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(54) Title: FUSED TRICYCLIC COMPOUNDS FOR USE AS INHIBITORS OF JANUS KINASES

(57) Abstract: The invention provides novel compounds of formula (I) having the general formula (I) wherein R_1, V, W, X, Y and Z are as described herein. Accordingly, the compounds may be provided in pharmaceutically acceptable compositions and used for the treatment of immunological or hyperproliferative disorders.

FUSED TRICYCLIC COMPOUNDS FOR USE AS INHIBITORS OF JANUS KINASES

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., IFNalpha), type II interferon (e.g., IFNgamma), 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).

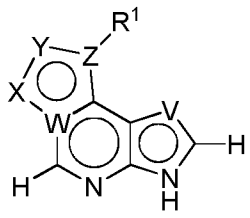
Biochemical and genetic studies have shown an association between JAK2 and single-chain (e.g., EPO), IL-3 and interferon gamma cytokine receptor families (Kisseleva et al., 2002, gene 285:1-24; Levy et al., 2005, Nat. Rev. Mol. Cell Biol. 3:651-662; O'Shea et al., 2002, Cell, 109 (suppl.): S121-S131). 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 R^1, V, W, X, Y and Z are defined herein.

Another aspect includes a pharmaceutical composition that includes a compound of 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 pharmaceutically acceptable salt thereof, for use 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 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 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 substituents described herein. In one example, the alkyl radical is one to eighteen carbon atoms (C_1-C_{18}). In other examples, the alkyl radical is C_0-C_6, C_0-C_5, C_0-C_3, C_1-C_{12}, C_1-C_{10}, C_1-C_8, C_1-C_6, C_1-C_5, C_1-C_4, or C_1-C_3. C_0 alkyl refers to a bond. Examples of alkyl groups include methyl (Me, $-CH_3$), ethyl (Et, $-CH_2CH_3$), 1-propyl (n-Pr, n-propyl, $-CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, $-CH(CH_3)_2$), 1-butyl (n-Bu, n-butyl, $-CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, $-CH_2CH(CH_3)_2$), 2-butyl (s-Bu, s-butyl, $-CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl, -

$C(CH_3)_3$), 1-pentyl (n-pentyl, $-CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($-CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($-CH(CH_2CH_3)_2$), 2-methyl-2-butyl ($-C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl ($-CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl ($-CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl ($-CH_2CH(CH_3)CH_2CH_3$), 1-hexyl ($-CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl ($-CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl ($-CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl ($-C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl ($-CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl ($-CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl ($-C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl ($-CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl ($-C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl ($-CH(CH_3)C(CH_3)_3$, 1-heptyl and 1-octyl.

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 (C_2-C_{18}). In other examples, the alkenyl radical is C_2-C_{12}, C_2-C_{10}, C_2-C_8, C_2-C_6 or C_2-C_3. Examples include, but are not limited to, ethenyl or vinyl ($-CH=CH_2$), prop-1-enyl ($-CH=CHCH_3$), prop-2-enyl ($-CH_2CH=CH_2$), 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.

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 (C_2-C_{18}). In other examples, the alkynyl radical is C_2-C_{12}, C_2-C_{10}, C_2-C_8, C_2-C_6 or C_2-C_3. Examples include, but are not limited to, ethynyl ($-C\equiv CH$), prop-1-ynyl ($-C\equiv CCH_3$), prop-2-ynyl (propargyl, $-CH_2C\equiv CH$), but-1-ynyl, 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 (C_1-C_{18}). In other examples, the divalent alkylene group is C_0-C_6,

C_0-C_5, C_0-C_3, C_1-C_{12}, C_1-C_{10}, C_1-C_8, C_1-C_6, C_1-C_5, C_1-C_4, or C_1-C_3. The group C_0 alkylene refers to a bond. Example alkylene groups include methylene (-CH_2-), 1,1-ethyl (-$CH(CH_3)$-), (1,2-ethyl (-CH_2CH_2-), 1,1-propyl (-$CH(CH_2CH_3)$-), 2,2-propyl (-$C(CH_3)_2$-), 1,2-propyl (-$CH(CH_3)CH_2$-), 1,3-propyl (-$CH_2CH_2CH_2$-), 1,1-dimethyleth-1,2-yl (-$C(CH_3)_2CH_2$-), 1,4-butyl (-$CH_2CH_2CH_2CH_2$-), and the like.

"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 (C_2-C_{18}). In other examples, the alkenylene group is C_2-C_{12}, C_2-C_{10}, C_2-C_8, C_2-C_6 or C_2-C_3. 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 (C_2-C_{18}). In other examples, the alkynylene radical is C_2-C_{12}, C_2-C_{10}, C_2-C_8, C_2-C_6 or C_2-C_3. Example alkynylene radicals include: acetylene (-C≡C-), propargyl (-CH_2C≡C-), and 4-pentynyl (-$CH_2CH_2CH_2$C≡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)-NH_2.

"Amino" means primary (i.e., –NH_2) , 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 inlcudes aryl groups having 6-10 carbon atoms. Examples of 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 herein. In one example, optional substituents on aryl are selected from halogen (F, Cl, Br, I), hydroxy, protected hydroxy, cyano, nitro, alkyl (for example C_1-C_6 alkyl), alkoxy (for example C_1-C_6 alkoxy), benzyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, aminomethyl, protected aminomethyl, trifluoromethyl, alkylsulfonylamino, alkylsulfonylaminoalkyl, arylsulfonylamino, arylsulfonylaminoalkyl, heterocyclylsulfonylamino, heterocyclylsulfonylaminoalkyl, heterocyclyl, aryl, or other groups specified. One or more methyne (CH) and/or methylene (CH_2) 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-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 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-(isopropoxy)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 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-benzyloxy-6-methyl sulfonylamino, 3-methoxy-4-benzyloxy-6-phenyl sulfonylamino, and tetrasubstituted phenyl groups where the substituents are different such as 3-methoxy-4-benzyloxy-5-methyl-6-phenyl sulfonylamino. Particular substituted phenyl groups include the 2-chlorophenyl, 2-aminophenyl, 2-bromophenyl, 3-methoxyphenyl, 3-ethoxy-phenyl, 4-benzyloxyphenyl, 4-methoxyphenyl, 3-ethoxy-4-benzyloxyphenyl, 3,4-diethoxyphenyl, 3-methoxy-4-benzyloxyphenyl, 3-methoxy-4-(1-chloromethyl)benzyloxy-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, betamethasone sodium phosphate, dexamethasone, dexamethasone sodium phosphate, fluocortolone, hydrocortisone-17-butyrate, hydrocortisone-17-valerate, aclometasone dipropionate, betamethasone valerate, betamethasone dipropionate, prednicarbate, clobetasone-17-butyrate, clobetasol-17-propionate, fluocortolone caproate, fluocortolone pivalate and fluprednidene acetate; immune selective anti-inflammatory peptides (ImSAIDs) such as 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 (TNFα) blockers such as etanercept (Enbrel), infliximab (Remicade), 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 such as rhuMAb Beta7; IgE pathway blockers such as Anti-M1 prime; Secreted homotrimeric LTa3 and membrane bound heterotrimer LTa1/β2 blockers such as Anti-lymphotoxin alpha (LTa); hormone antagonists, such as tamoxifen, finasteride or LHRH antagonists; radioactive isotopes (e.g., At^{211}, I^{131}, I^{125}, Y^{90}, Re^{186}, Re^{188}, Sm^{153}, Bi^{212}, P^{32}, Pb^{212} and radioactive isotopes of Lu); miscellaneous investigational agents such as thioplatin, PS-341, phenylbutyrate, ET-18- OCH_3, 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 cyclosphosphamide (CYTOXAN®); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide and trimethylomelamine; acetogenins (especially bullatacin and bullatacinone); delta-9-tetrahydrocannabinol (dronabinol, MARINOL®); beta-lapachone; lapachol; colchicines; betulinic acid; a camptothecin (including the synthetic analogue topotecan

(HYCAMTIN®), CPT-11 (irinotecan, CAMPTOSAR®), acetylcamptothecin, scopolectin, and 9-aminocamptothecin); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and 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, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosoureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimnustine; antibiotics such as the enediyne antibiotics (e. g., calicheamicin, especially calicheamicin gamma1I and calicheamicin omegaI1 (see, e.g., Nicolaou *et al.*, *Angew. Chem Intl. Ed. Engl.*, 33: 183-186 (1994)); CDP323, an oral alpha-4 integrin inhibitor; dynemicin, including dynemicin A; an 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-doxorubicin, doxorubicin HCl liposome injection (DOXIL®), liposomal doxorubicin TLC D-99 (MYOCET®), peglylated liposomal doxorubicin (CAELYX®), and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, porfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate, 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, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfornithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; 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; pipobroman; gacytosine; arabinoside ("Ara-C"); thiotepa; taxoid, *e.g.*, paclitaxel (TAXOL®), albumin-engineered nanoparticle formulation of paclitaxel (ABRAXANE™), and docetaxel (TAXOTERE®); chloranbucil; 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®), vincristine (ONCOVIN®), vindesine (ELDISINE®, FILDESIN®), and vinorelbine (NAVELBINE®); etoposide (VP-16); ifosfamide; mitoxantrone; leucovorin; novantrone; edatrexate; 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 OSTAC®), etidronate (DIDROCAL®), NE-58095, zoledronic acid/zoledronate (ZOMETA®), alendronate (FOSAMAX®), pamidronate (AREDIA®), tiludronate (SKELID®), or risedronate (ACTONEL®); troxacitabine (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 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); 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, SARASAR™); 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 abbreviation for a treatment regimen with oxaliplatin (ELOXATIN™) 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

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, inhibit DNA binding, increase ER turnover, and/or suppress ER levels); aromatase inhibitors, including steroidal 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 hormone-releaseing hormone agonists, including leuprolide (LUPRON® and ELIGARD®), goserelin, buserelin, and tripterelin; sex steroids, including progestines such as megestrol acetate and medroxyprogesterone acetate, estrogens such as diethylstilbestrol and premarin, and androgens/retinoids such as fluoxymesterone, all transretionic acid and fenretinide; onapristone; anti-progesterones; estrogen receptor down-regulators (ERDs); anti-androgens such as flutamide, 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), 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, cidfusituzumab, cidtuzumab, daclizumab, eculizumab, efalizumab, epratuzumab, erlizumab, felvizumab, fontolizumab, gemtuzumab ozogamicin, inotuzumab ozogamicin, ipilimumab, labetuzumab, lintuzumab, matuzumab, mepolizumab, motavizumab, motovizumab, natalizumab, nimotuzumab, nolovizumab, numavizumab, ocrelizumab, omalizumab, palivizumab, pascolizumab, pecfusituzumab, pectuzumab, pexelizumab, ralivizumab, ranibizumab, reslivizumab, reslizumab, resyvizumab, rovelizumab, 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 IgG_1 λ antibody genetically modified to recognize interleukin-12 p40 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 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; ERBUTIX®) 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. 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 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 (IRESSAJ) 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-quinolinyl]-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 (GLEEVECℑ, 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); 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 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 (GLEEVECℑ); 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, 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).

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, diclofenac, enolic acid derivatives such as piroxicam, meloxicam, tenoxicam, droxicam, lornoxicam and isoxicam, fenamic acid derivatives such as mefenamic acid, meclofenamic acid, flufenamic acid, tolfenamic 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 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.

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 (C_3-C_{12}). In other examples, cycloalkyl is C_3-C_8, C_3-C_{10} or C_5-C_{10}. In other examples, the cycloalkyl group, as a monocycle, is C_3-C_8, C_3-C_6 or C_5-C_6. In another example, the cycloalkyl group, as a bicycle, is C_7-C_{12}. In another example, the cycloalkyl group, as a spiro system, is C_5-C_{12}. 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, 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 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)-NH_2.

"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 tetrahydropyranyloxy, 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 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 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 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, SO_2), and any nitrogen heteroatom may optionally be quaternized (e.g. $[NR_4]^+Cl^-$, $[NR_4]^+OH^-$). Example 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, hexahydropyrimidinyl, oxazinanyl, thiazinanyl, thioxanyl, 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, oxatriazinyl, dithiadiazinyl, imidazolinyl, dihydropyrimidyl, tetrahydropyrimidyl, 1-pyrrolinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 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, tetrahydroindazolyl, 1,1-dioxohexahydrothiopyranyl. 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 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-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, *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 another embodiment, heteroaryl includes 5-6 membered monocyclic aromatic groups where one or more ring atoms is nitrogen, sulfur or oxygen. Example heteroaryl 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, 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-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 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-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.

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 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.

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.

"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, 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 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 another embodiment an optionally substituted group has 2 substituents. In another embodiment an optionally substituted group has 3 substituents.

In certain embodiments, divalent groups are described generically without specific bonding configurations, for example in the group $–CH_2C(O)–$. It is understood that the generic description is meant to include both bonding configurations, unless specified otherwise. For example, in the group $R^w–R^x–R^y$, if the group R^x is described as $–CH_2C(O)–$, then it is understood that this group can be bonded both as $R^w–CH_2C(O)–R^y$, and as $R^w–C(O)CH_2–R^y$, 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, glucosamine, methylglucamine, theobromine, purines, piperizine, 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 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.

"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.

"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 have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L, or *R* and *S,* are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

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

A "solvate" refers to an association or complex of one or more solvent molecules and a 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), 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, or (iii) prevents or delays the onset of one or more symptoms of the particular disease, condition or disorder described herein. In the case of cancer, the therapeutically effective amount of the drug may reduce the number of cancer cells; reduce the tumor size; inhibit (i.e., slow to some extent and preferably stop) cancer cell infiltration into peripheral organs; inhibit (i.e., slow to

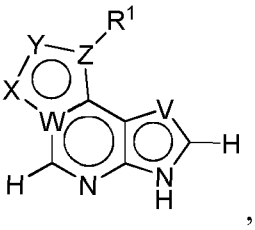
some extent and preferably stop) tumor metastasis; inhibit, to some extent, tumor growth; and/or relieve to some extent one or more of the symptoms associated with the cancer. To the extent the drug may prevent growth and/or kill existing cancer cells, it may be cytostatic and/or cytotoxic. For cancer therapy, efficacy can, for example, be measured by assessing the time to disease progression (TTP) and/or determining the response rate (RR). In 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.

"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) 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 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), and prodrugs 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 formulas I, II and III, wherein one or more hydrogen atoms are replaced by deuterium or tritium, or one or more carbon atoms are replaced by ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention.

INHIBITORS OF JAK1 KINASE

One aspect of the invention provides compounds of formula I:



I

stereoisomers, tautomers and pharmaceutically acceptable salts thereof, wherein

V is CR^4 or N, W is C, X and Z are N, and Y is CR^5 or N; or

V is CR^4 or N, W is N, X is CH, Y is CR^5, and Z is C;

R^1 is C_{3-12} cycloalkyl or 3-12 membered heterocyclyl, wherein R^1 is independently optionally substituted by halogen, oxo, −CN, $-OR^a$, $-S(O)_{0-2}R^a$, $-NR^aR^b$, C_{1-3} alkylene, C_{1-6} alkyl, $-(C_{0-3}$ alkylene)C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-(C_{0-3}$ alkylene)phenyl, or $-(C_{0-3}$ alkylene)3-6 membered heterocyclyl, wherein said alkyl, alkylene, alkenyl and alkynyl are independently optionally substituted by oxo, $-NR^cR^d$, $-OR^c$, −CN or halogen and said C_{3-6} cycloalkyl, phenyl and 3-6 membered heterocyclyl are independently optionally substituted by R^6;

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

R^5 is 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)$S(O)_{1-2}R^a$, $-(C_{0-3}$ alkylene)$NR^aS(O)_{1-2}R^b$, $-(C_{0-3}$ alkylene)$S(O)_{1-2}NR^aR^b$, $-(C_{0-3}$ alkylene)$NR^aS(O)_{1-2}NR^aR^b$, $-(C_{0-3}$ alkylene)C_{3-12} cycloalkyl, $-(C_{0-3}$ alkylene)C_{6-14} 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, 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)$S(O)_{0-2}R^c$, $-(C_{0-3}$ alkylene)$NR^cS(O)_{1-2}R^d$, $-(C_{0-3}$ alkylene)$S(O)_{1-2}NR^cR^d$, $-(C_{0-3}$ alkylene)$NR^cS(O)_{1-2}NR^cR^d$ or C_{1-6} alkyl optionally substituted by oxo, −CN or halogen;

each R^6 is independently oxo, halogen, $-CN$, $-C(O)R^a$, $-C(O)OR^a$, $-NR^aC(O)R^b$, $-C(O)NR^aR^b$, $-NR^aC(O)NR^aR^b$, $-OC(O)NR^aR^b$, $-NR^aC(O)OR^b$, $-S(O)_{1-2}R^a$, $-NR^aS(O)_2R^b$, $-S(O)_2NR^aR^b$, $-OR^a$, $-SR^a$, $-NR^aR^b$, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3-7 membered heterocycly or C_{6-14} aryl, and wherein said alkyl, alkenyl, alkynyl, cycloalkyl, 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)C_{3-6} cycloalkyl, $-S(O)_{1-2}R^i$, $-(C_{0-3}$ alkylene)3-12 membered heterocyclyl, $-(C_{0-3}$ alkylene)C(O)3-12 membered heterocyclyl or $-(C_{0-3}$ 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, $-(C_{0-3}$ alkylene)C_{3-6} cycloalkyl, $-(C_{0-3}$ alkylene)3-12 membered heterocyclyl, $-(C_{0-3}$ alkylene)C(O)3-12 membered heterocyclyl or $-(C_{0-3}$ alkylene)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, R^i are independently hydrogen or C_{1-6} alkyl optionally substituted by halogen or oxo.

In certain embodiments, Formula I includes compounds other than:

N-[(1S,3S,4R)-3-(2-aminoimidazo[4,5-d]pyrrolo[2,3-b]pyridin-1(6H)-yl)-4-ethylcyclopentyl]-cyclopropanesulfonamide;

N-((1R,3S,4R)-3-ethyl-4-(pyrrolo[2,3-b][1,2,3]triazolo[4,5-d]pyridin-1(6H)-yl)cyclopentyl)cyclopropanesulfonamide;

N-[(1S,3R,4S)-3-ethyl-4-[2-(trifluoromethyl)imidazo[4,5-d]pyrrolo[2,3-b]pyridin-1(6H)-yl]cyclopentyl]-cyclopropanesulfonamide;

N-[(1S,3R,4S)-3-ethyl-4-(2-methylimidazo[4,5-d]pyrrolo[2,3-b]pyridin-1(6H)-yl)cyclopentyl]-Cyclopropanesulfonamide;

N-[(1S,3S,4R)-3-[2-(difluoromethyl)imidazo[4,5-d]pyrrolo[2,3-b]pyridin-1(6H)-yl]-4-ethylcyclopentyl]-cyclopropanesulfonamide;

N-[(1S,3R,4S)-3-methyl-4-[2-(trifluoromethyl)imidazo[4,5-d]pyrrolo[2,3-b]pyridin-1(6H)-yl]cyclopentyl]-cyclopropanesulfonamide;

N-[(1S,3S,4R)-3-(2-cyclopropylimidazo[4,5-d]pyrrolo[2,3-b]pyridin-1(6H)-yl)-4-methylcyclopentyl]-cyclopropanesulfonamide;

N-[(1S,3R,4S)-3-methyl-4-(2-methylimidazo[4,5-d]pyrrolo[2,3-b]pyridin-1(6H)-yl)cyclopentyl]-cyclopropanesulfonamide;

1-cyclohexyl-1,6-dihydro-2-(trifluoromethyl)-imidazo[4,5-d]pyrrolo[2,3-b]pyridine; and

1-cyclohexyl-1,6-dihydro-2-methyl-imidazo[4,5-d]pyrrolo[2,3-b]pyridine, and

with the proviso that R^5 in Formula I is other than OH.

In certain embodiments, R^5 is other than NH_2, OH, methyl, difluoromethyl, trifluoromethyl or cyclopropyl. In certain embodiments, R^5 is other than OH.

In certain embodiments, V is CR^4 or N, W is N, X is CH, Y is CR^5, and Z is C.

In certain embodiments, V is CR^4, W is N, X is CH, Y is CR^5, and Z is C.

In certain embodiments, V is CR^4 or N, W is C, X and Z are N, and Y is CR^5 or N.

In certain embodiments, V is CR^4, W is C, X and Z are N, and Y is CR^5 or N.

In certain embodiments, V is N, W is C, X and Z are N, and Y is CR^5 or N.

In certain embodiments, V is CR^4, W is C, X and Z are N, and Y is CR^5.

In certain embodiments, V is CR^4, W is C, X and Z are N, and Y is N.

In certain embodiments, V is N, W is C, X and Z are N, and Y is N.

In certain embodiments, V is CR^4, W is C, X and Z are N, and Y is N.

In certain embodiments R^1 is 3-12 membered heterocyclyl, wherein R^1 is independently optionally substituted by halogen, oxo, −CN, $-OR^a$, $-S(O)_{0-2}R^a$, $-NR^aR^b$, C_{1-3} alkylene, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, or 3-6 membered heterocyclyl, wherein said alkyl, alkenyl and alkynyl are independently optionally substituted by oxo, $-NR^cR^d$, $-OR^c$, −CN or halogen and said C_{3-6} cycloalkyl, phenyl and 3-6 membered heterocyclyl are independently optionally substituted by R^6.

In certain embodiments R^1 is 6-membered heterocyclyl, optionally substituted by halogen, oxo, −CN, $-OR^a$, $-S(O)_{0-2}R^a$, $-NR^aR^b$, C_{1-3} alkylene, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, or 3-6 membered heterocyclyl, wherein said alkyl, alkenyl and alkynyl are independently optionally substituted by oxo, $-NR^cR^d$, $-OR^c$, −CN or halogen and said C_{3-6} cycloalkyl, phenyl and 3-6 membered heterocyclyl are independently optionally substituted by R^6.

In certain embodiments, R^1 is tetrahydropyranyl, tetrahydro-2H-thiopyranyl or piperidinyl, optionally substituted by halogen, oxo, −CN, $-OR^a$, $-S(O)_{0-2}R^a$, $-NR^aR^b$, C_{1-3} alkylene, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, or 3-6 membered heterocyclyl, wherein said alkyl, alkenyl and alkynyl are independently optionally substituted by oxo, $-NR^cR^d$, $-OR^c$, −CN or halogen and said C_{3-6} cycloalkyl, phenyl and 3-6 membered heterocyclyl are independently optionally substituted by R^6.

In certain embodiments R^1 is C_{3-12} cycloalkyl, wherein R^1 is independently optionally substituted by halogen, oxo, −CN, $-OR^a$, $-S(O)_{0-2}R^a$, $-NR^aR^b$, C_{1-3} alkylene, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, or 3-6 membered heterocyclyl, wherein said alkyl, alkenyl and alkynyl are independently optionally substituted by oxo, $-NR^cR^d$, $-OR^c$, −CN or halogen and said C_{3-6} cycloalkyl, phenyl and 3-6 membered heterocyclyl are independently optionally substituted by R^6.

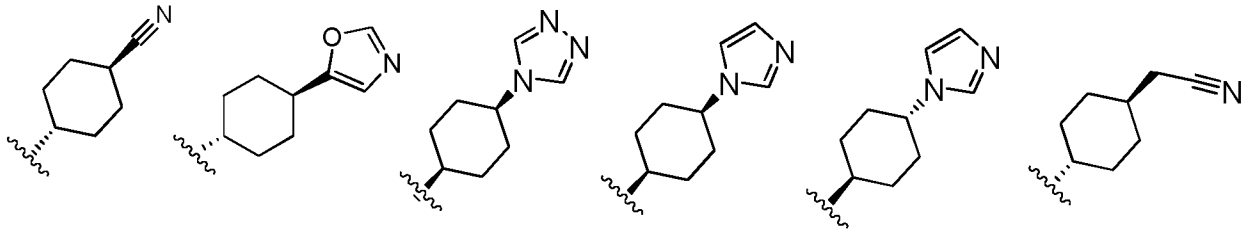
In certain embodiments R^1 is cyclopentyl or cyclohexyl, wherein R^1 is independently optionally substituted by halogen, oxo, −CN, $-OR^a$, $-S(O)_{0-2}R^a$, $-NR^aR^b$, C_{1-3} alkylene, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, or 3-6 membered heterocyclyl, wherein said alkyl, alkenyl and alkynyl are independently optionally substituted by oxo, $-NR^cR^d$, $-OR^c$, −CN or halogen and said C_{3-6} cycloalkyl, phenyl and 3-6 membered heterocyclyl are independently optionally substituted by R^6.

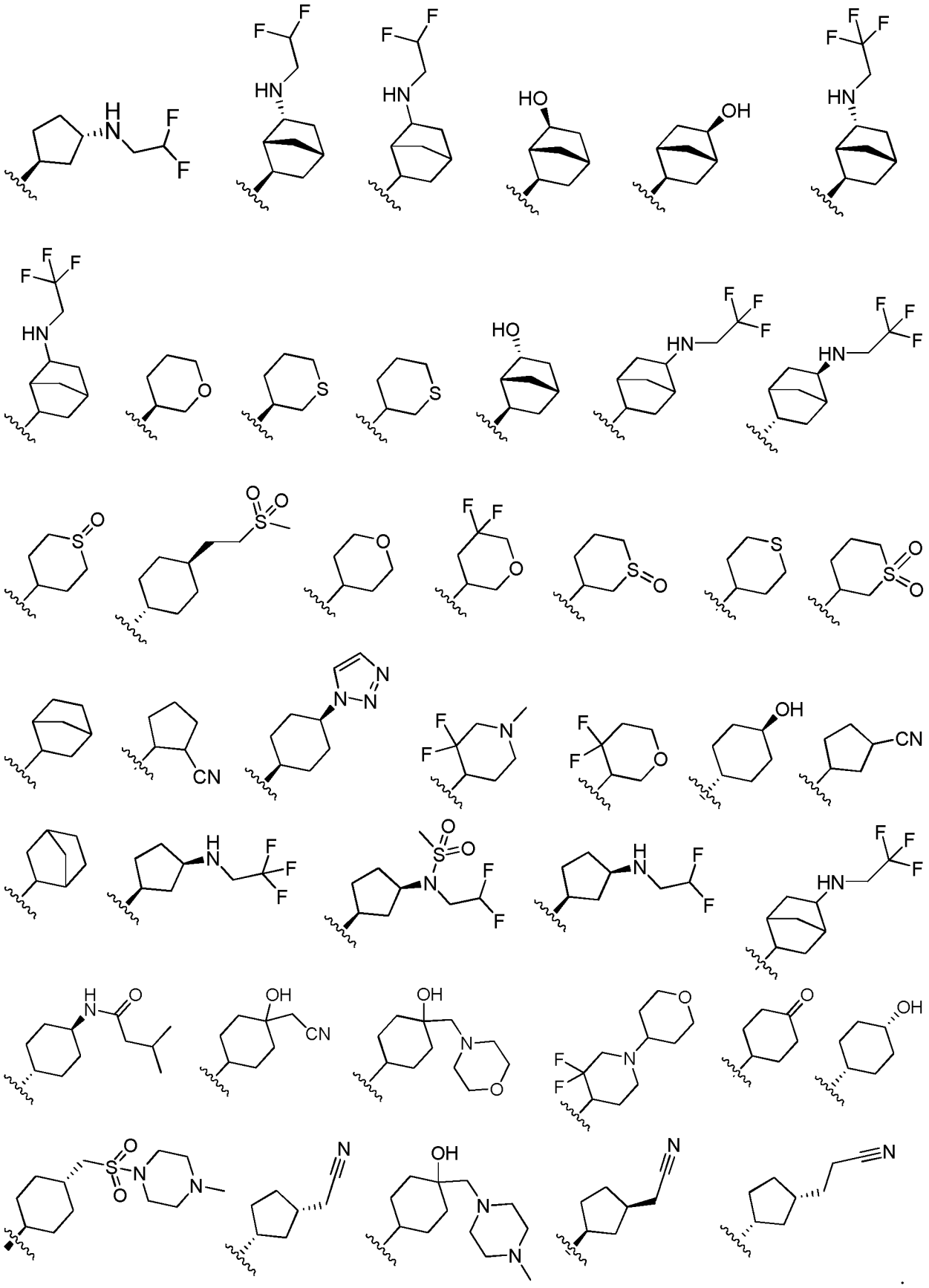
In another embodiment, R^1 is cyclohexyl optionally substituted by halogen, oxo, −CN, $-OR^a$, $-S(O)_{0-2}R^a$, $-NR^aR^b$, C_{1-3} alkylene, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, or 3-6 membered heterocyclyl, wherein said alkyl, alkenyl and alkynyl are independently optionally substituted by oxo, $-NR^cR^d$, $-OR^c$, −CN or halogen and said C_{3-6} cycloalkyl, phenyl and 3-6 membered heterocyclyl are independently optionally substituted by R^6. In another embodiment, R^1 is cyclohexyl optionally substituted by halogen, oxo, −CN, $-OR^a$, $-NR^aR^b$, C_{1-3} alkylene or C_{1-6} alkyl optionally substituted by halogen. In another embodiment, R^1 is cyclohexyl optionally substituted by halogen, oxo, C_{1-3} alkylene or C_{1-6} alkyl optionally substituted by halogen. In another embodiment, R^1 is cyclohexyl. In certain embodiments, R^1 is selected from cyclohexyl, 2-hydroxycyclohexyl, 3-hydroxycyclohexyl, 4-hydroxycyclohexyl, bicyclo[2.2.1]heptanyl, 2-methylcyclohexyl or 4,4-difluorocyclohexyl, wherein R^1 is optionally substituted by halogen, oxo, −CN, $-OR^a$, $-NR^aR^b$, C_{1-3} alkylene or C_{1-6} alkyl optionally substituted by halogen, and wherein the wavy line represents the point of attachment in formula I.

In another embodiment, R^1 is cyclopentyl halogen, oxo, −CN, $-OR^a$, $-S(O)_{0-2}R^a$, $-NR^aR^b$, C_{1-3} alkylene, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, or 3-6 membered heterocyclyl, wherein said alkyl, alkenyl and alkynyl are independently optionally substituted by oxo, $-NR^cR^d$, $-OR^c$, −CN or halogen and said C_{3-6} cycloalkyl, phenyl and 3-6 membered heterocyclyl are independently optionally substituted by R^6. In another embodiment, R^1 is cyclopentyl optionally substituted by halogen, oxo, −CN, $-OR^a$, $-NR^aR^b$, C_{1-3} alkylene or C_{1-6} alkyl optionally substituted by halogen. In another embodiment, R^1 is cyclopentyl.

In certain embodiments R^1 is tetrahydropyranyl, tetrahydro-2H-thiopyranyl, piperidinyl, cyclopentyl or cyclohexyl, wherein R^1 is independently optionally substituted by halogen, oxo, −CN, $-OR^a$, $-S(O)_{0-2}R^a$, $-NR^aR^b$, C_{1-3} alkylene, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, or 3-6 membered heterocyclyl, wherein said alkyl, alkenyl and alkynyl are independently optionally substituted by oxo, $-NR^cR^d$, $-OR^c$, −CN or halogen and said C_{3-6} cycloalkyl, phenyl and 3-6 membered heterocyclyl are independently optionally substituted by R^6.

In certain embodiments, $-R^1$ is selected from:





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

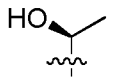
In certain embodiments, R^4 is hydrogen, methyl, CN or F. In another embodiment, R^4 is hydrogen or CN. In certain embodiments, R^4 is hydrogen.

In certain embodiments, R^5 is 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)$S(O)_{1-2}R^a$, $-(C_{0-3}$ alkylene)$NR^aS(O)_{1-2}R^b$, $-(C_{0-3}$ alkylene)$S(O)_{1-2}NR^aR^b$, $-(C_{0-3}$ alkylene)$NR^aS(O)_{1-2}NR^aR^b$, $-(C_{0-3}$ alkylene)C_{3-6} cycloalkyl, $-(C_{0-3}$ alkylene)C_{6-14} 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, 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)$S(O)_{0-2}R^c$, $-(C_{0-3}$ alkylene)$NR^cS(O)_{1-2}R^d$, $-(C_{0-3}$ alkylene)$S(O)_{1-2}NR^cR^d$, $-(C_{0-3}$ alkylene)$NR^cS(O)_{1-2}NR^cR^d$ or C_{1-6} alkyl optionally substituted by oxo, $-CN$ or halogen, with the proviso that R^5 is other than NH_2, OH, methyl, difluoromethyl, trifluoromethyl or cyclopropyl.

In certain embodiments, R^5 is C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, $-(C_{1-3}$ alkylene)CN, $-(C_{1-3}$ alkylene)NR^aR^b, $-(C_{1-3}$ alkylene)OR^a, $-(C_{1-3}$ alkylene)SR^a, $-(C_{1-3}$ alkylene)$C(O)R^a$, $-(C_{1-3}$ alkylene)$NR^aC(O)R^b$, $-(C_{1-3}$ alkylene)$C(O)NR^aR^b$, $-(C_{1-3}$ alkylene)$C(O)OR^a$, $-(C_{1-3}$ alkylene)$OC(O)R^a$, $-(C_{1-3}$ alkylene)$NR^aC(O)NR^aR^b$, $-(C_{1-3}$ alkylene)$OC(O)NR^aR^b$, $-(C_{1-3}$ alkylene)$NR^aC(O)OR^b$, $-(C_{1-3}$ alkylene)$S(O)_{1-2}R^a$, $-(C_{1-3}$ alkylene)$NR^aS(O)_{1-2}R^b$, $-(C_{1-3}$ alkylene)$S(O)_{1-2}NR^aR^b$, $-(C_{1-3}$ alkylene)$NR^aS(O)_{1-2}NR^aR^b$, $-(C_{1-3}$ alkylene)C_{3-6} cycloalkyl, $-(C_{1-3}$ alkylene)C_{6-14} aryl, $-(C_{1-3}$ alkylene)3-12 membered heterocyclyl or $-(C_{1-3}$ alkylene)C(O)3-12 membered heterocyclyl, wherein said alkyl, alkenyl, alkynyl, alkylene, cycloalkyl, aryl and heterocyclyl are independently optionally substituted by halogen, oxo, $-(C_{0-3}$ 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)$S(O)_{0-2}R^c$, $-(C_{0-3}$ alkylene)$NR^cS(O)_{1-2}R^d$, $-(C_{0-3}$ alkylene)$S(O)_{1-2}NR^cR^d$, $-(C_{0-3}$ alkylene)$NR^cS(O)_{1-2}NR^cR^d$ or C_{1-6} alkyl optionally substituted by oxo, $-CN$ or halogen, with the proviso that R^5 is other than methyl, difluoromethyl, trifluoromethyl or cyclopropyl.

In certain embodiments, R^5 is $-(C_{1-3}$ alkylene)CN, $-(C_{1-3}$ alkylene)NR^aR^b, $-(C_{1-3}$ alkylene)OR^a, $-(C_{1-3}$ alkylene)SR^a, $-(C_{1-3}$ alkylene)$C(O)R^a$, $-(C_{1-3}$ alkylene)$NR^aC(O)R^b$, $-(C_{1-3}$

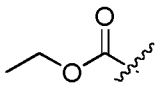
alkylene)C(O)NR^{a}R^b, −(C$_{1-3}$ alkylene)C(O)OR^a, −(C$_{1-3}$ alkylene)OC(O)R^a, −(C$_{1-3}$ alkylene)NR^{a}C(O)NR^{a}R^b, −(C$_{1-3}$ alkylene)OC(O)NR^{a}R^b, −(C$_{1-3}$ alkylene)NR^{a}C(O)OR^b, −(C$_{1-3}$ alkylene)S(O)$_{1-2}$R^a, −(C$_{1-3}$ alkylene)NR^{a}S(O)$_{1-2}$R^b, −(C$_{1-3}$ alkylene)S(O)$_{1-2}$NR^{a}R^b, −(C$_{1-3}$ alkylene)NR^{a}S(O)$_{1-2}$NR^{a}R^b, −(C$_{1-3}$ alkylene)C$_{4-6}$ cycloalkyl, −(C$_{1-3}$ alkylene)C$_{6-14}$ aryl, −(C$_{1-3}$ alkylene)3-12 membered heterocyclyl or −(C$_{1-3}$ alkylene)C(O)3-12 membered heterocyclyl, wherein said alkylene, 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^{c}R^d, −(C$_{0-3}$ alkylene)C(O)R^c, −(C$_{0-3}$ alkylene)C(O)OR^c, −(C$_{0-3}$ alkylene)C(O)NR^{c}R^d, −(C$_{0-3}$ alkylene)NR^{c}C(O)R^d, −(C$_{0-3}$ alkylene)OC(O)NR^{c}R^d, −(C$_{0-3}$ alkylene)NR^{c}C(O)NR^{c}R^d, −(C$_{0-3}$ alkylene)NR^{c}C(O)OR^d, −(C$_{0-3}$ alkylene)S(O)$_{0-2}$R^c, −(C$_{0-3}$ alkylene)NR^{c}S(O)$_{1-2}$R^d, −(C$_{0-3}$ alkylene)S(O)$_{1-2}$NR^{c}R^d, −(C$_{0-3}$ alkylene)NR^{c}S(O)$_{1-2}$NR^{c}R^d or C$_{1-6}$ alkyl optionally substituted by oxo, −CN or halogen.

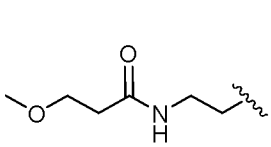
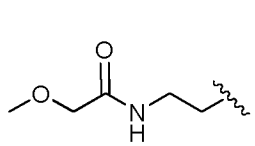
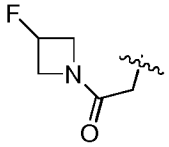
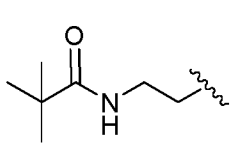
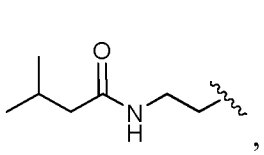
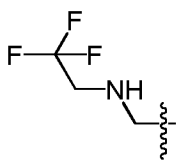
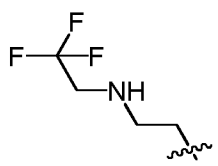
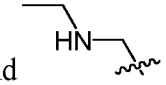
In certain embodiments, R^5 is C$_{1-12}$ alkyl, C$_{2-12}$ alkenyl, C$_{2-12}$ alkynyl, wherein said alkyl, alkenyl and alkynyl are independently optionally substituted by halogen, oxo, −(C$_{0-3}$ alkylene)CN, −(C$_{0-3}$ alkylene)OR^c, −(C$_{0-3}$ alkylene)NR^{c}R^d, −(C$_{0-3}$ alkylene)C(O)R^c, −(C$_{0-3}$ alkylene)C(O)OR^c, −(C$_{0-3}$ alkylene)C(O)NR^{c}R^d, −(C$_{0-3}$ alkylene)NR^{c}C(O)R^d, −(C$_{0-3}$ alkylene)OC(O)NR^{c}R^d, −(C$_{0-3}$ alkylene)NR^{c}C(O)NR^{c}R^d, −(C$_{0-3}$ alkylene)NR^{c}C(O)OR^d, −(C$_{0-3}$ alkylene)S(O)$_{0-2}$R^c, −(C$_{0-3}$ alkylene)NR^{c}S(O)$_{1-2}$R^d, −(C$_{0-3}$ alkylene)S(O)$_{1-2}$NR^{c}R^d, −(C$_{0-3}$ alkylene)NR^{c}S(O)$_{1-2}$NR^{c}R^d or C$_{1-6}$ alkyl optionally substituted by oxo, −CN or halogen. In certain embodiments, R^5 is selected from methyl, ethyl, –CH$_2$OH,  ,  , wherein the wavy line represents the point of attachment in formula I.

In certain embodiments, R^5 is C$_{1-12}$ alkyl, C$_{2-12}$ alkenyl, C$_{2-12}$ alkynyl, wherein said alkyl, alkenyl and alkynyl are independently substituted by one or more of halogen, oxo, −(C$_{0-3}$ alkylene)CN, −(C$_{0-3}$ alkylene)OR^c, −(C$_{0-3}$ alkylene)NR^{c}R^d, −(C$_{0-3}$ alkylene)C(O)R^c, −(C$_{0-3}$ alkylene)C(O)OR^c, −(C$_{0-3}$ alkylene)C(O)NR^{c}R^d, −(C$_{0-3}$ alkylene)NR^{c}C(O)R^d, −(C$_{0-3}$ alkylene)OC(O)NR^{c}R^d, −(C$_{0-3}$ alkylene)NR^{c}C(O)NR^{c}R^d, −(C$_{0-3}$ alkylene)NR^{c}C(O)OR^d, −(C$_{0-3}$ alkylene)S(O)$_{0-2}$R^c, −(C$_{0-3}$ alkylene)NR^{c}S(O)$_{1-2}$R^d, −(C$_{0-3}$ alkylene)S(O)$_{1-2}$NR^{c}R^d, −(C$_{0-3}$ alkylene)NR^{c}S(O)$_{1-2}$NR^{c}R^d and C$_{1-6}$ alkyl optionally substituted by oxo, −CN or halogen. In certain embodiments, R^5 is methyl or ethyl substituted by one or more OH.

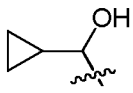
In certain embodiments, R^5 is −(C$_{0-3}$ alkylene)CN, wherein said alkylene is independently optionally substituted by halogen, oxo, −(C$_{0-3}$ alkylene)CN, −(C$_{0-3}$ alkylene)OR^c, −(C$_{0-3}$ alkylene)NR^{c}R^d, −(C$_{0-3}$ alkylene)C(O)R^c, −(C$_{0-3}$ alkylene)C(O)OR^c, −(C$_{0-3}$ alkylene)C(O)NR^{c}R^d,

$-(C_{0-3}$ 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)$S(O)_{0-2}R^c$, $-(C_{0-3}$ alkylene)$NR^cS(O)_{1-2}R^d$, $-(C_{0-3}$ alkylene)$S(O)_{1-2}NR^cR^d$, $-(C_{0-3}$ 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 $-CN$.

In certain embodiments, R^5 is $-(C_{0-3}$ alkylene)OR^a or $-(C_{0-3}$ alkylene)SR^a, wherein said alkylene is 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)$S(O)_{0-2}R^c$, $-(C_{0-3}$ alkylene)$NR^cS(O)_{1-2}R^d$, $-(C_{0-3}$ alkylene)$S(O)_{1-2}NR^cR^d$, $-(C_{0-3}$ 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 $-CH_2OH$,  and $-CH_2CH_2OH$.

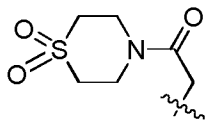
In certain embodiments, R^5 is $-(C_{0-3}$ alkylene)NR^aR^b, wherein said alkylene is independently optionally substituted by halogen, oxo, $-(C_{0-3}$ alkylene)CN, $-(C_{0-3}$ alkylene)OR^c, $-(C_{0-3}$ alkylene)NR^cR^d, $-(C_{0-3}$ alkylene)$C(O)R^c$, $-(C_{0-3}$ alkylene)$C(O)OR^c$, $-(C_{0-3}$ alkylene)$C(O)NR^cR^d$, $-(C_{0-3}$ 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)$S(O)_{0-2}R^c$, $-(C_{0-3}$ alkylene)$NR^cS(O)_{1-2}R^d$, $-(C_{0-3}$ alkylene)$S(O)_{1-2}NR^cR^d$, $-(C_{0-3}$ alkylene)$NR^cS(O)_{1-2}NR^cR^d$ or C_{1-6} alkyl optionally substituted by oxo, $-CN$ or halogen. In one embodiment, R^5 is $-(C_{0-3}$ alkylene)NR^aR^b, wherein said alkylene is optionally substituted by halogen, oxo, $-CN$, $-OR^c$, $-NR^cR^d$, $-C(O)OR^c$, or C_{1-6} alkyl optionally substituted by oxo, $-CN$ or halogen. In certain embodiments, R^5 is selected from $-NHCH_2CH_2OH$, $-CF_2CH_2NH_2$, $-CH_2C(O)NH_2$,  ,  ,  ,  ,  ,  ,  , and  , wherein the wavy line represents the point of attachment in formula I.

In certain embodiments, R^5 is $-(C_{0-3}$ alkylene)C_{3-12} cycloalkyl, wherein said alkylene and cycloalkyl 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^{c}R^d, −(C$_{0-3}$ alkylene)NR^{c}C(O)R^d, −(C$_{0-3}$ alkylene)OC(O)NR^{c}R^d, −(C$_{0-3}$ alkylene)NR^{c}C(O)NR^{c}R^d, −(C$_{0-3}$ alkylene)NR^{c}C(O)OR^d, −(C$_{0-3}$ alkylene)S(O)$_{0-2}$R^c, −(C$_{0-3}$ alkylene)NR^{c}S(O)$_{1-2}$R^d, −(C$_{0-3}$ alkylene)S(O)$_{1-2}$NR^{c}R^d, −(C$_{0-3}$ alkylene)NR^{c}S(O)$_{1-2}$NR^{c}R^d or C$_{1-6}$ alkyl optionally substituted by oxo, −CN or halogen. In one embodiment, R^5 is −(C$_{0-3}$ alkylene)C$_{3-6}$ cycloalkyl, wherein said alkylene and cycloalkyl are independently optionally substituted by halogen, oxo, −CN, −OR^c, −NR^{c}R^d, −C(O)OR^c, or C$_{1-6}$ alkyl optionally substituted by oxo, −CN or halogen. In certain embodiments, R^5 is other than cyclopropyl. In certain embodiments, R^5 is 

In certain embodiments, R^5 is −(C$_{0-3}$ alkylene)C$_{3-7}$ cycloalkyl. In another embodiment, R^5 is cyclopropyl or cyclobutyl.

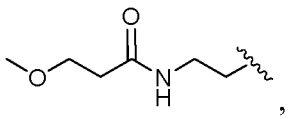
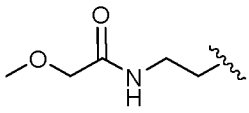
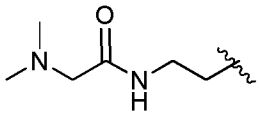
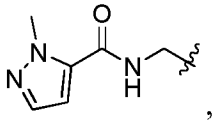
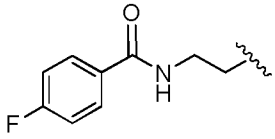
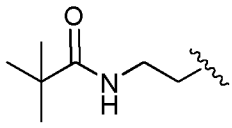
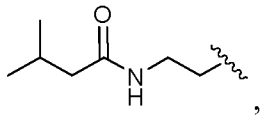
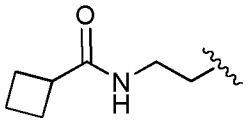
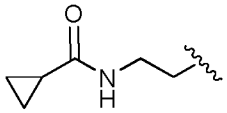
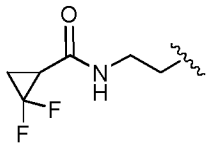
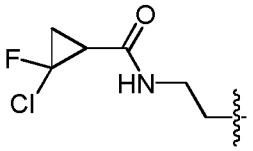
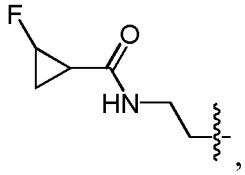
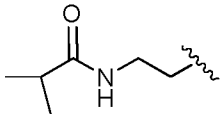
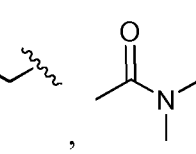
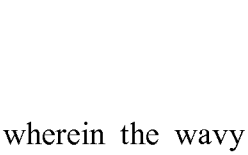
In certain embodiments, R^5 is −(C$_{0-3}$ alkylene)C(O)NR^{a}R^b, wherein said alkylene is independently optionally substituted by halogen, oxo, −(C$_{0-3}$ alkylene)CN, −(C$_{0-3}$ alkylene)OR^c, −(C$_{0-3}$ alkylene)NR^{c}R^d, −(C$_{0-3}$ alkylene)C(O)R^c, −(C$_{0-3}$ alkylene)C(O)OR^c, −(C$_{0-3}$ alkylene)C(O)NR^{c}R^d, −(C$_{0-3}$ alkylene)NR^{c}C(O)R^d, −(C$_{0-3}$ alkylene)OC(O)NR^{c}R^d, −(C$_{0-3}$ alkylene)NR^{c}C(O)NR^{c}R^d, −(C$_{0-3}$ alkylene)NR^{c}C(O)OR^d, −(C$_{0-3}$ alkylene)S(O)$_{0-2}$R^c, −(C$_{0-3}$ alkylene)NR^{c}S(O)$_{1-2}$R^d, −(C$_{0-3}$ alkylene)S(O)$_{1-2}$NR^{c}R^d, −(C$_{0-3}$ alkylene)NR^{c}S(O)$_{1-2}$NR^{c}R^d or C$_{1-6}$ alkyl optionally substituted by oxo, −CN or halogen. In one embodiment, R^5 is −(C$_{0-3}$ alkylene)C(O)NR^{a}R^b, wherein said alkylene is optionally substituted by halogen, oxo, −CN, −OR^c, −NR^{c}R^d, −C(O)OR^c, or C$_{1-6}$ alkyl optionally substituted by oxo, −CN or halogen. In certain embodiments, R^5 is selected from –CH$_2$C(O)NH$_2$, –CH$_2$C(O)NHcyclopentyl, −CH$_2$C(O)N(CH$_3$)(cyclopentyl), –CH$_2$C(O)NHCH$_3$, –CH(CH$_3$)C(O)NHCH(CH$_3$)$_2$, −CH$_2$C(O)(pyrrolidin-1-yl), −CH$_2$C(O)(4,4-difluorpiperidin-1-yl), −CH$_2$C(O)(morpholinyl) and



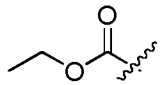
, wherein the wavy line represents the point of attachment in formula I.

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

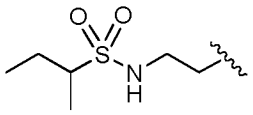
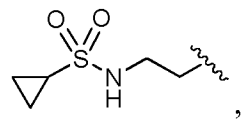
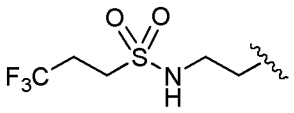
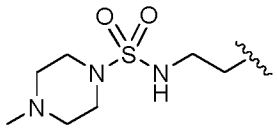
alkylene)$NR^aC(O)R^b$, wherein said alkylene is optionally substituted by halogen, oxo, −CN, $-OR^c$, $-NR^cR^d$, $-C(O)OR^c$, or C_{1-6} alkyl optionally substituted by oxo, −CN or halogen. In certain embodiments, R^5 is selected from $-CH_2NHC(O)CH_3$, $-CH_2NHC(O)CH(CH_3)_2$, $-CH_2NHC(O)CH_2CH_3$, $-CH_2NHC(O)CH_2OCH_3$, $-CH_2NHC(O)$pyridin-3-yl, $-CH_2NHC(O)$pyridin-4-yl,

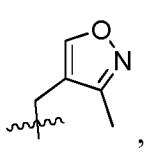
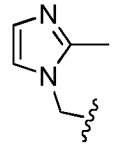
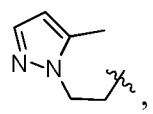
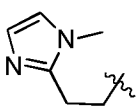
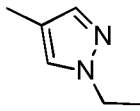
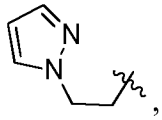
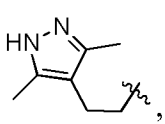
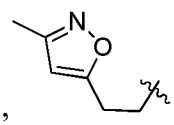
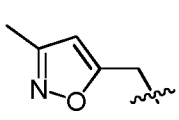
















, wherein the wavy line represents the point of attachment in formula I.

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

In certain embodiments, R^5 is $-(C_{0-3}$ alkylene)$NR^aS(O)_{1-2}R^b$, wherein said alkylene is 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)$S(O)_{0-2}R^c$, $-(C_{0-3}$ alkylene)$NR^cS(O)_{1-2}R^d$, $-(C_{0-3}$ alkylene)$S(O)_{1-2}NR^cR^d$, $-(C_{0-3}$ alkylene)$NR^cS(O)_{1-2}NR^cR^d$ or C_{1-6}

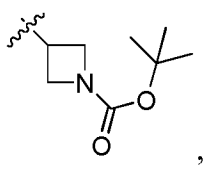
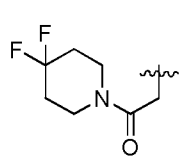
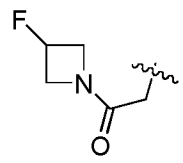
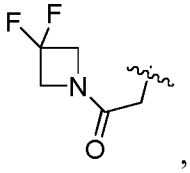
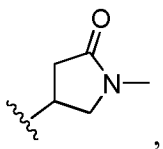
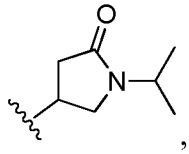
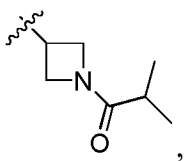
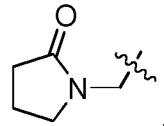
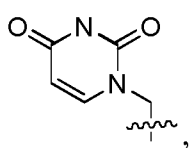
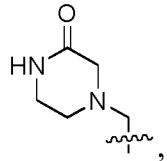
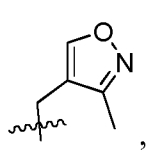
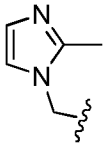
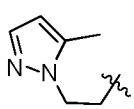
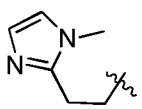
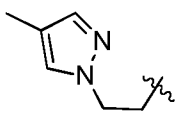
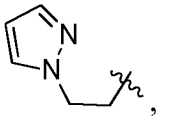
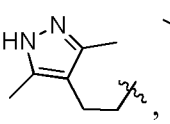
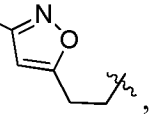
alkyl optionally substituted by oxo, −CN or halogen. In certain embodiments, R^5 is −(C_{0-3} alkylene)$NR^aS(O)_{1-2}R^b$, wherein said alkylene is optionally substituted by halogen, oxo, −CN, $-OR^c$, $-NR^cR^d$, $-C(O)OR^c$, or C_{1-6} alkyl optionally substituted by oxo, −CN or halogen. In certain embodiments, R^5 is selected from $-CH_2NHS(O)_2CH_3$, $-CH_2NHS(O)_2CH_2CH_3$, $-CH_2NHS(O)_2CH_2CH(CH_3)_2$, $-CH_2NHS(O)_2CH(CH_3)_2$, $-CH_2NHS(O)_2CH(CH_3)CH_2CH_3$, $-CH_2NHS(O)_2$cyclopropyl, $-CH_2NHS(O)_2$cyclopentyl, $-CH_2N(CH_3)S(O)_2CH_3$, $-CH_2CH_2NHS(O)_2CH_3$, $-CH_2CH_2NHS(O)_2CH_2CH_3$,  ,  ,  ,  , wherein the wavy line represents the point of attachment in formula I.

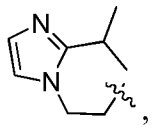
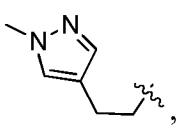
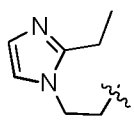
In certain embodiments, R^5 is −(C_{0-3} alkylene)5-12 membered heteroaryl, wherein said alkylene and heteroaryl are independently optionally substituted by halogen, oxo, −(C_{0-3} alkylene)CN, −(C_{0-3} alkylene)OR^c, −(C_{0-3} alkylene)NR^cR^d, −(C_{0-3} alkylene)$C(O)R^c$, −(C_{0-3} alkylene)$C(O)OR^c$, −(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)$S(O)_{0-2}R^c$, −(C_{0-3} alkylene)$NR^cS(O)_{1-2}R^d$, −(C_{0-3} alkylene)$S(O)_{1-2}NR^cR^d$, −(C_{0-3} 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 −(C_{0-3} alkylene)5-6 membered heteroaryl, wherein said alkylene and heteroaryl are independently optionally substituted by halogen, oxo, −CN, $-OR^c$, $-NR^cR^d$, $-C(O)OR^c$, or C_{1-6} alkyl optionally substituted by oxo, −CN or halogen. In certain embodiments, R^5 is selected from $-CH_2CH_2$triazolyl, triazolyl, pyridinyl, $-CH_2$pyrazolyl, $-CH_2$pyridinyl,  ,  ,  ,  ,  ,  ,  ,  ,  , wherein the wavy line represents the point of attachment in formula I.

In certain embodiments, R^5 is −(C_{0-3} alkylene)4-6 membered heteroaryl, wherein said alkylene is 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}

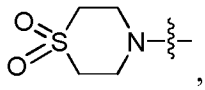
alkylene)$NR^cC(O)NR^cR^d$, $-(C_{0-3}$ alkylene)$NR^cC(O)OR^d$, $-(C_{0-3}$ alkylene)$S(O)_{0-2}R^c$, $-(C_{0-3}$ alkylene)$NR^cS(O)_{1-2}R^d$, $-(C_{0-3}$ alkylene)$S(O)_{1-2}NR^cR^d$, $-(C_{0-3}$ alkylene)$NR^cS(O)_{1-2}NR^cR^d$ or C_{1-6} alkyl optionally substituted by oxo, −CN or halogen. In certain embodiments, R^5 is $-(C_{0-3}$ alkylene)4-6 membered heteroaryl, wherein said alkylene is optionally substituted by oxo or halogen, and said heteroaryl is optionally substituted by oxo, halogen, C_{1-3} alkyl, $-OR^c$ or $-NR^cR^d$. In certain embodiments, R^5 is pyridinyl.

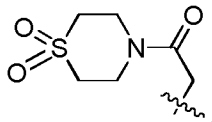
In certain embodiments, R^5 is $-(C_{0-3}$ alkylene)3-12 membered heterocyclyl, wherein said alkylene and heterocyclyl are independently optionally substituted by halogen, oxo, $-(C_{0-3}$ alkylene)CN, $-(C_{0-3}$ alkylene)OR^c, $-(C_{0-3}$ alkylene)NR^cR^d, $-(C_{0-3}$ alkylene)$C(O)R^c$, $-(C_{0-3}$ 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)$S(O)_{0-2}R^c$, $-(C_{0-3}$ alkylene)$NR^cS(O)_{1-2}R^d$, $-(C_{0-3}$ alkylene)$S(O)_{1-2}NR^cR^d$, $-(C_{0-3}$ 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 $-(C_{0-3}$ alkylene)3-7 membered heterocyclyl, wherein said alkylene and heterocyclyl are independently optionally substituted by halogen, oxo, −CN, $-OR^c$, $-NR^cR^d$, $-C(O)OR^c$, or C_{1-6} alkyl optionally substituted by oxo, −CN or halogen. In certain embodiments, R^5 is selected from oxetanyl, 1,1-dioxothiomorpholinyl, $-CH_2CH_2$(1,1-dioxothiomorpholinyl), $-CH_2CH_2$triazolyl, triazolyl, $-CH_2$pyrazolyl, $-CH_2$pyridinyl, pyridinyl, pyrrolidinyl, piperidinyl, $-CH_2$(4-hydroxypiperidin-1-yl), morpholinyl, azetidinyl, 2-acetylpyrrolidin-3-yl, $-CH_2$tetrahydropyranyl, $-CH_2$tetrahydropyran-4-yl, tetrahydropyranyl, tetrahydrofuranyl, $-CH_2$tetrahydrofuran-2-yl, $-CH_2CH_2$tetrahydrofuranyl, $-CH_2$morpholinyl, 1-acetylpiperidin-4-yl, −C(O)morpholinyl, $-CH_2C(O)$morpholinyl, $-CH_2C(O)$(1,1-dioxothiomorpholin-4-yl), $-CH_2C(O)$pyrrolidinyl,

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

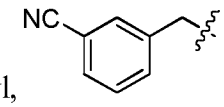
In certain embodiments, R^5 is $-(C_{0-3}$ alkylene)4-6 membered heterocyclyl, wherein said alkylene is independently optionally substituted by halogen, oxo, $-(C_{0-3}$ alkylene)CN, $-(C_{0-3}$ alkylene)OR^c, $-(C_{0-3}$ alkylene)NR^cR^d, $-(C_{0-3}$ alkylene)$C(O)R^c$, $-(C_{0-3}$ alkylene)$C(O)OR^c$, $-(C_{0-3}$ 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)$S(O)_{0-2}R^c$, $-(C_{0-3}$ alkylene)$NR^cS(O)_{1-2}R^d$, $-(C_{0-3}$ alkylene)$S(O)_{1-2}NR^cR^d$, $-(C_{0-3}$ 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 $-(C_{0-3}$ alkylene)4-6 membered heterocyclyl, wherein said alkylene is optionally substituted by oxo or halogen, and said heterocyclyl is optionally substituted by oxo, halogen, C_{1-3} alkyl, $-OR^c$ or $-NR^cR^d$. In certain embodiments, R^5 is $-CH_2C(O)$(4-6 membered heterocyclyl) or $-CH_2$(4-6 membered heterocyclyl), wherein said heterocyclyl is optionally substituted by oxo, halogen, C_{1-3} alkyl, $-OR^c$ or $-NR^cR^d$. In another embodiment, said heterocyclyl is oxetanyl, pyridinyl, pyrrolindinyl, pyranyl, piperidinyl, morpholinyl or

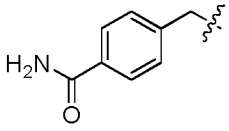
 , wherein the wavy line represents the point of attachment in formula I. In another embodiment, R^5 is pyridin-3-yl, pyrrolidin-1-yl, pyran-4-yl, $-CH_2C(O)$(pyrrolidin-1-yl), $-CH_2C(O)$(4,4-difluorpiperidin-1-yl), $-CH_2$ (morpholinyl), $-CH_2C(O)$(morpholinyl), $-CH_2$(pyrrolidin-2-on-1-yl) or

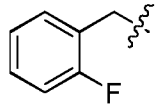
 , wherein the wavy line represents the point of attachment in formula I.

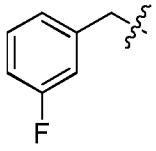
In certain embodiments, R^5 is $-(C_{0-3}$ alkylene)$S(O)_{1-2}R^a$, wherein said alkylene is independently optionally substituted by halogen, oxo, $-(C_{0-3}$ alkylene)CN, $-(C_{0-3}$ alkylene)OR^c, $-(C_{0-3}$ alkylene)NR^cR^d, $-(C_{0-3}$ alkylene)$C(O)R^c$, $-(C_{0-3}$ alkylene)$C(O)OR^c$, $-(C_{0-3}$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

$-NR^cR^d$, $-C(O)OR^c$, 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 $-(C_{0-3}$ alkylene)C_{6-12} aryl, wherein said alkylene and aryl 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)$S(O)_{0-2}R^c$, $-(C_{0-3}$ alkylene)$NR^cS(O)_{1-2}R^d$, $-(C_{0-3}$ alkylene)$S(O)_{1-2}NR^cR^d$, $-(C_{0-3}$ 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 $-(C_{0-3}$ alkylene)phenyl, wherein said alkylene and phenyl are independently optionally substituted by halogen, oxo, −CN, $-OR^c$, $-NR^cR^d$, $-C(O)OR^c$, or C_{1-6} alkyl optionally substituted by oxo, −CN or halogen. In certain embodiments, R^5 is selected from $-CH_2$phenyl, phenyl, 

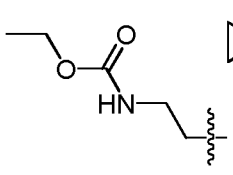
, 

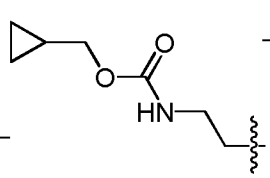
, 

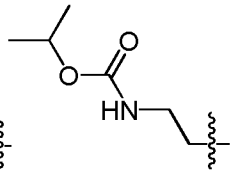
, 

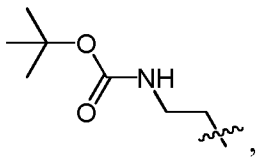
, wherein the wavy line represents the point of attachment in formula I.

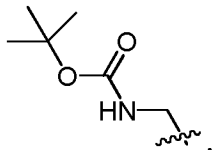
In certain embodiments, R^5 is $-(C_{0-3}$ alkylene)phenyl, wherein said alkylene is optionally substituted by oxo or halogen, and said phenyl is optionally substituted by halogen, C_{1-3} alkyl, $-OR^c$ or $-NR^cR^d$.

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







, 

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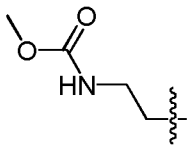
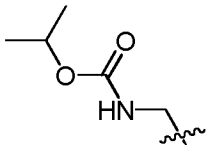
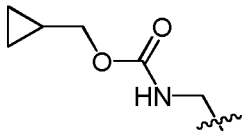
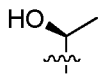
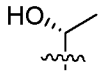



, wherein the wavy line represents the point of attachment in formula I.

In certain embodiments, R^5 is C_{1-12} alkyl optionally substituted by OR^c, $-(C_{1-3}$ alkylene)NR^aR^b, $-(C_{1-3}$ alkylene)OR^a, $-(C_{1-3}$ alkylene)$NR^aC(O)R^b$, $-(C_{1-3}$ alkylene)$NR^aC(O)NR^aR^b$, $-(C_{1-3}$ alkylene)$NR^aC(O)OR^b$, $-(C_{1-3}$ alkylene)$NR^aC(O)OR^b$, $-(C_{1-3}$ alkylene)$NR^aS(O)_{1-2}R^b$ or $-(C_{1-3}$ alkylene)3-12 membered heterocyclyl, wherein said alkylene and heterocyclyl are independently optionally substituted by halogen, oxo or C_{1-6} alkyl optionally substituted by halogen.

In certain embodiments, R^5 is ethyl substituted by OH, $-(C_{1-3}$ alkylene)NR^aR^b, $-(C_{1-3}$ alkylene)OR^a, $-(C_{1-3}$ alkylene)$NR^aC(O)R^b$, $-(C_{1-3}$ alkylene)$NR^aC(O)NR^aR^b$, $-(C_{1-3}$ alkylene)$NR^aC(O)OR^b$, $-(C_{1-3}$ alkylene)$NR^aS(O)_{1-2}R^b$ or $-(C_{1-3}$ alkylene)3-12 membered heterocyclyl, wherein said alkylene and heterocyclyl are independently optionally substituted by halogen, oxo or C_{1-6} alkyl optionally substituted by halogen.

In certain embodiments, R^5 is selected from methyl, ethyl, 

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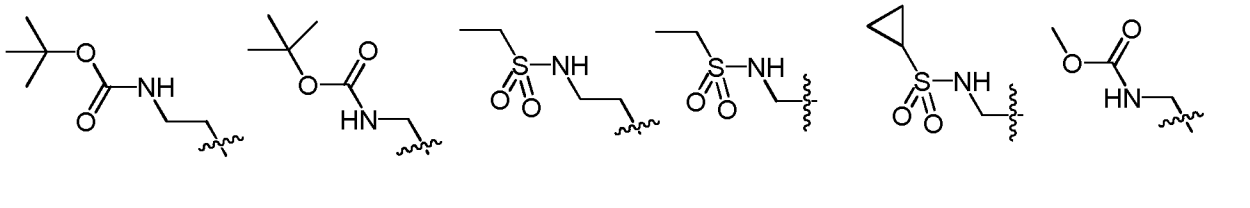
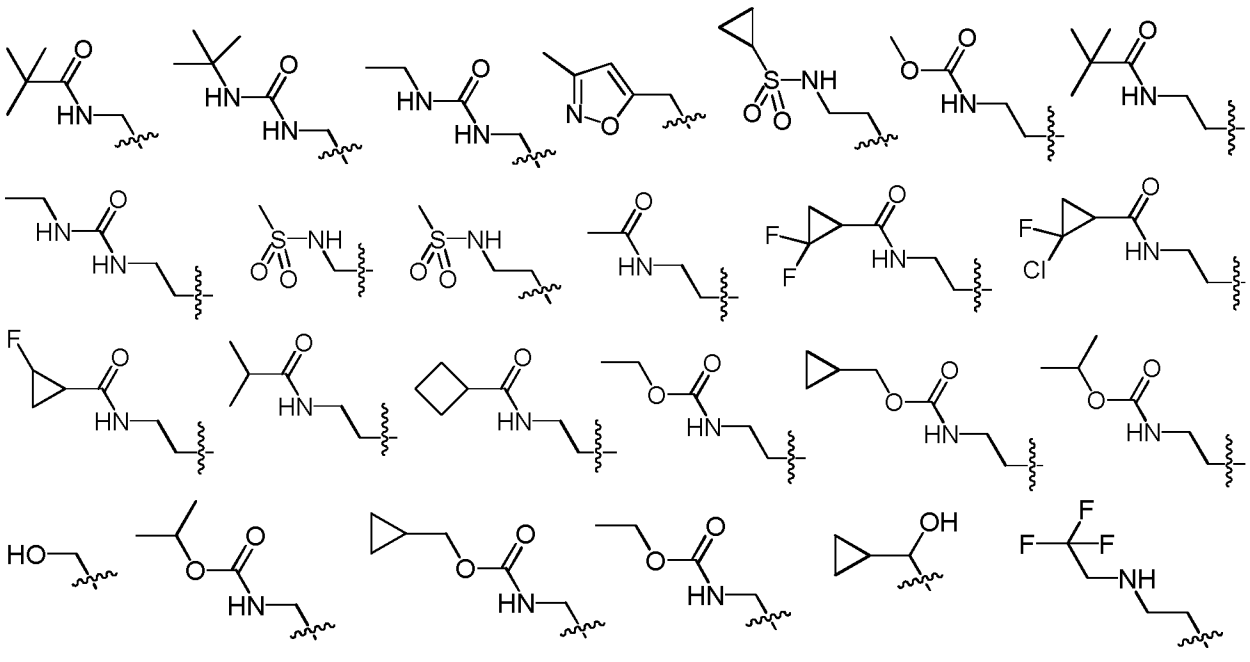
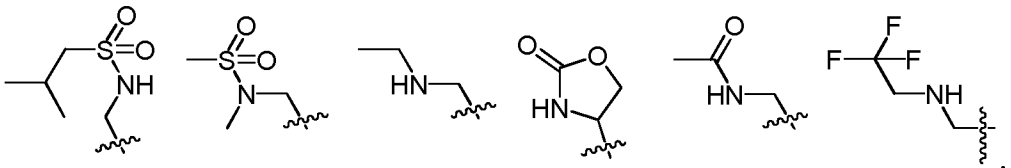
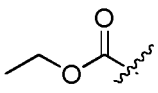








,wherein the wavy line represents the point of attachment in formula I.

In certain embodiments, R^6 is independently oxo, halogen, −CN, $-C(O)R^a$, $-C(O)OR^a$, $-NR^aC(O)R^b$, $-C(O)NR^aR^b$, $-NR^aC(O)NR^aR^b$, $-OC(O)NR^aR^b$, $-NR^aC(O)OR^b$, $-S(O)_{1-2}R^a$, $-NR^aS(O)_2R^b$, $-S(O)_2NR^aR^b$, $-OR^a$, $-SR^a$, $-NR^aR^b$, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3-7 membered heterocycly or C_{6-14} aryl, and wherein said alkyl, alkenyl, alkynyl, cycloalkyl, 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.

In certain embodiments, R^6 is independently oxo, halogen, −CN, $-C(O)(C_{1-6}$ alkyl), $-C(O)O(C_{1-6}$ alkyl), $-S(O)_2(C_{1-6}$ alkyl), $-NR^aS(O)_2(C_{1-6}$ alkyl), $-O(C_{1-6}$ alkyl), C_{1-6} alkyl, C_{3-6} cycloalkyl or 3-7 membered heterocyclyl, wherein said alkyl, cycloalkyl and heterocyclyl are independently optionally substituted by halogen, oxo, −CN, $-OR^c$, $-NR^cR^d$ or C_{1-6} alkyl optionally substituted by halogen. In certain embodiments, R^6 is independently oxo, F, Cl, −CN, −OH, $-C(O)CH_3$, $-CH_2CN$, $-CH_2CH_2CN$, cyclopropyl, cyclobutyl, $-CF_3$, $-NHS(O)_2CH_3$, $-S(O)_2CH_3$, $-C(O)OCH_3$, pyrrolidinyl or pyrrolidinonyl.

In certain embodiments, R^6 is independently oxo, halogen, −CN, $-C(O)(C_{1-6}$ alkyl), $-S(O)_2(C_{1-6}$ alkyl), $-OR^a$, $-NR^aR^b$, C_{1-6} alkyl or C_{3-6} cycloalkyl, and wherein said alkyl, alkenyl and alkynyl are independently optionally substituted by halogen, oxo, −CN, $-OR^c$ or $-NR^cR^d$. In certain embodiments, R^6 is halogen, $-S(O)_2CH_3$ or −CN.

In certain embodiments, each R^a and R^b are independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-S(O)_{1-2}R^i$, $-C_{3-6}$ cycloalkyl, −3-12 membered heterocyclyl, −C(O)3-12 membered heterocyclyl or $-C_{6-14}$ 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.

In certain embodiments, each R^a and R^b are independently hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, 3-6 membered heterocyclyl, $-C(O)$3-6 membered heterocyclyl or phenyl, wherein said alkyl, cycloalkyl, heterocyclyl and phenyl are independently optionally substituted by halogen, oxo, $-CN$, $-OR^e$, $-NR^eR^f$, $-C(O)R^g$, $-C(O)OR^g$, $-C(O)NR^gR^h$, $-NR^gC(O)R^h$, $-OC(O)NR^gR^h$, $-NR^gC(O)NR^gR^h$, $-NR^gC(O)OR^h$, $-S(O)_{1-2}R^g$, $-NR^gS(O)_{1-2}R^h$, $-S(O)_{1-2}NR^gR^h$, $-NR^gS(O)_{1-2}NR^gR^h$, C_{3-6} cycloalkyl, 3-6 membered heterocyclyl, phenyl or C_{1-3} alkyl optionally substituted by oxo or halogen.

In certain embodiments, each R^a and R^b are independently hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, 3-6 membered heterocyclyl, 5-6 membered heteroaryl or phenyl, wherein said alkyl, cycloalkyl, heterocyclyl, heteroaryl and phenyl are independently optionally substituted by halogen, oxo, $-CN$, $-OR^e$, $-NR^eR^f$ or C_{1-3} 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, $-S(O)_2CH_3$, $-CF_3$, $-CH_2CF_3$, $-CH_2F$, $-CHF_2$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2NH_2$, $-CH_2CH_2NH_2$, $-CH_2CH_2N(CH_3)_2$, $-CH_2N(CH_3)_2$, 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.

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, $-C(O)C_{1-6}$ alkyl or C_{1-6} 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, $-C(O)C_{1-6}$ alkyl or C_{1-6} alkyl optionally substituted by halogen. In certain 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, $-C(O)C_{1-6}$ alkyl or C_{1-6} alkyl.

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

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, $-C(O)C_{1-6}$ alkyl or C_{1-6} alkyl.

In certain embodiments, one R^a is H and one R^b is C_{1-6} alkyl 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.

In certain embodiments, each R^c and R^d are independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-C_{3-6}$ cycloalkyl, $-$3-12 membered heterocyclyl, $-C(O)$3-12 membered heterocyclyl or $-C_{6-14}$ 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.

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

In certain embodiments, each R^c and R^d are independently hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, 3-6 membered heterocyclyl, 5-6 membered heteroaryl or phenyl, wherein said alkyl, cycloalkyl, heterocyclyl, heteroaryl and phenyl are independently optionally substituted by halogen, oxo, $-CN$, $-OR^g$, $-NR^gR^h$ or C_{1-6} alkyl optionally substituted by halogen.

In certain embodiments, each R^c and R^d are independently hydrogen, methyl, ethyl, isopropyl, butyl, t-butyl, sec-butyl, $-CF_3$, $-CH_2CF_3$, $-CH_2F$, $-CHF_2$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2NH_2$, $-CH_2CH_2NH_2$, $-CH_2CH_2N(CH_3)_2$, $-CH_2N(CH_3)_2$, 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.

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, $-C(O)C_{1-6}$ alkyl or C_{1-6} alkyl optionally substituted by oxo or halogen.

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, a R^c and a R^d are 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 halogen. In certain embodiments, said heterocyclyl is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, piperidinonyl, morpholinyl and 1,1-dioxomorpholinyl.

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

In certain embodiments, each R^e, R^f, R^g, R^h and R^i 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 and R^i are independently hydrogen, methyl or ethyl.

In certain embodiments, R^1 is C_{5-7} cycloalkyl independently substituted by one NR^aR^b wherein R^a is H and R^b is C_{1-6} alkyl 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.

Another embodiment includes a compound selected from Examples 1-146.

Another embodiment includes a compound selected from Examples 1-147.

Another embodiment includes a compound selected from:

trans 1-(4-Cyano-cyclohexyl)-2-((R)-1-hydroxy-ethyl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacene-8-carbonitrile;

trans (R)-1-[1-(4-Oxazol-5-yl-cyclohexyl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol;

cis (R)-1-[1-(4-[1,2,4]Triazol-4-yl-cyclohexyl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol;

cis (R)-1-[1-(4-Imidazol-1-yl-cyclohexyl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol;

trans (R)-1-[1-(4-Imidazol-1-yl-cyclohexyl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol;

trans [4-(2-Methyl-6H-1,3,5,6-tetraaza-as-indacen-1-yl)-cyclohexyl]-acetonitrile;

(R)-1-{1-[(1S,3S)-3-(2,2-Difluoro-ethylamino)-cyclopentyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethanol;

(2-{1-[6-(2,2-Difluoro-ethylamino)-bicyclo[2.2.1]hept-2-yl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-carbamic acid tert-butyl ester;

{2-[1-(5-Hydroxy-bicyclo[2.2.1]hept-2-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-carbamic acid tert-butyl ester;

{2-[1-(6-Hydroxy-bicyclo[2.2.1]hept-2-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-carbamic acid tert-butyl ester;

{1-[6-(2,2,2-Trifluoro-ethylamino)-bicyclo[2.2.1]hept-2-yl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-carbamic acid tert-butyl ester;

[1-(5-Hydroxy-bicyclo[2.2.1]hept-2-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-carbamic acid tert-butyl ester;

(2-{1-[5-(2,2,2-Trifluoro-ethylamino)-bicyclo[2.2.1]hept-2-yl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-carbamic acid tert-butyl ester;

{2-[1-(6-Hydroxy-bicyclo[2.2.1]hept-2-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-carbamic acid tert-butyl ester;

Ethanesulfonic acid {2-[(S)-1-(tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-amide;

Ethanesulfonic acid [(S)-1-(tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-amide;

Cyclopropanesulfonic acid [(S)-1-(tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-amide;

[(S)-1-(Tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-carbamic acid methyl ester;

2,2-Dimethyl-N-[(S)-1-(tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-propionamide;

1-tert-Butyl-3-[(S)-1-(tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-urea;

1-Ethyl-3-[(S)-1-(tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-urea;

2-(3-Methyl-isoxazol-5-ylmethyl)-1-(S)-tetrahydro-pyran-3-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacene;

Cyclopropanesulfonic acid {2-[(S)-1-(tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-amide;

{2-[(S)-1-(Tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-carbamic acid methyl ester;

2,2-Dimethyl-N-{2-[(S)-1-(tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-propionamide;

1-tert-Butyl-3-{2-[(S)-1-(tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-urea;

1-Ethyl-3-{2-[(S)-1-(tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-urea;

N-[1-(Tetrahydro-thiopyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-methanesulfonamide;

trans Cyclopropanesulfonic acid (2-{1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-amide;

trans N-(2-{1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-methanesulfonamide;

trans N-(2-{1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-acetamide;

trans 2,2-Difluoro-cyclopropanecarboxylic acid (2-{1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-amide;

trans Ethanesulfonic acid (2-{1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-amide;

Trans (2-{1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-carbamic acid methyl ester;

trans 2-Chloro-2-fluoro-cyclopropanecarboxylic acid (2-{1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-amide;

trans 2,2-Dimethyl-N-(2-{1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-propionamide;

2-Fluoro-cyclopropanecarboxylic acid (2-{1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-amide;

trans N-(2-{1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-isobutyramide;

trans Cyclobutanecarboxylic acid (2-{1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-amide;

trans (2-{1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-carbamic acid ethyl ester;

trans (2-{1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-carbamic acid cyclopropylmethyl ester;

trans (2-{1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-carbamic acid tert-butyl ester;

2-Fluoro-cyclopropanecarboxylic acid (2-{1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-amide;

Trans (2-{1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-carbamic acid isopropyl ester;

N-{2-[1-(Tetrahydro-thiopyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-methanesulfonamide;

N-[1-(5,5-Difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-methanesulfonamide;

Trans (2,2,2-Trifluoro-ethyl)-(4-{2-[2-(2,2,2-trifluoro-ethylamino)-ethyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclohexyl)-amine;

(R)-1-[1-(1,1-Dioxo-hexahydro-thiopyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol;

(R)-1-[1-(Tetrahydro-thiopyran-4-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol;

(R)-1-[1-(Tetrahydro-thiopyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol;

Cyclopropyl-[1-(tetrahydro-pyran-4-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-methanol;

trans Cyclopropyl-{1-[4-(2-methanesulfonyl-ethyl)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-methanol;

2-Methyl-1-(tetrahydro-thiopyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacene;

2-Methyl-1-(1-oxo-hexahydro-thiopyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacene;

1-(1,1-Dioxo-hexahydro-thiopyran-3-yl)-2-methyl-1,6-dihydro-1,3,5,6-tetraaza-as-indacene;

2-Methyl-1-(tetrahydro-thiopyran-4-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacene;

2-Methyl-1-(1-oxo-hexahydro-thiopyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacene;

2-Methyl-1-(1-oxo-hexahydro-thiopyran-4-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacene;

N-{1-[(1S,3R)-3-(2,2,2-Trifluoro-ethylamino)-cyclopentyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-methanesulfonamide;

trans N-{4-[2-((R)-1-Hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclohexyl}-3-methyl-butyramide;

N-(1-{(1S,3R)-3-[(2,2-Difluoro-ethyl)-methanesulfonyl-amino]-cyclopentyl}-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl)-methanesulfonamide;

{1-[(1S,3R)-3-(2,2-Difluoro-ethylamino)-cyclopentyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-carbamic acid methyl ester;

trans Ethanesulfonic acid {1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-amide;

trans N-{1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-methanesulfonamide;

trans Cyclopropanesulfonic acid {1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-amide;

trans {1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-carbamic acid methyl ester;

trans {1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-carbamic acid ethyl ester;

trans {1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-carbamic acid tert-butyl ester;

trans {1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-carbamic acid cyclopropylmethyl ester;

trans {1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-carbamic acid isopropyl ester;

(1-Bicyclo[2.2.1]hept-2-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl)-carbamic acid methyl ester;

trans 2-Methyl-propane-1-sulfonic acid {1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-amide;

Ethanesulfonic acid (1-bicyclo[2.2.1]hept-2-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl)-amide;

N-(1-Bicyclo[2.2.1]hept-2-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl)-acetamide;

N-(2-{1-[(1S,3R)-3-(2,2,2-Trifluoro-ethylamino)-cyclopentyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-methanesulfonamide;

N-(2,2-Difluoro-ethyl)-N-{(1R,3S)-3-[2-(2-methanesulfonylamino-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentyl}-methanesulfonamide;

N-(1-Bicyclo[2.2.1]hept-2-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl)-methanesulfonamide;

trans (2,2,2-Trifluoro-ethyl)-(4-{2-[(2,2,2-trifluoro-ethylamino)-methyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclohexyl)-amine;

Trans 2-[2-((R)-1-Hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentanecarbonitrile;

Cis 2-[2-((R)-1-Hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentanecarbonitrile;

(R)-3-[2-(1-Hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentanecarbonitrile;

N-(1-Bicyclo[2.2.1]hept-2-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl)-N-methyl-methanesulfonamide;

[1-(4,4-Difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-ethyl-amine;

N-[1-(-3,3-Difluoro-1-methyl-piperidin-4-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-methanesulfonamide;

Ethanesulfonic acid [1-(-4,4-difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-amide;

Cyclopropanesulfonic acid [1-(-4,4-difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-amide;

[1-(4,4-Difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-carbamic acid methyl ester;

N-{2-[1-(-3,3-Difluoro-1-methyl-piperidin-4-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-methanesulfonamide;

Ethanesulfonic acid {2-[1-(4,4-difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-amide;

Cyclopropanesulfonic acid {2-[1-(4,4-difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-amide;

N-{2-[1-(4,4-Difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-methanesulfonamide;

{2-[1-(4,4-Difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-carbamic acid methyl ester;

cis (R)-1-[1-(4-[1,2,3]Triazol-1-yl-cyclohexyl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol

(R)-1-[1-((S)-3,3-Difluoro-1-methyl-piperidin-4-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol;

(R)-1-[1-(-3,3-Difluoro-1-methyl-piperidin-4-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol;

Trans 4-[2-((R)-1-Hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclohexanol;

3-{(1R,3R)-3-[2-((R)-1-Hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentyl}-propionitrile;

Cis 4-[2-((R)-1-Hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclohexanol;

4-[2-((R)-1-Hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclohexanone;

(R)-1-{1-[-3,3-Difluoro-1-(tetrahydro-pyran-4-yl)-piperidin-4-yl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethanol;

{1-Hydroxy-4-[2-((R)-1-hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclohexyl}-acetonitrile (single stereoisomer, cyclohexane stereochemistry unknown)

[1-(3,3-Difluoro-1-methyl-piperidin-4-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-methanol;

[1-(4,4-Difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-methanol;

[1-Hydroxy-4-(2-methyl-6H-1,3,5,6-tetraaza-as-indacen-1-yl)-cyclohexyl]-acetonitrile;

{(1R,3S)-3-[2-((R)-1-Hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentyl}-acetonitrile;

{(1S,3R)-3-[2-((R)-1-Hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentyl}-acetonitrile;

(R)-1-{1-[(1S,3R)-3-(2,2,2-Trifluoro-ethylamino)-cyclopentyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethanol;

(R)-1-{1-[(1S,3R)-3-(2,2-Difluoro-ethylamino)-cyclopentyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethanol;

Trans 2-Methyl-1-[4-(4-methyl-piperazine-1-sulfonylmethyl)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacene;

Trans 4-{1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-oxazolidin-2-one;

(9-Cyclohexyl-3H-dipyrrolo[1,2-c;3',2'-e]pyrimidin-8-yl)-methanol;

9-Cyclohexyl-3H-dipyrrolo[1,2-c;3',2'-e]pyrimidine-8-carboxylic acid ethyl ester; and

8-Cyclohexyl-7-methyl-3,8-dihydro-1,3,4,6,8-pentaaza-as-indacene.

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 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 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 alkoxycarbonyl (-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 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 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 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 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, including supplements (also available via the Beilstein online database)), or *Comprehensive Heterocyclic Chemistry*, Editors Katrizky and Rees, Pergamon Press, 1984.

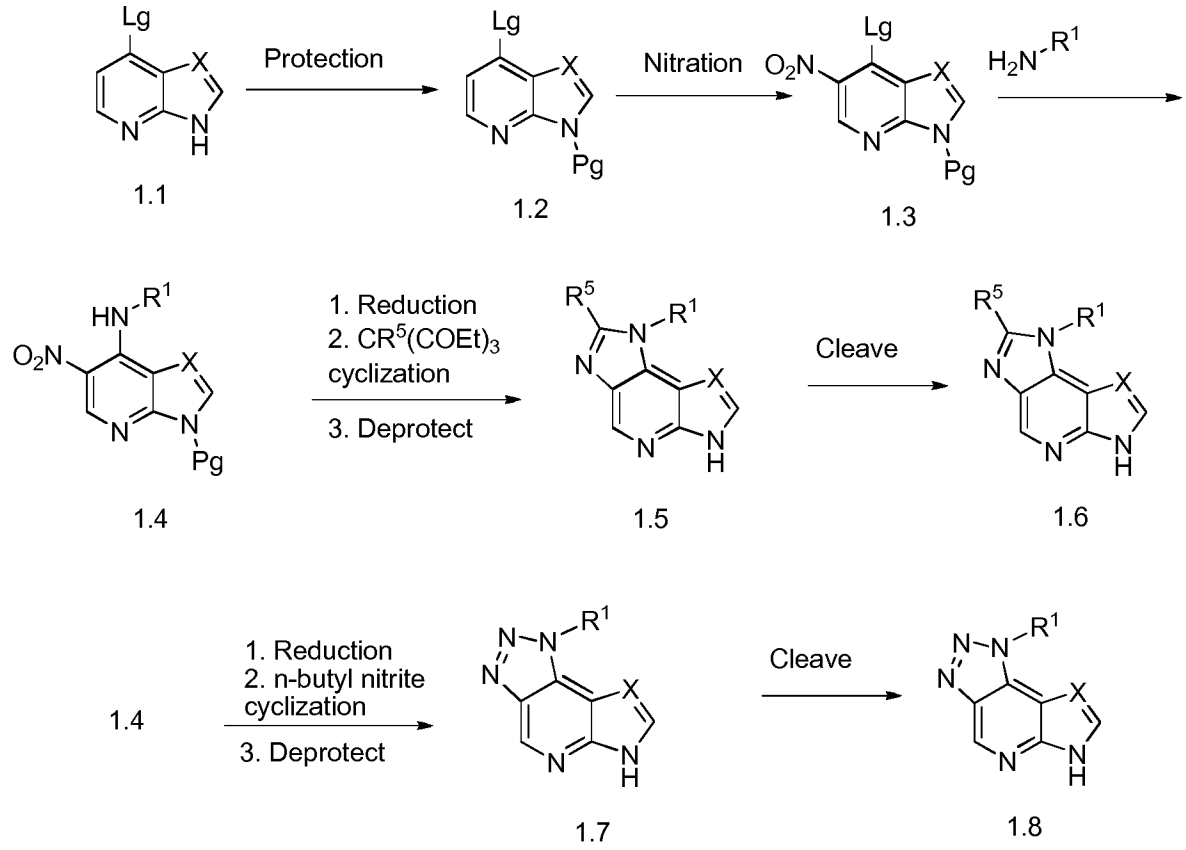
Compounds of formula I may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds, or 10 to 100 compounds of formula I. Libraries of compounds of formula I may be prepared by a combinatorial `split and mix` approach or by multiple parallel syntheses using 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 1-25 depicted below provide routes for 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 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 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. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.

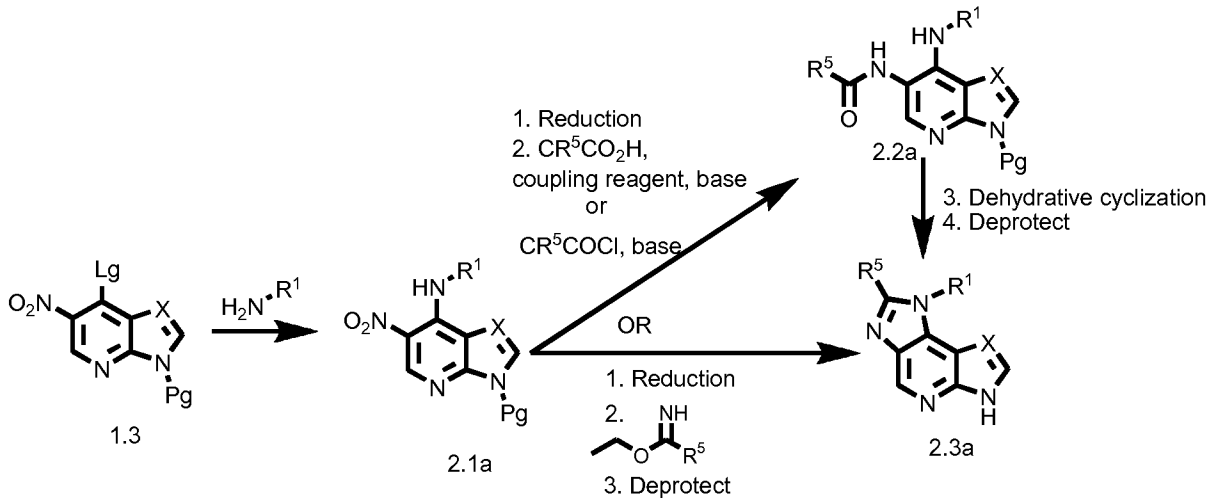
Compounds of the invention may be prepared from readily available starting materials using the general methods illustrated in Reaction Schemes 1-25 below.

Reaction Scheme 1



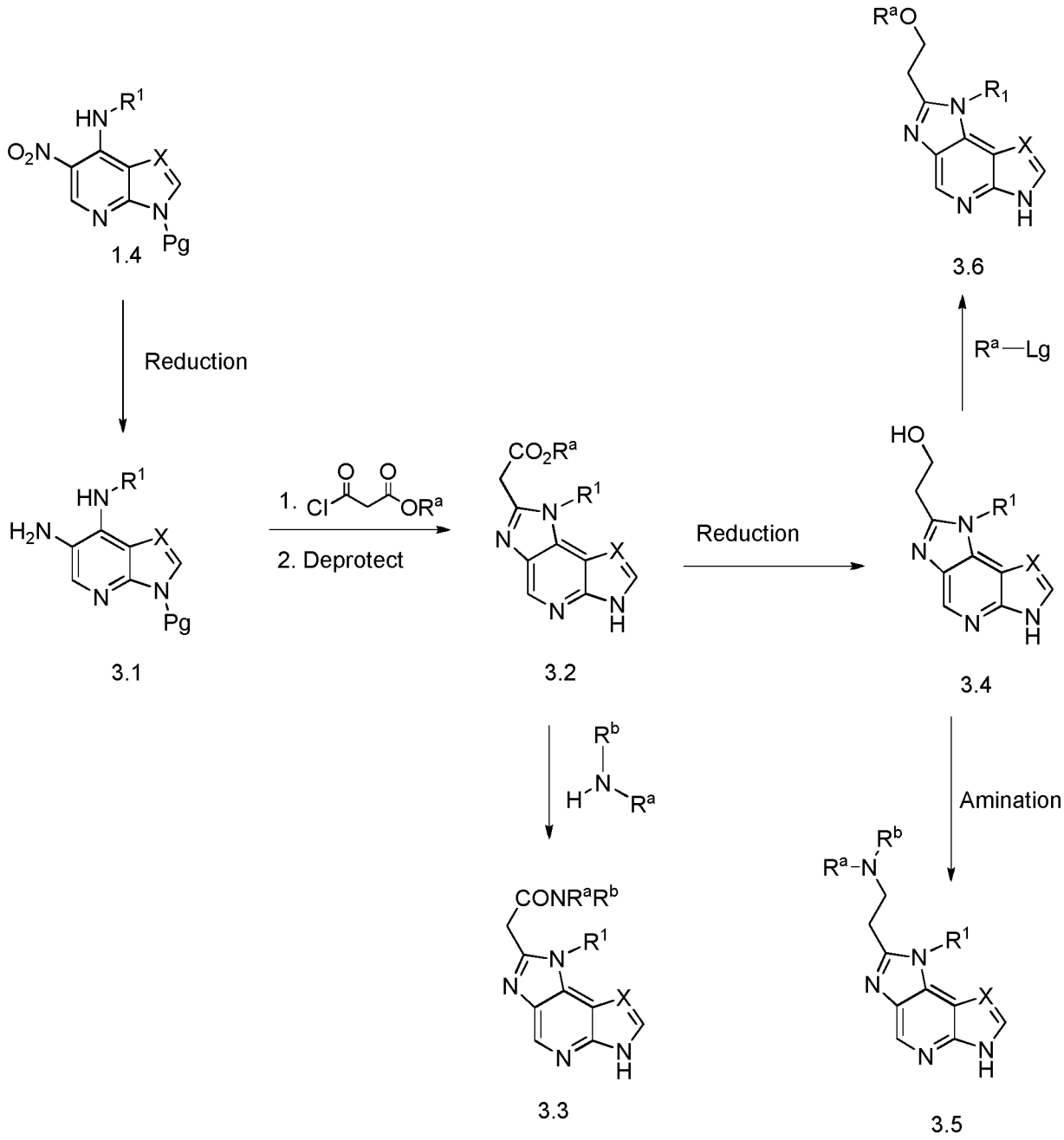
Compounds of formula I can be synthesized as shown in Reaction Scheme 1. For example, commercially available 4-substituted azaindole (where X is CR^4) or imidazopyridine (where X is N) (Lg is a leaving group, for example chloro) can be protected with an appropriate amino protecting group (Pg), to give amino-protected 1.2. Nitration of 1.2 gives nitro compound 1.3. Compound 1.4 can be prepared by treatment of compound 1.3 with a suitably substituted amine (wherein R^1 is defined herein) in the presence of base. Compound 1.4 can be cyclized via two different routes to obtain tricyclic derivatives. In one route, reduction of compounds 1.4, cyclization with triethyl ortho formyl derivative (where R^5 is defined herein), and deprotection gives compounds 1.5. In another route, reduction of compounds 1.4, cyclization with n-butyl nitrite, and deprotection gives compounds 1.7. Independent treatment of compounds 1.5 or 1.7 with suitable cleavage conditions provides compounds 1.6 or 1.8.

Scheme 2



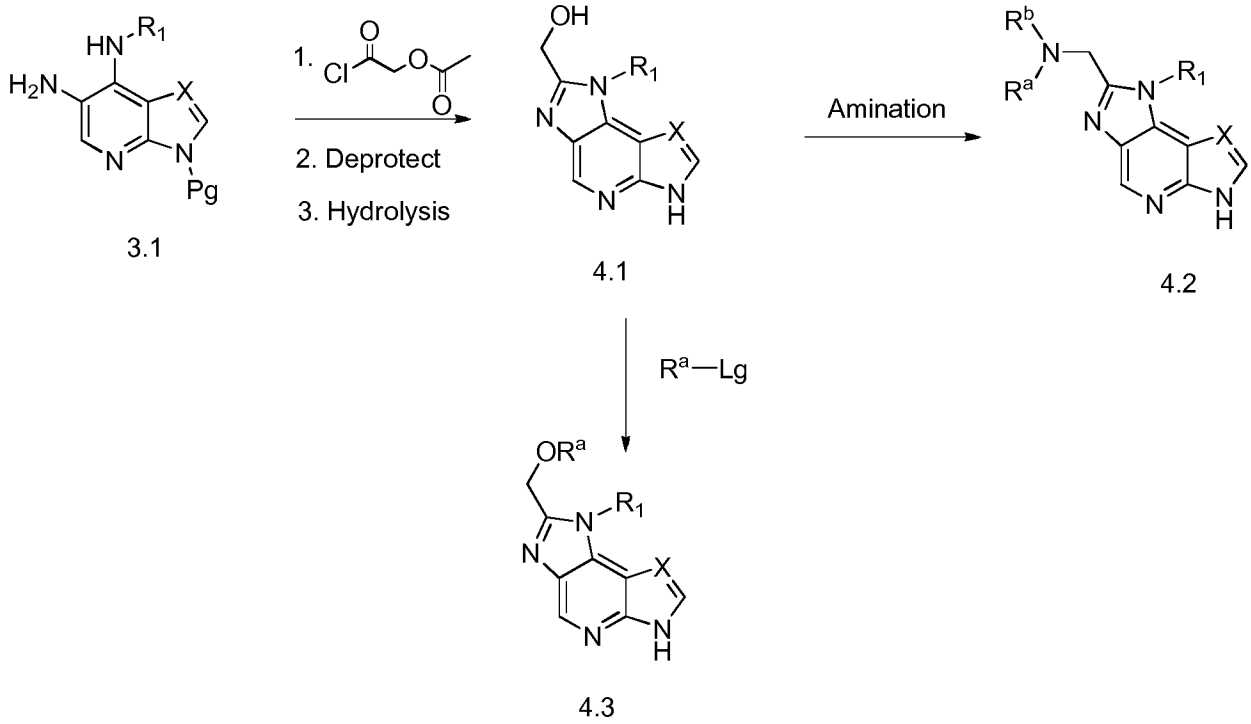
Compounds of formula I can also be synthesized as shown in Reaction Scheme 2a. For example, azaindole (where X is CR^4) or imidazopyridine (where X is N) 1.3 can be reacted with a substituted amine, for example $-NH_2R^1$, in the presence of base to give compound 2.1a. After reduction, imidazole formation can be achieved using two general methods. i) Amide bond formation by treatment with an acid chloride or a carboxlic acid in the presence of a suitable coupling reagent such as EDCI or HATU will give an amide which can then be dehydratively cyclized by treating with a reagent such as glacial acetic acid. Deprotection will give compound 2.3a. ii) Treatment with an imidate, followed by deprotection will give compound 2.3a. Further independent derivatization of compound 2.3a gives compound 2.4a.

Scheme 3



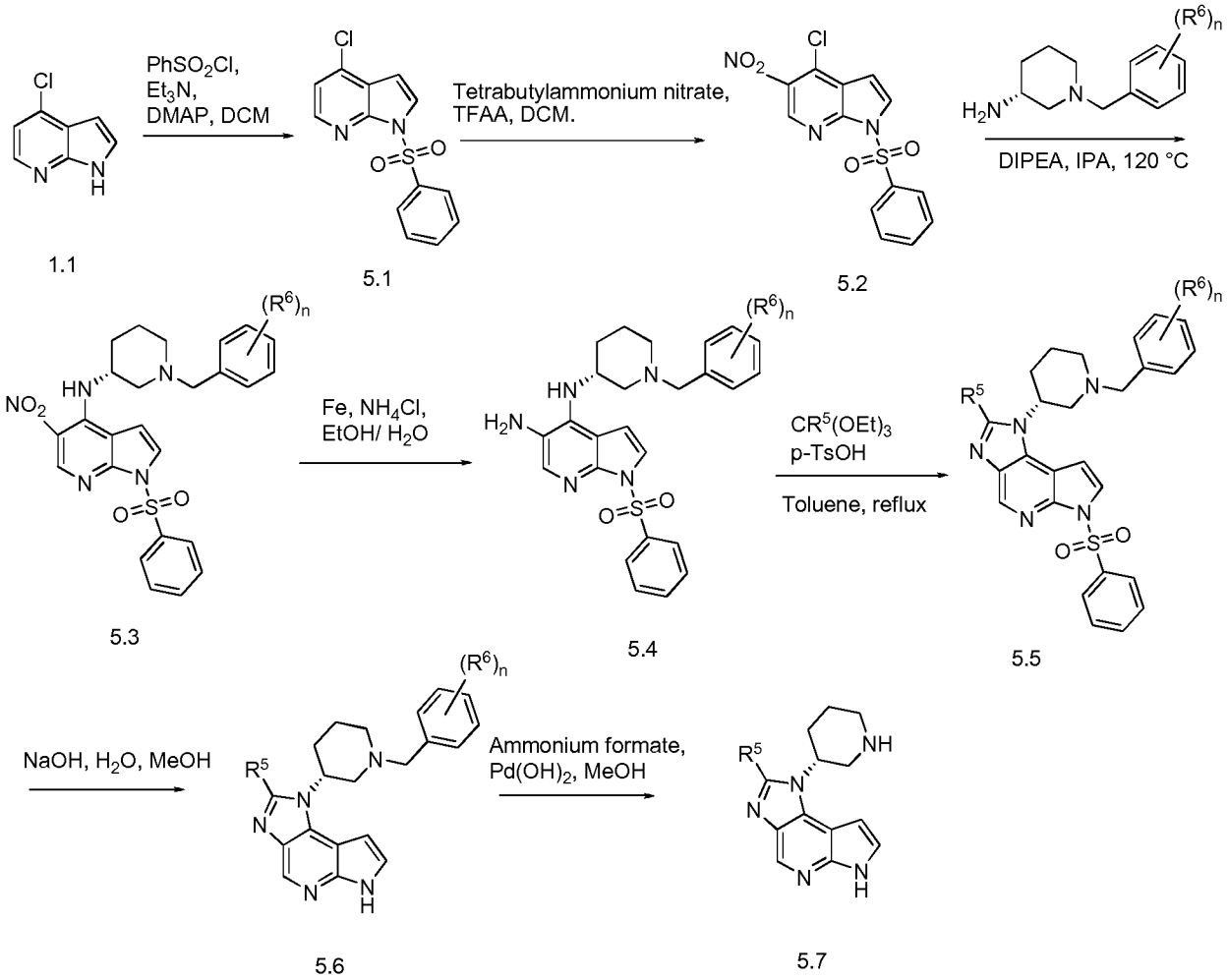
Compounds of formula I can also be synthesized as shown in Reaction Scheme 3. For example, azaindole (where X is CR^4) or imidazopyridine (where X is N) 1.4 can undergo reduction to produce the amine 3.1. Compound 3.1 can be cyclized, for example with malonyl chlorides, and deprotected to give compounds 3.2. Amidation of 3.2 with substituted amines (wherein R^a and R^b are defined herein) gives compounds 3.3. Reduction of 3.2 gives the alcohol 3.4. Alcohols 3.4 can undergo amination to give compounds 3.5, or further derivatized with R^a-Lg (where Lg is a leaving group) to give compounds 3.6.

Reaction Scheme 4



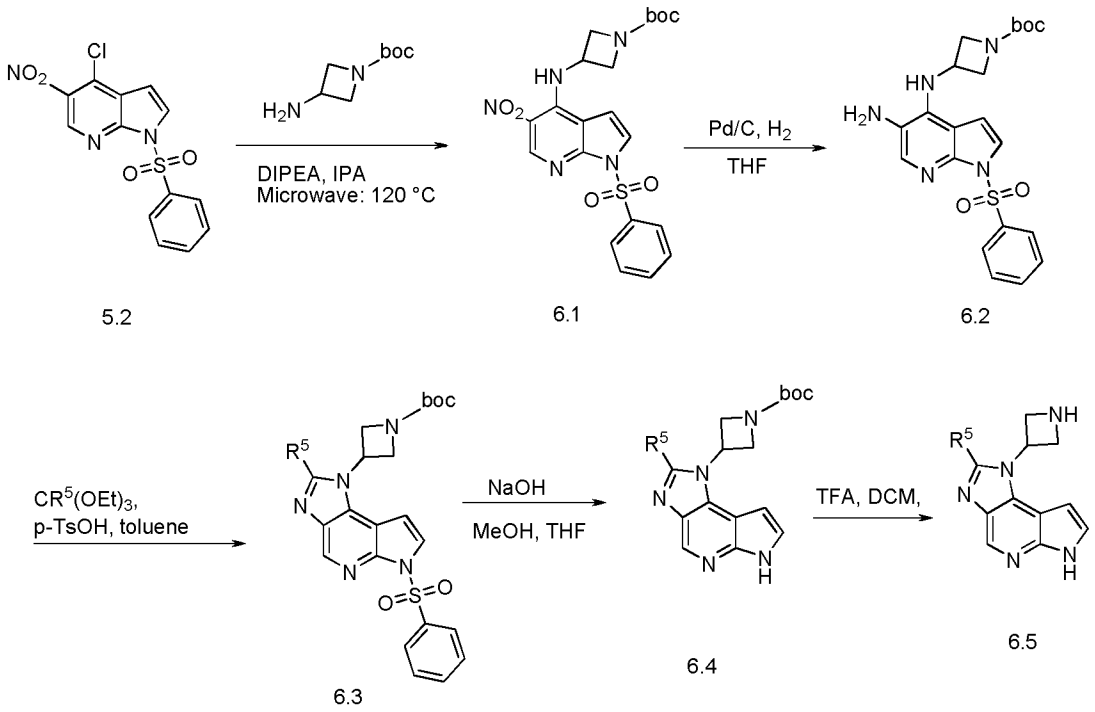
Compounds of formula I can also be synthesized as shown in Reaction Scheme 4. For example, compound 3.1 can be cyclized, for example with 2-chloro-2-oxoethyl acetate, deprotected and hydrolyzed to give tricyclic alcohol compounds 4.1. Alcohols 4.1 can undergo amination to give compounds 4.2, or further derivatized with R^a-Lg (where Lg is a leaving group) to give compounds 4.3.

Reaction Scheme 5



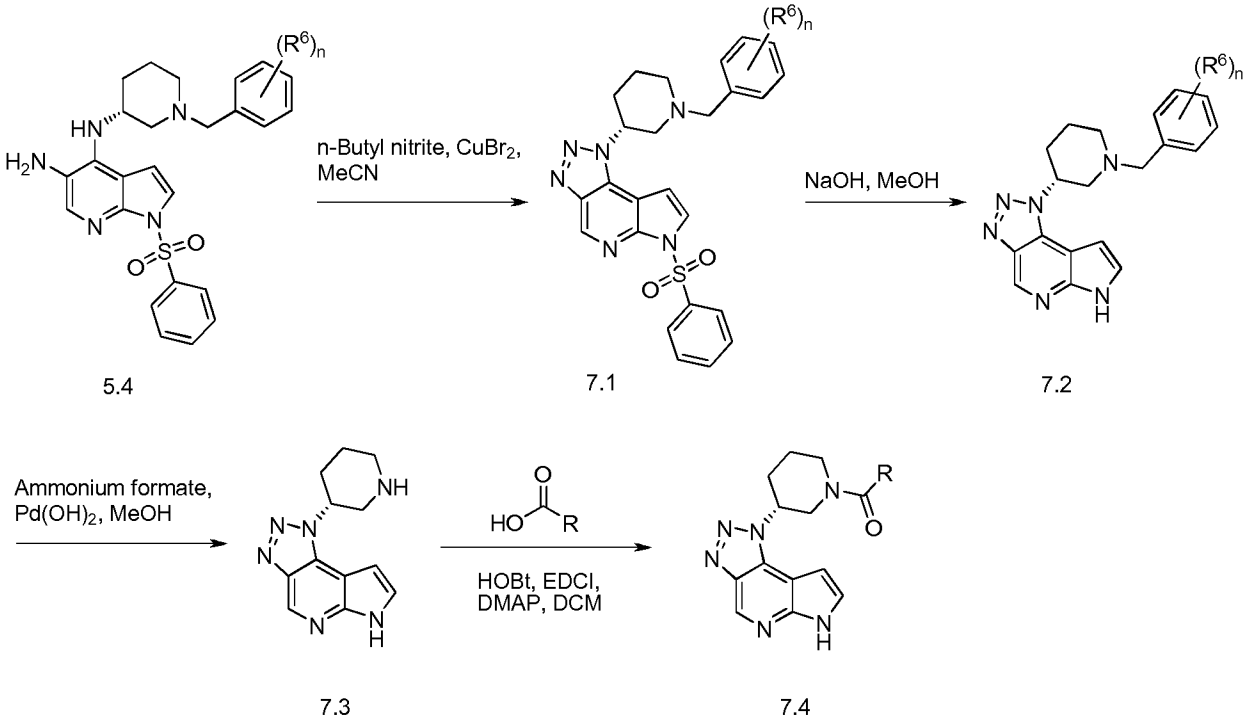
Compounds of formula I, for example 5.7, can be synthesized as shown in Reaction Scheme 5. For example, commercially available 4-chloroazaindole can be protected with phenylsulfonyl chloride in the presence of 4-(dimethylamino)pyridine (DMAP) and triethylamine to give sulfonamide 5.1. Compound 5.1 can be nitrated with tetrabutylammonium nitrate and trifluoroacetic anhydride (TFAA) to give nitro compound 5.2. Compound 5.2 can be derivatized with an amine having the formula H_2NR^1, for example with commercially available (*R*)-1-benzyl-3-aminopiperidine, in the presence of base such as diisopropylethylamine. Reduction of compound 5.3, with iron in the presence of ammonium chloride, affords diamine compound 5.4. Cyclization of compound 5.4 with R^5-substituted orthoformate, for example triethyl orthoformate (where R^5 is hydrogen), in presence of *p*-toluenesulfonic acid gives 1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine compound 5.5. Hydrolysis of compound 5.5 with aqueous sodium hydroxide in methanol provides compound 5.6. Treatment of compound 5.6 with a suitable hydrogen source such as ammonium formate in the presence of a suitable catalyst such as palladium (II) hydroxide in refluxing methanol provides compound 5.7.

Reaction Scheme 6



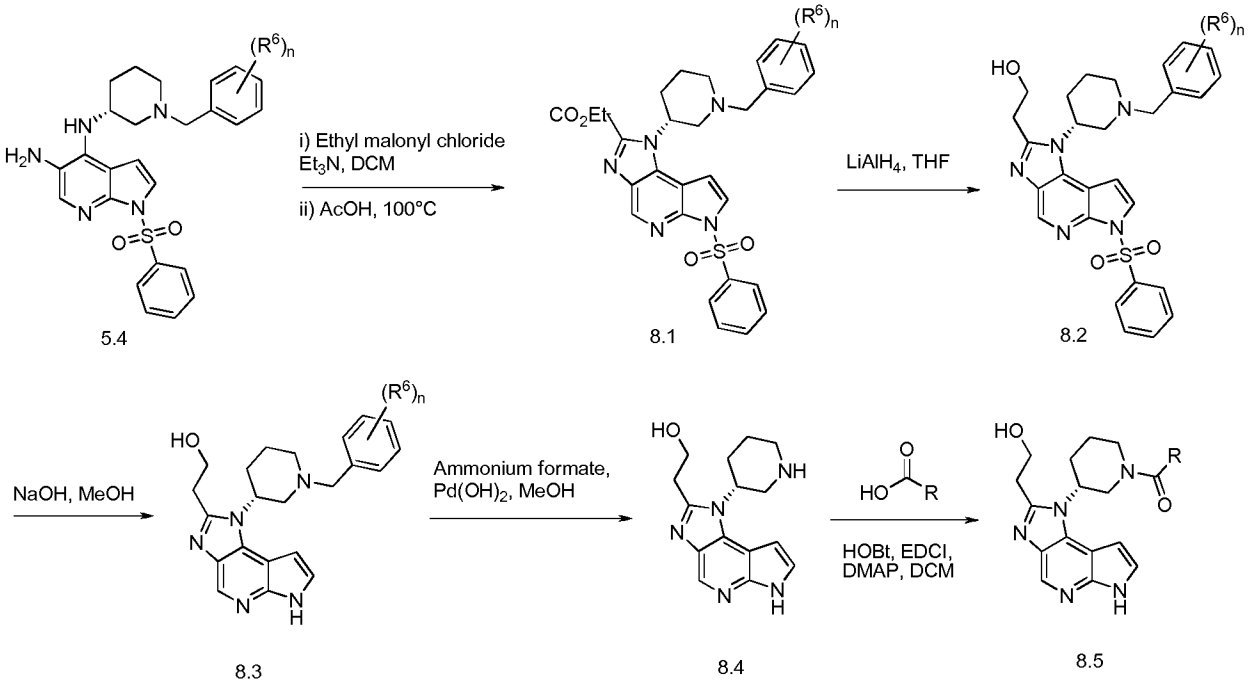
Reaction Scheme 6 illustrates the synthesis of compounds of formula I, for example compounds 6.5. Compound 6.1 can be prepared by treatment of compound 5.2 with a suitably protected diamine, for example commercially available 1-Boc-3-aminoazetidine, in the presence of base such as diisopropylethylamine. Reduction of compound 6.1 with hydrogen in the presence of palladium on carbon gives diamine compound 6.2. Cyclization of compound 6.2 with R^5-substituted orthoformate, for example triethyl orthoformate (where R^5 is hydrogen), in presence of *p*-toluenesulfonic acid gives tricyclic compound 6.3. Hydrolysis of compound 6.3 with aqueous sodium hydroxide in methanol/tetrahydrofuran (THF) provides compound 6.4. Deprotection of 6.4 with an acid, such as trifluoroacetic acid, gives compound 6.5.

Reaction Scheme 7



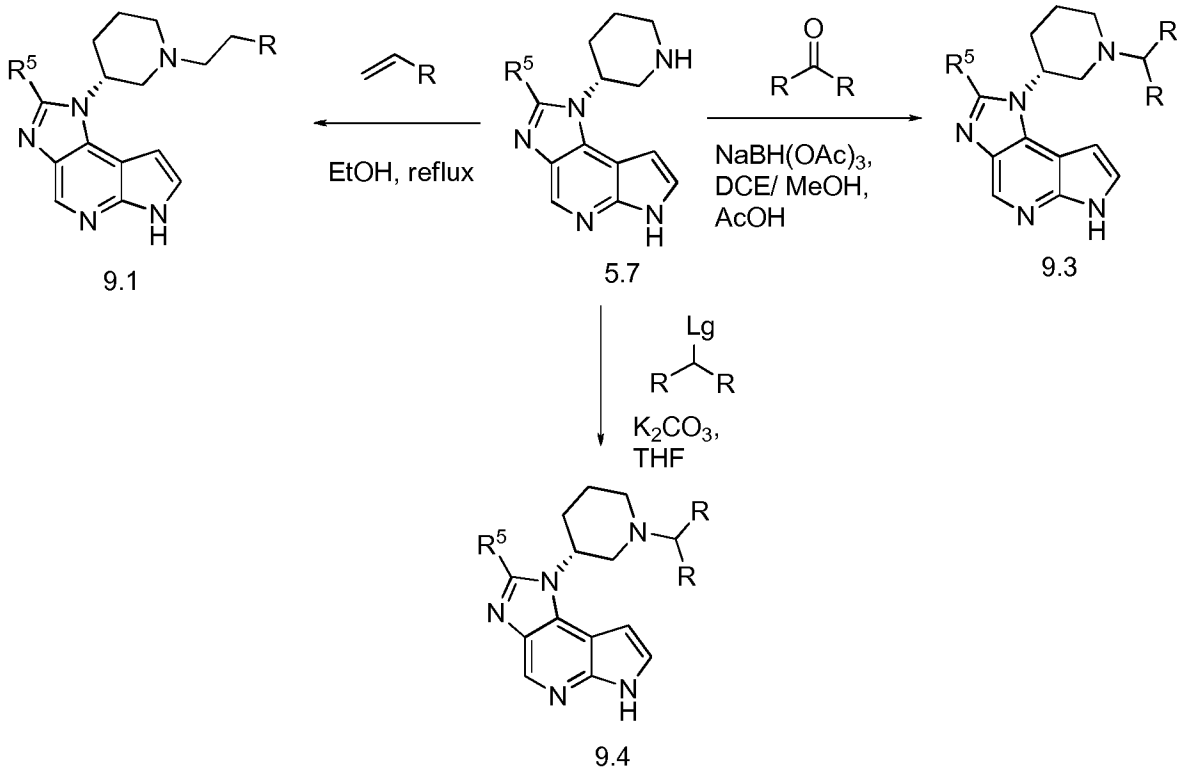
Reaction Scheme 7 illustrates the synthesis of compounds of formula I, for example compounds 7.4. Protected 3,4-diaminoazaindole 5.4 can be cyclised using n-butyl nitrite in the presence of copper (II) bromide to give 1,6-dihydropyrrolo[2,3-b][1,2,3]triazolo[4,5-d]pyridine compound 7.1. Deprotection of compound 7.1 using aqueous sodium hydroxide in methanol provides compounds 7.2. Treatment of compound 7.2 with ammonium formate and palladium (II) hydroxide in refluxing methanol provides compounds 7.3. Compounds 7.3 can be derivatized by reacting with compounds of the formula Lg-R (where Lg is a leaving group), for example, carboxylic acids of the formula RCO_2H (where each R is independently an optionally substituted group, such as alkyl, alkenyl, alkynyl, cycloalkyl, aryl or heterocyclyl) in the presence of suitable coupling reagents such as *N*-hydroxybenzotriazole (HOBt), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) and DMAP in dichloromethane (DCM).

Reaction Scheme 8



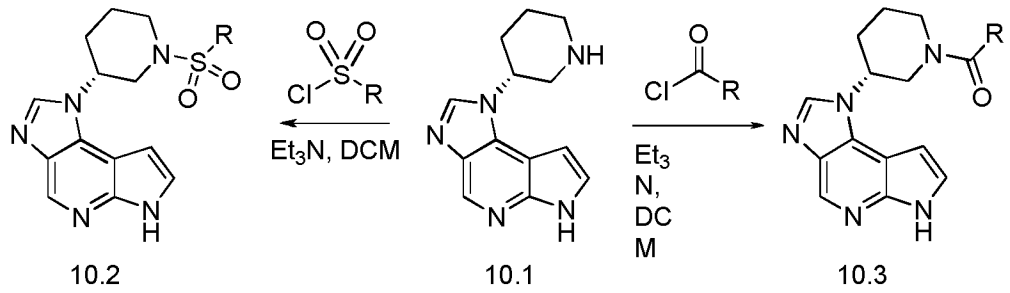
Reaction Scheme 8 illustrates the synthesis of compounds 8.5. For example, protected 3,4-diaminoazaindole 5.4 can be treated with ethyl malonyl chloride in the presence of base such as triethylamine and then cyclized in the presence of acetic acid to give imidazolo compound 8.1. Compound 8.1 can be reduced with a reducing agent, such as lithium aluminium hydride, to provide alcohol 8.2. Deprotection of compound 8.2 using aqueous sodium hydroxide in methanol provides compounds 8.3. Treatment of compound 8.3 with ammonium formate and palladium (II) hydroxide in refluxing methanol provides compounds 8.4. Compounds 8.4 can be converted using, for example, carboxylic acids in the presence of suitable coupling reagents such as HOBt and EDCI in DCM, to provide compounds 8.5.

Reaction Scheme 9



Reaction Scheme 9 illustrates the synthesis of compounds 9.4. Amino compounds such as 5.7 can be alkylated to give compounds 9.1 using a 2-substituted ethene in ethanol heated under reflux. Compounds 5.7 can be alkylated to give compounds 9.3 using an appropriate aldehyde or ketone, or an oxo-substitued compound such as R-C(O)-R, in the presence of a suitable reducing agent such as sodium triacetoxyborohydride either in the presence or absence of acetic acid. Alternatively compounds 5.7 can be alkylated with a suitable haloalkane (where Lg is a leaving group such as a halogen) in the presence of base such as potassium carbonate in THF to provide compounds of 9.4.

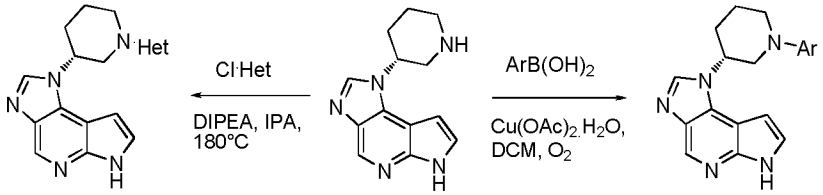
Reaction Scheme 10



Reaction Scheme 10 illustrates the synthesis of compounds 10.2 and 10.3. For example, amino compounds 10.1 can be treated with various functionalized sulfonyl chlorides in presence

of base such as triethylamine to give compounds 10.2. Compounds 10.1 can be coupled to various acid chlorides in the presence of base such as triethylamine to give compounds 10.3.

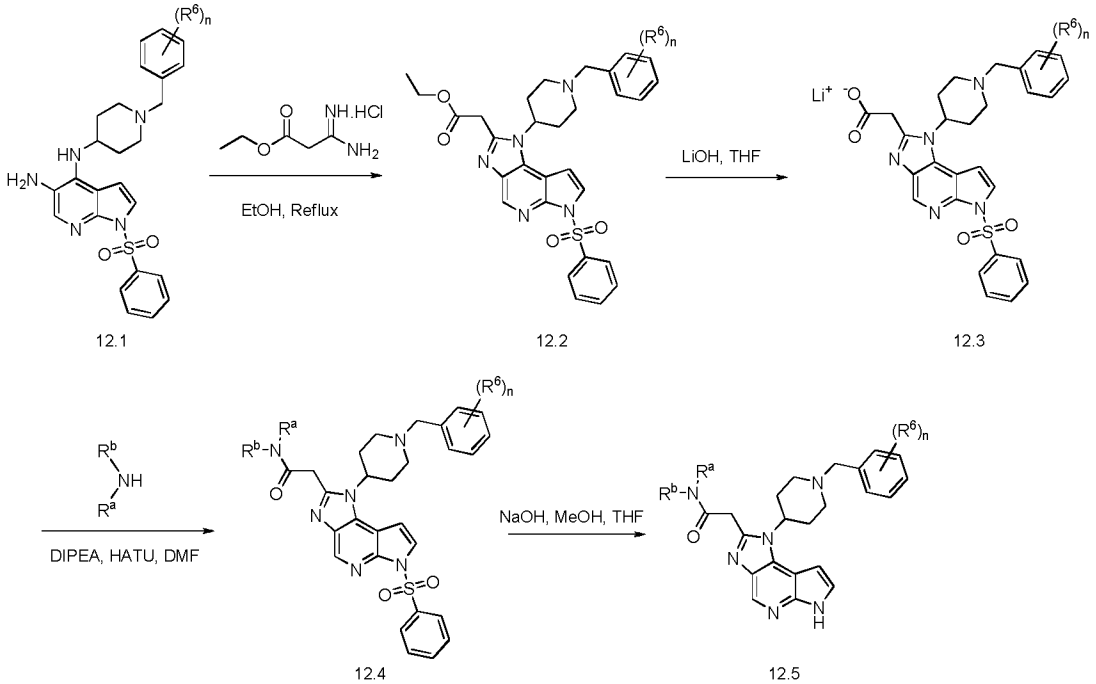
Reaction Scheme 11



11.1 10.1 11.2

Reaction Scheme 11 illustrates the synthesis of compounds 11.1 and 11.2. Amino compounds 10.1 can be treated with a suitable heteroaryl chloride, such as 4-chloropyridine, in presence of base, such as diisopropylethylamine, to provide compounds 11.1. Compounds 10.1 can be coupled to aryl or heteroaryl boronic acids in the presence of copper (II) acetate, either in the presence or absence of an oxygen atmosphere, using a suitable solvent, such as dichloromethane, to give compounds 11.2.

Reaction Scheme 12



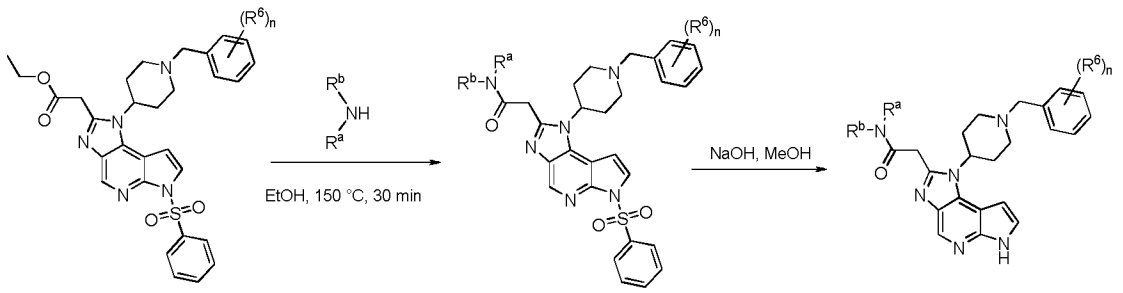
12.1 12.2 12.3

12.4 12.5

Reaction Scheme 12 illustrates the synthesis of compounds 12.5. A suitably protected 3,4-diaminoazaindole, such as compound 12.1, can be cyclised with a suitable amidine in the presence of a suitable solvent, such as ethanol, to give substituted imidazolo compound 12.2. Compound 12.2 can be hydrolysed using an aqueous base such as lithium hydroxide in a compatible solvent, such as THF, to provide acid salt compound 12.3. Compound 12.4 can be

prepared from compound 12.3 using suitable primary or secondary amines in the presence of a suitable coupling reagent, such as HATU, in a compatible solvent, such as DMF. Compound 12.4 can be hydrolysed using aqueous sodium hydroxide to give compounds 12.5.

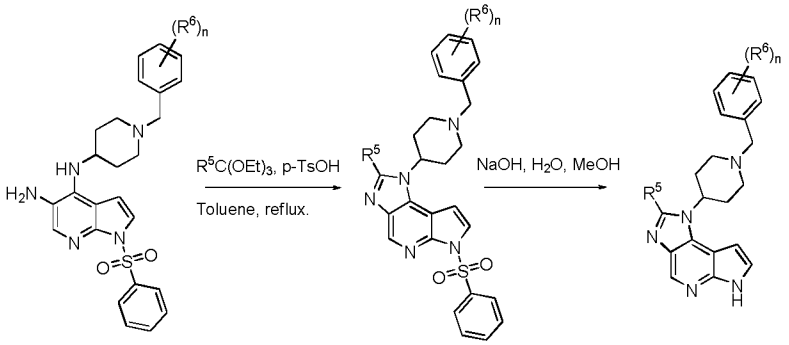
Reaction Scheme 13



12.2 12.4 12.5

Reaction Scheme 13 illustrates an alternative synthesis of compounds 12.5. Compound 14 can be treated with suitable amines, such as methylamine, in a compatible solvent, such as ethanol, at elevated temperatures to directly provide amide compound 12.4. Compound 12.4 can be hydrolysed using aqueous sodium hydroxide to give compound 12.5.

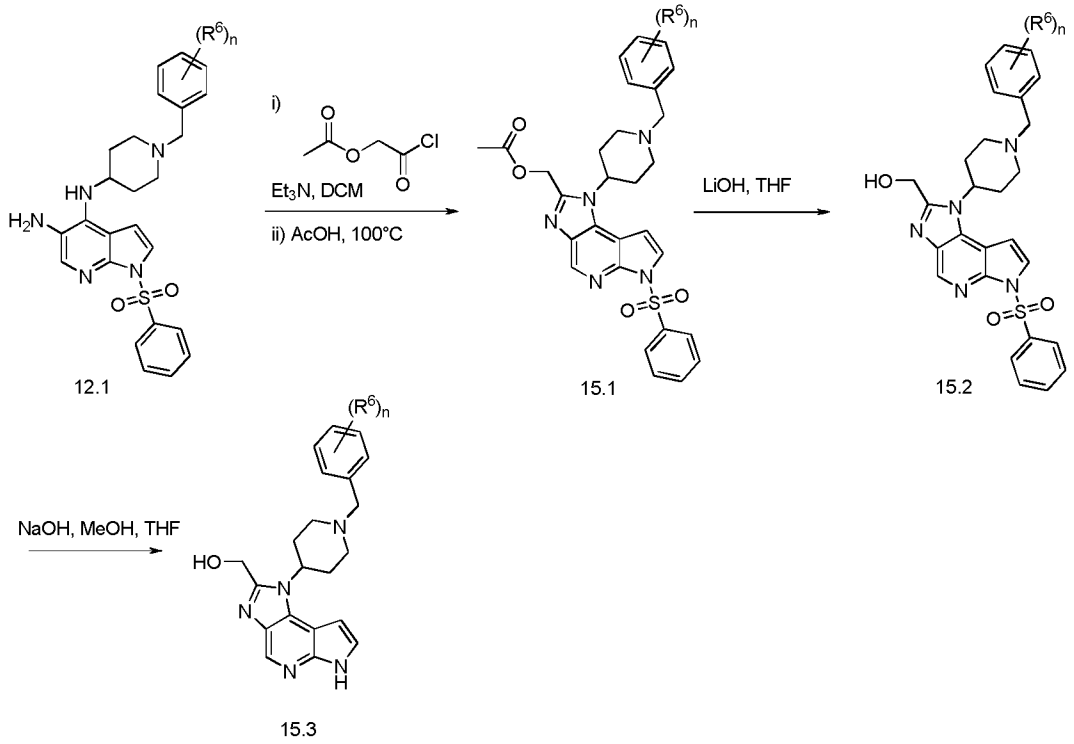
Reaction Scheme 14



12.1 14.1 14.2

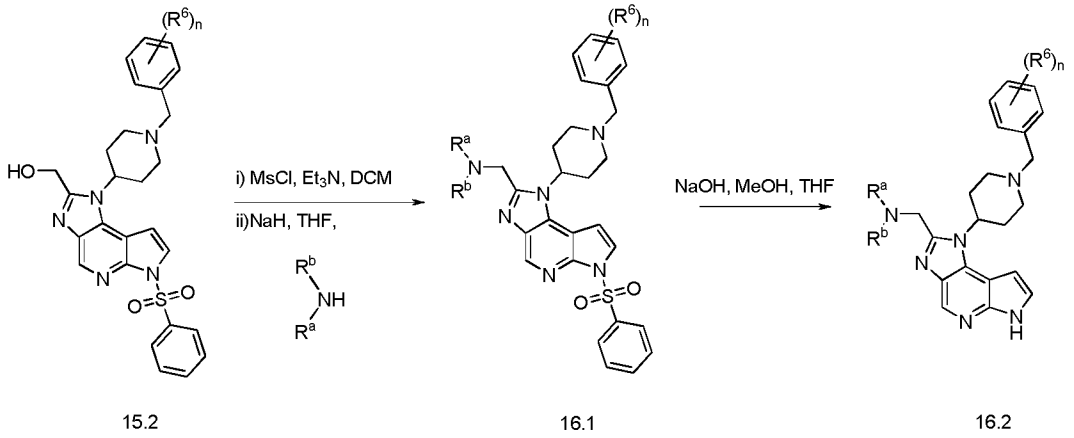
Reaction Scheme 14 illustrates the synthesis of compounds 14.2. A protected 3,4-diaminoazaindole, such as compound 12.1, can be cyclised with a triethyl orthoalkane, such as triethyl orthoacetate, in the presence of catalytic *p*-toluenesulfonic acid with prolonged heating to give substituted imidazolo compound 14.1. Hydrolysis of compound 14.1 with aqueous sodium hydroxide in methanol provides compounds 14.2.

Reaction Scheme 15



Reaction Scheme 15 illustrates the synthesis of compounds 15.3. A suitably protected 3,4-diaminoazaindole, such as compound 12.1, can be treated with acetoxyacetyl chloride in the presence of base, such as triethylamine, and then cyclized in the presence of acetic acid to give substituted imidazolo compound 15.1. Compound 15.1 can be hydrolysed using an aqueous base such as lithium hydroxide in a compatible solvent, such as THF, to provide alcohol compound 15.2. Hydrolysis of compound 15.2 with aqueous sodium hydroxide in methanol provides compounds 15.3.

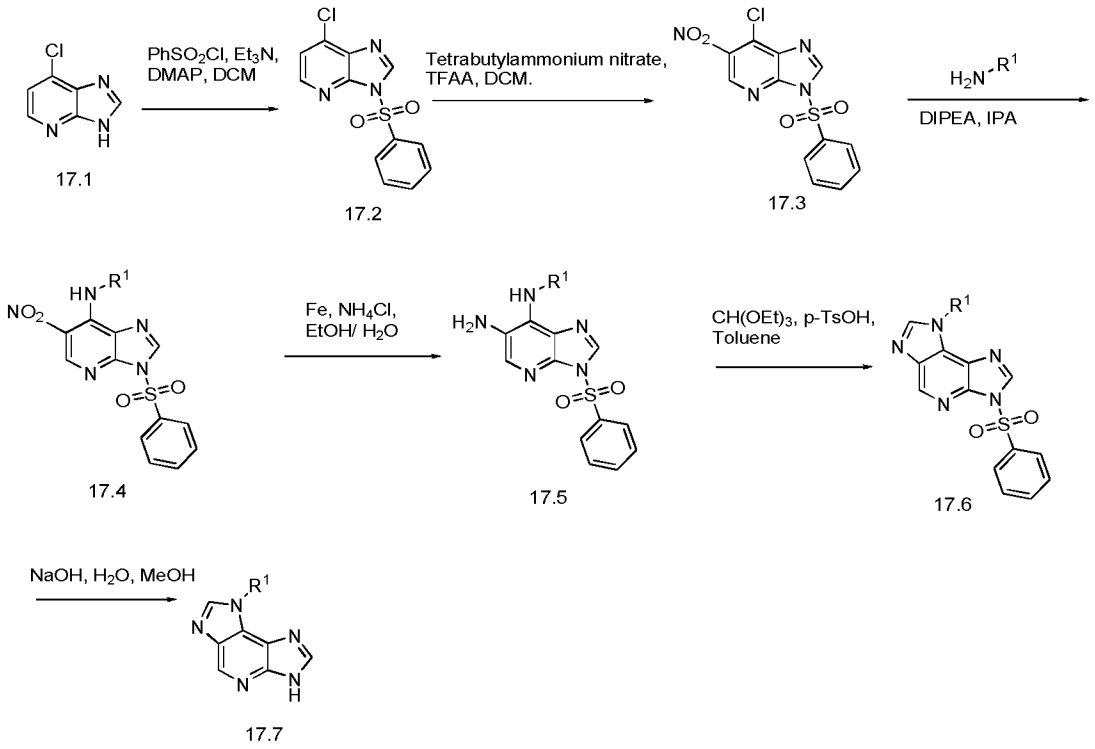
Reaction Scheme 16



Reaction Scheme 16 illustrates the synthesis of compounds 16.2. For example, alcohol compound 15.2 can be treated with methanesulfonyl chloride in the presence of a suitable base,

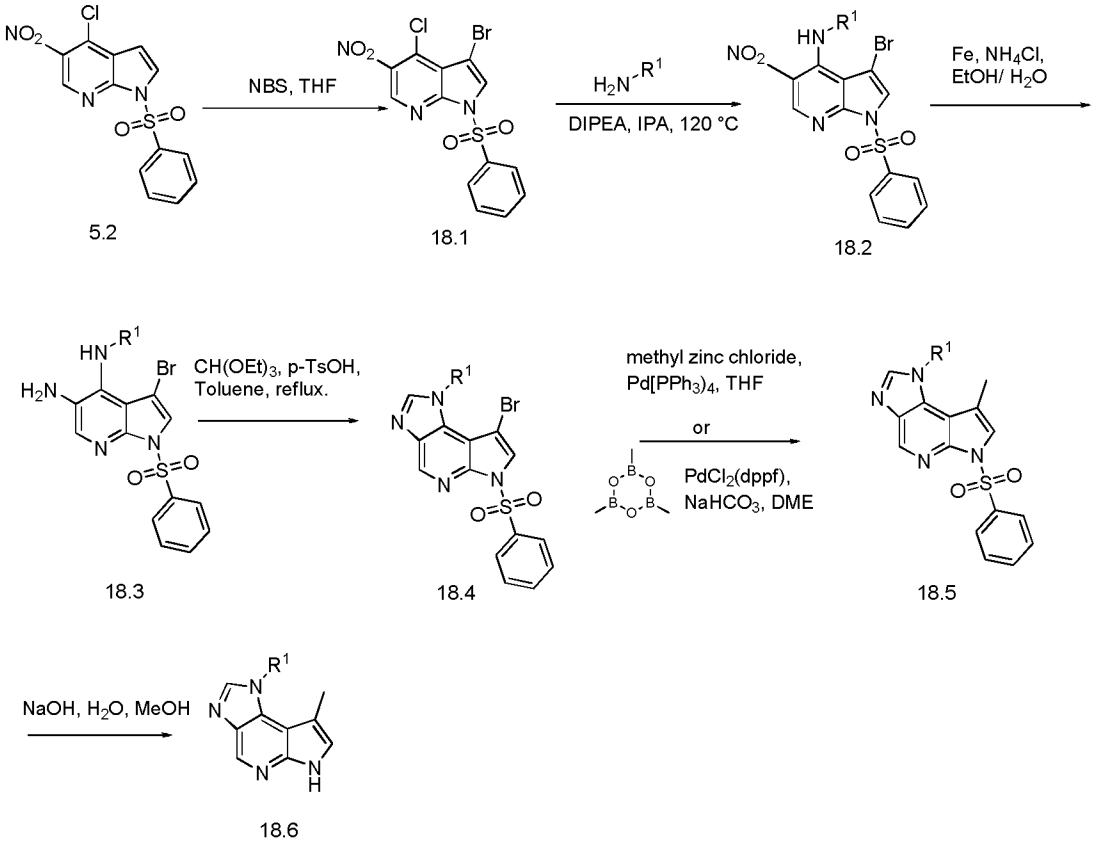
such as triethylamine, and the resulting product can be reacted with a compatible amine or lactam, such as 2-pyrrolidinone, in the presence of a suitable base, such as sodium hydride, to provide compound 16.1. Hydrolysis of compound 16.1 with aqueous sodium hydroxide provides compounds 16.2.

Reaction Scheme 17



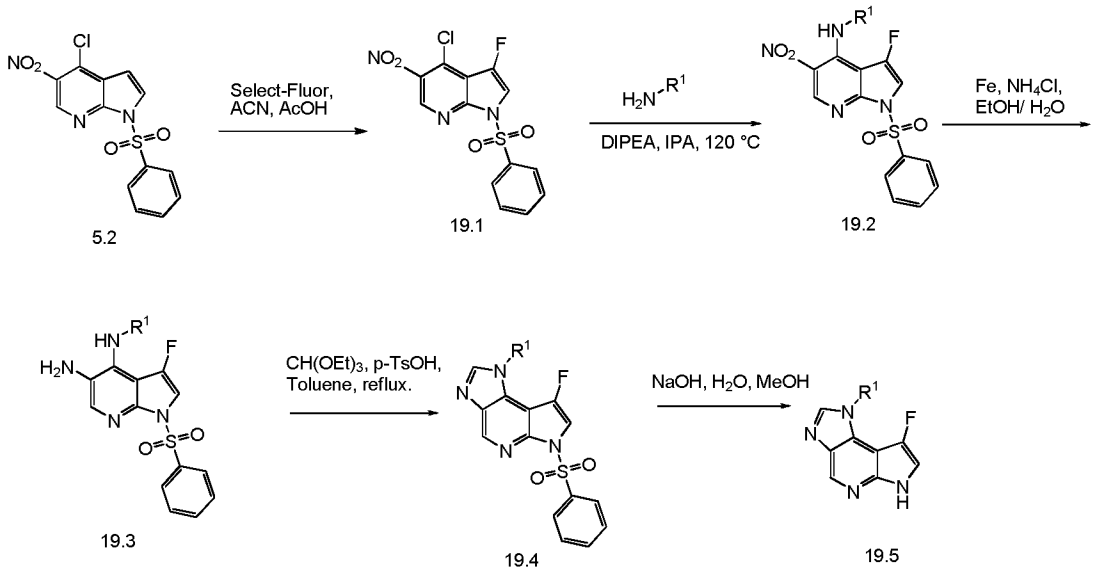
Reaction Scheme 17 illustrates the synthesis of compounds 17.7. The preparation of compound 17.1 has been previously described (see: Itoh et. al., *J. Heterocyclic Chem.*, **19**, 513-517 (1982)). Compound 17.1 can be treated with methanesulfonyl chloride in the presence of a suitable base, such as triethylamine, to give compound 17.2. Nitration of 17.2 using tetrabutylammonium nitrate in the presence of trifluoroacetic anhydride gives compound 17.3. Compound 17.3 can be reacted with an appropriate primary amine to give compound 17.4, which can then be treated with a reducing reagent, such as iron, in the presence of ammonium chloride to give aniline 17.5. Compound 17.5 can be cyclized to give imidazole 17.6, which can then be hydrolyzed with aqueous sodium hydroxide to give compound 17.7.

Reaction Scheme 18



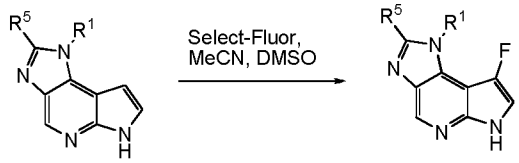
Reaction Scheme 18 illustrates the synthesis of compound 18.6. Compound 5.2 can be treated with a brominating reagent such as *N*-bromosuccinimide to give compound 18.1, which can then be treated with an appropriate primary amine to give intermediate 18.2. Compound 18.2 can be treated with a reducing agent, such as iron, in the presence of ammonium chloride to give aniline 18.3, which then can be cyclized to give imidazole 18.4. Compound 18.4 can be treated with alkylating reagents, such as methyl zinc chloride and tetrakis(triphenylphosphine)palladium(0), or trimethylboroxine in the presence of [1,1'-Bis(diphenylphosphino)ferrocene] dichloropalladium(II) and sodium hydrogen carbonate, to give alkylated compound 18.5. Compound 18.5 can then be hydrolyzed with aqueous sodium hydroxide to give compounds 18.6.

Reaction Scheme 19



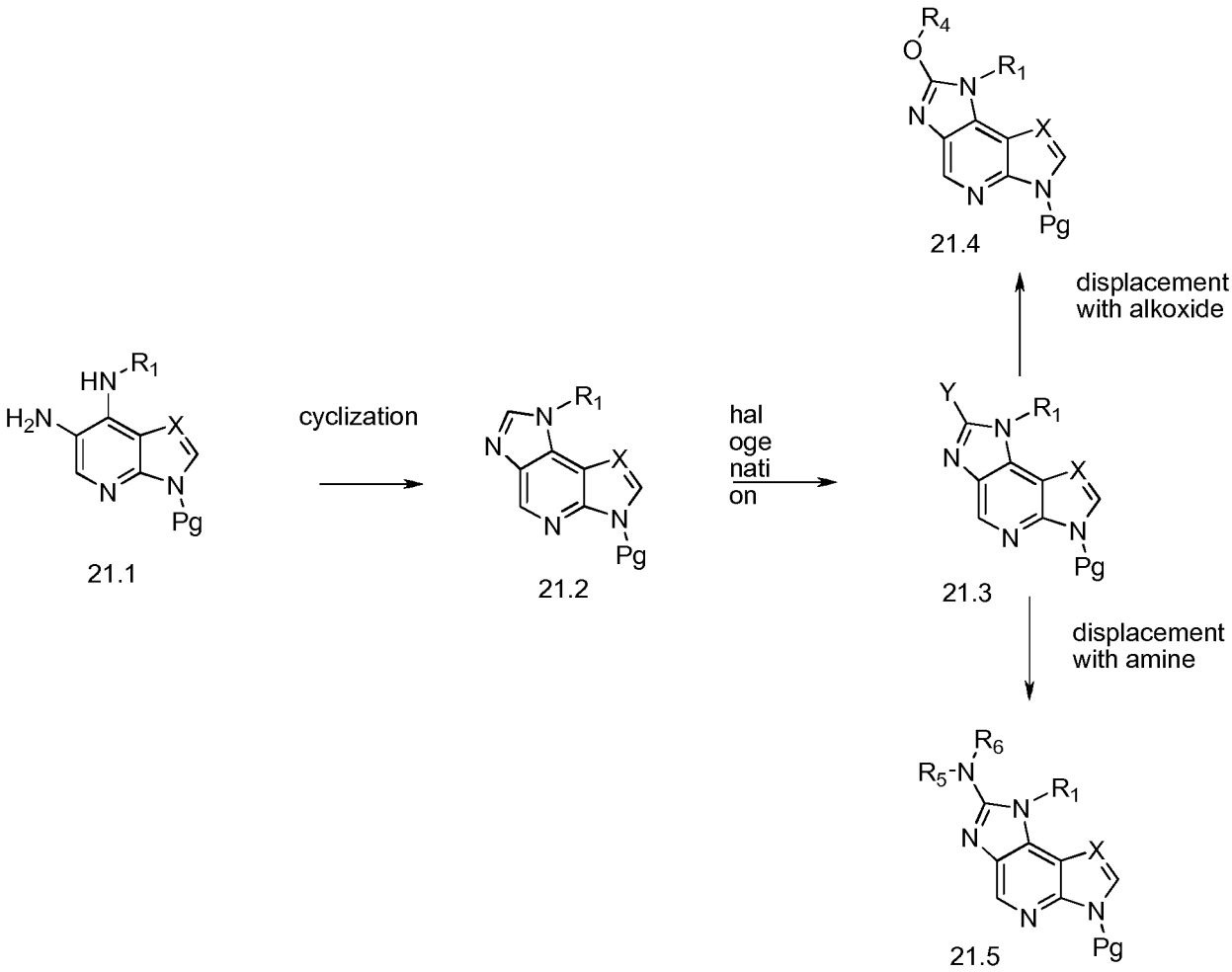
Reaction Scheme 19 illustrates the synthesis of compounds 19.5. Compound 5.2 can be treated with a fluorinating reagent, such as Select-Fluor, to give compound 19.1, which can then be treated with an appropriate primary amine to give intermediate 19.2. Compound 19.2 can then be treated with a reducing agent, such as iron in the presence of ammonium chloride, to give aniline 19.3, which then can be cyclized to give imidazole 19.4. Compound 19.4 can be hydrolyzed with aqueous sodium hydroxide to give compounds 19.5.

Reaction Scheme 20



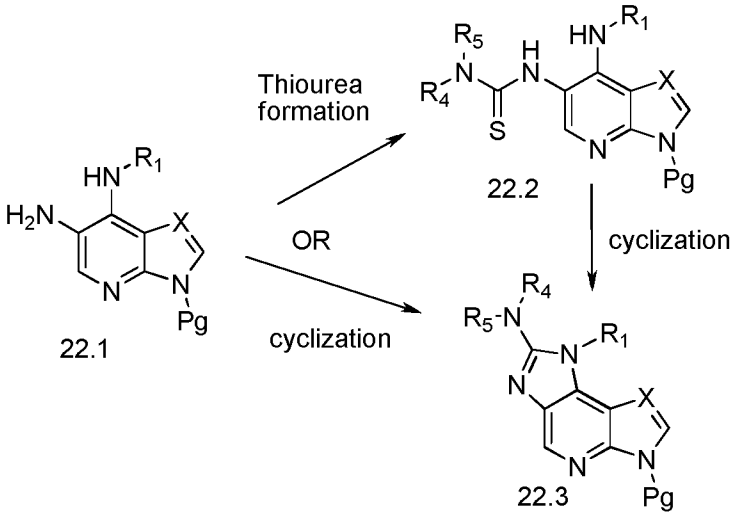
Reaction Scheme 20 illustrates the synthesis of compounds 20.2. For example, compound 20.1 can be treated with a fluorinating agent, such as Select-Fluor, to directly provide compounds 20.2.

Reaction Scheme 21



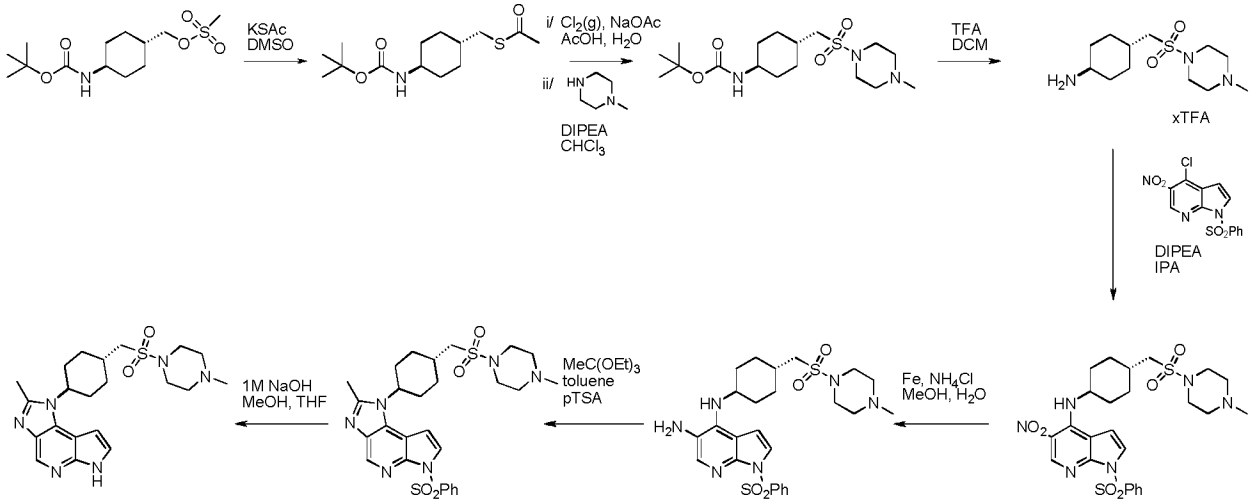
Compounds of type 21.4 and 21.5 can be synthesized from compounds of type 21.1 by cyclization for example with triethyl orthoformate. Halogenenation of 21.2 can be achieved for example by treating 21.2 with a suitable base such as lithium diisopropylamide then quenching with a suitable halogen source such as an N-halosuccinimide. Compounds of type 21.4 can be prepared by displacing the halogen in 21.3 with a suitable nucleophile such as sodium methoxide. Compounds of type 21.5 can similarly be prepared by displacement of the halogen in 21.3 with a suitable amine such as ethanolamine.

Reaction Scheme 22



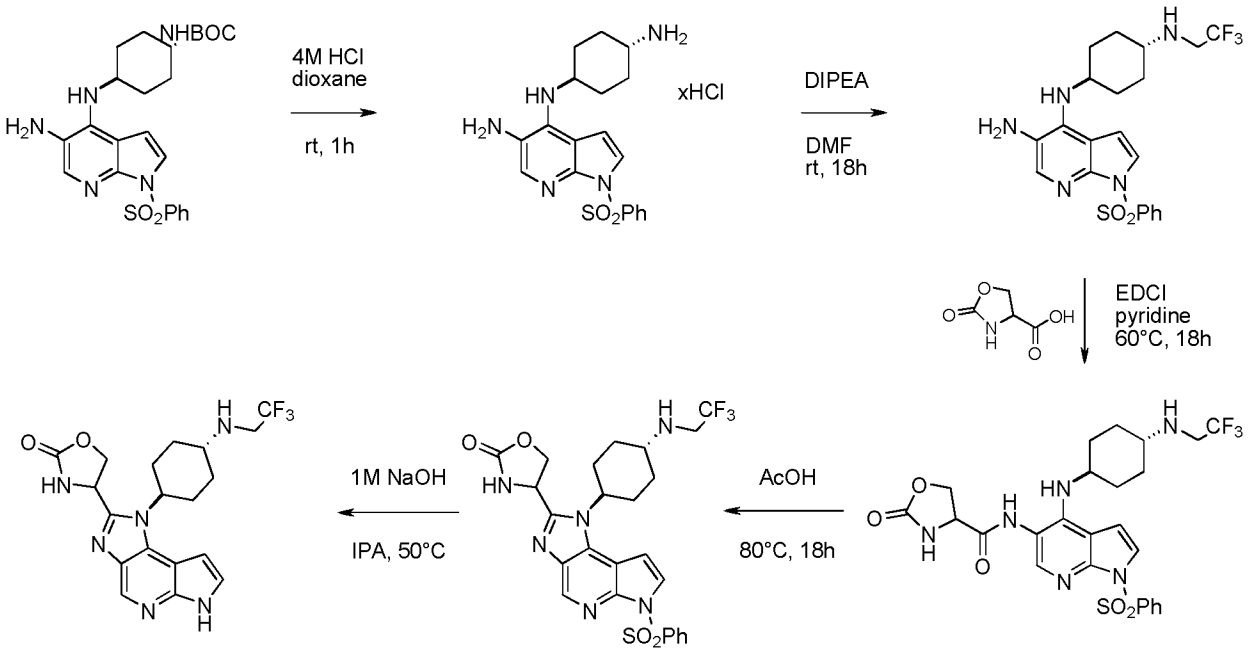
Compounds of type 22.3 can be prepared directly from compounds of type 22.1 by reaction with a reagent such as dichloromethylene-dimethyliminium chloride. Alternatively, compounds of type 22.3 can be prepared by first reacting compounds of type 22.1 with a reagent such as an alkyl isothiocyanate. Compounds of type 22.3 may be prepared by cyclisation of a compound of type 22.2 by reaction with a reagent such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

Reaction Scheme 23



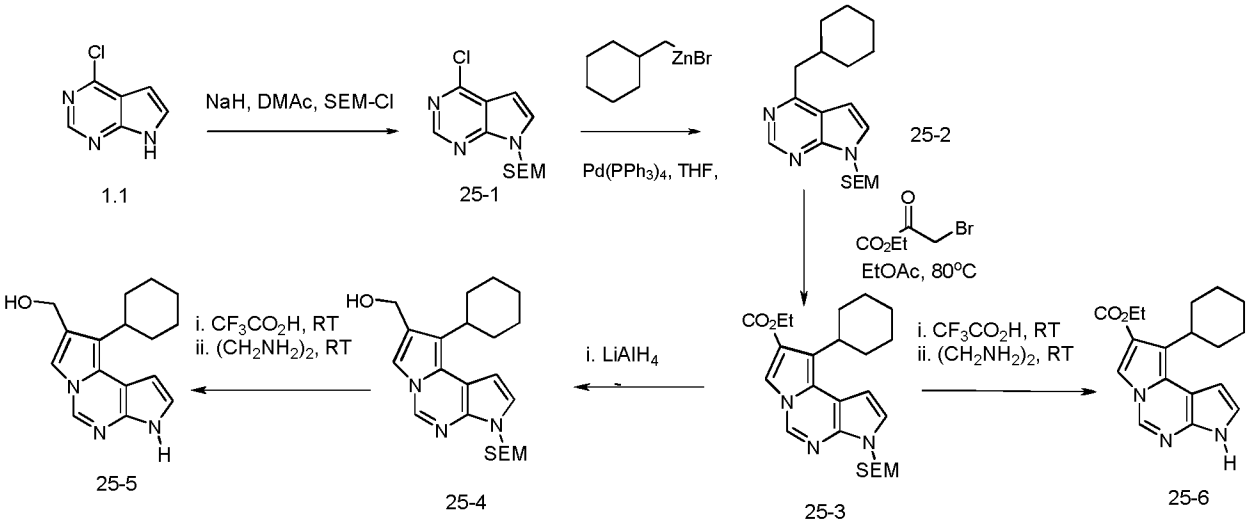
Compounds wherein R^5 is alkyl and R^1 is substituted cycloalkyl can be made according to reaction Scheme 23.

Reaction Scheme 24



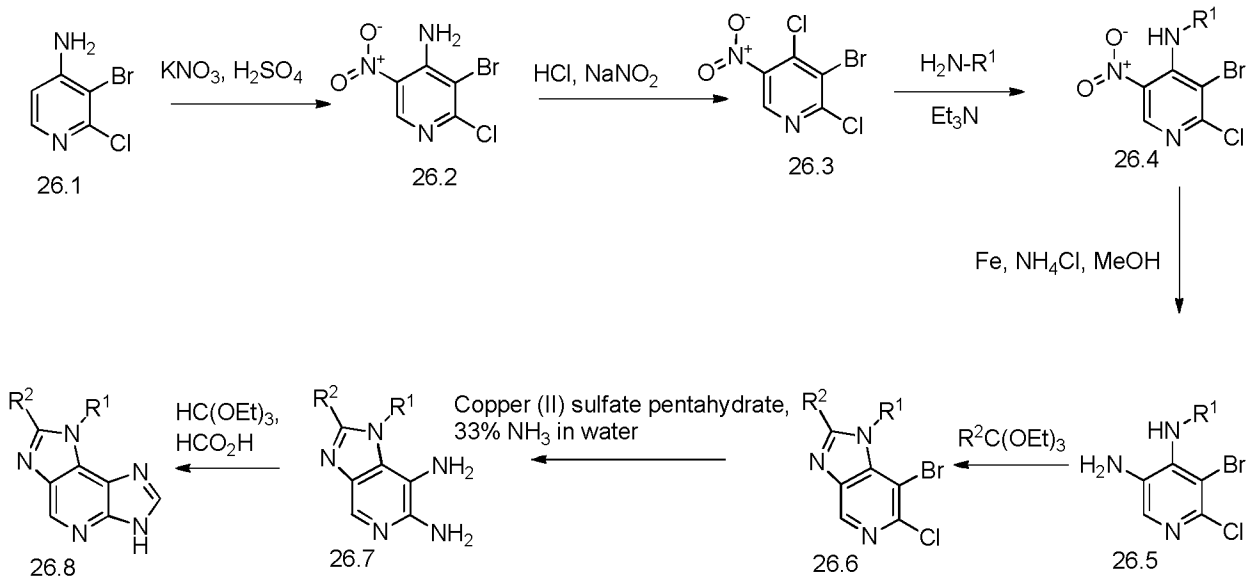
Compounds wherein R^5 is heterocyclyl can be made according to reaction Scheme 24.

Reaction Scheme 25



Compounds of type 25-5 and 25-6 can be prepared as shown in Scheme 25. Starting from compound 1.1, introduction of nitrogen protecting group, such as SEM, gives protected compound 25-1. Cross-coupling of 25-1 with organometallic reagents, such as alkylzinc compounds, give compounds 25-2. Cyclization of 25-2 with ethyl 3-bromo-2-oxopropanoate gives 25-3 with heating. Compound 25-3 can be reduced to the hydroxymethyl derivative and deprotected in two steps to give 25-5. Likewise, compound 25-3 can be directly deprotected to give the ester derivative 25.6.

Reaction Scheme 26



Reaction Scheme 26 illustrates the synthesis of compounds 17.8. Nitration of 26.1 provides 26.2. The aniline group present in 26.2 may be converted to aryl chloride 26.3 under standard conditions. Treatment of activated aryl chloride 26.3 with a primary amine in the presence of a base such as triethylamine provides anilines 26.4. Reduction of the nitro group under conditions such as iron and ammonium chloride provides dianilines 26.5. Cyclization of the dianilines with a reagent such as a triethyl orthoalkane provides imidazoles 26.6. Displacement of the aryl halide groups of 26.6 with amino groups provides dianilines 26.7, which may be further cyclized with triethylorthoacetate in the presence of formic acid to provide compounds 26.8.

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.

METHODS OF SEPARATION

In each of the exemplary Schemes it may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified (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:

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 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 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, 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 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 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)

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 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 be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the pure or enriched enantiomer. A method of determining optical purity involves making chiral esters, such as a menthyl ester, e.g. (-) menthyl chloroformate in the presence of base, or Mosher ester, α-methoxy-α-(trifluoromethyl)phenyl acetate (Jacob, *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 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 chiral molecules with asymmetric carbon atoms, such as optical rotation and circular dichroism. The absolute stereochemistry of chiral centers and enatiomers 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 sufficiently high, the E and Z isomers may be separated, for example by preparatory HPLC.

PHARMACEUTICAL COMPOSITIONS AND ADMINISTRATION

Another embodiment 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 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 mainly on the particular use and the concentration of compound, but preferably ranges anywhere from about 3 to about 8. In one example, a compound of formula I is formulated in an acetate buffer, at pH 5. In another embodiment, 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 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 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 another embodiment, 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 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, 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; 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, 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, 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 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 a pharmaceutically acceptable carrier or excipient.

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

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 pathways, such as IL-6, IL-15, IL-7, IL-2, IL-4, IL-9, IL-10, IL-13, IL-21, G-CSF, IFNalpha, IFNbeta 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, IFNbeta or IFNgamma cytokine signaling.

Another embodiment 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.

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.

In certain embodiments, the disease or condition is cancer.

In certain embodiments, the disease is a myeloproliferative disorder.

In certain embodiments, the myeloproliferative disorder is polycythemia vera, essential thrombocytosis, 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, hepatocellular cancer, head cancer, neck cancer, Hodgkin's or leukemia.

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, 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 kinase is rheumatoid arthritis, asthma, systemic lupus erythematosus, psoriasis, IBD or transplant rejection.

Another embodiment 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.

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

Another embodiment 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.

Another embodiment 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).

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-cancer, cytostatic, cytotoxic, anti-inflammatory or chemotherapeutic agent. The second compound of the pharmaceutical combination formulation or dosing regimen preferably 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 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 another embodiment, the cytostatic compound is doxorubicin. In another embodiment, compounds of the present invention are coadministered with an anti-inflammatory agent selected from a NSAID and corticosteroid. In another embodiment, compounds of the present invention are coadministered with an anti-rheumatoid agent, in one example, RITUXAN®. In another embodiment, compounds of the present invention are coadministered with a chemotherapeutic agent selected from etanercept (Enbrel), infliximab (Remicade),

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 such as rhuMAb Beta7; IgE pathway blockers such as Anti-M1 prime; Secreted homotrimeric LTa3 and membrane bound heterotrimer LTa1/β2 blockers such as Anti-lymphotoxin alpha (LTa)

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 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 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), 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.

ARTICLES OF MANUFACTURE

Another embodiment 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.

In another embodiment, 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 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 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 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.

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 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 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 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.

EXAMPLES

Abbreviations:

aq.	Aqueous
Bn	Benzyl
Boc_2O	Di-tert-butyl dicarbonate
$CDCl_3$	Deuterated chloroform
DCM	Dichloromethane
DIAD	Diisopropyl azodicarboxylate
DIPEA	Diisopropylethylamine
DMAP	4-(Dimethylamino)pyridine
DMAW 90	DCM/MeOH/AcOH/H_2O (90:18:3:2)
DMAW 240	DCM/MeOH/AcOH/H_2O (240:20:3:2)
DMSO	Dimethylsulfoxide
DMSO-*d6*	Deuterated DMSO
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
EDCI	1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride
eq	equivalents
ESI	Electrospray
Et	Ethyl
EtOAc	Ethyl acetate
EtOH	Ethanol
Et_3N	Triethylamine

Et_2O	Diethyl ether
h	Hour
hr	Hour
HATU	2-(7-aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HCl	Hydrochloric acid
HM-N	Isolute® HM-N is a modified form of diatomaceous earth
HOBt	Hydroxybenzotriazole
HPLC	High performance liquid chromatography
IMS	Industrial methylated spirit
IPA	Isopropyl alcohol
LDA	Lithium diisopropylamide
LiOH	Lithium Hydroxide
min	minutes
MeOH	Methanol
MeOD	Deuterated methanol
$MgSO_4$	Magnesium sulphate
MMPP	Magnesium monoperoxyphthalate
NaH	Sodium Hydride
NaOH	Sodium Hydroxide
Na_2SO_4	Sodium sulfate
$NaHCO_3$	Sodium bicarbonate / Sodium hydrogen carbonate
NaOH	Sodium hydroxide
NEt_3	Triethylamine
NH_3	Ammonia
NH4Cl	Ammonium chloride
p-TsOH	*para*-toluenesulfonic acid
RT	Retention time in minutes
SCX-2	Pre-packed Isolute® silica-based sorbent with a chemically bonded propylsulfonic acid functional group

SFC	Supercritical fluid chromatography
Si-SPE	Pre-packed Isolute® silica flash chromatography cartridge
Si-ISCO	Pre-packed ISCO® silica flash chromatography cartridge
TBAF	Tetrabutylammonium fluoride
TBS	tert-butyl dimethylsilyl
TBDMS-OTf	Trifluoromethanesulfonic acid tert-butyldimethylsilyl ester
TEA	Triethylamine
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMSCl	Trimethylsilyl chloride
Ts	Toluene sulfonyl

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.

^{1}H 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, a Bruker Avance DPX 300 (300MHz) equipped with a standard 5mm dual frequency probe for detection of ^{1}H and ^{13}C, a Bruker AVIII (400 MHz) using a BBI Broad Band Inverse 5mm probe, or a Bruker AVIII (500 MHz) using a QNP (Quad Nucleus detect) 5mm probe. Chemical shifts are expressed in ppm relative to an internal standard; tetramethylsilane (ppm = 0.00). The following abbreviations have been used: br = broad signal, s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet.

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

Method A: 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 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: Experiments performed 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 a Luna 3 micron C18(2) 30 x 4.6mm column at ambient temperature and a 2.0 ml / minute flow rate. The initial solvent system was 95% water containing 0.1% formic acid (solvent A) and 5% methanol 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.

Method C:

HPLC-Agilent 1200	
Mobile phase A	H_2O with 0.05%TFA
Mobile phase B	Acetonitrile with 0.05%TFA
Column	Agilent SD-C18, 1.8um, 2.1*30mm
Column temperature	40 °C

LC gradient	3-95%B in 8.5 min, 95% in 2.5 min
LC Flowrate	700uL/min
UV wavelength	220nm and 254nm
Mass Spec - Agilent quadrupole 6140	
Ionization	ESI+
Scan range	110-800amu

Method D:

HPLC-Agilent 1200	
Mobile phase A	H_2O with 0.05%TFA
Mobile phase B	Acetonitrile with 0.05%TFA
Column	Agilent SD-C18, 3.5µm, 3.0*100mm
Column temperature	40 °C
LC gradient	2-98%B in 25.5 min, hold for 4.5 min
LC Flowrate	700µL/min
UV wavelength	220nm and 254nm
Mass Spec - Agilent quadrupole 6140	
Ionization	ESI+
Scan range	110-800amu

Method E:

HPLC-Agilent 1200	
Mobile phase A	H2O with 0.1%Formic Acid
Mobile phase B	Acetonitrile with 0.1%Formic Acid
Column	XBridge C18 2.5 µm 3.0*30mm

Column temperature	40 °C
LC gradient	2-95%B in 2.2 min, 95% in 0.3 min
LC Flowrate	2mL/min
UV wavelength	220nm and 254nm
Mass Spec - Agilent quadrupole 6140	
Ionization	ESI+
Scan range	110-800amu

Method F:

Waters Acquity UPLC	
Mobile phase A	H_2O with 0.1%Formic Acid
Mobile phase B	Acetonitrile with 0.1%Formic Acid
Column	Acquity UPLC BEH C18, 1.7µm, 2.1*30mm
Column temperature	40 degree C
LC gradient	5-95%B in 1.4 min, 95% in 0.3 min
LC Flowrate	800uL/min
UV wavelength	220nm and 254nm
Mass Spec - Waters SQ Detector	
Ionization	ESI+
Scan range	100-800amu

Method G: HPLC instrument: Waters Acquity UPLC; mobile phase A: H_2O with 0.1% formic acid; mobile phase B: CH_3CN with 0.1% formic acid; column: Acquity UPLC BEH C18, 1.7 um, 2.1 x 30 mm; column temperature: 80 °C; LC gradient: 5-95% B in 1.4 min, 95% in 0.3 min; LC flowrate: 800uL/min; UV wavelength: 220 nm and 254 nm; mass spectrometer: Waters SQ detector; ionization: ESI+; scan range: 100-800 amu.

Method H: Experiments were performed on a Waters Platform LC quadrupole mass spectrometer linked to a Hewlett Packard HP1100 LC system with diode array detector and 100 position autosampler. The spectrometer has an electrospray source operating in positive and negative ion mode. Additional detection is achieved using a Sedex 85 evaporative light scattering detector. This system uses an Phenomenex 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 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 minutes. This was maintained for 1 minute before returning to 95% solvent A and 5% solvent B over the next 0.5 minute. Total run time was 6 minutes.

Method I: Experiments were performed on a Waters ZMD quadrupole mass spectrometer linked to a Waters 1525 LC system with Waters 996 diode array detector. The spectrometer has an electrospray source operating in positive and negative ion mode. Additional detection is achieved using a Sedex 85 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 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 minutes. This was maintained for 1 minute before returning to 95% solvent A and 5% solvent B over the next 0.5 minute. Total run time was 6 minutes.

Method J:

LCMS	SHIMADZU LC/20A or Agilent 1200 Series
Mobile phase A	H_2O with 0.375% TFA
Mobile phase B	Acetonitrile with 0.187% TFA
Column	Shimpack ODS XR-ODS,3*30mm or Xtimate 3μm,2.1*30mm SN:3u410901511
Column temperature	50 °C
LC gradient	10-80%B in 2 min, 80% in 0.9 min
LC Flowrate	1200μL/min
UV wavelength	220nm

Mass Spec - SHIMADZU 2010MSD or Agilent MSD VL	
Ionization	ESI+
Scan range	100-1000amu

Method K:

LCMS	SHIMADZU LC/20A or Agilent 1200 Series
Mobile phase A	H_2O with 0.375%TFA
Mobile phase B	Acetonitrile with 0.187% TFA
Column	Shimpack ODS XR-ODS,3*30mm or Xtimate 3µm,2.1*30mm SN:3u410901511
Column temperature	50 °C
LC gradient	0-60%B in 2min, 60% in 0.9min
LC Flowrate	1200µL/min
UV wavelength	220nm
Mass Spec - SHIMADZU 2010MSD or Agilent MSD VL	
Ionization	ESI+
Scan range	100-1000amu

Method L:

LCMS	SHIMADZU LC/20A or Agilent 1200 Series
Mobile phase A	H_2O with 0.375%TFA
Mobile phase B	Acetonitrile with 0.187%TFA
Column	Shimpack ODS XR-ODS,3*30mm or Xtimate 3µm,2.1*30mm SN:3u410901511
Column temperature	50 °C

LC gradient	0-30%B in 2 min, 30% in 0.9 min
LC Flowrate	1200µL/min
UV wavelength	220nm
Mass Spec - SHIMADZU 2010MSD or Agilent MSD VL	
Ionization	ESI+
Scan range	100-1000amu

Method M:

System	Shimadzu HPLC
Mobile phase A	H_2O with 0.05%TFA
Mobile phase B	Acetonitrile with 0.0375%TFA
Column	Phenomenex Onyx Monolithic C18 4.6*50mm
Column temperature	Room temperature
LC gradient	5-85%B in 4.0 min, 85% in 0.5 min
LC Flowrate	3000µL/min
UV wavelength	214nm and 254nm
Mass Spec - Waters SQ Detector	
Ionization	ESI+
Scan range	150-1250amu

Method N:

System	Waters Acquity UPLC
Mobile phase A	Waters with 0.05%TFA
Mobile phase B	Acetonitrile with 0.05%TFA
Column	Acquity UPLC BEH C18, 1.7µm, 2.1*50mm

Column temperature	40 °C
LC gradient	2-98%B in 17.0 min, 98% in 1.5 min
LC Flowrate	600µL/min
UV wavelength	254nm
Mass Spec - Waters LCT Premier XE	
Ionization	ESI positive
Scan range	100-800amu

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Method O:

System	HPLC-Agilent 1200
Mobile phase A	Water with 0.05%TFA
Mobile phase B	Acetonitrile with 0.05%TFA
Column	Agilent ZORBAX SD-C18, 1.8µm, 2.1*30mm
Column temperature	40 °C
LC gradient	3-95%B in 8.5 min, 95% in 2.5 min
LC Flowrate	400µL/min
UV wavelength	220nm and 254nm
Mass Spec - Agilent quadrupole 6140	
Ionization	ESI positive
Scan range	110-800amu

Method P:

System	HPLC-Agilent 1200
Mobile phase A	H_2O with 0.05%TFA
Mobile phase B	Acetonitrile with 0.05%TFA

Column	Onyx-C18, 2.0*50mm
Column temprature	35 °C
LC gradient	5-65%B in 4 min
LC Flowrate	785µL/min
UV wavelength	220nm and 254nm
Mass Spec - Agilent quadrupole 6140	
Ionization	ESI+
Scan range	60-1000amu

Method Q: Experiments were performed on a system consists of a Waters ZMD single quadrupole mass spectrometer linked to a Hewlett Packard HP1100 LC system with UV diode array detector and 100 position autosampler. The spectrometer has an electrospray source operating in positive and negative ion mode. This system uses an Phenomenex 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 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 minutes. This was maintained for 1 minute before returning to 95% solvent A and 5% solvent B over the next 0.5 minute. Total run time was 6 minutes.

Method R: Experiments were performed on a VG Platform II quadrupole spectrometer is linked to a Hewlett Packard HP1050 LC system with diode array detector and 100 position autosampler. The spectrometer has an electrospray source operating in positive and negative ion mode. Additional detection is achieved using a Sedex 85 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 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 minutes. This was maintained for 1 minute before returning to 95% solvent A and 5% solvent B over the next 0.5 minute. Total run time was 6 minutes.

Method S:

Waters Acquity/LCT short method - 10 min run

Waters Acquity UPLC

Mobile phase A

Waters with 0.1%FA

Mobile phase B

Acetonitrile with 0.1%FA

Column

Acquity UPLC BEH C18, 1.7um, 2.1*50mm

Column temperature

40 degree C

LC gradient

2-98%B in 7.5 min, 98% in 1.0 min

LC Flowrate

600uL/min

UV wavelength

254nm

Mass Spec - Waters LCT Premier XE

Ionization

ESI positive

Scan range

100-800amu

Chiral supercritical fluid chromatography (SFC) was performed using one of the following methods, unless specified otherwise:

Method A1:

System: Berger Analytical SFC

Column: 4.6x100mm, 5µm, Chiralpak AD from Chiral Technologies

Flowrate: 5mL/min

Solvent A: CO_2

Solvent B: Methanol

Method: 35%B over 3 minutes

Pressure: 120 Bar

Temperature: 40 °C

Detection: UV at 230nm

Method A2:

System	Mettler-Toledo MGII
Mobile phase A	Methanol with 0.1% Diethylamine
Mobile phase B	Super-critical CO_2
Column	Chiral Technologies Chiralpak IC, 5µm
Column temperature	40 °C
LC gradient	Isocratic 30%B, 3 min
LC Flowrate	50 g/min
UV wavelength	230 nm

Method A3:

Instrument: Berger analytical and Waters ZQ

Column: Phenomenex Lux Cellulose-2, 4.6x100mm, 5µm

Detection: UV 220nm

Mobile Phase: 30% EtOH containing 0.1%TEA, 70% CO_2

Flowrate: 5g/min

Runtime: 3 minutes

Back pressure setting: 120 bar

Temperature: 40 °C

Method A4:

Mobile Phase A: CO_2

Mobile phase B: Methanol with 0.1%dimethylamine

Isocratic conditions with 30% Mobile phase B

Flow Rate: 200mL/min

Column: Lux Cellulose-1, 3x25cm, 5 µM

Outlet pressure: 100 Bar

Temperatuer: 40 °C

System: Thar 350

Uv: 230nm

Runtime: 5.2 minutes

Method A5:

System	Mettler-Toledo MGII
Mobile phase A	Methanol with 0.1% NH4OH
Mobile phase B	Super-critical CO_2
Column	Chiral Technologies Chiralpak IC, 3µm
Column temperature	40 °C
LC gradient	Isocratic 35%B, 3 min
LC Flowrate	50 g/min
UV wavelength	230 nm

Method A6:

System	Mettler-Toledo MGII
Mobile phase A	Methanol with 0.1% NH4OH

Mobile phase B	Super-critical CO_2
Column	Chiral Technologies Chiralpak IC, 3µm
Column temperature	40 °C
LC gradient	Isocratic 30%B, 3 min
LC Flowrate	50 g/min
UV wavelength	230 nm

Method A7:

System	Mettler-Toledo MGII
Mobile phase A	Methanol with 0.1% NH4OH
Mobile phase B	Super-critical CO_2
Column	Chiral Technologies Chiralpak IC, 3µm
Column temperature	40 °C
LC gradient	Isocratic 25%B, 3 min
LC Flowrate	50 g/min
UV wavelength	230 nm

Method A8

Mobile Phase A: CO_2

Mobile phase B: Methanol with 0.1% ammonium hydroxide

Isocratic conditions with 40% Mobile phase B

Flow Rate: 200mL/min

Column: Lux Cellulose-1, 3x25cm, 5 µM

Outlet pressure: 100 Bar

Temperatuer: 40 °C

System: Thar 350

Uv: 230nm

Runtime: 5.2 minutes

Method A9

Mobile Phase A: CO_2

Mobile phase B: Methanol with 0.1% ammonium hydroxide

Isocratic conditions with 30% Mobile phase B

Flow Rate: 200mL/min

Column: L Chiralpak AD, 3x25cm, 5 μM

Outlet pressure: 100 Bar

Temperatuer: 40 °C

System: Thar 350

Uv: 230nm

Runtime: 5.2 minutes

Method A10

Mobile Phase A: CO_2

Mobile phase B: methanol with 0.1% ammonium hydroxide

Isocratic conditions with 30% Mobile phase B

Flow Rate: 200mL/min

Column: Lux Cellulose-1, 3x25cm, 5 μM

Outlet pressure: 100 Bar

Temperatuer: 40 °C

System: Thar 350

Uv: 230nm

Runtime: 5.2 minutes

Method A11:

Mobile Phase A: CO_2

Mobile phase B: Ethanol with 0.1%diethylethylamine

Isocratic conditions with 35% Mobile phase B

Flow Rate: 200mL/min

Column: Phenomenex Amylose-2, 3x25cm, 5 μM

Outlet pressure: 100 Bar

Temperatuer: 40 °C

System: Thar 350

Uv: 230nm

Runtime: 5.2 minutes

Method A12

Mobile Phase A: CO_2

Mobile phase B: methanol with 0.1% ammonium hydroxide

Isocratic conditions with 20% Mobile phase B

Flow Rate: 200mL/min

Column: Lux Cellulose-1, 3x25cm, 5 μM

Outlet pressure: 100 Bar

Temperatuer: 40 °C

System: Thar 350

Uv: 230nm

Runtime: 5.2 minutes

Method A13:

Column: Chiralpak AD-H 250×4.6mm I.D., 5um

Mobile phase: methanol (0.05% DEA) in CO2, from5% to 40% over 15 min

Flow rate: 2.35mL/min

Wavelength: 220nm

Method A14:

Column: Chiralcel OJ-H or OD-H 50×4.6mm I.D., 3um

Mobile phase: ethanol (0.05% DEA) in CO2, from5% to 40% over 3 min

Flow rate: 4mL/min

Wavelength: 220nm

Method A15:

Column: Chiralcel OJ-H 250×4.6mm I.D., 5um

Mobile phase: ethanol (0.05% DEA) in CO2, from5% to 40% over 16 min

Flow rate: 2.5mL/min

Wavelength: 220nm

Method A16:

Column: Chiralpak AD-H or OD-H 150×4.6mm I.D., 3um

Mobile phase: methanol or iso-propanol (0.05% DEA) in CO2, from5% to 40% over 16 min

Flow rate: 2.5mL/min

Wavelength: 220nm

Method A17:

Column: Chiralcel OD-H 250×4.6mm I.D., 5um

Mobile phase: methanol (0.05% DEA) in CO2, from5% to 40% over 15 min

Flow rate: 2.35mL/min

Wavelength: 220nm

Reverse Phase High Performance Liquid Chromatography (HPLC) was used to purify compounds where indicated. Unless otherwise indicated, the conditions were: 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®) which uses a single-mode resonator and dynamic field tuning. Temperature from 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., 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 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 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

JAK2 Inhibition Assay Protocol

The activity of the isolated JAK2 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 labelled on the N-terminus with 5-carboxyfluorescein using the Caliper LabChip technology (Caliper Life Sciences, Hopkinton, MA). To determine the inhibition constants (K_i), compounds were diluted serially in DMSO and added to 50 μL kinase reactions containing 0.2 nM purified JAK2 enzyme, 100 mM Hepes pH7.2, 0.015% Brij-35, 1.5 μM peptide substrate, 25 μM ATP, 10 mM $MgCl_2$, 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 μL 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. K_i 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

JAK1 and TYK2 Inhibition Assay Protocol

The activity of the isolated JAK1 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 labelled on the N-terminus with 5-carboxyfluorescein using the Caliper LabChip technology (Caliper Life Sciences, Hopkinton, MA). To determine inhibition constants (K_i), compounds were diluted serially in DMSO and added to 50 uL kinase reactions containing 1.5 nM JAK1 or 1 nM purified TYK2 enzyme, 100 mM Hepes pH7.2, 0.015% Brij-35, 1.5 μM 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. K_i 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

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 labelled on the N-terminus with 5-carboxyfluorescein using the Caliper LabChip technology (Caliper Life Sciences, Hopkinton, MA). To determine inhibition constants (K_i), 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. K_i 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 D

Cell-based Pharmacology Assays

The activities of compounds were determined in cell-based assays that are designed to measure JAK2- dependent signaling or proliferation. Compounds were serially diluted in DMSO and incubated with Set-2 cells (German Collection of Microorganisms and Cell Cultures (DSMZ); Braunschweig, Germany), which express the JAK2V617F mutant protein, in 96-well microtiter plates for 1 hr at 37°C in RPMI medium at a final cell density of 100,000 cells per well and a final DMSO concentration of 0.57%. Compound-mediated effects on STAT5 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. Alternatively, serially diluted compounds were added to 384-well microtiter plates in RPMI medium with 10% fetal bovine serum (Invitrogen Corp.; Carlsbad, CA) at a final cell density of 2500 cells per well and a final DMSO concentration of 0.3% and incubated at 37°C for 72 hours. Cell viability was then determined using the CellTiter-Glo® Luminescent Cell Viability Assay according to the manufacturer's protocol (Promega; Madison, WI) and EC50 values were determined.

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 with NK92 cells (American Type Culture Collection (ATCC); Manassas, VA) in 96-well microtiter plates in RPMI medium at a final cell density of 100,000 cells per well and a final DMSO concentration of 0.57%. Human recombinant IL-12 (R&D systems; Minneapolis, MN) was then added at a final concentration of 10ng/mL to the microtiter plates containing the NK92 cells and compound and the plates were incubated for 1 hr at 37 °C. Compound-mediated 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

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 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 37 °C. 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 and EC50 values were determined.

Example E

Alternative Cell-based Pharmacology Assay

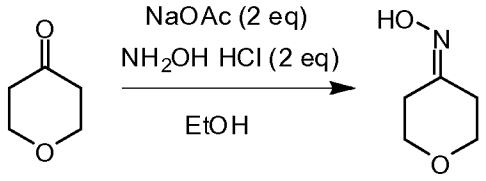
The activities of compounds were determined in cell-based assays that are designed to measure TYK2-dependent signaling. Compounds were serially diluted in DMSO and incubated with NK92 cells (American Type Culture Collection (ATCC); Manassas, VA) in 384-well microtiter plates in RPMI medium at a final 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 37°C. Compound-mediated 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.

PREPARATIVE EXAMPLES

Example F

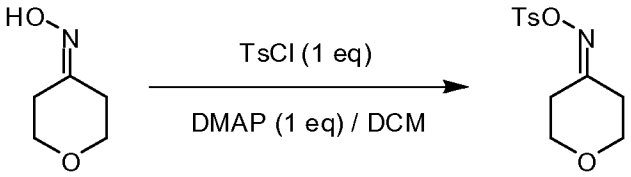
4,4-difluorotetrahydro-2*H*-pyran-3-amine (4,4-Difluoro-tetrahydro-pyran-3-ylamine)

Dihydro-2*H*-pyran-4(3*H*)-one oxime



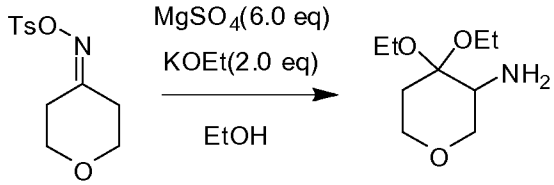
A mixture of dihydro-2*H*-pyran-4(3*H*)-one (75 g, 0.75 mol), hydroxylamine hydrochloride (104 g, 1.5 mol) and sodium acetate (82 g, 1.5 mol) in ethanol (500 mL) was refluxed for 10 h. After being cooled to room temperature, ethanol was removed under reduced pressure, and the residue was dissolved in ethyl acetate. The organic solution was washed with water and brine, dried over anhydrous sodium sulfate and concentrated to give dihydro-2*H*-pyran-4(3*H*)-one oxime (65 g, 0.56 mol, yield 75%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.83-3.75 (m, 4H), 2.68 (t, *J*=5.6, 2H), 2.39 (t, *J*=5.6, 2H).

Dihydro-2*H*-pyran-4(3*H*)-one *O*-tosyl oxime



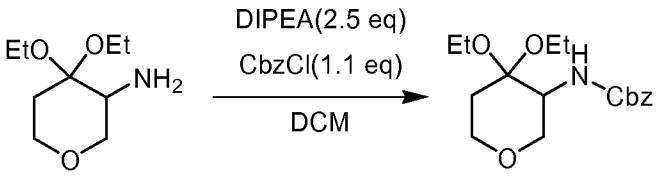
To a solution of dihydro-2*H*-pyran-4(3*H*)-one oxime (37 g, 0.32 mol) and 4-dimethylaminopyridine (39 g, 0.32 mol) in anhydrous dichloromethane (100 mL) was added 4-methylbenzene-1-sulfonyl chloride (64 g, 0.32 mol) in portions at room temperature, and the reaction mixture was stirred at room temperature for 3 h. Dichloromethane was removed under reduced pressure, and the residue was suspended in water and stirred for 20 minutes. The mixture was filtered, and the filter cake was dried to give dihydro-2*H*-pyran-4(3*H*)-one *O*-tosyl oxime (42 g, 0.15 mol, yield 49%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.83 (d, *J*=8.4, 2H), 7.31 (d, *J*=8.0, 2H), 3.75 (t, *J*=5.6, 2H), 3.69 (t, *J*=5.6, 2H), 2.63 (t, *J*= 5.6, 2H), 2.40 (s, 3H), 2.36 (d, *J*=5.6, 2H). LCMS (Method 0-60AB, ESI): RT=1.205 min, m+H=269.9

4,4-diethoxytetrahydro-2*H*-pyran-3-amine



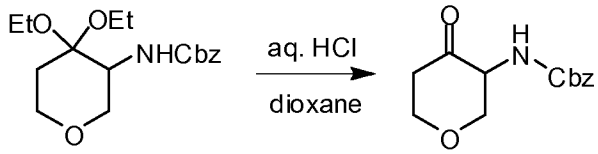
To a solution of potassium ethanolate (13 mL, 24% w/w in ethanol, 37 mmol) and magnesium sulfate (13.7 g, 114 mmol) in ethanol (50 mL) was added dihydro-2*H*-pyran-4(3*H*)-one *O*-tosyl oxime (5 g, 19 mmol) in portions at room temperature, and the mixture was refluxed for 2 h. After being cooled to room temperature, the mixture was filtered and the filtrate was concentrated to give 4,4-diethoxytetrahydro-2*H*-pyran-3-amine (3.4 g) without further purification.

Benzyl 4,4-diethoxytetrahydro-2*H*-pyran-3-ylcarbamate



To a solution of 4, 4-diethoxytetrahydro-2*H*-pyran-3-amine (3.4 g) and *N*,*N*-diisopropylethylamine (7.4 mL, 45 mmol) in anhydrous dichloromethane was added benzyl chloroformate (2.8 mL, 19.8 mmol) dropwise at 0 °C, and the mixture was stirred at 0 °C for 2 h. Then the solution was washed with saturated aqueous sodium bicarbonate solution and brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography on silica gel (eluting with petroleum ether/ethyl acetate from 10/1 to 2/1) to give benzyl 4,4-diethoxytetrahydro-2*H*-pyran-3-ylcarbamate (1.3 g, 4.02 mmol, yield 21% for two steps).

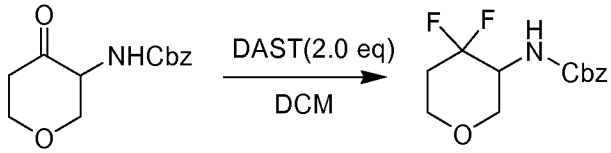
Benzyl 4-oxotetrahydro-2*H*-pyran-3-ylcarbamate



To a solution of benzyl 4, 4-diethoxytetrahydro-2*H*-pyran-3-ylcarbamate (1.2 g, 3.7 mmol) in dioxane (15 mL) was added aqueous hydrochloride acid (5 mL, 1 N), and the reaction mixture was heated to 100 °C for 2 h. After being cooled to room temperature, the solution was extracted with ethyl acetate and water, the organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography on silica gel (eluting with petroleum ether/ethyl acetate from 10/1 to 1/1) to give benzyl 4-oxotetrahydro-2*H*-pyran-3-ylcarbamate (0.5 g, 2 mmol, yield 54%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.39-7.31 (m, 5H), 5.71 (s, 1H), 5.07 (s, 2H), 4.66-4.62 (m, 1H), 4.51-4.45 (m, 1H), 4.33-4.31

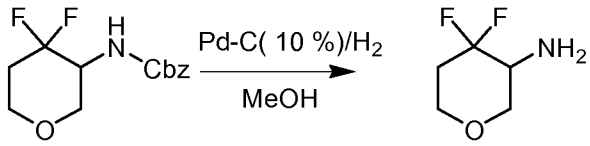
(m, 1H), 3.65-3.59 (m, 1H), 3.20 (t, *J*=10.4, 1H), 2.82-2.73 (m, 1H), 2.54-2.49 (m, 1H). LCMS (Method 0-60AB, ESI): RT = 1.349 min, m-44=205.9, m+H=249.9.

Benzyl 4,4-difluorotetrahydro-2*H*-pyran-3-ylcarbamate



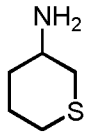
To a solution of benzyl 4-oxo-tetrahydro-2H-pyran-3-ylcarbamate (5.1 g, 20 mmol) in anhydrous dichloromethane (60 mL) was added diethylaminosulphur trifluoride (6.4 g, 40 mmol) dropwise at -50 °C and the mixture was warmed to room temperature and stirred for 4 h. The reaction was quenched with saturated sodium thiosulfate in ice bath, and the aqueous mixture was extracted with dichloromethane. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography on silica gel (eluting with petroleum ether/ethyl acetate from 10/1 to 2/1) to give benzyl 4,4-difluorotetrahydro-2*H*-pyran-3-ylcarbamate (1.6 g, 5.9 mmol, yield 30%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.38-7.32 (m, 5H), 5.16-5.09 (m, 3H), 4.17-4.08 (m, 1H), 3.79-3.85 (m, 2H), 3.69-3.63 (m, 1H), 3.42-3.38 (m, 1H), 2.20-2.02 (m, 2H). LCMS (Method 0-60AB, ESI): RT = 1.188 min, m-44=227.8

4,4-difluorotetrahydro-2*H*-pyran-3-amine (4,4-Difluoro-tetrahydro-pyran-3-ylamine)

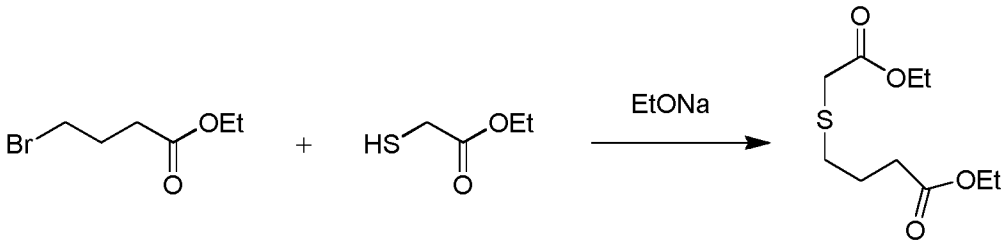


A mixture of benzyl 4,4-difluorotetrahydro-2*H*-pyran-3-ylcarbamate (1.2 g, 4.4 mmol) and palladium on carbon (10% w/w, 400 mg) in methanol (50 mL) was stirred at room temperature under hydrogen balloon overnight. The catalyst was filtered off, and methanolic hydrochloride (2 N, 1 mL) was added. The solvent was removed to give 4,4-difluorotetrahydro-2*H*-pyran-3-amine (4,4-Difluoro-tetrahydro-pyran-3-ylamine) (0.6 g) as a hydrochloride salt. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.06 (s, 3H), 3.95-3.91 (m, 1H), 3.76-3.67 (m, 4H), 2.43-2.31 (m, 1H), 2.18-2.07 (m, 1H).

Example G



tetrahydro-thiopyran-3-ylamine



i ii iii

To a mixture of EtONa (34.9 g, 0.51 mol) in EtOH (300 mL) at 0 °C was added compound **ii** (61.6 g, 0.51 mol) and compound **i** (100 g, 0.51 mol) dropwise. The resulting mixture was stirred at r.t. overnight. The solvent was removed under vaccum and the residue was diluted with water, then extracted with EtOAc. The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated to give compound **iii** (105 g, 88%), which was used for the next reaction directly without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz) : δ 4.13 - 4.05 (m, 4H), 3.14 (s, 2H), 2.63 - 2.61 (m, 2H), 2.37 - 2.35 (m, 2H), 1.88 - 1.86 (m, 2H), 1.23 - 1.16 (m, 4H)

ethyl 3-oxotetrahydro-2H-thiopyran-2-carboxylate

To a mixture of t-BuOK (4.8 g, 0.043 mol) in THF (100 mL) at r.t. was added compound iii (5 g, 0.021 mol) dropwise. The mixture was refluxed for 2 hrs and concentrated in vaccum. The residue was diluted with water and adjusted to pH=5 with 2M HCl. The mixture was extracted with EtOAc. The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated to give ethyl 3-oxotetrahydro-2H-thiopyran-2-carboxylate (2.1 g, 52 %) as yellow oil, which was used for the next reaction directly without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz) : δ12.22 (s, 1H), 4.24 - 4.22 (m, 2H), 2.78 - 2.74 (m, 2H), 2.38 - 2.37 (m, 2H), 2.11 - 2.07 (m, 2H), 1.31 - 1.28 (m, 3H)

dihydro-2H-thiopyran-3(4H)-one

A mixture of ethyl 3-oxotetrahydro-2H-thiopyran-2-carboxylate (2.1 g, 11.2 mmol) in 15 % sulfuric acid (10 mL) was refluxed for 14 hrs. A 10% NaOH solution in water was added dropwise to reach pH=6. The mixture was extracted with EtOAc. The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated to give dihydro-2H-thiopyran-3(4H)-one (0.84 g, 65%). ^{1}H NMR ($CDCl_3$, 400 MHz) : δ3.19 (s, 2H), 2.78 - 2.75 (m, 2H), 2.45 - 2.43 (m, 4H)

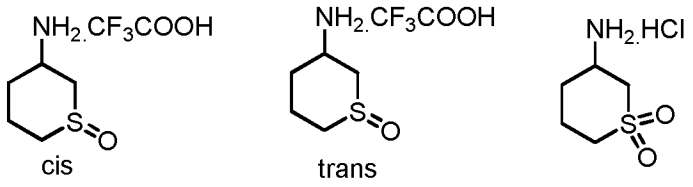
(E)-dihydro-2H-thiopyran-3(4H)-one oxime

To a solution of dihydro-2H-thiopyran-3(4H)-one (1 g, 8.6 mmol) in EtOH (7 mL) at r.t. was added a solution of $NH_2OH.HCl$ (1.2g, 17.2 mmol) and NaOH (0.69 g, 17 mmol) in H_2O (2.5 mL). The mixture was stirred at r.t. for 2 hrs. EtOH was removed in vaccum and the mixture was extracted with EtOAc. The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated in vacuum. The crude product was purified by chromatography on silica (Petroleum ether:EtOAc=15:1) to give (E)-dihydro-2H-thiopyran-3(4H)-one oxime (1 g, 87%). ^{1}H NMR ($CDCl_3$, 400 MHz) : δ 8.92 (s, 1H), 3.45 - 3.43 (m, 2H), 2.88 - 2.85 (m, 2H), 2.80 - 2.74 (m, 2H), 2.57 - 2.54 (m, 2H)

tetrahydro-thiopyran-3-ylamine

To a mixture of $LiAlH_4$ (19 g, 0.50 mol) in THF (1 L) was added (E)-dihydro-2H-thiopyran-3(4H)-one oxime (33 g, 0.25 mol) dropwise at -20 °C. The mixture was stirred at 80 °C overnight. Water (20 mL) and NaOH (15%, 20 mL) was added dropwise at 0 °C. The mixture was filtered and filtrate was concentrated in vaccum to give the crude product, which was purified by chromatograph on silica (DCM:MeOH=10:1) to give tetrahydro-thiopyran-3-ylamine (49 g, 83%). ^{1}H NMR ($CDCl_3$, 400 MHz) : δ 2.92 - 2.87 (m, 1H), 2.62 - 2.58 (m, 1H), 2.42 - 2.39 (m, 2H), 2.24 - 2.29 (m, 1H), 2.01 - 1.97 (m, 1H), 1.85 - 1.80 (m, 1H), 1.70 - 1.66 (m, 1H), 1.38 (s, 2H), 1.17 - 1.13 (m, 1H)

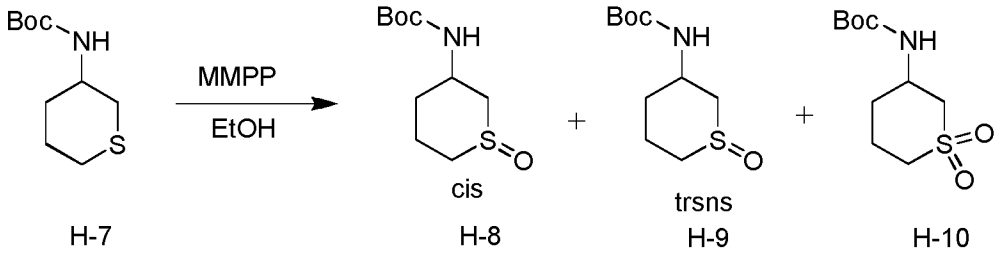
Example H



Cis 1-Oxo-hexahydro-thiopyran-3-ylamine trifluoroacetic acid; Trans 1-Oxo-hexahydro-thiopyran-3-ylamine trifluoroacetic acid; 1,1-Dioxo-hexahydro-thiopyran-3-ylamine hydrochloride

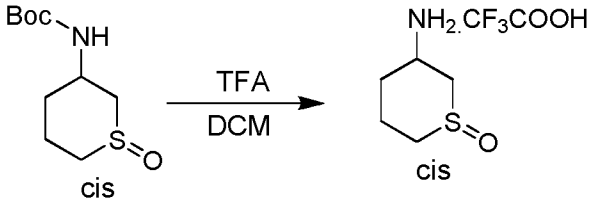
tert-butyl tetrahydro-2H-thiopyran-3-ylcarbamate

To a solution of tetrahydro-thiopyran-3-ylamine (35 g, 0.299 mol) in DCM (500 mL) was added Boc_2O (71.7 g, 0.328 mol). The mixture was stirred at r.t. overnight. The mixture was washed with brine, dried over Na_2SO_4 and concentrated to give the crude product, which was purified by chromatograph on silica (Petroleum ether:EtOAc =20:1) to give tert-butyl tetrahydro-2H-thiopyran-3-ylcarbamate (62.8 g, 97%). ^1H NMR ($CDCl_3$, 400 MHz) : δ 5.02 (s, 1H), 3.78 (s, 2H), 2.85 - 2.81 (m, 1H), 2.48 - 2.36 (m, 3H), 2.01 - 1.96 (m, 2H), 1.76 - 1.74 (m, 2H), 1.49 (s, 9H).



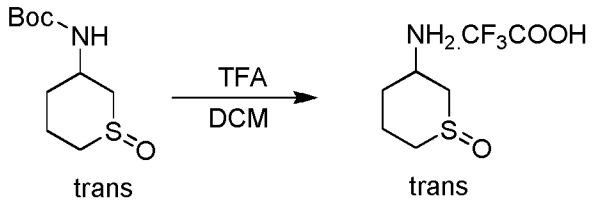
To a solution of compound H-7 (31 g, 0.14 mol) in EtOH (1.5 L) at -20 °C was added MMPP (35.3 g, 0.057 mol). The mixture was stirred at -20 °C for 2 hrs. Aqueous $NaHCO_3$ was added and the mixture was extracted with EtOAc. The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated in vacuum. The crude product was purified by chromatography on silica (Petroleum ether:EtOAc=1:2~1:5) to give compound H-8 (12 g, 37%), compound 9 (7 g, 21%) and compound 10 (6 g, 18%). (Compound H-8 ^1H NMR ($CDCl_3$, 400 MHz) : δ6.53 (s, 1H), 4.21 (s, 1H), 3.00 -2.98 (m, 2H), 2.73 - 2.67 (m, 2H), 2.53 - 2.49 (m, 1H), 1.89 - 1.88 (m, 1H), 1.73 - 1.71 (m, 2H), 1.42 (s, 9H); Compound H-9 ^1H NMR ($CDCl_3$, 400 MHz) : δ 4.67 (s, 1H), 4.24 (m, 1H), 3.17 (d, J = 12.4 Hz, 1H), 2.89 (d, J = 8.0 Hz, 1H), 2.61 (s, 1H), 2.47 - 2.45 (m, 2H), 2.01 - 1.98 (m, 1H), 1.92 - 1.88 (m, 1H), 1.59 - 1.58 (m, 1H), 1.43 (s, 9H); Compound H-10 ^1H NMR ($CDCl_3$, 400 MHz): δ 5.52 (s, 1H), 4.33 (s, 1H), 3.32 - 3.27 (m,

1H), 3.01- 2.99 (m, 3H), 2.25 -2.22 (m, 1H), 2.11 - 2.08 (m, 1H), 1.81 - 1.79 (s, 2H), 1.45 (s, 9H).



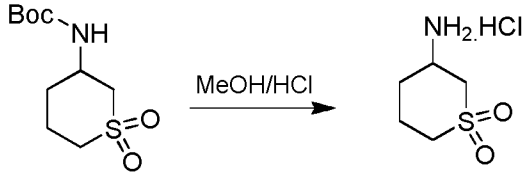
H-8

To a solution of compound H-8 (18 g, 0.077 mol) in DCM (100 mL) at r.t. was added TFA (44 g, 0.38 mol) dropwise. The reaction mixture was stirred at r.t. for 2 hrs. TLC indicated compound H-8 was consumed completely. The mixture was concentrated in vaccum to give cis 1-oxo-hexahydro-thiopyran-3-ylamine trifluoroacetic acid (19 g, 100%). ^{1}H NMR (MeOD, 400 MHz) : δ3.73 - 3.72 (m, 1H), 3.31 - 3.23 (m, 1H), 3.15-3.05 (m, 2H), 2.98 - 2.96 (m, 1H), 2.44 - 2.40 (m, 1H), 2.10 - 2.06 (m, 1H), 1.87 - 1.82 (m, 2H).



H-9

To a solution of compound H-9 (12 g, 0.05 mol) in DCM (100 mL) at r.t. was added TFA (29 g, 0.26 mol) dropwise. The reaction mixture was stirred at r.t. for 2 hrs. TLC indicated compound 9 was consumed completely. The mixture was concentrated in vaccum to give Trans 1-Oxo-hexahydro-thiopyran-3-ylamine trifluoroacetic acid (12 g, 100%). ^{1}H NMR (MeOD, 400 MHz) : δ3.85 - 3.83 (m, 1H), 3.29 - 3.28 (m, 1H), 2.99 - 2.97 (m, 1H), 2.77 - 2.70 (m, 1H), 2.65 - 2.60 (m, 1H), 2.41 - 2.37 (m, 1H), 2. 10 - 2.01 (m, 2H), 1.69 - 1.64 (m, 1H)

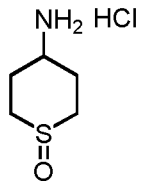


H-10

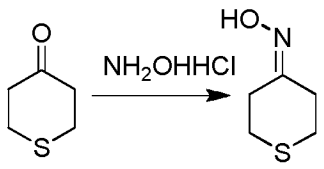
A solution of compound H-10 (9 g, 0.036 mol) in methanol (100 mL) saturated with HCl was stirred at r.t. for 3 hrs. TLC indicated compound 10 was consumed completely. The

mixture was concentrated in vaccum to give 1,1-Dioxo-hexahydro-thiopyran-3-ylamine hydrochloride (6.5 g, 97%). ^{1}H NMR (D_2O, 400 MHz): δ 3.87 - 3.89 (m, 1H), 3.67 - 3.63 (m, 1H), 3.47 - 3.40 (m, 1H), 3.32 - 3.25 (m, 2H), 2.37 - 2.31 (m, 1H), 2.26 - 2.22 (m, 1H), 2.07 - 2.03 (m, 1H), 1.80 - 1.76 (m, 1H).

EXAMPLE I

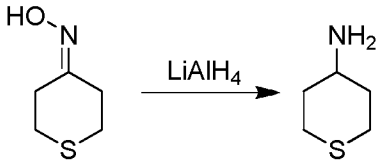


1-Oxo-hexahydro-thiopyran-4-ylamine hydrochloride (mixture of cis and trans)



I-1 I-2

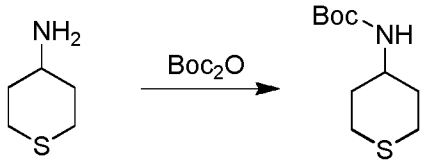
To a solution of compound I-1 (87.4 g, 0.75 mol) in EtOH (610 mL) at r.t. was added a solution of $NH_2OH.HCl$ (104.5 g, 1.5 mol) and NaOH (60 g, 1.5 mol) in H_2O (218 mL). The mixture was stirred at r.t. for 2 hrs. EtOH was removed in vaccum and the mixture was extracted with EtOAc. The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated in vacuum to give compound I-2 (91.4 g, 93%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.33 (s, 1H), 2.87 - 2.85 (m, 2H), 2.78 - 2.75 (m, 2H), 2.73 - 2.70 (m, 2H), 2.56 - 2.53 (m, 2H).



I-2 I-3

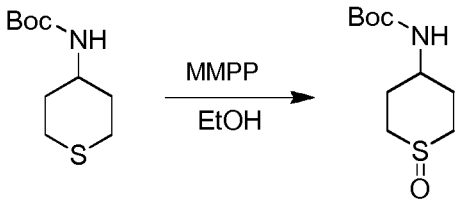
To a mixture of $LiAlH_4$ (17.63 g, 0.46 mol) in THF (1.3L) was added compound I-2 (30.47 g, 0.23 mol) dropwise at -20 °C. The mixture was stirred at 80 °C overnight. Water (18 mL) and NaOH (15%, 18mL) was added dropwise at 0 °C. The mixture was filtered and filtrate was concentrated in vaccumto give the crude product, which was purified by chromatograph on

silica (DCM:MeOH=10:1) to give the compound I-3 (22.3 g, 81%). ^{1}H NMR ($CDCl_3$, 400 MHz) : δ2.58 - 2.55 (m, 2H), 2.04 - 2.00 (m, 1H), 1.42 - 1.32 (m, 2H).



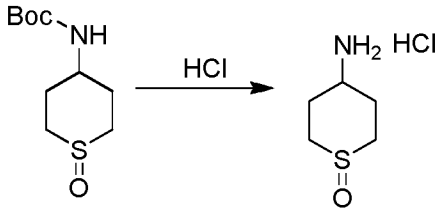
I-3 I-4

To a solution of compound I-3 (81.6 g, 0.7 mol) in DCM (500 mL) was added triethylamine (212.5 g, 2.1mol), followed by Boc_2O (182 g, 0.836 mol) at 0°C. The mixture was stirred at r.t. overnight. The mixture was washed with brine, dried over Na_2SO_4 and concentrated togive the crude product, was purified by chromatograph on silica (Petroleum ether:EtOAc =20:1) to give compound I-4 (90 g, 59%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.48 (d, J = 3.6 Hz, 1H), 3.43 (s, 1H), 2.70 - 2.63 (m, 4H), 2.22 - 2.19 (m, 2H), 1.51 - 1.49 (m, 2H), 1.43 (s, 9H).



I-4 I-5

To a solution of compound I-4 (30 g, 0.138 mol) in EtOH (1.5 L) at -20 °C was added MMPP (54 g, 0.11 mol). The mixture was stirred at -20 °C for 2 hrs. Aqueous $NaHCO_3$ was added and the mixture was extracted with EtOAc. The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated in vacuum to give the crude product, which was purified by chromatograph on silica (Petroleum ether:EtOAc =10:1~1:1) to give the compound I-5 (25 g, 79%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.58 - 4.48 (m, 0.5H), 3.60 - 3.58 (m, 0.5H), 3.06 - 3.03 (m, 2H), 2.56 - 2.52 (m, 2H), 2.22 - 2.16 (m, 2H), 1.99 - 1.95 (m, 2H), 1.44 (s, 9H).

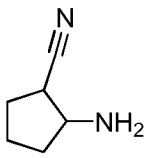


I-5

A solution of compound I-5 (76 g, 0.326 mol) in methol (500 mL) saturated with HCl was stirred at r.t. for 3 hrs. The precipitate was colected by filtration to give 1-oxo-hexahydro-

thiopyran-4-ylamine hydrochloride (28.9 g, 52.3%). ^{1}H NMR (D_2O, 400 MHz): δ 3.40 - 3.34 (m, 1H), 3.16 - 3.12 (m, 2H), 2.79 - 2.72 (m, 2H), 3.15 - 2.02 (m, 4H).

EXAMPLE J

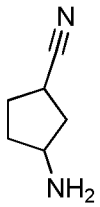


2-Amino-cyclopentanecarbonitrile

To a suspension of sodium (38.9 g) in dry toluene (1700 ml) was added adiponitrile (170ml) dropwise at 100 -110 °C over 1h. After the addition was complete, the reaction mixture was refluxed overnight, then cooled to rt and filtered. The cake was washed with toluene, then to the suspended solution of the cake in toluene was added water slowly. The mixture was stirred for 30min and filtered, then cake was washed with water, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was concentrated to yield an oil (120 g), which was used without further purification in the next step.

To a solution of the above intermediate (51.9 g) in MeOH (500 ml) was added bromocresol green and then a solution of HCl in MeOH was added and a yellow solution appeared. To this was added $NaCNBH_3$ (25.0 g) in portions while maintaining the temperature at 30 °C and the pH was kept acidic using MeOH·HCl. After stirring 30min at rt, the reaction mixture was concentrated under reduced pressure and the residue was diluted with DCM and NaOH (1N). The organic layer separated and was dried with Na_2SO_4, filtered, and evaporated under vacuum to afford 2-cyanocyclopentaneamine (39.0 g) as tan oil.

The above crude product (67.7 g) was dissolved in MeOH (1600 ml), and then a solution of oxalic acid dihydrate (43 g) in MeOH (100 ml) was added slowly. The mixture was stirred at rt overnight, then filtered and washed with MeOH. The cake was suspended in water (300 ml), and basified to pH 12 to 14 with 1N NaOH, then the aqueous layer was extracted with DCM. The DCM phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated to yield a yellow oil (58.0 g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.58 – 2.72 (m, 1H), 2.45 – 2.08 (m, 1H), 2.03 – 1.54 (m, 4H), 1.65 – 1.27 (m, 2H).



3-Amino-cyclopentanecarbonitrile

A mixture of KCN (19.0 g), water (200 ml), MeOH (200 ml) and $Et_3N{\cdot}HCl$ (50.0 g) was stirred at rt, and cyclopentenone was added dropwise slowly. After the addition was completed the mixture was stirred at rt overnight. The solution was concentrated to remove most of methanol and to the aqueous layer was added acetic acid (2 ml) to bring the pH to 6 -7, followed by extraction with DCM (three times). The combined organic layer was concentrated, and the resulting residue was purified by column chromatography on silica gel (PE/EA=5/1 to 4/1) to afford 3-cyanocyclopentanone (11.5 g) as a yellow oil.

To the solution of 3-cyanocyclopentanone prepared above (91.6 g) in MeOH (1300 ml) was added $NaBH_4$ (32.0 g) in portions while maintaining the temperature between 20- 30 °C. After the addition was completed the mixture was stirred at rt for 30min. The mixture was evaporated and purification of the residue by column chromatography on silica gel (50 % petroleum ether/EtOAc) afforded 3-Hydroxy-cyclopentanecarbonitrile (62.0 g) as a colorless oil.

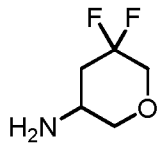
To a solution of the 3-cyanocyclopentanol prepared above (62.0 g) and Et_3N (60.0 g) in DCM (620 ml) was added methanesulfonyl chloride (67.2 g) in portions while maintaining the temperature at 10 °C. After stirring at rt overnight, the reaction mixture was diluted with water, and extracted with DCM (two times). The combined DCM phase was concentrated to yield methanesulfonic acid 3-cyano-cyclopentyl ester (94.4 g), which was used directly in the next step without be further purification.

NaN_3 (40.0 g) was added to the methanesulfonic acid 3-cyano-cyclopentyl ester prepared above (94.4 g) in DMF (470 ml) and the reaction mixture was stirred at 80 °C for 2h. After cooling to room temperature, the mixture was poured into water (2500 ml) and extracted with ethyl acetate (three times). The ethyl acetate layer was washed brine, dried over Na_2SO_4, filtered, and evaporated to yield 3-azido-cyclopentanecarbonitrile (73 g), which was used directly in the next step without further purification.

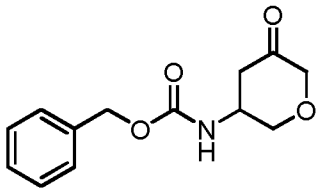
10% Pd/C (20 g) was added to the 3-azido-cyclopentanecarbonitrile prepared above (93.6 g) in MeOH (700 ml), and the reaction mixture was stirred under an atmosphere of hydrogen for 60 h. The reaction mixture was then filtered and concentrated, and the residue was purified by

column chrmatography to yield racemic 3-cyanocyclopentaneamine (51.0 g) as a mixture of cis and trans isomers.^{1}H NMR (400 MHz, $CDCl_3$) δ 3.58 – 2.72 (m, 1H), 2.45 – 2.08 (m, 1H), 2.03 – 1.54 (m, 4H), 1.65 – 1.27 (m, 2H).

EXAMPLE K

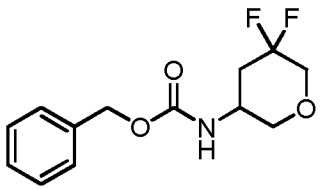


5,5-Difluoro-tetrahydro-pyran-3-ylamine



(5-Oxo-tetrahydro-pyran-3-yl)-carbamic acid benzyl ester

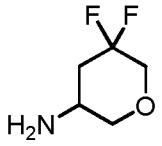
This material was prepared as reported in J. Org. Chem. Vol. 74, No. 5, 2009 1932-1938



(5,5-Difluoro-tetrahydro-pyran-3-yl)-carbamic acid benzyl ester

(5-Oxo-tetrahydro-pyran-3-yl)-carbamic acid benzyl ester (117 mg, 0.469 mmol) was dissolved into dichloromethane (3 mL) and cooled to -78° C for fifteen minutes. A solution of DAST (0.129 mL, 0.939 mmol) in dichloromethane (1 mL) was added to the cooled reaction mixture in a dropwise fashion. Upon completion of the DAST addition, the reaction was allowed to stir at room temperature for four hours before being quenched with the addition of 5 mL of 1 N sodium thiosulfate solution. The quenched reaction mixture was passed through a ChemElut column with dichloromethane elution and concentrated to dryness. Purification of the residue by column chromatography on silica gel (gradient: 0 to 60% EtOAc in Hept) afforded (5,5-Difluoro-tetrahydro-pyran-3-yl)-carbamic acid benzyl ester (42 mg, 32.99% yield) as a white solid, 1H NMR (400 MHz, DMSO) δ 7.44 – 7.28 (m, 5H), 5.29 (s, 1H), 5.11 (s, 2H), 4.13

(s, 1H), 3.85 (dd, J = 19.7, 10.8, 1H), 3.76 (d, J = 11.1, 1H), 3.61 (d, J = 11.5, 1H), 3.59 – 3.47 (m, 1H), 2.21 (ddd, J = 34.4, 14.8, 6.5, 2H).

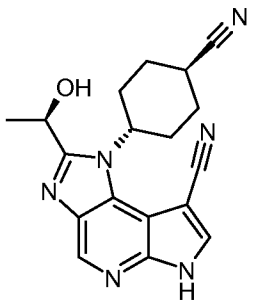


5,5-Difluoro-tetrahydro-pyran-3-ylamine

(5,5-Difluoro-tetrahydro-pyran-3-yl)-carbamic acid benzyl ester (492 mg; 1.813 mmol) was dissolved in methanol (10 mL) and purged with nitrogen. Palladium on activated carbon (100 mg) was added and the resulting heterogeneous mixture was placed under a hydrogen atmosphere at ambient temperature and pressure for 12 h before being filtered through Celite, washed with 100 mL of methanol and concentrated to yield 5,5-Difluoro-tetrahydro-pyran-3-ylamine (243 mg, 97.7% yield) as a colorless oil that was used without further purification. 1H NMR (400 MHz, CDCl3) δ 3.88 – 3.70 (m, 2H), 3.54 (dd, J = 25.5, 11.9, 1H), 3.26 – 3.14 (m, 2H), 2.36 (dd, J = 13.8, 11.8, 1H), 1.88 – 1.70 (m, 1H), 1.23 (s, 2H).

Product Examples

Example 1



Trans 1-(4-Cyano-cyclohexyl)-2-((R)-1-hydroxy-ethyl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacene-8-carbonitrile

Trans 4-[2-((R)-1-Hydroxy-ethyl)-8-iodo-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclohexanecarbonitrile

A mixture of trans 4-[2-((R)-1-hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclohexanecarbonitrile (2.50 g, 8.08 mmol) and THF (120 mL) was treated with N-iodosuccinimide (2.00 g, 8.89 mmol). The solution was stirred at room temperature for 18 hours, then concentrated onto diatomaceous earth and purified by column chromatography on silica gel

(gradient: DCM to 10% MeOH in DCM) to afford 3.35 g (95%) of trans 4-[2-((R)-1-hydroxy-ethyl)-8-iodo-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclohexanecarbonitrile as a brown solid. LCMS (Method Q, ESI): RT = 2.74 min, m+H = 436.2; ^{1}H NMR (400 MHz, DMSO) δ: 12.29 (s, 1 H), 8.56 (s, 1 H), 7.70 (d, 1 H), 6.06 (m, 1 H), 5.47 (s, 1 H), 5.14 (m, 1 H), 3.05 (m, 1 H), 2.45 (m, 1 H, partially obscured by DMSO), 2.36-1.93 (m, 7 H),1.62 (d, 3 H).

Trans 4-[6-Benzenesulfonyl-2-((R)-1-hydroxy-ethyl)-8-iodo-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclohexanecarbonitrile

A mixture of trans 4-[2-((R)-1-hydroxy-ethyl)-8-iodo-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclohexanecarbonitrile (3.30 g, 7.58 mmol), benzenesulfonyl chloride (1.45 mL, 11.4 mmol), triethylamine (2.10 mL, 15.2 mmol) and DMAP (93.0 mg, 0.76 mmol) in DCM/THF (100 mL, 1:1) was stirred at room temperature for 18 hours. DCM was then added and the mixture washed (water, saturated sodium hydrogencarbonate solution and brine), dried (sodium sulfate) and concentrated *in vacuo*. Purification by column chromatography on silica gel (gradient: DCM to ethyl acetate) afforded 1.94 g (44%) of trans 4-[6-benzenesulfonyl-2-((R)-1-hydroxy-ethyl)-8-iodo-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclohexanecarbonitrile as an orange solid. LCMS (Method Q, ESI): RT = 3.69 min, m+H = 576.2; ^{1}H NMR (400 MHz, DMSO) δ: 8.70 (s, 1 H), 8.19 (s, 1 H), 8.15 (d, 2 H), 7.71 (m, 1 H), 7.62 (m, 2 H), 5.98 (m, 1 H), 5.55 (m, 1 H), 5.15 (m, 1 H), 3.04 (m, 1 H), 2.27-1.88 (m, 8 H), 1.59 (d, 3 H).

Trans 6-Benzenesulfonyl-1-(4-cyano-cyclohexyl)-2-((R)-1-hydroxy-ethyl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacene-8-carbonitrile

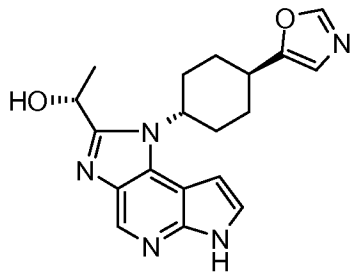
A mixture of trans 4-[6-benzenesulfonyl-2-((R)-1-hydroxy-ethyl)-8-iodo-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclohexanecarbonitrile (1.00 g, 1.74 mmol), copper (I) cyanide (623 mg, 6.95 mmol), 1,1'-bis-(diphenylphosphino)ferrocene (193 mg, 348 µmol) and tris(dibenzylideneacetone)dipalladium(0) (319 mg, 348 µmol) in dioxane (25 mL) was degassed and purged with nitrogen and then heated to 100 °C for 18 hours. LCMS indicated the reaction was incomplete, therefore additional copper (I) cyanide (623 mg, 6.95 mmol), 1,1'-bis-(diphenylphosphino)ferrocene (193 mg, 348 µmol) and tris(dibenzylideneacetone)dipalladium(0) (319 mg, 348 µmol) were added and heating continued for 24 hours. After cooling, the mixture was filtered through Celite®, the filtrate diluted with ethyl acetate and washed (water and brine), dried (sodium sulfate) and concentrated *in vacuo*. Purification by column chromatography on silica gel (gradient: DCM to 10% MeOH in DCM) followed by trituration (diether ether/DCM) afforded 458 mg (55%) of trans 6-benzenesulfonyl-1-(4-cyano-cyclohexyl)-2-((R)-1-hydroxy-ethyl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacene-8-carbonitrile as a beige solid. LCMS (Method

Q, ESI): RT = 3.55 min, m+H = 475.3; ^{1}H NMR (400 MHz, DMSO) δ: 9.10 (s, 1 H), 8.82 (s, 1 H), 8.21 (m, 2 H), 7.77 (m, 1 H), 7.66 (m, 2 H), 5.66 (s, 1 H), 5.26 (s, 1 H), 5.14 (s, 1 H), 2.94 (s, 1 H), 2.43-2.03 (m, 6 H), 1.99-1.76 (m, 2 H), 1.61 (d, 3 H).

trans 1-(4-Cyano-cyclohexyl)-2-((R)-1-hydroxy-ethyl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacene-8-carbonitrile

A mixture of trans 6-benzenesulfonyl-1-(4-cyano-cyclohexyl)-2-((R)-1-hydroxy-ethyl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacene-8-carbonitrile (200 mg, 0.42 mmol) and aqueous potassium carbonate solution (1.05 mL, 2.11 mmol, 2M) in methanol (10 mL) was heated to 70 °C for 1 hour. After cooling, the mixture was concentrated *in vacuo* and the resulting aqueous residue diluted with water and extracted with ethyl acetate (3x). The combined organic extracts were dried (sodium sulfate) and concentrated *in vacuo*. Purfication by HPLC (5 to 70% acetonitrile in H_2O + 0.1% HCO_2H) followed by lyophilisation afforded 28.0 mg (23%) of trans 1-(4-cyano-cyclohexyl)-2-((R)-1-hydroxy-ethyl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacene-8-carbonitrile as a white solid. LCMS (Method A, ESI): RT = 2.88 min, m+H = 335.1; ^{1}H NMR (400 MHz, DMSO) δ: 13.10 (br s, 1 H), 8.72 (s, 1 H), 8.51 (s, 1 H), 5.61 (s, 1 H), 5.36 (s, 1 H), 5.14 (m, 1 H), 2.95 (s, 1 H), 2.48-2.19 (m, 4 H), 2.17-1.78 (m, 4 H), 1.65 (d, 3 H).

Example 2



Trans (R)-1-[1-(4-Oxazol-5-yl-cyclohexyl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol

Trans (4-Oxazol-5-yl-cyclohexyl)-carbamic acid tert-butyl ester

Trans (4-formyl-cyclohexyl)-carbamic acid tert-butyl ester (1.00 g, 3.60 mmol) dissolved in methanol (15 mL) was treated sequentially with potassium carbonate (1.24 g, 9.00 mmol) and toluenesulfonylmethyl isocyanide (711 mg, 3.60 mmol) at room temperature. The resulting mixture was heated to 65 °C for 2 hours. After cooling, the solvent was removed *in vacuo*. The residue was partitioned between water and DCM and then separated. The organic phase was concentrated to dryness to afford crude trans (4-oxazol-5-yl-cyclohexyl)-carbamic acid tert-butyl ester which was used for the next step without purification or charectorisation.

Trans 4-Oxazol-5-yl-cyclohexylamine

Trans (4-oxazol-5-yl-cyclohexyl)-carbamic acid tert-butyl ester (assumed to be 3.60 mmol) was treated with trifluoroacetic acid (7 mL) in DCM (15 mL) at room temperature for 40 minutes. The solvent was removed *in vacuo* and the residue purified by column chromatography using an Isolute® SCX-2 cartridge (gradient: MeOH to 2M NH_3 in MeOH) to provide crude trans 4-oxazol-5-yl-cyclohexylamine which was used for the next step without further purification or charectorisation.

Trans (1-Benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-yl)-(4-oxazol-5-yl-cyclohexyl)-amine

A mixture of 1-benzenesulfonyl-4-chloro-5-nitro-1H-pyrrolo[2,3-b]pyridine (1.30 g, 3.83 mmol), crude trans 4-oxazol-5-yl-cyclohexylamine (assumed to be 3.60 mmol) and diisopropylethylamine (0.99 mL, 5.36 mmol) in propan-2-ol (15 mL) was heated to 80 °C for 3 hours. After cooling, the mixture was concentrated *in vacuo* and the resulting residue triturated (water) to provide a yellow solid. Purification by column chromatography on silica gel (gradient: cyclohexane to ethyl acetate), followed by an additional column (gradient: DCM to 10% ethyl acetate in DCM) afforded 128 mg (7%) of trans (1-benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-yl)-(4-oxazol-5-yl-cyclohexyl)-amine as a yellow solid. LCMS (Method Q, ESI): RT = 4.20 min, m+H = 468.0; ^{1}H NMR (400 MHz, DMSO) δ: 8.91 (s, 1 H), 8.84 (d, 1 H), 8.24 (s, 1 H), 8.12 (m, 2 H), 7.81 (d, 1 H), 7.76 (m, 1 H), 7.65 (m, 2 H), 7.07 (d, 1 H), 6.90 (s, 1 H), 4.11 (m, 1 H), 2.78 (m, 1 H), 2.15-2.01 (m, 4 H), 1.75-1.54 (m, 4 H).

Trans 1-Benzenesulfonyl-N*4*-(4-oxazol-5-yl-cyclohexyl)-1H-pyrrolo[2,3-b]pyridine-4,5-diamine

To a mixture of trans (1-benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-yl)-(4-oxazol-5-yl-cyclohexyl)-amine (128 mg, 0.274 mmol) in ethanol (1.4 mL, IMS grade) and water (0.46 mL), ammonium chloride (87.9 mg, 1.64 mmol) and iron powder (61.0 mg, 1.09 mmol) were sequentially added. The mixture was heated to reflux for 90 minutes. After cooling, the mixture was diluted with DCM/methanol and then filtered through Celite® (washing the filter cake with DCM/methanol (1:1)). The filtrate was concentrated *in vacuo* to provide crude trans 1-benzenesulfonyl-N*4*-(4-oxazol-5-yl-cyclohexyl)-1H-pyrrolo[2,3-b]pyridine-4,5-diamine which was used without further purification. LCMS (Method Q, ESI): RT = 2.67 min, m+H = 438.3.

Trans (R)-1-[6-Benzenesulfonyl-1-(4-oxazol-5-yl-cyclohexyl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol

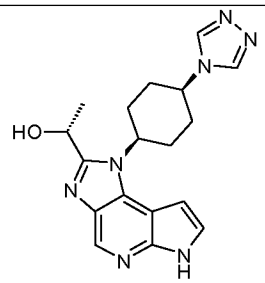
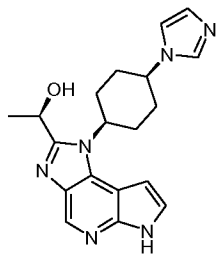
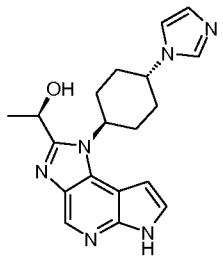
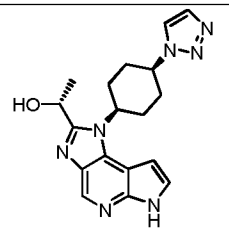
A suspension of triethyloxonium tetrafluoroborate (256 mg, 1.35 mmol) in DCM (2 mL) was treated with R-lactamide (124 mg, 1.39 mmol) and stirred at room temperature for 2 hours. The solvent was removed *in vacuo*. The residue was dissolved in ethanol (1 mL) and added to a stirred solution of trans 1-benzenesulfonyl-N*4*-(4-oxazol-5-yl-cyclohexyl)-1H-pyrrolo[2,3-b]pyridine-4,5-diamine (197 mg, 0.45 mmol) in ethanol (3 mL) at room temperature. The mixture was then heated to 80 °C for 20 hours, LCMS indicated remaining starting material, and additional triethyloxonium tetrafluoroborate (256 mg, 1.35 mmol) and R-lactamide (124 mg, 1.39 mmol) prepared as above was added. Heating was continued for 2 hours. After cooling, the solvent was removed *in vacuo* and the residue purified by column chromatography using an Isolute® SCX-2 cartridge (gradient: MeOH to 2M NH_3 in MeOH) to provide crude product. Further purification by column chromatography on silica gel (gradient: DCM to ethyl acetate, then 2% [2M NH_3 in MeOH] in DCM) afforded 40 mg (18%) of trans (R)-1-[6-benzenesulfonyl-1-(4-oxazol-5-yl-cyclohexyl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol as a pale brown glass. LCMS (Method Q, ESI): RT = 3.13 min, m+H = 492.3.

Trans (R)-1-[1-(4-Oxazol-5-yl-cyclohexyl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol

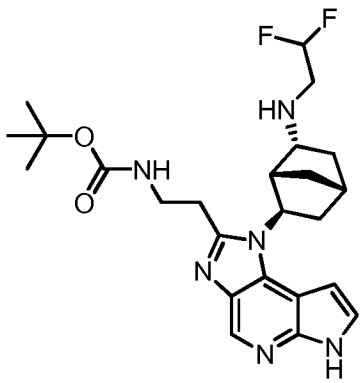
To a stirred solution of trans (R)-1-[6-benzenesulfonyl-1-(4-oxazol-5-yl-cyclohexyl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol (40.0 mg, 80.0 μmol) in THF (1 mL) and methanol (0.2 mL), aqueous sodium hydroxide solution (250 μL, 0.50 mmol) was added. The mixture was stirred at ambient temperature for 24 hours and then concentrated *in vacuo*. The resulting residue was purified by HPLC (10 to 35% acetonitrile in H_2O) and lyophilised to provide 5.2 mg (18%) of trans (R)-1-[1-(4-oxazol-5-yl-cyclohexyl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol as a white solid. LCMS (Method A, ESI): RT = 2.44 min, m+H = 352.1; ^{1}H NMR (400 MHz, DMSO) δ: 11.84 (s, 1 H), 8.55 (s, 1 H), 8.27 (s, 1 H), 7.46 (t, 1 H), 6.97 (s, 1 H), 6.81 (s, 1 H), 5.67 (m, 1 H), 5.14 (m, 1 H), 4.91 (m, 1 H), 3.16 (m, 1 H), 2.57-2.42 (m, 2 H, obscured by DMSO), 2.28-2.17 (m, 2 H), 2.07-1.94 (m, 2 H), 1.77-1.59 (m, 2 H), 1.63 (d, 3 H).

The following examples in Table 1 were made similarly to Example 2 above, and to Examples 653 in U.S. Pat. Appl. Serial No. 13/004,808, filed 1/11/2011.

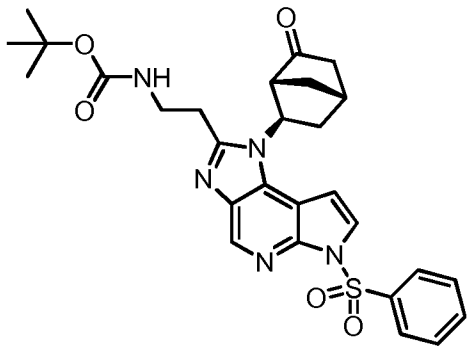
Table 1

Structure	Ex #	Name	LCMS RT (min)/ Method	LCMS (ESI) *m/z*
	3	cis (R)-1-[1-(4-[1,2,4]Triazol-4-yl-cyclohexyl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol	1.75 / A	352.1
	4	cis (R)-1-[1-(4-Imidazol-1-yl-cyclohexyl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol	1.49 / A	351.0
	5	trans (R)-1-[1-(4-Imidazol-1-yl-cyclohexyl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol	1.64 / A	351.0
	6	cis (R)-1-[1-(4-[1,2,3]Triazol-1-yl-cyclohexyl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol	2.08 / A	352.1

Example 7

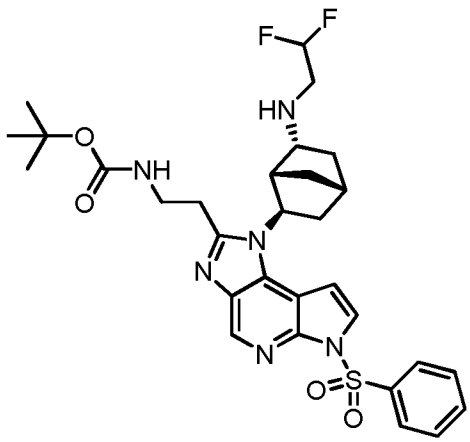


(2-{1-[6-(2,2-Difluoro-ethylamino)-bicyclo[2.2.1]hept-2-yl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-carbamic acid tert-butyl ester (racemic, single diastereomer)



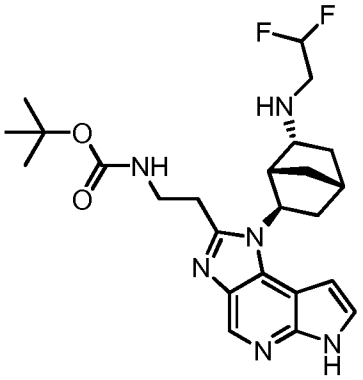
Racemic-{2-[6-Benzenesulfonyl-1-((1R,2R,4S)-6-oxo-bicyclo[2.2.1]hept-2-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-carbamic acid tert-butyl ester

See preparative example for {2-[1-(6-Hydroxy-bicyclo[2.2.1]hept-2-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-carbamic acid tert-butyl ester for relevant synthetic procedures. Dess-Martin periodinane (0.326 g, 0.761 mmol) was added to a solution of racemic-{2-[6-benzenesulfonyl-1-((1R,2R,4S,6S)-6-hydroxy-bicyclo[2.2.1]hept-2-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-carbamic acid tert-butyl ester (0.210 g. 0.381 mmol) in CH_2Cl_2 at 25 °C. The reaction mixture was stirred for 1.5 h at 25 °C, then was partitioned between half-saturated $NaHCO_3$ (100 ml) and EtOAc (2 x 100 ml). The organic layers were dried over $MgSO_4$, filtered and was concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (gradient: 0 to 7% CH_3OH in CH_2Cl_2) afforded racemic-{2-[6-benzenesulfonyl-1-((1R,2R,4S)-6-oxo-bicyclo[2.2.1]hept-2-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-carbamic acid tert-butyl ester (0.183 g, 88%) as a clear oil/foam.



Racemic-(2-{6-Benzenesulfonyl-1-[(1S,2R,4R,6R)-6-(2,2-difluoro-ethylamino)-bicyclo[2.2.1]hept-2-yl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-carbamic acid tert-butyl ester

Sodium triacetoxyborohydride (0.145 g, 0.684 mmol) was added to a solution of racemic-{2-[6-benzenesulfonyl-1-((1R,2R,4S)-6-oxo-bicyclo[2.2.1]hept-2-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-carbamic acid tert-butyl ester (0.188 g, 0.342 mmol) and diflurorethylamine (0.275 g, 3.42 mmol) in 1,2-dichloroethane (8 ml) at 25 °C. The reaction mixture was stirred for 18 h at 25 °C, then was partitioned between half-saturated $NaHCO_3$ (100 ml) and EtOAc (2 x 100 ml). The organic layers were dried over $MgSO_4$, filtered and was concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (gradient: 0 to 6% CH_3OH in CH_2Cl_2) afforded racemic-(2-{6-benzenesulfonyl-1-[(1S,2R,4R,6R)-6-(2,2-difluoro-ethylamino)-bicyclo[2.2.1]hept-2-yl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-carbamic acid tert-butyl ester (0.116 g, 55%) as a clear oil/foam. A minor amount of two other isomeric products were also isolated as an inseparable mixture from the silica gel chromatography.

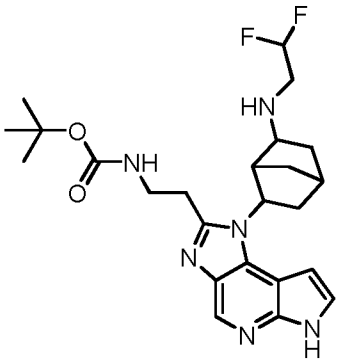


(2-{1-[6-(2,2-Difluoro-ethylamino)-bicyclo[2.2.1]hept-2-yl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-carbamic acid tert-butyl ester (racemic, single diastereomer)

Sodium hydroxide (2 ml of a 1.0 M solution in water, 2 mmol) was added to a solution of racemic-(2-{6-benzenesulfonyl-1-[(1S,2R,4R,6R)-6-(2,2-difluoro-ethylamino)-bicyclo[2.2.1]hept-2-yl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-carbamic acid tert-butyl ester (0.116 g, 0.189 mmol) in a 1:1 mixture of iPrOH and THF (8 ml) at 25 °C. The reaction mixture was stirred at 50 °C for 26 h, then was cooled to 25 °C. HCl (2.0 ml of a 1.0 M solution in water) and saturated NaHCO3 (0.50 ml) were added sequentially. The resulting mixture was concentrated under reduced pressure overnight at 50 °C (GeneVacc). The residue was suspended in DMF (2 ml) and was thoroughly mixed via vortexing and spatula scraping.

The suspension was filtered through a 1.2 u syringe filter and the resulting solution was purified by preparative HPLC (Method G) to give (2-{1-[6-(2,2-difluoro-ethylamino)-bicyclo[2.2.1]hept-2-yl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-carbamic acid tert-butyl ester (racemic, single diastereomer, 0.027 g, 31%) as white solid. LCMS (Method A, ESI): 3.23 min, m/z = 475.3 (100%). ^{1}H NMR (400 MHz, DMSO) δ 11.74 (s, 1H), 8.49 (s, 1H), 7.41 (t, J = 3.0 Hz, 1H), 6.91 (t, J = 5.3 Hz, 1H), 6.70 (s, 1H), 5.97 (tt, J = 56.4, 4.2 Hz, 1H), 5.46 – 5.37 (m, 1H), 3.57 – 3.48 (m, 2H), 3.25 – 3.05 (m, 3H), 2.99 – 2.85 (m, 2H), 2.68 (s, 1H), 2.24 – 1.88 (m, 4H), 1.47 (d, J = 10.2 Hz, 1H), 1.38 (s, 9H), 0.92 – 0.82 (m, 1H).

Examples 8 and 9



Racemic tert-butyl 2-(1-(6-(2,2-difluoroethylamino)bicyclo[2.2.1]heptan-2-yl)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2-yl)ethylcarbamate (stereochem unknown) and racemic tert-butyl 2-(1-(6-(2,2-difluoroethylamino)bicyclo[2.2.1]heptan-2-yl)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2-yl)ethylcarbamate (stereochem unknown)

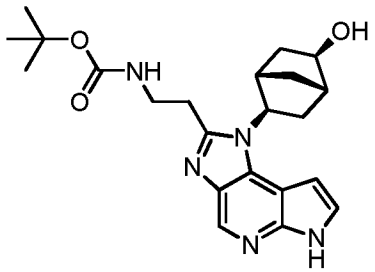
Removal of the sulfonamide protecting groups present in the minor isomers isolated during the preparation of racemic-(2-{6-benzenesulfonyl-1-[(1S,2R,4R,6R)-6-(2,2-difluoro-ethylamino)-bicyclo[2.2.1]hept-2-yl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-carbamic acid tert-butyl ester was accomplished in a manner analogous to that described for the preparation of racemic-(2-{1-[6-(2,2-difluoro-ethylamino)-bicyclo[2.2.1]hept-2-yl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-carbamic acid tert-butyl ester. The resulting products were separated and purified by preparative HPLC (Method G) to give two isomers of (2-{1-[6-

(2,2-difluoro-ethylamino)-bicyclo[2.2.1]hept-2-yl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-carbamic acid tert-butyl ester (racemic, unknown diastereomers) as white solids.

Isomer 1 (Example 8): LCMS (Method A, ESI): 3.06 min, m/z = 475.3 (100%). ^{1}H NMR (400 MHz, DMSO) δ 11.78 (s, 1H), 8.50 (s, 1H), 7.43 (t, J = 3.0 Hz, 1H), 6.97 (t, J = 5.4 Hz, 1H), 6.56 (s, J = 9.4 Hz, 1H), 5.97 (tt, J = 56.4, 4.3 Hz, 1H), 4.55 (dd, J = 8.6, 4.0 Hz, 1H), 3.49 (dd, J = 13.2, 6.8 Hz, 2H), 3.21 – 3.02 (m, 2H), 3.00 – 2.85 (m, 3H), 2.59 – 2.52 (m, 1H), 2.46 (s, 1H), 2.45 – 2.37 (m, 1H), 2.10 – 1.91 (m, 2H), 1.81 (d, J = 10.4 Hz, 1H), 1.78 – 1.69 (m, 1H), 1.65 (d, J = 10.2 Hz, 1H), 1.39 (s, 9H), 1.26 – 1.14 (m, 1H).

Isomer 2: (Example 9): LCMS (Method A, ESI): 2.99 min, m/z = 475.3 (100%).

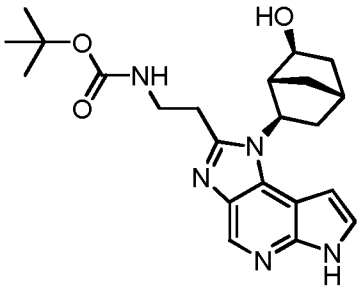
Example 10



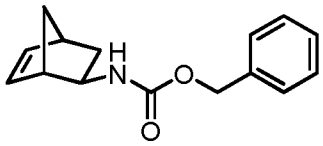
{2-[1-(5-Hydroxy-bicyclo[2.2.1]hept-2-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-carbamic acid tert-butyl ester (racemic, single diastereomer)

See preparative example for {2-[1-(6-Hydroxy-bicyclo[2.2.1]hept-2-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-carbamic acid tert-butyl ester for relevant synthetic procedures. This material was prepared from racemic-(1S,2R,4S,5R)-5-(1-benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-bicyclo[2.2.1]heptan-2-ol in a manner analogous to that described for the conversion of racemic-(1R,2S,4S,6R)-6-(1-benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-bicyclo[2.2.1]heptan-2-ol to racemic-{2-[1-(6-hydroxy-bicyclo[2.2.1]hept-2-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-carbamic acid tert-butyl ester. LCMS (Method A, ESI): 3.20 min, m/z = 412.2 (100%). ^{1}H NMR (400 MHz, DMSO) δ 11.77 (s, 1H), 8.49 (s, 1H), 7.42 (d, J = 3.2 Hz, 1H), 6.94 (t, J = 5.4 Hz, 1H), 6.52 (d, J = 3.3 Hz, 1H), 4.77 (s, 1H), 4.57 – 4.48 (m, 1H), 3.80 (d, J = 6.0 Hz, 1H), 3.48 (dd, J = 13.6, 6.9 Hz, 2H), 3.18 – 2.97 (m, 2H), 2.47 – 2.37 (m, 2H), 1.94 – 1.65 (m, 4H), 1.38 (s, 9H).

Example 11

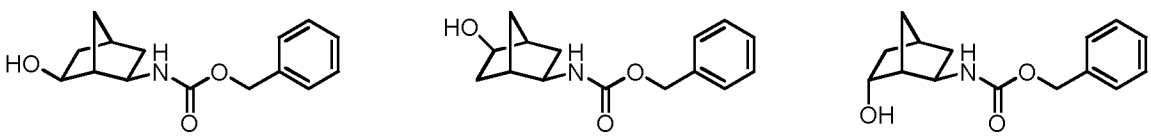


{2-[1-(6-Hydroxy-bicyclo[2.2.1]hept-2-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-carbamic acid tert-butyl ester (racemic, single diastereomer)



Exo-Bicyclo[2.2.1]hept-5-en-2-yl-carbamic acid benzyl ester

Ethyl chloroformate (7.13 ml, 74.2 mmol) was added to a solution of exo-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (5.00 g, 36.2 mmol) and triethylamine (15.3 ml, 109 mmol) in THF (200 ml) at 0 °C. The resulting suspension was stirred at 0 °C for 45 min, then a solution of sodium azide (7.13 g, 109 mmol) in water (25 ml) was added dropwise via addition funnel over 15 min. The reaction mixture was warmed to 25 °C and stirred for 1.5 h, then was partitioned between water (200 ml) and EtOAc (2 x 225 ml). The combined organic layers were dried over $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure to give a pale yellow liquid. This material was dissolved in benzene (80 ml) at 25 °C and the resulting solution was refluxed for 2 h. After cooling to 25 °C, the reaction mixture was concentrated under reduced pressure to afford a yellow oil. This material was dissolved in CH_2Cl_2 (70 ml) at 25 °C and triethylamine (10.2 ml, 72.7 mmol) and benzyl alcohol (4.16 ml, 40.0 mmol) were added sequentially. The mixture was refluxed for 18 h, then was cooled to 25 °C and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (gradient: 0 to 40% EtOAc in heptanes) afforded exo-bicyclo[2.2.1]hept-5-en-2-yl-carbamic acid benzyl ester (6.48 g, 74%) as a pale yellow oil.

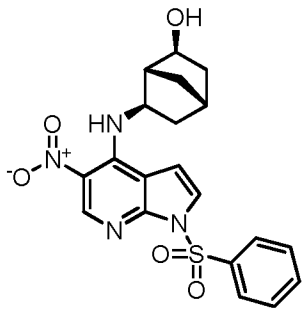
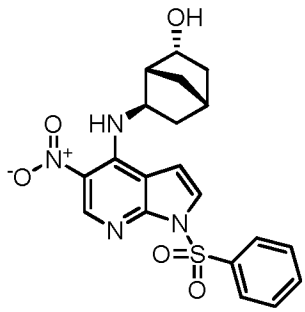
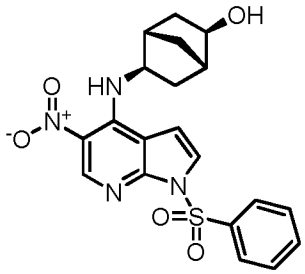


6-exo-2-exo-(6-Hydroxy-bicyclo[2.2.1]hept-2-yl)-carbamic acid benzyl ester

5-exo-2-exo-(5-Hydroxy-bicyclo[2.2.1]hept-2-yl)-carbamic acid benzyl ester

6-endo-2-exo-(6-Hydroxy-bicyclo[2.2.1]hept-2-yl)-carbamic acid benzyl ester

9-BBN (70 ml of a 0.5 M sol in THF, 33.3 mmol) was added to a solution of exo-bicyclo[2.2.1]hept-5-en-2-yl-carbamic acid benzyl ester (6.48 g, 26.6 mmol) in THF (150 ml) at 25 °C. The resulting mixture was stirred at 25 °C for 2.5 h, then $NaBO_3x4H_2O$ (5.65 g, 35.0 mmol) was added in small portions. After stirring for 1.5 h at 25 °C, the mixture was partitioned between water (100 ml) and EtOAc (2 x 150 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (gradient: 50 to 100% EtOAc in heptanes) afforded an inseparable mixture of the title compounds (4.06 g, 58%) as a clear oil.

Racemic-(1R,2S,4S,6R)-6-(1-Benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-bicyclo[2.2.1]heptan-2-ol

Racemic-(1R,2R,4S,6R)-6-(1-Benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-bicyclo[2.2.1]heptan-2-ol

Racemic-(1S,2R,4S,5R)-5-(1-Benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-bicyclo[2.2.1]heptan-2-ol

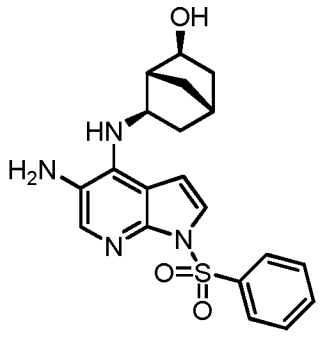
A suspension of 6-exo-2-exo-(6-hydroxy-bicyclo[2.2.1]hept-2-yl)-carbamic acid benzyl ester, 5-exo-2-exo-(5-hydroxy-bicyclo[2.2.1]hept-2-yl)-carbamic acid benzyl ester, and 6-endo-2-exo-(6-hydroxy-bicyclo[2.2.1]hept-2-yl)-carbamic acid benzyl ester (prepared above, 4.00 g, 16.3 mmol) and palladium on carbon (1.0 g, 10%, wet, Degussa, E101 NE/W) in THF (60 ml) and EtOH (20 ml) was stirred under a hydrogen atmosphere (2 balloons) at 50 °C for 2.5 h. The reaction mixture was filtered through Celite, and the Celite was washed with THF (2 x 20 ml). The combined filtrate and washings were concentrated under reduced pressure to afford a colorless oil. This material was dissolved in iPrOH (75 ml) at 50 °C and 1-benzenesulfonyl-4-chloro-5-nitro-1H-pyrrolo[2,3-b]pyridine (5.18 g, 15.3 mmol) and diisopropylethylamine (5.90

ml, 33.7 mmol) were added sequentially. The resulting suspension was heated at 85 °C for 13 h, then was cooled to 25 °C and concentrated under reduced pressure. The mixture was partitioned between water (150 ml) and CH_2Cl_2 (225 ml). The organic layer was dried over $MgSO_4$, filtered and was concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (gradient: 0 to 40% EtOAc in CH_2Cl_2) afforded the separated title compounds as yellow solids.

First isomer eluted = racemic-(1R,2R,4S,6R)-6-(1-benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-bicyclo[2.2.1]heptan-2-ol; 0.432 g (6.6%). Structure assigned as described below.

Second isomer eluted = racemic-(1R,2S,4S,6R)-6-(1-benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-bicyclo[2.2.1]heptan-2-ol; 1.73 g (26%). Structure assigned via 1D and 2D NMR experiments. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.97 (d, J = 6.5 Hz, 1H), 8.19 (d, J = 7.7 Hz, 2H), 7.67 – 7.58 (m, 2H), 7.56 – 7.48 (m, 2H), 6.84 (d, J = 4.2 Hz, 1H), 4.06 – 3.96 (m, 1H), 3.89 – 3.78 (m, 1H), 2.51 – 2.43 (m, 1H), 2.40 (s, 1H), 1.88 (ddd, J = 12.8, 7.6, 2.0 Hz, 1H), 1.83 – 1.69 (m, 2H), 1.59 – 1.48 (m, 3H), 1.48 – 1.37 (m, 2H).

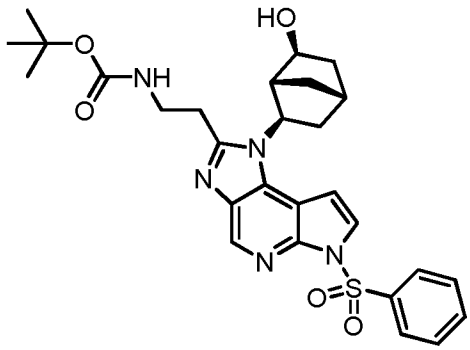
Third isomer eluted = racemic-(1S,2R,4S,5R)-5-(1-benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-bicyclo[2.2.1]heptan-2-ol; 0.63 g (9.6%). Structure inferred based on exo preference for hydroboration reaction and know assignment of second eluted isomer as other exo-OH compound.



Racemic-(1R,2S,4S,6R)-6-(5-Amino-1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-bicyclo[2.2.1]heptan-2-ol

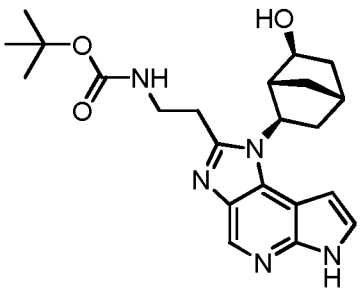
A suspension of racemic-(1R,2S,4S,6R)-6-(1-benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-bicyclo[2.2.1]heptan-2-ol (1.72 g, 4.01 mmol) and palladium on carbon (0.80 g, 10%, wet, Degussa, E101 NE/W) in 3:1 THF:EtOH (60 ml) was stirred under a hydrogen atmosphere (2 balloons) at 50 °C for 13 h. The reaction mixture was cooled to 25 °C and was filtered through Celite. The Celite was washed with THF (3 x 20 ml), and the combined

filtrate and washings were concentrated under reduced pressure to give crude racemic-(1R,2S,4S,6R)-6-(5-amino-1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-bicyclo[2.2.1]heptan-2-ol (1.50 g 94%) as a yellow/brown foam.



Racemic-{2-[6-Benzenesulfonyl-1-((1R,2R,4S,6S)-6-hydroxy-bicyclo[2.2.1]hept-2-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-carbamic acid tert-butyl ester

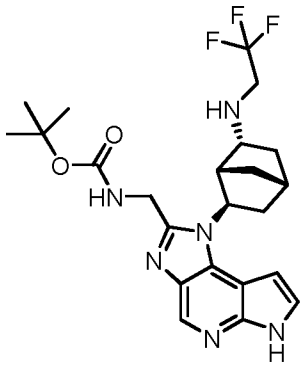
Triethyloxonium tetrafluoroborate (0.527 g 2.63 mmol) was added to a suspension of (2-carbamoyl-ethyl)-carbamic acid tert-butyl ester (0.496 g, 2.63 mmol) in CH_2Cl_2 (10 ml) at 25 °C. The reaction mixture was stirred for 1 h at 25 °C, then was concentrated under reduced pressure. EtOH (anhydrous, 10 ml) and crude racemic-(1R,2S,4S,6R)-6-(5-amino-1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-bicyclo[2.2.1]heptan-2-ol (0.350 g, 0.878 mmol) were added sequentially and the resulting mixture was heated at 75 °C for 1 h. After cooling to 25 °C, the reaction mixture was partitioned between half-saturated $NaHCO_3$ (150 ml) and EtOAc (2 x 100 ml). The organic layers were dried over $MgSO_4$, filtered and was concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (gradient: 0 to 6% CH_3OH in CH_2Cl_2) afforded racemic-{2-[6-benzenesulfonyl-1-((1R,2R,4S,6S)-6-hydroxy-bicyclo[2.2.1]hept-2-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-carbamic acid tert-butyl ester (0.261 g, 54%) as a clear oil/foam.



{2-[1-(6-Hydroxy-bicyclo[2.2.1]hept-2-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-carbamic acid tert-butyl ester (racemic, single diastereomer)

Sodium hydroxide (2 ml of a 1.0 M solution in water, 2 mmol) was added to a solution of racemic-{2-[6-benzenesulfonyl-1-((1R,2R,4S,6S)-6-hydroxy-bicyclo[2.2.1]hept-2-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-carbamic acid tert-butyl ester (0.050 g. 0.091 mmol) in a 1:1 mixture of iPrOH and THF (6 ml) at 25 °C. The reaction mixture was stirred at 50 °C for 24 h, then was cooled to 25 °C. HCl (2.0 ml of a 1.0 M solution in water) and saturated $NaHCO_3$ (0.50 ml) were added sequentially. The resulting mixture was concentrated under reduced pressure overnight at 50 °C (GeneVacc). The residue was suspended in DMF (2 ml) and was thoroughly mixed via vortexing and spatula scraping. The suspension was filtered through a 1.2 u syringe filter and the resulting solution was purified by preparative HPLC (Method G) to give {2-[1-(6-hydroxy-bicyclo[2.2.1]hept-2-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-carbamic acid tert-butyl ester (racemic, single diastereomer, 0.013 g, 36%) as white solid. LCMS (Method A, ESI): 3.39 min, m/z = 412.2 (100%). ^{1}H NMR (400 MHz, DMSO) δ 11.78 (s, 1H), 8.49 (s, 1H), 7.43 (d, J = 3.1 Hz, 1H), 6.95 (t, J = 5.3 Hz, 1H), 6.58 (d, J = 3.3 Hz, 1H), 4.88 – 4.75 (m, 1H), 4.52 (dd, J = 8.7, 4.8 Hz, 1H), 3.95 (d, J = 6.2 Hz, 1H), 3.51 (dd, J = 13.4, 6.3 Hz, 2H), 3.20 – 3.00 (m, 2H), 2.54 (s, 1H), 2.41 (s, 1H), 2.30 – 2.19 (m, 1H), 1.97 – 1.67 (m, 4H), 1.39 (s, 9H).

Example 12

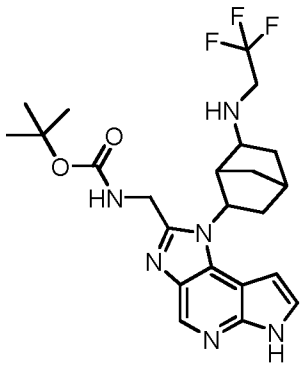


{1-[6-(2,2,2-Trifluoro-ethylamino)-bicyclo[2.2.1]hept-2-yl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-carbamic acid tert-butyl ester (racemic, single diastereomer)

This material was prepared from racemic-(1R,2S,4S,6R)-6-(5-amino-1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-bicyclo[2.2.1]heptan-2-ol in a manner analogous to that described for the preparation of racemic-(2-{1-[6-(2,2-difluoro-ethylamino)-bicyclo[2.2.1]hept-2-yl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-carbamic acid tert-butyl ester (employing trifluoroethylamine and carbamoylmethyl-carbamic acid tert-butyl ester where appropriate). LCMS (Method A, ESI): 4.19 min, m/z = 479.2 (100%). ^{1}H NMR (400 MHz, DMSO) δ 11.78 (s, 1H), 8.50 (s, 1H), 7.42 (t, J = 3.0 Hz, 1H), 7.28 (t, J = 4.8 Hz, 1H), 6.69 (s, 1H), 5.37 (t, J = 6.9 Hz, 1H), 4.55 (d, J = 5.3 Hz, 2H), 3.29 – 3.20 (m, 2H), 2.96 – 2.88 (m, 1H),

2.78 (s, 1H), 2.45 (s, 1H), 2.19 – 1.92 (m, 4H), 1.51 (d, J = 10.4 Hz, 1H), 1.41 (s, 9H), 1.36 – 1.24 (m, 1H), 0.94 – 0.85 (m, 1H).

Examples 13 and 14



{1-[6-(2,2,2-Trifluoro-ethylamino)-bicyclo[2.2.1]hept-2-yl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-carbamic acid tert-butyl ester (racemic, single unknown diastereomer)

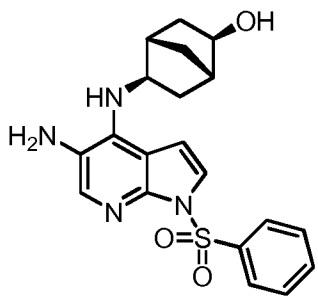
{1-[6-(2,2,2-Trifluoro-ethylamino)-bicyclo[2.2.1]hept-2-yl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-carbamic acid tert-butyl ester (racemic, single unknown diastereomer)

These materials were isolated during the preparation of racemic-{1-[6-(2,2,2-trifluoro-ethylamino)-bicyclo[2.2.1]hept-2-yl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-carbamic acid tert-butyl ester in a manner analogous to that described for the isolation of racemic isomers of tert-butyl 2-(1-(6-(2,2-difluoroethylamino)bicyclo[2.2.1]heptan-2-yl)-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2-yl)ethylcarbamate (stereochem unknown) .

Isomer 1 (Example 13): LCMS: 3.45 min, m/z = 479.2 (100%).

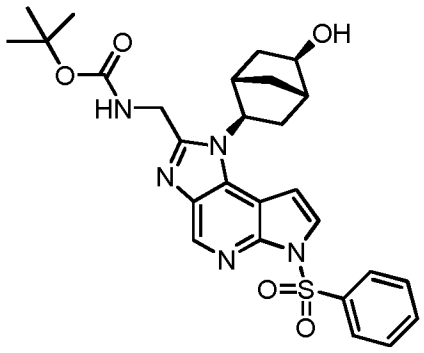
Isomer 2 (Example 14): LCMS: 3.43 min, m/z = 479.2 (100%).

Example 15



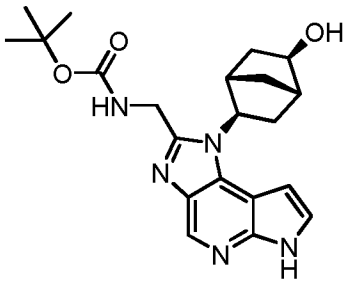
Racemic-(1S,2R,4S,5R)-5-(5-Amino-1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-bicyclo[2.2.1]heptan-2-ol

A suspension of racemic-(1S,2R,4S,5R)-5-(1-benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-bicyclo[2.2.1]heptan-2-ol (0.63 g, 1.50 mmol) and palladium on carbon (0.40 g, 10%, wet, Degussa, E101 NE/W) in 3:1 THF:EtOH (50 ml) was stirred under a hydrogen atmosphere (2 balloons) at 50 °C for 8 h. The reaction mixture was cooled to 25 °C and was filtered through Celite. The Celite was washed with THF (3 x 20 ml), and the combined filtrate and washings were concentrated under reduced pressure to give crude racemic-(1S,2R,4S,5R)-5-(5-amino-1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-bicyclo[2.2.1]heptan-2-ol (0.501 g 86%) as a purple/brown foam.



Racemic-[6-Benzenesulfonyl-1-((1S,2R,4S,5R)-5-hydroxy-bicyclo[2.2.1]hept-2-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-carbamic acid tert-butyl ester

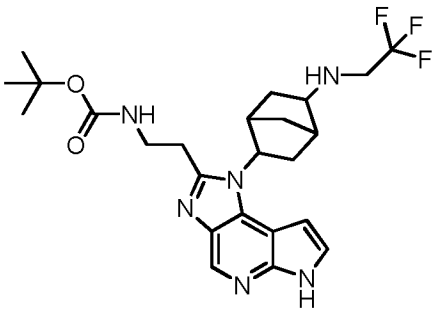
Triethyloxonium tetrafluoroborate (0.310 g 1.60 mmol) was added to a suspension of carbamoylmethyl-carbamic acid tert-butyl ester (0.270 g, 1.6 mmol) in CH_2Cl_2 (10 ml) at 25 °C. The reaction mixture was stirred for 1 h at 25 °C, then was concentrated under reduced pressure. EtOH (anhydrous, 10 ml) and crude racemic-(1S,2R,4S,5R)-5-(5-amino-1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-bicyclo[2.2.1]heptan-2-ol (0.250 g, 0.630 mmol) were added sequentially and the resulting mixture was heated at 75 °C for 1 h. After cooling to 25 °C, the reaction mixture was partitioned between half-saturated $NaHCO_3$ (150 ml) and EtOAc (2 x 100 ml). The organic layers were dried over $MgSO_4$, filtered and was concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (gradient: 0 to 6% CH_3OH in CH_2Cl_2) afforded racemic-[6-benzenesulfonyl-1-((1R,2R,4S,6S)-6-hydroxy-bicyclo[2.2.1]hept-2-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-carbamic acid tert-butyl ester (0.160 g, 47%) as a clear oil/foam.



[1-(5-Hydroxy-bicyclo[2.2.1]hept-2-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-carbamic acid tert-butyl ester (racemic, single diastereomer)

This material was prepared from racemic-[6-benzenesulfonyl-1-((1R,2R,4S,6S)-6-hydroxy-bicyclo[2.2.1]hept-2-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-carbamic acid tert-butyl ester in a manner analogous to that described for the preparation of racemic-(2-{1-[6-(2,2-difluoro-ethylamino)-bicyclo[2.2.1]hept-2-yl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-carbamic acid tert-butyl ester. LCMS (Method A, ESI): 3.16 min, m/z = 398.2 (100%). ^{1}H NMR (400 MHz, DMSO) δ 11.82 (s, 1H), 8.51 (s, 1H), 7.44 (d, J = 3.4 Hz, 1H), 7.41 – 7.35 (m, 1H), 6.52 (d, J = 3.2 Hz, 1H), 4.83 – 4.71 (m, 1H), 4.55 – 4.45 (m, 3H), 3.77 (d, J = 5.9 Hz, 1H), 2.43 (s, 2H), 1.92 – 1.78 (m, 3H), 1.69 (d, J = 10.3 Hz, 1H), 1.32 (dd, J = 13.3, 3.5 Hz, 2H).

Example 16

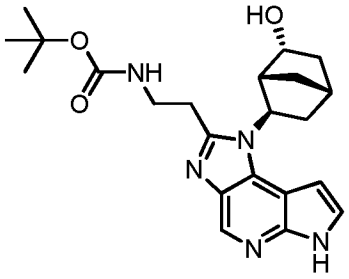


(2-{1-[5-(2,2,2-Trifluoro-ethylamino)-bicyclo[2.2.1]hept-2-yl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-carbamic acid tert-butyl ester (racemic, single unknown diastereomer)

This material was prepared from racemic-(1S,2R,4S,5R)-5-(5-Amino-1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-bicyclo[2.2.1]heptan-2-ol in a manner analogous to that described for the preparation of racemic-(2-{1-[6-(2,2-difluoro-ethylamino)-bicyclo[2.2.1]hept-2-yl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-carbamic acid tert-butyl ester (employing trifluoroethylamine where appropriate). LCMS (Method A, ESI): 3.48 min, m/z = 493.2 (96%). ^{1}H NMR (400 MHz, DMSO) δ 11.77 (s, 1H), 8.49 (s, 1H), 7.42 (t, J = 3.0 Hz, 1H), 6.93 (t, J = 5.4 Hz, 1H), 6.60 (dd, J = 2.8, 1.8 Hz, 1H), 4.65 (dd, J = 8.5, 3.7 Hz, 1H), 3.51 (dd, J = 13.1, 7.0 Hz, 2H), 3.30 – 3.21 (m, 2H), 3.20 – 3.00 (m, 3H), 2.72 (dd, J = 13.4, 7.4 Hz,

1H), 2.66 – 2.54 (m, 2H), 2.43 (d, J = 4.5 Hz, 1H), 2.30 – 2.21 (m, 1H), 2.07 – 1.92 (m, 2H), 1.43 (d, J = 10.3 Hz, 1H), 1.38 (s, 9H), 1.04 – 0.96 (m, 1H).

Example 17

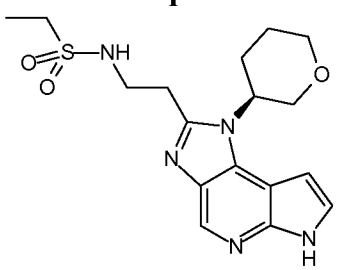


{2-[1-(6-Hydroxy-bicyclo[2.2.1]hept-2-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-carbamic acid tert-butyl ester (racemic, single diastereomer)

This material was prepared from racemic-(1R,2R,4S,6R)-6-(1-benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-bicyclo[2.2.1]heptan-2-ol in a manner analogous to that described for the conversion of racemic-(1R,2S,4S,6R)-6-(1-benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-bicyclo[2.2.1]heptan-2-ol to racemic-{2-[1-(6-hydroxy-bicyclo[2.2.1]hept-2-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-carbamic acid tert-butyl ester. LCMS (Method A, ESI): 3.53 min, m/z = 412.2 (92%). ^{1}H NMR (400 MHz, DMSO) δ 11.75 (s, 1H), 8.49 (s, 1H), 7.44 – 7.38 (m, 1H), 6.89 (t, J = 5.2 Hz, 1H), 6.72 (d, J = 2.8 Hz, 1H), 5.45 (dd, J = 8.7, 5.3 Hz, 1H), 5.17 (s, 1H), 4.26 – 4.16 (m, 1H), 3.52 (dd, J = 13.0, 6.8 Hz, 2H), 3.18 – 3.06 (m, 2H), 2.43 – 2.30 (m, 1H), 2.13 (dd, J = 12.4, 9.6 Hz, 1H), 2.05 – 1.93 (m, 2H), 1.43 (d, J = 10.7 Hz, 1H), 1.38 (s, 9H), 0.97 (dt, J = 6.5, 3.0 Hz, 1H).

Assignment of stereochemistry was performed as follows. Analytical scale Dess-Martin oxidation of racemic-{2-[6-benzenesulfonyl-1-((1R,2R,4S,6S)-6-hydroxy-bicyclo[2.2.1]hept-2-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-carbamic acid tert-butyl ester precursor and corresponding intermediate derived from racemic-(1R,2R,4S,6R)-6-(1-benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-bicyclo[2.2.1]heptan-2-ol (see example 11) afforded norbornyl ketones with identical LCMS retention times. This result suggested that the two norbornyl alcohols are epimers (vs alcohol regioisomers).

Example 18



Ethanesulfonic acid {2-[(S)-1-(tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-amide

((S)-6-Benzenesulfonyl-1-tetrahydro-pyran-3-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl)-acetonitrile

(2-cyano-1-methoxy-ethylidene)ammonium chloride (144.5 mg, 1.07 mmol) was added to a solution of 1-Benzenesulfonyl-N-4-(S)-tetrahydro-pyran-3-yl-1H-pyrrolo[2,3-b]pyridine-4,5-diamine (200 mg, 0.53 mmol) in ethanol (3.0 mL). The reaction mixture was stirred at 75 °C for 48 h, then the resulting precipitate was collected by filtration and washed with cold ethanol to afford crude ((S)-6-Benzenesulfonyl-1-tetrahydro-pyran-3-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl)-acetonitrile as a pale brown solid. LCMS (Method E, ESI): RT = 1.40 min, m+H = 422.2; ^{1}H NMR (400 MHz, DMSO) δ 8.75 (s, 1H), 8.15 (d, *J* = 7.7 Hz, 2H), 8.02 (d, *J* = 4.0 Hz, 1H), 7.72 (t, *J* = 7.4 Hz, 1H), 7.62 (t, *J* = 7.7 Hz, 2H), 7.25 (d, *J* = 4.1 Hz, 1H), 4.76 (s, 2H), 4.09 – 3.79 (m, 3H), 3.67 (dd, *J* = 17.8, 7.7 Hz, 1H), 3.52 – 3.35 (m, 1H), 2.39 – 2.19 (m, 1H), 2.12 (d, *J* = 10.9 Hz, 1H), 1.84 (d, *J* = 15.1 Hz, 2H). This material was used in the next step below without additional purification or characterization.

2-((S)-6-Benzenesulfonyl-1-tetrahydro-pyran-3-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl)-ethylamine

Raney nickel (0.80 mL, 121.0 mmol) was added to a solution of ((S)-6-Benzenesulfonyl-1-tetrahydro-pyran-3-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl)-acetonitrile (170 mg, 0.40 mmol) in tetrahydrofuran (3.0 mL) and ethanol (3.0 mL). The reaction mixture was stirred at room temperature, under an atmosphere of hydrogen for 16h, then filtered over a bed of celite and washed with dichloromethane. The resulting filtrate was concentrated to afford crude 2-((S)-6-Benzenesulfonyl-1-tetrahydro-pyran-3-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl)-ethylamine as a white solid. LCMS (Method E, ESI): RT = 1.21 min m+H = 426.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 – 8.71 (m, 1H), 8.23 (t, *J* = 10.2 Hz, 2H), 7.82 (t, *J* = 11.3 Hz, 1H), 7.64 – 7.36 (m, 3H), 7.09 – 6.86 (m, 1H), 4.61 (s, 1H), 4.11-3.92 (m, 4H), 3.71 – 3.50 (m, 1H), 3.35-3.11 (m, 2H), 2.46 (s, 1H), 1.91 (d, *J* = 44.5 Hz, 6H). This material was used in the next step below without additional purification or characterization.

Ethanesulfonic acid [2-((S)-6-benzenesulfonyl-1-tetrahydro-pyran-3-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl)-ethyl]-amide

Ethanesulfonyl chloride (0.070 mL, 0.73 mmol) and triethylamine (0.103 mL, 0.73 mmol) were added to a solution of 2-((S)-6-Benzenesulfonyl-1-tetrahydro-pyran-3-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl)-ethylamine (250 mg, 0.61 mmol) in tetrahydrofuran

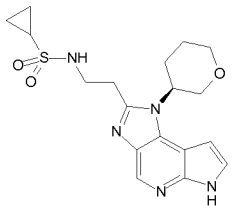
(3.0 mL). The reaction mixture was stirred at room temperature for 18h then filtered and washed with tetrahydrofuran. The resulting filtrate was concentrated to afford crude ethanesulfonic acid [2-((S)-6-benzenesulfonyl-1-tetrahydro-pyran-3-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl)-ethyl]-amide as a pale brown solid. LCMS (Method E, ESI): RT = 1.38 min, m+H = 504.2. This material was used in the next step below without additional purification or characterization.

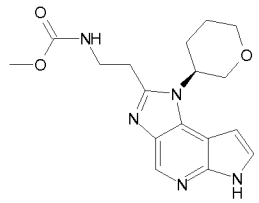
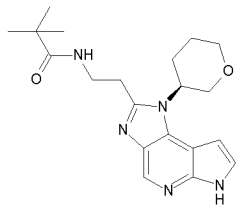
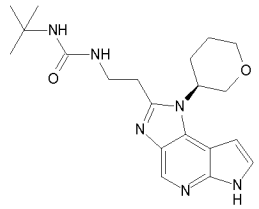
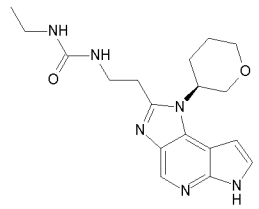
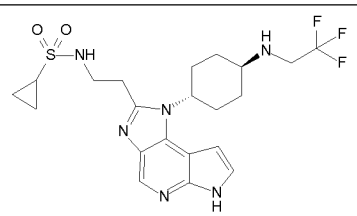
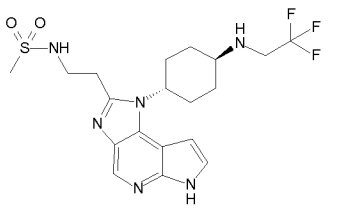
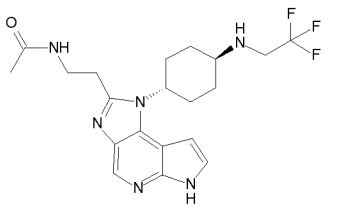
Ethanesulfonic acid {2-[(S)-1-(tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-amide

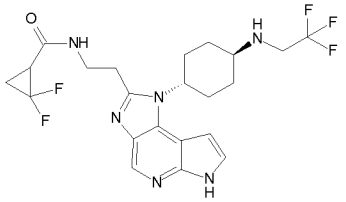
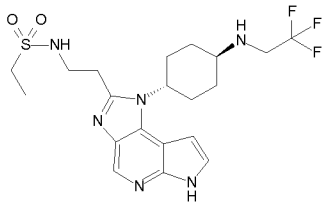
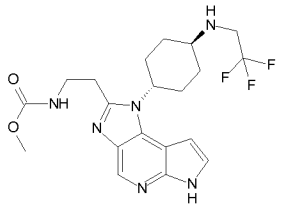
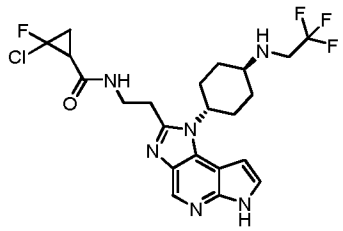
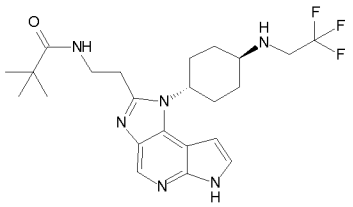
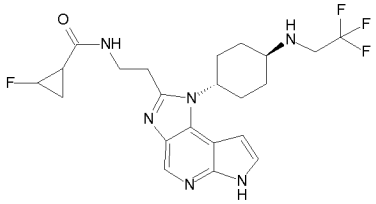
Sodium hydroxide (1.5 ml of a 1.0 M solution in water, 1.5 mmol) was added to a solution of ethanesulfonic acid [2-((S)-6-benzenesulfonyl-1-tetrahydro-pyran-3-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl)-ethyl]-amide (160 mg, 0.32 mmol) in isopropanol (2 ml) at 25 °C. The reaction mixture was stirred at 50 °C for 14 h, then was cooled to 5 °C. Aqueous 1.0 M hydrochloric acid (1.5 ml) was then added and the mixture was concentrated under reduced pressure. Purification of the resulting solution by preparative HPLC (column: Gemini-NX, 21.2 x 100 mm, 10 um; detection: UV 220 nm and mass, mobile phase A: water containing 0.1% NH_4OH; mobile phase B: CH_3CN; flowrate: 35 mL/min; gradient 5-85% B over 10 min) afforded Ethanesulfonic acid {2-[(S)-1-(tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-amide (87.5 mg, 76%) as a white solid. LCMS (Method C, ESI): RT = 2.90 min, m+H = 364.2 1H NMR (400 MHz, DMSO) δ 11.92 (s, 1H), 8.57 (d, J = 11.0 Hz, 1H), 7.80 (s, 1H), 7.56 – 7.45 (m, 1H), 6.86 (s, 1H), 4.87 – 4.70 (m, 1H), 4.57 (qd, J = 15.2, 5.2 Hz, 2H), 4.10 (t, J = 10.9 Hz, 1H), 4.06 – 3.89 (m, 2H), 3.77 – 3.60 (m, 1H), 3.11 (q, J = 7.3 Hz, 2H), 2.13 (d, J = 11.6 Hz, 1H), 1.87 (d, J = 19.3 Hz, 2H), 1.20 (t, J = 7.3 Hz, 3H).

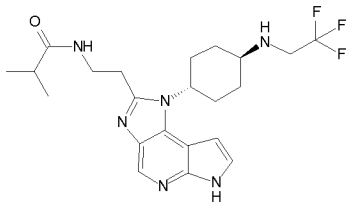
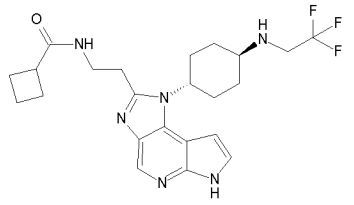
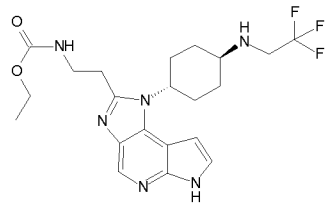
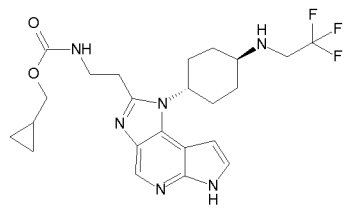
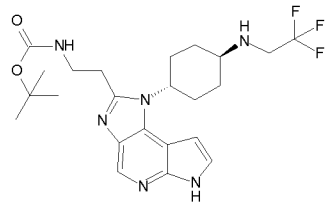
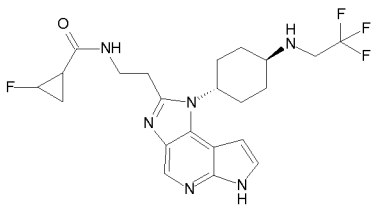
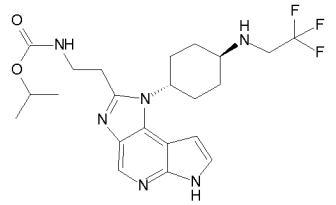
The following examples in Table 2 were made similarly to Example 18 above.

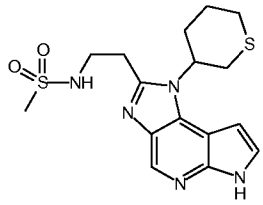
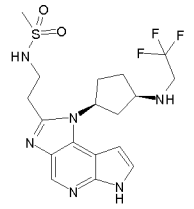
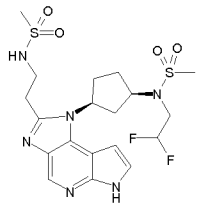
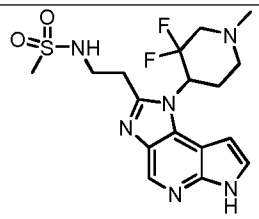
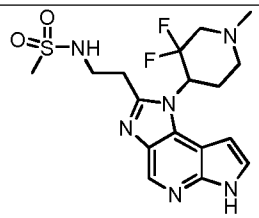
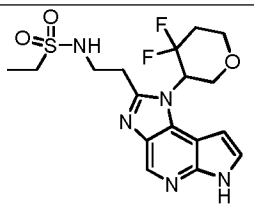
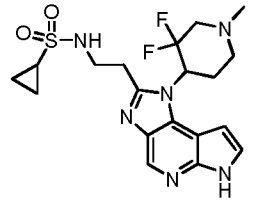
Table 2

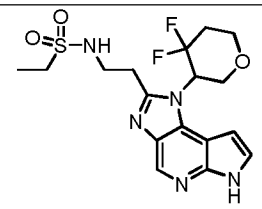
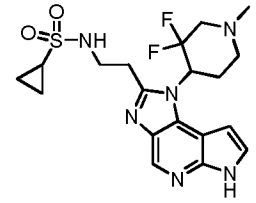
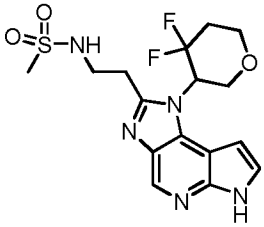
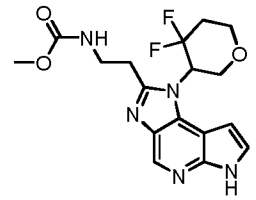
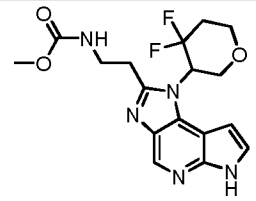
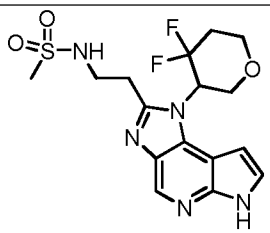
Structure	Ex #	Name	LCMS RT (min)/ Method	LCMS (ESI) *m/z*
	19	Cyclopropanesulfonic acid {2-[(S)-1-(tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-amide	2.09/B	390.0

	20	{2-[(S)-1-(Tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-carbamic acid methyl ester	1.98/B	344.2
	21	2,2-Dimethyl-N-{2-[(S)-1-(tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-propionamide	3.14/B	370.2
	22	1-tert-Butyl-3-{2-[(S)-1-(tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-urea	3.25/B	385.2
	23	1-Ethyl-3-{2-[(S)-1-(tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-urea	2.77/B	357.2
	24	trans Cyclopropanesulfonic acid (2-{1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-amide	3.54 / N	485.1
	25	trans N-(2-{1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-methanesulfonamide	2.72 / N	459.1
	26	trans N-(2-{1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-acetamide	2.71 / N	423.1

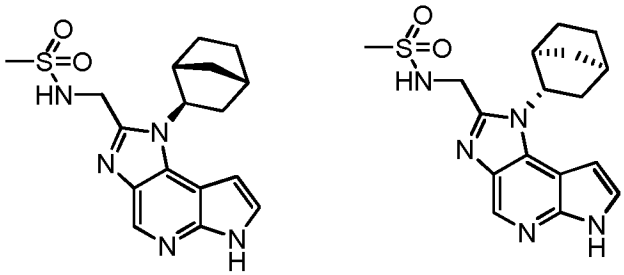
	27	trans 2,2-Difluoro-cyclopropanecarboxylic acid (2-{1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-amide (mixture of enantiomers)	3.74 /N	485.1
	28	trans Ethanesulfonic acid (2-{1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-amide	3.20 / N	473.1
	29	Trans (2-{1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-carbamic acid methyl ester	3.15 / N	439.1
	30	trans 2-Chloro-2-fluoro-cyclopropanecarboxylic acid (2-{1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-amide (cyclohexane is trans, cyclopropane is a mixture of diastereomers)	1.94 / A	501.2
	31	trans 2,2-Dimethyl-N-(2-{1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-propionamide	1.97 / A	465.3
	32	2-Fluoro-cyclopropanecarboxylic acid (2-{1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-amide (racemic mixture, both cyclohexane and cyclopropane are trans)	1.78 /A	467.2

	33	trans N-(2-{1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-isobutyramide	1.78 / A	451.2
	34	trans Cyclobutanecarboxylic acid (2-{1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-amide	1.88 /A	463.2
	35	Trans (2-{1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-carbamic acid ethyl ester	1.82 / A	453.2
	36	Trans (2-{1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-carbamic acid cyclopropylmethyl ester	2.08 / A	479.2
	37	Trans (2-{1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-carbamic acid tert-butyl ester	2.19 / A	481.2
	38	2-Fluoro-cyclopropanecarboxylic acid (2-{1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-amide (racemic mixture, cyclohexane is trans, cyclopropane is cis)	1.65 / A	467.2
	39	Trans (2-{1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-carbamic acid isopropyl ester	1.99 / A	467.2

	40	N-{2-[1-(Tetrahydro-thiopyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-methanesulfonamide (racemic)	3.10 / C	380.1
	41	N-(2-{1-[(1S,3R)-3-(2,2,2-Trifluoro-ethylamino)-cyclopentyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-methanesulfonamide	2.51/O	445.2
	42	N-(2,2-Difluoro-ethyl)-N-{(1R,3S)-3-[2-(2-methanesulfonylamino-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentyl}-methanesulfonamide	3.25 /O	505.1
	43	N-{2-[1-(-3,3-Difluoro-1-methyl-piperidin-4-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-methanesulfonamide (single unknown stereoisomer)	1.934 / K 7.917 / A13	413.1
	44	N-{2-[1-(-3,3-Difluoro-1-methyl-piperidin-4-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-methanesulfonamide (single unknown stereoisomer)	0.848 / K 8.834 / A13	413.1
	45	Ethanesulfonic acid {2-[1-(4,4-difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-amide (single unknown stereoisomer)	0.955 / K 7.01 / A16	414.0
	46	Cyclopropanesulfonic acid {2-[1-(4,4-difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-amide (single unknown stereoisomer)	0.968 / K 7.53 / A16	426.0

	47	Ethanesulfonic acid {2-[1-(4,4-difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-amide (single unknown stereoisomer)	0.940 / K 7.71 / A16	414.0
	48	Cyclopropanesulfonic acid {2-[1-(4,4-difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-amide (single unknown stereoisomer)	0.971 / K 8.55 / A16	426.0
	49	N-{2-[1-(4,4-Difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-methanesulfonamide (single unkown stereoisomer)	0.907 / K 11.15 / A16	400.0
	50	{2-[1-(4,4-Difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-carbamic acid methyl ester (single unknown stereoisomer)	0.948 / K 6.79 / A16	380.1
	51	{2-[1-(4,4-Difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-carbamic acid methyl ester (single unknown stereoisomer)	0.942 / K 7.64 / A16	380.1
	52	N-{2-[1-(4,4-Difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-methanesulfonamide (single unkown stereoisomer)	0.909 / K 10.09 / A16	400.0

Examples 53 and 54



N-(1-Bicyclo[2.2.1]hept-2-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl)-methanesulfonamide (single unknown exo stereoisomers)

(1-Benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-yl)-bicyclo[2.2.1]hept-2-yl-amine

A mixture of 1-benzenesulfonyl-4-chloro-5-nitro-1H-pyrrolo[2,3-b]pyridine (3.00 g, 8.8 mmol), racemic exo-bicyclo[2.2.1]hept-2-ylamine (1.0 ml, 9.0 mmol), and diisopropylethylamine (3.0 ml, 17.8 mmol) in propan-2-ol (30 ml) was heated at 90 °C for 20h. The mixture was then cooled to 25 °C and diluted with water The solid was collected by filtration, washed with water and dried in vac-oven at 50 °C to afford (1-benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-yl)-bicyclo[2.2.1]hept-2-yl-amine (3.0 g, 82%) as a yellow solid. This material was used in the next step below without additional characterization.

1-Benzenesulfonyl-N-4-bicyclo[2.2.1]hept-2-yl-1H-pyrrolo[2,3-b]pyridine-4,5-diamine

A suspension of (1-benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-yl)-bicyclo[2.2.1]hept-2-yl-amine (3.0 g, 7.3 mmol) and palladium on carbon (0.60 g, 10%, wet, Degussa, E101 NE/W) in a 2:1 mixture of THF and ethanol (60 ml) was stirred under a hydrogen atmosphere at 50 °C for 24 h. The reaction mixture was cooled to 25 °C, filtered through Celite, and the Celite was washed with THF (2 x 20 ml). The filtrate and washings were concentrated under reduced pressure to afford crude 1-benzenesulfonyl-N-4-bicyclo[2.2.1]hept-2-yl-1H-pyrrolo[2,3-b]pyridine-4,5-diamine as an orange-brown oil. This material was used in the next step below without further purification or characterization.

6-Benzenesulfonyl-1-bicyclo[2.2.1]hept-2-yl-2-chloromethyl-1,6-dihydro-1,3,5,6-tetraaza-as-indacene

A mixture of 1-benzenesulfonyl-N-4-bicyclo[2.2.1]hept-2-yl-1H-pyrrolo[2,3-b]pyridine-4,5-diamine (0.8 g, 2 mmol) and 1,1,1-triethoxychloroethane (0.8 g, 4 mmol) in acetic acid (5 mL) in 50 mL RB flask was lowered into a bath at 125 °C and heated for 20 min. The reaction mixture was cooled, diluted with DCM (200 mL) and stirred over saturated sodium bicarbonate until the bubbling stopped. The organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the resulting residue by column chromatography on silica gel (0-70% EtOAc in heptane) afforded 6-Benzenesulfonyl-1-bicyclo[2.2.1]hept-2-yl-2-chloromethyl-1,6-dihydro-1,3,5,6-tetraaza-as-indacene (0.7 g, 80 %). LCMS (Method G, ESI): RT = 1.22 min, m+H = 441.2

1-Bicyclo[2.2.1]hept-2-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl)-methanesulfonamide

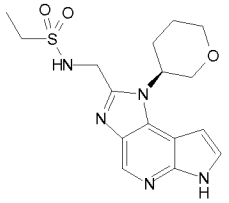
A mixture of 6-benzenesulfonyl-1-bicyclo[2.2.1]hept-2-yl-2-chloromethyl-1,6-dihydro-1,3,5,6-tetraaza-as-indacene (0.9 g, 2 mmol) and N-boc-methanesulfonamide (0.5 g, 2.5 mmol) and K_2CO_3 (0.60 g, 4.3 mmol) in DMF (10 mL) was heated at 50 °C for 24h. Cooled, diluted with water and the solid was collected by filtration. The solid was dissolved in DCM (20 mL) and 4N HCl/dioxane (20 mL) was added and stirred at 25 °C for 20 h. The solid was collected by filtration, washed with ethyl acetate. The solid was dissolved in a mixture of isopropyl alcohol (10 ml) and aqueos sodium hydroxide (5 mL, 1.0 M) and heated at 50 °C for 20h. Cooled, diluted with ethyl acetate. Organic layer was washed with brine, dried over sodium sulfate and concentrated under reduced pressure. Purification by chiral SFC yielded the separated enantiomers.

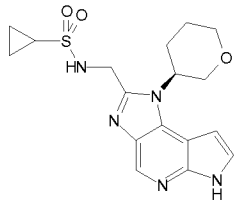
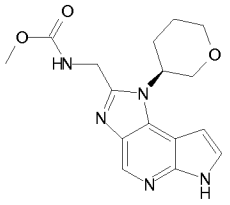
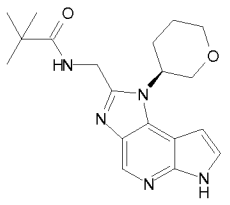
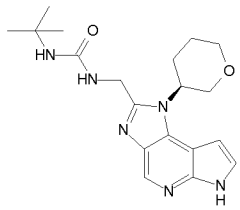
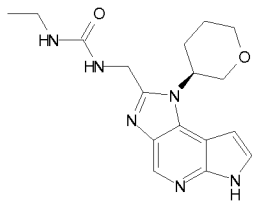
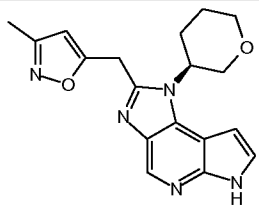
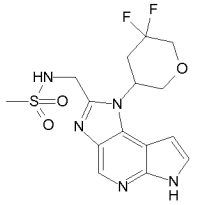
Peak #1 (ex. 53): SFC (Method A8): RT = 0.97 min. LC/MS (Method N, ESI): 6.74 min, m+H = 360.1. ^{1}H NMR (400 MHz, DMSO) δ 11.87 (s, 1H), 8.55 (s, 1H), 7.70 (s, 1H), 7.46 (t, *J* = 2.8 Hz, 1H), 6.58 (d, *J* = 2.1 Hz, 1H), 4.75 (dd, *J* = 8.9, 3.4 Hz, 1H), 4.63 – 4.51 (m, 2H), 3.02 (s, 3H), 2.70 – 2.52 (m, 3H), 2.10 – 1.92 (m, 2H), 1.69 – 1.50 (m, 3H), 1.41 – 1.25 (m, 2H).

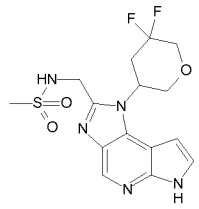
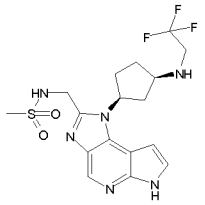
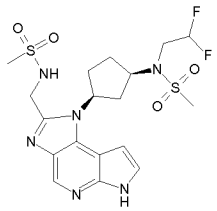
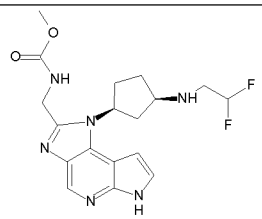
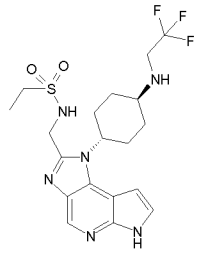
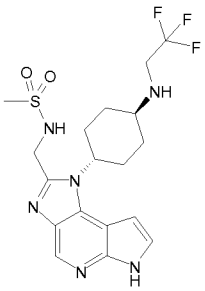
Peak #2 (Ex 54): SFC (Method A8): RT = 1.19 min.. LC/MS (Method N, ESI): 6.70 min.; m+H = 360.1. ^{1}H NMR (400 MHz, DMSO) δ 11.87 (s, 1H), 8.55 (s, 1H), 7.70 (s, 1H), 7.46 (t, *J* = 2.8 Hz, 1H), 6.58 (d, *J* = 2.1 Hz, 1H), 4.75 (dd, *J* = 8.9, 3.4 Hz, 1H), 4.63 – 4.51 (m, 2H), 3.02 (s, 3H), 2.70 – 2.52 (m, 3H), 2.10 – 1.92 (m, 2H), 1.69 – 1.50 (m, 3H), 1.41 – 1.25 (m, 2H).

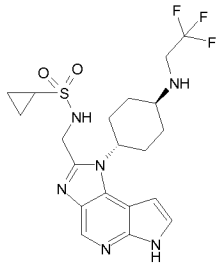
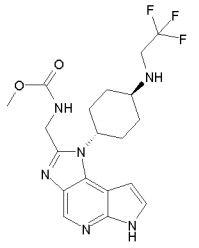
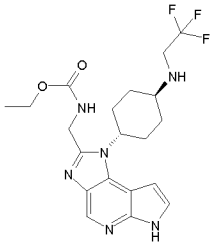
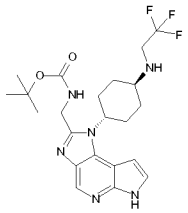
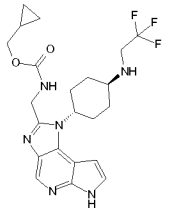
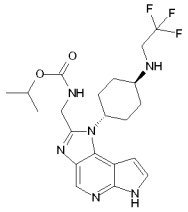
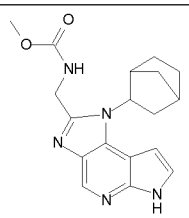
The following examples in Table 3 were made similarly to Example 53 and 54 above.

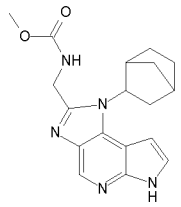
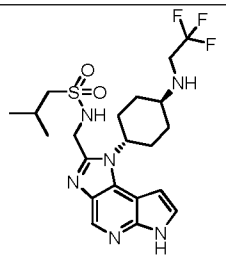
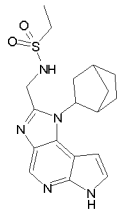
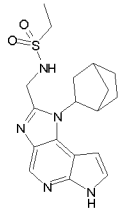
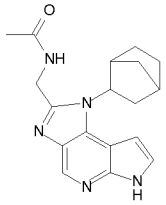
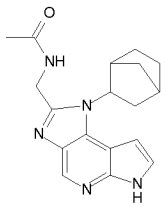
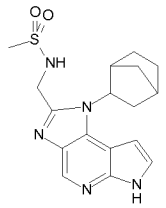
Table 3

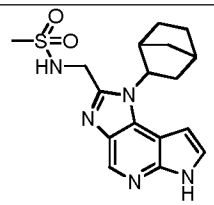
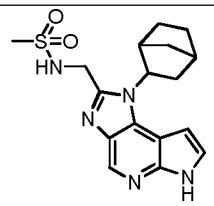
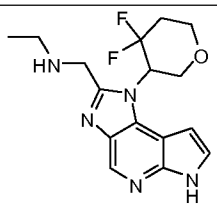
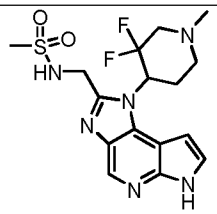
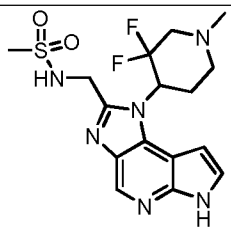
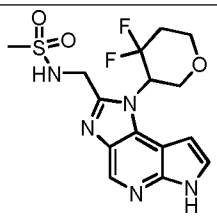
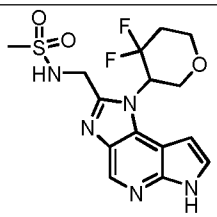
Structure	Ex #	Name	LCMS RT (min)/ Method	LCMS (ESI) *m/z*
	55	Ethanesulfonic acid [(S)-1-(tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-amide	2.90/B	364.2

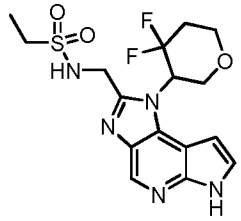
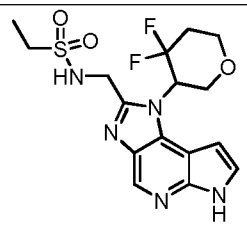
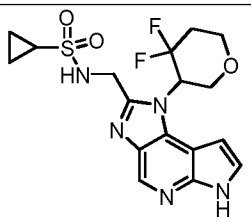
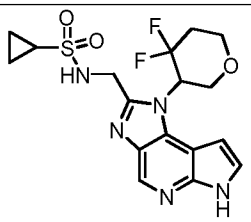
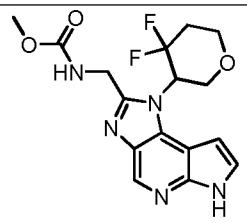
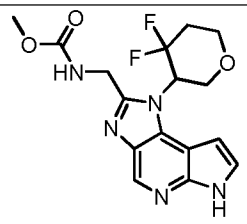
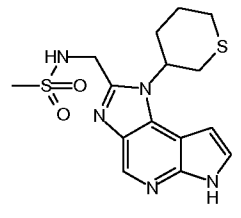
	56	Cyclopropanesulfonic acid [(S)-1-(tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-amide	2.08/B	376.0
	57	[(S)-1-(Tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-carbamic acid methyl ester	1.89/B	330.1
	58	2,2-Dimethyl-N-[(S)-1-(tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-propionamide	3.14/B	356.2
	59	1-tert-Butyl-3-[(S)-1-(tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-urea	3.24/B	371.2
	60	1-Ethyl-3-[(S)-1-(tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-urea	2.32/B	343.2
	61	2-(3-Methyl-isoxazol-5-ylmethyl)-1-(S)-tetrahydro-pyran-3-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacene	3.08/B	352.4
	62	N-[1-(5,5-Difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-methanesulfonamide (single unknown stereoisomer)	4.37 / N 1.03 / A7	386.1

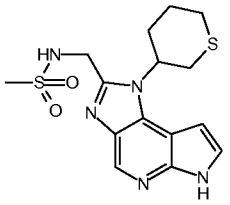
	63	N-[1-(5,5-Difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-methanesulfonamide (single unknown stereoisomer)	4.38 / N 0.65 / A7	386.1
	64	N-{1-[(1S,3R)-3-(2,2,2-Trifluoro-ethylamino)-cyclopentyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-methanesulfonamide	2.48/ O	431.1
	65	N-(1-{(1S,3R)-3-[(2,2-Difluoro-ethyl)-methanesulfonyl-amino]-cyclopentyl}-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl)-methanesulfonamide	5.80/N	491.1
	66	{1-[(1S,3R)-3-(2,2-Difluoro-ethylamino)-cyclopentyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-carbamic acid methyl ester	2.29/O	393.2
	67	trans Ethanesulfonic acid {1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-amide	3.05/N	459.3
	68	trans N-{1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-methanesulfonamide	2.53/N	445.3

	69	trans Cyclopropanesulfonic acid {1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-amide	4.80/O	471.2
	70	trans {1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-carbamic acid methyl ester	2.76/N	425.4
	71	trans {1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-carbamic acid ethyl ester	3.5/N	439.5
	72	trans {1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-carbamic acid tert-butyl ester	5.15/N	467.5
	73	trans {1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-carbamic acid cyclopropylmethyl ester	6.72/N	465.5
	74	trans {1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-carbamic acid isopropyl ester	4.29/O	453.4
	75	(1-Bicyclo[2.2.1]hept-2-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl)-carbamic acid methyl ester (single unknown exo stereoisomer)	1.04/A9 6.91/N	340.4

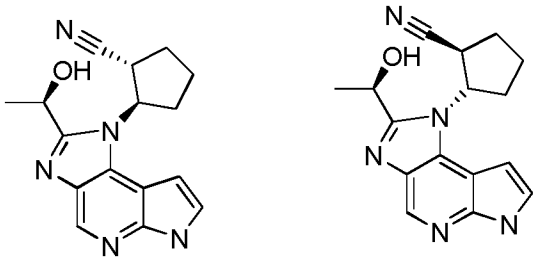
	76	(1-Bicyclo[2.2.1]hept-2-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl)-carbamic acid methyl ester (single unknown exo stereoisomer)	1.21/A9 6.93 /N	340.4
	77	trans 2-Methyl-propane-1-sulfonic acid {1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-amide	4.97/N	487.4
	78	Ethanesulfonic acid (1-bicyclo[2.2.1]hept-2-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl)-amide (single unknown exo stereoisomer)	0.61/A12 7.41/N	374.4
	79	Ethanesulfonic acid (1-bicyclo[2.2.1]hept-2-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl)-amide (single unknown exo stereoisomer)	0.67/A10 7.41/N	374.4
	80	N-(1-Bicyclo[2.2.1]hept-2-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl)-acetamide (single unknown exo stereoisomer)	0.66/A11 5.74/N	324.4
	81	N-(1-Bicyclo[2.2.1]hept-2-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl)-acetamide (single unknown exo stereoisomer)	0.87/A11 5.73/N	324.4
	82	N-(1-Bicyclo[2.2.1]hept-2-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl)-methanesulfonamide (racemic endo)	3.34/O	360.2

	83	N-(1-Bicyclo[2.2.1]hept-2-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl)-methanesulfonamide (single unknown exo stereoisomer)	0.97/A8 6.74/N	360.1
	84	N-(1-Bicyclo[2.2.1]hept-2-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl)-methanesulfonamide (single unknown exo stereoisomer)	1.19/A8 6.70/N	360.1
	85	[1-(4,4-Difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-ethyl-amine (racemic)	0.826 / K	336.0
	86	N-[1-(-3,3-Difluoro-1-methyl-piperidin-4-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-methanesulfonamide (single unknown stereoisomer)	0.789 / K 8.232 / A13	399.0
	87	N-[1-(-3,3-Difluoro-1-methyl-piperidin-4-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-methanesulfonamide (single unknown stereoisomer)	0.784 / K 9.059 / A13	399.0
	88	N-[1-(-3,3-Difluoro-1-methyl-piperidin-4-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-methanesulfonamide (single unknown stereoisomer)	0.972 / K 1.281 / A14	385.9
	89	N-[1-(-3,3-Difluoro-1-methyl-piperidin-4-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-methanesulfonamide (single unknown stereoisomer)	0.977 / K 1.406 / A14	385.9

	90	Ethanesulfonic acid [1-(-4,4-difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-amide (single unknown stereoisomer)	0.946 / K 7.66 / A15	400.0
	91	Ethanesulfonic acid [1-(-4,4-difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-amide (single unknown stereoisomer)	0.944 / K 8.32 / A15	400.1
	92	Cyclopropanesulfonic acid [1-(-4,4-difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-amide (single unknown stereoisomer)	0.988 / K 8.77 / A16	412.0
	93	Cyclopropanesulfonic acid [1-(-4,4-difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-amide (single unknown stereoisomer)	0.988 / K 9.39 / A16	412.0
	94	[1-(4,4-Difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-carbamic acid methyl ester (single unknown stereoisomer)	0.956 / K 7.828 / A13	366.0
	95	[1-(4,4-Difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-carbamic acid methyl ester (single unknown stereoisomer)	0.954 / K 9.357 / A13	366.0
	96	N-[1-(Tetrahydro-thiopyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-methanesulfonamide (single unknown stereoisomer)	89	5.10 / N 1.06/ A5

	97	N-[1-(Tetrahydro-thiopyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-methanesulfonamide (single unknown stereoisomer)	89	5.09 / N 0.85 / A5

Examples 98 and 99



Trans 2-[2-((R)-1-Hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentanecarbonitrile (absolute stereochemistry of cyclopentanes is unknown, relative stereochemistry is trans).

A mixture of 1-benzenesulfonyl-4-chloro-5-nitro-1H-pyrrolo[2,3-b]pyridine (2.00 g, 5.9 mmol), 2-Amino-cyclopentanecarbonitrile (0.98 g, 8.9 mmol) and diisopropylethylamine (2.0 mL, 11.8 mmol) in isopropyl alcohol was heated at 90 °C for 20h. The reaction mixture was cooled and the solid was collected by filtration, washed with water and dried in vac-oven at 50 °C to afford *trans*-2-(1-benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-cyclopentanecarbonitrile (1.4 g, 57%): LC/MS (Method G, ESI): RT = 1.15 min, m+H = 412.2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (d, *J* = 5.2 Hz, 1H), 9.04 (d, *J* = 7.3 Hz, 1H), 8.21 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 4.1 Hz, 1H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 2H), 6.92 (d, *J* = 4.1 Hz, 1H), 4.82 – 4.72 (m, 1H), 2.94 (dt, *J* = 8.3, 4.2 Hz, 1H), 2.50 – 1.77 (m, 6H).

The filtrate from above was diluted with water, and extracted with ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulfate and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (0-10% EtOAc/heptane) afforded *cis*-2-(1-benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-cyclopentanecarbonitrile (0.5 g g, 20%). LC/MS (Method G, ESI): RT = 1.13 min, m+H = 412.2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (d, *J* = 8.1 Hz, 1H), 9.13 (s, 1H), 8.20 (d, *J* = 7.9 Hz, 2H), 7.70 – 7.47 (m, 4H), 6.70 (d, *J* = 4.1 Hz, 1H), 4.73 – 4.61 (m, 1H), 3.30 – 3.12 (m, 1H), 2.38 – 1.77 (m, 6H).

2-[6-Benzenesulfonyl-2-((R)-1-hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentanecarbonitrile

A suspension of *trans*-2-(1-Benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-cyclopentanecarbonitrile (1.3 g, 3.2 mmol) and palladium on carbon (0.30 g, 10%, wet, Degussa, E101 NE/W) in a 2:1 mixture of THF and ethanol (60 ml) was stirred under a hydrogen atmosphere at 50 °C for 24 h. The reaction mixture was cooled to 25 °C, filtered through Celite, and the Celite was washed with THF (2 x 20 ml). The filtrate were concentrated under reduced pressure to afford crude trans-2-(5-amino-1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-cyclopentanecarbonitrile as foam. This material was used in the next step below without further purification or characterization.

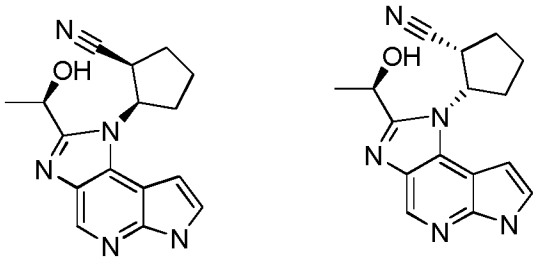
Triethyloxonium tetrafluoroborate (1.30 g, 6.8 mmol) was added to a solution of (*R*)-(+)-lactamide (0.61 g, 6.8 mmol) in THF (40 ml) at 25 °C. The resulting suspension was stirred at 25 °C for 1.5 h and then was concentrated under reduced pressure to afford an oil. This material was dissolved in EtOH (30 ml) at 25 °C and added to *trans*-2-(5-amino-1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-cyclopentanecarbonitrile (1.3 g, 3.4 mmol) of was added. The reaction mixture was heated at 80 °C for 0.5 h, then was cooled to 25 °C and concentrated under reduced pressure. The residue was dissolved in EtOAc and washed with half-saturated $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure. Purification of the resulting solid by column chromatography on silica gel (gradient: 0 to 5% CH_3OH in CH_2Cl_2) and trituration of the residue with ethyl acetate/heptane afforded trans-2-[6-benzenesulfonyl-2-((R)-1-hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentanecarbonitrile (0.6 g, 40 %) as a off-white solid. LC/MS (Method G: RT = 0.90 min, m+H = 436.2.

A mixture of trans-2-[6-benzenesulfonyl-2-((R)-1-hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentanecarbonitrile (0.6 g, 1.3 mmol) and potassium carbonate (0.4 g, 2.8 mmol) in methanol was stirred at 40 °C for 48h and then cooled and concentrated under reduced pressure. The residue was dissolved in EtOAc, washed with water, brine, dried over sodium sulfate and concentrated. Purification by chiral SFC afforded the two diastereomers.

Peak #1 (Ex No. 98): SFC (Method A5): RT = 0.75 min, LC/MS (Method O, ESI): 3.00 min, m+H = 296.2.1H NMR (400 MHz, DMSO) δ 11.97 (s, 1H), 9.34 – 9.26 (m, 1H), 8.61 (s, 1H), 7.51 (t, J = 3.0 Hz, 1H), 6.53 (s, 1H), 5.81 (d, J = 7.1 Hz, 1H), 5.68 – 5.56 (m, 1H), 5.19 – 5.06 (m, 1H), 3.78 – 3.62 (m, 1H), 3.49 – 3.39 (m, 1H), 2.64 – 2.53 (m, J = 8.6, 4.3 Hz, 1H), 2.45 – 1.97 (m, 5H), 1.69 (d, J = 6.4 Hz, 3H).

Peak #1 (Ex No 99): SFC (Method A5): RT = 1.17 min,. LC/MS (Method O, ESI): 2.99 min, m+H = 296.2.1H NMR (400 MHz, DMSO) δ 11.96 (s, 1H), 8.59 (s, 1H), 7.51 (t, J = 3.0 Hz, 1H), 6.52 (s, 1H), 5.82 (d, J = 6.1 Hz, 1H), 5.76 – 5.35 (m, 1H), 5.23 – 5.05 (m, 1H), 3.90 – 3.56 (m, 1H), 2.74 – 2.56 (m, 1H), 2.38 – 1.97 (m, 5H), 1.68 (d, J = 6.9 Hz, 3H).

Exampes 100 and 101



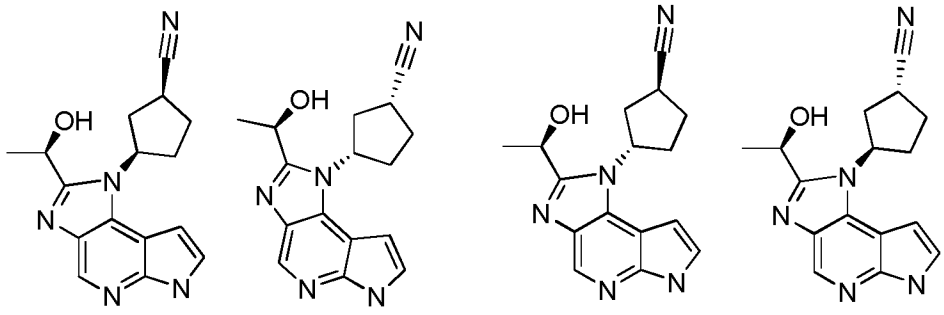
Cis 2-[2-((R)-1-Hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentanecarbonitrile (single stereoisomers: absolute stereochemistry of cyclopentanes is unknown, relative stereochemistry is cis)

These were synthesized following the procedure described in Examples 98 and 99, using cis-2-(1-benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-cyclopentanecarbonitrile, and the diastereomers were separated by SFC.

Peak#1 (100): SFC (Method A5): RT = 0.74 min. LC/MS (Method O, ESI): RT = 3.02, m+H = 296.2. 1H NMR (400 MHz, DMSO) δ 11.97 (s, 1H), 8.61 (s, 1H), 7.51 (t, J = 3.0 Hz, 1H), 6.53 (s, 1H), 5.80 (d, J = 7.1 Hz, 1H), 5.70 – 5.50 (m, 1H), 5.21 – 5.06 (m, 1H), 3.75 – 3.63 (m, 1H), 2.56 (dd, J = 8.7, 4.3 Hz, 1H), 2.46 – 1.99 (m, 5H), 1.69 (d, J = 6.4 Hz, 3H).

Peak#2 (101): SFC (Method A5): RT = 1.14 min LC/MS(Method O, ESI): RT = 2.99, m+H = 296.2.1H NMR (400 MHz, DMSO) δ 11.96 (s, 1H), 8.59 (s, 1H), 7.51 (t, J = 3.0 Hz, 1H), 6.51 (d, J = 7.8 Hz, 1H), 5.82 (d, J = 6.1 Hz, 1H), 5.74 – 5.63 (m, 1H), 5.23 – 5.09 (m, 1H), 3.87 – 3.67 (m, 1H), 2.70 – 2.56 (m, 1H), 2.35 – 1.92 (m, 5H), 1.68 (d, J = 7.0 Hz, 3H).

Examples 102, 103, 104 and 105

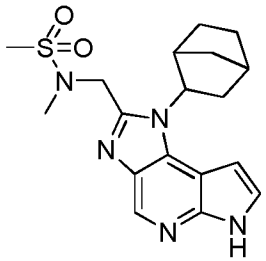


(R)-3-[2-(1-Hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentanecarbonitrile (single stereoisomers: stereochemistry of cyclopentanes is unknown)

A mixture of 1-benzenesulfonyl-4-chloro-5-nitro-1H-pyrrolo[2,3-b]pyridine (2.00 g, 5.9 mmol), 2-Amino-cyclopentanecarbonitrile (0.78 g, 7.2 mmol) and diisopropylethylamine (2.05 mL, 11.8 mmol) in isopropyl alcohol was heated at 90 °C for 20h and cooled. The reaction mixture was diluted with water and the solid collected by filtration. The solid was dissolved in DCM, washed with water, brine dried over sodium sulfate and concentrated under reduced pressure. Trituration with EtOAc/heptane afforded a while solid of cis/trans mixture of 3-(1-Benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-cyclopentanecarbonitrile (2.2 g, 90%) as a yellow solid. LC/MS (Method G, ESI): RT = 1.09, 1.12 min, m+H = 412.2

This mixture was carried on to the final products, as described above for Examples 92 and 93, and the four diastereomers were separated by chiral SFC. LC/MS (Method A12, ESI): four single isomers, RT = 0.82, 0.88, 1.1 and 1.37 mins, m+H = 296.2. (Method O, ESI): RT = 2.75, 2.77, 2.77, 2.80, m+H = 296.2.

Example 106



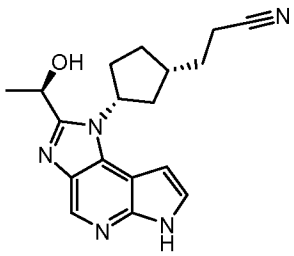
N-(1-Bicyclo[2.2.1]hept-2-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl)-N-methyl-methanesulfonamide (racemic exo)

A mixture of 6-benzenesulfonyl-1-bicyclo[2.2.1]hept-2-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl)-methanesulfonamide (0.2 g, 0.4 mmol), iodomethane (0.2 mL, 3.2 mmol) and potassium carbonate (0.11 g, 0.8 mmol) in DMF (5 mL) was heated at 50 °C for 20h.

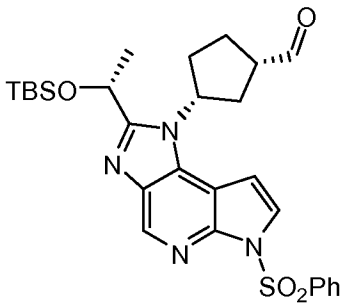
The reaction mixture was cooled, diluted with water, extracted with ethyl acetate, brine, dried over sodium sulfate and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (50-100% EtOAc/heptane) afforded 6-benzenesulfonyl-1-bicyclo[2.2.1]hept-2-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl)-N-methyl-methanesulfonamide (0.11 g, 53%).

A mixture of 6-benzenesulfonyl-1-bicyclo[2.2.1]hept-2-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl)-N-methyl-methanesulfonamide (0.11 g, 0.2 mmol), aqueous sodium hydroxide (0.5 mL, 1M) and ethanol (2 mL) was heated at 60 °C for 1h. The reaction mixture was cooled, concentrated and the purification of the residue by column chromatography and trituration of the residue with ethyl acetate afforded N-(1-Bicyclo[2.2.1]hept-2-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl)-N-methyl-methanesulfonamide (55 mg, 67%). LC/MS (Method O, ESI): RT = 3.51 min, m+H = 374.2. ^{1}H NMR (400 MHz, DMSO) δ 11.88 (s, 1H), 8.57 (s, 1H), 7.46 (t, *J* = 3.0 Hz, 1H), 6.56 (s, 1H), 4.79 (d, *J* = 6.7 Hz, 1H), 4.65 (t, *J* = 8.6 Hz, 2H), 3.08 (s, 3H), 2.79 (s, 3H), 2.63 (d, *J* = 18.6 Hz, 2H), 2.45 (s, 1H), 2.00 (dd, *J* = 13.5, 9.7 Hz, 2H), 1.59 (s, 3H), 1.42 – 1.20 (m, 2H).

Example 107

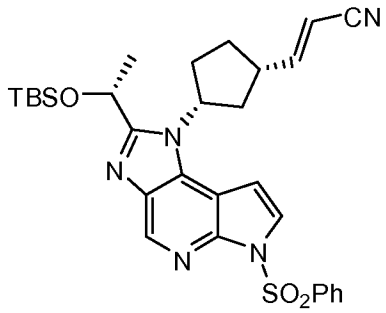


3-{(1R,3R)-3-[2-((R)-1-Hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentyl}-propionitrile



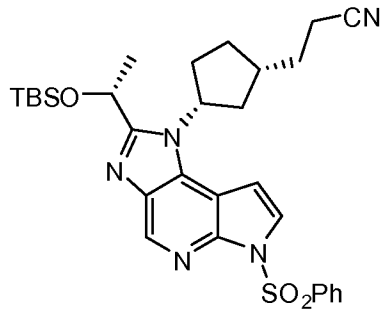
(1S,3R)-3-{6-Benzenesulfonyl-2-[(R)-1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclopentanecarbaldehyde

To a solution of ((1S,3R)-3-{6-Benzenesulfonyl-2-[(R)-1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclopentyl)-methanol (400 mg, 0.72 mmol) in dichloromethane (15 mL) was added Dess-Martin Periodinane (366 mg, 0.86 mmol) at 0 °C. The reaction mixture was stirred at room temperature overnight and purified by column chromatography on silica gel (eluting with hexanes / ethyl acetate = 3: 1) to give (1S,3R)-3-{6-Benzenesulfonyl-2-[(R)-1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclopentanecarbaldehyde (360 mg, yield 90%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.71 (d, 1H), 8.15 (d, 2H), 8.00 (d, 1H), 7.71 (m, 1H), 7.62 (t, 3H), 5.40 – 5.37 (m, 2H), 2.46 – 1.92 (m, 7H), 1.64 (t, 3H), 0.90 (d, 9H), 0.12 – 0.00 (m, 6H).



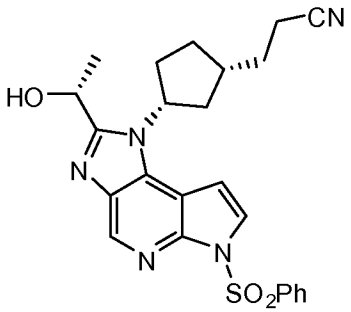
3-((1S,3R)-3-{6-Benzenesulfonyl-2-[(R)-1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclopentyl)-acrylonitrile

To the solution of sodium hydride (54.7 mg, 2.28 mmol) in THF (8 mL) was added Cyanomethyl-phosphonic acid diethyl ester (345 mg, 1.95 mmol), and the mixture was stirred at room temperature for 1 h. A solution of (1S,3R)-3-{6-Benzenesulfonyl-2-[(R)-1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclopentanecarbaldehyde (360 mg, 0.65 mmol) in tetrahydrofuran (2 mL) was added, and then the reaction was stirred at room temperature for another 1 h. To the reaction mixture was added water, followed by extraction with ethyl acetate. The organic phase was concentrated to give 3-((1S,3R)-3-{6-Benzenesulfonyl-2-[(R)-1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclopentyl)-acrylonitrile (320 mg, yield 85%). This material was used in the next step without additional purification or characterization.



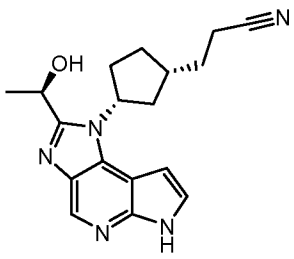
3-((1R,3R)-3-{6-Benzenesulfonyl-2-[(R)-1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclopentyl)-propionitrile

To the solution of 3-((1S,3R)-3-{6-Benzenesulfonyl-2-[(R)-1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclopentyl)-acrylonitrile (320 mg, 0.56 mmol) in ethanol (8 mL) was added palladium on carbon (10%, 50 mg,), and the mixture was stirred at room temperature under a hydrogen balloon for 1 h. The catalyst was filtered off and the filtrate was concentrated to give 3-((1R,3R)-3-{6-Benzenesulfonyl-2-[(R)-1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclopentyl)-propionitrile (300 mg, yield 93%). LCMS (Method K, ESI): RT = 1.709 min, m+H = 578.2.



3-{(1R,3R)-3-[6-Benzenesulfonyl-2-((R)-1-hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentyl}-propionitrile

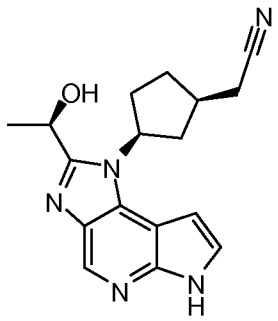
To the solution of 3-((1R,3R)-3-{6-Benzenesulfonyl-2-[(R)-1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclopentyl)-propionitrile (240 mg, 0.424 mmol) in tetrahydrofuran (5mL) was added tetrabutylammonium fluoride (500 mg, 0.234 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate and washed with water (5 mL) three times. This material was used in the next step without additional purification or characterization.



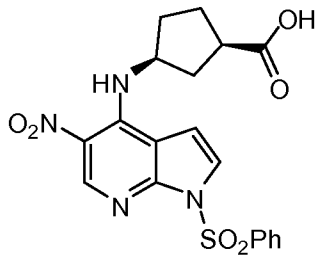
3-{(1R,3R)-3-[2-((R)-1-Hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentyl}-propionitrile

To the solution of 3-{(1R,3R)-3-[6-Benzenesulfonyl-2-((R)-1-hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentyl}-propionitrile (170 mg, 0.378 mmol) in methanol (20 mL) was added a solution of sodium hydroxide (151 mg, 3.78 mmol) in water (5 mL). The reaction mixture was stirred at 60 °C for 2 h. The reaction mixture was neutralized with 1M hydrochloric acid and purified by HPLC ($CH_3CN/H_2O/NH_3H_2O$) to give 3-{(1R,3R)-3-[2-((R)-1-Hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentyl}-propionitrile (25.6 mg, yield 12.5% for three steps). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.99 (s, 1H), 8.57 (s, 1H), 7.48 (d, 1H), 6.55 (d, 1H), 5.71 (br, 1H), 5.39 – 5.29 (m, 1H), 5.17 – 5.12 (m, 1H), 2.67 (t, 2H), 2.41 – 1.77 (m, 9H), 1.97 – 1.84 (m, 1H), 1.64 (d, 3H). LCMS (Method K, ESI): RT = 0.976 min, m+H = 324.1.

Example 108



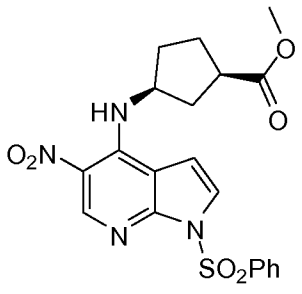
{(1R,3S)-3-[2-((R)-1-Hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentyl}-acetonitrile



(1R,3S)-3-(1-Benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-cyclopentanecarboxylic acid

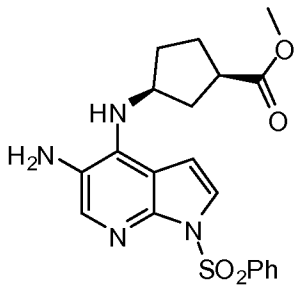
To a solution of 1-Benzenesulfonyl-4-chloro-5-nitro-1H-pyrrolo[2,3-b]pyridine (3.35 g, 10.23 mmol) in ethanol (50 mL) was added (1R,3S)-3-Amino-cyclopentanecarboxylic acid (1.20 g, 9.30 mmol) and Diisopropylethylamine (3.96 g, 30.96 mmol). The reaction mixture was heated at 80 °C for 3 h. After being cooled room temperature, the mixture was condensed and the residue was purified by column chromatography on silica gel (eluting with 10% to 30% ethyl acetate in petroleum ether) to give compound 3 (4.00 g, yield 93.7%). LCMS (Method K, ESI):

RT = 1.300 min, m+H = 430.9. This material was used in the next step below without additional characterization.



(1R,3S)-3-(1-Benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-cyclopentanecarboxylic acid methyl ester

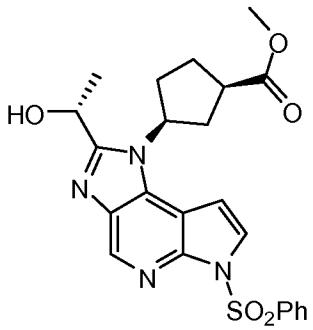
A solution of (1R,3S)-3-(1-Benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-cyclopentanecarboxylic acid (4.00 g, 9 mmol) and thionyl chloride (2 mL) in methanol (60 mL) was heated at 80 °C for 1 hour. Then the resulting mixture was concentrated under vacuum to give (1R,3S)-3-(1-Benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-cyclopentanecarboxylic acid methyl ester (3.60 g, yield 87%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 9.23 (d, J = 4.0 Hz, 1H), 9.10 (s, 1H), 8.21 (d, J = 8.0 Hz, 2H), 7.61 – 7.59 (m, 2H), 7.54 – 7.52 (m, 2H), 6.81 (d, J = 4.0 Hz, 1H), 4.54 (m, 1H), 3.72 (s, 3H), 3.02 – 2.98 (m, 1H), 2.46 – 2.38 (m, 1H), 2.13 – 2.11 (m, 4H), 1.97 – 1.92 (m, 1H).



(1R,3S)-3-(5-Amino-1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-cyclopentanecarboxylic acid methyl ester

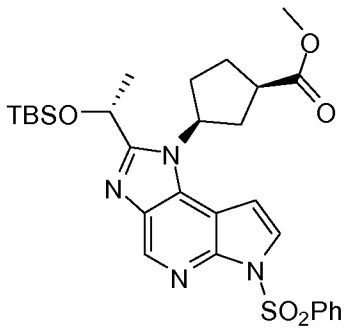
A solution of (1R,3S)-3-(1-Benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-cyclopentanecarboxylic acid methyl ester (3.6 g, 8.1 mmol), ammonium chloride (2.8 g, 40.5 mmol) and iron powder (1.8 g, 32.4 mmol) in methanol (30 mL) and water (10 mL) was heated at 80 °C for 3 h. After being cooled to room temperature, the resulting mixture was filtered and the filtrate was concentrated. The residue was dissolved in ethyl acetate. The solution was washed with water and brine. The organic layer was dried over sodium sulfate, filtered and concentrated under vacuum to give (1R,3S)-3-(5-Amino-1-benzenesulfonyl-1H-

pyrrolo[2,3-b]pyridin-4-ylamino)-cyclopentanecarboxylic acid methyl ester (2.0 g, yield 60%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.12 – 8.10 (m, 2H), 7.78 (s, 1H), 7.51 – 7.49 (m, 1H), 7.44 – 7.40 (m, 3H), 6.60 (d, J = 8.0 Hz, 1H), 5.23 – 5.22 (brs, 1H), 4.37 (brs, 1H), 3.66 (s, 3H), 2.98 – 2.92 (m, 1H), 2.16 – 2.18 (m, 2H), 2.14 (m, 1H), 2.10 – 2.05 (m, 2H), 1.95 – 1.91 (m, 2H).



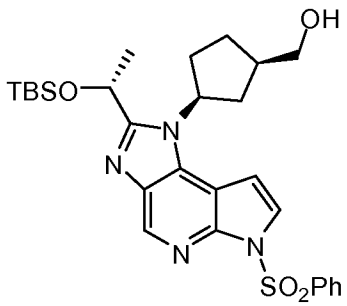
(1R,3S)-3-[6-Benzenesulfonyl-2-((R)-1-hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentanecarboxylic acid methyl ester

A solution of (R)-2-Hydroxy-propionamide (2.14 g, 24 mmol) and Triethyl-oxonium tetrafluoroborate (4.56 g, 24 mmol) in tetrahydrofuran (30 mL) was stirred at room temperature for 2 hours, and the mixture was concentrated under vacuum. The residue was mixed with (1R,3S)-3-(5-Amino-1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-cyclopentanecarboxylic acid methyl ester (2.0 g, 4.8 mmol) in ethanol (30 mL). The mixture was heated at 80 °C for 2 hours. The resulting mixture was concentrated under vacuum and extracted with ethyl acetate. The organic layer was washed with water, then dried over sodium sulfate, filtered and concentrated under vacuum to give (1R,3S)-3-[6-Benzenesulfonyl-2-((R)-1-hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentanecarboxylic acid methyl ester (2.1 g, yield 93%). This material was used in the next step below without additional purification or characterization.



(1R,3S)-3-{6-Benzenesulfonyl-2-[(R)-1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclopentanecarboxylic acid methyl ester

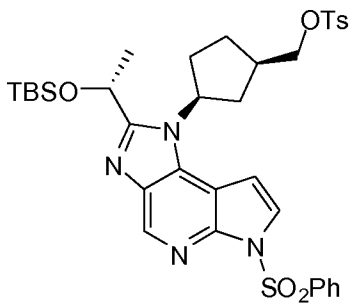
To a solution of (1R,3S)-3-[6-Benzenesulfonyl-2-((R)-1-hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentanecarboxylic acid methyl ester (2.10 g, 4.49 mmol) and imidazole (611 mg, 8.98 mmol) in anhydrous dichloromethane (40 mL) was added tert-Butyl-chloro-dimethyl-silane (1.02 g, 6.74 mmol), and the reaction mixture was stirred at room temperature overnight. The resulting mixture was washed with water and brine, dried over sodium sulfate and purified by column chromatography on silica gel (eluting with 10% to 30% ethyl acetate in petroleum ether) to give (1R,3S)-3-{6-Benzenesulfonyl-2-[(R)-1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclopentanecarboxylic acid methyl ester (2.17 g, yield 83%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.85 (s, 1H), 8.25 – 8.23 (d, J = 8.4 Hz, 2H), 7.86 – 7.84 (m, 1H), 7.57 – 7.53 (m, 1H), 7.49 – 7.45 (m, 2H), 7.05 – 7.01 (m, 1H), 5.66 – 5.62 (m, 1H), 5.41 – 5.35 (q, J = 6.8 Hz, 1H), 3.78 (s, 3H), 3.07 – 3.00 (m, 1H), 2.71 – 2.62 (m, 1H), 2.47 – 2.18 (m, 5H), 1.63 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.12 (s, 3H), 0.01(s, 3H).



((1R,3S)-3-{6-Benzenesulfonyl-2-[(R)-1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclopentyl)-methanol

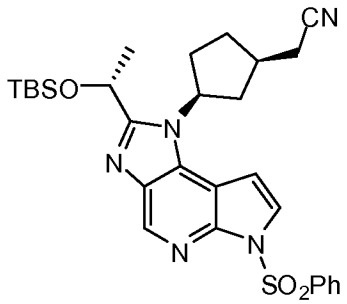
To a solution of (1R,3S)-3-{6-Benzenesulfonyl-2-[(R)-1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclopentanecarboxylic acid methyl ester (2.17 g, 3.72 mmol) in ethanol (20 mL) was added sodium borohydride (1.38 g, 37.2 mmol) and the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, and the residue was extracted with ethyl acetate and water. The organic layer was concentrated under vacuum, and purified by column chromatography on silica gel (eluting with 10% to 80% ethyl acetate in petroleum ether) to give ((1R,3S)-3-{6-Benzenesulfonyl-2-[(R)-1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclopentyl)-methanol (0.90 g, yield 45%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.82 (s, 1H), 8.20 (d, J = 8.8 Hz, 2H), 7.81 (d, J = 4.0 Hz, 1H), 7.57 – 7.53 (m, 1H), 7.49 – 7.45 (m, 2H), 6.96 (d, J = 4.0 Hz, 1H), 5.63 – 5.55 (m, 1H), 5.35 (q, J = 6.8 Hz, 1H), 3.80 (d, J = 4.8 Hz,

2H), 2.36 – 2.24 (m, 5H), 2.18 – 2.05 (m, 2H), 1.61 (d, J = 6.8 Hz, 3H), 0.86 (s, 9H), 0.10 (s, 3H), 0.04 (s, 3H).



Toluene-4-sulfonic acid (1R,3S)-3-{6-benzenesulfonyl-2-[(R)-1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclopentylmethyl ester

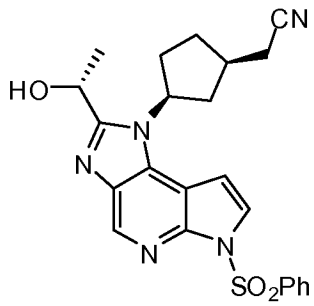
To a solution of ((1R,3S)-3-{6-Benzenesulfonyl-2-[(R)-1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclopentyl)-methanol (800 mg, 1.44 mmol) and 4-dimethylaminopyridine (351 mg, 2.88 mmol) in dichloromethane (30 mL) was added 4-Methyl-benzenesulfonyl chloride (549 mg, 2.88 mmol) and the mixture was stirred at room temperature for 30 hours. Then the reaction mixture was extracted with dichloromethane, concentrated under vacuum, purified by column chromatography (eluting with 10% to 30% ethyl acetate in petroleum ether) to give Toluene-4-sulfonic acid (1R,3S)-3-{6-benzenesulfonyl-2-[(R)-1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclopentylmethyl ester (720 mg, yield 70%). LCMS (Method J, ESI): RT = 1.410 min, m+H = 709.2.



((1R,3S)-3-{6-Benzenesulfonyl-2-[(R)-1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclopentyl)-acetonitrile

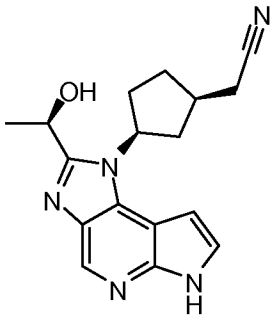
To a solution of Toluene-4-sulfonic acid (1R,3S)-3-{6-benzenesulfonyl-2-[(R)-1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclopentylmethyl ester (300 mg, 0.42 mmol) in DMSO (15 mL) and water (2 mL) was added potassium cyanide (136 mg, 2.1 mmol). The reaction mixture was heated at 60 °C for 3 h, and quenched with aqueous

sodium hydroxide solution. The mixture was extracted with ethyl acetate. The organic layer was concentrated and the residue was purified by column chromatography on silica gel (eluting with 10% to 50% ethyl acetate in petroleum ether) to give ((1R,3S)-3-{6-Benzenesulfonyl-2-[(R)-1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclopentyl)-acetonitrile (200 mg, yield 84%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.90 (s, 1H), 8.31 – 8.28 (m, 2H), 7.91 – 7.89 (m, 1H), 7.63 – 7.59 (m, 1H), 7.55 – 7.51 (m, 2H), 6.86 – 6.84 (m, 1H), 5.75 – 5.71 (m, 1H), 5.43 – 5.35 (q, J = 6.8 Hz, 1H), 2.68 (d, J = 4.8 Hz, 2H), 2.51 – 2.47 (m, 2H), 2.40 – 2.33 (m, 3H), 2.30 – 2.24 (m, 1H), 2.10 – 2.09 (m, 1H), 1.65 (d, J = 6.8 Hz, 3H), 0.94 (s, 9H), 0.17 (s, 3H), 0.04 (s, 3H).



{(1R,3S)-3-[6-Benzenesulfonyl-2-((R)-1-hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentyl}-acetonitrile

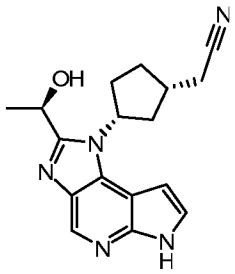
To a solution of ((1R,3S)-3-{6-Benzenesulfonyl-2-[(R)-1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclopentyl)-acetonitrile (200 mg, 0.36 mmol) in tetrahydrofuran (15 mL) was added tetrabutylammonium fluoride (173 mg, 0.72 mmol). The reaction mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate. The organic solution was washed with water and brine, dried over sodium sulfate and concentrated under vacuum to give {(1R,3S)-3-[6-Benzenesulfonyl-2-((R)-1-hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentyl}-acetonitrile (100 mg, yield 63%). LCMS (Method J, ESI): RT = 0.895 min, m+H = 450.1.



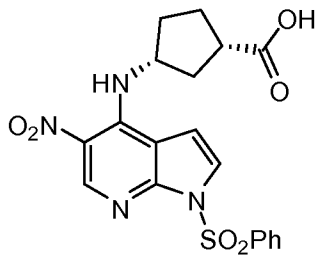
{(1R,3S)-3-[2-((R)-1-Hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentyl}-acetonitrile

To a solution of {(1R,3S)-3-[6-Benzenesulfonyl-2-((R)-1-hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentyl}-acetonitrile (100 mg, 0.22 mmol) in methanol (20 mL) was added aqueous sodium hydroxide solution (2 N, 10 mL). Then the reaction mixture was heated at 60 °C for 3 hours, and neutralized with 1M aqueous hydrochloric acid. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified by a reverse-phase preparatory HPLC ($CH_3CN/H_2O/NH_3H_2O$) to give {3-[2-((R)-1-Hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentyl}-acetonitrile (50 mg, yield 69%). ^1H NMR (DMSO-d_6, 400 MHz) δ: 11.86 (brs, 1H), 8.55 (s, 1H), 7.44 (d, J = 3.2 Hz, 1H), 6.66 (d, J = 3.2 Hz, 1H), 5.72 – 5.70 (m, 1H), 5.43 – 5.38 (m, 1H), 5.13 (q, J = 6.4 Hz, 1H), 2.82 (d, J = 6.4 Hz, 2H), 2.21 – 2.18 (m, 2H), 2.16 (m, 4H), 1.93 – 1.90 (m, 1H), 1.63 (d, J = 6.4 Hz, 3H). LCMS (Method K, ESI): RT = 0.918 min, m+H = 310.1.

Example 109



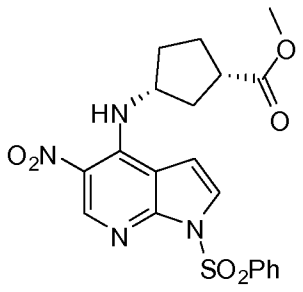
{(1S,3R)-3-[2-((R)-1-Hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentyl}-acetonitrile



(1S,3R)-3-(1-Benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-cyclopentanecarboxylic acid

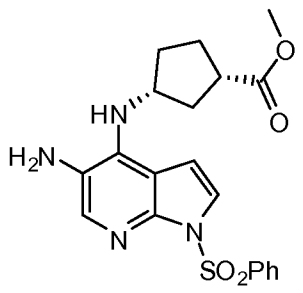
To a solution of 1-Benzenesulfonyl-4-chloro-5-nitro-1H-pyrrolo[2,3-b]pyridine (2.47 g, 7.35 mmol) in ethanol (30 mL) was added (1S,3R)-3-Amino-cyclopentanecarboxylic acid (1.0 g, 7.74 mmol) and Diisopropylethylamine (3 g, 23.2 mmol). The reaction mixture was stirred at 80

°C for 3 h. The reaction mixture was cooled to 0 °C, and the desired product crystallized from the solvent (3.4 g, yield 96%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.25 (s, 1H), 9.01 (m, 1H), 8.99 (s, 1H), 8.12 (m, 2H), 7.77 (m, 1H), 7.73 (m, 1H), 7.62 (m, 2H), 7.12 (m, 1H), 4.61 – 4.52 (m, 1H), 2.90 – 2.82 (m, 1H), 2.33 – 1.65 (m, 6H).



(1S,3R)-3-(1-Benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-cyclopentanecarboxylic acid methyl ester

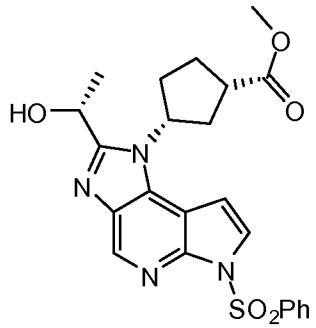
To a solution of (1S,3R)-3-(1-Benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-cyclopentanecarboxylic acid (3.4 g, 7.9 mmol) in methanol (60 mL) was added thionyl chloride (0.94 g, 7.9 mmol) in THF, and the reaction mixture was heated at 60 °C for 1 h. The resulting mixture was concentrated under reduced pressure. The residue was washed by ethyl acetate to give (1S,3R)-3-(1-Benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-cyclopentanecarboxylic acid methyl ester (3.35 g, yield 96%). ^{1}H NMR (DMSO- d_6, 400 MHz) : 8.98 (d, J = 7.2 Hz, 1H), 8.87 (s, 1H), 8.12 (d, J = 7.6 Hz, 2H), 7.79 (s, 1H), 7.75 (t, 1H), 7.65 (t, J = 7.2 Hz, 2H), 7.14 (d, J = 8.4 Hz, 1H), 4.60 – 4.59 (m, 1H), 3.57 (s, 3H), 3.00 – 2.97 (m, 1H), 2.38 – 1.75 (m, 6H).



(1S,3R)-3-(5-Amino-1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-cyclopentanecarboxylic acid methyl ester

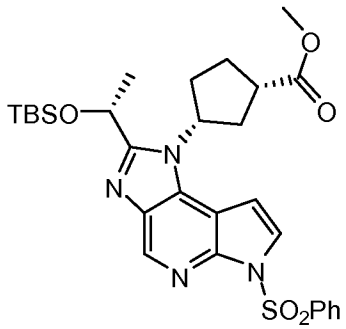
To a solution of (1S,3R)-3-(1-Benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-cyclopentanecarboxylic acid methyl ester (3.35 g, 7.54 mmol) in ethanol (20 mL) was added palladium on carbon (350 mg, 10%), and the mixture was stirred at room temperature under a hydrogen balloon overnight. The catalyst was filtered off and the filtrate was

concentrated under reduce pressure to give (1S,3R)-3-(5-Amino-1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-cyclopentanecarboxylic acid methyl ester (3.0 g, yield 87%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.02 (m, 2H), 7.68 (m, 1H), 7.59 (m, 3H), 7.47 (m, 1H), 6.81 (m, 1H), 5.31 (m, 1H), 4.49 – 4.26 (m, 3H), 3.59 (s, 3H), 2.92 – 2.88 (m, 1H), 2.30 – 1.58 (m, 6H).



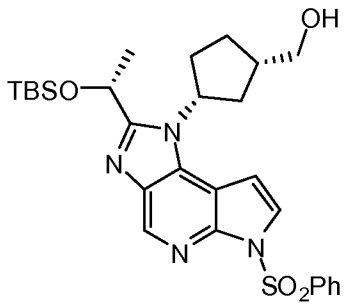
(1S,3R)-3-[6-Benzenesulfonyl-2-((R)-1-hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentanecarboxylic acid methyl ester

To a solution of (R)-2-Hydroxy-propionamide (1.9 g, 21.71 mmol) in THF (5 mL) was added Triethyl-oxonium tetrafluoroborate (4.2 g, 21.71 mmol), and the reaction mixture was stirred at room temperature for 1 h. A solution of (1S,3R)-3-(5-Amino-1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-cyclopentanecarboxylic acid methyl ester (1.5 g, 3.62 mmol) in ethanol (25 mL) was added. The reaction mixture was stirred at 90 °C for another 3 hours. After being cooled to room temperature, the reaction mixture was concentrated and the residue was dissovled in ethyl acetate. The organic solution was washed with water and brine, dried over sodium sulfate and purified by column chromatography on silica gel (eluting with hexanes / ethyl acetate = 1: 1) to give (1S,3R)-3-[6-Benzenesulfonyl-2-((R)-1-hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentanecarboxylic acid methyl ester (1.46 g, yield 93%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.72 (s, 1H), 8.16 (m, 2H), 8.05 (m, 1H), 7.73 (m, 1H), 7.64 (m, 2H), 7.07 (m, 1H), 5.78 (m, 1H), 5.42 – 5.31 (m, 1H), 5.16 (m, 1H) 3.71 (s, 3H), 3.21 – 3.09 (s, 1H), 2.46 – 2.17 (m, 6H), 1.62 (m, 3H).



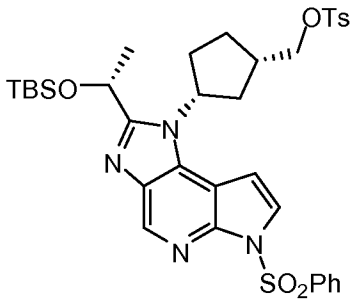
(1S,3R)-3-{6-Benzenesulfonyl-2-[(R)-1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclopentanecarboxylic acid methyl ester

To a solution of (1S,3R)-3-[6-Benzenesulfonyl-2-((R)-1-hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentanecarboxylic acid methyl ester (1.46 g, 3.12 mmol) in anhydrous dichloromethane (20 mL) was added tert-Butyl-chloro-dimethyl-silane (702 mg, 4.68 mmol) and imidazole (424 mg, 6.24 mmol), and the reaction mixture was stirred at room temperature overnight. The resulting mixture was washed with water and brine, dried over sodium sulfate and purified by column chromatography on silica gel (eluting with hexanes / ethyl acetate = 3: 1) to give (1S,3R)-3-{6-Benzenesulfonyl-2-[(R)-1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclopentanecarboxylic acid methyl ester (1.6 g, yield 93%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.72 (s, 1H), 8.19 (m, 2H), 8.09 (m, 1H), 7.74 (m, 1H), 7.63 (m, 2H), 7.07 (m, 1H), 5.49 – 5.35 (m, 2H), 3.72 (s, 3H), 3.23 – 3.15 (m, 1H), 2.39 – 2.09 (m, 6H), 1.62 – 1.59 (m, 3H), 0.82 (s, 9H), 0.06 (s, 6H).



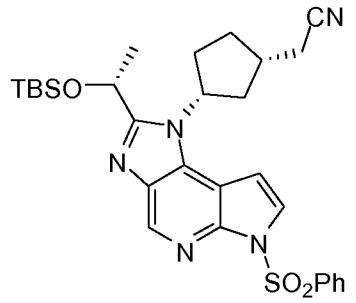
((1S,3R)-3-{6-Benzenesulfonyl-2-[(R)-1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclopentyl)-methanol

To the solution of (1S,3R)-3-{6-Benzenesulfonyl-2-[(R)-1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclopentanecarboxylic acid methyl ester (1.6 g, 2.75mmol) in EtOH (15 mL) was added sodium borohydride (1.04 g, 27.5 mmol) and cerium(III) chloride (0.2 g, 0.82 mmol). Then the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was purified by column chromatography on silica gel (eluting with hexanes / ethyl acetate = 1: 1) to give ((1S,3R)-3-{6-Benzenesulfonyl-2-[(R)-1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclopentyl)-methanol (1.0 g, yield 93%). ^{1}H NMR (DMSO-$_{d6}$, 400 MHz): δ 8.72 (s, 1H), 8.66 (m, 3H), 7.62 (m, 3H), 7.16 (m, 1H), 5.42 – 5.34 (m, 1H), 3.58 (m, 2H), 2.34 – 1.98 (m, 6H), 1.61 (m, 3H), 0.86 (s, 9H), 0.07 (s, 6H).



Toluene-4-sulfonic acid (1S,3R)-3-{6-benzenesulfonyl-2-[(R)-1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclopentylmethyl ester

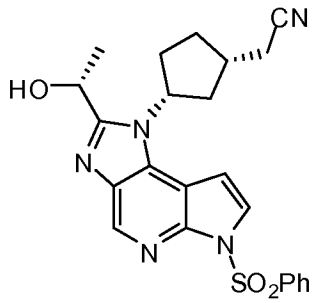
To the solution of ((1S,3R)-3-{6-Benzenesulfonyl-2-[(R)-1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclopentyl)-methanol (400 mg, 0.72 mmol) in dichloromethane (15 mL) was added 4-Methyl-benzenesulfonyl chloride (687 mg, 3.61 mmol) and 4-dimethylaminopyridine (462 mg, 3.61mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was purified by column chromatography on silica gel (eluting with hexanes / ethyl acetate = 3 : 1) to give Toluene-4-sulfonic acid (1S,3R)-3-{6-benzenesulfonyl-2-[(R)-1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclopentylmethyl ester (420 mg, yield 93%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.83 (s, 1H), 8.23 (m, 2H), 7.81 (m, 2H), 7.73 (m, 1H), 7.59 (m, 1H), 7.49 (m, 2H), 7.34 (m, 2H), 6.76 (m, 1H), 5.69 – 5.58 (m, 1H), 5.39 (m, 1H), 4.24 – 4.16 (m, 1H), 2.60 – 2.52 (m, 1H), 2.44 (s, 3H), 2.38 – 1.94 (m, 6H), 1.63- 1.58 (m, 3H), 0.90 – 0.89 (s, 2H), 0.87 (s, 9H), 0.12 (s, 6H).



((1S,3R)-3-{6-Benzenesulfonyl-2-[(R)-1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclopentyl)-acetonitrile

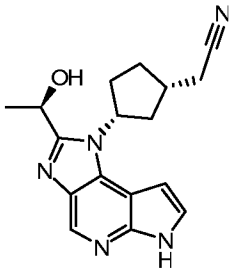
To the solution of Toluene-4-sulfonic acid (1S,3R)-3-{6-benzenesulfonyl-2-[(R)-1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclopentylmethyl ester (400 mg, 0.564 mmol) in DMSO (8 mL) was added a solution of potassium cyanide (92mg, 1.411 mmol) in water (2 mL). The reaction mixture was stirred at 60 °C for 5 h, then a 1M

aqueous solution of sodium carbonate was added, followed by extraction with ethyl acetate. The organic phase was concentrated under reduced pressure and used directly in the next step. LCMS (Method J, ESI): RT = 1.214 min, m+H = 564.1.



{(1S,3R)-3-[6-Benzenesulfonyl-2-((R)-1-hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentyl}-acetonitrile

To the solution of ((1S,3R)-3-{6-Benzenesulfonyl-2-[(R)-1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclopentyl)-acetonitrile (240 mg, 0.424 mmol) in tetrahydrofuran (5 mL) was added tetrabutylammonium fluoride (500 mg, 0.234 mmol). The reaction mixture was stirred at room temperature overnight, then the reaction mixture was extracted with ethyl acetate and washed with water (5 mL) three times. The organic phase was directly used for next step.

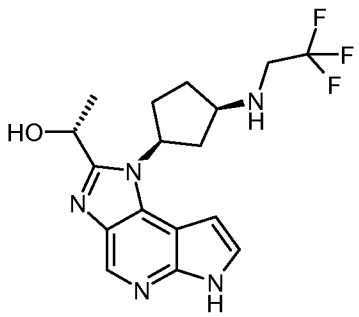


{(1S,3R)-3-[2-((R)-1-Hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentyl}-acetonitrile

To the solution of {(1S,3R)-3-[6-Benzenesulfonyl-2-((R)-1-hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentyl}-acetonitrile (170 mg, 0.378 mmol) in methanol (20 mL) was added a solution of sodium hydroxide (151 mg, 3.78 mmol) in water (5 mL). The reaction mixture was stirred at 60 °C for 2 h. The reaction mixture was neutralized with 1M aqueous hydrochloric acid and purified by HPLC ($CH_3CN/H_2O/NH_3H_2O$) to give {3-[2-((R)-1-Hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentyl}-acetonitrile (25.6 mg, yield 12.5% for three steps). ^1H NMR (DMSO-d_6, 400 MHz): δ 11.87 (s, 1H), 8.58 (s, 1H), 7.45 (d, J = 3.2 Hz, 1H), 6.68 (d, J = 3.2 Hz, 1H), 5.69 (br, 1H), 5.41 – 5.31 (m, 1H), 5.16 – 5.11 (m, 1H), 2.81 (d, J

= 6.4 Hz, 2H), 2.47 – 2.10 (m, 6H), 1.97 – 1.84 (m, 1H), 1.64 (d, J = 6.8 Hz, 3H). LCMS (Method K, ESI): RT = 0.924 min, m+H = 310.1.

Example 110



(R)-1-{1-[(1S,3R)-3-(2,2,2-Trifluoro-ethylamino)-cyclopentyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethanol

((1R,3S)-3-Benzyloxycarbonylamino-cyclopentyl)-carbamic acid tert-butyl ester

A solution of (1S,3R)-3-tert-butoxycarbonylamino-cyclopentanecarboxylic acid (3.09 g, 16.5 mmol) in toluene (30 mL) was treated with triethylamine (2.82 mL, 20.2 mmol), followed by diphenylphosphoryl azide (5.00 g, 18.2 mmol) and the mixture was stirred, under nitrogen, at room temperature for 1 hour. Benzyl alcohol (7.00 mL, 67.5 mmol) was added and the reaction mixture was heated at 85 °C overnight. The solvent was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (gradient: 0 to 40% ethyl actetate in cyclohexane) to afford 4.11 g (91%) of ((1R,3S)-3-benzyloxycarbonylamino-cyclopentyl)-carbamic acid tert-butyl ester as a white solid. LCMS (Method Q, ESI): RT = 3.89 min, m+Na = 357.1; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.28 (m, 5 H), 5.09 (s, 2 H), 5.00 (m, 1 H), 4.70 (m, 1 H), 3.98 (m,1 H), 3.90 (m, 1 H), 2.45-2.34 (m, 1 H), 2.02-1.89 (m, 2 H), 1.64-1.54 (m, 1 H, partially obscured by water), 1.45-1.30 (m, 2 H), 1.44 (s, 9 H).

((1R,3S)-3-Amino-cyclopentyl)-carbamic acid *tert*-butyl ester

A solution of ((1R,3S)-3-benzyloxycarbonylamino-cyclopentyl)-carbamic acid tert-butyl ester (4.11 g, 12.3 mmol) in ethanol (IMS grade, 50 mL) was added to a flask containing palladium hydroxide (20% wt/C, 801 mg, 1.20 mmol) and ethanol (5 mL, IMS grade), under an atmosphere of nitrogen. The reaction mixture was evacuated and stirred under an atmosphere of hydrogen at room temperature overnight. The mixture was filtered through a pad of Celite® and washed through with ethanol (IMS grade). The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (gradient: 0 to10% [2M NH_3 in MeOH] in

DCM) to afford 1.85 g (75%) of ((1R,3S)-3-amino-cyclopentyl)-carbamic acid *tert*-butyl ester as a colourless gum. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.40-5.27 (m, 1 H), 4.08-3.95 (m, 1 H), 2.13-2.03 (m, 1 H), 2.02-1.90 (m, 1 H), 1.89-1.78 (m, 1 H), 1.74-1.60 (m, 1 H), 1.51-1.38 (m, 1 H), 1.44 (s, 9 H), 1.32-1.22 (m, 1 H).

[(1R,3S)-3-(1-Benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-cyclopentyl]-carbamic acid *tert*-butyl ester

A mixture of 1-benzenesulfonyl-4-chloro-5-nitro-1H-pyrrolo[2,3-b]pyridine (3.29 g, 9.74 mmol), ((1R,3S)-3-amino-cyclopentyl)-carbamic acid *tert*-butyl ester (1.86 g, 9.27 mmol) and DIPEA (2.42 mL, 13.9 mmol) in propan-2-ol (35 mL) was heated at reflux (90°C) for 2.5 hours. After cooling, the solvent was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (gradient: 0 to 50% ethyl acetate in cyclohexane) to afford 3.54 g (73%) of [(1R,3S)-3-(1-benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-cyclopentyl]-carbamic acid *tert*-butyl ester as a yellow solid. LCMS (Method Q, ESI): RT = 4.36 min, m+H = 502.0; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.15 (m, 1 H), 9.10 (s, 1 H), 8.20 (m, 2 H), 7.66-7.58 (m, 2 H), 7.53 (m, 2 H), 6.79 (d, 1 H), 4.59 (m, 1 H), 4.45 (m, 1 H), 4.09 (m, 1 H), 2.70-2.58 (dt, 1 H), 2.23-2.10 (m, 2 H), 1.94-1.83 (m, 1 H), 1.74-1.58 (m, 2 H, partially obscured by water), 1.43 (s, 9 H).

[(1R,3S)-3-(5-Amino-1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-cyclopentyl]-carbamic acid *tert*-butyl ester

A mixture of [(1R,3S)-3-(1-benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-cyclopentyl]-carbamic acid *tert*-butyl ester (3.54 g, 7.06 mmol) in ethanol (100 mL, IMS grade) and water (50 mL) was treated with ammonium chloride (2.27 g, 42.4 mmol), followed by iron powder (1.58 g, 28.3 mmol) and the reaction mixture was heated at reflux for 2.5 hours. After cooling, the iron residue was collected on a pad of Celite ® and washed several times with ethanol (IMS grade). The combined filtrates were concentrated *in vacuo* and the residue partitioned between water and DCM (3x). The combined organic phases were washed with brine, dried (sodium sulfate), filtered and concentrated *in vacuo* to give a red gum. Purification by column chromatography on silica gel (gradient: 0 to 50% ethyl acetate in DCM) to afford 2.65 g (79%) of [(1R,3S)-3-(5-amino-1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-cyclopentyl]-carbamic acid *tert*-butyl ester as a pale brown solid. LCMS (Method Q, ESI): RT = 2.93 min, m+H = 472.0; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (m, 2 H), 7.82 (s, 1 H), 7.53 (m, 1 H), 7.48-7.40 (m, 3 H), 6.60 (d, 1 H), 4.73 (m, 1 H), 4.30 (m, 1 H), 3.93 (m, 1

H), 2.54-2.44 (m, 1 H), 2.07-1.89 (m, 2 H), 1.81-1.69 (m, 1 H), 1.60-1.51 (m, 1 H),1.48-1.39 (m, 1 H), 1.42 (s, 9 H).

{(1R,3S)-3-[6-Benzenesulfonyl-2-((R)-1-hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentyl}-carbamic acid *tert*-butyl ester

A solution of (R)-(+)-lactamide (1.00 g, 18.2 mmol) in anhydrous DCM (25 mL), under an atmosphere of nitrogen, was treated with triethyloxonium tetrafluoroborate (3.20 g, 16.8 mmol) and stirred at room temperature for 2 hours. The volatiles were removed *in vacuo* and the residue was dissolved in ethanol (12 mL, absolute grade). This solution was added to a mixture of [(1R,3S)-3-(5-amino-1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-4-ylamino)-cyclopentyl]-carbamic acid *tert*-butyl ester (2.65 g, 5.62 mmol) in ethanol (40 mL, absolute grade) at room temperature. The reaction mixture was heated to 75 °C, under an atmosphere of nitrogen, for 2 hours. The volatiles were removed *in vacuo* and the residue partitioned between EtOAc and saturated sodium hydrogencarbonate solution. The phases were separated and the aqeous phase extracted with EtOAc (3x). The combined organic phases were washed with brine, dried (sodium sulfate), filtered and concentrated *in vacuo* to give a pale yellow solid. Purification by column chromatography on silica gel (gradient: 0 to 10% MeOH in DCM) afforded 1.86 g (63%) of {(1R,3S)-3-[6-benzenesulfonyl-2-((R)-1-hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentyl}-carbamic acid *tert*-butyl ester as a pale yellow solid. LCMS (Method Q, ESI): RT = 3.56 min, m+H = 526.1; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.84 (s, 1 H), 8.21 (m, 2 H), 7.83 (d, 1 H), 7.55 (m, 1 H), 7.46 (m, 2 H), 6.83 (d, 1 H), 5.19-5.06 (m, 2 H), 4.81 (m, 1 H), 4.15 (m, 1 H), 2.49-2.33 (m, 3 H), 2.31-2.17 (m, 2 H), 2.02-1.90 (m, 1 H), 1.72 (d, 3 H), 1.46 (s, 9 H).

(R)-1-[1-((1S,3R)-3-Amino-cyclopentyl)-6-benzenesulfonyl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol

A stirred solution of {(1R,3S)-3-[6-benzenesulfonyl-2-((R)-1-hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentyl}-carbamic acid *tert*-butyl ester (1.86 g, 3.54 mmol) in DCM (32 mL) was treated with TFA (8 mL) at room temperature for 1 hour. The solvent was concentrated *in vacuo* and the residue purified by column chromatography using an Isolute® SCX-2 cartridge (eluting with 2M NH_3 in MeOH solution) to afford 1.28 g (85%) of (R)-1-[1-((1S,3R)-3-amino-cyclopentyl)-6-benzenesulfonyl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol as a pale yellow solid. LCMS (Method Q, ESI): RT = 2.15 min; ^{1}H NMR (400 MHz, DMSO): δ 8.70 (s, 1 H), 8.13 (m, 2 H), 7.95 (d, 1 H), 7.76-7.66 (m, 2 H), 7.64-7.57 (m, 2 H), 5.34-5.22 (m, 1 H), 5.17-5.09 (m, 1 H), 3.60-3.51 (m, 1 H), 2.37-2.22 (m, 2 H), 2.07-1.87 (m, 3 H), 1.78-1.68 (m, 1 H), 1.59 (d, 3 H).

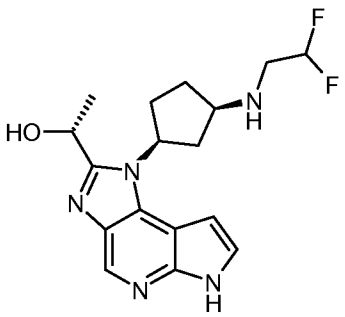
(R)-1-{6-Benzenesulfonyl-1-[(1S,3R)-3-(2,2,2-trifluoro-ethylamino)-cyclopentyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethanol

A stirred solution of (R)-1-[1-((1S,3R)-3-amino-cyclopentyl)-6-benzenesulfonyl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol (0.64 g, 1.51 mmol) in DCM/DMF (10 mL, 1:1) was treated with triethylamine (838 µL, 5.97 mmol) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (434 µL, 3.01 mmol) at room temperature for 18 hours. The mixture was partitioned between DCM and water and the phases were separated. The organic layer was washed with water, dried (sodium sulfate), filtered and concentrated *in vacuo*. The residue was azeotroped with toluene to provide a colourless gum. Purification by column chromatography on silica gel (gradient: 0 to 20% MeOH in DCM)) afforded 0.69 g (91%) of (R)-1-{6-benzenesulfonyl-1-[(1S,3R)-3-(2,2,2-trifluoro-ethylamino)-cyclopentyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethanol as a white solid. LCMS (Method H, ESI): RT = 2.67 min, m+H = 508.1; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.84 (s, 1 H), 8.21 (m, 2 H), 7.79 (d, 1 H), 7.54 (m, 1 H), 7.46 (m, 3 H), 5.22-5.06 (m, 2 H), 3.63-3.53 (m, 1 H), 3.22 (q, 2 H), 2.62-2.48 (m, 1 H), 2.44-2.33 (m, 1 H), 2.22-2.05 (m, 3 H), 1.96-1.85 (m, 1 H), 1.71 (d, 3 H).

(R)-1-{1-[(1S,3R)-3-(2,2,2-Trifluoro-ethylamino)-cyclopentyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethanol

A stirred mixture of (R)-1-{6-benzenesulfonyl-1-[(1S,3R)-3-(2,2,2-trifluoro-ethylamino)-cyclopentyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethanol (690 mg, 1.36 mmol) in THF (6 mL) and MeOH (6 mL) was treated with 2M aqueous NaOH solution (6 mL) at room temperature for 5 hours. The mixture was quenched with 1M aqueous HCl solution (12 mL) and then concentrated *in vacuo*. The resultant residue was treated with water and the pH was adjusted to 7 using 2M NaOH solution. Ethyl acetate was added and a white solid precipitated from solution, upon sonication. The solid was collected, washed (water and ethyl acetate) and dried *in vacuo* at 40 °C overnight to afford 146 mg (29%) of (R)-1-{1-[(1S,3R)-3-(2,2,2-trifluoro-ethylamino)-cyclopentyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethanol as a white solid. A second batch (140 mg, 28%) was obtained from re-filtering the filtrate and drying the solid *in vacuo* at 40 °C overnight. Both batches were analytically identical: LCMS (Method A, ESI): RT = 2.11 min, m+H = 368.1; ^{1}H NMR (400 MHz, DMSO): δ 11.83 (s, 1 H), 8.57 (s, 1 H), 7.45 (m, 1 H), 6.99 (m, 1 H), 5.68 (d, 1 H), 5.33 (m, 1 H), 5.15 (m, 1 H), 3.40 (m, 1 H), 3.30 (m, 2 H), 2.87-2.78 (m, 1 H), 2.51-2.40 (m, 1 H), 2.39-2.29 (m, 1 H), 2.27-2.05 (m, 3 H), 1.95-1.84 (m, 1 H), 1.64 (d, 3 H).

Example 111



(R)-1-{1-[(1S,3R)-3-(2,2-Difluoro-ethylamino)-cyclopentyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethanol

(R)-1-{6-Benzenesulfonyl-1-[(1S,3R)-3-(2,2-difluoro-ethylamino)-cyclopentyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethanol

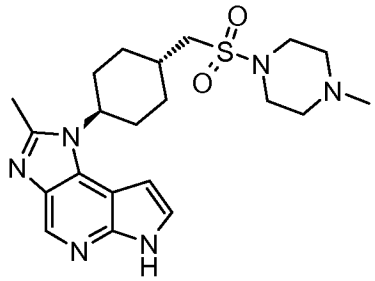
A stirred solution of (R)-1-[1-((1S,3R)-3-amino-cyclopentyl)-6-benzenesulfonyl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol (607 mg, 1.43 mmol) in DCM/DMF (16 mL, 1:1) was treated with triethylamine (794 μL, 5.71 mmol) and 2,2-difluoroethyl trifluoromethanesulfonate (382 μL, 2.86 mmol) at room temperature for 6 hours. The mixture was partitioned between DCM and water and the phases were separated. The organic layer was washed with water, dried (sodium sulfate) and concentrated *in vacuo*. The residue was azeotroped with toluene to provide a colourless gum. Purification by column chromatography on silica gel (gradient: 0 to 20% MeOH in DCM) afforded 584 mg (84%) of (R)-1-{6-benzenesulfonyl-1-[(1S,3R)-3-(2,2-difluoro-ethylamino)-cyclopentyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethanol as a white solid. LCMS (Method H, ESI): RT = 2.04 min, m+H = 490.0; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.84 (s, 1 H), 8.22 (m, 2 H), 7.79 (d, 1 H), 7.54 (m, 1 H), 7.50-7.42 (m, 3 H), 6.09-5.75 (tt, 1 H), 5.22-5.05 (m, 2 H), 3.54-3.45 (m, 1 H), 3.06-2.83 (m, 3 H), 2.59-2.46 (m, 1 H), 2.42-2.30 (m, 1 H), 2.21-2.05 (m, 3 H), 1.94-1.84 (m, 1 H), 1.71 (d, 3 H).

(R)-1-{1-[(1S,3R)-3-(2,2-Difluoro-ethylamino)-cyclopentyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethanol

A stirred mixture of (R)-1-{6-benzenesulfonyl-1-[(1S,3R)-3-(2,2-difluoro-ethylamino)-cyclopentyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethanol (584 mg, 1.19 mmol) in THF (6 mL) and MeOH (6mL) was treated with 2M aqueous NaOH solution (6 mL) at room temperature for 5 hours. The mixture was quenched with 1M aqueous HCl solution (12 mL) and then concentrated *in vacuo*. The resultant residue was treated with water and the pH was adjusted to 7 using 2M aqueous NaOH solution. Ethyl acetate was added and a white solid precipitated

from solution, upon sonication. The solid was collected, washed (water and ethyl acetate) and dried *in vacuo* at 40°C to afford 156 mg (37%) of (R)-1-{1-[(1S,3R)-3-(2,2-difluoro-ethylamino)-cyclopentyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethanol as a white solid. LCMS (Method A, ESI): RT = 1.60 min, m+H = 350.0; ^{1}H NMR (400 MHz, DMSO): δ 11.80 (s, 1 H), 8.54 (s, 1 H), 7.44 (m, 1 H), 7.00 (m, 1 H), 6.20-5.88 (tt, 1 H), 5.65 (d, 1 H), 5.37-5.24 (m, 1 H), 5.17-5.08 (m, 1 H), 3.40-3.32 (m, 1 H, partially obscured by water), 2.93 (t, 2 H), 2.48-2.38 (m, 2 H), 2.35-2.26 (m, 1 H), 2.23-2.00 (m, 3 H), 1.91-1.81 (m, 1 H), 1.62 (d, 3 H).

Example 112



Trans 2-Methyl-1-[4-(4-methyl-piperazine-1-sulfonylmethyl)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacene

Trans Thioacetic acid S-(4-tert-butoxycarbonylamino-cyclohexylmethyl) ester

A solution of methanesulfonic acid 4-tert-butoxycarbonylamino-cyclohexylmethyl ester (12.0 g, 39.1 mmol) and potassium thioacetate (4.9 g, 43.2 mmol) in DMSO was stirred at room temperature for two days. The reaction mixture was then partitioned between a saturated aqueous solution of NaHCO3 at 5 °C and DCM. The aqueous layer was separated and extracted with two portions of DCM. The combined organic extracts were washed with brine, dried over Na2SO4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient: 5 to 20% cyclohexane in EtOAc) to afford trans thioacetic acid S-(4-tert-butoxycarbonylamino-cyclohexylmethyl) ester as a white solid (8.1 g). ^{1}H NMR (400 MHz, d-$CHCl_3$): δ 4.34 (br s, 1H), 3.37 (br s, 1H), 2.78 (d, 2H), 2.32 (s, 3H), 2.07-1.95 (m, 2H), 1.88-1.79 (m, 2H), 1.43 (s, 9H), 1.06 (t, 4H).

Trans [4-(4-Methyl-piperazine-1-sulfonylmethyl)-cyclohexyl]-carbamic acid tert-butyl ester

A solution of trans thioacetic acid S-(4-tert-butoxycarbonylamino-cyclohexylmethyl) ester (1.32 g, 4.60 mmol) and sodium acetate (4.29 g, 52.3 mmol) in water (6 mL) and acetic

acid (30 mL) was cooled to -10 °C. Chlorine was bubbled into the reaction mixture until the colour changed. Nitrogen was then bubbled into the solution for 30 minutes and the reaction mixture was stirred for a further 20 minutes. The reaction mixture was concentrated *in vacuo* to give a residue that was partitioned between EtOAc and water. The organic layer was separated and washed with a water and brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was taken up in chloroform (20 mL) and DIPEA (5.2 mL, 30.0 mmol) and 1-methylpiperazine (1.1 mL, 10.0 mmol) added. The reaction mixture was stirred at room temperature for 3 hours and concentrated *in vacuo*. The residue was partitioned between DCM and a saturated aqueous solution of $NaHCO_3$. The organic layer was separated and added onto a solution of sodium sulphite (2. 0g, 15.9 mmol) in water (8 mL) and the resulting mixture was stirred vigorously at room temperature for 1 hour. The organic phase was separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (gradient: 0 to 10% MeOH in DCM) to afford trans [4-(4-methyl-piperazine-1-sulfonylmethyl)-cyclohexyl]-carbamic acid tert-butyl ester as a white solid (1.49 g). LCMS (Method R, ESI): RT = 2.05 min, m+H = 376.3.

Trans 4-(4-Methyl-piperazine-1-sulfonylmethyl)-cyclohexylamine

A solution of trans [4-(4-methyl-piperazine-1-sulfonylmethyl)-cyclohexyl]-carbamic acid tert-butyl ester (1.47 g, 3.92 mmol) in TFA (3 mL) and DCM (12 mL) was stirred at room temperature for 2.5 hours. The mixture was concentrated *in vacuo* to afford trans 4-(4-methyl-piperazine-1-sulfonylmethyl)-cyclohexylamine (TFA salt) as a colourless oil (3.4 g). LCMS (Method H, ESI): RT = 0.41 min, m+H = 276.0.

Trans (1-Benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-yl)-[4-(4-methyl-piperazine-1-sulfonylmethyl)-cyclohexyl]-amine

A solution of 1-benzenesulfonyl-4-chloro-5-nitro-1H-pyrrolo[2,3-b]pyridine (1.32 g, 3.9 mmol), trans 4-(4-methyl-piperazine-1-sulfonylmethyl)-cyclohexylamine (TFA salt, 3.3 g, 3.9 mmol) and DIPEA (9.9 mL, 58.1 mmol) in propan-2-ol was stirred at reflux for 3 hours and cooled to room temperature. The reaction mixture was concentrated *in vacuo* to give a residue that was partitioned between DCM and a saturated aqueous solution of $NaHCO_3$. The organic layer was separated and washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (gradient: 0 to 7% MeOH in DCM) to afford trans (1-benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-yl)-[4-(4-methyl-piperazine-1-sulfonylmethyl)-cyclohexyl]-amine as a yellow solid (2.2 g). LCMS (Method H, ESI): RT = 2.70 min, m+H = 577.2.

Trans 1-Benzenesulfonyl-N*4*-[4-(4-methyl-piperazine-1-sulfonylmethyl)-cyclohexyl]-1H-pyrrolo[2,3-b]pyridine-4,5-diamine

To a suspension of trans (1-benzenesulfonyl-5-nitro-1H-pyrrolo[2,3-b]pyridin-4-yl)-[4-(4-methyl-piperazine-1-sulfonylmethyl)-cyclohexyl]-amine (2.15 g, 3.73 mmol) in MeOH (120 mL) was added a solution of ammonium chloride (1.28 g, 23.9 mmol) in water (40 mL). Iron power (896 mg, 16.0 mmol) was added and the resulting mixture was stirred at 85 °C for 1.5 hours and cooled to room temperature. The reaction mixture was filtered through Celite® and the filtrate was concentrated *in vacuo*. The residue was partitioned between EtOAc and a saturated aqueous solution of $NaHCO_3$. The resulting precipitate was filtered off and washed with water and EtOAc. The residue was dried *in vacuo* to afford trans 1-benzenesulfonyl-N*4*-[4-(4-methyl-piperazine-1-sulfonylmethyl)-cyclohexyl]-1H-pyrrolo[2,3-b]pyridine-4,5-diamine as a pale pink solid (1.63 g). LCMS (Method H, ESI): RT = 1.90 min, m+H = 547.4.

Trans 6-Benzenesulfonyl-2-methyl-1-[4-(4-methyl-piperazine-1-sulfonylmethyl)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacene

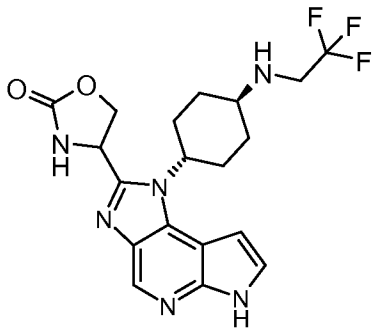
A mixture of trans 1-benzenesulfonyl-N*4*-[4-(4-methyl-piperazine-1-sulfonylmethyl)-cyclohexyl]-1H-pyrrolo[2,3-b]pyridine-4,5-diamine (300 mg, 0.55 mmol), triethyl orthoacetate (0.25 mL, 1.37 mmol) and *para*-toluene sulfonic acid monohydrate (10 mg, 0.05 mmol) in toluene (5 mL) was stirred at 105 °C for 18 hours and cooled to room temperature. The reaction mixture was concentrated *in vacuo* to give a residue that was taken up in acetic acid (5 mL). The resulting mixture was stirred at reflux for 1 hour and concentrated *in vacuo*. The residue was partitioned between EtOAc and a saturated aqueous solution of $NaHCO_3$. The aqueous layer was separated and extracted with two portions of EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford trans 6-benzenesulfonyl-2-methyl-1-[4-(4-methyl-piperazine-1-sulfonylmethyl)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacene as an off-white solid (280 mg). LCMS (Method R, ESI): RT = 2.05 min, m+H = 571.4.

Trans 2-Methyl-1-[4-(4-methyl-piperazine-1-sulfonylmethyl)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacene

To a solution of trans 6-benzenesulfonyl-2-methyl-1-[4-(4-methyl-piperazine-1-sulfonylmethyl)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacene (275 mg, 0.48 mmol) in methanol (3 mL) and THF (3 mL) was added a 1M aqueous solution of sodium hydroxide (2 mL, 2.00 mmol). The resulting mixture was stirred at room temperature for 5 hours and

concentrated *in vacuo*. The residue was suspended in water and a 1M aqueous hydrochloric acid solution was added until pH 8. After extraction with several portions of EtOAc, the combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting solid was recrystallised (EtOAc) to afford trans 2-methyl-1-[4-(4-methyl-piperazine-1-sulfonylmethyl)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacene as an white solid (79 mg). LCMS (Method A, ESI): RT = 1.72 min, m+H = 431.1; ^{1}H NMR (400 MHz, DMSO): δ 11.75 (br s, 1H), 8.41 (s, 1H), 7.43 (t, 1H), 6.61 (br s, 1H), 4.41 (br s, 1H), 3.15 (t, 4H), 3.00 (d, 2H), 2.59 (s, 3H), 2.35 (t, 4H), 2.30-2.23 (m, 1H), 2.18 (s, 3H), 2.15-2.09 (m, 4H), 1.94-1.88 (m, 2H), 1.43 (q, 2H).

Example 113



Trans 4-{1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-oxazolidin-2-one

Trans 2-Oxo-oxazolidine-4-carboxylic acid {1-benzenesulfonyl-4-[4-(2,2,2-trifluoro-ethylamino)-cyclohexylamino]-1H-pyrrolo[2,3-b]pyridin-5-yl}-amide

A solution of trans 1-benzenesulfonyl-N*4*-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1H-pyrrolo[2,3-b]pyridine-4,5-diamine (150 mg, 0.32 mmol) and 2-oxo-oxazolidine-4-carboxylic acid (51 mg, 0.38 mmol) in pyridine (2 mL) was treated with EDCI (73 mg, 0.80 mmol), and the mixture was stirred at 60 °C for 1.5 hours. The solvent was removed *in vacuo* and the residue partitioned between EtOAc and water. The organic layer was separated and washed with a saturated aqueous solution of $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (gradient: 0 to 5% MeOH in EtOAc) to afford trans 2-oxo-oxazolidine-4-carboxylic acid {1-benzenesulfonyl-4-[4-(2,2,2-trifluoro-ethylamino)-cyclohexylamino]-1H-pyrrolo[2,3-b]pyridin-5-yl}-amide as an off-white solid (144 mg). LCMS (Method I, ESI): RT = 1.98 min, m+H = 581.1.

Trans 4-{6-Benzenesulfonyl-1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-oxazolidin-2-one

A solution of trans 2-oxo-oxazolidine-4-carboxylic acid {1-benzenesulfonyl-4-[4-(2,2,2-trifluoro-ethylamino)-cyclohexylamino]-1H-pyrrolo[2,3-b]pyridin-5-yl}-amide (144 mg, 0.25 mmol) in acetic acid (2.5 mL) was stirred at 80 °C for 18 hours, then concentrated *in vacuo*. The residue was partitioned between EtOAc and a saturated aqueous solution of sodium hydrogencarbonate. The organic layer was separated and washed with water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (gradient: 0 to 10% MeOH in EtOAc) to afford 130 mg (90%) of trans 4-{6-benzenesulfonyl-1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-oxazolidin-2-one as a white solid. LCMS (Method R, ESI): RT = 2.35 min, m+H = 563.2

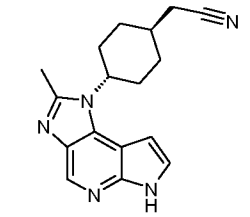
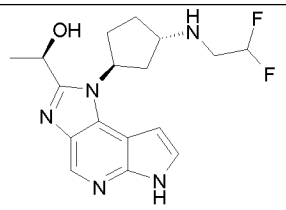
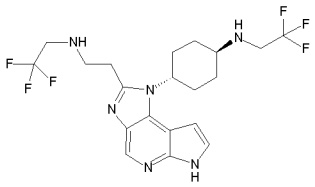
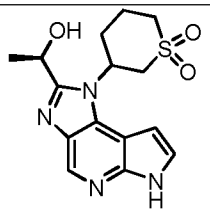
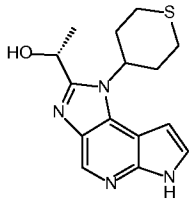
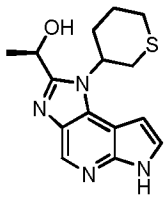
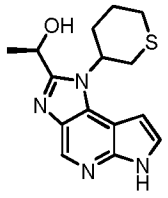
Trans 4-{1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-oxazolidin-2-one

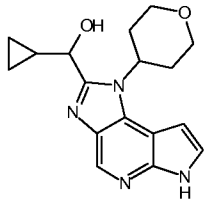
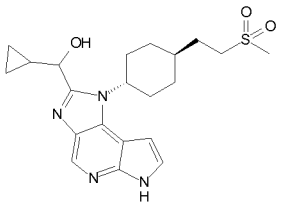
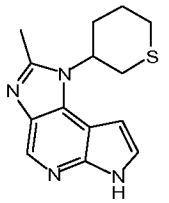
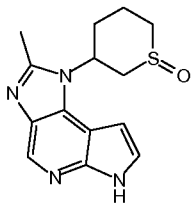
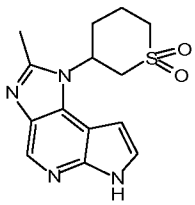
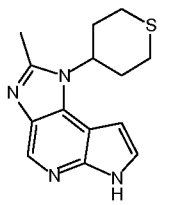
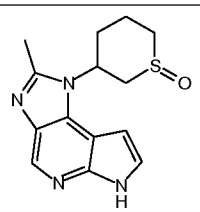
To a solution of trans 4-{6-benzenesulfonyl-1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-oxazolidin-2-one (125 mg, 0.22 mmol) in propan-2-ol was added a 1N aqueous solution of NaOH. The reaction mixture was stirred at 50 °C for 18 hours and then cooled to room temperature and neutralised by addition of 1N aqueous HCl (*ca.* 0.5 mL). The solvents were removed *in vacuo*. The residue was purified by HPLC chromatography (gradient: MeCN/H_2O [+ 0.1% NH_3]) to afford trans 4-{1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-oxazolidin-2-one as a white solid (5 mg): LCMS (Method A, ESI): RT = 1.84 min, m+H = 423.0; ^{1}H NMR (400 MHz, DMSO): δ 11.89 (s, 1 H), 8.55 (s, 1 H), 8.36 (br s, 1 H), 7.46 (m, 1 H), 6.65 (br s, 1 H), 5.49 (t, 1 H), 4.68 (d, 1 H), 4.40 (br s, 1 H), 3.36-3.25 (m, 2 H, partially obscured by water), 2.84-2.73 (m, 1 H), 2.42-2.19 (m, 3 H), 2.09-1.84 (m, 4 H), 1.46-1.23 (m, 2 H).

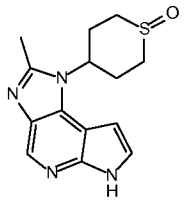
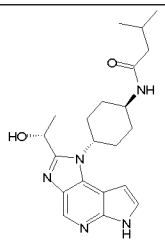
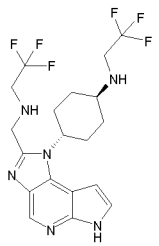
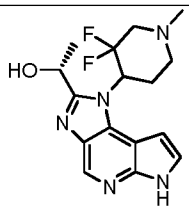
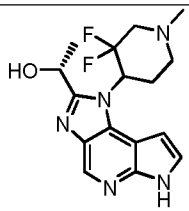
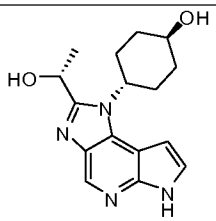
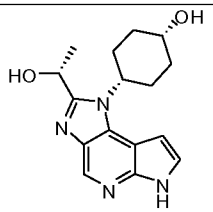
Additional examples shown in Table 4 were made according to the above procedures, and to Examples in U.S. Pat. Appl. Serial No. 13/004,808, filed 1/11/2011.

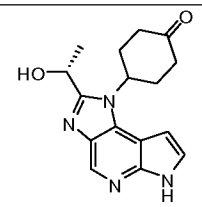
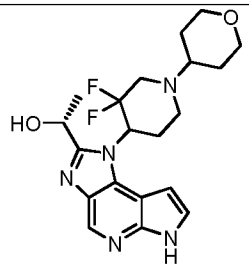
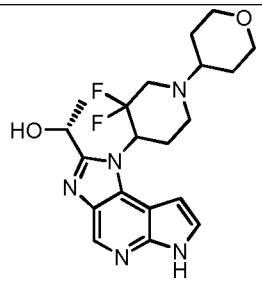
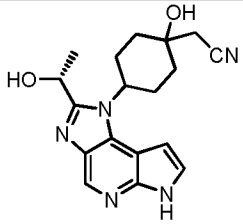
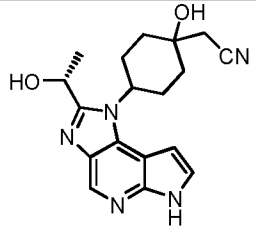
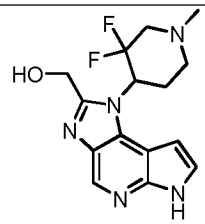
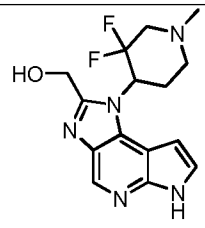
Table 4

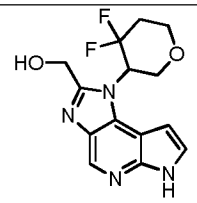
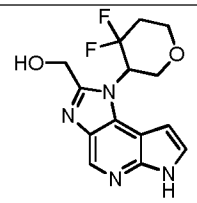
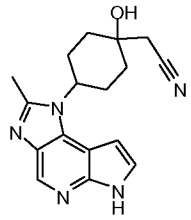
Structure	Ex #	Name	LCMS RT (min)/ Method	LCMS (ESI) *m/z*

	114	trans [4-(2-Methyl-6H-1,3,5,6-tetraaza-as-indacen-1-yl)-cyclohexyl]-acetonitrile	2.33 / A	294.1
	115	(R)-1-{1-[(1S,3S)-3-(2,2-Difluoro-ethylamino)-cyclopentyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethanol	1.57 / A	350.0
	116	Trans (2,2,2-Trifluoro-ethyl)-(4-{2-[2-(2,2,2-trifluoro-ethylamino)-ethyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclohexyl)-amine	2.494 / C	463.2
	117	(R)-1-[1-(1,1-Dioxo-hexahydro-thiopyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol (mixture of diastereomers)	2.73 / C	335.1
	118	(R)-1-[1-(Tetrahydro-thiopyran-4-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol	3.37 / C	303.2
	119	(R)1-[1-(Tetrahydro-thiopyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol (single isomer, stereochemistry of thiopyran unknown)	3.07 / C 1.11 / A6	303.1
	120	(R)-1-[1-(Tetrahydro-thiopyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol (single isomer, stereochemistry of thiopyran unknown)	3.08 / C 1.28 / A6	303.1

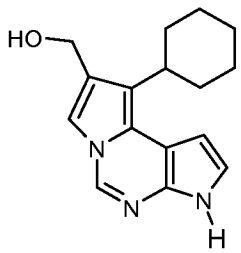
	121	Cyclopropyl-[1-(tetrahydro-pyran-4-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-methanol (racemic)	3.11 / C	313.2
	122	trans Cyclopropyl-{1-[4-(2-methanesulfonyl-ethyl)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-methanol (racemic)	3.41 /C	417.2
	123	2-Methyl-1-(tetrahydro-thiopyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacene (racemic)	3.34 /C	273.1
	124	2-Methyl-1-(1-oxo-hexahydro-thiopyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacene (racemic, single unknown diastereomer)	2.44 / C	289.1
	125	1-(1,1-Dioxo-hexahydro-thiopyran-3-yl)-2-methyl-1,6-dihydro-1,3,5,6-tetraaza-as-indacene (racemic)	2.63 / C	305.1
	126	2-Methyl-1-(tetrahydro-thiopyran-4-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacene	3.32 / C	273.1
	127	2-Methyl-1-(1-oxo-hexahydro-thiopyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacene (racemic, single unknown diastereomer)	2.53 / C	289.1

	128	2-Methyl-1-(1-oxo-hexahydro-thiopyran-4-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacene (mixture of cis and trans)	2.44 / C	289.2
	129	trans N-{4-[2-((R)-1-Hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclohexyl}-3-methyl-butyramide	2.35/S	384.1
	130	trans (2,2,2-Trifluoro-ethyl)-(4-{2-[(2,2,2-trifluoro-ethylamino)-methyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclohexyl)-amine	6.08/N	449.4
	131	(R)-1-[1-((S)-3,3-Difluoro-1-methyl-piperidin-4-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol (single unknown stereoisomer)	1.86 / K 6.12 / A17	336.1
	132	(R)-1-[1-(-3,3-Difluoro-1-methyl-piperidin-4-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol (single unknown stereoisomer)	1.896 / K 7.27 / A17	336.1
	133	Trans 4-[2-((R)-1-Hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclohexanol	1.729 / K	301.1
	134	Cis 4-[2-((R)-1-Hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclohexanol	1.780 / K	301.1

	135	4-[2-((R)-1-Hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclohexanone	0.875 / K	298.9
	136	(R)-1-{1-[-3,3-Difluoro-1-(tetrahydro-pyran-4-yl)-piperidin-4-yl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethanol (single unknown stereoisomer)	0.931 / K 1.327 / A14	406.0
	137	(R)-1-{1-[-3,3-Difluoro-1-(tetrahydro-pyran-4-yl)-piperidin-4-yl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethanol (single unknown stereoisomer)	0.923 / K 1.307 / A14	406.2
	138	{1-Hydroxy-4-[2-((R)-1-hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclohexyl}-acetonitrile (single stereoisomer, cyclohexane stereochemistry unknown)	1.849 / K	340.1
	139	{1-Hydroxy-4-[2-((R)-1-hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclohexyl}-acetonitrile (single stereoisomer, cyclohexane stereochemistry unknown)	1.924 / K	340.1
	140	[1-(3,3-Difluoro-1-methyl-piperidin-4-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-methanol (single unknown stereoisomer)	1.826 / K 7.029 / A13	322.1
	141	[1-(-3,3-Difluoro-1-methyl-piperidin-4-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-methanol (single unknown stereoisomer)	1.821 / K 8.097 / A13	322.1

	142	[1-(-4,4-Difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-methanol (single unknown stereoisomer)	0.912 / K 2.930 / A13	308.8
	143	[1-(-4,4-Difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-methanol (single unknown stereoisomer)	0.907 / K 3.522 / A13	308.8
	144	[1-Hydroxy-4-(2-methyl-6H-1,3,5,6-tetraaza-as-indacen-1-yl)-cyclohexyl]-acetonitrile (mixture of diastereomers)	0.866 / K	310.1

Example 145



(9-Cyclohexyl-3H-dipyrrolo[1,2-c;3',2'-e]pyrimidin-8-yl)-methanol

a. 4-Chloro-7-(2-trimethylsilanyl-ethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidine

4-Chloro-7H-pyrrolo[2,3-d]pyrimidine (1.5g, 9.77 mmol) was stirred in anhydrous N,N-dimethylacetamide (30ml), under nitrogen, with cooling to between 0°C and 5 °C as sodium hydride (60% dispersion, 430mg, 10.75 mmol) was added in portions. After all effervescence had ceased (25 min.), (2-chloromethoxy-ethyl)-trimethylsilane (1.79g, 10.75 mmol) was added dropwise, maintaining the temperature between 4 °C and 7 °C. After stirring for a further 1h 45 min. saturated aqueous NH_4Cl and a little water were added and the product was extracted with 2 portions of t-butyl methyl ether. The extracts were washed with water, brine, dried over Na_2SO_4 and the solvent evaporated. Purification on a Si-SPE ® cartridge (70g) eluting with EtOAc-cyclohexane (1:10 followed by 1:6) afforded the title compound as a colourless oil (2.19g, 79%) LCMS (Method 1, ESI): Rt 4.11 min., m/z 325 $[M+42]^+$, 284 $[M+H]^+$, ^1H NMR (400 MHz,

$CDCl_3$): δ 8.67 (1H, s), 7.39 (1H, d, J = 3.5Hz), 6.67 (1H, d, J = 3.5Hz), 5.65 (2H, s), 3.50-3.56 (2H, m), 0.88-0.93 (2H, m), -0.06 (9H, s).

b. 4-Cyclohexylmethyl-7-(2-trimethylsilanyl-ethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidine

To a solution of 4-chloro-7-(2-trimethylsilanyl-ethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidine (709 mg, 2.5 mmol) stirred in anhydrous THF (5ml) under nitrogen was added tetrakis(triphenylphosphine)palladium(0) (145 mg, 0.125 mmol), followed by (cyclohexylmethyl)zinc bromide (0.5M in THF, 15ml, 7.5 mmol). The mixture was heated at 50°C for 3.75h. After cooling, the mixture was quenched with aqueous NH_4Cl and extracted with EtOAc. The extracts were washed with brine, dried over Na_2SO_4 and the solvent evaporated. Chromatography on a 50g Biotage ® silica column eluting with EtOAc-cyclohexane (gradient 5% to 30%) afforded partially purified material (720mg) which was further purified by chromatography on a 40g Redisep ® silica column eluting with 0% to 3% MeOH in DCM to afford the title compound as an oil (619mg, 72%). LCMS (Method 2, ESI): Rt 3.80 min., m/z 346 $[M+H]^+$, ^1H NMR (400 MHz, $CDCl_3$): δ8.83 (1H, s), 7.29 (1H, d, *J* = 3.7 Hz), 6.60 (1H, d, *J* = 3.7 Hz), 5.64 (2H, s), 3.52-3.56 (2H, m), 2.89 (2H, d, *J* = 7.2 Hz), 1.89-2.03 (1H, m), 1.60-1.76 (5H, m), 1.00-1.30 (5H, m), 0.87-0.93 (2H, m), -0.08 (9H, s).

c. 9-Cyclohexyl-3-(2-trimethylsilanyl-ethoxymethyl)-3H-dipyrrolo[1,2-c;3',2'-e]pyrimidine-8-carboxylic acid ethyl ester

4-Cyclohexylmethyl-7-(2-trimethylsilanyl-ethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidine (505 mg, 1.46 mmol) and ethyl bromopyruvate (360 mg, 1.85 mmol) were heated in EtOAc (7.5 ml) in a sealed tube at 80°C for 4.5h. After standing overnight at room temperature, heating at 80°C was resumed for a further 3h. The cooled mixture was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic phase was separated, washed with brine, dried over Na_2SO_4 and the solvent evaporated. Chromatography on a 25g Biotage ® silica column eluting with 3% to 15% EtOAc in cyclohexane afforded the title compound as an oil (225mg, 35%). LCMS (Method 2, ESI): Rt 5.31 min., m/z 442 $[M+H]^+$, ^1H NMR (400 MHz, $CDCl_3$): δ8̃39 (1H, s̱7.81 (1H, s), 7.10 (1H, d, *J* = 3.4 Hz), 6.80 (1H, d, *J* = 3.4 Hz), 5.58 (2H, s), 4.35 (2H, q, *J* = 7.0 Hz), 3.52-3.64 (3H, m), 2.07-2.20 (2H, m), 1.85-1.94 (2H, m), 1.71-1.82 (3H, m), 1.41-1.61 (3H, m), 1.40 (3H, t, *J* = 7.0 Hz), 0.90-0.94 (2H, m), -0.04 (9H, s).

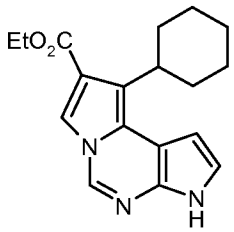
d. [9-Cyclohexyl-3-(2-trimethylsilanyl-ethoxymethyl)-3H-dipyrrolo[1,2-c;3',2'-e]pyrimidin-8-yl]-methanol

9-Cyclohexyl-3-(2-trimethylsilanyl-ethoxymethyl)-3H-dipyrrolo[1,2-c;3',2'-e]pyrimidine-8-carboxylic acid ethyl ester (180 mg, 0.41 mmol) was stirred under N_2 in anhydrous THF (6ml) at 0°C as $LiAlH_4$ (1M in THF, 0.4 ml, 0.4 mmol) was added. After 10 min. the mixture was allowed to warm to room temperature and, after 1.5h, a further 0.3ml of 1M $LiAlH_4$ solution was added. After 10 min. the dark solution was poured into water and EtOAc and the mixture filtered through celite. The organic phase was separated, washed with brine, dried (Na_2SO_4) and evaporated. Purification by on a Si-SPE ® cartridge (5g) eluting with EtOAc-cyclohexane (1:3 followed by 1:2) gave the title compound (63 mg, 38%, pink gum). LCMS (Method 2, ESI): Rt 4.55 min., m/z 400 $[M+H]^+$, ^1H NMR (400 MHz, $CDCl_3$): δ 8.40 (1H, s), 7.29 (1H, s), 7.11 (1H, d, J = 3.5 Hz), 6.75 (1H, d, J = 3.5 Hz), 5.62 (2H, s), 4.87 (2H, s), 3.55-3.62 (2H, m), 3.05-3.17 (1H, m), 1.80-2.00 (7H, m), 1.30-1.58 (3H, m), 0.93-1.00 (2H, m), 0.00 (9H, s).

e. (9-Cyclohexyl-3H-dipyrrolo[1,2-c;3',2'-e]pyrimidin-8-yl)-methanol

[9-Cyclohexyl-3-(2-trimethylsilanyl-ethoxymethyl)-3H-dipyrrolo[1,2-c;3',2'-e]pyrimidin-8-yl]-methanol (63 mg, 0.158 mmol) was stirred in TFA (1 ml) for 30 min. The mixture was partitioned between EtOAc and aqueous $NaHCO_3$ and the organic phase was dried over Na_2SO_4 and the solvent evaporated. The residue was dissolved in THF (3 ml) and ethylenediamine (0.25 ml) was added. After stirring for 4h 20 min. the mixture was partitioned between EtOAc and water. The organic phase was washed with water, brine, dried and evaporated. The brown solid was purified on a Si-SPE ® cartridge (2g) eluting with EtOAc-cyclohexane (2:1), then 100% EtOAc, furnishing a solid which was taken up in methanol, filtered and the filtrate evaporated to afford title compound (12.5 mg). LCMS (Method 3, ESI): Rt 3.45 min.(br.), m/z 270 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6): δ 11.60 (1H, s), 8.58 (1H, s), 7.30 (1H, s), 6.99-7.03 (1H, m), 6.45-6.48 (1H, m), 4.85 (1H, t, J = 5 Hz), 4.55 (2H, d, J = 5 Hz), 2.85-2.97 (1H, m), 1.62-1.82 (7H, m), 1.20-1.45 (3H, m).

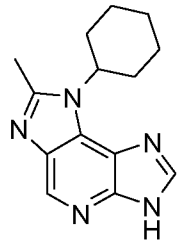
Example 146



9-Cyclohexyl-3H-dipyrrolo[1,2-c;3',2'-e]pyrimidine-8-carboxylic acid ethyl ester

9-Cyclohexyl-3-(2-trimethylsilanyl-ethoxymethyl)-3H-dipyrrolo[1,2-c;3',2'-e]pyrimidine-8-carboxylic acid ethyl ester (30 mg, 0.068 mmol) was stirred in TFA (0.5 ml) at room temperature for 30 min. The mixture was partitioned between EtOAc and saturated aqueous $NaHCO_3$ and the organic phase was washed with brine, dried over Na_2SO_4 and the solvent evaporated. The resulting product was dissolved in THF (1ml) and stirred with 0.1 ml of ethylenediamine for 1h 25 min. The mixture was diluted with EtOAc, washed with water, brine, dried (Na_2SO_4) and solvent evaporated. The crude product was dissolved in the minimum of THF-EtOAc mixture and purified on a Si-SPE ® cartridge (5g) sing EtOAc-cyclohexane (1:2) to afford title compound (13 mg) as a pale yellow solid. LCMS (Method 3, ESI): Rt 5.50 min., m/z 312 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6): δ 11.87 (1H, s), 8.77 (1H, s), 7.14-7.17 (1H, m), 6.62-6.65 (1H, m), 4.26 (2H, q, J = 7 Hz), 3.46-3.57 (1H, m), 2.02-2.18 (2H, m), 1.70-1.90 (3H, m), 1.57-1.67 (2H, m), 1.35-1.47 (3H, m), 1.32 (3H, t, J = 7 Hz).

Example 147



8-Cyclohexyl-7-methyl-3,8-dihydro-1,3,4,6,8-pentaaza-as-indacene

3-Bromo-2-chloro-5-nitro-pyridin-4-ylamine

To a stirred solution of 3-bromo-2-chloro-pyridin-4-ylamine (5.00 g, 24.10 mmol) in concentrated H_2SO_4 (36 mL) at ~5 °C was added KNO_3 (4.87 g, 48.20 mmol). The resultant solution was allowed to warm to room temperature and stir for 20 hours. The reaction mixture was poured onto ice chips (~400 mL) giving a pale yellow precipitate. The precipitate was collected by filtration and washed with water then dried under reduced pressure before being added portionwise to concentrated H_2SO_4 (30 mL) at ~5 °C. The reaction mixture was stirred at 90 °C for 2 hours then cooled to room temperature and allowed to stand for 18 hours. The solution was poured onto ice chips (~400 mL) giving a precipitate which was collected by filtration and washed with water. The solid was dissolved in a mixture of MeOH and ethyl acetate and the solution dried (Na_2SO_4) then concentrated *in vacuo* affording 3-bromo-2-chloro-

5-nitro-pyridin-4-ylamine (5.20 g, 85%) as a pale orange solid. LCMS (Method I, ESI): RT = 2.79 min, M+H = 251.9/253.9/255.9; ^{1}H NMR (400 MHz, DMSO): δ 8.86 (1 H, s).

3-Bromo-2,4-dichloro-5-nitro-pyridine

To a suspension of 3-bromo-2-chloro-5-nitro-pyridin-4-ylamine (5.20 g, 20.60 mmol) in concentrated HCl (42 mL) at ~5 °C was added sodium nitrite (6.40 g, 92.69 mmol) portionwise. The resultant reaction mixture was stirred at ~5 °C for 45 minutes then at room temperature for 3 hours. To the reaction was added acetonitrile (20 mL) and the reaction stirred at room temperature for 20 hours before the reaction mixture was concentrated *in vacuo*. The resultant residue was diluted with water (50 mL) then extracted with ethyl acetate (1 x 100 mL, 2 x 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to afford 3-bromo-2,4-dichloro-5-nitro-pyridine (5.05 g, 90%) as a peach solid. LCMS (Method R, ESI): RT = 3.53 min, M+H = none observed; ^{1}H NMR (400 MHz, DMSO): δ 9.12 (1 H, s)

(3-Bromo-2-chloro-5-nitro-pyridin-4-yl)-cyclohexyl-amine

To a solution of 3-bromo-2,4-dichloro-5-nitro-pyridine (3.00 g, 11.03 mmol) in DMF (25 mL) at ~5 °C was added triethylamine (1.69 mL, 12.13 mmol) followed by cyclohexylamine (1.26 mL, 11.03 mmol). The reaction was allowed to warm to room temperature and stirred for 2 hours. The reaction mixture was concentrated *in vacuo* before the resultant residue was taken up into ethyl acetate (50 mL) and washed with 1:1 brine/water (20 mL), brine (x3), dried (Na_2SO_4) and concentrated *in vacuo* to afford (3-bromo-2-chloro-5-nitro-pyridin-4-yl)-cyclohexyl-amine (3.67 g, 99%) as a brown oil. LCMS (Method I, ESI): RT = 4.29 min, M+H = 334.1/336.1/338.1; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.84 and 8.73 (1 H, s), 7.96 and (1 H, brs), 4.30-4.18 and 4.04-3.91 (1 H, m), 2.09-1.93 (2 H, m), 1.83-1.69 (2 H, m), 1.69-1.58 (1 H, m), 1.49-1.19 (5 H, m).

5-Bromo-6-chloro-N*4*-cyclohexyl-pyridine-3,4-diamine

A mixture of 3-bromo-2-chloro-5-nitro-pyridin-4-yl)-cyclohexyl-amine (2.00 g, 5.98 mmol), iron powder (1.34 g, 23.91 mmol), ammonium chloride (1.92 g, 35.86 mmol) in MeOH (110 mL) and water (40 mL) was stirred at reflux for 1 hour. The reaction mixture was cooled to room temperature before being filtered through a pad of celite and loaded onto a SCX-2 cartridge. The cartridge was eluted with MeOH, the desired compound did not retain therefore the obtained solution was concentrated *in vacuo* and the resultant residue was taken up into MeOH then loaded onto another SCX-2 cartridge. The cartridge was washed with MeOH then eluted with 2M NH_3 in MeOH before the basic fractions were combined and concentrated *in vacuo* affording

5-bromo-6-chloro-N*4*-cyclohexyl-pyridine-3,4-diamine (2.69 g, quantitative) as a red brown solid. LCMS (Method H, ESI): RT = 3.89 min, M+H = 304.0/306.0/308.0; ^{1}H NMR (400 MHz, DMSO): δ 7.59 and 7.56 (1 H, s), 5.11 and 5.09 (2 H, s), 4.50 and 4.34 (1 H, d, J = 10.00 Hz), 3.60-3.45 (1 H, m), 1.85-1.73 (2 H, m), 1.73-1.61 (2 H, m), 1.59-1.49 (1 H, m), 1.31-1.05 (5 H, m).

7-Bromo-6-chloro-1-cyclohexyl-2-methyl-1H-imidazo[4,5-c]pyridine

To a mixture of 5-bromo-6-chloro-N*4*-cyclohexyl-pyridine-3,4-diamine (1.00 g, 3.28 mmol) and concentrated HCl (328 μL) in IMS (20mL) at reflux was added a solution of trimethyl orthoacetate (3.34 mL, 26.26 mmol) in IMS (4.5 mL). The resultant mixture was stirred at reflux for 1 hour before the reaction was cooled to room temperature and loaded onto a SCX-2 cartridge. The cartridge was washed with MeOH before being eluted with 2M NH_3 in MeOH. The basic fractions were combined and concentrated *in vacuo* to afford 7-bromo-6-chloro-1-cyclohexyl-2-methyl-1H-imidazo[4,5-c]pyridine (961mg, 89%) as a red solid. LCMS (Method I, ESI): RT = 3.63 min, M+H = 328.0/330.0/332.0; ^{1}H NMR (400 MHz, DMSO): δ 8.60 (1 H, s), 5.59-5.47 (1 H, m), 2.73 (3 H, s), 2.11-1.83 (4 H, m), 1.76-1.63 (1 H, m), 1.56-1.06 (5H).

1-Cyclohexyl-2-methyl-1H-imidazo[4,5-c]pyridine-6,7-diamine

A stainless steel autoclave was charged with 7-bromo-6-chloro-1-cyclohexyl-2-methyl-1H-imidazo[4,5-c]pyridine (250 mg, 0.76 mmol), copper (II) sulphate pentahydrate (57 mg, 0.23 mmol) and 33% NH_3 in water (10 mL). The mixture was stirred at 170 °C for 18 hours before being cooled to room temperature. The suspension was filtered and the filtrate concentrated *in vacuo* to afford crude 1-cyclohexyl-2-methyl-1H-imidazo[4,5-c]pyridine-6,7-diamine as a brown solid. LCMS (Method I, ESI): RT = 1.69 min, M+H = 246.1.

8-Cyclohexyl-7-methyl-3,8-dihydro-1,3,4,6,8-pentaaza-as-indacene

A mixture of crude 1-cyclohexyl-2-methyl-1H-imidazo[4,5-c]pyridine-6,7-diamine, triethyl orthoformate (5 mL) and formic acid (100 μL) was stirred at 100 °C for 2 hours. The reaction mixture was cooled to room temperature before being concentrated *in vacuo* and the resultant residue purified by column chromatography on silica gel (gradient: 0-10% MeOH in DCM) then further purified by reverse-phase HPLC (column: C6 phenyl, mobile phase A: 0.1% formic acid in water, mobile phase B: 0.1% formic acid in MeCN, gradient: 10-30%) afforded 8-cyclohexyl-7-methyl-3,8-dihydro-1,3,4,6,8-pentaaza-as-indacene (18 mg, 9% over 2 steps) as a white solid. LCMS (Method A, ESI): RT = 2.60 min, M+H = 256.1; ^{1}H NMR (400 MHz,

DMSO): 13.16 (1 H, s), 8.57 (1 H, s), 8.35 (1 H, s), 4.49-4.33 (1 H, m), 2.92-2.74 (2 H, s), 2.64 (3 H, s), 1.95-1.85 (2 H, s), 1.83-1.66 (3 H, m), 1.60-1.42 (3 H, m).

The corresponding JAK1, JAK2, JAK3 and TYK2 inhibitions are shown in Table 5 for representative compounds of formula I.

Table 5

Example	JAK1 Ki, μM	JAK2 Ki, μM	JAK3 Ki, μM	TYK2 Ki, μM
1	0.26122	0.420557	0.237634	0.513142
2	0.001138	0.016486	0.049056	0.004304
3	0.009722	0.047982	0.021032	0.02497
4	0.004052	0.044471	0.012708	0.014269
5	0.005924	0.111159	0.149888	0.050533
18	0.008434	0.108721	0.22263	0.206268
19	0.009995	0.139436	0.279036	0.239237
20	0.01399	0.107342	0.176976	0.237784
21	0.011024	0.457367	0.685897	0.927659
22	0.014681	0.267865	0.778538	0.234874
23	0.008612	0.146286	0.241134	0.232245
25	0.001239	0.016185	0.104421	0.017179
26	0.003051	0.029113	0.117086	0.045052
27	0.001695	0.032221	0.276159	0.032175
28	0.001848	0.022389	0.165336	0.027469
29	0.002214	0.01704	0.076635	0.023599
31	0.002826	0.119716	0.647903	0.18333
32	0.001879	0.042711	0.292422	0.038786
33	0.001781	0.059561	0.326576	0.052209
34	0.00149	0.036426	0.239682	0.037727
35	0.002396	0.033579	0.196122	0.044292

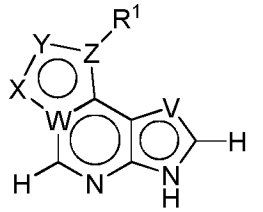
36	0.003305	0.043821	0.215563	0.056783
37	0.004516	0.060419	0.170286	0.01813
38	0.001232	0.028771	0.205437	0.026481
39	0.003133	0.056443	0.282875	0.069109
40	0.004489	0.071086	0.063674	0.067326
65	0.701868	1.277494	1.061825	2.96572
66	0.012527	0.174406	0.030622	0.149414
67	0.00242	0.040847	0.442057	0.034951
68	0.001602	0.024197	0.279822	0.016382
69	0.003818	0.054382	0.591353	0.040465
70	0.004269	0.030873	0.155592	0.034699
71	0.002805	0.024491	0.13598	0.021534
72	0.008508	0.03826	0.202533	0.143759
73	0.002751	0.029103	0.137863	0.02651
74	0.003694	0.032416	0.172245	0.032552
75	0.017948	0.050148	0.085545	0.107103
76	0.001361	0.009369	0.031313	0.024253
78	0.00034	0.008338	0.033115	0.008934
79	0.006221	0.045441	0.100955	0.08471
80	0.002306	0.02146	0.032864	0.013076
81	0.016765	0.071529	0.072254	0.08478
82	0.003238	0.0229	0.116645	0.072051
83	0.00016	0.004364	0.02308	0.004133
84	0.003756	0.035552	0.084921	0.0577
85	0.032327	0.784572	0.82741	1.191435
106	0.003342	0.044543	0.087385	0.092889
107	0.00251	0.007692	0.018385	0.002973

109	0.002094	0.004699	0.005365	0.001031
110	0.002014	0.0701	0.053402	0.019996
111	0.002135	0.083966	0.026961	0.018193
112	0.000764	0.004733	0.07026	0.011152
114	0.000085	0.00015	0.001388	0.00026
115	0.00099	0.015858	0.074436	0.006419
123	0.001193	0.004493	0.004712	0.006053
124	0.024527	0.10608	0.158411	0.494058
125	0.007567	0.039795	0.008847	0.137939
126	0.005218	0.01638	0.005774	0.010138
127	0.021903	0.099777	0.030526	0.082547
128	0.012219	0.052016	0.01025	0.008608
129	0.008236	0.181891	0.059604	0.372421
144	0.00090	0.003233	0.024081	0.003561
145	0.0204	0.017	0.0109	0.0101
146	0.07943	0.0424	0.0519	0.0714
147	0.0223	0.0532	0.00893	0.0107

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 the claims.

WHAT IS CLAIMED IS:

1. A compound of formula I:



I

stereoisomers, tautomers and pharmaceutically acceptable salts thereof, wherein

V is CR^4 or N, W is C, X and Z are N, and Y is CR^5 or N, or

V is CR^4 or N, W is N, X is CH, Y is CR^5, and Z is C;

R^1 is C_{3-12} cycloalkyl or 3-12 membered heterocyclyl, wherein R^1 is independently optionally substituted by halogen, oxo, $-CN$, $-OR^a$, $-S(O)_{0-2}R^a$, $-NR^aR^b$, C_{1-3} alkylene, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-(C_{0-3}$ alkylene)phenyl, or $-(C_{0-3}$ alkylene)3-6 membered heterocyclyl, wherein said alkyl, alkylene, alkenyl and alkynyl are independently optionally substituted by oxo, $-NR^cR^d$, $-OR^c$, $-CN$ or halogen and said C_{3-6} cycloalkyl, phenyl and 3-6 membered heterocyclyl are independently optionally substituted by R^6;

R^4 is hydrogen, halogen, C_{1-6} alkyl or $-CN$.

R^5 is 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)$S(O)_{1-2}R^a$, $-(C_{0-3}$ alkylene)$NR^aS(O)_{1-2}R^b$, $-(C_{0-3}$ alkylene)$S(O)_{1-2}NR^aR^b$, $-(C_{0-3}$ alkylene)$NR^aS(O)_{1-2}NR^aR^b$, $-(C_{0-3}$ alkylene)C_{3-12} cycloalkyl, $-(C_{0-3}$ alkylene)C_{6-14} 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, 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)$S(O)_{0-2}R^c$, $-(C_{0-3}$ alkylene)$NR^cS(O)_{1-2}R^d$, $-(C_{0-3}$ alkylene)$S(O)_{1-2}NR^cR^d$, $-(C_{0-3}$ alkylene)$NR^cS(O)_{1-2}NR^cR^d$ or C_{1-6} alkyl optionally substituted by oxo, $-CN$ or halogen;

each R^6 is independently oxo, halogen, −CN, $-C(O)R^a$, $-C(O)OR^a$, $-NR^aC(O)R^b$, $-C(O)NR^aR^b$, $-NR^aC(O)NR^aR^b$, $-OC(O)NR^aR^b$, $-NR^aC(O)OR^b$, $-S(O)_{1-2}R^a$, $-NR^aS(O)_2R^b$, $-S(O)_2NR^aR^b$, $-OR^a$, $-SR^a$, $-NR^aR^b$, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3-7 membered heterocycly or C_{6-14} aryl, and wherein said alkyl, alkenyl, alkynyl, cycloalkyl, 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)C_{3-6} cycloalkyl, $-S(O)_{1-2}R^i$, $-(C_{0-3}$ alkylene)3-12 membered heterocyclyl, $-(C_{0-3}$ alkylene)C(O)3-12 membered heterocyclyl or $-(C_{0-3}$ 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, $-(C_{0-3}$ alkylene)C_{3-6} cycloalkyl, $-(C_{0-3}$ alkylene)3-12 membered heterocyclyl, $-(C_{0-3}$ alkylene)C(O)3-12 membered heterocyclyl or $-(C_{0-3}$ alkylene)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, R^i are independently hydrogen or C_{1-6} alkyl optionally substituted by halogen or oxo, with the proviso that R^5 is not OH and Formula I includes compounds other than:

N-[(1S,3S,4R)-3-(2-aminoimidazo[4,5-d]pyrrolo[2,3-b]pyridin-1(6H)-yl)-4-ethylcyclopentyl]-cyclopropanesulfonamide;

N-((1R,3S,4R)-3-ethyl-4-(pyrrolo[2,3-b][1,2,3]triazolo[4,5-d]pyridin-1(6H)-yl)cyclopentyl)cyclopropanesulfonamide;

N-[(1S,3R,4S)-3-ethyl-4-[2-(trifluoromethyl)imidazo[4,5-d]pyrrolo[2,3-b]pyridin-1(6H)-yl]cyclopentyl]-cyclopropanesulfonamide;

N-[(1S,3R,4S)-3-ethyl-4-(2-methylimidazo[4,5-d]pyrrolo[2,3-b]pyridin-1(6H)-yl)cyclopentyl]-Cyclopropanesulfonamide;

N-[(1S,3S,4R)-3-[2-(difluoromethyl)imidazo[4,5-d]pyrrolo[2,3-b]pyridin-1(6H)-yl]-4-ethylcyclopentyl]-cyclopropanesulfonamide;

N-[(1S,3R,4S)-3-methyl-4-[2-(trifluoromethyl)imidazo[4,5-d]pyrrolo[2,3-b]pyridin-1(6H)-yl]cyclopentyl]-cyclopropanesulfonamide;

N-[(1S,3S,4R)-3-(2-cyclopropylimidazo[4,5-d]pyrrolo[2,3-b]pyridin-1(6H)-yl)-4-methylcyclopentyl]-cyclopropanesulfonamide;

N-[(1S,3R,4S)-3-methyl-4-(2-methylimidazo[4,5-d]pyrrolo[2,3-b]pyridin-1(6H)-yl)cyclopentyl]-cyclopropanesulfonamide;

1-cyclohexyl-1,6-dihydro-2-(trifluoromethyl)-imidazo[4,5-d]pyrrolo[2,3-b]pyridine; and

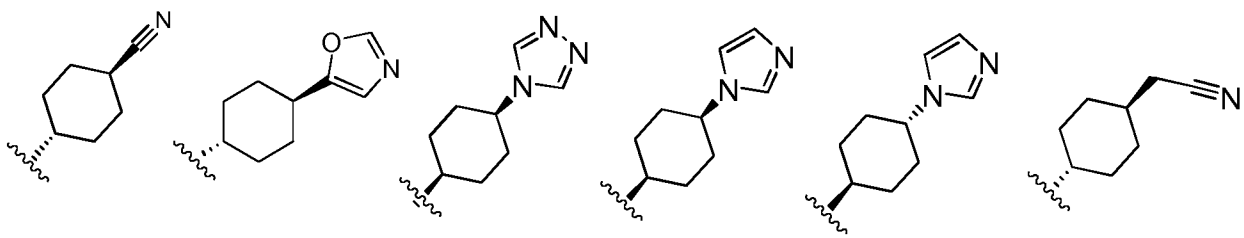
1-cyclohexyl-1,6-dihydro-2-methyl-imidazo[4,5-d]pyrrolo[2,3-b]pyridine.

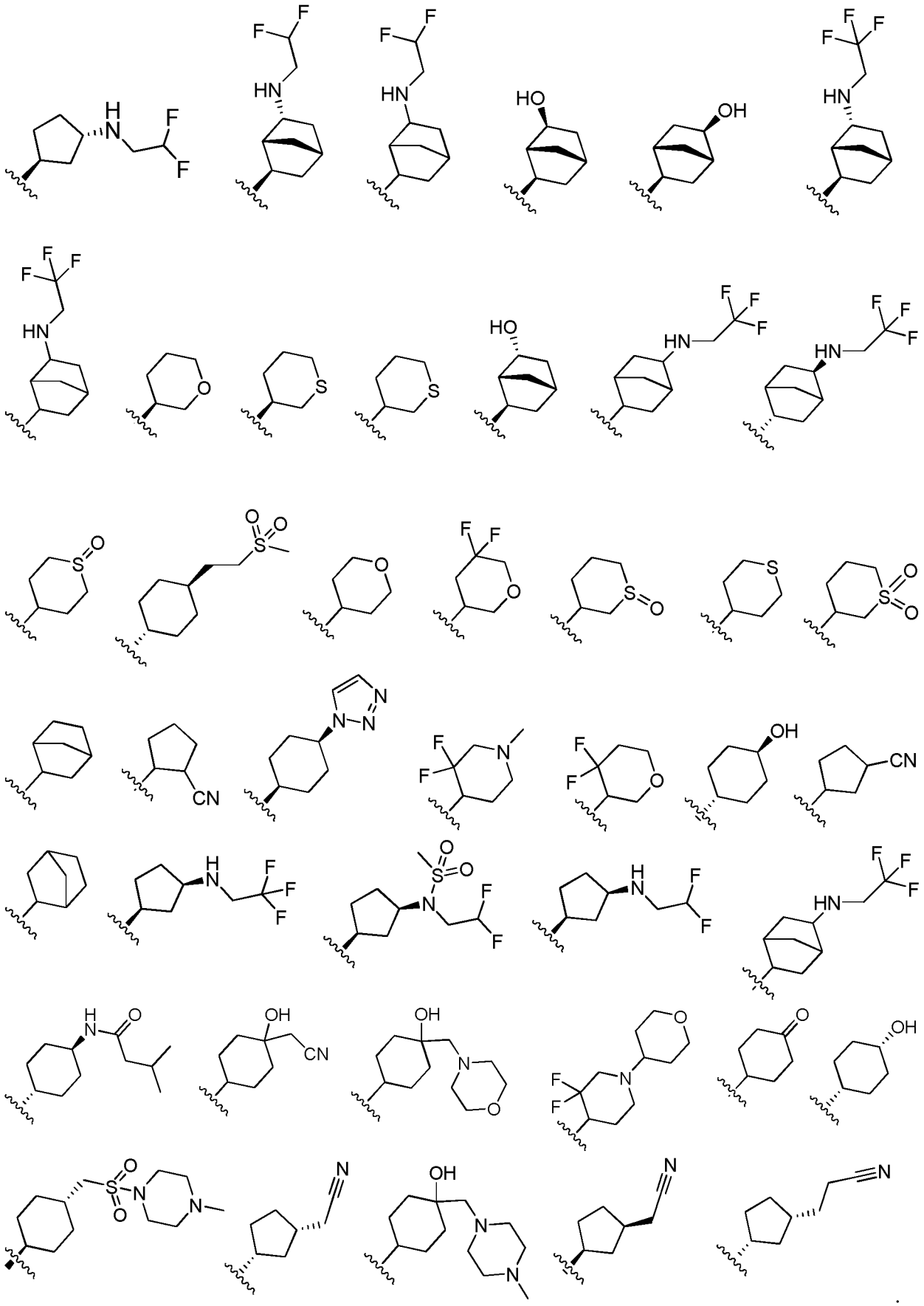
2. The compound of claim 1, wherein V is CR^4, W is C, X and Z are N, and Y is CR^5.

3. The compound of claim 1, wherein V is CR^4, W is N, X is CH, Y is CR^5, and Z is C.

4. The compound of claims 1-3, wherein R^1 is tetrahydropyranyl, tetrahydro-2H-thiopyranyl, piperidinyl, cyclopentyl or cyclohexyl, wherein R^1 is independently optionally substituted by halogen, oxo, $-CN$, $-OR^a$, $-S(O)_{0-2}R^a$, $-NR^aR^b$, C_{1-3} alkylene, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, or 3-6 membered heterocyclyl, wherein said alkyl, alkenyl and alkynyl are independently optionally substituted by oxo, $-NR^cR^d$, $-OR^c$, $-CN$ or halogen and said C_{3-6} cycloalkyl, phenyl and 3-6 membered heterocyclyl are independently optionally substituted by R^6.

5. The compound of claims 1-4, wherein R^1 is selected from:





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

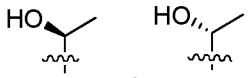
6. The compound of claims 1-5, wherein R^4 is hydrogen or CN.

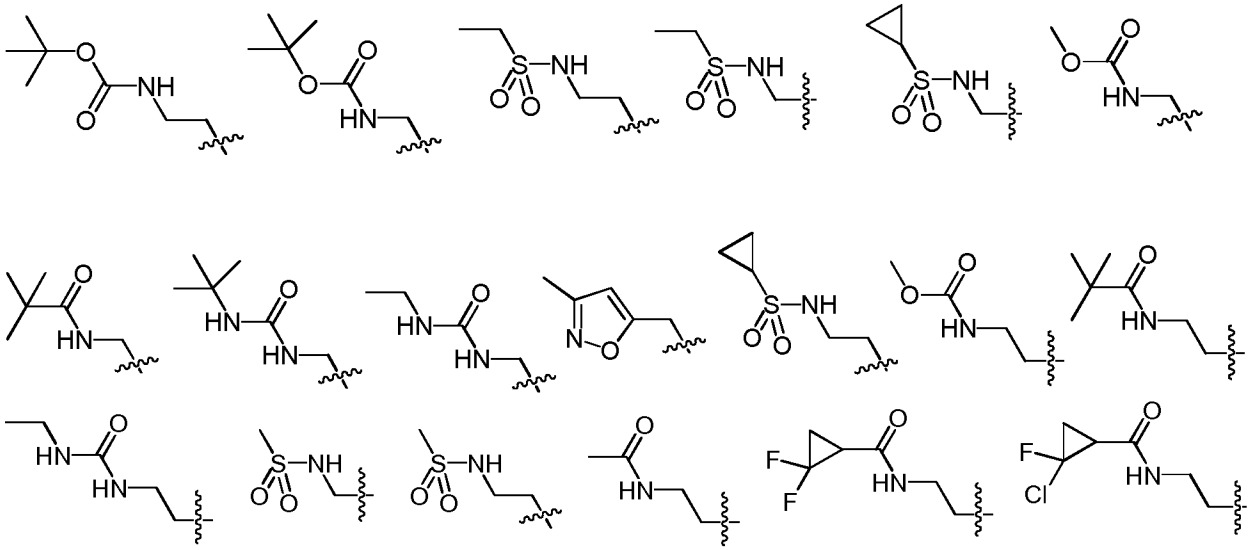
7. The comound of claims 1-6, wherein R^4 is hydrogen.

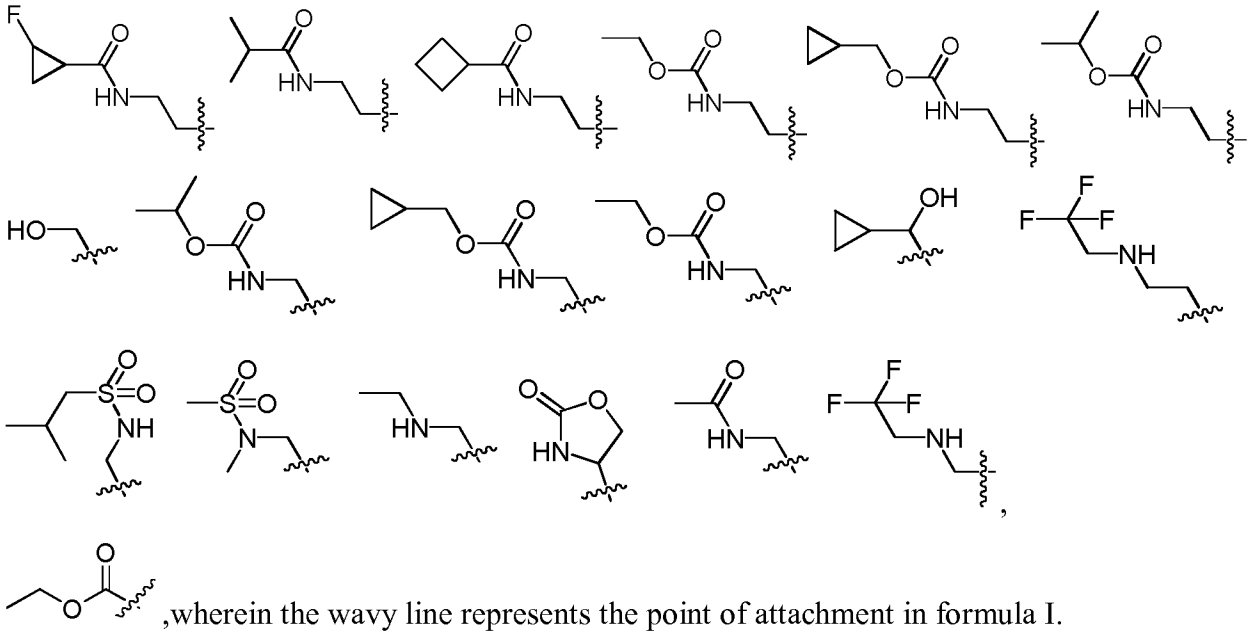
8. The compound of claims 1-7, wherein R^5 is C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, $-(C_{1-3}$ alkylene)CN, $-(C_{1-3}$ alkylene)NR^aR^b, $-(C_{1-3}$ alkylene)OR^a, $-(C_{1-3}$ alkylene)SR^a, $-(C_{1-3}$ alkylene)$C(O)R^a$, $-(C_{1-3}$ alkylene)$NR^aC(O)R^b$, $-(C_{1-3}$ alkylene)$C(O)NR^aR^b$, $-(C_{1-3}$ alkylene)$C(O)OR^a$, $-(C_{1-3}$ alkylene)$OC(O)R^a$, $-(C_{1-3}$ alkylene)$NR^aC(O)NR^aR^b$, $-(C_{1-3}$ alkylene)$OC(O)NR^aR^b$, $-(C_{1-3}$ alkylene)$NR^aC(O)OR^b$, $-(C_{1-3}$ alkylene)$S(O)_{1-2}R^a$, $-(C_{1-3}$ alkylene)$NR^aS(O)_{1-2}R^b$, $-(C_{1-3}$ alkylene)$S(O)_{1-2}NR^aR^b$, $-(C_{1-3}$ alkylene)$NR^aS(O)_{1-2}NR^aR^b$, $-(C_{1-3}$ alkylene)C_{3-6} cycloalkyl, $-(C_{1-3}$ alkylene)C_{6-14} aryl, $-(C_{1-3}$ alkylene)3-12 membered heterocyclyl or $-(C_{1-3}$ alkylene)C(O)3-12 membered heterocyclyl, wherein said alkyl, alkenyl, alkynyl, alkylene, cycloalkyl, aryl and heterocyclyl are independently optionally substituted by halogen, oxo, $-(C_{0-3}$ 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)$S(O)_{0-2}R^c$, $-(C_{0-3}$ alkylene)$NR^cS(O)_{1-2}R^d$, $-(C_{0-3}$ alkylene)$S(O)_{1-2}NR^cR^d$, $-(C_{0-3}$ alkylene)$NR^cS(O)_{1-2}NR^cR^d$ or C_{1-6} alkyl optionally substituted by oxo, $-CN$ or halogen.

9. The compound of claims 1-8, wherein R^5 is ethyl substituted by OH, $-(C_{1-3}$ alkylene)NR^aR^b, $-(C_{1-3}$ alkylene)OR^a, $-(C_{1-3}$ alkylene)$NR^aC(O)R^b$, $-(C_{1-3}$ alkylene)$NR^aC(O)NR^aR^b$, $-(C_{1-3}$ alkylene)$NR^aC(O)OR^b$, $-(C_{1-3}$ alkylene)$NR^aS(O)_{1-2}R^b$ or $-(C_{1-3}$ alkylene)3-12 membered heterocyclyl, wherein said alkylene and heterocyclyl are independently optionally substituted by halogen, oxo or C_{1-6} alkyl optionally substituted by halogen.

10. The compound of claims 1-8, wherein R^5 is selected from methyl, ethyl,







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

11. The compound of claims 1-10, wherein R^6 is independently oxo, halogen, −CN, $-C(O)R^a$, $-C(O)OR^a$, $-NR^aC(O)R^b$, $-C(O)NR^aR^b$, $-NR^aC(O)NR^aR^b$, $-OC(O)NR^aR^b$, $-NR^aC(O)OR^b$, $-S(O)_{1-2}R^a$, $-NR^aS(O)_2R^b$, $-S(O)_2NR^aR^b$, $-OR^a$, $-SR^a$, $-NR^aR^b$, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3-7 membered heterocycly or C_{6-14} aryl, and wherein said alkyl, alkenyl, alkynyl, cycloalkyl, 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.

12. The compound of claims 1-11, wherein each R^a and R^b are independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-S(O)_{1-2}R^i$, $-C_{3-6}$ cycloalkyl, −3-12 membered heterocyclyl, −C(O)3-12 membered heterocyclyl or $-C_{6-14}$ 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.

13. The compound of claims 1-12, wherein each R^a and R^b are independently selected from hydrogen, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, sec-butyl, $-S(O)_2CH_3$, $-CF_3$, $-CH_2CF_3$, $-CH_2F$, $-CHF_2$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2NH_2$, $-CH_2CH_2NH_2$, $-CH_2CH_2N(CH_3)_2$, $-CH_2N(CH_3)_2$, 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.

14. The compound of claims 1-13, one R^a is H and one R^b is C_{1-6} alkyl 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.

15. The compound of claims 1-14, wherein each R^c and R^d are independently hydrogen, methyl, ethyl, isopropyl, butyl, t-butyl, sec-butyl, $-CF_3$, $-CH_2CF_3$, $-CH_2F$, $-CHF_2$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2NH_2$, $-CH_2CH_2NH_2$, $-CH_2CH_2N(CH_3)_2$, $-CH_2N(CH_3)_2$, 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.

16. The compound of claims 1-15, wherein each R^e, R^f, R^g, R^h and R^i are independently hydrogen, methyl, ethyl, propyl or isopropyl, optionally substituted by halogen or oxo.

17. The compound of claim 1, wherein R^1 is C_{5-7} cycloalkyl independently substituted by one NR^aR^b wherein R^a is H and R^b is C_{1-6} alkyl 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.

18. The compound of claim 1, selected from:

trans 1-(4-Cyano-cyclohexyl)-2-((R)-1-hydroxy-ethyl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacene-8-carbonitrile;

trans (R)-1-[1-(4-Oxazol-5-yl-cyclohexyl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol;

cis (R)-1-[1-(4-[1,2,4]Triazol-4-yl-cyclohexyl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol;

cis (R)-1-[1-(4-Imidazol-1-yl-cyclohexyl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol;

trans (R)-1-[1-(4-Imidazol-1-yl-cyclohexyl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol;

trans [4-(2-Methyl-6H-1,3,5,6-tetraaza-as-indacen-1-yl)-cyclohexyl]-acetonitrile;

(R)-1-{1-[(1S,3S)-3-(2,2-Difluoro-ethylamino)-cyclopentyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethanol;

(2-{1-[6-(2,2-Difluoro-ethylamino)-bicyclo[2.2.1]hept-2-yl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-carbamic acid tert-butyl ester;

{2-[1-(5-Hydroxy-bicyclo[2.2.1]hept-2-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-carbamic acid tert-butyl ester;

{2-[1-(6-Hydroxy-bicyclo[2.2.1]hept-2-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-carbamic acid tert-butyl ester;

{1-[6-(2,2,2-Trifluoro-ethylamino)-bicyclo[2.2.1]hept-2-yl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-carbamic acid tert-butyl ester;

[1-(5-Hydroxy-bicyclo[2.2.1]hept-2-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-carbamic acid tert-butyl ester;

(2-{1-[5-(2,2,2-Trifluoro-ethylamino)-bicyclo[2.2.1]hept-2-yl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-carbamic acid tert-butyl ester;

{2-[1-(6-Hydroxy-bicyclo[2.2.1]hept-2-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-carbamic acid tert-butyl ester;

Ethanesulfonic acid {2-[(S)-1-(tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-amide;

Ethanesulfonic acid [(S)-1-(tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-amide;

Cyclopropanesulfonic acid [(S)-1-(tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-amide;

[(S)-1-(Tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-carbamic acid methyl ester;

2,2-Dimethyl-N-[(S)-1-(tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-propionamide;

1-tert-Butyl-3-[(S)-1-(tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-urea;

1-Ethyl-3-[(S)-1-(tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-urea;

2-(3-Methyl-isoxazol-5-ylmethyl)-1-(S)-tetrahydro-pyran-3-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacene;

Cyclopropanesulfonic acid {2-[(S)-1-(tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-amide;

{2-[(S)-1-(Tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-carbamic acid methyl ester;

2,2-Dimethyl-N-{2-[(S)-1-(tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-propionamide;

1-tert-Butyl-3-{2-[(S)-1-(tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-urea;

1-Ethyl-3-{2-[(S)-1-(tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-urea;

N-[1-(Tetrahydro-thiopyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-methanesulfonamide;

trans Cyclopropanesulfonic acid (2-{1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-amide;

trans N-(2-{1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-methanesulfonamide;

trans N-(2-{1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-acetamide;

trans 2,2-Difluoro-cyclopropanecarboxylic acid (2-{1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-amide;

trans Ethanesulfonic acid (2-{1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-amide;

Trans (2-{1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-carbamic acid methyl ester;

trans 2-Chloro-2-fluoro-cyclopropanecarboxylic acid (2-{1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-amide;

trans 2,2-Dimethyl-N-(2-{1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-propionamide;

2-Fluoro-cyclopropanecarboxylic acid (2-{1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-amide;

trans N-(2-{1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-isobutyramide;

trans Cyclobutanecarboxylic acid (2-{1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-amide;

trans (2-{1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-carbamic acid ethyl ester;

trans (2-{1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-carbamic acid cyclopropylmethyl ester;

trans (2-{1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-carbamic acid tert-butyl ester;

2-Fluoro-cyclopropanecarboxylic acid (2-{1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-amide;

Trans (2-{1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-carbamic acid isopropyl ester;

N-{2-[1-(Tetrahydro-thiopyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-methanesulfonamide;

N-[1-(5,5-Difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-methanesulfonamide;

Trans (2,2,2-Trifluoro-ethyl)-(4-{2-[2-(2,2,2-trifluoro-ethylamino)-ethyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclohexyl)-amine;

(R)-1-[1-(1,1-Dioxo-hexahydro-thiopyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol;

(R)-1-[1-(Tetrahydro-thiopyran-4-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol;

(R)-1-[1-(Tetrahydro-thiopyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol;

Cyclopropyl-[1-(tetrahydro-pyran-4-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-methanol;

trans Cyclopropyl-{1-[4-(2-methanesulfonyl-ethyl)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-methanol;

2-Methyl-1-(tetrahydro-thiopyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacene;

2-Methyl-1-(1-oxo-hexahydro-thiopyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacene;

1-(1,1-Dioxo-hexahydro-thiopyran-3-yl)-2-methyl-1,6-dihydro-1,3,5,6-tetraaza-as-indacene;

2-Methyl-1-(tetrahydro-thiopyran-4-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacene;

2-Methyl-1-(1-oxo-hexahydro-thiopyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacene;

2-Methyl-1-(1-oxo-hexahydro-thiopyran-4-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacene;

N-{1-[(1S,3R)-3-(2,2,2-Trifluoro-ethylamino)-cyclopentyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-methanesulfonamide;

trans N-{4-[2-((R)-1-Hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclohexyl}-3-methyl-butyramide;

N-(1-{(1S,3R)-3-[(2,2-Difluoro-ethyl)-methanesulfonyl-amino]-cyclopentyl}-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl)-methanesulfonamide;

{1-[(1S,3R)-3-(2,2-Difluoro-ethylamino)-cyclopentyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-carbamic acid methyl ester;

trans Ethanesulfonic acid {1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-amide;

trans N-{1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-methanesulfonamide;

trans Cyclopropanesulfonic acid {1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-amide;

trans {1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-carbamic acid methyl ester;

trans {1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-carbamic acid ethyl ester;

trans {1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-carbamic acid tert-butyl ester;

trans {1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-carbamic acid cyclopropylmethyl ester;

trans {1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-carbamic acid isopropyl ester;

(1-Bicyclo[2.2.1]hept-2-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl)-carbamic acid methyl ester;

trans 2-Methyl-propane-1-sulfonic acid {1-[4-(2,2,2-trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl}-amide;

Ethanesulfonic acid (1-bicyclo[2.2.1]hept-2-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl)-amide;

N-(1-Bicyclo[2.2.1]hept-2-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl)-acetamide;

N-(2-{1-[(1S,3R)-3-(2,2,2-Trifluoro-ethylamino)-cyclopentyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethyl)-methanesulfonamide;

N-(2,2-Difluoro-ethyl)-N-{(1R,3S)-3-[2-(2-methanesulfonylamino-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentyl}-methanesulfonamide;

N-(1-Bicyclo[2.2.1]hept-2-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl)-methanesulfonamide;

trans (2,2,2-Trifluoro-ethyl)-(4-{2-[(2,2,2-trifluoro-ethylamino)-methyl]-6H-1,3,5,6-tetraaza-as-indacen-1-yl}-cyclohexyl)-amine;

Trans 2-[2-((R)-1-Hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentanecarbonitrile;

Cis 2-[2-((R)-1-Hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentanecarbonitrile;

(R)-3-[2-(1-Hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentanecarbonitrile;

N-(1-Bicyclo[2.2.1]hept-2-yl-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl)-N-methyl-methanesulfonamide;

[1-(4,4-Difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-ethyl-amine;

N-[1-(-3,3-Difluoro-1-methyl-piperidin-4-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-methanesulfonamide;

Ethanesulfonic acid [1-(-4,4-difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-amide;

Cyclopropanesulfonic acid [1-(-4,4-difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-amide;

[1-(4,4-Difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-ylmethyl]-carbamic acid methyl ester;

N-{2-[1-(-3,3-Difluoro-1-methyl-piperidin-4-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-methanesulfonamide;

Ethanesulfonic acid {2-[1-(4,4-difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-amide;

Cyclopropanesulfonic acid {2-[1-(4,4-difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-amide;

N-{2-[1-(4,4-Difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-methanesulfonamide;

{2-[1-(4,4-Difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethyl}-carbamic acid methyl ester;

cis (R)-1-[1-(4-[1,2,3]Triazol-1-yl-cyclohexyl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol

(R)-1-[1-((S)-3,3-Difluoro-1-methyl-piperidin-4-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol;

(R)-1-[1-(-3,3-Difluoro-1-methyl-piperidin-4-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-ethanol;

Trans 4-[2-((R)-1-Hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclohexanol;

3-{(1R,3R)-3-[2-((R)-1-Hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentyl}-propionitrile;

Cis 4-[2-((R)-1-Hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclohexanol;

4-[2-((R)-1-Hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclohexanone;

(R)-1-{1-[-3,3-Difluoro-1-(tetrahydro-pyran-4-yl)-piperidin-4-yl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethanol;

{1-Hydroxy-4-[2-((R)-1-hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclohexyl}-acetonitrile (single stereoisomer, cyclohexane stereochemistry unknown)

[1-(3,3-Difluoro-1-methyl-piperidin-4-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-methanol;

[1-(4,4-Difluoro-tetrahydro-pyran-3-yl)-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl]-methanol;

[1-Hydroxy-4-(2-methyl-6H-1,3,5,6-tetraaza-as-indacen-1-yl)-cyclohexyl]-acetonitrile;

{(1R,3S)-3-[2-((R)-1-Hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentyl}-acetonitrile;

{(1S,3R)-3-[2-((R)-1-Hydroxy-ethyl)-6H-1,3,5,6-tetraaza-as-indacen-1-yl]-cyclopentyl}-acetonitrile;

(R)-1-{1-[(1S,3R)-3-(2,2,2-Trifluoro-ethylamino)-cyclopentyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethanol;

(R)-1-{1-[(1S,3R)-3-(2,2-Difluoro-ethylamino)-cyclopentyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-ethanol;

Trans 2-Methyl-1-[4-(4-methyl-piperazine-1-sulfonylmethyl)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacene;

Trans 4-{1-[4-(2,2,2-Trifluoro-ethylamino)-cyclohexyl]-1,6-dihydro-1,3,5,6-tetraaza-as-indacen-2-yl}-oxazolidin-2-one;

(9-Cyclohexyl-3H-dipyrrolo[1,2-c;3',2'-e]pyrimidin-8-yl)-methanol;

9-Cyclohexyl-3H-dipyrrolo[1,2-c;3',2'-e]pyrimidine-8-carboxylic acid ethyl ester; and

8-Cyclohexyl-7-methyl-3,8-dihydro-1,3,4,6,8-pentaaza-as-indacene.

19. A pharmaceutical composition comprising a compound of any one of claims 1-18, a stereoisomer, tautomer or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant or vehicle.

20. A compound of any one of claims 1-18, a stereoisomer, tautomer, prodrug or pharmaceutically acceptable salt thereof, for use in therapy.

21. A compound of any one of claims 1-18, a stereoisomer, tautomer, prodrug or pharmaceutically acceptable salt thereof, for use in treating an immunological disease.

22. A compound of any one of claims 1-18, a stereoisomer, tautomer, prodrug or pharmaceutically acceptable salt thereof, for use in treating an immunological disease selected from rheumatoid arthritis, asthma, systemic lupus erythematosus, psoriasis, IBD and transplant rejection.

23. The use of a compound of any one of claims 1-18, 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.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/063621

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/437 A61P37/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2011/086053 A1 (HOFFMANN LA ROCHE [CH]; BABU SRINIVASAN [US]; BERGERON PHILLIPPE [US];) 21 July 2011 (2011-07-21) claims 1,20,21; compounds 82,86,87,99-103,217,223,224,231-233 -----	1,2,4-23
X,P	MARK ZAK ET AL: "Discovery and Optimization of C -2 Methyl Imidazopyrrolopyridines as Potent and Orally Bioavailable JAK1 Inhibitors with Selectivity over JAK2", JOURNAL OF MEDICINAL CHEMISTRY, vol. 55, no. 13, 14 June 2012 (2012-06-14) , pages 6176-6193, XP055037261, ISSN: 0022-2623, DOI: 10.1021/jm300628c table 1 ----- -/--	1,2,4-23

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 September 2012	24/10/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Johnson, Claire

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2012/063621

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

2(completely); 1, 4-23(partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/063621

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/068881 A1 (ABBOTT LAB [US]; WISHART NEIL [US]; ARGIRIADI MARIA A [US]; CALDERWOOD) 9 June 2011 (2011-06-09) page 43 - page 45; claims 22,23 page 1, paragraph 3 page 49 - page 50 -----	1,2,4-23

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2012/063621

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011086053 A1	21-07-2011	AR 079984 A1	07-03-2012
		CA 2781578 A1	21-07-2011
		CN 102712640 A	03-10-2012
		US 2011201593 A1	18-08-2011
		WO 2011086053 A1	21-07-2011
WO 2011068881 A1	09-06-2011	AR 079234 A1	04-01-2012
		AU 2010326108 A1	14-06-2012
		CA 2781891 A1	09-06-2011
		CN 102711476 A	03-10-2012
		DO P2012000151 A	30-09-2012
		EP 2506716 A1	10-10-2012
		TW 201125869 A	01-08-2011
		US 2011311474 A1	22-12-2011
		UY 33071 A	31-05-2011
		WO 2011068881 A1	09-06-2011

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 2(completely); 1, 4-23(partially)

   Compounds of Formula I wherein V is CR4, W is C, X and Z are N and Y is CR5 or N, their pharmaceutical compositions and uses.

   ---

2. claims: 3(completely); 1, 4-23(partially)

   Compounds of present Formula I in which W is N, their pharmaceutical compositions and uses

   ---

3. claims: 1, 4-23(all partially)

   Compounds of present Formula I in which W is C and V is N, their pharmaceutical compositions and uses.
