl are independently optionally substituted by halogen, oxo, -CN, -OR^g, -NR^gR^h, -C(O)R^g, -C(O)OR^g, -C(O)NR^gR^h, -NR^gC(O)R^h, -OC(O)NR^gR^h, -NR^gC(O)NR^gR^h, -NR^gC(O)OR^h, -S(O)₁₋₂R^g, -NR^gS(O)₁₋₂R^h, -S(O)₁₋₂NR^gR^h, -NR^gS(O)₁₋₂NR^gR^h, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl or C₁₋₆ alkyl optionally substituted by oxo or halogen, or taken together with the atom to which they are attached to form a 3-6 membered heterocyclyl optionally substituted by oxo, halogen, -C(O)C₁₋₆ alkyl or C₁₋₆ alkyl optionally substituted by oxo or halogen.

10 In certain embodiments, each R^c and R^d are independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -C₃₋₆ cycloalkyl, -3-6 membered heterocyclyl, -C(O)3-6 membered heterocyclyl or phenyl, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl and phenyl are independently optionally substituted by halogen, oxo, -CN, -OR^g, -NR^gR^h, -C(O)R^g, -C(O)OR^g, -C(O)NR^gR^h, -NR^gC(O)R^h, -OC(O)NR^gR^h, -NR^gC(O)NR^gR^h, -NR^gC(O)OR^h, -S(O)₁₋₂R^g, -NR^gS(O)₁₋₂R^h, -S(O)₁₋₂NR^gR^h, -NR^gS(O)₁₋₂NR^gR^h, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl or C₁₋₆ alkyl optionally substituted by oxo or halogen.

In certain embodiments, each R^c and R^d are independently hydrogen, methyl, ethyl, isopropyl, butyl, t-butyl, sec-butyl, -CF₃, -CH₂CF₃, -CH₂F, -CHF₂, -CH₂OH, -CH₂CH₂OH, -CH₂NH₂, -CH₂CH₂NH₂, -CH₂CH₂N(CH₃)₂, -CH₂N(CH₃)₂, cyclopropyl, 2,2-difluorocyclopropyl, 2-fluorocyclopropyl, 2-methylcyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, piperidinyl, morpholinyl, piperazinyl, N-methylpiperazinyl, pyrazolyl, N-methylpyrazolyl, azetidinyl, 1,1-dioxothiomorpholinyl, pyrrolidinyl, pyrrolidinonyl, pyridinyl, cyanopyridinyl, phenyl and fluorophenyl.

25 In certain embodiments, a R^c and a R^d are independently taken together with the atom to which they are attached to form a 3-6 membered heterocyclyl optionally substituted by oxo, halogen, -C(O)C₁₋₆ alkyl or C₁₋₆ alkyl optionally substituted by oxo or halogen. In certain embodiments, said heterocyclyl is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, piperidinonyl, morpholinyl and 1,1-dioxomorpholinyl.

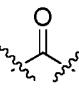
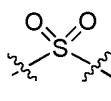
In certain embodiments, each R^c and R^d are independently hydrogen, methyl or ethyl, optionally substituted by fluoro or oxo. In certain embodiments, each R^c and R^d are independently hydrogen, methyl or ethyl.

In certain embodiments, R^c, R^d, R^e, R^f, R^g and R^h are independently hydrogen or methyl.

5 In certain embodiments, each R^e, R^f, R^g, R^h are independently hydrogen, methyl, ethyl, propyl or isopropyl, optionally substituted by halogen or oxo. In certain embodiments, each R^e, R^f, R^g, R^h are independently hydrogen, methyl or ethyl.

In certain embodiments, X is CR⁴,

R¹ is piperidinyl, cyclopentyl or cyclohexyl;

10 R² absent, methylene, ethylene, -NHCH₂-, , , -C(O)O-, -C(O)NH-, -NHC(O)O-, -NHC(O)CH₂-, -NHC(O)CH₂C(O)- or -NHC(O)NH-;

R³ is absent, hydrogen, methyl, ethyl, -CF₃, -CH₂CF₃, -CH₂CN, -(CH₂)₂CN, -CH₂cyclopropyl, cyclopropyl, phenyl, 3-cyanophenyl, 5-cyanopyridin-2-yl or pyridin-3-yl;

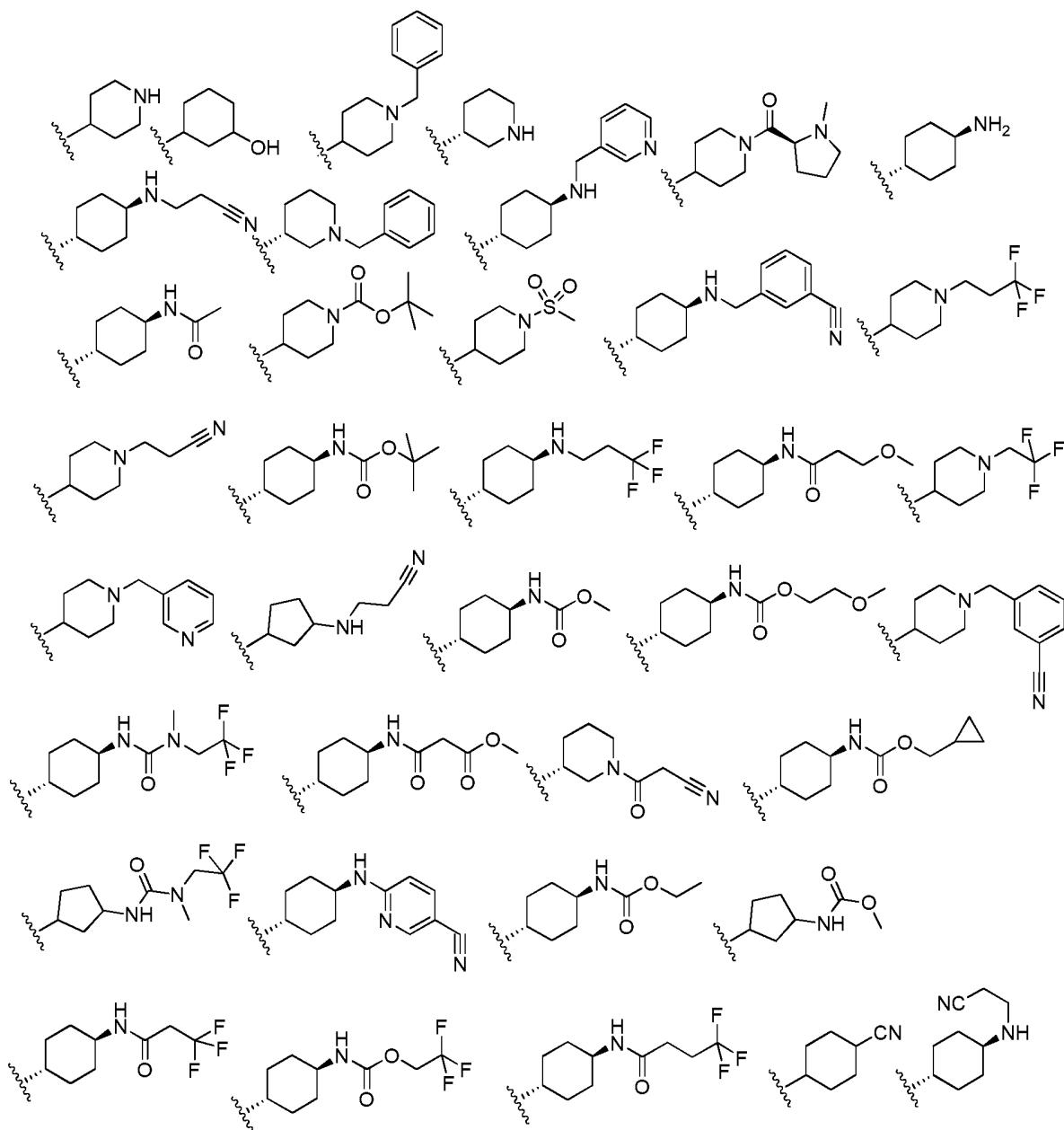
R⁴ is hydrogen, F or methyl;

15 R⁵ is methyl, ethyl, propyl, butyl, isopropyl, tert-butyl, cyclopropyl, -NH₂, -NH(CH₃), -N(CH₃)₂, -OCH₃ or -C(O)OEt;

each R^a and R^b are independently hydrogen, C₁₋₃ alkyl or C₃₋₆ cycloalkyl, wherein said alkyl and cycloalkyl are independently optionally substituted by oxo or halogen; or are taken together with the atom to which they are attached to form a 3-6 membered heterocycl¹
20 optionally substituted by oxo, halogen or C₁₋₃ alkyl; and

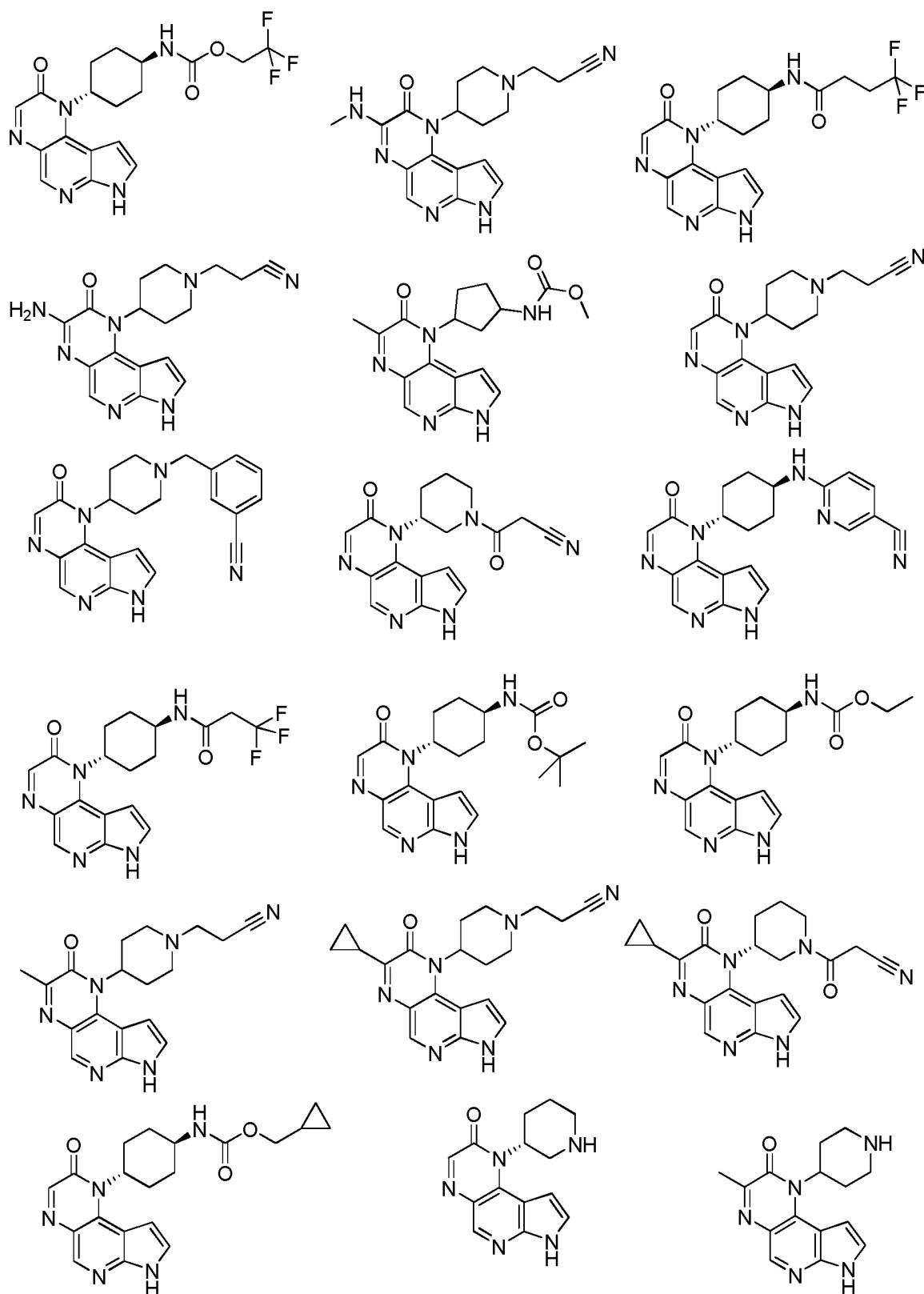
each R^c and R^d are independently hydrogen or C₁₋₆ alkyl; or are taken together with the atom to which they are attached to form a 3-6 membered heterocycl¹ optionally substituted by oxo, halogen, or C₁₋₃ alkyl, wherein the wavy line represents the point of attachment in formula I.

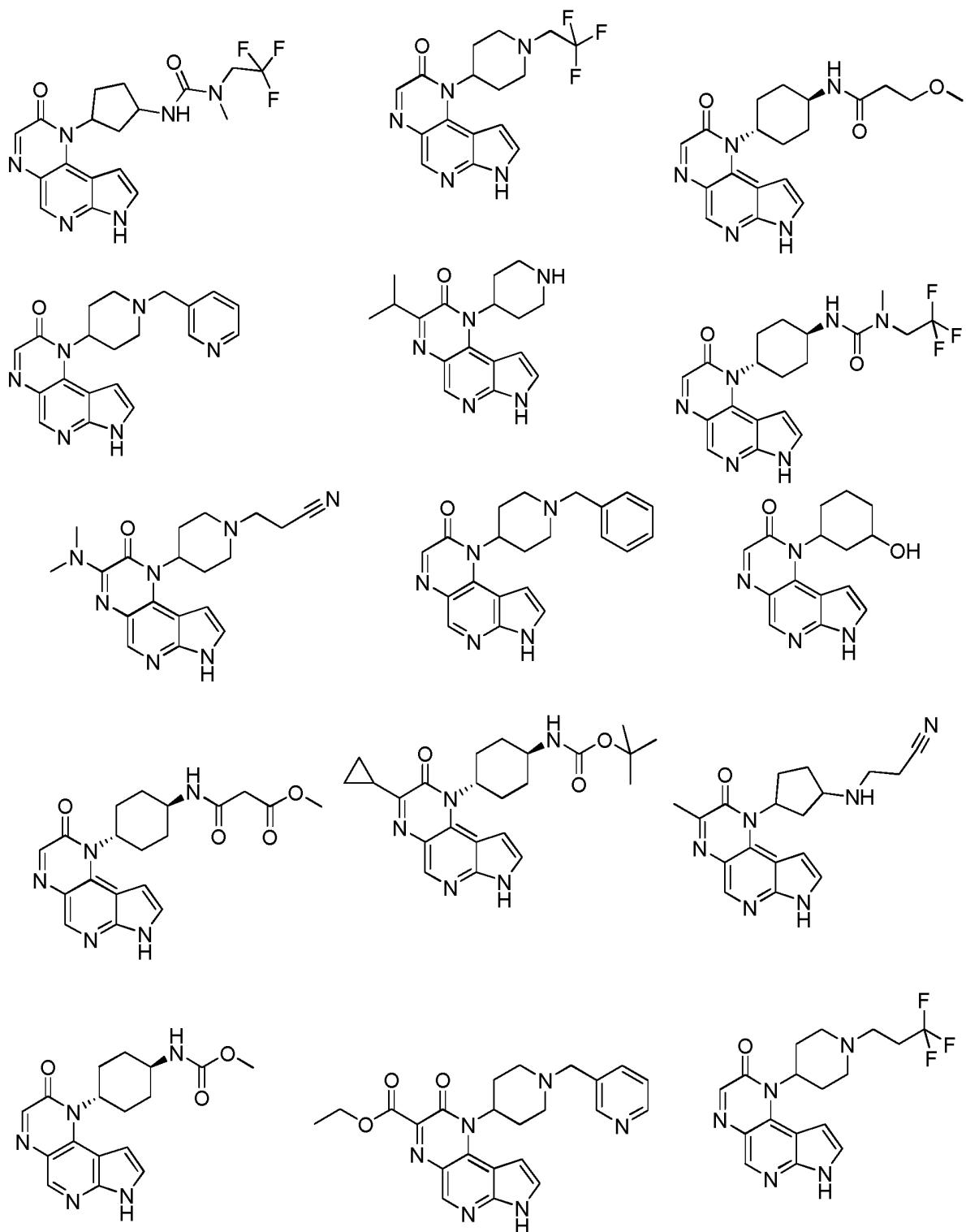
25 In certain embodiments, -R¹-R²-R³ taken together are:

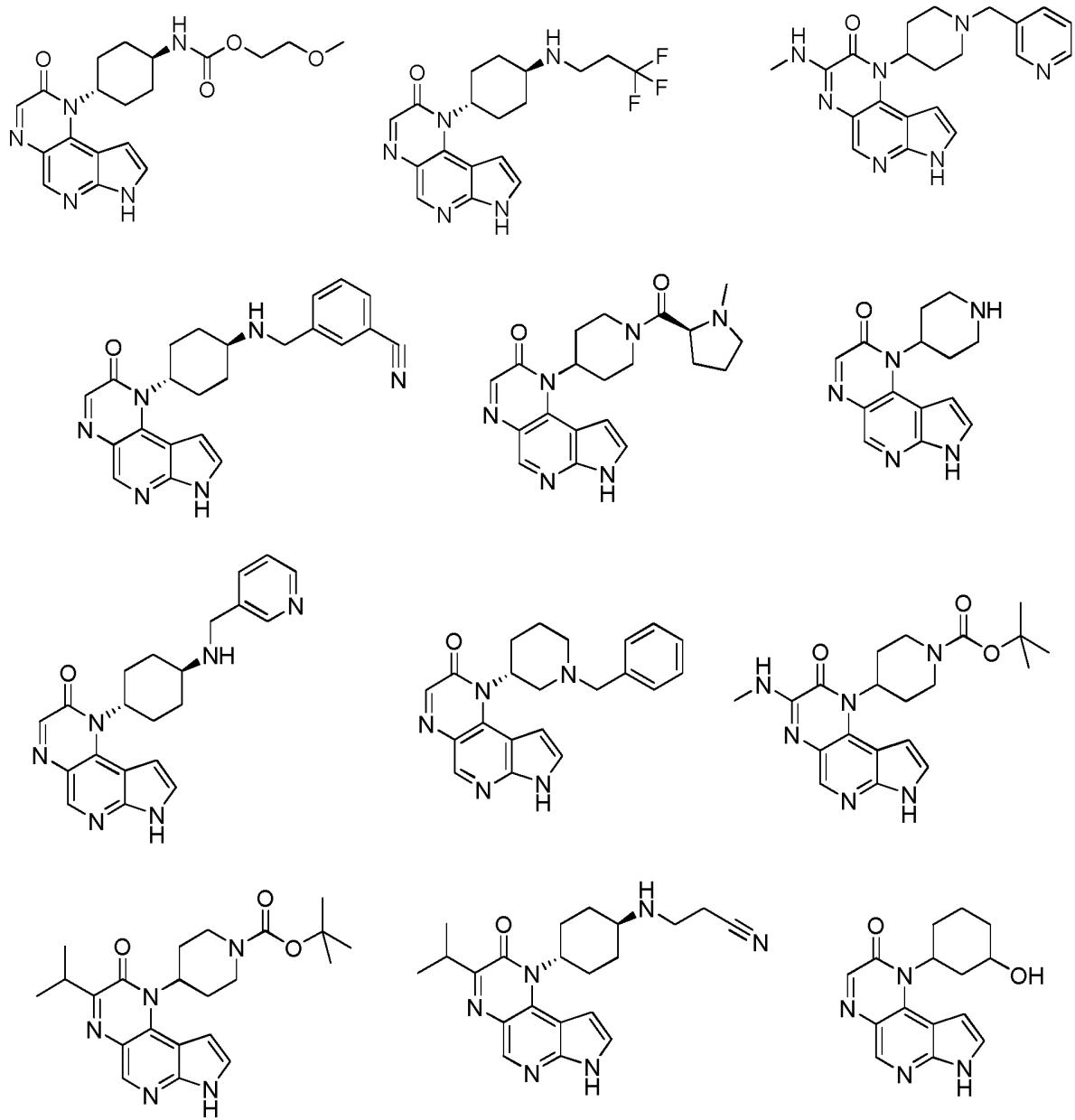


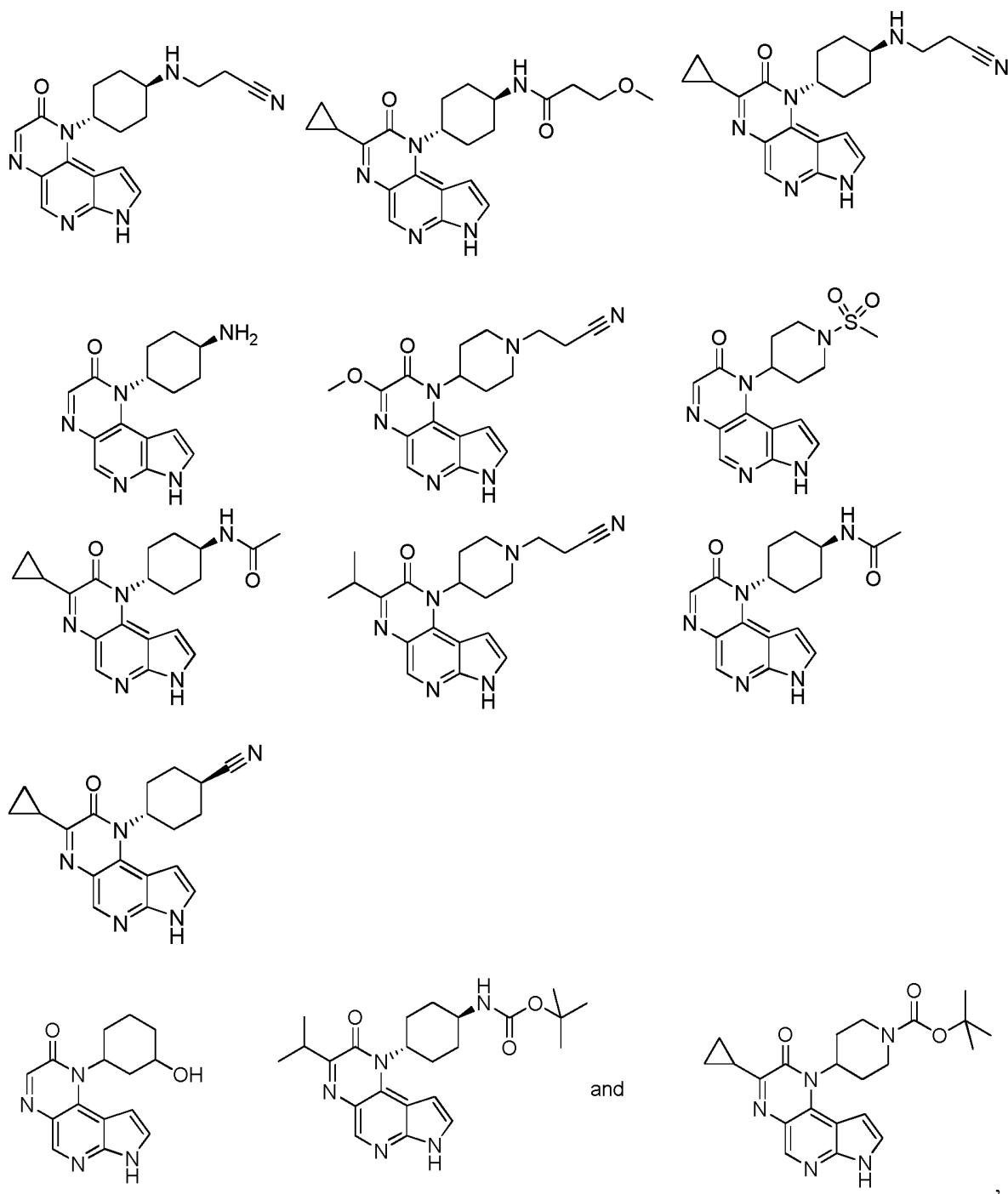
, wherein the wavy line represents the point of attachment in formula I.

Certain embodiments include a compound selected from:









and stereoisomers, tautomers and pharmaceutically acceptable salts thereof.

5 Compounds of the invention may contain one or more asymmetric carbon atoms. Accordingly, the compounds may exist as diastereomers, enantiomers or mixtures thereof. The syntheses of the compounds may employ racemates, diastereomers or enantiomers as starting

materials or as intermediates. Mixtures of particular diastereomeric compounds may be separated, or enriched in one or more particular diastereomers, by chromatographic or crystallization methods. Similarly, enantiomeric mixtures may be separated, or enantiomerically enriched, using the same techniques or others known in the art. Each of the asymmetric carbon 5 or nitrogen atoms may be in the R or S configuration and both of these configurations are within the scope of the invention.

Another aspect includes prodrugs of the compounds of formula I, including known amino-protecting and carboxy-protecting groups which are released, for example hydrolyzed, to yield the compound of formula I under physiologic conditions. A particular class of prodrugs are 10 compounds in which a nitrogen atom in an amino, amidino, aminoalkyleneamino, iminoalkyleneamino or guanidino group is substituted with a hydroxy (OH) group, an alkylcarbonyl (-CO-R) group, an alkoxy carbonyl (-CO-OR), an acyloxyalkyl-alkoxycarbonyl (-CO-O-R-O-CO-R) group where R is a monovalent or divalent group, for example alkyl, alkylene or aryl, or a group having the formula -C(O)-O-CP1P2-haloalkyl, where P1 and P2 are the same 15 or different and are hydrogen, alkyl, alkoxy, cyano, halogen, alkyl or aryl. In a particular embodiment, the nitrogen atom is one of the nitrogen atoms of the amidino group of the compounds of formula I. Prodrugs may be prepared by reacting a compound of formula I with an activated group, such as acyl groups, to bond, for example, a nitrogen atom in the compound of formula I to the exemplary carbonyl of the activated acyl group. Examples of activated 20 carbonyl compounds are those containing a leaving group bonded to the carbonyl group, and include, for example, acyl halides, acyl amines, acyl pyridinium salts, acyl alkoxides, acyl phenoxides such as p-nitrophenoxy acyl, dinitrophenoxy acyl, fluorophenoxy acyl, and difluorophenoxy acyl. The reactions are generally carried out in inert solvents at reduced temperatures such as -78 to about 50°C. The reactions may also be carried out in the presence of 25 an inorganic base, for example potassium carbonate or sodium bicarbonate, or an organic base such as an amine, including pyridine, trimethylamine, triethylamine, triethanolamine, or the like.

SYNTHESIS OF JAK1 INHIBITOR COMPOUNDS

Compounds of formula I may be synthesized by synthetic routes described herein. In certain embodiments, processes well-known in the chemical arts can be used, in addition to, or in 30 light of, the description contained herein. The starting materials are generally available from

commercial sources such as Aldrich Chemicals (Milwaukee, Wis.) 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. 1-19, Wiley, N.Y. (1967-1999 ed.), Beilsteins Handbuch der organischen Chemie, 4, Aufl. ed. Springer-Verlag, Berlin, 5 including supplements (also available via the Beilstein online database)), or *Comprehensive Heterocyclic Chemistry*, Editors Kritzky and Rees, Pergamon Press, 1984.

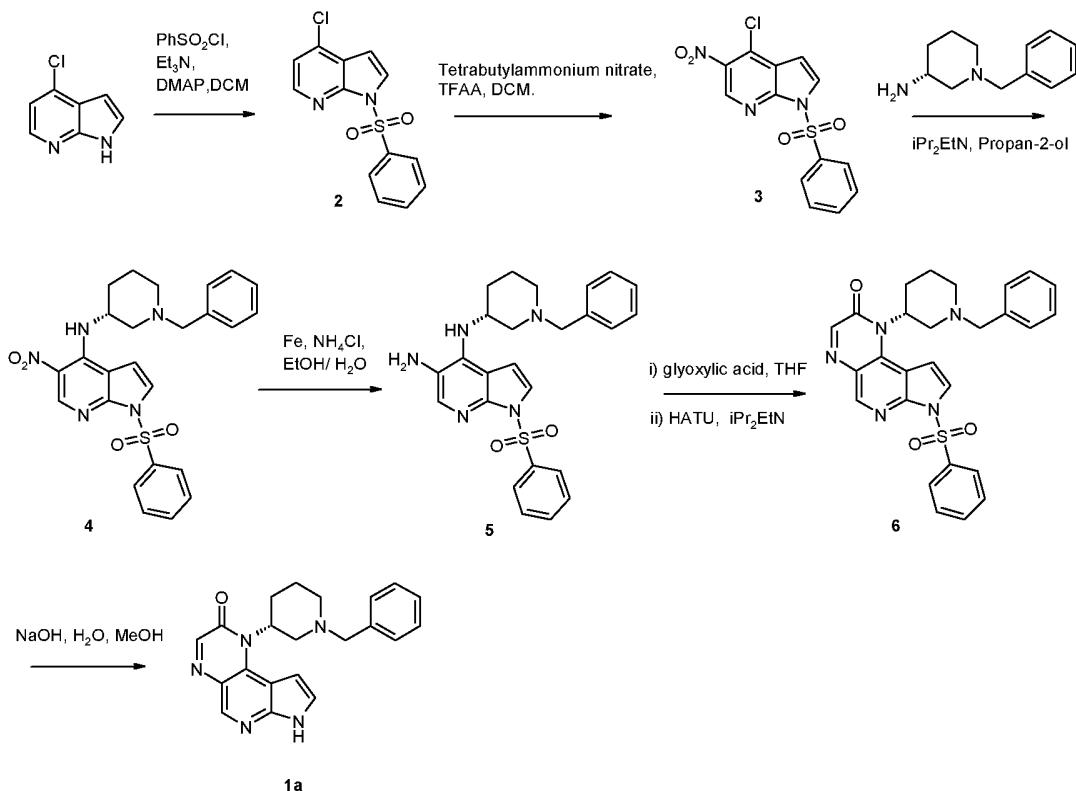
Compounds of formula I may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds, or 10 to 100 compounds of formula I. Libraries of compounds of formula I may be prepared by a combinatorial `split and mix` approach or by 10 multiple parallel syntheses using 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 of formula I, enantiomers, diastereomers, tautomers or pharmaceutically acceptable salts thereof.

For illustrative purposes, reaction schemes 1-10 depicted below provide routes for 15 synthesizing the compounds of the present invention as well as key intermediates. For a more detailed description of the individual reaction steps, see the Examples section below. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the inventive compounds. Although specific starting materials and reagents are depicted in the Schemes and discussed below, other starting materials and reagents can be easily substituted to 20 provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art.

In the preparation of compounds of the present invention, protection of remote functionality (e.g., primary or secondary amine) of intermediates may be necessary. The need for 25 such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. Suitable amino-protecting groups (NH-Pg) include acetyl, trifluoroacetyl, benzyl, phenylsulfonyl, 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. 30 Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York, 1991.

Compounds of the invention may be prepared from readily available starting materials using the general methods illustrated in Reaction Schemes 1-6 below.

Reaction Scheme 1

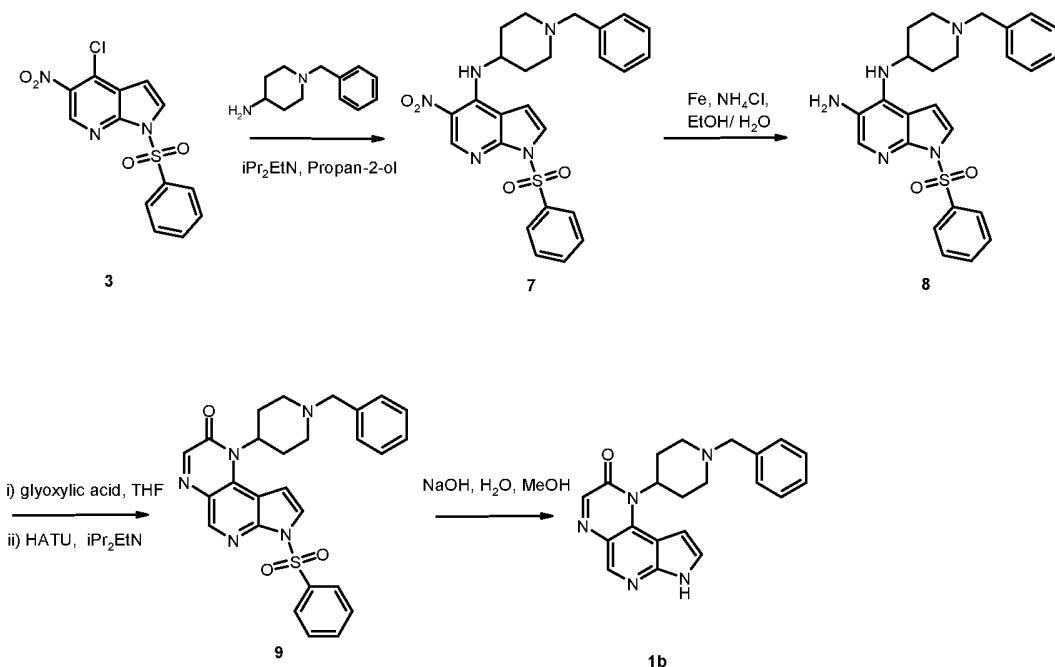


- 5 Compounds of Formula 1a can be synthesized as shown in Reaction Scheme 1. For example, commercially available 4-chloroazaindole can be protected with benzenesulfonyl chloride in the presence of 4-(dimethylamino)pyridine (DMAP) and a base such as triethylamine in a suitable solvent such as dichloromethane to give sulfonamide 2. Compound 2 can be treated with tetrabutylammonium nitrate and trifluoroacetic anhydride (TFAA) to give nitro compound 3. Compound 4 can be prepared by treatment of compound 3 with a suitably protected diamine such as (*R*)-1-benzyl-3-aminopiperidine in the presence of a base such as diisopropylethylamine in a compatible solvent such as propan-2-ol at temperatures between ambient and 150 °C. Reduction of compound 4 can be accomplished using a suitable reducing agent such as iron in the presence of ammonium chloride in a compatible solvent such as aqueous ethanol to afford 10 diamine compound 5. Reaction of compound 5 with a 2-oxocarboxylic acid such as glyoxylic acid followed by cyclisation using a suitable amide coupling reagent such as O-(7-15

azabenzotriazol-1-yl)-N,N,N',N'-tetramethyl uronium hexafluorophosphate (HATU) and a base such as diisopropylethylamine gives compound 6. Hydrolysis of compound 6 with aqueous sodium hydroxide in methanol provides compounds of Formula 1a.

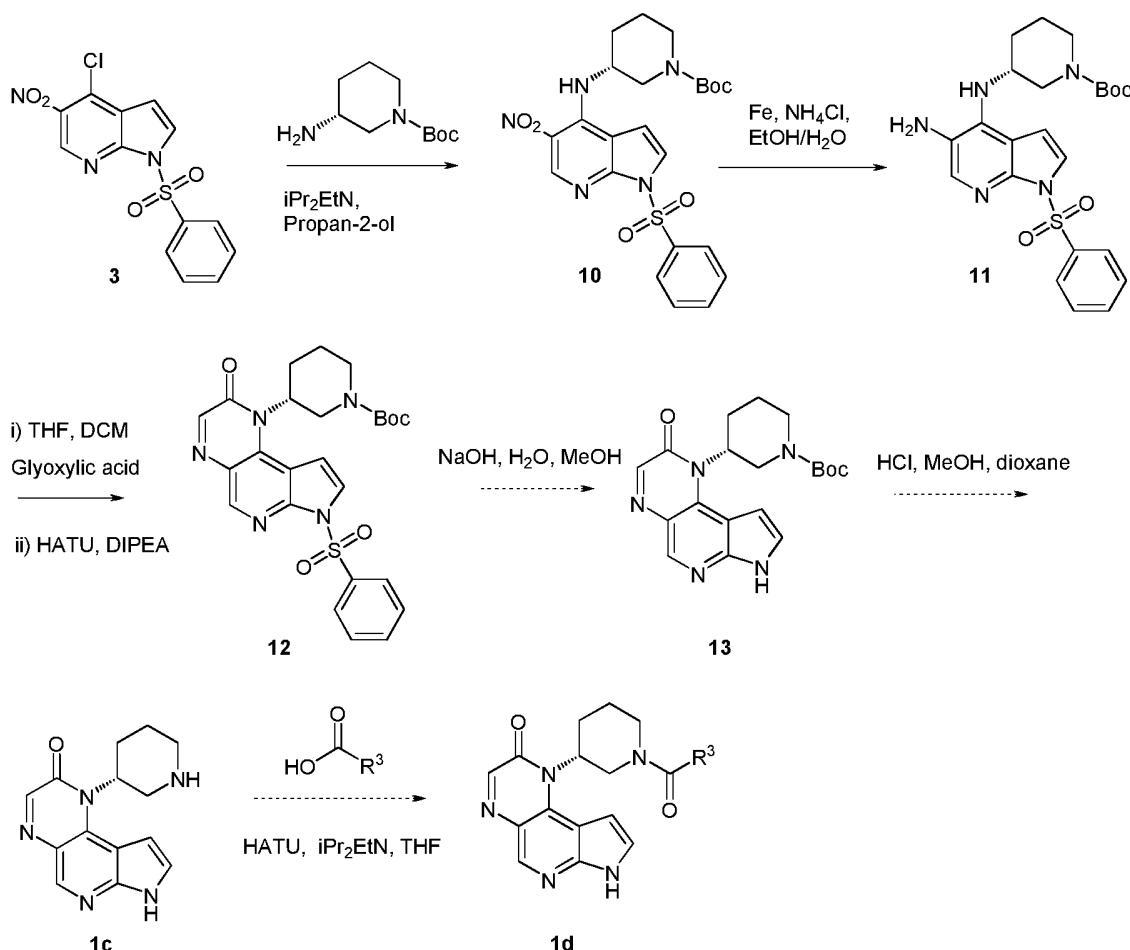
Reaction Scheme 2

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Compounds of Formula 1b can be synthesized as shown in Reaction Scheme 2. For example, compound 7 can be prepared by treatment of compound 3 with a suitably protected 10 diamine such as 1-benzyl-4-aminopiperidine in the presence of a base such as diisopropylethylamine in a suitable solvent such as propan-2-ol at temperatures between ambient and 150 °C. Reduction of compound 7 can be accomplished using a suitable reducing agent such as iron in the presence of ammonium chloride in a solvent such as aqueous ethanol to afford 15 diamine compound 8. Reaction of compound 8 with a 2-oxocarboxylic such as glyoxylic acid followed by cyclisation using a suitable amide coupling reagent such as HATU and a base such as diisopropylethylamine gives compound 9. Hydrolysis of compound 9 with aqueous sodium hydroxide in methanol provides compounds of Formula 1b.

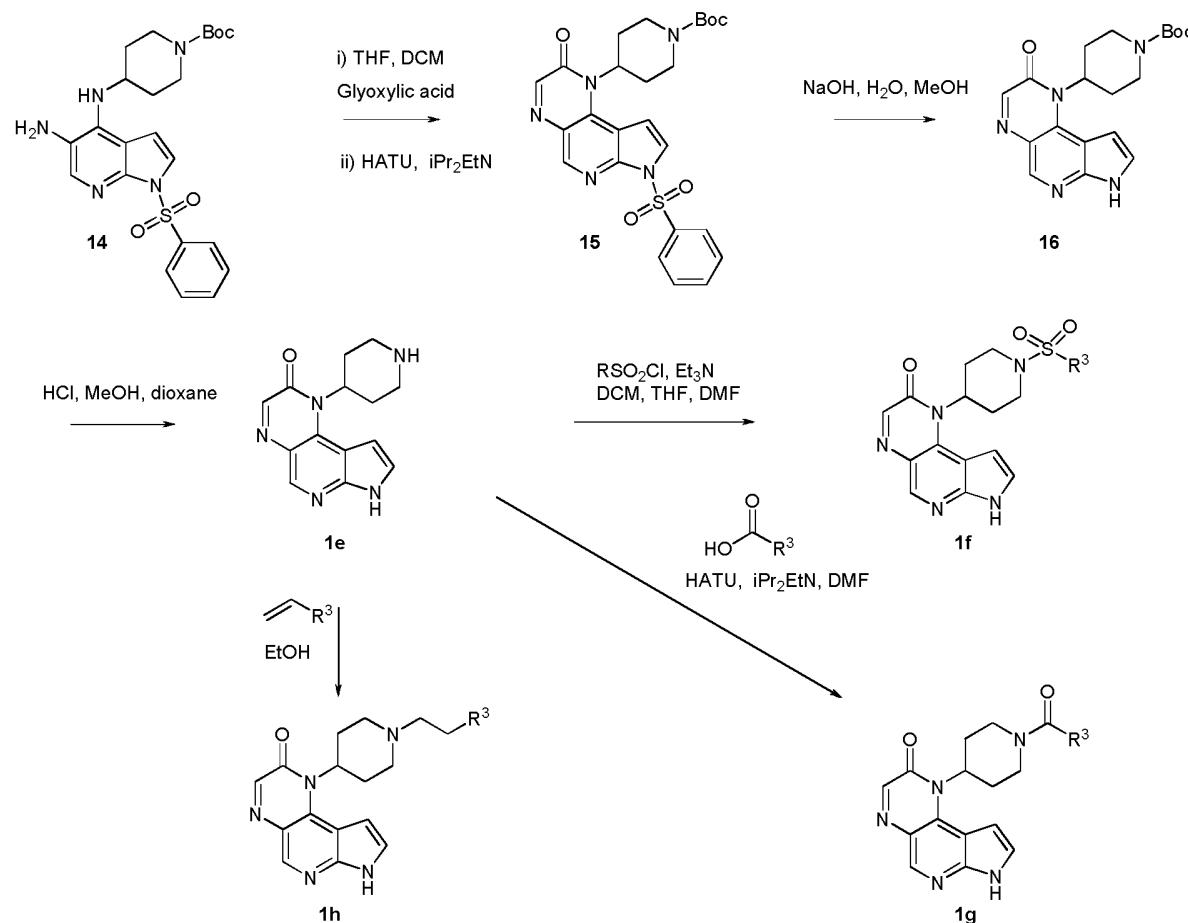
Reaction Scheme 3



Compounds of Formula 1c and 1d can be synthesized as shown in Reaction Scheme 3. For example, compound 10 can be prepared by treatment of compound 3 with a suitably protected diamine such as (R)-1-boc-3-aminopiperidine in the presence of a base such as diisopropylethylamine. Reduction of compound 10 can be accomplished using a suitable reducing agent such as iron in the presence of ammonium chloride in a solvent such as aqueous ethanol to afford diamine compound 11. Reaction of compound 11 with a 2-oxocarboxylic such as glyoxylic acid followed by cyclisation using a suitable amide coupling reagent such as HATU and a base such as diisopropylethylamine gives compound 12. Hydrolysis of compound 12 with aqueous sodium hydroxide in methanol gives compound 13. Deprotection under acidic conditions such as HCl in dioxane provides compound of Formula 1c. Amides can be prepared

for example reaction of 1c with a suitable carboxylic acid in the presence of a suitable coupling reagent such as HATU and a base such as diisopropylethylamine to provide compounds of Formula 1d.

Reaction Scheme 4

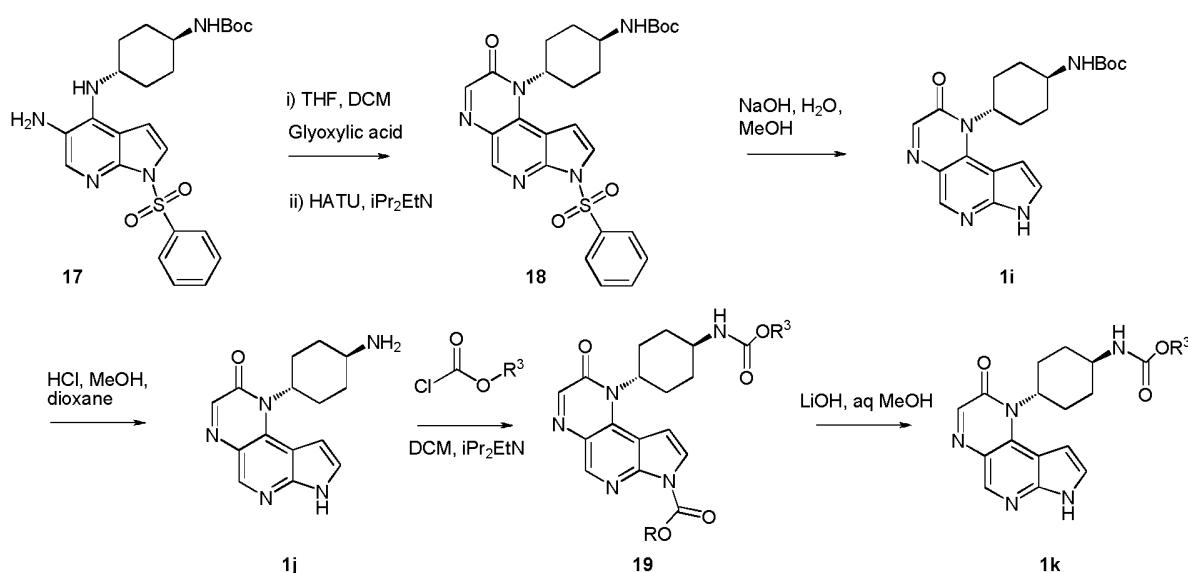


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Compounds of Formula 1e, 1f, 1g and 1h can be prepared as shown in Reaction Scheme 4. Reaction of compound 14 with a 2-oxocarboxylic acid such as glyoxylic acid followed by cyclisation using a suitable amide coupling reagent such as HATU and a base such as diisopropylethylamine gives compound 15. Hydrolysis of compound 15 with aqueous sodium hydroxide in methanol gives compound 16. Deprotection under acidic conditions such as HCl in dioxane provides compound of Formula 1e. Sulfonamides can be prepared from compounds of Formula 1e by reaction with for example a suitable sulfonyl chloride in the presence of a base such as triethylamine to give compounds of Formula 1f. Amides can be prepared from

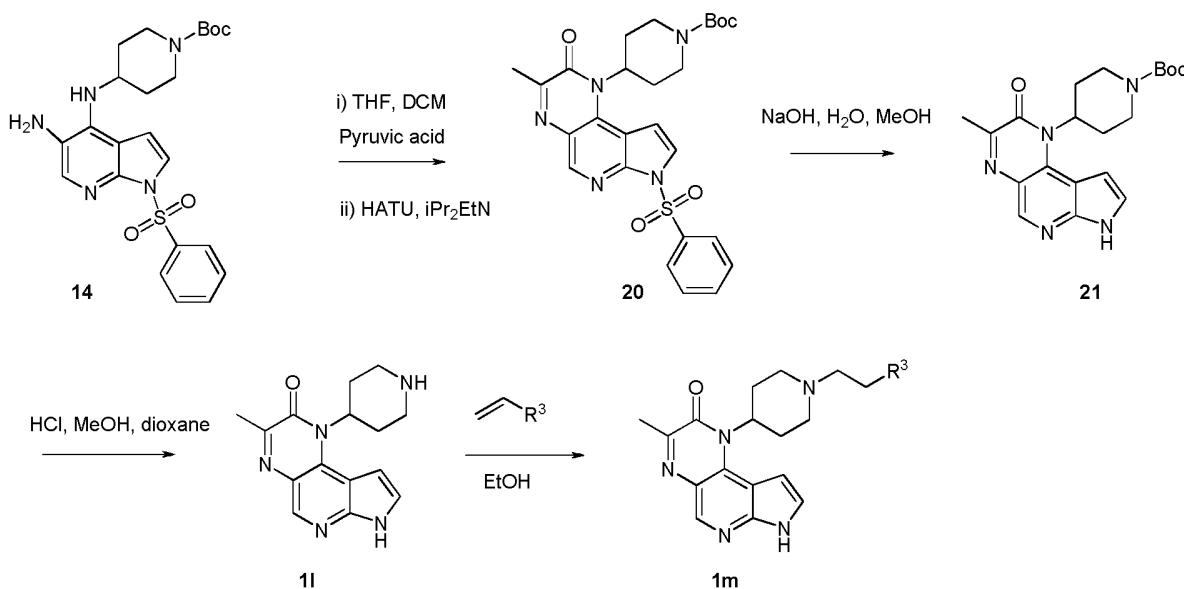
compounds of Formula 1e by reaction with for example a suitable carboxylic acid and in the presence of a suitable coupling reagent such as HATU and base such as diisopropylethylamine to give compounds of Formula 1g. Compounds of Formula 1e can be alkylated with for example a suitable 2-substituted ethene in a suitable solvent such as ethanol at a temperature between 5 ambient and 100 °C to give compounds of Formula 1h.

Reaction Scheme 5



Compounds of Formula 1i, 1j and 1k can be synthesized as shown in Reaction Scheme 5. For example, reaction of compound 17 with a 2-oxocarboxylic acid such as glyoxylic acid 10 followed by cyclisation using a suitable amide coupling reagent such as HATU and a base such as diisopropylethylamine gives compound 18. Hydrolysis of compound 18 with aqueous sodium hydroxide in methanol gives compound of Formula 1i. Deprotection of compound 1i under acidic conditions such as HCl in dioxane provides compounds of Formula 1j. Compound 1j can be treated with a suitable chloroformate in the presence of base such as diisopropylethylamine to 15 give compound 19. Hydrolysis of compound 21 using lithium hydroxide provides compounds of Formula 1k.

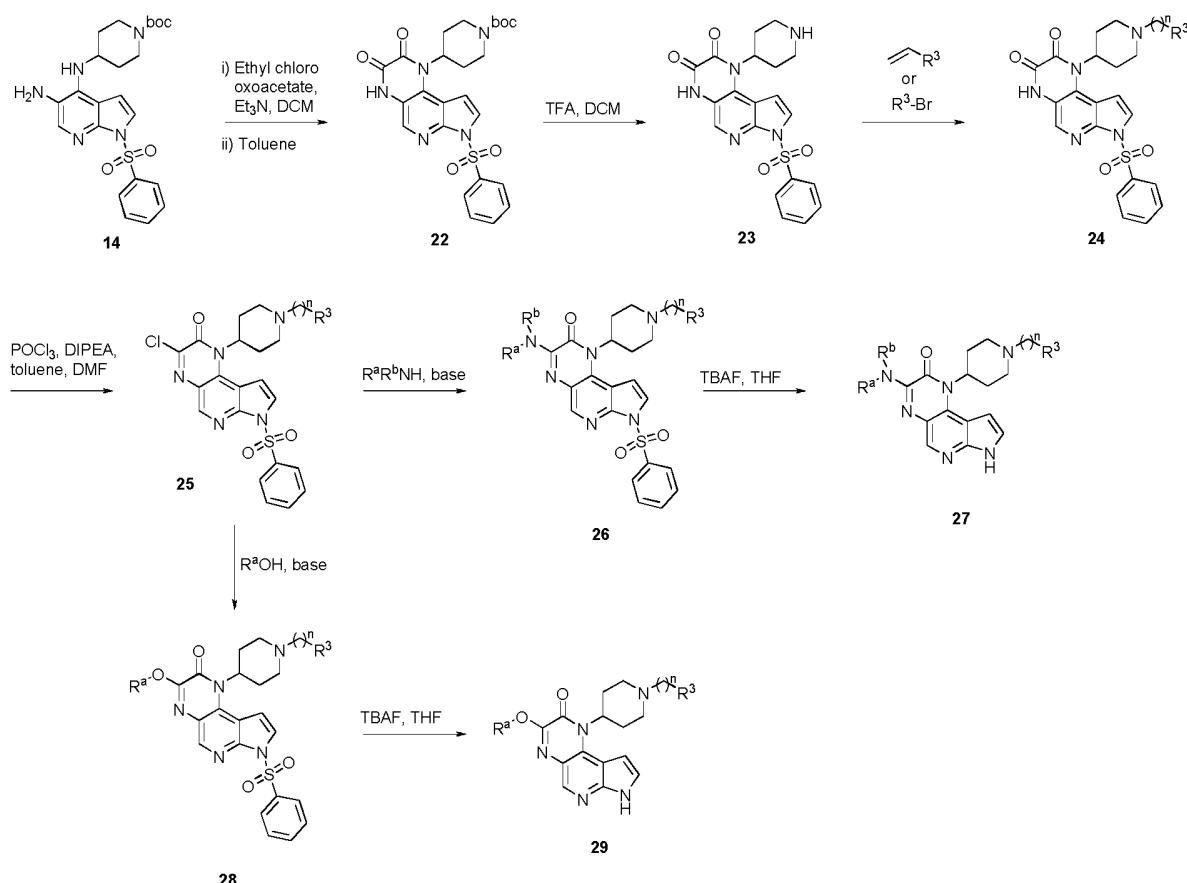
Reaction Scheme 6



Compounds of Formula 11 and 1m can be prepared as shown in Reaction Scheme 6. For example, reaction of compound 14 with a 2-oxocarboxylic acid such as pyruvic acid followed by cyclisation using a suitable amide coupling reagent such as HATU and a base such as diisopropylethylamine gives compound 20. Hydrolysis of compound 20 with aqueous sodium hydroxide in methanol gives compound 21. Deprotection of compound 21 under acidic conditions such as HCl in dioxane provides compounds of Formula 11. Compounds of Formula 11 can be alkylated with for example a suitable 2-substituted ethene in a suitable solvent such as ethanol at a temperature between ambient and 100 °C to give compounds of Formula 1m.

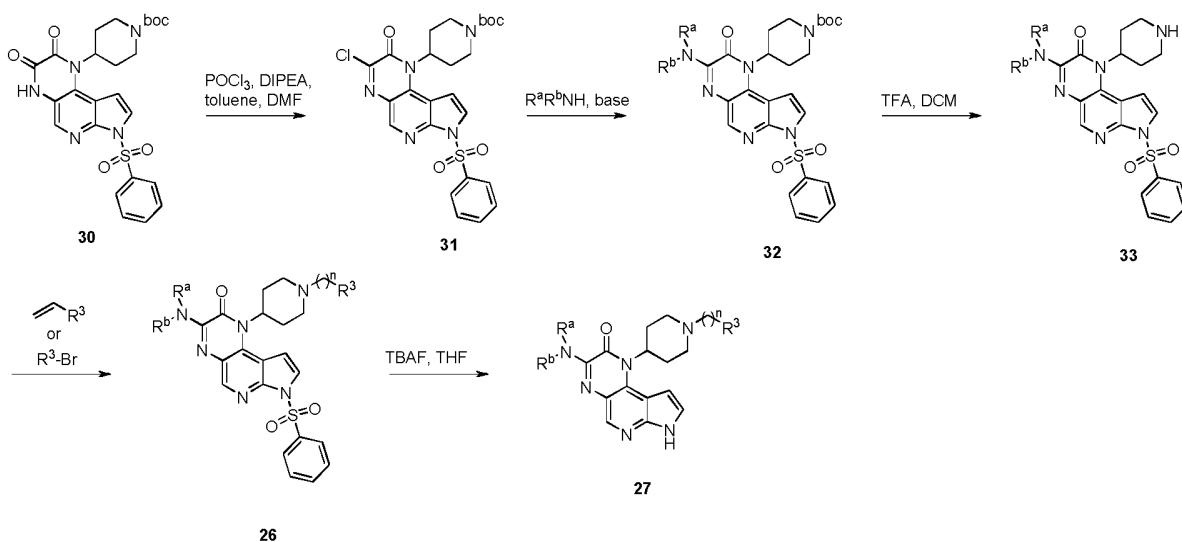
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Reaction Scheme 7



Compounds 27 and 29 can be prepared as shown in Reaction Scheme 7. For example, cyclisation of 14 followed by deprotection gives 23. Derivitizing the unprotected amine of 23 gives compound 24. Halogenation, amination and deprotection gives compound 27. Halogenation of 24 followed by reaction with an appropriate alcohol and deprotection gives 29.

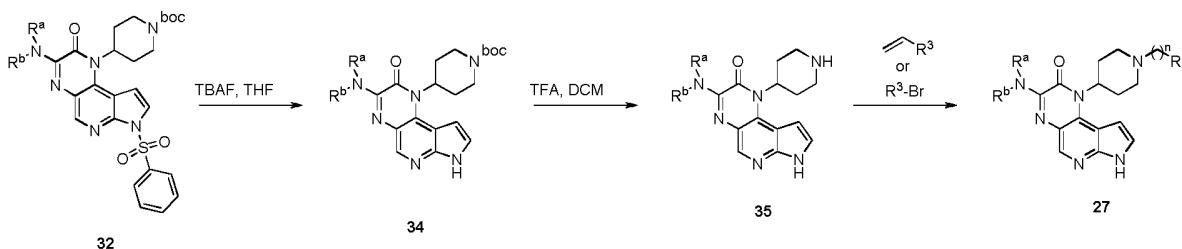
Reaction Scheme 8



Compound 27 can also be prepared as shown in Reaction Scheme 8. For example, halogenation, amination and deprotection gives compound 33. Derivitizing the deprotected amine and deprotection gives 27.

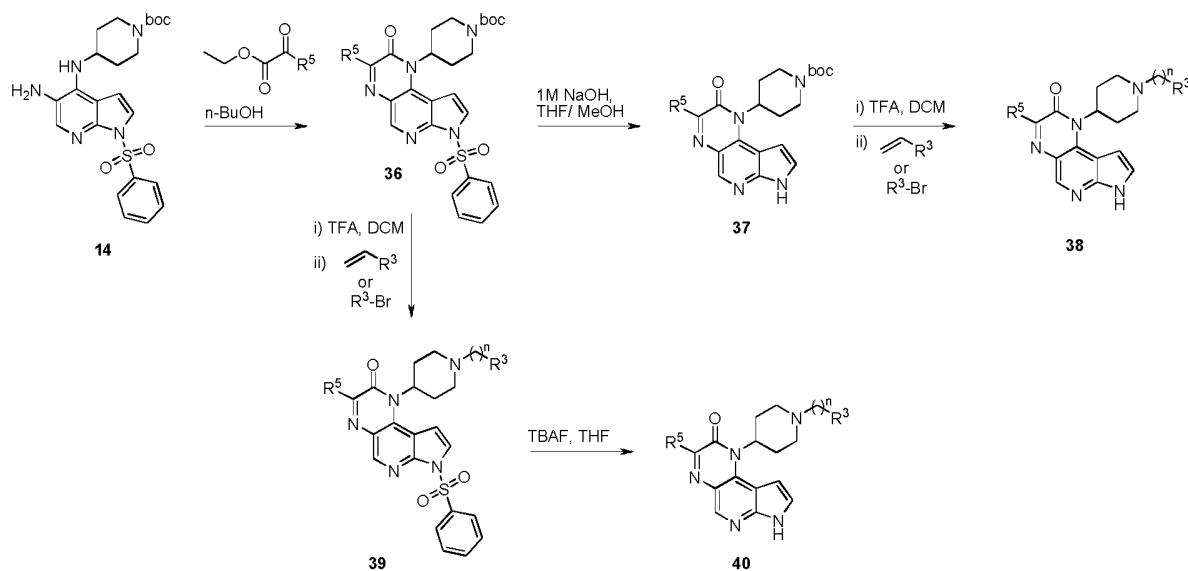
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Reaction Scheme 9



Alternatively, as shown in Scheme 9, starting from compound 32, sequential deprotection followed by derivitizing the deprotected amine gives compound 27.

Reaction Scheme 10



Compounds 38 and 40 can be prepared as shown in Scheme 10. Starting from compound 14, cyclisation to add R^5 gives 36. Sequential deprotection followed by derivitizing the deprotected amine gives compound 38. Alternatively, deprotection followed by derivitizing the deprotected amine gives compound 39. Deprotection of 39 gives compound 40.

It will be appreciated that where appropriate functional groups exist, compounds of various formulae or any intermediates used in their preparation may be further derivatized by one or more standard synthetic methods employing condensation, substitution, oxidation, reduction, or cleavage reactions. Particular substitution approaches include conventional alkylation, arylation, heteroarylation, acylation, sulfonylation, halogenation, nitration, formylation and coupling procedures.

In a further example, primary amine or secondary amine groups may be converted into amide groups ($-NHCOR'$ or $-NRCOR'$) by acylation. Acylation may be achieved by reaction with an appropriate acid chloride in the presence of a base, such as triethylamine, in a suitable solvent, such as dichloromethane, or by reaction with an appropriate carboxylic acid in the presence of a suitable coupling agent such as HATU (O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate) in a suitable solvent such as dichloromethane. Similarly, amine groups may be converted into sulfonamide groups ($-NHSO_2R'$ or $-NR''SO_2R'$) groups by reaction with an appropriate sulfonyl chloride in the presence of a suitable base, such as triethylamine, in a suitable solvent such as dichloromethane. Primary or secondary amine

groups can be converted into urea groups ($-\text{NHCONR}'\text{R}''$ or $-\text{NRCONR}'\text{R}''$) by reaction with an appropriate isocyanate in the presence or absence of a suitable base such as triethylamine, in a suitable solvent, such as dichloromethane.

An amine ($-\text{NH}_2$) may be obtained by reduction of a nitro ($-\text{NO}_2$) group, for example by 5 catalytic hydrogenation, using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as ethyl acetate or an alcohol e.g. methanol. Alternatively, the transformation may be carried out by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

In a further example, amine ($-\text{CH}_2\text{NH}_2$) groups may be obtained by reduction of nitriles (-CN), for example by catalytic hydrogenation using for example hydrogen in the presence of a 10 metal catalyst, for example palladium on a support such as carbon, or Raney nickel, in a solvent such as an ether e.g. a cyclic ether such as tetrahydrofuran, at an appropriate temperature, for example from about -78°C to the reflux temperature of the solvent.

In a further example, amine ($-\text{NH}_2$) groups may be obtained from carboxylic acid groups 15 ($-\text{CO}_2\text{H}$) by conversion to the corresponding acyl azide ($-\text{CON}_3$), Curtius rearrangement and hydrolysis of the resultant isocyanate ($-\text{N}=\text{C}=\text{O}$).

Aldehyde groups ($-\text{CHO}$) may be converted to amine groups ($-\text{CH}_2\text{NR}'\text{R}''$) by reductive amination employing an amine and a borohydride, for example sodium triacetoxyborohydride or sodium cyanoborohydride, in a solvent such as a halogenated hydrocarbon, for example 20 dichloromethane, or an alcohol such as methanol, where necessary in the presence of an acid such as acetic acid at around ambient temperature.

In a further example, aldehyde groups may be converted into alkenyl groups ($-\text{CH=CHR}'$) by the use of a Wittig or Wadsworth-Emmons reaction using an appropriate phosphorane or phosphonate under standard conditions known to those skilled in the art.

25 Aldehyde groups may be obtained by reduction of ester groups (such as $-\text{CO}_2\text{Et}$) or nitriles (-CN) using diisobutylaluminum hydride in a suitable solvent such as toluene. Alternatively, aldehyde groups may be obtained by the oxidation of alcohol groups using any suitable oxidising agent known to those skilled in the art.

Ester groups ($-\text{CO}_2\text{R}'$) may be converted into the corresponding acid group ($-\text{CO}_2\text{H}$) by acid- or base-catalysed hydrolysis, depending on the nature of R. If R is *t*-butyl, acid-catalysed hydrolysis can be achieved for example by treatment with an organic acid such as trifluoroacetic acid in an aqueous solvent, or by treatment with an inorganic acid such as hydrochloric acid in an 5 aqueous solvent.

Carboxylic acid groups ($-\text{CO}_2\text{H}$) may be converted into amides (CONHR' or $-\text{CONR}'\text{R}''$) by reaction with an appropriate amine in the presence of a suitable coupling agent, such as HATU, in a suitable solvent such as dichloromethane.

In a further example, carboxylic acids may be homologated by one carbon (i.e. $-\text{CO}_2\text{H}$ to 10 $-\text{CH}_2\text{CO}_2\text{H}$) by conversion to the corresponding acid chloride ($-\text{COCl}$) followed by Arndt-Eistert synthesis.

In a further example, -OH groups may be generated from the corresponding ester (e.g. $-\text{CO}_2\text{R}'$), or aldehyde ($-\text{CHO}$) by reduction, using for example a complex metal hydride such as 15 lithium aluminium hydride in diethyl ether or tetrahydrofuran, or sodium borohydride in a solvent such as methanol. Alternatively, an alcohol may be prepared by reduction of the corresponding acid ($-\text{CO}_2\text{H}$), using for example lithium aluminium hydride in a solvent such as tetrahydrofuran, or by using borane in a solvent such as tetrahydrofuran.

Alcohol groups may be converted into leaving groups, such as halogen atoms or sulfonyloxy groups such as an alkylsulfonyloxy, e.g. trifluoromethylsulfonyloxy or 20 arylsulfonyloxy, e.g. *p*-toluenesulfonyloxy group using conditions known to those skilled in the art. For example, an alcohol may be reacted with thionyl chloride in a halogenated hydrocarbon (e.g. dichloromethane) to yield the corresponding chloride. A base (e.g. triethylamine) may also be used in the reaction.

In another example, alcohol, phenol or amide groups may be alkylated by coupling a 25 phenol or amide with an alcohol in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl-, diisopropyl, or dimethylazodicarboxylate. Alternatively alkylation may be achieved by deprotonation using a suitable base e.g. sodium hydride followed by subsequent addition of an alkylating agent, such as an alkyl halide.

Aromatic halogen substituents in the compounds may be subjected to halogen-metal exchange by treatment with a base, for example a lithium base such as *n*-butyl or *t*-butyl lithium, optionally at a low temperature, e.g. around -78 °C, in a solvent such as tetrahydrofuran, and then quenched with an electrophile to introduce a desired substituent. Thus, for example, a 5 formyl group may be introduced by using *N,N*-dimethylformamide as the electrophile. Aromatic halogen substituents may alternatively be subjected to metal (e.g. palladium or copper) catalysed reactions, to introduce, for example, acid, ester, cyano, amide, aryl, heteroaryl, alkenyl, alkynyl, thio- or amino substituents. Suitable procedures which may be employed include those described by Heck, Suzuki, Stille, Buchwald or Hartwig.

10 Aromatic halogen substituents may also undergo nucleophilic displacement following reaction with an appropriate nucleophile such as an amine or an alcohol. Advantageously, such a reaction may be carried out at elevated temperature in the presence of microwave irradiation.

METHODS OF SEPARATION

In each of the exemplary Schemes it may be advantageous to separate reaction products 15 from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization or trituration from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, for example: 20 reverse-phase and normal phase; size exclusion; ion exchange; supercritical fluid; 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 25 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. Example separation methods include boiling point, and molecular weight in 5 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. One skilled in the art will apply techniques most likely to achieve the desired separation.

Diastereomeric mixtures can be separated into their individual diastereoisomers on the basis of their physical chemical differences by methods well known to those skilled in the art, 10 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 diastereoisomers and converting (e.g., hydrolyzing) the individual diastereoisomers to the corresponding pure enantiomers. Also, some of the compounds of the 15 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 or supercritical fluid chromatography.

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 20 using optically active resolving agents (Eliel, E. and Wilen, S., *Stereochemistry of Organic Compounds*, John Wiley & Sons, Inc., New York, 1994; Lochmuller, C. H., *J. Chromatogr.*, 113(3):283-302 (1975)). 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) 25 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).

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 5 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, the substrate to be resolved is reacted with one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E. and Wilen, S., *Stereochemistry of Organic Compounds*, John Wiley & Sons, Inc., New York, 1994, p. 322). Diastereomeric compounds can 10 be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthol 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 menthol ester, e.g. (-) menthol chloroformate in the 15 presence of base, or Mosher ester, α -methoxy- α -(trifluoromethyl)phenyl acetate (Jacob, *J. Org. Chem.* 47:4165 (1982)), of the racemic mixture, and analyzing the 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 20 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* W. J. Lough, Ed., Chapman and Hall, New York, (1989); Okamoto, *J. of Chromatogr.* 513:375-378 (1990)). Enriched or purified enantiomers can be distinguished by methods used to distinguish other 25 chiral molecules with asymmetric carbon atoms, such as optical rotation and circular dichroism. The absolute stereochemistry of chiral centers and enantiomers can be determined by x-ray crystallography.

Positional isomers, for example E and Z forms, of compounds of formula I, and intermediates for their synthesis, may be observed by characterization methods such as NMR and analytical HPLC. For certain compounds where the energy barrier for interconversion is 30 sufficiently high, the E and Z isomers may be separated, for example by preparatory HPLC.

PHARMACEUTICAL COMPOSITIONS AND ADMINISTRATION

Certain embodiments provides pharmaceutical compositions or medicaments containing the compounds of the invention and a therapeutically inert carrier, diluent or excipient, as well as methods of using the compounds of the invention to prepare such compositions and 5 medicaments. In one example, compounds of formula I may be formulated 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 into a galenical administration form. The pH of the formulation depends on the particular use and the concentration of compound, and can range anywhere from about 3 to about 10 8. In one example, a compound of formula I is formulated in an acetate buffer, at pH 5. In certain embodiments, the compounds of formula I are sterile. The compound may be stored, for example, as a solid or amorphous composition, as a lyophilized formulation or as an aqueous solution.

Compositions are formulated, dosed, and administered in a fashion consistent with good 15 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.

In one example, the therapeutically effective amount of the compound of the invention 20 administered parenterally per dose will be in the range of about 0.01-100 mg/kg, alternatively 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. In certain embodiments, oral unit dosage forms, such as tablets and capsules, contain from about 5 to about 100 mg of the compound of the invention.

The compounds of the invention may be administered by any suitable means, including 25 oral, topical (including buccal and sublingual), rectal, vaginal, transdermal, parenteral, subcutaneous, intraperitoneal, intrapulmonary, intradermal, intrathecal, inhaled and epidural and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration.

The compounds of the present invention may be administered in any convenient administrative form, e.g., tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, vapors, suppositories, gels, emulsions, patches, etc. Such compositions may contain components conventional in pharmaceutical preparations, e.g., diluents, carriers, pH modifiers, 5 sweeteners, bulking agents, and further active agents.

A typical formulation is prepared by mixing a compound of the present invention and a carrier or excipient. Suitable carriers and excipients are well known to those skilled in the art and are described in detail in, e.g., Ansel, Howard C., et al., *Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems*. Philadelphia: Lippincott, Williams & Wilkins, 2004; 10 Gennaro, Alfonso R., et al. *Remington: The Science and Practice of Pharmacy*. Philadelphia: Lippincott, Williams & Wilkins, 2000; and Rowe, Raymond C. *Handbook of Pharmaceutical Excipients*. Chicago, Pharmaceutical Press, 2005. 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, 15 colorants, sweeteners, perfuming agents, flavoring agents, diluents 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).

An example of a suitable oral dosage form is a tablet containing about 2 mg, 5 mg, 25mg, 20 50mg, 100mg, 250mg, or 500mg of the compound of the present invention compounded with about 95-30 mg anhydrous lactose, about 5-40 mg sodium croscarmellose, about 5-30mg polyvinylpyrrolidone (PVP) K30, and about e.g., 1-10 mg magnesium stearate. The powdered ingredients are first mixed together and then mixed with a solution of the PVP. The resulting composition can be dried, granulated, mixed with the magnesium stearate and compressed to 25 tablet form using conventional equipment. An example of an aerosol formulation can be prepared by dissolving the compound of the present invention, for example 5-400 mg, in a suitable buffer solution, e.g. a phosphate buffer, adding a tonicifier, e.g. a salt such sodium chloride, if desired. The solution may be filtered, e.g. using a 0.2 micron filter, to remove impurities and contaminants.

An embodiment, therefore, includes a pharmaceutical composition comprising a compound of formula I, stereoisomers, tautomers or pharmaceutically acceptable salts thereof. In a further embodiment includes a pharmaceutical composition comprising a compound of formula I, or stereoisomers, tautomers or pharmaceutically acceptable salts thereof, together with 5 a pharmaceutically acceptable carrier or excipient.

Certain embodiments includes a pharmaceutical composition comprising a compound of formula I stereoisomers, tautomers or pharmaceutically acceptable salts thereof for use in the treatment of a hyperproliferative disease. Certain embodiments includes a pharmaceutical composition comprising a compound of formula I stereoisomers, tautomers or pharmaceutically acceptable salts thereof for use in the treatment of cancer. Certain embodiments includes a pharmaceutical composition comprising a compound of formula I stereoisomers, tautomers or pharmaceutically acceptable salts thereof for use in the treatment of an immunological disorder. Certain embodiments includes a pharmaceutical composition comprising a compound of formula I stereoisomers, tautomers or pharmaceutically acceptable salts thereof for use in the treatment of 10 rheumatoid arthritis, psoriasis, inflammatory bowel disease (IBD) or asthma. Certain embodiments includes a pharmaceutical composition comprising a compound of formula I stereoisomers, tautomers or pharmaceutically acceptable salts thereof for use in the treatment of 15 rheumatoid arthritis, asthma, systemic lupus erythematosus, psoriasis, IBD and transplant rejection.

20 METHODS OF TREATMENT WITH AND USES OF JAK1 INHIBITORS

The compounds of Formula I inhibit the activity of JAK1 kinase. Accordingly, the compounds of Formula I inhibit the phosphorylation of signal transducers and activators of transcription (STATs) by JAK1 kinase as well as STAT mediated cytokine production. Compounds of Formula I are useful for inhibiting JAK1 kinase activity in cells through cytokine 25 pathways, such as IL-6, IL-15, IL-7, IL-2, IL-4, IL-9, IL-10, IL-13, IL-21, G-CSF, IFNalpha, IFNbta or IFNgamma pathways. The compounds of Formula I can be used for the treatment of immunological disorders driven by aberrant IL-6, IL-15, IL-7, IL-2, IL-4, IL9, IL-10, IL-13, IL-21, G-CSF, IFNalpha, IFNbta or IFNgamma cytokine signaling.

Certain embodiments includes a method of treating or lessening the severity of a disease or condition responsive to the inhibition of JAK1 kinase activity in a patient. The method includes the step of administering to a patient a therapeutically effective amount of a compound of the present invention.

5 In certain embodiments, the disease or condition is cancer, stroke, diabetes, hepatomegaly, cardiovascular disease, multiple sclerosis, Alzheimer's disease, cystic fibrosis, viral disease, autoimmune diseases, atherosclerosis, restenosis, psoriasis, rheumatoid arthritis, inflammatory bowel disease, asthma, allergic disorders, inflammation, neurological disorders, a hormone-related disease, conditions associated with organ transplantation, immunodeficiency disorders, destructive bone disorders, proliferative disorders, infectious diseases, conditions associated with cell death, thrombin-induced platelet aggregation, liver disease, pathologic immune conditions involving T cell activation, CNS disorders or a myeloproliferative disorder.

10

In certain embodiments, the disease or condition is cancer.

In certain embodiments, the disease is a myeloproliferative disorder.

15 In certain embodiments, the myeloproliferative disorder is polycythemia vera, essential thrombocythosis, myelofibrosis or chronic myelogenous leukemia (CML).

In certain embodiments, the cancer is breast, ovary, cervix, prostate, testis, penile, genitourinary tract, seminoma, esophagus, larynx, gastric, stomach, gastrointestinal, skin, keratoacanthoma, follicular carcinoma, melanoma, lung, small cell lung carcinoma, non-small cell lung carcinoma (NSCLC), lung adenocarcinoma, squamous carcinoma of the lung, colon, pancreas, thyroid, papillary, bladder, liver, biliary passage, kidney, bone, myeloid disorders, lymphoid disorders, hairy cells, buccal cavity and pharynx (oral), lip, tongue, mouth, salivary gland, pharynx, small intestine, colon, rectum, anal, renal, prostate, vulval, thyroid, large intestine, endometrial, uterine, brain, central nervous system, cancer of the peritoneum, 20 hepatocellular cancer, head cancer, neck cancer, Hodgkin's or leukemia.

25

In certain embodiments, the cardiovascular disease is restenosis, cardiomegaly, atherosclerosis, myocardial infarction or congestive heart failure.

In certain embodiments, the neurodegenerative disease is Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, and cerebral ischemia, and neurodegenerative disease caused by traumatic injury, glutamate neurotoxicity or hypoxia.

In certain embodiments, the inflammatory diseases is rheumatoid arthritis, psoriasis, 5 asthma, inflammatory bowel disease, contact dermatitis or delayed hypersensitivity reactions.

In certain embodiments, the autoimmune disease is lupus or multiple sclerosis.

In certain embodiments, the disease or condition responsive to the inhibition of JAK1 kinase is rheumatoid arthritis.

In certain embodiments, the disease or condition responsive to the inhibition of JAK1 10 kinase is asthma, inflammatory bowel disease, Crohn's disease, pouchitis, microscopic colitis, ulcerative colitis, rheumatoid arthritis, psoriasis, allergic rhinitis, atopic dermatitis, contact dermatitis, delayed hypersensitivity reactions, lupus or multiple sclerosis.

In certain embodiments, the disease or condition responsive to the inhibition of JAK1 kinase is rheumatoid arthritis, asthma, systemic lupus erythematosus, psoriasis, IBD or transplant 15 rejection.

Certain embodiments includes a method of treating cancer in a mammal in need of such treatment, wherein the method comprises administering to said mammal a therapeutically effective amount of a compound of formula I, a stereoisomer, tautomer, prodrug or pharmaceutically acceptable salt thereof.

20 Certain embodiments includes compounds of formula I, a stereoisomer, tautomer, prodrug or pharmaceutically acceptable salt thereof, for use in therapy. In certain embodiments, the therapy is the treatment of an immunological disorder, for example rheumatoid arthritis. In certain embodiments, the therapy is the treatment of cancer.

25 Certain embodiments includes compounds of formula I, a stereoisomer, tautomer, prodrug or pharmaceutically acceptable salt thereof, for use in treating a disease selected from rheumatoid arthritis, asthma, systemic lupus erythematosus, psoriasis, IBD and transplant rejection.

Certain embodiments includes the use of a compound of formulas I, a stereoisomer, tautomer, prodrug or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease described herein (e.g., cancer or immunological disorder).

- 5 [0100] Evaluation of drug-induced immunosuppression by the compounds of the invention may be performed using *in vivo* functional tests, such as rodent models of induced arthritis and therapeutic or prophylactic treatment to assess disease score, T cell-dependent antibody response (TDAR), and delayed-type hypersensitivity (DTH). Other *in vivo* systems including murine models of host defense against infections or tumor resistance (Burleson GR, Dean JH, and Munson AE. *Methods in Immunotoxicology*, Vol. 1. Wiley-Liss, New York, 1995) may be considered to elucidate the nature or mechanisms of observed immunosuppression. The *in vivo* test systems can be complemented by well-established *in vitro* or *ex vivo* functional assays for the assessment of immune competence. These assays may comprise B or T cell proliferation in response to mitogens or specific antigens, measurement of signaling through one or more of the Janus kinase pathways in B or T cells or immortalized B or T cell lines, measurement of cell surface markers in response to B or T cell signaling, natural killer (NK) cell activity, mast cell activity, mast cell degranulation, macrophage phagocytosis or kill activity, and neutrophil oxidative burst and/or chemotaxis. In each of these tests determination of cytokine production by particular effector cells (e.g., lymphocytes, NK, monocytes/macrophages, neutrophils) may be included. The *in vitro* and *ex vivo* assays can be applied in both preclinical and clinical testing using lymphoid tissues and/or peripheral blood (House RV. "Theory and practice of cytokine assessment in immunotoxicology" (1999) Methods 19:17-27; Hubbard AK. "Effects of xenobiotics on macrophage function: evaluation in vitro" (1999) Methods;19:8-16; Lebrec H, et al (2001) Toxicology 158:25-29).
- 10 15 20 25 30
- [0101] Collagen-induced arthritis (CIA) is an animal model of human rheumatoid arthritis (RA). Joint inflammation, which develops in animals with CIA, strongly resembles inflammation observed in patients with rheumatoid arthritis (RA). Blocking tumor necrosis factor (TNF) is an efficacious treatment of CIA, just as it is a highly efficacious therapy in treatment of RA patients. CIA is mediated by both T-cells and antibodies (B-cells). Macrophages are believed to play an important role in mediating tissue damage during disease development. CIA is induced by

immunizing animals with collagen emulsified in Complete Freund's Adjuvant (CFA). It is most commonly induced in the DBA/1 mouse strain, but the disease can also be induced in Lewis rats.

[0102] The T-cell Dependent Antibody Response (TDAR) is An assay for immune function testing when potential immunotoxic effects of compounds need to be studied. The IgM-Plaque

5 Forming Cell (PFC) assay, using Sheep Red Blood Cells (SRBC) as the antigen, is currently a widely accepted and validated standard test. TDAR is an assay for adult exposure immunotoxicity detection in mice based on the US National Toxicology Program (NTP) database (M.I. Luster et al (1992) Fundam. Appl. Toxicol. 18:200–210). The utility of this assay stems from the fact that it is a holistic measurement involving several important components of
10 an immune response. A TDAR is dependent on functions of the following cellular compartments: (1) antigen-presenting cells, such as macrophages or dendritic cells; (2) T-helper cells, which are critical players in the genesis of the response, as well as in isotype switching; and (3) B-cells, which are the ultimate effector cells and are responsible for antibody production. Chemically-induced changes in any one compartment can cause significant changes in the
15 overall TDAR (M.P. Holsapple In: G.R. Burleson, J.H. Dean and A.E. Munson, Editors, *Modern Methods in Immunotoxicology, Volume 1*, Wiley-Liss Publishers, New York, NY (1995), pp. 71–108). Usually, this assay is performed either as an ELISA for measurement of soluble antibody (R.J. Smialowicz et al (2001) Toxicol. Sci. 61:164–175) or as a plaque (or antibody) forming cell assay (L. Guo et al (2002) Toxicol. Appl. Pharmacol. 181:219–227) to detect plasma cells
20 secreting antigen specific antibodies. The antigen of choice is either whole cells (e.g. sheep erythrocytes) or soluble protein antigens (T. Miller et al (1998) Toxicol. Sci. 42:129–135).

[0103] A compound of Formula I may be administered by any route appropriate to the disease or condition to be treated. Suitable routes include oral, parenteral (including subcutaneous, intramuscular, intravenous, intraarterial, intradermal, intrathecal and epidural), transdermal,

25 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 route may vary with for example the condition of the recipient. Where the compound of Formula I is administered orally, it may
30 be formulated as a pill, capsule, tablet, etc. with a pharmaceutically acceptable carrier or excipient. Where the compound of Formula I 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 5 mg to about 1000 mg of a compound of Formula I. A typical dose may be about 5 mg to about 300 mg of a compound of 5 Formula I. A dose may be administered once a day (QD), 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 10 time. The regimen may be repeated for a number of cycles of therapy.

COMBINATION THERAPY

The compounds of formula I may be employed alone or in combination with other chemotherapeutic agents for treatment. The compounds of the present invention can be used in combination with one or more additional drugs, for example an anti-hyperproliferative, anti-15 cancer, cytostatic, cytotoxic, anti-inflammatory or chemotherapeutic agent. The second compound of the pharmaceutical combination formulation or dosing regimen, in one example, has complementary activities to the compound of this invention such that they do not adversely affect each other. Such agents are suitably present in combination in amounts that are effective for the purpose intended. The compounds may be administered together in a unitary 20 pharmaceutical composition or separately and, when administered separately this may occur simultaneously or sequentially. Such sequential administration may be close or remote in time. In certain embodiments, compounds of the present invention are coadministered with a cytostatic compound selected from the group consisting of cisplatin, doxorubicin, taxol, taxotere and mitomycin C. In certain embodiments, the cytostatic compound is doxorubicin. In certain 25 embodiments, compounds of the present invention are coadministered with an anti-inflammatory agent selected from a NSAID and corticosteroid. In certain embodiments, compounds of the present invention are coadministered with an anti-rheumatoid agent, in one example, RITUXAN®. In certain embodiments, compounds of the present invention are coadministered with a chemotherapeutic agent selected from etanercept (Enbrel), infliximab (Remicade), 30 adalimumab (Humira), certolizumab pegol (Cimzia), golimumab (Simponi), Interleukin 1 (IL-1)

blockers such as anakinra (Kineret), monoclonal antibodies against B cells such as rituximab (RITUXAN®), T cell costimulation blockers such as abatacept (Orencia), Interleukin 6 (IL-6) blockers such as tocilizumab (ACTEMERA®); Interleukin 13 (IL-13) blockers such as lebrikizumab; Interferon alpha (IFN) blockers such as Rontalizumab; Beta 7 integrin blockers 5 such as rhuMAb Beta7; IgE pathway blockers such as Anti-M1 prime; Secreted homotrimeric LT_a3 and membrane bound heterotrimer LT_a1/β2 blockers such as Anti-lymphotoxin alpha (LT_a)

The compounds of the present invention can be also used in combination with radiation therapy. The phrase "radiation therapy" refers to the use of electromagnetic or particulate 10 radiation in the treatment of neoplasia. Radiation therapy delivers doses of radiation sufficiently high to a target area to cause death of reproducing cells, in both tumor and normal tissues. The radiation dosage regimen is generally defined in terms of radiation absorbed dose (rad), time and fractionation, and must be carefully defined by the oncologist. The amount of radiation a patient receives will depend on various considerations but two of the most important considerations are 15 the location of the tumor in relation to other critical structures or organs of the body, and the extent to which the tumor has spread. Examples of radiotherapeutic agents are provided in Hellman, Principles of Radiation Therapy, Cancer, in Principles I and Practice of Oncology, 24875 (Devita et al., 4th ed., vol 1, 1993). Alternative forms of radiation therapy include three-dimensional conformal external beam radiation, intensity modulated radiation therapy (IMRT), 20 stereotactic radiosurgery and brachytherapy (interstitial radiation therapy), the latter placing the source of radiation directly into the tumor as implanted "seeds". These alternative treatment modalities deliver greater doses of radiation to the tumor, which accounts for their increased effectiveness when compared to standard external beam radiation therapy.

In one embodiment, compounds of the present invention are coadministered with any of 25 anti-IBD agents, including but not limited to anti-inflammatory drugs, such as sulfasalazine, mesalamine or corticosteroids, such as budesonide, prednisone, cortisone or hydrocortisone, immune suppressing agents, such as azathioprine, mercaptopurine, infliximab, adalimumab, certolizumab pegol, methotrexate, cyclosporine or natalizumab, antibiotics, such as metronidazole or ciprofloxacin, anti-diarrheals, such as psyllium powder, loperamide or 30 methylcellulose, laxatives, pain relievers, such as NSAIDs or acetaminophen, iron supplements,

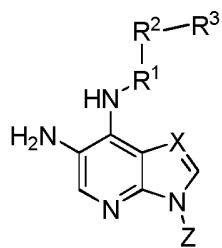
vitamin B supplements, vitamin D supplements and any combination of the above. In another example, compounds of the present invention are administered with (e.g. before, during or after) other anti-IBD therapies, such as surgery.

In one embodiment, compounds of the present invention are coadministered with any of 5 anti-psoriasis agents, including but not limited to topical corticosteroids, vitamin D analogues, such as calcipotriene or calcitriol, anthralin, topical retinoids, such as tazarotene, calcineurin inhibitors, such as tacrolimus or pimecrolimus, salicylic acid, coal tar, NSAIDs, moisturizing creams and ointments, oral or injectible retinoids, such as acitretin, methotrexate, cyclosporine, hydroxyurea. immunomodulator drugs, such as alefacept, etanercept, infliximab or ustekinumab, 10 thioguanine, and any combinations of the above. In another example, compounds of the present invention are administered with (e.g. before, during or after) other anti-psoriasis therapies, such as light therapy, sunlight therapy, UVB therarpy, narrow-band UVB therapy, Goeckerman therapy, photochemotherapy, such as psoralen plus ultraviolet A (PUVA), excimer and pulsed dye laser therapy, or in any combination of antipsoriasis agents and anti-psoriasis therapies.

15 In one embodiment, compounds of the present invention are coadministered with any of anti-asthmatic agents, including but not limited to beta2-adrenergic agonists, inhaled and oral corticosteroids, leukotriene receptor antagonist, and omalizumab. In another embodiment, compounds of the present invention are coadministered with an anti-asthmatic agent selected from a NSAID, combinations of fluticasone and salmeterol, combinations of budesonide and 20 formoterol, omalizumab, lebrikizumab and corticosteroid selected from fluticasone, budesonide, mometasone, flunisolide and beclomethasone.

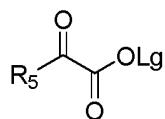
ARTICLES OF MANUFACTURE

Another embodiment includes a method of manufacturing a compound of formula I. The method inclcudes: (a) reacting a compound of formula i:



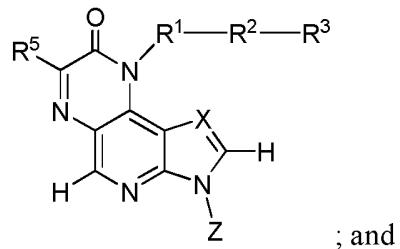
i ;

wherein R¹, R², R³ and X are as defined in formula I, and Z is hydrogen or an amino protecting group, with a compound of formula ii:



ii;

wherein R⁵ is defined in formula I and Lg is a leaving group, under conditions sufficient to form a compound of formula iii:



iii

10 (b) optionally deprotecting said amino protecting group to form a compound of formula I.

In certain embodiments of formula ii, Lg is hydrogen, halogen or C₁₋₃ alkyl. In certain embodiments of formulas ii and iii, R⁵ is hydrogen or C₁₋₁₂ alkyl optionally substituted by halogen, oxo, -(C₀₋₃ alkylene)CN, -(C₀₋₃ alkylene)OR^c, -(C₀₋₃ alkylene)NR^cR^d, -(C₀₋₃ alkylene)C(O)R^c, -(C₀₋₃ alkylene)C(O)OR^c, -(C₀₋₃ alkylene)C(O)NR^cR^d, -(C₀₋₃ alkylene)NR^cC(O)R^d, -(C₀₋₃ alkylene)OC(O)NR^cR^d, -(C₀₋₃ alkylene)NR^cC(O)NR^cR^d, -(C₀₋₃ alkylene)NR^cC(O)OR^d, -(C₀₋₃ alkylene)S(O)₀₋₂R^c, -(C₀₋₃ alkylene)NR^cS(O)₁₋₂R^d, -(C₀₋₃ alkylene)S(O)₁₋₂NR^cR^d, -(C₀₋₃ alkylene)NR^cS(O)₁₋₂NR^cR^d or C₁₋₆ alkyl optionally substituted by oxo, -CN or halogen. In certain embodiments of formulas ii and iii, R⁵ is hydrogen or methyl.

Certain embodiments includes a kit for treating a disease or disorder responsive to the inhibition of JAK1 kinase. The kit includes:

- (a) a first pharmaceutical composition comprising a compound of formula I; and
- (b) instructions for use.

5 In certain embodiments, the kit further includes:

- (c) a second pharmaceutical composition, which includes a chemotherapeutic agent.

In certain embodiments, the instructions describe the simultaneous, sequential or separate administration of said first and second pharmaceutical compositions to a patient in need thereof.

In certain embodiments, the first and second compositions are contained in separate
10 containers.

In certain embodiments, the first and second compositions are contained in the same container.

Containers for use include, for example, bottles, vials, syringes, blister pack, etc. The containers may be formed from a variety of materials such as glass or plastic. The container
15 includes a compound of formula I or 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). The container includes a composition comprising at least one compound of formula I. The label or package insert indicates that the composition is used for treating the condition of choice, such as
20 cancer. In certain embodiments, the label or package inserts indicates that the composition comprising the compound of formula I can be used to treat a disorder. In addition, the label or package insert may indicate that the patient to be treated is one having a disorder characterized by overactive or irregular kinase activity. The label or package insert may also indicate that the composition can be used to treat other disorders.

25 The article of manufacture may comprise (a) a first container with a compound of formula I contained therein; and (b) a second container with a second pharmaceutical formulation contained therein, wherein the second pharmaceutical formulation comprises a

chemotherapeutic agent. The article of manufacture in this embodiment of the invention may further comprise a package insert indicating that the first and second compounds can be used to treat patients at risk of stroke, thrombus or thrombosis disorder. Alternatively, or additionally, the article of manufacture may further comprise a second (or third) container comprising a 5 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 order to illustrate the invention, the following examples are included. However, it is to 10 be understood that these examples do not limit the invention and are only meant to suggest a method of practicing the invention. Persons skilled in the art will recognize that the chemical reactions described may be readily adapted to prepare other compounds of formula I, and alternative methods for preparing the compounds of formula I are within the scope of this invention. For example, the synthesis of non-exemplified compounds according to the invention 15 may be successfully performed by modifications apparent to those skilled in the art, e.g., by appropriately protecting interfering groups, by utilizing other suitable reagents known in the art other than those described, and/or by making routine modifications of reaction conditions. Alternatively, other reactions disclosed herein or known in the art will be recognized as having applicability for preparing other compounds of the invention.

20

EXAMPLES

The invention will be more fully understood by reference to the following examples. They should not, however, be construed as limiting the scope of the invention. Abbreviations used herein are as follows:

Abbreviations:

25

BOC	tert-Butyloxycarbonyl group
CDCl ₃	Deuterated chloroform
DCM	Dichloromethane
DIPEA	Diisopropylethylamine

	DMAP	4-(Dimethylamino)pyridine
	DMSO	Dimethylsulfoxide
	DMSO- <i>d</i> 6	Deuterated DMSO
	DME	1,2-Dimethoxyethane
5	DMF	Dimethylformamide
	ESI	Electrospray
	EtOAc	Ethyl acetate
	EtOH	Ethanol
	HATU	2-(7-aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
10	HCl	Hydrochloric acid
	HM-N	Isolute® HM-N is a modified form of diatomaceous earth
	IMS	Industrial methylated spirit
	MeOH	Methanol
15	min	Minutes
	NaH	Sodium Hydride
	Na ₂ SO ₄	Sodium sulfate
	NaHCO ₃	Sodium bicarbonate / Sodium hydrogen carbonate
	NaOH	Sodium hydroxide
20	NEt ₃	Triethylamine
	NH ₃	Ammonia
	RT	LCMS retention time in minutes
	SCX-2	Pre-packed Isolute® silica-based sorbent with a chemically bonded propylsulfonic acid functional group

Si-SPE	Pre-packed Isolute® silica flash chromatography cartridge
Si-ISCO	Pre-packed ISCO® silica flash chromatography cartridge
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

5 General Experimental Conditions:

All temperatures are in degrees Celsius (°C). Unless otherwise stated, operations were carried out at room or ambient temperature (18-25 °C).

Unless otherwise noted, the solvents used in preparing the example compounds were commercial anhydrous grade and were used without further drying or purification.

10 ¹H NMR spectra were recorded at ambient temperature or at 80 °C where indicated using one of the following machines: Varian Unity Inova (400MHz) spectrometer with a triple resonance 5mm probe, Bruker Avance DRX400 (400MHz) spectrometer with a triple resonance 5mm probe or a Bruker Avance DPX 300 (300MHz) equipped with a standard 5mm dual frequency probe for detection of H1 and C13. Chemical shifts are expressed in ppm relative to an internal standard; tetramethylsilane (ppm = 0.00). The following abbreviations have been used:
15 br = broad signal, s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet.

20 High Pressure Liquid Chromatography - Mass Spectrometry (LCMS) experiments to determine retention times (RT) and associated mass ions were performed using one of the following methods:

Method A: Example compounds were analysed using the following conditions: Experiments performed on a Waters Micromass ZQ2000 quadrupole mass spectrometer linked to a Waters Acquity UPLC system with a PDA UV detector. The spectrometer has an electrospray source operating in positive and negative ion mode. This system uses an Acquity BEH C18 1.7um 25 100 x 2.1mm column, maintained at 40°C or an Acquity BEH Shield RP18 1.7 µm 100 x 2.1mm column, maintained at 40°C and a 0.4 ml / minute flow rate. The initial solvent system was 95% water containing 0.1% formic acid (solvent A) and 5% acetonitrile containing 0.1%

formic acid (solvent B) for the first 0.4 minute followed by a gradient up to 5% solvent A and 95% solvent B over the next 5.6 minutes. This was maintained for 0.8 minute before returning to 95% solvent A and 5% solvent B over the next 1.2 minutes. Total run time was 8 minutes.

Method B: Intermediates were analysed using the following conditions: Experiments performed
5 on a Finnigan AQA single quadrupole mass spectrometer linked to a Hewlett Packard 1050 LC system with UV diode array detector and autosampler. The spectrometer has an electrospray source operating in positive ion mode. Additional detection is achieved using a Sedex 65 evaporative light scattering detector. This system uses an Luna 3micron C18(2) 30 x 4.6mm column at ambient temperature, and a 2.0 ml / minute flow rate. The initial solvent system was
10 95% water containing 0.1% formic acid (solvent A) and 5% acetonitrile containing 0.1% formic acid (solvent B) for the first 0.5 minute followed by a gradient up to 5% solvent A and 95% solvent B over the next 4.0 minutes. This was maintained for 1.0 minute before returning to 95% solvent A and 5% solvent B over the next 0.5 minute. Total run time was 6 minutes.

LCMS Method C:

15 run time - 10 min

HPLC-Agilent 1200

Mobile phase A: Water with 0.05%TFA

Mobile phase B: Acetonitrile with 0.05%TFA

Column: Agilent ZORBAX SD-C18, 1.8um, 2.1*30mm

20 Column temperature: 40 °C

LC gradient: 3-95%B in 8.5 min, 95% in 2.5 min

LC Flowrate: 400uL/min

UV wavelength: 220nm and 254nm

Mass Spec - Agilent quadrupole 6140, Ionization: ESI positive, Scan range 110-800amu

25 Reverse Phase High Pressure Liquid Chromatography (HPLC) was used to purify compounds where indicated. Separation using gradient elution on a Phenomenex Gemini C18

column (250 x 21.2 mm, 5 micron) as stationary phase and using mobile phase indicated, operating at a 18 ml/min flow rate using a Gilson UV/Vis -155 dual channel detector and Gilson GX-271 automated liquid handler.

Microwave experiments were carried out using a Biotage Initiator 2.0 (400 W magnetron)TM which uses a single-mode resonator and dynamic field tuning. Temperature from 5 40-250°C can be achieved, and pressures of up to 20 bar can be reached.

BIOLOGICAL EXAMPLES

Previous studies have shown that the isolated kinase domains of human JAK1, JAK2, JAK3 or TYK2 phosphorylate peptide substrates in *in vitro* kinase assays (Saltzman et al., 10 Biochem. Biophys. Res. Commun. 246:627-633 (2004)). The catalytically active kinase domain of human JAK1, JAK2, JAK3 or TYK2 was purified from extracts of SF9 insect cells infected with a recombinant baculovirus expression vector encoding the human JAK1, JAK2, JAK3 or TYK2 kinase domains (JAK1 amino acid residues N852-D1154 according to the numbering of GenBank sequence accession number P23458, JAK2 amino acid residues D812-G1132 15 according to the numbering of GenBank sequence accession number NP_004963.1; JAK3 amino acid residues S783-S1124 according to the numbering of GenBank sequence accession number P52333, and TYK2 amino acid residues N873-C1187 according to the numbering of GenBank sequence accession number P29597). The activity of the JAK1, JAK2, JAK3 or TYK2 kinase domains can be measured by a number of direct and indirect methods, including quantification of 20 phosphorylation of peptide substrates derived from the human JAK3 protein (Saltzman et al., Biochem. Biophys. Res. Commun. 246:627-633 (2004)). The activity of the JAK1, JAK2, JAK3 or TYK2 kinase domains was measured in vitro by monitoring phosphorylation of JAK3 derived peptides using the Caliper LabChip technology.

Example A

25 JAK1, JAK2 and TYK2 Inhibition Assay Protocol

The activity of the isolated JAK1, JAK2 or TYK2 kinase domain was measured by monitoring phosphorylation of a peptide derived from JAK3 (Val-Ala-Leu-Val-Asp-Gly-Tyr-Phe-Arg-Leu-Thr-Thr) fluorescently labeled on the N-terminus with 5-carboxyfluorescein using

the Caliper LabChip technology (Caliper Life Sciences, Hopkinton, MA). To determine the inhibition constants (Ki), compounds were diluted serially in DMSO and added to 50 uL kinase reactions containing 1.5 nM JAK1, 0.2 nM purified JAK2 or 1 nM purified TYK2 enzyme, 100 mM Hepes pH7.2, 0.015% Brij-35, 1.5µM peptide substrate, 25 µM ATP, 10 mM MgCl₂, 4 mM DTT at a final DMSO concentration of 2%. Reactions were incubated at 22 °C in 384-well polypropylene microtiter plates for 30 minutes and then stopped by addition of 25 uL of an EDTA containing solution (100 mM Hepes pH 7.2, 0.015% Brij-35, 150 mM EDTA), resulting in a final EDTA concentration of 50 mM. After termination of the kinase reaction, the proportion of phosphorylated product was determined as a fraction of total peptide substrate using the Caliper LabChip 3000 according to the manufacturer's specifications. Ki values were then determined using the Morrison tight binding model. Morrison, J.F., *Biochim. Biophys. Acta.* 185:269-296 (1969); William, J.W. and Morrison, J.F., *Meth. Enzymol.*, 63:437-467 (1979).

EXAMPLE B

JAK3 Inhibition Assay Protocol

The activity of the isolated JAK3 kinase domain was measured by monitoring phosphorylation of a peptide derived from JAK3 (Leu-Pro-Leu-Asp-Lys-Asp-Tyr-Tyr-Val-Val-Arg) fluorescently labeled on the N-terminus with 5-carboxyfluorescein using the Caliper LabChip technology (Caliper Life Sciences, Hopkinton, MA). To determine the inhibition constants (Ki), compounds were diluted serially in DMSO and added to 50 uL kinase reactions containing 5 nM purified JAK3 enzyme, 100 mM Hepes pH7.2, 0.015% Brij-35, 1.5 µM peptide substrate, 5 µM ATP, 10 mM MgCl₂, 4 mM DTT at a final DMSO concentration of 2%. Reactions were incubated at 22 °C in 384-well polypropylene microtiter plates for 30 minutes and then stopped by addition of 25 uL of an EDTA containing solution (100 mM Hepes pH 7.2, 0.015% Brij-35, 150 mM EDTA), resulting in a final EDTA concentration of 50 mM. After termination of the kinase reaction, the proportion of phosphorylated product was determined as a fraction of total peptide substrate using the Caliper LabChip 3000 according to the manufacturer's specifications. Ki values were then determined using the Morrison tight binding model. Morrison, J.F., *Biochim. Biophys. Acta.* 185:269-296 (1969); William, J.W. and Morrison, J.F., *Meth. Enzymol.*, 63:437-467 (1979).

Example C

Cell-based Pharmacology Assays

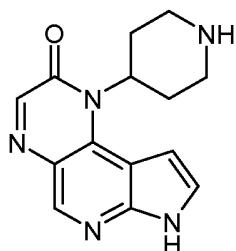
The activities of compounds were determined in cell-based assays that are designed to measure TYK2- dependent signaling. Compounds were serially diluted in DMSO and incubated 5 with NK92 cells (American Type Culture Collection (ATCC); Manassas, VA) in 384-well microtiter plates in RPMI medium at a final cell density of 50,000 cells per well and a final DMSO concentration of 0.2%. Human recombinant IL-12 (R&D systems; Minneapolis, MN) was then added at a final concentration of 30ng/ml to the microtiter plates containing the NK92 cells and compound and the plates were incubated for 45 min at 37oC. Compound-mediated 10 effects on STAT4 phosphorylation were then measured in the lysates of incubated cells using the Meso Scale Discovery (MSD) technology (Gaithersburg, Maryland) according to the manufacturer's protocol and EC50 values were determined.

The activities of compounds were determined in cell-based assays that are designed to measure JAK1 or JAK2- dependent signaling. Compounds were serially diluted in DMSO and 15 incubated with TF-1 cells (American Type Culture Collection (ATCC); Manassas, VA) in 384-well microtiter plates in OptiMEM medium without phenol red, 1% Charcoal/Dextran stripped FBS, 0.1 mM NEAA, 1mM sodium pyruvate (Invitrogen Corp.; Carlsbad, CA) at a final cell density of 100,000 cells per well and a final DMSO concentration of 0.2%. Human recombinant IL-6 (R&D systems; Minneapolis, MN) or EPO (Invitrogen Corp.; Carlsbad, CA) was then 20 added at a final concentration of 30 ng/ml or 10 Units/ml, respectively, to the microtiter plates containing the TF-1 cells and compound and the plates were incubated for 30 min at 37oC. Compound-mediated effects on STAT3 or STAT5 phosphorylation were then measured in the lysates of cells incubated in the presence of IL-6 or EPO, respectively, using the Meso Scale Discovery (MSD) technology (Gaithersburg, Maryland) according to the manufacturer's protocol 25 and EC50 values were determined.

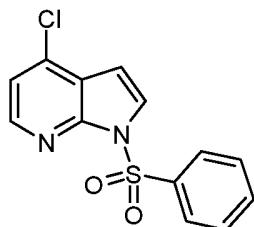
The compounds of Examples 1-56 and 58 were tested for their capacity to inhibit JAK1 kinase activity. The compounds of Examples 1-56 and 58 were found to have a K_i of about 1 μ M or less in a JAK1 kinase activity assay (Example A).

PREPARATIVE EXAMPLES

Example 1



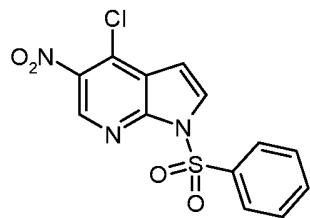
9-Piperidin-4-yl-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-8-one



5

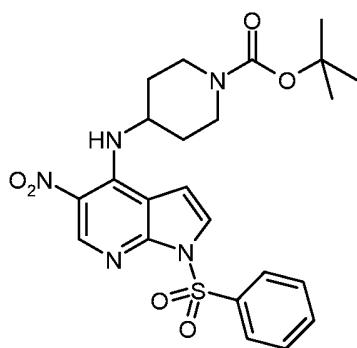
1-Benzenesulfonyl-4-chloro-1H-pyrrolo[2,3-b]pyridine

A stirred suspension of 4-chloro-7-azaindole (1.00 g, 6.55 mmol) in DCM (50 ml) was treated with 4-(dimethylamino)pyridine (80.0 mg, 0.66 mmol), triethylamine (1.36 ml, 9.83 mmol) and benzenesulfonyl chloride (0.93 ml, 7.21 mmol) at ambient temperature. The mixture 10 was left to stand overnight and then diluted with DCM and washed with 1M aqueous HCl solution, saturated sodium hydrogen carbonate solution, water, and brine, dried with sodium sulfate and concentrated under vacuum to give a brown solid. Trituration (diethyl ether) afforded 1.59 g (83%) of 1-benzenesulfonyl-4-chloro-1H-pyrrolo[2,3-b]pyridine as a beige solid. LCMS (Method B, ESI): RT = 4.48 min, m+H = 293.3; ¹H NMR (400MHz, CDCl₃) δ: 8.31 (1 H, d), 8.18 (2H, m), 7.78 (1H, m), 7.62-7.56 (1 H, m), 7.52-7.45 (2 H, m), 7.20 (1 H, m), 6.72 (1 H, m).



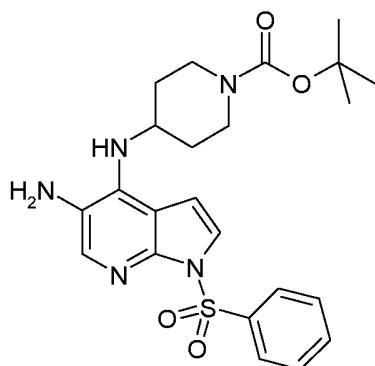
1-Benzenesulfonyl-4-chloro-5-nitro-1H-pyrrolo[2,3-b]pyridine

Tetrabutylammonium nitrate (381 mg, 1.25 mmol) dissolved in DCM (5 ml) was added dropwise to a stirred solution of 1-benzenesulfonyl-4-chloro-1H-pyrrolo[2,3-b]pyridine (293 mg, 1.00 mmol) in DCM (5 ml) at -5 °C. Trifluoroacetic anhydride (180 µl, 1.29 mmol) was added whilst maintaining the reaction temperature below 0 °C. The mixture was then stirred at -5 °C for 30 minutes and ambient temperature for 5 hours. TLC indicated incomplete reaction, therefore 0.25 eq of tetrabutylammonium nitrate and trifluoroacetic anhydride were added and the resulting mixture left to stand for 18 h at ambient temperature. DCM was added and the mixture washed with water, dried with sodium sulfate and concentrated under vacuum to give a yellow solid. Purification by column chromatography on silica gel (gradient: 0 to 25% ethyl acetate in cyclohexane) gave 266 mg (79%) of 1-benzenesulfonyl-4-chloro-5-nitro-1H-pyrrolo[2,3-b]pyridine as a white solid. LCMS (Method B, ESI): RT = 4.57 min, m+H = 338.4; ¹H NMR (400MHz, CDCl₃) δ: 9.00 (1 H, s), 8.23-8.17 (2 H, m), 7.94 (1 H, dd), 7.68-7.62 (1 H, m), 7.58-7.52 (2 H, m), 6.88-6.85 (1 H, m).



4-(1-Benzenesulphonyl-5-nitro-1H-pyrrolo[2,3-b]pyridine-4ylamino)-piperidine-1-carboxylic acid tert-butyl ester

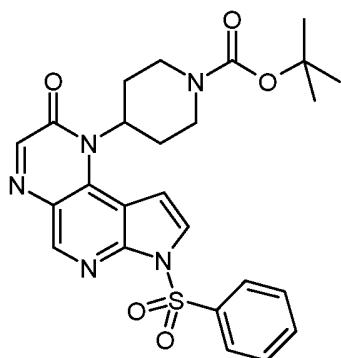
A stirred solution of 1-benzenesulphonyl-4-chloro-5-nitro-1H-pyrrolo[2,3-b]pyridine (7.90 g, 23.4 mmol), 1-Boc-4-aminopiperidine (5.15 g, 25.7 mmol), diisopropylethylamine (5.50 mL, 32.1 mmol) in propan-2-ol (80 mL) was heated to reflux for two hours. After cooling, the mixture was concentrated to dryness under vacuum. The resulting residue was partitioned 5 between DCM and 1M aqueous HCl, the organic layer was washed with water, brine, dried with sodium sulphate and concentrated under vacuum. The residue was triturated (diethyl ether), filtered and air dried to afford 11.6 g (Quantitative) of 4-(1-benzenesulphonyl-5-nitro-1H-pyrrolo[2,3-b]pyridine-4ylamino)-piperidine-1-carboxylic acid tert-butyl ester as a yellow solid.
¹H NMR (400MHz, CDCl₃) δ: 9.12 (1 H, br d), 9.09 (1 H, s), 8.21-8.19 (2 H, m), 7.66-7.61 (2 H, m), 7.53 (2 H, t), 6.69 (1 H, d), 4.14-4.12 (1 H, m), 4.01 (2 H, d), 3.12 (2 H, t), 2.11-2.08 (2 H, m), 1.65-1.64 (2 H, m), 1.48 (9 H, s).



4-(5-Amino-1-benzenesulphonyl-1H-pyrrolo[2,3-b]pyridine-4ylamino)-piperidine-1-carboxylic acid tert-butyl ester

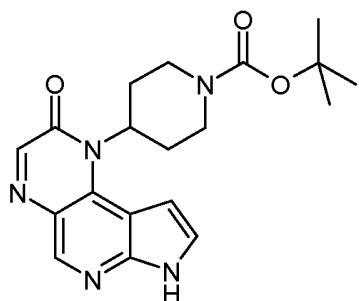
Palladium hydroxide (20 wt% on carbon, 2.20 g, 4.13 mmol) was added to a solution of 4-(1-benzenesulphonyl-5-nitro-1H-pyrrolo[2,3-b]pyridine-4ylamino)-piperidine-1-carboxylic acid tert-butyl ester (22.0 g, 43.9 mmol) in acetic acid (220 mL) under nitrogen. The reaction vessel was evacuated and purged with hydrogen and then warmed to 50 °C for 24 hours. After cooling, the mixture was filtered through Celite® and the filtrate concentrated to dryness under vacuum. The resulting residue was partitioned between DCM and sodium hydrogen carbonate (sat.aq.), the organic layer was dried with sodium sulphate and concentrated under vacuum. The residue was triturated (methanol), washed with diethyl ether and air dried to afford 16.9 g (82%) of
of 4-(5-amino-1-benzenesulphonyl-1H-pyrrolo[2,3-b]pyridine-4ylamino)-piperidine-1-

carboxylic acid tert-butyl ester. ^1H NMR (400MHz, CDCl_3) δ : 8.14 (2 H, dd), 7.85 (1 H, s), 7.54-7.54 (1 H, m), 7.49 (1 H, d), 7.45-7.44 (2 H, m), 6.52 (1 H, d), 4.80 (1 H, br s), 4.05 (2 H, s), 3.86 (1 H, m), 2.97 (2 H, t), 2.61 (2 H, m), 2.03 (2 H, d), 1.46 (9 H, s).



- 5 4-(3-Benzenesulphonyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-
piperidine-1-carboxylic acid tert-butyl ester

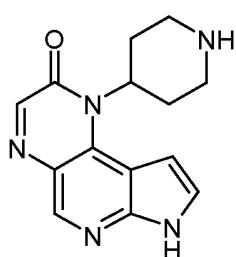
Glyoxylic acid mono hydrate (0.20 g, 2.12 mmol) was added to a suspension of 4-(5-amino-1-benzenesulphonyl-1H-pyrrolo[2,3-b]pyridine-4ylamino)-piperidine-1-carboxylic acid tert-butyl ester (1.00 g, 2.12 mmol) in THF (14 mL) and stirred under argon for 30 mins. 10 Diisopropylethylamine (728 μL , 4.25 mmol) and HATU (0.89 g, 2.31 mmol) were added and stirred for 2 hours. The mixture was concentrated under vacuum and the resulting residue passed through a silica gel column (eluting: 0 to 10% methanol in DCM) to afford crude 4-(3-benzenesulphonyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-piperidine-1-carboxylic acid tert-butyl ester as a yellow solid. LCMS (Method B, ESI): RT = 15 4.15 min, $m+\text{H} = 510$.



4-(8-Oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-piperidine-1-carboxylic acid tert-butyl ester

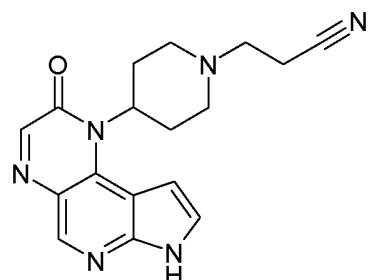
Sodium hydroxide (1M in water, 15 mL) was added to a suspension of crude 4-(3-benzenesulphonyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-piperidine-1-carboxylic acid tert-butyl ester (assumed to be 2.12 mmol) in methanol (10 mL) and stirred for 18 hours. THF (10 mL) was added and the mixture stirred for an additional 2 hours. The mixture was partially concentrated under vacuum, the resulting solid was filtered and washed with methanol affording 0.30 g (38%) of 4-(8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-piperidine-1-carboxylic acid tert-butyl ester as a white solid.

LCMS (Method B, ESI): RT = 3.26 min, m+H = 370; ¹H NMR (400MHz, DMSO-*d*₆) δ: 8.60 (1 H, s), 7.98 (1 H, s), 7.60 (1 H, d), 6.83 (1 H, d), 5.09 (1 H, m), 4.12 (2 H, m), 3.00 (2 H, m), 2.78-2.66 (2 H, m), 1.82 (2 H, d), 1.44 (9 H, s).



9-Piperidin-4-yl-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-8-one

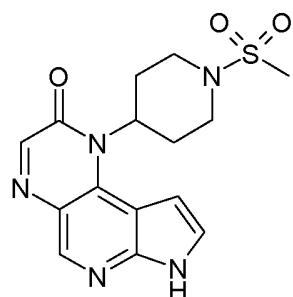
A suspension of 4-(8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-piperidine-1-carboxylic acid tert-butyl ester (0.29 g, 0.78 mmol) in 4M HCl in dioxane (4 mL) was stirred for 30 minutes, before 1.25M HCl in methanol (5 mL) was added and stirred for an additional 2 hours. Diethyl ether was added and the solid was isolated by filtration and washed with diethyl ether. The resulting solid was purified by HPLC (gradient: 5 to 50% acetonitrile in water with 0.1% ammonium hydroxide) to afford 9-piperidin-4-yl-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-8-one as a white solid. LCMS (Method A, ESI): RT = 1.62 min, m+H = 270.09; ¹H NMR (400MHz, DMSO-*d*₆) δ: 12.34 (1 H, br s), 8.61 (1 H, s), 8.01 (1 H, s), 7.62 (1 H, d), 6.77 (1 H, s), 4.93 (1 H, m), 3.12 (2 H, d), 2.75-2.74 (2 H, m), 2.66-2.64 (2 H, m), 1.74 (2 H, d).

Example 2

3-[4-(8-Oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-piperidin-1-yl]-propionitrile

5 Acrylonitrile (25.0 μ L, 0.31 mmol) was added to a suspension of 9-piperidin-4-yl-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-8-one (85.0 mg, 0.31 mmol) in propan-2-ol (2 mL) and heated to 75 °C for 1.5 hours. After cooling, water was added and the resulting solid isolated by filtration, washed with water and diethyl ether, and air dried to afford 27.0 mg (27 %) of 3-[4-(8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-piperidin-1-yl]-propionitrile as a white solid. LCMS (Method A, ESI): RT = 1.72 min, m+H = 323.10; 1 H NMR (400MHz, DMSO-*d*₆) δ : 12.36 (1 H, br s), 8.63 (1 H, s), 8.03 (1 H, s), 7.63 (1 H, d), 6.77 (1 H, s), 4.88 (1 H, m), 3.09 (2 H, d), 2.91-2.88 (2 H, m), 2.73-2.72 (2 H, m), 2.67 (2 H, t), 2.26 (2 H, t), 1.80 (2 H, d).

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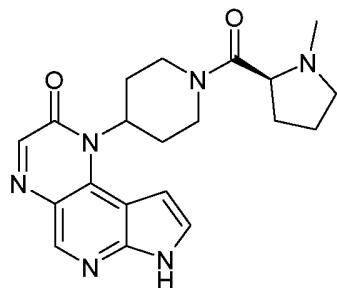
Example 3

15

9-(1-Methylsulphonyl-piperidin-4-yl)-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-8-one

Methanesulfonyl chloride (17.0 μ L, 0.22 mmol) was added to a suspension of 9-piperidin-4-yl-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-8-one (57.0 mg, 0.21 mmol) and triethylamine (60.0 μ L, 0.43 mmol) in THF (2 mL) and stirred under argon for 5 hours. Additional methanesulfonyl chloride (0.22 mmol) in DMF (0.5 mL) was added and stirred 5 for 18 hours. The resulting suspension was filtered and the isolated solid washed with diethyl ether and water then air dried to give 40.4 mg (55%) 9-(1-methylsulphonyl-piperidin-4-yl)-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-8-one as a white solid. LCMS (Method A, ESI): RT = 2.81 min, m+H = 348.07; 1 H NMR (400MHz, DMSO-*d*₆) δ : 12.37 (1 H, br s), 8.62 (1 H, s), 8.02 (1 H, s), 7.62 (1 H, t), 6.86 (1 H, s), 5.02 (1 H, m), 3.74 (2 H, d), 3.06 (2 H, t), 2.95 (3 H, s), 2.89-2.88 (2 H, m), 1.94 (2 H, d).

Example 4

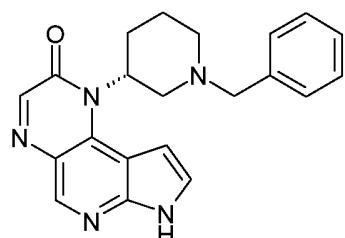


9-[1-((S)-1-Methyl-pyrrolidine-2-carbonyl)-piperidin-4-yl]-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-8-one

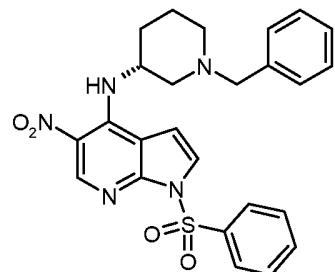
15 HATU (116 mg, 0.30 mmol) was added to a mixture of 9-piperidin-4-yl-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-8-one (75.0 mg, 0.27 mmol), N-methyl-l-proline (36.0 mg, 0.28 mmol) and diisopropylethylamine (95.0 μ L, 0.55 mmol) in DMF (2 mL) and stirred under argon for 3 hours. Methanol was added and the resulting suspension was filtered and the isolated solid was air dried. Purification by HPLC (gradient: 5 to 60% acetonitrile in water with 20 0.1% ammonium hydroxide) gave 9-[1-((S)-1-methyl-pyrrolidine-2-carbonyl)-piperidin-4-yl]-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-8-one as a white solid. LCMS (Method A, ESI): RT = 1.96 min, m+H = 381.16; 1 H NMR (400MHz, DMSO-*d*₆) δ : 12.34 (1 H, br s), 8.60 (1 H, s), 7.97 (1 H, s), 7.60 (1 H, d), 6.85 (1 H, d), 5.13 (1 H, m), 4.58 (1 H, d), 4.42 (1 H,

m), 3.30-3.08 (2 H, m), 2.96 (1 H, t), 2.76 (2 H, m), 2.64 (1 H, m), 2.24 (3 H, s), 2.19 - 2.07 (2 H, m), 1.85 (2 H, m), 1.73 (3 H, m).

Example 5

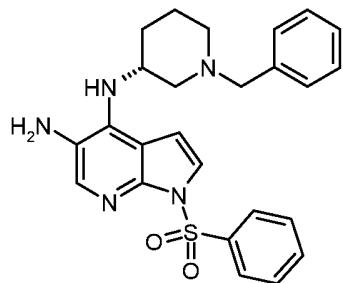


5 9-(R)-1-Benzyl-piperidin-3-yl)-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-8-one



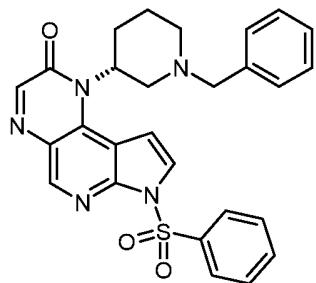
(1-Benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-yl)-((R)-1-benzyl-piperidin-3-yl)amine

A mixture of 1-benzenesulfonyl-4-chloro-5-nitro-1H-pyrrolo[2,3-b]pyridine (260 mg, 0.77 mmol), (R)-1-benzyl-3-aminopiperidine (175 mg, 0.92 mmol), diisopropylethylamine (197 µl, 1.16 mmol) in propan-2-ol (5 ml) was heated in a microwave reactor at 120 °C for 10 minutes. The mixture was diluted with DCM and then purified by column chromatography on silica gel (gradient: 0 to 40% ethyl acetate in cyclohexane) affording 429 mg of (1-benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-yl)-((R)-1-benzyl-piperidin-3-yl)amine as an orange residue which was used for the next step without further purification. LCMS (Method B, ESI): RT = 3.58 min, m+H = 492.5; ¹H NMR (400MHz, CDCl₃) δ: 9.53 (1 H, br s), 9.10 (1 H, s), 8.19-8.15 (2 H, m), 7.69-7.33 (9 H, m), 6.68-6.61 (1 H, m), 4.24-4.15 (1 H, br m), 3.54 (2 H, s), 2.77-2.27 (4 H, br m), 1.88-1.74 (3 H, br m), 1.69-1.52 (1 H, br m).



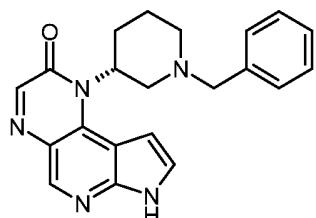
1-Benzenesulfonyl-N*4*-((R)-1-benzyl-piperidin-3-yl)-1H-pyrrolo[2,3-b]pyridine-4,5-diamine

A mixture of (1-benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-yl)-((R)-1-benzyl-piperidin-3-yl)amine (assumed to be 0.77 mmol), iron powder (129 mg, 2.31 mmol) and 5 ammonium chloride (206 mg, 3.85 mmol) in ethanol/water (8 ml, 3 : 1) was heated to reflux for 4 hours. After cooling, the mixture was filtered through Celite®, thoroughly washing the filter cake with ethanol. The filtrate and washings were combined and concentrated under vacuum. The resulting residue was partitioned between ethyl acetate and water, and the organic layer dried with sodium sulfate and concentrated under vacuum. Purification by column 10 chromatography on silica gel (gradient: 0 to 10% methanol in DCM) gave a brown residue which was re-purified by column chromatography on silica gel (gradient: 0 to 5% methanol in ethyl acetate) affording 303 mg (84%) of 1-benzenesulfonyl-N*4*-((R)-1-benzyl-piperidin-3-yl)-1H-pyrrolo[2,3-b]pyridine-4,5-diamine as an orange/brown residue. LCMS (Method B, ESI): RT = 2.48 - 2.68 min, $m+\text{H} = 462.6$; ^1H NMR (400MHz, CDCl_3) δ : 8.12-8.08 (2 H, m), 7.79 (1 H, s), 15 7.55-7.49 (1 H, m), 7.46-7.38 (3 H, m), 7.37-7.22 (5 H, m), 6.47 (1 H, s), 5.32-5.26 (1 H, br m), 4.00-3.87 (1 H, br m), 3.58-3.46 (2 H, br m), 2.94-2.28 (6 H, br m), 1.82-1.67 (2 H, br m).



3-Benzenesulphonyl-9-(R)-1-benzyl-piperidin-3-yl)-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-8-one

Following the procedure for 4-(3-benzenesulphonyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-piperidine-1-carboxylic acid tert-butyl ester the title compound was prepared from 1-benzenesulfonyl-N*4*-((R)-1-benzyl-piperidin-3-yl)-1H-pyrrolo[2,3-b]pyridine-4,5-diamine with further purification by column chromatography on silica gel (gradient: 0 to 100% DCM in cyclohexane then 5% methanol in DCM) to afford 3-benzenesulphonyl-9-(R)-1-benzyl-piperidin-3-yl)-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-8-one as a yellow solid. LCMS (Method B, ESI): RT = 2.63 min, m+H = 500.17.

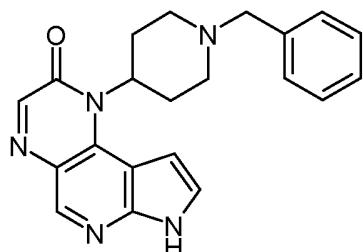


9-(R)-1-Benzyl-piperidin-3-yl)-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-8-one

Following the procedure for 4-(8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-piperidine-1-carboxylic acid tert-butyl ester the title compound was prepared from 3-benzenesulphonyl-9-(R)-1-benzyl-piperidin-3-yl)-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-8-one to afford 9-(R)-1-benzyl-piperidin-3-yl)-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-8-one as a yellow solid. LCMS (Method A, ESI): RT = 2.49 min, m+H = 360.07; ¹H NMR (400MHz, DMSO-d₆) δ: 12.25 (1H, br s), 8.57 (1 H, s),

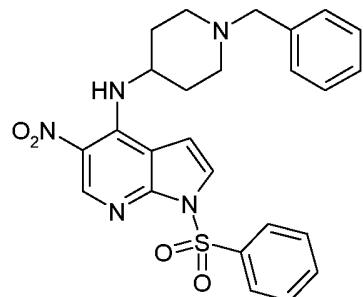
7.97 (1 H, s), 7.58 (1 H, d), 7.36 (2 H, d), 7.30 (2 H, t), 7.20 (1 H, t), 6.72 (1 H, d), 4.96 (1 H, m), 3.69 (1 H, d), 3.48 (1 H, d), 2.95-2.93 (3 H, m), 2.76 (1 H, m), 2.10 (1 H, t), 1.82 (2 H, s), 1.67 (1 H, d).

Example 6



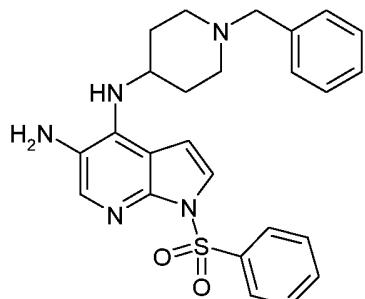
5

9-(1-Benzyl-piperidin-4-yl)-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-8-one



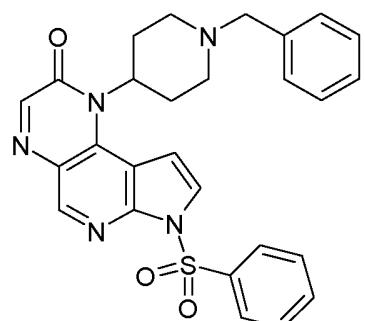
(1-Benzenesulphonyl-5-nitro-1H-pyrrolo[2,3-b]pyridine-4-yl)-(1-benzyl-piperidin-4-yl)-amine

Following the procedure for (1-benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-yl)-((R)-1-benzyl-piperidin-3-yl)amine the title compound was prepared using 1-benzenesulphonyl-4-chloro-5-nitro-1H-pyrrolo[2,3-b]pyridine and 4-amino-1-benzyl piperidine to afford (1-benzenesulphonyl-5-nitro-1H-pyrrolo[2,3-b]pyridine-4-yl)-(1-benzyl-piperidin-4-yl)-amine as a yellow foam. ^1H NMR (400MHz, CDCl_3) δ : 9.11 (1 H, s), 8.19 (2 H, dd), 7.62-7.60 (2 H, m), 7.52 (3 H, t), 7.33 (4 H, m), 6.70 (1 H, d), 4.01 (1 H, s), 3.57 (2 H, s), 2.85 (2 H, s), 2.31 (2 H, s), 2.10 (2 H, s), 1.79 (2 H, s).



1-Benzenesulphonyl-N*4*-(1-benzyl-piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridine-4,5-diamine

Following the procedure for 1-benzenesulfonyl-N*4*-(R)-1-benzyl-piperidin-3-yl)-1H-pyrrolo[2,3-b]pyridine-4,5-diamine the title compound was prepared using (1-benzenesulphonyl-5-nitro-1H-pyrrolo[2,3-b]pyridine-4-yl)-(1-benzyl-piperidin-4-yl)-amine to afford 1-benzenesulphonyl-N*4*-(1-benzyl-piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridine-4,5-diamine as brown foam. LCMS (Method B, ESI): RT = 2.63 min, m+H = 462.33; ¹H NMR (400MHz, CDCl₃) δ: 8.12 (2 H, d), 7.81 (1 H, s), 7.53 (1 H, t), 7.48-7.41 (5 H, m), 7.35 (3 H, m), 6.47 (1 H, d), 4.80 (1 H, br, s), 3.80 (3 H, m), 3.10 (2 H, m), 2.49 (2 H, m), 2.12 (2 H, m), 1.87 (2H, m).

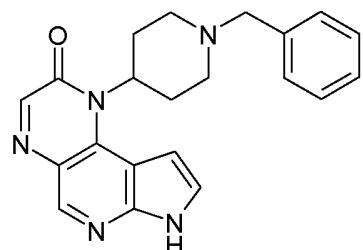


10

3-Benzenesulphonyl-9-(1-benzyl-piperidin-4-yl)-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-8-one

Following the procedure for 4-(3-benzenesulphonyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-piperidine-1-carboxylic acid tert-butyl ester the title compound was prepared from 1-benzenesulphonyl-N*4*-(1-benzyl-piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridine-4,5-diamine to afford 3-benzenesulphonyl-9-(1-benzyl-piperidin-4-yl)-3,9-dihydro-

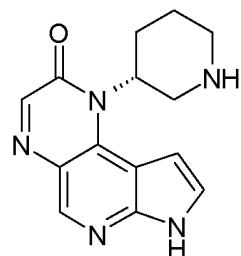
3,4,6,9-tetraaza-cyclopenta[a]naphthalene-8-one as a yellow solid. LCMS (Method B, ESI): RT = 2.61 min, m+H = 500.



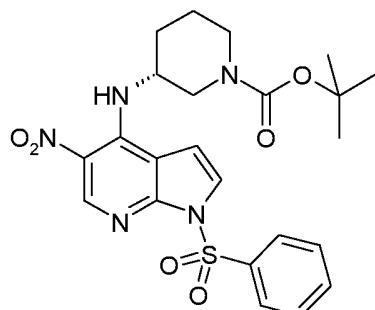
9-(1-Benzyl-piperidin-4-yl)-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-8-one

5 Following the procedure for 4-(8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-piperidine-1-carboxylic acid tert-butyl ester the title compound was prepared from 3-benzenesulphonyl-9-(1-benzyl-piperidin-4-yl)-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-8-one to afford 9-(1-benzyl-piperidin-4-yl)-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-8-one as a white solid. LCMS (Method A, ESI): RT = 2.43
10 min, m+H = 360.10; ¹H NMR (400MHz, DMSO-*d*₆) δ: 12.35 (1 H, br s), 8.61 (1 H, s), 8.01 (1 H, s), 7.62 (1 H, d), 7.36-7.33 (4 H, m), 7.26-7.25 (1 H, m), 6.74 (1 H, s), 4.88 (1 H, m), 3.55 (2 H, s), 3.00 (2 H, d), 2.92-2.88 (2 H, m), 2.18 (2 H, t), 1.78 (2 H, d).

Example 7

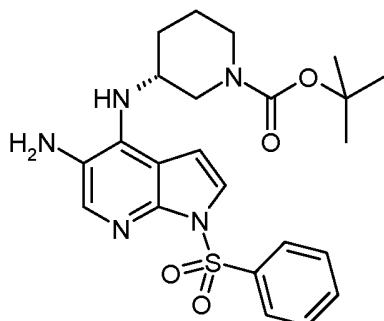


15 (R)-9-Piperidin-3-yl-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-8-one



(R)-3-(1-Benzenesulphonyl-5-nitro-1H-pyrrolo[2,3-b]pyridine-4-ylamino)-piperidine-1-carboxylic acid tert-butyl ester

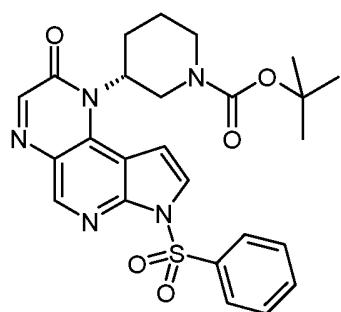
Following the procedure for 4-(1-benzenesulphonyl-5-nitro-1H-pyrrolo[2,3-b]pyridine-4-ylamino)-piperidine-1-carboxylic acid tert-butyl ester the title compound was prepared using 1-benzenesulphonyl-4-chloro-5-nitro-1H-pyrrolo[2,3-b]pyridine and (R)-1-Boc-3-aminopiperidine to afford 22.2 g (93%) of (R)-3-(1-benzenesulphonyl-5-nitro-1H-pyrrolo[2,3-b]pyridine-4-ylamino)-piperidine-1-carboxylic acid tert-butyl ester. ^1H NMR (400MHz, CDCl_3) δ : 8.24 (1 H, s), 8.21 (1 H, d), 7.31-7.31 (2 H, m), 6.77 (1 H, d), 6.74 (1 H, d), 6.64 (2 H, t), 6.02 (1H, br m), 3.17 (2 H, m), 2.79 (1 H, m), 2.37 (2 H, m), 1.24 (1 H, m), 0.92-0.89 (2 H, m), 0.75 (1 H, m), 0.56 (9 H, s).



(R)-3-(5-Amino-1-benzenesulphonyl-pyrrolo[2,3-b]pyridine-4-ylamino)-piperidine-1-carboxylic acid tert-butyl ester

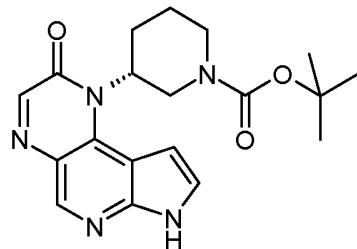
Following the procedure for 4-(5-Amino-1-benzenesulphonyl-1H-pyrrolo[2,3-b]pyridine-4-ylamino)-piperidine-1-carboxylic acid tert-butyl ester the title compound was prepared using (R)-3-(1-benzenesulphonyl-5-nitro-1H-pyrrolo[2,3-b]pyridine-4-ylamino)-piperidine-1-

carboxylic acid tert-butyl ester. Further purification by column chromatography on silica gel (ethyl acetate), then repurified by column chromatography on silica gel (gradient : 5 to 15% acetone in toluene) affording 15.8 g (75%) of (R)-3-(5-amino-1-benzenesulphonyl-pyrrolo[2,3-b]pyridine-4-ylamino)-piperidine-1-carboxylic acid tert-butyl ester. ^1H NMR (400MHz, CDCl_3) δ: 8.15-8.14 (2 H, m), 7.86 (1 H, s), 7.55-7.55 (1 H, m), 7.51 (1 H, d), 7.47-7.46 (2 H, m), 7.28-7.24 (1 H, m), 7.19-7.18 (1 H, m), 6.68 (1 H, br s), 4.94 (1 H, br d), 3.96 (1 H, dd), 3.85 (1 H, m), 3.65 (1 H, m), 3.18 (1 H, m), 2.82 (1 H, m), 2.04 (1 H, m), 1.76 (1 H, m), 1.65-1.54 (2 H, m), 1.42 (9 H, s).



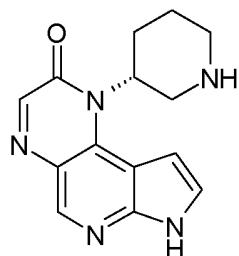
10 (R)-3-(3-Benzenesulphonyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidine-1-carboxylic acid tert-butyl ester

Following the procedure for 4-(3-benzenesulphonyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-piperidine-1-carboxylic acid tert-butyl ester the title compound was prepared using (R)-3-(5-amino-1-benzenesulphonyl-pyrrolo[2,3-b]pyridine-4-ylamino)-piperidine-1-carboxylic acid tert-butyl ester to afford (R)-3-(3-benzenesulphonyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidine-1-carboxylic acid tert-butyl ester. LCMS (Method B, ESI): RT = 4.26 min, $m+\text{H} = 510$.



(R)-3-(8-Oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-piperidine-1-carboxylic acid tert-butyl ester.

Following the procedure for 4-(8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-piperidine-1-carboxylic acid tert-butyl ester the title compound was prepared using (R)-3-(3-benzenesulphonyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-piperidine-1-carboxylic acid tert-butyl ester with additional purification by column chromatography on silica gel (gradient: 0 to 6% methanol in DCM) to provide (R)-3-(8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-piperidine-1-carboxylic acid tert-butyl ester. LCMS (Method B, ESI): RT = 3.32 min, m+H = 370.3.

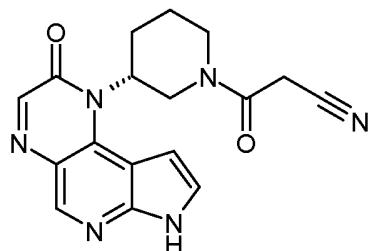


(R)-9-Piperidin-3-yl-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-8-one

Following the procedure for 9-piperidin-4-yl-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-8-one the title compound was prepared using (R)-3-(8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-piperidine-1-carboxylic acid tert-butyl ester to afford (R)-9-piperidin-3-yl-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-8-one as a white solid. LCMS (Method A, ESI): RT = 1.79 min, m+H = 270.18; ¹H NMR (400MHz, DMSO-d₆) δ: 12.34 (1 H, br s), 8.62 (1 H, s), 8.00 (1 H, s), 7.63 (1 H, d), 6.94 (1 H, d), 4.91 (1

H, d), 3.62 (1 H, t), 3.05 (1 H, d), 2.94 (1 H, d), 2.77 (1 H, m), 2.47 (1 H, m), 1.91 (1 H, d), 1.80 (1 H, d), 1.61-1.60 (1 H, m).

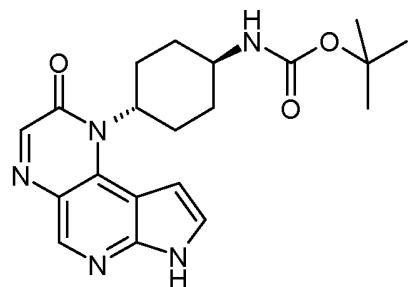
Example 8



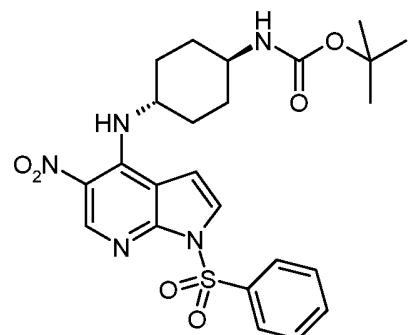
5 3-Oxo-3-[(R)-3-(8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-piperidine-1-yl]-propionitrile

HATU (57.0 mg, 0.15 mmol) was added to a suspension of (R)-9-piperidin-3-yl-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-8-one (37.0 mg, 0.14 mmol), cyanoacetic acid (12.0 mg, 0.14 mmol) and diisopropylethylamine (47.0 μ L, 0.27 mmol) in THF (3 mL) under argon and stirred for 18 hours. The mixture was concentrated to dryness under vacuum and the resulting residues purified by HPLC (gradient : 5 to 75% acetonitrile in water with 0.1% ammonium hydroxide) and further purified by SCX-2 column (eluting 2M ammonia in methanol) to give 5 mg (11%) of 3-oxo-3-[(R)-3-(8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-piperidine-1-yl]-propionitrile. LCMS (Method A, ESI): RT = 2.92 min, m+H = 337; 1 H NMR (400MHz, DMSO- d_6) δ : Rotamers: 12.36 (1 H, br s), 8.63 (1 H, d), 8.03 (1 H, d), 7.62 (1 H, dd), 6.72 (1 H, dd), 4.95-4.76 (1 H, m), 4.69-4.37 (1 H, m), 4.15-3.70 (4 H, multiple signals), 3.18-2.56 (2 H, multiple signals), 2.20-1.65 (3 H, multiple signals).

Example 9

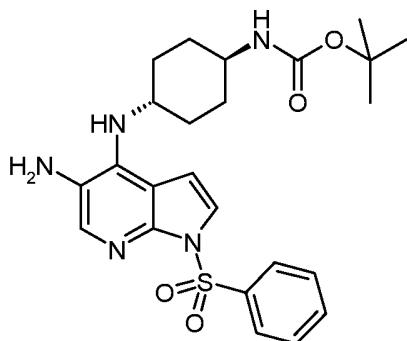


[4-(8-Oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-cyclohexyl]-carbamic acid tert-butyl ester



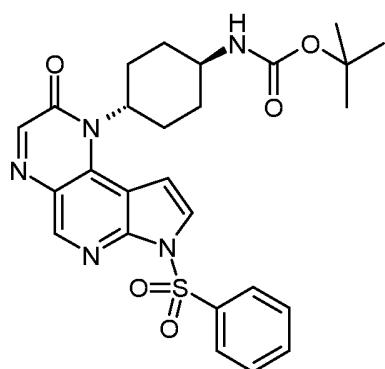
5 [4-(1-benzenesulphonyl-5-nitro-1H-pyrrolo[2,3-b]pyridine-4-ylamino)-cyclohexyl]-carbamic acid tert-butyl ester

Following the procedure for 4-(1-benzenesulphonyl-5-nitro-1H-pyrrolo[2,3-b]pyridine-4-ylamino)-piperidine-1-carboxylic acid tert-butyl ester the title compound was prepared using 1-benzenesulphonyl-4-chloro-5-nitro-1H-pyrrolo[2,3-b]pyridine and N-boc-trans-1,4-10 cyclohexanediamine to afford [4-(1-benzenesulphonyl-5-nitro-1H-pyrrolo[2,3-b]pyridine-4-ylamino)-cyclohexyl]-carbamic acid tert-butyl ester as a yellow solid. ¹H NMR (400MHz, CDCl₃) δ: 9.09 (1 H, s), 8.97 (1 H, d), 8.18 (2 H, dd), 7.61-7.58 (2 H, m), 7.51 (2 H, t), 6.66 (1 H, d), 4.41 (1 H, br s), 3.88-3.84 (1 H, m), 3.51 (1 H, br s), 2.18 (4 H, t), 1.54 (2 H, m), 1.45 (9H, s), 1.32 (2 H, m).



[4-(5-Amino-1-benzenesulphonyl-1H-pyrrolo[2,3-b]pyridine-4-ylamino)-cyclohexyl]-carbamic acid tert-butyl ester

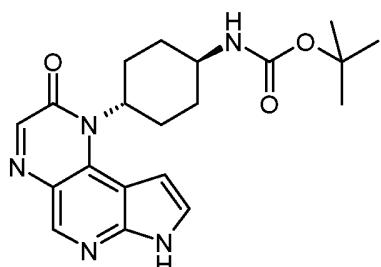
Following the procedure for 4-(5-amino-1-benzenesulphonyl-pyrrolo[2,3-b]pyridine-4-ylamino)-piperidine-1-carboxylic acid tert-butyl ester the title compound was prepared using [4-(1-benzenesulphonyl-5-nitro-1H-pyrrolo[2,3-b]pyridine-4-ylamino)-cyclohexyl]-carbamic acid tert-butyl ester to afford [4-(5-amino-1-benzenesulphonyl-1H-pyrrolo[2,3-b]pyridine-4-ylamino)-cyclohexyl]-carbamic acid tert-butyl ester as a purple solid. ^1H NMR (400MHz, CDCl_3) δ : 8.13-8.13 (2 H, m), 7.84 (1 H, s), 7.56-7.51 (1 H, m), 7.47 (2 H, d), 7.44 (1 H, d), 6.52 (1 H, d), 4.76 (1 H, br s), 4.42 (1 H, br s), 3.65 (1 H, br s), 3.49-3.46 (1 H, m), 2.13 (4 H, t), 1.45 (9 H, s), 1.30-1.26 (4 H, m).



[4-(3-Benzenesulphonyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-cyclohexyl]-carbamic acid tert-butyl ester

Following the procedure for 4-(3-benzenesulphonyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-piperidine-1-carboxylic acid tert-butyl ester the title compound

was prepared using [4-(5-amino-1-benzenesulphonyl-1H-pyrrolo[2,3-b]pyridine-4-ylamino)-cyclohexyl]-carbamic acid tert-butyl ester to afford [4-(3-benzenesulphonyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-cyclohexyl]-carbamic acid tert-butyl ester. LCMS (Method B, ESI): RT = 4.08 min, m+H = 524.



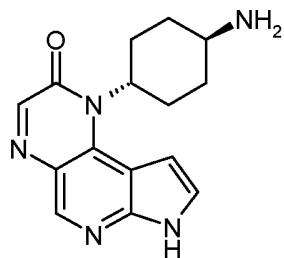
5

[4-(8-Oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-cyclohexyl]-carbamic acid tert-butyl ester

Following the procedure for 4-(8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-piperidine-1-carboxylic acid tert-butyl ester the title compound 10 was prepared using [4-(3-benzenesulphonyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-cyclohexyl]-carbamic acid tert-butyl. The crude reaction mixture was partially concentrated under vacuum and the resulting suspension was filtered and the solid washed with water and diethyl ether. The isolated solid was suspended in acetonitrile and water (1:1), filtered and air dried, then triturated (DCM with minimal methanol) and air dried to give 15 [4-(8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-cyclohexyl]-carbamic acid tert-butyl ester as a white solid. LCMS (Method A, ESI): RT = 8.64 min, m+H = 384.24; ¹H NMR (400MHz, DMSO-*d*₆) δ: 12.37 (1 H, br s), 8.62 (1 H, s), 8.01 (1 H, s), 7.66 (1 H, d), 6.80 (1 H, br d), 6.68 (1 H, d), 4.83 (1 H, t), 2.72 (2 H, q), 1.99 (2 H, d), 1.86 (2 H, d), 1.47-1.44 (3 H, m), 1.41 (9 H, s).

20

Example 10

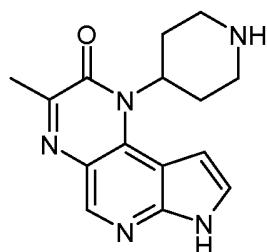


9-(4-Amino-cyclohexyl)-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-8-one

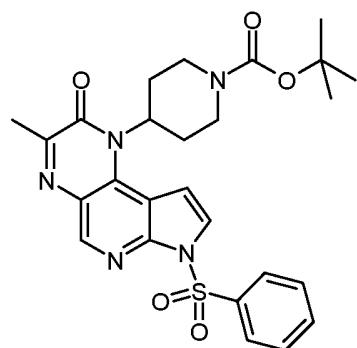
Following the procedure for 9-piperidin-4-yl-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-8-one the title compound was prepared using [4-(8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-cyclohexyl]-carbamic acid tert-butyl ester to afford 9-(4-amino-cyclohexyl)-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-8-one as a white solid. LCMS (Method A, ESI): RT = 3.83 min, m+H = 284.14; ¹H NMR (400MHz, DMSO-*d*₆) δ: 8.62 (1 H, s), 8.00 (1 H, s), 7.64 (1 H, d), 6.74 (1 H, d), 4.91-4.80 (1 H, m), 2.71-2.68 (3 H, m), 1.95 (2 H, d), 1.81 (2 H, d), 1.31-1.27 (2 H, m).

10

Example 11

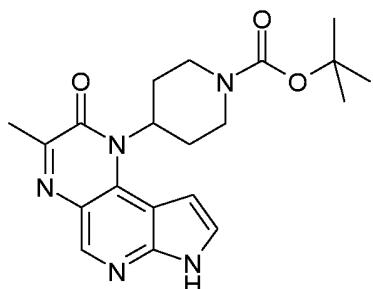


7-Methyl-9-piperidin-4-yl-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-8-one



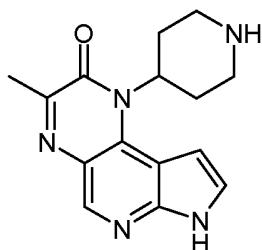
4-(3-Benzenesulphonyl-7-methyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-piperidine-1-carboxylic acid tert-butyl ester

Following the procedure for 4-(3-benzenesulphonyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-piperidine-1-carboxylic acid tert-butyl ester the title compound 5 was prepared using 4-(5-amino-1-benzenesulphonyl-1H-pyrrolo[2,3-b]pyridine-4ylamino)-piperidine-1-carboxylic acid tert-butyl ester and pyruvic acid with additional purification by column chromatography on silica gel (gradient: 0 to 5% methanol in DCM) to afford 4-(3-benzenesulphonyl-7-methyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-piperidine-1-carboxylic acid tert-butyl ester as a yellow solid. LCMS (Method B, ESI): RT = 10 4.25 min, m+H = 524.



4-(7-Methyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-piperidine-1-carboxylic acid tert-butyl ester

Following the procedure for 4-(8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-piperidine-1-carboxylic acid tert-butyl ester the title compound 15 was prepared using 4-(3-benzenesulphonyl-7-methyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-piperidine-1-carboxylic acid tert-butyl ester with additional purification by column chromatography on silica gel (gradient: 0 to 6% methanol in DCM) to afford 4-(7-methyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-piperidine-1-carboxylic acid tert-butyl ester as a yellow solid. LCMS (Method B, ESI): RT = 20 3.37 min, m+H = 384.

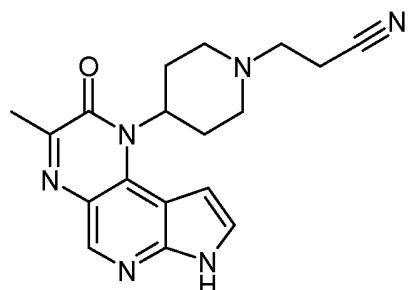


7-Methyl-9-piperidin-4-yl-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-8-one

Following the procedure for 9-piperidin-4-yl-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-8-one the title compound was prepared using 4-(7-methyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-piperidine-1-carboxylic acid tert-butyl ester to afford 7-methyl-9-piperidin-4-yl-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-8-one as a white solid. LCMS (Method A, ESI): RT = 1.78 min, m+H = 284.10; ¹H NMR (400MHz, DMSO-*d*₆) δ: 12.25 (1 H, br s), 8.56 (1 H, s), 7.59 (1 H, d), 6.75 (1 H, s), 4.93 (1 H, m), 3.13 (2 H, d), 2.77-2.74 (2 H, m), 2.66 (2 H, t), 2.41 (3 H, s), 1.73 (2 H, d).

10

Example 12



3-[4-(7-Methyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-piperidin-1-yl]-propionitrile

Following the procedure for 3-[4-(8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-piperidin-1-yl]-propionitrile the title compound was prepared using 7-methyl-9-piperidin-4-yl-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-8-one and acrylonitrile (1.5 eq) to afford 3-[4-(7-methyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-9-yl)-piperidin-1-yl]-propionitrile as a white solid. LCMS (Method A,

ESI): RT = 1.88 min, m+H = 337.09; ^1H NMR (400MHz, DMSO-*d*6) δ : 12.26 (1 H, br s), 8.56 (1 H, s), 7.60 (1 H, d), 6.73 (1 H, s), 4.88 (1 H, m), 3.09 (2 H, d), 2.96-2.85 (2 H, m), 2.74 (2 H, t), 2.68 (2 H, t), 2.41 (3 H, s), 2.26 (2 H, t), 1.78 (2 H, d).

The Examples shown in Table 1 were prepared generally following the above-described

- 5 Examples and making non-critical variations where necessary. The LCMS method used for each compound is indicated in the Method column.

Table 1

Example	Structure	Name	Method	RT/MS
13		[4-(8-Oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-cyclohexyl]-carbamic acid 2,2,2-trifluoro-ethyl ester	A	3.79/ 410.3
14		4,4,4-Trifluoro-N-[4-(8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-cyclohexyl]-butyramide	A	3.37/ 408.3
16		3-[4-(8-Oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidin-1-ylmethyl]-benzonitrile	A	2.35/ 385.2

17		3,3,3-Trifluoro-N-[4-(8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-cyclohexyl]-propionamide	A	3.17/ 394.3
18		[3-(7-Methyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-cyclopentyl]-carbamic acid methyl ester racemic, trans	A	3.06/ 342.3
19		6-[4-(8-Oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-cyclohexylamino]-nicotinonitrile	A	3.47/ 386.3
20		[4-(8-Oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-cyclohexyl]-carbamic acid ethyl ester	A	3.30/ 356.3
21		[4-(8-Oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-cyclohexyl]-carbamic acid cyclopropylmethyl ester	A	3.69/ 382.3

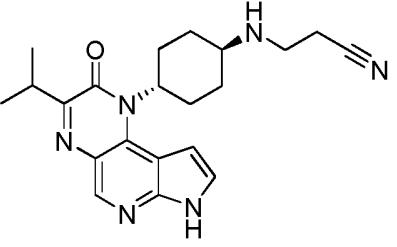
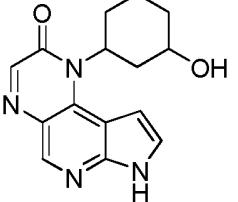
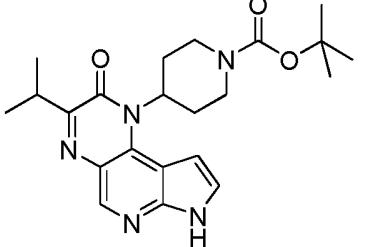
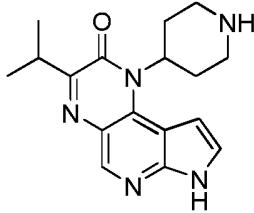
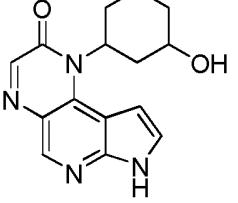
22		1-Methyl-3-[3-(8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-cyclopentyl]-1-(2,2,2-trifluoro-ethyl)-urea racemic, trans	A	3.31/ 409.1
23		3-[(R)-3-(7-Cyclopropyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidin-1-yl]-3-oxo-propionitrile	A	3.63/ 377.3
24		3-[4-(7-Methylamino-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidin-1-yl]-3-oxo-propionitrile	A	1.78/ 352.3
25		9-[1-(2,2,2-Trifluoro-ethyl)-piperidin-4-yl]-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-8-one	A	3.46/ 352.1
26		3-[4-(7-Cyclopropyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidin-1-yl]-3-oxo-propionitrile	A	2.43/ 363.3

28		3-Methoxy-N-[4-(8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-cyclohexyl]-propionamide	A	2.67/ 370.3
29		1-Methyl-3-[4-(8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-cyclohexyl]-1-(2,2,2-trifluoro-ethyl)-urea	A	3.43/ 423.1
30		N-[4-(8-Oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-cyclohexyl]-malonamic acid methyl ester	A	2.71/ 384.3
31		9-(1-Pyridin-3-ylmethyl-piperidin-4-yl)-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-8-one	A	1.82/ 361.2
32		[4-(7-Cyclopropyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-cyclohexyl]-carbamic acid tert-butyl ester	A	4.77/ 424.4

33		9-(3-Hydroxy-cyclohexyl)-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-8-one	C	3.11/ 285.0
34		3-[3-(7-Methyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-cyclopentylamino]-propionitrile	A	2.05/ 337.3
35		[4-(8-Oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-cyclohexyl]-carbamic acid methyl ester	A	3.02/ 342.2
36		[4-(8-Oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-cyclohexyl]-carbamic acid 2-methoxy-ethyl ester	A	3.04/ 386.3
37		3-[4-(8-Oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-cyclohexylamino]-propionitrile	A	1.96/ 337.2

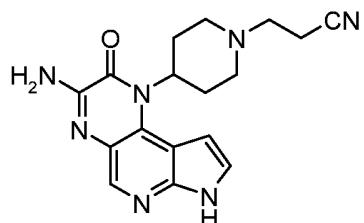
39		9-[4-(3,3,3-Trifluoropropylamino)-cyclohexyl]-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-8-one	A	2.36/ 380.2
40		N-[4-(7-Cyclopropyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-cyclohexyl]-3-methoxypropionamide	A	3.40/ 410.4
41		9-[1-(3,3,3-Trifluoropropyl)-piperidin-4-yl]-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-8-one	A	2.10/ 366.2
43		3-[4-(7-Cyclopropyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-cyclohexylamino]-propionitrile	A	2.63/ 377.3
44		N-[4-(8-Oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-cyclohexyl]-acetamide	A	2.53/ 326.2

46		3-[4-(7-Isopropyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidin-1-yl]-propionitrile	A	2.53/ 365.3
47		N-[4-(7-Cyclopropyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-cyclohexyl]-acetamide	A	3.26/ 366.4
48		3-{[4-(8-Oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-cyclohexylamino]-methyl}-benzonitrile	A	2.47/ 399.3
49		9-{4-[(Pyridin-3-ylmethyl)-amino]-cyclohexyl}-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-8-one	A	1.94/ 375.3
51		[4-(7-Isopropyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-cyclohexyl]-carbamic acid tert-butyl ester	A	5.00/ 426.4

52		3-[4-(7-Isopropyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-cyclohexylamino]-propionitrile	A	2.76/ 379.3
53	 Single stereoisomer, absolute stereochemistry unknown	9-(3-Hydroxy-cyclohexyl)-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-8-one	C	3.11/ 285.0
55		4-(7-Isopropyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidine-1-carboxylic acid tert-butyl ester	A	5.12/ 412.4
56		7-Isopropyl-9-piperidin-4-yl-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-8-one	A	2.44/ 313.8
57	 Single stereoisomer, absolute stereochemistry unknown	9-(3-Hydroxy-cyclohexyl)-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-8-one	C	3.28/ 285.0

58		4-(7-Cyclopropyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-cyclohexanecarbonitrile		
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Example 15



5 3-[4-(7-Amino-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidin-1-yl]-propionitrile

4-(3-Benzenesulfonyl-7,8-dioxo-3,6,7,8-tetrahydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidine-1-carboxylic acid tert-butyl ester

A solution of 4-(5-amino-1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-10 piperidine-1-carboxylic acid tert-butyl ester (2.50 g, 5.30 mmol) and triethylamine (1.10 mL, 8.00 mmol) in DCM (70 mL) was treated with ethyl chloro oxoacetate (710 μ L, 6.36 mmol) and stirred at ambient temperature for 1 hour. The mixture was diluted with DCM, washed (saturated sodium bicarbonate solution, water and brine), dried (sodium sulfate) and concentrated under vacuum to leave a yellow/ orange foam. This was taken up in toluene and heated at reflux for 70 hours. After cooling the resulting precipitate was collected, washed with toluene and diethyl ether and air dried to afford 2.20 g (79%) of 4-(3-benzenesulfonyl-7,8-dioxo-3,6,7,8-tetrahydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidine-1-carboxylic acid tert-butyl ester as an off-white solid. LCMS (Method B, ESI): RT = 3.56 min, m+H = 526.25; 1 H NMR (400MHz, DMSO- d_6) δ : 12.11 (br s, 1 H), 8.18 (s, 1 H), 8.12 (m, 2 H), 7.95 (d, 1 H), 7.72 (m, 1 H), 7.63

(m, 2 H), 6.86 (d, 1 H), 4.59 (m, 1 H), 4.07 (d, 2 H), 2.94 (s, 2 H), 2.55 (m, 2 H), 1.79 (d, 2 H), 1.43 (s, 9 H).

3-Benzenesulfonyl-9-piperidin-4-yl-6,9-dihydro-3H-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-7,8-dione

5 A solution of 4-(3-benzenesulfonyl-7,8-dioxo-3,6,7,8-tetrahydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidine-1-carboxylic acid tert-butyl ester (600 mg, 1.14 mmol) in DCM (5 mL) and trifluoroacetic acid (4 mL) was stirred at ambient temperature for 1 hour. The mixture was concentrated under vacuum to leave an off white solid. This was basified with ammonium hydroxide and the solid collected by filtration, washed with water and air dried to afford 514 mg (100%) of 3-benzenesulfonyl-9-piperidin-4-yl-6,9-dihydro-3H-3,4,6,9-tetraazacyclopenta[a]naphthalene-7,8-dione as an off-white solid. LCMS (Method B, ESI): RT = 1.97 and 2.14 min, m+H = 426.24; ¹H NMR (400MHz, DMSO-*d*₆) δ: 8.17 (s, 1 H), 8.12 (m, 2 H), 7.98 (d, 1 H), 7.72 (m, 1 H), 7.63 (m, 2 H), 6.81 (d, 1 H), 4.45 (m, 1 H), 3.25 (s, 1 H), 3.10 (d, 2 H), 2.62 (m, 4 H), 1.73 (d, 2 H).

10 15 3-[4-(3-Benzenesulfonyl-7,8-dioxo-3,6,7,8-tetrahydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidin-1-yl]-propionitrile

A mixture of 3-benzenesulfonyl-9-piperidin-4-yl-6,9-dihydro-3H-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-7,8-dione (500 mg, 1.18 mmol) and acrylonitrile (1 mL) in ethanol (IMS grade, 5 mL) and THF (5 mL) was heated at reflux for 18 hours. An additional portion of acrylonitrile (2 mL) was added and the mixture heated at reflux for 24 hours. The cooled mixture was concentrated under vacuum and the solid obtained triturated with diethyl ether, collected by filtration, washed with diethyl ether and air dried to afford 579 mg (100%) of 3-[4-(3-benzenesulfonyl-7,8-dioxo-3,6,7,8-tetrahydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidin-1-yl]-propionitrile as a white solid. LCMS (Method B, ESI): RT = 2.23 min, m+H = 479.36; ¹H NMR (400MHz, DMSO-*d*₆) δ: 12.12 (br s, 1 H), 8.17 (s, 1 H), 8.12 (m, 2 H), 7.98 (d, 1 H), 7.72 (m, 1 H), 7.63 (t, 2 H), 6.80 (d, 1 H), 4.39 (m, 1 H), 3.04 (d, 2 H), 2.67 (m, 6 H), 2.17 (t, 2 H), 1.76 (d, 2 H).

3-[4-(3-Benzenesulfonyl-7-chloro-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidin-1-yl]-propionitrile

A suspension of 3-[4-(3-benzenesulfonyl-7,8-dioxo-3,6,7,8-tetrahydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidin-1-yl]-propionitrile (400 mg, 836 μ mol) in toluene (25 mL) and DMF (5 mL) was treated with diisopropylethylamine (429 μ L, 2.51 mmol) and phosphorus oxychloride (234 μ L, 2.51 mmol) and heated at 100 °C for 45 minutes. The cooled mixture was diluted with DCM, washed with a saturated sodium bicarbonate solution, water and brine, dried with sodium sulfate and concentrated under vacuum to leave an orange/ brown residue. Purification by column chromatography on silica gel (gradient: 0 to 50% ethyl acetate in DCM) afforded 261 mg (63%) of 3-[4-(3-benzenesulfonyl-7-chloro-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidin-1-yl]-propionitrile as a pale orange solid.

LCMS (Method B, ESI): RT = 2.65 min, m+H = 497.30; 1 H NMR (400MHz, CDCl₃) δ : 8.79 (s, 1 H), 8.23 (d, 2 H), 7.91 (d, 1 H), 7.61 (t, 1 H), 7.53 (t, 2 H), 6.82 (br s, 1 H), 4.71 (br s, 1 H), 3.16 (d, 2 H), 3.07 (m, 2 H), 2.81 (t, 2 H), 2.57 (t, 2 H), 2.36 (t, 2 H), 1.78 (d, 2 H).

3-[4-(7-Amino-3-benzenesulfonyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidin-1-yl]-propionitrile

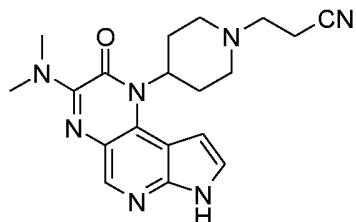
A mixture of 3-[4-(3-benzenesulfonyl-7-chloro-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidin-1-yl]-propionitrile (60 mg, 121 μ mol) in 2M ammonia in propan-2-ol (3 mL) was heated at reflux in a sealed vessel for 18 hours. A further portion of 2M ammonia in propan-2-ol (3 mL) was added and heating continued for 6 hours. The cooled mixture concentrated under vacuum and purified by column chromatography on silica gel (gradient: 0 to 100% ethyl acetate in DCM) to afford 49 mg (85%) of 3-[4-(7-amino-3-benzenesulfonyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidin-1-yl]-propionitrile as an off-white solid. LCMS (Method B, ESI): RT = 2.32 min, m+H = 478.37; 1 H NMR (400MHz, DMSO-*d*6) δ : 8.32 (s, 1 H), 8.12 (m, 2 H), 7.94 (d, 1 H), 7.72 (m, 1 H), 7.63 (dd, 2 H), 7.17 (br s, 2 H), 6.86 (br s, 1 H), 4.58 (br s, 1 H), 3.06 (d, 2 H), 2.83 (m, 2 H), 2.69 (m, 4 H), 2.22 (t, 2 H), 1.77 (d, 2 H).

3-[4-(7-Amino-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidin-1-yl]-propionitrile

A solution of 3-[4-(7-amino-3-benzenesulfonyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidin-1-yl]-propionitrile (45 mg, 94.0 μ mol) in THF (4 mL)

was treated with a 1M solution of tetrabutylammonium fluoride in THF (283 μ L, 283 μ mol) and heated at reflux for 18 hours. The cooled mixture was diluted with ethyl acetate, washed (water and brine), dried (sodium sulfate) and concentrated under vacuum. Purification by column chromatography on silica gel (gradient: 0 to 15% [2M ammonia in methanol solution] in DCM) 5 afforded 24 mg (76%) of 3-[4-(7-amino-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidin-1-yl]-propionitrile as an off-white solid. LCMS (Method A, ESI): RT = 1.72 min, m+H = 338.22; 1 H NMR (400MHz, DMSO-*d*6) δ : 11.92 (br s, 1 H), 8.25 (s, 1 H), 7.49 (m, 1 H), 6.84 (br s, 2 H), 6.59 (br s, 1 H), 4.87 (br m, 1 H), 3.09 (d, 2 H), 2.91 (m, 2 H), 2.70 (m, 4 H), 2.25 (t, 2 H), 1.79 (d, 2 H).

10

Example 27

3-[4-(7-Dimethylamino-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidin-1-yl]-propionitrile

15 4-(3-Benzenesulfonyl-7-chloro-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidine-1-carboxylic acid tert-butyl ester

A suspension of 4-(3-benzenesulfonyl-7,8-dioxo-3,6,7,8-tetrahydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidine-1-carboxylic acid tert-butyl ester (1.00 g, 1.90 mmol) in toluene (50 mL) and DMF (10 mL) was treated with diisopropylethylamine (980 μ L, 5.70 mmol) and phosphorus oxychloride (530 μ L, 5.70 mmol) and heated at 100 °C for 30 minutes. 20 The cooled mixture was diluted with DCM, washed with water (2x) and brine, dried with sodium sulfate and concentrated under vacuum to leave an orange/ brown solid. Purification by column chromatography on silica gel (gradient: 0 to 15% ethyl acetate in DCM) afforded 519 mg (50%) of 4-(3-benzenesulfonyl-7-chloro-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidine-1-carboxylic acid tert-butyl ester as a pale yellow solid. LCMS (Method B, ESI): 25 RT = 4.37 min, m+H = 544.35; 1 H NMR (400MHz, CDCl₃) δ : 8.79 (s, 1 H), 8.23 (dd, 2 H),

7.91 (d, 1 H), 7.62 (m, 1 H), 7.53 (m, 2 H), 6.79 (d, 1 H), 4.84 (br m, 1 H), 4.39 (br s, 2 H), 2.90 (br m, 4 H), 1.79 (br d, 2 H), 1.50 (s, 9 H).

4-(3-Benzenesulfonyl-7-dimethylamino-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidine-1-carboxylic acid tert-butyl ester

5 A mixture of 4-(3-benzenesulfonyl-7-chloro-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidine-1-carboxylic acid tert-butyl ester (200 mg, 368 µmol), dimethylamine hydrochloride (60 mg, 737 µmol) and triethylamine (127 µL, 920 µmol) in THF (5 mL) was heated at reflux in a sealed vessel for 5 hours. The cooled mixture was diluted with ethyl acetate, washed (water and brine), dried (sodium sulfate) and concentrated under vacuum.

10 Purification by column chromatography on silica gel (gradient: 0 to 50% ethyl acetate in DCM) afforded 203 mg (100%) of 4-(3-benzenesulfonyl-7-dimethylamino-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidine-1-carboxylic acid tert-butyl ester as a pale yellow solid. LCMS (Method B, ESI): RT = 4.55 min, m+H = 553.42; ¹H NMR (400MHz, CDCl₃) δ: 8.56 (s, 1 H), 8.20 (dd, 2 H), 7.75 (d, 1 H), 7.57 (m, 1 H), 7.48 (m, 2 H), 6.65 (d, 1 H), 4.69 (br m, 1 H), 4.36 (br s, 2 H), 3.30 (s, 6 H), 2.89 (m, 4 H), 1.77 (d, 2 H), 1.49 (s, 9 H).

15

3-BenzeneSulfonyl-7-dimethylamino-9-piperidin-4-yl-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-8-one

A solution of 4-(3-benzenesulfonyl-7-dimethylamino-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidine-1-carboxylic acid tert-butyl ester (195 mg, 353 µmol) in DCM (5 mL) and trifluoroacetic acid (3 mL) was stirred at ambient temperature for 30 minutes. The mixture was concentrated under vacuum and purified by SCX-2 column (eluting 2M ammonia in methanol) to afford 146 mg (91%) of 3-benzenesulfonyl-7-dimethylamino-9-piperidin-4-yl-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-8-one as an off-white solid.

20

LCMS (Method B, ESI): RT = 2.59 min, m+H = 453.33; ¹H NMR (400MHz, DMSO-d₆) δ: 8.36 (s, 1 H), 8.12 (m, 2 H), 7.94 (d, 1 H), 7.72 (m, 1 H), 7.62 (m, 2 H), 6.88 (br s, 1 H), 4.59 (br s, 1 H), 3.22 (s, 6 H), 3.08 (m, 2 H), 2.63 (m, 4 H), 1.69 (d, 2 H).

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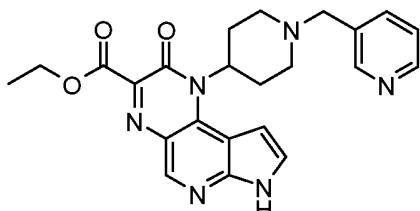
3-[4-(3-BenzeneSulfonyl-7-dimethylamino-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidin-1-yl]-propionitrile

A solution of 3-benzenesulfonyl-7-dimethylamino-9-piperidin-4-yl-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-8-one (140 mg, 309 µmol) in ethanol (IMS grade, 3 mL) and THF (3 mL) was treated with acrylonitrile (102 µL, 155 mmol) and heated at reflux for 5 hours. After cooling the mixture was concentrated under vacuum and purified by column chromatography on silica gel (gradient: 0 to 100% ethyl acetate in DCM) to afford 158 mg (100%) of 3-[4-(3-benzenesulfonyl-7-dimethylamino-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidin-1-yl]-propionitrile as a pale yellow solid. LCMS (Method B, ESI): RT = 2.65 min, m+H = 506.37; ¹H NMR (400MHz, DMSO-d6) δ: 8.37 (s, 1 H), 8.12 (m, 2 H), 7.94 (d, 1 H), 7.72 (m, 1 H), 7.62 (t, 2 H), 6.86 (br s, 1 H), 4.55 (br s, 1 H), 3.22 (s, 6 H), 3.04 (m, 2 H), 2.80 (m, 2 H), 2.68 (d, 4 H), 2.21 (t, 2 H), 1.75 (d, 2 H).

3-[4-(7-Dimethylamino-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidin-1-yl]-propionitrile

A solution of 3-[4-(3-benzenesulfonyl-7-dimethylamino-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidin-1-yl]-propionitrile (154 mg, 305 µmol) in THF (5 mL) was treated with a 1M solution of tetrabutylammonium fluoride in THF (914 µL, 914 µmol) and heated at reflux for 18 hours. After cooling the mixture was diluted with ethyl acetate, washed (water and brine), dried (sodium sulfate) and concentrated under vacuum. Purification by column chromatography on silica gel (gradient: 0 to 8% methanol in DCM) afforded 88 mg (79%) of 3-[4-(7-dimethylamino-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidin-1-yl]-propionitrile as a white solid. LCMS (Method A, ESI): RT = 2.11 min, m+H = 366.30; ¹H NMR (400MHz, DMSO-d6) δ: 11.94 (br s, 1 H), 8.32 (s, 1 H), 7.50 (t, 1 H), 6.60 (br s, 1 H), 4.82 (br m, 1 H), 3.19 (s, 6 H), 3.08 (d, 2 H), 2.90 (m, 2 H), 2.69 (m, 4 H), 2.24 (t, 2 H), 1.77 (d, 2 H).

Example 38



8-Oxo-9-(1-pyridin-3-ylmethyl-piperidin-4-yl)-8,9-dihydro-3H-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-7-carboxylic acid ethyl ester

3-Benzenesulfonyl-9-(1-tert-butoxycarbonyl-piperidin-4-yl)-8-oxo-8,9-dihydro-3H-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-7-carboxylic acid ethyl ester

5 A mixture of 4-(5-amino-1-benzenesulphonyl-1H-pyrrolo[2,3-b]pyridine-4ylamino)-piperidine-1-carboxylic acid tert-butyl ester (2.50 g, 5.30 mmol) and diethyl ketomalonate (890 µL, 5.8 mmol) in toluene (25 mL) was heated at reflux for 18 hours. After cooling the resulting precipitate was collected and washed with toluene and diethyl ether and air dried to afford 2.01 g (65%) of 3-benzenesulfonyl-9-(1-tert-butoxycarbonyl-piperidin-4-yl)-8-oxo-8,9-dihydro-3H-10 3,4,6,9-tetraaza-cyclopenta[a]naphthalene-7-carboxylic acid ethyl ester as a pale yellow solid. ¹H NMR (400MHz, CDCl₃) δ: 8.90 (s, 1 H), 8.22 (m, 2 H), 7.90 (d, 1 H), 7.61 (m, 1 H), 7.53 (t, 2 H), 6.80 (d, 1 H), 4.80 (br s, 1 H), 4.48 (q, 2 H), 4.36 (s, 2 H), 2.90 (m, 4 H), 1.79 (d, 2 H), 1.48 (s, 9 H), 1.43 (t, 3 H).

15 3-Benzenesulfonyl-8-oxo-9-piperidin-4-yl-8,9-dihydro-3H-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-7-carboxylic acid ethyl ester

A solution of 3-benzenesulfonyl-9-(1-tert-butoxycarbonyl-piperidin-4-yl)-8-oxo-8,9-dihydro-3H-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-7-carboxylic acid ethyl ester (582 mg, 1.00 mmol) in DCM (10 mL) and trifluoroacetic acid (5 mL) was stirred at ambient temperature for 1 hour. The mixture was concentrated under vacuum and the residue basified with 20 ammonium hydroxide. The resulting solid was collected by filtration, washed with water and dried at 50 °C under vacuum to afford 458 mg (100%) of 3-benzenesulfonyl-8-oxo-9-piperidin-4-yl-8,9-dihydro-3H-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-7-carboxylic acid ethyl ester as a yellow/ beige solid. LCMS (Method B, ESI): RT = 2.59 min, m+H = 482.33; ¹H NMR (400MHz, DMSO-d6) δ: 8.78 (s, 1 H), 8.18 (m, 2 H), 8.09 (m, 1 H), 7.75 (m, 1 H), 7.66 (m, 2 H), 7.06 (br s, 1 H), 4.75 (br s, 1 H), 4.37 (q, 2 H), 3.15 (d, 2 H), 2.70 (m, 4 H), 1.79 (d, 2 H), 25 1.31 (t, 3 H).

3-Benzenesulfonyl-8-oxo-9-(1-pyridin-3-ylmethyl-piperidin-4-yl)-8,9-dihydro-3H-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-7-carboxylic acid ethyl ester

A mixture of 3-benzenesulfonyl-8-oxo-9-piperidin-4-yl-8,9-dihydro-3H-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-7-carboxylic acid ethyl ester (450 mg, 935 µmol), 3-(bromomethyl)-

pyridine hydrochloride (260 mg, 1.03 mmol) and potassium carbonate (297 mg, 2.15 mmol) in DMF (15 mL) was stirred at ambient temperature for 18 hours. The mixture was diluted with ethyl acetate, washed (water (2x) and brine), dried (sodium sulfate) and concentrated under vacuum. Purification by column chromatography on silica gel (gradient: 0 to 12% methanol in DCM) afforded 324 mg (61%) of 3-benzenesulfonyl-8-oxo-9-(1-pyridin-3-ylmethyl-piperidin-4-yl)-8,9-dihydro-3H-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-7-carboxylic acid ethyl ester as a yellow solid. LCMS (Method B, ESI): RT = 2.65 min, m+H = 573.31; ¹H NMR (400MHz, DMSO-d6) δ: 8.77 (s, 1 H), 8.53 (s, 1 H), 8.49 (dd, 1 H), 8.18 (m, 2 H), 8.11 (d, 1 H), 7.76 (m, 2 H), 7.66 (t, 2 H), 7.39 (dd, 1 H), 6.99 (br s, 1 H), 4.66 (br s, 1 H), 4.37 (q, 2 H), 3.58 (s, 2 H), 2.97 (d, 2 H), 2.79 (m, 2 H), 2.21 (t, 2 H), 1.81 (d, 2 H), 1.31 (t, 3 H).

8-Oxo-9-(1-pyridin-3-ylmethyl-piperidin-4-yl)-8,9-dihydro-3H-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-7-carboxylic acid ethyl ester

A solution of 3-benzenesulfonyl-8-oxo-9-(1-pyridin-3-ylmethyl-piperidin-4-yl)-8,9-dihydro-3H-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-7-carboxylic acid ethyl ester (120 mg, 210 μmol) in THF (5 mL) was treated with 1M solution of tetrabutylammonium fluoride in THF (630 μL, 630 μmol) and heated at reflux for 3 hours. The cooled mixture was diluted with ethyl acetate, washed (water and brine), dried (sodium sulfate) and concentrated under vacuum. Purification by column chromatography on silica gel (gradient: 0 to 10% [2M ammonia in methanol solution] in DCM) afforded 70 mg (77%) of 8-oxo-9-(1-pyridin-3-ylmethyl-piperidin-4-yl)-8,9-dihydro-3H-3,4,6,9-tetraaza-cyclopenta[a]naphthalene-7-carboxylic acid ethyl ester as a yellow solid. LCMS (Method A, ESI): RT = 2.18 min, m+H = 433.29; ¹H NMR (400MHz, DMSO-d6) δ: 12.50 (br s, 1 H), 8.65 (s, 1 H), 8.54 (d, 1 H), 8.49 (dd, 1 H), 7.77 (m, 1 H), 7.67 (d, 1 H), 7.39 (dd, 1 H), 6.78 (br s, 1 H), 4.92 (br m, 1 H), 4.37 (q, 2 H), 3.60 (s, 2 H), 3.00 (d, 2 H), 2.87 (m, 2 H), 2.23 (t, 2 H), 1.84 (s, 2 H), 1.33 (t, 3 H).

25

Example 42



7-Methylamino-9-(1-pyridin-3-ylmethyl-piperidin-4-yl)-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-8-one

4-(3-Benzenesulfonyl-7-methylamino-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidine-1-carboxylic acid tert-butyl ester

5 Following the procedure for 4-(3-benzenesulfonyl-7-dimethylamino-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidine-1-carboxylic acid tert-butyl ester the title compound was prepared using 4-(3-benzenesulfonyl-7-chloro-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidine-1-carboxylic acid tert-butyl ester and 2M methylamine in THF to afford 127 mg (88%) of 4-(3-benzenesulfonyl-7-methylamino-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidine-1-carboxylic acid tert-butyl ester as a white solid. LCMS (Method B, ESI): RT = 4.15 min, m+H = 539.33; ¹H NMR (400MHz, CDCl₃) δ: 8.63 (s, 1 H), 8.20 (dd, 2 H), 7.77 (d, 1 H), 7.56 (m, 1 H), 7.48 (m, 2 H), 6.66 (d, 1 H), 6.25 (m, 1 H), 4.77 (m, 1 H), 4.36 (m, 2 H), 3.09 (d, 3 H), 2.91 (m, 4 H), 1.79 (d, 2 H), 1.50 (s, 9 H).

10

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Example 45



3-[4-(7-Methoxy-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidin-1-yl]-propionitrile

20 3-[4-(3-Benzenesulfonyl-7-methoxy-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidin-1-yl]-propionitrile

A mixture of 3-[4-(3-benzenesulfonyl-7-chloro-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidin-1-yl]-propionitrile (50 mg, 100 μmol) and diisopropylethylamine (21.0 μL, 125 μmol) in methanol (3 mL) was heated at reflux in a sealed vessel for 3 hours. The cooled mixture was concentrated under vacuum and purified by column chromatography on silica gel (gradient: 0 to 100% ethyl acetate in DCM) to afford 42 mg (85%) of

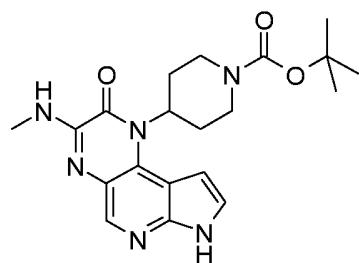
25 3-[4-(3-benzenesulfonyl-7-methoxy-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-

cyclopenta[a]naphthalen-9-yl)-piperidin-1-yl]-propionitrile as an off-white solid. LCMS (Method B, ESI): RT = 2.59 min, m+H = 493.39; ¹H NMR (400MHz, CDCl₃) δ: 8.66 (s, 1 H), 8.22 (d, 2 H), 7.84 (d, 1 H), 7.60 (t, 1 H), 7.50 (t, 2 H), 6.77 (br s, 1 H), 4.68 (br s, 1 H), 4.08 (s, 3 H), 3.14 (m, 4 H), 2.81 (t, 2 H), 2.57 (t, 2 H), 2.33 (t, 2 H), 1.78 (d, 2 H).

5 3-[4-(7-Methoxy-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidin-1-yl]-propionitrile

A solution of 3-[4-(3-benzenesulfonyl-7-methoxy-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidin-1-yl]-propionitrile (40 mg, 81 μmol) in THF (5 mL) was treated with a 1M solution of tetrabutylammonium fluoride in THF (244 μL, 244 μmol) and 10 heated at reflux for 18 hours. The cooled mixture was diluted with ethyl acetate, washed (water and brine), dried (sodium sulfate) and concentrated under vacuum. Purification by column chromatography on silica gel (gradient: 0 to 10% methanol in DCM) afforded 17 mg (60%) of 3-[4-(7-methoxy-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidin-1-yl]-propionitrile as an off-white solid. LCMS (Method A, ESI): RT = 1.96 min, m+H = 353.23; 15 ¹H NMR (400MHz, DMSO-d6) δ: 12.13 (br s, 1 H), 8.43 (s, 1 H), 7.58 (m, 1 H), 6.67 (br s, 1 H), 4.88 (br m, 1 H), 3.97 (s, 3 H), 3.09 (d, 2 H), 2.88 (m, 2 H), 2.69 (m, 4 H), 2.24 (t, 2 H), 1.80 (d, 2 H).

Example 50



20 4-(7-Methylamino-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidine-1-carboxylic acid tert-butyl ester

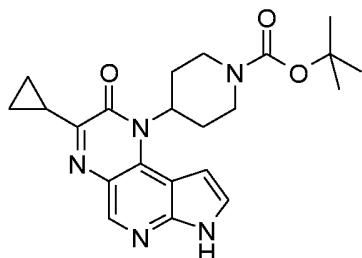
A solution of 4-(3-benzenesulfonyl-7-methylamino-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidine-1-carboxylic acid tert-butyl ester (118 mg, 219 μmol) in THF (5 mL) was treated with a 1M solution of tetrabutylammonium fluoride in THF (548 μL, 25 548 μmol) and heated at reflux for 18 hours. The cooled mixture was diluted with ethyl acetate,

washed (water and brine), dried (sodium sulfate) and concentrated under vacuum. Purification by column chromatography on silica gel (eluent: DMAW 360 - DCM, MeOH, AcOH and water in a ratio of 360:20:3:2). The resulting white solid obtained was basified with 2M ammonia in methanol solution and concentrated under vacuum. The residue was slurried in water, collected 5 by filtration, washed with water and air dried to afford 49 mg (56%) of 4-(7-methylamino-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidine-1-carboxylic acid tert-butyl ester as an off-white solid. LCMS (Method A, ESI): RT = 3.93 min, m+H = 399.35; ¹H NMR (400MHz, DMSO-*d*6) δ: 11.90 (br s, 1 H), 8.33 (s, 1 H), 7.48 (t, 1 H), 7.40 (m, 1 H), 6.65 (s, 1 H), 5.08 (m, 1 H), 4.13 (m, 2 H), 2.99 (m, 2 H), 2.90 (d, 3 H), 2.73 (m, 2 H), 1.82 10 (d, 2 H), 1.45 (s, 9 H).

7-Methylamino-9-(1-pyridin-3-ylmethyl-piperidin-4-yl)-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-8-one

A solution of 4-(7-methylamino-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidine-1-carboxylic acid tert-butyl ester (41 mg, 103 μmol) in 15 DCM (5 mL) and trifluoroacetic acid (3 mL) was stirred at ambient temperature for 1 hour. The mixture was concentrated under vacuum and the residue dissolved in DMF (5 mL). Diisopropylethylamine (88 μL, 515 μmol) and 3-(bromomethyl)-pyridine hydrochloride (29 mg, 113 μmol) were added and the mixture stirred at ambient temperature for 18 hours. The mixture was diluted with ethyl acetate, washed (water and brine), dried (sodium sulfate) and concentrated 20 under vacuum. Purification by column chromatography on silica gel (gradient: 0 to 15% methanol in DCM) afforded 23 mg (57%) of 7-methylamino-9-(1-pyridin-3-ylmethyl-piperidin-4-yl)-3,9-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-8-one as an off-white solid. LCMS (Method A, ESI): RT = 1.85 min, m+H = 390.26; ¹H NMR (400MHz, DMSO-*d*6) δ: 11.89 (br s, 1 H), 8.55 (m, 1 H), 8.49 (m, 1 H), 8.32 (s, 1 H), 7.77 (d, 1 H), 7.50 (t, 1 H), 7.38 (m, 2 H), 6.56 (br s, 1 H), 4.88 (br m, 1 H), 3.60 (s, 2 H), 2.90 (m, 7 H), 2.21 (t, 2 H), 1.80 (d, 2 H). 25

Example 54



4-(7-Cyclopropyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidine-1-carboxylic acid tert-butyl ester

5 4-(3-Benzenesulfonyl-7-cyclopropyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidine-1-carboxylic acid tert-butyl ester

A solution of 4-(5-amino-1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-piperidine-1-carboxylic acid tert-butyl ester (500 mg, 1.06 mmol) and cyclopropyl-oxo-acetic acid ethyl ester (196 mg, 1.38 mmol) in 1-butanol (5 mL) was heated at reflux for 48 hours. After cooling the resulting precipitate was collected and washed with cold 1-butanol and diethyl ether to afford 363 mg (62%) of 4-(3-benzenesulfonyl-7-cyclopropyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidine-1-carboxylic acid tert-butyl ester as a pale yellow solid. LCMS (Method B, ESI): RT = 4.65 min, m+H = 550.36; ¹H NMR (400MHz, CDCl₃) δ 8.69 (s, 1 H), 8.20 (m, 2 H), 7.82 (d, 1 H), 7.58 (m, 1 H), 7.50 (m, 2 H), 6.75 (d, 1 H), 4.75 (m, 1 H), 4.39 (m, 2 H), 2.98 (m, 2 H), 2.85 (m, 2 H), 2.70 (m, 1 H), 1.77 (m, 2 H), 1.50 (s, 9 H), 1.19 (m, 2 H), 1.09 (m, 2 H).

15 4-(7-Cyclopropyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidine-1-carboxylic acid tert-butyl ester

A solution of 4-(3-benzenesulfonyl-7-cyclopropyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidine-1-carboxylic acid tert-butyl ester (358 mg, 650 μmol) in a methanol/ THF mixture (1:1, 20 mL) was treated with a 1M sodium hydroxide solution and stirred at ambient temperature for 1 hour. The mixture was concentrated under vacuum and the aqueous residue extracted into DCM (2x). The combined extracts were washed (water brine), dried (sodium sulfate) and concentrated under vacuum. Purification by column chromatography on silica gel (gradient: 0 to 50% ethyl acetate in DCM) afforded 223 mg (84%) of 4-(7-cyclopropyl-8-oxo-3,8-dihydro-3,4,6,9-tetraaza-cyclopenta[a]naphthalen-9-yl)-piperidine-1-carboxylic acid tert-butyl ester as an off white solid. LCMS (Method A, ESI): RT = 4.89 min,

$m+H = 410.30$; ^1H NMR (400MHz, DMSO-d6) δ : 12.22 (br s, 1 H), 8.47 (s, 1 H), 7.57 (d, 1 H), 6.80 (d, 1 H), 5.08 (m, 1 H), 4.14 (m, 2 H), 3.01 (m, 2 H), 2.76 (m, 2 H), 2.63 (m, 1 H), 1.82 (d, 2 H), 1.45 (s, 9 H), 1.04 (d, 4 H).

Examples of the JAK1 inhibition (Example A) are shown in the below Table 2.

5

Table 2

Example no.	JAK1 Ki (μM)
1	0.0818
2	0.0035
3	0.0481
4	0.0863
5	0.1267
6	0.0089
7	0.2273
8	0.0024
9	0.0025
10	0.0495
11	0.4979
12	0.0044
13	0.0005
14	0.0006
15	0.0007
16	0.0011
17	0.0014
18	0.0023
19	0.0041
20	0.0041

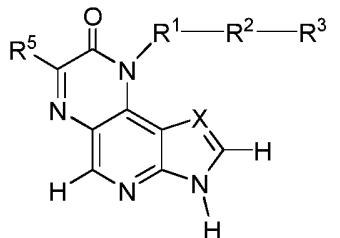
21	0.0044
22	0.005
23	0.0055
24	0.0063
25	0.0064
26	0.0067
27	0.0069
28	0.0073
29	0.0075
30	0.0086
31	0.0089
32	0.0098
33	0.0107
34	0.0125
35	0.0127
36	0.0133
37	0.0154
38	0.0156
39	0.0169
40	0.017
41	0.019
42	0.0218
43	0.026
44	0.0279
45	0.0368
46	0.048
47	0.05

48	0.0623
49	0.0887
50	0.0915
51	0.1369
52	0.2024
53	0.284
54	0.3682
55	0.6225
56	1.083
58	0.0554

Although the invention has been described and illustrated with a certain degree of particularity, it is understood that the present disclosure has been made only by way of example, and that numerous changes in the combination and arrangement of parts can be resorted to by those skilled in the art without departing from the spirit and scope of the invention, as defined by
5 the claims.

WHAT IS CLAIMED IS:

1. A compound of formula I:



I

5 stereoisomers, tautomers and pharmaceutically acceptable salts thereof, wherein

X is N or CR⁴;

R¹ is absent, C₁₋₁₂ alkyl, C₁₋₁₂ alkenyl, C₁₋₁₂ alkynyl, C₃₋₁₂ cycloalkyl, C₆₋₁₄ aryl or 3-20 membered heterocyclyl, wherein R¹ is independently optionally substituted by halogen, oxo, -CN, -OR^a, -SR^a, -NR^aR^b, C₁₋₃ alkylene or C₁₋₆ alkyl optionally substituted by oxo, -CN or 10 halogen;

R² is absent, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -(C₁₋₆ alkylene)-, -(C₂₋₆ alkenylene)-, -(C₂₋₆ alkynylene)-, -(C₀₋₆ alkylene)CN, -(C₀₋₃ alkylene)NR^a(C₀₋₃ alkylene)-, -(C₀₋₃ alkylene)O(C₀₋₃ alkylene)-, -(C₀₋₃ alkylene)C(O)(C₀₋₃ alkylene)-, -(C₀₋₃ alkylene)NR^aC(O)(C₀₋₃ alkylene)-, -(C₀₋₃ alkylene)C(O)NR^a(C₀₋₃ alkylene)-, -(C₀₋₃ alkylene)C(O)O(C₀₋₃ alkylene)-, 15 -(C₀₋₃ alkylene)OC(O)(C₀₋₃ alkylene)-, -(C₀₋₃ alkylene)NR^aC(O)NR^b(C₀₋₃ alkylene)-, -(C₀₋₃ alkylene)OC(O)NR^a(C₀₋₃ alkylene)-, -(C₀₋₃ alkylene)NR^aC(O)O(C₀₋₃ alkylene)-, -(C₀₋₃ alkylene)S(O)₁₋₂(C₀₋₃ alkylene)-, -(C₀₋₃ alkylene)NR^aS(O)₁₋₂(C₀₋₃ alkylene)-, -(C₀₋₃ alkylene)S(O)₁₋₂NR^a(C₀₋₃ alkylene)- or -(C₀₋₃ alkylene)NR^aS(O)₁₋₂NR^b(C₀₋₃ alkylene)-, whereon said alkyl, alkenyl, alkynyl, alkylene, alkenylene and alkynylene are independently optionally 20 substituted by halogen, oxo, -CN, -OR^c, -SR^c, -NR^cR^d or C₁₋₃ alkyl optionally substituted by halogen;

R³ is absent, hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₆₋₁₄ aryl or 3-20 membered heterocyclyl, wherein R³ is independently optionally substituted by R⁶;

R^4 is hydrogen, halogen or C_{1-3} alkyl;

R^5 is hydrogen, halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, $-(C_{0-3}$ alkylene)CN, $-(C_{0-3}$ alkylene)NR^aR^b, $-(C_{0-3}$ alkylene)OR^a, $-(C_{0-3}$ alkylene)SR^a, $-(C_{0-3}$ alkylene)C(O)R^a, $-(C_{0-3}$ alkylene)NR^aC(O)R^b, $-(C_{0-3}$ alkylene)C(O)NR^aR^b, $-(C_{0-3}$ alkylene)C(O)OR^a, $-(C_{0-3}$ alkylene)OC(O)R^a, $-(C_{0-3}$ alkylene)NR^aC(O)NR^aR^b, $-(C_{0-3}$ alkylene)OC(O)NR^aR^b, $-(C_{0-3}$ alkylene)NR^aC(O)OR^b, $-(C_{0-3}$ alkylene)S(O)₁₋₂R^a, $-(C_{0-3}$ alkylene)NR^aS(O)₁₋₂R^b, $-(C_{0-3}$ alkylene)S(O)₁₋₂NR^aR^b, $-(C_{0-3}$ alkylene)NR^aS(O)₁₋₂NR^aR^b, $-(C_{0-3}$ alkylene)C₃₋₁₂ cycloalkyl, $-(C_{0-3}$ alkylene)C₆₋₁₄ aryl, $-(C_{0-3}$ alkylene)3-12 membered heterocyclyl or $-(C_{0-3}$ alkylene)C(O)3-12 membered heterocyclyl, wherein said alkyl, alkenyl, alkynyl, alkylene, 10 cycloalkyl, aryl and heterocyclyl are independently optionally substituted by halogen, oxo, $-(C_{0-3}$ alkylene)CN, $-(C_{0-3}$ alkylene)OR^c, $-(C_{0-3}$ alkylene)NR^cR^d, $-(C_{0-3}$ alkylene)C(O)R^c, $-(C_{0-3}$ alkylene)C(O)OR^c, $-(C_{0-3}$ alkylene)C(O)NR^cR^d, $-(C_{0-3}$ alkylene)NR^cC(O)R^d, $-(C_{0-3}$ alkylene)OC(O)NR^cR^d, $-(C_{0-3}$ alkylene)NR^cC(O)NR^cR^d, $-(C_{0-3}$ alkylene)NR^cC(O)OR^d, $-(C_{0-3}$ alkylene)S(O)₀₋₂R^c, $-(C_{0-3}$ alkylene)NR^cS(O)₁₋₂R^d, $-(C_{0-3}$ alkylene)S(O)₁₋₂NR^cR^d, $-(C_{0-3}$ alkylene)NR^cS(O)₁₋₂NR^cR^d, 15 $-(C_{0-3}$ alkylene)NR^cS(O)₁₋₂NR^cR^d or C_{1-6} alkyl optionally substituted by oxo, -CN or halogen;

R^6 is independently oxo, halogen, -CN, -C(O)R^a, -C(O)OR^a, -NR^aC(O)R^b, -C(O)NR^aR^b, -NR^aC(O)NR^aR^b, -OC(O)NR^aR^b, -NR^aC(O)OR^b, -S(O)₁₋₂R^a, -NR^aS(O)₂R^a, -S(O)₂NR^aR^b, -OR^a, -SR^a, -NR^aR^b, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3-7 membered heterocyclyl or C_{6-14} aryl, and wherein said alkyl, alkenyl, alkynyl, cycloalkyl, 20 heterocyclyl and aryl are independently optionally substituted by halogen, oxo, -CN, -OR^c, -SR^c, -NR^cR^d or C_{1-6} alkyl optionally substituted by oxo or halogen;

each R^a and R^b are independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-(C_{0-3}$ alkylene)C₃₋₆ cycloalkyl, $-(C_{0-3}$ alkylene)3-12 membered heterocyclyl, $-(C_{0-3}$ alkylene)C(O)3-12 membered heterocyclyl or $-(C_{0-3}$ alkylene)C₆₋₁₄ aryl, wherein said alkyl, cycloalkyl, heterocyclyl 25 and aryl are independently optionally substituted by halogen, oxo, -CN, -OR^e, -NR^eR^f, -C(O)R^g, -C(O)OR^g, -C(O)NR^gR^h, -NR^gC(O)R^h, -OC(O)NR^gR^h, -NR^gC(O)NR^gR^h, -NR^gC(O)OR^h, -S(O)₁₋₂R^g, -NR^gS(O)₁₋₂R^h, -S(O)₁₋₂NR^gR^h, -NR^gS(O)₁₋₂NR^gR^h, C_{3-6} cycloalkyl, 3-6 membered heterocyclyl, phenyl or C_{1-3} alkyl optionally substituted by oxo or halogen, or taken together with the atom to which they are attached to form a 3-6 membered

heterocyclyl optionally substituted by oxo, halogen, $-\text{C}(\text{O})\text{C}_{1-6}$ alkyl or C_{1-6} alkyl optionally substituted by oxo, halogen, OR^g or NR^gNR^h ;

each R^c and R^d are independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-(\text{C}_{0-3}$ alkylene) C_{3-6} cycloalkyl, $-(\text{C}_{0-3}$ alkylene)3-12 membered heterocyclyl, $-(\text{C}_{0-3}$ alkylene) $\text{C}(\text{O})$ 3-12 membered heterocyclyl or $-(\text{C}_{0-3}$ alkylene) C_{6-14} aryl, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl and aryl are independently optionally substituted by halogen, oxo, $-\text{CN}$, $-\text{OR}^g$, $-\text{NR}^g\text{R}^h$, $-\text{C}(\text{O})\text{R}^g$, $-\text{C}(\text{O})\text{OR}^g$, $-\text{C}(\text{O})\text{NR}^g\text{R}^h$, $-\text{NR}^g\text{C}(\text{O})\text{R}^h$, $-\text{OC}(\text{O})\text{NR}^g\text{R}^h$, $-\text{NR}^g\text{C}(\text{O})\text{NR}^g\text{R}^h$, $-\text{NR}^g\text{C}(\text{O})\text{OR}^h$, $-\text{S}(\text{O})_{1-2}\text{R}^g$, $-\text{NR}^g\text{S}(\text{O})_{1-2}\text{R}^h$, $-\text{S}(\text{O})_{1-2}\text{NR}^g\text{R}^h$, $-\text{NR}^g\text{S}(\text{O})_{1-2}\text{NR}^g\text{R}^h$, C_{3-6} cycloalkyl, 3-6 membered heterocyclyl, phenyl or C_{1-6} alkyl optionally substituted by oxo or halogen, or taken together with the atom to which they are attached to form a 3-6 membered heterocyclyl optionally substituted by oxo, halogen, $-\text{C}(\text{O})\text{C}_{1-6}$ alkyl or C_{1-6} alkyl optionally substituted by oxo or halogen; and

each R^e , R^f , R^g , R^h are independently hydrogen or C_{1-6} alkyl optionally substituted by halogen or oxo.

15 2. The compound of claim 1, wherein X is CR^4 .

3. The compound of any one of claims 1-2, wherein R^1 is selected from piperidinyl, cyclopentyl or cyclohexyl.

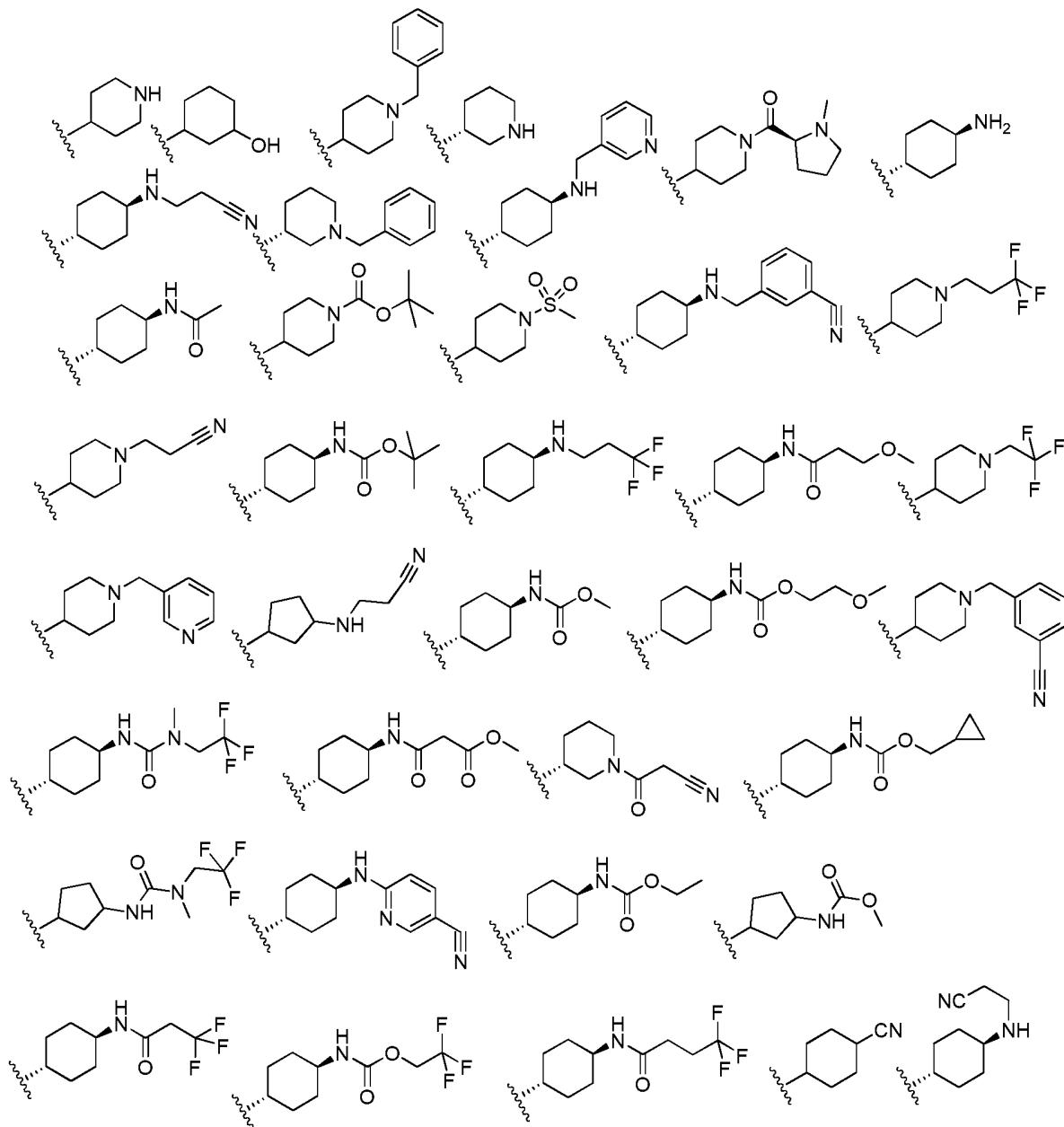
4. The compound of any one of claims 1-3, wherein R^2 is absent, methylene,

ethylene, $-\text{NH}-$, $-\text{NHCH}_2-$, , , $-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{NH}-$, $-\text{NHC}(\text{O})\text{O}-$,

20 $-\text{NHC}(\text{O})\text{CH}_2-$ or $-\text{NHC}(\text{O})\text{N}(\text{CH}_3)-$, wherein the wavy line represents the point of attachment in formula I.

5. The compound of any one of claims 1-4, wherein R^3 is absent, hydrogen, methyl, ethyl, t-butyl, $-\text{CF}_3$, $-\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{CN}$, $-(\text{CH}_2)_2\text{CN}$, $-\text{CH}_2$ cyclopropyl, cyclopropyl, phenyl, 3-cyanophenyl, 5-cyanopyridin-2-yl, N-methylpyrrolidin-2-yl or pyridin-3-yl.

25 6. The compound of any one of claims 1-5, wherein $-\text{R}^1\text{-R}^2\text{-R}^3$ taken together are:



7. The compound of any one of claims 1-6 wherein R⁴ is hydrogen.

8. The compound of any one of claims 1-7, wherein R⁵ is hydrogen, methyl,
5 isopropyl, cyclopropyl, -NH₂, -NH(CH₃), -N(CH₃)₂, -OCH₃ or -C(O)OEt.

9. The compound of any one of claims 1-8, wherein R⁶ is independently oxo,
halogen, -CN, -C(O)R^a, -C(O)OR^a, -NR^aC(O)R^b, -C(O)NR^aR^b, -NR^aC(O)NR^aR^b,

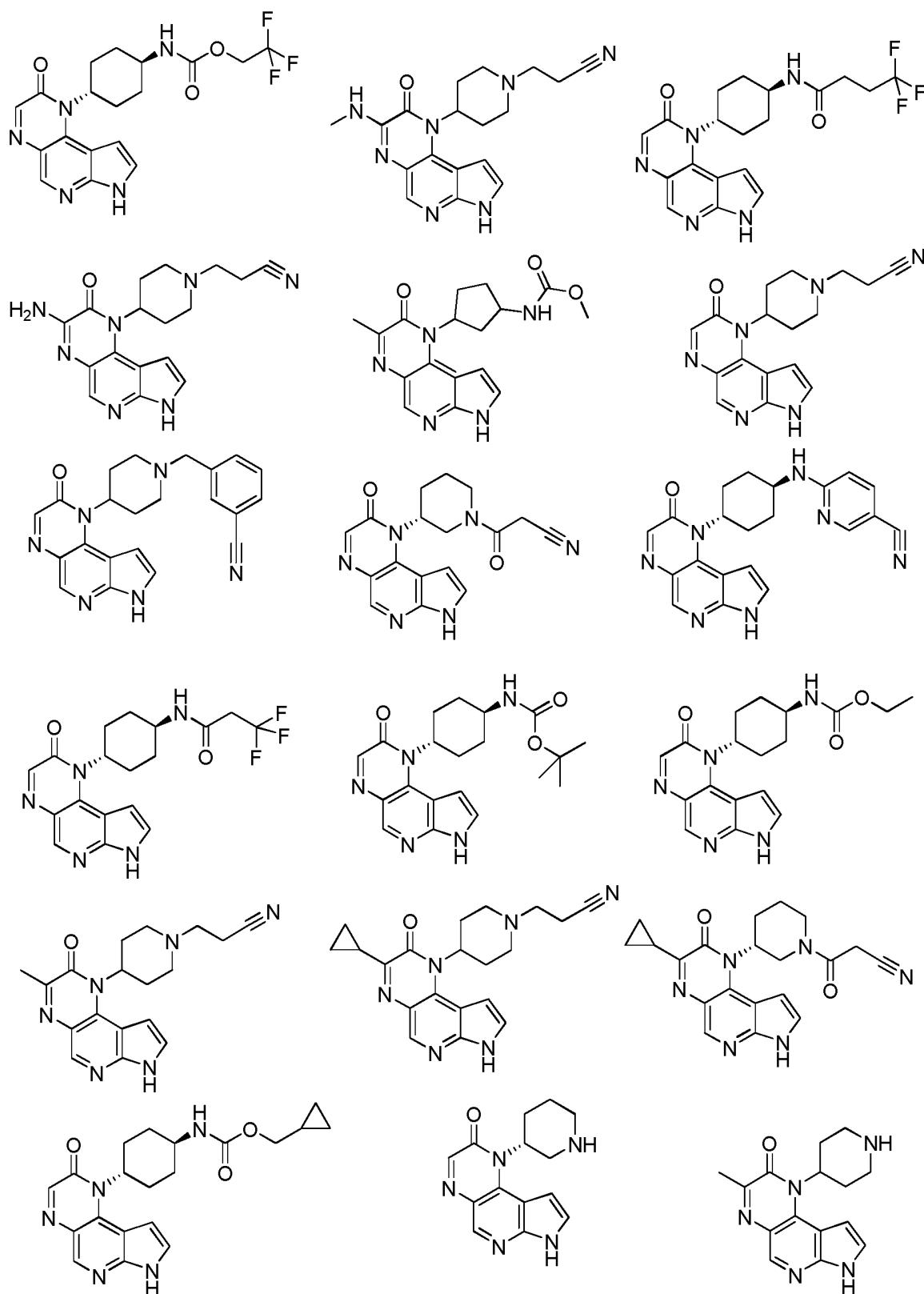
–OC(O)NR^aR^b, –NR^aC(O)OR^b, –S(O)₁₋₂R^a, –NR^aS(O)₂R^b, –S(O)₂NR^aR^b, –OR^a, –SR^a, –NR^aR^b, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, 3-7 membered heterocycl or C₆₋₁₄ aryl, and wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocycl and aryl are independently optionally substituted by halogen, oxo, –CN, –OR^c, –SR^c, –NR^cR^d or C₁₋₆ alkyl
5 optionally substituted by oxo or halogen.

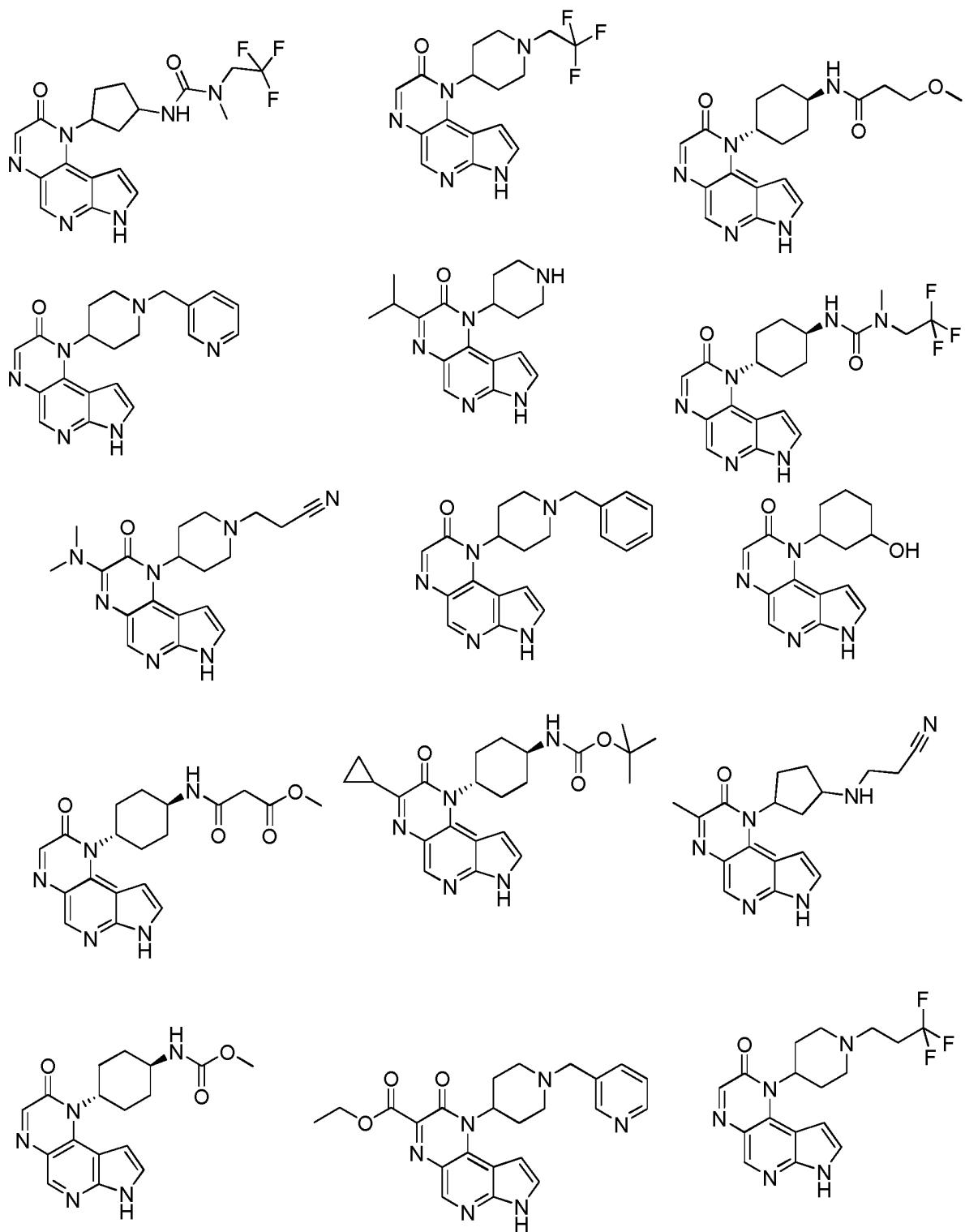
10. The compound of any one of claims 1-9, wherein each R^a and R^b are independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, –C₃₋₆ cycloalkyl, –3-12 membered heterocycl, –C(O)3-12 membered heterocycl or –C₆₋₁₄ aryl, wherein said alkyl, cycloalkyl, heterocycl and aryl are independently optionally substituted by halogen, oxo, –CN, –OR^e, –NR^eR^f,
10 –C(O)R^g, –C(O)OR^g, –C(O)NR^gR^h, –NR^gC(O)R^h, –OC(O)NR^gR^h, –NR^gC(O)NR^gR^h, –NR^gC(O)OR^h, –S(O)₁₋₂R^g, –NR^gS(O)₁₋₂R^h, –S(O)₁₋₂NR^gR^h, –NR^gS(O)₁₋₂NR^gR^h, C₃₋₆ cycloalkyl, 3-6 membered heterocycl, phenyl or C₁₋₃ alkyl optionally substituted by oxo or halogen, or taken together with the atom to which they are attached to form a 3-6 membered heterocycl optionally substituted by oxo, halogen, –C(O)C₁₋₆ alkyl or C₁₋₆ alkyl optionally substituted by oxo, halogen, OR^g or NR^gNR^h.
15

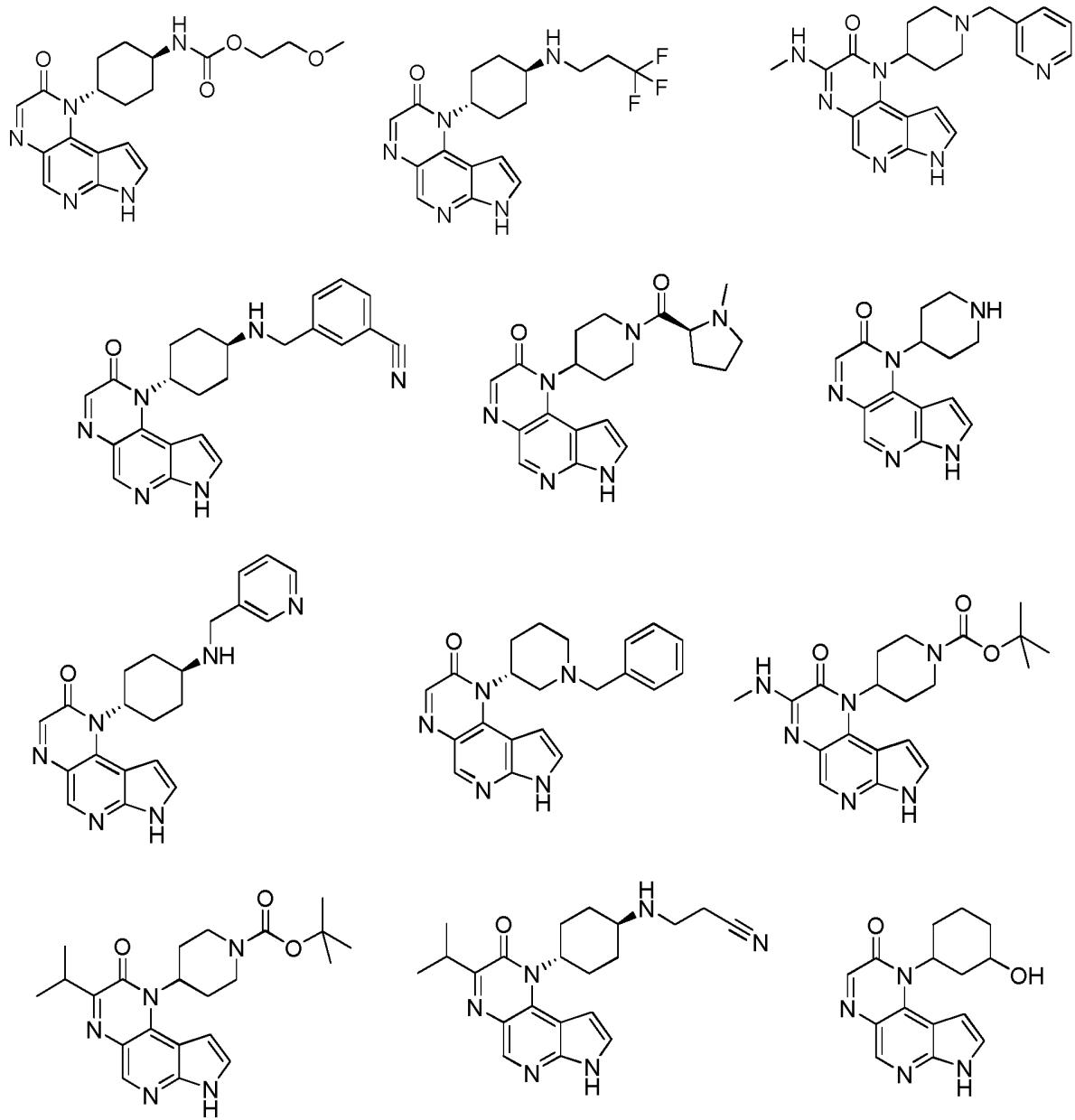
11. The compound of any one of claims 1-10, wherein each R^c and R^d are independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, –C₃₋₆ cycloalkyl, –3-12 membered heterocycl, –C(O)3-12 membered heterocycl or –C₆₋₁₄ aryl, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocycl and aryl are independently optionally substituted by halogen, oxo, –CN, –OR^g, –NR^gR^h, –C(O)R^g, –C(O)OR^g, –C(O)NR^gR^h, –NR^gC(O)R^h, –OC(O)NR^gR^h,
20 –NR^gC(O)NR^gR^h, –NR^gC(O)OR^h, –S(O)₁₋₂R^g, –NR^gS(O)₁₋₂R^h, –S(O)₁₋₂NR^gR^h, –NR^gS(O)₁₋₂NR^gR^h, C₃₋₆ cycloalkyl, 3-6 membered heterocycl, phenyl or C₁₋₆ alkyl optionally substituted by oxo or halogen, or taken together with the atom to which they are attached to form a 3-6 membered heterocycl optionally substituted by oxo, halogen, –C(O)C₁₋₆ alkyl or C₁₋₆ alkyl
25 optionally substituted by oxo or halogen.

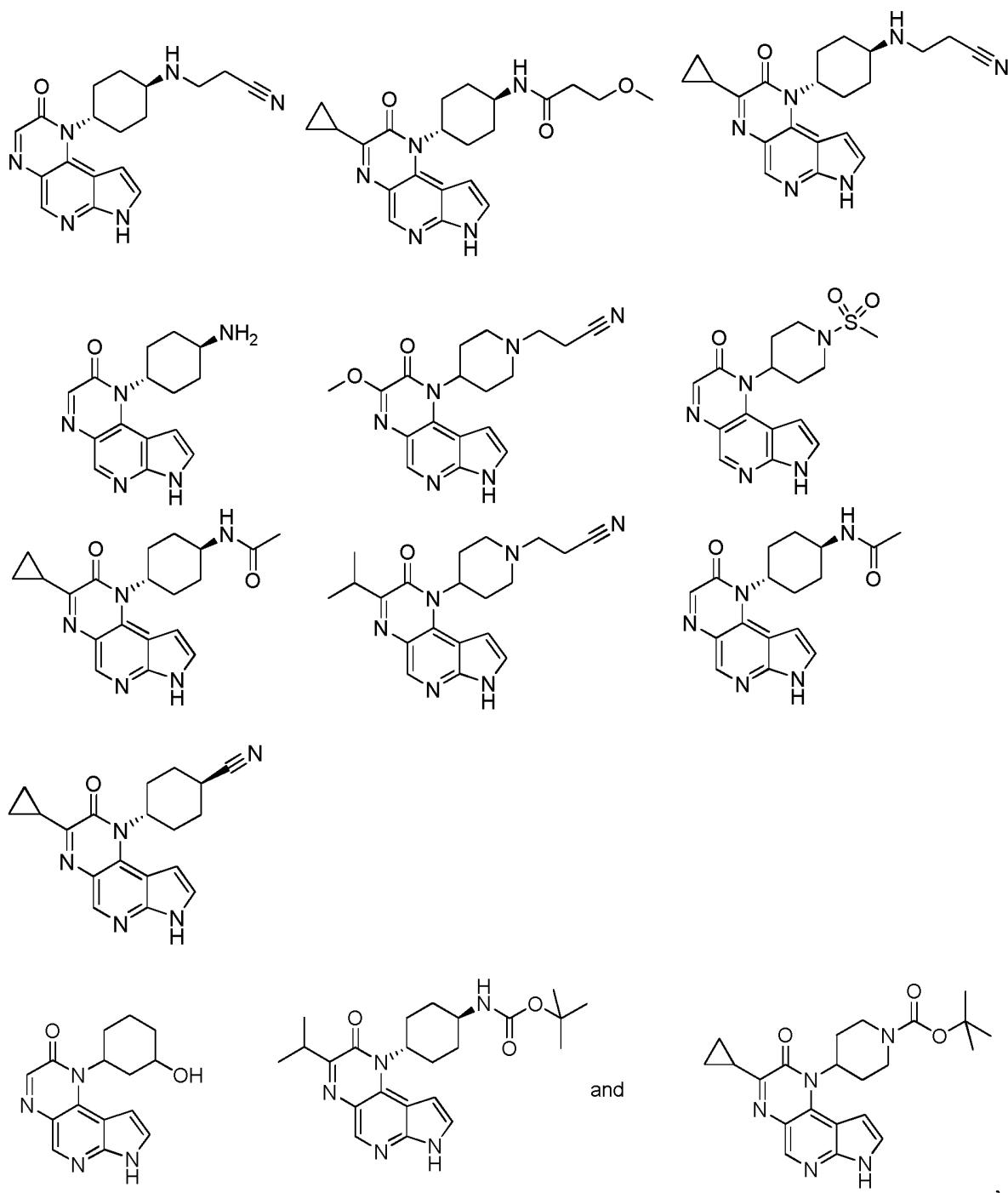
12. The compound of any one of claims 1-11, wherein each R^e, R^f, R^g, R^h are independently hydrogen, methyl, ethyl, propyl or isopropyl, optionally substituted by halogen or oxo.

13. A compound of claim 1, selected from:









and pharmaceutically acceptable salts thereof.

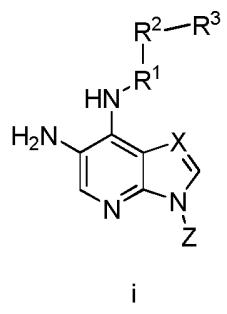
- 5 14. A pharmaceutical composition comprising a compound of any one of claims 1-13, a stereoisomer, tautomer or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant or vehicle.

15. A compound of any one of claims 1-13, a stereoisomer, tautomer, prodrug or pharmaceutically acceptable salt thereof, for use in therapy.

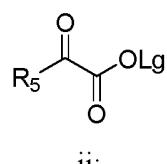
16. A compound of any one of claims 1-13, a stereoisomer, tautomer, prodrug or pharmaceutically acceptable salt thereof, for use in treating an immunological disease selected
5 from rheumatoid arthritis, asthma, systemic lupus erythematosus, psoriasis, IBD and transplant rejection.

17. The use of a compound of any one of claims 1-13, a stereoisomer, tautomer, prodrug or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease responsive to the inhibition of JAK1 kinase activity.

10 18. A method of manufacturing a compound of claim 1, comprising: (a) reacting a compound of formula i:

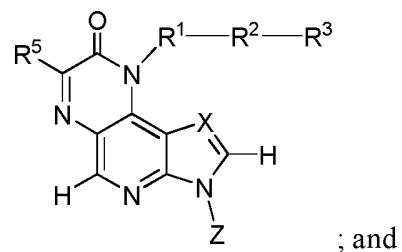


wherein R^1 , R^2 , R^3 and X are as defined in formula I, and Z is hydrogen or an amino protecting group, with a compound of formula ii:



15

wherein R^5 is defined in formula I and Lg is a leaving group, under conditions sufficient to form a compound of formula iii:



iii

(b) optionally deprotecting said amino protecting group to form a compound of formula I.

19. The method of claim 18, wherein Lg is hydrogen, halogen or C₁₋₃ alkyl.

5 20. The method of any one of claims 18 or 19, wherein R⁵ is hydrogen or methyl.

21. The invention as hereinbefore described.

INTERNATIONAL SEARCH REPORT

International application No PCT/EP2011/073734

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D487/12 A61K31/4985 A61P11/00 A61P29/00 ADD.
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT
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Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007/145957 A1 (MERCK & CO INC [US]; YOUNG JONATHAN R [US]; HAIDLE ANDREW [US]; TEMPES) 21 December 2007 (2007-12-21) the whole document -----	1-21
A	WO 2008/079521 A2 (VERTEX PHARMA [US]; BENNANI YOUSSEFF [US]; WANG TIANSHENG [US]; SALITU) 3 July 2008 (2008-07-03) the whole document -----	1-21
A	WO 2008/112217 A1 (MERCK & CO INC [US]; KOZINA EKATERINA [US]; DINSMORE CHRISTOPHER [US];) 18 September 2008 (2008-09-18) the whole document ----- -/-	1-21

Further documents are listed in the continuation of Box C.

See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 February 2012	28/02/2012
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Baston, Eckhard

INTERNATIONAL SEARCH REPORTInternational application No
PCT/EP2011/073734

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2009/035575 A1 (MERCK & CO INC [US]; SIU TONY [US]; YOUNG JONATHAN [US]; ALTMAN MICHAEL) 19 March 2009 (2009-03-19) the whole document -----	1-21

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Information on patent family members

International application No
PCT/EP2011/073734

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