

HETEROCYCLIC PAD4 INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of Indian Provisional Application No.

- 5 202041006146, filed February 12, 2020, the contents of which is specifically incorporated by reference herein.

FIELD OF THE INVENTION

- 10 The invention generally relates to substituted heterocyclic compounds, methods for preparing these compounds, pharmaceutical compositions comprising these compounds, and use of these compounds in the treatment of a disease or a disorder associated with PAD4 enzyme activity.

BACKGROUND OF THE INVENTION

- 15 PAD4 is a member of the peptidylarginine deiminase (PAD) family of enzymes capable of catalysing the citrullination of arginine into citrulline within peptide sequences. PAD4 is responsible for the deimination or citrullination of a variety of proteins *in vitro* and *in vivo*, with consequences of diverse functional responses in a variety of diseases (*Jones J.E. et al, Curr. Opin. Drug Discov. Devel., 12(5), (2009), 616-*
20 *627*). Examples of exemplar diseases or disorders include rheumatoid arthritis, diseases with neutrophilic contributions to pathogenesis (for example vasculitis, systemic lupus erythematosus, ulcerative colitis) in addition to oncology indications. PAD4 inhibitors also have wider applicability as tools and therapeutics for human diseases and disorders through epigenetic mechanisms.
- 25 Inhibitors of PAD4 have utility against Rheumatoid Arthritis (RA). RA is an autoimmune disease affecting approximately 1% of the population (*Wegner N. et al, Immunol. Rev., 233(1), (2010), 34-54*). It is characterized by inflammation of articular joints leading to debilitating destruction of bone and cartilage. A weak genetic association between PAD4 polymorphisms and susceptibility to RA has been suggested, albeit
30 inconsistently, in a number of population studies (*Kochi Y. et al, Ann. Rheum. Dis., 70, (2011), 512-515*). PAD4 (along with family member PAD2) has been detected in synovial tissue where it is responsible for the deimination of a variety of joint proteins. This process is presumed to lead to a break of tolerance to, and initiation of immune responses

to, citrullinated substrates such as fibrinogen, vimentin and collagen in RA joints. These anti-citrullinated protein antibodies (ACPA) contribute to disease pathogenesis and may also be used as a diagnostic test for RA (e.g. the commercially available CCP2 or cyclic citrullinated protein 2 test). In addition, increased citrullination may also offer additional

5 direct contributions to disease pathogenesis through its ability to affect directly the function of several joint and inflammatory mediators (e.g. fibrinogen, anti-thrombin, and multiple chemokines). In a smaller subset of RA patients, anti-PAD4 antibodies can be measured and may correlate with a more erosive form of the disease.

PAD4 inhibitors are also useful for the reduction of pathological neutrophil

10 activity in a variety of diseases. Studies suggest that the process of Neutrophil Extracellular Trap (NET) formation, an innate defense mechanism by which neutrophils are able to immobilize and kill pathogens, is associated with histone citrullination and is deficient in a PAD4 knockout mice (*Neeli I. et al, J. Immunol., 180, (2008), 1895-1902,* and *Li P. et al, J. Exp. Med., 207(9), (2010), 1853-1862*). PAD4 inhibitors may therefore

15 have applicability for diseases where NET formation in tissues contributes to local injury and disease pathology. Such diseases include, but are not limited to, small vessel vasculitis (*Kessenbrock K. et al, Nat. Med., 15(6), (2009), 623-625*), systemic lupus erythematosus (*Hakim A. et al, Proc. Natl. Acad. Sci. USA, 107(21), (2010), 9813-9818,* and *Villanueva E. et al, J. Immunol., 187(1), (2011), 538-52*), ulcerative colitis

20 (*Savchenko A. et al, Pathol. Int., 61(5), (2011), 290-7*), cystic fibrosis, asthma (*Dworski R. et al, J. Allergy Clin. Immunol., 127(5), (2011), 1260-6*), deep vein thrombosis (*Fuchs T. et al, Proc. Natl. Acad. Sci. USA, 107(36), (2010), 15880-5*), periodontitis (*Vitkov L. et al, Ultrastructural Pathol., 34(1), (2010), 25-30*), sepsis (*Clark S.R. et al, Nat. Med., 13(4), (2007), 463-9*), appendicitis (*Brinkmann V. et al, Science, 303, (2004), 1532-5*),

25 and stroke. In addition, there is evidence that NETs may contribute to pathology in diseases affecting the skin, e.g., in cutaneous lupus erythematosus (*Villanueva E. et al, J. Immunol., 187(1), (2011), 538-52*) and psoriasis (*Lin A.M. et al., J. Immunol., 187(1), (2011), 490-500*), so a PAD4 inhibitor may show benefit to tackle NET skin diseases, when administered by a systemic or cutaneous route. PAD4 inhibitors may affect

30 additional functions within neutrophils and have wider applicability to neutrophilic diseases.

Studies have demonstrated efficacy of tool PAD inhibitors (for example, chloro-amidine) in a number of animal models of disease, including collagen-induced arthritis (*Willis V.C. et al, J. Immunol., 186(7), (2011), 4396-4404*), dextran sulfate sodium (DSS)-induced experimental colitis (*Chumanevich A.A. et al, Am. J. Physiol.*

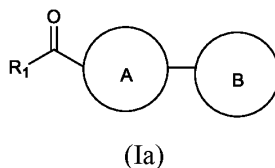
5 *Gastrointest. Liver Physiol., 300(6), (2011), G929-G938*), spinal cord repair (*Lange S. et al, Dev. Biol., 355(2), (2011), 205-14*), and experimental autoimmune encephalomyelitis (EAE). The DSS colitis report also demonstrates that chloro-amidine drives apoptosis of inflammatory cells both *in vitro* and *in vivo*, suggesting that PAD4 inhibitors may be effective more generally in widespread inflammatory diseases.

10 PAD4 inhibitors are also useful in the treatment of cancers (*Slack J.L. et al, Cell. Mol. Life Sci., 68(4), (2011), 709-720*). Over-expression of PAD4 has been demonstrated in numerous cancers (*Chang X. et al, BMC Cancer, 9, (2009), 40*). An anti-proliferative role has been suggested for PAD4 inhibitors from the observation that PAD4 citrullinates arginine residues in histones at the promoters of p53-target genes such as p21, which are
15 involved in cell cycle arrest and induction of apoptosis (*Li P. et al, Mol. Cell Biol., 28(15), (2008), 4745-4758*).

The aforementioned role of PAD4 in deiminating arginine residues in histones may be indicative of a role for PAD4 in epigenetic regulation of gene expression. PAD4 is the primary PAD family member observed to be resident in the nucleus as well as the
20 cytoplasm. Early evidence that PAD4 may act as a histone demethyliminase as well as a deiminase is inconsistent and unproven. However, it may reduce histone arginine methylation (and hence epigenetic regulation associated with this mark) indirectly *via* depletion of available arginine residues by conversion to citrulline. PAD4 inhibitors are useful as epigenetic tools or therapeutics for affecting expression of varied target genes in
25 additional disease settings. Through such mechanisms, PAD4 inhibitors may also be effective in controlling citrullination levels in stem cells and may therefore therapeutically affect the pluripotency status and differentiation potential of diverse stem cells including, but not limited to, embryonic stem cells, neural stem cells, haematopoietic stem cells and cancer stem cells. Accordingly, there remains an unmet need to identify
30 and develop PAD4 inhibitors for the treatment of PAD4-mediated diseases or disorders.

SUMMARY OF THE INVENTION

Accordingly, there are provided compounds of Formula (Ia):



or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof.

In another general aspect, there are provided pharmaceutical compositions comprising at least one compound of Formula (I), or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers.

In another general aspect, there is provided a method of treating a disease or a disorder associated with PAD4 enzyme activity, comprising administering to a subject in need of such treatment, a therapeutically effective amount of at least one compound of Formula (I), or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof.

The details of one or more embodiments of the invention are set forth in the description below. Other features, objects and advantages of the invention will be apparent from the following description including claims.

DETAILED DESCRIPTION OF THE INVENTION

1. Definitions

The following are definitions of terms used in this specification. The initial definition provided for a group or term herein applies to that group or term throughout the specification, individually or as part of another group, unless otherwise indicated. Although the invention is described with reference to exemplary embodiments, it should nevertheless be understood that no limitation of the scope of the invention is thereby intended. Numerous alterations and further modifications of the inventive features of the invention can be envisaged by one skilled in the relevant art, and having possession of this disclosure. All such alterations and modifications are to be considered within the scope of the invention. It must be noted that, as used in this specification and the appended claims, the singular forms “a”, “an”, and “the” include plural references unless the content clearly dictates otherwise. All references including patents, patent

applications, and literature cited in the specification are expressly incorporated herein by reference in their entirety.

The term “C₁₋₆ alkyl” as used herein refers to and includes cyclic, straight and branched chain hydrocarbon groups containing 1 to 6 carbon atoms. Typical, non-limiting
5 examples of C₁₋₆ alkyl include methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

The term “alkenyl” as used herein refers to and includes straight or branched chain hydrocarbon groups containing 2 to 20 carbons, which include 1 to 6 double bonds. Typical, non-limiting examples of alkenyl include vinyl, 2-propenyl, 3-butenyl, 2-
10 butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-nonenyl, 4-decenyl, 3-undecenyl, 4-dodecenyl, and the like.

The term “alkynyl” as used herein refers to and includes straight or branched chain hydrocarbon groups containing 2 to 12 carbon atoms, and at least one carbon to carbon triple bond. Typical, non-limiting examples of alkynyl include ethynyl, 2-
15 propynyl, 3-butylnyl, 2-butylnyl, 4-pentylnyl, 3-pentylnyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonylnyl, 4-decynyl, and the like.

The term “cycloalkyl” as used herein refers to and includes a saturated or partially unsaturated (containing 1 or 2 double bonds) cyclic hydrocarbon group containing 1 to 3 rings (for example, monocyclic, bicyclic, or tricyclic), and containing a total of 3 to 20
20 carbon atoms forming the rings. The cycloalkyl may be optionally substituted. The rings of multi-ring cycloalkyls may exist as fused, bridged and/or joined through one or more spiro union to 1 or 2 aromatic cycloalkyl or heterocyclic rings. Typical, non-limiting examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl, cyclododecyl, cyclopentenyl, cyclohexenyl,
25 cycloheptenyl, cyclooctenyl, cyclohexadienyl, cycloheptadienyl, and the like.

The terms “heterocyclic”, “heterocyclyl” or “heterocyclo” as used herein refers to and includes optionally substituted, saturated, unsaturated or partially unsaturated 3 to 20 member cyclic groups (for example, 3 to 13 member monocyclic, 7 to 17 member bicyclic, or 10 to 20 member tricyclic ring systems), which have at least one heteroatom
30 in at least one carbon atom-containing ring. The heteroatom is selected from nitrogen, oxygen and/or sulfur atoms. Each ring of the heterocyclic group may have 1, 2, 3, 4 or 5 heteroatoms, subject to a condition that that at least one ring contains at least one

heteroatom. The nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. The rings of multi-ring heterocycles may be fused, bridged and/or joined through one or more spiro unions. Typical, non-limiting examples of heterocyclic groups include azetidiny, pyrrolidinyl, oxetanyl, imidazolinyl, oxazolidinyl, isoxazolinyl, thiazolidinyl, isothiazolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, 4-piperidonyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothienyl, and the like.

10 The term “aryl” as used herein refers to and includes aromatic homocyclic (i.e., hydrocarbon) monocyclic, bicyclic or tricyclic aromatic groups containing 6 to 14 carbons in the ring portion, and may optionally include one to three additional rings (either cycloalkyl, heterocyclo or heteroaryl) fused thereto. Typical, non-limiting examples of aryl groups includes phenyl, biphenyl, naphthyl (including 1-naphthyl, and 2-naphthyl), anthracenyl, and the like.

 The above-defined groups may optionally have one or more hydrogen atoms that are attached to a carbon atom substituted with any group known to one of skill in the art. Throughout the specification, groups and substituents thereof may be chosen to provide stable moieties and compounds.

20 The term “subject” as used herein refers to and includes any human or non-human organism that could potentially benefit from treatment with a PAD4 inhibitor. Exemplary subjects include humans and animals.

 The terms “treating” or “treatment” as used herein refer to and include treatment of a disease-state in a subject, for example in a human or animal, and include: (a) inhibiting the disease-state, i.e., arresting it’s development; (b) relieving the disease-state, i.e., causing regression of the disease state; and/or (c) preventing the disease-state from occurring in a subject.

 The terms “preventing” or “prevention” as used herein refer to and include preventive treatment (i.e. prophylaxis and/or risk reduction) of a subclinical disease-state in a subject, for example in a human or animal, aimed at reducing the probability of the occurrence of a clinical disease-state. Subjects may be selected for preventative therapy based on factors that are known to increase risk of suffering a clinical disease state

compared to the general population. “Prophylaxis” therapies can be divided into (a) primary prevention, and (b) secondary prevention. Primary prevention is defined as treatment in a subject that has not yet presented with a clinical disease state, whereas secondary prevention is defined as preventing a second occurrence of the same or similar
5 clinical disease state.

The term “therapeutically effective amount” refers to and includes an amount of a compound or a composition according to the invention that is effective when administered alone or in combination to prevent or treat the disease or disorder associated with PAD4 enzyme activity. When applied to a combination, the term refers to combined
10 amounts of the active ingredients that result in the preventive or therapeutic effect, whether administered in combination, serially, or simultaneously.

A “pharmaceutically acceptable carrier” refers to media generally accepted in the art for the delivery of biologically active agents to humans and/or animals. Pharmaceutically acceptable carriers are formulated according to a number of factors well within the purview of those of ordinary skill in the art. These include, without limitation,
15 the type and nature of the active agent being formulated, the subject to which the agent-containing composition is to be administered, the intended route of administration of the compound or composition, and, the therapeutic indication being targeted. Pharmaceutically acceptable carriers include both aqueous and non-aqueous liquid media. Such carriers can include a number of different ingredients and additives in addition to
20 the active agent, such additional ingredients being included in the formulation for a variety of reasons, e.g., stabilization of the active agent, binders, etc., well known to those of ordinary skill in the art. Typical, non-limiting examples of such carriers include diluents, preserving agents, fillers, flow regulating agents, disintegrating agents, wetting
25 agents, emulsifying agents, suspending agents, sweetening agents, flavouring agents, perfuming agents, anti-bacterial agents, anti-fungal agents, lubricating agents, dispensing agents, coating agents, and the like. Descriptions of suitable pharmaceutically acceptable carriers, and factors involved in their selection, are found in a variety of readily available sources such as, for example, *Allen, L. V., Jr. et al., Remington: The Science and Practice of Pharmacy (2 Volumes), 22nd Edition, Pharmaceutical Press (2012)*.
30

Prodrugs and solvates of the compounds of the invention are also contemplated herein. The term “prodrug”, as employed herein, denotes a compound, which, upon

administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of Formula (I), or a salt and/or solvate thereof. Solvates of the compounds of Formula (Ia) include hydrates.

Any tautomer, which may exist, is also contemplated herein as a part of the present invention. All stereoisomers of the compound of Formula (Ia), such as those, which may exist due to asymmetric carbons, including enantiomeric forms (which may exist even in the absence of asymmetric carbons, e.g., atropisomers) and diastereomeric forms are contemplated within the scope of this invention. Individual stereoisomers of the compound of Formula (Ia) may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centres in these compounds may have the S or R configuration as defined by the IUPAC 1974 Recommendations. In general, the compounds according to the invention may be described herein without specific stereochemistry for convenience, however all stereoisomeric forms are included within the scope of the invention.

The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium (symbol D or ^2H) and tritium (symbol T or ^3H). For example, a methyl group may be represented by CH_3 or CD_3 . Isotopes of carbon include ^{13}C and ^{14}C . Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed.

The compound of Formula (I) forms salts which are also within the scope of this invention. Reference to a compound of the Formula (I) herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. In addition, when a compound of Formula (I) contains both a basic moiety and an acidic moiety, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable salts include those generally acceptable in the art of pharmaceutical sciences for administration in a subject, including

humans and animals. In general, the pharmaceutically acceptable salts are non-toxic and physiologically acceptable salts. Salts of the compounds according to the invention may be formed, for example, by reacting the compound with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

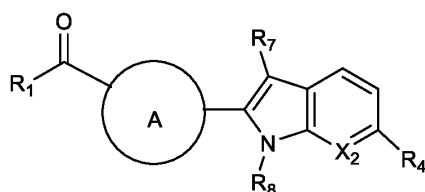
The compounds of Formula (Ia) which contain a basic moiety may form salts with a variety of organic and inorganic acids. Exemplary acid addition salts include acetates (such as those formed with acetic acid or trihaloacetic acid, for example, trifluoroacetic acid), adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides (formed with hydrochloric acid), hydrobromides (formed with hydrogen bromide), hydroiodides, 2-hydroxyethanesulfonates, lactates, maleates (formed with maleic acid), methanesulfonates (formed with methanesulfonic acid), 2-naphthalenesulfonates, nicotines, nitrates, oxalates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates (such as those formed with sulfuric acid), sulfonates (such as those mentioned herein), tartrates, thiocyanates, toluenesulfonates such as tosylates, undecanoates, and the like.

The compounds of Formula (Ia) which contain an acidic moiety may form salts with a variety of organic and inorganic bases. Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as benzathines, dicyclohexylamines, hydrabamines (formed with N,N-bis(dehydroabietyl)-ethylenediamine), N-methyl-D-glucamines, N-methyl-D-glucamides, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (e.g. methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (e.g. decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

The invention encompasses compounds of Formula (I), including their stereoisomers, enantiomers, diastereomers, tautomers, and pharmaceutically acceptable salts, methods for preparing these compounds, pharmaceutical compositions comprising these compounds, and use of these compounds in the treatment of diseases or disorders associated with PAD4 enzyme activity.

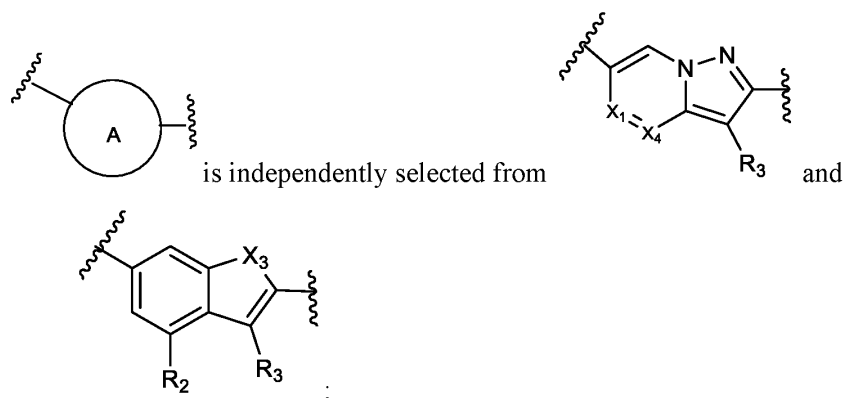
2. Description of Certain Aspects of the Invention

In a first aspect, the invention provides a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:



X_1 and X_2 are independently selected from CH and N;

X_3 is independently selected from O and S;

X_4 is independently selected from CR_2 and N; provided X_1 and X_4 are not both N;

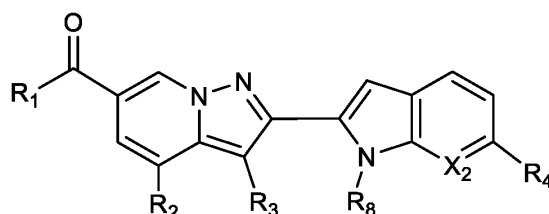
R_1 is independently selected from $-NH-C_{1-5}$ alkyl optionally substituted with one or more substituents selected from F, Cl, and NH_2 , 4-10 membered heterocyclyl, and $-NH-$ 4-10 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with one or more substituents selected from F, Cl, CN, C_{1-3} alkyl, $=N-OR_b$, $-(CH_2)_rOR_b$, $-(CH_2)_rNR_aR_a$, $-NR_aC(=NH)C_{1-3}$ alkyl, $-NR_aC(=O)OR_b$, carbocyclyl, and heterocyclyl;

R_2 is independently selected from H, F, Cl, C_{1-4} alkyl, and $-OC_{1-4}$ alkyl;

- R₃ is independently selected from H, F, Cl, -CN, -C(=O)OR_b, and C₁₋₃ alkyl optionally substituted with one or more substituents selected from F, Cl, and OH;
- R₄ is independently selected from H, F, Cl, Br, -C(=O)R_b, C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, -OH, -NH-C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, and OH, and C₃₋₆ cycloalkyl, -(CH₂)_r-aryl substituted with one or more R₅, -(CH₂)_r-C₃₋₁₂ cycloalkyl substituted with one or more R₅, and -(CH₂)_r-4-10 membered heterocyclyl comprising carbon atoms and 1-5 heteroatoms selected from N, NR₆, O, and S and substituted with one or more R₅;
- 10 R₅ is independently selected from H, F, Cl, Br, -CN, =O, C₁₋₄alkyl optionally substituted with one or more R_e, C₂₋₄alkenyl optionally substituted with one or more R_e, C₂₋₄alkynyl optionally substituted with one or more R_e, -(CR_dR_d)_rOR_b, -(CR_dR_d)_rS(O)_pR_c, -(CR_dR_d)_rS(O)_pNR_aR_a, -(CR_dR_d)_rNR_aS(O)_pR_c, -(CR_dR_d)_rNR_aR_a, -(CR_dR_d)_rNR_aC(=O)R_b, -(CR_dR_d)_rNR_aC(=O)OR_b, -(CR_dR_d)_rNR_aC(=O)NR_aR_a, -(CR_dR_d)_rC(=O)R_b, -(CR_dR_d)_rC(=O)OR_b, -(CR_dR_d)_rC(=O)NR_aR_a, -(CR_dR_d)_rOC(=O)R_b, -(CR_dR_d)_rOC(=O)OR_b, -(CR_dR_d)_rO(CH₂)_rC(=O)NR_aR_a, C₃₋₆cycloalkyl optionally substituted with one or more R_e, aryl optionally substituted with one or more R_e, and heterocyclyl optionally substituted with one or more R_e;
- 15 R₆ is independently selected from H, C₁₋₆alkyl optionally substituted with one or more R_e, -S(O)_pR_c, -S(O)_pNR_aR_a, -C(=O)R_b, -C(=O)OR_b, -C(=O)NR_aR_a, C₃₋₆cycloalkyl optionally substituted with one or more R_e, aryl optionally substituted with one or more R_e, and heterocyclyl optionally substituted with one or more R_e;
- 20 R₇ is independently selected from H, F, and Cl;
- R₈ is independently selected from H and C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, and C₃₋₆ cycloalkyl;
- 25 R_a is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more R_e, C₂₋₆ alkenyl optionally substituted with one or more R_e, C₂₋₆ alkynyl optionally substituted with one or more R_e, -(CH₂)_r-C₃₋₁₀carbocyclyl optionally substituted with one or more R_e, and -(CH₂)_r-heterocyclyl optionally substituted with one or more R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring optionally substituted with one or more R_e;
- 30

- R_b is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , C_{2-6} alkenyl optionally substituted with one or more R_e , C_{2-6} alkynyl optionally substituted with one or more R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_e ;
- R_c is independently selected from C_{1-6} alkyl optionally substituted with one or more R_e , C_{2-6} alkenyl optionally substituted with one or more R_e , C_{2-6} alkynyl optionally substituted with one or more R_e , $-(CH_2)_r-C_{3-6}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_e ;
- R_d is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e ,
- R_e is independently selected from F, Cl, Br, $-CN$, $-NH_2$, $-NHC_{1-4}$ alkyl, $-N(C_{1-4}alkyl)_2$, $=O$, OH, OC_{1-6} alkyl, $-CO_2H$, C_{1-6} alkyl optionally substituted with one or more R_f , C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_r-C_{3-6}$ cycloalkyl optionally substituted with one or more R_f , $-(CH_2)_r$ -aryl optionally substituted with one or more R_f , $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_f ;
- R_f is independently selected from F, Cl, Br, $-CN$, $-OH$, C_{1-5} alkyl optionally substituted with $-OH$, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-6} cycloalkyl, and phenyl;
- p , at each occurrence, is independently selected from zero, 1, and 2; and
- r , at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

In a second aspect, the invention provides a compound of Formula (II):

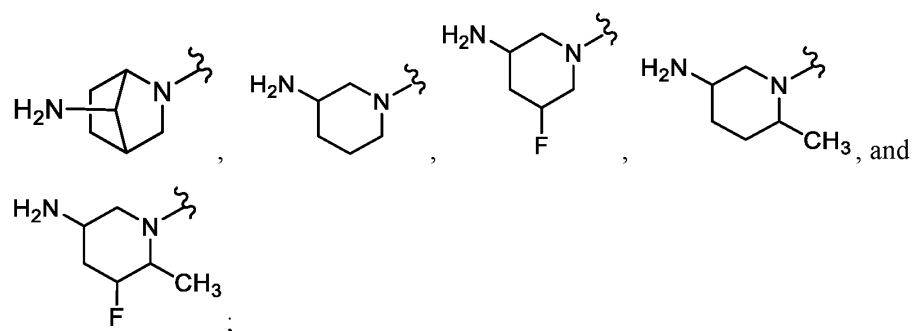


(II)

- or a pharmaceutically acceptable salt thereof, within the scope of the first aspect, wherein:

X_2 is independently selected from CH and N;

R_1 is independently selected from



R_2 is independently selected from H, F, Cl, $-\text{CH}_3$, and $-\text{OCH}_3$;

R_3 is independently selected from H, F, Cl, $-\text{CN}$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$;

- 5 R_4 is independently selected from H, C_{1-5} alkyl optionally substituted with one or more substituents selected from F, Cl, and $-\text{OH}$, phenyl substituted with one or more R_5 , C_{3-6} cycloalkyl, and a 4-10 membered heterocyclyl comprising carbon atoms and 1-5 heteroatoms selected from N, NR_6 , O, and S and substituted with one or more R_5 ;
- 10 R_5 is independently selected from H, F, Cl, Br, $-\text{CN}$, $=\text{O}$, C_{1-4} alkyl optionally substituted with one or more R_e , C_{2-4} alkenyl optionally substituted with one or more R_e , $-(\text{CHR}_d)_r\text{OR}_b$, $-(\text{CHR}_d)_r\text{S}(\text{O})_p\text{R}_c$, $-(\text{CHR}_d)_r\text{NR}_a\text{S}(\text{O})_p\text{R}_c$, $-(\text{CHR}_d)_r\text{NR}_a\text{R}_a$, $-(\text{CHR}_d)_r\text{NR}_a\text{C}(=\text{O})\text{R}_b$, $-(\text{CHR}_d)_r\text{NR}_a\text{C}(=\text{O})\text{OR}_b$, $-(\text{CHR}_d)_r\text{C}(=\text{O})\text{R}_b$, $-(\text{CHR}_d)_r\text{C}(=\text{O})\text{OR}_b$, $-(\text{CHR}_d)_r\text{C}(=\text{O})\text{NR}_a\text{R}_a$, $-(\text{CHR}_d)_r\text{OC}(=\text{O})\text{R}_b$, $-(\text{CHR}_d)_r\text{OC}(=\text{O})\text{OR}_b$, $-(\text{CHR}_d)_r\text{O}(\text{CH}_2)_r\text{C}(=\text{O})\text{NR}_a\text{R}_a$;
- 15

R_6 is independently selected from H and C_{1-4} alkyl optionally substituted with one or more R_e ;

R_8 is independently selected from H and $-\text{CH}_2-\text{C}_{3-6}$ cycloalkyl;

- R_a is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , $-(\text{CH}_2)_r-\text{C}_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(\text{CH}_2)_r$ -heterocyclyl optionally substituted with one or more R_e ; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring optionally substituted with one or more R_e ;
- 20
- R_b is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , $-(\text{CH}_2)_r-\text{C}_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(\text{CH}_2)_r$ -heterocyclyl optionally substituted with one or more R_e ;
- 25

R_e is independently selected from C_{1-6} alkyl optionally substituted with one or more R_e , $-(CH_2)_r-C_{3-6}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_e ;

R_d is independently selected from H and C_{1-4} alkyl optionally substituted with one or more R_e ;

R_e is independently selected from F, Cl, Br, $-CN$, $-NO_2$, $=O$, OH, OC_{1-4} alkyl, C_{1-4} alkyl optionally substituted with one or more R_f , C_{3-6} cycloalkyl optionally substituted with one or more R_f , $-(CH_2)_r$ -aryl optionally substituted with one or more R_f , $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_f ;

R_f is independently selected from F, Cl, Br, $-CN$, and $-OH$;

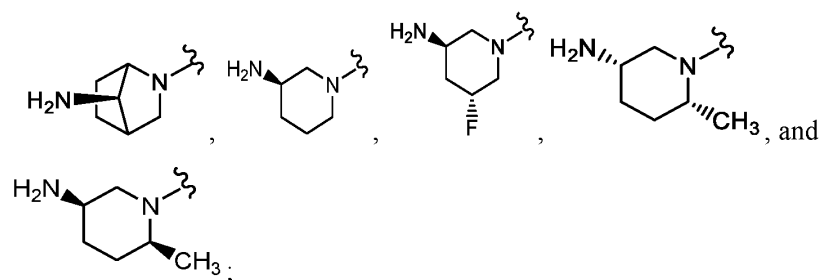
p , at each occurrence, is independently selected from zero, 1, and 2; and

r , at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

In a third aspect, the invention provides a compound within the scope of the second aspect,

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is independently selected from



R_2 is independently selected from H, F, $-CH_3$, and $-OCH_3$;

R_3 is independently selected from H, Cl, $-CH_3$, and $-CH_2OH$;

R_4 is independently selected from H, C_{1-5} alkyl optionally substituted with one or more substituents selected from F, Cl, and $-OH$, phenyl substituted with one or more R_5 , C_{3-6} cycloalkyl, and a 4-10 membered heterocyclyl comprising carbon atoms and 1-5 heteroatoms selected from N, NR_6 , O, and S and substituted with one or more

R_5 ;

R_5 , at each occurrence, is independently selected from H, F, Cl, $-CN$, $=O$, C_{1-4} alkyl optionally substituted with one or more R_e , $-(CH_2)_rOR_b$, $-(CH_2)_rNR_aS(O)_pR_c$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-$

$(\text{CH}_2)_r\text{NR}_a\text{C}(=\text{O})\text{NR}_a\text{R}_a$, $-(\text{CH}_2)_r\text{C}(=\text{O})\text{R}_b$, $-(\text{CH}_2)_r\text{C}(=\text{O})\text{OR}_b$, $-(\text{CH}_2)_r\text{C}(=\text{O})\text{NR}_a\text{R}_a$, $-(\text{CH}_2)_r\text{OC}(=\text{O})\text{R}_b$, $-(\text{CH}_2)_r\text{OC}(=\text{O})\text{OR}_b$, and $-(\text{CH}_2)_r\text{O}(\text{CH}_2)_r\text{C}(=\text{O})\text{NR}_a\text{R}_a$;

5 R_6 is independently selected from H and C_{1-3} alkyl optionally substituted with one or more R_e ;

R_8 is $-\text{CH}_2$ -cyclopropyl;

R_a is independently selected from H and C_{1-6} alkyl optionally substituted with one or more R_e ; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring optionally substituted with one or more R_e ;

10 R_b is independently selected from H and C_{1-6} alkyl optionally substituted with one or more R_e ;

R_c is C_{1-6} alkyl optionally substituted with one or more R_e ;

15 R_e is independently selected from F, Cl, Br, $-\text{CN}$, $=\text{O}$, OH, OC_{1-3} alkyl, C_{1-3} alkyl optionally substituted with one or more R_f , C_{3-6} cycloalkyl optionally substituted with one or more R_f , $-(\text{CH}_2)_r$ -aryl optionally substituted with one or more R_f , $-(\text{CH}_2)_r$ -heterocyclyl optionally substituted with one or more R_f ;

R_f is independently selected from F, Cl, Br, $-\text{CN}$, and $-\text{OH}$;

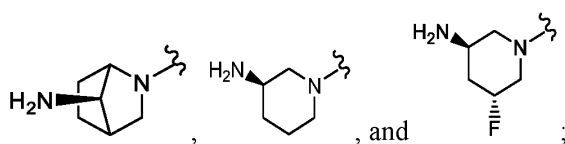
p , at each occurrence, is independently selected from zero, 1, and 2; and

r , at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

20 In a fourth aspect, the invention provides a compound within the scope of the third aspect,

or a pharmaceutically acceptable salt thereof, wherein:

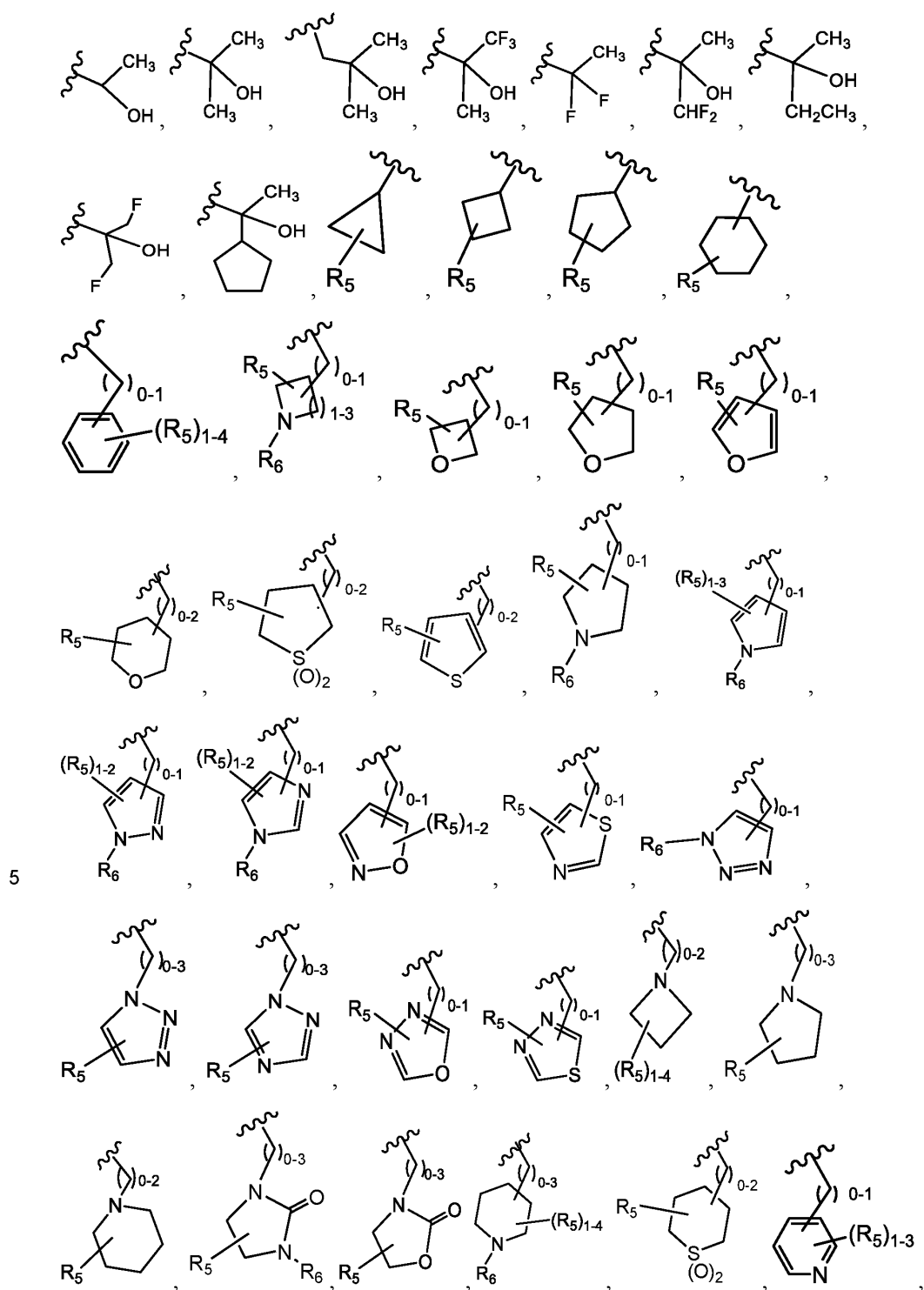
R_1 is independently selected from

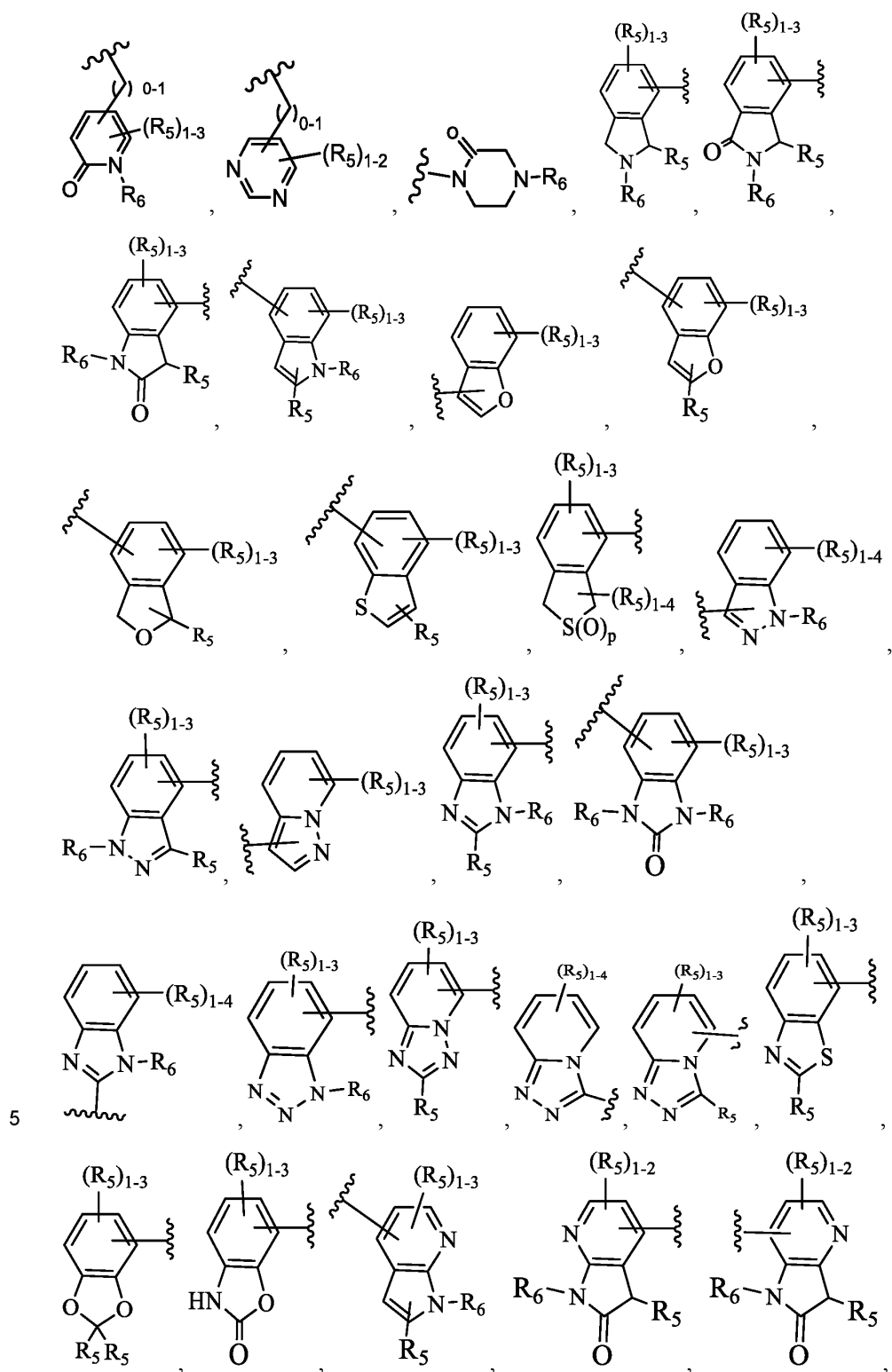


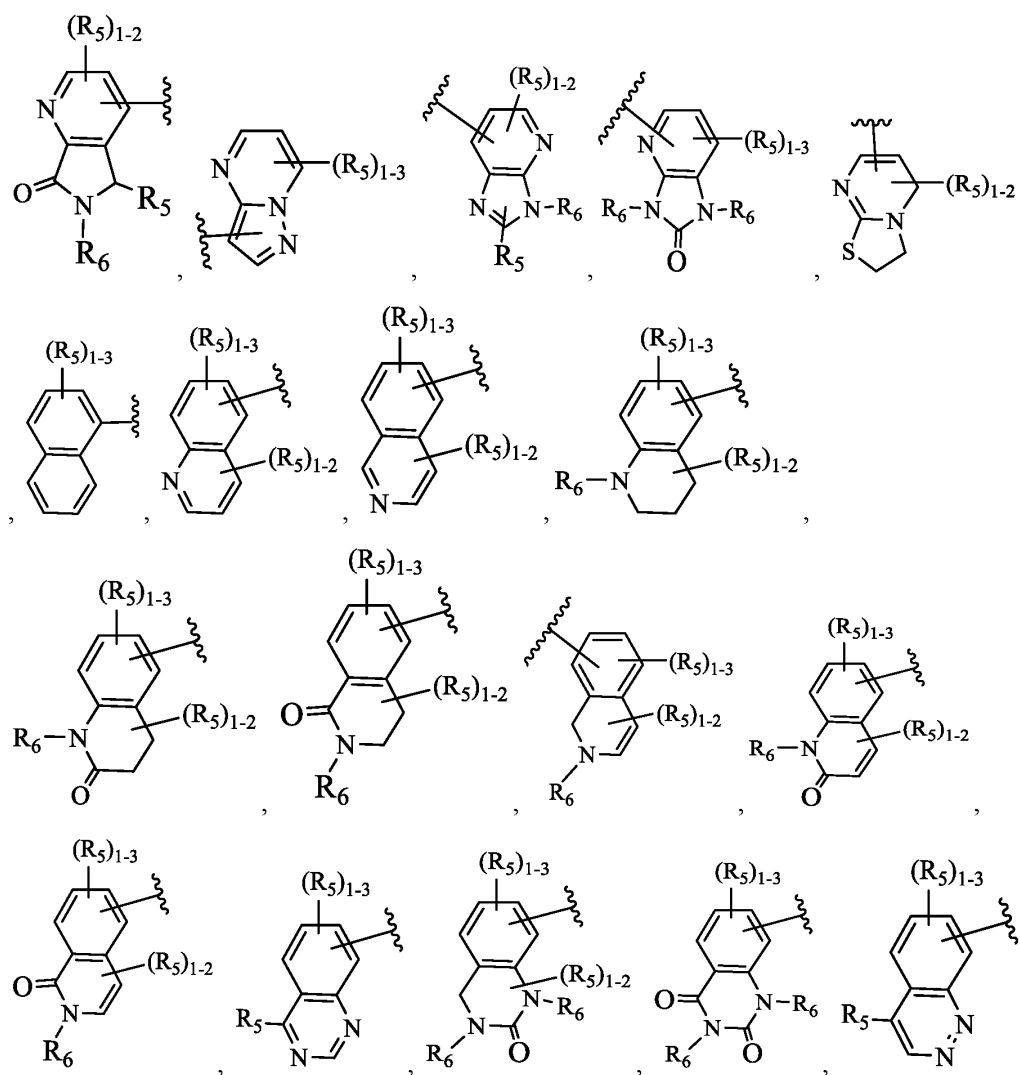
25 R_2 is independently selected from H, F, and $-\text{OCH}_3$;

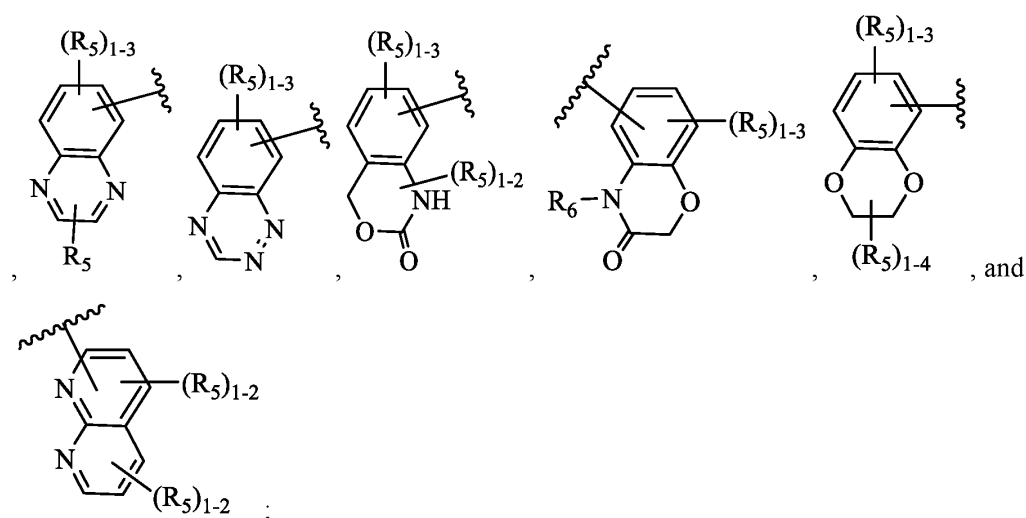
R_3 is CH_3 ;

R_4 is selected from F, Cl, C_{1-3} alkyl,









R_5 , at each occurrence, is independently selected from H, F, Cl, $-\text{CN}$, $=\text{O}$, C_{1-4} alkyl

optionally substituted with one or more R_e , $-\text{OR}_b$, $-\text{NR}_a\text{S}(\text{O})_2\text{R}_c$, $-\text{NR}_a\text{R}_a$, $-\text{NR}_a\text{C}(=\text{O})\text{R}_b$, $-\text{NR}_a\text{C}(=\text{O})\text{OR}_b$, $-\text{NR}_a\text{C}(=\text{O})\text{NR}_a\text{R}_a$, $-\text{C}(=\text{O})\text{R}_b$, $-\text{C}(=\text{O})\text{OR}_b$, $-\text{C}(=\text{O})\text{NR}_a\text{R}_a$, $-\text{OC}(=\text{O})\text{R}_b$, and $-\text{OC}(=\text{O})\text{OR}_b$;

5

R_6 is independently selected from H and C_{1-3} alkyl;

R_a is independently selected from H and C_{1-5} alkyl; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring optionally substituted with one or more R_e ;

10

R_b is independently selected from H and C_{1-5} alkyl optionally substituted with one or more R_e ;

R_c is C_{1-5} alkyl optionally substituted with one or more R_e ;

R_e is independently selected from F, Cl, Br, $-\text{CN}$, $=\text{O}$, OH, C_{1-4} alkyl optionally

15

substituted with one or more R_f , C_{3-6} cycloalkyl optionally substituted with one or more R_f , aryl optionally substituted with one or more R_f , heterocyclyl optionally substituted with one or more R_f ; and

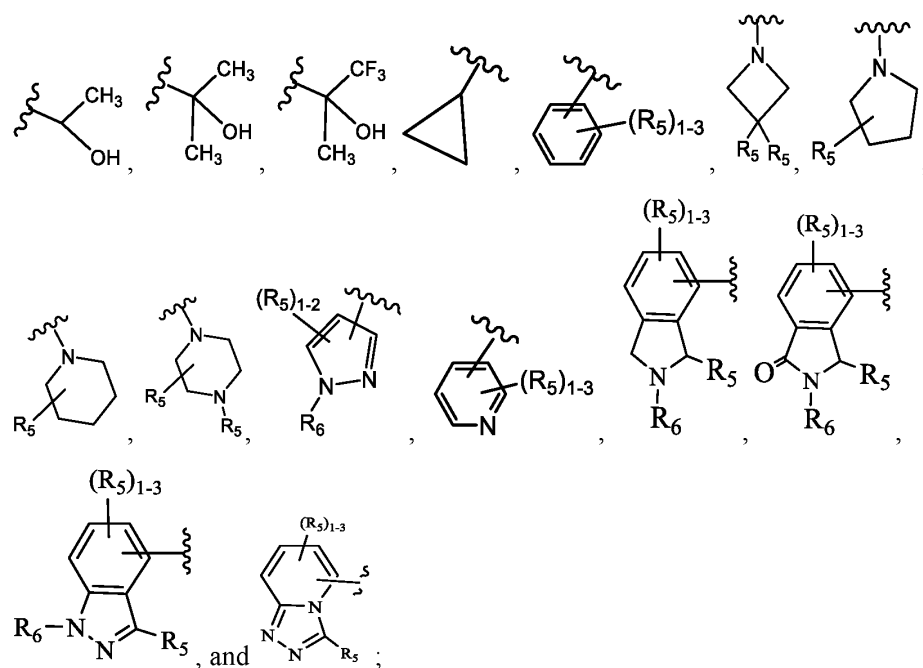
R_f is independently selected from F, Cl, Br, $-\text{CN}$, and $-\text{OH}$.

20

In a fifth aspect, the invention provides a compound within the scope of the fourth aspect,

or a pharmaceutically acceptable salt thereof, wherein:

R_4 is selected from C_{1-2} alkyl,



R_5 is independently selected from H, F, Cl, =O, C_{1-4} alkyl optionally substituted with one

5 or more R_e , $-OR_b$, $-NR_aS(O)_2R_c$, $-NR_aR_a$, $-NR_aC(=O)R_b$, and $C(=O)NR_aR_a$;

R_6 is independently selected from H and C_{1-4} alkyl optionally substituted with one or more substituents selected from F, Cl, and OH;

R_a is independently selected from H and C_{1-4} alkyl optionally substituted with one or more R_e ;

10 R_b is independently selected from H and C_{1-4} alkyl optionally substituted with one or more R_e ;

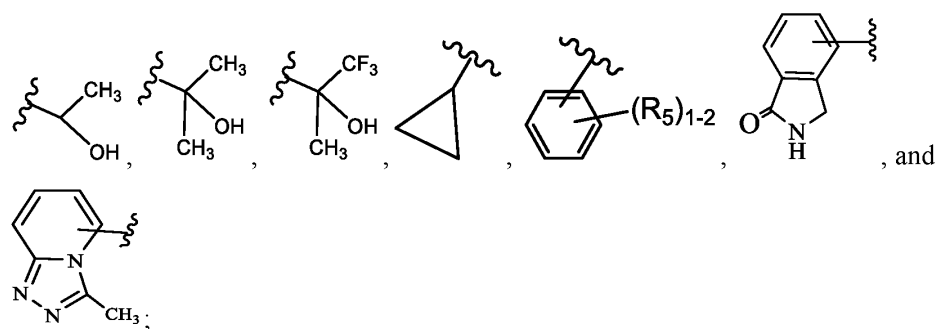
R_c is independently selected from H and C_{1-4} alkyl optionally substituted with one or more R_e ; and

R_e is independently selected from F, Cl, Br, $-CN$, =O, OH, and C_{1-6} alkyl.

15 In a sixth aspect, the invention provides a compound within the scope of the fifth aspect,

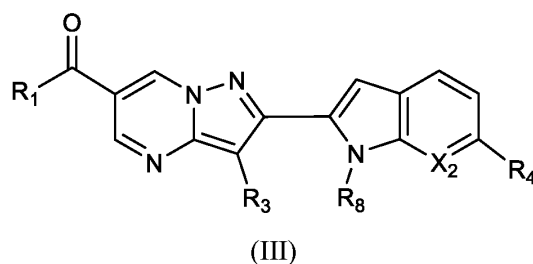
or a pharmaceutically acceptable salt thereof, wherein:

R_4 is independently selected from CH_3 ,



R_5 is independently selected from F, Cl, -OH, and $C(=O)NH_2$.

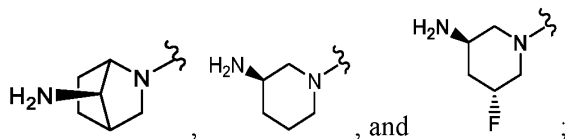
In a seventh aspect, the invention provides a compound of Formula (III):



or a pharmaceutically acceptable salt thereof, within the scope of the first aspect, wherein:

X_2 is independently selected from CH and N;

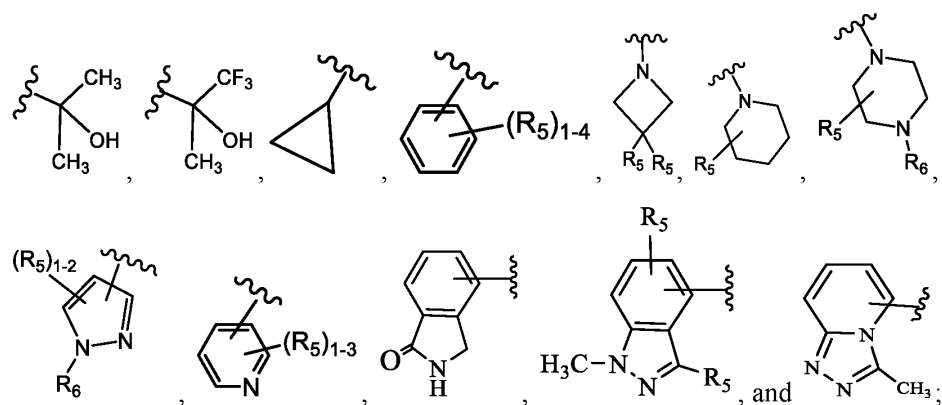
10 R_1 is independently selected from



R_2 is independently selected from H, F, Cl, -CH₃, and -OCH₃;

R_3 is independently selected from H, F, Cl, -CN, -CH₃, and -CH₂OH;

R_4 is independently selected from H, F, Cl, C₁₋₃ alkyl,



R_5 is independently selected from H, F, Cl, =O, -OH, -OCHF₂, C(=O)NH₂, and -NHS(O)₂C₁₋₄alkyl;

- 5 R_6 is independently selected from H and C₁₋₄alkyl optionally substituted with one or more substituents selected from F, Cl, and OH;

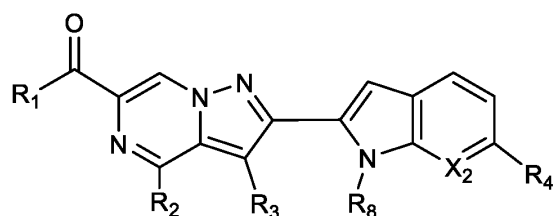
R_8 is -CH₂-cyclopropyl;

R_a is independently selected from H and C₁₋₄ alkyl optionally substituted with one or more R_e ;

- 10 R_b is independently selected from H and C₁₋₄ alkyl optionally substituted with one or more R_e ; and

R_e is independently selected from F, Cl, Br, -CN, =O, OH, and C₁₋₆ alkyl.

In an eighth aspect, the invention provides a compound of Formula (IV):



(IV)

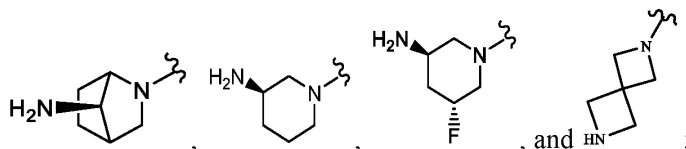
15

or a pharmaceutically acceptable salt thereof, within the scope of the first aspect, wherein:

X_2 is independently selected from CH and N;

R_1 is independently selected from -NHCH₂CHFCH₂NH₂,

20



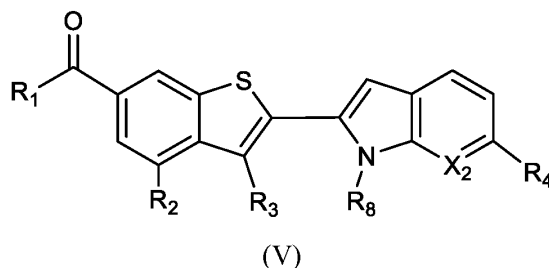
R₂ is independently selected from H, F, Cl, -CH₃, and -OCH₃;

R₃ is independently selected from H, F, Cl, -CN, -CH₃, and -CH₂OH;

R₄ is independently selected from H, F, Cl, and C₁₋₃ alkyl; and

R₈ is -CH₂-cyclopropyl.

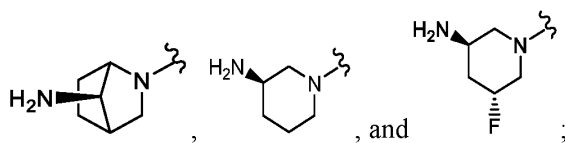
- 5 In a ninth aspect, the invention provides a compound of Formula (V):



or a pharmaceutically acceptable salt thereof, within the scope of the first aspect, wherein:

- 10 X₂ is independently selected from CH and N;

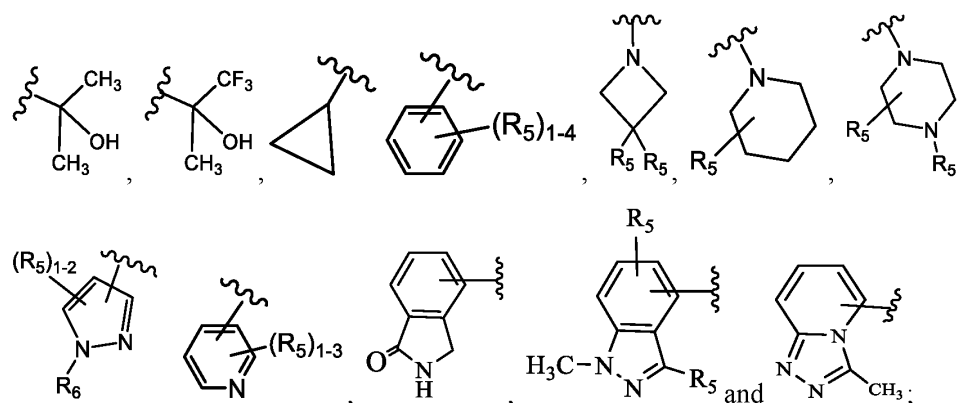
R₁ is independently selected from



R₂ is independently selected from H, F, Cl, -CH₃, and -OCH₃;

R₃ is independently selected from H, F, Cl, -CN, -CH₃, and -CH₂OH;

- 15 R₄ is independently selected from H, F, Cl, Br, C₁₋₃ alkyl,



R₅ is independently selected from H, F, Cl, =O, -OH, -OCHF₂, NH₂, and C(=O)NH₂;

R₆ is independently selected from H and C₁₋₄alkyl optionally substituted with one or
20 more substituents selected from F, Cl, and OH;

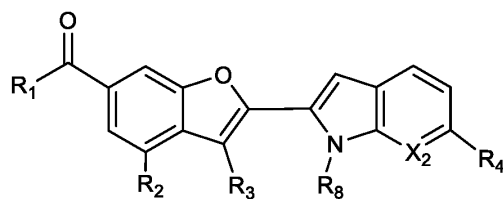
R₈ is -CH₂-cyclopropyl;

R_a is independently selected from H and C₁₋₄ alkyl optionally substituted with one or more R_e;

R_b is independently selected from H and C₁₋₄ alkyl optionally substituted with one or more R_c; and

R_c is independently selected from F, Cl, Br, -CN, =O, OH, and C₁₋₆ alkyl.

In a tenth aspect, the invention provides a compound of Formula (VI):

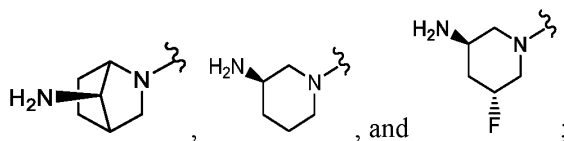


(VI)

10 or a pharmaceutically acceptable salt thereof, within the scope of the first aspect,
wherein:

X_2 is independently selected from CH and N;

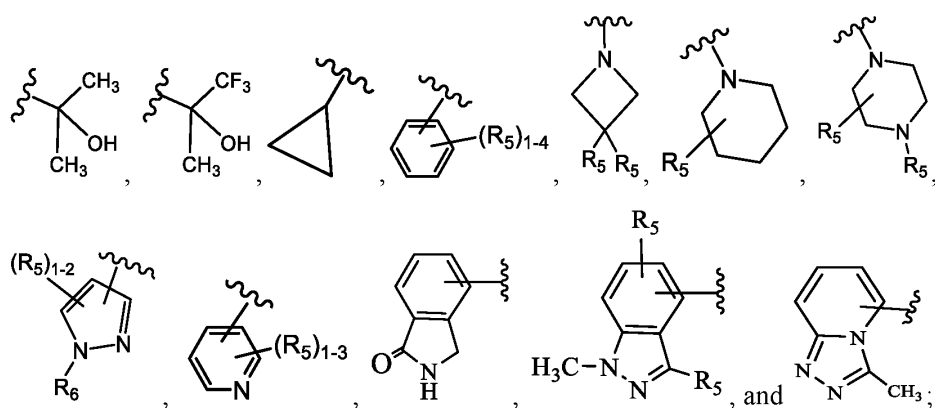
R_1 is independently selected from



15 R₂ is independently selected from H, F, Cl, -CH₃, and -OCH₃;

R₃ is independently selected from H, F, Cl, -CN, -CH₃, and -CH₂OH;

R₄ is independently selected from H, F, Cl, C₁₋₃ alkyl,



20 R₅ is independently selected from H, F, Cl, =O, -OH, -OCHF₂, and -C(=O)NH₂;

R_6 is independently selected from H and C_{1-4} alkyl optionally substituted with one or more substituents selected from F, Cl, and OH;

R_8 is $-\text{CH}_2\text{-cyclopropyl}$;

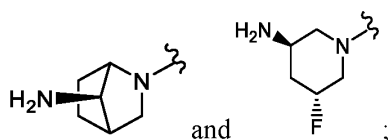
R_a is independently selected from H and C_{1-4} alkyl optionally substituted with one or more R_c ;

R_b is independently selected from H and C_{1-4} alkyl optionally substituted with one or more R_c ; and

R_c is independently selected from F, Cl, Br, $-\text{CN}$, $=\text{O}$, OH, and C_{1-6} alkyl.

In an eleventh aspect, the invention provides a compound within the scope of the tenth aspect, or a pharmaceutically acceptable salt thereof, wherein:

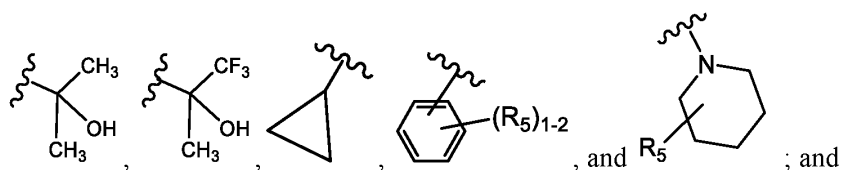
R_1 is independently selected from



R_2 is independently selected from H, F, and $-\text{OCH}_3$;

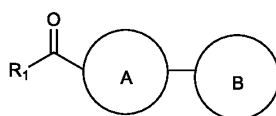
R_3 is $-\text{CH}_3$;

R_4 is independently selected from



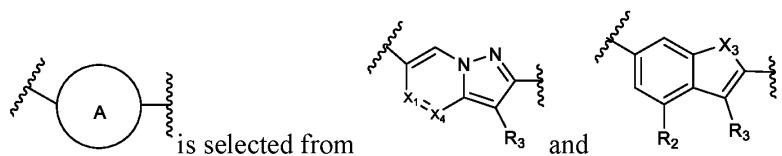
R_5 is independently selected from F, Cl, $-\text{OH}$, $-\text{NH}_2$, $-\text{OC}_{1-4}\text{alkyl}$, and $\text{C}(=\text{O})\text{NH}_2$.

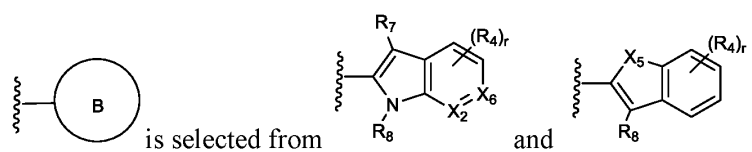
In one aspect, the invention provides a compound of Formula (Ia):



(Ia)

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





- is selected from
- X_1 is independently selected from CR₂ and N;
- X_2 is independently selected from CR₄ and N;
- X_3 is independently selected from O and S;
- 5 X_4 is independently selected from CR₂ and N; provided X_1 and X_4 are not both N;
- X_5 is independently selected from O and S;
- X_6 is independently selected from CR₄, and N; provided 1) X_2 and X_6 are not both N; 2) when X_2 and X_6 are both CR₄, one of R₄ is H;
- R₁ is independently selected from -NH-C₁₋₅ alkyl optionally substituted with one or more
- 10 substituents selected from F, Cl, and NH₂, 4-10 membered heterocyclyl, and -NH-4-10 membered heterocyclyl, wherein said heterocyclyl is optionally substituted with one or more substituents selected from F, Cl, CN, C₁₋₃ alkyl, =N-OR_b, -(CH₂)_rOR_b, -(CH₂)_rNR_aR_a, -NR_aC(=NH)C₁₋₃ alkyl, -NR_aC(=O)OR_b, carbocyclyl, and heterocyclyl;
- 15 R₂ is independently selected from H, F, Cl, C₁₋₄ alkyl optionally substituted with one or more substituents selected from F, Cl, and OH, and -OC₁₋₄ alkyl;
- R₃ is independently selected from H, F, Cl, CN, -C(=O)OR_b, and C₁₋₃ alkyl optionally substituted with one or more substituents selected from F, Cl, OH, NH₂, and N₃;
- R₄ is independently selected from H, F, Cl, Br, -C(=O)R_b, C₁₋₆ alkyl optionally substituted
- 20 with one or more substituents selected from F, Cl, OH, and C₃₋₆ cycloalkyl, -NH-C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C₃₋₆ cycloalkyl, -(CH₂)_r-aryl substituted with one or more R₅, -O-C₁₋₆ alkyl substituted with one or more R₅, -(CH₂)_r-C₃₋₁₂ cycloalkyl substituted with one or more R₅, and -(CH₂)_r-4-10 membered heterocyclyl comprising carbon atoms
- 25 and 1-5 heteroatoms selected from N, NR₆, O, and S and substituted with one or more R₅;
- R₅ is independently selected from H, F, Cl, Br, CN, =O, C₁₋₄ alkyl optionally substituted with one or more R_e, C₂₋₄ alkenyl optionally substituted with one or more R_e, C₂₋₄ alkynyl optionally substituted with one or more R_e, -(CR_dR_d)_rOR_b, -
- 30 (CR_dR_d)_rS(O)_pR_c, -(CR_dR_d)_rS(O)_pNR_aR_a, -(CR_dR_d)_rNR_aS(O)_pR_c, -(CR_dR_d)_rNR_aR_a,

- $-(\text{CR}_d\text{R}_d)_r\text{NR}_a\text{C}(=\text{O})\text{R}_b$, $-(\text{CR}_d\text{R}_d)_r\text{NR}_a\text{C}(=\text{O})\text{OR}_b$, $-(\text{CR}_d\text{R}_d)_r\text{NR}_a\text{C}(=\text{O})\text{NR}_a\text{R}_a$, $-(\text{CR}_d\text{R}_d)_r\text{C}(=\text{O})\text{R}_b$, $-(\text{CR}_d\text{R}_d)_r\text{C}(=\text{O})\text{OR}_b$, $-(\text{CR}_d\text{R}_d)_r\text{C}(=\text{O})\text{NR}_a\text{R}_a$, $-(\text{CR}_d\text{R}_d)_r\text{OC}(=\text{O})\text{R}_b$, $-(\text{CR}_d\text{R}_d)_r\text{OC}(=\text{O})\text{OR}_b$, $-(\text{CR}_d\text{R}_d)_r\text{O}(\text{CH}_2)_r\text{C}(=\text{O})\text{NR}_a\text{R}_a$, C₃₋₆ cycloalkyl optionally substituted with one or more R_e, aryl optionally substituted with one or more R_e, and heterocyclyl optionally substituted with one or more R_e;
- 5 R₆ is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more R_e, -S(O)_pR_c, -S(O)_pNR_aR_a, -C(=O)R_b, -C(=O)OR_b, -C(=O)NR_aR_a, C₃₋₆ cycloalkyl optionally substituted with one or more R_e, aryl optionally substituted with one or more R_e, and heterocyclyl optionally substituted with one or more R_e;
- 10 R₇ is independently selected from H, F, and Cl;
- R₈ is independently selected from H, and C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, and C₃₋₆ cycloalkyl;
- R_a is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more R_e, C₂₋₆ alkenyl optionally substituted with one or more R_e, C₂₋₆ alkynyl optionally substituted with one or more R_e, -(CH₂)_r-C₃₋₁₀ carbocyclyl optionally substituted with one or more R_e, and -(CH₂)_r-heterocyclyl optionally substituted with one or more R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring optionally substituted with one or more R_e;
- 15 R_b is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more R_e, C₂₋₆ alkenyl optionally substituted with one or more R_e, C₂₋₆ alkynyl optionally substituted with one or more R_e, -(CH₂)_r-C₃₋₁₀ carbocyclyl optionally substituted with one or more R_e, and -(CH₂)_r-heterocyclyl optionally substituted with one or more R_e;
- 20 R_c is independently selected from C₁₋₆ alkyl optionally substituted with one or more R_e, C₂₋₆ alkenyl optionally substituted with one or more R_e, C₂₋₆ alkynyl optionally substituted with one or more R_e, -(CH₂)_r-C₃₋₁₀ carbocyclyl optionally substituted with one or more R_e, and -(CH₂)_r-heterocyclyl optionally substituted with one or more R_e;
- 25 R_d is independently selected from H, and C₁₋₆ alkyl optionally substituted with one or more R_e;
- 30 R_e is independently selected from F, Cl, Br, CN, NH₂, -NH-C₁₋₄ alkyl, -N(C₁₋₄ alkyl)₂, =O, OH, -OC₁₋₆ alkyl, -CO₂H, C₁₋₆ alkyl optionally substituted with one or more R_f,

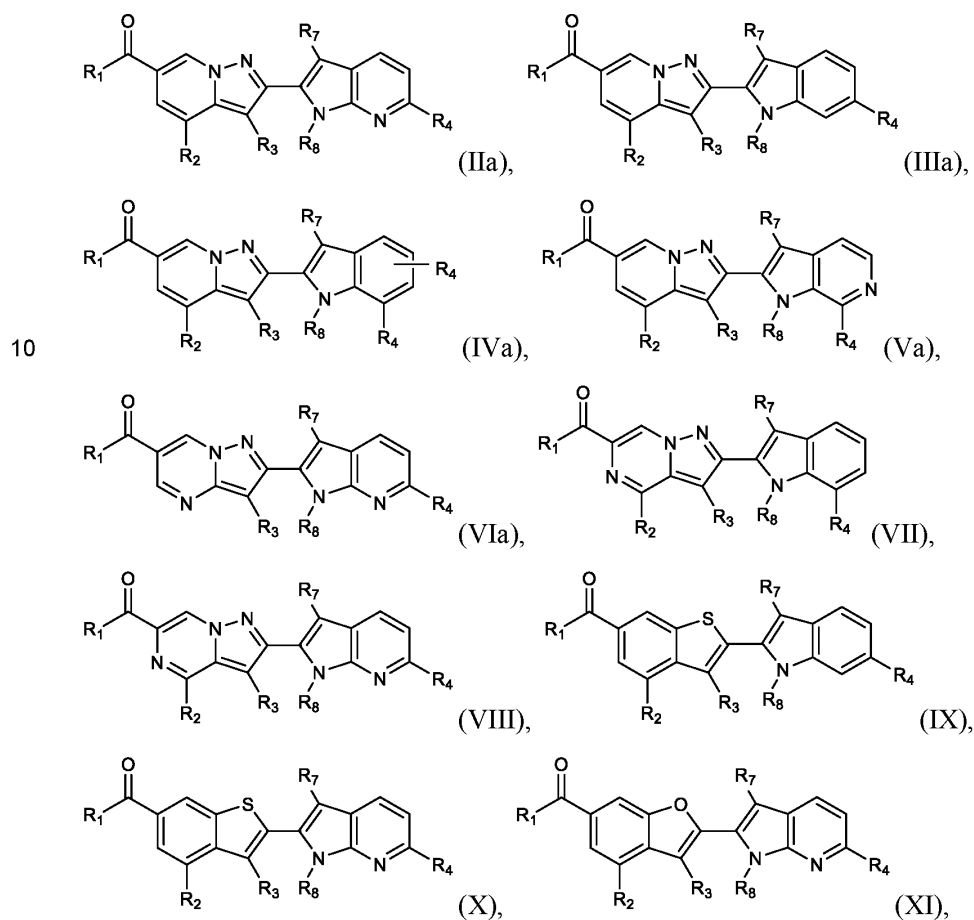
C₂₋₆ alkenyl, C₂₋₆ alkynyl, $-(CH_2)_r$ -C₃₋₆ cycloalkyl optionally substituted with one or more R_f, $-(CH_2)_r$ -aryl optionally substituted with one or more R_f, and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_f;

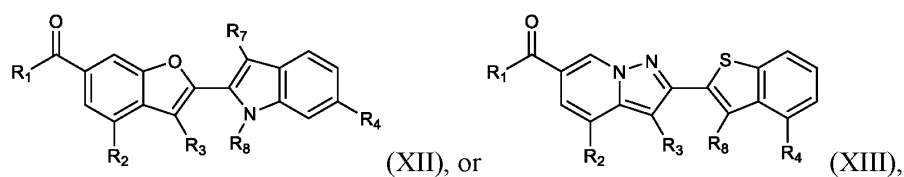
R_f is independently selected from F, Cl, Br, CN, OH, OC₁₋₅ alkyl, C₁₋₅ alkyl optionally substituted with OH, C₂₋₅ alkenyl, C₂₋₅ alkynyl, C₃₋₆ cycloalkyl, and phenyl;

p, at each occurrence, is independently selected from zero, 1, and 2; and

r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

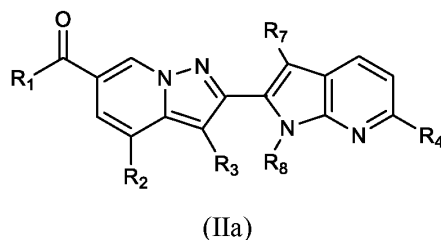
In another aspect, the invention provides a compound of Formulae (IIa)-(XIII):



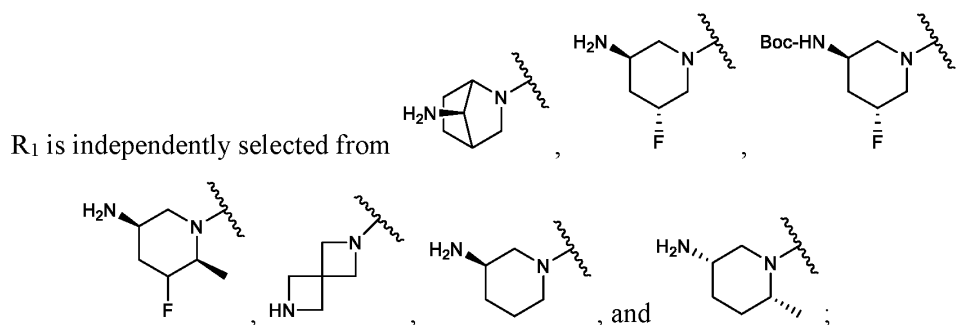


or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof. R_1 , R_2 , R_3 , R_4 , R_7 , and R_8 are as defined in Formula (Ia).

In another aspect, the invention provides a compound having Formula (IIa):



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



R_2 is independently selected from H, F, Cl, C_{1-3} alkyl optionally substituted with one or more substituents selected from F, Cl, and OH, and OC_{1-3} alkyl;

R_3 is independently selected from H, F, Cl, CH_3 , and CH_2OH ;

R_4 is independently selected from H, F, Cl, $-C(=O)R_b$, C_{1-6} alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C_{3-6} cycloalkyl, $-NH-C_{1-6}$ alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C_{3-6} cycloalkyl, $-(CH_2)_r$ -aryl substituted with one or more R_5 , $-O-C_{1-6}$ alkyl substituted with one or more R_5 , $-(CH_2)_r-C_{3-12}$ cycloalkyl substituted with one or more R_5 , and $-(CH_2)_r$ -4–10 membered heterocyclyl comprising carbon atoms and 1–5 heteroatoms selected from N, NR_6 , O, and S and substituted with one or more R_5 ;

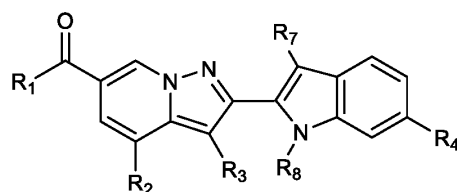
15

20

- R₅ is independently selected from H, F, Cl, =O, C₁₋₄ alkyl optionally substituted with one or more R_e, $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rC(=O)NR_aR_a$, $-(CH_2)_rOC(=O)R_b$, $-(CH_2)_rOC(=O)OR_b$, $-(CH_2)_rO(CH_2)_rC(=O)NR_aR_a$, C₃₋₆ cycloalkyl optionally substituted with one or more R_e, aryl optionally substituted with one or more R_e, and heterocyclyl optionally substituted with one or more R_e;
- R₆ is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more R_e, C(=O)R_b, -C(=O)NR_aR_a, C₃₋₆ cycloalkyl optionally substituted with one or more R_e, aryl optionally substituted with one or more R_e, and heterocyclyl optionally substituted with one or more R_e;
- R₇ is independently selected from H, F, and Cl;
- R₈ is independently selected from H, and C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, and C₃₋₆ cycloalkyl;
- R_a is independently selected from H, and C₁₋₆ alkyl optionally substituted with one or more R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring optionally substituted with one or more R_e;
- R_b is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more R_e, $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e, and $-(CH_2)_r$ heterocyclyl optionally substituted with one or more R_e;
- R_c is independently selected from C₁₋₆ alkyl optionally substituted with one or more R_e, $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e, and $-(CH_2)_r$ heterocyclyl optionally substituted with one or more R_e;
- R_e is independently selected from F, Cl, Br, NH₂, -NH-C₁₋₄ alkyl, -N(C₁₋₄ alkyl)₂, =O, OH, -OC₁₋₆ alkyl, C₁₋₆ alkyl optionally substituted with one or more R_f, $-(CH_2)_r-C_{3-6}$ cycloalkyl optionally substituted with one or more R_f, $-(CH_2)_r$ -aryl optionally substituted with one or more R_f, and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_f;
- R_f is independently selected from F, Cl, OH, OC₁₋₅ alkyl, C₁₋₅ alkyl optionally substituted with OH, C₃₋₆ cycloalkyl, and phenyl;
- p, at each occurrence, is independently selected from zero, 1, and 2; and

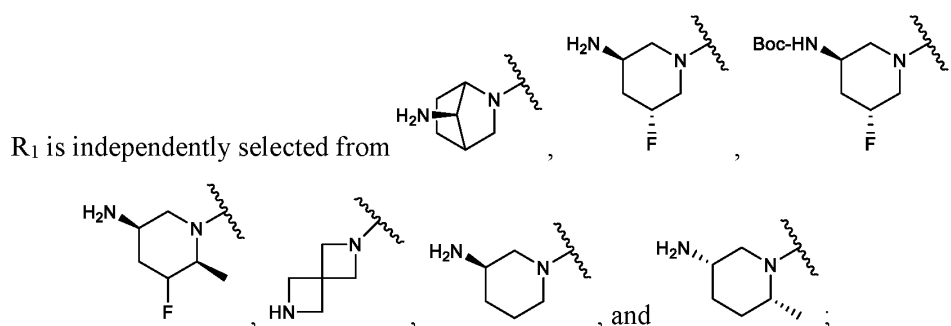
r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

In another aspect, the invention provides a compound having Formula (IIIa):



(IIIa)

- 5 or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof, wherein:



- R₂ is independently selected from H, F, Cl, C₁₋₃ alkyl optionally substituted with one or
 10 more substituents selected from F, Cl, and OH, and OC₁₋₃ alkyl;
 R₃ is independently selected from H, F, Cl, and C₁₋₃ alkyl optionally substituted with one
 or more substituents selected from F, Cl, and OH;
 R₄ is independently selected from H, F, Cl, -C(=O)R_b, C₁₋₆ alkyl optionally substituted
 with one or more substituents selected from F, Cl, OH, and C₃₋₆ cycloalkyl, -NH-
 15 C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl,
 OH, and C₃₋₆ cycloalkyl, -(CH₂)_r-aryl substituted with one or more R₅, -O-C₁₋₆
 alkyl substituted with one or more R₅, -(CH₂)_r-C₃₋₁₂ cycloalkyl substituted with one
 or more R₅, and -(CH₂)_r-4-10 membered heterocyclyl comprising carbon atoms
 20 and 1-5 heteroatoms selected from N, NR₆, O, and S and substituted with one or
 more R₅;
 R₅ is independently selected from H, F, Cl, =O, C₁₋₄ alkyl optionally substituted with one
 or more R_c, -(CH₂)_rOR_b, -(CH₂)_rS(O)_pR_c, -(CH₂)_rS(O)_pNR_aR_a, -(CH₂)_rNR_aS(O)_pR_c,
 -(CH₂)_rNR_aR_a, -(CH₂)_rNR_aC(=O)R_b, -(CH₂)_rNR_aC(=O)OR_b, -
 (CH₂)_rNR_aC(=O)NR_aR_a, -(CH₂)_rC(=O)R_b, -(CH₂)_rC(=O)OR_b, -

$(\text{CH}_2)_r\text{C}(=\text{O})\text{NR}_a\text{R}_a$, $-(\text{CH}_2)_r\text{OC}(=\text{O})\text{R}_b$, $-(\text{CH}_2)_r\text{OC}(=\text{O})\text{OR}_b$, $-(\text{CH}_2)_r\text{O}(\text{CH}_2)_r\text{C}(=\text{O})\text{NR}_a\text{R}_a$, C_{3-6} cycloalkyl optionally substituted with one or more R_e , aryl optionally substituted with one or more R_e , and heterocyclyl optionally substituted with one or more R_e ;

- 5 R_6 is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , $-\text{C}(=\text{O})\text{R}_b$, $-\text{C}(=\text{O})\text{OR}_b$, $-\text{C}(=\text{O})\text{NR}_a\text{R}_a$, C_{3-6} cycloalkyl optionally substituted with one or more R_e , aryl optionally substituted with one or more R_e , and heterocyclyl optionally substituted with one or more R_e ;

R_7 is independently selected from H, F, and Cl;

- 10 R_8 is independently selected from H, and C_{1-6} alkyl optionally substituted with one or more substituents selected from F, Cl, and C_{3-6} cycloalkyl;

R_a is independently selected from H, and C_{1-6} alkyl optionally substituted with one or more R_e ; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring optionally substituted with one or more R_e ;

- 15 R_b is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , $-(\text{CH}_2)_r\text{C}_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(\text{CH}_2)_r$ heterocyclyl optionally substituted with one or more R_e ;

R_c is independently selected from C_{1-6} alkyl optionally substituted with one or more R_e , $-(\text{CH}_2)_r\text{C}_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(\text{CH}_2)_r$ heterocyclyl optionally substituted with one or more R_e ;

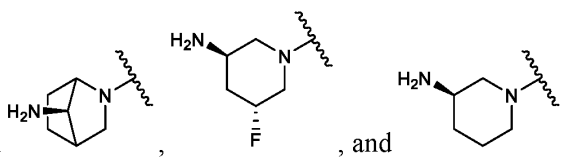
- 20 R_e is independently selected from F, Cl, Br, CN, NH_2 , $-\text{NH}-\text{C}_{1-4}$ alkyl, $-\text{N}(\text{C}_{1-4} \text{ alkyl})_2$, $=\text{O}$, OH, $-\text{OC}_{1-6}$ alkyl, C_{1-6} alkyl optionally substituted with one or more R_f , $-(\text{CH}_2)_r\text{C}_{3-6}$ cycloalkyl optionally substituted with one or more R_f , $-(\text{CH}_2)_r$ aryl optionally substituted with one or more R_f , and $-(\text{CH}_2)_r$ heterocyclyl optionally substituted with one or more R_f ;

25 R_f is independently selected from F, Cl, OH, OC_{1-5} alkyl, C_{1-5} alkyl optionally substituted with OH, C_{3-6} cycloalkyl, and phenyl;

p , at each occurrence, is independently selected from zero, 1, and 2; and

r , at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

- 30 In another aspect, the invention provides a compound having Formulae (IIa)-(IIIa), or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof, wherein:



R₁ is independently selected from

R₂ is independently selected from H, F, Cl, CH₃, and OCH₃;

R₃ is independently selected from H, F, Cl, CH₃, and CH₂OH;

R₄ is independently selected from H, F, Cl, C₁₋₅ alkyl optionally substituted with one or

- 5 more substituents selected from F, Cl, OH, and C₃₋₆ cycloalkyl, -(CH₂)_r-aryl substituted with one or more R₅, -O-C₁₋₆ alkyl substituted with one or more R₅, -(CH₂)_r-C₃₋₁₂ cycloalkyl substituted with one or more R₅, and -(CH₂)_r-4-10 membered heterocyclyl comprising carbon atoms and 1-5 heteroatoms selected from N, NR₆, O, and S and substituted with one or more R₅;
- 10 R₅ is independently selected from H, F, Cl, =O, C₁₋₄ alkyl optionally substituted with one or more R_e, -(CH₂)_rOR_b, -(CH₂)_rS(O)₂R_c, -(CH₂)_rS(O)_pNR_aR_a, -(CH₂)_rNR_aS(O)₂R_c, -(CH₂)_rNR_aR_a, -(CH₂)_rNR_aC(=O)R_b, -(CH₂)_rNR_aC(=O)OR_b, -(CH₂)_rNR_aC(=O)NR_aR_a, -(CH₂)_rC(=O)R_b, -(CH₂)_rC(=O)OR_b, -(CH₂)_rC(=O)NR_aR_a, -(CH₂)_rOC(=O)R_b, -(CH₂)_rOC(=O)OR_b, -(CH₂)_rO(CH₂)_rC(=O)NR_aR_a, C₃₋₆ cycloalkyl optionally substituted with one or more R_e, aryl optionally substituted with one or more R_e, and heterocyclyl optionally substituted with one or more R_e;

R₆ is independently selected from H and C₁₋₆₅ alkyl optionally substituted with one or more R_e;

- 20 R₇ is H;

R₈ is C₁₋₃ alkyl substituted with one C₃₋₆ cycloalkyl;

R_a is independently selected from H, and C₁₋₄ alkyl;

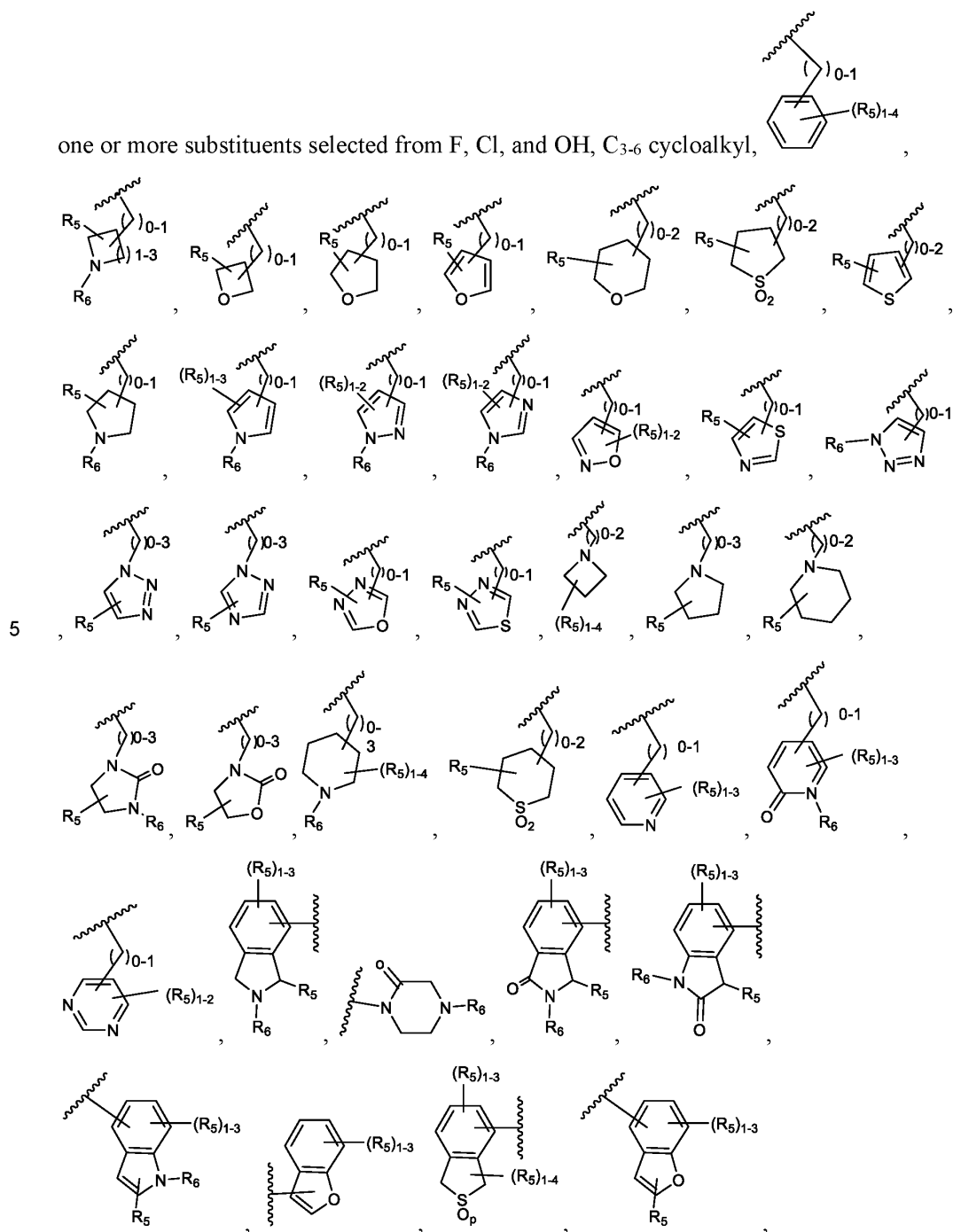
R_b is independently selected from H, C₁₋₄ alkyl;

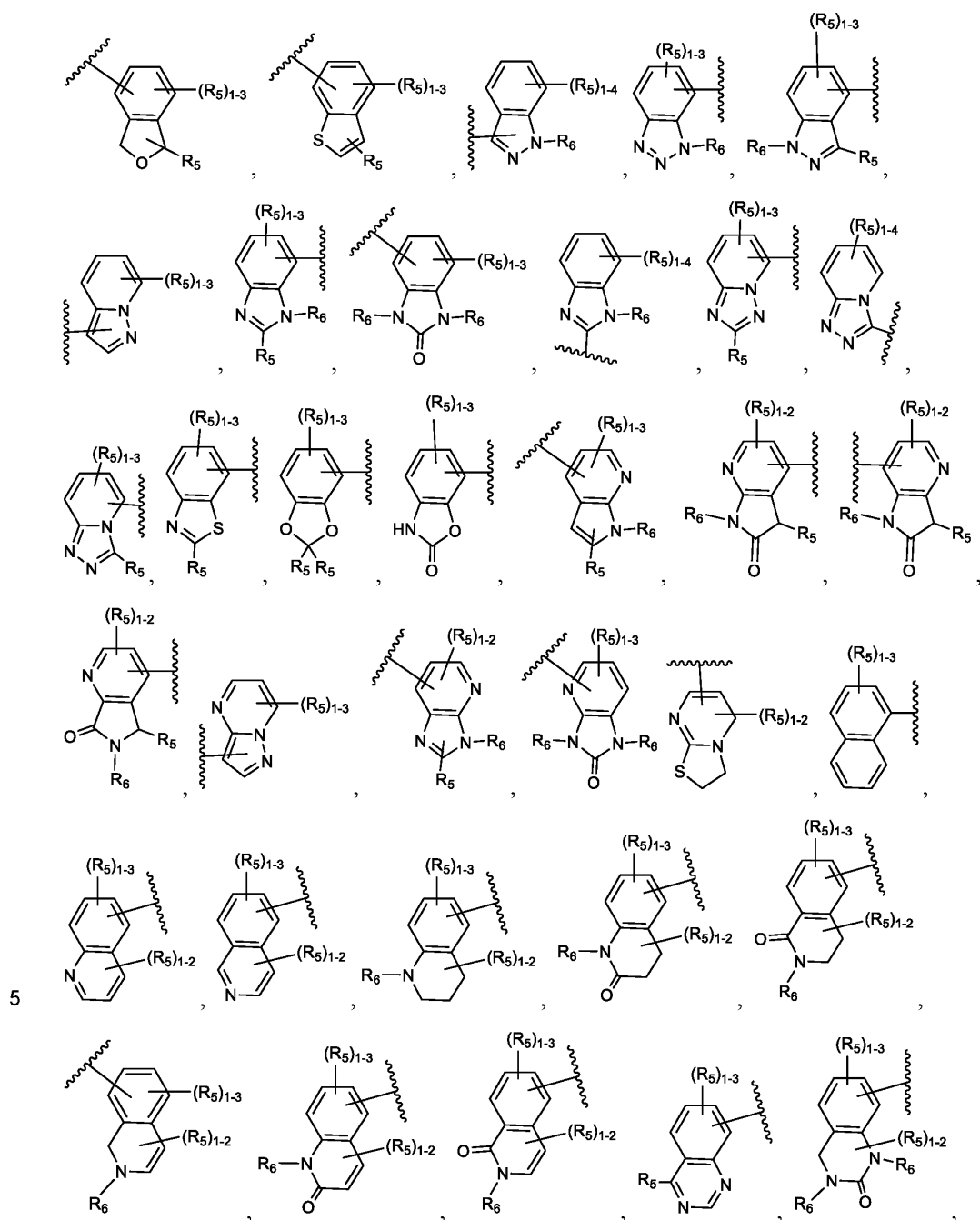
R_c is C₁₋₄ alkyl; and

- 25 r, at each occurrence, is independently selected from zero, 1, and 2.

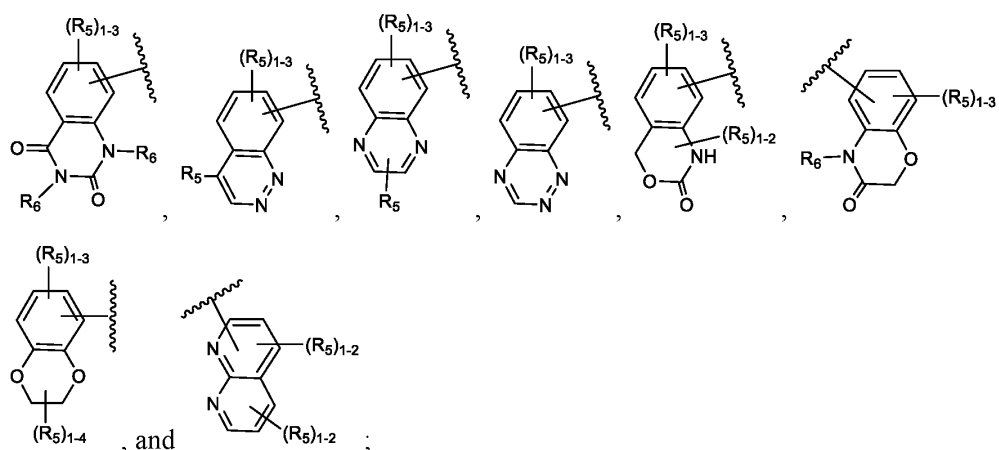
In another aspect, the invention provides a compound having Formulae (IIa)-(IIIa), or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof, wherein:

R₄ is independently selected from H, F, Cl, C₁₋₅ alkyl optionally substituted with





5

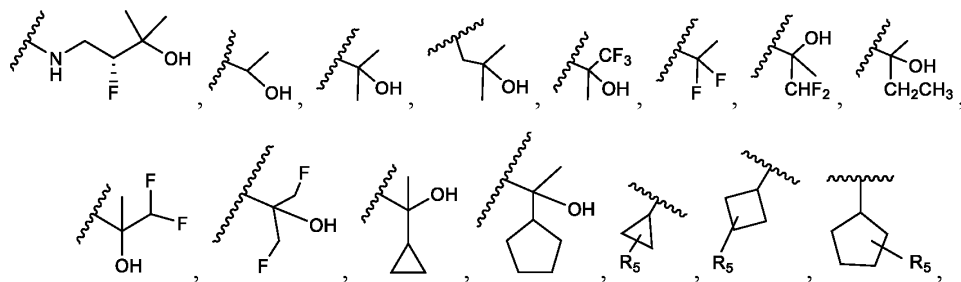


R_5 is independently selected from H, F, Cl, =O, C_{1-4} alkyl optionally substituted with one or more R_e , $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rC(=O)NR_aR_a$, $-(CH_2)_rOC(=O)R_b$, $-(CH_2)_rOC(=O)OR_b$, $-(CH_2)_rO(CH_2)_rC(=O)NR_aR_a$, C_{3-6} cycloalkyl optionally substituted with one or more R_e , aryl optionally substituted with one or more R_e , and heterocyclyl optionally substituted with one or more R_e ; and

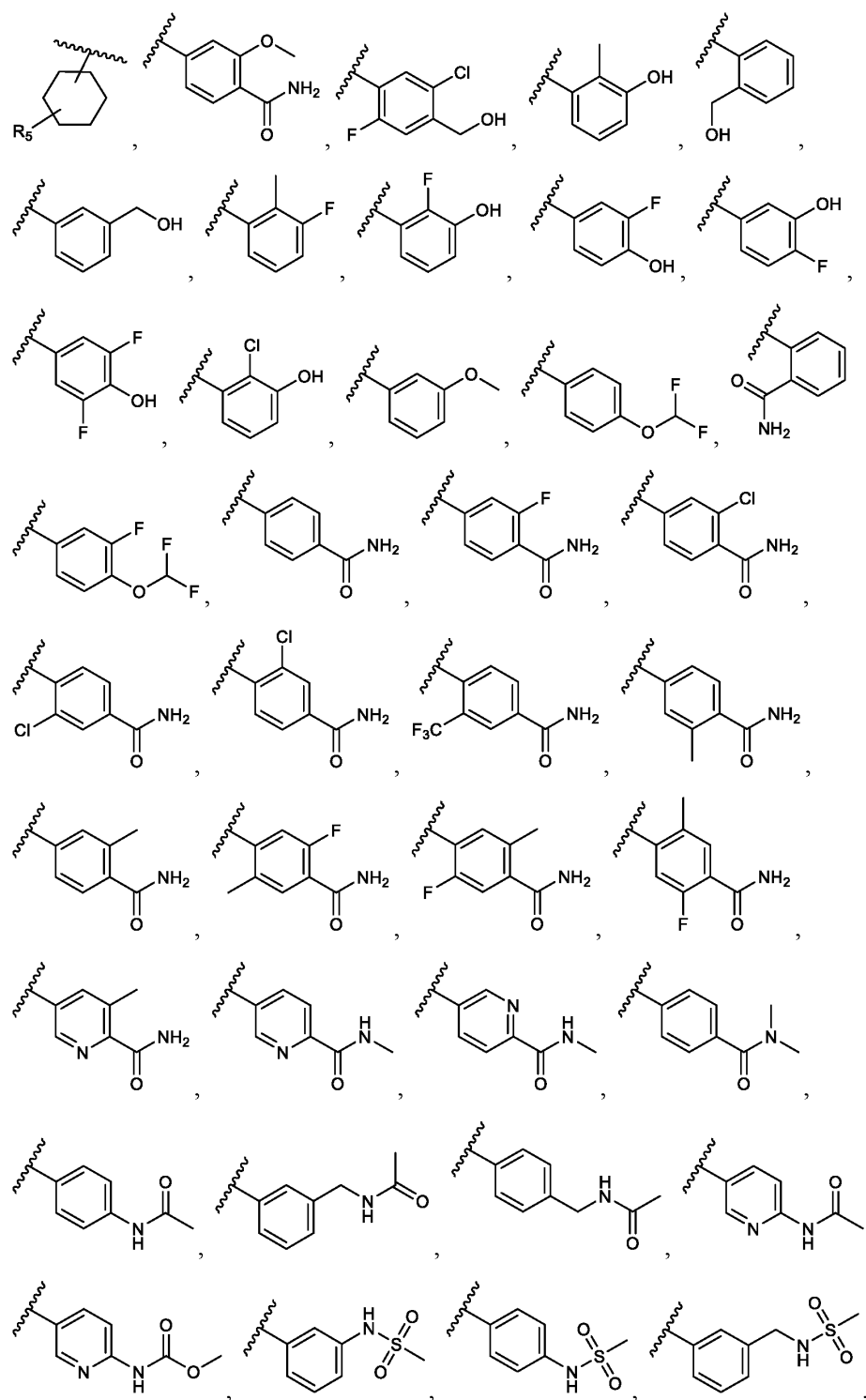
R_6 is independently selected from H and C_{1-5} alkyl; and other variables are as defined in Formulae (IIa)-(IIIa).

In another aspect, the invention provides a compound having Formulae (IIa)-(IIIa), or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof, wherein:

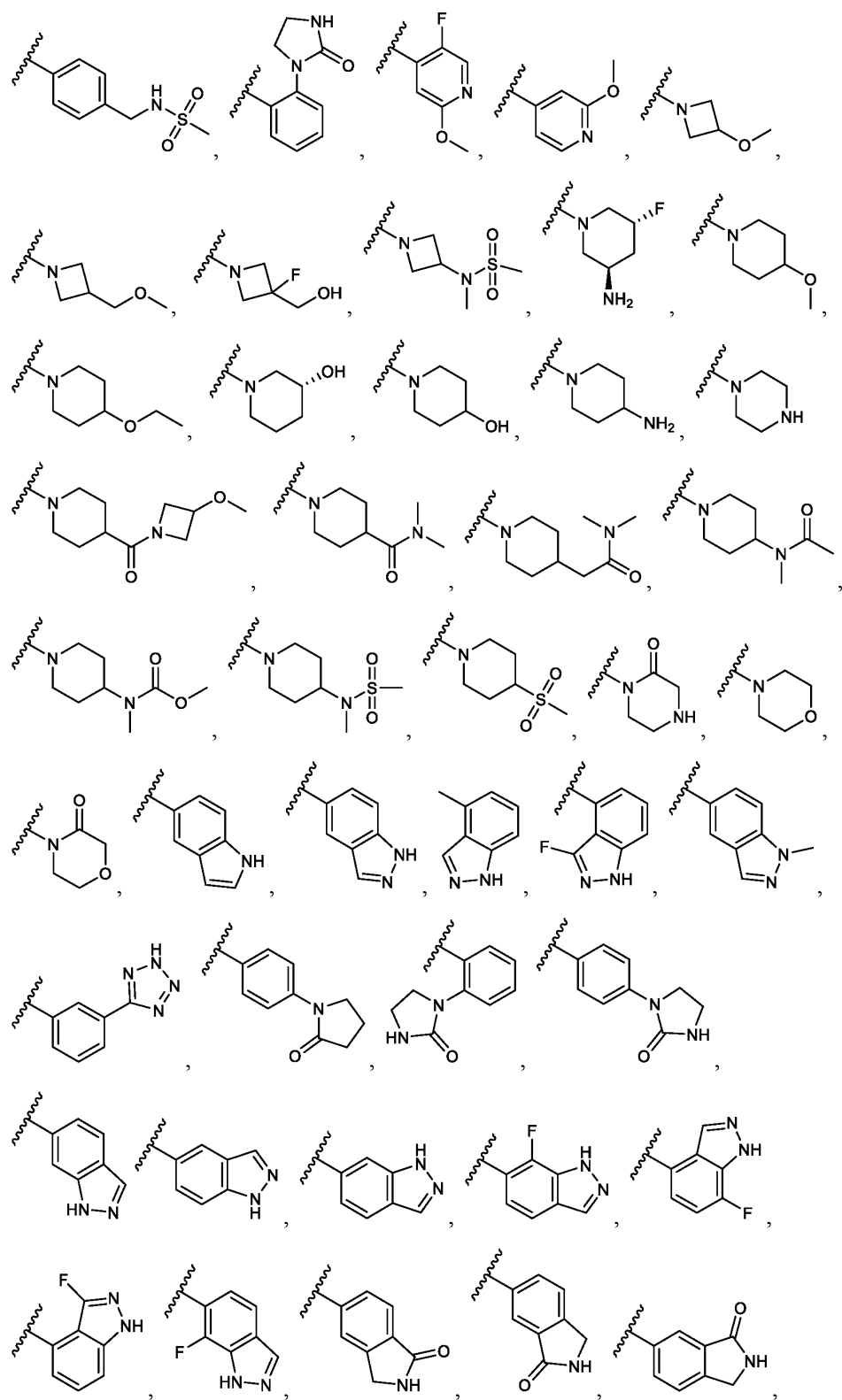
R_4 is independently selected from

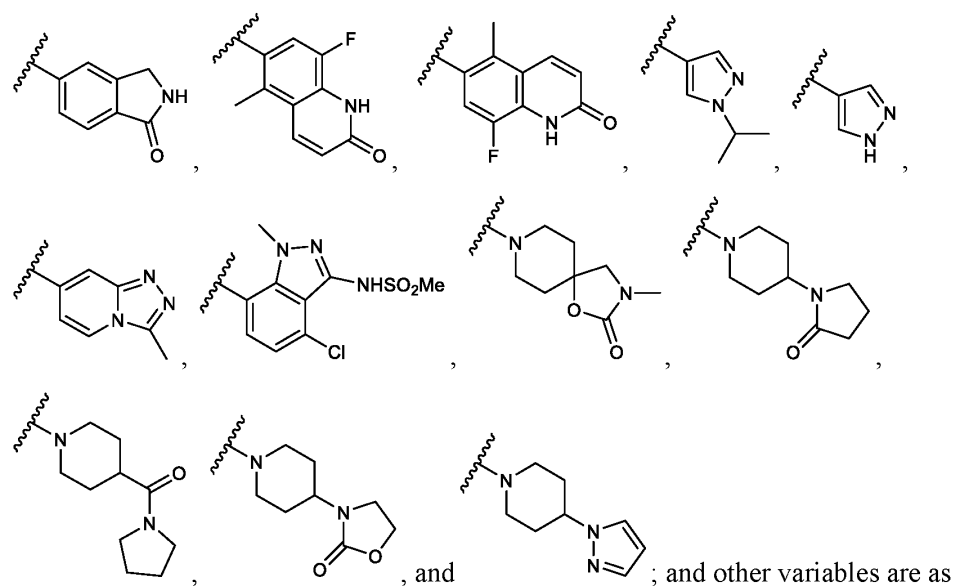


5



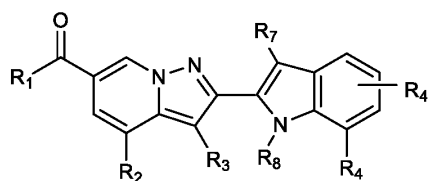
5





defined in Formulae (IIa)-(IIIa).

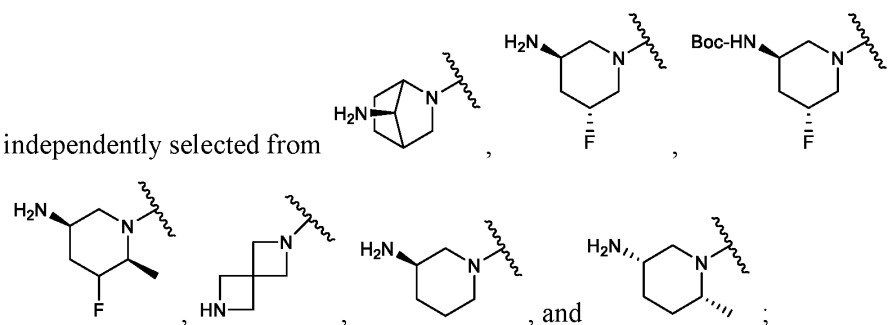
5 In another aspect, the invention provides a compound having Formula (IVa):



(IVa)

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

10 R₁ is independently selected from



R₂ is independently selected from H, F, Cl, C₁₋₃ alkyl optionally substituted with one or more substituents selected from F, Cl, and OH, and OC₁₋₃ alkyl;

R₃ is independently selected from H, F, Cl, and C₁₋₃ alkyl optionally substituted with one or more substituents selected from F, Cl, and OH;

15

- R_4 is independently selected from H, F, Cl, $-C(=O)R_b$, C_{1-6} alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C_{3-6} cycloalkyl, $-NH-$ C_{1-6} alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C_{3-6} cycloalkyl, $-(CH_2)_r$ -aryl substituted with one or more R_5 , $-O-C_{1-6}$ alkyl substituted with one or more R_5 , $-(CH_2)_r-C_{3-12}$ cycloalkyl substituted with one or more R_5 , and $-(CH_2)_r-4-10$ membered heterocyclyl comprising carbon atoms and 1-5 heteroatoms selected from N, NR_6 , O, and S and substituted with one or more R_5 ;
- R_5 is independently selected from H, F, Cl, $=O$, C_{1-4} alkyl optionally substituted with one or more R_e , $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rC(=O)NR_aR_a$, $-(CH_2)_rOC(=O)R_b$, $-(CH_2)_rOC(=O)OR_b$, $-(CH_2)_rO(CH_2)_rC(=O)NR_aR_a$, C_{3-6} cycloalkyl optionally substituted with one or more R_e , aryl optionally substituted with one or more R_e , and heterocyclyl optionally substituted with one or more R_e ;
- R_6 is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , $-S(O)_pR_c$, $-S(O)_pNR_aR_a$, $-C(=O)R_b$, $-C(=O)OR_b$, $-C(=O)NR_aR_a$, C_{3-6} cycloalkyl optionally substituted with one or more R_e , aryl optionally substituted with one or more R_e , and heterocyclyl optionally substituted with one or more R_e ;
- R_7 is independently selected from H, F, and Cl;
- R_8 is independently selected from H, and C_{1-6} alkyl optionally substituted with one or more substituents selected from F, Cl, and C_{3-6} cycloalkyl;
- R_a is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_e ; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring optionally substituted with one or more R_e ;
- R_b is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ heterocyclyl optionally substituted with one or more R_e ;

R_c is independently selected from C_{1-6} alkyl optionally substituted with one or more R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_e ;

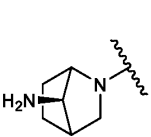
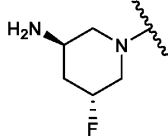
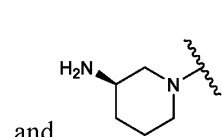
R_e is independently selected from F, Cl, Br, NH_2 , $-NH-C_{1-4}$ alkyl, $-N(C_{1-4}$ alkyl) $_2$, $=O$,
 5 OH, $-OC_{1-6}$ alkyl, C_{1-6} alkyl optionally substituted with one or more R_f , $-(CH_2)_r-C_{3-6}$ cycloalkyl optionally substituted with one or more R_f , $-(CH_2)_r$ -aryl optionally substituted with one or more R_f , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_f ;

R_f is independently selected from F, Cl, OH, OC_{1-5} alkyl, C_{1-5} alkyl optionally substituted
 10 with OH, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-6} cycloalkyl, and phenyl;

p , at each occurrence, is independently selected from zero, 1, and 2; and

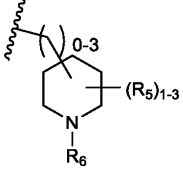
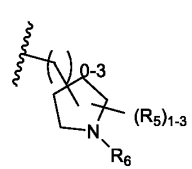
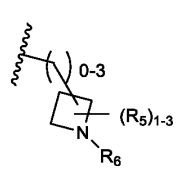
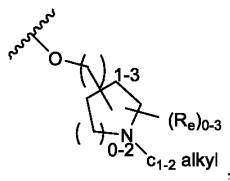
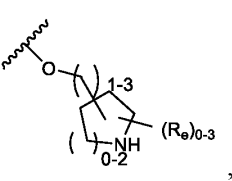
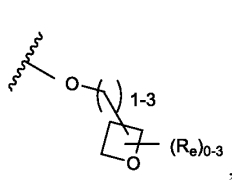
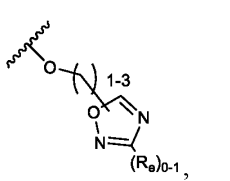
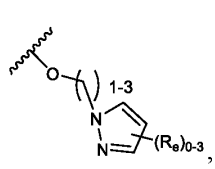
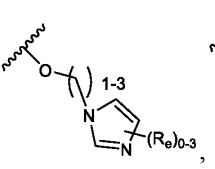
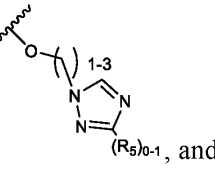
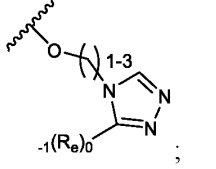
r , at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

In another aspect, the invention provides a compound having Formulae (IVa), or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable
 15 salt thereof, wherein:

R_1 is independently selected from , , and ;

R_2 is independently selected from H, F, Cl, and OCH_3 ;

R_3 is independently selected from F, Cl, and CH_3 ;

R_4 is independently selected from H,
, , ,
, , , ,
, , , and ;

R₅ is independently selected from H, =O, C₁₋₄ alkyl, OH, and NH₂;

R₆ is independently selected from H, C₁₋₅ alkyl optionally substituted with one or more R_e, and -C(=O)R_b;

R₇ is H;

5 R₈ is C₁₋₂ alkyl optionally substituted with cyclopropyl;

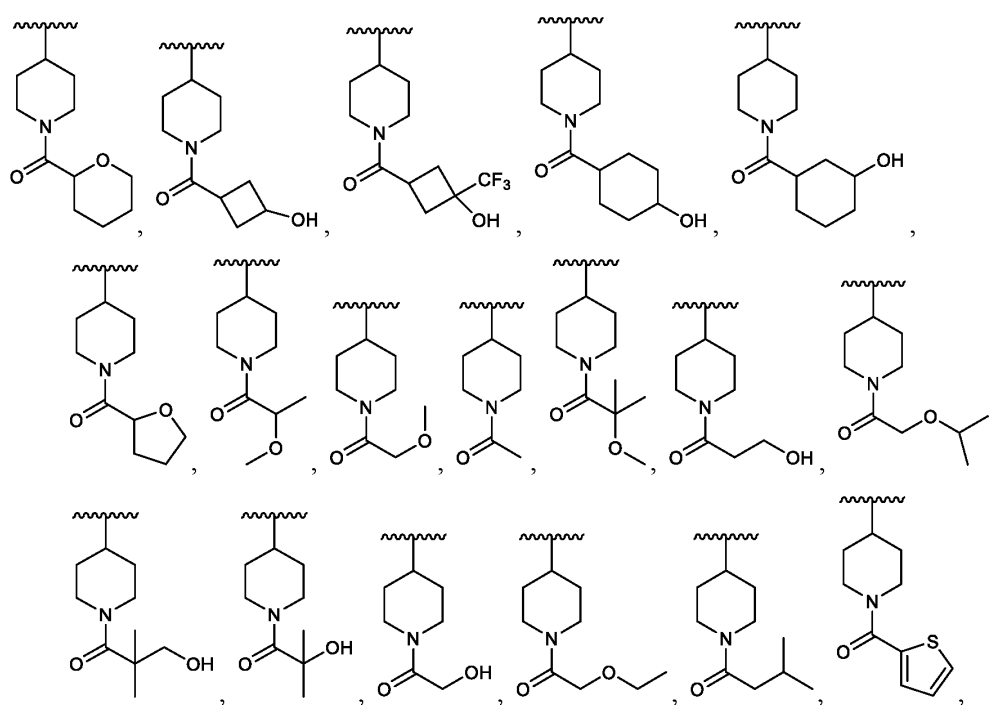
R_b is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more R_e, -(CH₂)_r-C₃₋₁₀ carbocyclyl optionally substituted with one or more R_e, and -
(CH₂)_r heterocyclyl optionally substituted with one or more R_e;

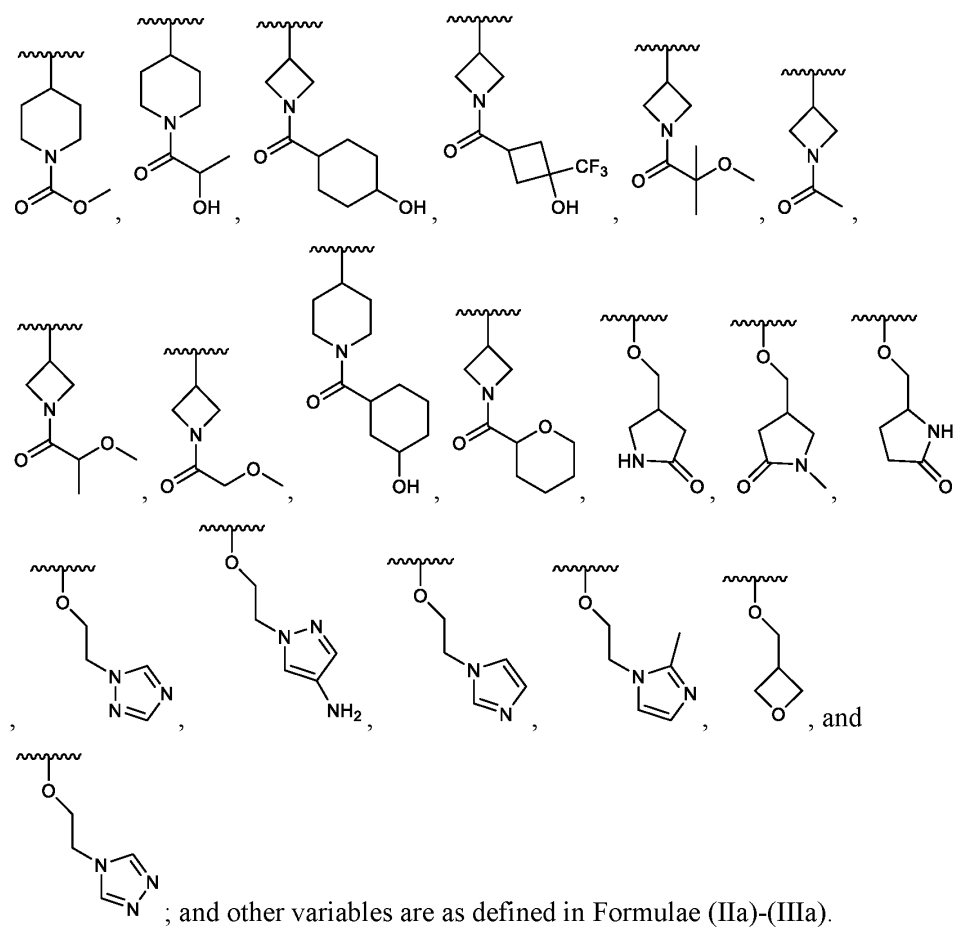
R_e is independently selected from NH₂ and C₁₋₅ alkyl optionally substituted with one or
10 more R_f; and

R_f is independently selected from F, Cl, OH, and OC₁₋₅ alkyl.

In another aspect, the invention provides a compound having Formulae (IIa)-(IIIa), or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof, wherein:

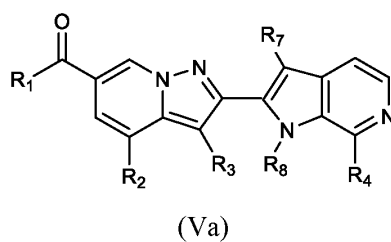
15 R₄ is independently selected from



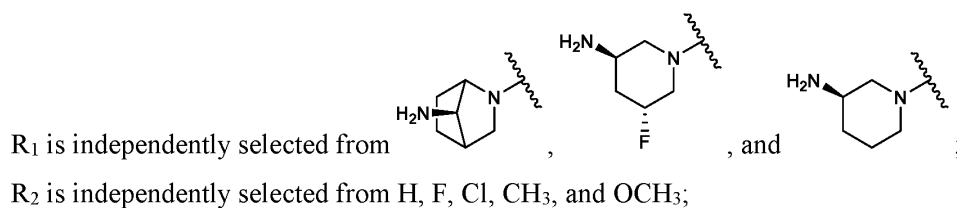


5

In another aspect, the invention provides a compound having Formula (Va):



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



- R_3 is independently selected from H, F, Cl, CN, CH_3 , and CH_2OH ;
- R_4 is independently selected from H, F, Cl, $-C(=O)R_b$, C_{1-6} alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C_{3-6} cycloalkyl, $-NH-$ C_{1-6} alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C_{3-6} cycloalkyl, $-(CH_2)_r$ -aryl substituted with one or more R_5 , $-O-C_{1-6}$ alkyl substituted with one or more R_5 , $-(CH_2)_r-C_{3-12}$ cycloalkyl substituted with one or more R_5 , and $-(CH_2)_r-4-10$ membered heterocyclyl comprising carbon atoms and 1-5 heteroatoms selected from N, NR_6 , O, and S and substituted with one or more R_5 ;
- R_5 is independently selected from H, F, Cl, $=O$, C_{1-4} alkyl optionally substituted with one or more R_e , $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rC(=O)NR_aR_a$, $-(CH_2)_rOC(=O)R_b$, $-(CH_2)_rOC(=O)OR_b$, $-(CH_2)_rO(CH_2)_rC(=O)NR_aR_a$, C_{3-6} cycloalkyl optionally substituted with one or more R_e , aryl optionally substituted with one or more R_e , and heterocyclyl optionally substituted with one or more R_e ;
- R_6 is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , $-C(=O)R_b$, $-C(=O)OR_b$, $-C(=O)NR_aR_a$, C_{3-6} cycloalkyl optionally substituted with one or more R_e , aryl optionally substituted with one or more R_e , and heterocyclyl optionally substituted with one or more R_e ;
- R_7 is independently selected from H, F, and Cl;
- R_8 is independently selected from H, and C_{1-6} alkyl optionally substituted with one or more substituents selected from F, Cl, and C_{3-6} cycloalkyl;
- R_a is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_e ; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring optionally substituted with one or more R_e ;
- R_b is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ heterocyclyl optionally substituted with one or more R_e ;

R_e is independently selected from C_{1-6} alkyl optionally substituted with one or more R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_e ;

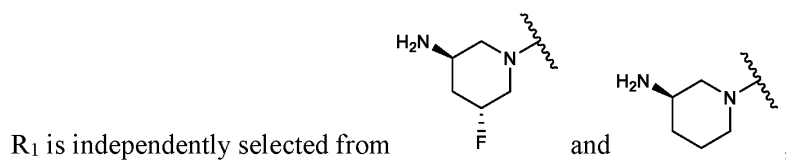
R_e is independently selected from F, Cl, Br, NH_2 , $-NH-C_{1-4}$ alkyl, $-N(C_{1-4}$ alkyl) $_2$, $=O$,
 5 OH, $-OC_{1-6}$ alkyl, $-CO_2H$, C_{1-6} alkyl optionally substituted with one or more R_f , $-(CH_2)_r-C_{3-6}$ cycloalkyl optionally substituted with one or more R_f , $-(CH_2)_r$ -aryl optionally substituted with one or more R_f , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_f ;

R_f is independently selected from F, Cl, Br, CN, OH, C_{1-5} alkyl optionally substituted
 10 with OH, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-6} cycloalkyl, and phenyl;

p , at each occurrence, is independently selected from zero, 1, and 2; and

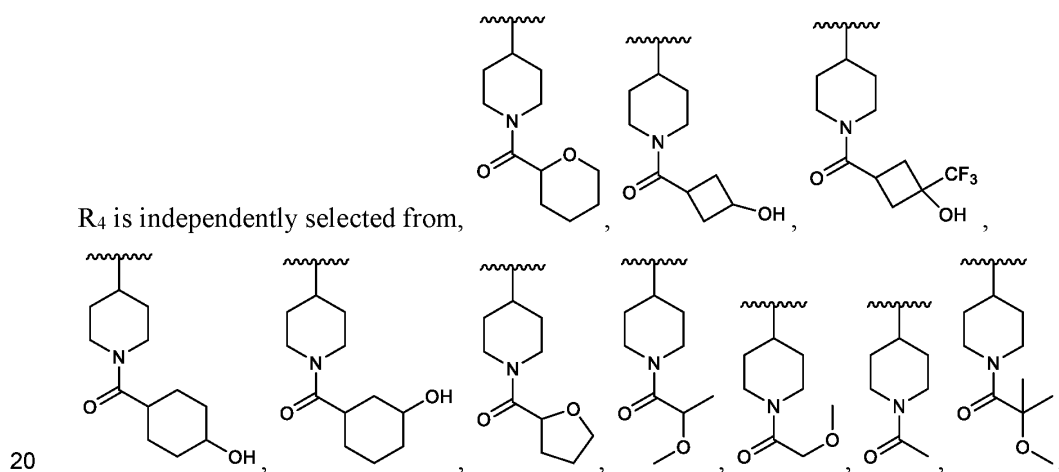
r , at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

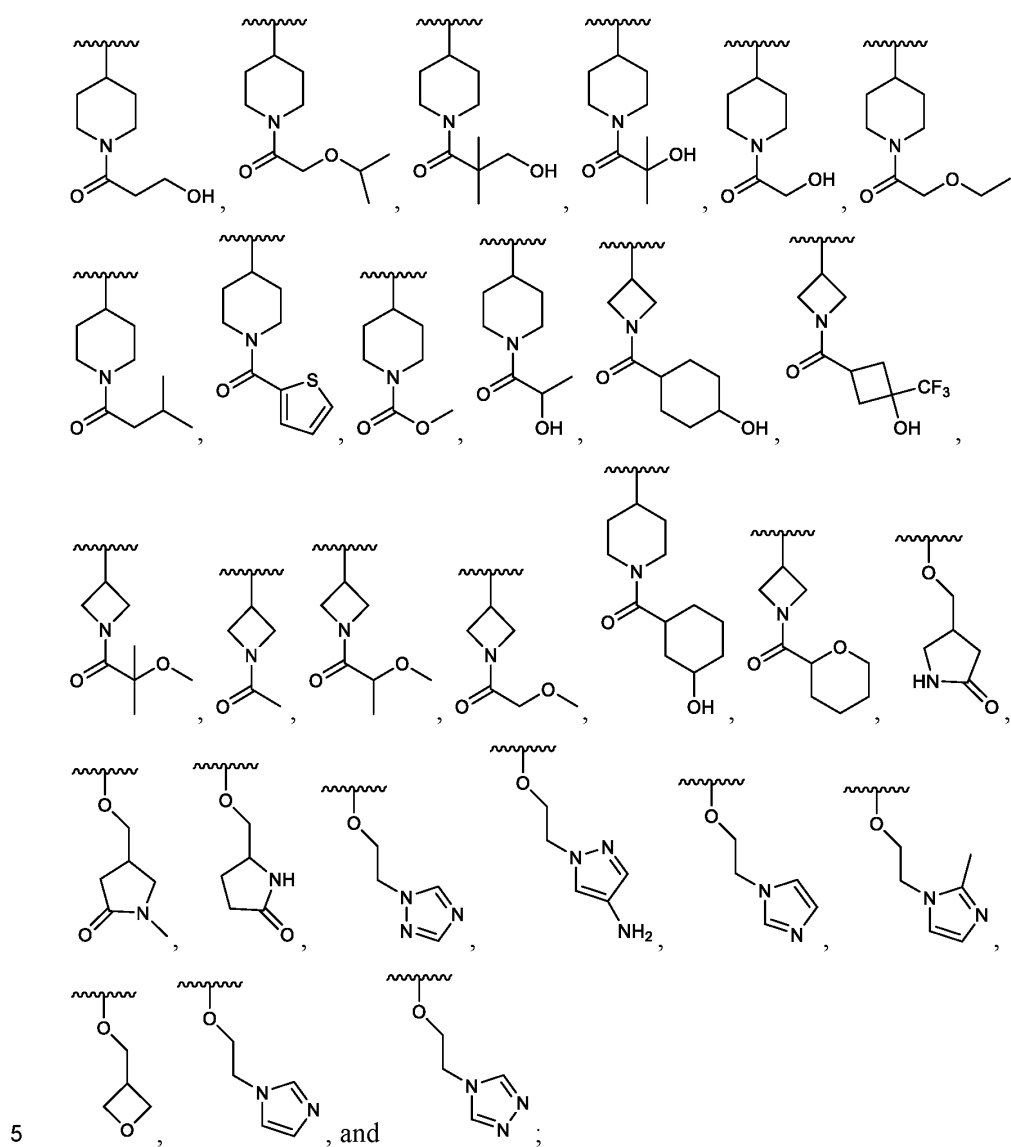
In another aspect, the invention provides a compound having Formula (Va), or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable
 15 salt thereof, wherein:



R_2 is CH_3 ;

R_3 is CH_3 ; and

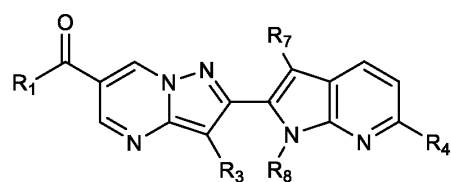




R_7 is H; and

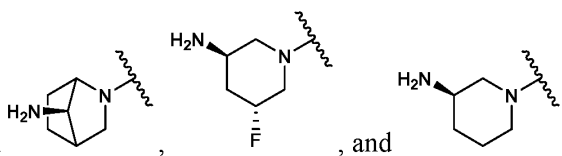
R_8 is C_{1-2} alkyl optionally substituted with cyclopropyl.

In another aspect, the invention provides a compound having Formula (VIa):



(VIa)

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



R₁ is independently selected from

R₃ is independently selected from H, F, and CH₃;

- 5 R₄ is independently selected from H, F, Cl, -C(=O)R_b, C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C₃₋₆ cycloalkyl, -NH-C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C₃₋₆ cycloalkyl, -(CH₂)_r-aryl substituted with one or more R₅, -O-C₁₋₆ alkyl substituted with one or more R₅, -(CH₂)_r-C₃₋₁₂ cycloalkyl substituted with one or more R₅, and -(CH₂)_r-4-10 membered heterocyclyl comprising carbon atoms and 1-5 heteroatoms selected from N, NR₆, O, and S and substituted with one or more R₅;

- R₅ is independently selected from H, F, Cl, Br, CN, =O, C₁₋₄ alkyl optionally substituted with one or more R_e, C₂₋₄ alkenyl optionally substituted with one or more R_e, C₂₋₄ alkynyl optionally substituted with one or more R_e, -(CH₂)_rOR_b, -(CH₂)_rS(O)_pR_c, -(CH₂)_rS(O)_pNR_aR_a, -(CH₂)_rNR_aS(O)_pR_c, -(CH₂)_rNR_aR_a, -(CH₂)_rNR_aC(=O)R_b, -(CH₂)_rNR_aC(=O)OR_b, -(CH₂)_rNR_aC(=O)NR_aR_a, -(CH₂)_rC(=O)R_b, -(CH₂)_rC(=O)OR_b, -(CH₂)_rC(=O)NR_aR_a, -(CH₂)_rOC(=O)R_b, -(CH₂)_rOC(=O)OR_b, -(CH₂)_rO(CH₂)_rC(=O)NR_aR_a, C₃₋₆ cycloalkyl optionally substituted with one or more R_e, aryl optionally substituted with one or more R_e, and heterocyclyl optionally substituted with one or more R_e;

- R₆ is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more R_e, -C(=O)R_b, -C(=O)OR_b, -C(=O)NR_aR_a, C₃₋₆ cycloalkyl optionally substituted with one or more R_e, aryl optionally substituted with one or more R_e, and heterocyclyl optionally substituted with one or more R_e;

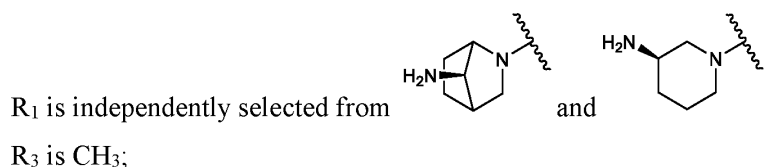
R₇ is independently selected from H, F, and Cl;

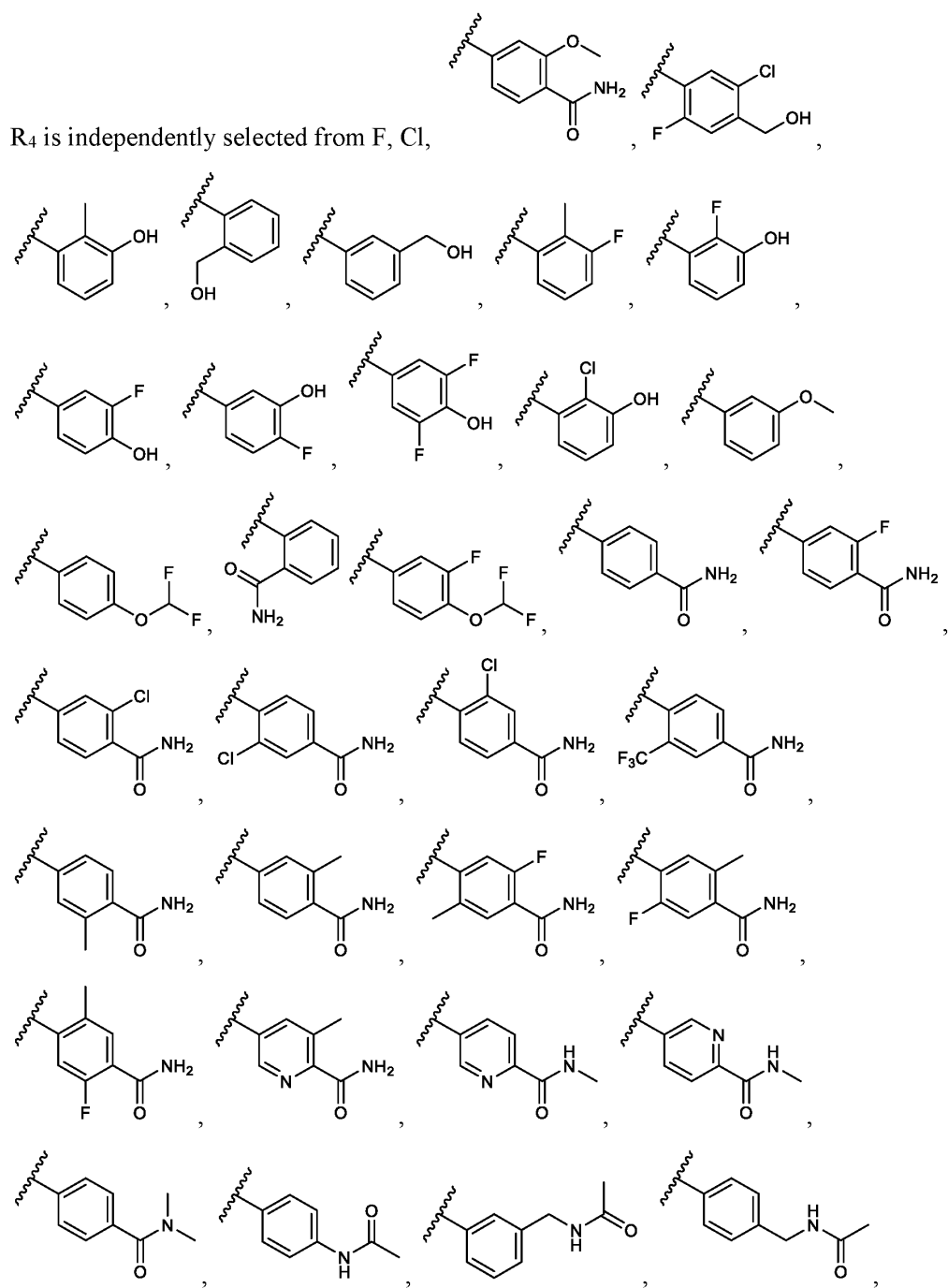
R₈ is independently selected from H, and C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, and C₃₋₆ cycloalkyl;

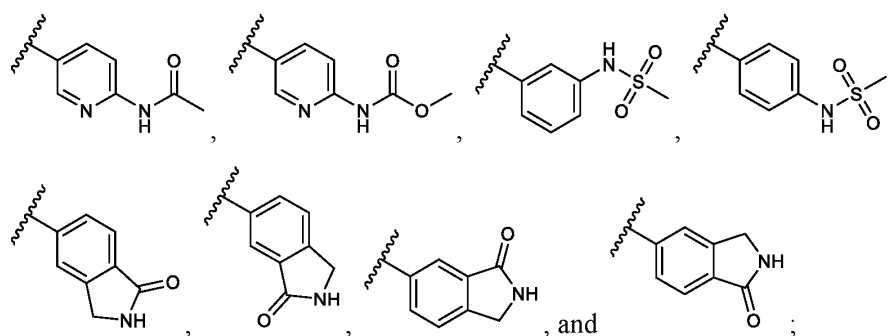
- R_a is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more R_e, C₂₋₆ alkenyl optionally substituted with one or more R_e, C₂₋₆ alkynyl optionally

- substituted with one or more R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_e ; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring optionally substituted with one or more R_e ;
- 5 R_b is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , C_{2-6} alkenyl optionally substituted with one or more R_e , C_{2-6} alkynyl optionally substituted with one or more R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ heterocyclyl optionally substituted with one or more R_e ;
- 10 R_c is independently selected from C_{1-6} alkyl optionally substituted with one or more R_e , C_{2-6} alkenyl optionally substituted with one or more R_e , C_{2-6} alkynyl optionally substituted with one or more R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_e ;
- 15 R_e is independently selected from F, Cl, Br, CN, NH_2 , $-NH-C_{1-4}$ alkyl, $-N(C_{1-4}$ alkyl) $_2$, $=O$, OH, $-OC_{1-6}$ alkyl, $-CO_2H$, C_{1-6} alkyl optionally substituted with one or more R_f , C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_r-C_{3-6}$ cycloalkyl optionally substituted with one or more R_f , $-(CH_2)_r$ -aryl optionally substituted with one or more R_f , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_f ;
- 20 R_f is independently selected from F, Cl, Br, CN, OH, C_{1-5} alkyl optionally substituted with OH, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-6} cycloalkyl, and phenyl;
- p , at each occurrence, is independently selected from zero, 1, and 2; and
- r , at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

In another aspect, the invention provides a compound having Formula (VIa), or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof, wherein:



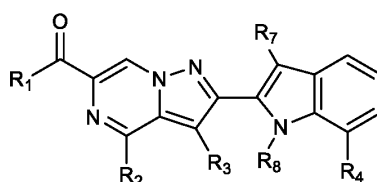




R_7 is H; and

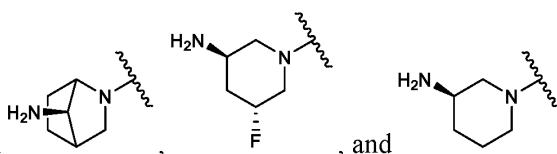
R_8 is C_{1-2} alkyl optionally substituted with cyclopropyl.

- 5 In another aspect, the invention provides a compound having Formula (VII):



(VII)

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



- 10 R_1 is independently selected from , , and ;
 R_2 is independently selected from H, F, Cl, CH_3 , and OCH_3 ;
 R_3 is independently selected from H, F, and CH_3 ;
 R_4 is independently selected from H, F, Cl, Br, $-C(=O)R_b$, C_{1-6} alkyl optionally substituted
 with one or more substituents selected from F, Cl, OH, and C_{3-6} cycloalkyl, $-NH-$
 15 C_{1-6} alkyl optionally substituted with one or more substituents selected from F, Cl,
 OH, and C_{3-6} cycloalkyl, $-(CH_2)_r$ -aryl substituted with one or more R_5 , $-O-C_{1-6}$
 alkyl substituted with one or more R_5 , $-(CH_2)_r-C_{3-12}$ cycloalkyl substituted with one
 or more R_5 , and $-(CH_2)_r-4-10$ membered heterocyclyl comprising carbon atoms
 and 1-5 heteroatoms selected from N, NR_6 , O, and S and substituted with one or
 20 more R_5 ;
 R_5 is independently selected from H, F, Cl, Br, CN, $=O$, C_{1-4} alkyl optionally substituted
 with one or more R_6 , C_{2-4} alkenyl optionally substituted with one or more R_6 , C_{2-4}

alkynyl optionally substituted with one or more R_e , $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rC(=O)NR_aR_a$, $-(CH_2)_rOC(=O)R_b$, $-(CH_2)_rOC(=O)OR_b$, $-(CH_2)_rO(CH_2)_rC(=O)NR_aR_a$, C_{3-6} cycloalkyl optionally substituted with one or more R_e , aryl optionally substituted with one or more R_e , and heterocyclyl optionally substituted with one or more R_e ;

R_6 is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , $-S(O)_pR_c$, $-S(O)_pNR_aR_a$, $-C(=O)R_b$, $-C(=O)OR_b$, $-C(=O)NR_aR_a$, C_{3-6} cycloalkyl optionally substituted with one or more R_e , aryl optionally substituted with one or more R_e , and heterocyclyl optionally substituted with one or more R_e ;

R_7 is independently selected from H, F, and Cl;

R_8 is independently selected from H, and C_{1-6} alkyl optionally substituted with one or more substituents selected from F, Cl, and C_{3-6} cycloalkyl;

R_a is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , C_{2-6} alkenyl optionally substituted with one or more R_e , C_{2-6} alkynyl optionally substituted with one or more R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_e ; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring optionally substituted with one or more R_e ;

R_b is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , C_{2-6} alkenyl optionally substituted with one or more R_e , C_{2-6} alkynyl optionally substituted with one or more R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ heterocyclyl optionally substituted with one or more R_e ;

R_c is independently selected from C_{1-6} alkyl optionally substituted with one or more R_e , C_{2-6} alkenyl optionally substituted with one or more R_e , C_{2-6} alkynyl optionally substituted with one or more R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_e ;

R_e is independently selected from F, Cl, Br, CN, NH_2 , $-NH-C_{1-4}$ alkyl, $-N(C_{1-4}$ alkyl) $_2$, $=O$, OH, $-OC_{1-6}$ alkyl, $-CO_2H$, C_{1-6} alkyl optionally substituted with one or more R_f ,

C₂₋₆ alkenyl, C₂₋₆ alkynyl, -(CH₂)_r-C₃₋₆ cycloalkyl optionally substituted with one or more R_f, -(CH₂)_r-aryl optionally substituted with one or more R_f, and -(CH₂)_r-heterocyclyl optionally substituted with one or more R_f;

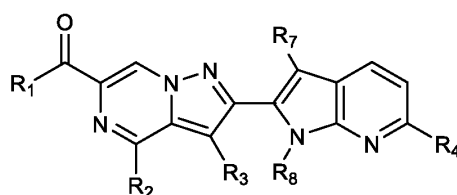
R_f is independently selected from F, Cl, Br, CN, OH, C₁₋₅ alkyl optionally substituted

5 with OH, C₂₋₅ alkenyl, C₂₋₅ alkynyl, C₃₋₆ cycloalkyl, and phenyl;

p, at each occurrence, is independently selected from zero, 1, and 2; and

r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

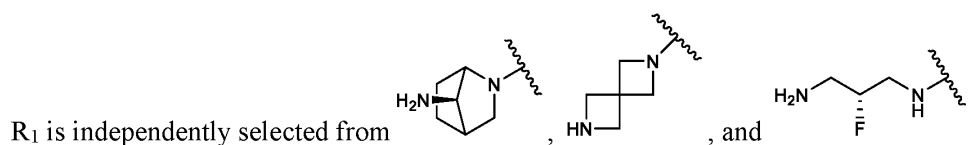
In another aspect, the invention provides a compound having Formula (VIII):



10

(VIII)

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



R₁ is independently selected from

R₂ is independently selected from H, F, and OCH₃;

15 R₃ is independently selected from H, F, and CH₃;

R₄ is independently selected from H, F, Cl, Br, -C(=O)R_b, C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C₃₋₆ cycloalkyl, -NH-C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C₃₋₆ cycloalkyl, -(CH₂)_r-aryl substituted with one or more R₅, -O-C₁₋₆ alkyl substituted with one or more R₅, -(CH₂)_r-C₃₋₁₂ cycloalkyl substituted with one or more R₅, and -(CH₂)_r-4-10 membered heterocyclyl comprising carbon atoms and 1-5 heteroatoms selected from N, NR₆, O, and S and substituted with one or more R₅;

20

R₅ is independently selected from H, F, Cl, Br, CN, =O, C₁₋₄ alkyl optionally substituted with one or more R_e, C₂₋₄ alkenyl optionally substituted with one or more R_e, C₂₋₄ alkynyl optionally substituted with one or more R_e, -(CH₂)_rOR_b, -(CH₂)_rS(O)_pR_c, -(CH₂)_rS(O)_pNR_aR_a, -(CH₂)_rNR_aS(O)_pR_c, -(CH₂)_rNR_aR_a, -(CH₂)_rNR_aC(=O)R_b, -

25

- $(\text{CH}_2)_r\text{NR}_a\text{C}(=\text{O})\text{OR}_b$, $-(\text{CH}_2)_r\text{NR}_a\text{C}(=\text{O})\text{NR}_a\text{R}_a$, $-(\text{CH}_2)_r\text{C}(=\text{O})\text{R}_b$, $-(\text{CH}_2)_r\text{C}(=\text{O})\text{OR}_b$, $-(\text{CH}_2)_r\text{C}(=\text{O})\text{NR}_a\text{R}_a$, $-(\text{CH}_2)_r\text{OC}(=\text{O})\text{R}_b$, $-(\text{CH}_2)_r\text{OC}(=\text{O})\text{OR}_b$, $-(\text{CH}_2)_r\text{O}(\text{CH}_2)_r\text{C}(=\text{O})\text{NR}_a\text{R}_a$, C_{3-6} cycloalkyl optionally substituted with one or more R_e , aryl optionally substituted with one or more R_e , and heterocyclyl optionally substituted with one or more R_e ;
- 5 R_6 is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , $-\text{C}(=\text{O})\text{R}_b$, $-\text{C}(=\text{O})\text{OR}_b$, $-\text{C}(=\text{O})\text{NR}_a\text{R}_a$, C_{3-6} cycloalkyl optionally substituted with one or more R_e , aryl optionally substituted with one or more R_e , and heterocyclyl optionally substituted with one or more R_e ;
- 10 R_7 is independently selected from H, F, and Cl;
- R_8 is independently selected from H, and C_{1-6} alkyl optionally substituted with one or more substituents selected from F, Cl, and C_{3-6} cycloalkyl;
- R_a is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , C_{2-6} alkenyl optionally substituted with one or more R_e , C_{2-6} alkynyl optionally substituted with one or more R_e , $-(\text{CH}_2)_r\text{-C}_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(\text{CH}_2)_r\text{-heterocyclyl}$ optionally substituted with one or more R_e ; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring optionally substituted with one or more R_e ;
- 15 R_b is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , C_{2-6} alkenyl optionally substituted with one or more R_e , C_{2-6} alkynyl optionally substituted with one or more R_e , $-(\text{CH}_2)_r\text{-C}_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(\text{CH}_2)_r\text{-heterocyclyl}$ optionally substituted with one or more R_e ;
- 20 R_c is independently selected from C_{1-6} alkyl optionally substituted with one or more R_e , C_{2-6} alkenyl optionally substituted with one or more R_e , C_{2-6} alkynyl optionally substituted with one or more R_e , $-(\text{CH}_2)_r\text{-C}_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(\text{CH}_2)_r\text{-heterocyclyl}$ optionally substituted with one or more R_e ;
- 25 R_d is independently selected from H, and C_{1-6} alkyl optionally substituted with one or more R_e ;
- 30 R_e is independently selected from F, Cl, Br, CN, NH_2 , $-\text{NH-C}_{1-4}$ alkyl, $-\text{N}(\text{C}_{1-4} \text{ alkyl})_2$, $=\text{O}$, OH, $-\text{OC}_{1-6}$ alkyl, $-\text{CO}_2\text{H}$, C_{1-6} alkyl optionally substituted with one or more R_f ,

C₂₋₆ alkenyl, C₂₋₆ alkynyl, -(CH₂)_r-C₃₋₆ cycloalkyl optionally substituted with one or more R_f, -(CH₂)_r-aryl optionally substituted with one or more R_f, and -(CH₂)_r-heterocyclyl optionally substituted with one or more R_f;

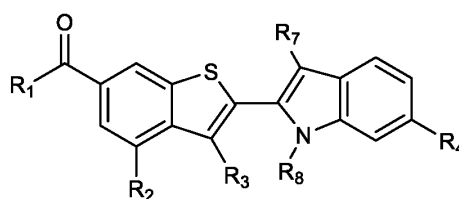
R_f is independently selected from F, Cl, Br, CN, OH, C₁₋₅ alkyl optionally substituted

5 with OH, C₂₋₅ alkenyl, C₂₋₅ alkynyl, C₃₋₆ cycloalkyl, and phenyl;

p, at each occurrence, is independently selected from zero, 1, and 2; and

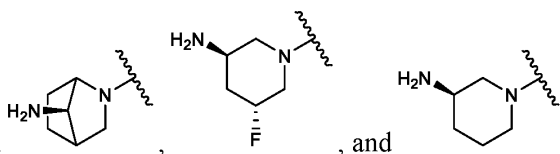
r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

In another aspect, the invention provides a compound having Formula (IX):



(IX)

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



R₁ is independently selected from

R₂ is independently selected from H, F, CH₃, CH₂OH, CH₂CH₂OH, and OCH₃;

15 R₃ is independently selected from H, F, Cl, CH₃, CH₂OH, CH₂CH₂OH, CH₂NH₃, CH₂CH₂NH₂, and CH₂CH₂N₃;

R₄ is independently selected from H, F, Cl, Br, -C(=O)R_b, C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C₃₋₆ cycloalkyl, -NH-C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C₃₋₆ cycloalkyl, -(CH₂)_r-aryl substituted with one or more R₅, -O-C₁₋₆ alkyl substituted with one or more R₅, -(CH₂)_r-C₃₋₁₂ cycloalkyl substituted with one or more R₅, and -(CH₂)_r-4-10 membered heterocyclyl comprising carbon atoms and 1-5 heteroatoms selected from N, NR₆, O, and S and substituted with one or more R₅;

25 R₅ is independently selected from H, F, Cl, Br, CN, =O, C₁₋₄ alkyl optionally substituted with one or more R_e, C₂₋₄ alkenyl optionally substituted with one or more R_e, C₂₋₄

alkynyl optionally substituted with one or more R_e , $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rC(=O)NR_aR_a$, $-(CH_2)_rOC(=O)R_b$, $-(CH_2)_rOC(=O)OR_b$, $-(CH_2)_rO(CH_2)_rC(=O)NR_aR_a$, C_{3-6} cycloalkyl optionally substituted with one or more R_e , aryl optionally substituted with one or more R_e , and heterocyclyl optionally substituted with one or more R_e ;

R_6 is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , $-S(O)_pR_c$, $-S(O)_pNR_aR_a$, $-C(=O)R_b$, $-C(=O)OR_b$, $-C(=O)NR_aR_a$, C_{3-6} cycloalkyl optionally substituted with one or more R_e , aryl optionally substituted with one or more R_e , and heterocyclyl optionally substituted with one or more R_e ;

R_7 is independently selected from H, F, and Cl;

R_8 is independently selected from H, and C_{1-6} alkyl optionally substituted with one or more substituents selected from F, Cl, and C_{3-6} cycloalkyl;

R_a is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , C_{2-6} alkenyl optionally substituted with one or more R_e , C_{2-6} alkynyl optionally substituted with one or more R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_e ; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring optionally substituted with one or more R_e ;

R_b is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , C_{2-6} alkenyl optionally substituted with one or more R_e , C_{2-6} alkynyl optionally substituted with one or more R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ heterocyclyl optionally substituted with one or more R_e ;

R_c is independently selected from C_{1-6} alkyl optionally substituted with one or more R_e , C_{2-6} alkenyl optionally substituted with one or more R_e , C_{2-6} alkynyl optionally substituted with one or more R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_e ;

R_e is independently selected from F, Cl, Br, CN, NH_2 , $-NH-C_{1-4}$ alkyl, $-N(C_{1-4} \text{ alkyl})_2$, $=O$, OH, $-OC_{1-6}$ alkyl, $-CO_2H$, C_{1-6} alkyl optionally substituted with one or more R_f ,

C₂₋₆ alkenyl, C₂₋₆ alkynyl, $-(CH_2)_r-C_{3-6}$ cycloalkyl optionally substituted with one or more R_f, $-(CH_2)_r$ -aryl optionally substituted with one or more R_f, and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_f;

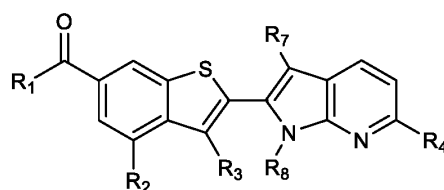
R_f is independently selected from F, Cl, Br, CN, OH, C₁₋₅ alkyl optionally substituted

5 with OH, C₂₋₅ alkenyl, C₂₋₅ alkynyl, C₃₋₆ cycloalkyl, and phenyl;

p, at each occurrence, is independently selected from zero, 1, and 2; and

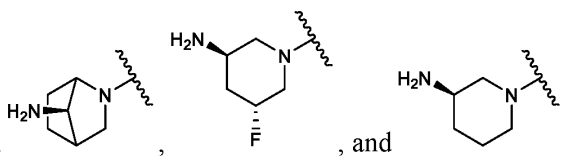
r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

In another aspect, the invention provides a compound having Formula (X):



(X)

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



R₁ is independently selected from , , and ;

R₂ is independently selected from H, F, CH₃, CH₂OH, CH₂CH₂OH, and OCH₃;

15 R₃ is independently selected from H, F, CH₃, CH₂OH, CH₂CH₂OH, CH₂NH₃, CH₂CH₂NH₂, and CH₂CH₂N₃;

R₄ is independently selected from H, F, Cl, Br, $-C(=O)R_b$, C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C₃₋₆ cycloalkyl, $-NH-C_{1-6}$ alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C₃₋₆ cycloalkyl, $-(CH_2)_r$ -aryl substituted with one or more R₅, $-O-C_{1-6}$ alkyl substituted with one or more R₅, $-(CH_2)_r-C_{3-12}$ cycloalkyl substituted with one or more R₅, and $-(CH_2)_r-4-10$ membered heterocyclyl comprising carbon atoms and 1-5 heteroatoms selected from N, NR₆, O, and S and substituted with one or more R₅;

25 R₅ is independently selected from H, F, Cl, Br, CN, =O, C₁₋₄ alkyl optionally substituted with one or more R_e, C₂₋₄ alkenyl optionally substituted with one or more R_e, C₂₋₄ alkynyl optionally substituted with one or more R_e, $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-$

- $(\text{CH}_2)_i\text{S}(\text{O})_p\text{NR}_a\text{R}_a$, $-(\text{CH}_2)_i\text{NR}_a\text{S}(\text{O})_p\text{R}_c$, $-(\text{CH}_2)_i\text{NR}_a\text{R}_a$, $-(\text{CH}_2)_i\text{NR}_a\text{C}(=\text{O})\text{R}_b$, $-(\text{CH}_2)_i\text{NR}_a\text{C}(=\text{O})\text{OR}_b$, $-(\text{CH}_2)_i\text{NR}_a\text{C}(=\text{O})\text{NR}_a\text{R}_a$, $-(\text{CH}_2)_i\text{C}(=\text{O})\text{R}_b$, $-(\text{CH}_2)_i\text{C}(=\text{O})\text{OR}_b$, $-(\text{CH}_2)_i\text{C}(=\text{O})\text{NR}_a\text{R}_a$, $-(\text{CH}_2)_i\text{OC}(=\text{O})\text{R}_b$, $-(\text{CH}_2)_i\text{OC}(=\text{O})\text{OR}_b$, $-(\text{CH}_2)_i\text{O}(\text{CH}_2)_i\text{C}(=\text{O})\text{NR}_a\text{R}_a$, C₃₋₆ cycloalkyl optionally substituted with one or more R_e, aryl optionally substituted with one or more R_e, and heterocyclyl optionally substituted with one or more R_e;
- 5 R₆ is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more R_e, $-\text{S}(\text{O})_p\text{R}_c$, $-\text{S}(\text{O})_p\text{NR}_a\text{R}_a$, $-\text{C}(=\text{O})\text{R}_b$, $-\text{C}(=\text{O})\text{OR}_b$, $-\text{C}(=\text{O})\text{NR}_a\text{R}_a$, C₃₋₆ cycloalkyl optionally substituted with one or more R_e, aryl optionally substituted with one or more R_e, and heterocyclyl optionally substituted with one or more R_e;
- 10 R₇ is independently selected from H, F, and Cl;
- R₈ is independently selected from H, and C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, and C₃₋₆ cycloalkyl;
- 15 R_a is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more R_e, C₂₋₆ alkenyl optionally substituted with one or more R_e, C₂₋₆ alkynyl optionally substituted with one or more R_e, $-(\text{CH}_2)_i\text{-C}_{3-10}$ carbocyclyl optionally substituted with one or more R_e, and $-(\text{CH}_2)_i\text{-heterocyclyl}$ optionally substituted with one or more R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring optionally substituted with one or more R_e;
- 20 R_b is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more R_e, C₂₋₆ alkenyl optionally substituted with one or more R_e, C₂₋₆ alkynyl optionally substituted with one or more R_e, $-(\text{CH}_2)_i\text{-C}_{3-10}$ carbocyclyl optionally substituted with one or more R_e, and $-(\text{CH}_2)_i\text{-heterocyclyl}$ optionally substituted with one or more R_e;
- 25 R_c is independently selected from C₁₋₆ alkyl optionally substituted with one or more R_e, C₂₋₆ alkenyl optionally substituted with one or more R_e, C₂₋₆ alkynyl optionally substituted with one or more R_e, $-(\text{CH}_2)_i\text{-C}_{3-10}$ carbocyclyl optionally substituted with one or more R_e, and $-(\text{CH}_2)_i\text{-heterocyclyl}$ optionally substituted with one or more R_e;
- 30 R_e is independently selected from F, Cl, Br, CN, NH₂, $-\text{NH-C}_{1-4}$ alkyl, $-\text{N}(\text{C}_{1-4} \text{ alkyl})_2$, $=\text{O}$, OH, $-\text{OC}_{1-6}$ alkyl, $-\text{CO}_2\text{H}$, C₁₋₆ alkyl optionally substituted with one or more R_f, C₂₋₆ alkenyl, C₂₋₆ alkynyl, $-(\text{CH}_2)_i\text{-C}_{3-6}$ cycloalkyl optionally substituted with one

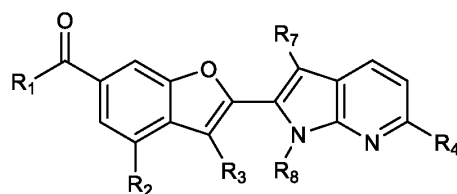
or more R_f , $-(CH_2)_r$ -aryl optionally substituted with one or more R_f , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_f ;

R_f is independently selected from F, Cl, Br, CN, OH, C_{1-5} alkyl optionally substituted with OH, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-6} cycloalkyl, and phenyl;

5 p, at each occurrence, is independently selected from zero, 1, and 2; and

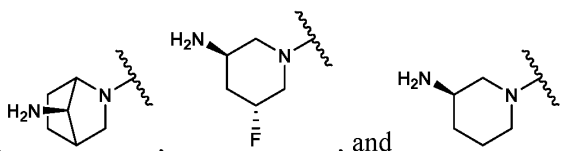
r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

In another aspect, the invention provides a compound having Formula (XI):



(XI)

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



R_1 is independently selected from

R_2 is independently selected from H, F, CH_3 , CH_2OH , CH_2CH_2OH , and OCH_3 ;

R_3 is independently selected from H, F, CH_3 , CH_2OH , CH_2CH_2OH , CH_2NH_3 ,

15 $CH_2CH_2NH_2$, and $CH_2CH_2N_3$;

R_4 is independently selected from H, F, Cl, Br, $-C(=O)R_b$, C_{1-6} alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C_{3-6} cycloalkyl, $-NH-C_{1-6}$ alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C_{3-6} cycloalkyl, $-(CH_2)_r$ -aryl substituted with one or more R_5 , $-O-C_{1-6}$ alkyl substituted with one or more R_5 , $-(CH_2)_r-C_{3-12}$ cycloalkyl substituted with one or more R_5 , and $-(CH_2)_r-4-10$ membered heterocyclyl comprising carbon atoms and 1-5 heteroatoms selected from N, NR_6 , O, and S and substituted with one or more R_5 ;

20 R_5 is independently selected from H, F, Cl, Br, CN, $=O$, C_{1-4} alkyl optionally substituted with one or more R_e , C_{2-4} alkenyl optionally substituted with one or more R_e , C_{2-4} alkynyl optionally substituted with one or more R_e , $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-$

- $(\text{CH}_2)_r\text{NR}_a\text{C}(=\text{O})\text{OR}_b$, $-(\text{CH}_2)_r\text{NR}_a\text{C}(=\text{O})\text{NR}_a\text{R}_a$, $-(\text{CH}_2)_r\text{C}(=\text{O})\text{R}_b$, $-(\text{CH}_2)_r\text{C}(=\text{O})\text{OR}_b$, $-(\text{CH}_2)_r\text{C}(=\text{O})\text{NR}_a\text{R}_a$, $-(\text{CH}_2)_r\text{OC}(=\text{O})\text{R}_b$, $-(\text{CH}_2)_r\text{OC}(=\text{O})\text{OR}_b$, $-(\text{CH}_2)_r\text{O}(\text{CH}_2)_r\text{C}(=\text{O})\text{NR}_a\text{R}_a$, C₃₋₆ cycloalkyl optionally substituted with one or more R_e, aryl optionally substituted with one or more R_e, and heterocyclyl optionally substituted with one or more R_e;
- 5 R₆ is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more R_e, -S(O)_pR_c, -S(O)_pNR_aR_a, -C(=O)R_b, -C(=O)OR_b, -C(=O)NR_aR_a, C₃₋₆ cycloalkyl optionally substituted with one or more R_e, aryl optionally substituted with one or more R_e, and heterocyclyl optionally substituted with one or more R_e;
- 10 R₇ is independently selected from H, F, and Cl;
- R₈ is independently selected from H, and C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, and C₃₋₆ cycloalkyl;
- R_a is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more R_e, C₂₋₆ alkenyl optionally substituted with one or more R_e, C₂₋₆ alkynyl optionally substituted with one or more R_e, $-(\text{CH}_2)_r\text{-C}_{3-10}$ carbocyclyl optionally substituted with one or more R_e, and $-(\text{CH}_2)_r\text{-heterocyclyl}$ optionally substituted with one or more R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring optionally substituted with one or more R_e;
- 15 R_b is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more R_e, C₂₋₆ alkenyl optionally substituted with one or more R_e, C₂₋₆ alkynyl optionally substituted with one or more R_e, $-(\text{CH}_2)_r\text{-C}_{3-10}$ carbocyclyl optionally substituted with one or more R_e, and $-(\text{CH}_2)_r\text{-heterocyclyl}$ optionally substituted with one or more R_e;
- 20 R_c is independently selected from C₁₋₆ alkyl optionally substituted with one or more R_e, C₂₋₆ alkenyl optionally substituted with one or more R_e, C₂₋₆ alkynyl optionally substituted with one or more R_e, $-(\text{CH}_2)_r\text{-C}_{3-10}$ carbocyclyl optionally substituted with one or more R_e, and $-(\text{CH}_2)_r\text{-heterocyclyl}$ optionally substituted with one or more R_e;
- 25 R_d is independently selected from H, and C₁₋₆ alkyl optionally substituted with one or more R_e;
- 30 R_e is independently selected from F, Cl, Br, CN, NH₂, -NH-C₁₋₄ alkyl, -N(C₁₋₄ alkyl)₂, =O, OH, -OC₁₋₆ alkyl, -CO₂H, C₁₋₆ alkyl optionally substituted with one or more R_f,

C₂₋₆ alkenyl, C₂₋₆ alkynyl, $-(CH_2)_r-C_{3-6}$ cycloalkyl optionally substituted with one or more R_f, $-(CH_2)_r$ -aryl optionally substituted with one or more R_f, and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_f;

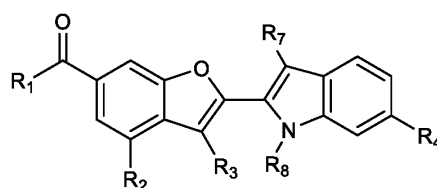
R_f is independently selected from F, Cl, Br, CN, OH, C₁₋₅ alkyl optionally substituted

5 with OH, C₂₋₅ alkenyl, C₂₋₅ alkynyl, C₃₋₆ cycloalkyl, and phenyl;

p, at each occurrence, is independently selected from zero, 1, and 2; and

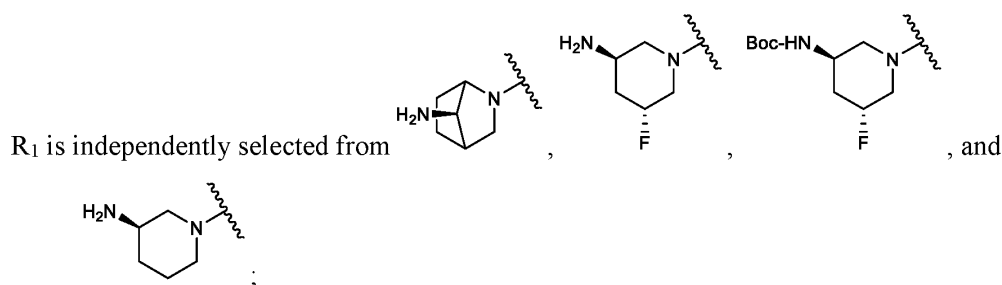
r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

In another aspect, the invention provides a compound having Formula (XII):



(XII)

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



15 R₂ is independently selected from H, F, CH₃, CH₂OH, CH₂CH₂OH and OCH₃;

R₃ is independently selected from H, F, CH₃, CH₂OH, CH₂CH₂OH, CH₂NH₃, CH₂CH₂NH₂, and CH₂CH₂N₃;

R₄ is independently selected from H, F, Cl, Br, $-C(=O)R_b$, C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C₃₋₆ cycloalkyl, $-NH-$

20 C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C₃₋₆ cycloalkyl, $-(CH_2)_r$ -aryl substituted with one or more R₅, $-O-C_{1-6}$

alkyl substituted with one or more R₅, $-(CH_2)_r-C_{3-12}$ cycloalkyl substituted with one or more R₅, and $-(CH_2)_r-4-10$ membered heterocyclyl comprising carbon atoms

25 and 1-5 heteroatoms selected from N, NR₆, O, and S and substituted with one or more R₅;

- R_5 is independently selected from H, F, Cl, Br, CN, =O, C_{1-4} alkyl optionally substituted with one or more R_e , C_{2-4} alkenyl optionally substituted with one or more R_e , C_{2-4} alkynyl optionally substituted with one or more R_e , $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rC(=O)NR_aR_a$, $-(CH_2)_rOC(=O)R_b$, $-(CH_2)_rOC(=O)OR_b$, $-(CH_2)_rO(CH_2)_rC(=O)NR_aR_a$, C_{3-6} cycloalkyl optionally substituted with one or more R_e , aryl optionally substituted with one or more R_e , and heterocyclyl optionally substituted with one or more R_e ;
- R_6 is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , $-S(O)_pR_c$, $-S(O)_pNR_aR_a$, $-C(=O)R_b$, $-C(=O)OR_b$, $-C(=O)NR_aR_a$, C_{3-6} cycloalkyl optionally substituted with one or more R_e , aryl optionally substituted with one or more R_e , and heterocyclyl optionally substituted with one or more R_e ;
- R_7 is independently selected from H, F, and Cl;
- R_8 is independently selected from H, and C_{1-6} alkyl optionally substituted with one or more substituents selected from F, Cl, and C_{3-6} cycloalkyl;
- R_a is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , C_{2-6} alkenyl optionally substituted with one or more R_e , C_{2-6} alkynyl optionally substituted with one or more R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_e ; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring optionally substituted with one or more R_e ;
- R_b is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , C_{2-6} alkenyl optionally substituted with one or more R_e , C_{2-6} alkynyl optionally substituted with one or more R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ heterocyclyl optionally substituted with one or more R_e ;
- R_c is independently selected from C_{1-6} alkyl optionally substituted with one or more R_e , C_{2-6} alkenyl optionally substituted with one or more R_e , C_{2-6} alkynyl optionally substituted with one or more R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_e ;

R_d is independently selected from H, and C₁₋₆ alkyl optionally substituted with one or more R_e;

R_e is independently selected from F, Cl, Br, CN, NH₂, -NH-C₁₋₄ alkyl, -N(C₁₋₄ alkyl)₂, =O, OH, -OC₁₋₆ alkyl, -CO₂H, C₁₋₆ alkyl optionally substituted with one or more R_f, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -(CH₂)_r-C₃₋₆ cycloalkyl optionally substituted with one or more R_f, -(CH₂)_r-aryl optionally substituted with one or more R_f, and -(CH₂)_r-heterocyclyl optionally substituted with one or more R_f.

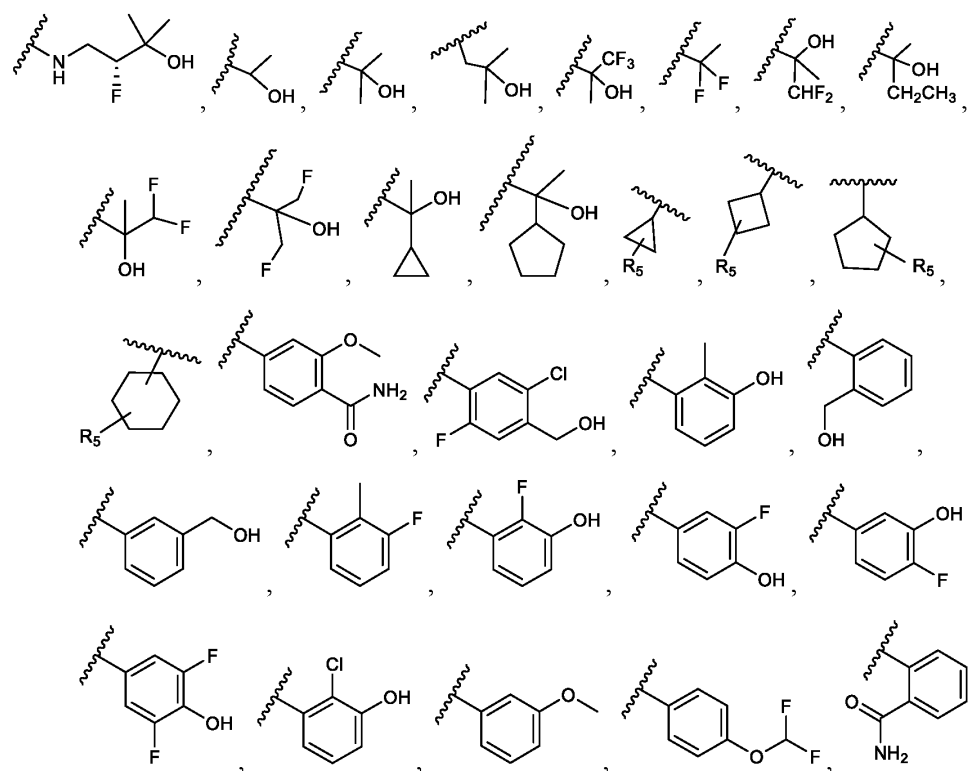
R_f is independently selected from F, Cl, Br, CN, OH, C₁₋₅ alkyl optionally substituted with OH, C₂₋₅ alkenyl, C₂₋₅ alkynyl, C₃₋₆ cycloalkyl, and phenyl;

10 p, at each occurrence, is independently selected from zero, 1, and 2; and

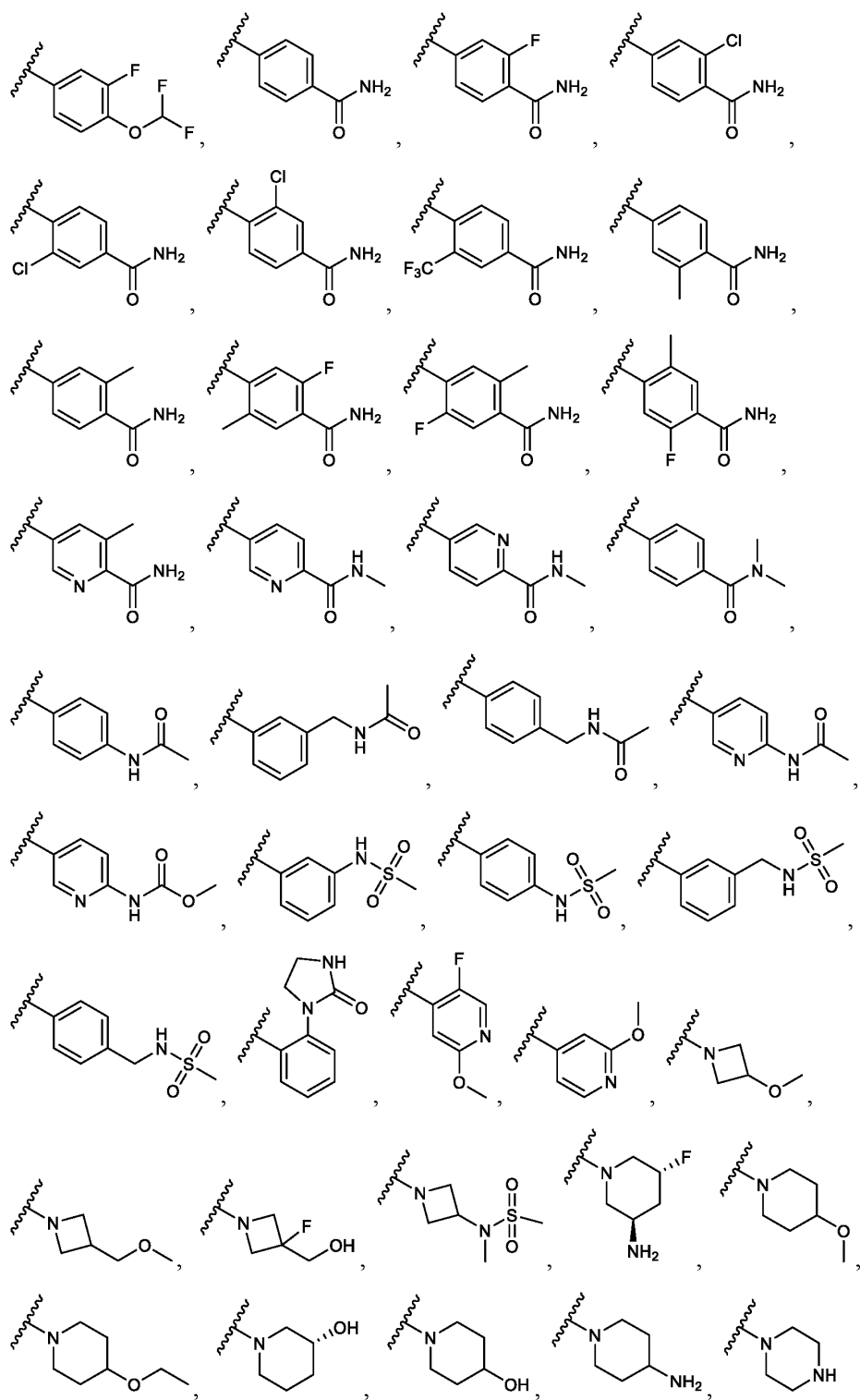
r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

In another aspect, the invention provides a compound having Formulae (IX)-(XII), or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof, wherein;

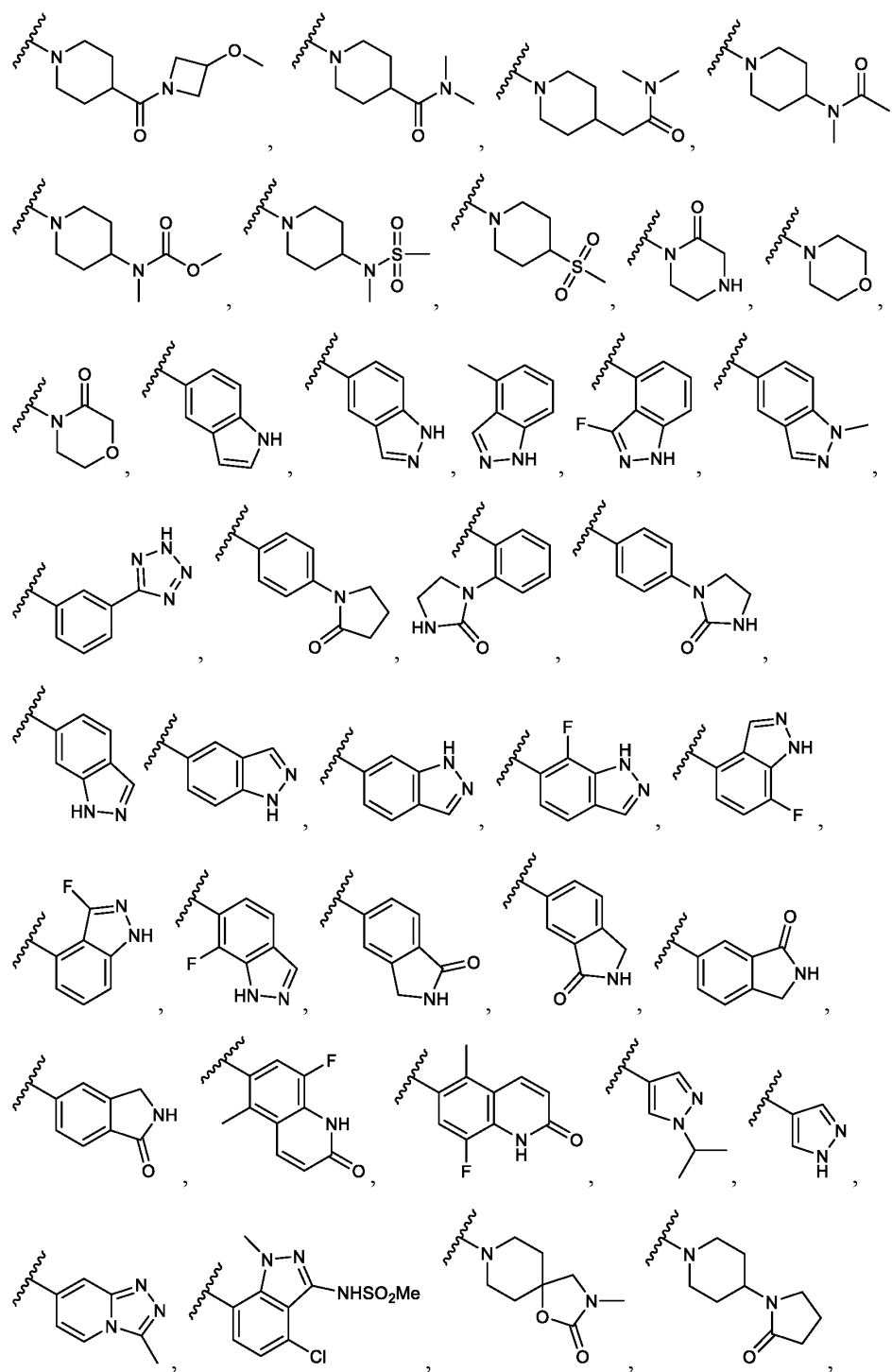
15 R_4 is independently selected from H, F, Cl, Br,

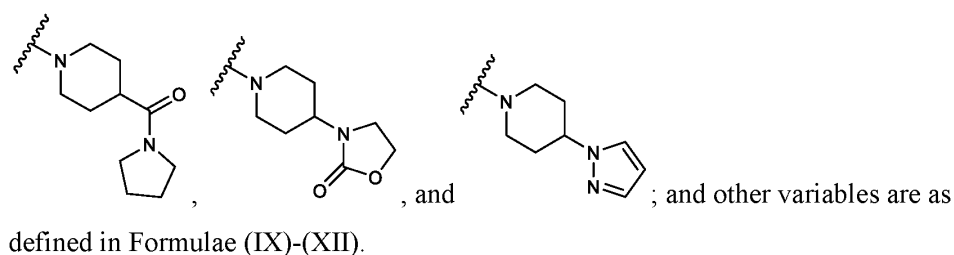


5

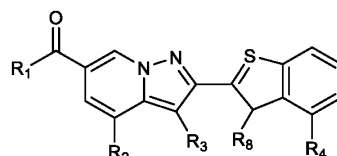


5



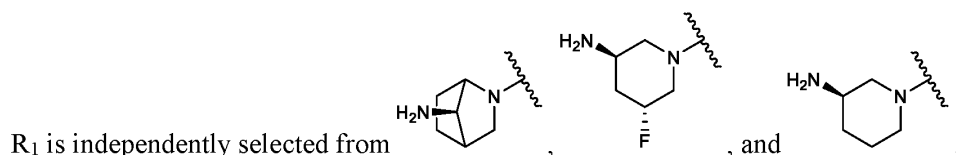


In another aspect, the invention provides a compound having Formula (XIII):



(XIII)

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



R_2 is independently selected from H, F, CH_3 , and OCH_3 ;

10 R_3 is independently selected from H, F, and CH_3 ;

R_4 is independently selected from H, F, Cl, Br, $-\text{C}(=\text{O})\text{R}_b$, C_{1-6} alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C_{3-6} cycloalkyl, $-\text{NH}-\text{C}_{1-6}$ alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C_{3-6} cycloalkyl, $-(\text{CH}_2)_r$ -aryl substituted with one or more R_5 , $-\text{O}-\text{C}_{1-6}$ alkyl substituted with one or more R_5 , $-(\text{CH}_2)_r-\text{C}_{3-12}$ cycloalkyl substituted with one or more R_5 , and $-(\text{CH}_2)_r$ -4-10 membered heterocyclyl comprising carbon atoms and 1-5 heteroatoms selected from N, NR_6 , O, and S and substituted with one or more R_5 ;

20 R_5 is independently selected from H, F, Cl, Br, CN, $=\text{O}$, C_{1-4} alkyl optionally substituted with one or more R_e , C_{2-4} alkenyl optionally substituted with one or more R_e , C_{2-4} alkynyl optionally substituted with one or more R_e , $-(\text{CH}_2)_r\text{OR}_b$, $-(\text{CH}_2)_r\text{S}(\text{O})_p\text{R}_c$, $-(\text{CH}_2)_r\text{S}(\text{O})_p\text{NR}_a\text{R}_a$, $-(\text{CH}_2)_r\text{NR}_a\text{S}(\text{O})_p\text{R}_c$, $-(\text{CH}_2)_r\text{NR}_a\text{R}_a$, $-(\text{CH}_2)_r\text{NR}_a\text{C}(=\text{O})\text{R}_b$, $-(\text{CH}_2)_r\text{NR}_a\text{C}(=\text{O})\text{OR}_b$, $-(\text{CH}_2)_r\text{NR}_a\text{C}(=\text{O})\text{NR}_a\text{R}_a$, $-(\text{CH}_2)_r\text{C}(=\text{O})\text{R}_b$, $-(\text{CH}_2)_r\text{C}(=\text{O})\text{OR}_b$, $-(\text{CH}_2)_r\text{C}(=\text{O})\text{NR}_a\text{R}_a$, $-(\text{CH}_2)_r\text{OC}(=\text{O})\text{R}_b$, $-(\text{CH}_2)_r\text{OC}(=\text{O})\text{OR}_b$, $-$

$(\text{CH}_2)_r\text{O}(\text{CH}_2)_r\text{C}(=\text{O})\text{NR}_a\text{R}_a$, C_{3-6} cycloalkyl optionally substituted with one or more R_e , aryl optionally substituted with one or more R_e , and heterocyclyl optionally substituted with one or more R_e ;

R_6 is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , $-\text{S}(\text{O})_p\text{R}_c$, $-\text{S}(\text{O})_p\text{NR}_a\text{R}_a$, $-\text{C}(=\text{O})\text{R}_b$, $-\text{C}(=\text{O})\text{OR}_b$, $-\text{C}(=\text{O})\text{NR}_a\text{R}_a$, C_{3-6} cycloalkyl optionally substituted with one or more R_e , aryl optionally substituted with one or more R_e , and heterocyclyl optionally substituted with one or more R_e ;

R_8 is independently selected from H, and C_{1-6} alkyl optionally substituted with one or more substituents selected from F, Cl, and C_{3-6} cycloalkyl;

R_a is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , C_{2-6} alkenyl optionally substituted with one or more R_e , C_{2-6} alkynyl optionally substituted with one or more R_e , $-(\text{CH}_2)_r\text{-C}_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(\text{CH}_2)_r\text{-heterocyclyl}$ optionally substituted with one or more R_e ; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring optionally substituted with one or more R_e ;

R_b is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , C_{2-6} alkenyl optionally substituted with one or more R_e , C_{2-6} alkynyl optionally substituted with one or more R_e , $-(\text{CH}_2)_r\text{-C}_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(\text{CH}_2)_r\text{-heterocyclyl}$ optionally substituted with one or more R_e ;

R_c is independently selected from C_{1-6} alkyl optionally substituted with one or more R_e , C_{2-6} alkenyl optionally substituted with one or more R_e , C_{2-6} alkynyl optionally substituted with one or more R_e , $-(\text{CH}_2)_r\text{-C}_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(\text{CH}_2)_r\text{-heterocyclyl}$ optionally substituted with one or more R_e ;

R_d is independently selected from H, and C_{1-6} alkyl optionally substituted with one or more R_e ;

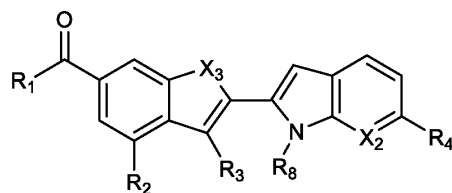
R_e is independently selected from F, Cl, Br, CN, NH_2 , $-\text{NH-C}_{1-4}$ alkyl, $-\text{N}(\text{C}_{1-4}$ alkyl)₂, $=\text{O}$, OH, $-\text{OC}_{1-6}$ alkyl, $-\text{CO}_2\text{H}$, C_{1-6} alkyl optionally substituted with one or more R_f , C_{2-6} alkenyl, C_{2-6} alkynyl, $-(\text{CH}_2)_r\text{-C}_{3-6}$ cycloalkyl optionally substituted with one or more R_f , $-(\text{CH}_2)_r\text{-aryl}$ optionally substituted with one or more R_f , and $-(\text{CH}_2)_r\text{-heterocyclyl}$ optionally substituted with one or more R_f ;

R_f is independently selected from F, Cl, Br, CN, OH, C_{1-5} alkyl optionally substituted with OH, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-6} cycloalkyl, and phenyl;

p , at each occurrence, is independently selected from zero, 1, and 2; and

r , at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

5 In another aspect, the invention provides a compound having Formula (XIV):

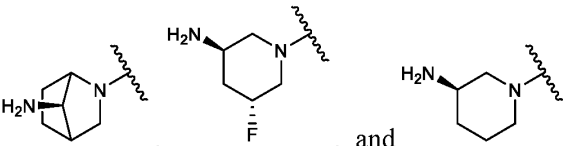


(XIV)

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

10 X_2 is independently selected from CR_4 and N;

X_3 is independently selected from O and S;

R_1 is independently selected from  , and

R_2 is independently selected from CH_2OH , CH_2CH_2OH and OCH_3 ;

R_3 is independently selected from CH_2OH , CH_2CH_2OH , CH_2NH_2 , $CH_2CH_2NH_2$, and

15 $CH_2CH_2N_3$;

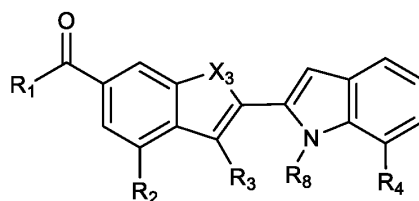
R_4 is independently selected from H and $-O-C_{1-4}$ alkyl substituted with one or more R_5 ;
provided R_4 is not both $-O-C_{1-4}$ alkyl substituted with one or more R_5 ;

R_5 is independently selected from OH and heterocyclyl optionally substituted with one or more R_6 ;

20 R_8 is independently selected from H, and C_{1-6} alkyl optionally substituted with C_{3-6} cycloalkyl; and

R_6 is independently selected from NH_2 and C_{1-3} alkyl.

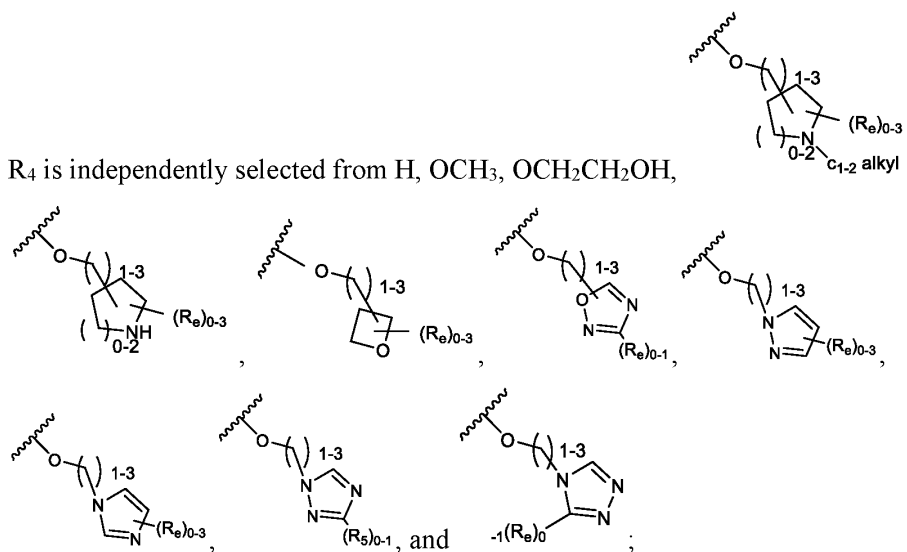
In another aspect, the invention provides a compound having Formula (XV):



(XV)

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

- 5 R_4 is independently selected from H, OCH_3 , OCH_2CH_2OH ,



R_8 is C_{1-3} alkyl substituted with C_{3-6} cycloalkyl; and

R_e is independently selected from NH_2 and C_{1-3} alkyl; and other variables are as defined in Formula (XIV).

10

Typical, non-limiting examples of the compounds according to the invention include:

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (1);

15

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (2);

6-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one (3);

5 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (4);

5-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one (5);

10 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-cyclopropyl-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (6);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(1-isopropyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (7);

15 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (8);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-fluoro-3-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (9);

20 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-fluoro-4-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (10);

25 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(4-(difluoromethoxy)phenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (11);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(4-(difluoromethoxy)-3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (12);

30

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-methoxyazetidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (13);

5 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (14);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (15);

10 6-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one (16);

15 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (17);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(1-isopropyl-1H-pyrazol-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (18);

20 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(6-cyclopropyl-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (19);

5-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one (20);

25 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (21);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (22);

30 6-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one (23);

5-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one (24);

5 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (25);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(4-(difluoromethoxy)phenyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (26);

10 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-methyl-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (27);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-cyclopropyl-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (28);

15 6-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one (29);

20 5-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one (30);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (31);

25 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(2-fluoro-3-hydroxyphenyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (32);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(3-(methoxymethyl)-azetidin-1-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (33);

30 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(6-((3R,5R)-3-amino-5-fluoropiperidin-1-yl)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (34);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(4-methoxypiperidin-1-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (35);

5 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(((R)-2-fluoro-3-hydroxy-3-methylbutyl)amino)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (36);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(3-fluoro-3-(hydroxymethyl)azetidin-1-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (37);

10 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (38);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (39);

15 3((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (40);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-cyclopropyl-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (41);

20 5-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one (42);

25 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (43);

30 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(4-(difluoromethoxy)-3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (44);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(5-fluoro-2-methoxypyridin-4-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (45);

5 6-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one (46);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(4-(difluoromethoxy)phenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (47);

10 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-fluoro-4-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (48);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-fluoro-3-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (49);

15 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-methoxyazetidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (50);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-((R)-3-hydroxypiperidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (51);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (52);

25 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (53);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (54);

30

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(2-fluoro-3-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (55);

4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorobenzamide (56);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(6-cyclopropyl-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (57);

10 N-(7-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide (58);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-fluoro-3-hydroxyphenyl)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (59);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-fluoro-4-hydroxyphenyl)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (60);

20 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(4-fluoro-3-hydroxyphenyl)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (61);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (62);

25 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (63);

5-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one (64);

30 6-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one (65);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (66);

5 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-fluoro-4-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (67);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-fluoro-3-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (68);

10 4-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorobenzamide (69);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (70);

15 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-cyclopropyl-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (71);

20 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(5-fluoro-2-methoxypyridin-4-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (72);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(4-(difluoromethoxy)-3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (73);

25 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3,5-difluoro-4-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (74);

30 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(4-fluoro-3-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (75);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(4-methoxypiperidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (76);

5 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(4-hydroxypiperidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (77);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-((R)-3-hydroxypiperidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (78);

10 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-methoxyazetidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (79);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (80);

15 5-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one (81);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (82);

20 6-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one (83);

25 4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorobenzamide (84);

4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-chlorobenzamide (85);

30 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(2-fluoro-3-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (86);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(4-methoxypiperidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (87);

5 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(4-hydroxypiperidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (88);

6-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one (89);

10 5-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one (90);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-fluoro-3-(hydroxymethyl)azetidin-1-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (91);

15 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(2-fluoro-3-hydroxyphenyl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (92);

4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)-2-fluorobenzamide (93);

20 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(3-fluoro-4-hydroxyphenyl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (94);

5-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one (95);

25 6-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one (96);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-hydroxypropan-2-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (97);

30 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(2-hydroxypropan-2-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (98);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(1,1,1-trifluoro-2-hydroxypropan-2-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (99);

5 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-hydroxypropan-2-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (100);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(1,1,1-trifluoro-2-hydroxypropan-2-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (101);

10 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-hydroxypropan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (102);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(1,1,1-trifluoro-2-hydroxypropan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (103);

15 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(1-hydroxyethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (104);

20 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(2-hydroxypropan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (105);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(1,1,1-trifluoro-2-hydroxypropan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (106, 107 as diastereomers);

25 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyrimidin-6-yl)methanone (108);

30 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-fluoro-3-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyrimidin-6-yl)methanone (109);

6-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyrimidin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one (110);

5 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-fluoro-4-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyrimidin-6-yl)methanone (111);

4-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyrimidin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorobenzamide (112);

10 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyrazin-6-yl)methanone (113);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyrazin-6-yl)methanone (114);

15 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyrazin-6-yl)methanone (115);

(2-(1-(Cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyrazin-6-yl)(2,6-diazaspiro[3.3]heptan-2-yl)methanone (116);

20 (R)-N-(3-Amino-2-fluoropropyl)-2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyrazine-6-carboxamide (117);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylbenzo[b]thiophen-6-yl)methanone (118);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylbenzo[b]thiophen-6-yl)methanone (119);

25 6-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylbenzo[b]thiophen-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one (120);

30 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-fluoro-3-hydroxyphenyl)-1H-indol-2-yl)-4-methoxy-3-methylbenzo[b]thiophen-6-yl)methanone (121);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)-1H-indol-2-yl)-4-methoxy-3-methylbenzo[b]thiophen-6-yl)methanone (122);

5 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-fluoro-4-hydroxyphenyl)-1H-indol-2-yl)-4-methoxy-3-methylbenzo[b]thiophen-6-yl)methanone (123);

4-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylbenzo[b]thiophen-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)-2-fluorobenzamide (124);

10 4-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylbenzo[b]thiophen-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)-2-chlorobenzamide (125);

5-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylbenzo[b]thiophen-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one (126);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-methyl-1H-indol-2-yl)-4-methoxy-3-methylbenzo[b]thiophen-6-yl)methanone (127);

20 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-fluoro-2-methylphenyl)-1H-indol-2-yl)-4-methoxy-3-methylbenzo[b]thiophen-6-yl)methanone (128);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-methoxypyridin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylbenzo[b]thiophen-6-yl)methanone (129);

25 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-(4-aminopiperidin-1-yl)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylbenzo[b]thiophen-6-yl)methanone (130);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(4-methoxypiperidin-1-yl)-1H-indol-2-yl)-4-methoxy-3-methylbenzo[b]thiophen-6-yl)methanone (131);

30 5-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylbenzo- [b]thiophen-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one (132);

4-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylbenzo[b]thiophen-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorobenzamide (133);

5 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-fluoro-3-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylbenzo[b]thiophen-6-yl)methanone (134);

6-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylbenzo[b]thiophen-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one (135);

10 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-fluoro-4-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylbenzo[b]thiophen-6-yl)methanone (136);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(4-methoxypiperidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylbenzo[b]thiophen-6-yl)methanone (137);

15 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylbenzo[b]thiophen-6-yl)methanone (138);

20 5-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylbenzo[b]thiophen-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one (139);

6-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylbenzo[b]thiophen-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one (140);

25 4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylbenzo[b]thiophen-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorobenzamide (141);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(4-methoxypiperidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylbenzo[b]thiophen-6-yl)methanone (142);

30 6-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylbenzo[b]thiophen-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one (143);

5-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylbenzo[b]thiophen-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one (144);

5 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylbenzofuran-6-yl)methanone (145);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylbenzofuran-6-yl)methanone (146);

10 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylbenzofuran-6-yl)methanone (147);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylbenzofuran-6-yl)methanone (148);

5-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one (149);

15 6-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one (150);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-methyl-1H-indol-2-yl)-4-methoxy-3-methylbenzofuran-6-yl)methanone (151);

20 4-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)-2-fluorobenzamide (152);

4-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)-2-chlorobenzamide (153);

25 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-fluoro-4-hydroxyphenyl)-1H-indol-2-yl)-4-methoxy-3-methylbenzofuran-6-yl)methanone (154);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (155);

30 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-cyclopropyl-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylbenzofuran-6-yl)methanone (156);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)-1H-indol-2-yl)-4-methoxy-3-methylbenzofuran-6-yl)methanone (157);

3- ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(4-ethoxypiperidin-1-yl)-1H-indol-2-yl)-4-methoxy-3-methylbenzofuran-6-yl)methanone (158);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(4-methoxypiperidin-1-yl)-1H-indol-2-yl)-4-methoxy-3-methylbenzofuran-6-yl)methanone (159);

10 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-(4-aminopiperidin-1-yl)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylbenzofuran-6-yl)methanone (160);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylbenzofuran-6-yl)methanone (161);

15 4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)-2-chlorobenzamide (162);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(2-fluoro-3-hydroxyphenyl)-1H-indol-2-yl)-4-methoxy-3-methylbenzofuran-6-yl)methanone (163);

20 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylbenzofuran-6-yl)methanone (164);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylbenzofuran-6-yl)methanone (165);

25 6-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one (166);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylbenzofuran-6-yl)methanonecyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one

30 (167);

5-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one (168);

5 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-fluoro-3-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylbenzofuran-6-yl)methanone (169);

4-(2-(6-((7R)-7-amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorobenzamide (170);

10 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylbenzofuran-6-yl)methanone (171);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-methoxy-pyridin-4-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylbenzofuran-6-yl)methanone (172);

15 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-methoxyazetidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylbenzofuran-6-yl)methanone (173);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylbenzofuran-6-yl)methanone (174);

20 6-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one (175);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone (176);

25 6-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one (177);

5-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one (178);

30 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone (179);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(1-isopropyl-1H-pyrazol-4-yl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone (180);

- ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-fluoro-3-hydroxyphenyl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone (181);
- ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-fluoro-4-hydroxyphenyl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone (182);
- 5 4-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)-2-chlorobenzamide (183);
- ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-methyl-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone (184);
- 4-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)-2-fluorobenzamide (185);
- 10 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-methoxypyridin-4-yl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone (186);
- ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-cyclopropyl-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone (187);
- 15 5-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)-3-methylpicolinamide (188);
- ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(4-methoxypiperidin-1-yl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone (189);
- 20 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-methoxyazetidin-1-yl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone (190);
- ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-(4-aminopiperidin-1-yl)-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone (191);
- ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(piperazin-1-yl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone (192);
- 25 1-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)piperazin-2-one (193);
- ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone (194);
- 30 5-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one (195);

- 4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)-2-fluorobenzamide (196);
- ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone
- 5 (197);
- ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(2-fluoro-3-hydroxyphenyl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone (198);
- 4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)-2-chlorobenzamide (199);
- 10 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(4-methoxypiperidin-1-yl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone (200);
- ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(piperazin-1-yl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone (201);
- ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(6-(4-aminopiperidin-1-yl)-1-
- 15 (cyclopropylmethyl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone (202);
- ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-hydroxypropan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylbenzofuran-6-yl)methanone (203);
- ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-
- 20 hydroxypropan-2-yl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone (204);
- 1-[2-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)phenyl]imidazolidin-2-one (205);
- 4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-methoxy-3-
- 25 methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-methylbenzamide (206);
- 4-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluoro-5-methylbenzamide (207);
- 30 4-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluoro-5-methylbenzamide (208);

[2-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methanol (209);

5 [3-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methanol (210);

N-{[3-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methyl}methanesulfonamide (211);

10 (3R,5R)-1-{2-[1-(Cyclopropylmethyl)-6-(3-methoxyphenyl)-1H-indol-2-yl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-5-fluoropiperidin-3-amine (212);

N-[3-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methanesulfonamide (213);

15 N-[4-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]acetamide (214);

20 N-{[3-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methyl}acetamide (215);

N-[4-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methanesulfonamide (216);

25 4-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-N,N-dimethylbenzamide (217);

(3R,5R)-1-{2-[1-(Cyclopropylmethyl)-6-(1H-indazol-5-yl)-1H-indol-2-yl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-5-fluoropiperidin-3-amine (218);

30 (3R,5R)-1-{2-[1-(Cyclopropylmethyl)-6-(1-methyl-1H-indazol-5-yl)-1H-indol-2-yl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-5-fluoropiperidin-3-amine (219);

(3R,5R)-1-{2-[1-(Cyclopropylmethyl)-6-[3-(2H-1,2,3,4-tetrazol-5-yl)phenyl]-1H-indol-2-yl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-5-fluoropiperidin-3-amine (220);

5 N-{[4-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methyl}acetamide (221);

(3R,5R)-1-{2-[1-(Cyclopropylmethyl)-6-(1H-indazol-4-yl)-1H-indol-2-yl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-5-fluoropiperidin-3-amine (222);

10 2-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)benzamide (223);

N-{[4-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methyl}methanesulfonamide (224);

15 6-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-8-fluoro-5-methyl-1,2-dihydroquinolin-2-one (225);

20 N-[5-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)pyridin-2-yl]acetamide (226);

[3-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methanol (227);

25 N-{[4-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methyl}acetamide (228);

4-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)benzamide (229);

4-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-N,N-dimethylbenzamide (230);

30 N-[4-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methanesulfonamide (231);

N-{[3-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methyl}acetamide (232);

5 [2-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methanol (233);

N-{[4-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methyl}methanesulfonamide (234);

10 N-{[3-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methyl}methanesulfonamide (235);

[3-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methanol (236);

15 a[2-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)benzamide (237);

(3R)-1-{2-[1-(Cyclopropylmethyl)-6-(1H-indazol-4-yl)-1H-indol-2-yl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}piperidin-3-amine (238);

20 6-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-8-fluoro-5-methyl-1,2-dihydroquinolin-2-one (239);

N-[5-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)pyridin-2-yl]acetamide (240);

25 (3R,5R)-1-{2-[1-(Cyclopropylmethyl)-6-(4-methanesulfonylpiperidin-1-yl)-1H-indol-2-yl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-5-fluoropiperidin-3-amine (241);

1-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-N,N-dimethylpiperidine-4-carboxamide (242);

30 N-[1-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-N-methylacetamide (243);

N-[1-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-N-methylacetamide (244);

5 Methyl N-[1-(2-{6-[(3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-N-methylcarbamate (245);

N-[1-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-N-methylmethanesulfonamide (246);

10 N-[1-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)azetidin-3-yl]-N-methylmethanesulfonamide (247);

(3R)-1-{2-[1-(Cyclopropylmethyl)-6-(4-methanesulfonylpiperidin-1-yl)-1H-indol-2-yl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}piperidin-3-amine (248);

15 (3R)-1-{2-[1-(Cyclopropylmethyl)-6-(4-methoxypiperidin-1-yl)-1H-indol-2-yl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}piperidin-3-amine (249);

2-[1-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-N,N-dimethylacetamide (250);

20 (3R)-1-{2-[1-(Cyclopropylmethyl)-6-[4-(3-methoxyazetidine-1-carbonyl)piperidin-1-yl]-1H-indol-2-yl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}piperidin-3-amine (251);

N-[1-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-N-methylacetamide (252);

25 N-[1-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-N-methylacetamide (253);

30 N-[1-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-N-methylmethanesulfonamide (254);

Methyl N-[1-(2-{6-[(3R)-3-aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-N-methylcarbamate (255);

5 N-[1-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)azetidin-3-yl]-N-methylmethanesulfonamide (256);

1-[2-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)phenyl]imidazolidin-2-one (257);

10 1-[4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)phenyl]pyrrolidin-2-one (258);

15 3-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-methylphenol (259);

4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluoro-5-methylbenzamide (260);

20 1-[4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)phenyl]imidazolidin-2-one (261);

4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-methylbenzamide (262);

25 4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)benzamide (263);

30 5-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-N-methylpyridine-2-carboxamide (264);

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-((R)-3-hydroxypiperidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (265);

(7R)-2-{2-[1-(Cyclopropylmethyl)-6-(morpholin-4-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine (266);

4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)morpholin-3-one (267);

(7R)-2-{2-[1-(Cyclopropylmethyl)-6-(4-methanesulfonylpiperidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine (268);

8-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-methyl-1-oxa-3,8-diazaspiro[4.5]decan-2-one (269);

(3R)-1-{2-[1-(Cyclopropylmethyl)-6-(4-methanesulfonylpiperidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}piperidin-3-amine (270);

N-[1-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)piperidin-4-yl]-N-methylacetamide (271);

Methyl N-[1-(2-{6-[(3R)-3-aminopiperidine-1-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)piperidin-4-yl]-N-methylcarbamate (272);

1-[1-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)piperidin-4-yl]pyrrolidin-2-one (273);

(5S)-5-{[(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)oxy]methyl}pyrrolidin-2-one (274);

4-{{(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)oxy)methyl}pyrrolidin-2-one (275);

(3R)-1-{4-Chloro-2-[1-(cyclopropylmethyl)-6-(4-methoxypiperidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}piperidin-3-amine (276);

4-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluoro-5-methylbenzamide (277);

10 3-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-chlorophenol (278);

4-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorobenzamide (279);

1-[4-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)phenyl]imidazolidin-2-one (280);

1-[2-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)phenyl]imidazolidin-2-one (281);

3-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-methylphenol (282);

25 3-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorophenol (283);

5-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2,3-dihydro-1H-isoindol-1-one (284);

30

6-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2,3-dihydro-1H-isoindol-1-one (285);

4-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-methylbenzamide (286);

5-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-N-methylpyridine-2-carboxamide (287);

(3R)-1-{2-[1-(Cyclopropylmethyl)-6-{3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl}-1H-pyrrolo[2,3-b]pyridin-2-yl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}piperidin-3-amine (288);

(3R,5R)-1-{4-Chloro-2-[6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-5-fluoropiperidin-3-amine (289);

(3R,5R)-1-{4-Chloro-2-[1-(cyclopropylmethyl)-6-(1H-indazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-5-fluoropiperidin-3-amine (290);

(3R)-1-{4-Chloro-2-[6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}piperidin-3-amine (291);

(3R)-1-{4-chloro-2-[1-(Cyclopropylmethyl)-6-(1H-indazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}piperidin-3-amine (292);

5-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-2,3-dihydro-1H-isoindol-1-one (293);

4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-3-chlorobenzamide (294);

(7R)-2-{2-[1-(Cyclopropylmethyl)-6-{3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl}-1H-indol-2-yl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine (295);

(7R)-2-{2-[1-(Cyclopropylmethyl)-6-(3-methoxyazetidin-1-yl)-1H-indol-2-yl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine (296);

5 (7R)-2-{2-[1-(Cyclopropylmethyl)-6-(3-fluoro-1H-indazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine (297);

(7R)-2-{2-[1-(Cyclopropylmethyl)-6-(1H-indazol-6-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine (298);

10 (7R)-2-{2-[1-(Cyclopropylmethyl)-6-(1H-indazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine (299);

(7R)-2-{2-[1-(Cyclopropylmethyl)-6-(1H-indazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine (300);

15 3-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-methylphenol (301);

20 1-[2-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)phenyl]imidazolidin-2-one (302);

4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-methoxybenzamide (303);

25 1-[4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)phenyl]pyrrolidin-2-one (304);

30 4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluoro-5-methylbenzamide (305);

(7R)-2-{2-[1-(Cyclopropylmethyl)-6-(7-fluoro-1H-indazol-6-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine (306);

5 5-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-N-methylpyridine-2-carboxamide (307);

Methyl N-[5-(2-{6-[(7R)-7-amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)pyridin-2-yl]carbamate (308);

10 (3R)-1-{2-[1-(Cyclopropylmethyl)-6-(1H-indazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}piperidin-3-amine (309);

(3R)-1-{2-[1-(Cyclopropylmethyl)-6-(1H-indazol-6-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}piperidin-3-amine (310);

15 (3R)-1-{2-[1-(Cyclopropylmethyl)-6-(1H-indazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}piperidin-3-amine (311);

6-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-8-fluoro-5-methyl-1,2-dihydroquinolin-2-one (312);

20 3-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-chlorophenol (313);

3-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorophenol (314);

25 6-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2,3-dihydro-1H-isoindol-1-one (315);

4-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-methylbenzamide (316);

30 5-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2,3-dihydro-1H-isoindol-1-one (317);

(7R)-2-{2-[1-(Cyclopropylmethyl)-6-(morpholin-4-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine (318);

5 4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)morpholin-3-one (319);

(7R)-2-{2-[1-(Cyclopropylmethyl)-6-(4-methanesulfonylpiperidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine (320);

10 (3R,5R)-1-{2-[1-(Cyclopropylmethyl)-6-(1H-indazol-6-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-5-fluoropiperidin-3-amine (321);

(3R,5R)-1-{2-[1-(Cyclopropylmethyl)-6-(1H-indazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-5-fluoropiperidin-3-amine (322);

15 (3R,5R)-1-{2-[1-(Cyclopropylmethyl)-6-(1H-indazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-5-fluoropiperidin-3-amine (323);

20 6-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-8-fluoro-5-methyl-1,2-dihydroquinolin-2-one (324);

Methyl N-[1-(2-{6-[(3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)piperidin-4-yl]-N-methylcarbamate (325);

25 (7R)-2-{2-[1-(Cyclopropylmethyl)-6-(7-fluoro-1H-indazol-4-yl)-1H-indol-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine (326);

(7R)-2-{2-[1-(Cyclopropylmethyl)-6-(3-fluoro-1H-indazol-4-yl)-1H-indol-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine (327);

30 1-[4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]imidazolidin-2-one (328);

- 1-[4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]pyrrolidin-2-one (329);
- (7R)-2-{2-[1-(Cyclopropylmethyl)-6-(7-fluoro-1H-indazol-6-yl)-1H-indol-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine (330);
- 5 4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-5-fluoro-2-methylbenzamide (331);
- (7R)-2-{2-[1-(Cyclopropylmethyl)-6-(1H-indazol-6-yl)-1H-indol-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine (332);
- 10 (7R)-2-{2-[1-(Cyclopropylmethyl)-6-(1H-indazol-5-yl)-1H-indol-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine (333);
- 4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-2-methylbenzamide (334);
- 15 4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-3-(trifluoromethyl)benzamide (335);
- (7R)-2-{2-[1-(Cyclopropylmethyl)-6-(7-fluoro-1H-indazol-6-yl)-1H-indol-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine (336);
- 20 N-[7-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-4-chloro-1-methyl-1H-indazol-3-yl]methanesulfonamide (337);
- 1-[2-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]imidazolidin-2-one (338);
- 25 4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-2-chlorobenzamide (339);
- 30 5-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-N-methylpyridine-2-carboxamide (340);

- (7R)-2-{2-[1-(Cyclopropylmethyl)-6-(1H-pyrazol-4-yl)-1H-indol-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine (341);
- N-{[4-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methyl}methanesulfonamide (342);
- 5 N-{[3-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methyl}acetamide (343);
- [3-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methanol (344);
- 10 (3R)-1-{2-[1'-(Cyclopropylmethyl)-1H,1'H-[5,6'-biindole]-2'-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}piperidin-3-amine (345);
- 6-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-8-fluoro-5-methyl-1,2-dihydroquinolin-2-one (346);
- 15 N-[4-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methanesulfonamide (347);
- N-[5-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)pyridin-2-yl]acetamide (348);
- (R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (349);
- 20 (7R)-2-{2-[1-(Cyclopropylmethyl)-6-(morpholin-4-yl)-1H-indol-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine (350);
- (7R)-2-{2-[1-(Cyclopropylmethyl)-6-(4-methanesulfonylpiperidin-1-yl)-1H-indol-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine (351);
- 25 Methyl N-[1-(2-{6-[(3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-N-methylcarbamate (352);
- 30 N-[1-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-N-methylacetamide (353);

N-[1-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-N-methylmethanesulfonamide (354);

(3R,5R)-1-{2-[1-(Cyclopropylmethyl)-6-[4-(pyrrolidine-1-carbonyl)piperidin-1-yl]-1H-indol-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-5-fluoropiperidin-3-amine (355);

1-[1-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]pyrrolidin-2-one (356);

3-[1-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-1,3-oxazolidin-2-one (357);

Methyl N-[1-(2-{6-[(3R)-3-aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-N-methylcarbamate (358);

N-[1-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-N-methylacetamide (359);

N-[1-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-N-methylmethanesulfonamide (360);

(3R)-1-{2-[1-(Cyclopropylmethyl)-6-[4-(pyrrolidine-1-carbonyl)piperidin-1-yl]-1H-indol-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}piperidin-3-amine (361);

N-[1-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-N-methylmethanesulfonamide (362);

1-[1-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]pyrrolidin-2-one (363);

3-[1-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-1,3-oxazolidin-2-one (364);

(3R)-1-{2-[1-(Cyclopropylmethyl)-6-[4-(1H-pyrazol-1-yl)piperidin-1-yl]-1H-indol-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}piperidin-3-amine (365);

N-[1-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)azetidin-3-yl]-N-methylmethanesulfonamide (366);

5 N-{[3-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methyl}methanesulfonamide (367);

(3R,5R)-1-{2-[1-(Cyclopropylmethyl)-6-[3-(2H-1,2,3,4-tetrazol-5-yl)phenyl]-1H-indol-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-5-fluoropiperidin-3-amine (368);

10 N-[4-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methanesulfonamide (369);

N-{[4-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methyl}methanesulfonamide (370);

15 [3-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methanol (371);

20 2-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)benzamide (372);

4-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)benzamide (373);

(3R,5R)-1-{2-[1'-(Cyclopropylmethyl)-1H,1'H-[5,6'-biindole]-2'-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-5-fluoropiperidin-3-amine (374);

25 [4-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-2-chloro-5-fluorophenyl]methanol (375);

6-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-8-fluoro-5-methyl-1,2-dihydroquinolin-2-one (376);

30 4-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-3-chlorobenzamide (377);

4-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-2-methylbenzamide (378);

(3R,5R)-1-{2-[1-(Cyclopropylmethyl)-6-{3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl}-1H-indol-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-5-fluoropiperidin-3-amine (379);

2-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)propan-2-ol (Homochiral) (380);

2-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-1,1-difluoropropan-2-ol (Diastereomeric mixture) (381);

2-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-1,1,1-trifluoropropan-2-ol (Diastereomeric mixture) (382);

2-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-1,1,1-trifluoropropan-2-ol (383);

1-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-1-cyclopropylethan-1-ol (384);

1-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)ethan-1-ol (Diastereomeric mixture) (385);

((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(tetrahydro-2H-pyran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (386);

((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(tetrahydro-2H-pyran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (387);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(tetrahydro-2H-pyran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (388);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(tetrahydro-2H-pyran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (389);

5 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxycyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (390);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1r,4r)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (391);

10 (R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxycyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (392);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxycyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (393);

15 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(tetrahydrofuran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (394);

20 (R)-1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxypropan-1-one (395);

(R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxycyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (396);

25 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(tetrahydrofuran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (397);

30 (R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxy-3-(trifluoromethyl)cyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (398);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxy-3-(trifluoromethyl)cyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (399);

5 ((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(tetrahydrofuran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (400);

((R)-1-(4-(2-(6-(3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxyethan-1-one (401);

10 ((R)-1-(4-(2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxypropan-1-one (402);

((S)-1-(4-(2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxypropan-1-one (403);

15 ((S)-1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxypropan-1-one (404);

20 1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxyethan-1-one (405);

((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1s,4s)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (406);

25 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1s,4s)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (407);

30 ((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1r,4r)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (408);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1r,4r)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (409);

(R)-1-(4-(2-(6-(3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)ethan-1-one (410);

1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)ethan-1-one (411);

1-(4-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)ethan-1-one (412);

(R)-1-(4-(2-(6-(3-Aminopiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)ethan-1-one (413);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1r,4r)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (414);

((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1r,4r)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (415);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1s,4s)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (416);

1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxy-2-methylpropan-1-one (417);

(R)-1-(4-(2-(6-(3-Aminopiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxy-2-methylpropan-1-one (418);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxycyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (419);

(R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxycyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (420);

5 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxy-3-(trifluoromethyl)cyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (421);

(R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxy-3-(trifluoromethyl)cyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (422);

10 (S)-1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxypropan-1-one (423);

(S)-1-(4-(2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxypropan-1-one (424);

(R)-1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxypropan-1-one (425);

20 (R)-1-(4-(2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxypropan-1-one (426);

1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)ethan-1-one (427);

25 1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxyethan-1-one (428);

(R)-1-(4-(2-(6-(3-Aminopiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxyethan-1-one (429);

30 Ethyl 2-(7-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate (430);

1-(4-(2-(6-((3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-3-hydroxypropan-1-one (430);

1-(4-(2-(6-((3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-isopropoxyethan-1-one (431);

(R)-1-(4-(2-(6-(3-aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-isopropoxyethan-1-one (432);

1-(4-(2-(6-((3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-3-hydroxy-2,2-dimethylpropan-1-one (433);

(R)-1-(4-(2-(6-(3-aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-3-hydroxy-2,2-dimethylpropan-1-one (434);

1-(4-(2-(6-((3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-hydroxy-2-methylpropan-1-one (435);

(R)-1-(4-(2-(6-(3-aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-hydroxy-2-methylpropan-1-one (436);

(R)-1-(4-(2-(6-(3-aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-3-hydroxypropan-1-one (437);

1-(4-(2-(6-((3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-hydroxyethan-1-one (438);

(R)-1-(4-(2-(6-(3-aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-hydroxyethan-1-one (439);

((R)-3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1R,3S)-3-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (440);

(R)-1-(4-(2-(6-(3-aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-ethoxyethan-1-one (441);

- 1-(4-(2-(6-((3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-ethoxyethan-1-one (442);
- 5 ((R)-3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1r,4r)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (443);
- ((3R,5R)-3-amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1s,4s)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (444);
- 10 1-(4-(2-(6-((3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-3-methylbutan-1-one (445);
- ((R)-1-(4-(2-(6-(3-aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-3-methylbutan-1-one (446);
- 15 ((R)-3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1S,3R)-3-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (447);
- ((3R,5R)-3-amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1S,3R)-3-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (448);
- 20 ((3R,5R)-3-amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1R,3S)-3-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (449);
- ((R)-3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1s,4s)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (450);
- 25 ((3R,5R)-3-amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1r,4r)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (451);
- 30 1-(4-(2-(6-((3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)ethan-1-one (452);

1-(4-(2-(6-((7R)-7-amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxyethan-1-one (453);

(S)-1-(4-(2-(6-((R)-3-aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxypropan-1-one (454);

(R)-1-(4-(2-(6-(3-aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxyethan-1-one (455);

(R)-(3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxy-3-(trifluoromethyl)cyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (456);

((R)-3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(tetrahydro-2H-pyran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (457);

((3R,5R)-3-amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(tetrahydro-2H-pyran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (458);

(S)-1-(4-(2-(6-((3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxypropan-1-one (459);

(R)-1-(4-(2-(6-((R)-3-aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxypropan-1-one (460);

(R)-1-(4-(2-(6-((3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxypropan-1-one (461);

((R)-3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(tetrahydrofuran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (462);

((3R,5R)-3-amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(tetrahydrofuran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (463);

(R)-(3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(thiophene-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (464);

(R)-(3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxycyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (465);

((3R,5R)-3-amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxycyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (466);

(4-(2-(6-((7R)-7-amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)(3-hydroxycyclobutyl)methanone (467);

Methyl (R)-4-(2-(6-(3-aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidine-1-carboxylate (468);

Methyl 4-(2-(6-((3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidine-1-carboxylate (469);

Methyl 4-(2-(6-((7R)-7-amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidine-1-carboxylate (470);

(R)-1-(4-(2-(6-((R)-3-aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-hydroxypropan-1-one (471);

(R)-1-(4-(2-(6-((3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-hydroxypropan-1-one (472);

(2R)-1-(4-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-hydroxypropan-1-one (473);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(thiophene-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (474);

(4-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)(thiophen-2-yl)methanone (475);

1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)ethan-1-one (476);

1-(4-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)ethan-1-one (477);

1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxyethan-1-one (478);

(R)-1-(4-(2-(6-(3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)ethan-1-one (479);

(R)-1-(4-(2-(6-(3-aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-7-yl)piperidin-1-yl)-2-methoxyethan-1-one (480);

1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-7-yl)piperidin-1-yl)-2-methoxyethan-1-one (481);

1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-7-yl)piperidin-1-yl)ethan-1-one (482);

(R)-1-(4-(2-(6-(3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-7-yl)piperidin-1-yl)ethan-1-one (483);

((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-((1r,4r)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (484);

((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-((1s,4s)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (485);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-((1s,4s)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (486);

5 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-((1r,4r)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (487);

((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-(tetrahydrofuran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (488);

10 ((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-(tetrahydrofuran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (489);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-(tetrahydrofuran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (490);

15 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-(tetrahydrofuran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (491);

20 ((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-(3-hydroxycyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (492);

((R)-1-(4-(2-(6-(3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-7-yl)piperidin-1-yl)-2-methoxy-2-methylpropan-1-one (493);

25 1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-7-yl)piperidin-1-yl)-3-methylbutan-1-one (494);

30 1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-7-yl)piperidin-1-yl)-3-methylbutan-1-one (495);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-(3-hydroxycyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (496);

(R)-1-(4-(2-(6-((R)-3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-7-yl)piperidin-1-yl)-2-methoxypropan-1-one (497);

(R)-1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-7-yl)piperidin-1-yl)-2-methoxypropan-1-one (498);

(S)-1-(4-(2-(6-((R)-3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-7-yl)piperidin-1-yl)-2-methoxypropan-1-one (499);

(S)-1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-7-yl)piperidin-1-yl)-2-methoxypropan-1-one (500);

1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-7-yl)piperidin-1-yl)-2-methoxy-2-methylpropan-1-one (501);

(R)-1-(4-(2-(6-(3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-7-yl)piperidin-1-yl)-2-methoxyethan-1-one (502);

1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-7-yl)piperidin-1-yl)-2-methoxyethan-1-one (503);

(R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-(3-hydroxy-3-(trifluoromethyl)cyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (504);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-(3-hydroxy-3-(trifluoromethyl)cyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (505);

(R)-1-(4-(2-(6-(3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-7-yl)piperidin-1-yl)ethan-1-one (506);

1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-7-yl)piperidin-1-yl)ethan-1-one (507);

5 ((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-(tetrahydro-2H-pyran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (508);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-(tetrahydro-2H-pyran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (509);

10 (R)-1-(4-(2-(6-(3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)piperidin-1-yl)-2-methoxyethan-1-one (510);

15 1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)piperidin-1-yl)-2-methoxyethan-1-one (511);

(R)-1-(4-(2-(6-(3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)piperidin-1-yl)-2-methoxyethan-1-one (512);

20 1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)piperidin-1-yl)-2-methoxyethan-1-one (513);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1r,4r)-4-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (514);

25 (R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxy-3-(trifluoromethyl)cyclobutane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (515);

30 (R)-1-(3-(2-(6-(3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)-2-methoxy-2-methylpropan-1-one (516);

((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1r,4r)-4-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (517);

1-(3-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)-2-methoxy-2-methylpropan-1-one (518);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1s,4s)-4-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (519);

10 ((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1s,4s)-4-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (520);

(R)-1-(3-(2-(6-(3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)ethan-1-one (521);

15 1-(3-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)ethan-1-one (522);

(S)-1-(3-(2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)-2-methoxypropan-1-one (523);

(S)-1-(3-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)-2-methoxypropan-1-one (524);

(R)-1-(3-(2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)-2-methoxypropan-1-one (525);

(R)-1-(3-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)-2-methoxypropan-1-one (526);

30 1-(3-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)-2-methoxyethan-1-one (527);

(R)-1-(3-(2-(6-(3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)-2-methoxyethan-1-one (528);

5 (R)-1-(3-(2-(6-(3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)-2-methoxyethan-1-one (529);

((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1r,4r)-4-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (530);

10 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1R,3S)-3-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (531);

((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1R,3S)-3-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (532);

15 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1S,3R)-3-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (533);

20 ((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1S,3R)-3-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (534);

(R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxy-3-(trifluoromethyl)cyclobutane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (535);

25 (R)-1-(3-(2-(6-(3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)-2-methoxy-2-methylpropan-1-one (536);

30 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1r,4r)-4-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (537);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-
((1s,4s)-4-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-3-
methylpyrazolo[1,5-a]pyridin-6-yl)methanone (538);

5 ((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1s,4s)-4-
hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-
a]pyridin-6-yl)methanone (539);

((R)-1-(3-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-
methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)-
2-methoxypropan-1-one (540);

10 ((R)-1-(3-(2-(6-((R)-3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-
a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)-2-methoxypropan-1-
one (541);

((S)-1-(3-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-
methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)-
15 2-methoxypropan-1-one (542);

((S)-1-(3-(2-(6-((R)-3-aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-
a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)-2-methoxypropan-1-
one (543);

20 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-
(tetrahydro-2H-pyran-2-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-
a]pyridin-6-yl)methanone (544);

((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(tetrahydro-2H-
pyran-2-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-
yl)methanone (545);

25 ((R)-1-(3-(2-(6-(3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-
2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)-2-methoxyethan-1-one (546);

1-(3-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-
methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)-
2-methoxyethan-1-one (547);

30 1-(3-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-
methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-
yl)ethan-1-one (548);

1-(3-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)ethan-1-one (549);

4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (550);

4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)-1-methylpyrrolidin-2-one (551);

4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)-1-methylpyrrolidin-2-one (552);

4-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)-1-methylpyrrolidin-2-one (553);

4-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)-1-methylpyrrolidin-2-one (554);

(R)-(2-(7-(2-(1H-1,2,4-Triazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)(3-aminopiperidin-1-yl)methanone (555);

(2-(7-(2-(1H-1,2,4-Triazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)((3R,5R)-3-amino-5-fluoropiperidin-1-yl)methanone (556);

(2-(7-(2-(4-Amino-1H-pyrazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)((3R,5R)-3-amino-5-fluoropiperidin-1-yl)methanone (557);

(R)-(2-(7-(2-(4-Amino-1H-pyrazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)(3-aminopiperidin-1-yl)methanone (558);

(S)-5-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (559);

(S)-5-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (560);

(R)-5-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (561);

4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (562);

4-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (563);

4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (564);

4-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (565);

4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (566);

4-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (567);

(S)-5-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (568);

(S)-5-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (569);

(R)-5-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (570);

4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (571);

4-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (572);

4-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (573);

(2-(7-(2-(1H-Imidazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)((3R,5R)-3-amino-5-fluoropiperidin-1-yl)methanone (574);

(R)-(2-(7-(2-(1H-Imidazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)(3-aminopiperidin-1-yl)methanone (575);

4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)-1-methylpyrrolidin-2-one (576);

4-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)-1-methylpyrrolidin-2-one (577);

4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)-1-methylpyrrolidin-2-one (578);

4-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)-1-methylpyrrolidin-2-one (579);

(R)-(2-(7-(2-(1H-1,2,4-Triazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)(3-aminopiperidin-1-yl)methanone (580);

(2-(7-(2-(1H-1,2,4-Triazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)((3R,5R)-3-amino-5-fluoropiperidin-1-yl)methanone (581);

(R)-(2-(7-(2-(4-Amino-1H-pyrazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)(3-aminopiperidin-1-yl)methanone (582);

(2-(7-(2-(4-Amino-1H-pyrazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)((3R,5R)-3-amino-5-fluoropiperidin-1-yl)methanone (583);

- (S)-5-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (584);
- (S)-5-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (585);
- (R)-5-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (586);
- (R)-5-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (587);
- 4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (588);
- 4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (589);
- 4-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (590);
- 4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one (591);
- (2-(7-(2-(1H-1,2,4-Triazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)((3R,5R)-3-amino-5-fluoropiperidin-1-yl)methanone (592);
- (R)-(2-(7-(2-(1H-1,2,4-Triazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)(3-aminopiperidin-1-yl)methanone (593);
- ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(2-(2-methyl-1H-imidazol-1-yl)ethoxy)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (594);
- (R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(2-(2-methyl-1H-imidazol-1-yl)ethoxy)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (595);

(R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(oxetan-3-ylmethoxy)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (596);

5 (2-(7-(2-(1H-Imidazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)((3R,5R)-3-amino-5-fluoropiperidin-1-yl)methanone (597);

(R)-(2-(7-(2-(1H-Imidazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)(3-aminopiperidin-1-yl)methanone (598);

10 (R)-(2-(7-(2-(4H-1,2,4-Triazol-4-yl)ethoxy)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)(3-aminopiperidin-1-yl)methanone (599);

(2-(7-(2-(4H-1,2,4-Triazol-4-yl)ethoxy)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)((3R,5R)-3-amino-5-fluoropiperidin-1-yl)methanone (600);

4-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one (601);

20 4-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one (602);

4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one (603);

25 (5R)-5-(((2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one (604);

30 4-(((2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one (605);

4-(((2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one (606);

(5R)-5-(((2-(6-((7S)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one (607);

4-(((2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one (608);

(R)-(2-(7-(2-(4H-1,2,4-Triazol-4-yl)ethoxy)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)(3-aminopiperidin-1-yl)methanone (609);

(2-(7-(2-(1H-1,2,4-Triazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)((3R,5R)-3-amino-5-fluoropiperidin-1-yl)methanone (610);

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(2-(2-methyl-1H-imidazol-1-yl)ethoxy)-1H-pyrrolo[2,3-c]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (611);

(R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(2-(2-methyl-1H-imidazol-1-yl)ethoxy)-1H-pyrrolo[2,3-c]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (612);

(2-(7-(2-(4H-1,2,4-Triazol-4-yl)ethoxy)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)((3R,5R)-3-amino-5-fluoropiperidin-1-yl)methanone (613);

4-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one (614);

4-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one (615);

(2-(7-(2-(1H-Imidazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)((3R,5R)-3-amino-5-fluoropiperidin-1-yl)methanone (616);

(R)-(2-(7-(2-(1H-Imidazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)(3-aminopiperidin-1-yl)methanone (617);

4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one (618);

4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one (619);

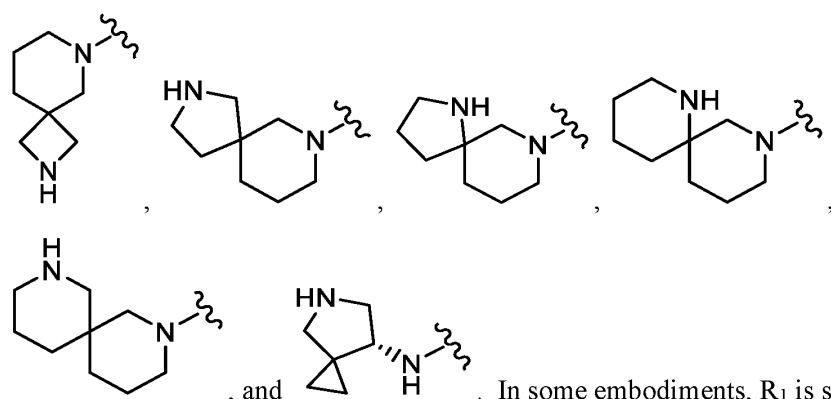
(2-(7-(2-(4H-1,2,4-Triazol-4-yl)ethoxy)-1-methyl-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)((3R,5R)-3-amino-5-fluoropiperidin-1-yl)methanone (620); and

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl) (2-(3-(cyclopropylmethyl)-4-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)benzo[b]thiophen-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (621);

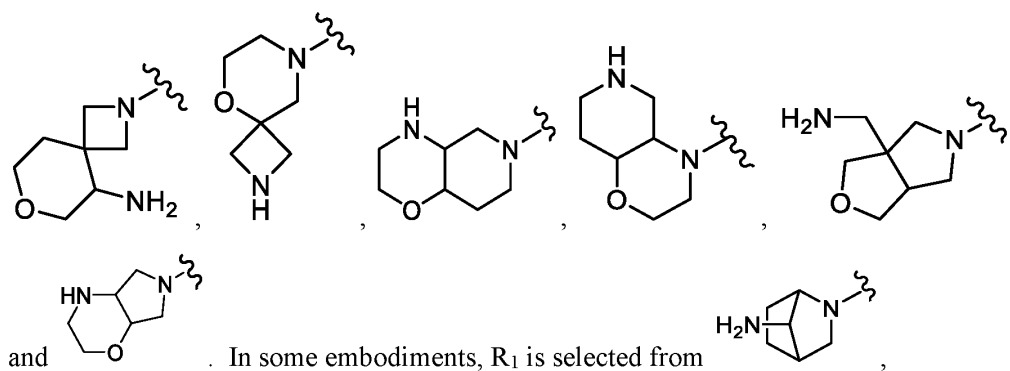
or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides compounds with IC₅₀ values ≤ 4.000 μM, using the RFMS PAD4 functional assay disclosed herein, preferably, IC₅₀ values ≤ 1.000 μM, preferably, IC₅₀ values ≤ 0.500 μM, preferably, IC₅₀ values ≤ 0.100 μM, more preferably, IC₅₀ values ≤ 0.050 μM, more preferably, IC₅₀ values ≤ 0.03 μM, more preferably, IC₅₀ values ≤ 0.02 μM, even more preferably, IC₅₀ values ≤ 0.01 μM.

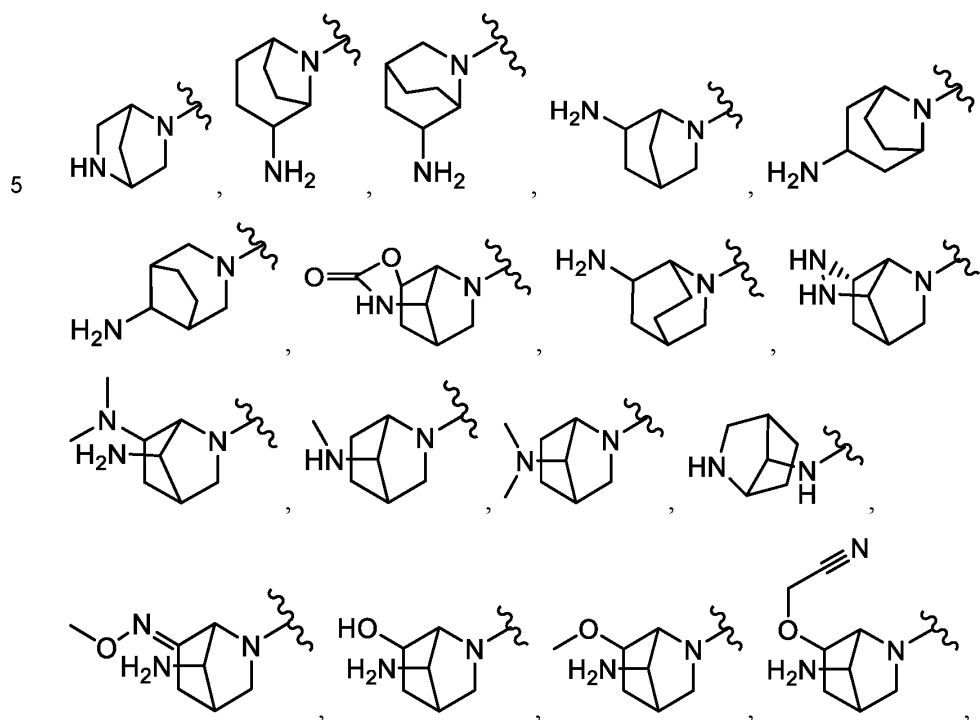
As defined above and described herein, X₂ is selected from N and CR₄. In some embodiments, X₂ is N. In some embodiments, X₂ is CR₄. In certain embodiments, X₂ is selected from those functional groups depicted in the examples below.

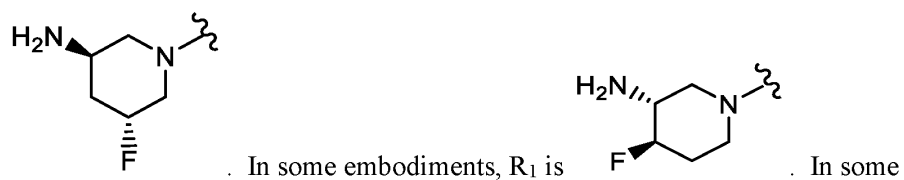
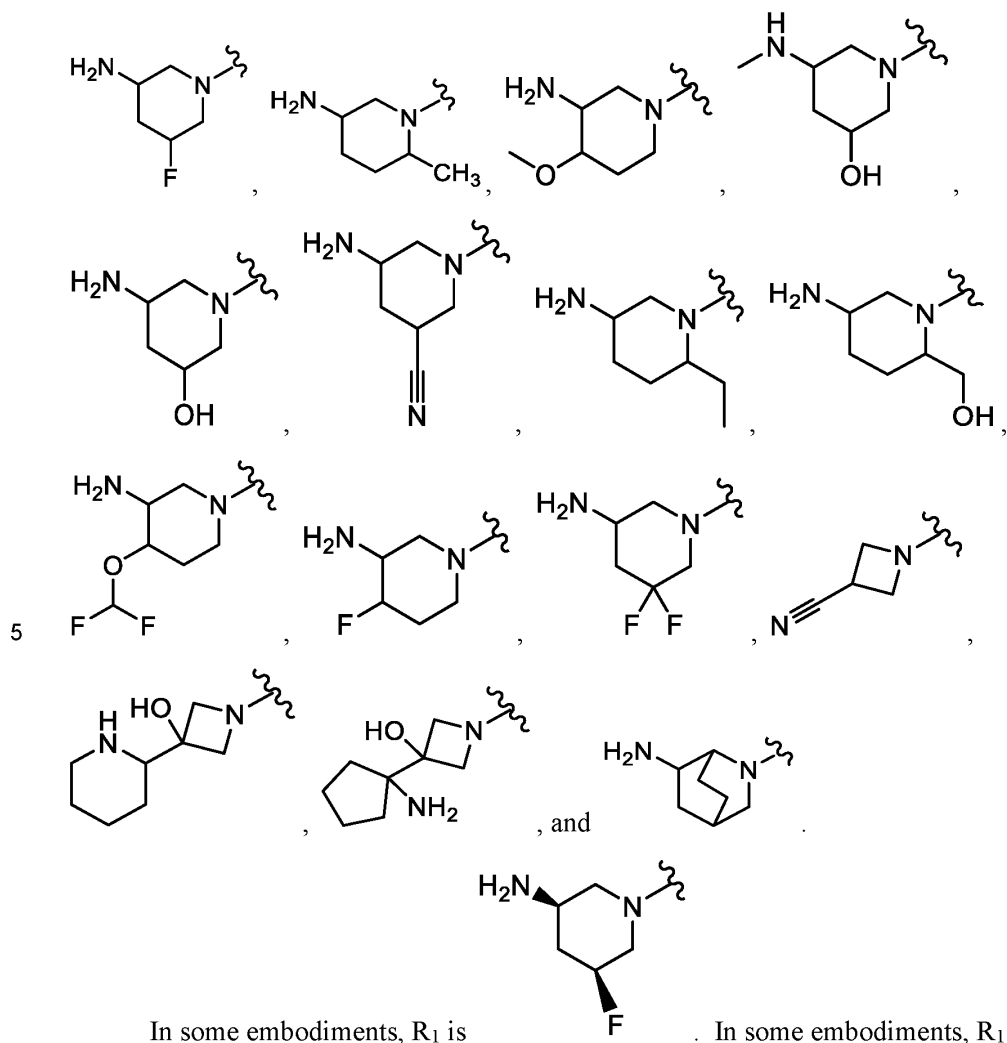
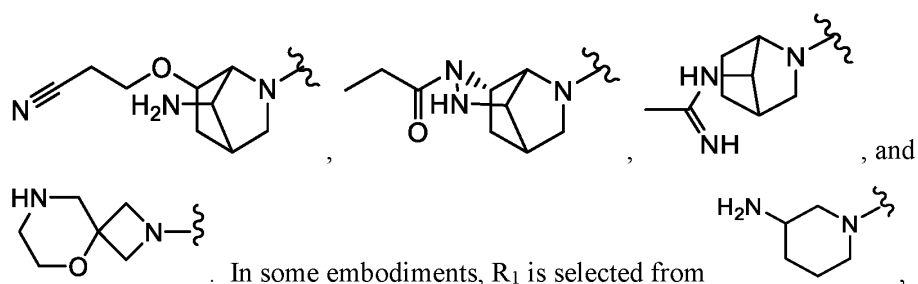


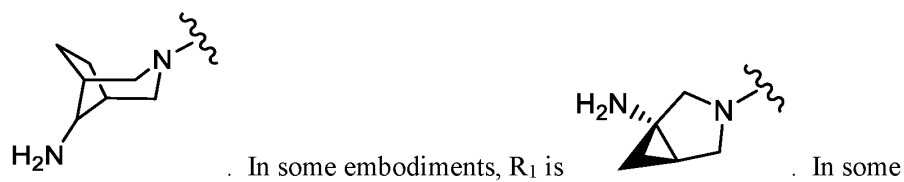
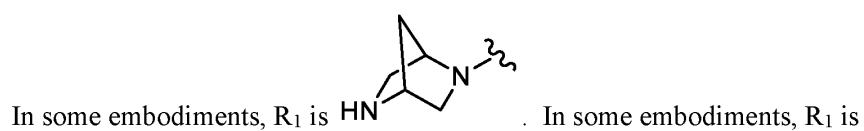
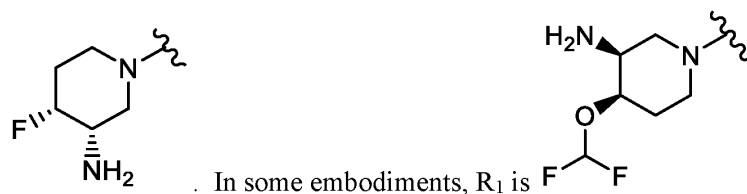
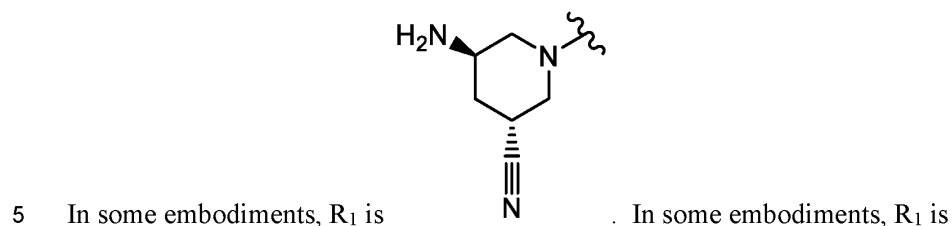
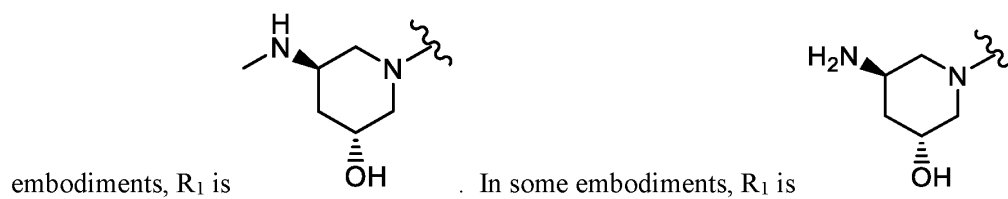
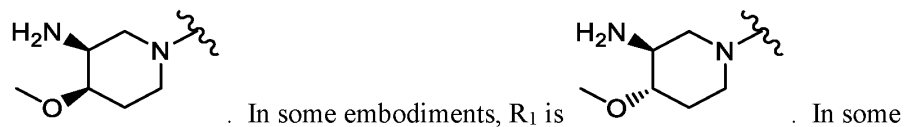
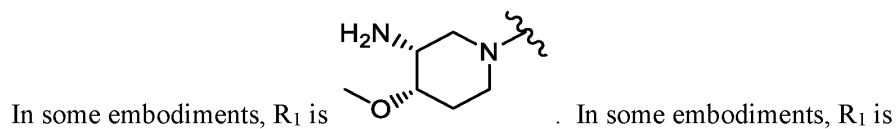
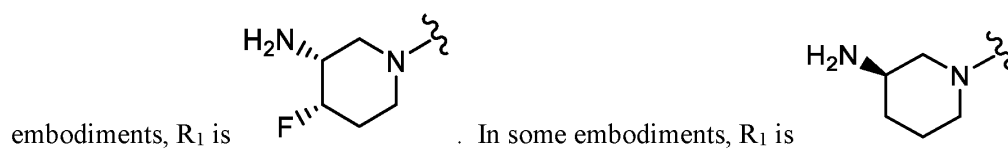
, and . In some embodiments, R_1 is selected from

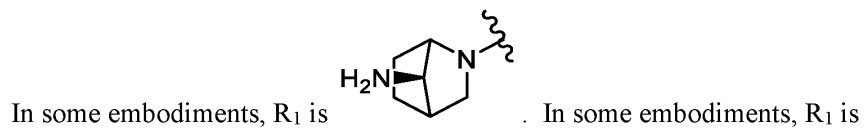
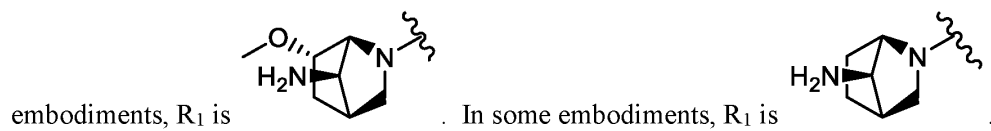
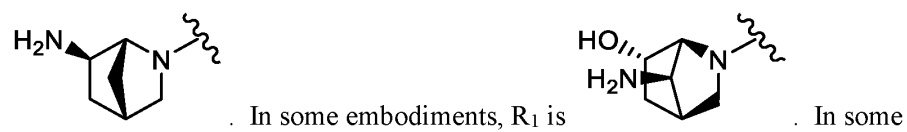
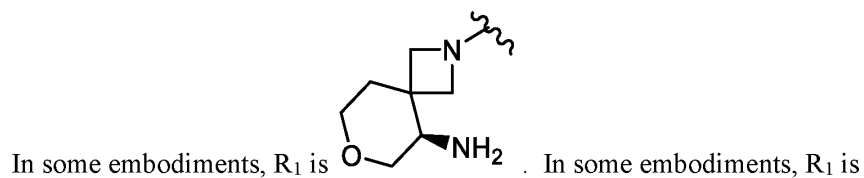
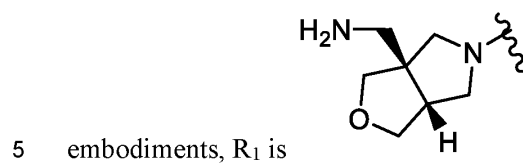
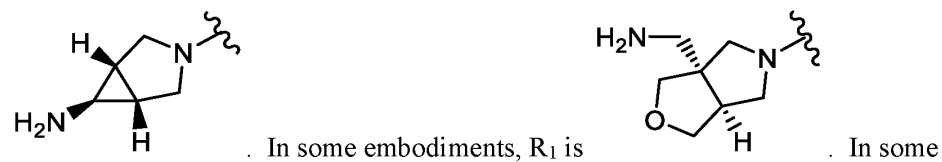
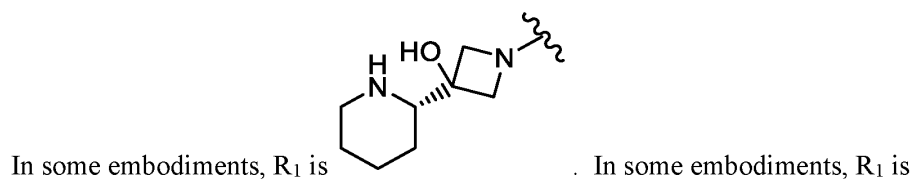
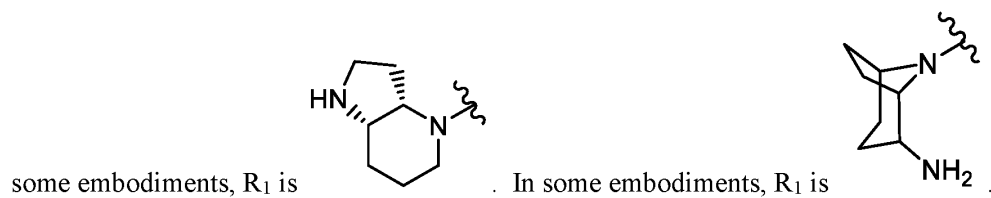
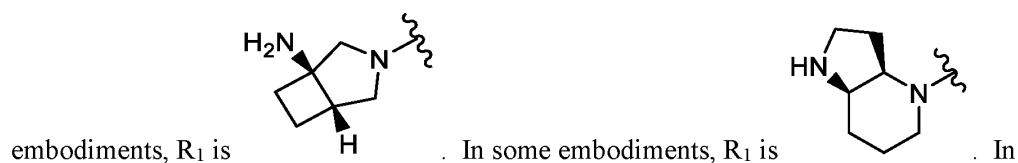


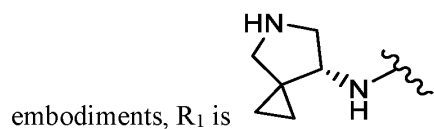
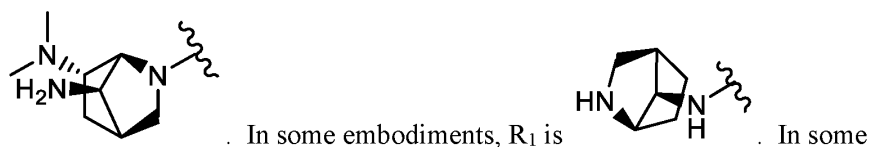
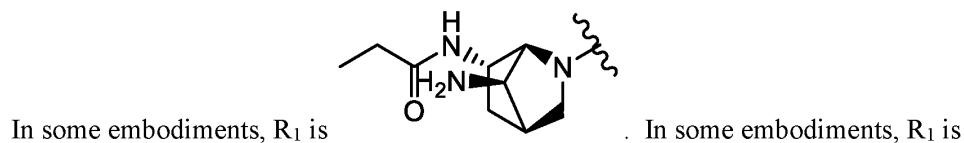
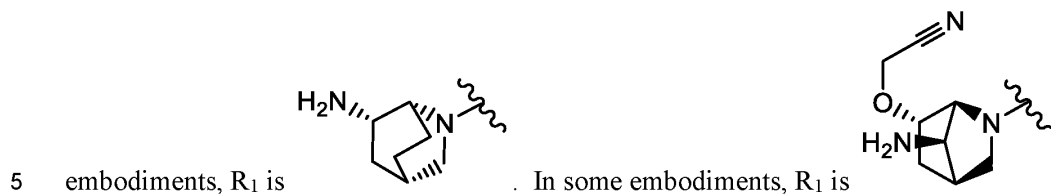
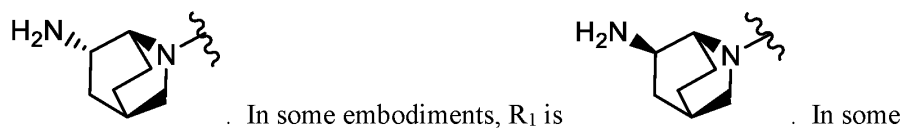
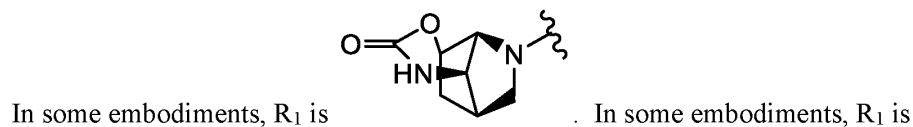
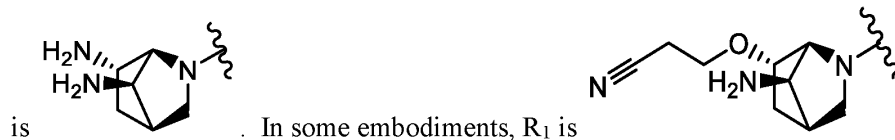
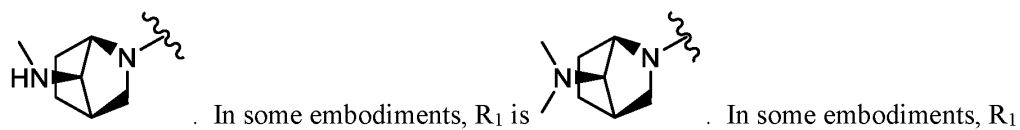
and . In some embodiments, R_1 is selected from

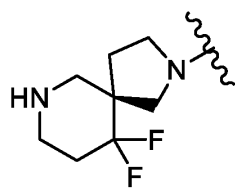






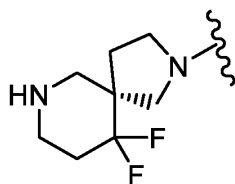




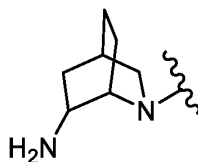


In some embodiments, R₁ is

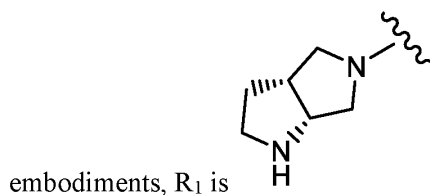
. In some embodiments, R₁ is



. In some embodiments, R₁ is

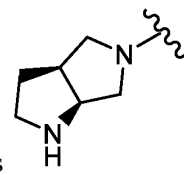


. In some

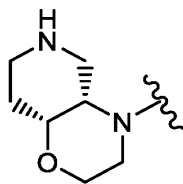


embodiments, R₁ is

. In some embodiments, R₁ is

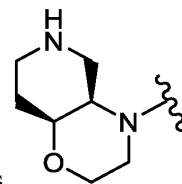


. In



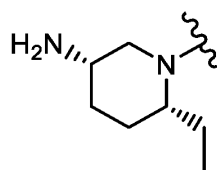
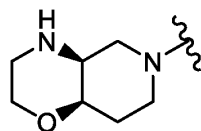
some embodiments, R₁ is

. In some embodiments, R₁ is



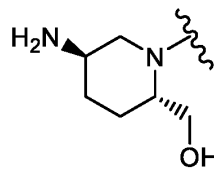
5 . In some embodiments, R₁ is

. In some embodiments, R₁ is

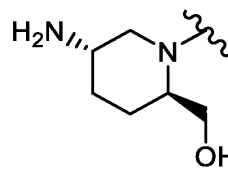


In some embodiments, R₁ is

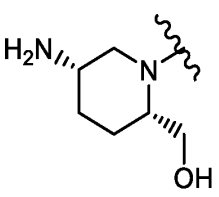
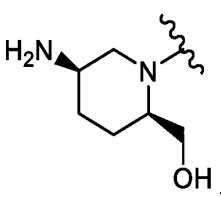
. In some embodiments, R₁ is

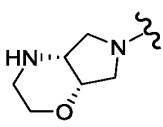
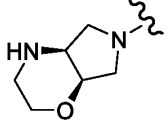


. In some embodiments, R₁ is

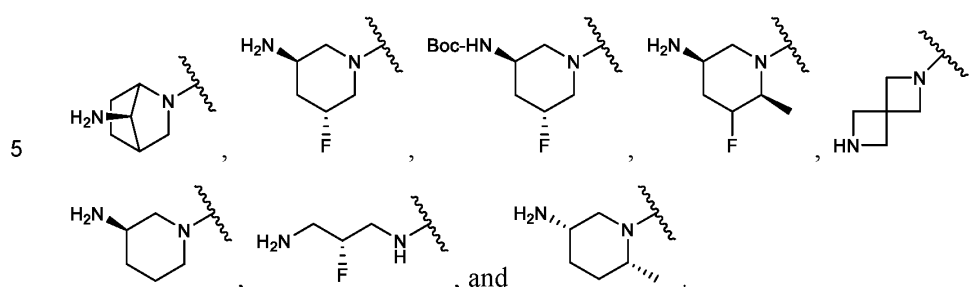


. In some

embodiments, R₁ is . In some embodiments, R₁ is .

In some embodiments, R₁ is . In some embodiments, R₁ is .

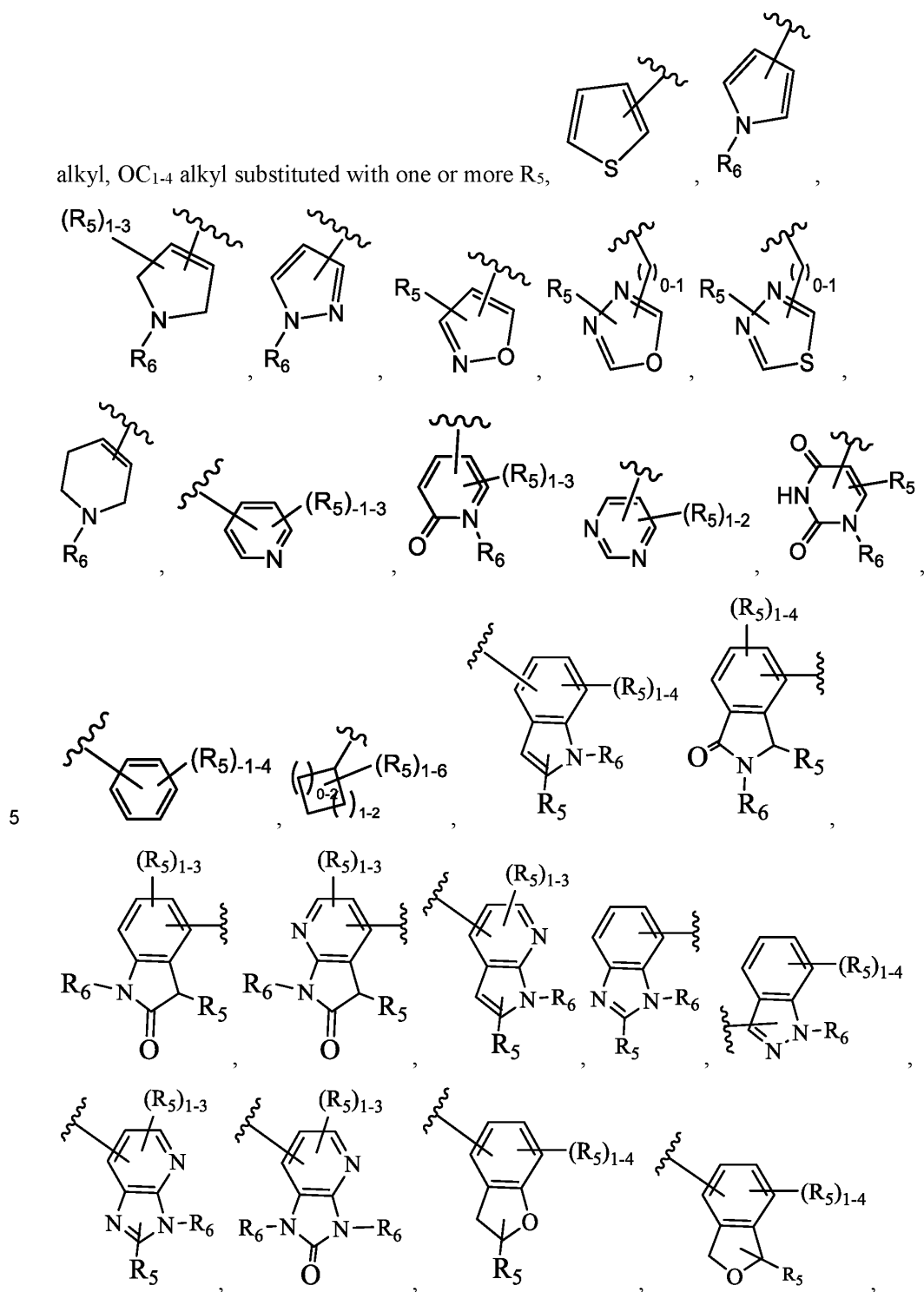
In certain embodiments, R₁ is selected from those functional groups depicted in the examples below. R₁ is preferably selected from

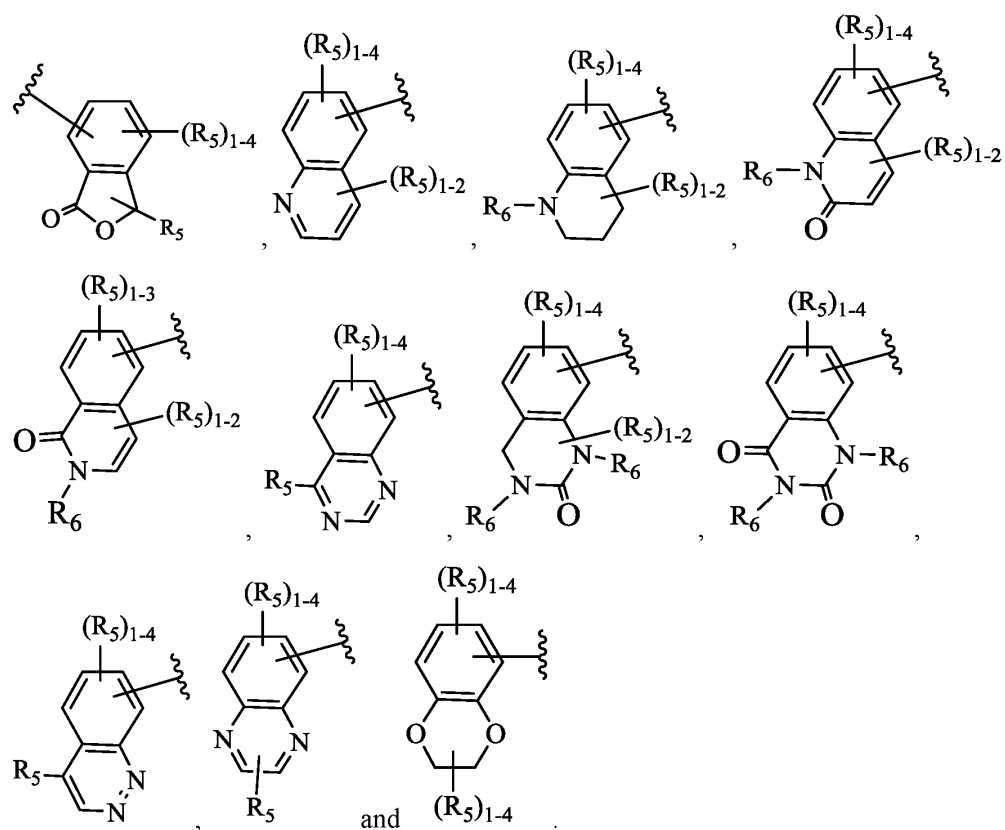


As defined above and described herein, R₂ is selected from H, F, Cl, Br, -OR_b, and C₁₋₃ alkyl optionally substituted with one or more R_c. In some embodiments, R₂ is H. In some embodiments, R₂ is F, Cl, Br. In some embodiments, R₂ is F. In some
 10 embodiments, R₂ is C₁₋₃ alkyl. In some embodiments, R₂ is methyl. In some embodiments, R₂ is ethyl. In some embodiments, R₂ is propyl. In some embodiments, R₂ is OR_b. In some embodiments, R₂ is -OCH₃. In some embodiments, R₂ is -OCH₂CH₃. In some embodiments, R₂ is -OCH₂CH₂CH₃. In certain embodiments, R₂ is -OCH(F)₂. In certain embodiments, R₂ is selected from those functional groups depicted in the
 15 examples below. R₂ is preferably selected from H, F, Cl, CH₃, and OCH₃.

As defined above and described herein, R₃ is selected from CH₃ and CD₃. In some embodiments, R₃ is CH₃. In some embodiments, R₃ is CD₃. In certain embodiments, R₃ is selected from those functional groups depicted in the examples below. R₃ is preferably selected from H, F, Cl, CH₃, and CH₂OH.

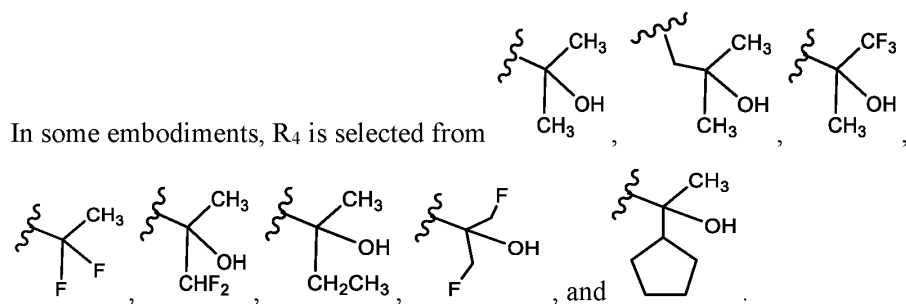
As defined above and described herein, R₄ is selected from H, F, Cl, Br, C₁₋₄



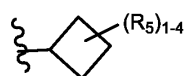


In some embodiments, R_4 is H. In some embodiments, R_4 is selected from F, Cl, and Br.

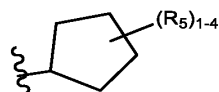
In some embodiments, R_4 is C_{1-3} alkyl. In some embodiments, R_4 is CH_3 .



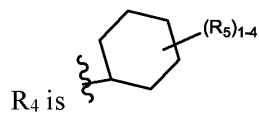
In some embodiments, R_4 is  $(R_5)_{1-4}$. In some embodiments, R_4 is



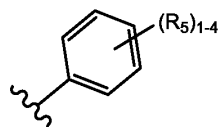
. In some embodiments, R_4 is



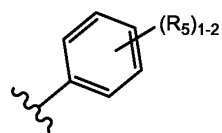
. In some embodiments,



In some embodiments, R_4 is

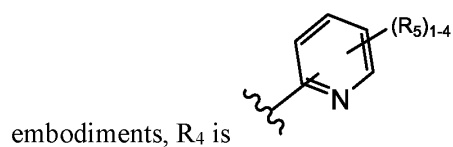


. In some embodiments, R_4 is

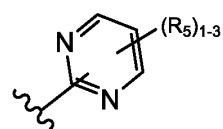


5

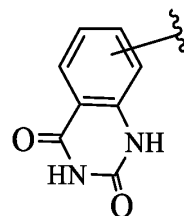
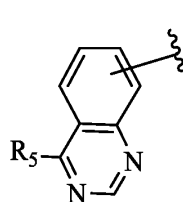
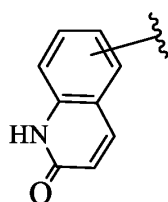
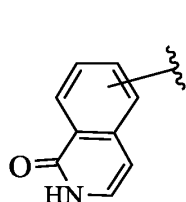
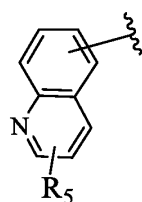
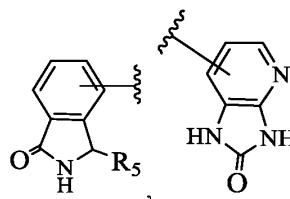
, wherein R_5 is selected from F, Cl, -OH, -C(=O)NH₂. In some

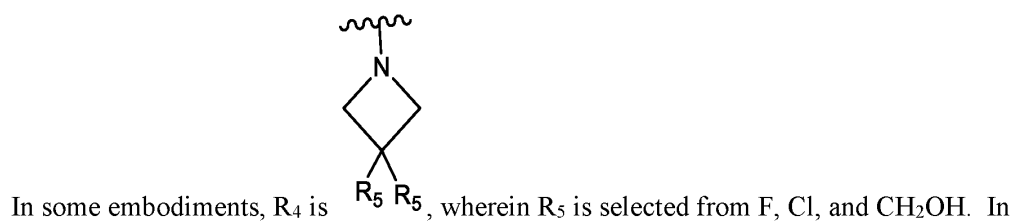
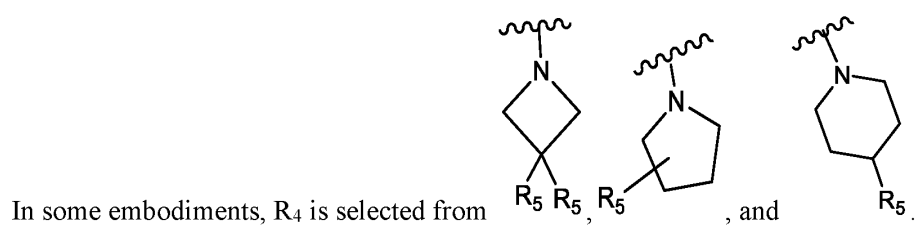
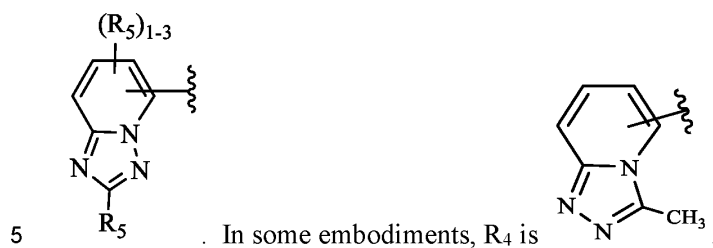
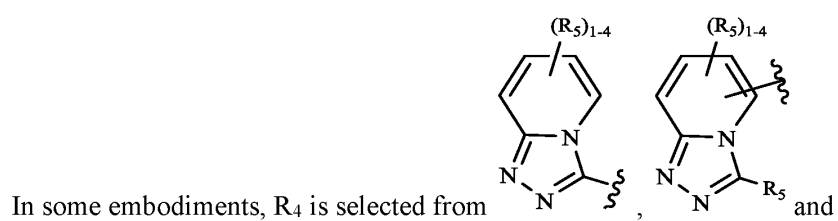
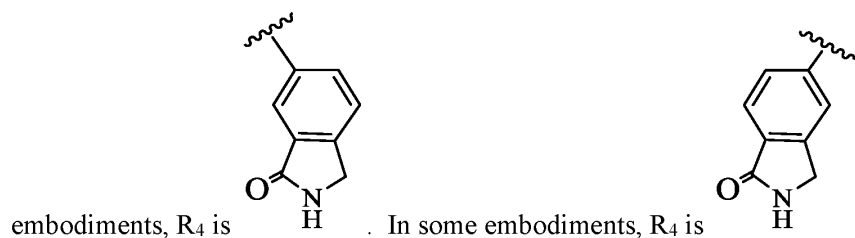
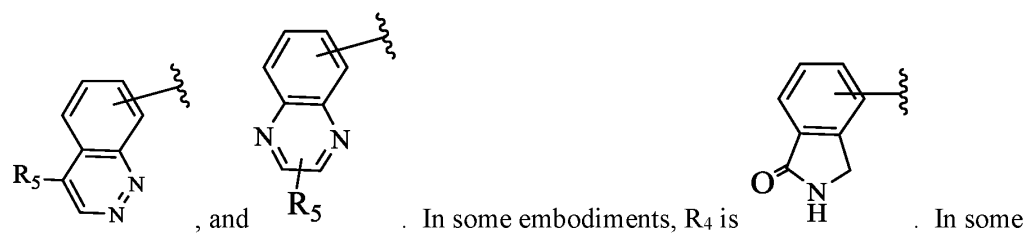


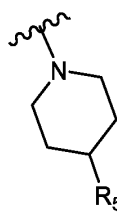
. In some embodiments, R_4 is



In some embodiments, R_4 is selected from

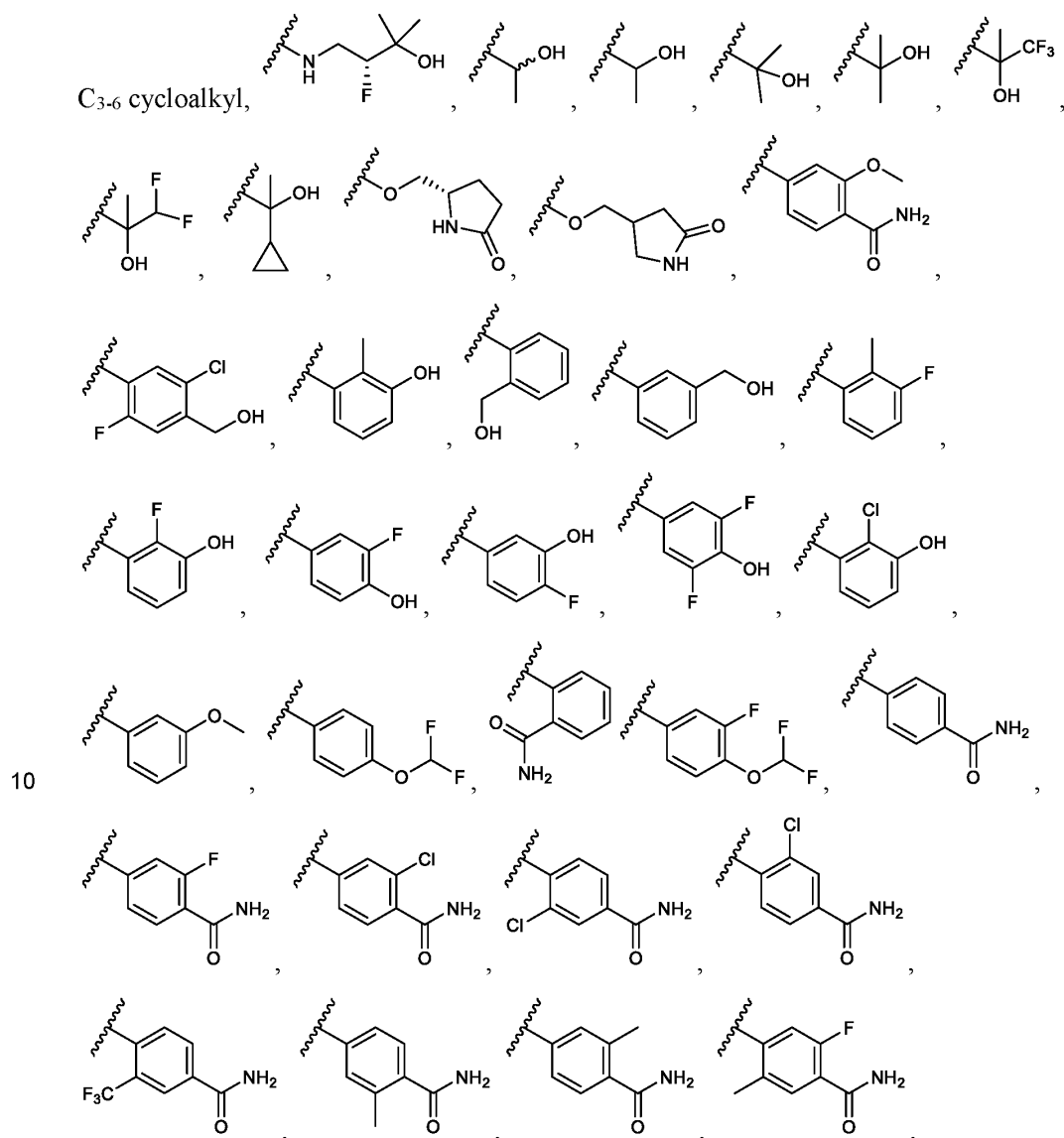


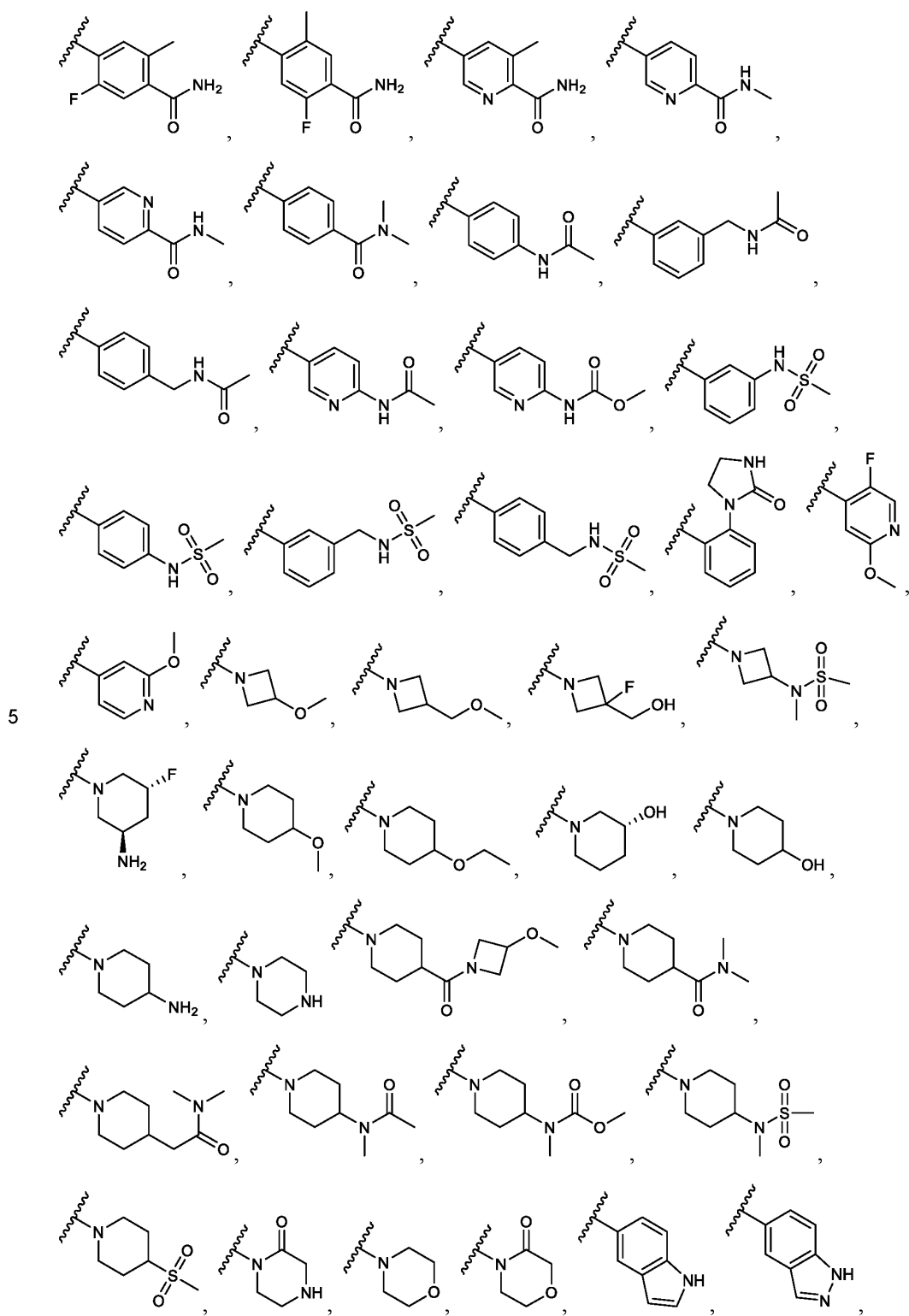


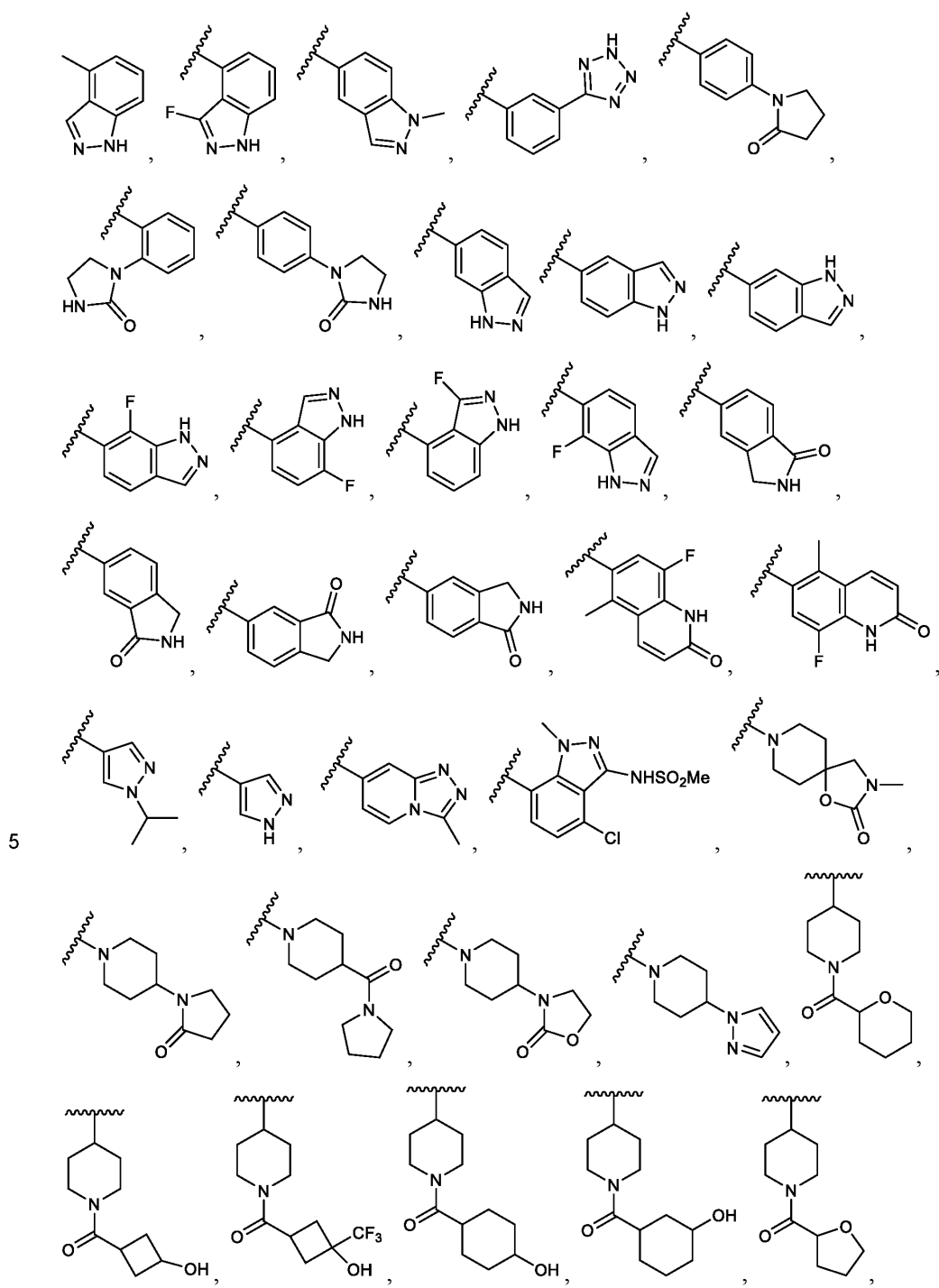


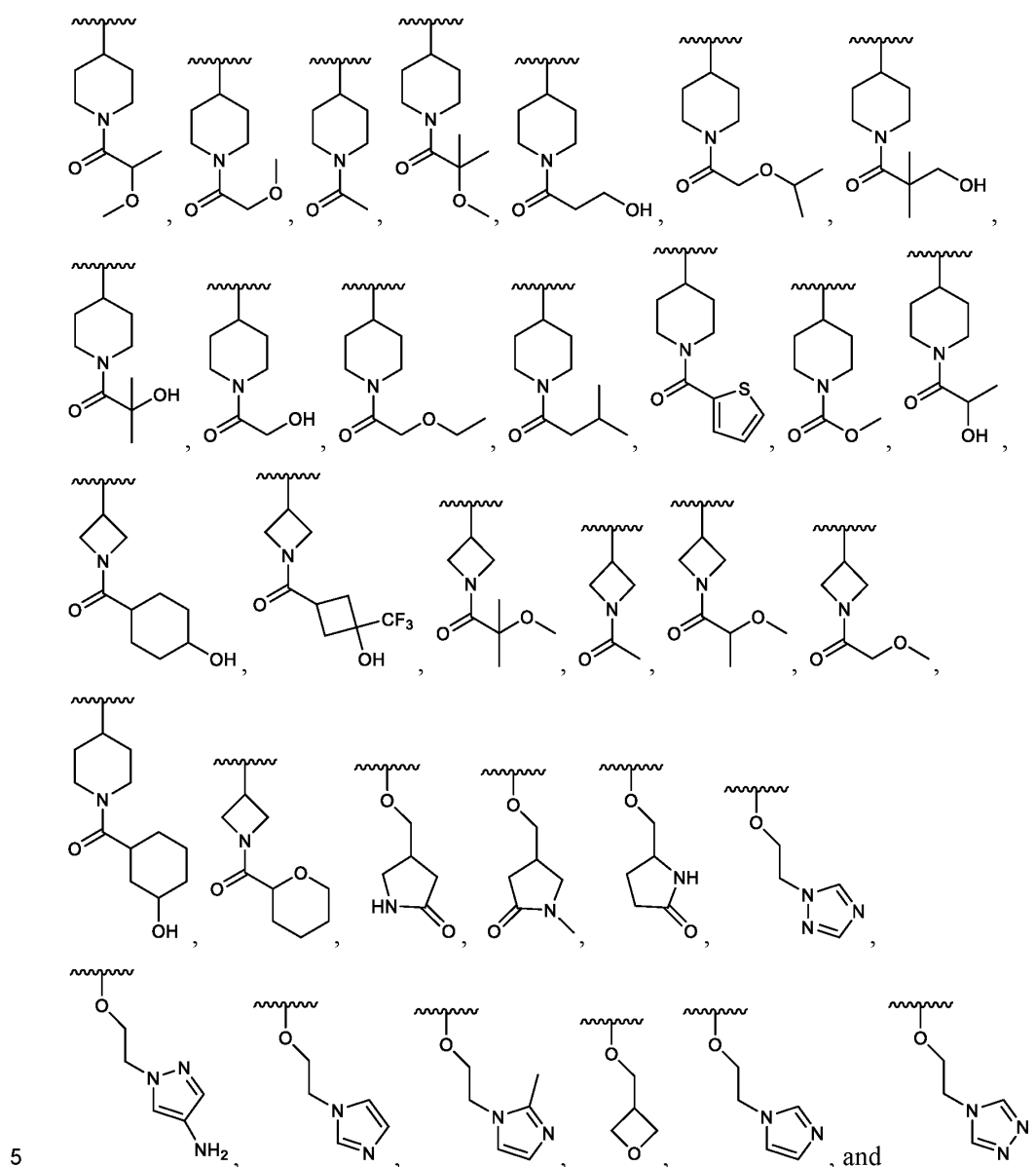
some embodiments, R₄ is R₅, wherein R₅ is selected from F, Cl, -OH, -OCH₃ – OCH₂CH₃, and NH₂. In certain embodiments, R₄ is selected from those functional groups depicted in the examples below.

R₄, alone or together with R₅ and R₆, is preferably selected from H, F, Cl, C₁₋₅ alkyl optionally substituted with one or more substituents selected from F, Cl, and OH,







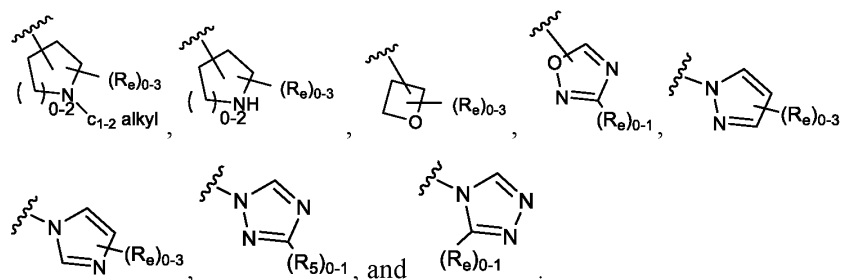


substituted with one or more R_e , aryl optionally substituted with one or more R_e , and heterocyclyl optionally substituted with one or more R_e .

In some embodiments, R_5 is selected from H, F, Cl, CN, C_{1-4} alkyl (optionally substituted with OH, NH_2 , and COOH), SC_{1-4} alkyl, $S(O)_2C_{1-4}$ alkyl, $S(O)_2NH$ -
 5 cyclopropyl, $-(CH_2)_{0-1}NHS(O)_2C_{1-4}$ alkyl, $-NR_aS(O)_2C_{2-4}$ alkenyl, $-(CH_2)_{0-1}OH$, OC_{1-4} alkyl, $-(CH_2)_{0-1}NH_2$, $-(CH_2)_{0-1}NHC(=O)C_{1-4}$ alkyl, $-NR_aC(=O)C_{2-4}$ alkenyl, $-NHC(=O)C_{2-4}$ alkynyl, $-(CH_2)_{0-1}C(=O)OH$, $-C(=O)OC_{1-4}$ alkyl, $-NHC(=O)OC_{1-4}$ alkyl, $-NHC(=O)O(CH_2)_2OC_{1-4}$ alkyl, $-NHC(=O)OCH_2$ -cyclopropyl, $-NHC(=O)NH_2$, $C(=O)NHC_{1-4}$ alkyl, $CONH(CH_2)_{1-2}C(=O)OH$, $-(CH_2)_{0-1}C(=O)NH_2$, $-(CH_2)_{0-1}C(=O)NHC_{1-4}$ alkyl, $C(=O)NH$ -pyridine, $-C(=O)NH(CH_2)_2N(C_{1-4}alkyl)_2$, $-C(=O)NH(CH_2)_2OH$, $-C(=O)NH(CH_2)_2S(O)_2C_{1-4}$ alkyl, and $-OC(=O)C_{1-4}$ alkyl.

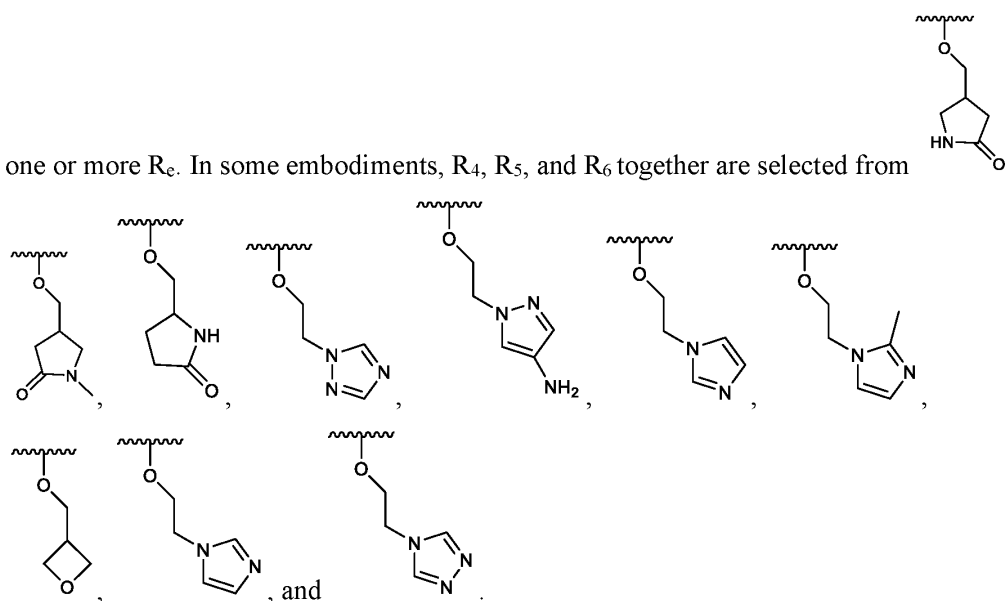
In some embodiments, R_5 is F. In some embodiments, R_5 is C_{1-4} alkyl. In some embodiments, R_5 is $-OH$ or $-OC_{1-3}$ alkyl. In some embodiments, R_5 is $-NHS(O)_2C_{1-4}$ alkyl. In certain embodiments, R_5 is selected from those functional groups depicted in the
 15 examples below.

In some embodiments, R_4 is OC_{1-3} alkyl substituted with one or more R_5 ; R_5 is



As defined above and described herein, R_6 is selected from H and C_{1-3} alkyl
 20 optionally substituted with one or more R_e , $-S(O)_pR_c$, $-C(=O)R_b$, $-(CH_2)_rC(=O)NR_aR_a$, $-C(=O)(CH_2)_rNR_aC(=O)R_b$, $-C(=O)OR_b$, $-S(O)_pNR_aR_a$, aryl optionally substituted with one or more R_e , or heterocyclyl optionally substituted with one or more R_e . In some embodiments, R_6 is H. In some embodiments, R_6 is methyl or isopropyl. In some embodiments, R_6 is $-(CH_2)_2OH$. In certain embodiments, R_6 is selected from those
 25 functional groups depicted in the examples below. R_6 is preferably selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , $-S(O)_pR_c$, $-S(O)_pNR_aR_a$, $-C(=O)R_b$, $-C(=O)OR_b$, $-C(=O)NR_aR_a$, C_{3-6} cycloalkyl optionally substituted with one or more R_e , aryl optionally substituted with one or more R_e , and heterocyclyl optionally substituted with

one or more R_e . In some embodiments, R_4 , R_5 , and R_6 together are selected from



As defined above and described herein, R_7 is selected from H, F, Cl, Br, and

- 5 C_{1-4} alkyl. In some embodiments, R_7 is H. In some embodiments, R_7 is C_{1-3} alkyl. In certain embodiments, R_7 is selected from those functional groups depicted in the examples below. R_7 is preferably selected from H, F, and Cl.

- As defined above and described herein, R_8 is selected from H and C_{1-3} alkyl optionally substituted with one or more substituents selected from F, Cl, and C_{3-6}
- 10 cycloalkyl. In some embodiments, R_8 is hydrogen. In some embodiments, R_8 is C_{1-2} alkyl substituted with C_{3-6} cycloalkyl. In some embodiments, R_8 is methyl. In some embodiments, R_8 is ethyl. In some embodiments, R_8 is cyclopropyl. Preferably, R_8 is $-CH_2$ -cyclopropyl or $-CH_2$ -cyclobutyl. In some embodiments, R_8 is $-CH_2$ -cyclobutyl optionally substituted with methyl and $-OH$. In certain embodiments, R_8 is selected from
- 15 those functional groups depicted in the examples below.

- As defined above and described herein, R_a is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , C_{2-6} alkenyl optionally substituted with one or more R_e , C_{2-6} alkynyl optionally substituted with one or more R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ -heterocyclyl
- 20 optionally substituted with one or more R_e ; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring optionally substituted with one or more R_e .

As defined above and described herein, R_b is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , C_{2-6} alkenyl optionally substituted with one or more R_e , C_{2-6} alkynyl optionally substituted with one or more R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ -heterocyclyl
5 optionally substituted with one or more R_e .

As defined above and described herein, R_c is independently selected from C_{1-6} alkyl optionally substituted with one or more R_e , C_{2-6} alkenyl optionally substituted with one or more R_e , C_{2-6} alkynyl optionally substituted with one or more R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ -heterocyclyl
10 optionally substituted with one or more R_e .

As defined above and described herein, R_d is independently selected from H, and C_{1-6} alkyl optionally substituted with one or more R_e .

As defined above and described herein, R_e is independently selected from F, Cl, Br, CN, NH_2 , $-NH-C_{1-4}$ alkyl, $-N(C_{1-4}$ alkyl) $_2$, $=O$, OH, $-OC_{1-6}$ alkyl, $-CO_2H$, C_{1-6} alkyl
15 optionally substituted with one or more R_f , C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_r-C_{3-6}$ cycloalkyl optionally substituted with one or more R_f , $-(CH_2)_r$ -aryl optionally substituted with one or more R_f , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_f .

As defined above and described herein, R_f is independently selected from F, Cl, Br, CN, OH, C_{1-5} alkyl optionally substituted with OH, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-6} cycloalkyl, and phenyl.
20

As defined above and described herein, p , at each occurrence, is independently selected from zero, 1, and 2.

As defined above and described herein, r is 0-4. In some embodiments, r is 0. In
25 some embodiments, r is 1. In some embodiments, r is 2. In some embodiments, r is 3. In some embodiments, r is 4.

In some embodiments, the compound of Formula (Ia) is selected from examples depicted below. In certain embodiments, the present invention provides any compound described above and herein, or a pharmaceutically acceptable salt thereof or a
30 composition for use in therapy. In some embodiments, the present invention provides any compound described above and herein in isolated form. In some embodiments, the

present invention provides the compounds according to any one of claims presented below.

3. Pharmaceutical Compositions

- 5 In another aspect, the invention provides a composition comprising a compound of this invention or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle. The amount of a compound in the compositions of this invention is such that it is effective to measurably inhibit PAD4 in a biological sample or in a patient.
- 10 In certain embodiments, the amount of compound in compositions of this invention is such that it is effective to measurably inhibit PAD4, in a biological sample or in a patient. In certain embodiments, a composition of this invention is formulated for administration to a patient in need of such composition. In some embodiments, a composition of this invention is formulated for oral administration to a patient.
- 15 The term “subject,” as used herein, is used interchangeably with the term “patient” and means an animal, preferably a mammal. In some embodiments, a subject or patient is a human. In other embodiments, a subject (or patient) is a veterinary subject (or patient). In some embodiments, a veterinary subject (or patient) is a canine, a feline, or an equine subject.
- 20 The term “pharmaceutically acceptable carrier, adjuvant, or vehicle” refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, 25 potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium 30 carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

Compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously. Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents that are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

Pharmaceutically acceptable compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for

oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

Alternatively, pharmaceutically acceptable compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared
5 by mixing the agent with a suitable non-irritating excipient that is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

Pharmaceutically acceptable compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs
10 readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs. Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used. For topical applications, provided
15 pharmaceutically acceptable compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water.

20 Alternatively, provided pharmaceutically acceptable compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

25 For ophthalmic use, provided pharmaceutically acceptable compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutically acceptable compositions may be formulated in an ointment such as
30 petrolatum.

Pharmaceutically acceptable compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to

techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

5 Preferably, pharmaceutically acceptable compositions of this invention are formulated for oral administration. Such formulations may be administered with or without food. In some embodiments, pharmaceutically acceptable compositions of this invention are administered without food. In other embodiments, pharmaceutically acceptable compositions of this invention are administered with food.

10 Pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, as an oral or nasal spray, or the like, as required. In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels of about 0.01 mg/kg
15 to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

 Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain
20 inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and
25 fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

 Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or
30 wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable

vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic
5 acid may also be used in the preparation of injectables.

Injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

10 In order to prolong the effect of a compound of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and
15 crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the
20 rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

Compositions for rectal or vaginal administration are preferably suppositories
25 which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature, and therefore melt in the rectum or vaginal cavity and release the active compound.

Solid dosage forms for oral administration include capsules, tablets, pills,
30 powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or (a) fillers or extenders such as starches, lactose, sucrose,

glucose, mannitol, and silicic acid, (b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, (c) humectants such as glycerol, (d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, 5 (e) solution retarding agents such as paraffin, (f) absorption accelerators such as quaternary ammonium compounds, (g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, (h) absorbents such as kaolin and bentonite clay, and (i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the 10 dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as 15 enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may 20 also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release 25 controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the 30 case of capsules, tablets and pills, the dosage forms may also comprise buffering agents.

Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays,

inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates
5 the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer
10 matrix or gel.

The amount of compounds of the present invention that may be combined with the carrier materials to produce a composition in a single dosage form will vary depending upon the host treated, the particular mode of administration. Preferably, provided compositions should be formulated so that a dosage of between 0.01 - 100 mg/kg body
15 weight/day of the inhibitor can be administered to a patient receiving these compositions.

A compound of the current invention can be administered alone or in combination with one or more other therapeutic compounds, possible combination therapy taking the form of fixed combinations or the administration of a compound of the invention and one or more other therapeutic compounds being staggered or given independently of one
20 another, or the combined administration of fixed combinations and one or more other therapeutic compounds. Exemplary of such other therapeutic agents include corticosteroids, rolipram, calphostin, cytokine-suppressive anti-inflammatory drugs (CSAIDs), Interleukin-10, glucocorticoids, salicylates, nitric oxide, and other immunosuppressants; nuclear translocation inhibitors, such as deoxyspergualin (DSG);
25 non-steroidal antiinflammatory drugs (NSAIDs) such as ibuprofen, celecoxib and rofecoxib; steroids such as prednisone or dexamethasone; antiviral agents such as abacavir; antiproliferative agents such as methotrexate, leflunomide, FK506 (tacrolimus, Prograf); cytotoxic drugs such as azathioprine and cyclophosphamide; TNF- α inhibitors such as tenidap, anti-TNF antibodies or soluble TNF receptor, and rapamycin (sirolimus
30 or Rapamune) or derivatives thereof. A compound of the current invention can besides or in addition be administered especially for tumor therapy in combination with chemotherapy, radiotherapy, immunotherapy, phototherapy, surgical intervention, or a

combination of these. Long-term therapy is equally possible as is adjuvant therapy in the context of other treatment strategies, as described above. Other possible treatments are therapy to maintain the patient's status after tumor regression, or even chemopreventive therapy, for example in patients at risk.

5 Those additional agents may be administered separately from an inventive compound-containing composition, as part of a multiple dosage regimen. Alternatively, those agents may be part of a single dosage form, mixed together with a compound of this invention in a single composition. If administered as part of a multiple dosage regime, the two active agents may be submitted simultaneously, sequentially or within a period of
10 time from one another normally within five hours from one another.

 As used herein, the term “combination,” “combined,” and related terms refer to the simultaneous or sequential administration of therapeutic agents in accordance with this invention. For example, a compound of the present invention may be administered with another therapeutic agent simultaneously or sequentially in separate unit dosage
15 forms or together in a single unit dosage form. Accordingly, the present invention provides a single unit dosage form comprising a compound of the current invention, an additional therapeutic agent, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

 The amount of both an inventive compound and additional therapeutic agent (in
20 those compositions which comprise an additional therapeutic agent as described above) that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Preferably, compositions of this invention should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of an inventive compound can be administered.

25 In those compositions which comprise an additional therapeutic agent, that additional therapeutic agent and the compound of this invention may act synergistically. Therefore, the amount of additional therapeutic agent in such compositions will be less than that required in a monotherapy utilizing only that therapeutic agent.

 The amount of additional therapeutic agent present in the compositions of this
30 invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably, the amount of additional therapeutic agent in the presently disclosed compositions will range

from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease or disorder being treated. The amount of a compound of the present invention in the composition will also depend upon the particular compound in the composition.

10

4. Uses of Compounds

Compounds and compositions described herein are generally useful for the inhibition of PAD4.

The activity of a compound utilized in this invention as an inhibitor of PAD4, may be assayed *in vitro*, *in vivo* or in a cell line. *In vitro* assays include assays that determine the inhibition of PAD4. Detailed conditions for assaying a compound utilized in this invention as an inhibitor of PAD4 are set forth in the Examples below. In some embodiments, a provided compound inhibits PAD4 selectively as compared to PAD2.

As used herein, the terms “treatment,” “treat,” and “treating” refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease or disorder, or one or more symptoms thereof, as described herein. In some embodiments, treatment may be administered after one or more symptoms have developed. In other embodiments, treatment may be administered in the absence of symptoms. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (e.g., in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved, for example to prevent or delay their recurrence.

Provided compounds are inhibitors of PAD4 and are therefore useful for treating one or more diseases or disorders associated with PAD4 enzyme activity. Thus, in certain embodiments, the present invention provides a method for treating a disease or a disorder associated with PAD4 enzyme activity, comprising the step of administering to a patient

in need thereof a compound of the present invention, or a pharmaceutically acceptable composition thereof.

In one embodiment, a disease or a disorder associated with PAD4 enzyme activity is a disease, condition, or disorder mediated by inappropriate PAD4 activity. In some
5 embodiments, a disease or a disorder associated with PAD4 enzyme activity is selected from the group consisting of rheumatoid arthritis, vasculitis, systemic lupus erythematosus, ulcerative colitis, cancer, cystic fibrosis, asthma, cutaneous lupus erythematosus, and psoriasis. In a further embodiment, the disease or a disorder associated with PAD4 enzyme activity is rheumatoid arthritis. In a further embodiment,
10 the disease or a disorder associated with PAD4 enzyme activity is systemic lupus. In a further embodiment, the disease or a disorder associated with PAD4 enzyme activity is vasculitis. In a further embodiment, the disease or a disorder associated with PAD4 enzyme activity cutaneous lupus erythematosus. In a further embodiment, the disease or a disorder associated with PAD4 enzyme activity is psoriasis.

15 In one embodiment there is provided a method of treatment of rheumatoid arthritis, vasculitis, systemic lupus erythematosus, ulcerative colitis, cancer, cystic fibrosis, asthma, cutaneous lupus erythematosus, or psoriasis, which method comprises administering to a human subject in need thereof, a therapeutically effective amount of a provided compound or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a
20 pharmaceutically acceptable salt thereof.

In one embodiment there is provided a method of treatment of rheumatoid arthritis, which method comprises administering to a human subject in need thereof, a therapeutically effective amount of a provided compound, a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof. In one
25 embodiment there is provided a method of treatment of systemic lupus, which method comprises administering to a human subject in need thereof, a therapeutically effective amount of a provided compound, a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof. In one embodiment there is provided a method of treatment of vasculitis, which method comprises administering to a
30 human subject in need thereof, a therapeutically effective amount of a provided compound, a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof. In one embodiment there is provided a method

of treatment of cutaneous lupus erythematosus, which method comprises administering to a human subject in need thereof, a therapeutically effective amount of a provided compound, a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof. In one embodiment there is provided a method
 5 of treatment of psoriasis, which method comprises administering to a human subject in need thereof, a therapeutically effective amount of a provided compound, a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof.

In some embodiments, a disease or a disorder associated with PAD4 enzyme activity is selected from the group consisting of acid-induced lung injury, acne (PAPA),
 10 acute lymphocytic leukemia, acute respiratory distress syndrome, Addison's disease, adrenal hyperplasia, adrenocortical insufficiency, ageing, AIDS, alcoholic hepatitis, alcoholic liver disease, allergen induced asthma, allergic bronchopulmonary, aspergillosis, allergic conjunctivitis, alopecia, Alzheimer's disease, amyloidosis, amyotrophic lateral sclerosis, weight loss, angina pectoris, angioedema, anhidrotic
 15 ecodermal dysplasia-ID, ankylosing spondylitis, anterior segment, inflammation, antiphospholipid syndrome, aphthous stomatitis, appendicitis, arthritis, asthma, atherosclerosis, atopic dermatitis, autoimmune diseases, autoimmune hepatitis, bee sting-induced inflammation, Bechet's disease, Bechet's syndrome, Bells Palsey, berylliosis, Blau syndrome, bone pain, bronchiolitis, burns, bursitis, cancer, cardiac hypertrophy,
 20 carpal tunnel syndrome, catabolic disorders, cataracts, cerebral aneurysm, chemical irritant-induced inflammation, chorioretinitis, chronic heart failure, chronic lung disease of prematurity, chronic lymphocytic leukemia, chronic obstructive pulmonary disease, colitis, complex regional pain syndrome, connective tissue disease, corneal ulcer, crohn's disease, cryopyrin-associated periodic syndromes, cryptococcosis, cystic fibrosis,
 25 deficiency of the interleukin-1-receptor antagonist (DIRA), dermatitis, dermatitis endotoxemia, dermatomyositis, diffuse intrinsic pontine glioma, endometriosis, endotoxemia, epicondylitis, erythroblastopenia, familial amyloidotic polyneuropathy, familial cold urticarial, familial Mediterranean fever, fetal growth retardation, glaucoma, glomerular disease, glomerular nephritis, gout, gouty arthritis, graft-versus-host disease,
 30 gut diseases, head injury, headache, hearing loss, heart disease, hemolytic anemia, Henoch-Scholein purpura, hepatitis, hereditary periodic fever syndrome, herpes zoster and simplex, HIV-1, Hodgkin's disease, Huntington's disease, hyaline membrane disease,

hyperammonemia, hypercalcemia, hypercholesterolemia, hyperimmunoglobulinemia D with recurrent fever (HIDS), hypoplastic and other anemias, hypoplastic anemia, idiopathic thrombocytopenic purpura, incontinentia pigmenti, infectious mononucleosis, inflammatory bowel disease, inflammatory lung disease, inflammatory neuropathy,

5 inflammatory pain, insect bite-induced inflammation, iritis, irritant-induced inflammation, ischemia/reperfusion, juvenile rheumatoid arthritis, keratitis, kidney disease, kidney injury caused by parasitic infections, kidney injury caused by parasitic infections, kidney transplant rejection prophylaxis, leptospirosis, leukemia, Loeffler's syndrome, lung injury, lupus, lupus nephritis, lymphoma, meningitis, mesothelioma, mixed connective

10 tissue disease, Muckle-Wells syndrome (urticaria deafness amyloidosis), multiple sclerosis, muscle wasting, muscular dystrophy, myasthenia gravis, myocarditis, mycosis fungoides, myelodysplastic syndrome, myositis, nasal sinusitis, necrotizing enterocolitis, neonatal onset multisystem inflammatory disease (NOMID), nephrotic syndrome, neuritis, neuropathological diseases, non-allergen induced asthma, obesity, ocular allergy,

15 optic neuritis, organ transplant, osteoarthritis, otitis media, Paget's disease, pain, pancreatitis, Parkinson's disease, pemphigus, pericarditis, periodic fever, periodontitis, peritoneal endometriosis, pertussis, pharyngitis and adenitis (PFAPA syndrome), plant irritant-induced inflammation, pneumonia, pneumonitis, pneumocystis infection, poison ivy/ urushiol oil-induced inflammation, polyarteritis nodosa, polychondritis, polycystic

20 kidney disease, polymyositis, psoriasis, psychosocial stress diseases, pulmonary disease, pulmonary hypertension, pulmonary fibrosis, pyoderma gangrenosum, pyogenic sterile arthritis, renal disease, retinal disease, rheumatic carditis, rheumatic disease, rheumatoid arthritis, sarcoidosis, seborrhea, sepsis, severe pain, sickle cell, sickle cell anemia, silica-induced disease, Sjogren's syndrome, skin diseases, sleep apnea, solid tumors, spinal cord

25 injury, Stevens-Johnson syndrome, stroke, subarachnoid hemorrhage, sunburn, temporal arteritis, tenosynovitis, thrombocytopenia, thyroiditis, tissue transplant, TNF receptor associated periodic syndrome (TRAPS), toxoplasmosis, transplant, traumatic brain injury, tuberculosis, type 1 diabetes, type 2 diabetes, ulcerative colitis, urticarial, uveitis, Wegener's granulomatosis, interstitial lung disease, psoriatic arthritis, juvenile idiopathic

30 arthritis, Sjögren's syndrome, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, antiphospholipid antibody syndrome, sepsis, deep vein thrombosis, fibrosis, Alzheimer's, scleroderma and CREST syndrome.

In one embodiment, the invention provides a compound, or a pharmaceutically acceptable salt thereof, for use in therapy. In another embodiment, the invention provides a compound, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease or a disorder mediated by inappropriate PAD4 activity. In another embodiment, the invention provides a compound, or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof, for use in the treatment of rheumatoid arthritis, vasculitis, systemic lupus erythematosus, ulcerative colitis, cancer, cystic fibrosis, asthma, cutaneous lupus erythematosus, or psoriasis. In another embodiment, the invention provides a compound, or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof, for use in the treatment of rheumatoid arthritis. In another embodiment, the invention provides a compound, or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof, for use in the treatment of systemic lupus. In another embodiment, the invention provides a compound, or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof, for use in the treatment of vasculitis. In another embodiment, the invention provides a compound, or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof, for use in the treatment of cutaneous lupus erythematosus. In another embodiment, the invention provides a compound, or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof, for use in the treatment of psoriasis. In another embodiment, the invention provides the use of a compound, or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of a disorder mediated by inappropriate PAD4 activity. In another embodiment, the invention provides the use of a compound, or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of rheumatoid arthritis, vasculitis, systemic lupus erythematosus, ulcerative colitis, cancer, cystic fibrosis, asthma, cutaneous lupus erythematosus, or psoriasis. In another embodiment, the invention provides the use of a compound, or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of rheumatoid arthritis. In another

embodiment, the invention provides the use of a compound, or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of systemic lupus. In another embodiment, the invention provides the use of a compound, or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of vasculitis. In another embodiment, the invention provides the use of a compound, or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of cutaneous lupus erythematosus. In another embodiment, the invention provides the use of a compound, or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of psoriasis. In a further embodiment, the invention provides a pharmaceutical composition for the treatment or prophylaxis of a disease or a disorder mediated by inappropriate PAD4 activity comprising a provided compound, or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof. In a further embodiment, the invention provides a pharmaceutical composition for the treatment or prophylaxis of rheumatoid arthritis, vasculitis, systemic lupus erythematosus, ulcerative colitis, cancer, cystic fibrosis, asthma, cutaneous lupus erythematosus, or psoriasis, comprising a provided compound, or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof. In a further embodiment, the invention provides a pharmaceutical composition for the treatment or prophylaxis of rheumatoid arthritis comprising a provided compound, or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof. In a further embodiment, the invention provides a pharmaceutical composition for the treatment or prophylaxis of systemic lupus comprising a provided compound, or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof. In a further embodiment, the invention provides a pharmaceutical composition for the treatment or prophylaxis of vasculitis comprising a provided compound, or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof. In a further embodiment, the invention provides a pharmaceutical composition for the treatment or prophylaxis of cutaneous lupus erythematosus

comprising a provided compound, or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof. In a further embodiment, the invention provides a pharmaceutical composition for the treatment or prophylaxis of psoriasis comprising a provided compound, or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof.

All features of each of the aspects of the invention apply to all other aspects *mutatis mutandis*. In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

5. Examples

The following Examples have been prepared, isolated and characterized using the methods disclosed herein. The following examples demonstrate a partial scope of the invention and are not meant to be limiting of the scope of the invention.

Details of various HPLC/LC-MS methods used in the analysis of compounds and intermediates is provided below.

Method A: SUNFIRE C18 (4.6×150) mm, 3.5 µm column; flow rate 1 ml/min; gradient time 15 min; 10-100% solvent B; monitoring at 254 nm and 220 nm (solvent A: 5% acetonitrile (ACN), 95% water, 0.05% trifluoroacetic acid (TFA); solvent B: 95% ACN, 5% water, 0.05% TFA).

Method B: X-Bridge Phenyl (4.6×150) mm, 3.5 µm column; flow rate 1 ml/min; gradient time 15 min; 10-100% solvent B; monitoring at 254 nm and 220 nm (solvent A: 5% ACN, 95% water, 0.05% TFA; solvent B: 95% ACN, 5% water, 0.05% TFA).

Method C: Kinetex EVO C18 (4.6×100) mm, 2.6 µm, buffer: 0.05% TFA in water, mobile phase C: buffer: ACN (95:5), mobile phase D: ACN: buffer (95:5).

Method D: Kinetex Biphenyl (4.6×100) mm, 2.6 µm, buffer: 0.05% TFA in water, mobile phase C: buffer: ACN (95:5), mobile phase D: ACN: buffer (95:5).

Method E: XBridge BEH XP C18 (50×2.1) mm, 2.5µm, Time (min): 0-3% B: 0-100 buffer A: 95% water: 5% ACN; 10 mM ammonium acetate (NH₄OAc) B: 5% water: 95% ACN; 10 mM NH₄OAc, flow: 1.1 ml/min, temperature: 50°C.

Method F: XBridge BEH XP C18 (50×2.1) mm, 2.5µm, time (min): 0-3%, B: 0-100, A: 95% water: 5% ACN; 0.1% TFA, B: 5% water: 95% ACN; 0.1%TFA, flow: 1.1 ml/min, temperature: 50°C.

Method G: ACQUITY UPLC® BEH C18 (3×50) mm, 1.7µm, buffer: 10 mM NH₄OAc, mobile phase A: buffer: ACN (95:5), mobile phase B: buffer: ACN (5:95), flow:0.7ml/min, method: 0 min-20% B, 20% to 100% B 2 min, 2 to 2.3min-100%.

Method H: Kinetex XB C18 (75×3) mm, 2.6µm, mobile phase A: 10 mM NH₄OAc in water, water: ACN (98:02), mobile phase B: 10 mM NH₄OAc in water: ACN (02:98), gradient: 20-100%B over 4 min, flow: 1.0ml/min.

Method I: ACQUITY UPLC® BEH C18 (3×50) mm, 1.7µm, buffer: 0.05% TFA in water, mobile phase A: buffer: ACN (95:5), mobile phase B: ACN: buffer (95:5).

Method J: Column: HALO C18, 3x30 mm, 2.7 µm; Mobile Phase A: water+0.05%TFA, Mobile Phase B: acetonitrile+0.05%TFA; Flow rate: 1.5 mL/min; Gradient: 5% B to 95% B in 2.5 min, hold at 95% for 1 min, 95% B to 5% B in 0.05 min; Detection: MS and UV (254 nm).

Method K: Column: Shim-pack XR-ODS, 3×50 mm, 2.2 µm; Mobile Phase A: water/0.05%TFA, Mobile Phase B: acetonitrile/0.05%TFA; Flow Rate: 1.2000 mL/min; Gradient: 5% B to 95% B in 3.3 min, hold at 95% for 0.7 min, 95% B to 5% B in 0.1 min; Detection: MS and UV (254 nm).

20

General procedure for purification using Reverse Phase HPLC (RP-HPLC) is as follows. Typically, the sample to be purified was dissolved in DCM:MeOH (2:1), 20% by weight of poly(4-vinylpyridine) (Aldrich # 226963) was added to this solution, and the container containing the solution was placed on a shaker for 2 hours. Thereafter, the contents were filtered through a 25 mm syringe filter fitted with a 0.45 µm nylon membrane (VWR # 28145-489) into a clean vial, and dried using centrifugal evaporation to afford the purified sample.

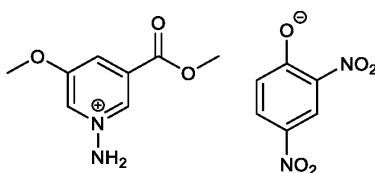
25

General synthetic procedures:

30

Intermediate 1

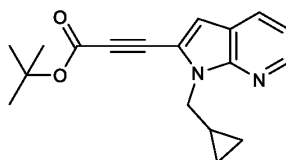
1-Amino-3-methoxy-5-(methoxycarbonyl)pyridin-1-ium 2,4-dinitrophenolate



O-(2,4-dinitrophenyl)hydroxylamine (10.01 g, 50.3 mmol) was added to a stirred solution of methyl 5-methoxynicotinate (7 g, 41.9 mmol) in tetrahydrofuran (THF, 50 ml) and water (50 ml). The reaction mixture was heated to 40°C, stirred for 12 hours, and
 5 filtered to afford 1-amino-3-methoxy-5-(methoxycarbonyl)pyridin-1-ium (10 g, 130%) as yellowish brown solid, which was used in the next step without further purification. Liquid chromatography–mass spectrometry (LC-MS) m/z: 183.1 [M+H]⁺.

Intermediate 2

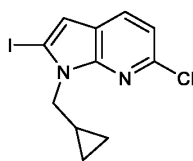
10 tert-Butyl-3-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)propiolate



tert-Butyl propiolate (0.605 g, 4.80 mmol) and bis(triphenylphosphine)palladium(II) dichloride (0.153 g, 0.218 mmol) were added to a stirred solution of 1-(cyclopropylmethyl)-2-iodo-1H-pyrrolo[2,3-b]pyridine (1.3 g, 4.36
 15 mmol) in a mixture of triethylamine (TEA, 5 ml) and THF (5 ml). The reaction mixture was heated to 65°C, stirred for 1 hour, and filtered through a celite bed. The filtrate was concentrated under reduced pressure to obtain a crude product, which was purified using a silica gel column (40 g, Redisep[®] SiO₂ column, eluting with 20% ethyl acetate (EtOAc) in hexane) to afford the title compound (1.2 g, 93%) as a brown liquid. LC-MS m/z:
 20 297.1 [M+H]⁺. ¹H NMR (300 MHz, chloroform-*d*) δ ppm: 8.55-8.38 (m, 1H), 7.99-7.87 (m, 1H), 7.26-6.99 (m, 1H), 7.04-6.99 (m, 1H), 4.43-4.06 (m, 2H), 3.26-3.16 (m, 1H), 1.65-1.38 (m, 10H), 1.34-1.07 (m, 1H), 0.59-0.39 (m, 4H).

Intermediate 3

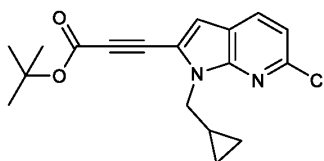
25 6-Chloro-1-(cyclopropylmethyl)-2-iodo-1H-pyrrolo[2,3-b]pyridine



- Sodium hydride (2.87 g, 71.8 mmol) was added to a stirred solution of 6-chloro-2-iodo-1H-pyrrolo[2,3-b]pyridine (10 g, 35.9 mmol) in dimethylformamide (DMF, 200 ml) at 0°C and the reaction mixture was stirred for 0.5 hours, followed by addition of
- 5 (bromomethyl)cyclopropane (4.50 ml, 46.7 mmol). The reaction mixture was stirred for 1 hour, poured into ice water (200 ml), and extracted with ethyl acetate (3×200 ml). The combined organic fractions were washed with water (2×300 ml) and brine (2×200 ml), dried over sodium sulfate (Na₂SO₄), filtered, and concentrated to obtain a crude product, which was purified using a silica gel column (80 g, Redisep[®] Silica column, 0-50%
- 10 EtOAc in hexane as an eluent) to afford the title compound (8 g, 67%) as yellow solid. LC-MS m/z: 332.9 [M+H]⁺. ¹H NMR (400 MHz, chloroform-*d*) δ ppm: 7.75 (d, J=8.1 Hz, 1H), 7.04 (d, J=8.3 Hz, 1H), 6.79 (s, 1H), 1.46-1.26 (m, 1H), 0.61-0.44 (m, 4H).

Intermediate 4

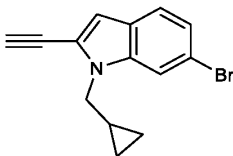
- 15 tert-Butyl 3-(6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)propiolate



- tert-Butyl propiolate (1.669 g, 13.23 mmol) and bis(triphenylphosphine)palladium(II) dichloride (0.422 g, 0.601 mmol) were added to a stirred solution of 6-chloro-1-(cyclopropyl-methyl)-2-iodo-1H-pyrrolo[2,3-b]pyridine
- 20 (Intermediate 3, 4 g, 12.03 mmol) in a mixture of TEA (10 ml) and THF (10 ml). The reaction mixture was stirred at 50°C for 1 hour, and filtered through a celite bed. The filtrate was concentrated under reduced pressure to obtain a crude compound, which was purified using a silica gel column (40 g, Redisep[®] SiO₂ column, eluting with 20% EtOAc in hexane) to afford the title compound (2.5 g, 63%) as yellow liquid. LC-MS m/z: 331.1
- 25 [M+H]⁺.

Intermediate 5

6-Bromo-1-(cyclopropylmethyl)-2-ethynyl-1H-indole

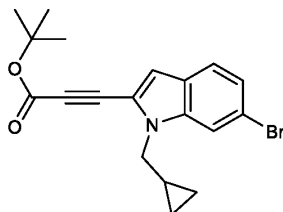


Potassium carbonate (K_2CO_3 , 11.18 g, 81 mmol) was added to a stirred solution of dimethyl (1-diazo-2-oxopropyl)phosphonate (51.8 g, 27.0 mmol, 10% solution in
 5 acetonitrile) in methanol (MeOH, 50 ml), followed by the addition of 6-bromo-1-(cyclopropylmethyl)-1H-indole-2-carbaldehyde (7.5g, 27.0 mmol) at 0°C. The reaction mixture was allowed to warm to a room temperature, stirred for 6 hours, and concentrated under vacuum to afford a crude residue, which was diluted with water and extracted with EtOAc (2×100 ml). The combined organic layers were dried over Na_2SO_4 , filtered, and
 10 the filtrate was concentrated under reduced pressure to obtain a crude product, which was purified using a silica gel column (40 g, Redisep[®] SiO_2 column, eluting with 0-5% EtOAc in hexane) to afford the title compound (6.3g, 85%) as a brown liquid. LC-MS m/z: 276.1 $[M+2H]^+$.

15

Intermediate 6

tert-Butyl-3-(6-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)propiolate



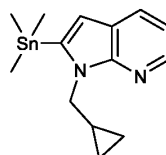
Lithium diisopropylamide (LDA, 17.23 ml, 34.5 mmol) was added to a stirred solution of 6-bromo-1-(cyclopropylmethyl)-2-ethynyl-1H-indole (Intermediate 5, 6.3g, 22.98 mmol) in THF (10 ml) at 0°C, and the reaction mixture was stirred for 30 min,
 20 followed by the addition of Boc_2O (5.34 ml, 22.98 mmol) slowly. The reaction mixture was stirred for 1 hour, quenched with water, and extracted with EtOAc (2×100 ml). The combined organic layers were washed with water (2×300 ml) and brine (2×200 ml), dried over Na_2SO_4 , filtered, and the filtrate was concentrated under reduced pressure. The crude
 25 product obtained was purified using a silica gel column (80 g, Redisep[®] Silica column, 0-5% EtOAc in hexane as an eluent) to afford the title compound (6.2 g, 72%). LC-MS m/z:

318.0 [M-isobutene+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 7.94 (s, 1H), 7.58 (d, J=8.5 Hz, 1H), 7.26 (dd, J=1.5, 8.5 Hz, 1H), 7.21 (s, 1H), 4.17 (d, J=7.0 Hz, 2H), 1.51 (s, 9H), 1.27-1.18 (m, 1H), 0.52-0.40 (m, 4H).

5

Intermediate 7

1-(Cyclopropylmethyl)-2-(trimethylstannyl)-1H-pyrrolo[2,3-*b*]pyridine

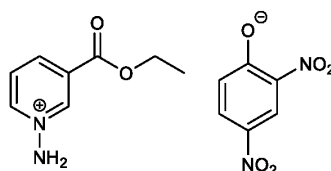


Hexamethylditin (0.278 ml, 1.342 mmol) was added to a stirred solution of 1-(cyclopropyl -methyl)-2-iodo-1*H*-pyrrolo[2,3-*b*]pyridine (0.2 g, 0.671 mmol) in 1,4-dioxane (1.5 ml), and the reaction mixture was degassed with argon for 5 min, followed by the addition of [1,1'-bis(di-*tert*-butylphosphino)-ferrocene]-dichloropalladium(II) (0.031 g, 0.047 mmol). The reaction mixture was stirred at 70°C for 2 hours, filtered through a celite bed, and the filtrate was concentrated to afford a crude product (250 mg), which was used in the next steps without further purification. LC-MS *m/z*: 337 [M+H]⁺.

15

Intermediate 8

1-Amino-3-(ethoxycarbonyl)pyridin-1-ium 2,4-dinitrophenolate

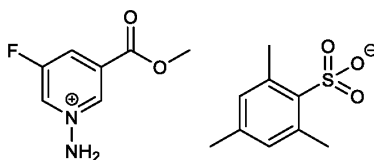


Intermediate 8 was prepared following a procedure similar to the preparation of Intermediate 1 (10 g, 28.5mmol, 100%). LC-MS *m/z*: 168 [M+H]⁺.

20

Intermediate 9

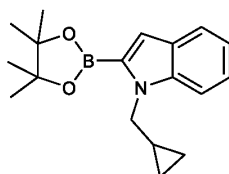
1-Amino-3-fluoro-5-(methoxycarbonyl)pyridin-1-ium 2,4,6-trimethylbenzenesulfonate



O-(mesitylsulfonyl)hydroxylamine (8.33 g, 38.7 mmol) was added to a stirred solution of methyl 5-fluoronicotinate (5 g, 32.2 mmol) in dichloromethane (DCM, 20 ml) at 0°C. The reaction mixture was stirred for 2 hours, and concentrated to afford 1-amino-3-fluoro-5-(methoxycarbonyl)pyridin-1-ium (5 g, 91%) as a brown solid, which was used in the next step without further purification. LC-MS m/z: 171.0 [M+H]⁺.

Intermediate 10

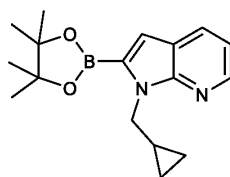
1-(Cyclopropylmethyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole



sec-Butyllithium (16.68 ml, 23.36 mmol) was added drop wise to a stirred solution of 1-(cyclopropylmethyl)-1H-indole (2 g, 11.68 mmol) in THF (20 ml) under argon atmosphere at -78°C. The reaction mixture was stirred further for 30 min, followed by the addition of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.173 g, 11.68 mmol). The reaction mixture was stirred at a room temperature for 2 hours, quenched with drop wise addition of water (50 ml), and extracted with EtOAc (2×50 ml). The combined organic extracts were washed with water (100 ml) and brine (100 ml), dried over Na₂SO₄, filtered, and the filtrate was evaporated to dryness under reduced pressure. The crude product thus obtained was purified using a silica gel column column (EtOAc in hexane), and the purified product was isolated at 15% EtOAc in hexane. Required fractions were collected and volatiles were evaporated to dryness under reduced pressure to afford the title compound (2 g, 58%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 0.32-0.44 (m, 4 H), 1.16-1.34 (m, 13 H), 4.32 (d, J=6.85 Hz, 2 H), 6.94-7.05 (m, 2 H), 7.16-7.25 (m, 1 H), 7.51-7.60 (m, 2 H).

Intermediate 11

1-(Cyclopropylmethyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine

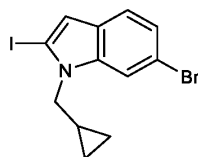


Intermediate 11 was prepared following a procedure similar to the preparation of Intermediate 10 (1.3 g, 31%). LC-MS (ESI) m/z : 300.3 $[M+H]^+$.

5

Intermediate 12

6-Bromo-1-(cyclopropylmethyl)-2-iodo-1H-indole



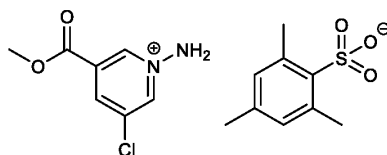
Sodium hydride (NaH, 1.372 g, 34.3 mmol) was added lot wise to a stirred solution of 6-bromo-2-iodo-1H-indole (5.52 g, 17.15 mmol, Ref: *Bioorg. Med. Chem.* 22(5), **2014**, 1708) in DMF (20 ml) at 0°C, and the reaction mixture was stirred for 10 minutes followed by drop wise the addition of (bromomethyl)-cyclopropane (2.498 ml, 25.7 mmol). The reaction mixture was stirred at a room temperature for 16 hours, diluted with cold water (50 ml), and extracted with EtOAc (3×50 ml). The combined organic layers were dried over anhydrous sodium sulphate, filtered, and the filtrate was

15 evaporated under reduced pressure. The crude product thus obtained was purified using a silica gel column (24g, Redisep® SiO₂ column, eluting with 10% EtOAc in n-hexane) to afford the title compound (5g, 78%). LC-MS m/z : 377 $[M+H]^+$. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 7.83 (s, 1H), 7.43 (d, J =8.3 Hz, 1H), 7.14 (dd, J =1.8, 8.5 Hz, 1H), 6.82 (s, 1H), 4.13 (d, J =6.8 Hz, 2H), 1.31-1.13 (m, 1H), 0.51-0.41 (m, 4H).

20

Intermediate 13

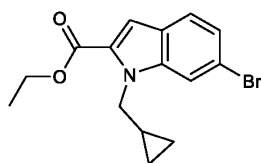
1-Amino-3-chloro-5-(methoxycarbonyl)pyridin-1-ium-2,4,6-trimethylbenzenesulfonate



O-(mesitylsulfonyl)hydroxylamine (2.6 g, 11.66 mmol) was added to a stirred solution of methyl 5-chloronicotinate (2 g, 11.66 mmol) in DCM (40 ml) at 0°C. The reaction mixture was stirred at a room temperature for 2 hours, and evaporated under reduced pressure to afford crude 1-amino-3-chloro-5-(methoxycarbonyl)pyridin-1-ium (2.1 g, 96%) as a white solid, which was used in the next step without further purification. LC-MS m/z: 187.2 [M+H]⁺.

Intermediate 14

Ethyl 6-bromo-1-(cyclopropylmethyl)-1H-indole-2-carboxylate



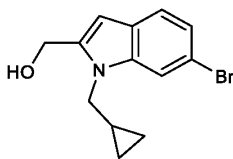
10

Potassium carbonate (10.3 g, 74.6 mmol) was added to a stirred solution of ethyl 6-bromo-1H-indole-2-carboxylate (10g, 37.3 mmol) in DMF (60 ml), followed by the addition of (bromomethyl)cyclopropane (5.0 g, 37.3 mmol). The reaction mixture was stirred for 16 hours, and potassium carbonate (5 g) and (bromomethyl)cyclopropane (2.5 g) were added. The resulting reaction mixture was heated to 50°C for 2 hours, diluted with water (150 ml), and extracted with ethyl acetate (3×150 ml). The combined organic layers were concentrated in vacuo to afford ethyl 6-bromo-1-(cyclopropylmethyl)-1H-indole-2-carboxylate (10 g, 83%) as a brown solid, which was used further without purification. LC-MS m/z: 322.0 [M+H]⁺.

20

Intermediate 15

(6-Bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)methanol



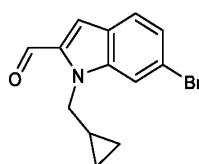
LiBH₄ (15.52 ml, 62.1 mmol, 4 M in THF) was added to a stirred solution of Intermediate 14 (10g, 31 mmol) in THF (50 ml) at 0°C. The reaction mixture was allowed to warm to a room temperature over 1 hour, stirred for 16 hours, cooled to 0°C and additional amount of LiBH₄ (15.52 ml, 62.1 mmol, 4 M in THF) was added dropwise.

25

The reaction mixture was stirred for 6 hours at a room temperature, cooled to 0°C, quenched by slow addition of saturated ammonium chloride solution (need to add carefully, sudden evolution of gas was noticed), stirred for ~ 45 minutes, and extracted with ethyl acetate (4×100 ml). The organic layers were separated, dried over Na₂SO₄,
5 filtered and concentrated to obtain a crude product, which was further purified using a silica gel column (0-30% ethyl acetate / petether) to afford 6-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)methanol (8.5g, 98%). LC-MS m/z: 280.1 [M+H]⁺.

Intermediate 16

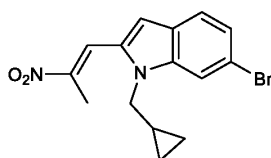
10 6-Bromo-1-(cyclopropylmethyl)-1H-indole-2-carbaldehyde



Manganese dioxide (10.3 g, 119 mmol) was added to a stirred solution of Intermediate 15 (8.3g, 29.6 mmol) in THF (50 ml). The reaction mixture was stirred at 45°C for 2 hours, and filtered through a celite bed. The filtrate was concentrated in vacuo
15 to obtain 6-bromo-1-(cyclopropylmethyl)-1H-indole-2-carbaldehyde (7.6g, 92%) as a brown syrup, which was used further without purification. LC-MS m/z: 278.1 [M+H]⁺.

Intermediate 17

(E)-6-Bromo-1-(cyclopropylmethyl)-2-(2-nitroprop-1-en-1-yl)-1H-indole

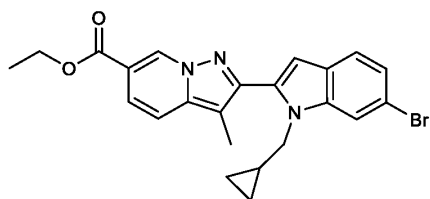


20 Ammonium acetate (122 mg, 1.582 mmol) was added to a stirred solution of Intermediate 16 (400 mg, 1.438 mmol) in nitroethane (2 ml, 28.0 mmol). The reaction mixture was stirred at 90°C for 2 hours, diluted with water (5ml), and extracted with ethyl acetate (2×10 ml). The combined organic layers were washed with brine, dried over
25 sodium sulfate, filtered, and concentrated in vacuum to afford (E)-6-bromo-1-(cyclopropylmethyl)-2-(2-nitroprop-1-en-1-yl)-1H-indole as yellow liquid (420 mg),

which was used in the next step without purification. LC-MS retention time: 1.26 min., $m/z = 335.1$ $[M+H]^+$

Intermediate 18

- 5 Ethyl 2-(6-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate

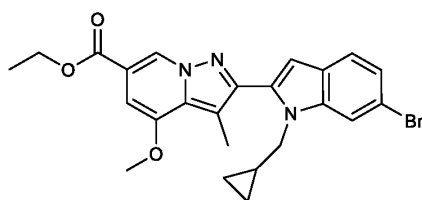


- Intermediate 8 (75 mg, 0.447 mmol) and copper (I) iodide (6 mg, 0.03 mmol) were added to a stirred solution of Intermediate 17 (50 mg, 0.149 mmol) in DMF (1 ml).
 10 The reaction mixture was stirred at 80°C for 30 hours, concentrated to remove DMF, and water (10 ml) was added, and the contents were extracted with ethyl acetate (3×50 ml). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuum to obtain a crude product, which was purified using a silica gel column (0-5% methanol in dichloromethane) to afford ethyl 2-(6-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate (20
 15 mg, 30%). LC-MS (ES): $m/z = 452.1$ $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ ppm: 9.19 (s, 1H), 7.90 (s, 1H), 7.83 (d, $J=9.5$ Hz, 1H), 7.62-7.58 (m, 2H), 7.24-7.20 (m, 1H), 6.91 (s, 1H), 4.50 (d, $J=7.0$ Hz, 2H), 4.36 (q, $J=7.0$ Hz, 2H), 2.42 (s, 3H), 1.36 (t, $J=7.0$ Hz, 3H), 1.11 (m, 1H), 0.32-0.26 (m, 2H), 0.18-0.13 (m, 2H).

20

Intermediate 19

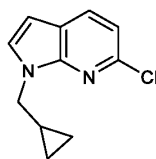
- Ethyl 2-(6-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate



Intermediate 19 was prepared following a procedure similar to the preparation of Intermediate 18 using appropriate reactants. LC-MS retention time: 1.76 min, m/z: 468.2 [M+H] (Method G). ¹H NMR (400 MHz, chloroform-*d*) δ ppm: 8.91 (s, 1H), 8.50 (s, 1H), 7.80 (dd, J=3.01, 1.51 Hz, 1H), 7.43-7.60 (m, 1H), 6.85-6.91 (m, 1H), 6.75 (s, 1H), 4.37 (d, J = 6.5 Hz, 2H), 4.02 (s, 3H), 3.93 (s, 3H), 2.56-2.62 (m, 3H), 1.15-1.34 (m, 1H), 0.33-0.46 (m, 2H), 0.13-0.18 (m, 2H).

Intermediate 20

6-Chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridine



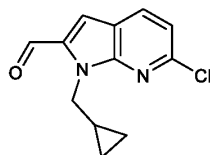
10

Sodium hydride in mineral oil (60% w/w, 1.31 g, 32.8 mmol) was added portion wise to a stirred solution of 6-chloro-1H-pyrrolo[2,3-b]pyridine (5g, 32.8 mmol) in DMF (25 ml) at 0°C, the reaction mixture was stirred for 15 minutes, followed by the slow addition of (bromomethyl)cyclopropane (4.42 g, 32.8 mmol) over 5 minutes. The reaction mixture was allowed to warm to a room temperature, stirred for 16 hours, quenched with water (50 ml), and extracted with ethyl acetate (3×50 ml). The combined organic layers were concentrated in vacuo to obtain a crude product, which was purified using a silica gel column (0-5% ethyl acetate / pet ether) to afford 6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridine (6.5g, 96%). LC-MS retention time: 1.85 min, m/z: 207.0 [M+H] (Method G).

20

Intermediate 21

6-Chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridine-2-carbaldehyde



25

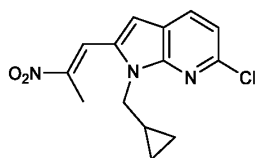
sec-Butyllithium (10.37 ml, 14.52 mmol, 1.4 M in cyclohexane) was added to a stirred solution of Intermediate 20 (2 g, 9.68 mmol) in THF (20 ml) at -78°C, the contents were stirred for 30 minutes, followed by the addition of DMF (2 ml, 25.8 mmol). The

reaction mixture was allowed to warm to -20°C, then to a room temperature, stirred for 12 hours, cooled to -10°C, and quenched by addition of saturated ammonium chloride solution. The reaction mixture was diluted with water (100 ml) and extracted with ethylacetate (3×100 ml). The combined organic layers were dried over sodium sulphate, filtered and the filtrate was concentrated in vacuo to obtain a crude product, which was purified using a silica gel column (0 to 15% ethyl acetate/pet ether) to afford 6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridine-2-carbaldehyde (1.45 g, 64%) as an off-white crystalline solid. LC-MS retention time: 1.85 min., m/z: 235.0 [M+H] (Method G).

10

Intermediate 22

(E)-6-Chloro-1-(cyclopropylmethyl)-2-(2-nitroprop-1-en-1-yl)-1H-pyrrolo[2,3-b]pyridine

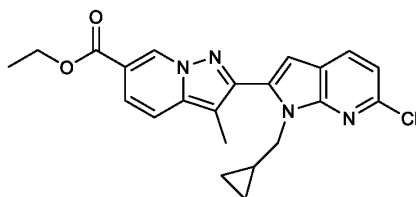


Intermediate 22 was prepared following a procedure similar to the preparation of Intermediate 17 using Intermediate 21. LC-MS retention time: 1.17 min, m/z: 292.2 [M+H] (Method G).

15

Intermediate 23

Ethyl 2-(6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate



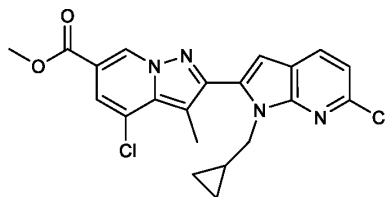
20

Intermediate 23 was prepared following a procedure similar to the preparation of Intermediate 18 using Intermediate 22 and Intermediate 8. LC-MS retention time: 1.66 min, m/z: 409.1 [M+H] (Method G).

25

Intermediate 24

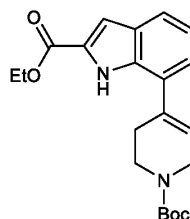
Methyl 2-(6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-chloro-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate



Intermediate 24 was prepared as a gummy liquid following a procedure similar to the preparation of Intermediate 18 using Intermediate 13 and Intermediate 22. LC-MS (ES): m/z : 429.1 $[M+H]^+$.

Intermediate 25

Ethyl 7-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole-2-carboxylate



10

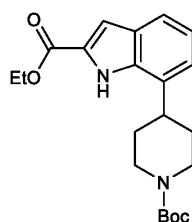
K_2CO_3 (15.46 g, 112 mmol) and $PdCl_2(dppf) \cdot CH_2Cl_2$ (3.05 g, 3.73 mmol) were added to a stirred solution of tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (11.53 g, 37.3 mmol) and ethyl 7-bromo-1H-indole-2-carboxylate (10 g, 37.3 mmol) in dioxane (200 ml). The reaction mixture was purged with nitrogen for 2 minutes, stirred at 100°C for 3 hours thereafter, filtered through a celite bed, and the celite bed was thoroughly washed with ethyl acetate. The combined filtrate was concentrated under reduced pressure to obtain a crude product, which was purified using a silica gel column (0-30% ethyl acetate in pet ether) to afford the title compound (11.3 g, 82%) as a gummy liquid. LC-MS m/z : 369.4 $[M-H]^+$. 1H NMR (300 MHz, $DMSO-d_6$) δ ppm: 11.43 (s, 1H), 7.57 (d, $J=7.2$ Hz, 1H), 7.21 (d, $J=4.0$ Hz, 1H), 7.24-7.04 (m, 2H), 5.96 (br, s, 1H), 4.34 (q, $J=7.1$ Hz, 2H), 4.08-3.99 (m, 2H), 3.62 (t, $J=5.7$ Hz, 2H), 1.51-1.45 (m, 2H), 1.46 (s, 9H), 1.34 (t, $J=7.2$ Hz, 3H).

20

Intermediate 26

Ethyl 7-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1H-indole-2-carboxylate

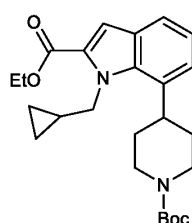
25



Pd/C (7.18 g, 6.75 mmol, 50% wet) was added to a stirred solution of Intermediate 25 (5.0 g, 13.50 mmol) in methanol (100 ml) purged with nitrogen, and the reaction mixture was stirred under H₂ atmosphere for 4 hours. The reaction mixture was filtered through a celite bed, and the filtrate was concentrated under reduced pressure to obtain ethyl 7-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1H-indole-2-carboxylate (4.95 g, 98%). LC-MS m/z: 371.4 [M-H]⁺. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm: 11.84 (s, 1H), 7.49 (d, J=7.6 Hz, 1H), 7.21-7.01 (m, 3H), 4.36 (q, J=7.1 Hz, 2H), 4.16-4.04 (m, 4H), 3.61-3.42 (m, 1H), 1.90-1.74 (m, 2H), 1.59-1.47 (m, 2H), 1.43 (s, 9H), 1.35 (t, J=7.2 Hz, 3H).

Intermediate 27

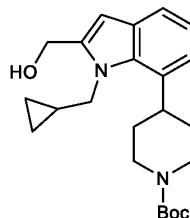
Ethyl 7-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1-(cyclopropylmethyl)-1H-indole-2-carboxylate



K₂CO₃ (14.47 g, 105 mmol) and (bromomethyl)cyclopropane (14.14 g, 105 mmol) were added to a stirred solution of Intermediate 26 (13 g, 34.9 mmol) in DMF (100 ml). The reaction mixture was stirred at 50°C for 12 hours, allowed to cool to a room temperature, diluted with water, and extracted with ethyl acetate (3×150 ml). The combined organic layers were washed with water and brine solution, dried over anhydrous sodium sulphate, and the volatiles were evaporated under reduced pressure to obtain a crude product, which was purified using a silica gel column (0-20% ethyl acetate in pet ether) to afford ethyl 7-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1-(cyclopropylmethyl)-1H-indole-2-carboxylate (4.8 g, 32%) as a gummy liquid. LC-MS m/z: 427.5 [M+H]⁺.

Intermediate 28

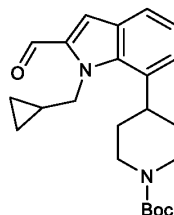
tert-Butyl 4-(1-(cyclopropylmethyl)-2-(hydroxymethyl)-1H-indol-7-yl)piperidine-1-carboxylate



- 5 LiBH₄ in tetrahydrofuran (10.08 ml, 40.3 mmol) was added to a stirred solution of Intermediate 27 (4.3 g, 10.08 mmol) in tetrahydrofuran (80 ml) at 0°C. The reaction mixture was allowed to warm to a room temperature, stirred for 48 hours, quenched with saturated ammonium chloride solution, and extracted with ethyl acetate (4×50 ml). The combined organic layers were washed with water and brine solution, dried over
- 10 anhydrous sodium sulphate, and evaporated under reduced pressure to obtain a crude product, which was purified using a silica gel column (0-70% ethyl acetate in pet ether) to afford tert-butyl 4-(1-(cyclopropylmethyl)-2-(hydroxymethyl)-1H-indol-7-yl)piperidine-1-carboxylate (3.7 g, 95%) as a gummy liquid. LC-MS m/z: 385.4 [M+H]⁺. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm: 7.33 (d, J=6.8 Hz, 1H), 7.03-6.90 (m, 2H), 6.38 (s, 1H),
- 15 5.24 (br, t, 1H), 4.60 (s, 2H), 4.30 (d, J=5.3 Hz, 2H), 4.22-3.98 (m, 2H), 3.59-3.38 (m, 1H), 3.02-2.74 (m, 2H), 1.88-1.80 (m, 2H), 1.74-1.50 (m, 2H), 1.43 (s, 9 H), 1.19-1.01 (m, 1H), 0.55-0.37 (m, 2H), 0.36-0.19 (m, 2H).

Intermediate 29

- 20 tert-Butyl 4-(1-(cyclopropylmethyl)-2-formyl-1H-indol-7-yl)piperidine-1-carboxylate

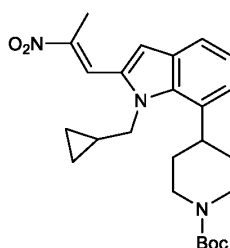


- Manganese dioxide (9.04 g, 104 mmol) was added to a stirred solution of Intermediate 28 (4 g, 10.40 mmol) in tetrahydrofuran (60 ml). The reaction mixture was heated to 40°C, stirred for 2 hours, filtered through a celite bed, and washed with ethyl
- 25 acetate. The combined filtrate was concentrated under reduced pressure to obtain tert-

butyl 4-(1-(cyclopropylmethyl)-2-formyl-1H-indol-7-yl)piperidine-1-carboxylate (3.8 g, 96%). LC-MS m/z: 383.4 [M+H]⁺. ¹H NMR (400 MHz, chloroform-*d*) δ ppm: 9.84 (s, 1H), 7.63 (dd, J=1.3, 7.8 Hz, 1H), 7.42-7.33 (m, 1H), 7.30 (s, 1H), 7.32 (s, 1H), 7.18 (t, J=7.6 Hz, 1H), 5.32 (s, 1H), 4.83 (d, J=6.0 Hz, 2H), 4.47-4.23 (m, 2H), 3.81-3.72 (m, 1H), 3.64-3.48 (m, 1H), 2.93 (br, t, J=12.3 Hz, 2H), 2.01-1.95 (m, 2H), 1.84-1.78 (m, 2H), 1.52 (s, 9H), 1.18-1.08 (m, 1H), 0.50-0.42 (m, 2H), 0.42-0.35 (m, 2H).

Intermediate 30

tert-Butyl (E)-4-(1-(cyclopropylmethyl)-2-(2-nitroprop-1-en-1-yl)-1H-indol-7-yl)piperidine-1-carboxylate

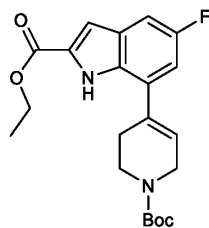


Ammonium acetate (0.937 g, 12.16 mmol) was added to a stirred solution of Intermediate 29 (3.1 g, 8.10 mmol) in nitroethane (20 ml, 280 mmol). The reaction mixture was heated to 80°C, stirred for 2 hours, diluted with water and extracted with ethyl acetate (2×50 ml). The combined organic layers were washed with water and brine solution, dried over anhydrous sodium sulphate, and evaporated under reduced pressure to obtain tert-butyl (E)-4-(1-(cyclopropylmethyl)-2-(2-nitroprop-1-en-1-yl)-1H-indol-7-yl)piperidine-1-carboxylate (3.5 g, 98%). LC-MS m/z: 440.4 [M+H]⁺. ¹H NMR (300 MHz, chloroform-*d*) δ ppm: 8.23 (s, 1H), 7.53 (d, J=6.80 Hz, 1H), 7.07-7.24 (m, 2H), 6.89 (s, 1H), 4.37 (br, s, 1H), 4.33 (br, d, J=5.3 Hz, 2H), 3.46-3.59 (m, 1H), 2.78-2.98 (m, 2H), 2.59 (s, 3H), 2.00-1.90 (m, 2H), 1.86-1.77 (m, 1H), 1.53-1.63 (m, 9H), 1.22-1.32 (m, 1H), 1.07-1.21 (m, 1H), 0.83 (br, d, J=2.27 Hz, 1H), 0.53-0.62 (m, 2H), 0.31 (q, J=5.16 Hz, 2H).

25

Intermediate 31

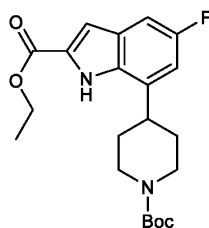
Ethyl 7-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-fluoro-1H-indole-2-carboxylate



tert-Butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (5.40 g, 17.48 mmol) and potassium carbonate (6.04 g, 43.7 mmol) were added to a stirred solution of ethyl 7-bromo-5-fluoro-1H-indole-2-carboxylate (5 g, 17.48 mmol) in 1,4-dioxane (45 ml) and water (5 ml). The reaction mixture was degassed with nitrogen for 2 min, followed by addition of PdCl₂(dppf) (1.279 g, 1.748 mmol). The reaction mixture was degassed for additional 2 min, heated to 100°C for 3 hours, filtered through a celite bed, and the celite bed was washed with ethyl acetate (300 ml). The combined filtrates were concentrated under reduced pressure to obtain a crude product, which was purified using a silica gel column (0-30% ethyl acetate in hexane) to afford ethyl 7-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)-5-fluoro-1H-indole-2-carboxylate (5.7 g, 84%). LC-MS m/z: 387.5 [M-H]⁺. ¹H NMR (300 MHz, chloroform-*d*) δ ppm: 8.92 (br, s, 1H), 7.25-7.20 (m, 1H), 7.18 (d, J=2.2 Hz, 1H), 6.95 (dd, J=2.3, 10.2 Hz, 1H), 6.12 (br, s, 1H), 4.42 (q, J=7.2 Hz, 2H), 4.16 (br, d, J=3.0 Hz, 2H), 3.71 (t, J=5.5 Hz, 2H), 2.63-2.42 (m, 2H), 1.53 (s, 9H), 1.42 (t, J=7.2 Hz, 3H).

Intermediate 32

Ethyl 7-(1-(tert-butoxycarbonyl)piperidin-4-yl)-5-fluoro-1H-indole-2-carboxylate

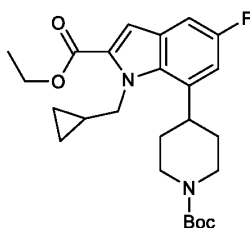


Pd/C (3.29 g, 15.45 mmol) was added to a solution of Intermediate 31 (6.0 g, 15.45 mmol) in methanol (60 ml) purged with nitrogen for 2 min. The reaction mixture was stirred under hydrogen atmosphere at 1 atmospheric pressure for 3 hours, filtered through a celite bed, and washed with ethyl acetate (300 ml). The combined organic layers were concentrated under reduced pressure to obtain ethyl 7-(1-(tert-

butoxycarbonyl)piperidin-4-yl)-5-fluoro-1H-indole-2-carboxylate (5.5 g, 91%). LC-MS
 m/z: 389.2 [M-H]⁺. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm: 12.00 (s, 1H), 7.25 (dd,
J=2.3, 9.1 Hz, 1H), 7.15 (d, *J*=1.9 Hz, 1H), 7.00 (dd, *J*=2.5, 10.8 Hz, 1H), 4.36 (q, *J*=7.2
 Hz, 2H), 4.11 (br d, *J*=12.5 Hz, 2H), 3.52 (br s, 1H), 3.34 (s, 1H), 3.07-2.74 (m, 2H), 1.81
 5 (br d, *J*=11.7 Hz, 2H), 1.62-1.50 (m, 1H), 1.43 (s, 9H), 1.34 (t, *J*=7.0 Hz, 3H).

Intermediate 33

Ethyl 7-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-
 indole-2-carboxylate



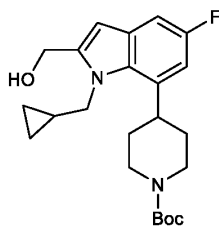
10

Cesium carbonate (10.43 g, 32.0 mmol), TBAI (4.73 g, 12.81 mmol) and
 (bromomethyl)cyclopropane (3.46 g, 25.6 mmol) were added to a stirred solution of
 Intermediate 32 (5 g, 12.81 mmol) in DMF (50 ml). The reaction mixture was heated to
 55°C for 16 hours, quenched with water (100 ml), and extracted with ethyl acetate (2×100
 15 ml). The combined organic layers were dried over sodium sulphate, filtered, and
 concentrated under reduced pressure to obtain a crude product, which was purified using
 a silica gel column (0-20% ethyl acetate in hexane) to afford ethyl 7-(1-(tert-
 butoxycarbonyl)piperidin-4-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indole-2-carboxylate
 (4.8 g, 84%). LC-MS m/z: 389.3 [M+H]⁺. ¹H NMR (400 MHz, chloroform-*d*) δ ppm:
 20 7.32 (s, 1H), 7.18 (dd, *J*=2.5, 8.5 Hz, 1H), 6.99 (dd, *J*=2.8, 10.8 Hz, 1H), 4.79 (d, *J*=6.0
 Hz, 2H), 4.44-4.34 (m, 2H), 3.55 (br s, 1H), 2.92 (br s, 2H), 2.00 (br d, *J*=13.0 Hz, 2H),
 1.76 (br, dd, *J*=4.0, 12.5 Hz, 2H), 1.52 (s, 9H), 1.45-1.40 (m, 3H), 1.05 (s, 1H), 0.48-0.39
 (m, 2H), 0.38-0.30 (m, 2H).

25

Intermediate 34

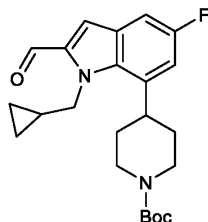
tert-Butyl 4-(1-(cyclopropylmethyl)-5-fluoro-2-(hydroxymethyl)-1H-indol-7-
 yl)piperidine-1-carboxylate



LiBH₄ (9.84 ml, 39.4 mmol) was added to a stirred solution of Intermediate 33 (3.5 g, 7.87 mmol) in THF (35 ml) at 0°C. The reaction mixture was stirred for 16 hours at a room temperature, filtered through a celite bed, and washed with ethyl acetate (70 ml). The combined organic layers were concentrated under reduced pressure to obtain crude tert-butyl 4-(1-(cyclopropylmethyl)-5-fluoro-2-(hydroxymethyl)-1H-indol-7-yl)piperidine-1-carboxylate (2.5 g, 79%). LC-MS m/z: 403.4 [M+H]⁺. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm: 7.10 (dd, J=9.07, 2.64 Hz, 1H), 6.74-6.92 (m, 1H), 6.38 (s, 1H), 5.29 (t, J=5.48 Hz, 1H), 4.59 (d, J=5.67 Hz, 1H), 4.28 (br d, J=5.29 Hz, 2H), 4.13 (br d, J=12.46 Hz, 1H), 3.51 (br t, J=10.58 Hz, 1H), 3.13-3.32 (m, 1H), 2.35 (s, 2H), 2.27 (d, J=5.29 Hz, 1H), 1.84 (br d, J=12.84 Hz, 2H), 1.51-1.74 (m, 2H), 1.35-1.51 (m, 9H), 0.74-1.04 (m, 1H), 0.21-0.51 (m, 4H).

Intermediate 35

tert-Butyl 4-(1-(cyclopropylmethyl)-5-fluoro-2-formyl-1H-indol-7-yl)piperidine-1-carboxylate

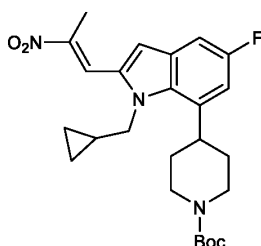


Manganese dioxide (0.691 g, 7.95 mmol) was added to a stirred solution of Intermediate 34 (3.2 g, 7.95 mmol) in tetrahydrofuran (32 ml). The reaction mixture was stirred for 16 hours, filtered through a celite bed, and washed with ethyl acetate (70 ml). The organic layers were concentrated under reduced pressure to obtain tert-butyl 4-(1-(cyclopropylmethyl)-5-fluoro-2-formyl-1H-indol-7-yl)piperidine-1-carboxylate (2.7 g, 85%). LC-MS m/z: 345.1 [M-tBu]⁺. ¹H NMR (300 MHz, chloroform-*d*) δ ppm: 9.81 (s, 1H), 7.25-7.20 (m, 2H), 7.05 (dd, J=2.3, 11.0 Hz, 1H), 4.78 (d, J=6.0 Hz, 2H), 4.48-4.22

(m, 2H), 3.52 (br, t, $J=11.5$ Hz, 1H), 3.02-2.77 (m, 2H), 2.05-1.89 (m, 2H), 1.86-1.64 (m, 2H), 1.50 (s, 9H), 1.15-1.01 (m, 1H), 0.49-0.31 (m, 4H).

Intermediate 36

- 5 tert-Butyl (E)-4-(1-(cyclopropylmethyl)-5-fluoro-2-(2-nitroprop-1-en-1-yl)-1H-indol-7-yl)piperidine-1-carboxylate

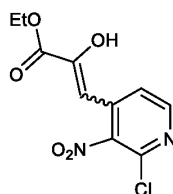


Intermediate 36 was prepared following a procedure similar to the preparation of Intermediate 30, using appropriate reactants. LC-MS m/z : 402.3 $[M+H]^+$. 1H NMR (300
10 MHz, chloroform- d) δ ppm: 8.18 (s, 1H), 7.15 (dd, $J=2.5, 8.1$ Hz, 1H), 6.94 (dd, $J=2.3, 11.0$ Hz, 1H), 6.82 (s, 1H), 4.47-4.26 (m, 4H), 3.60-3.44 (m, 1H), 3.01-2.79 (m, 2H), 2.58 (s, 3H), 2.01-1.90 (m, 2H), 1.84-1.70 (m, 2H), 1.50 (s, 9H), 1.15-1.05 (m, 1H), 0.62-0.52 (m, 2H), 0.29 (q, $J=5.3$ Hz, 2H).

15

Intermediate 37

Ethyl 3-(2-chloro-3-nitropyridin-4-yl)-2-hydroxyacrylate

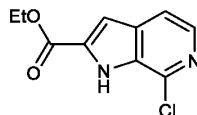


Sodium ethoxide in ethanol (28.2 g, 87 mmol) was added to diethyl oxalate (12.70 g, 87 mmol) in toluene (50 ml). The reaction mixture was stirred for 10 min at a room
20 temperature, followed by the addition of 2-chloro-4-methyl-3-nitropyridine (10 g, 57.9 mmol). The reaction mixture was stirred at a room temperature for 16 hours, concentrated, the residue thus obtained was diluted with water (20 ml), and acidified with acetic acid (10 ml) to bring pH to about 4. The solids thus obtained were filtered and dried to afford ethyl 3-(2-chloro-3-nitropyridin-4-yl)-2-hydroxyacrylate (15 g, 95%) as an
25 off-white solid. LC-MS m/z : 273.0 $[M+H]^+$. 1H NMR (300 MHz, DMSO- d_6) δ ppm: 8.61

(d, $J=5.7$ Hz, 1H), 8.31 (d, $J=5.7$ Hz, 1H), 5.92 (s, 1H), 4.30 (q, $J=7.1$ Hz, 2H), 1.28 (t, $J=7.0$ Hz, 3H).

Intermediate 38

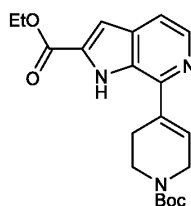
5 Ethyl 7-chloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate



Iron (15.36 g, 275 mmol) and ammonium chloride (23.54 g, 440 mmol) in water (30 ml) were added to a stirred solution of Intermediate 37 (15.0 g, 55.0 mmol) in ethanol (50 ml) and THF (100 ml). The reaction mixture was stirred at 65°C for 3 hours, filtered
 10 through a celite bed, the filtrate obtained was diluted with water (50 ml), and quenched with saturated NaHCO_3 solution, followed by extraction with ethyl acetate (2×100 ml). The combined organic layers were dried over sodium sulphate, filtered, and concentrated under reduced pressure to obtain a crude product, which was purified using a silica gel column (0-50% ethyl acetate in hexane) to afford ethyl 7-chloro-1H-pyrrolo[2,3-
 15 c]pyridine-2-carboxylate (6.5 g, 53%). LC-MS m/z : 225.0 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm: 12.73 (br, s, 1H), 7.99 (d, $J=5.5$ Hz, 1H), 7.68 (d, $J=5.5$ Hz, 1H), 7.30 (s, 1H), 4.39 (q, $J=7.0$ Hz, 2H), 1.36 (t, $J=7.0$ Hz, 3H).

Intermediate 39

20 Ethyl 7-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylate

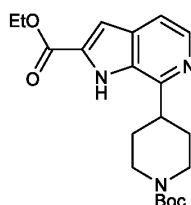


tert-Butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (11.63 g, 37.6 mmol) and K_2CO_3 in water (36.2 ml, 72.3 mmol) were
 25 added to a stirred solution of Intermediate 38 (6.5 g, 28.9 mmol) in 1,4-dioxane (65 ml). The reaction mixture was degassed with argon for 10 min, followed by the addition of $\text{PdCl}_2(\text{dppf})\text{-CH}_2\text{Cl}_2$ adduct (1.418 g, 1.736 mmol), and stirred at 110°C for 16 hours. The

reaction mixture was filtered through a celite bed, the filtrate was diluted with water (50 ml) and extracted with ethyl acetate (2×100 ml). The combined organic layers were dried over sodium sulphate, filtered, and concentrated under reduced pressure to obtain a crude product, which was purified using a silica gel column (0-60% ethyl acetate in hexane) to afford ethyl 7-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylate (10.2 g, 95%). LC-MS m/z: 372.2 [M+H]⁺. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm: 11.95 (br, s, 1H), 8.16 (d, J=5.3 Hz, 1H), 7.53 (d, J=5.7 Hz, 1H), 7.23 (s, 1H), 6.36 (br s, 1H), 4.38 (q, J=7.1 Hz, 2H), 4.15-4.08 (m, 2H), 4.03 (d, J=7.2 Hz, 1H), 3.94 (s, 2H), 3.59 (br t, J=5.3 Hz, 2H), 2.72-2.62 (m, 2H), 1.46 (s, 9H), 1.35 (t, J=7.2 Hz, 3H).

Intermediate 40

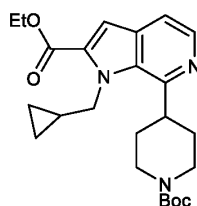
Ethyl 7-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylate



Pd/C (50% wet, 2.92 g, 2.75 mmol) was added to a stirred solution of Intermediate 39 (10.2 g, 27.5 mmol) in ethanol (10 ml). The reaction mixture was stirred under hydrogen atmosphere for 16 hours, filtered through a celite bed, and the filtrate was concentrated to obtain ethyl 7-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylate (8.1 g, 79%). LC-MS m/z: 374.1 [M+H]⁺. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm: 12.38 (s, 1H), 8.09 (d, J=5.3 Hz, 1H), 7.46 (d, J=5.7 Hz, 1H), 7.18 (d, J=1.5 Hz, 1H), 4.43-4.34 (m, 2H), 4.16-4.05 (m, 2H), 3.94 (s, 2H), 3.80-3.62 (m, 2H), 3.44-3.42 (m, 2H), 1.76 (br, s, 1H), 1.43 (s, 9H), 1.39-1.23 (m, 3H).

Intermediate 41

Ethyl 7-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylate

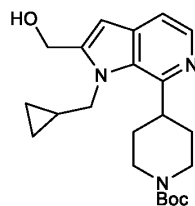


Cesium carbonate (4.45 g, 13.66 mmol) and TBAI (0.841 g, 2.276 mmol) were added to a stirred solution of Intermediate 40 (1.7 g, 4.55 mmol) in DMF (10 ml), followed by the addition of (bromomethyl)cyclopropane (1.229 g, 9.10 mmol). The reaction mixture was stirred at 60°C for 3 hours, diluted with water (20 ml), and extracted with ethyl acetate (3×20 ml). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuum to obtain a crude product, which was purified using a silica gel column (0-20% ethyl acetate in hexane) to afford ethyl 7-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylate (1.3 g, 67%). LC-MS m/z : 428.2 $[M+H]^+$. 1H NMR (300 MHz, DMSO- d_6) δ ppm: 8.18 (d, $J=5.3$ Hz, 1H), 7.53 (d, $J=5.3$ Hz, 1H), 7.33 (s, 1H), 4.80 (br, d, $J=6.4$ Hz, 2H), 4.35 (q, $J=7.2$ Hz, 2H), 4.19-3.98 (m, 2H), 3.68-3.52 (m, 1H), 2.94 (br, s, 2H), 1.85 (br, s, 4 H), 1.43 (s, 9H), 1.36-1.32 (m, 3H), 1.27-0.99 (m, 1H), 0.53-0.35 (m, 2H), 0.33-0.17 (m, 2H).

15

Intermediate 42

tert-Butyl 4-(1-(cyclopropylmethyl)-2-(hydroxymethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)piperidine-1-carboxylate



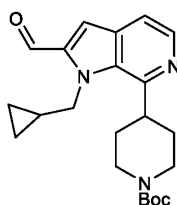
$LiBH_4$ (4.56 ml, 18.24 mmol) was added to a stirred solution of Intermediate 41 (1.3 g, 3.04 mmol) in THF (30 ml). The reaction mixture was stirred at a room temperature for 36 hours, quenched with saturated ammonium chloride solution (10 ml), diluted with water (20 ml), and extracted with ethyl acetate (3×20 ml). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuum to obtain a crude product, which was purified using a silica gel

25

column (0-20% ethyl acetate in hexane) to afford tert-butyl 4-(1-(cyclopropylmethyl)-2-(hydroxymethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)piperidine-1-carboxylate (1.02 g, 87%). LC-MS m/z: 386.2 [M+H]⁺. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm: 8.04 (d, J=5.3 Hz, 1H), 7.32 (d, J=5.3 Hz, 1H), 6.45 (s, 1H), 5.42 (t, J=5.3 Hz, 1H), 4.65 (d, J=5.7 Hz, 2H), 4.34 (br d, J=6.0 Hz, 2H), 4.11 (br d, J=10.6 Hz, 2H), 3.57 (br d, J=11.0 Hz, 1H), 2.90 (br s, 2H), 1.88 (br d, J=9.8 Hz, 2H), 1.83-1.64 (m, 2H), 1.43 (s, 9H), 1.24 (br s, 1H), 0.53-0.42 (m, 2H), 0.31 (q, J=4.9 Hz, 2H).

Intermediate 43

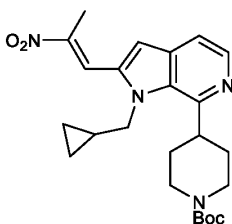
tert-Butyl 4-(1-(cyclopropylmethyl)-2-formyl-1H-pyrrolo[2,3-c]pyridin-7-yl)piperidine-1-carboxylate



Manganese dioxide (2.255 g, 25.9 mmol) was added to a stirred solution of Intermediate 42 (1 g, 2.59 mmol) in THF (10 ml). The reaction mixture was stirred at 40°C for 3 hours, filtered through a celite bed, and the filtrate was concentrated to obtain tert-butyl 4-(1-(cyclopropylmethyl)-2-formyl-1H-pyrrolo[2,3-c]pyridin-7-yl)piperidine-1-carboxylate (0.9 g, 90%). LC-MS m/z: 384.2[M+H]⁺. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm: 10.03 (s, 1H), 8.22 (d, J=5.3 Hz, 1H), 7.61 (d, J=5.3 Hz, 1H), 7.56 (s, 1H), 4.80 (d, J=6.0 Hz, 2H), 4.18-4.00 (m, 2H), 3.67-3.55 (m, 1H), 3.13-2.81 (m, 2H), 1.94-1.75 (m, 4H), 1.47-1.35 (m, 9H), 1.29-1.12 (m, 1H), 0.51-0.37 (m, 2H), 0.36-0.23 (m, 2H).

Intermediate 44

tert-Butyl (E)-4-(1-(cyclopropylmethyl)-2-(2-nitroprop-1-en-1-yl)-1H-pyrrolo[2,3-c]pyridin-7-yl)piperidine-1-carboxylate

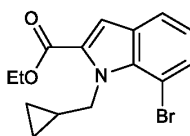


Ammonium acetate (0.271 g, 3.52 mmol) was added to a stirred solution of Intermediate 43 (0.9 g, 2.347 mmol) in nitroethane (1.678 ml, 23.47 mmol). The reaction mixture was stirred at 90°C for 2 hours, diluted with water (50 ml), and extracted with ethyl acetate (2×100 ml). The combined organic layers were dried over sodium sulphate, filtered, and concentrated under reduced pressure to obtain tert-butyl (E)-4-(1-(cyclopropylmethyl)-2-(2-nitroprop-1-en-1-yl)-1H-pyrrolo[2,3-c]pyridin-7-yl)piperidine-1-carboxylate (0.85 g, 82%). LC-MS m/z: 441.2 [M+H]⁺.

10

Intermediate 45

Ethyl 7-bromo-1-(cyclopropylmethyl)-1H-indole-2-carboxylate

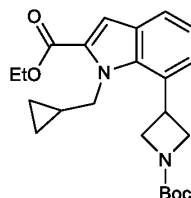


Potassium carbonate (41.2 g, 298 mmol) was added to a stirred solution of ethyl 7-bromo-1H-indole-2-carboxylate (20 g, 74.6 mmol) in DMF (80 ml), followed by addition of (bromomethyl)cyclopropane (14.47 ml, 149 mmol). The reaction mixture was stirred at 50°C for 16 hours, diluted with water (100 ml), and extracted with ethyl acetate (2×200 ml). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuum to obtain a crude product, which was purified using a silica gel column (0-10% ethyl acetate in hexane) to afford (22 g, 92%) of ethyl 7-bromo-1-(cyclopropylmethyl)-1H-indole-2-carboxylate as off white solid. LC-MS m/z: 322.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 7.76 (d, J=8.0 Hz, 1H), 7.59 (d, J=8.0 Hz, 1H), 7.41 (s, 1H), 7.07 (t, J=8.0 Hz, 1H), 5.01 (d, J=8.0 Hz, 2H), 4.34 (q, J=8.0 Hz, 2H), 2.33 (br, s, 1H), 1.34 (t, J=8.00 Hz, 3H), 1.27-1.15 (m, 1H), 0.42-0.29 (m, 4H).

25

Intermediate 46

Ethyl 7-(1-(tert-butoxycarbonyl)azetidin-3-yl)-1-(cyclopropylmethyl)-1H-indole-2-carboxylate

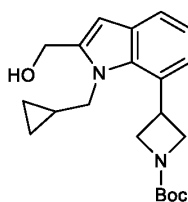


5 Tris(trimethylsilyl)silane (5.67 g, 22.81 mmol) and sodium carbonate (4.61 g, 43.5 mmol) were added to a stirred solution of Intermediate 45 (9.84 g, 34.8 mmol) in 1,2-dimethoxyethane (35 ml) in a first vial, and the reaction mixture was purged with argon followed by the addition of Ir[DF(CF₃)PPY]₂(DTBBPY)PF₆ (0.244 g, 0.217 mmol). A mixture of 4,4'-di-tert-butyl-2,2'-dipyridyl (0.292 g, 1.086 mmol) and Nickel(II) chloride ethylene glycol dimethyl ether complex (0.239 g, 1.086 mmol) in 1,2-dimethoxy ethane 10 (0.5 ml) was prepared in another vial and the contents were sonicated for 10 min to obtain a catalyst (green suspension). The catalyst was added into the reaction mixture in the first vial, and the vial containing the reaction mixture was placed under Blue LED light (34 W) for 16 hours. The reaction mixture was diluted with water (100 ml), and extracted 15 with ethyl acetate (2×200 ml). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuum to obtain a crude product, which was purified using a silica gel column (0-20% ethyl acetate in hexane) to afford (5.6 g, 64%) of ethyl 7-(1-(tert-butoxycarbonyl)azetidin-3-yl)-1-(cyclopropylmethyl)-1H-indole-2-carboxylate as pale yellow liquid. LC-MS m/z: 343.3 [M-56]⁺. ¹H NMR (400 20 MHz, DMSO-*d*₆) δ ppm: 7.63 (d, *J*=8.0 Hz, 1H), 7.49 (d, *J*=8.0 Hz, 1H), 7.36 (s, 1H), 7.19 (t, *J*=8.0 Hz, 1H), 4.63 (d, *J*=8.0 Hz, 2H), 4.57-4.52 (m, 1H), 4.41-4.29 (m, 2H), 4.12-3.94 (m, 2H), 3.82-3.80 (m, 2H), 2.12 (quin, *J*=7.5 Hz, 1H), 1.41 (s, 9H), 1.33(t, *J*=8.0 Hz, 3H), 0.94-0.84 (m, 1H), 0.39-0.27 (m, 2H), 0.21-0.02 (m, 2H).

25

Intermediate 47

tert-Butyl 3-(1-(cyclopropylmethyl)-2-(hydroxymethyl)-1H-indol-7-yl)azetidine-1-carboxylate

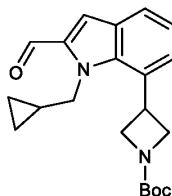


LiBH₄ (14.05 ml, 56.2 mmol) was added to a stirred solution of Intermediate 46 (5.6 g, 14.05 mmol) in THF (50 ml). The reaction mixture was stirred at a room temperature for 4 days, quenched with saturated ammonium chloride solution (10 ml),
 5 diluted with water (20 ml), and extracted with ethyl acetate (3×50 ml). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuum to obtain a crude product, which was purified using a silica gel column (0-20% ethyl acetate in hexane) to afford (2.0 g, 39%) of tert-butyl 3-(1-(cyclopropylmethyl)-2-(hydroxymethyl)-1H-indol-7-yl)azetidine-1-carboxylate. LC-MS
 10 m/z: 357.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 7.41 (d, J=8.0 Hz, 1H), 7.29 (d, J=8.0 Hz, 1H), 7.06 (t, J=8.0 Hz, 1H), 6.41 (s, 1H), 5.23 (t, J=4.0 Hz, 1H), 4.66-4.55 (m, 2H), 4.36 (br, t, J=8.5 Hz, 2H), 4.24 (d, J=6.0 Hz, 2H), 3.96 (br, t, J=8.0 Hz, 2H), 1.99 (s, 1H), 1.46-1.38 (m, 9H), 1.09-1.00 (m, 1H), 0.47-0.37 (m, 2H), 0.24 (q, J=5.0 Hz, 2H).

15

Intermediate 48

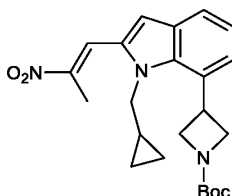
tert-Butyl 3-(1-(cyclopropylmethyl)-2-formyl-1H-indol-7-yl)azetidine-1-carboxylate



Manganese dioxide (4.88 g, 56.1 mmol) was added to a stirred solution of
 20 Intermediate 47 (2 g, 5.61 mmol) in THF (10 ml). The reaction mixture was stirred at 40°C for 3 hours, filtered through a celite bed, and the filtrate was concentrated to obtain (1.9 g, 96%) of tert-butyl 3-(1-(cyclopropylmethyl)-2-formyl-1H-indol-7-yl)azetidine-1-carboxylate. LC-MS m/z: 299 [M-56]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 9.86 (s, 1H), 7.72 (d, J=8.0 Hz, 1H), 7.60 (d, J=8.0 Hz, 1H), 7.56 (s, 1H), 7.23 (t, J=8.0 Hz, 1H),
 25 4.65 (d, J=8.0 Hz, 2H), 4.38 (br t, J=8.0 Hz, 2H), 4.06-3.96 (m, 2H), 1.77 (td, J=3.4, 6.3 Hz, 1H), 1.41 (s, 9H), 1.02-0.99 (m, 1H), 0.41-0.30 (m, 2H), 0.26-0.15 (m, 2H).

Intermediate 49

tert-Butyl (E)-3-(1-(cyclopropylmethyl)-2-(2-nitroprop-1-en-1-yl)-1H-indol-7-yl)azetidine-1-carboxylate



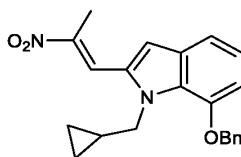
5

Ammonium acetate (0.620 g, 8.04 mmol) was added to a stirred solution of Intermediate 48 (1.9 g, 5.36 mmol) in nitroethane (3.83 ml, 53.6 mmol). The reaction mixture was stirred at 90°C for 2 hours, diluted with water (20 ml), and extracted with ethyl acetate (3×20 ml). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuum to afford (2.2 g, 100%) of tert-butyl (E)-3-(1-(cyclopropylmethyl)-2-(2-nitroprop-1-en-1-yl)-1H-indol-7-yl)azetidine-1-carboxylate. LC-MS m/z: 412.3 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.21 (s, 1H), 7.60 (d, J=8.0 Hz, 1H), 7.45 (d, J=8.0 Hz, 1H), 7.18 (t, J=8.0 Hz, 1H), 7.09 (s, 1H), 4.58-4.53 (m, 1H), 4.43-4.33 (m, 2H), 4.30 (d, J=6.0 Hz, 2H), 4.09-3.95 (m, 2H), 2.48-2.38 (m, 1H), 1.47-1.37 (m, 9H), 1.06-0.96 (m, 1H), 0.49-0.39 (m, 2H), 0.29-0.15 (m, 2H).

15

Intermediate 50

(E)-7-(benzyloxy)-1-(cyclopropylmethyl)-2-(2-nitroprop-1-en-1-yl)-1H-indole



20

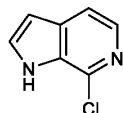
Ammonium acetate (0.606 g, 7.86 mmol) was added to a stirred solution of 7-(benzyloxy)-1-(cyclopropylmethyl)-1H-indole-2-carbaldehyde (2 g, 6.55 mmol) in nitroethane (18.73 ml, 262 mmol). The reaction mixture was heated to 90°C for 2 hours, allowed to cool to a room temperature, diluted with water (100 ml), and extracted with ethyl acetate (2×100 ml). The combined organic layers were dried over sodium sulphate, filtered, and concentrated under reduced pressure to obtain crude (E)-7-(benzyloxy)-1-

25

(cyclopropylmethyl)-2-(2-nitroprop-1-en-1-yl)-1H-indole (1.9 g, 80%) LC-MS m/z: 361.7 [M+H]⁺.

Intermediate 51

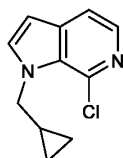
5

7-Chloro-1*H*-pyrrolo[2,3-*c*]pyridine

Vinyl magnesium bromide (189 ml, 189 mmol) was added to a stirred solution of 2-chloro-3-nitropyridine (10 g, 63.1 mmol) in THF (80 ml) at -78°C. The reaction mixture was stirred for 1 hour, warmed to -20°C, and the resulting solution was stirred at -20°C for 12 hours. The reaction mixture was quenched with saturated ammonium chloride solution (20 ml), diluted with water (2×50 ml), and extracted with ethyl acetate (3×50 ml). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuum to obtain a crude product, which was purified using a silica gel column (0-50% ethyl acetate in hexane) to afford 7-chloro-1*H*-pyrrolo[2,3-*c*]pyridine (3.4 g, 35%) as brown solid. LC-MS m/z: 153.1 [M+H]⁺. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm: 8.35-8.30 (m, 1H), 8.29 (s, 1H), 7.88-7.78 (m, 1H), 7.78-7.70 (m, 1H), 7.66 (s, 1H).

Intermediate 52

20

7-Chloro-1-(cyclopropylmethyl)-1*H*-pyrrolo[2,3-*c*]pyridine

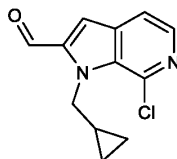
Sodium hydride (1.049 g, 26.2 mmol) was added to a stirred solution of Intermediate 51 (2 g, 13.11 mmol) in DMF (20 ml) at 0°C, the contents were stirred for 20 minutes, followed by the addition of (bromomethyl)cyclopropane (1.910 ml, 19.66 mmol). The resulting reaction mixture was stirred for 16 hours, quenched with ice-flakes and cold water (20 ml), and extracted with ethyl acetate (3×30 ml). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuum to obtain a crude product, which was purified using a silica gel column (0-20%

ethyl acetate in hexane) to afford 7-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridine (2.2 g, 81%) of. LC-MS m/z: 207.1 $[M+H]^+$. 1H NMR (300 MHz, DMSO- d_6) δ ppm: 7.90 (d, J=5.3 Hz, 1H), 7.76 (d, J=3.0 Hz, 1H), 7.58 (d, J=5.3 Hz, 1H), 6.63 (d, J=3.4 Hz, 1H), 4.40 (d, J=6.8 Hz, 2H), 1.40-1.22 (m, 1H), 0.53-0.39 (m, 4H).

5

Intermediate 53

7-Chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridine-2-carbaldehyde

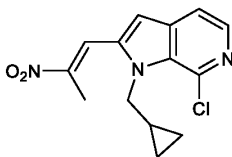


10 *sec*-Butyllithium (11.41 ml, 15.97 mmol) was added to a stirred solution of Intermediate 52 (2.2 g, 10.64 mmol) in tetrahydrofuran (30 ml) at -78°C, the contents were stirred for 1 hour, followed by the addition of DMF (1.236 ml, 15.97 mmol). The resulting reaction mixture was stirred at the same temperature for 1 hour, quenched with saturated ammonium chloride solution (10 ml), diluted with water (20 ml), and extracted with ethyl acetate (3×20 ml). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuum to obtain a crude product, which was purified using a silica gel column (eluting with 0-20% ethyl acetate in hexane) to afford 7-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridine-2-carbaldehyde (1.2 g, 78%) as an off white solid. LC-MS m/z: 235.0 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm: 10.10 (s, 1H), 8.08 (d, J=5.0 Hz, 1H), 7.84 (d, J=5.5 Hz, 1H), 7.67 (s, 1H), 4.92 (d, J=7.0 Hz, 2H), 1.35-1.24 (m, 1H), 0.47-0.41 (m, 2H), 0.41-0.33 (m, 2H).

20

Intermediate 54

(E)-7-Chloro-1-(cyclopropylmethyl)-2-(2-nitroprop-1-en-1-yl)-1H-pyrrolo[2,3-c]pyridine



25

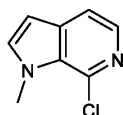
(E)-7-chloro-1-(cyclopropylmethyl)-2-(2-nitroprop-1-en-1-yl)-1H-pyrrolo[2,3-c]pyridine (1.2g, 97%) was prepared following a procedure similar to the preparation of

Intermediate 57. LC-MS m/z 292.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm: 8.18 (s, 1H), 8.01 (d, $J=5.5$ Hz, 1H), 7.69 (d, $J=5.5$ Hz, 1H), 7.14 (s, 1H), 4.64 (d, $J=7.0$ Hz, 2H), 2.54-2.52 (m, 3H), 1.33-1.09 (m, 1H), 0.43-0.23 (m, 4H).

5

Intermediate 55

7-Chloro-1-methyl-1H-pyrrolo[2,3-c]pyridine

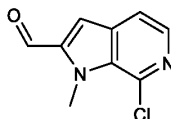


Sodium hydride (1.311 g, 32.8 mmol) was added to a stirred solution of Intermediate 51 (5 g, 32.8 mmol) in DMF (100 ml) at 0°C, the contents were stirred for 5 min, followed by the addition of iodomethane (2.049 ml, 32.8 mmol). The resulting reaction mixture was stirred at a room temperature for 16 hours, quenched with ice water, and extracted with ethyl acetate (3×100 ml). The combined organic layers were dried over Na₂SO₄, and concentrated to obtain a crude product, which was purified using a silica gel column (0-50% ethyl acetate in hexane) to afford 7-chloro-1-methyl-1H-pyrrolo[2,3-c]pyridine (4 g, 73%) as off-white solid. LC-MS m/z : 167.0 $[M+H]^+$.

15

Intermediate 56

7-Chloro-1-methyl-1H-pyrrolo[2,3-c]pyridine-2-carbaldehyde

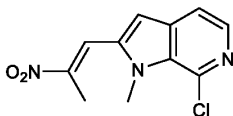


sec-Butyl lithium (6.43 ml, 9 mmol) was added to a solution of Intermediate 55 (1 g, 6 mmol) in tetrahydrofuran (10 ml) at -78°C, the contents were stirred for 0.5 hours, followed by the addition of DMF (0.697 ml, 9 mmol). The resulting reaction mixture was stirred for 1 hour, quenched with saturated NH₄Cl solution (50 ml), extracted with ethyl acetate (3×50 ml), dried over Na₂SO₄, and concentrated to obtain a crude product, which was purified using a silica gel column (0-50% ethyl acetate in hexane) to afford 7-chloro-1-methyl-1H-pyrrolo[2,3-c]pyridine-2-carbaldehyde (1.0 g, 86%) as a brown oil. LC-MS m/z : 195.0 $[M+H]^+$.

25

Intermediate 57

(E)-7-Chloro-1-methyl-2-(2-nitroprop-1-en-1-yl)-1H-pyrrolo[2,3-c]pyridine

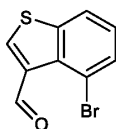


Ammonium acetate (0.594 g, 7.71 mmol) was added to a solution of Intermediate 56 (1 g, 5.14 mmol) in nitroethane (10 ml). The reaction mixture was heated to 90°C, stirred for 2 hours, diluted with ethyl acetate (50 ml), washed with saturated NH₄Cl, dried over Na₂SO₄, and concentrated to obtain a crude product, which was purified using a silica gel column (0-50% ethyl acetate in hexane) to afford (E)-7-chloro-1-methyl-2-(2-nitroprop-1-en-1-yl)-1H-pyrrolo[2,3-c]pyridine (1.1 g, 85%) as a yellow solid. LC-MS m/z: 252.3 [M+H]⁺.

10

Intermediate 58

4-Bromobenzo[b]thiophene-3-carbaldehyde

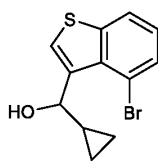


A solution of 4-bromobenzo[b]thiophene (10 g, 46.9 mmol) and dichloro(methoxy)methane (5.39 g, 46.9 mmol) in DCM (500 ml) was stirred and cooled to 0°C, followed by the addition of TiCl₄ (65.17 ml, 591 mmol) dropwise at a room temperature. The resulting reaction mixture was stirred for 16 hours at a room temperature. Thereafter, saturated ammonium chloride (500 ml) was added dropwise to the reaction mixture, and the contents were extracted with DCM (2×500 ml). The combined organic layers were washed with water (200 ml) and brine solution (200 ml), followed by drying over sodium sulphate. The organic layers were filtered, and volatiles were evaporated to dryness under reduced pressure to obtain a crude product, which was purified using a silica gel column (0-20% ethyl acetate in hexane) to afford 4-bromobenzo[b]thiophene-3-carbaldehyde (6 g, 53%). ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm: 10.80-10.95 (m, 1H), 8.80 (s, 1H), 8.21 (dd, *J*=8.31, 0.76 Hz, 1H), 7.79-7.85 (m, 1H), 7.41 (t, *J*=7.93 Hz, 1H).

25

Intermediate 59

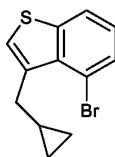
(4-Bromobenzo[b]thiophen-3-yl)(cyclopropyl)methanol



Cyclopropylmagnesium bromide (12.44 ml, 12.44 mmol) was added dropwise under nitrogen atmosphere to a stirred solution of Intermediate 58 (2 g, 8.30 mmol) in THF (30 ml) cooled to -20°C. The reaction mixture stirred for 2 hours, diluted with water (50 ml), and extracted with ethyl acetate (2×50 ml). The combined organic layers were washed with water (100 ml) and brine solution (100 ml), followed by drying over sodium sulphate. The organic layers were filtered, and volatiles were evaporated to dryness under reduced pressure to afford (4-bromobenzo[b]thiophen-3-yl)(cyclopropyl)methanol (2.2 g, 94%). ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm: 7.99-8.08 (m, 1H), 7.84-7.90 (m, 1H), 7.60-7.68 (m, 1H), 7.19-7.28 (m, 1H), 5.52-5.65 (m, 1H), 5.11-5.23 (m, 1H), 1.33-1.48 (m, 1H), 0.27-0.49 (m, 4H).

Intermediate 60

4-Bromo-3-(cyclopropylmethyl)benzo[b]thiophene



15

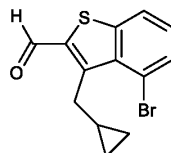
Triethylsilane (14 ml, 49.4 mmol) was added to a stirred solution of Intermediate 50 (14 g, 49.4 mmol) in DCM (200 ml), followed by the addition of TFA (14 ml, 182 mmol) after 5 minutes. The resulting reaction mixture was stirred for 1 hour at a room temperature. Thereafter, the volatiles were evaporated to dryness under reduced pressure, saturated NaHCO₃ (100 ml) was added, and the contents were extracted with DCM (2×150 ml). The combined organic extracts were washed with water (100 ml) and brine solution (100 ml), dried over sodium sulphate, filtered, and volatiles were evaporated to dryness under reduced pressure to obtain a crude product, which was purified using a silica gel column (0-10% ethyl acetate in hexane) to afford 4-bromo-3-(cyclopropylmethyl)benzo[b]thiophene (6 g, 45%). ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm: 8.02 (dd, J=7.93, 0.76 Hz, 1H), 7.70 (s, 1H), 7.63 (dd, J=7.55, 1.13 Hz, 1H), 7.24 (t,

25

J=7.74 Hz, 1H), 3.05 (d, J=6.80 Hz, 2H), 1.24 (br, d, J=3.78 Hz, 1H), 0.54-0.44 (m, 2H), 0.31-0.17 (m, 2H).

Intermediate 61

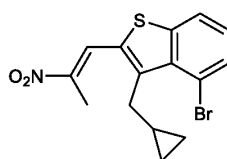
5 4-Bromo-3-(cyclopropylmethyl)benzo[b]thiophene-2-carbaldehyde



LDA (2M in THF, 11.23 ml, 22.46 mmol) was added dropwise to a stirred solution of Intermediate 60 (3 g, 11.23 mmol) in THF (30 ml) cooled to -78°C, the contents were stirred for 1 hour at -78°C, followed by the addition of DMF (1.739 ml, 22.46 mmol). The resulting reaction mixture was stirred for 3 hours, water (100 ml) was added, and the contents were extracted with ethyl acetate (2×100 ml). The combined organic layers were washed with water (100 ml) and brine solution (100 ml), dried over sodium sulphate, filtered, and volatiles were evaporated to dryness under reduced pressure to afford 4-bromo-3-(cyclopropylmethyl)benzo[b]thiophene-2-carbaldehyde (3g, 10 91%). ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm: 10.32 (s, 1H), 8.15 (dd, J=8.3, 0.70 Hz, 1H), 8.07-7.92 (m, 1H), 7.45 (t, J=8.0 Hz, 1H), 3.57 (d, J=6.4 Hz, 2H), 1.24-1.03 (m, 1H), 0.54-0.23 (m, 4H). LC-MS m/z: 295.31 [M+H]⁺.

Intermediate 62

20 (E)-4-Bromo-3-(cyclopropylmethyl)-2-(2-nitroprop-1-en-1-yl)benzo[b]thiophene



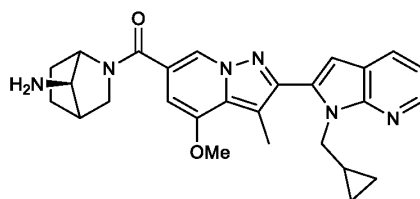
Ammonium acetate (0.261 g, 3.39 mmol) was added to a stirred solution of Intermediate 61 (1 g, 3.39 mmol) in nitroethane (0.242 ml, 3.39 mmol). The reaction mixture was stirred for 2 hours at 90°C, water (100 ml) was added to the reaction mixture, 25 and the contents were extracted with ethyl acetate (2×100 ml). The combined organic layers were washed with water (100 ml), dried over sodium sulphate, filtered, and volatiles were evaporated to dryness under reduced pressure to afford (E)-4-bromo-3-

(cyclopropylmethyl)-2-(2-nitroprop-1-en-1-yl)benzo[b]thiophene (1 g, 84%) as a yellow solid. ^1H NMR (300 MHz, DMSO- d_6) δ ppm: 8.39 (s, 1H), 8.14 (d, $J=8.3$ Hz, 1H), 7.76 (d, $J=7.6$ Hz, 1H), 7.44-7.34 (m, 1H), 3.34 (m, 2H), 1.29-1.2 (m, 1H), 0.47-0.42 (m, 2H), 0.27 (d, $J=4.5$ Hz, 2H).

5

Example 1

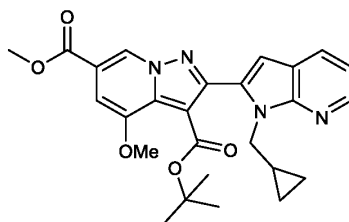
((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone



10

Intermediate 1A

3-(tert-Butyl)-6-methyl 2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxypyrazolo[1,5-a]pyridine-3,6-dicarboxylate

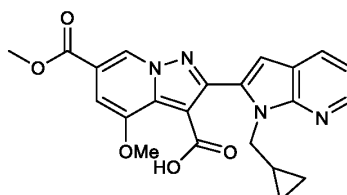


15 1-Amino-3-methoxy-5-(methoxycarbonyl)pyridin-1-ium (Intermediate 1, 0.618 g, 3.37 mmol) and K_2CO_3 (0.933 g, 6.75 mmol) were added to a stirred solution of tert-butyl 3-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)propiolate (Intermediate 2, 1 g, 3.37 mmol) in DMF (20 ml). The reaction mixture was stirred at a room temperature for 16 hours, diluted with EtOAc (50 ml), washed with water (3×50 ml) and brine (3×50 ml),
20 dried over Na_2SO_4 , and concentrated under reduced pressure to obtain a crude product. The crude product was purified using a silica gel column (24 g, Redisep[®] SiO_2 column, eluting with 30% EtOAc in hexane) to afford the title compound (650 mg, 40%) as a yellow solid. LC-MS m/z : 477.2 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, chloroform- d) δ ppm: 8.92 (d, $J=1.0$ Hz, 1H), 8.39 (d, $J=4.8$ Hz, 1H), 7.98-7.93 (m, 1H), 7.16-7.08 (m, 2H),

6.82 (s, 1H), 4.48 (d, J=7.0 Hz, 2H), 4.04 (s, 3H), 3.99 (s, 3H), 1.43 (m, 9 H), 1.37-1.21 (m, 5H), 0.38-0.25 (m, 4H).

Intermediate 1B

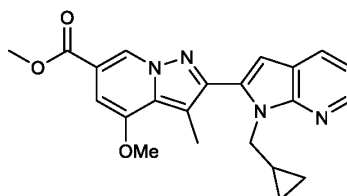
- 5 2-(1-(Cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-6-(methoxycarbonyl)pyrazolo[1,5-a]pyridine-3-carboxylic acid



- TFA (0.210 ml, 2.73 mmol) was added to a stirred solution of Intermediate 1A (650 mg, 1.364 mmol) in DCM (5 ml). The reaction mixture was stirred at a room temperature for 1 hour, and concentrated to afford the title compound (600 mg, 73%) as a brown solid. The crude compound was used in the next steps without further purification. LC-MS m/z: 421.1 [M+H]⁺.
- 10

Intermediate 1C

- 15 Methyl 2-(1-(cyclopropylmethyl)-1H-pyrrolo-[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate

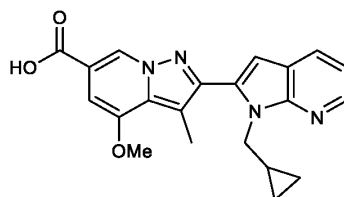


- Borane dimethyl sulfide complex (3.57 ml, 7.14 mmol) was added to a stirred solution of Intermediate 1B (600 mg, 1.427 mmol) in THF (10 ml) at 0°C. The reaction mixture was stirred for 30 min, followed by heating to 65°C and stirring for 5 hours, quenched with methanol (5 ml) at 0°C, and concentrated to afford the title compound (520 mg, 93%) as a brown solid. The crude compound was used in the next steps without further purification. LC-MS m/z: 391.2 [M+H]⁺. ¹H NMR (400 MHz, chloroform-*d*) δ ppm: 8.88-8.76 (m, 1H), 8.44-8.27 (m, 1H), 7.99-7.85 (m, 1H), 7.13-6.90 (m, 1H), 6.89-
- 20

6.85 (m, 1H), 6.76-6.69 (m, 1H), 4.62-4.44 (m, 2H), 4.07-3.96 (m, 6H), 2.58 (s, 3H), 1.05-0.78 (m, 1H), 0.45-0.11 (m, 4H).

Intermediate 1D

5 2-(1-(Cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylic acid

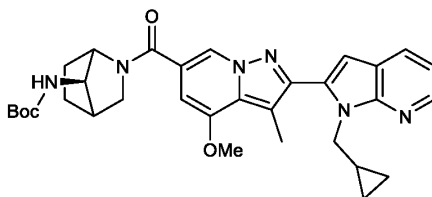


Lithium hydroxide (LiOH, 153 mg, 6.40 mmol) was added to a stirred solution of
 10 Intermediate 1C (500 mg, 1.281 mmol) in a mixture of THF (3 ml), methanol (3 ml) and water (3 ml). The reaction mixture was stirred at a room temperature for 30 min, concentrated, and the crude residue was acidified with 1.5 N HCl. The solid product obtained was filtered, and dried under vacuum to afford the title compound (360 mg, 75%) as an off-white solid. LC-MS m/z: 377.1 [M+H]⁺.

15

Intermediate 1E

tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



20 (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU, 707 mg, 1.860 mmol) and N,N-diisopropylethylamine (DIPEA, 0.487 ml, 2.79 mmol) were added to a stirred solution of Intermediate 1D (350 mg, 0.930 mmol) and tert-butyl ((7R)-2-azabicyclo[2.2.1]-heptan-7-yl)carbamate (197 mg, 0.930 mmol) in DMF (5 ml). The reaction mixture was stirred at a room temperature
 25 for 12 hours, poured into ice water (10 ml), and the solid product separated was filtered

and dried under vacuum to obtain a crude product, which was purified using a silica gel column (24 g, Redisep[®] SiO₂ column, eluting with 50% EtOAc in hexane) to afford the title compound (300 mg, 57%) as an off-white solid. LC-MS m/z: 571.2 [M+H]⁺.

5

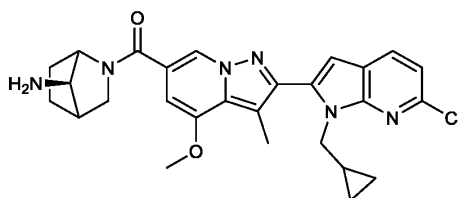
Example 1

TFA (0.364 ml, 4.73 mmol) was added to a stirred solution of Intermediate 1E (270 mg, 0.473 mmol) in DCM (5 ml). The reaction mixture was stirred at a room temperature for 1 hour, concentrated, and the crude compound obtained was purified using Prep-HPLC. The purified sample was further purified using RP-HPLC to afford the title compound (76 mg, 34%). LC-MS m/z: 471.2 [M+H]⁺. LC-MS retention time: 1.76 min (Method E). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.55 (s, 0.5 H), 8.39 (s, 0.5H), 8.31-8.33 (m, 1H), 8.03-8.05 (m, 1H), 7.14-7.17(m, 1H), 6.81 (s, 1H), 6.59-6.65 (m, 1H), 4.47 (br, d, J=7.03 Hz, 2H), 4.09 (br, s, 0.5H), 3.94-4.04 (m, 3H), 3.82 (br s, 0.5H), 3.62-3.77 (m, 0.5 H), 3.03-3.29 (m, 3.5H), 2.52-2.55 (m, 3H), 2.13-2.32 (m, 2H), 1.88-2.08 (m, 3H), 1.58-1.70 (m, 1H), 1.33-1.47 (m, 1H), 1.09-1.19 (m, 1H), 0.17-0.30 (m, 4H).

15

Example 2

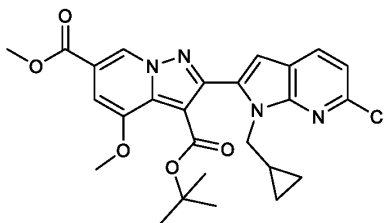
((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone



20

Intermediate 2A

3-(tert-Butyl)-6-methyl 2-(6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxypyrazolo[1,5-a]pyridine-3,6-dicarboxylate



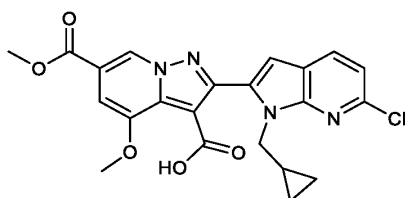
25

1-Amino-3-methoxy-5-(methoxycarbonyl)pyridin-1-ium (Intermediate 1, 1.384 g, 7.56 mmol) and K_2CO_3 (2.089 g, 15.11 mmol) were added to a stirred solution of tert-butyl 3-(6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)propiolate (Intermediate 4, 2.5 g, 7.56 mmol) in DMF (5 ml). The reaction mixture was stirred at a room temperature for 16 hours, diluted with EtOAc (50 ml), washed with water (3×50 ml), dried over Na_2SO_4 , and concentrated to obtain a crude product, which was purified using a silica gel column (40 g, Redisep[®] SiO_2 column, eluting with 30% EtOAc in hexane) to afford the title compound (1.5 g, 39%) as a yellow liquid. LC-MS m/z: 511.2 $[M+H]^+$.

10

Intermediate 2B

2-(6-Chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-6-(methoxycarbonyl)pyrazolo[1,5-a]pyridine-3-carboxylic acid

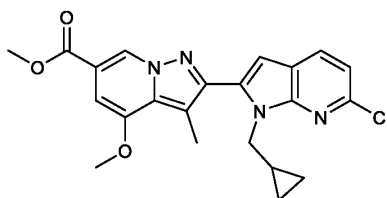


15 2,6-Lutidine (0.684 ml, 5.87 mmol) and trimethylsilyl trifluoromethanesulfonate (0.530 ml, 2.94 mmol) were added to a solution of Intermediate 2A (1.5 g, 2.94 mmol) in DCM (20 ml). The reaction mixture was stirred at a room temperature for 30 min, diluted with DCM (30 ml), washed with 10% $NaHCO_3$ solution (3×50 ml), dried over Na_2SO_4 , and concentrated to afford the title compound (1.5 g, 79%) as a brown solid. LC-MS m/z: 455.1 $[M+H]^+$.

20

Intermediate 2C

Methyl-2-(6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate

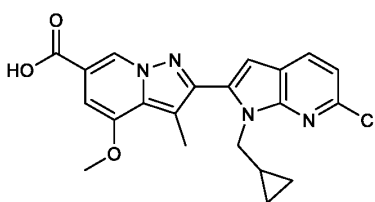


25

Borane dimethyl sulphide complex (3.30 ml, 6.60 mmol) was added to a stirred solution of Intermediate 2B (1 g, 2.198 mmol) in THF (10 ml) at 0°C. The reaction mixture was stirred at the same temperature for 30 min, then heated to 65°C and stirred for 5 hours, quenched with methanol (5 ml), and the reaction contents were concentrated to afford the title compound as an off-white solid (200 mg, 22%). The crude compound was used in the next steps without further purification. LC-MS m/z: 425.1 [M+H]⁺.

Intermediate 2D

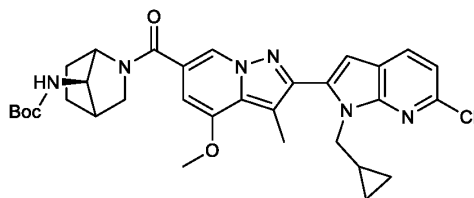
2-(6-Chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylic acid



LiOH (141 mg, 5.88 mmol) was added to a stirred solution of Intermediate 2C (500 mg, 1.177 mmol) in a mixture of THF (3 ml), methanol (3 ml) and water (3 ml), and the reaction mixture was stirred at a room temperature for 30 min. The reaction mixture was concentrated under reduced pressure and the residue obtained was acidified with 1.5 N HCl. The separated solids were filtered, and dried under vacuum to afford the title compound (400 mg, 83%) as an off-white solid. LC-MS m/z: 411.1 [M+H]⁺.

Intermediate 2E

tert-Butyl-((7R)-2-(2-(6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



HATU (555 mg, 1.460 mmol) and DIPEA (0.383 ml, 2.191 mmol) were added to a stirred solution of Intermediate 2D (300 mg, 0.730 mmol) and tert-butyl ((7R)-2-

azabicyclo[2.2.1]-heptan-7-yl)carbamate (155 mg, 0.730 mmol) in DMF (5 ml). The reaction mixture was stirred at a room temperature for 12 hours, poured into ice water (10 ml), the solid product thus obtained was filtered, and dried under vacuum to afford the title compound (400 mg, 91%). LC-MS m/z: 605.4 [M+H]⁺.

5

Example 2

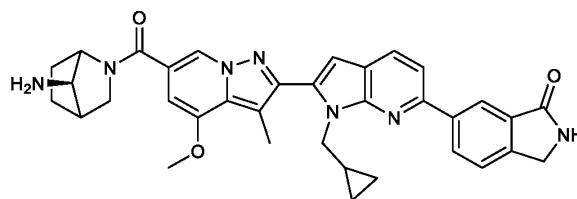
TFA (0.127 ml, 1.653 mmol) was added to a solution of Intermediate 2E (100 mg, 0.165 mmol) in DCM (5 ml). The reaction mixture was stirred at a room temperature for 1 hour, concentrated under reduced pressure, and the crude product obtained was purified using Prep-HPLC. The product was further purified using RP-HPLC to afford the title compound (12 mg, 14%). LC-MS m/z: 505.3 [M+H]⁺. LC-MS retention time: 1.79 min ((Method E). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.55 (s, 0.5H), 8.39 (s, 0.5 H), 8.11 (d, J=8.03 Hz, 1H), 7.22 (d, J=8.53 Hz, 1H), 6.87 (s, 1H), 6.60-6.66 (m, 1H), 4.42 (br, d, J=7.03 Hz, 2H), 4.09 (s, 0.5H), 3.99 (s, 3H), 3.81 (br, s, 0.5H), 3.48-61 (m, 2H), 3.12-3.29 (m, 2H), 3.06-3.25 (m, 2H), 2.57-2.66 (m, 1H), 2.53 (br, s, 3H), 1.60-2.23 (m, 4H), 1.39-1.41 (m, 1H), 1.13-1.15 (m, 1H), 0.31 (br, d, J=8.03 Hz, 2H), 0.20 (br, d, J=4.02 Hz, 2H).

15

Example 3

6-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one

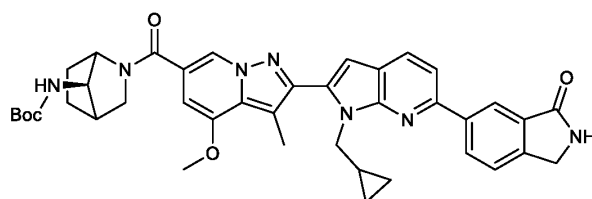
20



25

Intermediate 3A

tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-6-(3-oxoisoindolin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



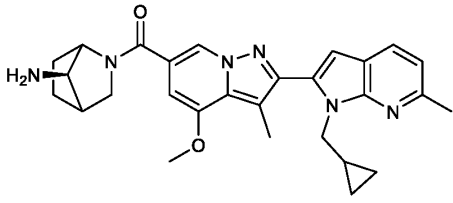
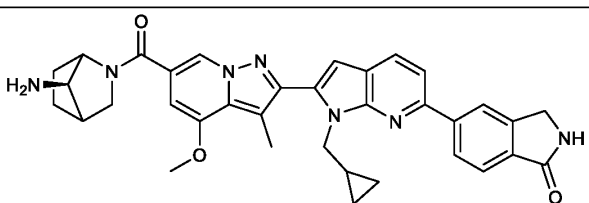
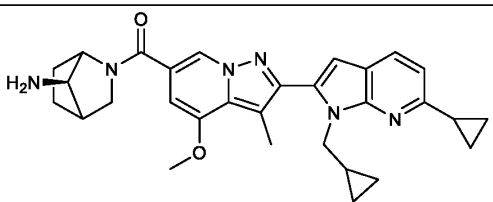
- PdCl₂(dppf).CH₂Cl₂ (13.50 mg, 0.017 mmol) was added to a degasified solution of Intermediate 2E (100 mg, 0.165 mmol), (3-oxoisindolin-5-yl)boronic acid (43.9 mg, 0.248 mmol) and K₂CO₃ (68.5 mg, 0.496 mmol) in dioxane (5 ml) and water (0.556 ml).
- 5 The reaction mixture was heated to 100°C and stirred for 12 hours, filtered through a celite bed, and the filtrate was concentrated to afford a crude product, which was purified using Prep-HPLC to afford the title compound (16 mg, 14%). LC-MS m/z: 702.4 [M+H]⁺. ¹H NMR (400 MHz, chloroform-*d*) δ ppm: 8.60 (s, 1H), 8.49-8.46 (m, 1H), 8.28-8.20 (m, 1H), 8.07-7.95 (m, 1H), 7.73-7.64 (m, 1H), 7.62-7.53 (m, 1H), 6.78 (s, 1H),
- 10 6.53 (s, 1H), 6.20-6.10 (m, 1H), 4.64-4.41 (m, 5H), 4.01 (s, 3H), 3.89-3.72 (m, 2H), 3.33-3.18 (m, 1H), 2.64-2.50 (m, 4H), 1.95 (br s, 2H), 1.41 (s, 9H), 1.34-1.14 (m, 2H), 0.38-0.25 (m, 4H).

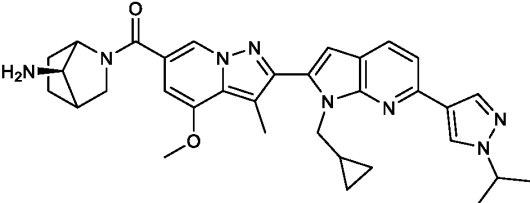
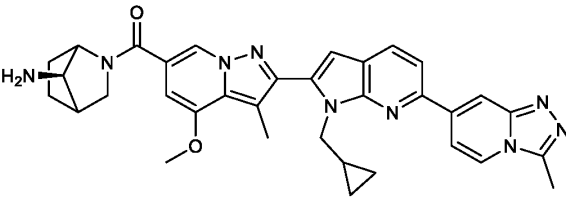
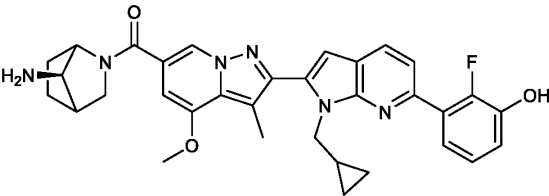
Example 3

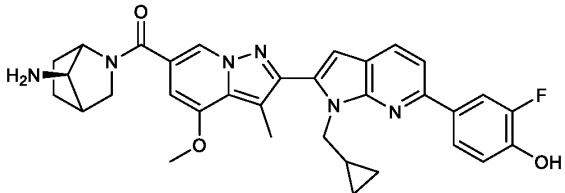
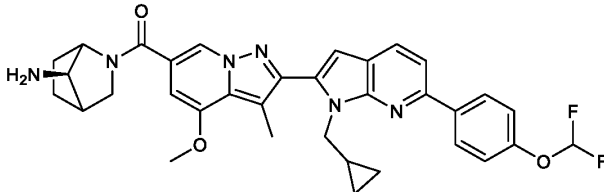
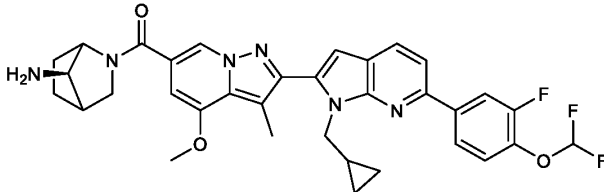
- 15 TFA (0.016 ml, 0.214 mmol) was added to a solution of Intermediate 3A (15 mg, 0.021 mmol) in DCM (5 ml). The reaction mixture was stirred for 1 hour, concentrated, and the crude product obtained was purified using Prep-HPLC. The purified product was further purified using RP-HPLC to afford the title compound (7.42mg, 57%). LC-MS m/z: 602.2 [M+H]⁺. HPLC retention time: 6.364 min (Method C). ¹H NMR (400 MHz,
- 20 DMSO-*d*₆) δ ppm: 8.70-8.57 (m, 1H), 8.46-8.32 (m, 3H), 8.18-8.08 (m, 1H), 7.88-7.77 (m, 1H), 7.72-7.58 (m, 1H), 6.89-6.76 (m, 1H), 6.66-6.52 (m, 1H), 4.71-4.48 (m, 2H), 4.47-4.35 (m, 2H), 4.10-3.88 (m, 5H), 3.87-3.42 (m, 1H), 3.06-3.22 (m, 1H), 2.54-2.41 (m, 3H), 1.76-2.26 (m, 4H), 1.48-1.31 (m, 1H), 1.27-1.15 (m, 1H), 0.44-0.20 (m, 4H).
- 25 Compounds of Examples 4 to 12 in Table 1 were prepared following a procedure similar to the preparation of a compound of Example 3, using Suzuki coupling reaction of Intermediate 2E with appropriate boronic acid.

Table 1

Example	Structure,
---------	------------

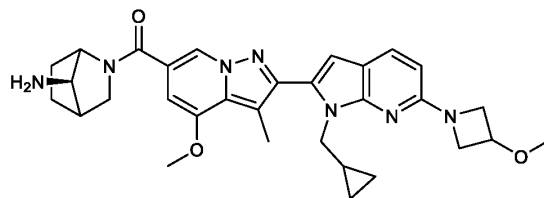
	Name, Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
4	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone. Analytical data: 485.2, 4.452 min (Method C)
5	 5-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one. Analytical data: 602.2, 6.281 min (Method C)
6	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-cyclopropyl-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical data: 511.4, 7.977 min (Method C)

7	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(1-isopropyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical data: 579.4, 6.603 min (Method C)
8	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone. Analytical data: 602.3, 4.761 min (Method C)
9	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-fluoro-3-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical data: 581.3, 7.259 min (Method C)

10	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-fluoro-4-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone. Analytical data: 581.4, 4.619 min (Method C)
11	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(4-(difluoromethoxy)phenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical data: 613.2, 5.878 min (Method C)
12	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(4-(difluoromethoxy)-3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone. Analytical data: 631.3, 2.417 min (Method E)

Example 13

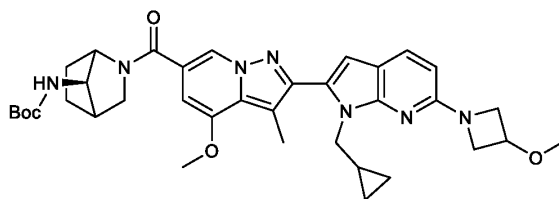
((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-methoxyazetidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone



5

Intermediate 13A

tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-6-(3-methoxyazetidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



10

$\text{Pd}_2(\text{dba})_3$ (5.67 mg, 6.20 μmol) and 2-Dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (RUPHOS, 15.42 mg, 0.033 mmol) were added to a degassed solution of Intermediate 2E (100 mg, 0.165 mmol), 3-methoxyazetidine (28.8 mg, 0.331 mmol) and caesium carbonate (162 mg, 0.496 mmol) in dioxane (5 ml). The reaction mixture was heated to 85°C and stirred for 12 hours, filtered, and the filtrate was concentrated under reduced pressure to afford the crude product, which was used in the next step without further purification. LC-MS m/z : 656.5 $[\text{M}+\text{H}]^+$.

15

Example 13

TFA (0.117 ml, 1.525 mmol) was added to a stirred solution of Intermediate 13A (100 mg, 0.152 mmol) in DCM (5 ml). The reaction mixture was stirred for 1 hour, concentrated under reduced pressure, and the crude product obtained was purified using Prep-HPLC. The purified sample was further purified using RP-HPLC to afford the title compound (8.5mg, 10%). LC-MS m/z : 556.4 $[\text{M}+\text{H}]^+$. HPLC retention time: 7.703 min (Method C). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm: 8.56-8.34 (m, 1H), 7.78 (d, $J=8.5$

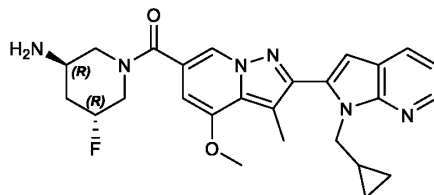
25

Hz, 1H), 6.62-6.57 (m, 2H), 6.27 (d, J=8.5 Hz, 1H), 4.35 (br, d, J=6.0 Hz, 4H), 4.27-4.13 (m, 2H), 3.98 (s, 6H), 3.84-3.58 (m, 5H), 3.29 3.06 (m, 1H), 2.67-2.57 (m, 3H), 2.20-1.40 (m, 5H), 1.24-1.12 (m, 1H), 0.32-0.22 (m, 4H).

5

Example 14

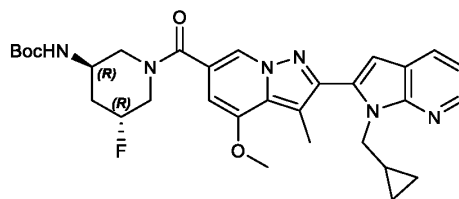
((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone



10

Intermediate 14A

tert-Butyl-((3R,5R)-1-(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



Intermediate 14A was prepared following a procedure similar to the preparation of Intermediate 2E (20 mg, 52%). LC-MS m/z: 577.1 [M+H]⁺.

15

Example 14

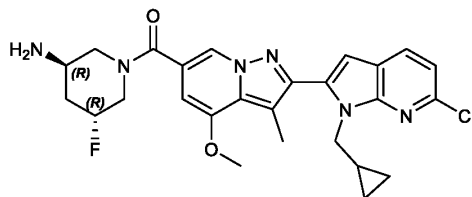
TFA (0.027 ml, 0.347 mmol) was added to a stirred solution of Intermediate 14A (20 mg, 0.035 mmol) in DCM (1 ml) at a room temperature. The reaction mixture was stirred for 1 hour, concentrated under reduced pressure, and the crude product obtained was purified using Prep-HPLC. The purified product was further purified using RP-HPLC to afford the title compound (6 mg, 36%). LC-MS m/z: 477.1 [M+H]⁺. LC-MS retention time: 1.374 min (method E). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.39 (s, 1H), 8.32 (dd, J=1.5, 4.6 Hz, 1H), 8.04 (dd, J=1.7, 7.8 Hz, 1H), 7.16 (dd, J=4.6, 7.8 Hz, 1H), 6.81

20

(s, 1H), 6.56 (s, 1H), 4.89 (br, s, 1H), 4.47 (d, J=7.1 Hz, 2H), 3.98 (s, 4H), 3.03-2.98 (m, 2H), 2.55 (s, 3H), 2.21-2.11 (m, 1H), 1.35-1.09, (m, 3H), 0.32-0.14 (m, 4H).

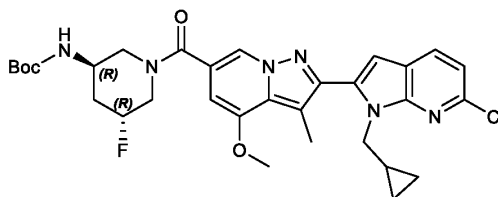
Example 15

- 5 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone



Intermediate 15A

- 10 tert-Butyl-((3R,5R)-1-(2-(6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



- 15 HATU (1296 mg, 3.41 mmol) and DIPEA (0.893 ml, 5.11 mmol) were added to a stirred solution of Intermediate 2D (700 mg, 1.704 mmol) and tert-butyl ((3R,5R)-5-fluoropiperidin-3-yl)carbamate (372 mg, 1.704 mmol) in DMF (5 ml). The reaction mixture was stirred at a room temperature for 12 hours, poured into ice water (40 ml), and the solids obtained were filtered, dried under vacuum to afford the title compound (1g, 67%) as an off-white solid. LC-MS m/z: 611.4 [M+H]⁺.
- 20

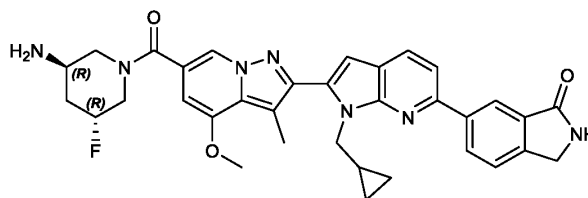
Example 15

- TFA (0.252 ml, 3.27 mmol) was added to a stirred solution of Intermediate 15A (200 mg, 0.327 mmol) in DCM (5 ml). The reaction mixture was stirred at a room temperature for 1 hour, concentrated under reduced pressure, and the crude product
- 25

obtained was purified using Prep-HPLC. The purified product was further purified using RP-HPLC to afford the title compound (21 mg, 12%). LC-MS m/z: 608.4 [M+H]⁺. LC-MS retention time: 2.054 min (Method E). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.38 (s, 1H), 8.10 (d, J=8.07 Hz, 1H), 7.22 (d, J=8.07 Hz, 1H), 6.87 (s, 1H), 6.56 (s, 1H), 4.96-4.78 (m, 1H), 4.41 (d, J=7.09 Hz, 3H), 3.98 (s, 4H), 2.97 (br, s, 2H), 2.52-2.55 (m, 3H), 2.14 (br, s, 1H), 1.41-1.60 (m, 1H), 1.12-1.20 (m, 1H), 0.27-0.34 (m, 2H), 0.20-0.26 (m, 2H).

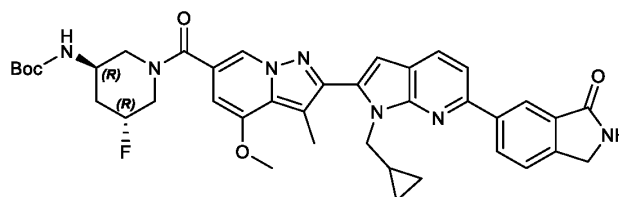
Example 16

6-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one



Intermediate 16A

tert-Butyl-((3R,5R)-1-(2-(1-(cyclopropylmethyl)-6-(3-oxoisoindolin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



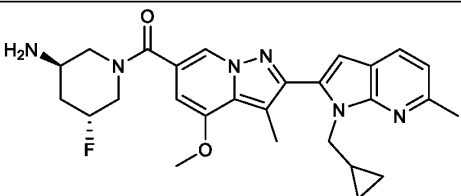
PdCl₂(dppf).CH₂Cl₂ (9.35 mg, 0.011 mmol) was added to a degassed solution of Intermediate 15A (70 mg, 0.115 mmol), (3-oxoisoindolin-5-yl)boronic acid (30.4 mg, 0.172 mmol) and K₂CO₃ (47.5 mg, 0.344 mmol) in dioxane (5 ml) and water (0.556 ml). The reaction mixture was stirred at 100°C for 12 hours, filtered, and the filtrate was concentrated under reduced pressure to afford a crude product. The crude product was used in next the step without further purification. LC-MS m/z: 708.5 [M+H]⁺.

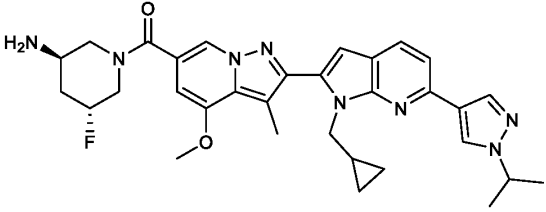
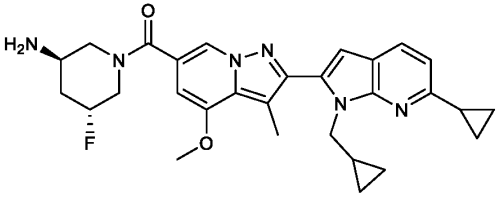
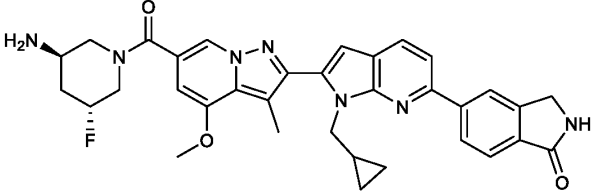
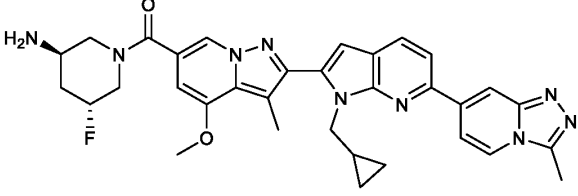
Example 16

TFA (0.076 ml, 0.989 mmol) was added to a solution of Intermediate 16A (70 mg, 0.099 mmol) in DCM (5 ml). The reaction mixture was stirred for 1 hour, concentrated under reduced pressure, and the crude product obtained was purified using Prep-HPLC. The purified product was further purified using RP-HPLC to afford the title compound (12 mg, 19%). LC-MS m/z: 608.4 [M+H]⁺. HPLC retention time: 6.559 min (method E). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.65 (s, 1H), 8.48-8.41 (m, 3H), 8.16 (d, J=8.4 Hz, 1H), 8.10-7.98 (m, 1H), 7.99 (brs, 1H), 7.88 (d, J=8.0 Hz, 1H), 7.73 (d, J=8.0 Hz, 1H), 6.95 (s, 1H), 6.59 (s, 1H), 5.08-4.55 (m, 1H), 4.59 (d, J=6.8 Hz, 3H), 4.46 (s, 3H), 4.00 (s, 3H), 3.20 (br d, J=10.5 Hz, 1H), 2.57-2.53 (m, 3H), 2.49-2.27 (m, 2H), 1.78-1.58 (m, 1H), 1.34-1.11 (m, 2H), 0.34-0.26 (m, 4H).

Compounds of Examples 17 to 21 in Table 2 were prepared following a procedure similar to the preparation of a compound of Example 16, using the Intermediate 15A and the appropriate boronic acid.

Table 2

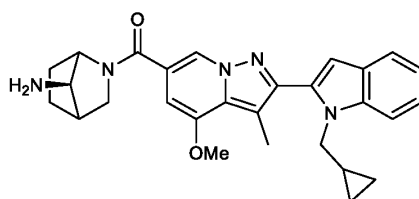
Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
17	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)-methanone. Analytical Data: 491.4, 4.563 min (Method C)

18	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(1-isopropyl-1H-pyrazol-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 585.5, 7.566 min (Method C)
19	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(6-cyclopropyl-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 585.5, 7.566 min (Method C)
20	 5-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one Analytical Data: 608.3, 5.958 min (Method C)
21	

	((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 608.4, 5.179 min (Method C)
--	---

Example 22

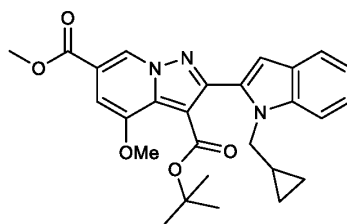
((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone



5

Intermediate 22A

3-(tert-Butyl)-6-methyl 2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxypyrazolo[1,5-a]pyridine-3,6-dicarboxylate

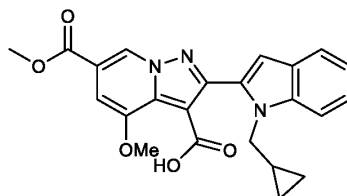


tert-Butyl-3-(1-(cyclopropylmethyl)-1H-indol-2-yl)propiolate (1g, 3.39 mmol) and K_2CO_3 (0.468 g, 3.39 mmol) were added to a stirred solution of 1-amino-3-methoxy-5-(methoxy-carbonyl)pyridin-1-ium (Intermediate 1, 0.620 g, 3.39 mmol) in DMF (10 ml). The reaction mixture was stirred at a room temperature for 48 hours, quenched with water (100 ml), and extracted with EtOAc (2×100 ml). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to obtain a crude product, which was purified using a silica gel column (EtOAc in hexane). The product was isolated at 10-20% EtOAc in hexane, required fractions were collected and volatiles were evaporated to dryness under reduced pressure to afford the title compound (480 mg, 30%). LC-MS m/z: 476.2 $[M+H]^+$.

20

Intermediate 22B

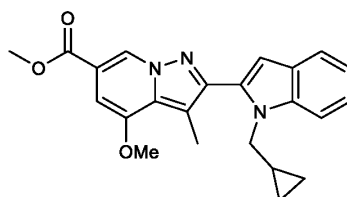
2-(1-(Cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-6-(methoxycarbonyl)pyrazolo[1,5-a]pyridine-3-carboxylic acid



- 5 Formic acid (0.028 ml, 0.736 mmol) was added to a solution of Intermediate 22A (350 mg, 0.736 mmol) in DCM (1 ml). The reaction mixture was stirred at a room temperature for 4 hours, quenched with saturated NaHCO₃ solution, and extracted with DCM (2×100 ml). The combined the organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford the crude title compound (150 mg, 49%)
- 10 LC-MS m/z: 420.2 [M+H]⁺.

Intermediate 22C

Methyl-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate

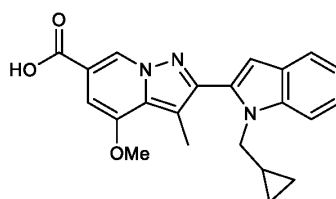


- 15 Borane dimethyl sulfide complex (0.834 ml, 1.669 mmol) was added to a stirred solution of Intermediate 22B (350 mg, 0.834 mmol) in THF (2 ml). The reaction mixture was stirred at 50°C for 5 hours, cooled to a room temperature, quenched with methanol, and concentrated under reduced pressure to afford a crude product, which was purified
- 20 using a silica gel column (EtOAc in hexane (10-20%)) to afford the title compound (100 mg, 31%) LC-MS /z: 390.2 [M+H]⁺.

Intermediate 22D

2-(1-(Cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylic acid

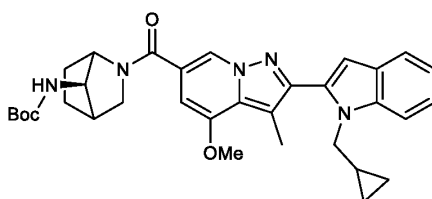
25



LiOH (9.39 mg, 0.392 mmol) was added to a stirred solution of Intermediate 22C (100 mg, 0.131 mmol) in THF (6 ml) and water (6 ml). The reaction mixture was stirred at a room temperature for 16 hours, concentrated under reduced pressure to evaporate THF, and acidified with 1N HCl. The solid product separated was filtered and dried under vacuum to afford the title compound (80 mg, 163%); LC-MS m/z: 376.2 [M+H]⁺.

Intermediate 22E

tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



HATU (161 mg, 0.424 mmol), DIPEA (0.185 ml, 1.060 mmol) and tert-butyl ((7R)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate (90 mg, 0.424 mmol) were added to a stirred solution of Intermediate 22D (260 mg, 0.353 mmol) in DMF (2 ml) at 0°C. The reaction mixture was stirred at a room temperature for 2 hours, quenched with water (100 ml), and extracted with EtOAc (2×100 ml). The combined the organic layers were dried over sodium sulphate, filtered, and concentrated under reduced pressure to afford the crude product (100 mg, 49%). LC-MS m/z: 570.3 [M+H]⁺.

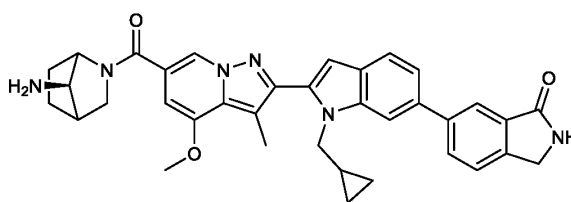
Example 22

TFA (0.022 ml, 0.281 mmol) was added to a stirred solution of Intermediate 24E (80 mg, 0.140 mmol) in DCM (2 ml). The reaction mixture was stirred at a room temperature for 16 hours, evaporated completely under reduced pressure, and the crude product obtained was purified using Prep-HPLC. The purified product was further purified using RP-HPLC to afford the title compound (13.4 mg, 20%). LC-MS m/z: 470.3

[M+H]⁺. LC-MS retention time: 2.0 min (Method E). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.63-8.40 (m, 1H), 8.32-8.01 (m, 1H), 7.62 (t, J=7.3 Hz, 2H), 7.33-6.93 (m, 2H), 6.76 (s, 1H), 6.67-6.50 (m, 1H), 4.58-4.25 (m, 3H), 4.08-3.96 (m, 3H), 3.90 (s, 1H), 3.87-3.80 (m, 1H), 3.67-3.54 (m, 2H), 3.30-3.14 (m, 1H), 2.97-2.60 (m, 2H), 2.05-1.58 (m, 2H), 1.29-1.13 (m, 2H), 1.13-1.03 (m, 1H), 0.34-0.21 (m, 2H), 0.12 (q, J=4.8 Hz, 2H).

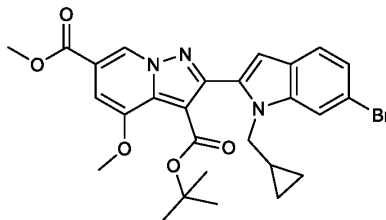
Example 23

6-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one



Intermediate 23A

3-(tert-Butyl)-6-methyl 2-(6-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxypyrazolo[1,5-a]pyridine-3,6-dicarboxylate



tert-Butyl 3-(6-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)propiolate

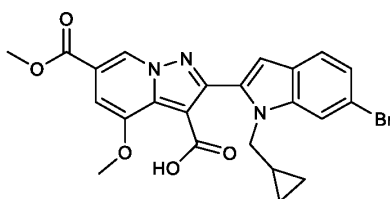
(Intermediate 6, 5.5g, 14.69 mmol) and K₂CO₃ (6.09 g, 44.1 mmol) were added to a solution of 1-amino-3-methoxy-5-(methoxycarbonyl)pyridin-1-ium 2,4-dinitrophenolate (Intermediate 1, 8.07 g, 22.04 mmol) in DMF (50 ml). The reaction mixture was stirred overnight, concentrated under a vacuum at ~45°C over a period of 1 hour, diluted with EtOAc, and filtered through a celite bed. The filtrate was further washed with water, dried over Na₂SO₄, filtered, and the organic layer was concentrated under vacuum to obtain a crude compound, which was purified using a silica gel column (40 g, Redisep[®] SiO₂ column, eluting with 30% EtOAc in hexane) to afford the title compound (5.3g, 65%).

LC-MS m/z: 500.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm: 9.04-8.91 (m, 1H), 8.56-7.96-7.84 (m, 1H), 7.63-7.53 (m, 1H), 7.30-7.06 (m, 2H), 6.80-6.70 (m, 1H), 4.44-4.30 (m, 2H), 3.96-3.86 (m, 6H), 1.43-1.36 (m, 8H), 1.12-1.02 (m, 1H), 0.34-0.24 (m, 2H), 0.18-0.12 (m, 2H).

5

Intermediate 23B

2-(6-Bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-6-(methoxycarbonyl)pyrazolo[1,5-a]pyridine-3-carboxylic acid

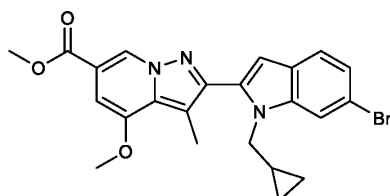


10 2,6-Lutidine (8.91 ml, 76 mmol) was added to a stirred solution of Intermediate 23A (5.3g, 9.56 mmol) in DCM (50 ml), followed by the addition of trimethylsilyl trifluoromethanesulfonate (6.91 ml, 38.2 mmol) at 0-5°C. The reaction mixture was stirred for 2 hours at the same temperature, quenched with 10% NaHCO₃ solution, stirred for 10 min, and diluted with EtOAc (50 ml). The organic layer was separated, and

15 aqueous layer was extracted with EtOAc (3×25 ml). The combined organic layers were dried over Na₂SO₄, and concentrated under vacuum at a room temperature to obtain the title compound as a pale yellow syrup (5.5 g, 102%). LC-MS m/z: 500 $[M+H]^+$.

Intermediate 23C

20 Methyl-2-(6-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate



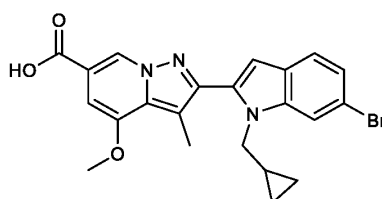
Borane-methyl sulfide complex (2.52 ml, 26.6 mmol) was added to a stirred solution of Intermediate 23B (5.3 g, 10.64 mmol) in THF (50 ml) at 0°C. The reaction

25 mixture was stirred for 30 min, slowly heated to 50°C and stirred for 4 hours, followed by

stirring at a room temperature for 12 hours. The reaction mixture was cooled to 0°C, quenched by careful addition of methanol, and concentrated under vacuum to obtain a crude residue. The crude product was triturated with water (3×25 ml), and the sticky off-white residue was purified using a silica gel column (40 g, Redisep® SiO₂ column, eluting with 0 to 50% EtOAc in hexane) to afford the title compound (1.1 g, 22%). LC-MS m/z: 470.1 [M+H]⁺.

Intermediate 23D

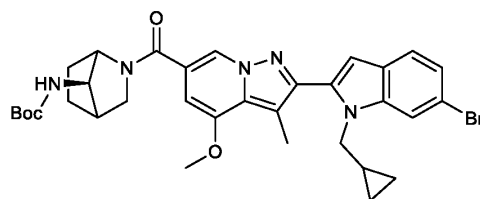
2-(6-Bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylic acid



LiOH (0.169 g, 7.05 mmol) in water (5 ml) was added to a stirred suspension of Intermediate 23C (1.1 g, 2.349 mmol) in a mixture of methanol (20 ml) and THF (5 ml). The reaction mixture was stirred for 4 hours, concentrated under vacuum to obtain a crude salt, which was neutralized using 1.5 N HCl. The solids obtained were filtered and dried under vacuum to afford the title compound (930 mg, 87%) as an off-white solid. LC-MS m/z: 455 [M+H]⁺.

Intermediate 23E

tert-Butyl-((7R)-2-(2-(6-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



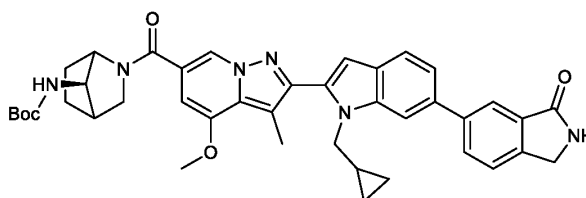
HATU (250 mg, 0.658 mmol), DIPEA (0.265 ml, 1.519 mmol) and tert-butyl ((7R)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate (107 mg, 0.506 mmol) were successively added to a stirred solution of Intermediate 23D (230 mg, 0.506 mmol) in DMF (2 ml).

The reaction mixture was stirred for 3 hours, cooled, and treated with ice-cold water and stirred for 10 min. The solids obtained were filtered, and dried in vacuum to afford the title compound (300 mg, 91%) as an off-white solid. LC-MS m/z : 650.3 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm: 8.59-8.50 (m, 1H), 8.42-8.31 (m, 1H), 7.89 (s, 1H), 7.59 (d, $J=8.3$ Hz, 1H), 7.22 (d, $J=8.8$ Hz, 1H), 7.14 -7.01 (m, 1H), 6.80 (s, 1H), 6.68-6.60 (m, 1H), 4.40 (br, d, $J=6.4$ Hz, 2H), 4.25-4.12 (m, 1H), 4.00 (br, s, 3H), 3.84-3.64 (m, 1H), 3.58-3.43 (m, 1H), 3.21-2.86 (m, 2H), 2.44 (br, s, 3H), 2.33 (br, s, 1H), 2.08-1.74 (m, 3H), 1.35 (br, s, 10H), 0.29 (br d, $J=7.6$ Hz, 2H), 0.11 (br, s, 2H).

10

Intermediate 23F

tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-6-(3-oxoisindolin-5-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



15

K_2CO_3 (29.8 mg, 0.216 mmol) and $PdCl_2(dppf)$ (7.90 mg, 10.79 μ mol) were added to a solution of Intermediate 23E (70 mg, 0.108 mmol) and 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isindolin-1-one (28.0 mg, 0.108 mmol) in dioxane (3 ml) in a 8 ml chemglass vial. The reaction mixture was degassed using argon, heated to 85°C and stirred for 8 hours, filtered, and concentrated under vacuum to afford a crude product, which was purified using Prep-HPLC to obtain the title compound (40 mg, 53%) as a white solid. LC-MS retention time: 0.94 min. LC-MS m/z : 701.5 $[M+H]^+$.

20

Example 23

TFA (0.1 ml, 1.298 mmol) was added to a solution of Intermediate 23F (40 mg, 0.057 mmol) in DCM (1 ml). The reaction mixture was stirred for 2 hours, concentrated under vacuum, the residue obtained was treated with 28% ammonia solution, and kept on standby for 30 min. The aqueous layer was decanted, and solids left in the flask were dried under vacuum. The crude product was further purified using RP-HPLC to afford the title compound (25 mg, 0.040 mmol, 70%), which was lyophilized to afford a white solid.

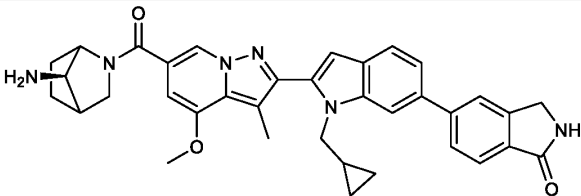
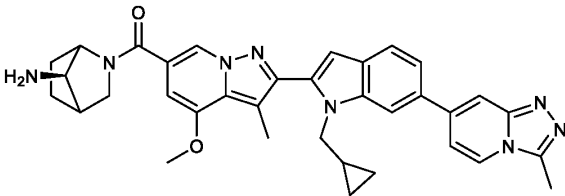
25

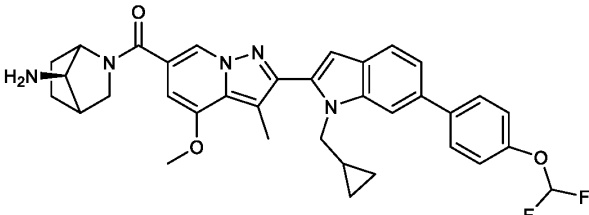
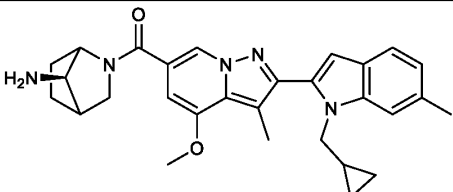
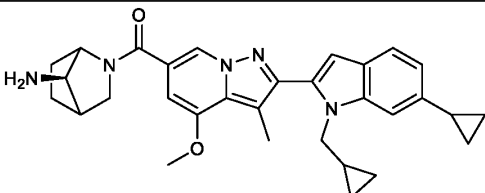
LC-MS m/z: 601.4 [M+H]⁺. HPLC retention time: 6.958 min (Method C). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.63-8.48 (m, 1H), 8.78-8.43 (m, 1H), 8.43-8.35 (m, 1H), 8.05-7.94 (m, 3H), 7.80-7.65 (m, 2H), 7.50-7.40 (m, 1H), 6.85-6.75 (m, 1H), 6.68-6.57 (m, 1H), 4.56-4.46 (m, 2H), 4.46-4.40 (m, 2H), 4.24-4.18 (m, 1H), 4.03-3.85 (m, 3H), 3.82-3.46 (m, 1H), 3.15-3.06 (m, 1H), 2.53 (s, 3H), 2.30-2.20 (m, 1H), 2.10-1.78 (m, 4H), 1.52-1.37 (m, 1H), 1.19-1.10 (m, 1H), 0.36-0.26 (m, 2H), 0.19-0.13 (m, 2H).

Compounds of Examples 24 to 28 in Table 3 were prepared following a procedure similar to the preparation of a compound of Example 23, using Suzuki coupling of Intermediate 23E with appropriate boronic acid.

10

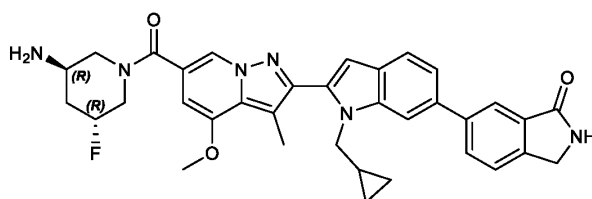
Table 3

Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
24	 5-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one Analytical Data: 601.4, 6.779 min (Method C)
25	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 601.4, 5.325 min (Method C)

26	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(4-(difluoromethoxy)phenyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 612.4, 5.954 min (Method C)
27	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-methyl-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 484.3, 5.698 min (Method C)
28	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-cyclopropyl-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 511.3, 4.777 min (Method C)

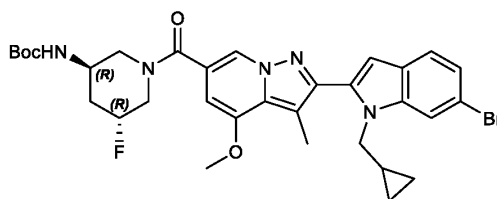
Example 29

6-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one



Intermediate 29A

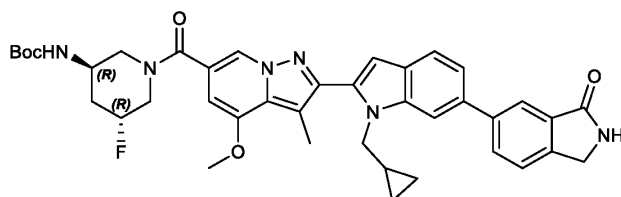
tert-Butyl-((3R,5R)-1-(2-(6-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



HATU (1742 mg, 4.58 mmol) followed by DIPEA (2.401 ml, 13.74 mmol) were added to a stirred solution of Intermediate 23D (2081 mg, 4.58 mmol) and tert-butyl ((3R,5R)-5-fluoropiperidin-3-yl)carbamate (1000 mg, 4.58 mmol) in DMF (3 ml). The reaction mixture was stirred at a room temperature overnight, cooled to 0°C, and ice-cold water was added. The solids obtained were filtered, washed with water, and purified using a silica gel column (0-1% methanol/chloroform) to afford the title compound (1.4g, 47%) as an off-white solid. LC-MS m/z: 655.4 [M+H]⁺.

Intermediate 29B

tert-Butyl-((3R,5R)-1-(2-(1-(cyclopropylmethyl)-6-(3-oxoisindolin-5-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



K₂CO₃ (29.6 mg, 0.214 mmol) and PdCl₂(dppf) (7.82 mg, 10.69 μmol) were added to a solution of Intermediate 29A (70 mg, 0.107 mmol) and 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isindolin-1-one (27.7 mg, 0.107 mmol) in dioxane (3 ml). The

reaction mixture was degassed using argon, heated to 85°C and stirred for 8 hours, filtered, and the filtrate was concentrated under vacuum to obtain a crude compound, which was purified using Prep-HPLC to afford the title compound (40 mg, 53%) as a white solid. LC-MS m/z: 707.5 [M+H]⁺.

5

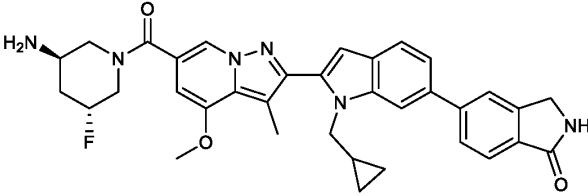
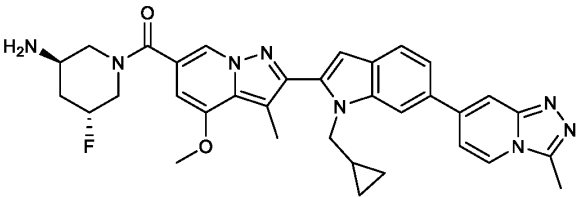
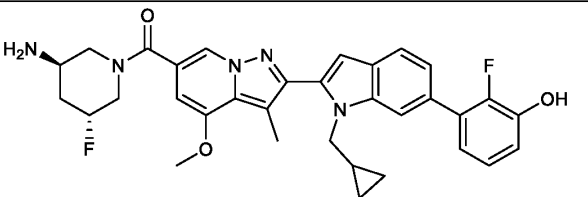
Example 29

TFA (0.1ml, 1.298 mmol) was added to a solution of Intermediate 29B (40 mg, 0.057 mmol) in DCM (1 ml). The reaction mixture was stirred for 2 hours, concentrated under vacuum, the crude compound obtained was treated with 28% ammonia solution, and kept on standby for 30 minutes. The aqueous layer was decanted, and the solids left in the flask were dried under vacuum. The product was further purified using RP-HPLC to afford the title compound (18 mg, 51%), which was lyophilized to afford white solid. LC-MS m/z: 607.4 [M+H]⁺. HPLC retention time: 7.167 min (Method C). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.54 (s, 1H), 8.38 (s, 1H), 7.98 (d, J=5.5 Hz, 2H), 7.89 (d, J=7.5 Hz, 1H), 7.78-7.65 (m, 2H), 7.49 (d, J=8.3Hz, 1H), 6.81 (s, 1H), 6.56 (s, 1H), 5.02-4.92 (m, 1H), 4.55-4.41 (m, 5H), 4.00 (s, 4H), 3.50-3.36 (m, 1H), 3.28-3.05 (m, 1H), 2.47-2.35 (m, 3H), 1.92-1.89 (m, 1H), 1.69 (br d, J=1.0 Hz, 1H), 1.24-1.20 (m, 1H), 0.40-0.29(m, 2H), 0.21-0.11 (m, 2H).

Compounds of Examples 30 to 33 in Table 4 were prepared following a procedure similar to the preparation of a compound of Example 29, by Suzuki coupling of Intermediate 29A with appropriate boronic acid.

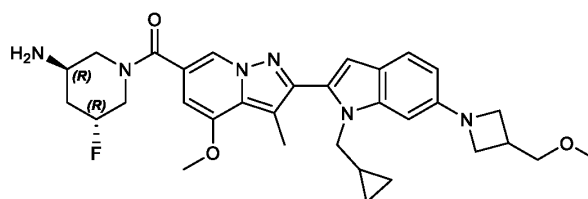
Table 4

Example	Structure
	Name
	Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method 1)

30	 5-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one Analytical Data: 607.2, 6.951 min (Method C)
31	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 674, 5.471 min (Method C)
32	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(2-fluoro-3-hydroxyphenyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 586.4, 1.964 min (Method E)

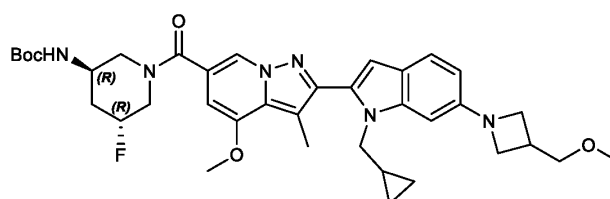
Example 33

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(3-(methoxymethyl)-azetidin-1-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone



Intermediate 33A

tert-Butyl-((3R,5R)-1-(2-(1-(cyclopropylmethyl)-6-(3-(methoxymethyl)azetidin-1-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



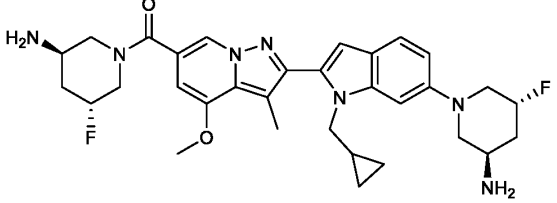
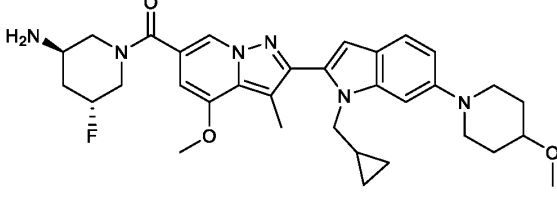
$\text{Pd}_2(\text{dba})_3$ (12 mg, 0.013 mmol), Cs_2CO_3 (100 mg, 0.307 mmol), and RUPHOS (13 mg, 0.028 mmol) were added to a solution of Intermediate 29A (65 mg, 0.099 mmol) and 3-(methoxymethyl)-azetidine (10.04 mg, 0.099 mmol) in dioxane (3 ml) in a 8 ml chemglass vial. The reaction mixture was degassed using argon, heated to 110°C and stirred for 14 hours, filtered, and concentrated under vacuum to afford a crude compound (70 mg, 104%), which was used in the next step without further purification. LC-MS m/z : 675.5 $[\text{M}+\text{H}]^+$.

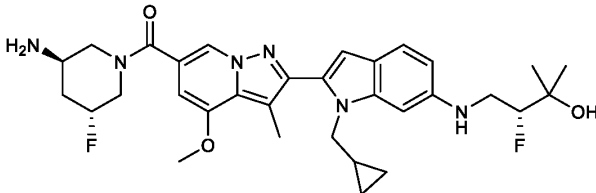
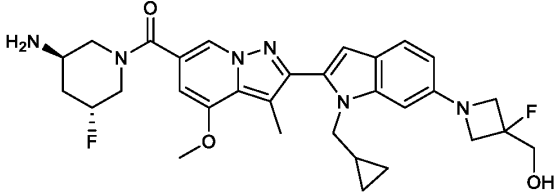
Example 33

TFA (0.3ml, 3.89 mmol) was added to a solution of Intermediate 33A (70 mg, 0.104 mmol) in DCM (1 ml). The reaction mixture was stirred for 2 hours, concentrated under vacuum, and the crude product obtained was purified using prep-HPLC. The product was further purified using RP-HPLC to afford the title compound (13 mg, 22%). LC-MS m/z : 575 $[\text{M}+\text{H}]^+$. LC-MS retention time: 1.963 min (Method E). ^1H NMR (400 MHz, methanol- d_4) δ ppm: 8.27 (d, $J=1.0$ Hz, 1H), 7.46 (d, $J=8.5$ Hz, 1H), 6.59 (s, 1H), 6.55 (s, 2H), 6.45 (dd, $J=2.0, 8.5$ Hz, 1H), 5.01 -4.96 (m, 1H), 4.27 (d, $J=6.5$ Hz, 2H), 4.09-3.96 (m, 6H), 3.72-3.64 (m, 4H), 3.51-3.35 (m, 1H), 3.31-3.14 (m, 2H), 3.06-2.88(m, 1H), 2.88-2.68 (m, 1H), 2.53 (s, 3H), 2.45-2.19 (m, 1H), 1.75-1.54 (m, 1H), 1.42-1.23 (m, 1H), 1.19-0.99 (m, 1H), 0.35-0.28 (m, 2H), 0.13 -0.01 (m, 2H),

Compounds of Examples 34 to 37 in Table 5 were prepared following a procedure similar to the preparation of a compound of Example 33, by Buchwald coupling of Intermediate 29A with appropriate amine.

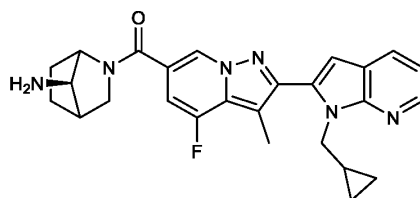
Table 5

Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
34	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(6-((3R,5R)-3-amino-5-fluoropiperidin-1-yl)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 592.4, 1.216 min (Method E)
35	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(4-methoxypiperidin-1-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 589.4, 1.970 min (Method E)

36	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(((R)-2-fluoro-3-hydroxy-3-methylbutyl)amino)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 595.4, 1.712 min (Method E)
37	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(3-fluoro-3-(hydroxymethyl)azetidin-1-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 579.4, 1.428 min (Method F)

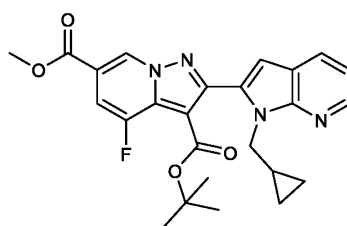
Example 38

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone



Intermediate 38A

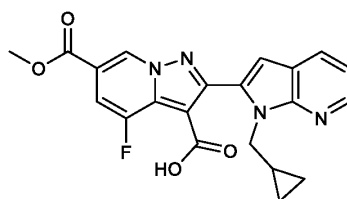
3-(tert-Butyl)-6-methyl 2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoropyrazolo[1,5-a]pyridine-3,6-dicarboxylate



Intermediate 38A was prepared following a procedure similar to the preparation of Intermediate 1A, and using 1-amino-3-fluoro-5-(methoxycarbonyl)pyridin-1-ium 2,4,6-trimethylbenzenesulfonate (Intermediate 9) and *tert*-butyl 3-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)propiolate (Intermediate 2), as a pale yellow solid (200 mg, 43%). LC-MS *m/z*: 465.1 [M+H]⁺.

Intermediate 38B

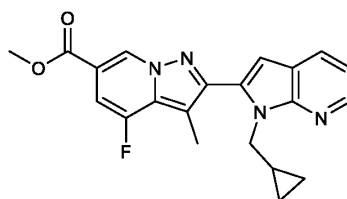
2-(1-(Cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-6-(methoxycarbonyl)pyrazolo[1,5-a]pyridine-3-carboxylic acid



Intermediate 38B was prepared following a procedure similar to the preparation of Intermediate 1B, as a pale yellow solid (170 mg, 56%). LC-MS *m/z*: 409.2 [M+H]⁺.

Intermediate 38C

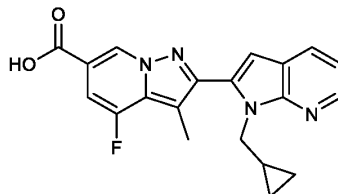
Methyl-2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate



Intermediate 38C was prepared following a procedure similar to the preparation of Intermediate 1C, as a brown solid (142 mg, 90%). LC-MS *m/z*: 379.2 [M+H]⁺.

Intermediate 38D

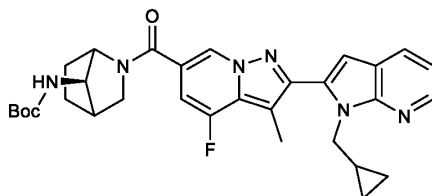
2-(1-(Cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carboxylic acid



5 Intermediate 38D was prepared following a procedure similar to the preparation of Intermediate, as an off white solid (125 mg, 93%). LC-MS m/z: 365.2 [M+H]⁺.

Intermediate 38E

tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



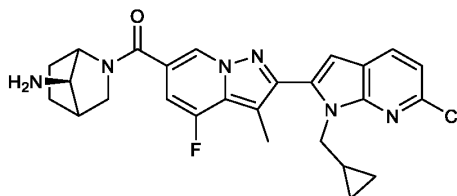
Intermediate 38E was prepared following a procedure similar to preparation of Intermediate 1E, as an off white solid (60 mg, 66%). LC-MS m/z: 559.3 [M+H]⁺.

15 Example 38

Compound of Example 38 was prepared following a procedure similar to the preparation of a compound of Example 1 (8.07 mg, 19%). LC-MS m/z: 459.3 [M+H]⁺. HPLC retention time: 5.349 min (Method C). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.87-8.72 (m, 1H), 8.34 (dd, *J*=4.52, 1.51 Hz, 1H), 8.07 (dd, *J*=7.78, 1.76 Hz, 1H), 7.13-7.19 (m, 2H), 6.88 (s, 1H), 4.50 (br, d, *J*=6.53 Hz, 2H), 4.08-3.81 (m, 1H), 3.75-3.45 (m, 20 2H), 3.10-3.29 (m, 3H), 2.53 (s, 3H), 2.09-2.32 (m, 2H), 1.96 (br, s, 3H), 1.87-1.65 (m, 1H), 1.36-1.46 (m, 1H), 1.24 (s, 1H), 0.21-0.45 (m, 4H).

Example 39

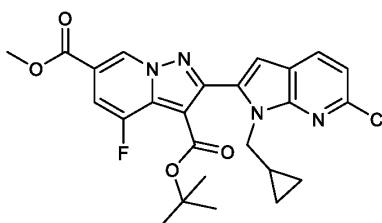
((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone



5

Intermediate 39A

3-(tert-Butyl)-6-methyl 2-(6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoropyrazolo[1,5-a]pyridine-3,6-dicarboxylate:

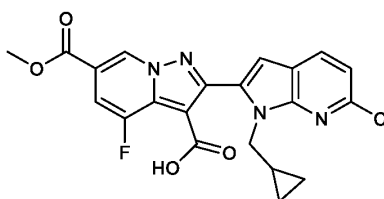


Intermediate 39A was prepared following a procedure similar to the preparation of Intermediate 2A, as a yellow solid (1.5 g, 33%). LC-MS m/z: 499.1 [M+H]⁺.

10

Intermediate 39B

2-(6-Chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-6-(methoxycarbonyl)pyrazolo[1,5-a]pyridine-3-carboxylic acid:



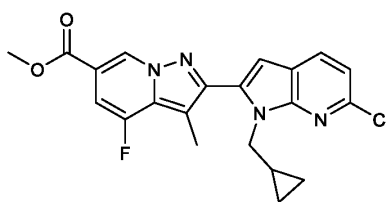
15

Intermediate 39B was prepared following a procedure similar to preparation of Intermediate 2B, as a brown solid (1.3 g, 98%). LC-MS m/z: 443.1 [M+H]⁺.

Intermediate 39C

Methyl-2-(6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate:

20

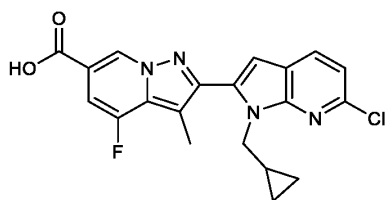


Intermediate 39B was prepared following a procedure similar to the preparation of Intermediate 2C, as a brown solid (1.21 g, 50%). LC-MS m/z: 413.2 [M+H]⁺.

5

Intermediate 39D

2-(6-Chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carboxylic acid:

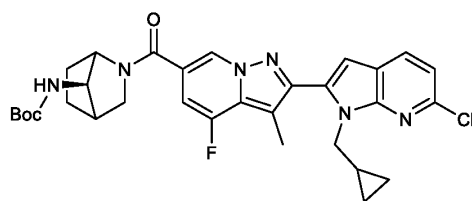


Intermediate 39D was prepared following a procedure similar to the preparation of Intermediate 2D, as a brown solid (1.2 g, 67%) as a brown solid. LC-MS m/z: 399.2 [M+H]⁺.

10

Intermediate 39E

tert-Butyl-((7R)-2-(2-(6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate:



Intermediate 39E was prepared following a procedure similar to the preparation of Intermediate 2E, as a brown solid (700 mg, 78%) as a brown solid. LC-MS m/z: 593.3 [M+H]⁺.

20

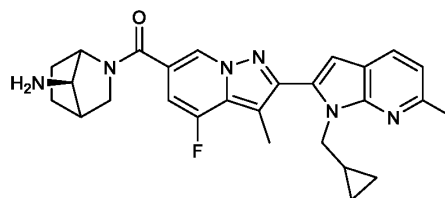
Example 39

Compound of Example 39 was prepared following a procedure similar to the preparation of a compound of Example 2 (7.2 mg, 8%). LC-MS m/z: 493.3 [M+H]⁺. LC-MS retention time: 2.105 min (Method E). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.95-8.71 (m, 1H), 8.13 (d, J=8.3 Hz, 1H), 7.29-7.11 (m, 2H), 6.95 (s, 1H), 4.56-4.18 (m, 2.5H), 4.28-4.21 (s, 0.5H), 3.84-3.75 (m, 0.5 H), 3.57 (br s, 1.5H), 3.19 (br d, J=10.8 Hz, 0.5H), 2.69-2.58 (m, 1.5H), 2.03-1.81 (m, 3H), 1.69-1.58 (m, 1H), 1.28 -1.10 (m, 2H), 0.40-0.14 (m, 4H).

10

Example 40

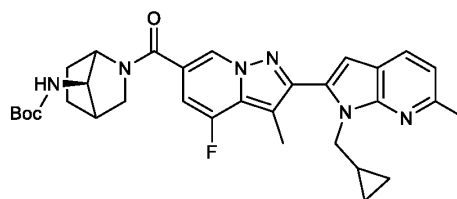
3((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone:



15

Intermediate 40A

tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-6-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate:



20

PdCl₂(dppf). DCM complex (13.77 mg, 0.017 mmol) was added to a degassed and stirred solution of Intermediate 39E (100 mg, 0.169 mmol), trimethylboraxine (31.7 mg, 0.253 mmol), and K₂CO₃ (69.9 mg, 0.506 mmol) in dioxane (5 ml) and water (0.556 ml). The reaction mixture was stirred at 100°C for 12 hours, filtered, and concentrated under reduced pressure to afford a crude compound. The crude compound was used in the next

25

step without further purification. LC-MS m/z: 573.3 [M+H]⁺.

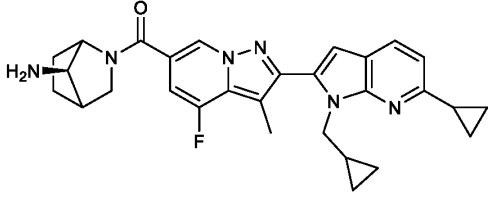
Example 40

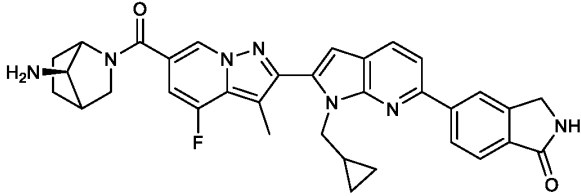
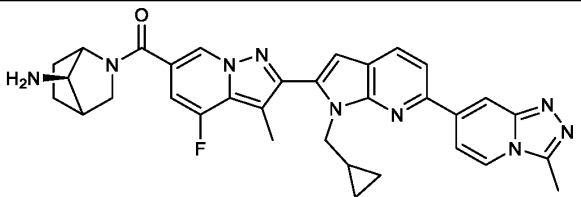
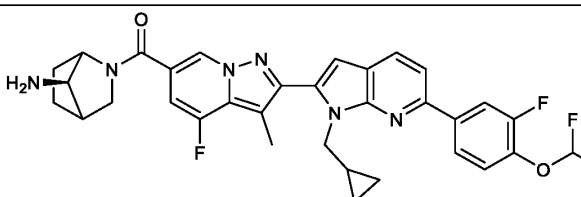
Compound of Example 40 was prepared following a procedure similar to the preparation of Example 3 to obtain the title compound as a brown solid (15 mg, 18%).

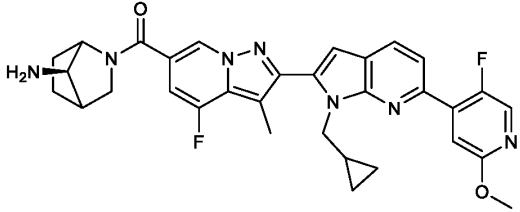
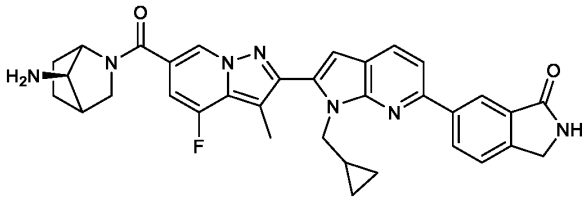
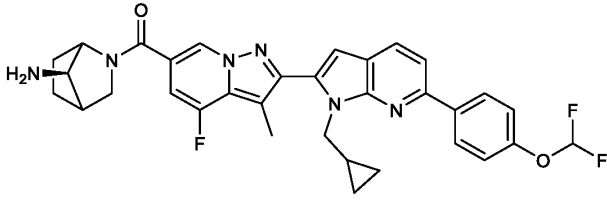
- 5 LC-MS m/z: 473.2 $[M+H]^+$. HPLC retention time: 4.76 min (Method C). 1H NMR (400 MHz, DMSO- d_6) δ ppm: 8.90-8.77 (m, 1H), 8.04-7.93 (m, 1H), 7.23 (s, 1H), 7.08-7.04 (m, 2H), 6.96-6.81 (m, 1H), 4.63-4.47 (m, 2.5H), 4.27 (brs, 0.5H), 3.80 (brs, 1H), 3.58 (brs, 2H), 2.62 (s, 3H), 2.53 (s, 3H), 2.02-1.85 (m, 2H), 1.70-1.66 (m, 1H), 1.28-1.02 (m, 3H), 0.41-0.19 (m, 4H).

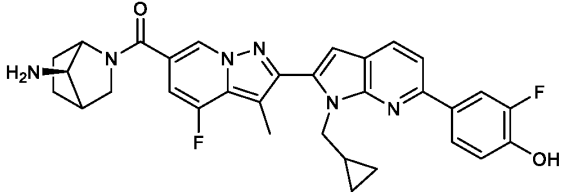
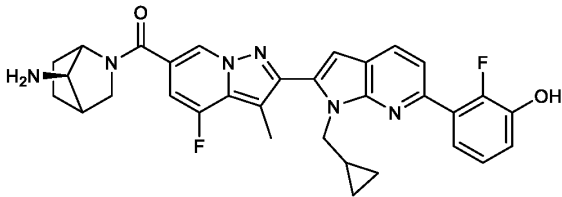
- 10 Compounds of Examples 41 to 49 in Table 6 were prepared following a procedure similar to the preparation of a compound of Example 40, using Suzuki coupling of Intermediate 39E with appropriate boronic acid.

Table 6

Example	Structure Name Analytical Data: LC-MS m/z $[M+H]^+$; HPLC retention time (HPLC method)
41	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-cyclopropyl-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 499.4, 6.953 min (Method C)

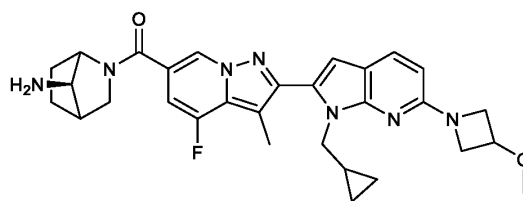
42	 5-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one Analytical Data: 590.2, 12.831 min (Method G)
43	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 587.2, 5.439 min (Method C)
44	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(4-(difluoromethoxy)-3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 619.4, 6.063 min (Method C)

45	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(5-fluoro-2-methoxypyridin-4-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 584.2, 5.467 min (Method C)
46	 6-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one Analytical Data: 590.3, 6.629 min (Method C)
47	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(4-(difluoromethoxy)phenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 601.4, 5.976 min (Method C)

48	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-fluoro-4-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 567.2, 7.351 min (Method C)
49	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-fluoro-3-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 569.3, 7.115 min (Method C)

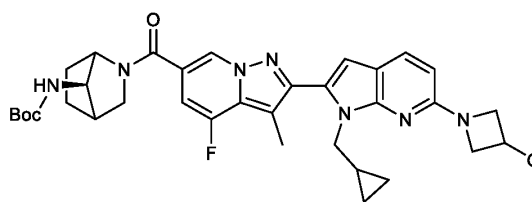
Example 50

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-methoxyazetidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone



Intermediate 50A

tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-6-(3-methoxyazetidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



Intermediate 50A was prepared following a procedure similar to the preparation of Intermediate 13A as a brown solid (crude 100 mg, 92%). LC-MS m/z: 644.5 [M+H]⁺.

5

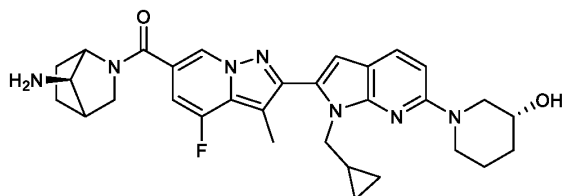
Example 50

Compound of Example 50 was prepared following a procedure similar to the preparation of a compound of Example 13, as a brown solid (23 mg, 26%). LC-MS m/z: 544.4 [M+H]⁺. HPLC retention time: 7.768 min (Method C). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.82 (s, 0.5H), 8.66 (s, 0.5 H), 7.80 (d, J=8.5 Hz, 1H), 7.13 (s, 1H), 7.10 (s, 1H), 6.68 (s, 1H), 6.29 (d, J=8.0 Hz, 1H), 4.53-4.28 (m, 4H), 4.27-4.14 (m, 2.5 H), 4.08 (br s, 0.5 H), 3.80 (dd, J=8.8, 4.3 Hz, 4H), 3.62-3.36 (m, 2H), 3.25-3.13 (m, 2H), 2.53 (m, 3H), 2.32-1.83 (m, 5H), 1.40-1.38 (m, 1H), 1.22-1.20 (m, 2H), 0.34-0.24 (m, 4H).

15

Example 51

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-((R)-3-hydroxypiperidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone

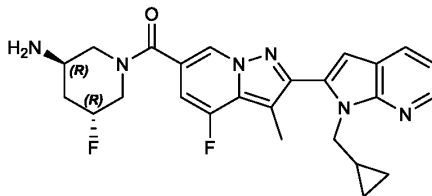


20

Compound of Example 51 was prepared following a procedure similar to the preparation of a compound of Example 50, by Buchwald coupling of Intermediate 39E with appropriate amine. LC-MS m/z: 558.4 [M+H]⁺, HPLC retention time: 5.795 min (method C).

Example 52

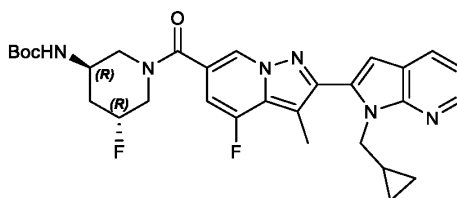
((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone



5

Intermediate 52A

tert-Butyl-((3R,5R)-1-(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



10 Intermediate 52A was prepared following a procedure similar to the preparation of Intermediate 14A as off-white solid (40 mg, 43%). LC-MS m/z : 565.3 $[M+H]^+$, LC-MS retention time: 2.01 min.

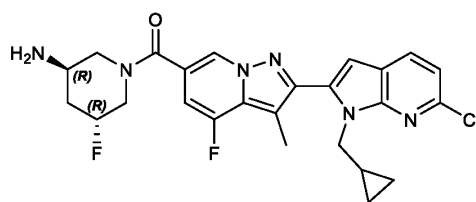
Example 52

15 Compound of Example 52 was prepared following a procedure similar to the preparation of a compound of Example 14 as off-white solid (7.73 mg, 23%). LC-MS m/z : 465.2 $[M+H]^+$. LC-MS retention time: 7.132 min (Method C). 1H NMR (400 MHz, DMSO- d_6) δ ppm: 8.65-8.74 (m, 1H), 8.23-8.35 (m, 1H), 7.96-8.06 (m, 1H), 7.00-7.20 (m, 2H), 6.84 (s, 1H), 4.80-5.04 (m, 1H), 4.37-4.56 (m, 4H), 2.84-3.03 (m, 4H), 2.57 (s, 3H), 2.04-2.23 (m, 1H), 1.40-1.64 (m, 1H), 1.12-1.24 (m, 2H), 0.14-0.42 (m, 4H).

20

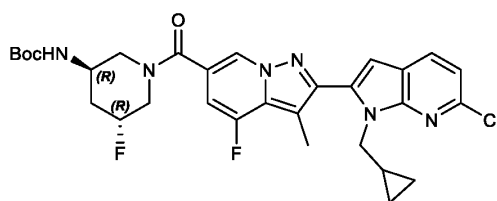
Example 53

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone



Intermediate 53A

tert-Butyl-((3R,5R)-1-(2-(6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



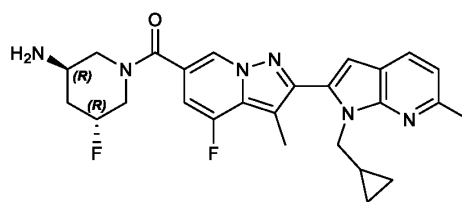
Intermediate 53A was prepared following a procedure similar to the preparation of Intermediate 15A, as off-white solid (130 mg, 87%). LC-MS m/z: 599.2 [M+H]⁺.

Example 53

Compound of Example 53 was prepared following a procedure similar to the preparation of a compound of Example 15, as off-white solid (10.1 mg, 9%). LC-MS m/z: 499.2 [M+H]⁺. LC-MS retention time: 2.058 min (Method E). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.79 (br s, 1H), 8.19-7.95 (m, 1H), 7.24 (d, J=8.3 Hz, 1H), 7.20-7.09 (m, 1H), 6.95 (s, 1H), 5.11-4.90 (m, 1H), 4.44 (d, J=7.1 Hz, 2H), 3.46-3.41 (m, 1H), 3.08-2.77 (m, 2H), 2.53 (s, 3H), 2.41-2.34 (m, 1H), 1.96-1.75 (m, 1H), 1.27-1.11 (m, 1H), 0.38-0.19 (m, 4H).

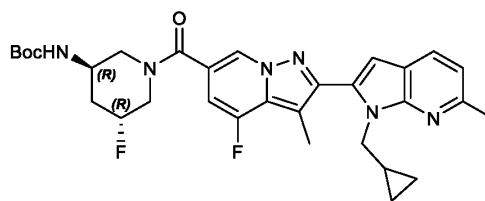
Example 54

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone



Intermediate 54A

tert-Butyl-((3R,5R)-1-(2-(1-(cyclopropylmethyl)-6-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



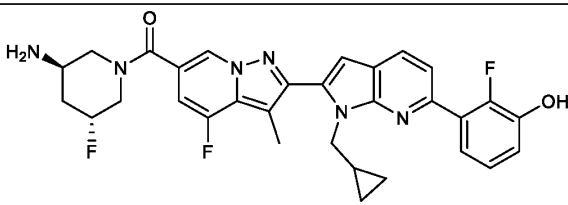
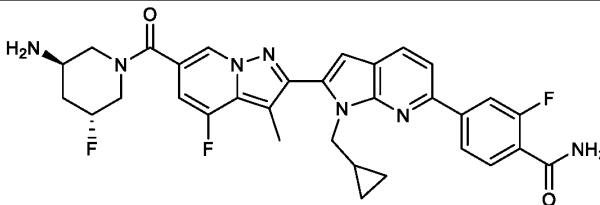
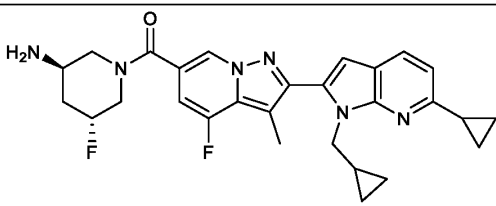
Intermediate 54A was prepared following a procedure similar to the preparation of Intermediate 16A, as off-white solid (70 mg, 91%). LC-MS m/z : 579.3 $[M+H]^+$.

Example 54

Compound of Example 54 was prepared following a procedure similar to the preparation of a compound of Example 16, as off-white solid (9.8 mg, 15%). LC-MS m/z : 479.3 $[M+H]^+$. LC-MS retention time: 1.19 min (Method E). 1H NMR (400 MHz, DMSO- d_6) δ ppm: 8.76-8.67 (m, 1H), 7.93 (d, $J=7.8$ Hz, 1H), 7.15-6.98 (m, 2H), 6.80 (s, 1H), 4.94-4.79 (m, 1H); 4.49-4.39 (m, 3H), 4.10 (ddd, $J=6.4, 5.0, 2.6$ Hz, 1H), 3.04-2.94 (m, 3H), 2.58 (s, 3H), 2.19-2.06 (m, 1H), 1.64-1.45 (m, 1H), 1.27-1.11 (m, 3H), 0.33-0.18 (m, 4H).

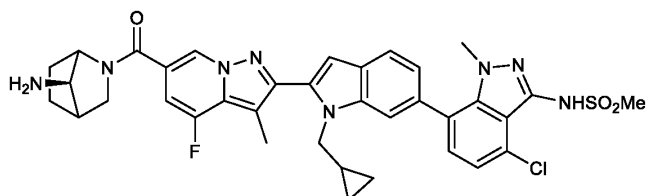
Compounds of Examples 55 to 57 in Table 7 were prepared following a procedure similar to the preparation of a compound of Example 54, by Suzuki coupling of Intermediate 53A with appropriate boronic acid.

Table 7

Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
55	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(2-fluoro-3-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 575.2, 7.279 min (Method C)
56	 4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorobenzamide Analytical Data: 602.3, 6.922 min (Method C)
57	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(6-cyclopropyl-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 505.3, 2.265 min (Method E)

Example 58

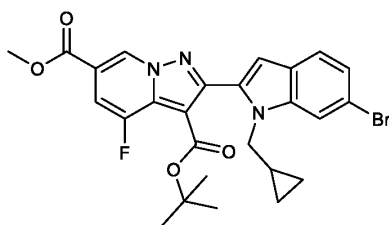
N-(7-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide



5

Intermediate 58A

3-(tert-Butyl)-6-methyl 2-(6-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-fluoropyrazolo[1,5-a]pyridine-3,6-dicarboxylate

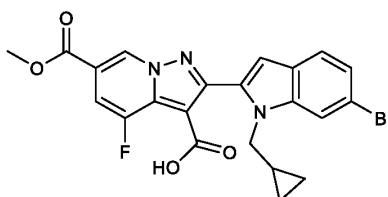


10 Intermediate 58A was prepared following a procedure similar to the preparation of Intermediate 23A, as a pale yellow solid (2.0 g, 27%). LC-MS m/z: 543.9 [M+H]⁺.

Intermediate 58B

2-(6-Bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-fluoro-6-(methoxycarbonyl)pyrazolo[1,5-a]pyridine-3-carboxylic acid

15

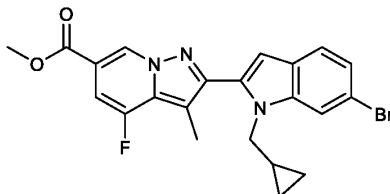


Intermediate 58B was prepared following a procedure similar to the preparation of Intermediate 23B, as a pale yellow solid (2 g, 3.07 mmol, 89%). LC-MS m/z: 488.0 [M+H]⁺.

20

Intermediate 58C

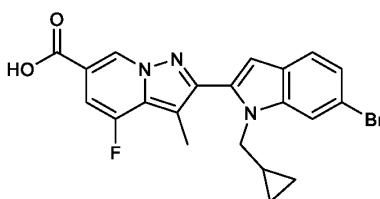
Methyl-2-(6-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate



5 Intermediate 58C was prepared following a procedure similar to the preparation of 23C as a pale yellow solid (crude 2.0g, 75%). LC-MS m/z: 458.1 [M+H]⁺.

Intermediate 58D

2-(6-Bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-
10 a]pyridine-6-carboxylic acid

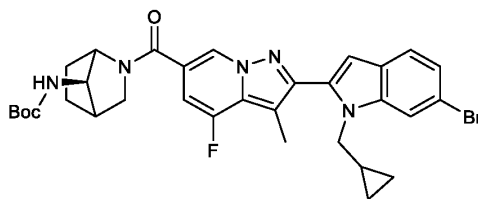


Intermediate 58D was prepared following a procedure similar to the preparation of Intermediate 23D, as a pale yellow solid (1.6 g, 83%). LC-MS m/z: 444.1 [M+H]⁺.

15

Intermediate 58E

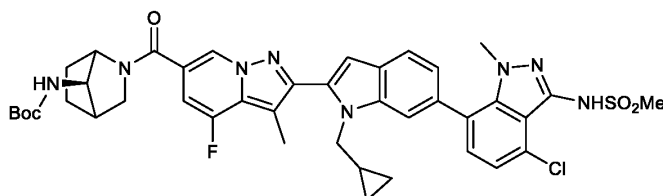
tert-Butyl-((7R)-2-(2-(6-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



Intermediate 58E was prepared following a procedure similar to the preparation of
20 Intermediate 23E, as a pale yellow solid (700 mg, 97%). LC-MS: m/z: 638.2 [M+H]⁺.

Intermediate 58F

tert-Butyl-((7R)-2-(2-(6-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



5

Intermediate 58F was prepared following a procedure similar to the preparation of Intermediate 23F as a pale yellow solid (70 mg, 95%). LC-MS m/z: 668.3 [M+H]⁺.

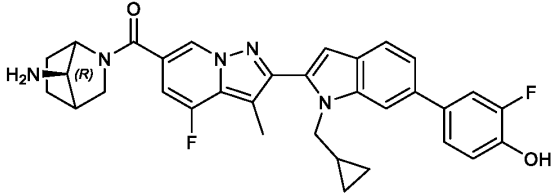
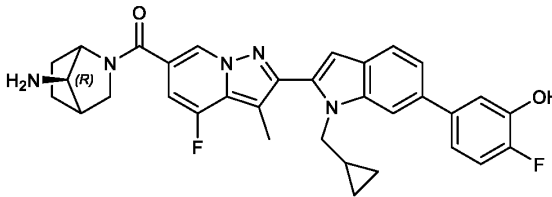
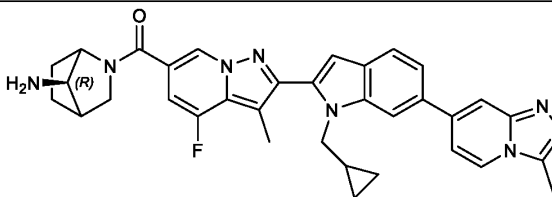
Example 58

10 Compound of Example 58 was prepared following a procedure similar to the preparation of a compound of Example 23, as a pale yellow solid (5 mg, 0.007 mmol, 8%). LC-MS m/z: 715.3 [M+H]⁺. LC-MS retention time: 0.85 min (Method G).

Compounds of Examples 59 to 62 in Table 8 were prepared following a procedure
15 similar to the preparation of a compound of Example 58, by Suzuki coupling of Intermediate 58E with appropriate boronic acid.

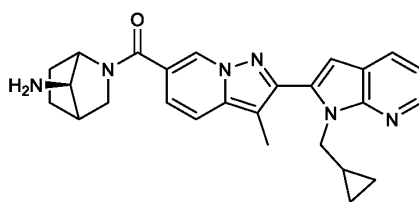
Table 8

Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
59	((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-fluoro-3-hydroxyphenyl)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 568.3, 3.8 min (Method C)

60	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-fluoro-4-hydroxyphenyl)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 568.3, 10.01 min (Method A)
61	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(4-fluoro-3-hydroxyphenyl)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 568.3, 3.5 min (Method C)
62	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 589.4, 1.16 min (Method C)

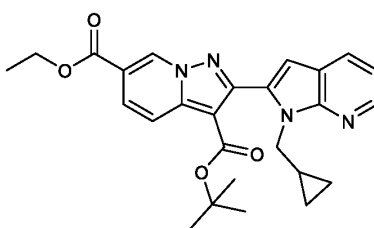
Example 63

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone



Intermediate 63A

3-(tert-Butyl)-6-ethyl 2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)pyrazolo[1,5-a]pyridine-3,6-dicarboxylate



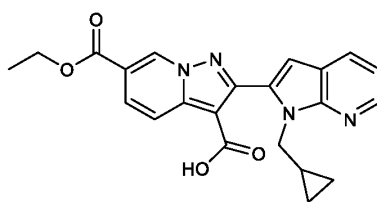
5

K_2CO_3 (839 mg, 6.07 mmol) and tert-butyl 3-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)propiolate (Intermediate 2, 600 mg, 2.024 mmol) were added to a stirred solution of 1-amino-3-(ethoxycarbonyl)pyridin-1-ium salt (Intermediate 8, 338 mg, 2.024 mmol) in acetone (25 ml). The reaction mixture was bubbled with air for 5 minutes, stirred overnight, filtered, and concentrated in vacuum to afford a crude compound, which was dissolved in EtOAc and washed with water. The organic layer was concentrated under vacuum to afford a crude compound, which was purified using a silica gel column to afford the title compound as a pale yellow solid (300 mg, 32%). LC-MS m/z : 461.2 $[M+H]^+$. 1H NMR (400 MHz, $DMSO-d_6$) δ ppm: 8.73 (s, 1H), 8.15 (d, $J=8.0$ Hz, 1H), 7.69-7.62 (m, 1H), 7.59-7.50 (m, 4H), 7.36 (t, $J=6.8$ Hz, 1H), 7.13 (br, t, $J=7.3$ Hz, 2H), 7.04-7.00 (m, 1H), 6.93 (s, 1H), 4.58-4.47 (m, 4H), 4.41 (d, $J=1.5$ Hz, 2H), 4.10 (s, 3H), 3.42 (s, 3H), 3.39-3.35 (m, 1H), 3.27 (br, s, 1H), 2.61-1.24 (s, 3H), 0.36-0.32 (m, 5H), 0.15 (s, 2H).

20

Intermediate 63B

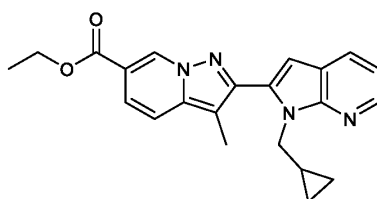
2-(1-(Cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-(ethoxycarbonyl)pyrazolo[1,5-a]pyridine-3-carboxylic acid



A solution of Intermediate 63A (300 mg, 0.651 mmol) in DCM (3 ml) and TFA (0.5 m) was stirred for 2 hours, and concentrated under reduced pressure at a room temperature to obtain a pale pink compound, which was dried over high vacuum to afford the title compound (200 mg, 76%). The crude compound was used in the next steps without further purification. LC-MS m/z: 405.2 [M+H]⁺.

Intermediate 63C

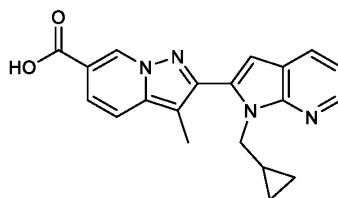
Ethyl-2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-
3-methylpyrazolo[1,5-a]pyridine-6-carboxylate



Intermediate 63C was prepared following a procedure similar to the preparation of Intermediate 1C, as a pale yellow solid (120 mg, 65%). LC-MS m/z: 375.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 9.27-9.22 (m, 1H), 8.35-8.31 (m, 1H), 8.08-8.03 (m, 1H), 7.87-7.81 (m, 1H), 7.62 (d, J=9.3 Hz, 1H), 7.19-7.13 (m, 1H), 6.94 (s, 1H), 4.59 (d, J=7.0 Hz, 2H), 4.40-4.34 (m, 2H), 2.48-2.45 (m, 3H), 1.37 (t, J=7.0 Hz, 3H), 1.29-1.19 (m, 1H), 0.35-0.24 (m, 4H).

Intermediate 63D

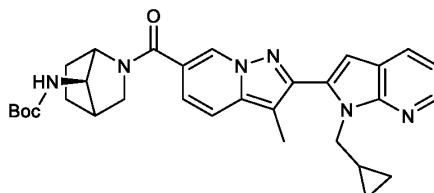
2-(1-(Cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylic acid



Intermediate 63D was prepared following a procedure similar to the preparation of Intermediate 1D, as off-white solid (110 mg, 99%). LC-MS m/z: 347 [M+H]⁺.

Intermediate 63E

- 5 tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



Intermediate 63C was prepared following a procedure similar to the preparation of Intermediate 1E (70 mg, 90%). LC-MS m/z: 541.3 [M+H]⁺.

10

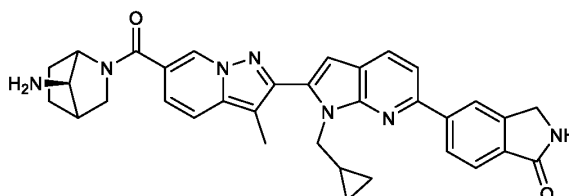
Example 63

- Compound of Example 63 was prepared following a procedure similar to preparation of Example 1 (9.0 mg, 15%). LC-MS m/z: 441.3 [M+H]⁺. LC-MS retention time: 1.570 min (Method E). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.94-8.78 (m, 1H), 8.32 (d, J=4.6 Hz, 1H), 8.05 (dd, J=1.1, 7.7 Hz, 1H), 7.85-7.75 (m, 1H), 7.39-7.24 (m, 1H), 7.16 (dd, J=4.5, 7.7 Hz, 1H), 6.87 (s, 1H), 4.56 (br d, J=7.1 Hz, 2H), 3.93-3.90 (m, 1H), 3.77-3.68 (m, 1H), 3.65-3.46 (m, 2H), 3.32-3.06 (m, 2H), 2.63-2.52 (m, 1H), 2.48-2.36 (m, 3H), 2.02-1.84 (m, 2H), 1.80-1.65 (m, 1H), 1.54-1.37 (m, 1H), 1.30-1.13 (m, 1H), 0.31-0.19 (m, 4H).

20

Example 64

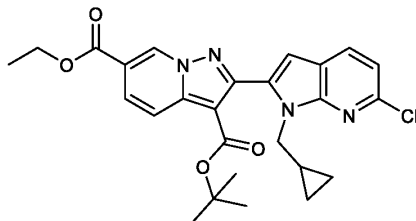
- 5-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one



25

Intermediate 64A

3-(tert-Butyl)-6-ethyl 2-(6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)pyrazolo[1,5-a]pyridine-3,6-dicarboxylate

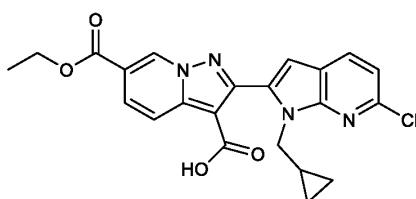


5

Intermediate 64A was prepared following a procedure similar to the preparation of Intermediate 2A (2 g, 30%). LC-MS m/z: 495.2 [M+H]⁺.

Intermediate 64B

2-(6-Chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-(ethoxycarbonyl)pyrazolo[1,5-a]pyridine-3-carboxylic acid

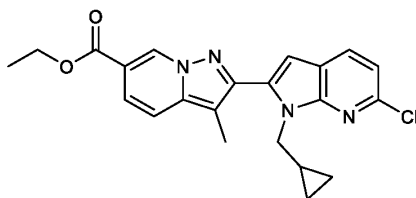


Intermediate 64B was prepared following a procedure similar to the preparation of Intermediate 2B (1.5 g, 85%). LC-MS m/z: 441.3 [M+H]⁺.

15

Intermediate 64C

Ethyl-2-(6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate

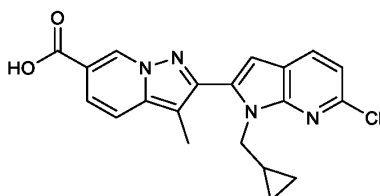


Intermediate 64C was prepared following a procedure similar to the preparation of Intermediate 2C (240 mg, 0.05 mmol, 86%). LC-MS m/z: 409.2 [M+H]⁺.

20

Intermediate 64D

2-(6-Chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylic acid

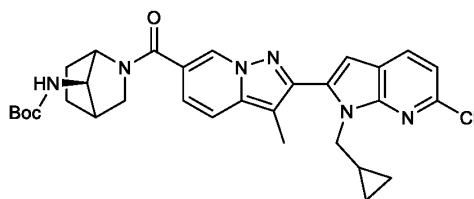


5

Intermediate 63D was prepared following a procedure similar to the preparation of Intermediate 2D (900 mg, 88%). LC-MS m/z: 381.1 [M+H]⁺.

Intermediate 64E

10 tert-Butyl-((7R)-2-(2-(6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate

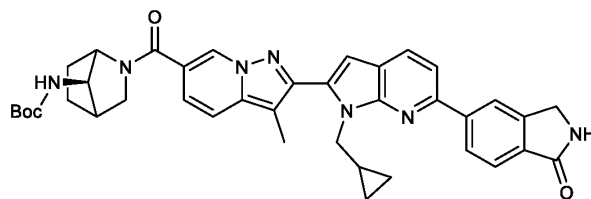


Intermediate 64E was prepared following a procedure similar to the preparation of Intermediate 2E (1.2 g, 88%). LC-MS m/z: 575.3 [M+H]⁺.

15

Intermediate 64F

tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-6-(1-oxoisindolin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



20

Intermediate 63F was prepared following a procedure similar to the preparation of Intermediate 3A (50 mg, 61%). LC-MS m/z: 672.4 [M+H]⁺.

Example 64

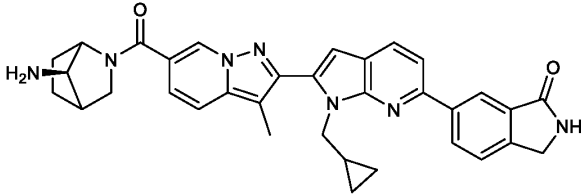
Compound of Example 64 was prepared following a procedure similar to the preparation of compound of Example 3 (8.88 mg, 17%). LC-MS m/z: 672.4 [M+H]⁺.

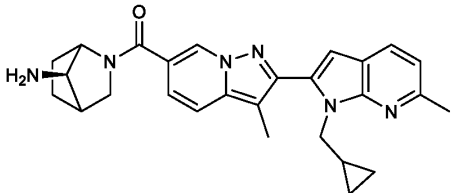
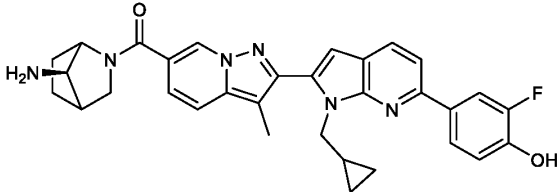
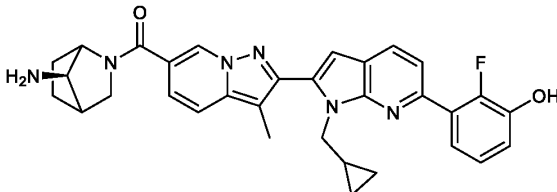
- 5 HPLC retention time: 5.956 min (Method C). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm:
 9.01-8.88 (m, 1H), 8.61 (s, 1H), 8.37 (s, 1H), 8.32 (d, J=7.8 Hz, 1H), 8.18 (d, J=8.0 Hz,
 1H), 8.12-7.91 (m, 3H), 7.90-7.77 (m, 2H), 7.40-7.28 (m, 1H), 6.95 (s, 1H), 4.69 (br d,
 J=6.0 Hz, 2H), 4.50 (s, 2H), 4.25 (br s, 1H), 3.82 (br dd, J=3.0, 9.5 Hz, 1H), 3.71-3.51 (m,
 2H), 3.48-3.36 (m, 1H), 3.19-3.07 (m, 1H), 2.70-2.53 (m, 1H), 2.46-2.43 (m, 3H), 2.06-
 10 1.80 (m, 3H), 1.77-1.60 (m, 1H), 1.34-1.15 (m, 1H), 0.38-0.30 (m, 4H).

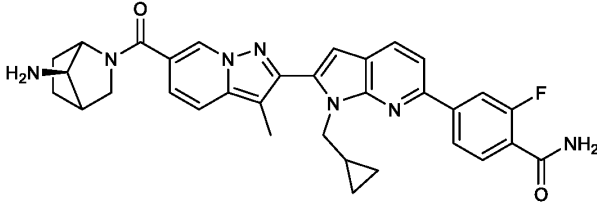
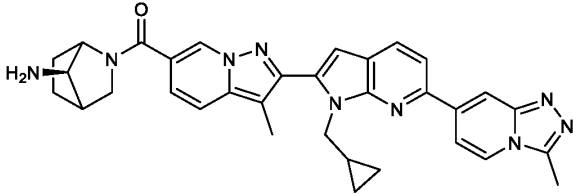
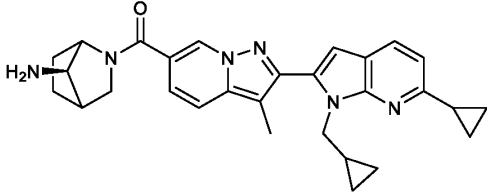
Compounds of Examples 65 to 75 in Table 9 were prepared following a procedure similar to the preparation of a compound of Example 64, by Suzuki coupling of Intermediate 64E with appropriate boronic acid.

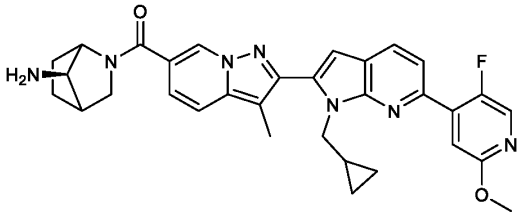
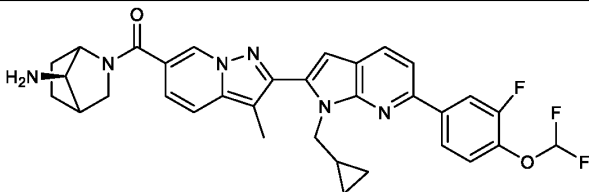
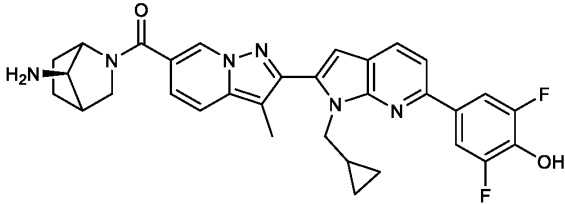
15

Table 9

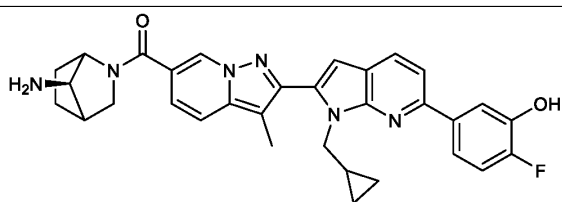
Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
65	 6-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one Analytical Data: 572.3, 6.015 min (Method C)

66	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 455.3, 5.696 min (Method C)
67	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-fluoro-4-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 551.3, 6.268 min (Method C)
68	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-fluoro-3-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 551.4, 6.502 min (Method C)

69	 4-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorobenzamide Analytical Data: 578.4, 7.954 min (Method C)
70	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 572.4, 5.613 min (Method C)
71	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-cyclopropyl-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 481.3, 1.588 min (Method F)

72	 <chem>CN1[C@H]2CC[C@@H]1C[C@H]2C(=O)c3ccc4c(c3)nnc4C5=C(C)N6C(=CC=CC=C6N7C8=CC=CC=C8N(CCC9CC9)C=C8C=C7C=C5C=C4)c1cc(F)c(OC)cn1</chem> ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(5-fluoro-2-methoxypyridin-4-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 566.3, 1.893 min (Method F)
73	 <chem>CN1[C@H]2CC[C@@H]1C[C@H]2C(=O)c3ccc4c(c3)nnc4C5=C(C)N6C(=CC=CC=C6N7C8=CC=CC=C8N(CCC9CC9)C=C8C=C7C=C5C=C4)c1cc(F)c(OC(F)F)cn1</chem> ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(4-(difluoromethoxy)-3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 601.3, 1.987 min (Method F)
74	 <chem>CN1[C@H]2CC[C@@H]1C[C@H]2C(=O)c3ccc4c(c3)nnc4C5=C(C)N6C(=CC=CC=C6N7C8=CC=CC=C8N(CCC9CC9)C=C8C=C7C=C5C=C4)c1cc(F)c(O)c(F)c1</chem> ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3,5-difluoro-4-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 569.3, 1.648 min (Method F)

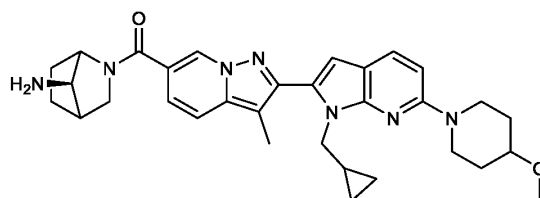
75



((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(4-fluoro-3-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone
Analytical Data: 551.3, 1.639 min (Method F)

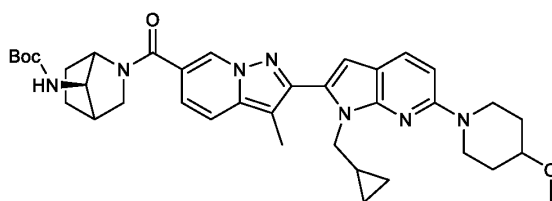
Example 76

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(4-methoxypiperidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone



Intermediate 76A

tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-6-(4-methoxypiperidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



Intermediate 76A was prepared following a procedure similar to the preparation of Intermediate 13A (50 mg, 63%). LC-MS m/z: 654.5 [M+H]⁺.

Example 76

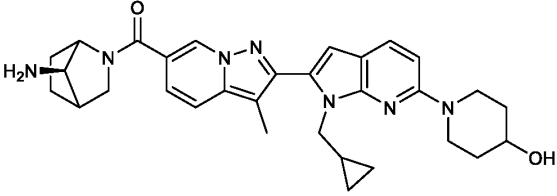
Compound of Example 76 was prepared following a procedure similar to the preparation of compound of Example 13 (9.1 mg, 16%). LC-MS m/z: 554.4 [M+H]⁺. LC-MS retention time: 1.994 min (Method E). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.99-8.71 (m, 1H), 8.11-7.93 (m, 2H), 7.87-7.67 (m, 1H), 7.56-7.20 (m, 2H), 6.82-6.72 (m, 1H), 6.66 (s, 1H), 4.48-4.41 (m, 2H), 4.27-4.20 (m, 1H), 4.09-3.98 (m, 3H), 3.65-3.54 (m, 2H), 3.49-3.41 (m, 2H), 3.26-3.22 (m, 3H), 3.24-3.16 (m, 1H), 2.72-2.59 (m, 2H), 2.42 (s, 3H), 2.02-1.84 (m, 5H), 1.76-1.61 (m, 1H), 1.54-1.41 (m, 2H), 1.27-1.24 (m, 1H), 0.39-0.22 (m, 4H).

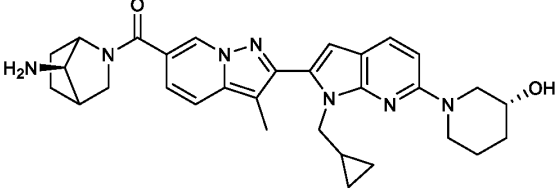
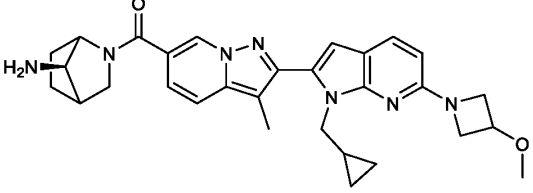
10

Compounds of Examples 77 to 79 in Table 10 were prepared following a procedure similar to the preparation of a compound of Example 76, by Buchwald coupling of Intermediate 64E with appropriate amines.

15

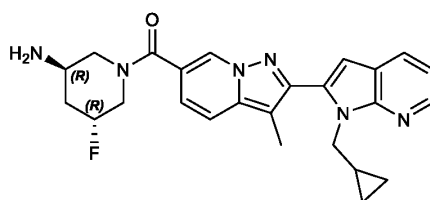
Table 10

Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
77	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(4-hydroxypiperidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 540.4, 1.078 min (Method F)

78	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-((R)-3-hydroxypiperidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 540.4, 1.235 min (Method F)
79	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-methoxyazetidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 526.4, 1.393 min (Method F)

Example 80

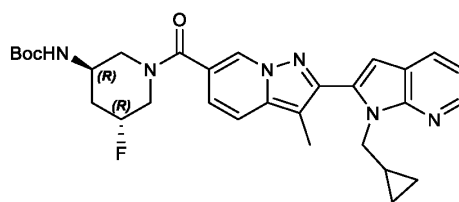
((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone



5

Intermediate 80A

tert-Butyl-((3R,5R)-1-(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



Intermediate 80A was prepared following a procedure similar to the preparation of Intermediate 14A (50 mg, 63%). LC-MS m/z : 547.3 $[M+H]^+$.

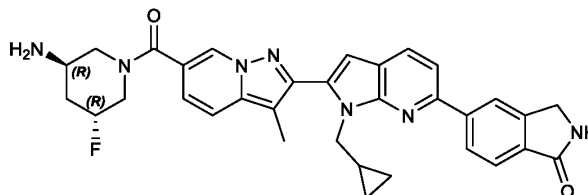
5

Example 80

Compound of Example 80 was prepared following a procedure similar to the preparation of Example 14 (21.2 mg, 43%). LC-MS m/z : 447.3 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm: 8.79 (s, 1H), 8.33 (dd, $J=1.6, 4.8$ Hz, 1H), 8.05 (dd, $J=1.5, 7.8$ Hz, 1H), 7.82 (d, $J=9.3$ Hz, 1H), 7.23 (dd, $J=1.2, 9.3$ Hz, 1H), 7.16 (dd, $J=4.6, 7.8$ Hz, 1H),
 10 6.87 (s, 1H), 5.04-4.80 (m, 1H), 4.55 (d, $J=7.1$ Hz, 3H), 3.91 (s, 2H), 3.03-2.95 (m, 1H), 2.45 (s, 3H), 2.22-2.09 (m, 1H), 1.65-1.41 (m, 1H), 1.29-1.15 (m, 1H), 0.34-0.21 (m, 4H).

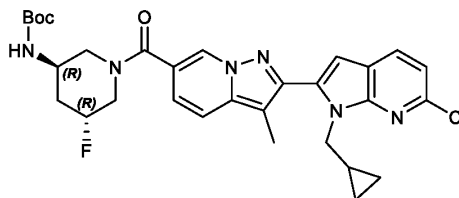
Example 81

5-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-
 15 a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one



Intermediate 81A

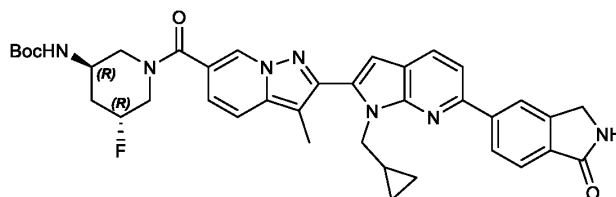
tert-Butyl-((3R,5R)-1-(2-(6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-
 20 yl)-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



Intermediate 81A was prepared following a procedure similar to the preparation of Intermediate 15A (600 mg, 79%). LC-MS m/z : 581.3 $[M+H]^+$.

Intermediate 81B

- 5 tert-Butyl-((3R,5R)-1-(2-(1-(cyclopropylmethyl)-6-(1-oxoisindolin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



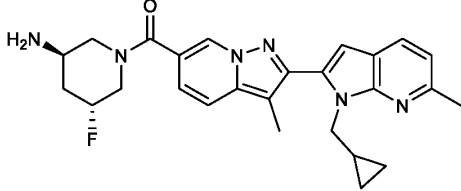
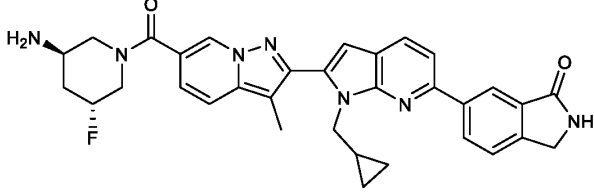
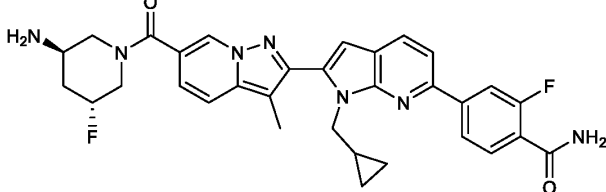
- 10 Intermediate 81B was prepared following a procedure similar to the preparation of Intermediate 16A (50 mg, 61%). LC-MS m/z : 678.4 $[M+H]^+$.

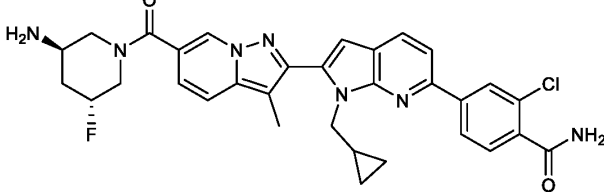
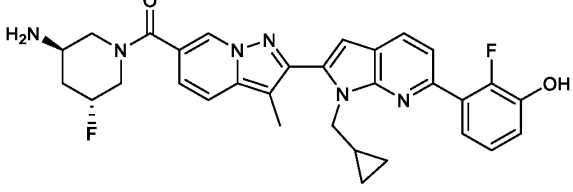
Example 81

- Compound of Example 81 was prepared following a procedure similar to the
 15 preparation of Example 16 (7.1 mg). LC-MS m/z : 578.4 $[M+H]^+$. LC-MS retention time: 1.576 min (Method E). 1H NMR (400 MHz, DMSO- d_6) δ ppm: 8.86-8.77 (m, 1H), 8.66-8.56 (m, 1H), 8.42-8.28 (m, 2H), 8.17 (d, $J=8.1$ Hz, 1H), 7.88-7.76 (m, 3H), 7.24 (d, $J=8.4$ Hz, 1H), 6.93 (s, 1H), 5.08-4.82 (m, 1H), 4.73-4.59 (m, 2H), 4.56-4.38 (m, 2H), 4.22-4.12 (m, 1H), 4.12-3.85 (m, 1H), 3.09-2.95 (m, 2H), 2.48-2.38 (m, 3H), 2.24-2.11
 20 (m, 1H), 1.98-1.82 (m, 1H), 1.68-1.42 (m, 1H), 1.39-1.14 (m, 1H), 0.37-0.30 (m, 4H).

Compounds of Examples 82 to 86 in Table 11 were prepared following a procedure similar to the preparation of a compound of Example 81, by Suzuki coupling of Intermediate 81A with appropriate boronic acid.

Table 11

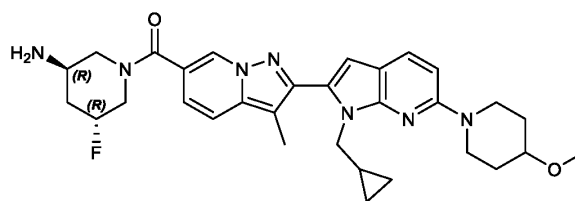
Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
82	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 461.4, 1.129 min (Method F)
83	 6-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one Analytical Data: 578.3, 1.440 min (Method F)
84	 4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorobenzamide Analytical Data: 584.3, 1.623 min (Method F)

85	 4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-chlorobenzamide Analytical Data: 600.3, 1.454 min (Method F)
86	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(2-fluoro-3-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 557.4, 1.603 min (Method F)

Example 87

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(4-methoxypiperidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone

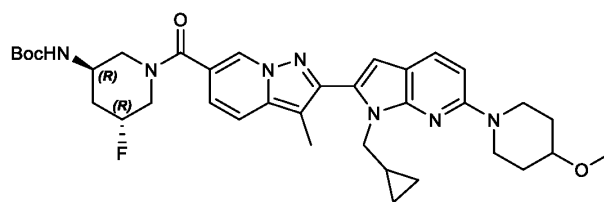
5



Intermediate 87A

tert-Butyl-((3R,5R)-1-(2-(1-(cyclopropylmethyl)-6-(4-methoxypiperidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate

10



Intermediate 87A was prepared following a procedure similar to the preparation of Intermediate 13A (60 mg, 75%). LC-MS m/z : 660.5 $[M+H]^+$.

5

Example 87

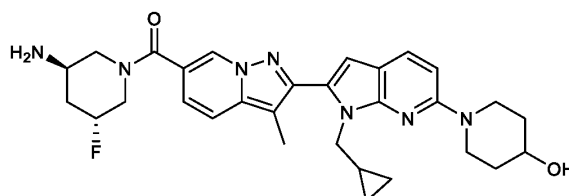
Compound of Example 87 was prepared following a procedure similar to the preparation of Example 13 (5 mg, 9%). LC-MS m/z : 560.4 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm: 8.72 (s, 1H), 7.79-7.69 (m, 2H), 7.22-7.14 (m, 1H), 6.75 (d, $J=8.6$ Hz, 1H), 6.65 (s, 1H), 5.10-4.80 (m, 1H), 4.46-4.38 (m, 3H), 4.06-3.97 (m, 4H), 3.28-3.30 (m, 5H), 3.22-3.18 (m, 2H), 2.98-2.93 (m, 1H), 2.41 (s, 3H), 1.99-1.89 (m, 3H), 1.51-1.42 (m, 3H), 1.32-1.09 (m, 1H), 0.96-0.84 (m, 1H), 0.31 (d, $J=6.6$ Hz, 4H).

10

Example 88

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(4-hydroxypiperidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone

15



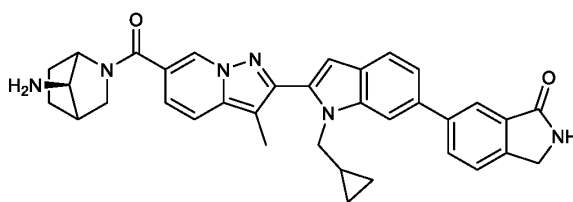
Compound of Example 88 was prepared following a procedure similar to the preparation of Example 87, by Buchwald coupling of Intermediate 81A with appropriate amine. LC-MS m/z : 546.3 $[M+H]^+$. LC-MS retention time: 1.573 min (Method F).

20

Example 89

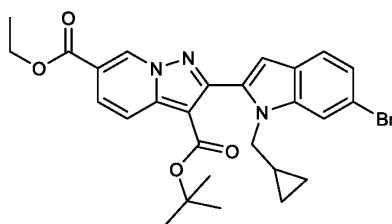
6-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one

25



Intermediate 89A

3-(tert-Butyl)-6-ethyl 2-(6-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)pyrazolo[1,5-a]pyridine-3,6-dicarboxylate



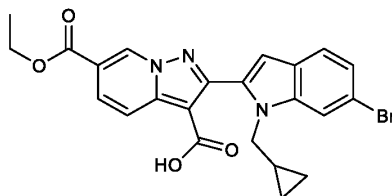
5

Intermediate 89A was prepared following a procedure similar to the preparation of Intermediate 23A, as a pale brown glassy solid (300 mg, 26%). LC-MS m/z: 538.2 [M+H]⁺.

10

Intermediate 89B

2-(6-Bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-6-(ethoxycarbonyl)pyrazolo[1,5-a]pyridine-3-carboxylic acid

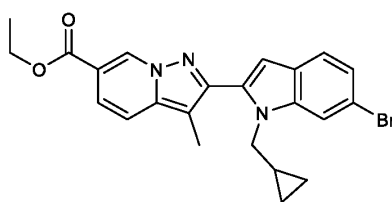


Intermediate 89B was prepared following a procedure similar to the preparation of Intermediate 23B, as pale yellow syrup (300 mg, 99%). LC-MS m/z: 484.0 [M+2H]⁺.

15

Intermediate 89C

Ethyl-2-(6-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate

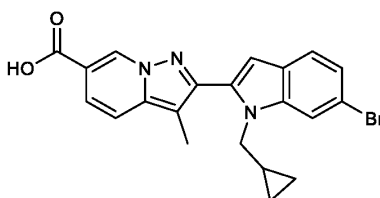


Intermediate 89C was prepared following a procedure similar to the preparation of Intermediate 23C (250 mg, 89%). LC-MS m/z : 454.1 $[M+2H]^+$.

5

Intermediate 89D

2-(6-Bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylic acid

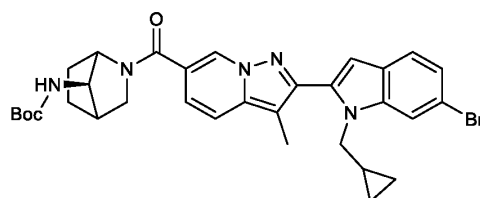


Intermediate 89D was prepared following a procedure similar to the preparation of Intermediate 23D, as brown syrup (230 mg, 98%). LC-MS m/z : 426.3 $[M+2H]^+$.

10

Intermediate 89E

tert-Butyl-((7R)-2-(2-(6-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



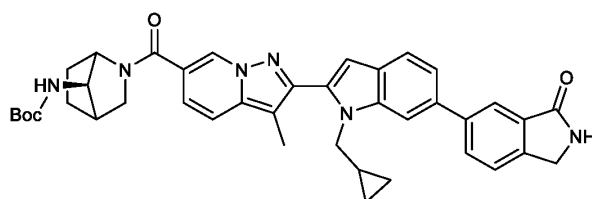
15

Intermediate 89E was prepared following a procedure similar to the preparation of Intermediate 23E, as a glassy solid (180 mg, 54%). LC-MS m/z : 620.3 $[M+2H]^+$.

Intermediate 89F

tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-6-(3-oxoisindolin-5-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate

20



Intermediate 89F was prepared following a procedure similar to the preparation of Intermediate 23F, as a white solid (40 mg, 53%). LC-MS m/z: 671.5 [M+H]⁺.

5

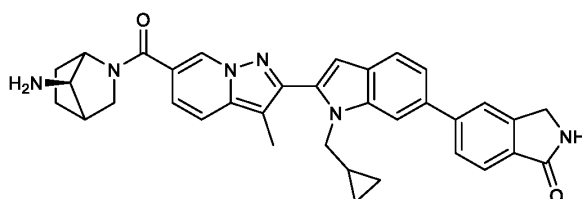
Example 89

Compound of Example 89 was prepared following a procedure similar to the preparation of the compound of Example 23, as a white solid (4 mg, 11%). LC-MS m/z: 571.3 [M+H]⁺. ¹H NMR (400 MHz, methanol-*d*₄) δ ppm: 8.82 (s, 1H), 8.75 (s, 1H), 8.14 (s, 1H), 8.02 (dd, J=1.8, 7.8 Hz, 1H), 7.83 (s, 1H), 7.75-7.64 (m, 3H), 7.57-7.42 (m, 1H), 7.40-7.22 (m, 1H), 6.82 (s, 1H), 5.07-4.88 (m, 1H), 4.83-4.80 (m, 1H), 4.59 (s, 1H), 4.56-4.50 (m, 4H), 4.35 (s, 1H), 4.02 (s, 1H), 3.85-3.58 (m, 1H), 3.57-3.39 (m, 1H), 3.34 (br, d, J=6.0 Hz, 1H), 3.29-3.22 (m, 1H), 2.50-2.43 (m, 3H), 2.40 (br, s, 1H), 2.34 (br, s, 1H), 2.13-1.89 (m, 3H), 1.71-1.48 (m, 1H), 1.42-1.24 (m, 1H), 1.24-1.11 (m, 1H), 0.41-0.30 (m, 2H), 0.18-0.08 (m, 2H).

15

Example 90

5-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one



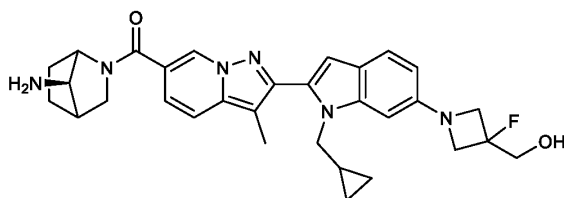
20

Compound of Example 90 was prepared following a procedure similar to the preparation of the compound of Example 89, by Suzuki coupling of Intermediate 89E with appropriate boronic acid. LC-MS m/z: 571.3 [M+H]⁺, LC-MS retention time: 7.662 min (Method C).

25

Example 91

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-fluoro-3-(hydroxymethyl)azetidin-1-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone

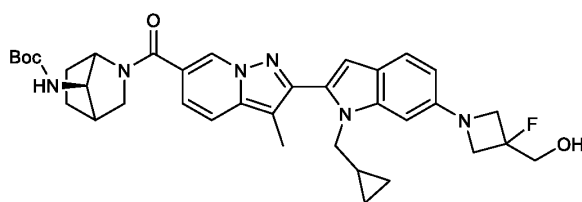


5

Intermediate 91A

tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-6-(3-fluoro-3-(hydroxymethyl)azetidin-1-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate

10



Intermediate 91A was prepared following a procedure similar to the preparation of Intermediate 33A (45 mg, 62%). LC-MS m/z: 643.5 [M+H]⁺.

15

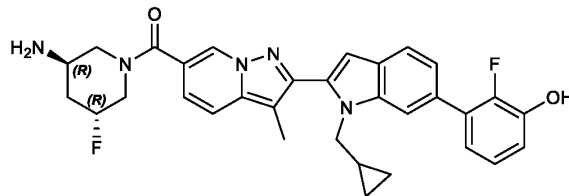
Example 91

Compound of Example 91 was prepared following a procedure similar to the preparation of the compound of 33 (9 mg, 7%). LC-MS m/z: 543.4 [M+H]⁺. LC-MS retention time: 1.285 min (Method E). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.74 (br, d, J=2.0 Hz, 1H), 7.77-7.66 (m, 1H), 7.45 (d, J=8.6 Hz, 1H), 7.34-7.14 (m, 2H), 6.68 (s, 1H), 6.59 (s, 1H), 6.45-6.35 (m, 1H), 5.37-5.27 (m, 1H), 4.48-4.36 (m, 2H), 4.11-3.98 (m, 3H), 3.90-3.73 (m, 5H), 2.39 (s, 3H), 2.03-1.80 (m, 4H), 1.58-1.45 (m, 2H), 1.38-1.07 (m, 3H), 0.34-0.23 (m, 2H), 0.20-0.05 (m, 2H).

20

Example 92

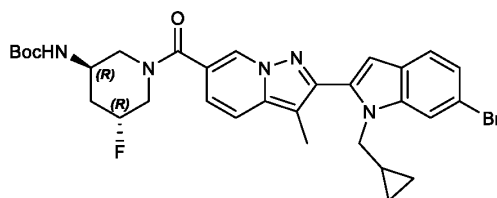
((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(2-fluoro-3-hydroxyphenyl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone



5

Intermediate 92A

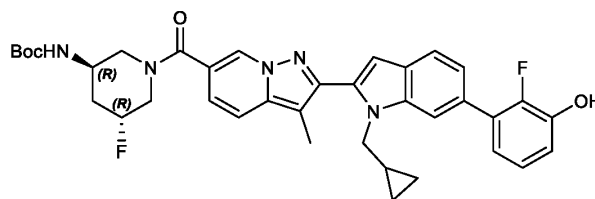
tert-Butyl-((3R,5R)-1-(2-(6-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



10 Intermediate 92A was prepared following a procedure similar to the preparation of Intermediate 29A (300 mg, 41%). LC-MS m/z: 657.3 [M+H]⁺.

Intermediate 92B

15 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(2-fluoro-3-hydroxyphenyl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone



Intermediate 92B was prepared following a procedure similar to the preparation of Intermediate 29B (50 mg, 68%). LC-MS m/z: 557.4 [M+H]⁺.

20

Example 92

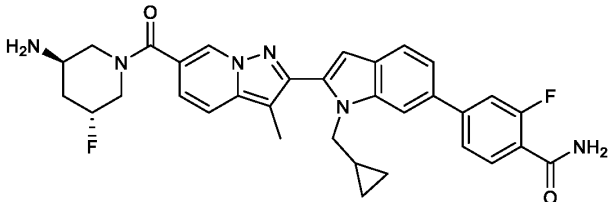
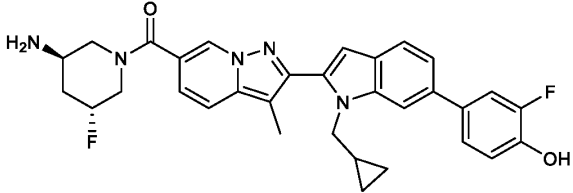
Compound of Example 92 was prepared following a procedure similar to the preparation of the compound of Example 29 (16.3 mg). LC-MS m/z: 556.3 [M+H]⁺. LC-

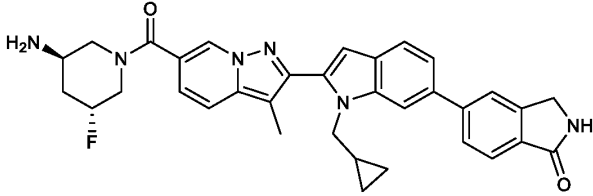
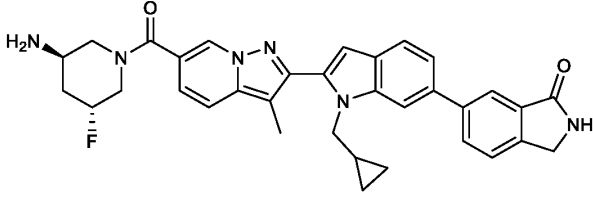
MS retention time: 1.843 min (method E). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 9.93-9.83 (m, 1H), 8.82 (s, 1H), 8.11-7.89 (m, 1H), 7.83 (d, J=9.3 Hz, 1H), 7.76-7.65 (m, 2H), 7.30-7.18 (m, 2H), 7.11-7.04 (m, 1H), 7.01-6.92 (m, 2H), 6.87 (s, 1H), 5.11-4.93 (m, 1H), 4.54-4.40 (m, 3H), 3.28-3.20 (m, 2H), 2.43 (s, 3H), 2.42-2.35 (m, 2H), 1.97-1.75 (m, 1H), 1.19-1.07 (m, 1H), 0.36-0.27 (m, 2H), 0.25-0.13 (m, 2H).

Compounds of Examples 93 to 96 in Table 12 were prepared following a procedure similar to the preparation of a compound of Example 92, by Suzuki coupling of Intermediate 92A with appropriate boronic acid.

10

Table 12

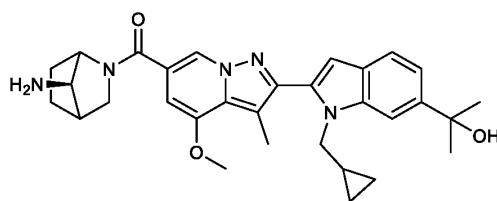
Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
93	 4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)-2-fluorobenzamide Analytical Data: 583.3, 1.530 min (Method F)
94	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(3-fluoro-4-hydroxyphenyl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 556.3, 1.668 min (Method F)

95	 5-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one Analytical Data: 577.4, 1.460 min (Method F)
96	 6-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one Analytical Data: 577.3, 7.422 min (Method F)

Example 97

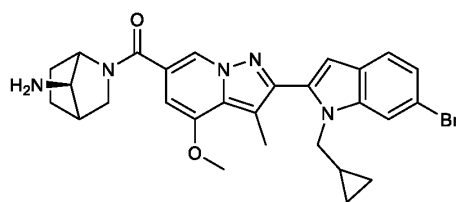
((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-hydroxypropan-2-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone

5



Intermediate 97A

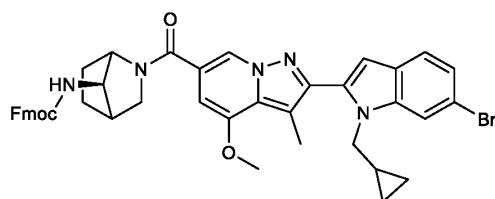
((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone



TFA (0.3ml, 3.89 mmol) was added to a solution of Intermediate 23E (200 mg, 0.308 mmol) in DCM (1 ml). The reaction mixture was stirred for 2 hours, and concentrated under vacuum to afford the crude title compound (180 mg, 100%), which
 5 was used in next step without further purification. LC-MS m/z: 548 [M+H]⁺.

Intermediate 97B

(9H-Fluoren-9-yl)methyl-((7R)-2-(2-(6-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate
 10

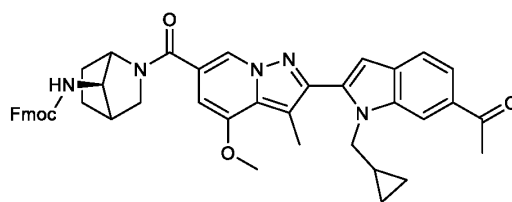


Sodium bicarbonate (115 mg, 1.367 mmol) was added to a stirred solution of Intermediate 97A (250 mg, 0.456 mmol) in a mixture of solvents dioxane (1 ml) and water (1 ml), followed by the addition of (9H-fluoren-9-yl)methyl carbonochloridate (118 mg, 0.456 mmol). The reaction mixture was diluted with DCM and stirred for about 5
 15 min. The organic layer was separated and concentrated under reduced pressure to afford crude compound, which was purified using a silica gel column (eluting with 0-60% EtOAc in hexane) to afford the title compound (70 mg, 20%) as off-white solid. LC-MS m/z: 772.3 [M+H]⁺.

20

Intermediate 97C

(9H-Fluoren-9-yl)methyl-((7R)-2-(2-(6-acetyl-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate

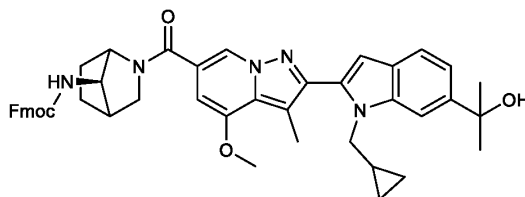


Tributyl(1-ethoxyvinyl)stannane (46.9 mg, 0.130 mmol) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (9.11 mg, 0.013 mmol) were added to a solution of Intermediate 97B (100 mg, 0.130 mmol) in toluene (3 m) in a vial. The reaction mixture was degassed with argon for 2 min, heated to 85°C and stirred for 16 hours, diluted in minimum amount of DCM and loaded onto a silica gel column for purification. Eluting with 0-100% EtOAc / petether afforded the ether cleaved title compound (70 mg, 74%) as a colourless syrup. LC-MS m/z : 734.4 $[\text{M}+\text{H}]^+$.

10

Intermediate 97D

(9H-Fluoren-9-yl)methyl-((7R)-2-(2-(1-(cyclopropylmethyl)-6-(2-hydroxypropan-2-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



15

Methyl magnesium bromide (0.127 ml, 0.382 mmol, 3 M in THF) was added to a stirred solution of Intermediate 97C (70 mg, 0.095 mmol) in THF (3 ml) at 0°C. The reaction mixture was stirred for 1 hour, quenched with saturated NH_4Cl solution at 0°C, extracted with EtOAc, dried over Na_2SO_4 , and concentrated under reduced pressure to afford a crude compound. Purification by prep-HPLC of the crude compound afforded the title compound (40 mg, 56%) as a white solid. LC-MS m/z : 750.4 $[\text{M}+\text{H}]^+$.

20

Example 97

Piperidine (10.56 μl , 0.107 mmol) was added drop wise to a stirred solution of Intermediate 97D (40 mg, 0.053 mmol) in DCM. The reaction mixture was stirred for 2 hours, and concentrated to afford a crude compound as off-white solid. Purification by

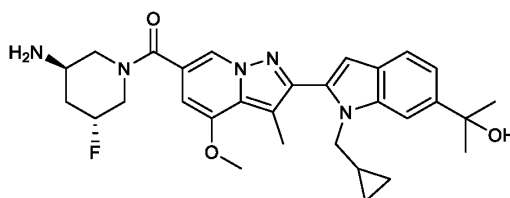
25

Prep-HPLC afforded the title compound. The purified compound was further purified using RP-HPLC to afford the title compound (3 mg, 10%) as off-white solid. LC-MS m/z : 534.4 $[M+H]^+$. HPLC retention time: 6.983 (Method C). 1H NMR (400 MHz, methanol- d_4) δ ppm: 8.33 (s, 1H), 7.69 (s, 1H), 7.58 (d, $J=8.0$ Hz, 1H), 7.24 (dd, $J=1.5, 8.5$ Hz, 1H), 6.68 (s, 1H), 6.65-6.61 (m, 1H), 4.60 (s, 2H), 4.43-4.27 (m, 2H), 4.16-4.00 (m, 4H), 3.76-3.62 (m, 1H), 3.62-3.54 (m, 1H), 3.53-3.41 (m, 1H), 3.30-3.06 (m, 1H), 2.54 (s, 3H), 2.48-2.34 (m, 1H), 2.18-1.90 (m, 5H), 1.23-1.03 (m, 2H), 1.01-0.81 (m, 1H), 0.37-0.30 (m, 2H), 0.14-0.06 (m, 2H).

10

Example 98

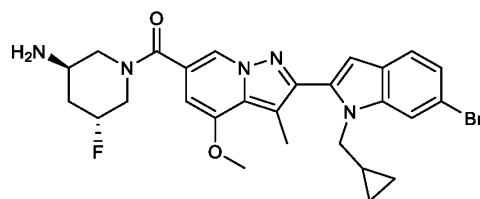
((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(2-hydroxypropan-2-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone



15

Intermediate 98A

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(6-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone

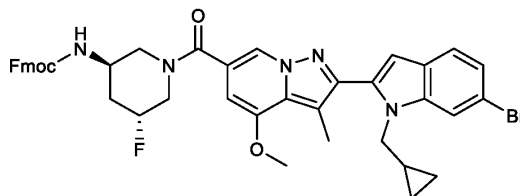


20

Intermediate 98A was prepared following a procedure similar to the preparation of Intermediate 97A (70 mg, 100%). LCMS m/z : 778.3 $[M+H]^+$.

Intermediate 98B

(9H-Fluoren-9-yl)methyl-((3R,5R)-1-(2-(6-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate

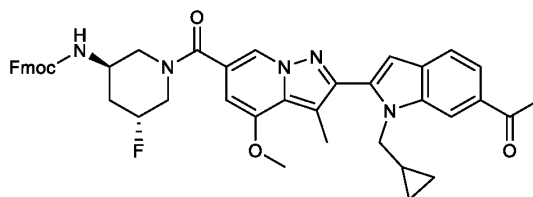


5

Intermediate 98B was prepared following a procedure similar to the preparation of Intermediate 97B (65 mg, 66%) as an off-white solid. LC-MS m/z : 778.3 $[M+H]^+$.

Intermediate 98C

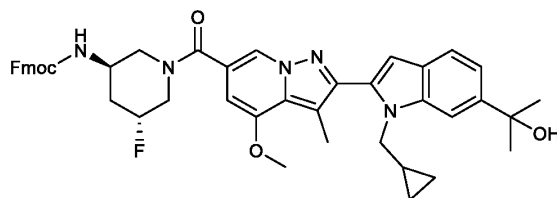
10 (9H-Fluoren-9-yl)methyl-((3R,5R)-1-(2-(6-acetyl-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



15 Intermediate 98C was prepared following a procedure similar to the preparation of Intermediate 97C (crude 70 mg) as black syrup. LC-MS m/z : 740.4 $[M+H]^+$.

Intermediate 98D

20 (9H-Fluoren-9-yl)methyl-((3R,5R)-1-(2-(1-(cyclopropylmethyl)-6-(2-hydroxypropan-2-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



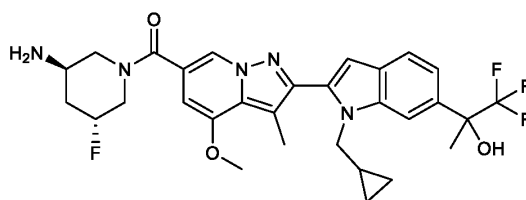
Intermediate 98D was prepared following a procedure similar to the preparation of Intermediate 97D (30 mg, 42%) as a pale yellow solid. LC-MS m/z: 756.2 [M+H]⁺.

Example 98

Compound of Example 98 was prepared following a procedure similar to the preparation of a compound of Example 97 (1.5 mg, 6%), as a pale yellow solid. LC-MS m/z: 534.2 [M+H]⁺. HPLC retention time: 6.983 min (Method C). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.34 (s, 1H), 7.65 (s, 1H), 7.52 (d, J=8.5 Hz, 1H), 7.19 (dd, J=1.3, 8.3 Hz, 1H), 6.68 (s, 1H), 6.53 (s, 1H), 5.01-4.93 (m, 2H), 4.35 (br d, J=6.5 Hz, 3H), 3.97 (s, 4H), 3.26-3.09 (m, 1H), 3.08-2.82 (m, 2H), 2.62 (m, 3H), 2.43-2.25 (m, 2H), 2.24-1.99 (m, 1H), 1.51 (s, 6H), 1.17-1.05 (m, 1H), 0.33-0.28 (m, 2H), 0.17-0.12 (m, 2H).

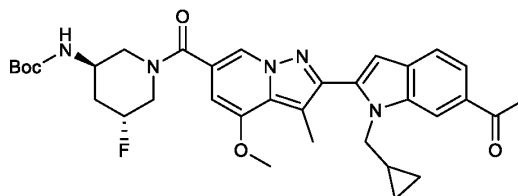
Example 99

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(1,1,1-trifluoro-2-hydroxypropan-2-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone



Intermediate 99A

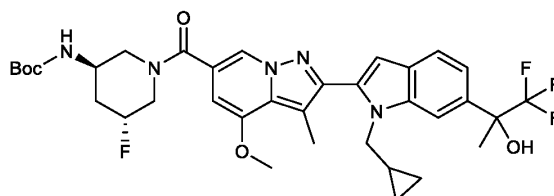
tert-Butyl-((3R,5R)-1-(2-(6-acetyl-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



Intermediate 99A was prepared following a procedure similar to the preparation of Intermediate 97C (200 mg, 66%) as a glassy solid. LC-MS m/z: 618.4 [M+H]⁺.

Intermediate 99B

tert-Butyl-((3R,5R)-1-(2-(1-(cyclopropylmethyl)-6-(1,1,1-trifluoro-2-hydroxypropan-2-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



5

Trimethyl(trifluoromethyl)silane (0.142 ml, 0.283 mmol, 2 M in THF) was added to a solution of Intermediate 99A (35 mg, 0.057 mmol) in DME (0.5 ml) in a 8 ml chemglass vial, followed by the addition of caesium fluoride (1 mg, 6.58 μ mol) on the walls of the vial. The vial was closed and the contents were mixed, stirred at a room temperature for 16 hours, and concentrated under vacuum to afford a crude title compound (30 mg, 70%), which was used in the next step without further purification. LC-MS m/z: 760 [M+H]⁺.

10

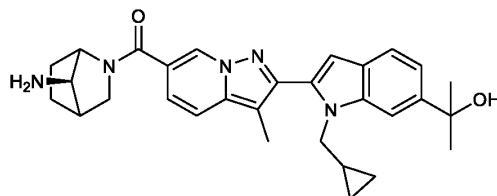
Example 99

2,6-Lutidine (0.018 ml, 0.158 mmol) was added to a stirred solution of Intermediate 99B (30 mg, 0.039 mmol) in DCM (1 ml), and the reaction mixture was cooled to 0°C, followed by the addition of TMS-OTf (0.014 ml, 0.079 mmol). The reaction mixture was stirred at 0°C for 30 minutes, and additional 28 μ l of TMS-OTf was added. The contents were allowed to warm to a room temperature, stirred for 30 minutes, quenched by the addition of 10% NaHCO₃ solution, and kept on standby over the weekend. The mixture was extracted with EtOAc (4×10 ml), dried over Na₂SO₄, concentrated under vacuum and the crude compound was purified using prep-HPLC. The purified compound was further purified using RP-HPLC to afford the title compound (2.2 mg, 10%). LC-MS m/z: 588 [M+H]⁺. LC-MS retention time: 1.889 min (Method E). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.39 (s, 1H), 7.80 (s, 1H), 7.61 (d, J=8.3 Hz, 1H), 7.30 (br, d, J=8.3 Hz, 1H), 6.75 (s, 1H), 6.55 (s, 1H), 5.10-4.92 (m, 1H), 4.41-4.36 (m, 2H), 3.98 (s, 3H), 3.80- 3.17 (m, 1H), 2.54 (s, 3H), 2.30-2.21 (m, 2H), 1.79 (br, s, 3H), 1.31-1.07 (m, 1H), 0.91-0.77 (m, 2H), 0.36-0.24 (m, 2H), 0.16 (br, d, J=5.1 Hz, 2H).

25

Example 100

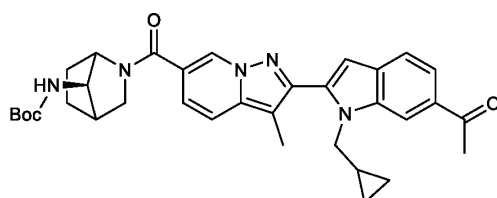
((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-hydroxypropan-2-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone



5

Intermediate 100A

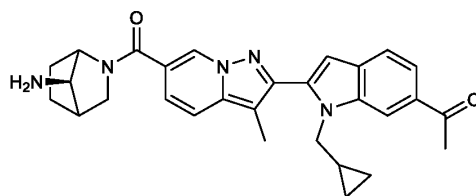
tert-Butyl-((7R)-2-(2-(6-acetyl-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



10 Intermediate 100A was prepared following a procedure similar to the preparation of Intermediate 97C (70 mg, 37%). LC-MS m/z: 582.4 [M+H]⁺.

Intermediate 100B

15 1-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)ethan-1-one



TFA (9.27 μ l, 0.120 mmol) was added to a stirred solution of Intermediate 100A (70 mg, 0.120 mmol) in DCM (0.5 ml). The reaction mixture was stirred at a room temperature for 2 hours, and concentrated under reduced pressure to afford a crude product (30 mg, 52%). LC-MS m/z: 482.3 [M+H]⁺.

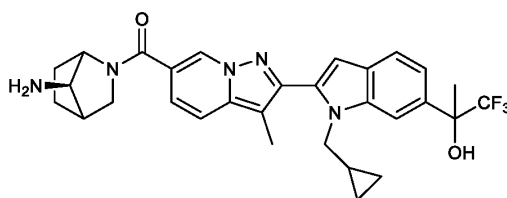
20

Example 100

Methyl magnesium bromide (0.415 ml, 0.415 mmol) was added to a stirred solution of Intermediate 100B (100 mg, 0.208 mmol) in THF (3 ml) at 0°C. The reaction mixture was stirred for 3 hours, allowed to warm to a room temperature, stirred for 3
 5 hours, quenched with saturated ammonium chloride (50 ml), and extracted with EtOAc (2×100 ml). The combined organic layers were dried over sodium sulphate, filtered, and the filtrate was concentrated under reduced pressure to afford the title compound. The crude compound was purified by prep-HPLC. The purified compound was further
 10 purified using RP-HPLC to afford the title compound (1.6 mg, 1.5%). LC-MS m/z: 498.4 [M+H]. HPLC retention time: 5.115 min (Method C). ¹H NMR (400 MHz, methanol-*d*₄) δ ppm: 8.73 (s, 1H), 7.74-7.64 (m, 2H), 7.57 (d, *J*=8.0 Hz, 1H), 7.31 (dd, *J*=1.0, 9.0 Hz, 1H), 7.24 (d, *J*=8.6 Hz, 1H), 6.72 (s, 1H), 4.42 (d, *J*=6.5 Hz, 2H), 4.33 (br s, 1H), 4.01 (s, 1H), 3.84-3.58 (m, 1H), 3.49 (s, 1H), 3.42 (s, 1H), 3.28-3.20 (m, 2H), 3.14 (d, *J*=1.5 Hz, 1H), 2.43 (s, 3H), 2.40-2.30 (m, 1H), 2.21 (s, 1H), 2.14-2.01 (m, 2H), 1.99-1.91 (m, 1H),
 15 1.90 (s, 1H), 1.64 (s, 7H), 1.29 (s, 6H), 1.18-1.09 (m, 1H), 0.36-0.28 (m, 2H), 0.10 (s, 2H).

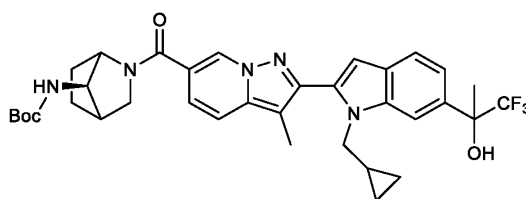
Example 101

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(1,1,1-
 20 trifluoro-2-hydroxypropan-2-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone



Intermediate 101A

tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-6-(1,1,1-trifluoro-2-hydroxypropan-2-yl)-
 25 1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



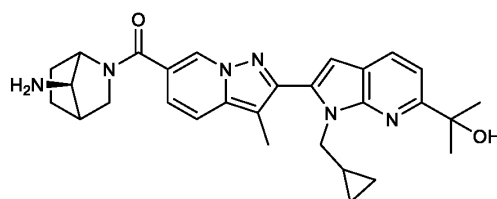
Me₃SiCF₃ (430 μ l, 0.860 mmol) was added to a stirred solution of Intermediate 100A (50 mg, 0.086 mmol) in THF (1 ml) at -78°C, followed by slow addition of TBAF (215 μ l, 0.430 mmol). The reaction mixture was allowed to warm to a room temperature, stirred for 3 hours, quenched with water (100 ml), and extracted with EtOAc (2 $\times$ 100 ml). The combined organic layers were dried over sodium sulphate, filtered, and the filtrate was concentrated under reduced pressure to afford a crude title compound (30 mg, 54%). LC-MS m/z: 652.3 [M+H]⁺.

Example 101

HCl (1 ml, 4 M in dioxane) was added to a stirred solution of Intermediate 101A (40 mg, 0.061 mmol) in dioxane (0.5 ml) at a room temperature. The reaction mixture was stirred for 2 hours, concentrated under reduced pressure, and the crude product obtained was purified using prep-HPLC. The purified product was further purified using RP-HPLC to afford the title compound (8.6 mg, 23%). LC-MS m/z: 552.3 [M+H]. HPLC retention time: 6.316 min (Method C). ¹H NMR (400 MHz, methanol-*d*₄) δ ppm: 8.80 (s, 1H), 8.73 (s, 1H), 7.82 (s, 1H), 7.73-7.59 (m, 2H), 7.36-7.29 (m, 2H), 6.76 (s, 1H), 5.05-4.88 (m, 1H), 4.43 (d, *J*=6.5 Hz, 2H), 4.33 (s, 1H), 4.00 (s, 1H), 3.72-3.63 (m, 1H), 3.29-3.20 (m, 4H), 2.43 (s, 3H), 2.31 (br s, 1H), 2.14-1.87 (m, 3H), 1.83 (s, 3H), 1.74-1.52 (m, 3H), 1.46-1.24 (m, 3H), 1.14-1.07 (m, 1H), 1.02 (t, *J*=7.5 Hz, 3H), 0.90 (s, 1H), 0.36-0.28 (m, 2H), 0.15-0.03 (m, 2H).

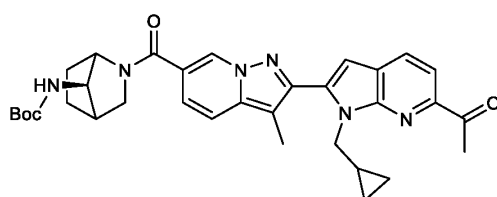
Example 102

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-hydroxypropan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone



Intermediate 102A

tert-Butyl-((7R)-2-(2-(6-acetyl-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate

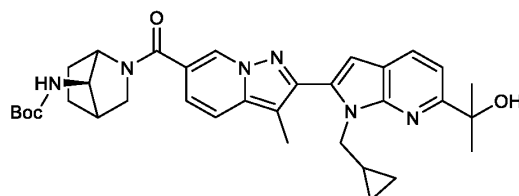


Intermediate 102A was prepared following a procedure similar to the preparation of Intermediate 97C (150 mg, 74%). LC-MS m/z : 583.34 $[M+H]^+$.

10

Intermediate 102B

tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-6-(2-hydroxypropan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



Intermediate 102B was prepared following a procedure similar to the preparation of Intermediate 97D (70 mg, 68%) LC-MS m/z : 599.4 $[M+H]^+$.

Example 102

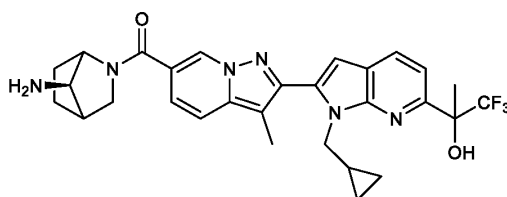
Compound of Example 102 was prepared following a procedure similar to the preparation of a compound of Example 1 (12.7 mg, 22%) LC-MS m/z : 499.4 $[M+H]^+$. HPLC retention time: 5.846 min (Method C). 1H NMR (400 MHz, DMSO- d_6) δ ppm: 9.14-8.85 (m, 1H), 8.06 (d, $J=8.5$ Hz, 1H), 7.93-7.79 (m, 1H), 7.54 (d, $J=8.5$ Hz, 1H),

7.48-7.27 (m, 1H), 6.88 (s, 1H), 4.71-4.47 (m, 2H), 4.36-4.21 (m, 1H), 3.92-3.78 (m, 1H), 3.69-3.56 (m, 2H), 2.73 (s, 2H), 2.54 (s, 3H), 2.52-2.31 (m, 6H), 2.15-1.83 (m, 4H), 1.78-1.70 (m, 1H), 1.59 (s, 6H), 1.39-1.14 (m, 1H), 0.43-0.34 (m, 4H).

5

Example 103

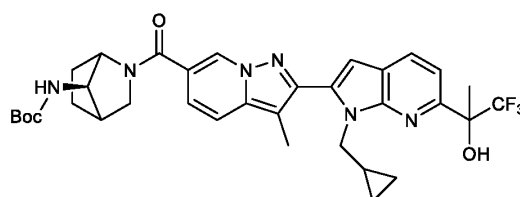
((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(1,1,1-trifluoro-2-hydroxypropan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone



10

Intermediate 103A

tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-6-(1,1,1-trifluoro-2-hydroxypropan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



15

Intermediate 103A was prepared following a procedure similar to the preparation of Intermediate 101A (50 mg, 45%). LC-MS m/z : 653.4 $[M+H]^+$.

Example 103

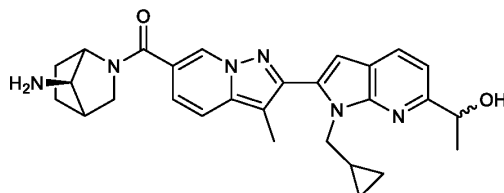
20

Compound of Example 103 was prepared following a procedure similar to the preparation of Example 101 (1.9 mg, 3%) LC-MS m/z : 553.4 $[M+H]^+$. HPLC retention time: 6.865 min (Method C). 1H NMR (400 MHz, methanol- d_4) δ ppm: 9.00-8.80 (m, 1H), 8.10 (d, $J=8.5$ Hz, 1H), 7.76 (br s, 1H), 7.52 (d, $J=8.0$ Hz, 1H), 7.39 (br s, 1H), 6.87 (s, 1H), 4.96-4.91 (m, 1H), 4.61 (dd, $J=7.0, 3.5$ Hz, 2H), 4.48-4.33 (m, 1H), 3.93 (s, 1H), 3.77 (br s, 1H), 2.72 – 2.84 (m, 2H), 2.49 (s, 3H), 2.23 (s, 1H), 2.01 (br s, 2H), 1.86 (s, 3H), 1.49-1.22 (m, 2H), 1.18 (br s, 1H), 0.35-0.12 (m, 4H).

25

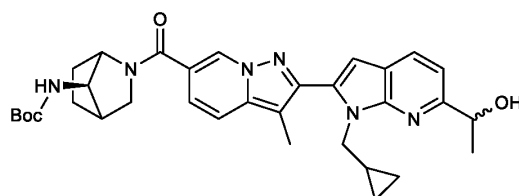
Example 104

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(1-hydroxyethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone



Intermediate 104A

tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-6-(1-hydroxyethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



Sodium borohydride (4.54 mg, 0.120 mmol) was added to a stirred solution of Intermediate 102A (70 mg, 0.120 mmol) in methanol. The reaction mixture was stirred at a room temperature for 3 hours, quenched with saturated ammonium chloride (100 ml), and extracted with EtOAc (2×100 ml). The combined organic layers were dried over sodium sulphate, filtered, and the filtrate was concentrated under reduced pressure to afford a crude title compound (40 mg, 57%). LC-MS m/z: 585.4 [M+H]⁺.

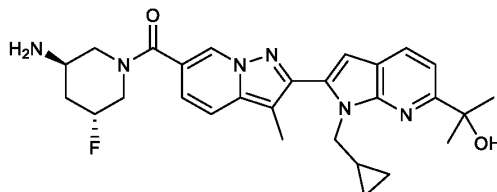
Example 104

Compound of Example 104 was prepared following a procedure similar to the preparation of Example 1 (5.6 mg, 10%). LC-MS m/z: 485.4 [M+H]⁺; HPLC retention time: 7.898 min (Method C). ¹H NMR (400 MHz, methanol-*d*₄) δ ppm: 8.89-8.83 (br, s, 1H), 8.03 (d, J=8.5 Hz, 1H), 7.75 (br, s, 1H), 7.37 (br, s, 1H), 7.31 (d, J=8.0 Hz, 1H), 6.80 (s, 1H), 5.10-4.92 (m, 1H), 4.74 (br, s, 1H), 4.60 (d, J=7.0 Hz, 1H), 4.44 (br, s, 1H), 3.92 (br, d, J=6.5 Hz, 1H), 3.77 (br, s, 1H), 3.67 (br, s, 1H), 3.58-3.38 (m, 1H), 2.87-2.63 (m,

1H), 2.48 (s, 3H), 2.21 (br, s, 1H), 1.87-2.02 (br, s, 2H), 1.64-1.53 (m, 3H), 1.42-1.24 (m, 2H), 1.24-1.06 (m, 1H), 0.34-0.18 (m, 4H).

Example 105

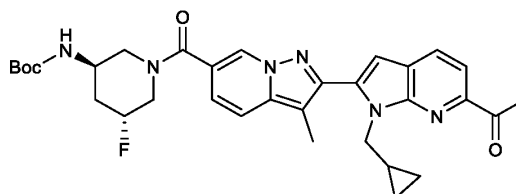
5 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(2-hydroxypropan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone



10

Intermediate 105A

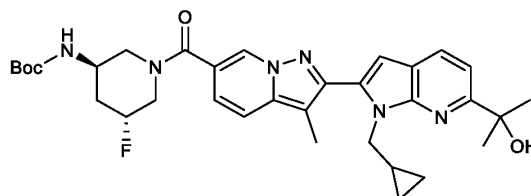
tert-Butyl-((3R,5R)-1-(2-(6-acetyl-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolof[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



Intermediate 105A was prepared following a procedure similar to the preparation
15 of Intermediate 97C (400 mg, 79%). LC-MS: 589.3 [M+H]⁺.

Intermediate 105B

tert-Butyl-((3R,5R)-1-(2-(1-(cyclopropylmethyl)-6-(2-hydroxypropan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



Intermediate 105B was prepared following a procedure similar to the preparation of Intermediate 97D (30 mg, 29%). LC-MS m/z: 605.3 [M+H]⁺.

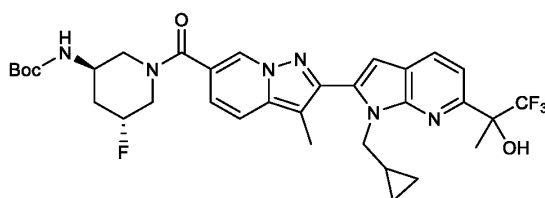
Example 105

Compound of Example 105 was prepared following a procedure similar to the preparation of the compound of Example 1 (14 mg, 20%). LC-MS m/z: 505.4 [M+H]⁺; HPLC retention time: 7.101 min (Method C). ¹H NMR (400 MHz, methanol-*d*₄) δ ppm: 8.74 (t, J=1.3 Hz, 1H), 8.01 (d, J=8.0 Hz, 1H), 7.75 (d, J=9.4 Hz, 1H), 7.42 (d, J=8.0 Hz, 1H), 7.28 (dd, J=1.5, 9.0 Hz, 1H), 6.78 (s, 1H), 5.06-5.01 (m, 1H), 4.98-4.88 (m, 1H), 4.84-4.73 (m, 2H), 4.57 (d, J=6.5 Hz, 3H), 4.51 (br d, J=3.5 Hz, 1H), 4.47-4.20 (m, 1H), 3.63 (s, 1H), 3.55-3.36 (m, 3H), 3.31-3.28 (m, 1H), 3.18-3.14 (m, 1H), 2.99-2.83 (m, 1H), 2.53-2.41 (m, 4H), 1.97 (s, 2H), 1.83-1.64 (m, 8H), 1.39-1.28 (m, 1H), 1.25-1.14 (m, 1H), 0.93 (d, J=6.5 Hz, 1H), 0.36-0.25 (m, 4H)

Examples 106 and 107

Intermediates 106A and 107A

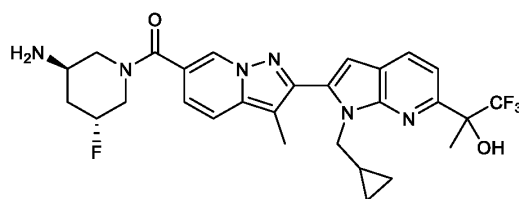
tert-Butyl-((3R,5R)-1-(2-(1-(cyclopropylmethyl)-6-(1,1,1-trifluoro-2-hydroxypropan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



Intermediates 106A and 107A were obtained following a procedure similar to the preparation of Intermediate 101A. Both the diastereomers were isolated by chiral SFC method. Diastereomer-1: (35 mg, 8%). LC-MS m/z: 659.4 [M+H]⁺. Diastereomer-2: (35 mg, 8%). LC-MS m/z: 659.4 [M+H]⁺.

Examples 106 and 107

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(1,1,1-trifluoro-2-hydroxypropan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone



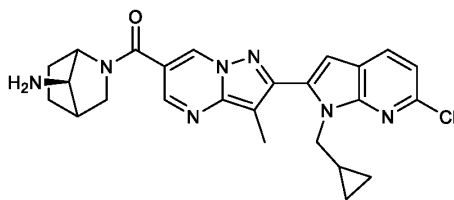
TFA was added to the diastereomer 106A (35mg) in DCM, and the reaction mixture was stirred at a room temperature for 2 hours. The volatiles were removed under vacuum and the crude product was purified by HPLC. The purified product was further purified using RP-HPLC to afford a compound of Example 106 (30 mg, 94%). LC-MS m/z: 559.27 [M+H]⁺; HPLC retention time: 7.046 min (Method C). ¹H NMR (400 MHz, methanol-*d*₄) δ ppm: 8.79 (s, 1H), 8.10 (d, J=8.0 Hz, 1H), 7.78 (d, J=9.1 Hz, 1H), 7.52 (d, J=8.0 Hz, 1H), 7.30 (dd, J=9.0, 1.5 Hz, 1H), 6.87 (s, 1H), 4.80-4.88 (m, 1H), 4.64-4.50 (m, 2H), 3.72-3.42 (m, 2H), 3.11-2.95 (m, 1H), 2.50 (s, 3H), 1.96 (s, 1H), 1.86 (s, 4H), 1.31 (s, 3H), 1.39-1.15 (m, 1H), 1.24-1.12 (m, 1H), 0.36-0.26 (m, 4H).

Compound of Example 107 was prepared analogous to the compound of Example 106 (21 mg, 66%). LC-MS m/z: 559.27 [M+H]⁺; HPLC retention time: 7.048 min (Method C). ¹H NMR (400 MHz, methanol-*d*₄) δ ppm: 8.79 (s, 1H), 8.10 (d, J=8.0 Hz, 1H), 7.78 (d, J=9.1 Hz, 1H), 7.52 (d, J=8.0 Hz, 1H), 7.30 (dd, J=9.0, 1.5 Hz, 1H), 6.87 (s, 1H), 4.80-4.88 (m, 1H), 4.64-4.50 (m, 2H), 3.72-3.42 (m, 2H), 3.11-2.95 (m, 1H), 2.50 (s, 3H), 1.96 (s, 1H), 1.86 (s, 4H), 1.31 (s, 3H), 1.39-1.15 (m, 1H), 1.24-1.12 (m, 1H), 0.36-0.26 (m, 4H).

20

Example 108

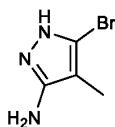
((7R)-7-Amino-2-azabicyclo [2.2.1] heptan-2-yl)(2-(6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyrimidin-6-yl)methanone



Intermediate 108A

25

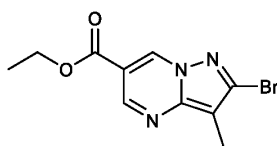
5-Bromo-4-methyl-1H-pyrazol-3-amine



Borane dimethyl sulfide complex (3.04 ml, 32.0 mmol) was added to a stirred solution of ethyl 3-amino-5-bromo-1H-pyrazole-4-carboxylate (3.0 g, 12.82 mmol) in THF (30 ml) at 0°C. The reaction mixture was stirred for 1 hour, heated to 65°C and stirred further for 16 hours, slowly quenched with methanol (5 ml) at a room temperature and stirred at 65°C for 1 hour, the volatiles were removed under vacuum, and the residue obtained was washed with saturated brine solution and extracted with DCM (2×50 ml). The combined organic extracts were dried over sodium sulphate, filtered, and the filtrate was evaporated under reduced pressure to afford the title compound (1.55g, 68%) as a white solid. LC-MS m/z: 176.0 [M+H]⁺.

Intermediate 108B

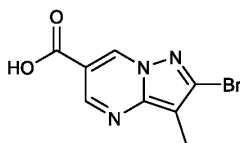
Ethyl-2-bromo-3-methylpyrazolo[1,5-a]pyrimidine-6-carboxylate



Acetic acid (5 ml) was added to a stirred solution of Intermediate 108A (0.8g, 4.55 mmol) and Ethyl 2-formyl-3-oxopropanoate (0.655 g, 4.55 mmol) in ethanol (25 ml) at 30°C. The reaction mixture was stirred at 80°C for 16 hours, evaporated to dryness, quenched with brine solution and extracted with DCM (2×50 ml). The combined organic extracts were dried over sodium sulphate, filtered, and the filtrate was evaporated under reduced pressure to afford the crude product, which was loaded onto a silica gel column (24g) and purified using EtOAc in hexane (0-100%) in a gradient manner to afford the title compound (460 mg, 36%). LC-MS m/z: 285.9 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ ppm: 9.2- 9.1 (m, 1H), 8.9- 8.8 (m, 1H), 4.5- 4.4 (m, 2H), 2.3 (s, 3H), 1.5-1.4 (m, 3H).

Intermediate 108C

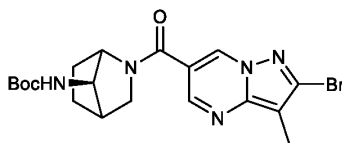
2-Bromo-3-methylpyrazolo[1,5-a]pyrimidine-6-carboxylic acid



LiOH (388 mg, 16.19 mmol) in water (1 ml) was added to a stirred solution of Intermediate 108B (460 mg, 1.619 mmol) in THF (6.00 ml) and methanol (3 ml). The reaction mixture was stirred at a room temperature for 16 hours, evaporated to dryness, acidified with citric acid solution, and extracted with DCM (2×50 ml). The combined organic extracts were dried over sodium sulphate, filtered, and the filtrate was evaporated under reduced pressure to afford the title compound as a crude product (380 mg, 92%). LC-MS *m/z*: 257.0 [M+H]⁺. ¹H NMR (400 MHz, MeOD) δ ppm: 9.21- 9.20 (d, 1H, *J*=2.4Hz), 8.95- 8.94 (d, 1H, *J*=2.8 Hz), 2.4 (s, 3H).

Intermediate 108D

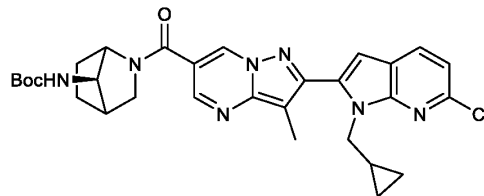
tert-Butyl-((7R)-2-(2-bromo-3-methylpyrazolo[1,5-a] pyrimidine-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



HATU (80 mg, 0.211 mmol) and DIPEA (0.092 ml, 0.527 mmol) were added to a stirred solution of Intermediate 108C (45 mg, 0.176 mmol), *tert*-butyl ((7R)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate (44.8 mg, 0.211 mmol) in DMF (3 ml). The reaction mixture was stirred at a room temperature for 16 hours, evaporated to dryness, quenched with brine solution, and extracted with DCM (2×50 ml). The combined organic extracts were dried over sodium sulphate, filtered, and the filtrate was evaporated under reduced pressure to afford the crude material. The crude material was loaded onto a silica gel column (12g) and purified using EtOAc in hexane (0-100%) in a gradient manner to afford the title compound (55 mg, 70%). LC-MS *m/z*: 396.1 [M-54]. ¹H NMR (400 MHz, MeOD) δ ppm: 8.73-8.72 (d, 1H, *J*=2.4Hz), 8.70-8.69 (d, 1H, *J*=2.8 Hz), 3.80-3.76 (m, 1H), 3.27-3.23 (m, 1H), 3.15-2.96 (m, 2H), 2.53 (m, 1H), 2.35-2.34 (s, 3H), 1.91-1.61 (m, 4H), 1.40 (s, 9H).

Intermediate 108E

tert-Butyl-((7R)-2-(2-(6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyrimidine-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



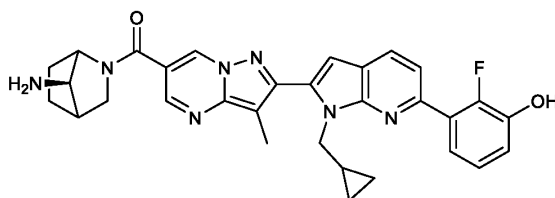
- 5 Pd(PPh₃)₄ (10.78 mg, 9.33 μmol) was added to a stirred solution of Intermediate 108D (210 mg, 0.466 mmol), 6-chloro-1-(cyclopropylmethyl)-2-(trimethylstannyl)-1H-pyrrolo[2,3-b]pyridine (Intermediate-7, 215 mg, 0.583 mmol) and CuI (17.76 mg, 0.093 mmol) in dioxane (5 ml), and the reaction mixture was heated to 110°C and stirred for 3 hours. The reaction mixture was evaporated to dryness to afford the crude material. The
- 10 crude material was loaded onto a silica gel column (12g) and purified using EtOAc in hexane (0-100%) in a gradient manner to afford the title compound (220 mg, 82%). LC-MS m/z: 576.3 [M+H]⁺. ¹H NMR (400 MHz, MeOD) δ ppm 7.7 – 7.6 (m, 1H), 7.5 – 7.3 (m, 1H), 7.2 – 7.1 (m, 1H), 7.0 (m, 1H), 6.6 – 6.4 (m, 1H), 4.02 – 4.00 (m, 2H), 3.96 – 3.94 (m, 2H), 3.69 – 3.66 (m, 2H), 2.16 – 2.06 (s, 3H), 1.92 (m, 1H), 1.8 – 1.5 (m, 4H),
- 15 0.90 – 0.85 (m, 1H), 0.65 – 0.61 (m, 2H), 0.40 – 0.37 (m, 2H).

Example 108

- TFA (0.033 ml, 0.434 mmol) was added to a stirred solution of Intermediate 108E (25 mg, 0.043 mmol) in DCM (5ml). The reaction mixture was stirred at a room
- 20 temperature for 16 hours, evaporated to dryness and the crude material was purified using prep-HPLC. The purified product was further purified using RP-HPLC to afford the title compound (5.5 mg, 27%). LC-MS m/z: 476.3 [M+H]⁺. LC-MS retention time: 2.76 min, (Method H). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 9.3-9.1 (m, 1H), 8.7-8.6 (m, 1H), 8.1-8.0 (m, 1H), 7.2-7.1 (m, 1H), 6.9 (s, 1H), 4.7-4.6 (m, 2H), 4.5 (m, 1H), 4.4-4.1 (m,
- 25 1H), 3.9-3.5 (m, 2H), 2.6 (s, 3H), 2.55-2.45 (m, 1H), 2.2-2.0 (m, 2H), 1.2-1.1 (m, 1H), 1.0-0.8 (m, 2H), 0.4-0.3 (m, 2H).

Example 109

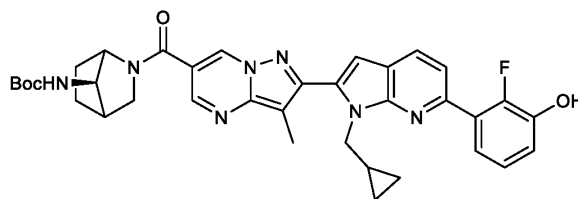
((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-fluoro-3-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyrimidin-6-yl)methanone



5

Intermediate 109A

tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-6-(2-fluoro-3-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyrimidine-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



10

Pd(PPh₃)₄ (3.51 mg, 3.04 μmol) was added to a stirred solution of Intermediate 108E (35 mg, 0.061 mmol), 2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (17.36 mg, 0.073 mmol) and K₂CO₃ (20.99 mg, 0.152 mmol) in 1,4-dioxane (4 ml). The reaction mixture was stirred at 85°C for 3 hours, filtered through a celite bed, and the filtrate was evaporated to dryness to afford a crude material. The crude compound was used in the next step without further purification. LC-MS m/z: 652.4 [M+H]⁺.

15

Example 109

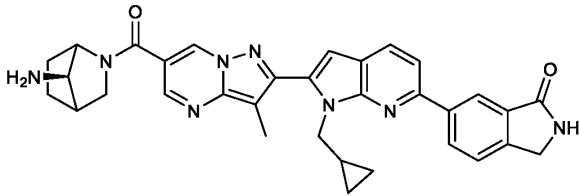
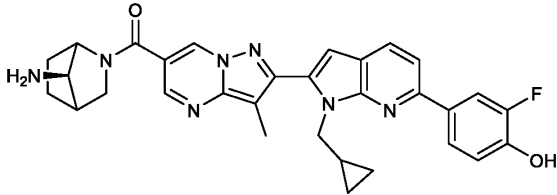
TFA (0.047 ml, 0.614 mmol) was added to a stirred solution of Intermediate 109A (40 mg, 0.061 mmol) in DCM (5 ml). The reaction mixture was stirred at a room temperature for 16 hours, evaporated to dryness, and the crude material obtained was purified using RP-HPLC to afford the title compound (1.2 mg, 22%). LC-MS m/z: 552.3 [M+H]⁺. LC-MS retention time: 1.70 min / 1.48 min. (Methods E / F). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 9.8 (s, 1H), 9.4-9.2 (m, 1H), 8.7-8.6 (m, 1H), 8.2-8.1 (m, 1H), 7.6-7.5 (m, 1H), 7.4-7.3 (m, 1H), 7.2-7.1 (m, 1H), 7.1-7.0 (m, 2H), 4.7-4.5 (m, 2H), 4.4-

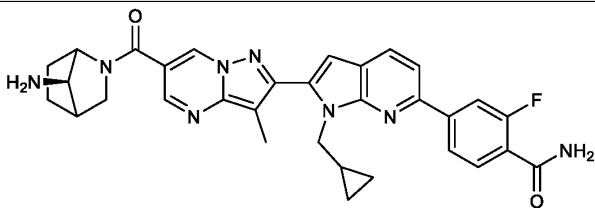
20

4.3 (m, 2H), 3.9-3.8 (m, 1H), 2.3 (s, 3H), 1.9-1.8 (m, 2H), 1.7-1.6 (m, 2H), 1.5 (m, 1H), 1.2-1.1 (m, 1H), 0.9-0.8 (m, 2H), 0.4- 0.3 (m, 2H).

- Compounds of Examples 110 to 112 in Table 13 were prepared following a procedure similar to the preparation of a compound of Example 109, by Suzuki coupling of Intermediate 108E with appropriate boronate acid.

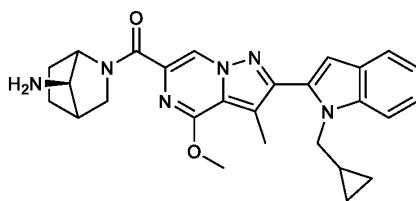
Table 13

Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time 1 (HPLC method 1), HPLC retention time 2 (HPLC method 2),
110	 6-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyrimidin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one Analytical Data: 573.3, 1.346 min (Method A), 1.341 min (Method B)
111	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-fluoro-4-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyrimidin-6-yl)methanone Analytical Data: 552.3, 1.626 min (Method A), 1.481min (Method B)

112	 4-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyrimidin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorobenzamide Analytical Data: 579.3, 1.567 min (Method A), 1.366 min (Method B)
-----	--

Example 113

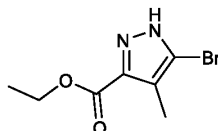
((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyrazin-6-yl)methanone



5

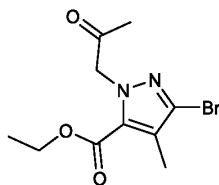
Intermediate 113A

Ethyl-5-bromo-4-methyl-1H-pyrazole-3-carboxylate:



Bromine (3.34 ml, 64.9 mmol) was added to a stirred suspension of ethyl 4-methyl-1H-pyrazole-3-carboxylate (10.0 g, 64.9 mmol) in water (50 ml). The reaction mixture was stirred at a room temperature for 2 hours, diluted with EtOAc (50 ml), washed with saturated NaHCO₃ solution (20 ml), brine, dried over sodium sulfate, filtered, and the filtrate was concentrated in vacuum. The crude product thus obtained was purified using a silica gel column (120 g, Redisep[®] SiO₂ column, eluting with 10% EtOAc in n-hexane) to obtain (9.0 g, 60%) of title compound as a white solid. LC-MS m/z: 231.0 [M-H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 14.08 (br s, 1 H), 4.32 (q, *J*=7.03 Hz, 2 H), 2.16 (s, 3 H), 1.31 (t, *J*=7.03 Hz, 3 H).

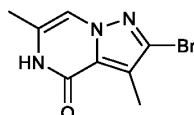
Intermediate 113B

Ethyl-3-bromo-4-methyl-1-(2-oxopropyl)-1*H*-pyrazole-5-carboxylate (A2115-423)

5 K₂CO₃ (6.40 g, 46.3 mmol) was added to a stirred solution of Intermediate 113A (9.0 g, 38.6 mmol) in DMF (30 ml), followed by the addition of 1-chloropropan-2-one (3.25 ml, 38.6 mmol). The resulting reaction mixture was stirred at a room temperature for 1 hour, diluted with water (20 ml), and extracted with EtOAc (3×30 ml). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and
10 the filtrate was concentrated under reduced pressure. The crude product thus obtained was purified using a silica gel column (120 g, Redisep[®] SiO₂ column, eluting with 14% EtOAc in n-hexane) to afford the title compound 6.5 g (58%) as off-white solid. LC-MS m/z: 288.9 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 5.38 (s, 2H), 4.26 (q, J=7.03 Hz, 2H), 2.18 (d, J=1.00 Hz, 6H), 1.28 (t, J=7.03 Hz, 3H).

15

Intermediate 113C

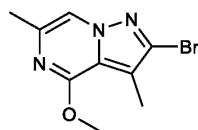
2-Bromo-3,6-dimethylpyrazolo[1,5-*a*]pyrazin-4(5*H*)-one

 Ammonium acetate (34.7 g, 450 mmol) was added to a stirred solution of
20 Intermediate 113B (6.5 g, 22.48 mmol) in acetic acid (15.0 ml). The reaction mixture was stirred at 120°C for 16 hours, diluted with water (100 ml), and the resulting solids were filtered off and dried under vacuum to obtain 4.2 g (77%) of the title compound as off-white solid. LC-MS m/z: 240.1 [M-H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 11.28 (br, s, 1H), 7.42 (s, 1H), 2.34 (s, 3H), 2.07 (s, 3H).

25

Intermediate 113D

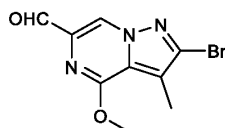
2-Bromo-4-methoxy-3,6-dimethylpyrazolo[1,5-*a*]pyrazine (A2115-429-1)



POCl₃ (2.310 ml, 24.79 mmol) was added to the Intermediate 113C (2.0 g, 8.26 mmol). The reaction mixture solution was stirred at 115°C for 2 hours, concentrated to dryness to obtain Intermediate 2-bromo-4-chloro-3,6-dimethylpyrazolo[1,5-a]pyrazine as a brown solid. LC-MS retention time: 1.72 min.; m/z: 259.9 [M+H]⁺. Sodium methoxide in methanol (5.4 M, 7.65 ml, 41.3 mmol) was added to the crude product obtained above in methanol (5 ml) at 0°C, and the reaction mixture was stirred at a room temperature for 16 hours, diluted with water (20 ml) and extracted with EtOAc (2×20 ml). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuum. The crude product was purified using a silica gel column (24 g, Redisp[®] SiO₂ column, eluting with 14% EtOAc in n-hexane) to afford 1.8 g (85%) of the title compound as a brown solid. LC-MS m/z: 256.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.12 (s, 1H), 4.01 (s, 3H), 2.43-2.33 (m, 6 H).

15

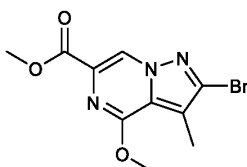
Intermediate 113E

2-Bromo-4-methoxy-3-methylpyrazolo[1,5-*a*]pyrazine-6-carbaldehyde

Selenium dioxide (1.430 g, 12.89 mmol) was added to a stirred solution of Intermediate 113D (3.0 g, 11.71 mmol) in 1,4-dioxane (10 ml). The reaction mixture was stirred at 110°C for 16 hours, filtered through a celite bed, and the filtrate was concentrated to obtain 2 g of the crude title compound, which was used in the next step without further purification. LC-MS m/z: 270.0 [M+H]⁺.

25

Intermediate 113F

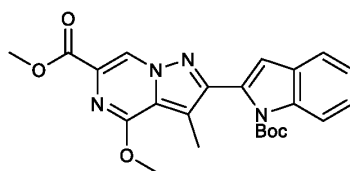
Methyl-2-bromo-4-methoxy-3-methylpyrazolo[1,5-*a*]pyrazine-6-carboxylate

Oxone (5.92 g, 9.63 mmol) was added to a stirred solution of Intermediate 113E (2.0 g, 7.41 mmol) in MeOH (8 ml). The reaction mixture was stirred at 70°C for 6 hours, concentrated under reduced pressure. The residue thus obtained was diluted with water (10 ml), and extracted with EtOAc (2× 20 ml). The combined organic layers were washed
 5 with brine, dried over sodium sulfate, filtered, and the filtrate was concentrated in vacuum. The crude product thus obtained was purified using a silica gel column (24 g Redisep[®] SiO₂ column, eluting with 14% EtOAc in n-hexane) to afford 0.32 g (14%) of the title compound as off-white solid. LC-MS m/z: 300 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.90 (s, 1 H), 4.09 (s, 3 H), 3.88 (s, 3 H), 2.34 (s, 3H).

10

Intermediate 113G

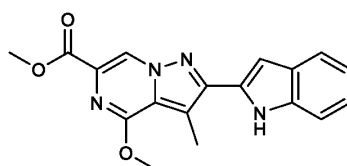
Methyl-2-(1-(tert-butoxycarbonyl)-1*H*-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-*a*]pyrazine-6-carboxylate



(1-(*tert*-Butoxycarbonyl)-1*H*-indol-2-yl)boronic acid (239 mg, 0.916 mmol) and potassium phosphate tribasic in water (2M, 1.041 ml, 2.083 mmol) were added to a stirred solution of Intermediate 113F (250 mg, 0.833 mmol) in 1,4-dioxane (4 ml). The solution was degassed with argon and Pd(Ph₃)₄ (67.4 mg, 0.058 mmol) was added to this solution. The reaction mixture was stirred at 100°C for 10 hours, diluted with water (10 ml), and
 20 extracted with 10% MeOH in DCM (2×30 ml). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuum to afford the title compound (280 mg, crude). The crude product was used in the next step without further purification. LC-MS m/z: 437.4 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 9.01(s, 1 H), 7.65-7.01 (m, 5H), 4.13 (s, 3H), 3.90 (s, 3 H), 2.70 (s, 3 H), 1.24 (s,
 25 9H).

Intermediate 113H

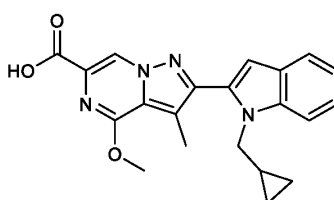
Methyl-2-(1*H*-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-*a*]pyrazine-6-carboxylate



TFA (0.494 ml, 6.42 mmol) was added to a stirred suspension of Intermediate 113G (280mg, 0.642 mmol) in DCM (5 ml). The reaction mixture was stirred at a room temperature for 16 hours, concentrated to remove the excess TFA, and the residue thus
 5 obtained was diluted with water (5 ml) and extracted with DCM (2×15 ml). The combined organic layers were washed with saturated NaHCO₃ solution, brine, dried over sodium sulfate, filtered, and the filtrate was concentrated in vacuum to afford 160 mg (56%) of the title compound as a brown solid. LC-MS m/z: 337.2 [M+H]⁺. ¹H NMR (400 MHz, methanol-*d*₄) δ ppm: 8.82 (s, 1H), 7.68-7.53 (m, 4H), 6.92 (s, 1H), 4.21 (s, 3H),
 10 3.98 (s, 3H), 2.72 (s, 3H).

Intermediate 113I

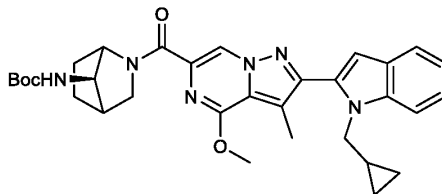
2-(1-(Cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyrazine-6-carboxylic acid



15 Sodium hydride (23.19 mg, 0.580 mmol) was added to a stirred solution of Intermediate 113H (130 mg, 0.387 mmol) in DMF (1 ml). The reaction mixture was stirred at 0°C for 5 min, followed by the addition of (Bromomethyl)cyclopropane (62.6 mg, 0.464 mmol). The reaction mixture was stirred at a room temperature for 16 hours,
 20 diluted with water (5 ml), and extracted with EtOAc (2×10 ml). The combined organic layers were washed with 1N HCl, brine, dried over sodium sulfate, filtered, and the filtrate was concentrated in vacuum to afford the crude title compound (140 mg) as brown solid. LC-MS m/z: 377 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 11.66 (s, 1 H), 8.84 (s, 1 H), 7.71- 7.27 (m, 4 H), 6.85 (s, 1 H), 4.40 (d, J=6.53 Hz, 2 H), 4.14 (s, 3 H),
 25 2.73 (s, 3 H), 0.86 (s, 1 H), 0.25-0.39 (m, 2 H), 0.15 (q, J=4.69 Hz, 2 H).

Intermediate 113J

tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-1*H*-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-*a*]pyrazine-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



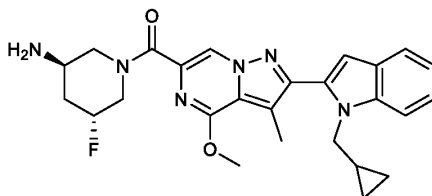
- 5 HATU (106 mg, 0.279 mmol), *tert*-butyl ((7R)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate (47.4 mg, 0.223 mmol) and DIPEA (0.065 ml, 0.372 mmol) were added to a stirred solution of Intermediate 113I (70 mg, 0.186 mmol) in DMF (1 ml). The reaction mixture was stirred at a room temperature for 2 hours, diluted with water (5 ml), and extracted with EtOAc (2×10 ml). The combined organic layers were washed with brine,
 10 dried over sodium sulfate, filtered, and the filtrate was concentrated in vacuum to afford the crude title compound (70 mg). LC-MS *m/z*: 571.3 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.82 (dd, *J*=4.27, 1.25 Hz, 1H), 8.67-8.60(m, 1H), 7.61-7.57 (m, 2H), 7.21-7.06 (m, 2H), 6.87 (s, 1H), 4.46-4.36 (m, 3H), 4.16-4.08 (m, 3 H), 3.58-3.48 (m, 1H), 3.39-3.35 (m, 1 H), 3.29-3.21 (m, 2 H), 2.72-2.68 (m, 1H), 2.58-2.55 (m, 2H), 2.46-
 15 2.42 (m, 2H), 1.98-1.82 (m, 1H), 1.31-1.48 (m, 9H), 0.92-0.86 (m, 1H), 0.50 (dd, *J*=8.03, 1.51 Hz, 2H), 0.13-0.33 (m, 2H).

Example 113

- TFA (0.094 ml, 1.227 mmol) was added to a stirred solution of Intermediate 113J
 20 (70 mg, 0.123 mmol) in DCM (3 ml). The resulting solution was stirred at a room temperature for 16 hours, concentrated, and the crude material thus obtained was purified using preparative LC-MS. The purified product was further purified using RP-HPLC to afford 14.7 mg (25%) of the title compound. LC-MS *m/z*: 471.3 [M+H]⁺. LC-MS retention time: 2.067 min (Method G), 1.780 min (Method F). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.72-8.56 (m, 1H), 7.62 (t, *J*=7.5 Hz, 2H), 7.22 (t, *J*=7.6 Hz, 1H), 7.13-
 25 7.04 (m, 1H), 6.83 (s, 1H), 4.57 (br, s, 1H), 4.39 (br d, *J*=6.6 Hz, 2H), 4.16-4.04 (m, 3H), 3.90 (s, 2H), 3.63-3.51 (m, 1H), 3.19 (br, s, 1H), 3.10 (br, d, *J* = 11.7 Hz, 1H), 2.54 (s, 3H), 2.26-2.04 (m,2H), 2.01-1.84 (m, 2H), 1.46-1.34 (m, 1H), 1.15-1.02 (m, 1H), 0.29 (br, d, *J* = 8.1 Hz, 2H), 0.14 (br, d, *J* = 4.6 Hz, 2H).

Example 114

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyrazin-6-yl)methanone



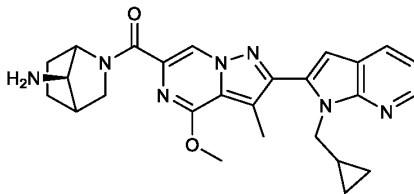
5

Compound of Example 114 was prepared following a procedure similar to the preparation of a compound of Example 113, by coupling Intermediate 113I with the appropriate amine. LC-MS m/z: 477.3 [M+H]⁺, LC-MS retention time: 1.7 min (UPLC).

10

Example 115

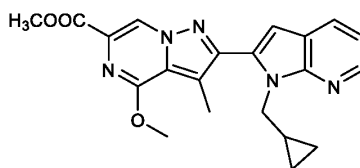
((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyrazin-6-yl)methanone



15

Intermediate 115A

Methyl-2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyrazine-6-carboxylate



1-(Cyclopropylmethyl)-2-(trimethylstannyl)-1H-pyrrolo[2,3-b]pyridine (Intermediate 7, 167 mg, 0.500 mmol) was added to a stirred solution of Intermediate 113F (150 mg, 0.500 mmol) in 1,4-dioxane (3 ml). The reaction mixture was degassed with argon, followed by the addition of Pd(Ph₃)₄ (57.8 mg, 0.050 mmol). The reaction mixture was stirred at 110°C for 16 hours, diluted with water (5 ml), and extracted with

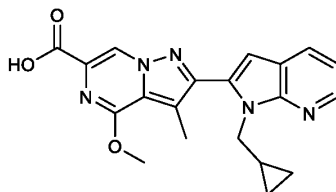
20

EtOAc (2×10 ml). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated in vacuum to obtain the crude title compound (200 mg). LC-MS m/z: 392.2 [M+H]⁺.

5

Intermediate 115B

2-(1-(Cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyrazine-6-carboxylic acid

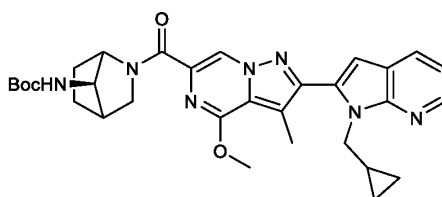


Sodium hydroxide in water (1.277 ml, 2.55 mmol) was added to a stirred solution of Intermediate 115A (200 mg, 0.511 mmol) in THF (3 ml). The resulting solution was stirred at a room temperature for 1 hour, acidified with 1N HCl (3.0 ml), and extracted with EtOAc (2×10 ml). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and the filtrate was concentrated in vacuum. The compound thus obtained was washed with diethyl ether (5 ml) to remove impurities and dried to afford (110 mg) of the title compound. LC-MS m/z: 378.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 13.31-13.14 (m, 1H), 8.90 (s, 1H), 8.40(s, 1H), 7.72-7.14 (m, 2H), 6.89 (s, 1H), 4.62-4.48 (m, 2H), 4.36-4.08 (m, 3H), 2.43-2.22 (m, 3H), 1.05-0.97 (m, 1H), 0.57-0.32 (m, 2H), 0.30-0.12 (m, 2H).

20

Intermediate 115C

tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyrazine-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



HATU (76 mg, 0.199 mmol), *tert*-butyl ((7R)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate (33.8 mg, 0.159 mmol) and DIPEA (0.046 ml, 0.265 mmol) were added to a stirred solution of Intermediate 115B (50 mg, 0.132 mmol) in DMF (1 ml). The reaction

mixture was stirred at a room temperature for 2 hours, diluted with water (5 ml), and extracted with EtOAc (2×10 ml). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and the filtrate was concentrated in vacuum. The crude product was purified using a silica gel column (24 g, Redisep[®] SiO₂ column, eluting with 4% methanol in DCM to afford the title compound (0.050 g, 66%). LC-MS m/z: 572.3 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.68 (s, 1H), 8.35-8.33 (m, 1H), 8.09-8.04 (m, 1H), 7.68-7.51 (m, 1H), 7.20-7.14 (m, 1H), 6.89 (s, 1H), 4.53-4.43 (m, 2H), 4.12 (s, 3H), 4.10-4.06 (m, 1H), 3.72-3.47 (m, 3H), 2.69 (s, 3H), 1.97-1.82 (m, 3H), 1.40-1.29 (m, 9H), 1.26-1.21 (m, 2H), 1.20-1.10 (m, 1H), 0.34-0.16 (m, 4H).

10

Example 115

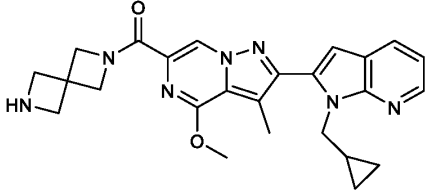
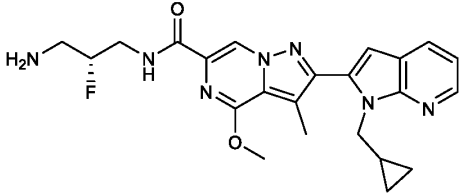
TFA (0.067 ml, 0.875 mmol) was added to a stirred solution of Intermediate 115C (50 mg, 0.087 mmol) in DCM (3 ml). The resulting solution was stirred at a room temperature for 16 hours, concentrated, and the crude product thus obtained was purified using preparative LC-MS. The purified product was further purified using RP-HPLC to afford 17.5 mg (42%) of the title compound. LC-MS m/z: 472.3 [M+H]⁺, retention time: 1.78 min (Method G), 1.338 min (Method F). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.65 (s, 1H), 8.34 (dd, *J*=1.5, 4.6 Hz, 1H), 8.06 (dd, *J*=1.5, 7.8 Hz, 1H), 7.17 (dd, *J*=4.6, 7.8 Hz, 1H), 6.89 (s, 1H), 4.54-4.44 (m, 3H), 4.20 (s, 1H), 4.16-4.05 (m, 3H), 3.60 (d, *J*=10.3 Hz, 1H), 3.56-3.51 (m, 1H), 3.17 (s, 1H), 3.09 (d, *J*=11.2 Hz, 1H), 2.61-2.55 (m, 3H), 2.24-2.06 (m, 2H), 2.01-1.83 (m, 2H), 1.64-1.34 (m, 1H), 1.25-1.12 (m, 1H), 0.33-0.16 (m, 4H).

20

Compounds of Examples 116 and 117 in Table 14 were prepared following a procedure similar to the preparation of a compound of Example 115, by coupling of Intermediate 115B with appropriate amine.

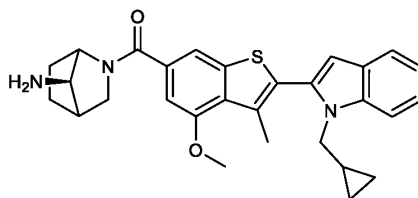
25

Table 14

Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
116	 (2-(1-(Cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyrazin-6-yl)(2,6-diazaspiro[3.3]heptan-2-yl)methanone Analytical Data: 472.3, 1.4 min (Method F)
117	 (R)-N-(3-Amino-2-fluoropropyl)-2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyrazine-6-carboxamide Analytical Data: 452.3, 1.6 min (Method G)

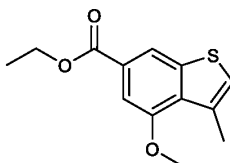
Example 118

- 5 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylbenzo[b]thiophen-6-yl)methanone



Intermediate 118A

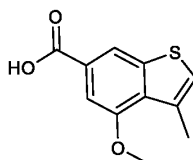
Ethyl-4-methoxy-3-methylbenzo[b]thiophene-6-carboxylate



K₂CO₃ (1.404 g, 10.16 mmol) was added to a stirred solution of ethyl 4-hydroxy-3-methylbenzo[b]thiophene-6-carboxylate (1.2 g, 5.08 mmol; U.S. Pub. 20080280875) in DMF (6 m). The reaction mixture was stirred for 10 min, followed by the addition of methyl iodide (0.381 ml, 6.09 mmol). The reaction mixture was further stirred for 5 hours at a room temperature, poured into water (70 ml, and extracted with EtOAc (2×25 ml). The combined organic layers were washed with water (50 ml) and brine solution (50 ml), dried over Na₂SO₄, filtered, and the volatiles were evaporated to dryness under reduced pressure. Residue thus obtained was purified using a silica gel column using a gradient of EtOAc in hexane. The product was isolated at 15% EtOAc in hexane, required fractions were collected and volatiles were evaporated to dryness under reduced pressure to afford the title compound as yellow solid (900 mg, 80%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.16 (s, 1H), 7.48 (s, 1H), 7.31 (s, 1H), 4.23-4.46 (m, 2H), 3.94 (s, 3H), 2.54-2.59 (m, 3H), 1.29-1.44 (m, 3H).

Intermediate 118B

4-Methoxy-3-methylbenzo[b]thiophene-6-carboxylic acid

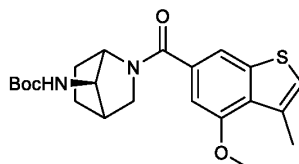


Lithium hydroxide (201 mg, 8.39 mmol) in water (2 ml) was added to a stirred solution of Intermediate 118A (700 mg, 2.80 mmol) in a mixture of ethanol (5 ml) and THF (5 ml). The reaction mixture was stirred at a room temperature for 17 hours, the volatiles were evaporated to dryness under reduced pressure, water (10 ml) was added, and pH of the reaction mixture was adjusted to pH 2 using 1.5 N aqueous HCl. The solids thus obtained were collected by vacuum filtration to afford 4-methoxy-3-methylbenzo[b]thiophene-6-carboxylic acid (620 mg, 80%). LC-MS m/z: 221.1 [M-H]⁺.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm: 12.9 (br, 1H), 8.12 (d, $J=1.51$ Hz, 1H), 7.45 (s, 1H), 7.32 (d, $J=1.00$ Hz, 1H), 3.93 (s, 3H), 2.57 (d, $J=1.00$ Hz, 3H).

Intermediate 118C

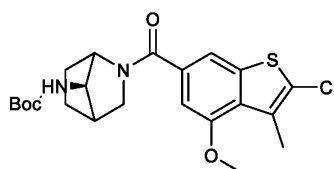
5 tert-Butyl-((7R)-2-(4-methoxy-3-methylbenzo[b]thiophene-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



HATU (1591 mg, 4.18 mmol), DIPEA (1.462 ml, 8.37 mmol) and tert-butyl ((7R)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate (592 mg, 2.79 mmol) were added to a stirred solution of Intermediate 118B (620 mg, 2.79 mmol) in DMF (10 ml). The reaction mixture was stirred further at a room temperature for 17 hours, water (30 ml) was added, and the reaction mixture was extracted with EtOAc (2×25 ml). The combined organic layers were washed with water (25 ml) and brine (50 ml), dried over Na_2SO_4 , filtered, and the volatiles were evaporated to dryness under reduced pressure to afford the title compound (800 mg, 60%). LC-MS m/z : 417.3 $[\text{M}+\text{H}]^+$.

Intermediate 118D

tert-Butyl-((7R)-2-(2-chloro-4-methoxy-3-methylbenzo[b]thiophene-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate

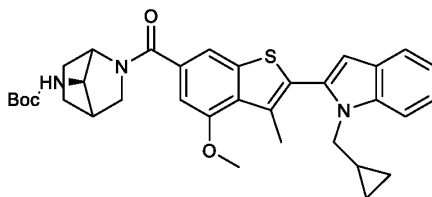


20 LDA (0.6 ml, 0.120 mmol) was added to a stirred solution of Intermediate 118C (50 mg, 0.120 mmol) in THF (4 ml) at -78°C , and the reaction mixture was stirred for 30 min. A solution of perchloroethane (28.7 mg, 0.120 mmol) in THF (4 ml) was added and the reaction mixture was further stirred for 5 hours. Later, the reaction mixture was allowed to warm to a room temperature, quenched with aqueous ammonium chloride solution (25 ml), and extracted with EtOAc (2×25 ml). The combined organic layers were washed with water (25 ml) and brine (50 ml), dried over Na_2SO_4 , filtered, and the

volatiles were evaporated to dryness under reduced pressure to afford the title compound (50 mg, 60%). LC-MS m/z: 451.2 [M+H]⁺.

Intermediate 118E

- 5 tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylbenzo[b]thiophene-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



- A solution of K₂CO₃ (92 mg, 0.665 mmol) in water (1 ml) was added to a stirred solution of Intermediate 118D (100 mg, 0.222 mmol) and 1-(cyclopropylmethyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (Intermediate-10, 65.9 mg, 0.222 mmol) in dioxane (3 ml), followed by the addition of tetrakis(triphenylphosphine)palladium(0) under argon atmosphere. The reaction mixture was heated at 120°C and stirred for 17 hours, allowed to cool to a room temperature, water (10 ml) was added, and extracted with EtOAc (2×15 ml). The combined organic layers were washed with water (15 ml) and brine (20 ml), dried over Na₂SO₄, filtered, and the volatiles were evaporated to dryness under reduced pressure to afford the title compound (120 mg, 85%). LC-MS m/z: 586.3 [M+H]⁺.

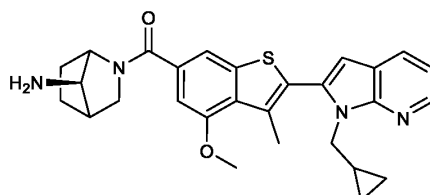
Example 118

- 20 TFA (0.158 ml, 2.049 mmol) was added to a stirred solution of Intermediate 118E (120 mg, 0.205 mmol) in DCM (2 ml). The reaction mixture was stirred at a room temperature for 17 hours, the volatiles were evaporated to dryness under reduced pressure, and the crude product thus obtained was purified using reverse phase column chromatography. The purified product was further purified using RP-HPLC to afford the title compound (2.2 mg, 2%). LC-MS m/z: 486.3 [M+H]⁺. LC-MS retention time: 1.8 min (Method F). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 7.79-7.54 (m, 3H), 7.23 (t, J=7.7 Hz, 1H), 7.14-7.06 (m, 1H), 7.06-6.88 (m, 1H), 6.64 (s, 1H), 4.07-3.99 (m, 2H), 3.97-3.91 (m, 3H), 3.76-3.71 (m, 1H), 3.61-3.56 (m, 1H), 3.51-3.47 (m, 1H), 3.18 (br, d, J=10.8 Hz,

1H), 2.55 (s, 2H), 2.48-2.41 (m, 3H), 2.04-1.81 (m, 3H), 1.62 (br, d, J=1.0 Hz, 1H), 1.23 (s, 1H), 0.98 (br, s, 1H), 0.38-0.22 (m, 2H), 0.10 (br, d, J=2.9 Hz, 2H).

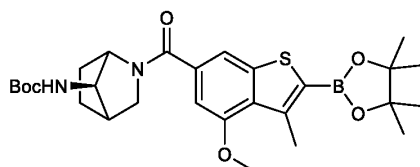
Example 119

- 5 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylbenzo[b]thiophen-6-yl)methanone



Intermediate 119A

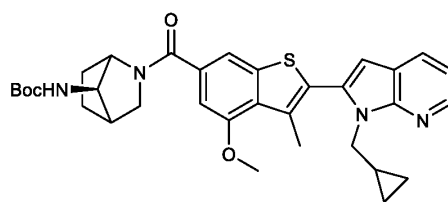
- 10 tert-Butyl-((7R)-2-(4-methoxy-3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[b]thiophene-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



- LDA (1.2 ml, 0.480 mmol) was added drop wise under argon atmosphere to a stirred solution of Intermediate 118C (200 mg, 0.480 mmol) in THF (4 ml) at -78°C. The reaction mixture was stirred for 45 min, followed by the addition of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.100 ml, 0.480 mmol). The reaction mixture was further stirred for 1 hours, allowed to warm to a room temperature, quenched with aqueous ammonium chloride solution (25 ml), and extracted with EtOAc (2×25 ml). The combined organic layers were washed with water (25 ml) and brine solution (50 ml), dried over Na₂SO₄, filtered and the volatiles were evaporated to dryness under reduced pressure to afford the title compound (200 mg, crude). LC-MS m/z: 543 [M+H]⁺.

Intermediate 119B

- tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylbenzo[b]thiophene-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



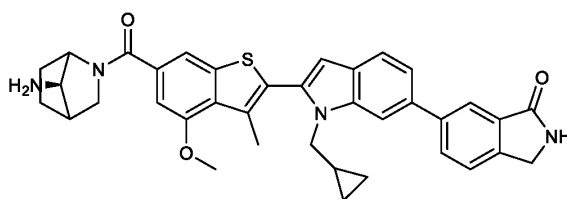
A solution of K_2CO_3 (184 mg, 1.330 mmol) in water (1 ml) was added to a stirred solution of Intermediate 119A (200 mg, 0.443 mmol) and 1-(cyclopropylmethyl)-2-iodo-1H-pyrrolo[2,3-b]pyridine (132 mg, 0.443 mmol) in dioxane (6 ml), followed by the addition of $PdCl_2(dppf)$ (20.23 mg, 0.028 mmol) under argon atmosphere. The reaction mixture was heated to $85^\circ C$ and stirred for 17 hours, allowed to cool to a room temperature, water (10 ml) was added, and extracted with EtOAc (2×15 ml). The combined organic layers were washed with water (15 ml) and brine (20 ml), dried over Na_2SO_4 , filtered, and the volatiles were evaporated to dryness under reduced pressure to afford the title compound (200 mg, crude). LC-MS m/z : 587.4 $[M+H]^+$.

Example 119

TFA (0.263 ml, 3.41 mmol) was added to a stirred solution of Intermediate 119B (200 mg, 0.341 mmol) in DCM (3 ml). The reaction mixture was stirred at a room temperature for 17 hours, the volatiles were evaporated to dryness under reduced pressure, and the residue thus obtained was purified using prep-HPLC. The purified product was further purified using RP-HPLC to afford the title compound (16.2 mg, 9%). LC-MS m/z : 487.2 $[M+H]^+$. LC-MS retention time: 1.4 min (Method F). 1H NMR (400 MHz, $DMSO-d_6$) δ ppm: 8.38-8.27 (m, 1H), 8.10-7.96 (m, 1H), 7.76-7.58 (m, 1H), 7.22-7.10 (m, 1H), 7.03-6.90 (m, 1H), 6.74-6.65 (m, 1H), 4.17-4.09 (m, 2H), 3.99-3.87 (m, 4H), 3.70 (s, 1H), 3.52-3.48 (m, 1H), 3.17 (br, d, $J=1.2$ Hz, 1H), 3.09-3.00 (m, 1H), 2.58-2.53 (m, 1H), 2.48-2.42 (m, 3H), 2.23-2.09 (m, 1H), 2.03-1.86 (m, 3H), 1.79-1.64 (m, 1H), 1.45-1.30 (m, 1H), 1.07-0.95 (m, 1H), 0.34-0.24 (m, 2H), 0.19-0.10 (m, 2H).

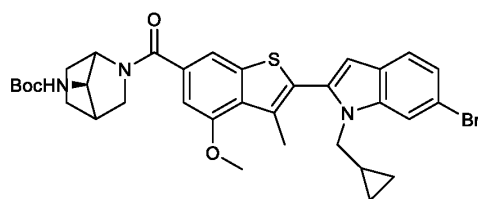
Example 120

6-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylbenzo[b]thiophen-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one



Intermediate 120A

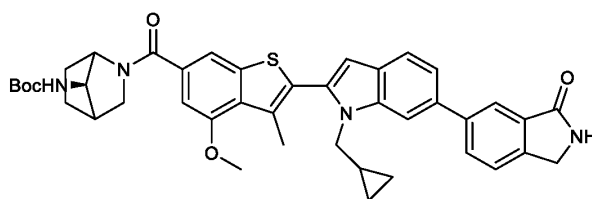
tert-Butyl-((7R)-2-(2-(6-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylbenzo[b]thiophene-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



A solution of K_2CO_3 (2.293 g, 16.59 mmol) in water (8 ml) was added to a stirred solution of Intermediate 119A (3 g, 5.53 mmol), 6-bromo-1-(cyclopropylmethyl)-2-iodo-1H-indole (Intermediate-12, 2.079 g, 5.53 mmol) and $PdCl_2(dppf)-CH_2Cl_2$ adduct (0.339 g, 0.415 mmol) in dioxane (50 ml). The reaction mixture was heated to 80°C and stirred for 14 hours, the volatiles were evaporated to dryness under reduced pressure, water (50 ml) was added to the reaction mixture, and extracted with EtOAc (2×50 ml). The combined organic extracts were washed with water (100 ml) and brine (100 ml), dried over sodium sulphate, filtered, and the filtrate was concentrated to dryness under reduced pressure. Residue thus obtained was purified using a silica gel column using a gradient of EtOAc in hexane. The product was isolated at 45% EtOAc in hexane, required fractions were collected and volatiles were evaporated to dryness under reduced pressure to afford the title compound (1.2 g, 33%). LCMS m/z: 666.4 $[M+2H]^+$.

Intermediate 120B

tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-6-(3-oxoisindolin-5-yl)-1H-indol-2-yl)-4-methoxy-3-methylbenzo[b]thiophene-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



A solution of K_2CO_3 (24.95 mg, 0.181 mmol) in water (1 ml) was added to a stirred solution of Intermediate 120A (40 mg, 0.060 mmol) and 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-1-one (15.59 mg, 0.060 mmol) in dioxane (2 ml),
 5 followed by the addition of $PdCl_2(dppf)$ DCM adduct (3.30 mg, 4.51 μ mol) under argon atmosphere. The reaction mixture was heated to 80°C and stirred for 14 hours, the volatiles were evaporated to dryness under reduced pressure, water (10 ml) was added and the reaction mixture was extracted with EtOAc (2×10 ml). The combined organic extracts were washed with water (20 ml) and brine (20 ml), dried over sodium sulphate,
 10 filtered, and the filtrate was evaporated to dryness under reduced pressure to afford title compound (40 mg, crude). LC-MS m/z: 715 $[M-H]^+$.

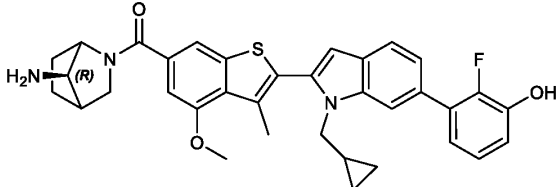
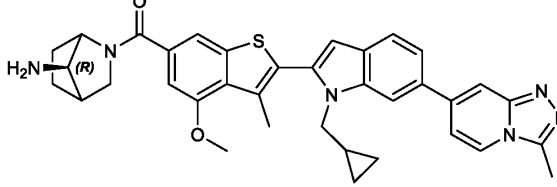
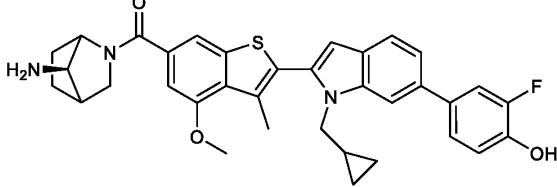
Example 120

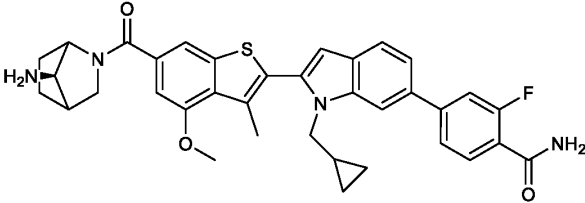
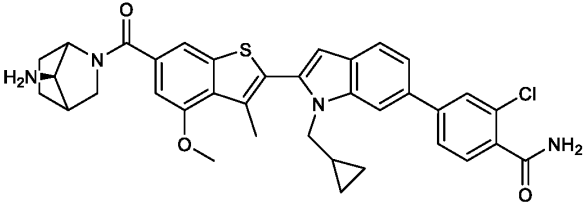
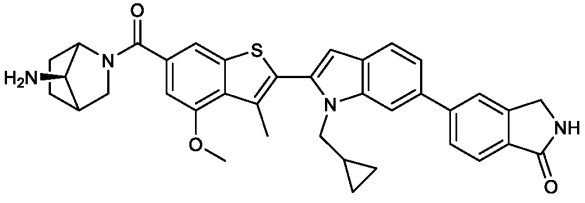
TFA (0.043 ml, 0.558 mmol) was added to a stirred solution of Intermediate 120B
 15 (40 mg, 0.056 mmol) in DCM (2 ml). The reaction mixture was stirred at a room temperature for 17 hours, the volatiles were evaporated to dryness under reduced pressure, and the crude product thus obtained was purified using RP-HPLC to afford the title compound (2.8mg, 8%). LC-MS m/z: 617.4 $[M-H]^+$. LC-MS retention time: 1.5 min (Method F). 1H NMR (400 MHz, $DMSO-d_6$) δ ppm: 8.60 (s, 1H), 8.06-7.96 (m, 3H),
 20 7.75-7.65 (m, 2H), 7.63 (s, 1H), 7.48 (d, $J=8.3$ Hz, 1H), 7.03-6.91 (m, 1H), 6.69 (s, 1H), 4.44 (s, 3H), 4.22-4.12 (m, 2H), 3.96 (s, 4H), 3.71 (br, s, 1H), 3.49 (br, d, $J=1.5$ Hz, 1H), 3.18 (br, d, $J=0.7$ Hz, 1H), 3.09-3.03 (m, 1H), 2.20 (br, s, 1H), 2.04-1.81 (m, 3H), 1.76-1.69 (m, 1H), 1.45-1.36 (m, 1H), 1.23 (s, 2H), 1.10-1.02 (m, 1H), 0.35 (br, d, $J=8.1$ Hz, 2H), 0.14 (br, d, $J=3.2$ Hz, 2H).

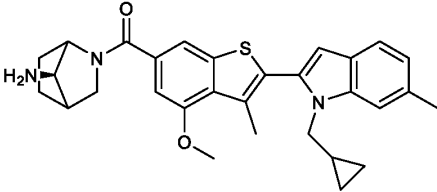
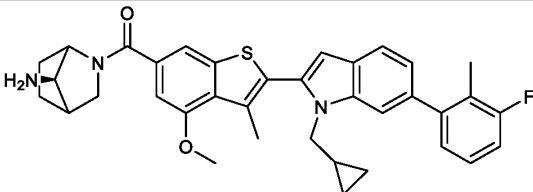
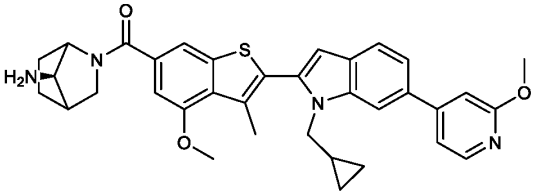
25

Compounds of Examples 121 to 129 in Table 15 were prepared following a procedure similar to the preparation of a compound of Example 120, by Suzuki coupling of the Intermediate 120A with appropriate boronic acid.

Table 15

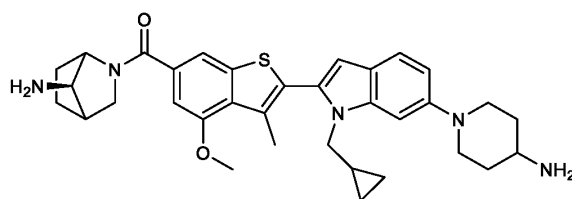
Example	Structure
	Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
121	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-fluoro-3-hydroxyphenyl)-1H-indol-2-yl)-4-methoxy-3-methylbenzo[b]thiophen-6-yl)methanone Analytical Data: 596.3, 2.075 min (Method E)
122	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)-1H-indol-2-yl)-4-methoxy-3-methylbenzo[b]thiophen-6-yl)methanone Analytical Data: 617.3, 1.7 min (Method E)
123	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-fluoro-4-hydroxyphenyl)-1H-indol-2-yl)-4-methoxy-3-methylbenzo[b]thiophen-6-yl)methanone Analytical Data: 596.3, 2.0 min (Method E)

124	 4-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylbenzo[b]thiophen-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)-2-fluorobenzamide Analytical Data: 623.3, 1.8 min (Method E)
125	 4-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylbenzo[b]thiophen-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)-2-chlorobenzamide Analytical Data: 639.3, 1.8 min (Method E)
126	 5-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylbenzo[b]thiophen-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one Analytical Data: 617.3, 1.7 min (Method E)

127	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-methyl-1H-indol-2-yl)-4-methoxy-3-methylbenzo[b]thiophen-6-yl)methanone Analytical Data: 500, 2.3 min (Method E)
128	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-fluoro-2-methylphenyl)-1H-indol-2-yl)-4-methoxy-3-methylbenzo[b]thiophen-6-yl)methanone Analytical Data: 594.3, 2.6 min (Method E)
129	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-methoxypyridin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylbenzo[b]thiophen-6-yl)methanone Analytical Data: 593, 2.0 min (Method E)

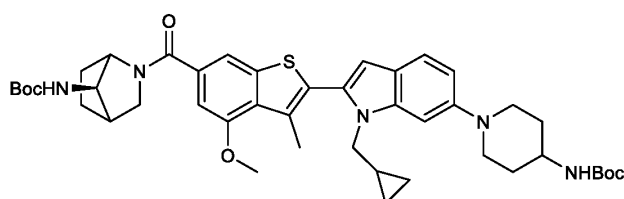
Example 130

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-(4-aminopiperidin-1-yl)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylbenzo[b]thiophen-6-yl)methanone



Intermediate 130A

tert-Butyl-((7R)-2-(2-(6-(4-((tert-butoxycarbonyl)amino)piperidin-1-yl)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylbenzo[b]thiophene-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



Caesium carbonate (147 mg, 0.451 mmol), RUPHOS (35.1 mg, 0.075mmol) and $\text{Pd}_2(\text{dba})_3$ (13.78 mg, 0.015 mmol) were added to a stirred solution of Intermediate 120A (100 mg, 0.150mmol) and tert-butyl piperidin-4-ylcarbamate (30.1 mg, 0.150 mmol) in dioxane (3 ml). The reaction mixture was degasified with argon for 5 min, stirred at 110°C for 16 hours, cooled to a room temperature, water (10 ml) was added and the reaction mixture was extracted with EtOAc (2×10 ml). The combined organic extracts were washed with water (20 ml) and brine (20 ml), dried over sodium sulphate, filtered, and volatiles were evaporated to dryness under reduced pressure to afford the title compound 100 mg (crude). LC-MS m/z: 784.5 $[\text{M}-\text{H}]^+$.

Example 130

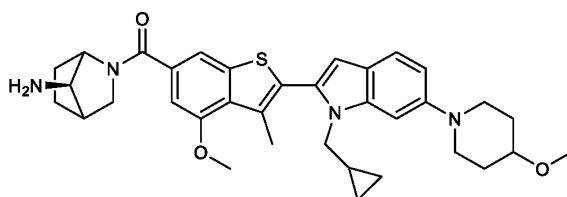
TFA (0.5 ml) was added to a stirred solution of Intermediate 130A (100 mg) in DCM (2 ml), and the reaction mixture was stirred at a room temperature for 17 hours. The volatiles were evaporated to dryness under reduced pressure and the residue thus obtained was purified using RP-HPLC to afford the title compound (9.4 mg, 13%). LC-MS m/z: 584.3 $[\text{M}-\text{H}]^+$. LCMS retention time: 1.5 min (Method E). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm: 8.13 (br, d, $J=4.2$ Hz, 1H), 8.03-7.85 (m, 4H), 7.76-7.59 (m, 1H), 7.45 (d, $J=8.3$ Hz, 1H), 7.11-7.04 (m, 1H), 7.04-6.93 (m, 1H), 6.90 (br, d, $J=7.6$ Hz, 1H), 6.50

(s, 1H), 4.56-4.12 (m, 3H), 4.03-3.92 (m, 3H), 3.81-3.73 (m, 2H), 3.63-3.55 (m, 1H), 3.20(br, d, J=11.5 Hz, 1H), 2.87-2.76 (m, 2H), 2.46-2.41 (m, 2H), 2.04-1.81 (m, 4H), 1.74-1.59 (m, 2H), 1.02-0.89 (m, 1H), 0.37-0.26 (m, 2H), 0.14-0.03 (m, 2H).

5

Example 131

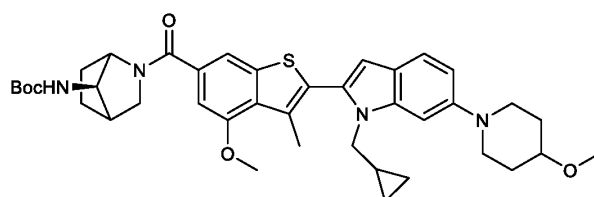
((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(4-methoxypiperidin-1-yl)-1H-indol-2-yl)-4-methoxy-3-methylbenzo[b]thiophen-6-yl)methanone



10

Intermediate 131A

tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-6-(4-methoxypiperidin-1-yl)-1H-indol-2-yl)-4-methoxy-3-methylbenzo[b]thiophene-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



15

2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (XPHOS, 10.76 mg, 0.023 mmol), potassium tert-butoxide (10.13 mg, 0.090 mmol) and palladium (II) acetate (3.04 mg, 0.014 mmol) were added to a stirred solution of Intermediate 120A (30 mg, 0.045 mmol) and 4-methoxypiperidine (5.20 mg, 0.045 mmol) in dioxane (1 ml). The reaction mixture was degasified under argon for 5 min and then stirred at 110°C for 16 hours. The reaction mixture was cooled to a room temperature, water (10 ml) was added, and extracted with EtOAc (2×10 ml). The combined organic extracts were washed with water (20 ml) and brine (20 ml), dried over sodium sulphate, filtered, and the filtrate was evaporated to dryness under reduced pressure to afford the title compound 100 mg (crude). LC-MS m/z: 699.5 [M+H]⁺.

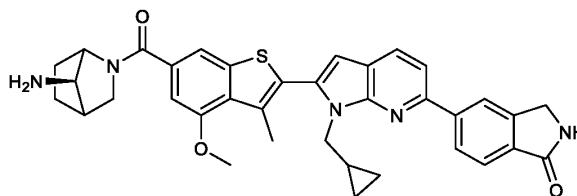
25

Example 131

TFA (0.5 ml) was added to a stirred solution of Intermediate 131A (100 mg) in DCM (2 ml). The reaction mixture was stirred at a room temperature for 17 hours, the volatiles were evaporated to dryness under reduced pressure, and the crude compound thus obtained was purified using RP-HPLC to afford the title compound (6.6 mg, 18%). LC-MS m/z : 599.3 $[M+H]^+$. LC-MS retention time: 2.1 min (Method E). 1H NMR (400 MHz, DMSO- d_6) δ ppm: 7.72-7.57 (m, 1H), 7.41 (d, $J=8.8$ Hz, 1H), 7.03 (s, 1H), 6.99-6.92 (m, 1H), 6.87 (dd, $J=9.0, 1.2$ Hz, 1H), 6.48 (s, 1H), 4.01-3.91 (m, 5H), 3.75 (br, s, 1H), 3.54-3.47 (m, 3H), 3.29 (s, 4H), 3.21 (br, d, $J=1.7$ Hz, 1H), 3.08 (br, d, $J=10.8$ Hz, 1H), 2.96-2.86 (m, 3H), 2.46-2.42 (m, 3H), 2.28-2.20 (m, 1H), 2.03-1.84 (m, 4H), 1.79-1.53 (m, 3H), 1.46-1.37 (m, 1H), 1.02-0.89 (m, 1H), 0.38-0.25 (m, 2H), 0.08 (br, d, $J=3.4$ Hz, 2H).

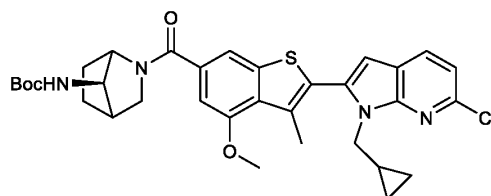
Example 132

5-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylbenzo- [b]thiophen-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-*b*]pyridin-6-yl)isoindolin-1-one



Intermediate 132A

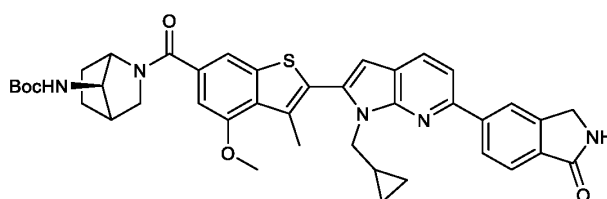
tert-Butyl-((7R)-2-(2-(6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-*b*]pyridin-2-yl)-4-methoxy-3-methylbenzo[*b*]thiophene-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



6-Chloro-1-(cyclopropylmethyl)-2-iodo-1*H*-pyrrolo[2,3-*b*]pyridine (Intermediate 3, 800 mg, 2.406 mmol) and potassium carbonate (831 mg, 6.01 mmol) in water (0.5 ml) were added to a degassed solution of Intermediate 119A (1696 mg, 3.13 mmol) in 1,4-dioxane (15 ml), followed by the addition of PdCl₂(dppf)-CH₂Cl₂ adduct (118 mg, 0.144 mmol). The resulting solution was stirred at 80°C for 10 hours, diluted with water (5 m), and extracted with EtOAc (2×10 ml). The combined organic layers were washed with brine (20 ml), dried over sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure. The crude product thus obtained was purified using a silica gel column (24 g, Redisep[®] SiO₂ column, eluting with 80% EtOAc in n-hexane) to afford the title compound (0.55 g, 36%) as a brown solid. LC-MS *m/z*: 621.3 [M+H]⁺.

Intermediate 132B

tert-Butyl- ((7*R*)-2-(2-(1-(cyclopropylmethyl)-6-(1-oxoisindolin-5-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)-4-methoxy-3-methylbenzo[*b*]thiophene-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isindolin-1-one (37.5 mg, 0.145 mmol), potassium phosphate tribasic (64.1 mg, 0.302 mmol) in water (0.3 ml) were added to a degassed solution of Intermediate 132A (75 mg, 0.121 mmol) in 1,4-dioxane (2 ml), followed by the addition of XPHOS Pd G2 (5.30 mg, 7.24 μmol). The resulting solution was heated to 80°C and stirred for 10 hours, diluted with water (5 ml), and extracted with EtOAc (2×10 ml). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and the filtrate was concentrated in vacuum. The crude product thus obtained was purified using a silica gel column (12 g, Redisep[®] SiO₂ column, eluting with 80% EtOAc in n-hexane) to afford the title compound (35 mg, 40%) as a brown solid. LC-MS *m/z*: 718.4 [M+H]⁺.

Example 132

TFA (0.032 ml, 0.418 mmol) was added to a stirred solution of Intermediate 132B (30 mg, 0.042 mmol) in DCM (5 ml) at a room temperature. The reaction mixture was stirred further for 16 hours, concentrated, and the crude product thus obtained was

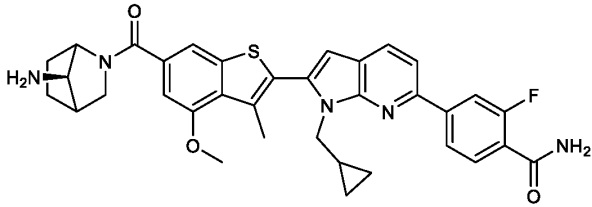
5 purified using RP-HPLC to afford the title compound (0.013 g, 48%). LC-MS m/z: 618.3 [M+H]⁺. HPLC retention time: 6.9 min (Method C). ¹H NMR (400 MHz, methanol-*d*₄) δ ppm: 8.34-8.44 (m, 2H), 8.12 (d, *J*=8.07 Hz, 1H), 7.92 (d, *J*=7.83 Hz, 1H), 7.82-7.87 (m, 1H), 7.65 (s, 1H), 6.97-7.11 (m, 1H), 6.69 (s, 1H), 4.60 (s, 2H), 4.31 (br, d, *J*=6.85 Hz, 2H), 4.04 (s, 3H), 3.73-3.83 (m, 1H), 3.56-3.71 (m, 1H), 2.69-2.90 (m, 1H) 2.59 (s, 3H),

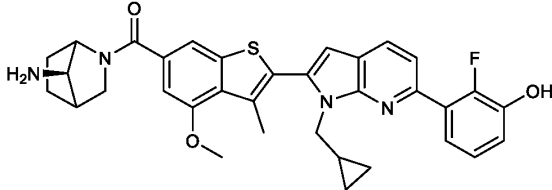
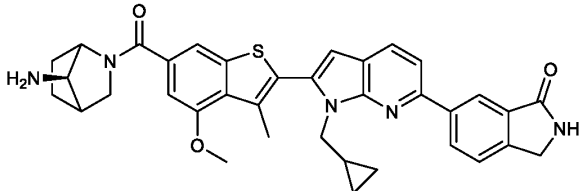
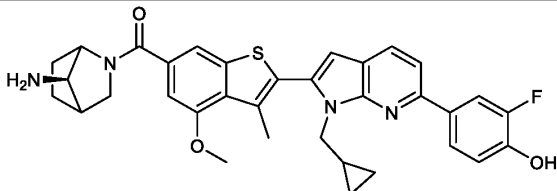
10 1.93-2.31 (m, 3H), 1.10-1.24 (m, 1H), 0.40 (br, d, *J*=8.07 Hz, 2H), 0.25 (br, d, *J*=5.62 Hz, 2H).

Compounds of Examples 133 to 136 in Table 16 were prepared following a procedure similar to the preparation of a compound of Example 132, by Suzuki coupling

15 of Intermediate 132A with appropriate boronic acid.

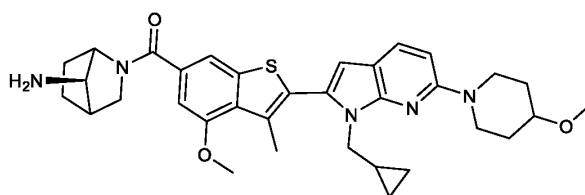
Table 16

Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
133	 4-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylbenzo[b]thiophen-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorobenzamide Analytical Data: 624.4, 2.9 min (UPLC)

134	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-fluoro-3-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylbenzo[b]thiophen-6-yl)methanone Analytical Data: 597.3, 7.5 min (Method C)
135	 6-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylbenzo[b]thiophen-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one Analytical Data: 618.2, 7.39 min (Method C)
136	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-fluoro-4-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylbenzo[b]thiophen-6-yl)methanone Analytical Data: 597.3, 7.0 min (Method C)

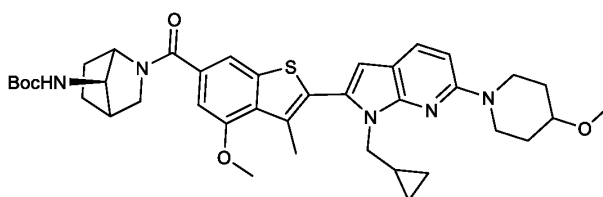
Example 137

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(4-methoxypiperidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylbenzo[b]thiophen-6-yl)methanone



Intermediate 137A

tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-6-(4-methoxypiperidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylbenzo[b]thiophene-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



4-Methoxypiperidine (19.47 mg, 0.169 mmol), potassium tert-butoxide (25.3 mg, 0.225 mmol), Pd(OAc)₂ (7.59 mg, 0.034 mmol), and XPHOS (32.2 mg, 0.068 mmol) were added to a degasified stirred solution of Intermediate 132A (70 mg, 0.113 mmol) in 1,4-dioxane (2 ml). The reaction mixture was heated to 110°C and stirred for 16 hours, concentrated, diluted with water (5ml), and extracted with EtOAc (2×10 ml). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and the filtrate was concentrated in vacuum. The crude product obtained was purified using a silica gel column (12 g, Redisep[®] SiO₂ column, eluting with 5% methanol in DCM) to afford the title compound as brown solid (40 mg, 50%). LC-MS m/z: 700 [M+H]⁺.

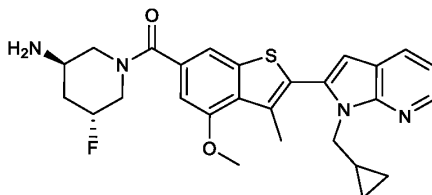
Example 137

TFA (4.40 μl, 0.057 mmol) was added to a stirred solution of Intermediate 137A (40 mg, 0.057 mmol) in DCM (5 ml). The reaction mixture was stirred at a room temperature for 16 hours, concentrated, and the crude compound thus obtained was purified using RP-HPLC to afford the title compound (11 mg, 31%) as off white solid. LC-MS m/z: 600.2 [M+H]⁺. LCMS retention time: 2.44 min (Method C). ¹H NMR (400 MHz, methanol-*d*₄) δ ppm: 7.76 (d, J=8.56 Hz, 1H), 7.58 (s, 1H), 7.01-6.98(m, 1H), 6.74 (d, J=8.80 Hz, 1H), 6.42 (s, 1H), 4.17-4.06 (m, 4H), 3.98 (s, 3H), 3.82-3.66 (m, 1H), 3.58-3.49 (m, 1H), 3.39 (s, 3H), 3.35 (s, 1H), 3.29- 3.12 (m, 3H), 2.57-2.47 (m, 4 H), 2.10

– 1.91 (m, 5H), 1.77-1.53 (m, 3H), 1.43-1.24 (m, 1H), 1.17-1.02 (m, 1H), 0.37-0.28 (m, 2H), 0.23-0.04 (m, 2H).

Example 138

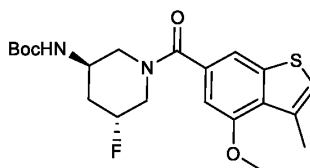
- 5 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylbenzo[b]thiophen-6-yl)methanone



10

Intermediate 138A

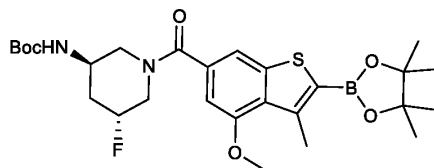
tert-Butyl-((3R,5R)-5-fluoro-1-(4-methoxy-3-methylbenzo[b]thiophene-6-carbonyl)-piperidin-3-yl)carbamate



- HATU (1026 mg, 2.70 mmol) and DIPEA (1.179 ml, 6.75 mmol) in DMF (14 ml) was added to a stirred solution of Intermediate 118B (500 mg, 2.250 mmol), and tert-butyl ((3R,5R)-5-fluoropiperidin-3-yl)carbamate (491 mg, 2.250 mmol). The reaction mixture was stirred at a room temperature for 17 hours, water (30 ml) was added, and extracted with EtOAc (2×25 ml). The combined organic layers were washed with water (25 ml) and brine (50 ml), dried over Na₂SO₄, filtered, and the volatiles were evaporated to dryness under reduced pressure. The crude product thus obtained was purified using a silica gel column (40 g, Redisep[®] SiO₂ column, eluting with 40% EtOAc in hexane) to afford the title compound (300 mg, crude). LC-MS m/z: 421.2 [M-H]⁺.

Intermediate 138B

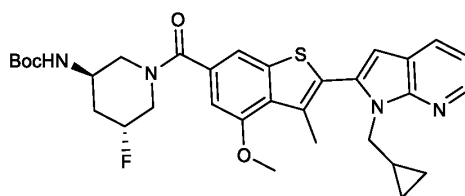
- 25 tert-Butyl-((3R,5R)-5-fluoro-1-(4-methoxy-3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[b]thiophene-6-carbonyl)piperidin-3-yl) carbamate



LDA (1 ml, 2 mmol) was added drop wise under argon atmosphere to a stirred
 5 solution of Intermediate 138A (200 mg, 0.473 mmol) in THF (13 ml) at -78°C, the
 reaction mixture was stirred for 45 min followed by the addition of 2-Isopropoxy-4,4,5,5-
 tetramethyl-1,3,2-dioxaborolane (0.4 ml, 0.473 mmol). The reaction mixture was stirred
 for 1 hour, allowed to warm to a room temperature, quenched with aqueous ammonium
 chloride solution (25 ml), and extracted with EtOAc (2×25 ml). The combined organic
 10 layers were washed with water (25 ml) and brine (50 ml), dried over Na₂SO₄, filtered, and
 the volatiles were evaporated to dryness under reduced pressure to afford the title
 compound (200 mg, crude). LC-MS m/z: 491.2 [M-57+H]⁺.

Intermediate 138C

15 tert-Butyl-((3R,5R)-1-(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-
 2-yl)-4-methoxy-3-methylbenzo[b]thiophene-6-carbonyl)-5-fluoropiperidin-3-
 yl)carbamate



20 A solution of K₂CO₃ (302 mg, 2.188 mmol) in water (1 ml) was added to a stirred
 solution of Intermediate 138B (400mg, 0.729 mmol) and 1-(cyclopropylmethyl)-2-iodo-
 1H-pyrrolo[2,3-b]pyridine (217 mg, 0.729 mmol) in dioxane (4 ml), followed by the
 addition of tetrakis-(triphenylphosphine)palladium(0) (63.2 mg, 0.055 mmol) under argon
 atmosphere. The reaction mixture was heated to 85°C and stirred for 17 hours, allowed to
 25 cool to a room temperature, water (10 ml) was added, and extracted with EtOAc (2×15
 ml). The combined organic layers were washed with water (15 ml) and brine (20 ml),

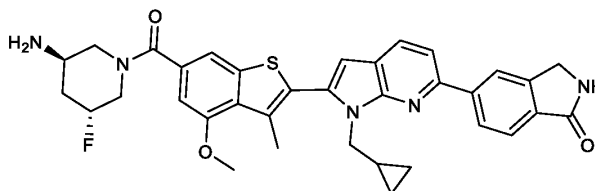
dried over Na₂SO₄, filtered and the volatiles were evaporated to dryness under reduced pressure to afford the title compound (200 mg, 50%). LC-MS m/z: 593.3 [M+H]⁺.

Example 138

5 TFA (0.260 ml, 3.37 mmol) was added to a stirred solution of Intermediate 138C (200 mg, 0.337 mmol) in DCM (2 ml). The reaction mixture was stirred at a room temperature for 17 hours, the volatiles were evaporated to dryness under reduced pressure, and the crude product thus obtained was purified using RP-HPLC to afford the title compound (13.8, 8%). LC-MS m/z: 493.3 [M+H]⁺. LC-MS retention time: 1.8 min
10 (Method E). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.34 (dd, J=1.6, 4.8 Hz, 1H), 7.63 (s, 1H), 7.31-6.99 (m, 2H), 6.93 (s, 1H), 6.69 (s, 1H), 5.13 -4.58 (m, 3H), 4.16 (br, d, J=7.1 Hz, 3H), 3.95 (s, 5H), 3.10-2.79 (m, 1H), 2.41-2.32 (m, 3H), 1.98-1.69 (m, 1H), 1.29-1.09 (m, 1H), 1.06-0.94 (m, 1H), 0.36-0.25 (m, 2H), 0.15 (br, d, J=4.6 Hz, 2H).

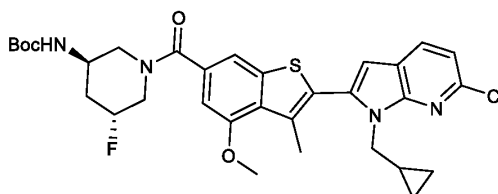
Example 139

5-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylbenzo[b]thiophen-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one



Intermediate 139A

tert-Butyl-((3R,5R)-1-(2-(6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylbenzo[b]thiophene-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate

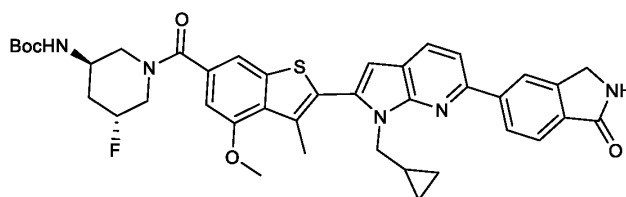


25 6-Chloro-1-(cyclopropylmethyl)-2-iodo-1H-pyrrolo[2,3-b]pyridine (Intermediate-3, 0.8 g, 2.406 mmol) and K₂CO₃ (0.831 g, 6.01 mmol) in water (0.8 ml) were added to a

degassed solution of Intermediate 138B (1.583 g, 2.89 mmol) in 1,4-dioxane (3 ml), followed by the addition of PdCl₂(dppf)-CH₂Cl₂ adduct (0.118 g, 0.144 mmol). The reaction mixture was heated to 90°C and stirred for 16 hours, diluted with water (5 ml), and extracted with EtOAc (2×10 ml). The combined organic layers were washed with
 5 brine (20 ml), dried over sodium sulphate, filtered, and the filtrate was concentrated under reduced pressure. The crude product thus obtained was purified using a silica gel column (24 g, Redisep[®] SiO₂ column, eluting with 80% EtOAc in n-hexane) to afford the title compound as brown solid (40 mg, 46%). LC-MS m/z: 627 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.10 (d, *J*=8.53 Hz, 1H), 7.63 (s, 1H), 7.25 (d, *J*=8.03 Hz, 1H), 6.93
 10 (s, 2H), 6.75 (s, 1H), 4.05 (dt, *J*=14.68, 7.47 Hz, 2H), 3.95 (br, s, 6H), 3.16-3.30 (m, 2H), 2.44-2.48 (m, 4H), 1.99 (s, 1H), 1.41 (br, s, 9H), 1.08 (s, 1H), 0.34 (br, d, *J*=6.53 Hz, 2H), 0.15 (br, d, *J*=6.02 Hz, 2H).

Intermediate 139B

15 tert-Butyl-((3R,5R)-1-(2-(1-(cyclopropylmethyl)-6-(1-oxoisindolin-5-yl)-1H-pyrrolo[2,3-*b*]pyridin-2-yl)-4-methoxy-3-methylbenzo[*b*]thiophene-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



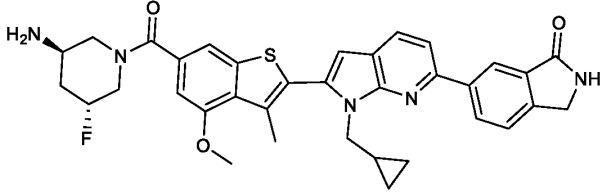
5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)isindolin-1-one (37.2 mg, 0.144
 20 mmol), K₂CO₃ (63.5 mg, 0.299 mmol) and XPHOS Pd G2 (5.25 mg, 7.18 μmol) were added to a degassed solution of Intermediate 139A (75 mg, 0.120 mmol) in 1,4-dioxane (2 ml). The reaction mixture stirred at 80°C for 10 hours, diluted with water (5 ml), and extracted with EtOAc (2×10 ml). The combined organic layers were washed with brine, dried over sodium sulphate, filtered, and concentrated under vacuum. The crude product
 25 was purified using a silica gel column (12 g, Redisep[®] SiO₂ column, eluting with 80% EtOAc in n-hexane) to afford the title compound as brown solid (40 mg, 46%). LC-MS m/z: 724 [M+H]⁺.

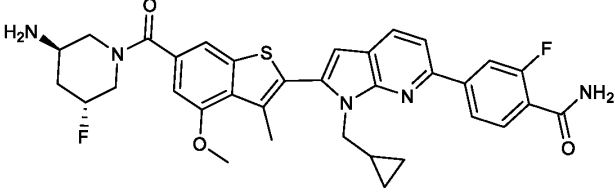
Example 139

TFA (0.043 ml, 0.553 mmol) was added to a solution of Intermediate 139B (40 mg, 0.055 mmol) in DCM (3.0 ml). The reaction mixture was stirred at a room temperature for 16 hours, concentrated, and the crude compound was purified using RP-HPLC to afford the title compound (10 mg, 28%) as off-white solid. LC-MS m/z: 624.3 [M+H]⁺. HPLC retention time: 2.37 min (Method I). ¹H NMR (400 MHz, methanol-*d*₄) δ ppm: 8.40 (s, 1H), 8.35 (d, J=8.2 Hz, 1H), 8.11 (d, J=8.3 Hz, 1H), 7.92 (d, J=8.1 Hz, 1H), 7.82 (d, J=8.3 Hz, 1H), 7.56 (d, J=1.0 Hz, 1H), 6.99-6.93 (m, 1H), 6.69 (s, 1H), 4.83-4.73 (m, 3H), 4.62-4.57 (m, 2H), 4.01(s, 3H), 2.58 (s, 3H), 2.45-2.36 (m, 1H), 1.96-1.93 (m, 1H), 1.75-1.57 (m, 1H), 1.47-1.26 (m, 3H), 1.25 -1.14 (m, 1H), 0.99-0.88 (m, 1H), 0.43-0.37 (m, 2H), 0.31-0.21 (m, 2H).

Compounds of Examples 140 and 141 in Table 17 were prepared following a procedure similar to the preparation of a compound of Example 139, by Suzuki coupling of Intermediate 139A with appropriate boronic acid.

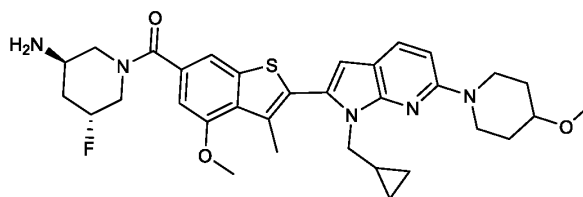
Table 17

Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
140	 6-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylbenzo[b]thiophen-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one Analytical Data: 624.2, 7.1 min (Method C)

141	 4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylbenzo[b]thiophen-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorobenzamide Analytical Data: 630.2, 7.3 min (Method C)
-----	---

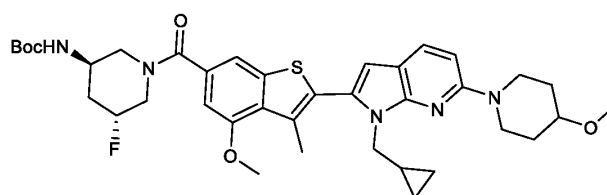
Example 142

- 5 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(4-methoxypiperidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylbenzo[b]thiophen-6-yl)methanone



Intermediate 142A

- 10 tert-Butyl-((3R,5R)-1-(2-(1-(cyclopropylmethyl)-6-(4-methoxypiperidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylbenzo[b]thiophene-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



- 15 4-Methoxypiperidine (19.28 mg, 0.167 mmol) and potassium tert-butoxide (25.05 mg, 0.223 mmol) were added to a solution of Intermediate 139A (70 mg, 0.112 mmol) in 1,4-dioxane (2 ml). The reaction mixture was degassed with argon for 10 min, followed

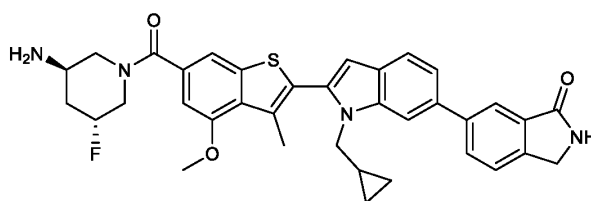
by the addition of XPHOS (31.9 mg, 0.067 mmol) and Pd(OAc)₂ (7.52 mg, 0.033 mmol). The resulting reaction mixture was stirred at 110°C for 12 hours, concentrated, diluted with water (5 ml), and extracted with EtOAc (2×10 ml). The combined organic layers were washed with brine (20 ml), dried over sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified using a silica gel column (12 g, Redisep[®] SiO₂ column, eluting with 90% EtOAc in hexane) to afford the title compound as brown solid (40 mg, 51%). LC-MS m/z: 706 [M+H]⁺.

Example 142

TFA (0.044 ml, 0.567 mmol) was added to a stirred solution of Intermediate 142A (40 mg, 0.057 mmol) in DCM (3 ml). The reaction mixture was stirred at a room temperature for 16 hours, concentrated, and the crude compound was purified using RP-HPLC to afford the title compound (7mg, 19%) as off-white solid. LC-MS m/z: 606 [M+H]⁺. LCMS retention time: 2.66 min (Method F). ¹H NMR (400 MHz, methanol-*d*₄) δ ppm: 7.76 (d, J=8.8 Hz, 1H), 7.56 (d, J=1.0 Hz, 1H), 6.96 (d, J=1.0 Hz, 1H), 6.75 (d, J=8.8 Hz, 1H), 6.42 (s, 1H), 4.19-4.06 (m, 4H), 4.02-3.98 (m, 3H), 3.52 (br, d, J=4.4 Hz, 2H), 3.68-3.47 (m, 2H), 3.45-3.39 (m, 4H), 3.30-3.15 (m, 2H), 2.54 (s, 3H), 2.03 (br, s, 2H), 1.73-1.56 (m, 2H), 1.51-1.28 (m, 4H), 1.13-1.00 (m, 1H), 0.38-0.27 (m, 2H), 0.18 (d, J=5.9 Hz, 2H).

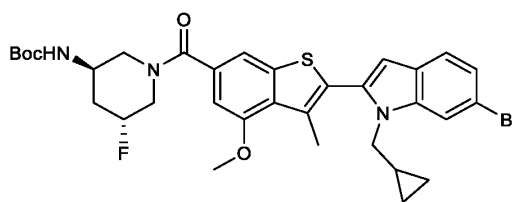
Example 143

6-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylbenzo[b]thiophen-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one



Intermediate 143A

tert-Butyl-((3R,5R)-1-(2-(6-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylbenzo[b]thiophene-6-carbonyl)-5-fluoropiperidin-3-yl) carbamate

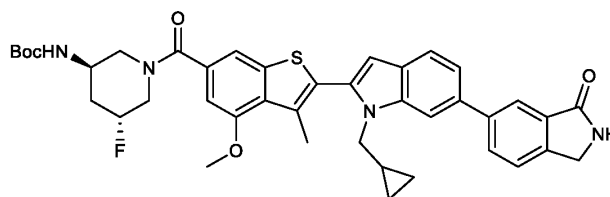


K₂CO₃ (287 mg, 2.078 mmol) and PdCl₂(dppf) (38.0 mg, 0.052 mmol) were added to a degasified solution of Intermediate 138B (380 mg, 0.693 mmol) and 6-bromo-1-(cyclopropylmethyl)-2-iodo-1H-indole (Intermediate 12, 261 mg, 0.693 mmol) in dioxane (3 ml). The reaction mixture was heated at 80°C for 17 hours, diluted with water (5 ml), and extracted with EtOAc (2×10 ml). The combined organic layers were washed with brine (20 ml), dried over sodium sulphate, filtered, and the filtrate was concentrated to afford the title compound (180 mg). LC-MS m/z: 670.3 [M-H]⁺.

10

Intermediate 143B

tert-Butyl-((3R,5R)-1-(2-(1-(cyclopropylmethyl)-6-(3-oxoisindolin-5-yl)-1H-indol-2-yl)-4-methoxy-3-methylbenzo[b]thiophene-6-carbonyl)-5-fluoropiperidin-3-yl) carbamate



PdCl₂(dppf) (9.82 mg, 0.013 mmol) and K₂CO₃ (55.6 mg, 0.403 mmol) in water (1 ml) were added to a degasified solution Intermediate 143A (90 mg, 0.134 mmol) and 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isindolin-1-one (34.8 mg, 0.134 mmol) in dioxane (2 ml). The reaction mixture was heated at 80°C for 17 hours, diluted with water (5 ml), and extracted with EtOAc (2×10 ml). The combined organic layers were washed with brine (20 ml), dried over sodium sulphate, filtered, and the filtrate was concentrated to afford title compound (80 mg). LC-MS m/z: 723.4 [M-H]⁺.

20

Example 143

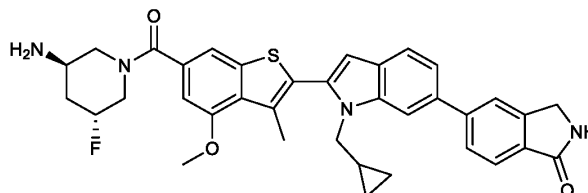
TFA (0.5 ml) was added to a stirred solution of Intermediate 143B (80 mg) in DCM (3 ml). The reaction mixture was stirred at a room temperature for 16 hours, concentrated, and the crude compound obtained was purified using RP-HPLC to afford

25

the title compound (4.8 mg, 7%). LC-MS m/z: 623.3 [M+H]⁺. LCMS retention time: 1.6 min (Method F).

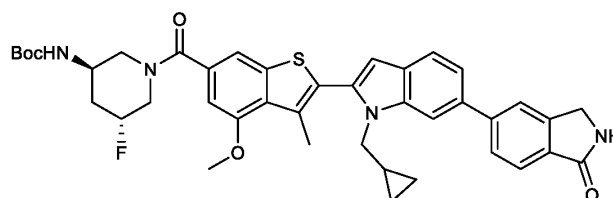
Example 144

5 5-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylbenzo[b]thiophen-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one



Intermediate 144A

tert-Butyl-((3R,5R)-1-(2-(1-(cyclopropylmethyl)-6-(1-oxoisoindolin-5-yl)-1H-indol-2-yl)-4-methoxy-3-methylbenzo[b]thiophene-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



PdCl₂(dppf) (9.82 mg, 0.013 mmol) and K₂CO₃ (55.6 mg, 0.403 mmol) in water (1 ml) were added to a degasified solution of Intermediate 143A (90 mg, 0.134 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-1-one (34.8 mg, 0.134 mmol) in dioxane (2 ml). The reaction mixture was heated at 80°C for 17 hours, diluted with water (5 ml), and extracted with EtOAc (2×10 ml). The combined organic layers were washed with brine (20 ml), dried over sodium sulphate, filtered, and the filtrate was concentrated to afford the title compound (80 mg). LC-MS m/z: 723.4 [M-H]⁺.

20

Example 144

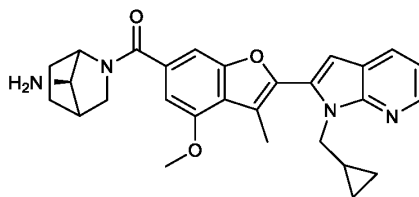
TFA (0.5 ml) was added to a stirred solution of Intermediate 144A (80 mg) in DCM (3 ml) and the reaction mixture was stirred at a room temperature for 16 hours, concentrated and the crude compound thus obtained was purified by using RP-HPLC to afford the title compound (3.2mg, 6%). LC-MS m/z: 623.3 [M+H]⁺. LCMS retention

25

time: 1.7 min (Method F). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.55 (s, 1H), 8.01 (s, 1H), 7.97 (s, 1H), 7.89 (d, *J*=7.8 Hz, 1H), 7.76 (d, *J*=7.8 Hz, 1H), 7.71 (d, *J*=8.3 Hz, 1H), 7.58 (s, 1H), 7.49 (dd, *J*=1.0, 8.3 Hz, 1H), 6.90 (s, 1H), 6.69 (s, 1H), 5.08-4.75 (m, 1H), 4.46 (s, 4H), 4.21-4.09 (m, 2H), 3.94 (s, 5H), 3.05-2.80 (m, 2H), 2.19-2.10 (m, 1H),
 5 1.65-1.41 (m, 1H), 1.11-0.97 (m, 1H), 0.41-0.25 (m, 2H), 0.19-0.05 (m, 2H).

Example 145

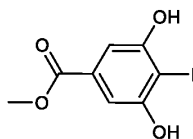
((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-*b*]pyridin-2-yl)-4-methoxy-3-methylbenzofuran-6-yl)methanone



10

Intermediate 145A

Methyl-3,5-dihydroxy-4-iodobenzoate

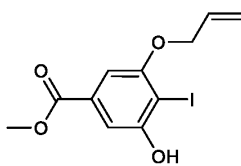


15 N-Iodosuccinimide (NIS, 26.8 g, 119 mmol) in MeOH (200 ml) was added to a stirred solution of methyl 3,5-dihydroxybenzoate (20g, 119 mmol) in MeOH (200 ml) at 0°C. The reaction mixture was stirred at a room temperature for 16 hours, quenched with aqueous sodium thiosulphate solution (200 ml), and stirred for 15 min. Organic solvents were removed under reduced pressure, diluted with water (100 ml) and extracted with
 20 EtOAc (2×200 ml). The combined organic layers were washed with water (200 ml) and brine (200 ml), dried over sodium sulphate, filtered, and the filtrate was evaporated under reduced pressure to afford a crude compound (40 g). LC-MS *m/z*: 294.9 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 10.51 (s, 2H), 6.94 (s, 2H), 3.32 (s, 3H).

25

Intermediate 145B

Methyl-3-(allyloxy)-5-hydroxy-4-iodobenzoate

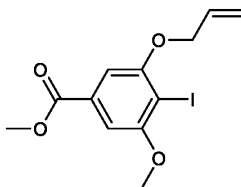


K_2CO_3 (5.44 g, 39.3 mmol) was added to a stirred solution of Intermediate 145A (11.57 g, 39.3 mmol) in DMF (100 ml). The contents were stirred for 10 min, followed by the addition of allyl bromide (3.40 ml, 39.3 mmol) drop wise. The reaction mixture
 5 was stirred at a room temperature for 16 hours, filtered, the filtrate was diluted with water (100 ml) and extracted with EtOAc (3×100 ml). The combined organic layers were dried over sodium sulphate, filtered and the filtrate was evaporated under reduced pressure. The crude material was purified using a silica gel column (80 g, Redisep® SiO₂ column, eluting with 30% EtOAc in n-hexane) to afford the title compound (9.3 g, 54%) as an off
 10 white solid. LC-MS m/z: 335 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 10.73 (s, 1H), 7.13 (d, *J*=1.51 Hz, 1H), 6.92 (d, *J*=2.01 Hz, 1H), 5.88-6.16 (m, 1H), 5.51 (dd, *J*=17.07, 2.01 Hz, 1H), 5.28 (dd, *J*=10.54, 1.51 Hz, 1H), 4.63-4.69 (m, 1H), 3.32 (s, 2H), 2.52-2.68 (m, 1H).

15

Intermediate 145C

Methyl-3-(allyloxy)-4-iodo-5-methoxybenzoate



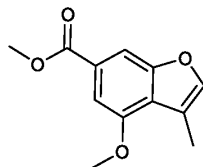
K_2CO_3 (5.77 g, 41.8 mmol) was added to a stirred solution of Intermediate 145B (9.3 g, 27.8 mmol) in DMF (100 ml), and the contents were stirred for 10 min, followed
 20 by the addition of methyl iodide (2.26 ml, 36.2 mmol). The reaction mixture was stirred at a room temperature for 16 hours, filtered, the filtrate was diluted with water (100 ml) and extracted with EtOAc (3×100 ml). The combined organic layers were dried over anhydrous sodium sulphate, filtered, and the volatiles were evaporated under reduced pressure to afford the crude compound. The crude compound was purified using a silica
 25 gel column (40 g, Redisep® SiO₂ column, eluting with 35% EtOAc in n-hexane) to afford the title compound (5.5g, 45%) as a colourless oil. LC-MS m/z: 349 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 7.13 (s, 2H), 6.06 (ddt, 1H), 5.45-5.58 (m, 1H), 5.30

(dd, $J=10.76, 1.71$ Hz, 1H), 4.67-4.77 (m, 2H), 3.89-3.92(m, 3H), 3.32 (s, 2H), 0.01 (s, 1H).

Intermediate 145D

5

Methyl-4-methoxy-3-methylbenzofuran-6-carboxylate

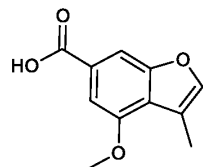


Palladium (II) acetate (0.177 g, 0.790 mmol) was added to a stirred solution of Intermediate 145C (5.5g, 15.80 mmol), sodium carbonate (4.19 g, 39.5 mmol), sodium formate (1.074 g, 15.80 mmol), and tetrabutylammonium chloride (4.83 g, 17.38 mmol) in DMF (2 ml). The reaction mixture was stirred at 80°C for 16 hours, filtered through a celite bed, and washed with EtOAc (50 ml). The filtrate was diluted with water (150 ml), and extracted with EtOAc (3×50 ml). The combined organic layers were dried over anhydrous sodium sulphate, filtered, and the filtrate was evaporated under reduced pressure. The crude compound thus obtained was purified using a silica gel column (24 g, 15 Redisep® SiO₂ column, eluting with 40-45% EtOAc in n-hexane) to afford the title compound (1.1g, 29%) as a colourless oil. LC-MS m/z : 221 $[M+H]^+$. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 7.83-7.86 (m, 1H), 7.71-7.74 (m, 1H), 7.25-7.31 (m, 1H), 3.94 (s, 4H), 3.84-3.91 (m, 5H), 2.53-2.69 (m, 1H), 2.41-2.49 (m, 3H), 2.32 (d, $J=1.47$ Hz, 5H).

20

Intermediate 145E

4-Methoxy-3-methylbenzofuran-6-carboxylic acid



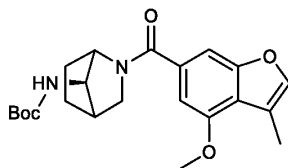
LiOH (1.631 g, 68.1 mmol) in water (5 ml) was added to a stirred solution of Intermediate 145D (5.0 g, 22.70 mmol) in THF (3 ml) and MeOH (3 ml). The reaction mixture was stirred at a room temperature for 3 hours, evaporated under reduced pressure to dryness, and the residue thus obtained was acidified to pH 3 using ice cold 1.5 N HCl. The resulting solids were filtered, washed with water, and vacuum dried to afford the title

compound (4.34g, 93%) as a white solid. LC-MS m/z : 205 $[M-H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm: 7.81 (d, $J=1.51$ Hz, 1H), 7.68 (d, $J=1.00$ Hz, 1H), 7.27 (s, 1H), 3.92 (s, 3H), 2.45-2.47 (m, 1H), 2.31 (d, $J=1.00$ Hz, 3H).

5

Intermediate 145F

tert-Butyl-((7R)-2-(4-methoxy-3-methylbenzofuran-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate

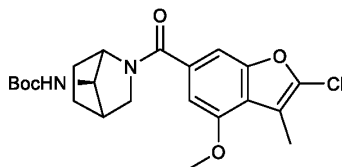


10 HATU (4.15 g, 10.91 mmol) in DMF (20 ml) and DIPEA (3.81 ml, 21.82 mmol) were added to a stirred solution of tert-butyl ((7R)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate (1.544 g, 7.27 mmol), 145E (1.5 g, 7.27 mmol). The reaction mixture was stirred at a room temperature for 16 hours, evaporated under reduced pressure to dryness, water (50 ml) was added, and extracted with EtOAc (2×50 ml). The combined organic
15 layers were washed with water (100 ml) and brine (100 ml), dried over anhydrous sodium sulphate, filtered, and the filtrate was evaporated under reduced pressure. The crude compound thus obtained was purified using a silica gel column (24 g, Redisep® SiO₂ column, eluting with 10-90% EtOAc in n-hexane) to afford the title compound (2.2 g, 76%) as an off-white solid. LC-MS m/z : 401.3 $[M+H]^+$.

20

Intermediate 145G

tert-Butyl-((7R)-2-(2-chloro-4-methoxy-3-methylbenzofuran-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate

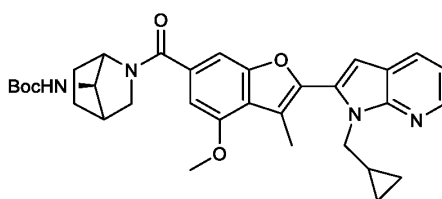


25 LDA at -78°C (0.7 ml, 1.400 mmol) was added to a stirred solution of Intermediate 145F (100mg, 0.250 mmol) in THF (15 ml) under nitrogen atmosphere. The reaction mixture was stirred for 45 min, followed by the addition of hexachloroethane

(65.0 mg, 0.275 mmol) in 2 ml of THF. The reaction mixture was allowed to warm to a room temperature and stirred for 4 hours, quenched with water (50 ml), and extracted with EtOAc (2×50 ml). The combined organic layers were washed with water (30 ml) and brine (30 ml), dried over anhydrous sodium sulphate, filtered, and the filtrate were
 5 evaporated to dryness under reduced pressure to afford the crude material (120 mg). LC-MS m/z: 435.3 [M+H]⁺.

Intermediate 145H

tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-
 10 3-methylbenzofuran-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



K₂CO₃ (95 mg, 0.690 mmol) in water (0.75 ml) was added to a stirred solution of Intermediate 145G (100 mg, 0.230 mmol), 1-(cyclopropylmethyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine (Intermediate 11, 68.6 mg, 0.230
 15 mmol) and tetrakis(triphenylphosphine)palladium(0) (266 mg, 0.230 mmol) in dioxane (2 ml). The reaction mixture was stirred and heated at 120°C for 6 hours, evaporated under reduced pressure to dryness, water (10 ml) was added, extracted with EtOAc (2×10 ml). The combined organic layers were washed with water (10 ml) and brine (10 ml), dried over anhydrous sodium sulphate, filtered, and the filtrate was evaporated under reduced
 20 pressure to afford the crude compound (100 mg). LC-MS m/z: 571.5 [M+H]⁺.

Example 145

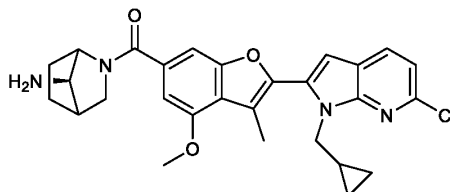
TFA (0.108 ml, 1.402 mmol) was added to a stirred solution of Intermediate 145H (80 mg, 0.140 mmol) in DCM (2 ml). The reaction mixture was stirred at a room
 25 temperature for 6 hours, evaporated under reduce pressure to dryness, and the crude product thus obtained was purified using RP-HPLC to afford the title compound (10 mg, 15%). LC-MS m/z: 471.3 [M+H]⁺. LC-MS retention time: 1.4 min. (Method F). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.35 (dd, *J*=1.5, 4.6 Hz, 1H), 8.07 (dd, *J*=1.5, 7.8 Hz, 1H), 7.44-6.91 (m, 2H), 6.88 (t, *J*=2.0 Hz, 2H), 4.36 (d, *J*=7.1Hz, 2H), 4.18 (s, 1H), 4.01-3.90

(m, 3H), 3.74 (s, 1H), 3.66-3.50 (m, 1H), 3.21 (s, 1H), 3.10-3.01 (m, 1H), 2.28-2.17 (m, 1H), 2.02-1.65 (m, 3H), 1.50 -1.34 (m, 1H), 1.18-1.06 (m, 1H), 0.39-0.29 (m, 2H), 0.27-0.13 (m, 2H).

5

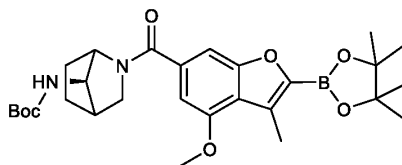
Example 146

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylbenzofuran-6-yl)methanone



Intermediate 146A

10 tert-Butyl-((7R)-2-(4-methoxy-3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



LDA (3.75 ml, 7.49 mmol) was drop wise added to a stirred solution of

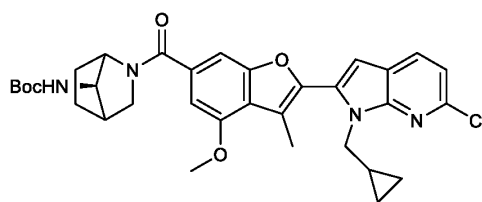
15 Intermediate 145F (0.6 g, 1.498 mmol) in THF (6 ml) at -78°C. The reaction mixture was stirred for 30 min, followed by the addition of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.254 g, 6.74 mmol). The reaction mixture was stirred at -78°C for 1 hour, quenched by water at -78°C, and extracted with EtOAc (3×50 ml). The combined organic layers were dried over anhydrous sodium sulphate, filtered, and filtrate was evaporated

20 under reduced pressure to afford the title compound (0.780 g, 99%) as brown oil. LC-MS m/z: 527 [M-H]⁺.

Intermediate 146B

tert-Butyl-((7R)-2-(2-(6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylbenzofuran-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate

25



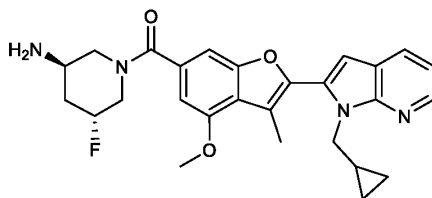
K₂CO₃ (37.3 mg, 0.270 mmol) in water (0.75 ml) was added to a stirred solution of Intermediate 146A (40 mg, 0.090 mmol), 6-chloro-1-(cyclopropylmethyl)-2-iodo-1H-pyrrolo[2,3-b]pyridine (Intermediate-3, 29.9 mg, 0.090 mmol) and PdCl₂(dppf)-CH₂Cl₂ adduct (5.51 mg, 6.75 μmol) in dioxane (3 ml). The reaction mixture was heated to 110°C and stirred for 6 hours, evaporated under reduced pressure to dryness, water (10 ml) was added, and extracted with EtOAc (2×10 ml). The combined organic layers were washed with water (10 ml) and brine solution (10 ml), dried over anhydrous sodium sulphate, filtered, and the filtrate was evaporated under reduced pressure to afford the crude compound (60 mg). LC-MS m/z: 605.3 [M+H]⁺.

Example 146

TFA (0.076 ml, 0.992 mmol) was added to a stirred solution of Intermediate 146B (60 mg, 0.099 mmol) in DCM (2 ml). The reaction mixture was stirred at a room temperature for 10 hours, concentrated under reduced pressure, and the crude product thus obtained was purified using RP-HPLC to afford the title compound (1.9 mg, 3.6%), LC-MS m/z: 505.2 [M+H]⁺; LC-MS retention time: 1.906 / 2.216 min. (Method E / F).

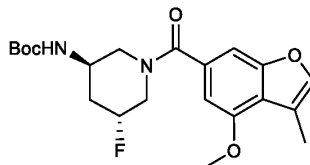
Example 147

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylbenzofuran-6-yl)methanone



Intermediate 147A

tert-Butyl-((3R,5R)-5-fluoro-1-(4-methoxy-3-methylbenzofuran-6-carbonyl)piperidin-3-yl)carbamate

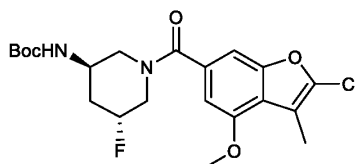


5 HATU (830 mg, 2.182 mmol) in DMF (15 ml) and DIPEA (0.762 ml, 4.36 mmol) were added to a stirred solution of Intermediate 145E (300 mg, 1.455 mmol) and tert-butyl ((3R,5R)-5-fluoropiperidin-3-yl)carbamate (318 mg, 1.455 mmol). The reaction mixture was stirred at a room temperature for 16 hours, evaporated under reduced pressure to dryness, water (50 ml) was added, and extracted with EtOAc (2×50 ml). The combined organic layers were washed with water (100 ml), brine solution (100 ml), dried over anhydrous sodium sulphate, filtered, and the filtrate was concentrated under reduced pressure to afford the crude material. The crude compound was purified using a silica gel column (24 g, Redisep® SiO₂ column, eluting with 40-45% EtOAc in n-hexane) to afford the title compound (450 mg, 76%) as an off-white solid. LC-MS m/z: 405.3 [M-H]⁺.

15

Intermediate 147B

tert-Butyl-((3R,5R)-1-(2-chloro-4-methoxy-3-methylbenzofuran-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



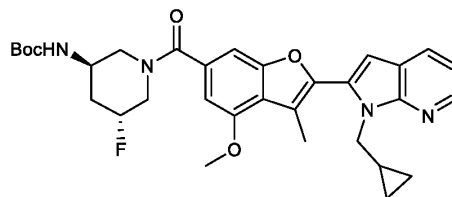
20 LDA (0.7 ml, 1.400 mmol) was added to a stirred solution of Intermediate 147A (110 mg, 0.271 mmol) in THF (10 ml) at -78°C under nitrogen atmosphere. The reaction mixture was stirred for 1 hour, followed by the addition of hexachloroethane (70.5 mg, 0.298 mmol) in 2 ml of THF at -78°C. The reaction mixture was allowed to warm to a room temperature and stirred for 4 hours, quenched with water, and extracted with EtOAc (2×50 ml). The combined organic layers were washed with water (30 ml) and brine (30 ml), dried over anhydrous sodium sulphate, filtered, and the filtrate was concentrated

25

under reduced pressure to afford the crude compound (112 mg). LC-MS m/z: 441.2 [M-H]⁺.

Intermediate 147C

- 5 tert-Butyl-((3R,5R)-1-(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylbenzofuran-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



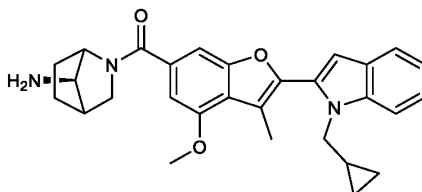
- K₂CO₃ (103 mg, 0.748 mmol) in water (0.75 ml) was added to a stirred solution of Intermediate 147B (110 mg, 0.249 mmol), 1-(cyclopropylmethyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine (Intermediate 11, 74.4 mg, 0.249 mmol), and tetrakis(triphenylphosphine)palladium(0) (288 mg, 0.249 mmol) in dioxane (3 ml). The reaction mixture was stirred and heated at 120°C for 6 hours, evaporated under reduced pressure to dryness, water (10 ml) was added, and extracted with EtOAc (2×10 ml). The combined organic layers were washed with water (10 ml) and brine (10 ml), dried over anhydrous sodium sulphate, filtered, and the filtrate was concentrated under reduced pressure to afford the crude material. The crude compound was purified using a silica gel column (24 g, Redisep® SiO₂ column, eluting with 50-75% EtOAc in n-hexane) to afford the title compound (100 mg). LC-MS m/z: 575.5 [M-H]⁺.

20 Example 147

- TFA (0.120 ml, 1.561 mmol) was added to a stirred solution of Intermediate 147C (90 mg, 0.156 mmol) in DCM (2 ml) and the reaction mixture was stirred at a room temperature for 5 hours. The reaction mixture was evaporated under reduced pressure, and the crude product thus obtained was purified using RP-HPLC to afford the title compound (0.8 mg, 1%). LC-MS m/z: 477.3 [M+H]⁺. LC-MS retention time: 1.5 min (Method F). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.35 (dd, *J*=1.3, 5.0 Hz, 1H), 8.17-7.86 (m, 1H), 7.30 (s, 1H), 7.19 (dd, *J*=4.5, 7.7 Hz, 1H), 6.88 (s, 1H), 6.84 (s, 1H), 5.04-4.66 (m, 1H), 4.35 (d, *J*=7.3 Hz, 2H), 3.95 (s, 4H), 2.39-2.33 (m, 1H), 1.93-1.77 (m, 1H), 1.33-1.06 (m, 5H), 0.90-0.77 (m, 1H), 0.41-0.31 (m, 2H), 0.28-0.19 (m, 2H).

Example 148

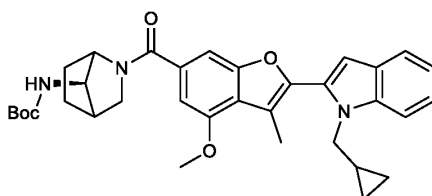
((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylbenzofuran-6-yl)methanone



5

Intermediate 148A

tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylbenzofuran-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



10 A solution of K_2CO_3 (95 mg, 0.690 mmol) in water (0.75 ml) was added to a stirred solution of Intermediate 145G (100 mg, 0.230 mmol), 1-(cyclopropylmethyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (Intermediate-10, 68.3 mg, 0.230 mmol), and tetrakis-(triphenylphosphine)palladium(0) (266 mg, 0.230 mmol) in dioxane (2 ml). The reaction mixture was heated to 120°C and stirred for 6 hours, evaporated

15 under reduced pressure to dryness, water (10 ml) was added, and extracted with EtOAc (2×10 ml). The combined organic layers were washed with water (10 ml) and brine (10 ml), dried over anhydrous sodium sulphate, filtered, and the filtrate was concentrated under reduced pressure to afford the crude compound (100 mg). LC-MS m/z: 570.4 $[M+H]^+$.

20

Example 148

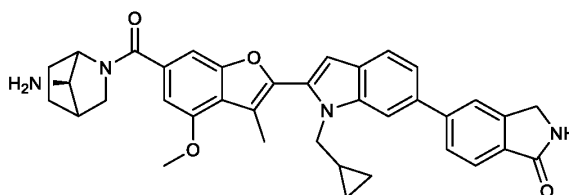
TFA (0.135 ml, 1.755 mmol) was added to a stirred solution of Intermediate 148A (100 mg, 0.176 mmol) in DCM (2 ml). The reaction mixture was stirred at a room temperature for 16 hours, evaporated under reduced pressure, and the crude product

25 obtained was purified using RP-HPLC to afford the title compound (11.1mg, 13%). LC-MS m/z: 470.3 $[M+H]^+$. LC-MS retention time: 1.8 min (Method F). 1H NMR (400 MHz,

DMSO-*d*₆) δ ppm: 7.64 (dd, *J*=3.1, 8.2 Hz, 2H), 7.29-7.22 (m, 2H), 7.13-7.09 (m, 1H), 6.91-6.82 (m, 2H), 4.24 (d, *J*=6.6 Hz, 2H), 4.00-3.91 (m, 3H), 3.70 (s, 1H), 3.67-3.54 (m, 1H), 3.50 (br, d, *J*=10.8 Hz, 2H), 3.18-3.15 (m, 2H), 3.12-3.01 (m, 1H), 2.21 (br, s, 1H), 2.03-1.85 (m, 2H), 1.84-1.64 (m, 1H), 1.47-1.31 (m, 1H), 1.13-1.04 (m, 1H), 0.37-0.32 (m, 2H), 0.16 (d, *J*=4.4 Hz, 2H)

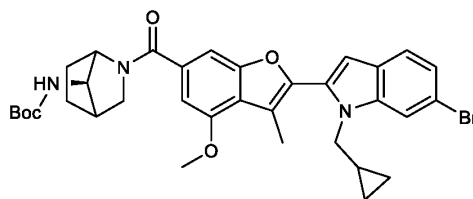
Example 149

5-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one



Intermediate 149A

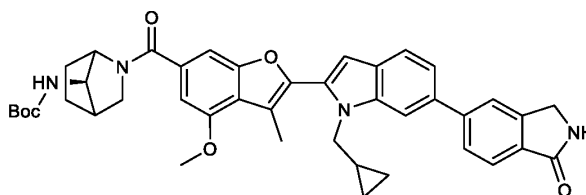
tert-Butyl-((7R)-2-(2-(6-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylbenzofuran-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



A solution of K_2CO_3 (622 mg, 4.50 mmol) in water (0.027 ml, 1.501 mmol) was added to a stirred and degasified solution of Intermediate 146A (790 mg, 1.501 mmol), 6-bromo-1-(cyclopropylmethyl)-2-iodo-1H-indole (Intermediate-12, 1016 mg, 2.70 mmol) in dioxane (8 ml), followed by the addition of $Pd(PPh_3)_4$ (130 mg, 0.113 mmol). The reaction mixture was heated to 80°C and stirred for 16 hours, diluted with water (50 ml), and extracted with EtOAc (3×50 ml). The combined organic layers were dried over anhydrous sodium sulphate, filtered, and the filtrate was evaporated under reduced pressure. The crude product was purified using a silica gel column (24 g, Redisep® SiO_2 column, eluting with 65% EtOAc in n-hexane) to afford the title compound (700 mg, 72%) as a brown oil. LC-MS *m/z*: 650 $[M-H]^+$.

Intermediate 149B

tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-6-(1-oxoisindolin-5-yl)-1H-indol-2-yl)-4-methoxy-3-methylbenzofuran-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



A solution of K_2CO_3 (60.7 mg, 0.439 mmol) in water (2.64 μ l, 0.146 mmol) was added to a stirred and degasified solution of Intermediate 149A (95 mg, 0.146 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isindolin-1-one (38.0 mg, 0.146 mmol) in dioxane (2 ml). The reaction mixture was degasified with argon, followed by the addition of $PdCl_2(dppf)-CH_2Cl_2$ adduct (8.97 mg, 10.99 μ mol). The reaction mixture was heated to 80°C and stirred for 16 hours, diluted with water (50 ml), and extracted with EtOAc (3 $\times$ 50 ml). The combined organic layers were dried over anhydrous sodium sulphate, filtered, and the filtrate was concentrated under reduced pressure. The crude product thus obtained was purified using prep HPLC to afford the title compound as off-white solid (0.040 g, 39%). LC-MS m/z : 701 $[M-H]^+$.

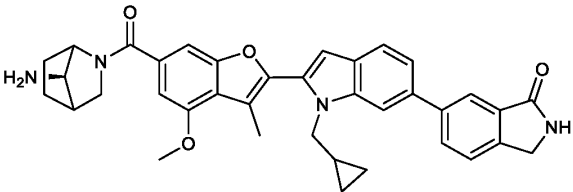
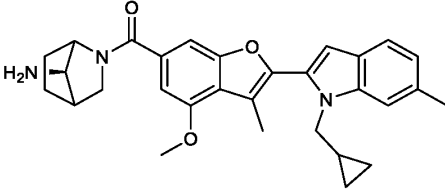
Example 149

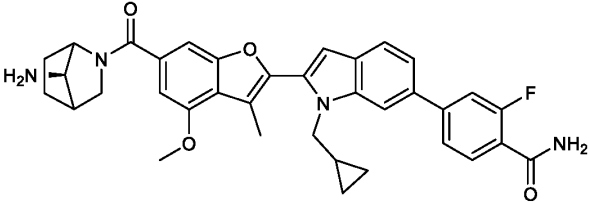
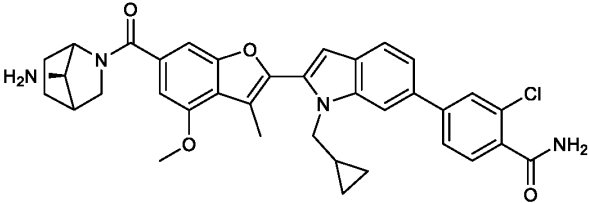
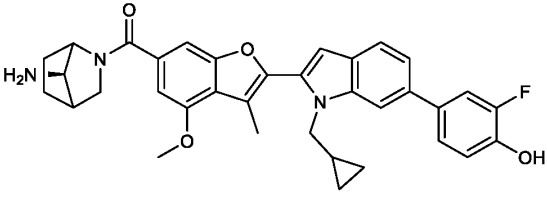
TFA (4.52 μ L, 0.059 mmol) was added to a stirred solution of Intermediate 149B (40 mg, 0.059 mmol) in DCM (2 ml), and the contents were stirred at a room temperature for 3 hours. The reaction mixture was evaporated under reduced pressure and the residue was stirred with aqueous ammonia solution (2 ml). The aqueous solution was decanted and the residue obtained was dried under vacuum and purified using RP-HPLC to afford the title compound (7.33 mg, 30%). LC-MS m/z : 601 $[M+H]^+$. LC-MS retention time: 2.664 min (Method H). 1H NMR (400 MHz, $DMSO-d_6$) δ ppm: 8.50-8.60 (m, 1H), 7.89-8.10 (m, 3H), 7.85-8.00 (m, 2H), 7.81-7.97 (m, 1H), 7.70-7.83 (m, 2H), 7.44-7.58 (m, 1H), 7.22-7.34 (m, 1H), 6.89 (s, 2H), 4.47 (s, 5 H), 4.30 (s, 2H), 4.23-4.39 (m, 1H), 3.97 (s, 4H), 3.66-3.79 (m, 2H), 3.44-3.59 (m, 2H), 2.97-3.17 (m, 3H), 2.53-2.61 (m, 15 H), 2.35-2.47 (m, 6 H), 2.18-2.29 (m, 2H), 1.83-2.05 (m, 3H), 1.24 (s, 10 H), 0.75-0.96 (m, 3H), 0.26-0.43 (m, 1H), 0.15-0.23 (m, 2H), 0.01-0.02 (m, 2H), -0.06-0.00 (m, 9 H).

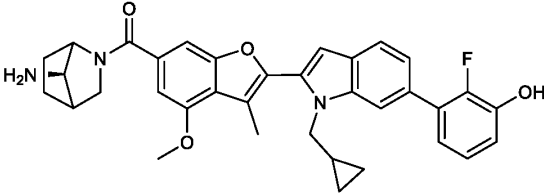
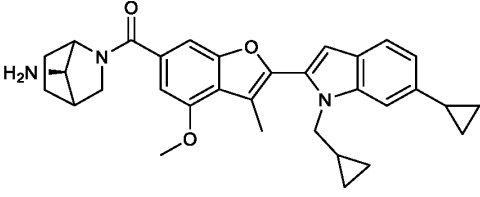
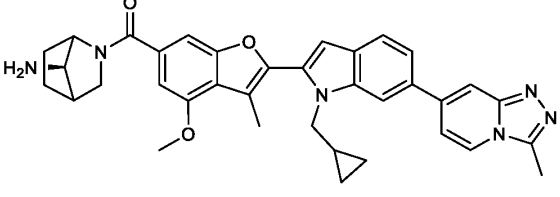
Compounds of Examples 150 to 157 in Table 18 were obtained following a procedure similar to the preparation of a compound of Example 149, by Suzuki coupling of Intermediate 149A with appropriate boronic ester or acid.

5

Table 18

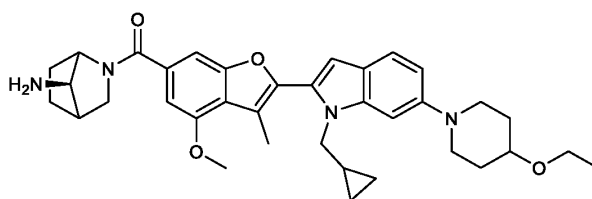
Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
150	 6-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one Analytical Data: 601.4, 2.720 min (Method H)
151	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-methyl-1H-indol-2-yl)-4-methoxy-3-methylbenzofuran-6-yl)methanone Analytical Data: 484.3, 3.512 min (Method H)

152	 4-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)-2-fluorobenzamide Analytical Data: 607.4, 2.853 min (Method H)
153	 4-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)-2-chlorobenzamide Analytical Data: 623.4, 2.801min (Method H)
154	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-fluoro-4-hydroxyphenyl)-1H-indol-2-yl)-4-methoxy-3-methylbenzofuran-6-yl)methanone Analytical Data: 580.3, 2.308 min (Method E)

155	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 580.3, 6.998 min (Method D)
156	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-cyclopropyl-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylbenzofuran-6-yl)methanone Analytical Data: 510.3, 2.358 min (Method E)
157	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)-1H-indol-2-yl)-4-methoxy-3-methylbenzofuran-6-yl)methanone Analytical Data: 601.4, 2.616 min (Method H)

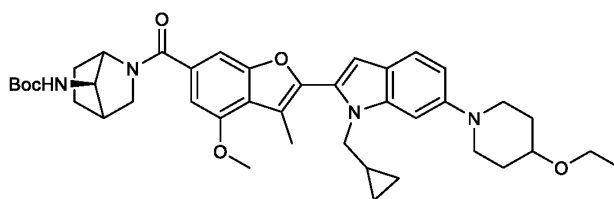
Example 158

3- ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(4-ethoxypiperidin-1-yl)-1H-indol-2-yl)-4-methoxy-3-methylbenzofuran-6-yl)methanone



Intermediate 158A

tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-6-(4-ethoxypiperidin-1-yl)-1H-indol-2-yl)-
 5 4-methoxy-3-methylbenzofuran-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



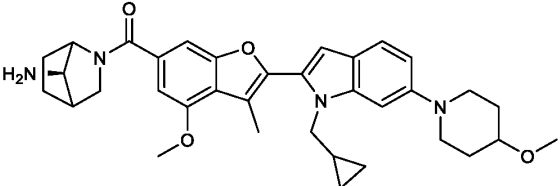
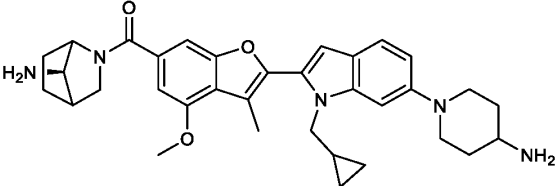
Pd(OAc)₂ (15.58 mg, 0.069 mmol) was added to a stirred and degassed solution of Intermediate 149A (150 mg, 0.231 mmol), 4-ethoxypiperidine (44.8 mg, 0.347 mmol), XPHOS (55.1 mg, 0.116 mmol) and KOtBu (51.9 mg, 0.463 mmol) in dioxane (2 ml).
 10 The reaction mixture was heated to 110°C and stirred for 16 hours, filtered through a celite bed, and the filtrate was evaporated under reduced pressure. The crude product thus obtained was purified using prep HPLC to afford the title compound as an off-white solid (20 mg). LC-MS m/z: 697 [M+H]⁺.

Example 158

TFA (0.022 ml, 0.287 mmol) was added to a stirred solution of Intermediate 158A
 15 (20 mg, 0.029 mmol) in DCM (1 ml). The reaction mixture was stirred at a room temperature for 3 hours, and evaporated under reduced pressure to afford the crude material, which was purified using RP-HPLC to afford the title compound (4.8 mg, 27%). LC-MS m/z: 597.4 [M+H]⁺. LC-MS retention time: 2.284 / 1.342 min (Methods E / F). ¹H
 20 NMR (400 MHz, DMSO-*d*₆) δ ppm: 7.45 (d, *J*=8.9 Hz, 1H), 7.25 (s, 1H), 7.02 (s, 1H), 6.93-6.85 (m, 2H), 6.67 (s, 1H), 4.22-4.03 (m, 4H), 4.02-3.88 (m, 5H), 3.84 (br, d, *J*=3.2 Hz, 2H), 3.59-3.38 (m, 13H), 3.30-3.22 (m, 4H), 3.17 (d, *J*=5.3 Hz, 2H), 3.09 (br, d, *J*=10.4 Hz, 3H), 3.00-2.74 (m, 5H), 2.66-2.53 (m, 4H), 2.47-2.40 (m, 5H), 2.08 (s, 1H), 2.03-1.74 (m, 7H), 1.67-1.53 (m, 4H), 1.50 (br, s, 2H), 1.32-1.20 (m, 9H), 1.20-1.03 (m,
 25 7H), 0.90-0.81 (m, 2H), 0.34 (br, d, *J*=7.5 Hz, 2H), 0.17-0.09 (m, 2H), 0.01 (s, 1H).

Compounds of Examples 159 and 160 in Table 19 were prepared following a procedure similar to the preparation of a compound of Example 158 by Buchwald coupling of Intermediate 149A with appropriate amines

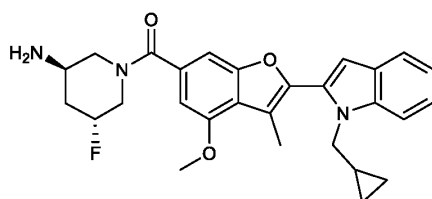
Table 19

Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
159	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(4-methoxypiperidin-1-yl)-1H-indol-2-yl)-4-methoxy-3-methylbenzofuran-6-yl)methanone Analytical Data: 583.4, 6.015 min (Method D)
160	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-(4-aminopiperidin-1-yl)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylbenzofuran-6-yl)methanone Analytical Data: 583.4, 8.803 min (Method D)

5

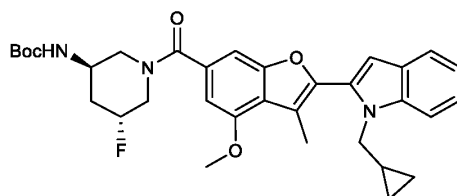
Example 161

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylbenzofuran-6-yl)methanone



Intermediate 161A

tert-Butyl-((3R,5R)-1-(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylbenzofuran-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



A solution of K_2CO_3 (103 mg, 0.748 mmol) in water (0.75 ml) was added to a stirred and degassed solution of Intermediate 147B (110 mg, 0.249 mmol), 1-(cyclopropylmethyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (Intermediate 10, 74.2 mg, 0.249 mmol) in dioxane (3 ml), followed by the addition of $Pd(PPh_3)_4$ (288 mg, 0.249 mmol). The reaction mixture was heated to 115°C and stirred for 6 hours, evaporated under reduced pressure to dryness, water (50 ml) was added, and extracted with EtOAc (2×50 ml). The combined organic layers were washed with water (10 ml) and brine (10 ml), dried over anhydrous sodium sulphate, filtered, and the filtrate was evaporated under reduced pressure. The crude compound thus obtained was purified using a silica gel column (24g, Redisep® SiO_2 column, eluting with 75% EtOAc in n-hexane) to afford the title compound (100 mg). LC-MS m/z: 576.4 $[M+H]^+$.

Example 161

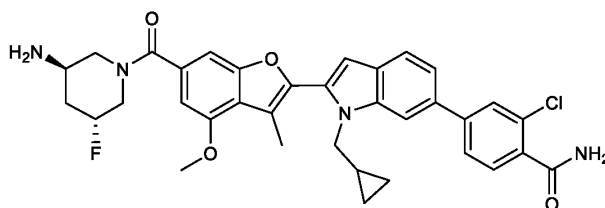
TFA (0.120 ml, 1.563 mmol) was added to a stirred solution of Intermediate 161A (90 mg, 0.156 mmol) in DCM (4 ml). The reaction mixture was stirred at a room temperature for 10 hours, and evaporated under reduced pressure to afford the crude material, which was purified using RP-HPLC to afford the title compound (6.4 mg, 8.4%). LC-MS m/z: 476.4 $[M+H]^+$. LC-MS retention time: 1.9 min (Method F). 1H NMR (400 MHz, $DMSO-d_6$) δ ppm: 7.64 (dd, $J=4.5, 7.7$ Hz, 2H), 7.25 (t, $J=7.2$ Hz, 1H), 7.22

(s, 1H), 7.11 (t, $J=7.4$ Hz, 1H), 6.82 (s, 1H), 6.82-6.79 (m, 1H), 5.02-4.77 (m, 1H), 4.58-4.40 (m, 1H), 4.23 (d, $J=6.8$ Hz, 2H), 3.94 (s, 3H), 3.17 (s, 3H), 2.97 (br, t, $J=10.4$ Hz, 2H), 2.67 (s, 1H), 2.49-2.46 (m, 3H), 2.33 (s, 1H), 2.15 (br, s, 1H), 1.90 (s, 1H), 1.23 (s, 1H), 1.16-0.99 (m, 1H), 0.39-0.29 (m, 2H), 0.18 (q, $J=4.7$ Hz, 2H).

5

Example 162

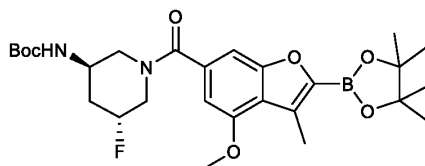
4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)-2-chlorobenzamide



10

Intermediate 162A

tert-Butyl-((3R,5R)-5-fluoro-1-(4-methoxy-3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-6-carbonyl)piperidin-3-yl)carbamate



15

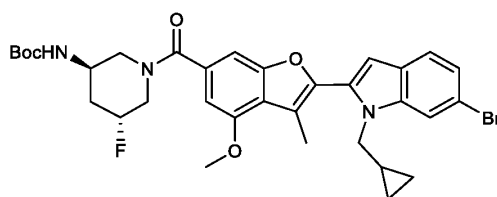
LDA (4.92 ml, 9.84 mmol) was added drop wise to a stirred solution of Intermediate 147A (0.4g, 0.984 mmol) in THF (4 ml) at -78°C . The reaction mixture was stirred for 30 min, followed by the addition of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.916 g, 4.92 mmol). The reaction mixture was stirred -78°C for 1 hour, quenched with water at -78°C , and extracted with EtOAc (3×50 ml). The combined organic layers were dried over anhydrous sodium sulphate, filtered, and the filtrate was evaporated under reduced pressure to afford the title compound (0.520 g, 99%) as brown oil. LC-MS $m/z = 533$ $[\text{M}-\text{H}]^{+}$.

20

Intermediate 162B

tert-Butyl-((3R,5R)-1-(2-(6-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylbenzofuran-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate

25

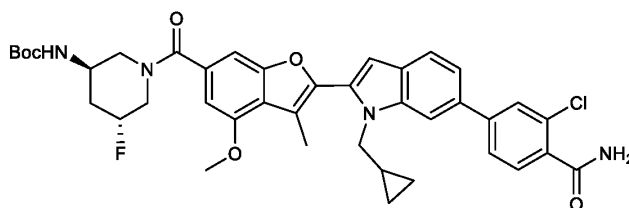


A solution of K_2CO_3 (37.3 mg, 0.270 mmol) in water (0.75 ml) was added to a stirred and degasified solution of Intermediate 162A (524 mg, 0.984 mmol), 6-bromo-1-(cyclopropylmethyl)-2-iodo-1H-indole (Intermediate-12, 444 mg, 1.181 mmol) in dioxane (8 ml). The reaction mixture was degasified using argon, followed by the addition of $Pd(PPh_3)_4$ (85 mg, 0.074 mmol). The reaction mixture was heated to $80^\circ C$ and stirred for 16 hours, evaporated under reduced pressure to dryness, water (50 ml) was added, and extracted with EtOAc (2×50 ml). The combined organic layers were washed with water (20 ml) and brine (20 ml), dried over anhydrous sodium sulphate, filtered, and the filtrate was evaporated under reduced pressure. The crude product thus obtained was purified using a silica gel column (12g, Rediseq® SiO_2 column, eluting with 5% MeOH in $CHCl_3$) to afford the title compound as a brown oil (400 mg, 62%). LC-MS m/z = 655.3 $[M+H]^+$.

15

Intermediate 162C

tert-Butyl-((3R,5R)-1-(2-(6-(4-carbamoyl-3-chlorophenyl)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylbenzofuran-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



A solution of K_2CO_3 (95 mg, 0.687 mmol) in water (4.13 μ l, 0.229 mmol) was added to a stirred and degasified solution of Intermediate 162B (150 mg, 0.229 mmol) and 2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (97 mg, 0.344 mmol) in dioxane (2 ml), followed by addition of $PdCl_2(dppf)-CH_2Cl_2$ adduct (14.04 mg, 0.017 mmol). The reaction mixture was heated to $80^\circ C$ and stirred for 16 hours, diluted with water (50 ml), and extracted with EtOAc (3×50 ml). The combined organic layers were dried over anhydrous sodium sulphate, filtered, and the filtrate was evaporated

under reduced pressure concentrated to afford the crude material, which was purified using preparative HPLC to afford the product as brown oil (0.015 g, 8%). LC/MS m/z: 729 [M-H]⁺.

5

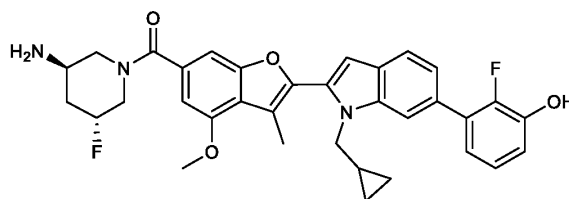
Example 162

TFA (0.120 ml, 1.561 mmol) was added to a stirred solution of Intermediate 162C (15 mg, 0.020 mmol) in DCM (2 ml). The reaction mixture was stirred at a room temperature for 1 hour, and evaporated under reduced pressure to afford the crude product, which was purified using RP-HPLC to afford the title compound (2.2mg, 14%).

10 LC-MS m/z: 629 [M+H]⁺. LC-MS retention time: 1.885 / 1.687 min (Method E / F).

Example 163

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(2-fluoro-3-hydroxyphenyl)-1H-indol-2-yl)-4-methoxy-3-methylbenzofuran-6-yl)methanone



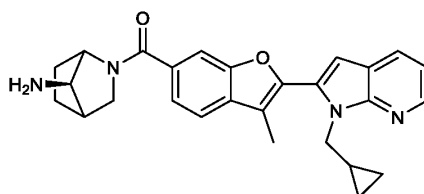
15

Compound of Example 163 was prepared following a procedure similar to the preparation of a compound of Example 162, using the Intermediate 162B and the appropriate boronic acid. LC-MS m/z: 586.3 [M+H]⁺. LC-MS retention time: 2.071 min (Method T).

20

Example 164

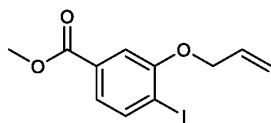
((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylbenzofuran-6-yl)methanone



25

Intermediate 164A

Methyl-3-(allyloxy)-4-iodobenzoate

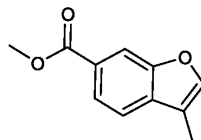


K₂CO₃ (5.47 g, 39.6 mmol) and 3-bromoprop-1-ene (3.42 ml, 39.6 mmol) were added to a stirred solution of methyl 3-hydroxy-4-iodobenzoate (5.5 g, 19.78 mmol) in DMF (100 ml). The reaction mixture was stirred at a room temperature for 2 hours, quenched with water (100 ml), and extracted with EtOAc (3×150 ml). The combined organic layers were washed with water (100 ml) and brine (100 ml), dried over anhydrous sodium sulphate, filtered, and the filtrate was evaporated under reduced pressure to afford the crude material, which was purified using flash chromatography (80g silica gel column, 50% EtOAc in pet ether) to afford the title compound as a white solid (6.1 g, 97%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 0.01 (d, *J*=0.73 Hz, 1H), 3.86 (s, 3H), 4.70-4.75 (m, 2H), 5.31 (dd, *J*=10.64, 1.10 Hz, 1H), 5.51 (dd, *J*=17.61, 1.47 Hz, 1H), 6.01-6.11 (m, 1H), 7.33 (dd, *J*=8.07, 0.98 Hz, 1H), 7.43 (s, 1H), 7.96 (d, *J*=8.07 Hz, 1H).

15

Intermediate 164B

Methyl-3-methylbenzofuran-6-carboxylate



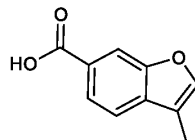
Palladium(II) acetate (0.071 g, 0.314 mmol), sodium carbonate (1.666 g, 15.72 mmol), and tetrabutylammonium chloride hydrate (2.047 g, 6.92 mmol) were added to a stirred and degassed solution of Intermediate 164A (2.0 g, 6.29 mmol) in DMF (30 ml). The reaction mixture was stirred and heated to 80°C for 48 hours, evaporated under reduced pressure to dryness, water (100 ml) was added, and extracted with EtOAc (2×100 ml). The combined organic layers were washed with water (50 ml) and brine (50 ml), dried over anhydrous sodium sulphate, and evaporated under reduced pressure to afford the crude material, which was purified using flash chromatography (40 g, silica gel column, 25% EtOAc in pet ether) to afford the title compound (1.0 g, 84%) as white solid. LC-MS *m/z*: 191 [M-H]. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 2.25 (d, *J*=1.51

Hz, 3H), 3.82-3.90 (m, 3H), 7.74 (d, $J=8.03$ Hz, 1H), 7.89 (d, $J=7.88$ Hz, 1H), 7.96-8.04 (m, 1H), 8.09 (d, $J=1.51$ Hz, 1H).

Intermediate 164C

5

3-Methylbenzofuran-6-carboxylic acid

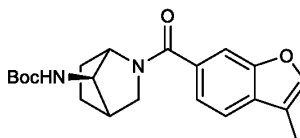


LiOH (0.378 g, 15.77 mmol) in water (5 ml) was added to a stirred solution of Intermediate 164B (1.0 g, 5.26 mmol) in THF (5 ml) and MeOH (5 ml). The reaction mixture was stirred at a room temperature for 12 hours, evaporated under reduced pressure to remove the volatile solvents, and 1.5N HCl solution was added till the solution turned acidic. The solids precipitated were filtered, and dried under high vacuum to afford the title compound (0.85 g, 92%) as a white solid. LC-MS m/z : 175.2 [M-H]. ^1H NMR (400 MHz, DMSO- d_6) δ ppm: 2.24 (d, $J=1.00$ Hz, 3H), 7.71 (d, $J=8.03$ Hz, 1H), 7.80-7.92 (m, 1H), 7.97 (d, $J=1.51$ Hz, 1H), 8.06 (s, 1H).

15

Intermediate 164D

tert-Butyl-((7R)-2-(3-methylbenzofuran-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate

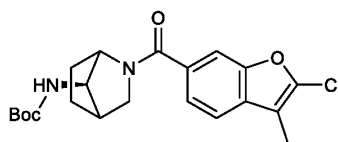


HATU (2.75 g, 7.24 mmol) in DMF (20 ml) and DIPEA (1.685 ml, 9.65 mmol) were added to a stirred solution of Intermediate 164C (0.85 g, 4.82 mmol) and tert-butyl ((7R)-2-azabicyclo- [2.2.1]heptan-7-yl)carbamate (1.024 g, 4.82 mmol). The reaction mixture was stirred at a room temperature for 12 hours, diluted with water (200 ml), and extracted with EtOAc (2 $\times$ 100 ml). The combined organic layers were washed with water (50 ml) and brine (50 ml), dried over anhydrous sodium sulphate, filtered, and the filtrate was evaporated under reduced pressure to afford the crude material, which was purified using a silica gel column (24 g, silica gel column, 70% EtOAc in pet ether) to afford the title compound (1.5 g, 84%). LC-MS m/z : 371 [M+H] $^+$.

25

Intermediate 164E

tert-Butyl-((7R)-2-(2-chloro-3-methylbenzofuran-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



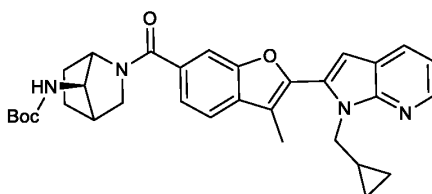
5

1M THF solution of lithium diisopropylamide (0.225 ml, 0.540 mmol) was added to a stirred solution of Intermediate 164D (100mg, 0.270 mmol) in THF (15 ml) at -78°C under nitrogen atmosphere. The reaction mixture was stirred for 1 hour, followed by the addition of hexachloroethane (70.3 mg, 0.297 mmol) in 2 ml of THF. The reaction mixture was allowed to warm up to a room temperature and stirred for further 4 hours, quenched with saturated aqueous ammonium chloride solution (50 ml), and extracted with EtOAc (2×50 ml). The combined organic layers were washed with water (100 ml) and brine (100 ml), dried over anhydrous sodium sulphate, filtered, and the filtrate was evaporated under reduced pressure to afford the crude compound (85 mg, 78%) as gummy liquid. LC-MS m/z: 405.1 [M+H]⁺.

15

Intermediate 164F

tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylbenzofuran-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



20

A solution of K₂CO₃ (103 mg, 0.748 mmol) in water (0.75 ml) and tetrakis-(triphenylphosphine)palladium(0) (14.27 mg, 0.012 mmol) were added to a stirred and degasified solution of Intermediate 164E (100 mg, 0.247 mmol) and 1-(cyclopropylmethyl)-2-(trimethylstannyl)-1H-pyrrolo[2,3-b]pyridine (Intermediate 7, 83 mg, 0.247 mmol) in dioxane (3 ml). The reaction mixture was heated to 100°C and stirred for 16 hours, evaporated under reduced pressure to dryness, water (10 ml) was added, and extracted with EtOAc (2×10 ml). The combined organic layers were washed with water

25

(10 ml) and brine (10 ml), dried over anhydrous sodium sulphate, filtered, and the filtrate was evaporated under reduced pressure to afford the crude title compound (40 mg) as a brown oil. LC-MS m/z : 541.3 $[M+H]^+$.

5

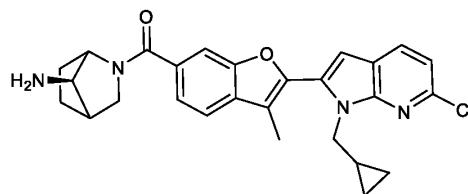
Example 164

TFA (0.057 ml, 0.740 mmol) was added to a stirred solution of Intermediate 164F (40 mg, 0.074 mmol) in DCM (2 ml). The reaction mixture was stirred at a room temperature for 6 hours, evaporated under reduced pressure to afford the crude material, which was purified using RP-HPLC to afford the title compound (1.5mg, 4%). LC-MS m/z : 441.3 $[M+H]^+$. LC-MS retention time: 1.3 min (Method F). 1H NMR (400 MHz, DMSO- d_6) δ ppm: 0.26 (br, s, 2H), 0.35 (br, d, $J=8.31$ Hz, 2H), 0.86 (s, 2H), 1.11-1.27 (m, 16 H), 1.30 (br, s, 2H), 1.38 (s, 4H), 1.90 (br, s, 4H), 2.41-2.47 (m, 4H), 3.11-3.28 (m, 4H), 4.43 (br, d, $J=7.09$ Hz, 2H), 6.96 (s, 2H), 7.17-7.23 (m, 2H), 7.77 (s, 2H), 7.82 (br, s, 1H), 7.86 (s, 2H), 8.09 (br, d, $J=7.58$ Hz, 2H), 8.37 (br, d, $J=4.40$ Hz, 1H).

15

Example 165

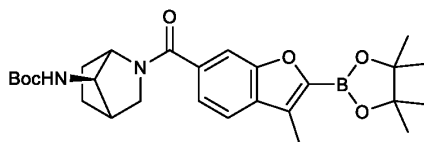
((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylbenzofuran-6-yl)methanone



20

Intermediate 165A

tert-Butyl-((7R)-2-(3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



25

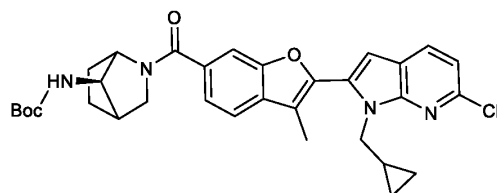
1M THF solution of lithium diisopropylamide (5.40 ml, 10.80 mmol) was added to a stirred solution of Intermediate 164D (1.0g, 2.70 mmol) in tetrahydrofuran (15 ml) at

-78°C. The reaction mixture was stirred for 5 min, followed by the addition of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.826 ml, 4.05 mmol) at -78°C, and the reaction mixture was stirred at the same temperature for another 2 hours. The reaction mixture was quenched with water (30 ml), and extracted with EtOAc (2 x 50 ml). The combined organic layers were washed with water (50 ml) and brine (50 ml), dried over anhydrous sodium sulphate, filtered, and the filtrate was evaporated under reduced pressure to afford the title compound (1.1 g, 82%) as a gummy liquid. LC-MS m/z: 497.3 [M+H]⁺.

10

Intermediate 165B

tert-Butyl-((7R)-2-(2-(6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylbenzofuran-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



A solution of K₂CO₃ (112 mg, 0.812 mmol) and water (1 ml) and tetrakis (triphenylphosphine)palladium(0) (23.45 mg, 0.020 mmol) was added to a stirred and degasified solution of Intermediate 165A (134 mg, 0.271 mmol), 6-chloro-1-(cyclopropylmethyl)-2-iodo-1H-pyrrolo[2,3-b]pyridine (Intermediate 3, 90 mg, 0.271 mmol) in dioxane (3 ml). The reaction mixture was heated to 85°C and stirred for 16 hours, diluted with water (25 ml), and extracted with EtOAc (2×25 ml). The combined organic layers were washed with water (20 ml) and brine (20 ml), dried over sodium sulphate, filtered, and the filtrate was evaporated under reduced pressure to afford the crude title compound (100 mg) as brown solid. LC-MS m/z: 575 [M+H]⁺.

20

Example 165

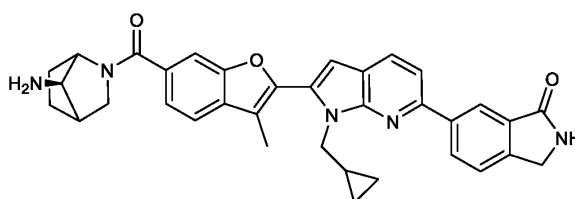
TFA (0.057 ml, 0.740 mmol) was added to a stirred solution of Intermediate 165B (100 mg, 0.074 mmol) in DCM (2 ml) and the reaction mixture was stirred at a room temperature for 6 hours. The reaction mixture was evaporated under reduced pressure to afford the crude material, which was purified using RP-HPLC to afford the title compound (5.1mg, 6%). LC-MS m/z: 475 [M+H]⁺. LC-MS retention time: 2.09 / 1.787

25

min (Method E / F). ^1H NMR (400 MHz, DMSO- d_6) δ ppm: 8.19-8.07 (m, 1H), 7.84-7.67 (m, 2H), 7.52-7.33 (m, 1H), 7.25 (dd, $J=0.9, 8.2$ Hz, 1H), 7.04-6.92 (m, 1H), 4.36 (d, $J=7.1$ Hz, 2H), 3.66 (br, d, $J=1.7$ Hz, 1H), 3.53-3.48 (m, 1H), 3.17 (br, d, $J=1.7$ Hz, 1H), 3.07 (d, $J=11.2$ Hz, 1H), 2.45-2.41 (m, 3H), 2.22-2.09 (m, 2H), 2.01-1.86 (m, 3H), 1.75-1.65 (m, 1H), 1.46-1.31 (m, 1H), 1.27-1.20 (m, 2H), 1.19-1.07 (m, 1H), 0.39-0.32 (m, 2H), 0.28-0.21 (m, 2H).

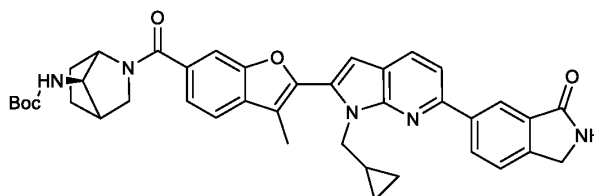
Example 166

6-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one



Intermediate 166A

tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-6-(3-oxoisoindolin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylbenzofuran-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



Potassium phosphate tribasic anhydrous (111 mg, 0.522 mmol) in water (1 ml) was added to a stirred and degasified solution of Intermediate 165B (100 mg, 0.174 mmol) and 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-1-one (45.1 mg, 0.174 mmol) in dioxane (2 ml). The reaction mixture was degasified with argon, followed by the addition of XPHOS Pd G₂ (8.29 mg, 0.017 mmol). The reaction mixture was heated to 100°C and stirred for 2 hours, cooled to a room temperature, water (25 ml) was added, and extracted with EtOAc (2×25 ml). The combined organic layers were washed with water (20 ml) and brine (20 ml), dried over anhydrous sodium sulphate, filtered, and

the filtrate was evaporated under reduced pressure to afford the crude compound (100 mg). LC-MS m/z: 672 [M+H]⁺.

Example 166

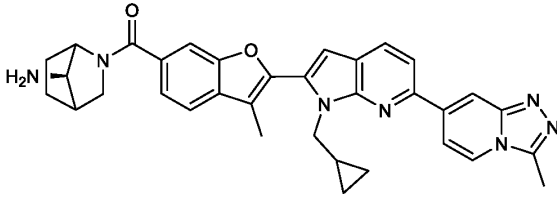
5 TFA (0.115 ml, 1.489 mmol) was added to a stirred solution of Intermediate 165A (100 mg, 0.149 mmol) in DCM (2 ml). The reaction mixture was stirred at a room temperature for 16 hours, evaporated under reduced pressure, and the crude compound was purified using RP-HPLC to afford the title compound (3.1mg, 3%). LC-MS m/z: 572 [M+H]⁺. LC-MS retention time: 1.72 / 1.49 min (Method E / F). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.66 (s, 1H), 8.49-8.38 (m, 3H), 8.18 (d, *J*=8.1 Hz, 1H), 8.02-7.62 (m, 7H), 7.50-7.31 (m, 2H), 6.98 (s, 1H), 6.94-6.85 (m, 1H), 4.51 (br, d, *J*=6.8 Hz, 2H), 4.46 (s, 3H), 4.30-4.18 (m, 1H), 3.71 (d, *J*=12.0 Hz, 2H), 3.51 (br, s, 1H), 3.16-3.04 (m, 1H), 2.63 (s, 1H), 2.47 (s, 3H), 2.28-2.20 (m, 1H), 2.01-1.82 (m, 3H), 1.77-1.41 (m, 4H), 1.32-1.16 (m, 6H), 0.92-0.82 (m, 2H), 0.60-0.49 (m, 1H), 0.43-0.31 (m, 4H).

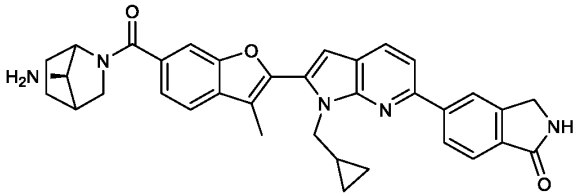
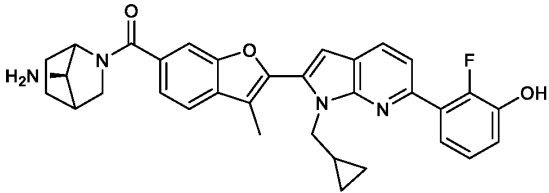
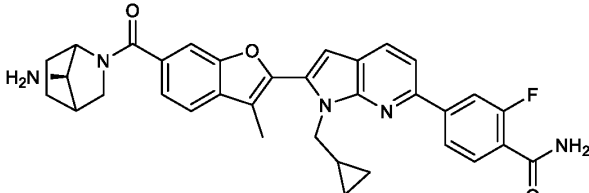
15

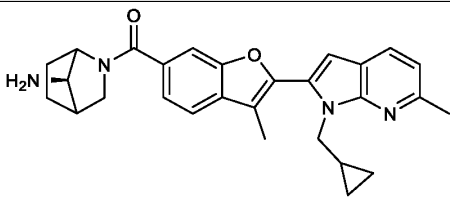
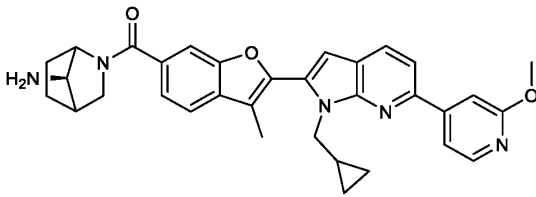
Compounds of Examples 167 to 172 in Table 20 were prepared following a procedure similar to the preparation of a compound of Example 166, by Suzuki coupling of Intermediate 165B with appropriate boronic acids.

20

Table 20

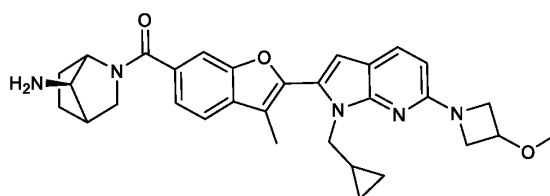
Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
167	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylbenzofuran-6-yl)methanonecyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one Analytical Data: 572.3, 1.679 min (Method E)

168	 5-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one Analytical Data: 572.4, 1.176 min (Method F)
169	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-fluoro-3-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylbenzofuran-6-yl)methanone Analytical Data: 551.3, 1.913 min (Method E)
170	 4-(2-(6-((7R)-7-amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorobenzamide Analytical Data: 578.3, 1.765 min (Method E)

171	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylbenzofuran-6-yl)methanone Analytical Data: 455.3, 1.342 min (Method F)
172	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-methoxypyridin-4-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylbenzofuran-6-yl)methanone Analytical Data: 548.3, 1.704 min (Method F)

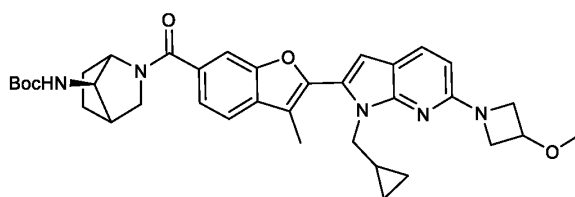
Example 173

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-methoxyazetidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylbenzofuran-6-yl)methanone



Intermediate 173A

tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-6-(3-methoxyazetidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylbenzofuran-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



RUPHOS (0.041 g, 0.087 mmol) and caesium carbonate (0.113 g, 0.348 mmol) were added to a stirred and degasified solution of Intermediate 165B (0.1 g, 0.174 mmol), 3-methoxyazetidine (0.015 g, 0.174 mmol) in dioxane (2 ml). The reaction mixture was
 5 purged with nitrogen for 5 min, followed by the addition of $\text{Pd}_2(\text{dba})_3$ (0.016 g, 0.017 mmol). The reaction mixture was heated to 110°C and stirred for 12 hours, filtered through a celite bed, washed using EtOAc, and the filtrate was evaporated under reduced pressure to afford a residue. Water (50 ml) was added to the residue obtained and extracted with EtOAc (2×50 ml). The combined organic layers were washed with water
 10 (50 ml) and brine (50 ml), dried over anhydrous sodium sulphate, filtered, and the filtrate was evaporated under reduced pressure to afford the crude compound (100 mg). LC-MS m/z : 626 $[\text{M}+\text{H}]^+$.

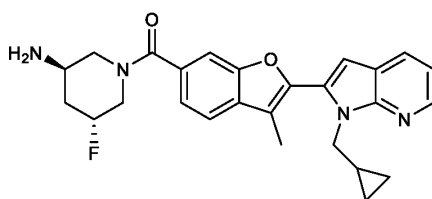
Example 173

TFA (0.031 ml, 0.400 mmol) was added to a stirred solution of Intermediate 173A (0.05 g, 0.080 mmol) in DCM (2 ml). The reaction mixture was stirred at a room temperature for 1 hour, evaporated under reduced pressure, and the crude product obtained was purified using RP-HPLC to afford the title compound (9.7mg, 19%). LC-MS m/z : 526 $[\text{M}+\text{H}]^+$. LC-MS retention time: 2.024 / 1.599 min (Method E / F). ^1H NMR
 20 (400 MHz, $\text{DMSO}-d_6$) δ ppm: 7.81 (d, $J=8.6$ Hz, 1H), 7.75-7.61 (m, 2H), 7.47-7.33 (m, 1H), 6.72 (s, 1H), 6.30 (d, $J=8.3$ Hz, 1H), 4.39-4.32(m, 1H), 4.27-4.16 (m, 4H), 3.83-3.77 (m, 2H), 3.71-3.49 (m, 2H), 3.27 (s, 3H), 3.20-3.15 (m, 2H), 3.07 (br, d, $J=11.0$ Hz, 1H), 2.39 (s, 3H), 2.24-2.15 (m, 1H), 2.00-1.65 (m, 3H), 1.45-1.32 (m, 1H), 1.20-1.10 (m, 1H), 0.39-0.31 (m, 2H), 0.31-0.22 (m, 2H).

25

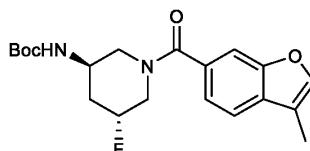
Example 174

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylbenzofuran-6-yl)methanone



Intermediate 174A

tert-Butyl-((3R,5R)-5-fluoro-1-(3-methylbenzofuran-6-carbonyl)piperidin-3-yl)carbamate



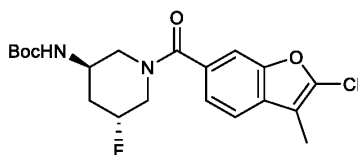
5

HATU (3.24 g, 8.51 mmol) in DMF (20 ml) and DIPEA (1.983 ml, 11.35 mmol) were added to a stirred solution of Intermediate 164C (1.0 g, 5.68 mmol), tert-butyl ((3R,5R)-5-fluoropiperidin-3-yl) carbamate (1.239 g, 5.68 mmol). The reaction mixture was stirred at a room temperature for 12 hours, quenched with water (200 ml), and extracted with EtOAc (2×200 ml). The combined organic layers were washed with water (100 ml) and brine (100 ml), dried over anhydrous sodium sulphate, filtered, and the filtrate was evaporated under reduced pressure. A crude product thus obtained was purified using flash chromatography (24 g, silica gel column, 70% EtOAc in pet ether) to afford the title compound (2.0 g, 94%) as a gummy liquid. LC-MS m/z: 377 [M+H]⁺.

15

Intermediate 174B

tert-Butyl-((3R,5R)-1-(2-chloro-3-methylbenzofuran-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



20

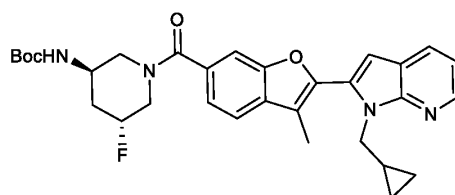
1M THF solution of LDA (0.266 ml, 0.531 mmol) was added to a stirred solution of Intermediate 174A (100 mg, 0.266 mmol) in THF (15 ml) at -78°C under nitrogen atmosphere and the reaction mixture was stirred for 1 hour, followed by the addition of hexachloroethane (69.2 mg, 0.292 mmol) in 2 ml of THF. The reaction mixture was allowed to warm to a room temperature and stirred for 4 hours, quenched with water (15

ml), and extracted with EtOAc (2×50 ml). The combined organic layers were washed with water (30 ml) and brine (30 ml), dried over anhydrous sodium sulphate, filtered, and the filtrate was evaporated under reduced pressure to afford the crude compound (120 mg) as a brown solid. LC-MS m/z: 409.3 [M-H]⁺.

5

Intermediate 174C

tert-Butyl-((3R,5R)-1-(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylbenzofuran-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



10 A solution of K₂CO₃ (121 mg, 0.876 mmol) in water (0.75 ml) was added to a stirred and degasified solution of Intermediate 174B (120 mg, 0.292 mmol) and 1-(cyclopropylmethyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine (87 mg, 0.292 mmol) in dioxane (3 ml). The reaction mixture was degasified with argon, followed by the addition of Pd(PPh₃)₄ (338 mg, 0.292 mmol). The reaction mixture was heated to 115°C and stirred for 6 hours, evaporated under reduced pressure to dryness, water (20 ml) was added, and extracted with EtOAc (2×30 ml). The combined organic layers were washed with water (20 ml) and brine (20 ml), dried over anhydrous sodium sulphate, filtered, and the filtrate was evaporated under reduced pressure to afford the crude compound (100 mg) as brown solid. LC/MS m/z: 547.4 [M+H]⁺.

20

Example 174

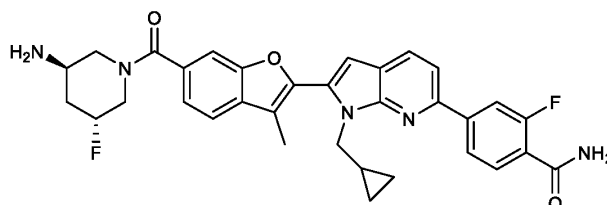
TFA (0.141 ml, 1.829 mmol) was added to a stirred solution of Intermediate 174C (100 mg, 0.183 mmol) in DCM (2 ml). The reaction mixture was stirred at a room temperature for 7 hours, evaporated under reduced pressure, and the crude product obtained was purified using RP-HPLC to afford the title compound (14.2mg, 17%). LC-MS m/z: 447.2 [M+H]⁺. LC-MS retention time: 1.4 min (Method F). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.37 (dd, J=1.5, 4.6 Hz, 1H), 8.17-7.99 (m, 3H), 7.83 (d, J=8.1 Hz, 1H), 7.73 (s, 1H), 7.40 (dd, J=1.2, 8.1 Hz, 1H), 7.27-7.18 (m, 1H), 7.01 (s, 1H), 6.95 (s, 1H), 5.07-4.85 (m, 1H), 4.81-4.66 (m, 1H), 4.42 (d, J=7.1 Hz, 2H), 3.57 (br, s, 2H), 3.17

25

(s, 1H), 2.62-2.52 (m, 1H), 2.45 (s, 3H), 2.35 (br, d, $J=13.9$ Hz, 1H), 2.08 (s, 1H), 1.90 (s, 1H), 1.80 (s, 1H), 1.25-1.14 (m, 1H), 0.38-0.31 (m, 2H), 0.31-0.25 (m, 2H).

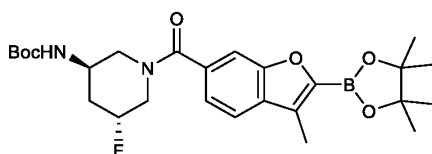
Example 175

- 5 6-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one



Intermediate 175A

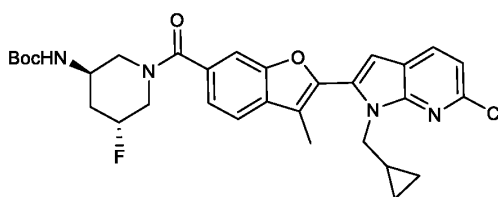
- 10 tert-Butyl-((3R,5R)-5-fluoro-1-(3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-6-carbonyl)piperidin-3-yl)carbamate



- 1M THF solution of LDA (5.31 ml, 10.63 mmol) was added to a stirred solution of Intermediate 174A (1.0g, 2.66 mmol) in THF (20 ml) at -78°C . The reaction mixture was stirred for 30 min, followed by the addition of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.084 ml, 5.31 mmol) at -78°C and stirring at -78°C for 2 hours. The reaction mixture was quenched with water (10 ml), and extracted with EtOAc (2×100 ml). The combined organic layers were washed with water (100 ml) and brine (100 ml), dried over anhydrous sodium sulphate, filtered, and the filtrate was evaporated under reduced pressure to afford the crude material (1.1 g, 82%) as a gummy liquid. LC-MS m/z : 503 $[\text{M}+\text{H}]^{+}$.

Intermediate 175B

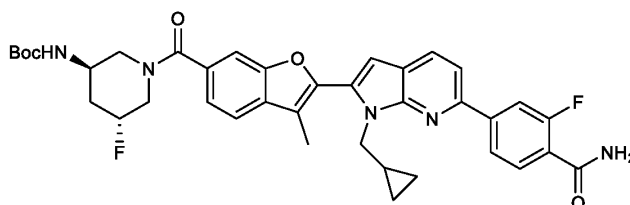
- tert-Butyl-((3R,5R)-1-(2-(6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylbenzofuran-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



A solution of K_2CO_3 (413 mg, 2.99 mmol) in water (1 ml) was added to a stirred and degasified solution of Intermediate 175A (500 mg, 0.995 mmol) and 6-chloro-1-(cyclopropylmethyl)-2-iodo-1H-pyrrolo[2,3-b]pyridine (Intermediate 3, 331 mg, 0.995 mmol) in dioxane (2 ml), followed by the addition of $PdCl_2(dppf)$ (72.8 mg, 0.100 mmol). The reaction mixture was heated to $80^\circ C$ and stirred for 17 hours, evaporated under reduced pressure to dryness, water (20 ml) was added, and extracted with EtOAc (2×30 ml). The combined organic layers were washed with water (20 ml) and brine (20 ml), dried over anhydrous sodium sulphate, filtered, and the filtrate was evaporated under reduced pressure to afford the crude (180mg, 40%) as a brown solid. LC-MS m/z: 581.3 $[M+H]^+$.

Intermediate 175C

tert-Butyl-((3R,5R)-1-(2-(1-(cyclopropylmethyl)-6-(3-oxoisindolin-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylbenzofuran-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



A solution of K_2CO_3 (64.2 mg, 0.465 mmol) in water (1 ml) was added to a stirred and degasified solution of Intermediate 175B (90 mg, 0.155 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (40.1 mg, 0.155 mmol) in dioxane (2 ml), followed by the addition of $PdCl_2(dppf)$ (56.7 mg, 0.077 mmol). The reaction mixture was heated to $80^\circ C$ and stirred for 16 hours, evaporated under reduced pressure to dryness, water (20 ml) was added, and extracted with EtOAc (2×30 ml). The combined organic layers were washed with water (20 ml) and brine (20 ml), dried over

anhydrous sodium sulphate, filtered, and the filtrate was evaporated under reduced pressure to afford the crude product (90mg) as a brown solid. LC-MS m/z 678.4 [M+H]⁺.

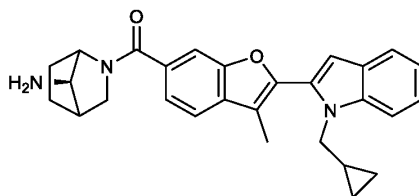
Example 175

5 TFA (0.141 ml, 1.829 mmol) was added to a stirred solution of Intermediate 175C (90 mg, 0.183 mmol) in DCM (2 ml). The reaction mixture was stirred at a room temperature for 7 hours, evaporated under reduced pressure, and the crude product thus obtained was purified using RP-HPLC to afford the title compound (6.9mg, 16%). LC-MS m/z: 578 [M+H]⁺. LC-MS retention time: 1.803 / 1.607 min. (Method E / F). ¹H
 10 NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.70-8.58 (m, 2H), 8.49-8.39 (m, 3H), 8.18 (d, J=8.3 Hz, 1H), 8.03-7.82 (m, 2H), 7.81 (d, J=8.1 Hz, 1H), 7.75- 7.62 (m, 3H), 7.37 (d, J=7.8 Hz, 1H), 6.98 (s, 1H), 4.56-4.41 (m, 6H), 3.02 (td, J=4.2, 1.6 Hz, 1H), 2.47 (s, 3H), 2.22-2.09 (m, 1H), 1.63-1.42 (m, 1H), 1.32-1.22 (m, 2H), 0.61-0.49 (m, 1H), 0.44-0.31 (m, 4H).

15

Example 176

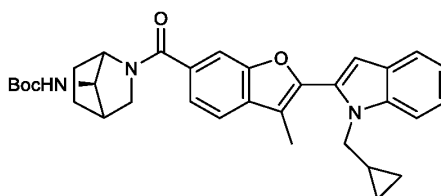
((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone



20

Intermediate 176A

tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylbenzofuran-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



25 A solution of K₂CO₃ (71.7 mg, 0.519 mmol) in water (0.75 ml) was added to a stirred and degasified solution of Intermediate 164E (70 mg, 0.173 mmol) and 1-

(cyclopropylmethyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (Intermediate 10, 51.4 mg, 0.173 mmol) in dioxane (2 ml), followed by the addition of Pd(PPh₃)₄ (200 mg, 0.173 mmol). The reaction mixture was heated to 120°C and stirred for 6 hours, evaporated under reduced pressure to dryness, water (25 ml) was added, and extracted with EtOAc (2×25 ml). The combined organic extracts were washed with water (25 ml) and brine (25 ml), dried over anhydrous sodium sulphate, filtered, and the filtrate was evaporated under reduced pressure to afford the title compound (100 mg) as a brown solid. LC/MS m/z: 540.3 [M+H]⁺.

10

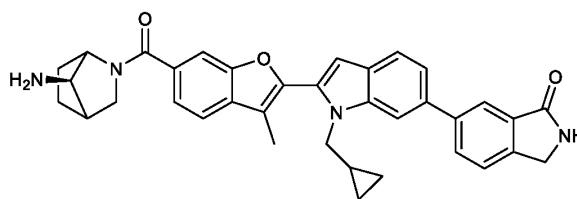
Example 176

TFA (0.143 ml, 1.853 mmol) was added to a stirred solution of Intermediate 176A (100 mg, 0.185 mmol) in DCM (3 ml). The reaction mixture was stirred at a room temperature for 10 hours, evaporated under reduced pressure, and the crude product thus obtained was purified using RP-HPLC to afford the title compound. LC-MS m/z: 441.2 [M+H]⁺. LC-MS retention time: 2.9 min. (Method H). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.29-7.99 (m, 3H), 8.28-7.98 (m, 2H), 7.82-7.67 (m, 2H), 7.54-7.37 (m, 1H), 7.23 (t, J=7.5 Hz, 1H), 7.16 (d, J=9.0 Hz, 1H), 6.8 (s, 1H), 4.55-4.50 (m, 2H), 4.30-4.24 (m, 2H), 4.27 (br, d, J=7.0 Hz, 1H), 4.14 (br, s, 1H), 4.12-4.02 (m, 1H), 3.75-3.41 (m, 2H), 3.25-3.04 (m, 1H), 2.68-2.60 (m, 1H), 2.38 (s, 3H), 1.99-1.82 (m, 3H), 1.74-1.51 (m, 1H), 1.16-0.96 (m, 1H), 0.39-0.27 (m, 2H), 0.15 (br, d, J=4.5 Hz, 2H).

20

Example 177

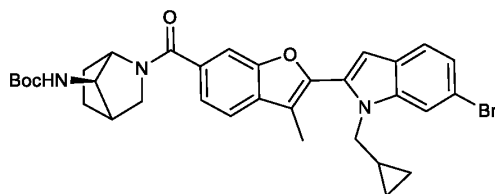
6-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one



25

Intermediate 177A

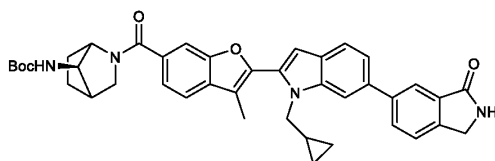
tert-Butyl-((7R)-2-(2-(6-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylbenzofuran-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



A solution of K_2CO_3 (0.368 g, 2.66 mmol) in water (0.1 ml) was added to a stirred and degasified solution of Intermediate 165A (0.551 g, 1.330 mmol) and 6-bromo-1-(cyclopropylmethyl)-2-iodo-1H-indole (Intermediate-12, 0.5 g, 1.330 mmol) in dioxane (10 ml), followed by the addition of $Pd(PPh_3)_4$ (0.123 g, 0.106 mmol). The reaction mixture was heated to $80^\circ C$ and stirred for 3 hours, filtered through a celite bed using EtOAc, and the filtrate was evaporated under reduced pressure. The crude product thus obtained was purified using flash chromatography (12g silica gel column, 70% EtOAc in pet ether) to afford the pure the title compound (0.28g, 34%) as a gummy liquid. LC-MS m/z: 620 $[M+H]^+$.

Intermediate 177B

tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-6-(3-oxoisindolin-5-yl)-1H-indol-2-yl)-3-methylbenzofuran-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



15

A solution of K_2CO_3 (0.045 g, 0.323 mmol) in water (0.1 ml) was added to a stirred and degasified solution of Intermediate 177A (0.1 g, 0.162 mmol) and 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-1-one (0.050 g, 0.194 mmol) in dioxane (2 ml), followed by the addition of $PdCl_2(dppf)-CH_2Cl_2$ adduct (0.013 g, 0.016 mmol). The reaction mixture was heated to $80^\circ C$ and stirred for 2 hours, filtered through a celite bed using EtOAc, and the filtrate was evaporated under reduced pressure to afford the title compound (100 mg) as a brown solid. LC-MS m/z: 672 $[M+H]^+$.

20

Example 177

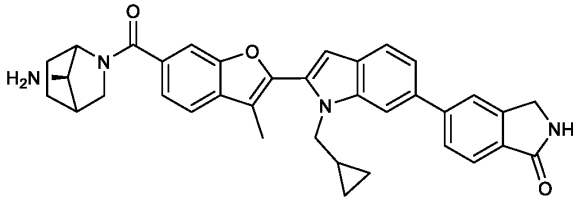
TFA (0.057 ml, 0.745 mmol) was added to a stirred solution of Intermediate 177B (0.1 g, 0.149 mmol) in DCM (2 ml). The reaction mixture was stirred at a room

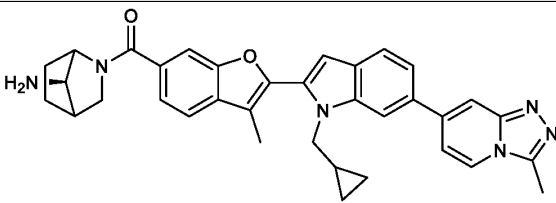
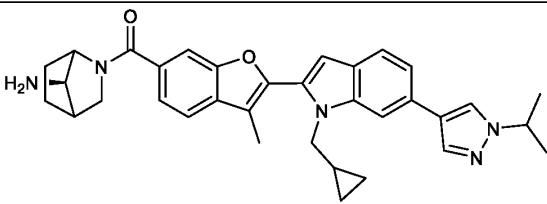
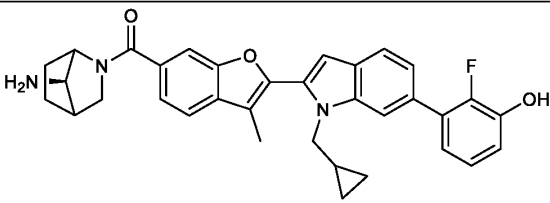
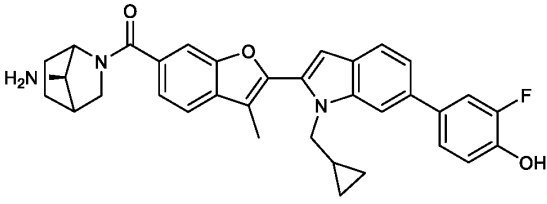
25

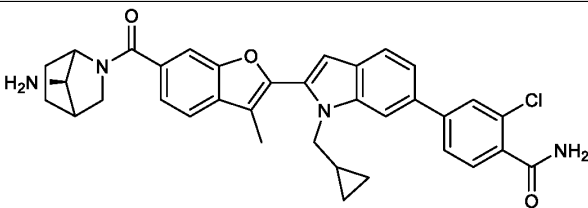
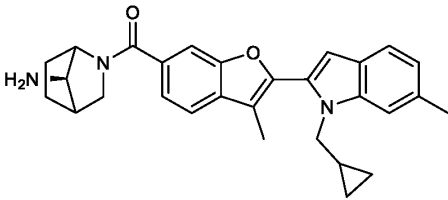
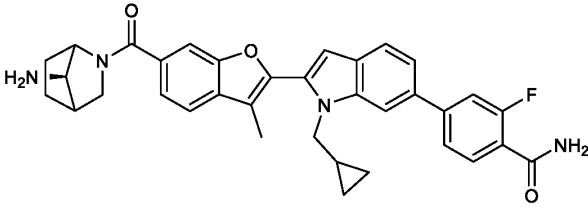
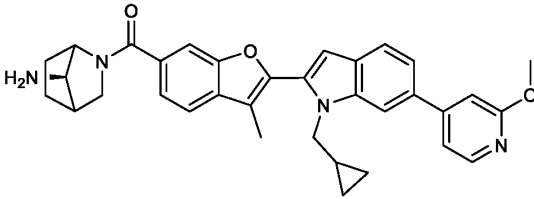
temperature for 1 hour, evaporated under reduced pressure, and the crude product obtained was purified using RP-HPLC to afford the title compound (5.6mg, 6.4%). LC-MS m/z: 572 [M+H]⁺. LC-MS Ret. Time: 1.739 / 1.532 min (Method E / F). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.60 (s, 1H), 8.08-7.99 (m, 2H), 7.81-7.65 (m, 2H), 7.54-7.38 (m, 3H), 6.93 (s, 1H), 4.54-4.38 (m, 5H), 3.68 (s, 1H), 3.52 (br, d, *J*=10.0 Hz, 1H), 3.17 (br, s, 2H), 3.07-2.99 (m, 1H), 2.45-2.38 (m, 4H), 2.25-2.12 (m, 1H), 2.03-1.81 (m, 3H), 1.75-1.65 (m, 1H), 1.48-1.30 (m, 1H), 1.19-1.04 (m, 1H), 0.41-0.33 (m, 2H), 0.21 (q, *J*=5.1 Hz, 2H).

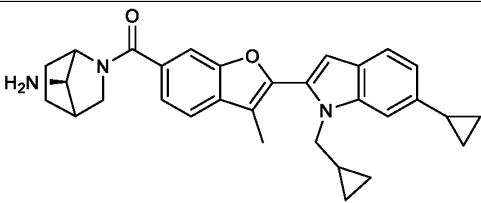
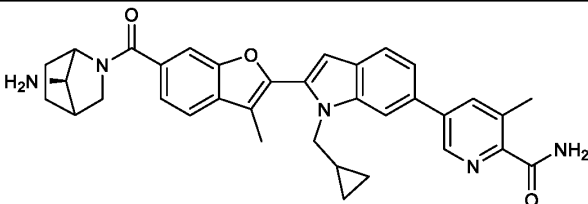
- 10 Compounds of Examples 178 to 188 in Table 21 were prepared following a procedure similar to the preparation of a compound of Example 177, by Suzuki coupling of Intermediate 177A with appropriate boronic ester or acid.

Table 21

Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
178	 5-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one Analytical Data: 571.3, 1.704 min (Method E)

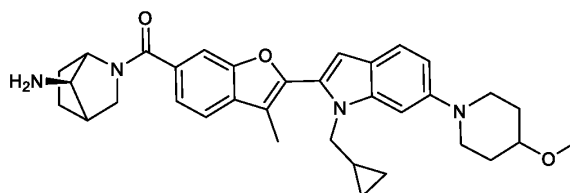
179	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone Analytical Data: 571.3, 1.578 min (Method E)
180	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(1-isopropyl-1H-pyrazol-4-yl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone Analytical Data: 548.4, 1.991 min (Method E)
181	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-fluoro-3-hydroxyphenyl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone Analytical Data: 550.3, 1.962 min (Method E)
182	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-fluoro-4-hydroxyphenyl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone Analytical Data: 550.3, 1.944 min (Method E)

183	 4-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)-2-chlorobenzamide Analytical Data: 593.4, 1.782 min (Method E)
184	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-methyl-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone Analytical Data: 454.3, 2.177 min (Method E)
185	 4-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)-2-fluorobenzamide Analytical Data: 577.3, 1.790 min (Method E)
186	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-methoxypyridin-4-yl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone Analytical Data: 547.4, 2.146 min (Method E)

187	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-cyclopropyl-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone Analytical Data: 480.3, 2.252 min (Method E)
188	 5-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)-3-methylpicolinamide Analytical Data: 574.3, 1.802 min (Method E)

Example 189

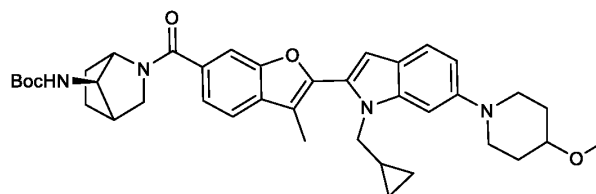
((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(4-methoxypiperidin-1-yl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone



5

Intermediate 189A

tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-6-(4-methoxypiperidin-1-yl)-1H-indol-2-yl)-3-methylbenzofuran-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



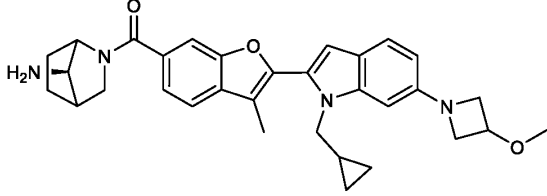
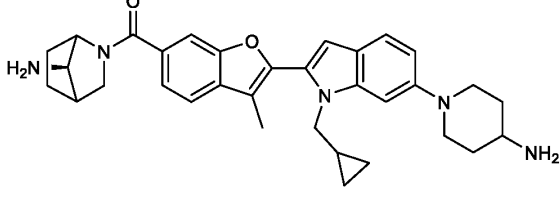
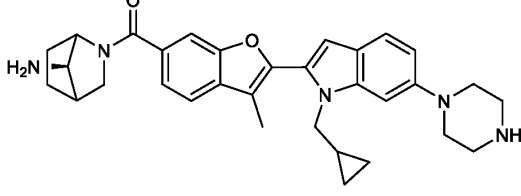
Potassium tert-butoxide (0.036 g, 0.323 mmol) and XPHOS (0.039 g, 0.081 mmol) were added to a stirred and degasified solution of Intermediate 177A (0.1 g, 0.162 mmol), 4-methoxy-piperidine (0.019 g, 0.162 mmol) in dioxane (2 ml). The reaction mixture was purged with nitrogen for 5 min, followed by the addition of Palladium(II) acetate (10.89 mg, 0.048 mmol). The reaction mixture was heated to 110°C and stirred for 12 hours, filtered through a celite bed using EtOAc (50 ml), and the filtrate was evaporated under reduced pressure to afford a residue. Water (50 ml) was added to the residue, and extracted with EtOAc (2×50 ml). The combined organic layers were washed with water (50 ml) and brine (50 ml), dried over anhydrous sodium sulphate, filtered, and the filtrate was evaporated under reduced pressure to afford the title compound (90 mg, 85%) as a brown solid. LC-MS m/z: 653 [M+H].

Example 189

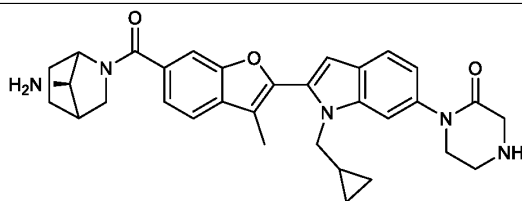
TFA (0.059 ml, 0.766 mmol) was added to a stirred solution of Intermediate 189A (0.1 g, 0.153 mmol) in DCM (2 ml). The reaction mixture was stirred at a room temperature for 1 hour, evaporated under reduced pressure, and the crude product obtained was purified using RP-HPLC to afford the title compound (9.6mg, 10%). LC-MS m/z: 553 [M+H]⁺. LC-MS retention time: 2.009 / 1.117 min (Method E / F). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 7.73 (s, 1H), 7.65 (s, 1H), 7.49-7.43 (m, 1H), 7.39 (dd, *J*=0.7, 7.6 Hz, 1H), 7.03 (d, *J*=1.0 Hz, 1H), 6.91-6.87 (m, 1H), 6.73 (s, 1H), 4.24 (br, d, *J*=6.8 Hz, 2H), 3.70 (br, d, *J*=1.2 Hz, 1H), 3.57-3.50 (m, 3H), 3.07 (br, d, *J*=10.8 Hz, 1H), 2.97-2.91 (m, 2H), 2.37 (s, 4H), 2.26-2.15 (m, 1H), 2.03-1.88 (m, 5H), 1.73-1.54 (m, 3H), 1.12-1.04 (m, 1H), 0.39-0.28 (m, 2H), 0.17 (br, d, *J*=4.2 Hz, 2H).

Compounds of Examples 190 to 193 in Table 22 were prepared following a procedure similar to the preparation of a compound of Example 189, using the Intermediate 177A and the appropriate amine.

Table 22

Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
190	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-methoxyazetidin-1-yl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone Analytical Data: 525.4, 1.389 min (Method F)
191	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-(4-aminopiperidin-1-yl)-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone Analytical Data: 538.3, 1.375 min (Method E)
192	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(piperazin-1-yl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone Analytical Data: 524.3, 1.377 min (Method E)

193

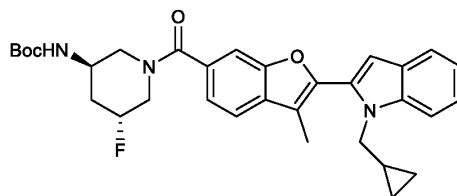


1-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)piperazin-2-one

Analytical Data: 538.3, 1.289 min (Method E)

Example-194

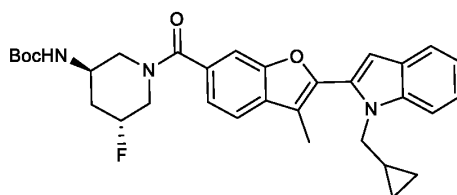
((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone



5

Intermediate 194A

tert-Butyl-((3R,5R)-1-(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylbenzofuran-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



10

A solution of K_2CO_3 (101 mg, 0.730 mmol) in water (0.75 ml) was added to a stirred and degasified solution of Intermediate 174B (100 mg, 0.243 mmol) and 1-(cyclopropylmethyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (Intermediate 10, 72.3 mg, 0.243 mmol) in dioxane (3 ml). The reaction mixture was degasified with argon, followed by the addition of $Pd(PPh_3)_4$ (281 mg, 0.243 mmol). The reaction mixture was heated to 115°C and stirred for 6 hours, evaporated under reduced pressure to dryness, water (25 ml) was added, and extracted with EtOAc (2×25 ml). The

15

combined organic layers were washed with water (10 ml) and brine (10 ml), dried over anhydrous sodium sulphate, filtered, and the filtrate was evaporated under reduced pressure to afford the title compound (100 mg) as brown solid. LC-MS m/z: 546.5 [M+H]⁺.

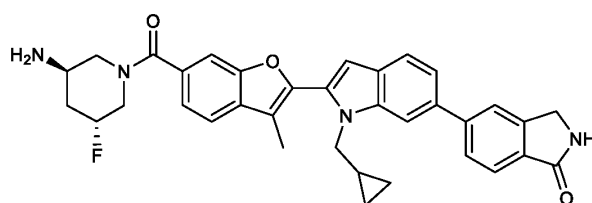
5

Example 194

TFA (0.141 ml, 1.833 mmol) was added to a stirred solution of Intermediate 194A (100 mg, 0.183 mmol) in DCM (2 ml). The reaction mixture was stirred at a room temperature for 7 hours, evaporated under reduced pressure, and the crude product
 10 obtained was purified using RP-HPLC to afford the title compound (1.3 mg, 1.4%). LC-MS m/z: 446.3 [M+H]⁺. LC-MS retention time: 1.8 min (Method F). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 7.79 (d, *J*=7.8 Hz, 1H), 7.71-7.63 (m, 3H), 7.37 (dd, *J*=1.3, 7.9 Hz, 1H), 7.30-7.23 (m, 1H), 7.16-7.06 (m, 1H), 6.90(s, 1H), 5.04-4.82 (m, 1H), 4.73-4.39 (m, 1H), 4.30 (d, *J*=6.8 Hz, 2H), 3.94-3.83 (m, 1H), 2.86-2.74 (m, 1H), 2.41 (s, 3H), 2.31-
 15 2.21 (m, 1H), 1.84 -1.64 (m, 1H), 1.24 (s, 2H), 1.18-1.07 (m, 1H), 0.41-0.27 (m, 2H), 0.24-0.11 (m, 2H).

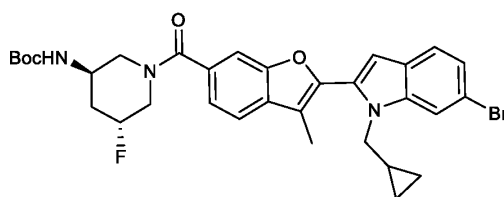
Example 195

5-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one
 20



Intermediate 195A

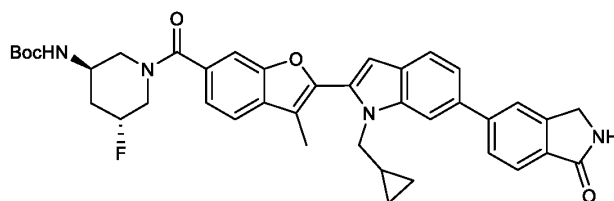
25 tert-Butyl-((3R,5R)-1-(2-(6-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylbenzofuran-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



A solution of K_2CO_3 (0.715 g, 5.18 mmol) in water (0.5 ml) was added to a stirred and degasified solution of Intermediate 175A (1.3 g, 2.59 mmol) and 6-bromo-1-(cyclopropylmethyl)-2-iodo-1H-indole (Intermediate-12, 0.973 g, 2.59 mmol) in dioxane (12 ml). The reaction mixture was degasified with argon, followed by the addition of $PdCl_2(dppf)-CH_2Cl_2$ adduct (0.190 g, 0.233 mmol). The reaction mixture was heated to $80^\circ C$ and stirred for 3 hours, diluted with water (100 ml) and extracted with EtOAc (2×100 ml). The combined organic layers were washed with water (100 ml) and brine (100 ml), dried over anhydrous sodium sulphate, filtered, and the filtrate was evaporated under reduced pressure. The crude material was purified using a silica gel column (40 g, silica gel column, 70% EtOAc in pet ether) to afford the title compound (1.1 g, 68%) as a gummy liquid. LC-MS m/z : 626 $[M+H]^+$.

Intermediate 195B

tert-Butyl-((3R,5R)-1-(2-(1-(cyclopropylmethyl)-6-(1-oxoisindolin-5-yl)-1H-indol-2-yl)-3-methylbenzofuran-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



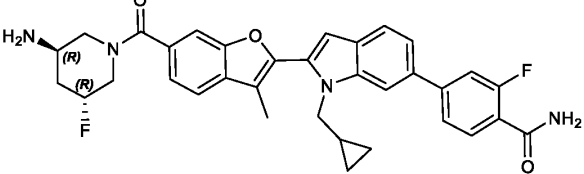
A solution of K_2CO_3 (0.044 g, 0.320 mmol) in water (0.5 ml) was added to a stirred and degasified solution of Intermediate 195A (0.1 g, 0.160 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isindolin-1-one (0.050 g, 0.192 mmol) in dioxane (2 ml). The reaction mixture was degasified with argon, followed by the addition of $PdCl_2(dppf)-CH_2Cl_2$ adduct (0.013 g, 0.016 mmol). The reaction mixture was heated to $80^\circ C$ and stirred for 12 hours, filtered through a celite bed using ethyl acetate, and the filtrate was concentrated under reduced pressure to afford the title compound (100mg, 91%). LC/MS $m/z=677.4$ $[M+H]^+$.

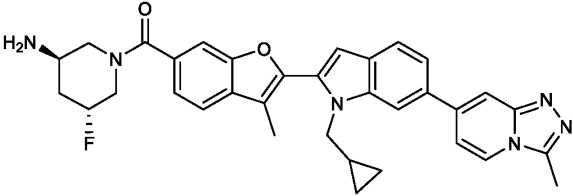
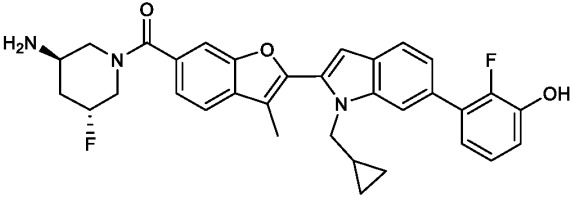
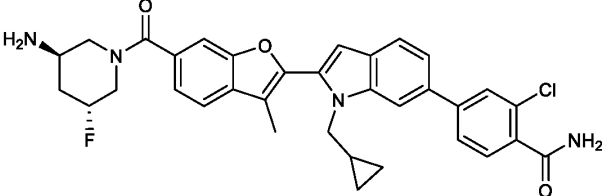
Example 195

TFA (0.056 ml, 0.732 mmol) was added to a stirred solution of 195B (0.1 g, 0.146 mmol) in DCM (2 ml). The reaction mixture was stirred at a room temperature for 1 hour, evaporated under reduced pressure, and the crude product obtained was purified using RP-HPLC to afford the title compound (2mg, 2.1%). LC/MS m/z: 577.3 [M+H]⁺. LC-MS retention time: 1.678 / 1.529 min (Method E / F); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.55 (s, 1H), 8.03 (s, 1H), 7.98 (s, 1H), 7.90 (br, dd, J=1.1, 8.4 Hz, 2H), 7.83-7.74 (m, 4H), 7.70 (br, d, J=0.7 Hz, 1H), 7.52 (d, J=9.0 Hz, 1H), 7.39 (d, J=7.6 Hz, 1H), 6.95 (s, 1H), 4.47 (s, 3H), 4.45-4.39 (m, 2H), 3.01-2.88 (m, 2H), 2.44 (s, 3H), 2.28 (br, t, J=7.5 Hz, 1H), 1.92-1.74 (m, 2H), 1.57-1.39 (m, 2H), 1.30-1.08 (m, 14H), 0.90-0.79 (m, 2H), 0.43-0.32 (m, 2H), 0.25-0.17 (m, 2H).

Compounds of Examples 196 to 199 in Table 23 were prepared following a procedure similar to the preparation of a compound of Example 195, using the Intermediate 195A and the appropriate boronic esters or acids

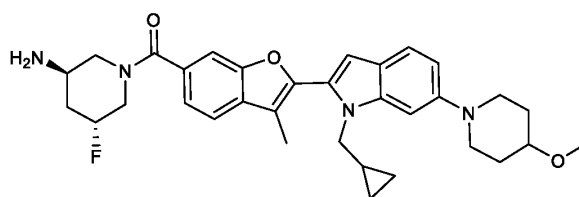
Table 23

Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
196	 4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)-2-fluorobenzamide Analytical Data: 583.4, 1.755 min (Method E)

197	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone Analytical Data: 577.3, 1.562 min (Method E)
198	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(2-fluoro-3-hydroxyphenyl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone Analytical Data: 556.3, 1.933 min (Method E)
199	 4-(2-(6-(((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)-2-chlorobenzamide Analytical Data: 599.3, 1.741 min (Method E)

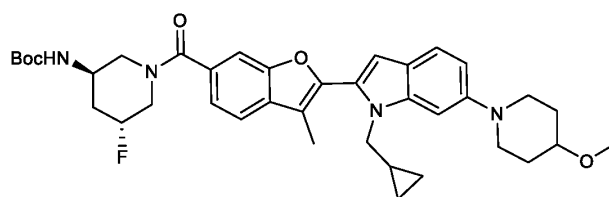
Example 200

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(4-methoxypiperidin-1-yl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone



Intermediate 200A

tert-Butyl-((3R,5R)-1-(2-(1-(cyclopropylmethyl)-6-(4-methoxypiperidin-1-yl)-1H-indol-2-yl)-3-methylbenzofuran-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



Potassium tert-butoxide (0.036 g, 0.320 mmol), XPHOS (0.038 g, 0.080 mmol) were added to a stirred and degassed solution of Intermediate 195A (0.1 g, 0.160 mmol), (0.018 g, 0.160 mmol) in dioxane (2 ml). The reaction mixture was purged with nitrogen for 5 min, followed by the addition of Palladium(II) acetate (10.89 mg, 0.048 mmol). The reaction mixture heated to 110°C and stirred for 12 hours, filtered through a celite bed using EtOAc (50 ml), and the filtrate was evaporated under reduced pressure. Water (50 ml) was added to the residue thus obtained, and extracted with EtOAc (2×50 ml). The combined organic layers were washed with water (50 ml) and brine (50 ml), dried over anhydrous sodium sulphate, filtered, and the filtrate was evaporated under reduced pressure to afford the title compound (90mg, 85%) as brown solid. LC-MS m/z: 659.4 [M+H]⁺.

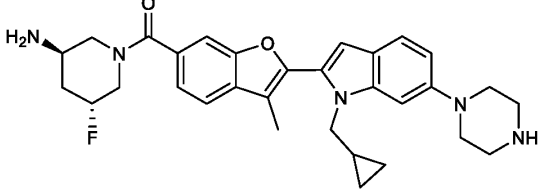
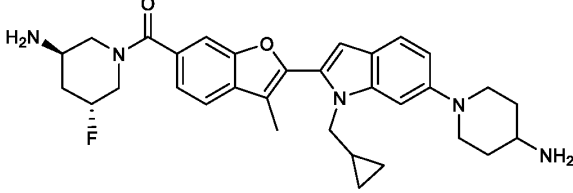
Example 200

TFA (0.029 ml, 0.379 mmol) was added to a stirred solution of Intermediate 200A (0.05 g, 0.076 mmol) in DCM (2 ml). The reaction mixture was stirred at a room temperature for 1 hour, evaporated under reduced pressure, and the crude product thus obtained was purified using RP-HPLC to afford the title compound (6.8mg, 15%). LC-MS m/z: 559 [M+H]⁺. LC-MS retention time: 1.959 / 1.161 min, (Method E / F). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.17-7.91 (m, 2H), 7.77 (d, *J*=8.3 Hz, 1H), 7.67 (s, 1H), 7.60-7.52 (m, 1H), 7.37 (d, *J*=7.8 Hz, 1H), 7.07-6.96 (m, 1H), 6.80 (s, 1H), 4.26 (br,

d, $J=6.8$ Hz, 2H), 3.57 (br, dd, $J=1.6, 4.5$ Hz, 3H), 3.31 (s, 6H), 3.12-2.87 (m, 2H), 2.38 (s, 5H), 2.11-2.01 (m, 2H), 1.89-1.58 (m, 1H), 1.23 (s, 1H), 1.11 (br, d, $J=7.1$ Hz, 1H), 0.41-0.30 (m, 2H), 0.19 (d, $J=4.6$ Hz, 2H).

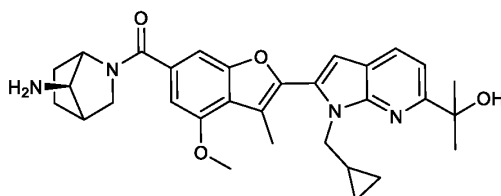
- 5 Compounds of Examples 201 and 202 in Table 24 were prepared following a procedure similar to the preparation of a compound of Example 200, using the Intermediate 195A and the appropriate amine.

Table 24

Example	Structure Name Analytical Data: LC-MS m/z $[M+H]^+$; HPLC retention time (HPLC method)
201	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(piperazin-1-yl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone Analytical Data: LC-MS m/z: 530.3 $[M+H]^+$; HPLC retention time: 1.171 min (Method E)
202	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(6-(4-aminopiperidin-1-yl)-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone Analytical Data: LC-MS m/z: 544.3 $[M+H]^+$; HPLC retention time: 2.007 min (Method E)

Example 203

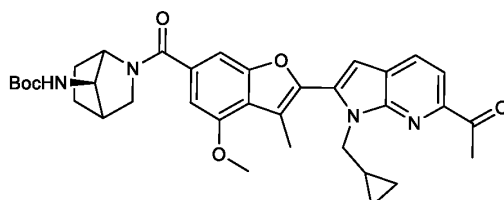
((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-hydroxypropan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylbenzofuran-6-yl)methanone



5

Intermediate 203A

tert-Butyl-((7R)-2-(2-(6-acetyl-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylbenzofuran-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



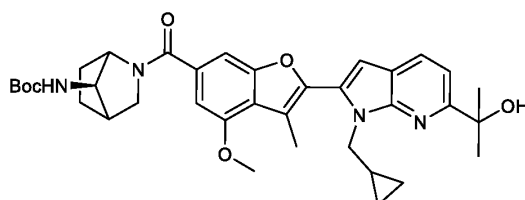
10 Tributyl (1-ethoxyvinyl)tin (119 mg, 0.331 mmol) and Pd(PPh₃)₄ (38.2 mg, 0.033 mmol) were added to a stirred and degasified solution of Intermediate 146B (200 mg, 0.331 mmol) in toluene (5 ml). The reaction mixture was heated to 85°C and stirred for 14 hours, evaporated under reduced pressure to dryness, and the crude product thus obtained was purified using a silica gel column (12 g, Redisep® SiO₂ column, eluting with 45% EtOAc in n-hexane) to afford the title compound (120 mg, 59%) as a brown solid. LC-MS m/z: 613.4 [M+H]⁺.

15

Intermediate 203B

tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-6-(2-hydroxypropan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylbenzofuran-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate

20



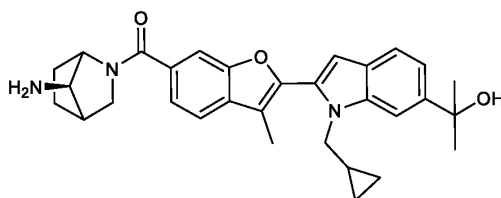
Methyl magnesium bromide (0.245 ml, 0.490 mmol, 2M in THF) was added to a stirred solution of Intermediate 203A (100 mg, 0.163 mmol) in THF at 0°C. The reaction mixture was stirred for 2 hours, quenched with saturated aqueous ammonium chloride solution (20 ml), and extracted with EtOAc (2×10 ml). The combined organic layers were washed with water (10 ml) and brine (10 ml), dried over anhydrous sodium sulphate, filtered, and the filtrate was evaporated under reduced pressure to afford the crude product (130 mg) as a brown solid. LC-MS m/z: 629.5 [M+H]⁺.

Example 203

TFA (0.123 ml, 1.590 mmol) was added to a solution of 203B (100 mg, 0.159 mmol) in DCM (3 ml) and the reaction mixture was stirred at a room temperature for 6 hours. The reaction mixture was evaporated under reduced pressure, and the crude product thus obtained was purified using RP-HPLC to afford the title compound (1.21 mg, 1%). LC-MS m/z: 529.3 [M+H]⁺. LC-MS retention time: 1.921 / 1.643 min (Method E / F).

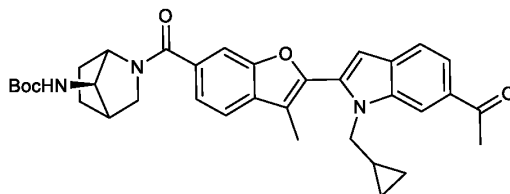
Example 204

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-hydroxypropan-2-yl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone



Intermediate 204A

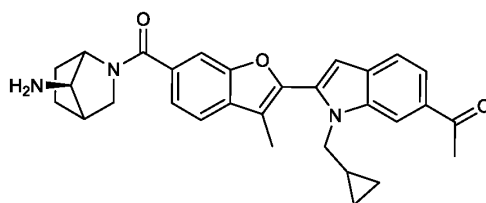
tert-Butyl-((7R)-2-(2-(6-acetyl-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylbenzofuran-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



Tributyl(1-ethoxyvinyl)stannane (0.234 g, 0.647 mmol) and Pd(PPh₃)₂Cl₂ (0.023 g, 0.032 mmol) were added to a stirred and degasified solution of Intermediate 177A (0.2 g, 0.323 mmol) in toluene (2 ml). The reaction mixture was heated to 90°C and stirred for 3 hours, evaporated under reduced pressure, and the crude product thus obtained was
5 purified using a silica gel column (4 g, Redisep® SiO₂ column, eluting with 70% EtOAc in n-hexane) to afford the title compound (0.13 g, 69%) as gummy liquid. LC-MS m/z: 582.4 [M+H]⁺.

Intermediate 204B

10 tert-Butyl-((7R)-2-(2-(1-(cyclopropylmethyl)-6-(2-hydroxypropan-2-yl)-1H-indol-2-yl)-3-methylbenzofuran-6-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate



TFA (0.040 ml, 0.516 mmol) was added to a stirred solution Intermediate 204A (0.06 g, 0.103 mmol) in DCM (2 ml). The reaction mixture was stirred at a room
15 temperature for 1 hour, evaporated under reduced pressure, diluted with 10% sodium bicarbonate solution (20 ml), and extracted with EtOAc (2×20 ml). The combined organic layers were washed with water (20 ml) and brine (20 ml), dried over anhydrous sodium sulphate, filtered, and the filtrate was evaporated under reduced pressure to afford the crude product (50 mg) as a gummy liquid. LC-MS m/z: 482.3 [M+H]⁺.

20

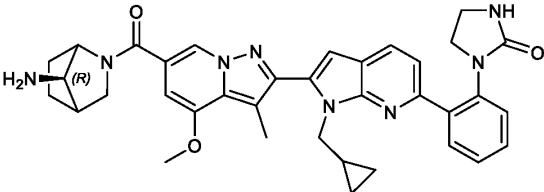
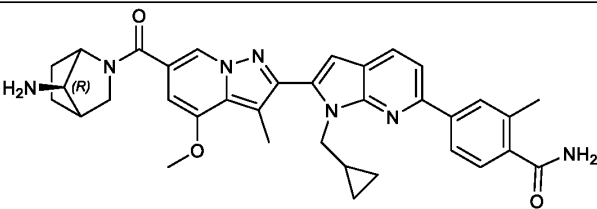
Example 204

Methyl magnesium bromide (0.125 ml, 0.125 mmol) was added to a stirred solution of Intermediate 204B (0.05 g, 0.104 mmol) in THF (2 ml) at 0°C. The reaction mixture was stirred at a room temperature for 2 hours, quenched with saturated aqueous
25 ammonium chloride solution (20 ml), and extracted with EtOAc (2× 20 ml). The combined organic layers were washed with water (20 ml) and brine (20 ml), dried over anhydrous sodium sulphate, filtered, and the filtrate was evaporated under reduced pressure. The crude product thus obtained was purified using RP-HPLC to afford the title compound (3.5 mg, 6%). LC/MS m/z: 498.4 [M+H]⁺, retention time: 3.476 min (Method

H). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 7.76 (s, 1H), 7.73-7.66 (m, 3H), 7.55 (d, J=8.0 Hz, 1H), 7.24 (s, 1H), 6.82 (s, 1H), 5.04 (s, 1H), 4.27 (d, J=7.0Hz, 2H), 3.51 (s, 4H), 2.39-2.36 (m, 4H), 2.29-2.19 (m, 4H), 1.83-1.69 (m, 2H), 1.66(s, 1H), 1.56-1.41 (m, 6H), 1.36 (br, d, J=8.0 Hz, 1H), 1.34-1.10 (m, 4H), 0.98-0.77 (m, 1H), 0.39-0.34 (m, 2H), 0.19 (br, d, J=4.0 Hz, 2H).

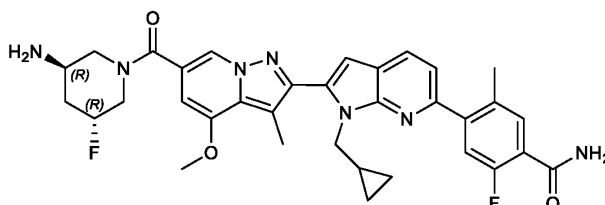
Compounds of Examples 205 and 206 in Table 25 were prepared following a procedure similar to the preparation of a compound of Example 3, using Suzuki coupling reaction of Intermediate 2E with appropriate boronic acid or boronate esters.

Table 25

Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
205	 1-[2-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)phenyl]imidazolidin-2-one Analytical Data: 631.4; 1.568 min (Method E)
206	 4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-methylbenzamide Analytical Data: 604.4; 1.781 min (Method E)

Example 207

4-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluoro-5-methylbenzamide



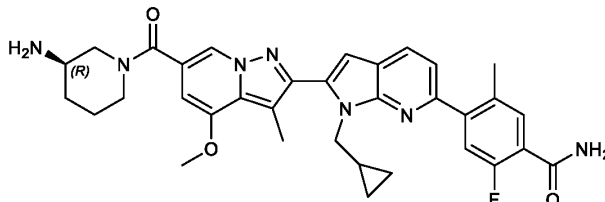
5

Compound of Example 207 was prepared following a procedure similar to the preparation compound of Example 16, using Intermediate 15A and appropriate boronic acid or boronate ester. LC-MS m/z : 627.3 $[M+H]^+$; HPLC retention time: 1.762 min (HPLC method E).

10

Example 208

4-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluoro-5-methylbenzamide



15

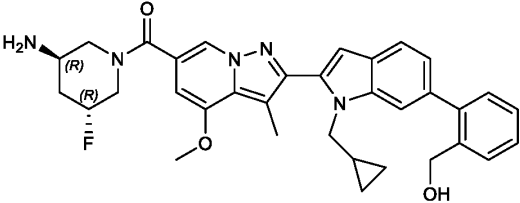
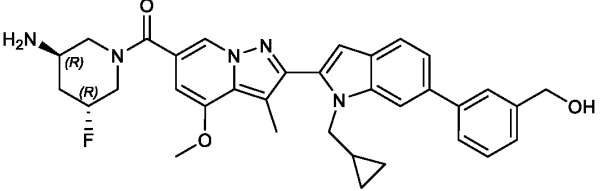
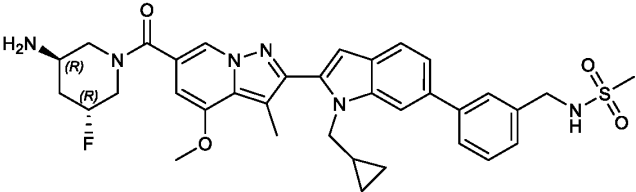
Compound of Example 208 was prepared following a procedure similar to the preparation of compound of Example 3, using Intermediate 2D and tert-butyl (R)-piperidin-3-ylcarbamate in amide formation reaction and the appropriate boronic acid or boronate ester in Suzuki coupling reaction. LC-MS m/z : 609.3 $[M+H]^+$; HPLC retention time: 1.710 min (HPLC Method E).

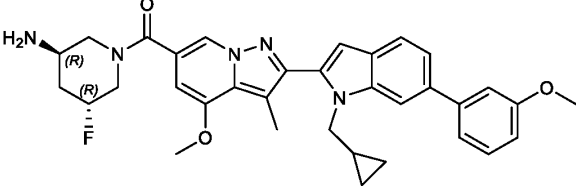
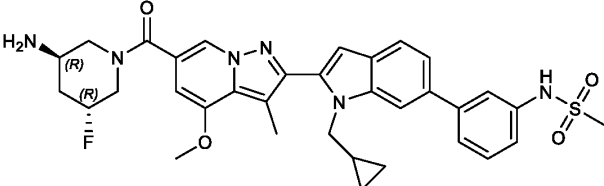
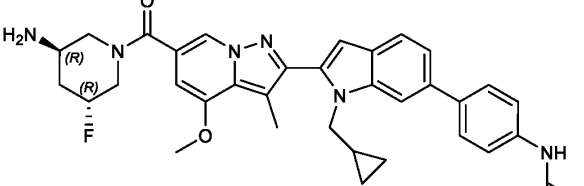
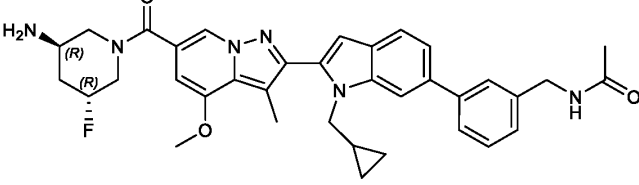
20

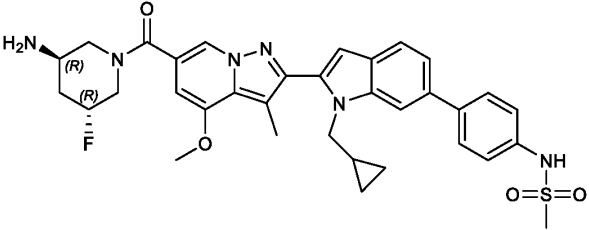
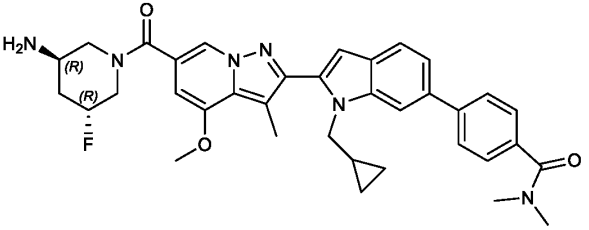
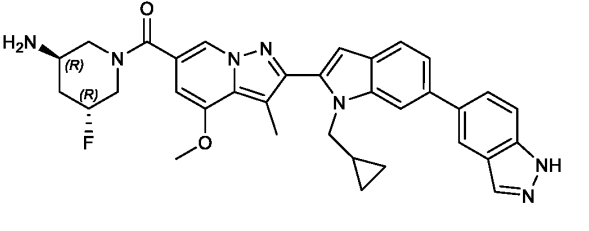
Compounds of Examples 209 to 226 in Table 26 were prepared following a procedure similar to the preparation of a compound of Example 29, by Suzuki coupling of Intermediate 29A with appropriate boronic acid or boronate ester.

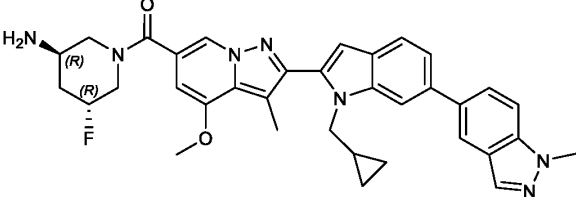
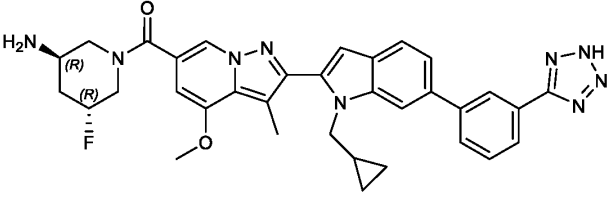
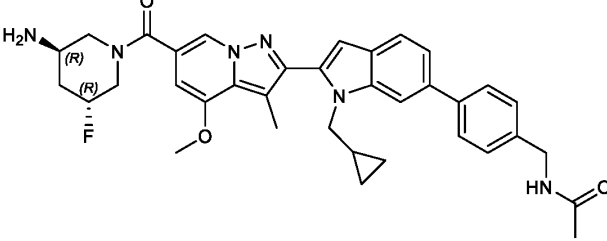
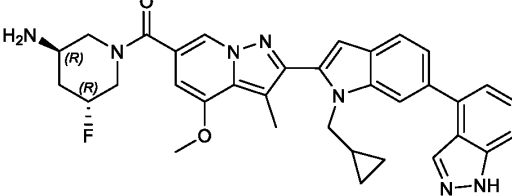
25

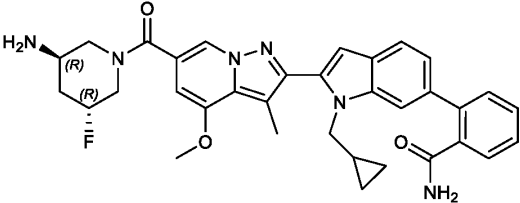
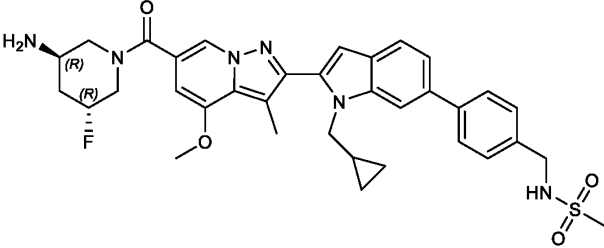
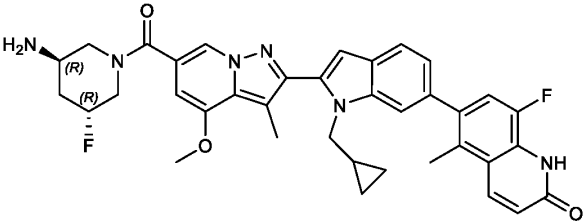
Table 26

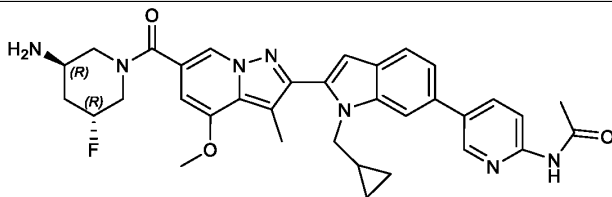
Example	Structure
	Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method 1)
209	 [2-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methanol Analytical Data: 582.3; 1.913 min (Method E)
210	 [3-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methanol Analytical Data: 582.3; 1.856 min (Method E)
211	 N-{[3-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methyl}methanesulfonamide Analytical Data: 659.3; 1.878 min (Method E)

212	 (3R,5R)-1-{2-[1-(Cyclopropylmethyl)-6-(3-methoxyphenyl)-1H-indol-2-yl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-5-fluoropiperidin-3-amine Analytical Data: 582.3; 2.275 min (Method E)
213	 N-[3-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methanesulfonamide Analytical Data: 645.3, 1.871 min (Method E)
214	 N-[4-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]acetamide Analytical Data: 609.3; 1.772 min (Method E)
215	

	N-{{3-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl)methyl}acetamide Analytical Data: 623.2.3; 1.782 min (Method E)
216	 N-[4-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methanesulfonamide Analytical Data: 645.2; 1.828 min (Method E)
217	 4-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-N,N-dimethylbenzamide Analytical Data: 623.3; 1.864 min (Method E)
218	 (3R,5R)-1-{2-[1-(Cyclopropylmethyl)-6-(1H-indazol-5-yl)-1H-indol-2-yl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-5-fluoropiperidin-3-amine Analytical Data: 592.3; 1.819 min (Method E)

219	 (3R,5R)-1-{2-[1-(Cyclopropylmethyl)-6-(1-methyl-1H-indazol-5-yl)-1H-indol-2-yl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-5-fluoropiperidin-3-amine Analytical Data: 606.3; 2.054 min (Method E)
220	 (3R,5R)-1-{2-[1-(Cyclopropylmethyl)-6-[3-(2H-1,2,3,4-tetrazol-5-yl)phenyl]-1H-indol-2-yl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-5-fluoropiperidin-3-amine Analytical Data: 620.3; 1.455 min (Method E)
221	 N-{[4-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methyl}acetamide Analytical Data: 623.3; 1.742 min (Method E)
222	

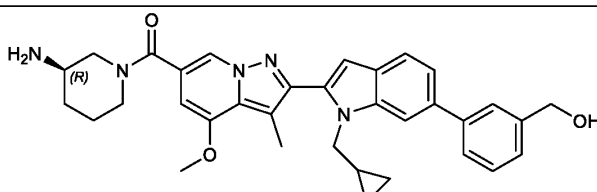
	(3R,5R)-1-{2-[1-(Cyclopropylmethyl)-6-(1H-indazol-4-yl)-1H-indol-2-yl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-5-fluoropiperidin-3-amine Analytical Data: 592.3; 1.876 min (Method E)
223	 2-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)benzamide Analytical Data: 595.3; 1.653 min (Method E)
224	 N-[4-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methyl}methanesulfonamide Analytical Data: 659.2; 1.865 min (Method E)
225	 6-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-8-fluoro-5-methyl-1,2-dihydroquinolin-2-one Analytical Data: 651.3, 1.807 min (Method E)

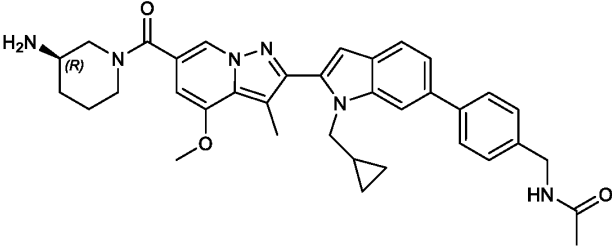
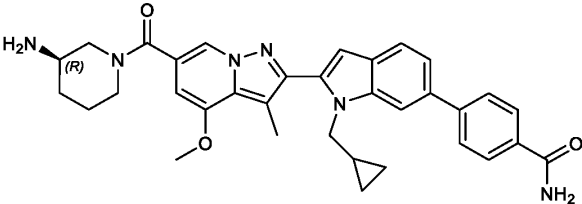
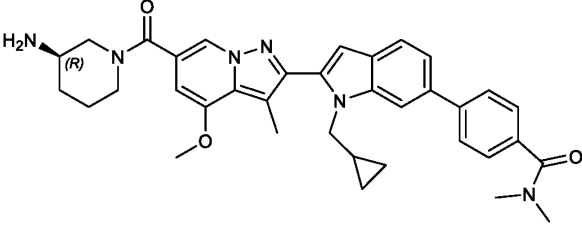
226	 N-[5-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)pyridin-2-yl]acetamide Analytical Data: 610.3; 1.721 min (Method E)
-----	--

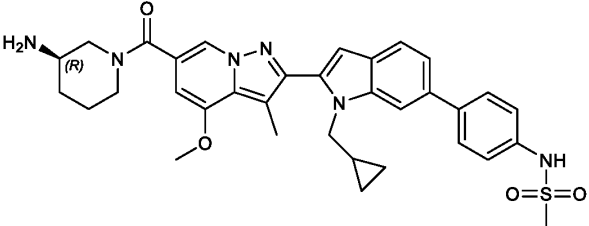
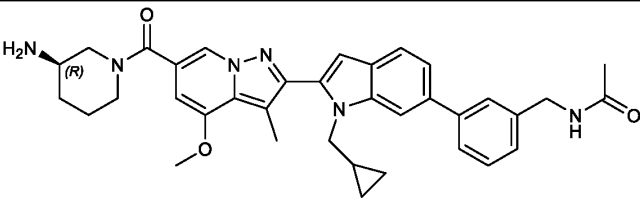
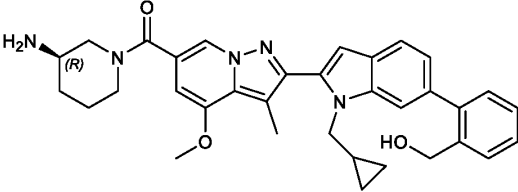
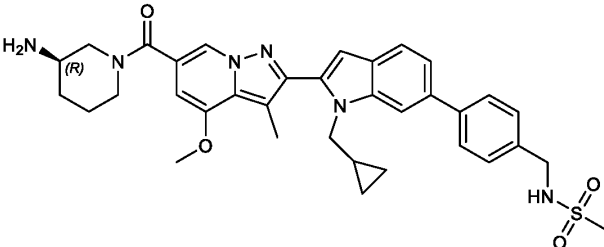
Compounds of Examples 227 to 240 in Table 27 were prepared following a procedure similar to the preparation of a compound of Example 29, using the Intermediate 23D and *tert*-butyl (R)-piperidin-3-ylcarbamate in amide formation and the

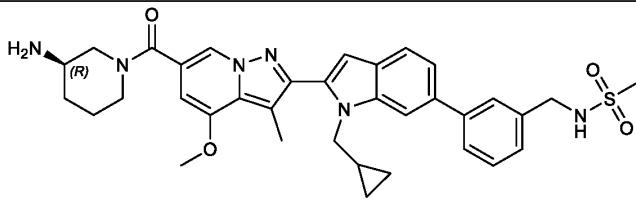
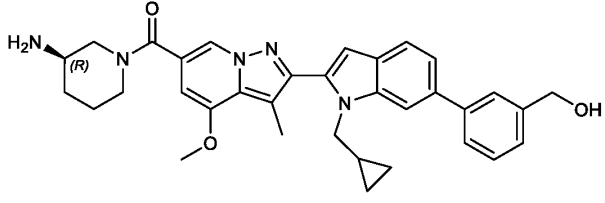
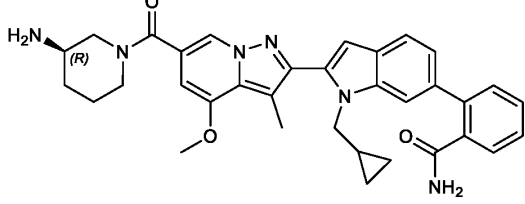
5 appropriate boronic acid/boronate ester in Suzuki coupling reaction.

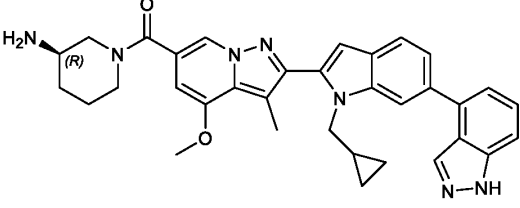
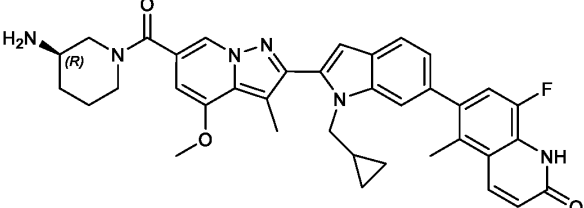
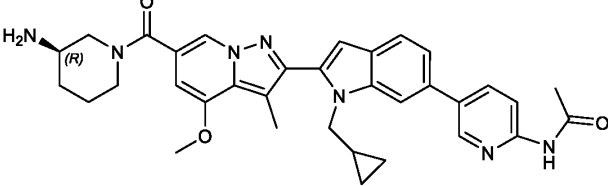
Table 27

Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method 1)
227	 [3-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methanol Analytical Data: 564.3; 1.777 min (Method E)

228	 N-{[4-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methyl}acetamide Analytical Data: 605.3; 1.602 min (Method E)
229	 4-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)benzamide Analytical Data: 577.3; 1.557 min (Method E)
230	 4-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-N,N-dimethylbenzamide Analytical Data: 605.3; 1.771 min (Method E)

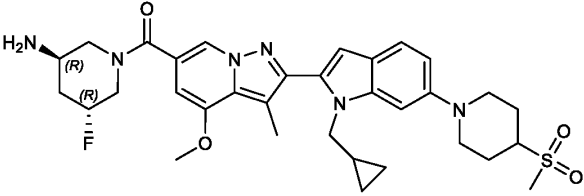
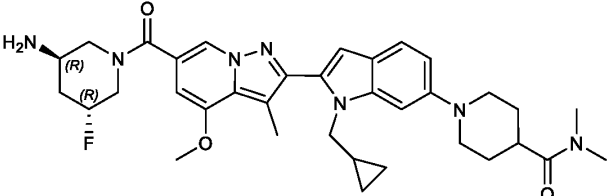
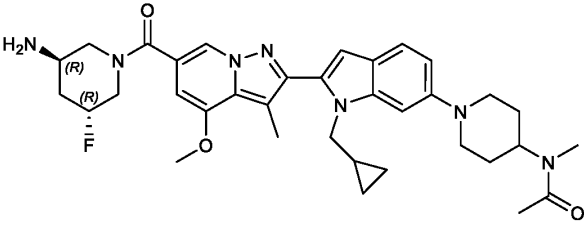
231	 N-[4-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methanesulfonamide Analytical Data: 625.3; 1.743min (Method E)
232	 N-{[3-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methyl}acetamide Analytical Data: 605.3, 1.699 min (Method E)
233	 [2-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methanol Analytical Data: 564.3; 1.831 min (Method E)
234	

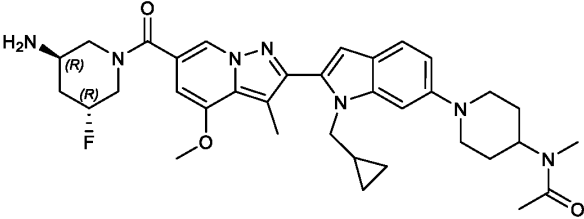
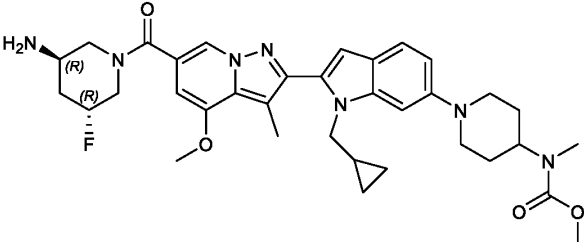
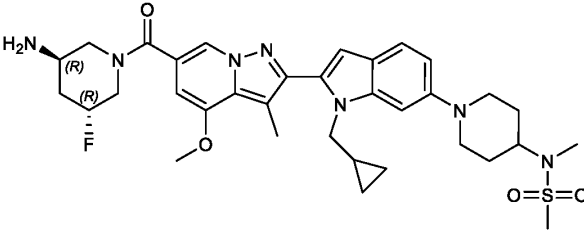
	N-{[4-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methyl}methanesulfonamide Analytical Data: 641.2; 1.763 min (Method E)
235	 N-{[3-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methyl}methanesulfonamide Analytical Data: 641.3; 1.802 min (Method E)
236	 [3-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methanol Analytical Data: 564.2; 1.738 min (Method E)
237	 2-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)benzamide Analytical Data: 577.3; 1.573 min (Method E)

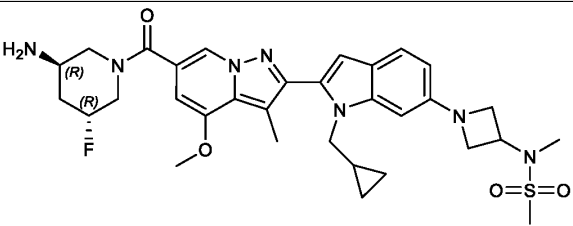
238	 (3R)-1-{2-[1-(Cyclopropylmethyl)-6-(1H-indazol-4-yl)-1H-indol-2-yl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}piperidin-3-amine Analytical Data: 574.3; 1.703 min (Method E)
239	 6-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-8-fluoro-5-methyl-1,2-dihydroquinolin-2-one Analytical Data: 633.3; 1.753 min (Method E)
240	 N-[5-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)pyridin-2-yl]acetamide Analytical Data: 592.3; 1.640 min (Method E)

Compounds of Examples 241 to 247 in Table 28 were prepared following a procedure similar to the preparation of a compound of Example 33, by Buchwald coupling of Intermediate 29A with appropriate amine.

Table 28

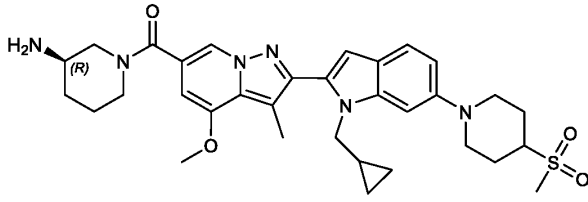
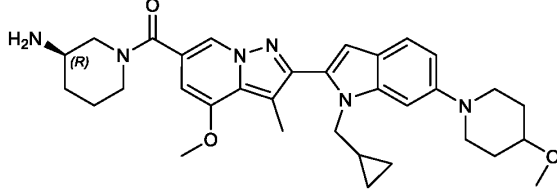
Example	Structure
	Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
241	 (3R,5R)-1-{2-[1-(Cyclopropylmethyl)-6-(4-methanesulfonylpiperidin-1-yl)-1H-indol-2-yl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-5-fluoropiperidin-3-amine Analytical Data: 637.2; 1.588 min (Method E)
242	 1-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-N,N-dimethylpiperidine-4-carboxamide Analytical Data: 630.4; 1.634 min (Method E)
243	 N-[1-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-N-methylacetamide Analytical Data: 630.4; 1.423min (Method E)

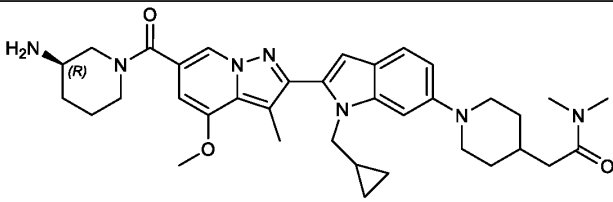
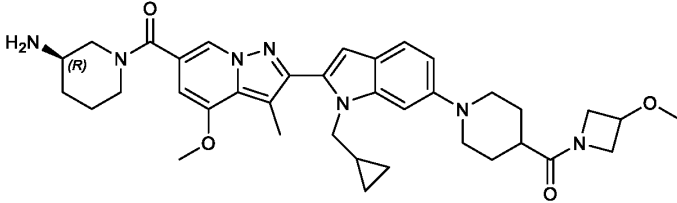
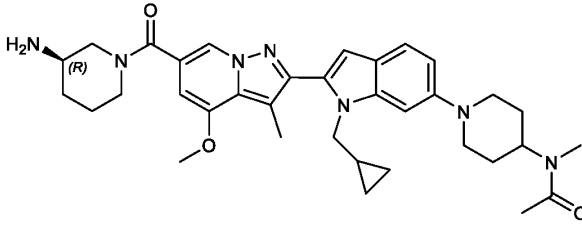
244	 N-[1-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-N-methylacetamide Analytical Data: 630.4; 1.617 min (Method E)
245	 Methyl N-[1-(2-{6-[(3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-N-methylcarbamate Analytical Data: 646.3; 1.895min (Method E)
246	 N-[1-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-N-methylmethanesulfonamide Analytical Data: 666.3; 1.733 min (Method E)

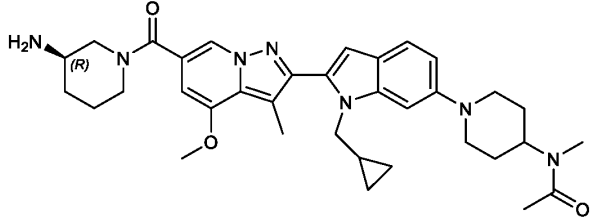
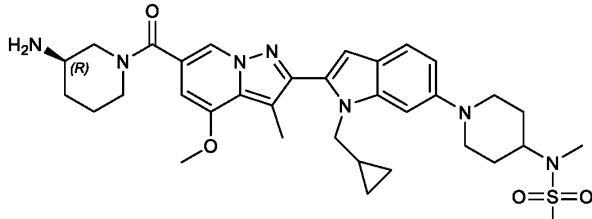
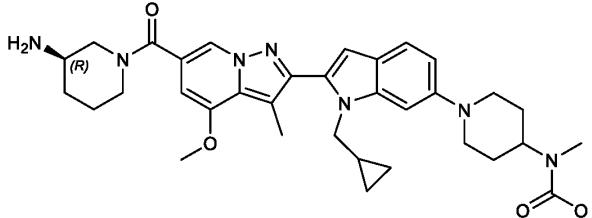
247	 N-[1-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)azetidin-3-yl]-N-methylmethanesulfonamide Analytical Data: 638.3; 1.670 min (Method E)
-----	---

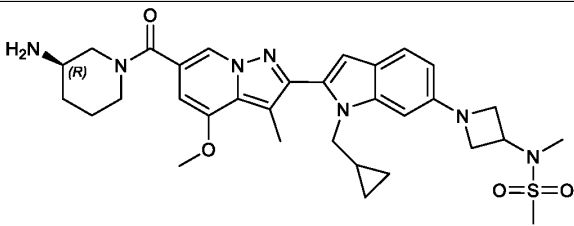
Compounds of Examples 248 to 256 in Table 29 were prepared following a procedure similar to the preparation of a compound of Example 33, by using Intermediate 23D and *tert*-butyl (R)-piperidin-3-ylcarbamate for amide formation and appropriate secondary amine in the Buchwald coupling reaction.

Table 29

Example	Structure Name Analytical Data: LC-MS m/z $[M+H]^+$; HPLC retention time (HPLC method)
248	 (3R)-1-{2-[1-(Cyclopropylmethyl)-6-(4-methanesulfonylpiperidin-1-yl)-1H-indol-2-yl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}piperidin-3-amine Analytical Data: 619.3; 1.530 min (Method E)
249	

	(3R)-1-{2-[1-(Cyclopropylmethyl)-6-(4-methoxypiperidin-1-yl)-1H-indol-2-yl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}piperidin-3-amine Analytical Data: 571.3, 1.837 min (Method E)
250	 2-[1-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-N,N-dimethylacetamide Analytical Data: 626.3; 1.647 min (Method E)
251	 (3R)-1-{2-[1-(Cyclopropylmethyl)-6-[4-(3-methoxyazetidine-1-carbonyl)piperidin-1-yl]-1H-indol-2-yl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}piperidin-3-amine Analytical Data: 654.4; 1.565 min (Method E)
252	 N-[1-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-N-methylacetamide Analytical Data: 612.4; 1.571 min (Method E)

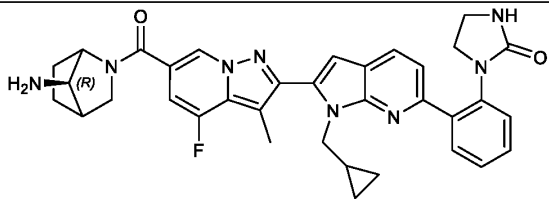
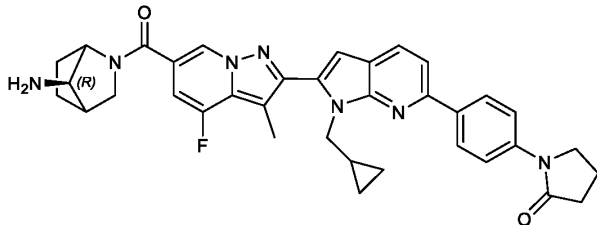
253	 N-[1-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-N-methylacetamide Analytical Data: 612.4; 1.566 min (Method E)
254	 N-[1-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-N-methylmethanesulfonamide Analytical Data: 648.3; 1.677 min (Method E)
255	 Methyl N-[1-(2-{6-[(3R)-3-aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-N-methylcarbamate Analytical Data: 628.4; 1.840 min (Method E)

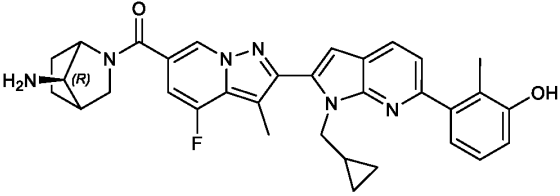
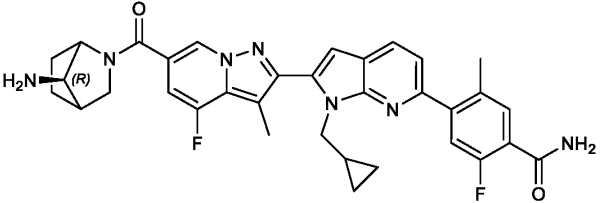
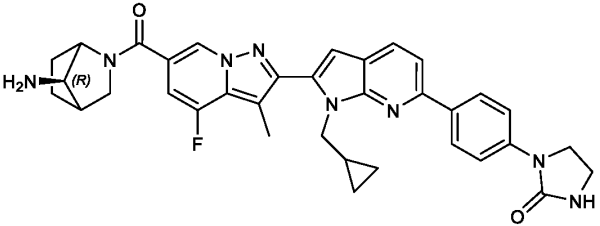
256	 N-[1-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)azetidin-3-yl]-N-methylmethanesulfonamide Analytical Data: 620.3; 1.631 min (Method E)
-----	---

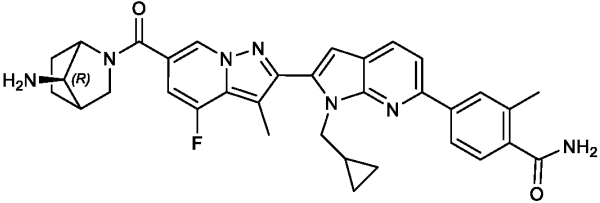
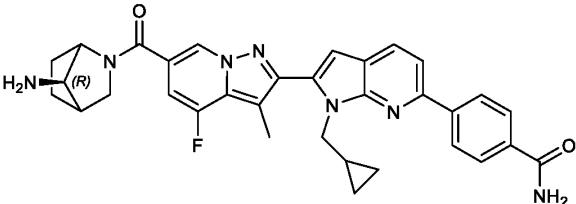
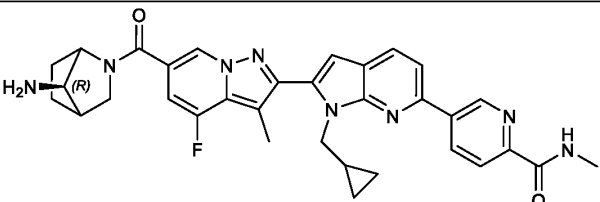
Compounds of Examples 257 to 264 in Table 30 were prepared following a procedure similar to the preparation of a compound of Example 40, using Suzuki coupling of Intermediate 39E with appropriate boronic acid or boronate ester.

5

Table 30

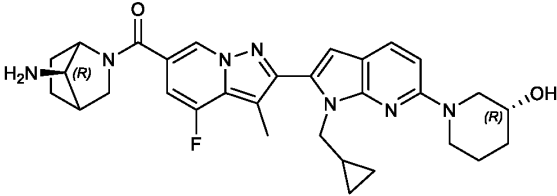
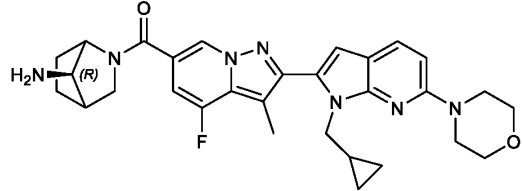
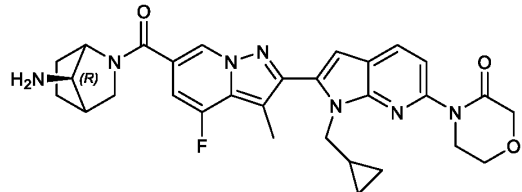
Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
257	 1-[2-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)phenyl]imidazolidin-2-one Analytical Data: 619.2; 1.678 min (Method E)
258	

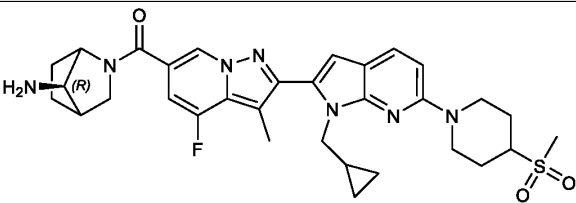
	1-[4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)phenyl]pyrrolidin-2-one Analytical Data: 618.3; 1.984 min (Method E)
259	 3-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-methylphenol Analytical Data: 565.3; 1.900 min (Method E)
260	 4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluoro-5-methylbenzamide Analytical Data: 610.3; 1.760 min (Method E)
261	 1-[4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)phenyl]imidazolidin-2-one Analytical Data: 619.4; 1.844 min (Method E)

262	 4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-methylbenzamide Analytical Data: 592.4; 1.734 min (Method E)
263	 4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)benzamide Analytical Data: 578.3; 1.682 min (Method E)
264	 5-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-N-methylpyridine-2-carboxamide Analytical Data: 593.3; 1.783 min (Method E)

Compounds of Examples 265 to 268 in Table 31 were prepared following a procedure similar to the preparation of a compound of Example 50, using Intermediate 5 39E and appropriate secondary amine in Buchwald coupling reaction.

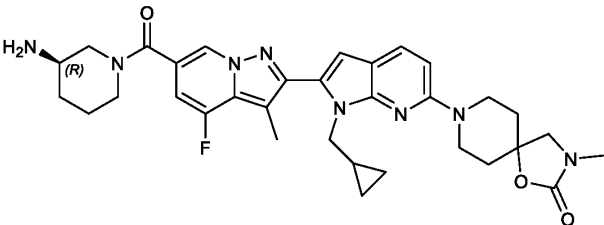
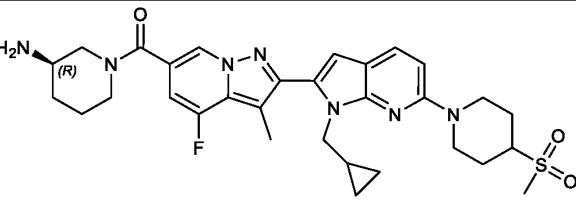
Table 31

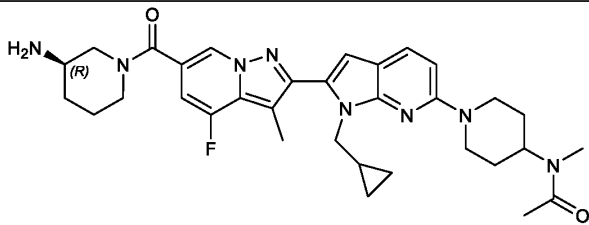
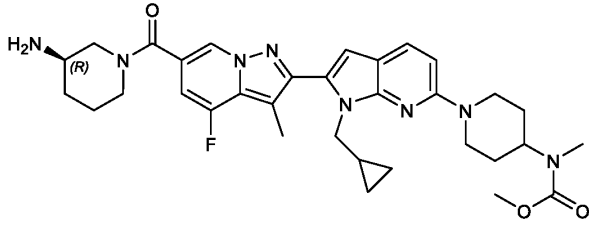
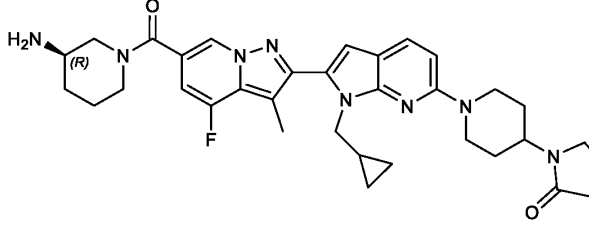
Example	Structure
	Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
265	 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-((R)-3-hydroxypiperidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 558.4; 5.795 min (Method C)
266	 (7R)-2-{2-[1-(Cyclopropylmethyl)-6-(morpholin-4-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine Analytical Data: 544.3; 1.668 min (Method E)
267	 4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)morpholin-3-one Analytical Data: 558.3; 1.595 min (Method E)

268	 (7R)-2-{2-[1-(Cyclopropylmethyl)-6-(4-methanesulfonylpiperidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine Analytical Data: 620.2; 1.713 min (Method E)
-----	--

Compounds of Examples 269 to 273 in Table 32 were prepared following a procedure similar to the preparation of a compound of Example 50, using Intermediate 39D and *tert*-butyl (R)-piperidin-3-ylcarbamate in amide formation and with appropriate secondary amine in Buchwald coupling reaction.

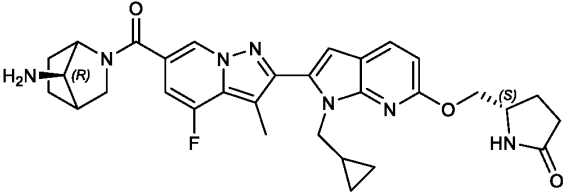
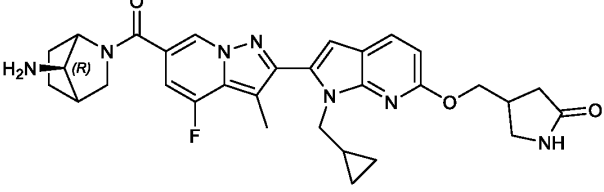
Table 32

Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
269	 8-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-methyl-1-oxa-3,8-diazaspiro[4.5]decan-2-one Analytical Data: 615.3; 1.703 min (Method E)
270	

	(3R)-1-{2-[1-(Cyclopropylmethyl)-6-(4-methanesulfonylpiperidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}piperidin-3-amine Analytical Data: 608.3; 1.558 min (Method E)
271	 N-[1-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)piperidin-4-yl]-N-methylacetamide Analytical Data: 601.3; 1.618 min (Method E)
272	 Methyl N-[1-(2-{6-[(3R)-3-aminopiperidine-1-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)piperidin-4-yl]-N-methylcarbamate Analytical Data: 617.3; 1.905min (Method E)
273	 1-[1-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)piperidin-4-yl]pyrrolidin-2-one Analytical Data: 613.3; 1.640 min (Method E)

Compounds of Examples 274 and 275 in Table 33 were prepared following a procedure similar to the preparation of a compound of Example 50, using Intermediate 39E with appropriate primary alcohol in Buchwald coupling reaction.

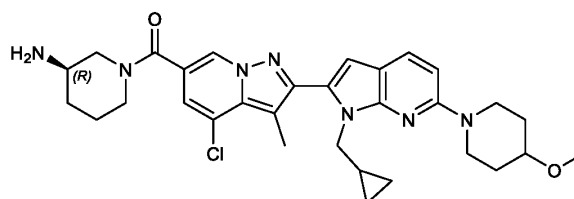
Table 33

Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
274	 (5S)-5-([(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)oxy)methyl]pyrrolidin-2-one Analytical Data: 572.2; 1.453 min (Method E)
275	 4-([(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)oxy)methyl]pyrrolidin-2-one (mixture of diastereomers) Analytical Data: 572.4; 1.519 min (Method E)

5

Example 276

(3R)-1-{4-Chloro-2-[1-(cyclopropylmethyl)-6-(4-methoxypiperidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}piperidin-3-amine

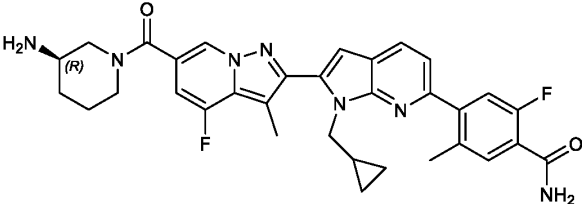
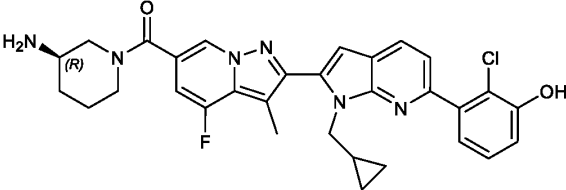


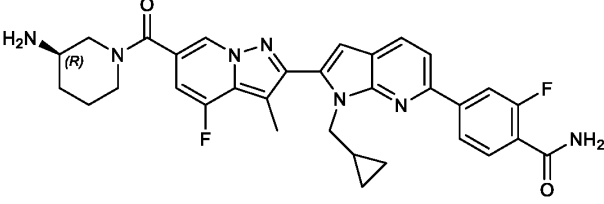
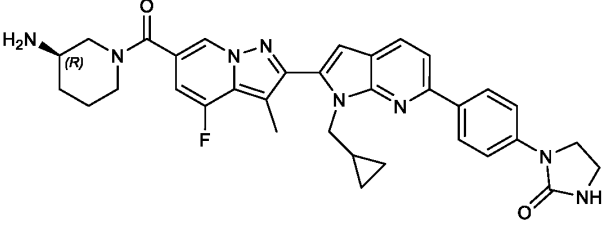
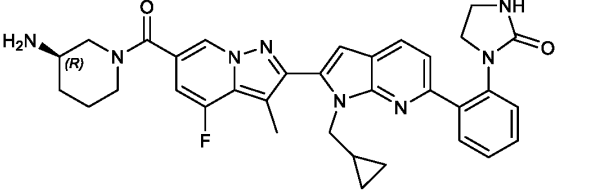
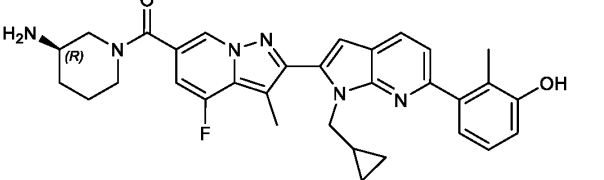
Compound of Example 276 was prepared following a procedure similar to the preparation of a compound of Example 50, using Intermediate 24 to carboxylic acid and tert-butyl (R)-piperidin-3-ylcarbamate in amide formation and with appropriate secondary amine in Buchwald coupling reaction. LC-MS m/z: 576.3 [M+H]⁺; HPLC retention time:

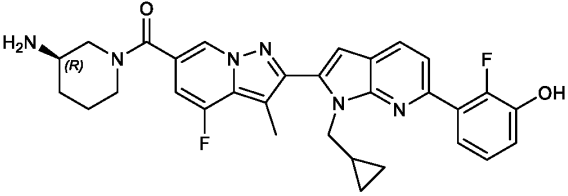
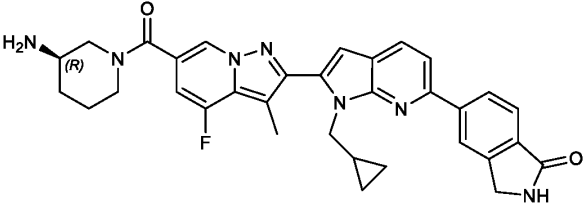
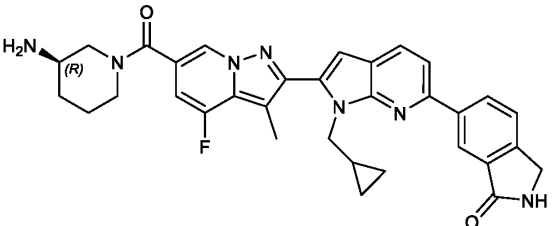
5 1.649 min (method F)

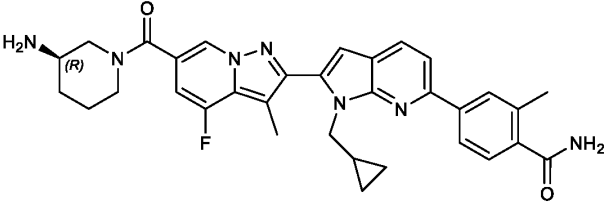
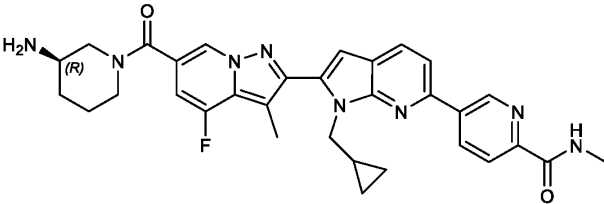
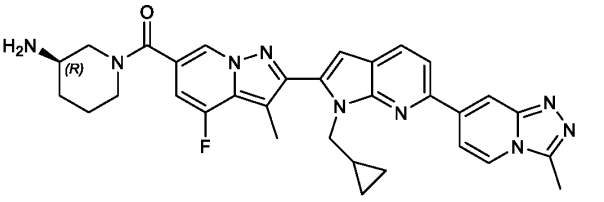
Compounds of Examples 277 to 288 in Table 34 were prepared following a procedure similar to the preparation of a compound of Example 54, by using Intermediate 39D and *tert-butyl* (R)-piperidin-3-ylcarbamate in amide formation and appropriate
 10 boronic acid or boronate ester in Suzuki coupling reaction.

Table 34

Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
277	 4-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluoro-5-methylbenzamide Analytical Data: 598.3; 1.689 min (Method E)
278	 3-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-chlorophenol Analytical Data: 573.2; 1.777 min (Method E)

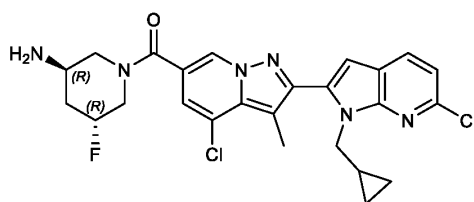
279	 4-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorobenzamide Analytical Data: 584.3; 1.603 min (Method E)
280	 1-[4-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)phenyl]imidazolidin-2-one Analytical Data: 607.3; 1.710 min (Method E)
281	 1-[2-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)phenyl]imidazolidin-2-one Analytical Data: 607.3; 1.554 min (Method E)
282	 1-[4-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)phenyl]-2-methylphenol

	3-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-methylphenol Analytical Data: 555.3; 1.782 min (Method E)
283	 3-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorophenol Analytical Data: 557.3; 1.735 min (Method E)
284	 5-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2,3-dihydro-1H-isoindol-1-one Analytical Data: 578.3; 1.533 min (Method E)
285	 6-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2,3-dihydro-1H-isoindol-1-one Analytical Data: 578.3, 1.625 min (Method E)

286	 4-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-methylbenzamide Analytical Data: 580.3; 1.618 min (Method E)
287	 5-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-N-methylpyridine-2-carboxamide Analytical Data: 581.2; 1.693 min (Method E)
288	 (3R)-1-{2-[1-(Cyclopropylmethyl)-6-{3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl]-1H-pyrrolo[2,3-b]pyridin-2-yl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}piperidin-3-amine Analytical Data: 578.3; 1.441 min (Method E)

Example 289

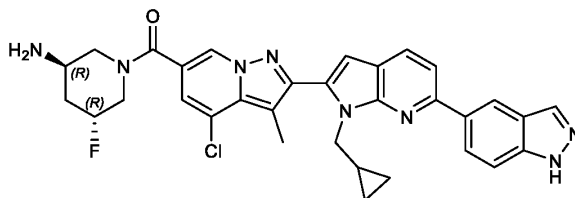
(3R,5R)-1-{4-Chloro-2-[6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-5-fluoropiperidin-3-amine



Compound of Example 289 was prepared following a procedure similar to the preparation of a compound of Example 53 by using Intermediate 24 to carboxylic acid and tert-butyl ((3R,5R)-5-fluoropiperidin-3-yl)carbamate in amide formation. LC-MS
 5 m/z: 515.1 [M+H]⁺; HPLC retention time: 2.048 min (Method E).

Example 290

(3R,5R)-1-((4-Chloro-2-[1-(cyclopropylmethyl)-6-(1H-indazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-amine

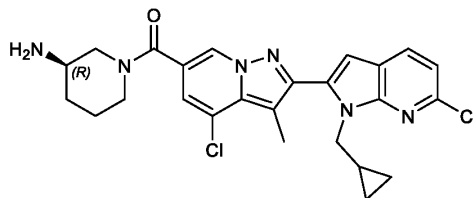


10

Compound of Example 290 was prepared following a procedure similar to the preparation of a compound of Example 54 by using Intermediate 24 to carboxylic acid and tert-butyl ((3R,5R)-5-fluoropiperidin-3-yl)carbamate in amide formation and appropriate boronic acid or boronate ester in Suzuki coupling reaction. LC-MS m/z: 597.2
 15 [M+H]⁺; HPLC retention time: 1.878 min (Method E).

Example 291

(3R)-1-((4-Chloro-2-[6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)piperidin-3-amine



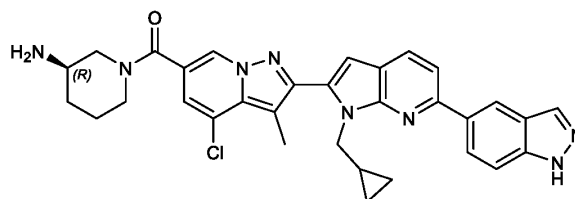
20

Compound of Example 291 was prepared following a procedure similar to the preparation of a compound of Example 53, by using Intermediate 24 to carboxylic acid

and tert-butyl (R)-piperidin-3-ylcarbamate in amide formation. LC-MS m/z: 497.1 [M+H]⁺; HPLC retention time: 1.992 min (Method E).

Example 292

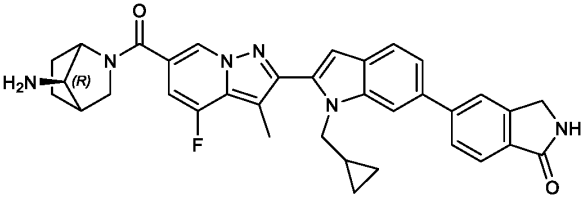
- 5 (3R)-1-{4-chloro-2-[1-(Cyclopropylmethyl)-6-(1H-indazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}piperidin-3-amine

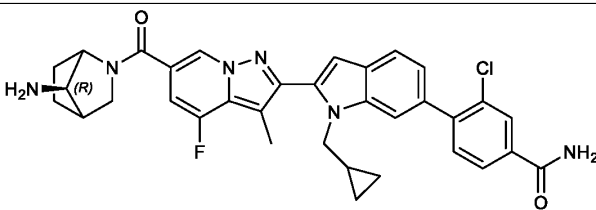
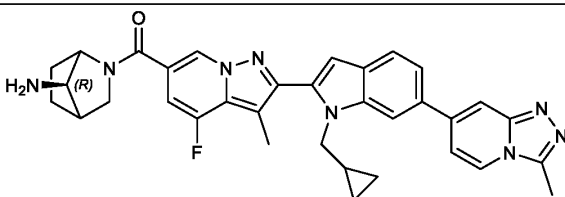


- Compound of Example 292 was prepared following a procedure similar to the preparation of a compound of Example 54 by using Intermediate 24 to carboxylic acid and tert-butyl (R)-piperidin-3-ylcarbamate in amide formation and appropriate boronic acid or boronate ester in Suzuki coupling reaction. LC-MS m/z: 579.2 [M+H]⁺; HPLC retention time: 1.787 min (Method E)

- Compounds of Examples 293 to 295 in Table 35 were prepared following a procedure similar to the preparation of a compound of Example 58, by Suzuki coupling of Intermediate 58E with appropriate boronic acid.

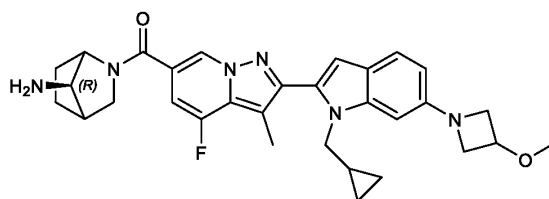
Table 35

Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
293	 5-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-2,3-dihydro-1H-isoindol-1-one Analytical Data: 589.3; 1.808 min (Method E)

294	 4-(2-({6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-3-chlorobenzamide Analytical Data: 611.3; 1.880 min (Method E)
295	 (7R)-2-{2-[1-(Cyclopropylmethyl)-6-{3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl}-1H-indol-2-yl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine Analytical Data: 589.4; 1.784 min (Method D)

Example 296

(7R)-2-{2-[1-(Cyclopropylmethyl)-6-(3-methoxyazetidin-1-yl)-1H-indol-2-yl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine

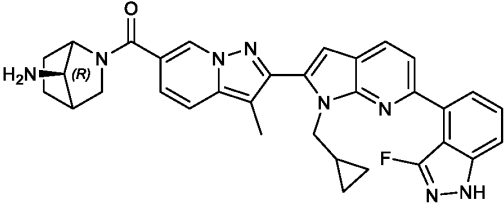
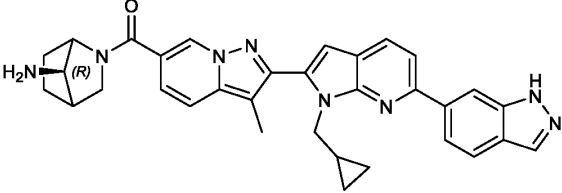
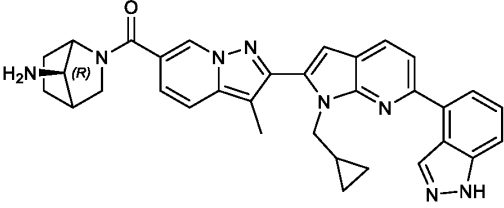


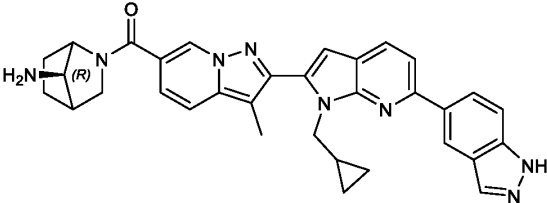
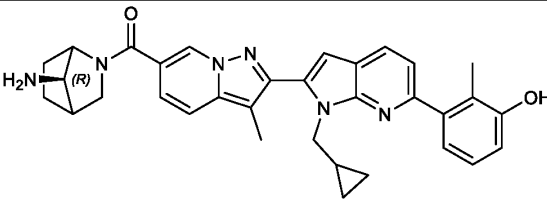
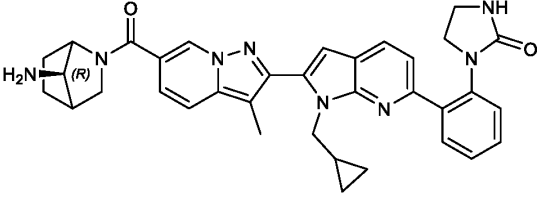
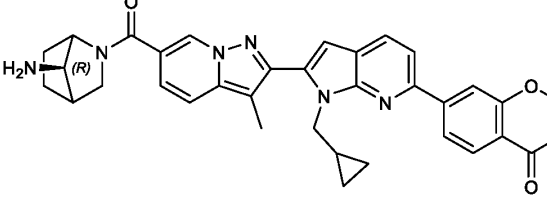
5

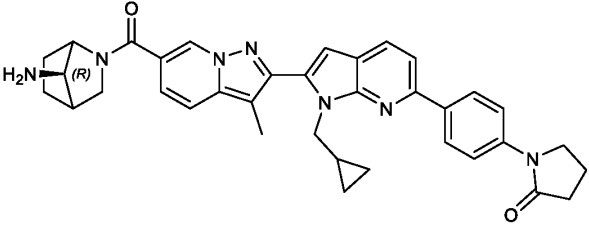
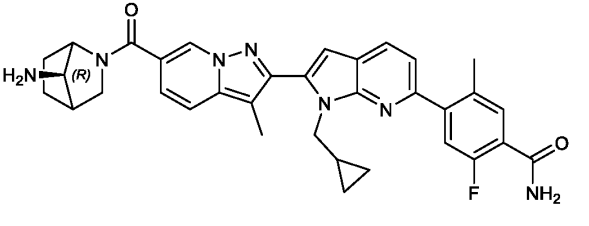
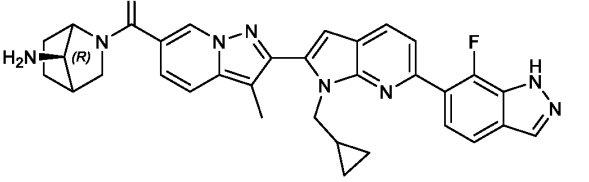
Compound of Example 296 was prepared following a procedure similar to the preparation of a compound of Example 50, by using Intermediate 58E and appropriate secondary amine in Buchwald coupling reaction. LC-MS m/z : 543.3 $[M+H]^+$; HPLC retention time: 2.028 min (Method E).

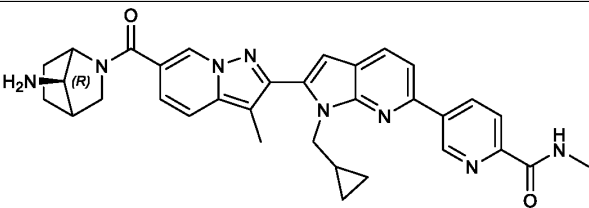
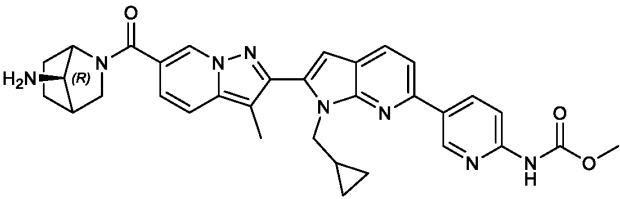
Compounds of Examples 297 to 308 in Table 36 were prepared following a procedure similar to the preparation of a compound of Example 64, by Suzuki coupling of Intermediate 64E with appropriate boronic acid.

Table 36

Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
297	 (7R)-2-{2-[1-(Cyclopropylmethyl)-6-(3-fluoro-1H-indazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine Analytical Data: 575.3; 1.56min (Method E)
298	 (7R)-2-{2-[1-(Cyclopropylmethyl)-6-(1H-indazol-6-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine Analytical Data: 557.2, 1.754min (Method E)
299	 (7R)-2-{2-[1-(Cyclopropylmethyl)-6-(1H-indazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine

	Analytical Data: 557.2; 1.749min (Method E)
300	 (7R)-2-{2-[1-(Cyclopropylmethyl)-6-(1H-indazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine Analytical Data: 557.2; 1.702 min (Method E)
301	 3-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-methylphenol Analytical Data: 547.3; 1.491min (Method E)
302	 1-[2-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)phenyl]imidazolidin-2-one Analytical Data: 601.3; 1.395 min (Method E)
303	

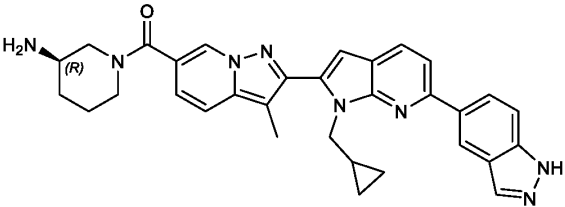
	4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-methoxybenzamide Analytical Data: 590.3; 1.752min (Method E)
304	 1-[4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)phenyl]pyrrolidin-2-one Analytical Data: 600.4; 1.875min (Method E)
305	 4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluoro-5-methylbenzamide Analytical Data: 592.3; 1.433min (Method E)
306	 (7R)-2-{2-[1-(Cyclopropylmethyl)-6-(7-fluoro-1H-indazol-6-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine Analytical Data: 575.3, 2.036 min (Method E)

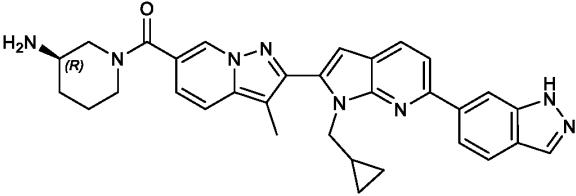
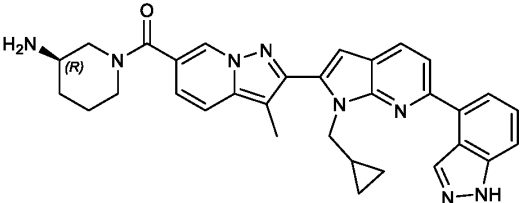
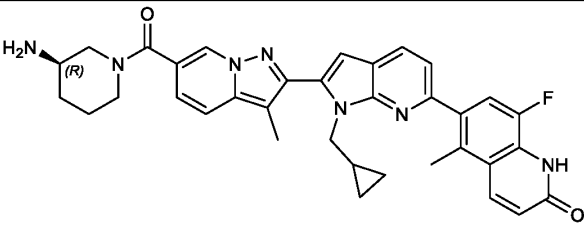
307	 5-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-N-methylpyridine-2-carboxamide Analytical Data: 575.4; 1.508 min (Method E)
308	 Methyl N-[5-(2-{6-[(7R)-7-amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)pyridin-2-yl]carbamate Analytical Data: 591.4; 1.748min (Method E)

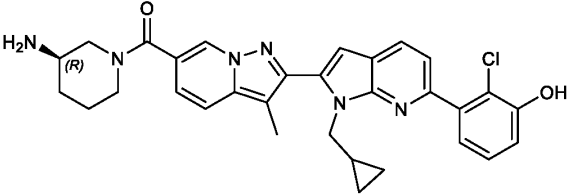
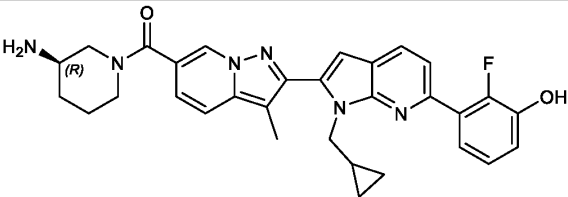
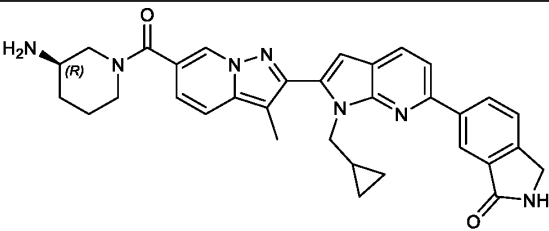
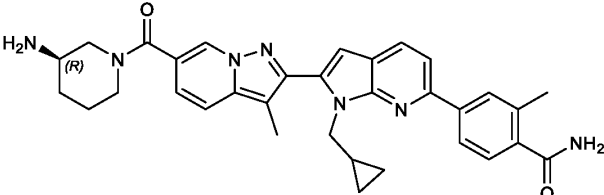
Compounds of Examples 309 to 317 in Table 37 were prepared following a procedure similar to the preparation of a compound of Example 64, by using Intermediate 64D and tert-butyl (R)-piperidin-3-ylcarbamate in amide formation and appropriate

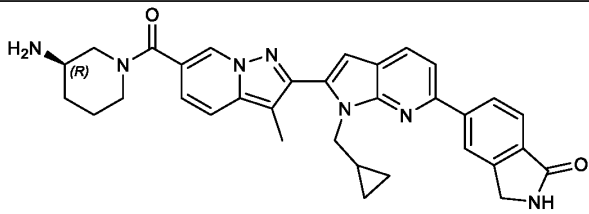
5 boronic acid / boronate ester in Suzuki coupling.

Table 37

Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
309	

	(3R)-1-{2-[1-(Cyclopropylmethyl)-6-(1H-indazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}piperidin-3-amine Analytical Data: 545.3; 1.523 min (Method E)
310	 (3R)-1-{2-[1-(Cyclopropylmethyl)-6-(1H-indazol-6-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}piperidin-3-amine Analytical Data: 545.3; 1.608min (Method E)
311	 (3R)-1-{2-[1-(Cyclopropylmethyl)-6-(1H-indazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}piperidin-3-amine Analytical Data: 545.3; 1.581 min (Method E)
312	 6-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-8-fluoro-5-methyl-1,2-dihydroquinolin-2-one Analytical Data: 604.4; 1.454min (Method E)

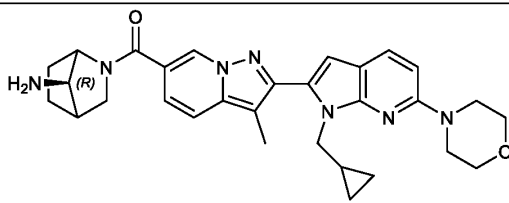
313	 3-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-chlorophenol Analytical Data: 555.3; 1.606 min (Method E)
314	 3-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorophenol Analytical Data: 539.3; 1.579 min (Method E)
315	 6-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2,3-dihydro-1H-isoindol-1-one Analytical Data: 560.4; 1.507 min (Method E)
316	

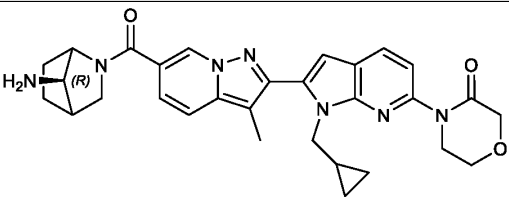
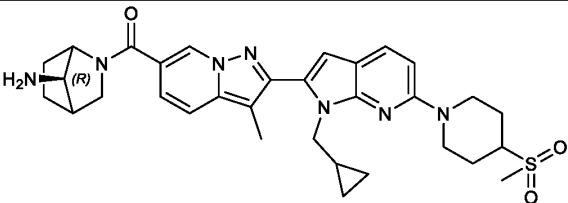
	4-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-methylbenzamide Analytical Data: 562.4; 1.415min (Method E)
317	 5-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2,3-dihydro-1H-isoindol-1-one Analytical Data: 560.4; 1.391 min (Method E)

Compounds of Examples 318 to 320 in Table 38 were prepared following a procedure similar to the preparation of a compound of Example 76, by Buchwald coupling of Intermediate 64E with appropriate amines.

5

Table 38

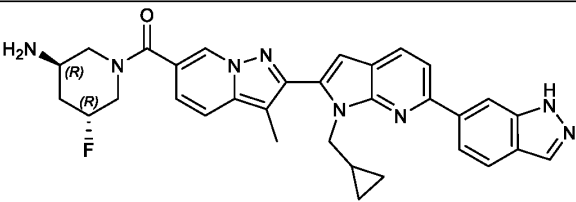
Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
318	 (7R)-2-{2-[1-(Cyclopropylmethyl)-6-(morpholin-4-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine Analytical Data: 526.3, 1.782 min (Method E)

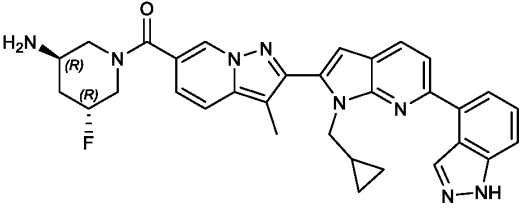
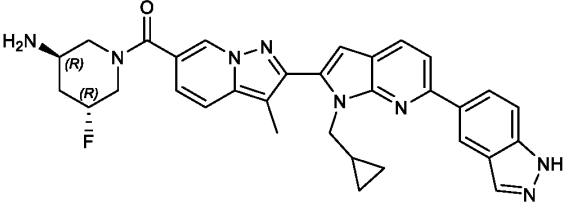
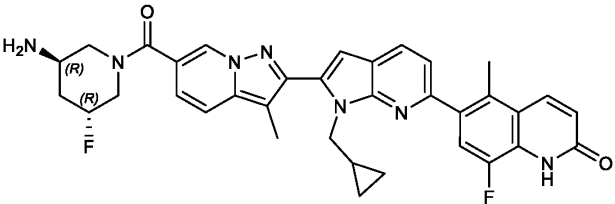
319	 4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)morpholin-3-one Analytical Data: 540.4; 1.458 min (Method E)
320	 (7R)-2-{2-[1-(Cyclopropylmethyl)-6-(4-methanesulfonylpiperidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine Analytical Data: 602.2; 1.326min (Method E)

Compounds of Examples 321 to 324 in Table 39 were prepared following a procedure similar to the preparation of a compound of Example 81, by Suzuki coupling of Intermediate 81A with appropriate boronic acid.

5

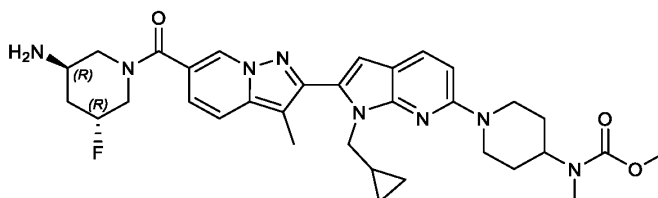
Table 39

Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
321	

	(3R,5R)-1-{2-[1-(Cyclopropylmethyl)-6-(1H-indazol-6-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-5-fluoropiperidin-3-amine Analytical Data: 563.3; 2.191 min (Method E)
322	 (3R,5R)-1-{2-[1-(Cyclopropylmethyl)-6-(1H-indazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-5-fluoropiperidin-3-amine Analytical Data: 563.2; 1.744min (Method E)
323	 (3R,5R)-1-{2-[1-(Cyclopropylmethyl)-6-(1H-indazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-5-fluoropiperidin-3-amine Analytical Data: 563.3; 1.670min (Method E)
324	 6-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-8-fluoro-5-methyl-1,2-dihydroquinolin-2-one Analytical Data: 622.3; 1.461min (Method E)

Example 325

Methyl N-[1-(2-{6-[(3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)piperidin-4-yl]-N-methylcarbamate



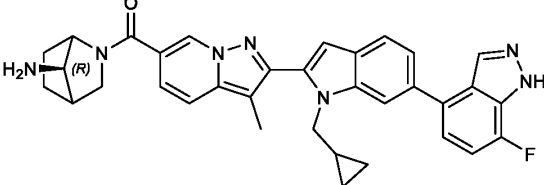
5

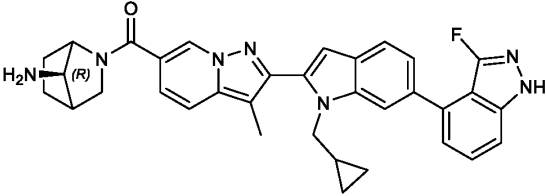
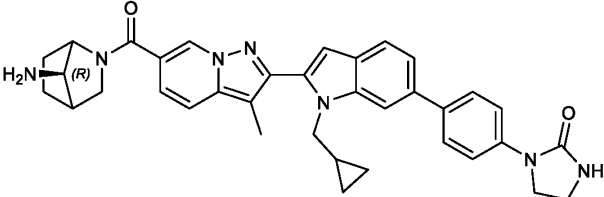
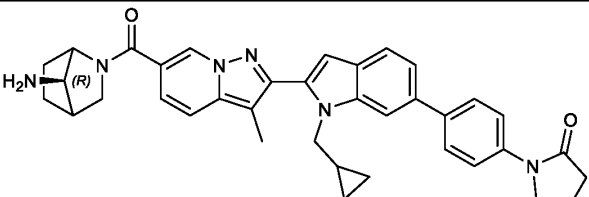
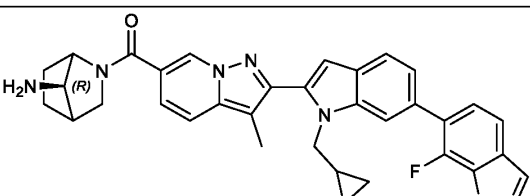
Compound of Example 325 was prepared following a procedure similar to the preparation of a compound of Example 87, by Buchwald coupling of Intermediate 81A with appropriate secondary amine. LC-MS m/z : 617 $[M+H]^+$; HPLC retention time: 1.530min (Method E).

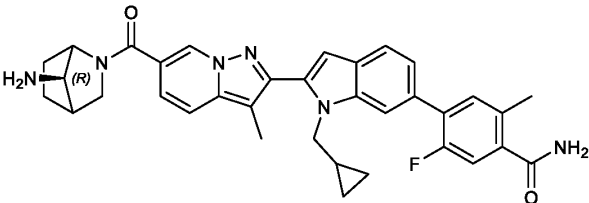
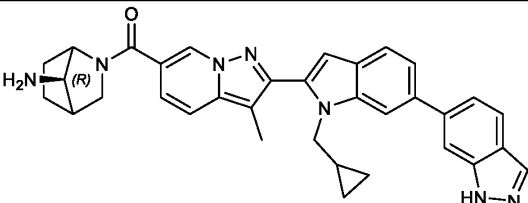
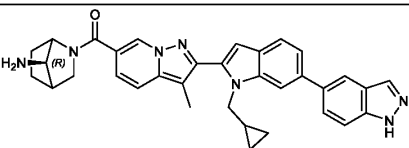
10

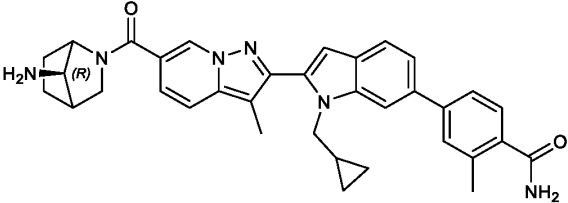
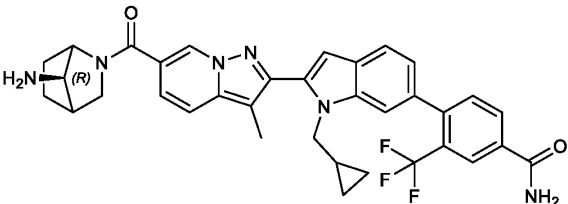
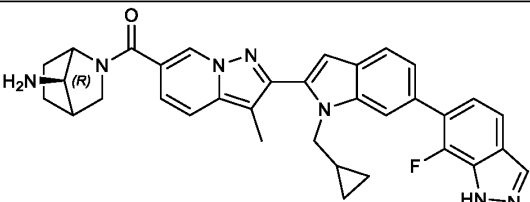
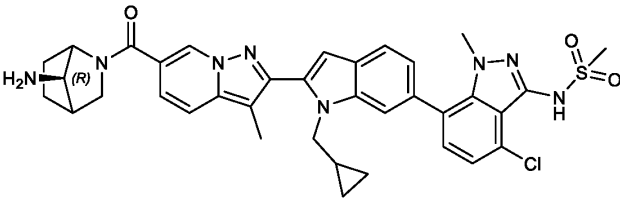
Compounds of Examples 326 to 341 in Table 40 were prepared following a procedure similar to the preparation of a compound of Example 89, by Suzuki coupling of Intermediate 89E with appropriate boronic acid or boronate ester.

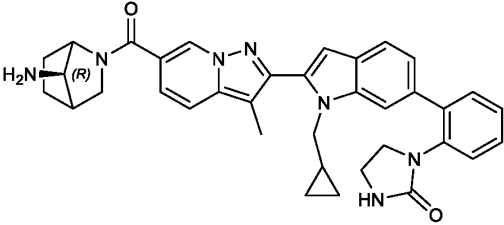
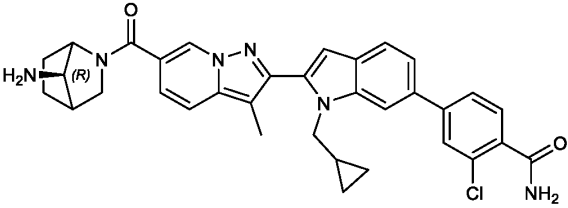
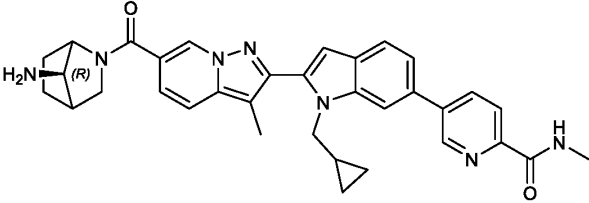
Table 40

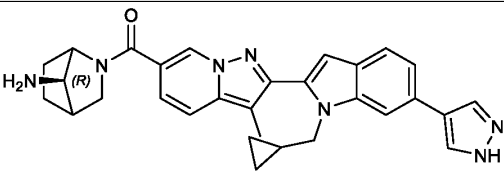
Example	Structure Name Analytical Data: LC-MS m/z $[M+H]^+$; HPLC retention time (HPLC method)
326	 (7R)-2-{2-[1-(Cyclopropylmethyl)-6-(7-fluoro-1H-indazol-4-yl)-1H-indol-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine Analytical Data: 574.3; 2.144 min (Method E)

327	 (7R)-2-{2-[1-(Cyclopropylmethyl)-6-(3-fluoro-1H-indazol-4-yl)-1H-indol-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine Analytical Data: 574.3; 2.173min (Method E)
328	 1-[4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]imidazolidin-2-one Analytical Data: 600.4; 1.762min (Method E)
329	 1-[4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]pyrrolidin-2-one Analytical Data: 599.4; 1.883 min (Method E)
330	

	(7R)-2-{2-[1-(Cyclopropylmethyl)-6-(7-fluoro-1H-indazol-6-yl)-1H-indol-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine Analytical Data: 574.4; 2.053min (Method E)
331	 4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-5-fluoro-2-methylbenzamide Analytical Data: 591.2; 1.481 min (Method E)
332	 (7R)-2-{2-[1-(Cyclopropylmethyl)-6-(1H-indazol-6-yl)-1H-indol-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine Analytical Data: 556.2; 1.772min (Method E)
333	 (7R)-2-{2-[1-(Cyclopropylmethyl)-6-(1H-indazol-5-yl)-1H-indol-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine Analytical Data: 556.2; 1.703 min (Method E)

334	 4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-2-methylbenzamide Analytical Data: 573.2; 1.383 min (Method E)
335	 4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-3-(trifluoromethyl)benzamide Analytical Data: 627.3; 1.493min (Method E)
336	 (7R)-2-{2-[1-(Cyclopropylmethyl)-6-(7-fluoro-1H-indazol-6-yl)-1H-indol-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine Analytical Data: 574.3; 2.128min (Method E)
337	

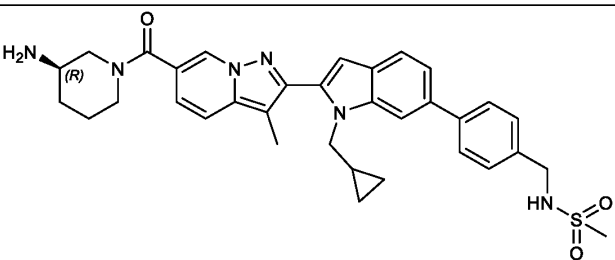
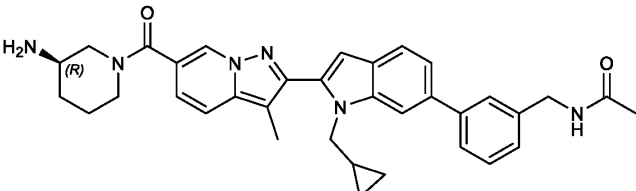
	N-[7-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-4-chloro-1-methyl-1H-indazol-3-yl]methanesulfonamide Analytical Data: 698.3; 2.217min (Method E)
338	 1-[2-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]imidazolidin-2-one Analytical Data: 601.4; 1.825min (Method E)
339	 4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-2-chlorobenzamide Analytical Data: 594.2; 1.755 min (Method E)
340	 5-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-N-methylpyridine-2-carboxamide Analytical Data: 574.2; 1.441min (Method E)

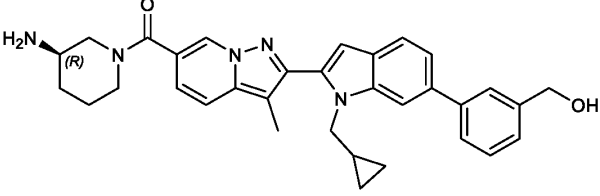
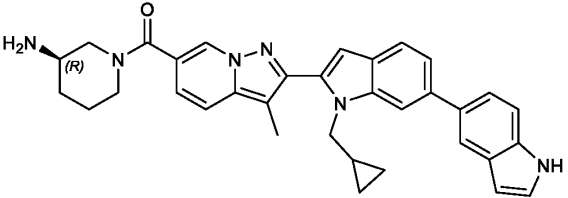
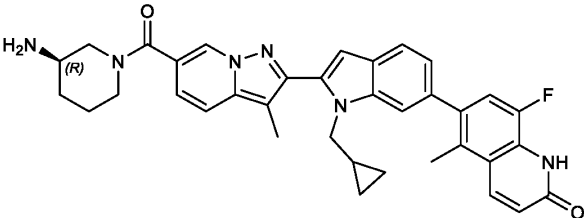
341	 (7R)-2-{2-[1-(Cyclopropylmethyl)-6-(1H-pyrazol-4-yl)-1H-indol-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine Analytical Data: 506.2; 1.554 min (Method E)
-----	--

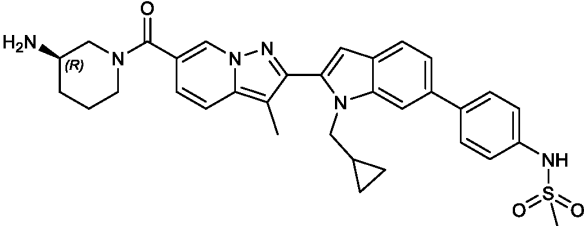
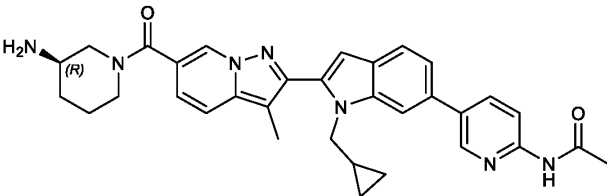
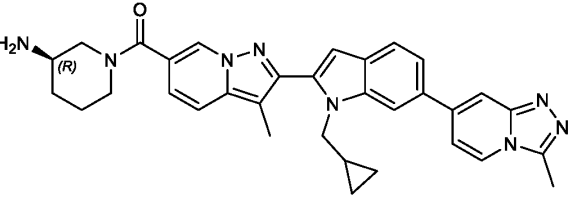
Compounds of Examples 342 to 349 in Table 41 were prepared following a procedure similar to the preparation of a compound of Example 92, by using Intermediate 89D and tert-butyl (R)-piperidin-3-ylcarbamate in amide formation and with appropriate

5 boronic acid or boronate ester in Suzuki coupling reaction.

Table 41

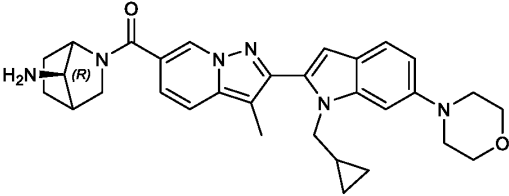
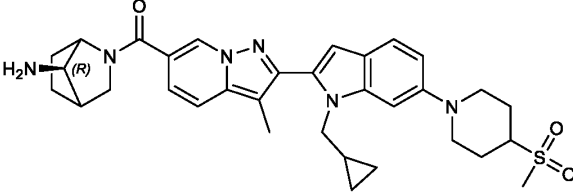
Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
342	 N-{[4-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methyl}methanesulfonamide Analytical Data: 611.2; 1.571min (Method E)
343	

	N-{[3-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methyl}acetamide Analytical Data: 575.3; 1.584 min (Method E)
344	 [3-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methanol Analytical Data: 534.3; 1.556 min (Method E)
345	 (3R)-1-{2-[1'-(Cyclopropylmethyl)-1H,1'H-[5,6'-biindole]-2'-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}piperidin-3-amine Analytical Data: 543.2; 1.869min (Method E)
346	 6-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-8-fluoro-5-methyl-1,2-dihydroquinolin-2-one Analytical Data: 603.3; 1.535 min (Method E)

347	 N-[4-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methanesulfonamide Analytical Data: 597.3; 1.625min (Method E)
348	 N-[5-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)pyridin-2-yl]acetamide Analytical Data: 562.3; 1.625min (Method E)
349	 (R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 559.3; 1.452min (Method E)

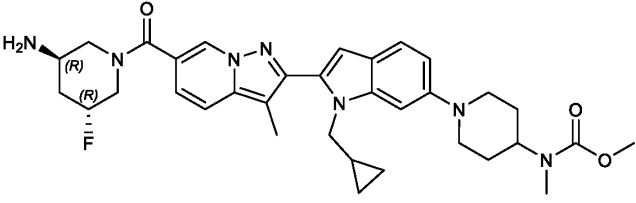
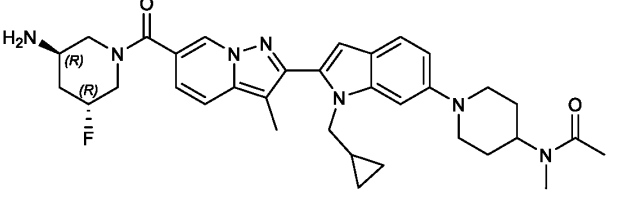
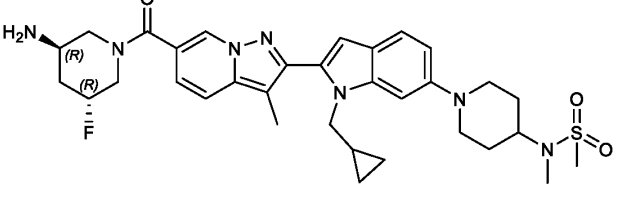
Compounds of Examples 350 and 351 in Table 42 were prepared following a procedure similar to the preparation of a compound of Example 91, by Buchwald coupling of Intermediate 89E with appropriate secondary amine.

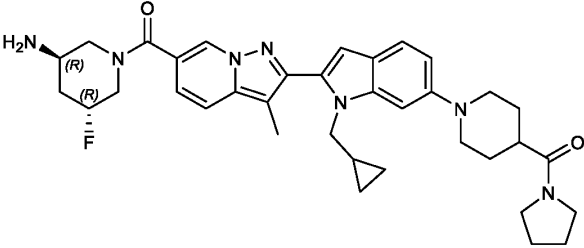
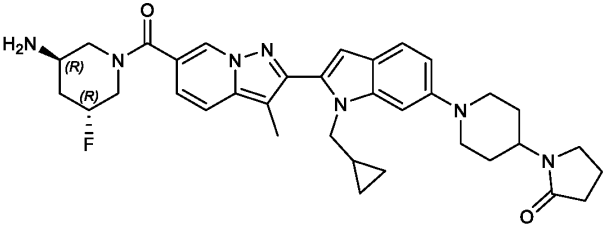
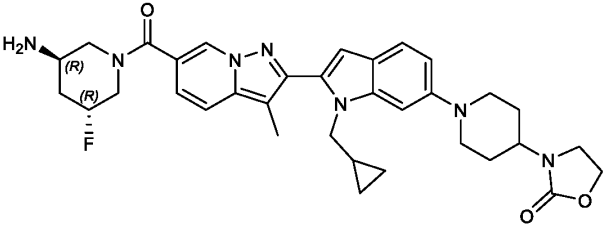
Table 42

Example	Structure
	Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
350	 (7R)-2-{2-[1-(Cyclopropylmethyl)-6-(morpholin-4-yl)-1H-indol-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine Analytical Data: 525.3; 1.755 min (Method E)
351	 (7R)-2-{2-[1-(Cyclopropylmethyl)-6-(4-methanesulfonylpiperidin-1-yl)-1H-indol-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine Analytical Data: 601.3; 1.500min (Method E)

Compounds of Examples 352 to 357 in Table 43 were prepared following a procedure similar to the preparation of a compound of Example 91, by using Intermediate 5 89D and tert-butyl ((3R,5R)-5-fluoropiperidin-3-yl)carbamate in amide formation and with appropriate secondary amine in Buchwald coupling reaction.

Table 43

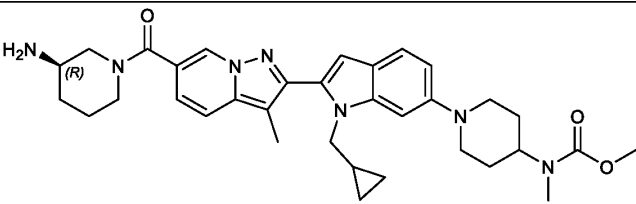
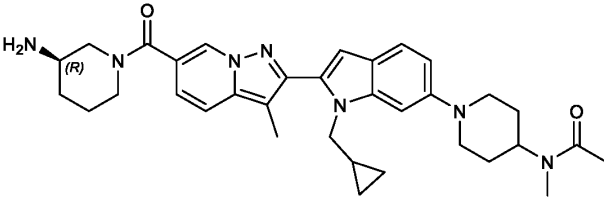
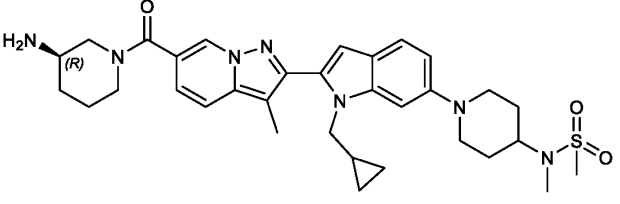
Example	Structure
	Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
352	 Methyl N-[1-(2-{6-[(3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-N-methylcarbamate Analytical Data: 616.3; 1.830min (Method E)
353	 N-[1-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-N-methylacetamide Analytical Data: 600.4, 1.059min (Method E)
354	 N-[1-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-N-methylmethanesulfonamide Analytical Data: 636.2; 1.656 min (Method E)

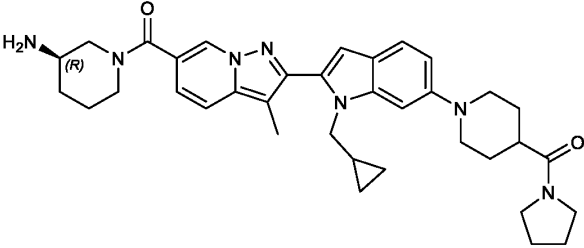
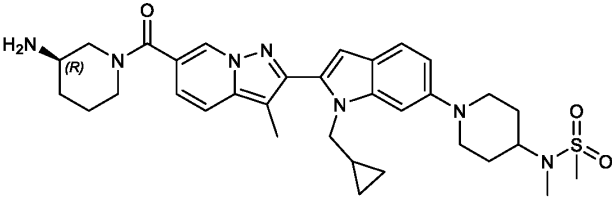
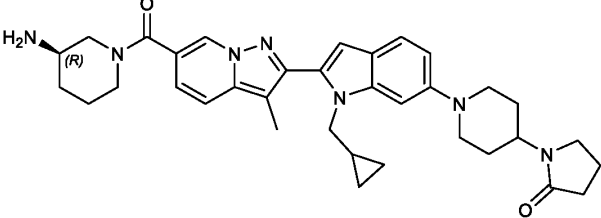
355	 (3R,5R)-1-{2-[1-(Cyclopropylmethyl)-6-[4-(pyrrolidine-1-carbonyl)piperidin-1-yl]-1H-indol-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-5-fluoropiperidin-3-amine Analytical Data: 626.4; 1.636 min (Method E)
356	 1-[1-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]pyrrolidin-2-one Analytical Data: 612.3; 1.512min (Method E)
357	 3-[1-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-1,3-oxazolidin-2-one Analytical Data: 614.3; 1.479 min (Method E)

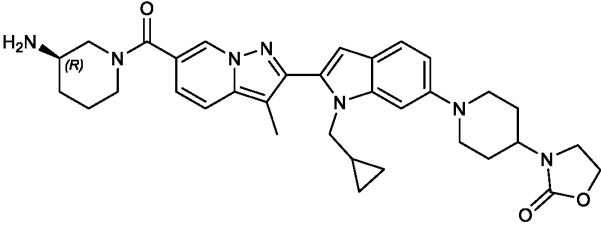
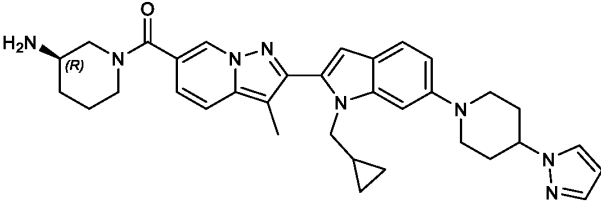
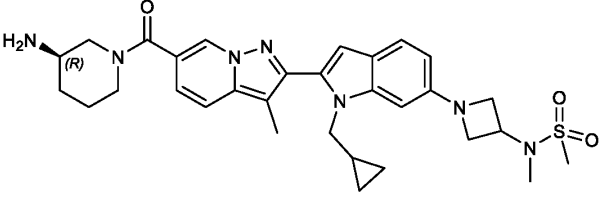
Compounds of Examples 358 to 366 in Table 44 were prepared following a procedure similar to the preparation of a compound of Example 91, by using Intermediate

89D and tert-butyl (R)-piperidin-3-ylcarbamate in amide formation and with appropriate secondary amine in Buchwald coupling reaction.

Table 44

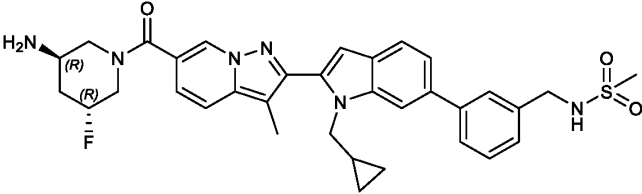
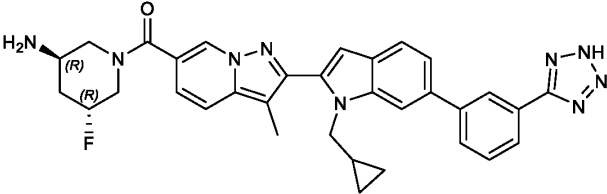
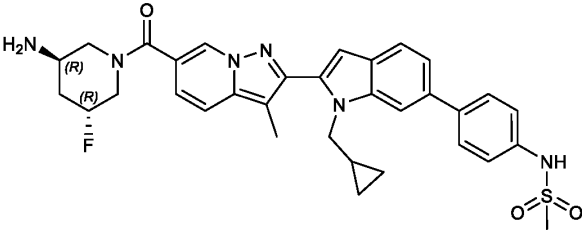
Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
358	 Methyl N-[1-(2-{6-[(3R)-3-aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-N-methylcarbamate Analytical Data: 598.4; 1.170 min (Method E)
359	 N-[1-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-N-methylacetamide Analytical Data: 582.4; 1.488 min (Method E)
360	 N-[1-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-N-methylmethanesulfonamide Analytical Data: 618.4; 1.063min (Method E)

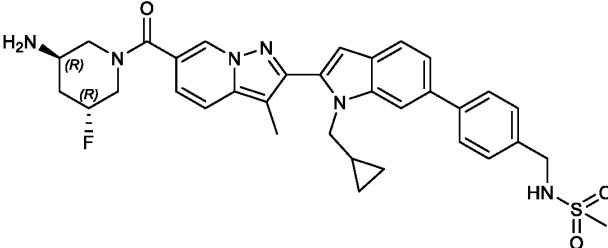
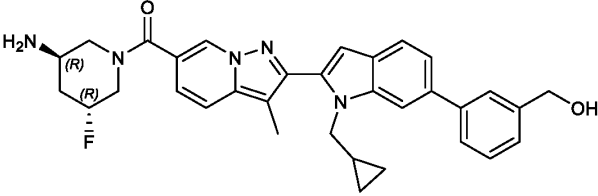
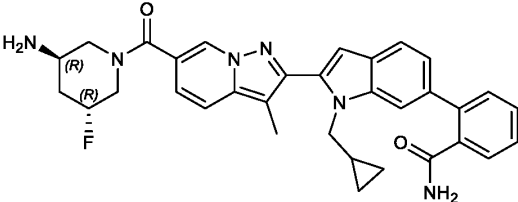
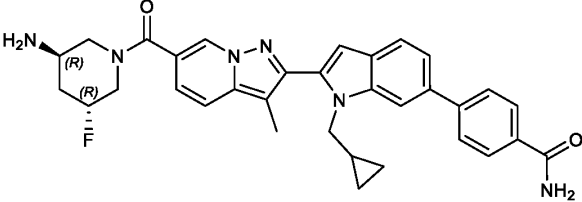
361	 (3R)-1-{2-[1-(Cyclopropylmethyl)-6-[4-(pyrrolidine-1-carbonyl)piperidin-1-yl]-1H-indol-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}piperidin-3-amine Analytical Data: 608.3; 1.591min (Method E)
362	 N-[1-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-N-methylmethanesulfonamide Analytical Data: 618.4; 1.063min (Method E)
363	 1-[1-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]pyrrolidin-2-one Analytical Data: 594.3; 1.448 min (Method E)

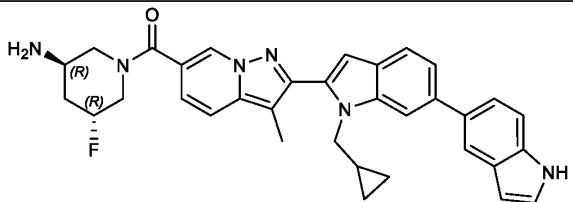
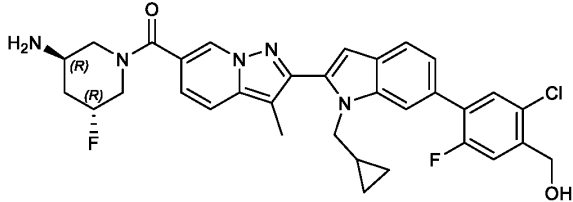
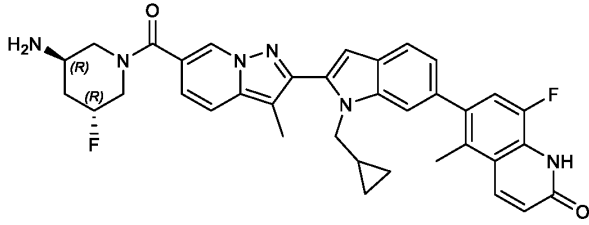
364	 3-[1-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-1,3-oxazolidin-2-one Analytical Data: 596.3; 1.412 min (Method E)
365	 (3R)-1-{2-[1-(Cyclopropylmethyl)-6-[4-(1H-pyrazol-1-yl)piperidin-1-yl]-1H-indol-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}piperidin-3-amine Analytical Data: 577.3; 1.628min (Method E)
366	 N-[1-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)azetidin-3-yl]-N-methylmethanesulfonamide Analytical Data: 590.3; 1.522min (Method E)

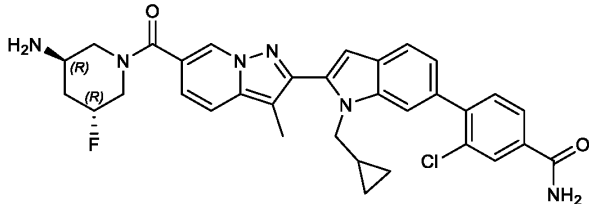
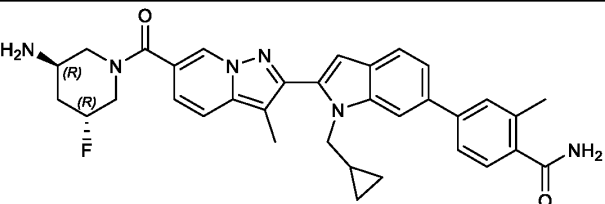
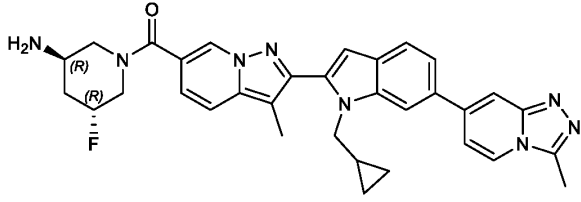
Compounds of Examples 367 to 379 in Table 45 were prepared following a procedure similar to the preparation of a compound of Example 92, by Suzuki coupling of Intermediate 92A with appropriate boronic acid or boronate ester.

Table 45

Example	Structure
	Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
367	 N-{[3-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methyl}methanesulfonamide Analytical Data: 629.2; 1.775min (Method E)
368	 (3R,5R)-1-{2-[1-(Cyclopropylmethyl)-6-[3-(2H-1,2,3,4-tetrazol-5-yl)phenyl]-1H-indol-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-5-fluoropiperidin-3-amine Analytical Data: 590.3; 1.369min (Method E)
369	 N-[4-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methanesulfonamide Analytical Data: 615.2; 1.713min (Method E)

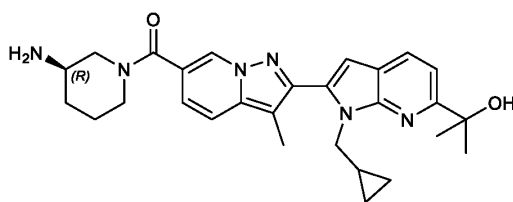
370	 N-{[4-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl)methyl}methanesulfonamide Analytical Data: 629.3; 1.738 min (Method E)
371	 [3-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]methanol Analytical Data: 552.3; 1.742 min (Method E)
372	 2-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)benzamide Analytical Data: 565.3; 1.536 min (Method E)
373	

	4-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)benzamide Analytical Data: 565.2; 1.531 min (Method E)
374	 (3R,5R)-1-{2-[1'-(Cyclopropylmethyl)-1H,1'H-[5,6'-biindole]-2'-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-5-fluoropiperidin-3-amine Analytical Data: 561.2; 1.943min (Method E)
375	 [4-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-2-chloro-5-fluorophenyl]methanol Analytical Data: 604.3; 1.915 min (Method E)
376	 6-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-8-fluoro-5-methyl-1,2-dihydroquinolin-2-one Analytical Data: 621.3; 1.557 min (Method E)

377	 4-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-3-chlorobenzamide Analytical Data: 599.3; 1.676 min (Method E)
378	 4-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-2-methylbenzamide Analytical Data: 579.4; 1.523min (Method E)
379	 (3R,5R)-1-{2-[1-(Cyclopropylmethyl)-6-{3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl}-1H-indol-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-5-fluoropiperidin-3-amine Analytical Data: 577.3; 1.501min (Method E)

Example 380

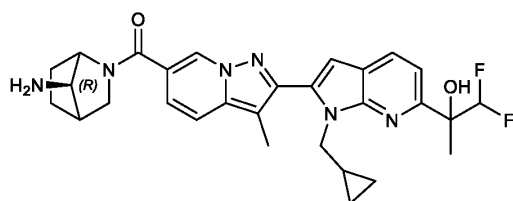
2-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)propan-2-ol (Homochiral)



Compound of Example 380 was obtained by amide formation of Intermediate 64D with tert-butyl (R)-piperidin-3-ylcarbamate followed the similar preparation of a compound of Example 100. LC-MS m/z: 487.4 [M+H]⁺; HPLC retention time: 1.453min (Method E).

Example 381

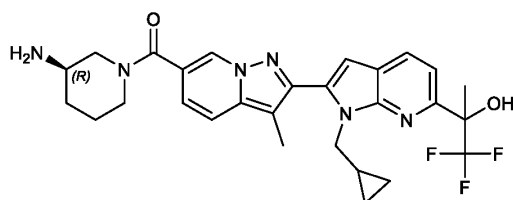
2-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-1,1-difluoropropan-2-ol (Diastereomeric mixture)



Compound of Example 381 was prepared following a procedure similar to the preparation of a compound of Example 101, by using Intermediate 100A with (Difluoromethyl)trimethylsilane reagent. LC-MS m/z: 535.2 [M+H]⁺; HPLC retention time: 1.503min (Method E).

Example 382

2-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-1,1,1-trifluoropropan-2-ol (Diastereomeric mixture)

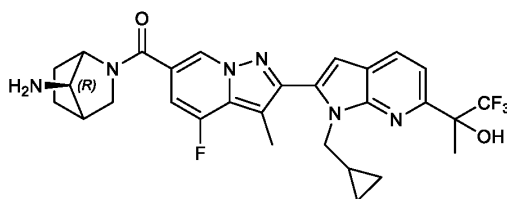


Compound of Example 382 was obtained by amide formation of Intermediate 64D with tert-butyl (R)-piperidin-3-ylcarbamate followed with the similar preparation of a compound of Example 101. LC-MS m/z: 541.3 [M+H]⁺; HPLC retention time: 1.746min (Method E).

5

Example 383

2-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-1,1,1-trifluoropropan-2-ol

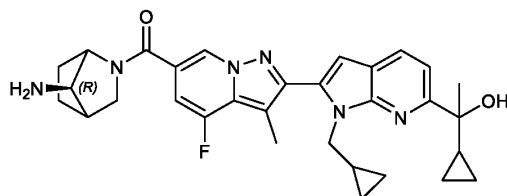


10

Compound of Example 383 obtained following a procedure similar to the preparation of Example 101, from Intermediate 39E. Analytical Data: LC-MS m/z: 571.3 [M+H]⁺; HPLC retention time: 2.147 min (Method E).

Example 384

1-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-1-cyclopropylethan-1-ol

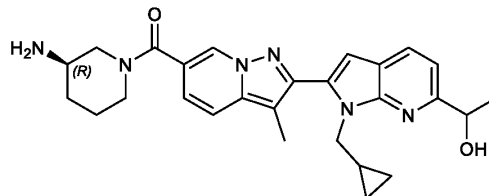


Compound of Example 384 was prepared following a procedure similar to the preparation of Example 102, from Intermediate 39E and using cyclopropyl magnesium bromide in Grignard addition reaction. LC-MS m/z: 543.2 [M+H]⁺; HPLC retention time: 1.812 min (Method E).

20

Example 385

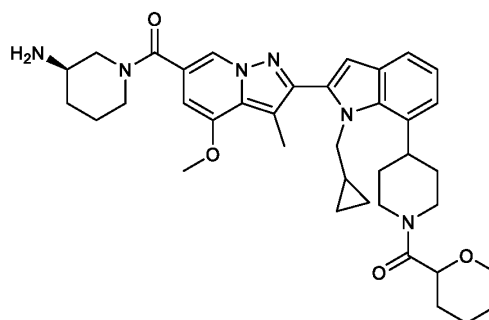
1-(2-{6-[(3R)-3-Aminopiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)ethan-1-ol (Diastereomeric mixture)



- 5 Compound of Example 385 was obtained by amide formation of Intermediate 64D with tert-butyl (R)-piperidin-3-ylcarbamate following the procedure to the preparation of Example 104. LC-MS m/z: 473.3 [M+H]⁺; HPLC retention time: 1.259min (Method E).

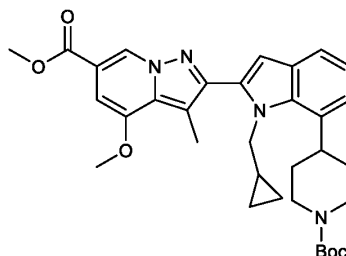
Examples 386 and 387

- 10 ((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(tetrahydro-2H-pyran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (isomer 1)



Intermediate 386A

- 15 Methyl 2-(7-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate

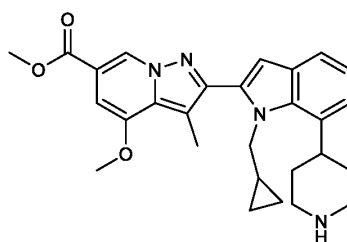


Intermediate 1 (1.042 g, 5.69 mmol) and copper(I) iodide (0.542 g, 2.84 mmol) were added to a stirred solution of Intermediate 30 (2.5 g, 5.69 mmol) in DMF (5 ml). The reaction mixture was heated to 80°C for 48 hours, allowed to cool to a room temperature, diluted with water (100 ml), and extracted with ethyl acetate (2×100 ml). The combined organic layers were dried over sodium sulphate, filtered, and concentrated under reduced pressure to obtain a crude product, which was purified using silica a gel column (0-20% ethyl acetate in hexane) to afford methyl 2-(7-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate (1.6 g, 49%). LC-MS 573.3 [M+H]⁺; ¹H NMR (400 MHz, chloroform-*d*) δ ppm: 8.84-8.86 (s, 1H), 7.53-7.61 (m, 1H), 7.14-7.19 (m, 2H), 6.87 (s, 1H), 6.77 (s, 1H), 4.44 (d, *J*=6.50 Hz, 2H), 4.04 (s, 3H), 4.01-3.97 (m, 4H), 3.93 (s, 3H), 2.89-3.00 (m, 1H), 2.55 (s, 3H), 2.08 – 2.05 (m, 2H), 1.76-1.94 (m, 2H), 1.53 (s, 9 H), 0.88-1.03 (m, 1H), 0.17-0.33 (m, 2H), 0.18-0.06 (m, 2H).

15

Intermediate 386B

Methyl 2-(1-(cyclopropylmethyl)-7-(piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate

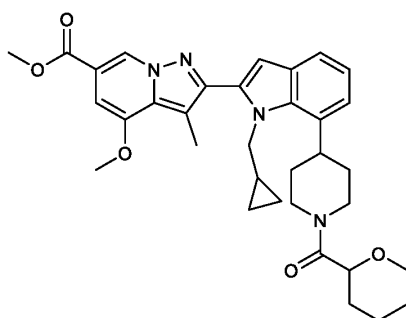


TFA (0.210 ml, 2.73 mmol) was added to a stirred solution of Intermediate 386A (1.6 g, 2.73 mmol) in DCM (15 ml) at 0°C. The reaction mixture was stirred for 3 hours at a room temperature, and concentrated under reduced pressure to obtain methyl 2-(1-(cyclopropylmethyl)-7-(piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate (1.1 g, 85%). LC-MS *m/z*: 473.4 [M+H]⁺.

25

Intermediate 386C

Methyl 2-(1-(cyclopropylmethyl)-7-(1-(tetrahydro-2H-pyran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate

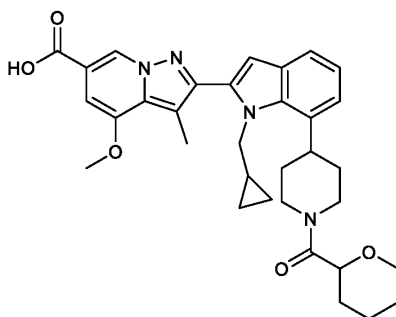


Racemic tetrahydro-2H-pyran-2-carboxylic acid (55.1 mg, 0.423 mmol), DIPEA (0.222 ml, 1.270 mmol) and HATU (241 mg, 0.635 mmol) were added to a stirred solution of Intermediate 386B (200 mg, 0.423 mmol) in DMF (2 ml). The reaction mixture was stirred for 3 hours, quenched with water, the solids obtained were filtered and dried in vacuo to obtain methyl 2-(1-(cyclopropylmethyl)-7-(1-(tetrahydro-2H-pyran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate (180 mg, 73%). LC-MS m/z: 585.4 [M+H]⁺.

10

Intermediate 386D

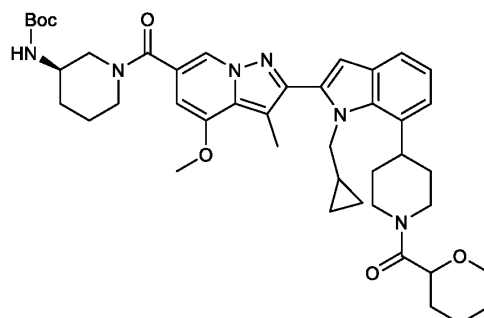
2-(1-(Cyclopropylmethyl)-7-(1-(tetrahydro-2H-pyran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylic acid



LiOH (7.37 mg, 0.308 mmol) was added to a stirred solution of Intermediate 386C (180 mg, 0.308 mmol) in a mixture of solvents [THF (1 ml), methanol (1.0 ml) and water (1 ml)]. The reaction mixture was stirred for 4 hours, concentrated under reduced pressure to obtain crude salts, which were acidified with 1 N HCl. The solids thus obtained were filtered through Buchner funnel and dried under vacuo to obtain 2-(1-(cyclopropylmethyl)-7-(1-(tetrahydro-2H-pyran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylic acid (160 mg, 91%). LC-MS m/z: 571.2 [M+H]⁺.

Intermediate 386E & Intermediate 386F

tert-Butyl ((3R)-1-(2-(1-(cyclopropylmethyl)-7-(1-(tetrahydro-2H-pyran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)piperidin-3-yl)carbamate



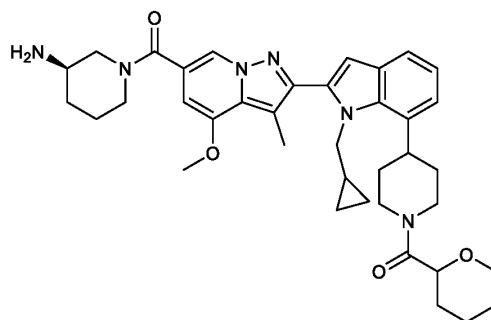
tert-Butyl (R)-piperidin-3-ylcarbamate (35.1 mg, 0.175 mmol), DIPEA (0.092 ml, 0.526 mmol) and HATU (100 mg, 0.263 mmol) were added to a stirred solution of Intermediate 386D (100 mg, 0.175 mmol) in DMF (1 ml). The reaction mixture was stirred for 3 hours, quenched with water (50 ml), and the solids obtained were filtered and dried to obtain a crude product, which was purified by SFC chiral purification to afford corresponding homochiral isomers. (*Preparative SFC Conditions* Column/dimensions: Whelk (R, R) (250×30) mm, 5u% CO₂: 60%, Co solvent: 40% of 5 mM Ammonium Acetate in [MeOH + ACN(1:1)], total flow: 170.0 g/min, back Pressure: 100 bar, temperature: 40°C, UV: 225 nm.

Isomer 1 (Intermediate 386E): tert-butyl ((3R)-1-(2-(1-(cyclopropylmethyl)-7-(1-(tetrahydro-2H-pyran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)piperidin-3-yl)carbamate (40 mg, 61%). LC-MS m/z: 753.7 [M+H]⁺.

Isomer 2 (Intermediate 386F): tert-butyl ((3R)-1-(2-(1-(cyclopropylmethyl)-7-(1-(tetrahydro-2H-pyran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)piperidin-3-yl)carbamate (40 mg, 61%). LC-MS m/z: 753.7 [M+H]⁺.

Example 386

((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(tetrahydro-2H-pyran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (isomer 1)

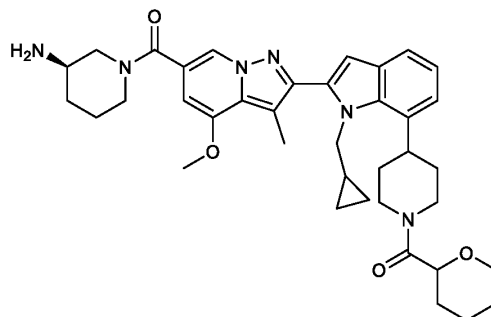


5

TFA (0.053 mmol) was added to a stirred solution of 386E (40 mg, 0.053 mmol) in DCM (1 ml) at 0°C. The reaction mixture was allowed to warm to a room temperature and stirred for 3 hours, concentrated in vacuo to obtain a crude product, which was purified using preparative LC/MS with the following conditions: Column: Waters X
 10 Bridge C18, 150 mm×19 mm, 5-μm particles; mobile phase A: 5:95 acetonitrile: water with 0.1% trifluoroacetic acid; mobile phase B: 95:5 acetonitrile: water with 0.1% trifluoroacetic acid; gradient: a 0-minute hold at 20% B, 20-40% B over 20 minutes, then a 5-minute hold at 100% B; flow rate: 20 ml/min, column temperature: 25°C. Fraction collection was triggered by signals. Fractions containing the desired product were
 15 combined and dried via centrifugal evaporation. The purified material was diluted with a 1:1 mixture of ethylene dichloride and methanol (EDM), treated with Si-Pyridine and shaken for a minimum of 2 hours, the resulting mixture was filtered and dried via centrifugal evaporation to afford ((R)-3-aminopiperidin-1-yl) (2-(1-(cyclopropylmethyl)-7-(1-(tetrahydro-2H-pyran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-
 20 methylpyrazolo[1,5-a]pyridin-6-yl)methanone (isomer 1, 3 mg, 8%). LC-MS m/z: 653.5 [M+H]⁺. LCMS retention time: 1.825 min (method E). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.46 (s, 1H), 7.49 (d, *J*=6.69 Hz, 1H), 7.08 (m, 2H), 6.72 (s, 1H), 6.62 (s, 1H), 4.62 – 4.57 (m, 1H), 4.41 (d, *J*=6.11 Hz, 2H), 4.24 – 4.14 (m, 2H), 3.99 (s, 3H), 3.93 – 3.85 (m, 2H), 3.68 – 3.58 (m, 1H), 3.55 – 3.45 (m, 1H), 3.30 – 3.20 (m, 4H), 2.53-2.56 (m, 2H), 2.47 (s, 3H), 2.05 – 1.95 (m, 4H), 1.87 – 1.72 (m, 4H), 1.70 – 1.55 (m, 6H), 1.53 – 1.44 (m, 2H), 1.0 – 0.9 (m, 1H), 0.23 (d, *J*=8.31 Hz, 2H), -0.18 (m, 2H).

Example 387

5 ((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(tetrahydro-2H-pyran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (isomer 2)

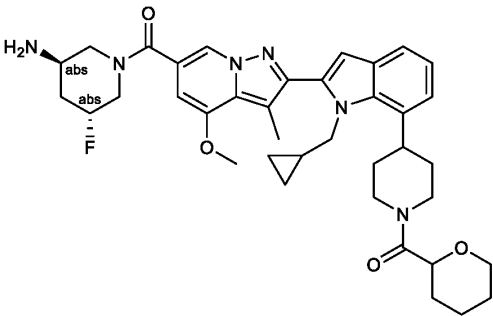
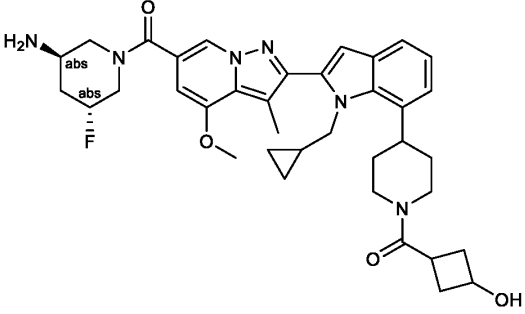


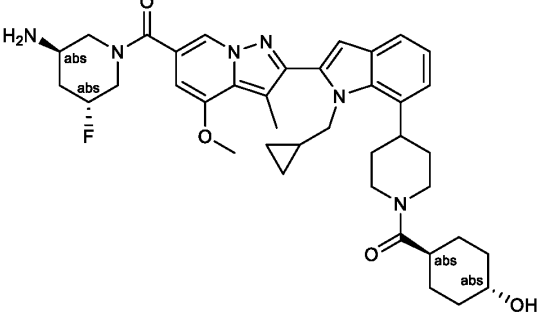
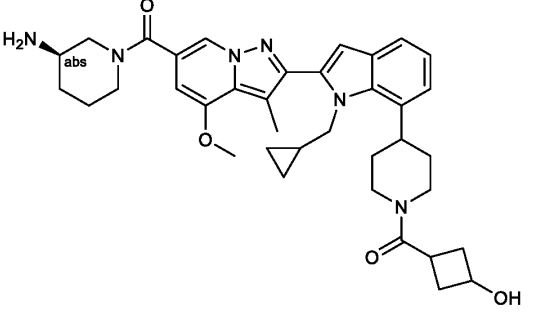
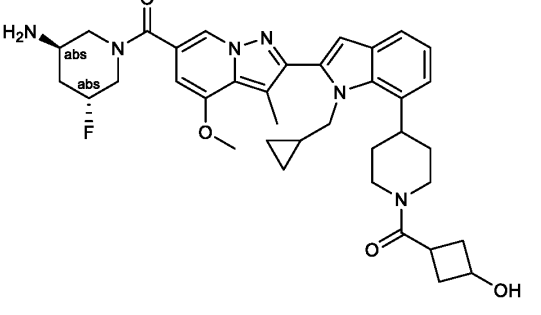
Compound of Example 387 was prepared in a similar fashion like Example 386 using the intermediate 386F.

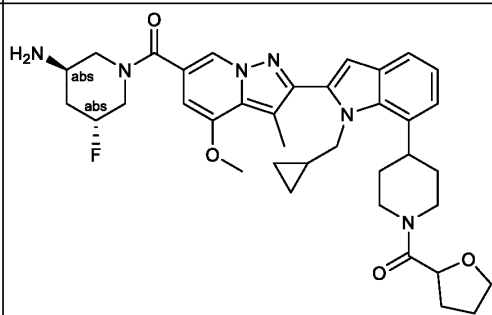
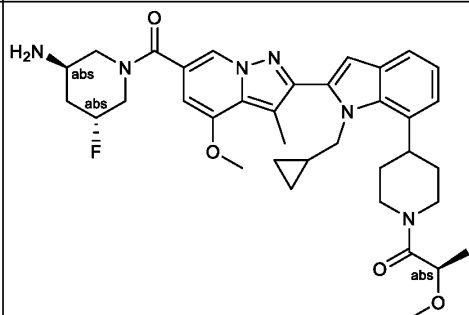
Compounds of Examples 388 to 412 in Table 46 were prepared following a procedure similar to the preparation of a compound of Example 386, by acid amine coupling of Intermediate 386B with appropriate carboxylic acid and amines.

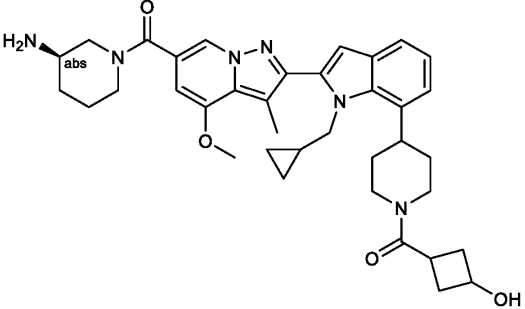
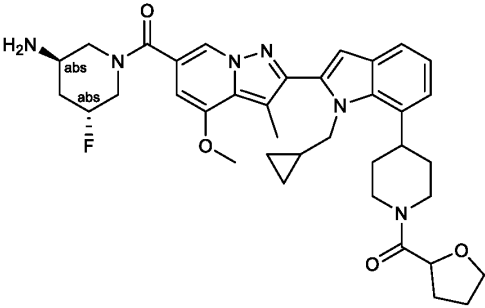
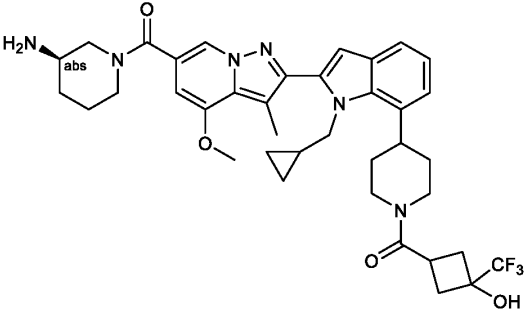
Table 46

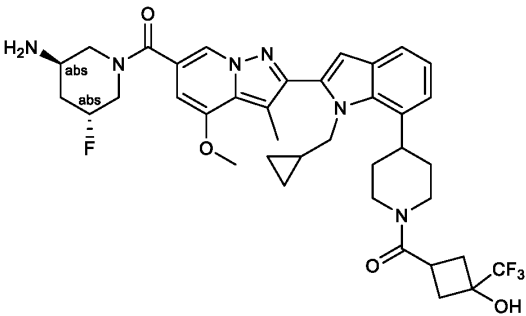
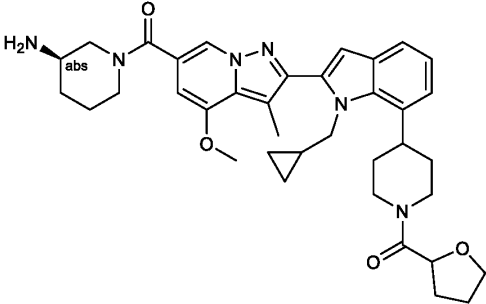
Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
388	

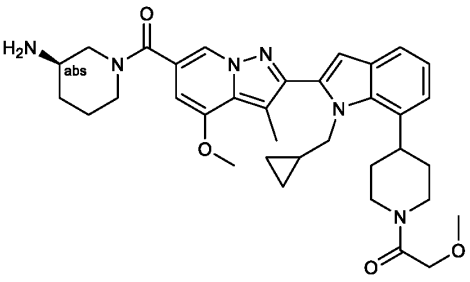
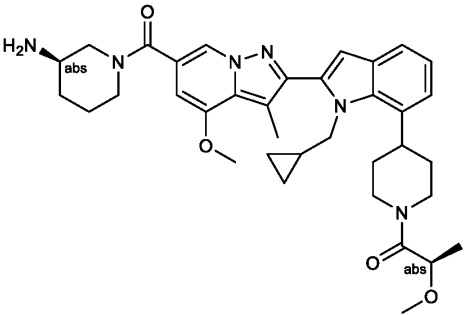
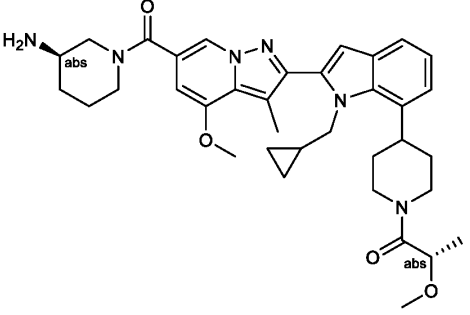
	((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(tetrahydro-2H-pyran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (isomer 1) Analytical Data: 671.; 1.953 min (Method E)
389	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(tetrahydro-2H-pyran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (isomer 2) Analytical Data: 671.4; 1.951 min (Method E)
390	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxycyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (isomer 1) Analytical Data: 657.3; 1.502 min (Method E)

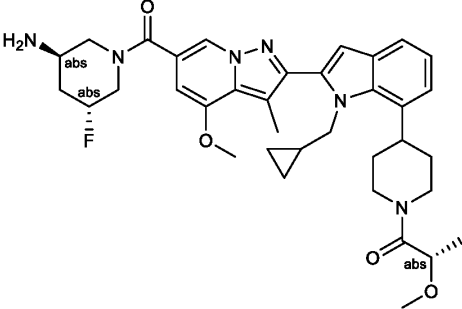
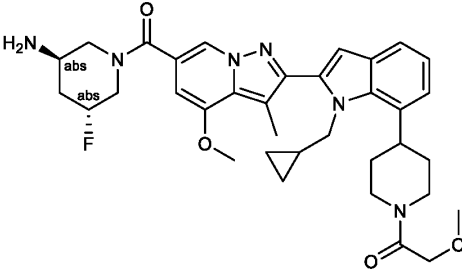
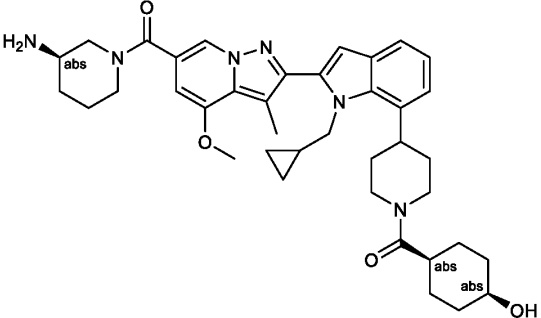
391	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1r,4r)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 685.3; 1.625 min (Method E)
392	 (R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxycyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (isomer 1) Analytical Data: 639.3; 1.512 min (Method E)
393	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxycyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (isomer 2)

	Analytical Data: 657.3; 1.534 min (Method E)
394	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(tetrahydrofuran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (isomer 1) Analytical Data: 657.3; 1.664 min (Method E)
395	 (R)-1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxypropan-1-one Analytical Data: 645.3; 1.735 min (Method E)

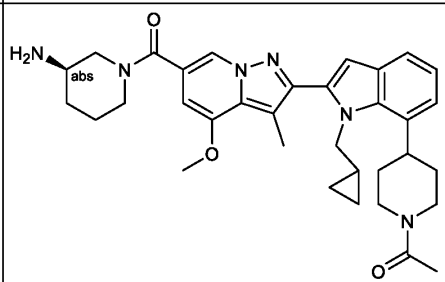
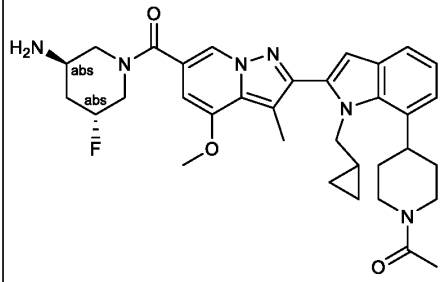
396	 (R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxycyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (isomer 1) Analytical Data: 639.3; 1.520 min (Method E)
397	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(tetrahydrofuran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (isomer 2) Analytical Data: 657.3; 1.676 min (Method E)
398	 (R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxy-3-(trifluoromethyl)cyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone

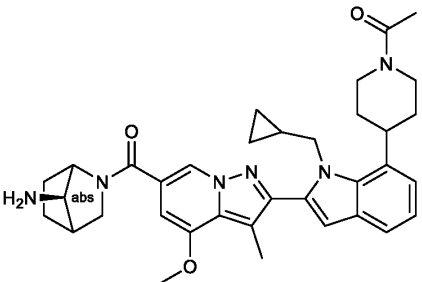
	methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (mixture of diastereomers) Analytical Data: 707.3; 1.774 min (Method E)
399	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxy-3-(trifluoromethyl)cyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (mixture of diastereomers) Analytical Data: 725.3; 1.793 min (Method E)
400	 ((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(tetrahydrofuran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (mixture of diastereomers) Analytical Data: 639.3; 1.657 min (Method E)

401	 (R)-1-(4-(2-(6-(3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxyethan-1-one Analytical Data: 613.3; 1.565 min (Method E)
402	 (R)-1-(4-(2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxypropan-1-one Analytical Data: 627.3; 1.603 min (Method E)
403	 (S)-1-(4-(2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxypropan-1-one Analytical Data: 627.3; 1.698 min (Method E)

404	 (S)-1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxypropan-1-one Analytical Data: 645.3; 1.751min (Method E)
405	 1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxyethan-1-one Analytical Data: 631.3; 1.681 min (Method E)
406	 ((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1s,4s)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 667.3; 1.672 min (Method E)

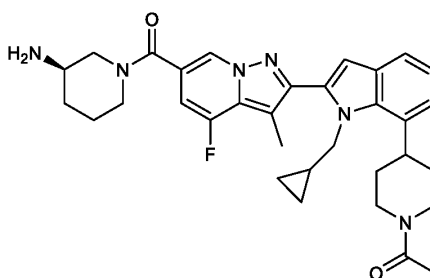
407	((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1s,4s)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 685.3; 1.721 min (Method E)
408	((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1r,4r)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 667.3; 1.583 min (Method E)
409	((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1r,4r)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone

	Analytical Data: 685.3; 1.625 min (Method E)
410	 (R)-1-(4-(2-(6-(3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)ethan-1-one Analytical Data: 583.4; 1.641 min (Method E)
411	 1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)ethan-1-one Analytical Data: 601.4; 1.696 min (Method E)

412	 1-(4-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)ethan-1-one Analytical Data: 595.4; 8.079 min (Method D)
-----	--

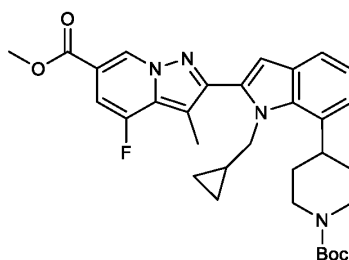
Example 413

(R)-1-(4-(2-(6-(3-Aminopiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)ethan-1-one



Intermediate 413A

Methyl 2-(7-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate



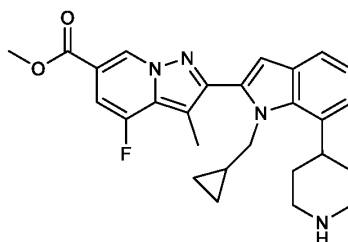
10

Copper(I) iodide (0.260 g, 1.365 mmol) was added to a stirred solution of Intermediate 9 (3.11 g, 18.20 mmol) and Intermediate 30 (2.0 g, 4.55 mmol) in DMF (40

ml). The reaction mixture was heated to 80°C for 16 hours, filtered through a celite bed, and washed with ethyl acetate. The combined filtrate was washed with water (2×100 ml), followed by 10% sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulphate and evaporated under reduced pressure to obtain a crude product, which was purified using a silica gel column (0-15% ethyl acetate in pet ether) to afford methyl 2-(7-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate (0.38 g, 15%) as a gummy liquid. LC-MS m/z: 561.4 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 9.14 (s, 1H), 9.15-9.13 (m, 1H), 7.52 (dd, *J*=1.3, 7.8 Hz, 1H), 7.42-7.35 (m, 1H), 7.22-7.04 (m, 3H), 6.85 (s, 1H), 4.44 (d, *J*=6.5 Hz, 2H), 4.15 (br, s, 2H), 3.94-3.90 (m, 3H), 2.49-2.46 (m, 4H), 2.41 (s, 1H), 2.00-1.83 (m, 3H), 1.78-1.56 (m, 3H), 1.53-1.35 (m, 9H), 1.26 (br, d, *J*=8.5 Hz, 2H), 0.99-0.80 (m, 1H), 0.25-0.21 (m, 2H), -0.01--0.18 (m, 2H).

Intermediate 413B

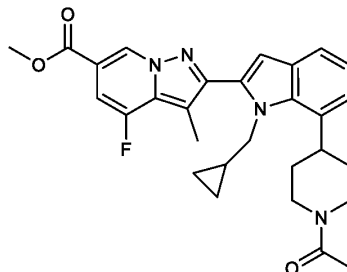
Methyl 2-(1-(cyclopropylmethyl)-7-(piperidin-4-yl)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate



TFA (0.254 ml, 3.30 mmol) was added to a stirred solution of Intermediate 413A (0.37g, 0.660 mmol) in DCM (2 ml). The reaction mixture was stirred for 1 hour, and concentrated under reduced pressure to obtain a crude product, which was neutralized using 10% sodium bicarbonate solution and the contents were extracted with ethyl acetate (4×25 ml). The combined organic layers were washed with water and brine solution, dried over anhydrous sodium sulphate, and evaporated under reduced pressure to obtain methyl 2-(1-(cyclopropylmethyl)-7-(piperidin-4-yl)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate (0.29 g, 95%). LC-MS m/z: 461.3 [M+H]⁺.

Intermediate 413C

Methyl 2-(7-(1-acetylpiperidin-4-yl)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate

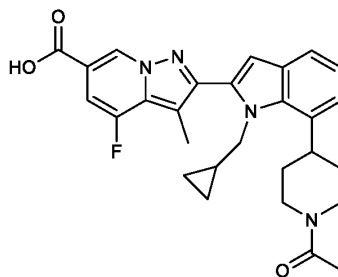


- 5 Triethylamine (0.039 ml, 0.282 mmol) was added to a stirred solution of Intermediate 413B (0.13 g, 0.282 mmol) in DCM (3 ml), followed by the addition of acetic anhydride (0.029 g, 0.282 mmol) at 0°C. The reaction mixture was allowed to warm to a room temperature and stirred for 1 hour, diluted with water, and extracted with DCM (3×15 ml). The combined organic layers were washed with water and brine
- 10 solution, dried over anhydrous sodium sulphate, and evaporated under reduced pressure to obtain methyl 2-(7-(1-acetylpiperidin-4-yl)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate (0.12 g, 85%) as gummy liquid, which was used further without purification. LC-MS m/z: 503.4 [M+H]⁺.

15

Intermediate 413D

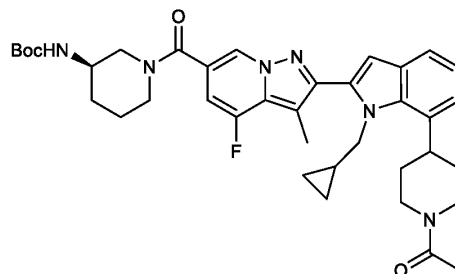
2-(7-(1-Acetylpiperidin-4-yl)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carboxylic acid



- Intermediate 413D (0.1 g, 94%) was prepared following a procedure similar to the
- 20 preparation of Intermediate 386D. LC-MS m/z: 489.4 [M+H]⁺

Intermediate 413E

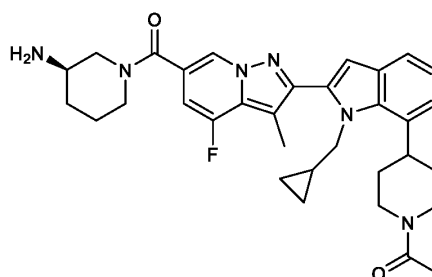
tert-butyl (R)-(1-(2-(7-(1-acetylpiperidin-4-yl)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)piperidin-3-yl)carbamate



- 5 Intermediate 413E was prepared following a procedure similar to the preparation of Intermediate 386E (0.07 g, 85%) as a gummy liquid. LC-MS m/z: 671.5[M+H]⁺

Example 413

- (R)-1-(4-(2-(6-(3-aminopiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)ethan-1-one
- 10

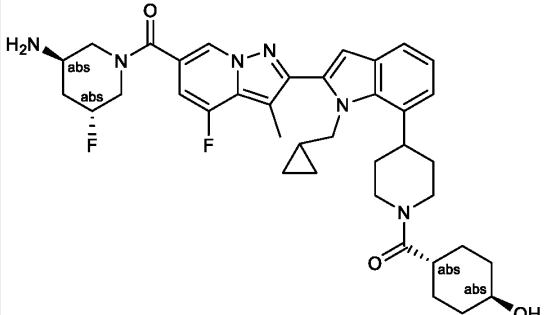
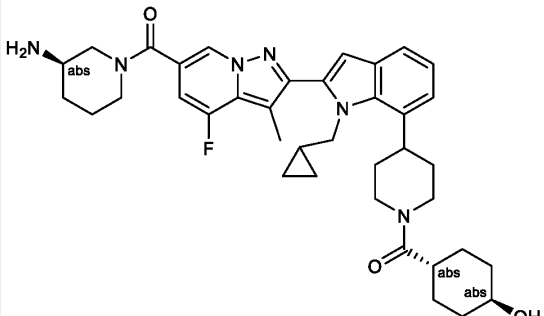


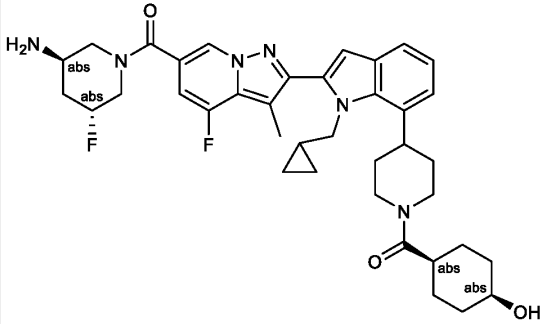
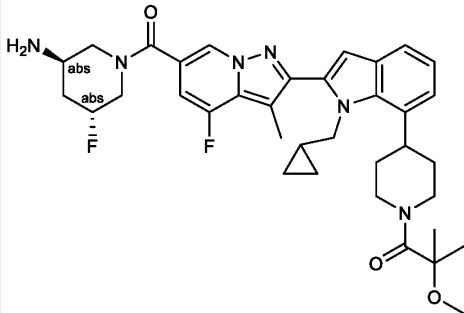
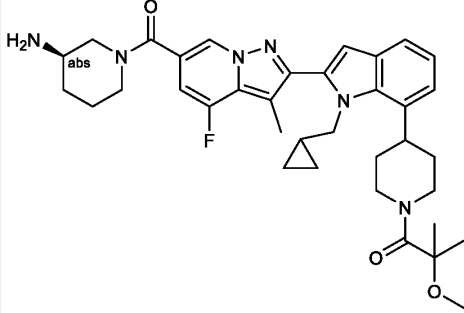
- (R)-1-(4-(2-(6-(3-aminopiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)ethan-1-one was prepared starting from intermediate 413 E following a procedure similar to the preparation of Example 386. LC-MS m/z: 571.3 [M+H]⁺. LCMS retention time: 1.64 min (method E). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.74 (s, 1H), 7.51 (dd, *J*=7.50, 1.00 Hz, 1H), 7.04-7.22 (m, 3H), 6.79 (s, 1H), 4.43 (d, *J*=6.00 Hz, 2H), 4.1 – 3.9 (m, 2H), 3.70-3.55 (m, 2H), 3.20-3.07 (m, 2H), 3.07 – 2.86 (m, 2H), 2.85-2.62 (m, 2H), 2.07 (s, 3H), 2.05 – 1.95 (m, 2H), 1.92 (s, 3H), 1.90 – 1.77 (m, 2H), 1.75 – 1.35 (m, 4H), 1.24-1.22 (m, 2H), 0.97 – 0.93 (m, 1H), 0.26 – 0.22 (m, 2H), -0.17--0.13 (m, 2H).
- 15
- 20

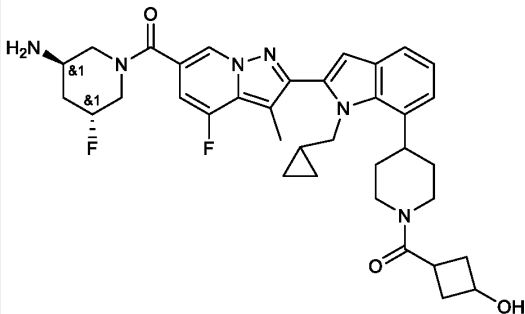
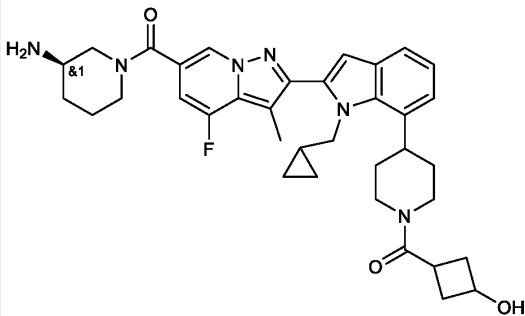
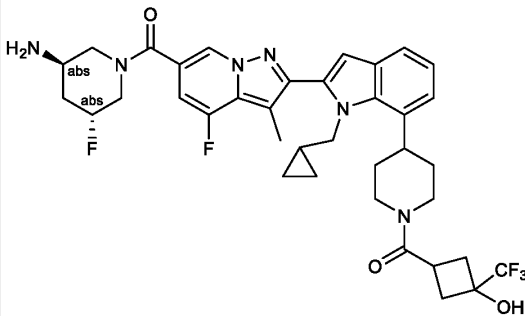
Compounds of Examples 414 to 429 in Table 47 were prepared following a procedure similar to the preparation of a compound of Example 413, by acid amine coupling of Intermediate 413B with appropriate carboxylic acid followed by ester hydrolysis and the coupling of resulting carboxylic acid with appropriate amines

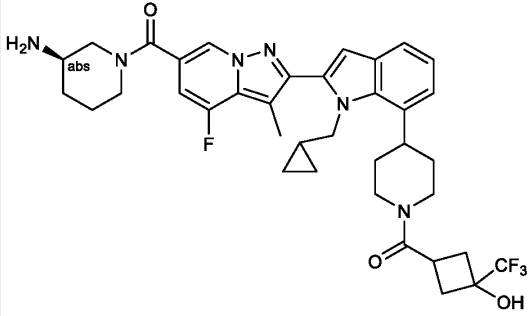
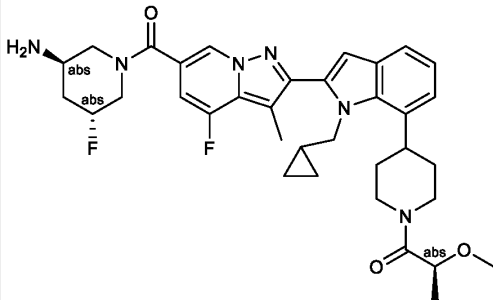
5

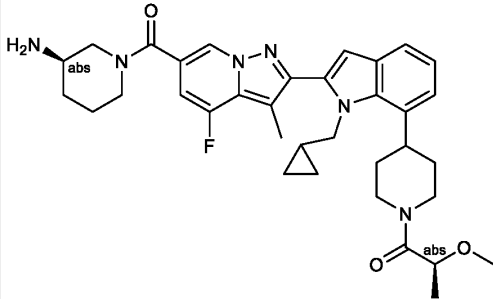
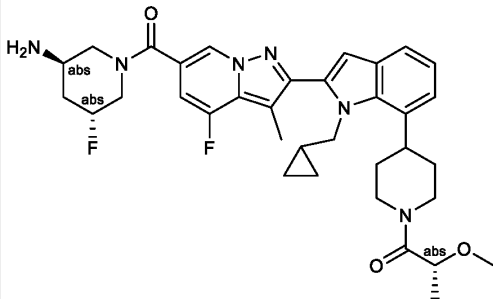
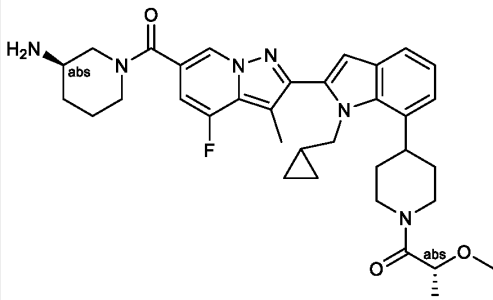
Table 47

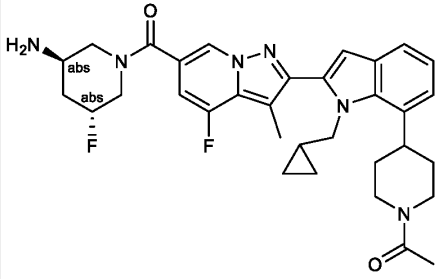
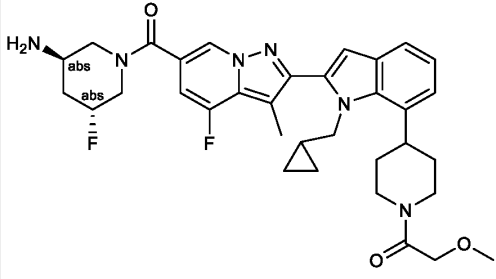
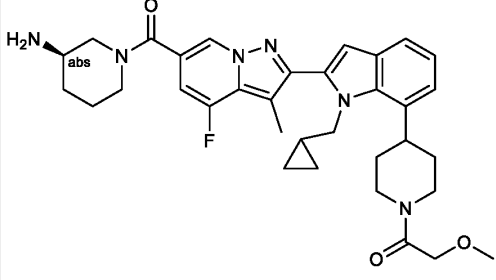
Example	Structure
	Name
	Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method 1)
414	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1r,4r)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical data: 673.3; 1.70 min (Method E)
415	 ((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1r,4r)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical data: 655.4; 1.63 min (Method E)

416	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1s,4s)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical data: 673.3; 1.78 min (Method E)
417	 1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxy-2-methylpropan-1-one Analytical data: 647.3; 2.0 min (Method E)
418	 (R)-1-(4-(2-(6-(3-Aminopiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxy-2-methylpropan-1-one

	Analytical data: 629.4; 1.96 min (Method E)
419	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxycyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (mixture of diastereomers) Analytical data: 645.4; 1.51 min (Method E)
420	 (R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxycyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (mixture of diastereomers) Analytical data: 627.4; 1.58 min (Method E)
421	

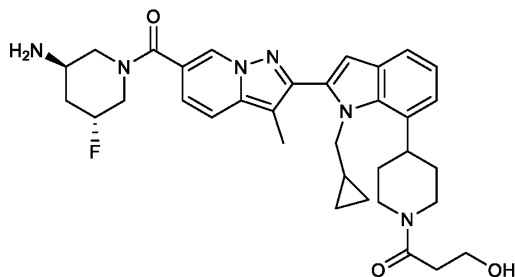
	((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxy-3-(trifluoromethyl)cyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (mixture of diastereomers) Analytical data: 713.3; 1.93 min (Method E)
422	 (R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxy-3-(trifluoromethyl)cyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (mixture of diastereomers) Analytical data: 695.3; 1.89 min (Method E)
423	 (S)-1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxypropan-1-one Analytical data: 633.3; 1.78 min (Method E)

424	 (S)-1-(4-(2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxypropan-1-one Analytical data: 615.4; 1.71 min (Method E)
425	 (R)-1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxypropan-1-one Analytical data: 633.4; 1.64 min (Method E)
426	 (R)-1-(4-(2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxypropan-1-one Analytical data: 615.4; 1.72 min (Method E)

427	 1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)ethan-1-one Analytical data: 589.3; 1.70 min (Method E)
428	 1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxyethan-1-one Analytical data: 619.3; 1.69 min (Method E)
429	 (R)-1-(4-(2-(6-(3-Aminopiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxyethan-1-one Analytical data: 601.3; 1.62 min (Method E)

Example 430

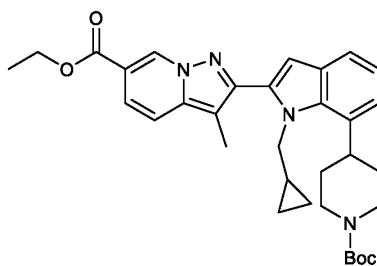
Ethyl 2-(7-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate



5

Intermediate 430A

Ethyl 2-(7-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate

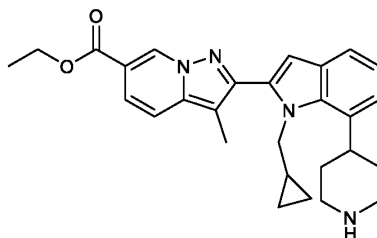


10

Intermediate 430A (2.1 g, 47%) was prepared following a procedure similar to the preparation of Intermediate 386A. LC-MS m/z : 557.3 $[M+H]^+$

Intermediate 430B

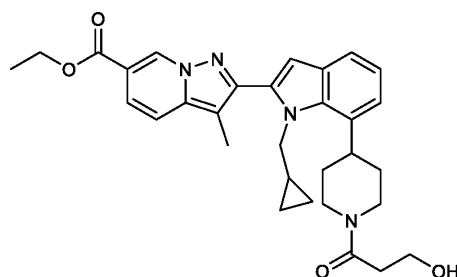
15 Ethyl 2-(1-(cyclopropylmethyl)-7-(piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate



Intermediate 430B (1.4 g, 81%) was prepared starting from Intermediate 430A following a procedure similar to the preparation of Intermediate 386B. LC-MS m/z: 457.3 [M+H]⁺

5 Intermediate 430C

1-(4-(2-(6-((3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-3-hydroxypropan-1-one

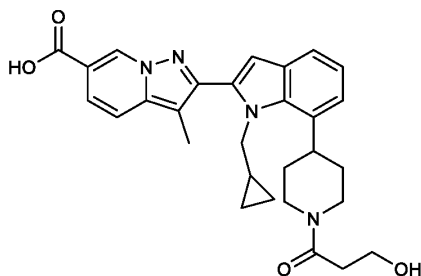


10 3-Hydroxypropanoic acid (59.2 mg, 0.657 mmol), DIPEA (0.344 ml, 1.971 mmol) and HATU (375 mg, 0.986 mmol) were added to a stirred solution of Intermediate 430B (300 mg, 0.657 mmol) in DMF (1 ml). The reaction was continued for 3 hours. The reaction mixture was cooled to 0°C, and quenched with ice cold water to obtain a solid, which was filtered through Buchner funnel and dried under reduced vacuum to afford the

15 title compound ethyl 2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxypropanoyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate (172 mg, 50%). LC-MS m/z: 529.3 [M+H]⁺.

Intermediate 430D

20 2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxypropanoyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylic acid

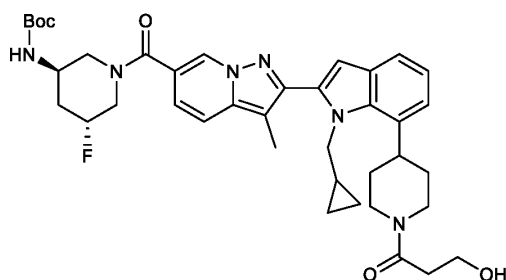


Intermediate 430D (140 mg, 92%) was prepared starting from Intermediate 430C following a procedure similar to the preparation of Intermediate 386D. LC-MS m/z : 501.4 $[M+H]^+$.

5

Intermediate 430E

tert-Butyl ((3R,5R)-1-(2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxypropanoyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate.



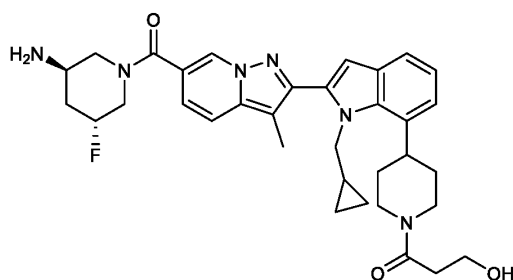
10

Intermediate 430E (60 mg, 86%) was prepared starting from Intermediate 430D following a procedure similar to the preparation of Intermediate 386E. LC-MS m/z : 645.4 $[M-tBu]^+$.

15

Example 430

1-(4-(2-(6-((3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-3-hydroxypropan-1-one



20

HCl (4 M in dioxane) (0.043 ml, 0.171 mmol) was added to a stirred solution of Intermediate 430E (60 mg, 0.086 mmol) in 1,4-dioxane (1 ml) at 0°C. The reaction was continued for 3 hours. The reaction mixture was concentrated in vacuo to obtain a crude

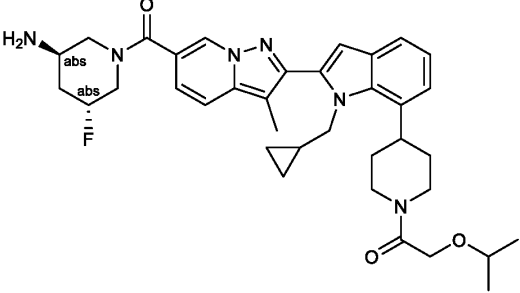
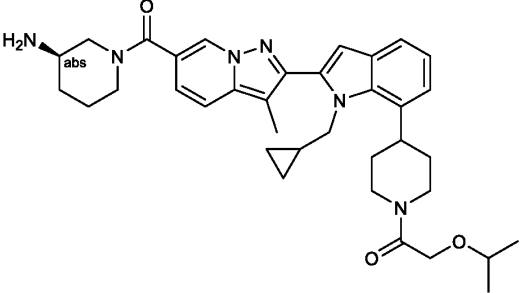
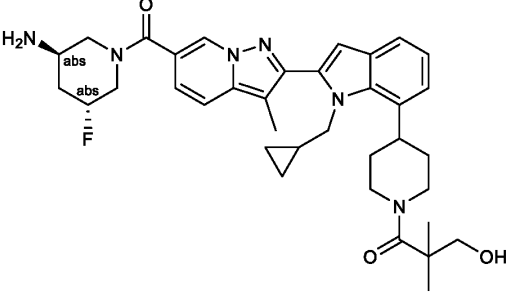
compound, which was purified using preparative LC/MS with the following conditions: Column: Waters X Bridge C18, 150 mm×19 mm, 5-μm particles; mobile phase A: 5:95 acetonitrile: water with 0.1% trifluoroacetic acid; mobile phase B: 95:5 acetonitrile: water with 0.1% trifluoroacetic acid; gradient: a 0-minute hold at 15% B, 15-30% B over 20 minutes, then a 5-minute hold at 100% B; flow rate: 20 ml/min; column temperature: 25°C. Fraction collection was triggered by signals. Fractions containing the desired product were combined and dried using centrifugal evaporation. The purified material was then diluted with a 1:1 mixture of ethylene dichloride and methanol (EDM), treated with Si-Pyridine and shaken for a minimum of 2 hours. The resulting mixture was filtered, and dried via centrifugal evaporation to afford 1-(4-(2-(6-((3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-3-hydroxypropan-1-one (6.9 mg, 11%). LC-MS m/z: 601.3 [M+H]⁺. LCMS retention time: 1.504 min (method E). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.76 (s, 1H), 7.80 (d, *J*=9.29 Hz, 1H), 7.50 (d, *J*=7.58 Hz, 1H), 7.23 (d, *J*=9.15 Hz, 1H), 7.07-7.14 (m, 2H), 6.78 (s, 1H), 6.32 (br, s, 1H), 4.50 (d, *J*=6.36 Hz, 2H), 3.67 (m, 4H), 3.39-3.54 (m, 4H), 3.25 (m, 3H), 2.80 – 2.60 (m, 2H), 2.38 (s, 3H), 2.25 – 2.10 (m, 2H), 2.08 – 1.90 (m, 2H), 1.85 – 1.75 (m, 2H), 1.70 – 1.50 (m, 2H), 1.26 – 1.22 (m, 2H), 0.98 – 0.90 (m, 1H), 0.22 (d, *J*=8.07 Hz, 2H), -0.17 (d, *J*=5.14 Hz, 2H).

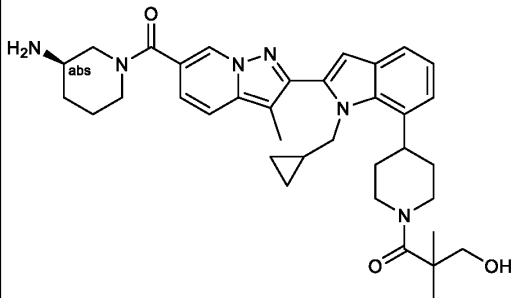
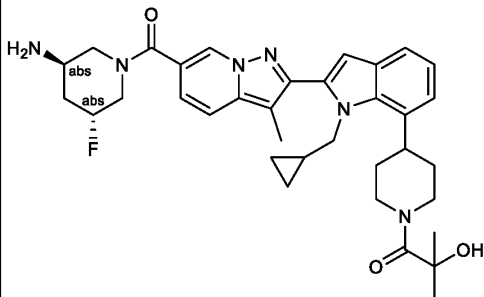
20

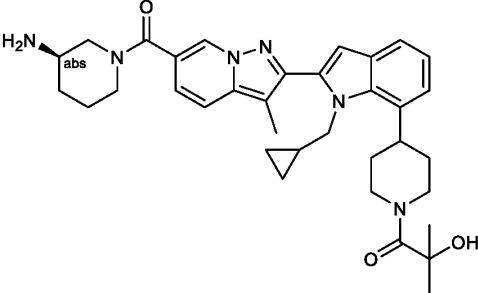
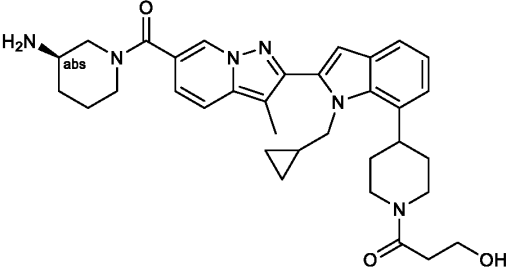
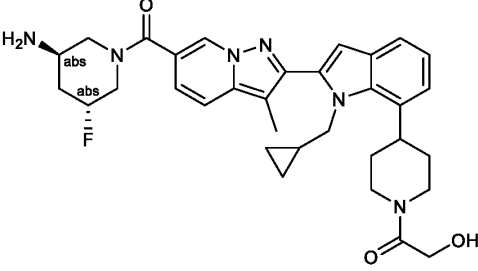
Compounds of Examples 431 to 479 in Table 48 were prepared following a procedure similar to the preparation of a compound of Example 430, by acid amine coupling of Intermediate 430B with appropriate carboxylic acid followed by ester hydrolysis and amide coupling of resulting carboxylic acid with appropriate amines.

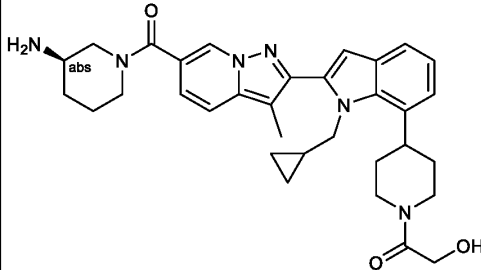
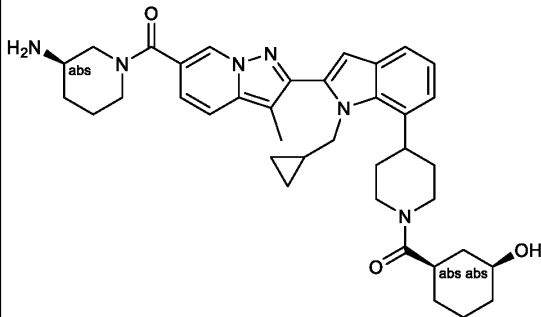
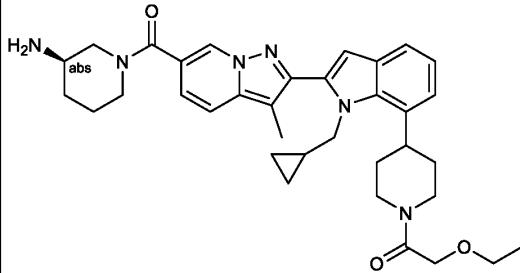
25

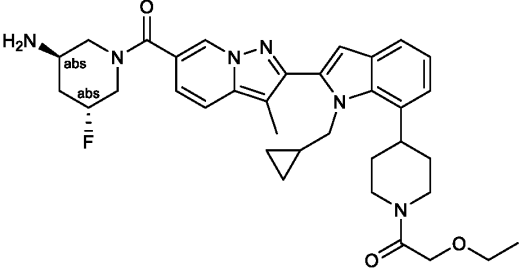
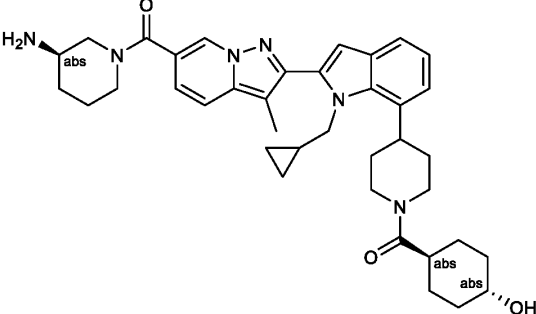
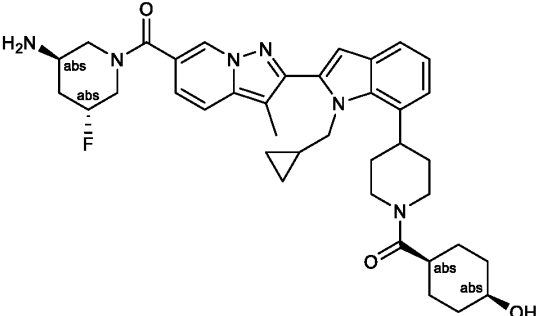
Table 48

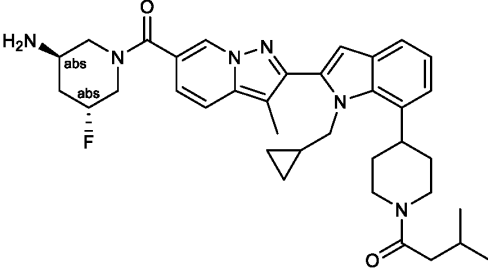
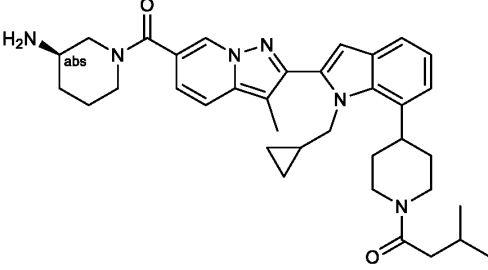
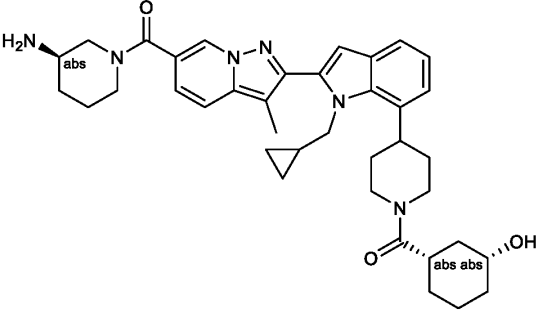
Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
431	 1-(4-(2-(6-((3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-isopropoxyethan-1-one Analytical Data: 629.4; 1.842min (Method E)
432	 (R)-1-(4-(2-(6-(3-aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-isopropoxyethan-1-one Analytical Data: 611.5; 1.760 min (Method E)
433	

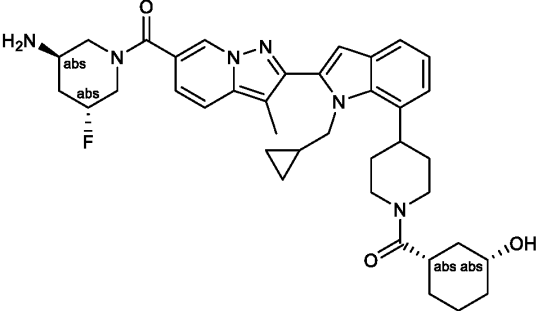
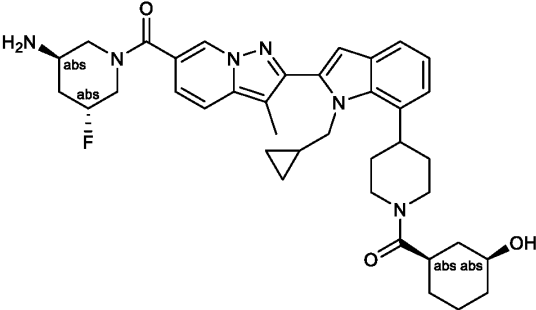
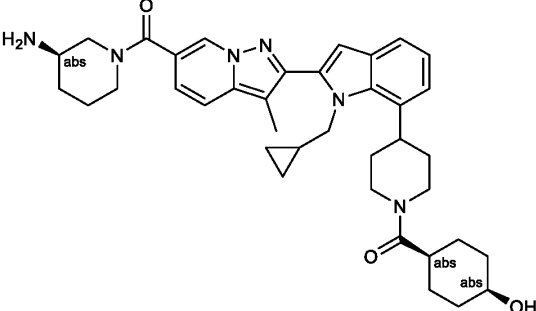
	1-(4-(2-(6-((3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-3-hydroxy-2,2-dimethylpropan-1-one Analytical Data: 629.3; 1.748 min (Method E)
434	 (R)-1-(4-(2-(6-(3-aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-3-hydroxy-2,2-dimethylpropan-1-one Analytical Data: 611.4; 1.663 min (Method E)
435	 1-(4-(2-(6-((3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-hydroxy-2-methylpropan-1-one Analytical Data: 615.3; 1.694 min (Method E)

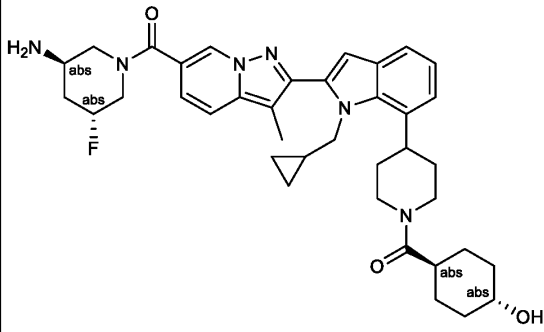
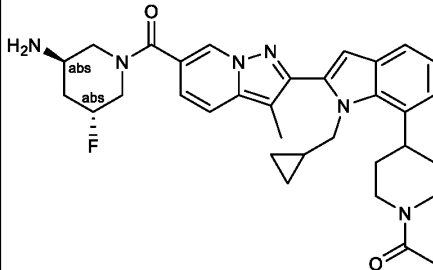
436	 (R)-1-(4-(2-(6-(3-aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-hydroxy-2-methylpropan-1-one Analytical Data: 597.3; 1.597min (Method E)
437	 (R)-1-(4-(2-(6-(3-aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-3-hydroxypropan-1-one Analytical Data: 583.4; 1.377 min (Method E)
438	 1-(4-(2-(6-((3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-hydroxyethan-1-one Analytical Data: 587.3; 1.544 min (Method E)

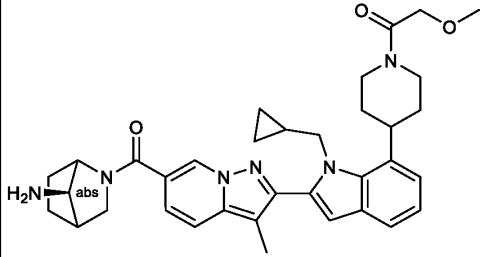
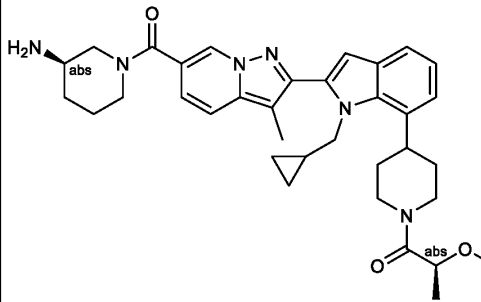
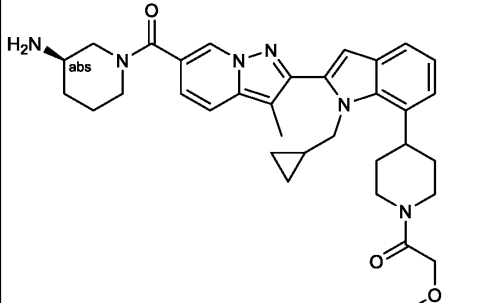
439	 (R)-1-(4-(2-(6-(3-aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-hydroxyethan-1-one Analytical Data: 569.3; 1.464 min (Method E)
440	 ((R)-3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1R,3S)-3-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 637.4; 1.521 min (Method E)
441	 (R)-1-(4-(2-(6-(3-aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-ethoxyethan-1-one Analytical Data: 597.3; 1.561 min (Method E)

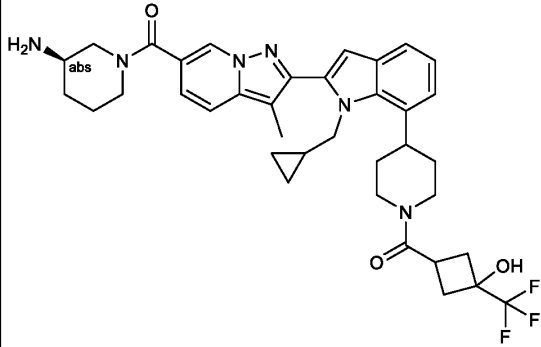
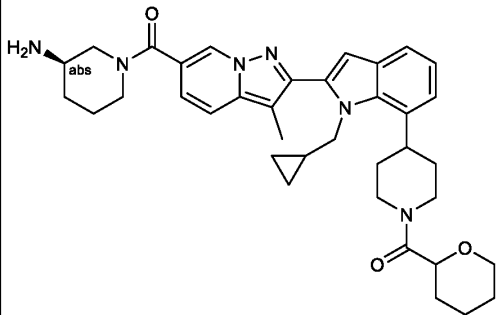
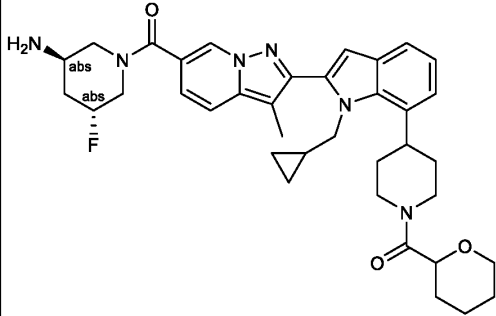
442	 1-(4-(2-(6-((3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-ethoxyethan-1-one Analytical Data: 615.3; 1.576 min (Method E)
443	 ((R)-3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1r,4r)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 637.3; 1.497 min (Method E)
444	 ((3R,5R)-3-amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1s,4s)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 655.4; 1.637 min (Method E)

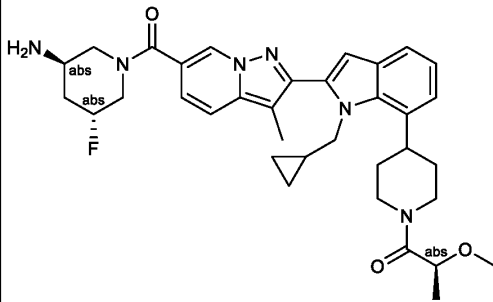
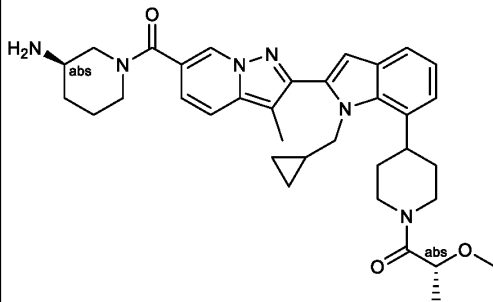
445	 1-(4-(2-(6-((3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-3-methylbutan-1-one Analytical Data: 613.4; 1.918 min (Method E)
446	 (R)-1-(4-(2-(6-(3-aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-3-methylbutan-1-one Analytical Data: 595.4; 1.861 min (Method E)
447	 ((R)-3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1S,3R)-3-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 637.4; 1.58 min (Method E)

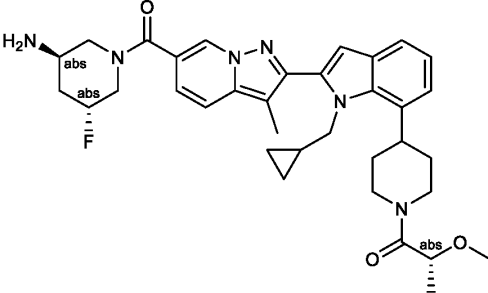
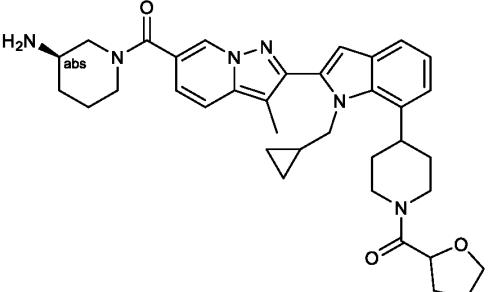
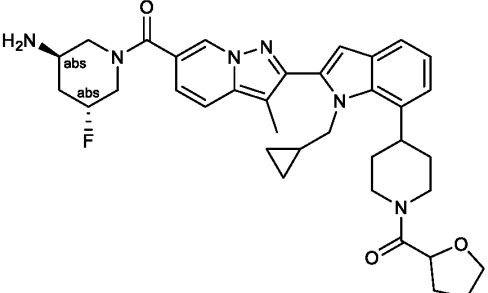
448	 ((3R,5R)-3-amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1S,3R)-3-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 655.4; 1.492 min (Method E)
449	 ((3R,5R)-3-amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1R,3S)-3-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 655.4; 1.494 min (Method E)
450	 ((R)-3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1S,4S)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone

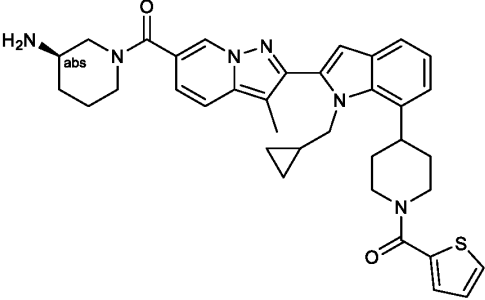
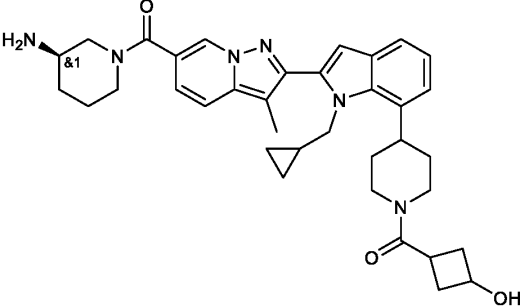
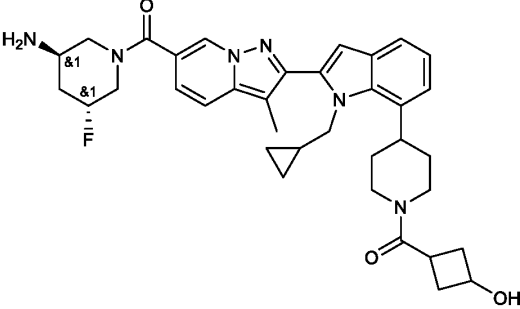
	Analytical Data: 637.5; 1.499 min (Method E)
451	 ((3R,5R)-3-amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1r,4r)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 655.4; 1.546 min (Method)
452	 1-(4-(2-(6-((3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)ethan-1-one Analytical Data: 571.4; 1.907 min (Method E)

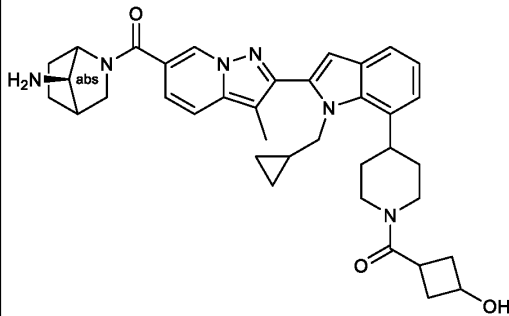
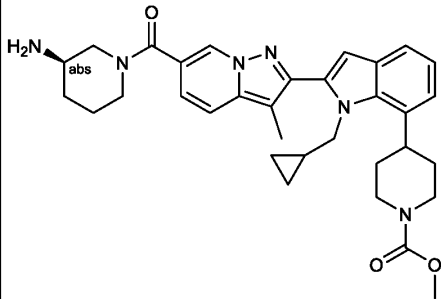
453	 1-(4-(2-(6-((7R)-7-amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxyethan-1-one Analytical Data: 595.4; 8.066 min (Method D)
454	 (S)-1-(4-(2-(6-((R)-3-aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxypropan-1-one Analytical Data: 597.3; 1.520 min (Method E)
455	 (R)-1-(4-(2-(6-(3-aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxyethan-1-one Analytical Data: 583.3; 1.505 min (Method E)

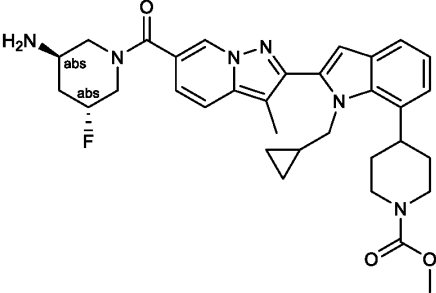
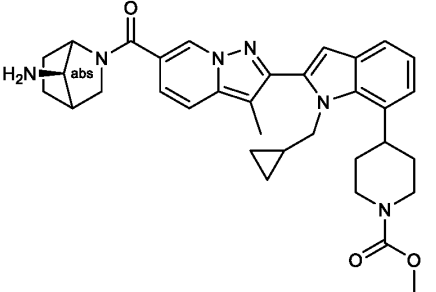
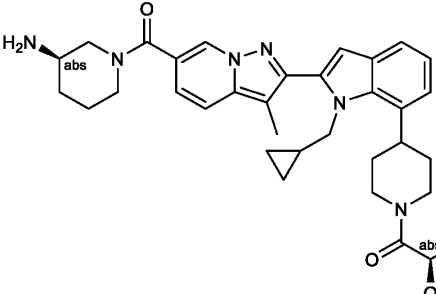
456	 (R)-(3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxy-3-(trifluoromethyl)cyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (mixture of diastereomers) Analytical Data: 677.4; 1.779 min (Method E)
457	 ((R)-3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(tetrahydro-2H-pyran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (mixture of diastereomers) Analytical Data: 623.3; 1.735 min (Method)
458	

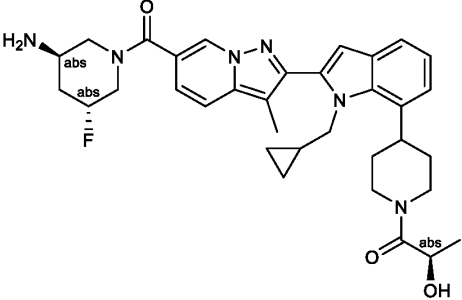
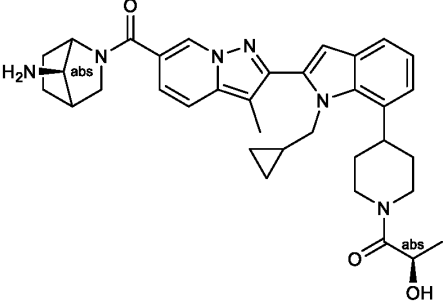
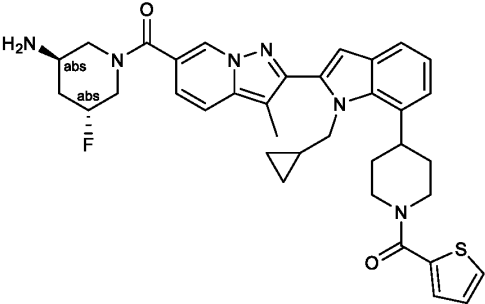
	((3R,5R)-3-amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(tetrahydro-2H-pyran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (mixture of diastereomers) Analytical Data: 641.5; 1.792 min (Method E)
459	 (S)-1-(4-(2-(6-((3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxypropan-1-one Analytical Data: 615.3; 1.649 min (Method E)
460	 (R)-1-(4-(2-(6-((R)-3-aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxypropan-1-one Analytical Data: 597.4; 1.521 min (Method E)

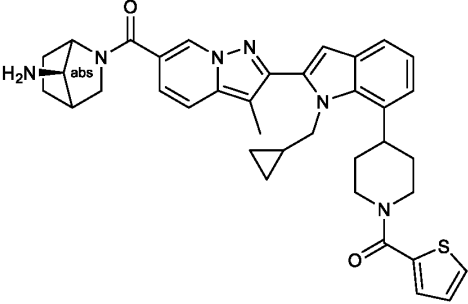
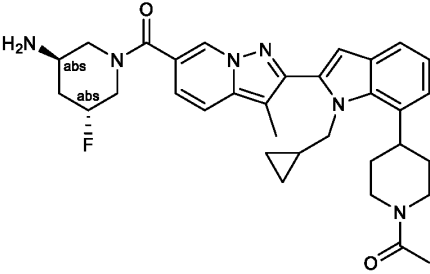
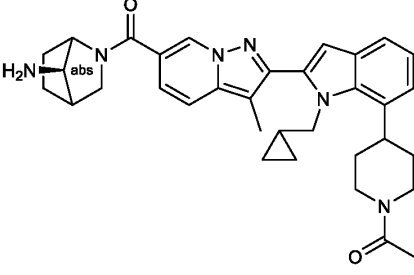
461	 (R)-1-(4-(2-(6-((3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxypropan-1-one Analytical Data: 615.3; 1.538 min (Method E)
462	 ((R)-3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(tetrahydrofuran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (mixture of diastereomers) Analytical Data: 609.3; 1.708 min (Method E)
463	 ((3R,5R)-3-amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(tetrahydrofuran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (mixture of diastereomers) Analytical Data: 627.3; 1.770 min (Method E)

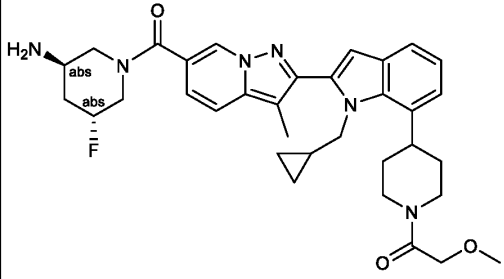
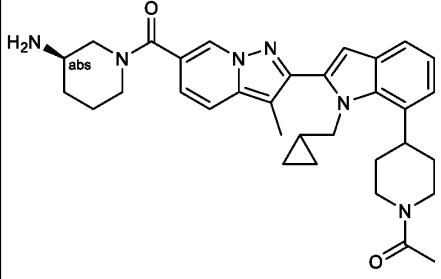
464	 (R)-(3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(thiophene-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 621.3; 1.819 min (Method E)
465	 (R)-(3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxycyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (mixture of diastereomers) Analytical Data: 609.3; 1.390 min (Method E)
466	 ((3R,5R)-3-amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxycyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (mixture of diastereomers)

	Analytical Data: 627.3; 1.406 min (Method E)
467	 (4-(2-(6-((7R)-7-amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)(3-hydroxycyclobutyl)methanone (mixture of diastereomers) Analytical Data: 621.3; 1.371 min (Method E)
468	 Methyl (R)-4-(2-(6-(3-aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidine-1-carboxylate Analytical Data: 569.3; 1.671 min (Method E)

469	 Methyl 4-(2-(6-((3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidine-1-carboxylate Analytical Data: 587.3; 1.699 min (Method E)
470	 Methyl 4-(2-(6-((7R)-7-amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidine-1-carboxylate Analytical Data: 581.3; 1.646 min (Method E)
471	 (R)-1-(4-(2-(6-((R)-3-aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-hydroxypropan-1-one Analytical Data: 583.3; 1.428 min (Method E)

472	 (R)-1-(4-(2-(6-((3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-hydroxypropan-1-one Analytical Data: 601.3; 1.554 min (Method E)
473	 (2R)-1-(4-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-hydroxypropan-1-one Analytical Data: 595.3; 1.406 min (Method E)
474	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(thiophene-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 639.2; 1.749 min (Method E)

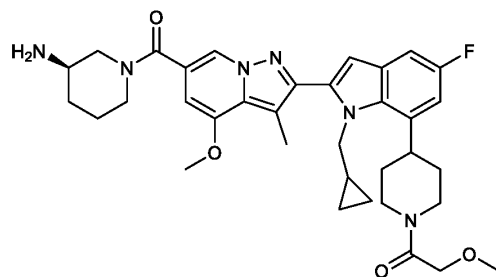
475	 (4-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)(thiophen-2-yl)methanone Analytical Data: 633.2; 1.911 min(Method E)
476	 1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)ethan-1-one Analytical Data: 571.4; 1.60 min(Method E)
477	 1-(4-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)ethan-1-one Analytical Data: 565.4; 1.640 min (Method E)

478	 1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxyethan-1-one Analytical Data: 601.4; 5.680 min (Method D)
479	 (R)-1-(4-(2-(6-(3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)ethan-1-one Analytical Data: 553.4; 1.484 min (Method E)

Example 480

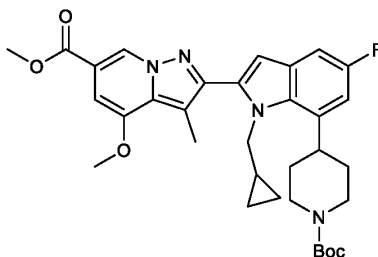
(R)-1-(4-(2-(6-(3-aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-7-yl)piperidin-1-yl)-2-methoxyethan-1-one

5



Intermediate 480A

methyl 2-(7-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate

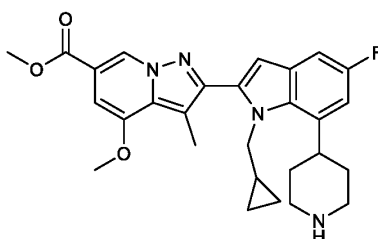


- 5 To a stirred solution of Intermediate 36 (900 mg, 1.967 mmol) in DMF (5 ml) was added Intermediate 1 (360 mg, 1.967 mmol) and copper(I) iodide (187 mg, 0.984 mmol) and heated to 80 °C for 48 hours. The reaction mixture was quenched with NaHCO₃ (300ml) and extracted with ethyl acetate (2 x 300 ml). The combined organic layers were dried over sodium sulphate, filtered and concentrated under reduced vacuum pressure to
- 10 give crude product. Purified using a silica gel column using 0-20% ethyl acetate in hexane to afford methyl 2-(7-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate (600 mg, 52%). LC-MS m/z: 591.2 [M+H]⁺

15

Intermediate 480B

Methyl 2-(1-(cyclopropylmethyl)-5-fluoro-7-(piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate

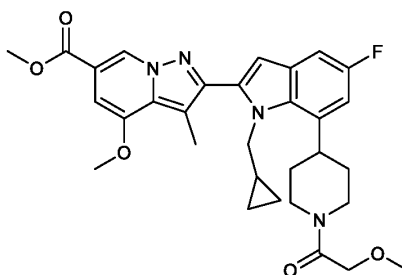


- TFA (0.078 ml, 1.016 mmol) was added to stirred solution of Intermediate 480A
- 20 (600 mg, 1.016 mmol) in DCM (5 ml) at 0°C. The reaction mixture was allowed to warm to a room temperature and stirred for 3 hours, concentrated under reduced pressure to obtain a crude title compound methyl 2-(1-(cyclopropylmethyl)-5-fluoro-7-(piperidin-4-

yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate (470 mg, 94%). LC-MS m/z: 491.3 [M+H]⁺.

Intermediate 480C

- 5 Methyl 2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-(2-methoxyacetyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate

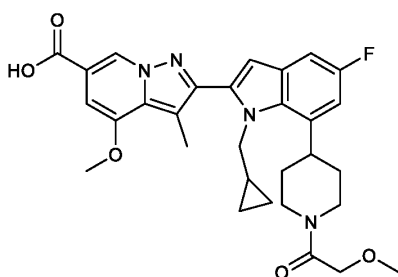


- DIPEA (0.128 ml, 0.734 mmol) and HATU (140 mg, 0.367 mmol) were added to a stirred solution of Intermediate 480B (24.24 mg, 0.269 mmol). The reaction was continued for 3 hours. The reaction mixture was quenched with water (50 ml), and the solids obtained were filtered and dried in vacuo to obtain the title compound methyl 2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-(2-methoxyacetyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate (110 mg, 80%). LC-MS m/z: 563.3 [M+H]⁺.

15

Intermediate 480D

- 2-(1-(Cyclopropylmethyl)-5-fluoro-7-(1-(2-methoxyacetyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylic acid

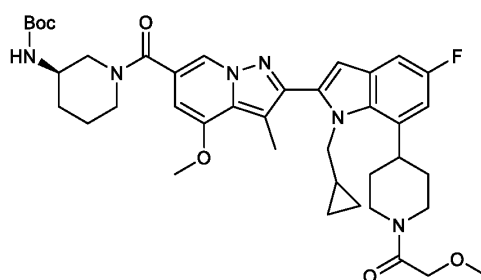


- 20 LiOH (13.83 mg, 0.578 mmol) was added to a stirred solution of Intermediate 480C (130 mg, 0.231 mmol) in a mixture of solvents: THF (1 ml), MeOH (1 ml) and water (1 ml). The reaction mixture was stirred for 3 hours, concentrated under reduced

pressure to obtain a crude residue, which was acidified with 1 N HCl. The solids precipitated were filtered through Buchner funnel, and dried in vacuum to afford the title compound 2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-(2-methoxyacetyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylic acid (105 mg, 83%). LC-MS m/z: 549.2 [M+H]⁺.

Intermediate 480E

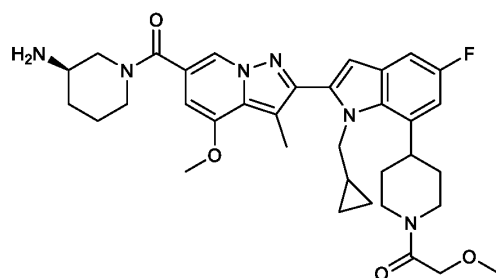
tert-Butyl (R)-(1-(2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-(2-methoxyacetyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)piperidin-3-yl)carbamate



tert-Butyl (R)-piperidin-3-ylcarbamate (18.25 mg, 0.091 mmol), DIPEA (0.048 ml, 0.273 mmol) and HATU (52.0 mg, 0.137 mmol) were added to a stirred solution of Intermediate 480D (50 mg, 0.091 mmol) in DMF (1 ml). The reaction mixture was stirred for 3 hours, quenched with ice cold water, and the solids obtained were filtered through Buchner funnel and dried under reduced pressure to afford the title compound tert-butyl (R)-(1-(2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-(2-methoxyacetyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)piperidin-3-yl)carbamate (43 mg, 65%). LC-MS m/z: 731.2 [M+H]⁺.

Example 480

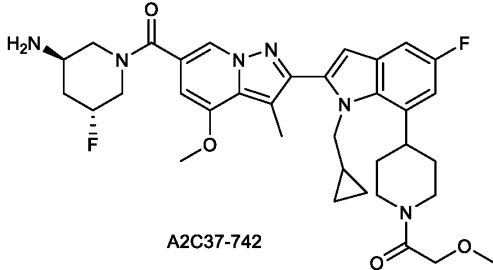
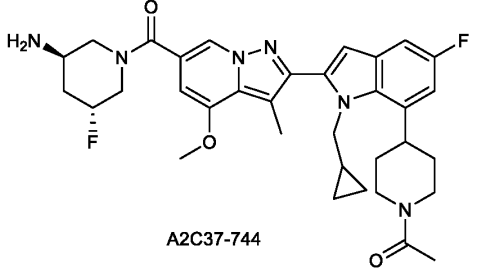
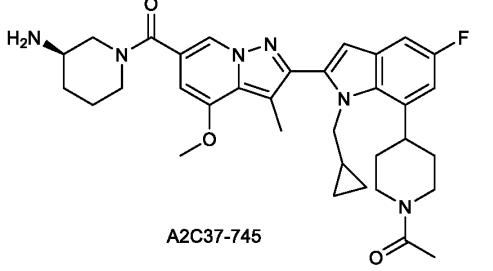
(R)-1-(4-(2-(6-(3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-7-yl)piperidin-1-yl)-2-methoxyethan-1-one



TFA (10.54 μ l, 0.137 mmol) was added to a solution of Intermediate 480E (50 mg, 0.068 mmol) in DCM (1 ml) at 0°C. The reaction mixture was stirred for 3 hours, and concentrated in vacuum to obtain a crude compound, which was purified using
5 preparative LC/MS with the following conditions: Column: Waters XBridge C18, 150 mm $\times$ 19 mm, 5- μ m particles; mobile phase A: 5:95 acetonitrile: water with 0.1% trifluoroacetic acid; mobile phase B: 95:5 acetonitrile: water with 0.1% trifluoroacetic acid; gradient: a 0-minute hold at 15% B, 15-30% B over 20 minutes, then a 5-minute hold at 100% B; flow rate: 20 ml/min; column temperature: 25°C. Fraction collection was
10 triggered by signals. Fractions containing the desired product were combined and dried using centrifugal evaporation. The purified material was then diluted with a 1:1 mixture of ethylene dichloride and methanol (EDM), treated with Si-Pyridine and shaken for a minimum of 2 hours. The resulting mixture was filtered and dried using centrifugal evaporation to afford (R)-1-(4-(2-(6-(3-aminopiperidine-1-carbonyl)-4-methoxy-3-
15 methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-7-yl)piperidin-1-yl)-2-methoxyethan-1-one.

Compounds of Examples 481 to 483 in Table 49 were prepared following a procedure similar to the preparation of a compound of Example 480, by acid amine
20 coupling of Intermediate 480B with appropriate carboxylic acid followed by ester hydrolysis and the resulting carboxylic acid with appropriate amines.

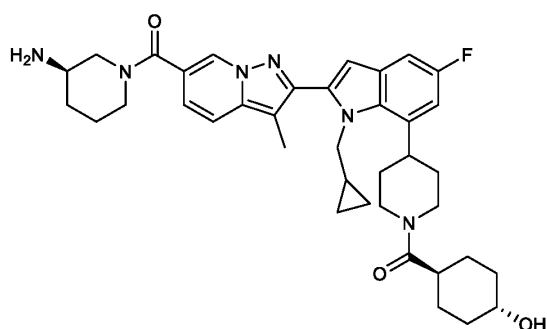
Table 49

Example	Structure
	Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method 1)
481	 A2C37-742 1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-7-yl)piperidin-1-yl)-2-methoxyethan-1-one Analytical Data: 633.2; 1.911 min(Method E)
482	 A2C37-744 1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-7-yl)piperidin-1-yl)ethan-1-one Analytical Data: 619.3; 1.703 min(Method E)
483	 A2C37-745

	(R)-1-(4-(2-(6-(3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-7-yl)piperidin-1-yl)ethan-1-one Analytical Data: 601.3; 1.629 min(Method E)
--	--

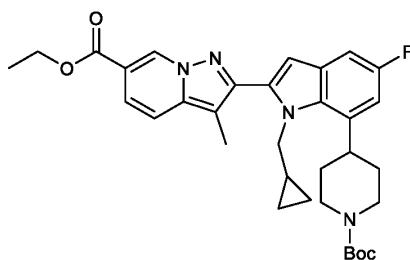
Example 484

5 ((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-((1r,4r)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone



Intermediate 484A

10 Ethyl 2-(7-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate

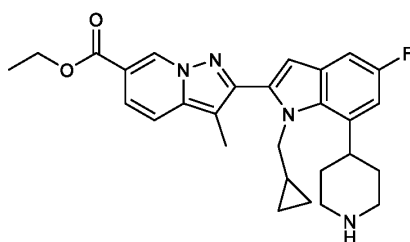


Intermediate 484A (3.0 g, 68%) was prepared following a procedure similar to the preparation of Intermediate 386A. LC-MS m/z: 575.5 [M+H]⁺.

15

Intermediate 484B

Ethyl 2-(1-(cyclopropylmethyl)-5-fluoro-7-(piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate

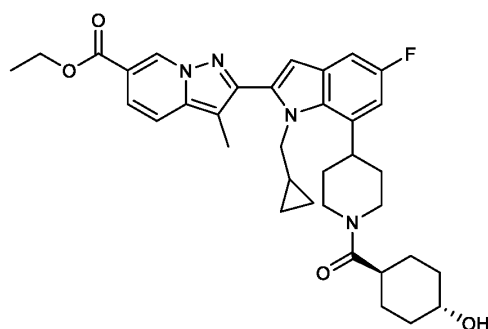


Intermediate 484B (500 mg, 76%) was obtained from intermediate 484A following a procedure similar to the preparation of Intermediate 386B. LC-MS m/z: 475.4 [M+H]⁺.

5

Intermediate 484C

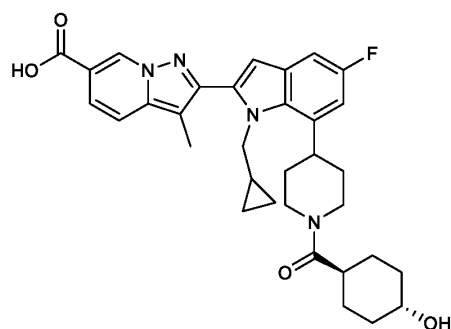
Ethyl 2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-((1*r*,4*r*)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1*H*-indol-2-yl)-3-methylpyrazolo[1,5-*a*]pyridine-6-carboxylate



10 (1*s*,4*s*)-4-Hydroxycyclohexane-1-carboxylic acid (30.4 mg, 0.211 mmol), DIPEA (0.110 ml, 0.632 mmol) and HATU (120 mg, 0.316 mmol) were added to a stirred solution of Intermediate 484B (100 mg, 0.211 mmol) in DMF (2 ml). The reaction mixture was stirred 3 hours, quenched with water (50 ml), and extracted with ethyl acetate (2×50 ml). The combined organic layers were dried over sodium sulphate, filtered,
15 and concentrated under reduced pressure to give afford crude ethyl 2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-((1*s*,4*s*)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1*H*-indol-2-yl)-3-methylpyrazolo[1,5-*a*]pyridine-6-carboxylate (100 mg, 79%). LC-MS m/z: 601.8 [M+H]⁺.

Intermediate 484D

2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-((1*r*,4*r*)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1*H*-indol-2-yl)-3-methylpyrazolo[1,5-*a*]pyridine-6-carboxylic acid



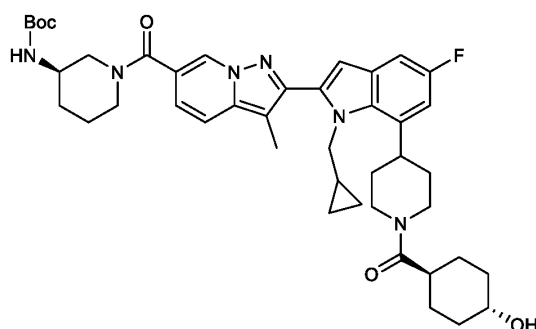
5

LiOH (3.99 mg, 0.166 mmol) was added to a stirred solution of Intermediate 484C (100 mg, 0.166 mmol) in a mixture of solvents: THF (1 ml), methanol (1 ml) and water (1 ml). The reaction mixture was stirred for 4 hours, concentrated in vacuo and the salts obtained were neutralized using 1 N HCl. The solids obtained was filtered through a Buchner funnel, and dried under reduced pressure to afford 2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-((1*r*,4*r*)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1*H*-indol-2-yl)-3-methylpyrazolo[1,5-*a*]pyridine-6-carboxylic acid (90 mg, 94%). LC-MS *m/z*: 573.5 [M+H]⁺.

15

Intermediate 484E

tert-butyl ((*R*)-1-(2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-((1*r*,4*r*)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1*H*-indol-2-yl)-3-methylpyrazolo[1,5-*a*]pyridine-6-carbonyl)piperidin-3-yl)carbamate



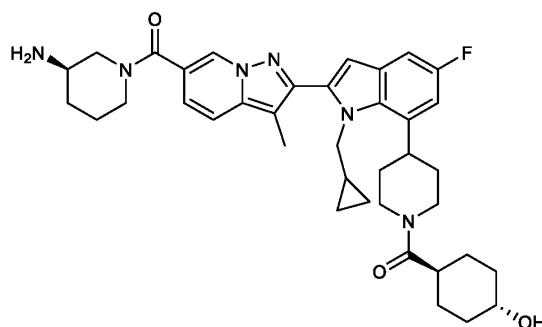
20

Intermediate 484E (100 mg, 76%) was prepared starting from Intermediate 484D following a procedure similar to the preparation of Intermediate 386E. LC-MS m/z : 755.6 $[M+H]^+$.

5

Example 484

((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-((1*r*,4*r*)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1*H*-indol-2-yl)-3-methylpyrazolo[1,5-*a*]pyridin-6-yl)methanone

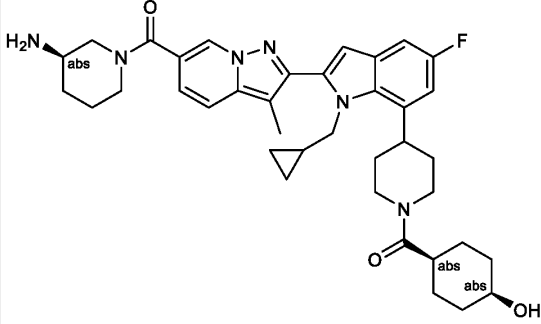
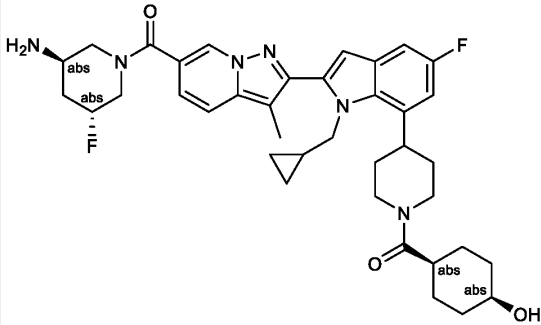


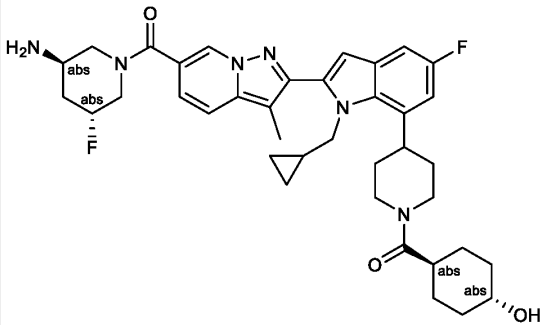
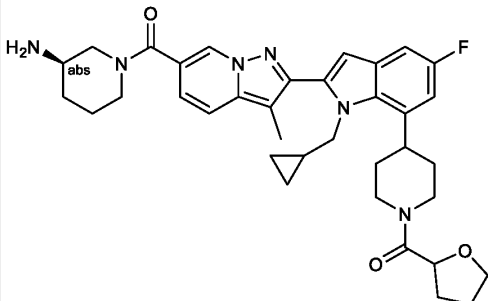
10 TFA (0.106 mmol) was added to a stirred solution of Intermediate 484E (80 mg, 0.106 mmol) in DCM (1 ml) at 0°C. The reaction mixture was stirred for 3 hours, concentrated in vacuo to obtain a crude compound, which was purified using preparative LC/MS with the following conditions: Column: Waters X Bridge C18, 19×150 mm, 5 μ m particles; mobile phase A: 10 mM ammonium acetate; mobile phase B: acetonitrile; 15 gradient: 12-47% B over 25 minutes, then a 5-minute hold at 100% B; flow rate: 15 ml/min. Fractions containing the desired product were combined, and dried using centrifugal evaporation. The purified material was then diluted with a 1:1 mixture of ethylene dichloride and methanol (EDM), treated with Si-Pyridine, and shaken for a minimum of 2 hours, filtered, and dried via centrifugal evaporation to afford ((R)-3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-((1*s*,4*s*)-4- 20 hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1*H*-indol-2-yl)-3-methylpyrazolo[1,5-*a*]pyridin-6-yl)methanone (7.3 mg, 10%). LCMS m/z : 655.4 $[M+H]^+$. LCMS retention time : 1.52 min (method E); 1H NMR (400 MHz, DMSO- d_6) δ ppm: 8.86 (s, 1H), 8.13-7.90 (m, 2H), 7.82 (d, $J=9.3$ Hz, 1H), 7.33-7.10 (m, 3H), 7.04-6.93 (m, 2H), 6.78 (s, 1H), 25 4.70-4.62 (m, 1H), 4.50-4.26 (m, 3H), 4.17-3.94 (m, 3H), 3.84-3.79 (m, 1H), 3.64-3.59

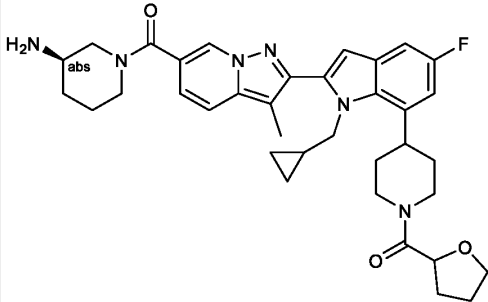
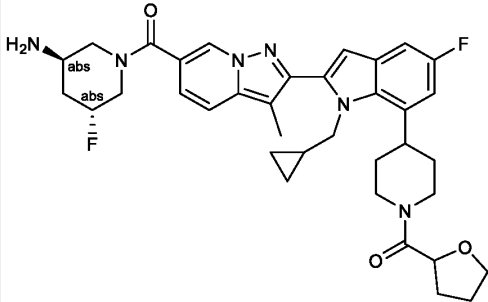
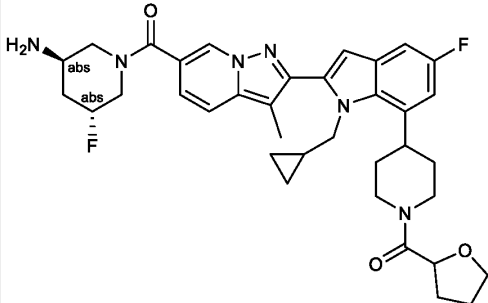
(m, 1H), 3.31-3.16 (m, 5H), 2.95-2.61 (m, 4H), 2.37 (s, 3H), 2.06-1.94 (m, 3H), 1.87-1.35 (m, 7H), 0.98-0.88 (m, 1H), 0.23 (br, d, J=8.8 Hz, 2H), 0.12-0.28 (m, 2H).

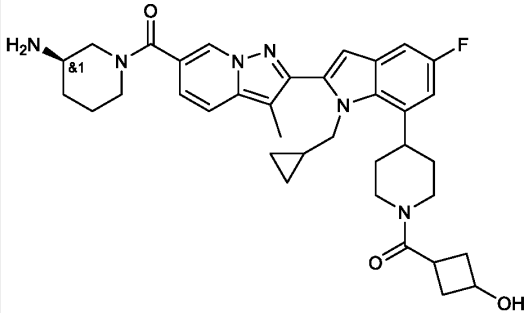
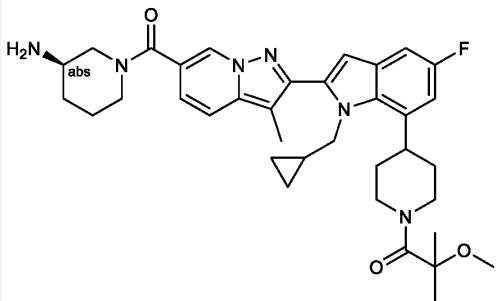
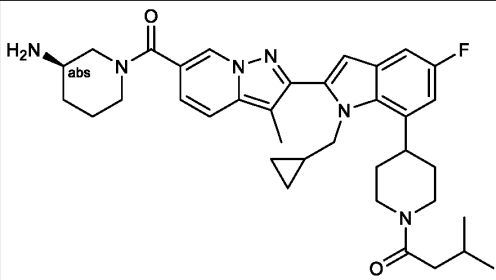
- Compounds of Examples 485 to 509 in Table 50 were prepared following a procedure similar to the preparation of a compound of Example 484, by acid amine coupling of Intermediate 484B with appropriate carboxylic acid followed by ester hydrolysis and coupling with appropriate amines

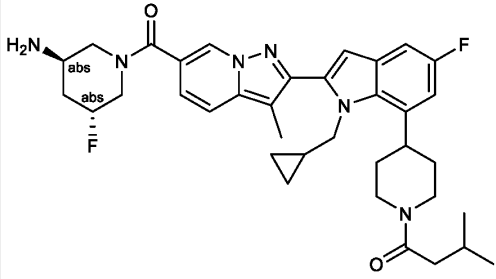
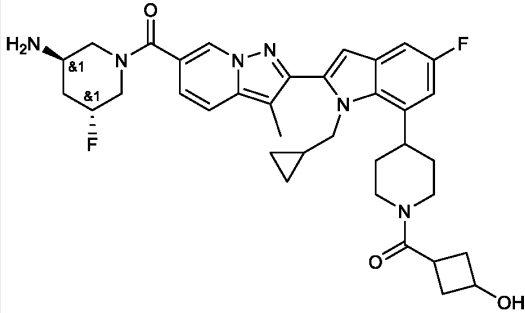
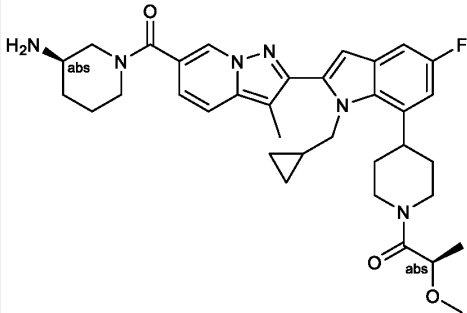
Table 50

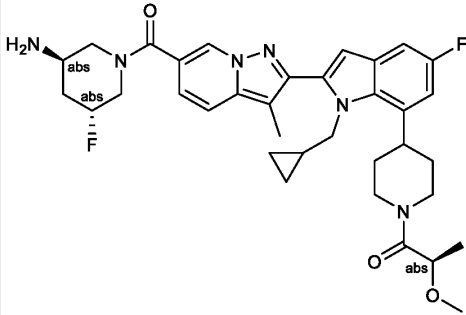
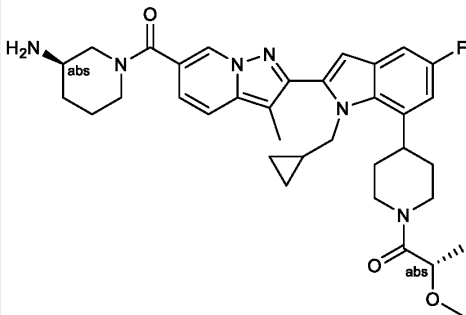
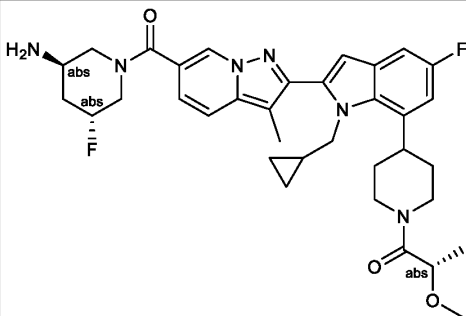
Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
485	 ((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-((1s,4s)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 655.4; 1.650 min (Method E)
486	

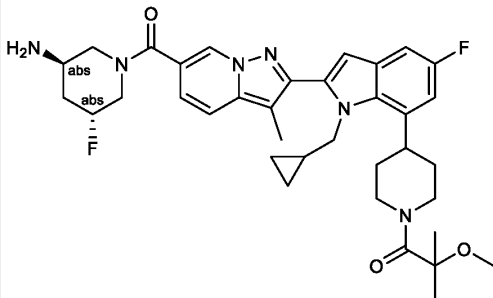
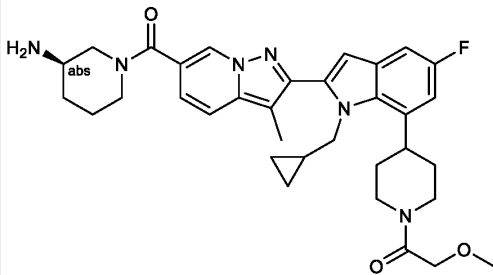
	((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-((1s,4s)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 673.4; 1.623 min (Method E)
487	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-((1r,4r)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 673.4; 1.627 min (Method E)
488	 ((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-(tetrahydrofuran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (isomer 1) Analytical Data: 627.4; 1.942 min (Method E)

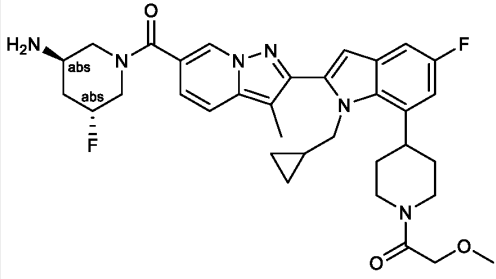
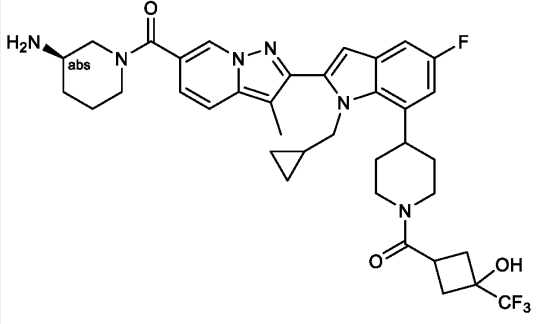
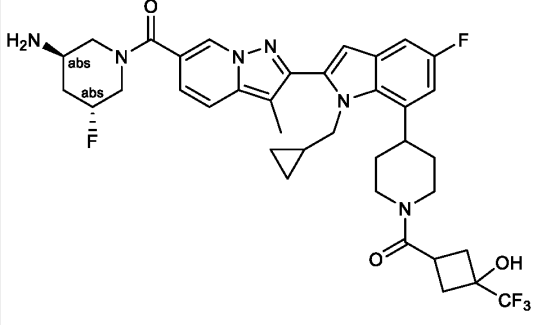
489	 ((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-(tetrahydrofuran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (isomer 2) Analytical Data: 627.4; 1.942 min (Method E)
490	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-(tetrahydrofuran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (isomer 1) Analytical Data: 645.45; 1.979 min (Method E)
491	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-(tetrahydrofuran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (isomer 2) Analytical Data: 645.45; 1.979 min (Method E)

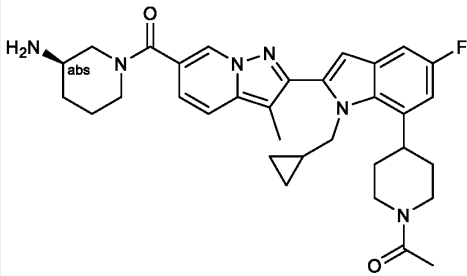
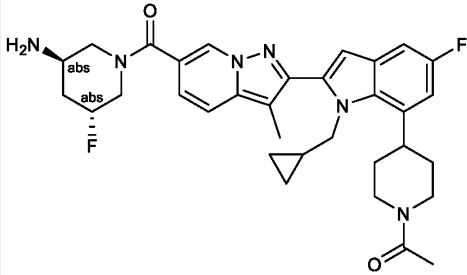
492	 (R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-(3-hydroxycyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (mixture of diastereomers) Analytical Data: 627.3; 1.509 min (Method E)
493	 (R)-1-(4-(2-(6-(3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-7-yl)piperidin-1-yl)-2-methoxy-2-methylpropan-1-one Analytical Data: 629.3; 1.868 min (Method E)
494	 1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-7-yl)piperidin-1-yl)-3-methylbutan-1-one Analytical Data: 613.3; 1.780 min (Method E)

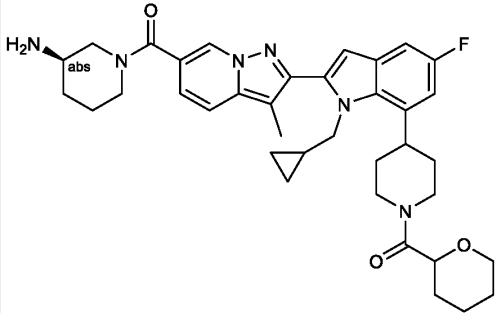
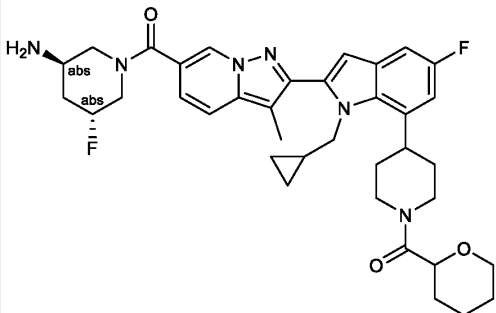
495	 1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-7-yl)piperidin-1-yl)-3-methylbutan-1-one Analytical Data: 631.3; 1.810 min (Method E)
496	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-(3-hydroxycyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (mixture of diastereomers) Analytical Data: 645.3; 1.447 min (Method E)
497	 (R)-1-(4-(2-(6-((R)-3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-7-yl)piperidin-1-yl)-2-methoxypropan-1-one Analytical Data: 615.3; 1.551 min (Method E)

498	 (R)-1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-7-yl)piperidin-1-yl)-2-methoxypropan-1-one Analytical Data: 633.3; 1.693 min (Method E)
499	 (S)-1-(4-(2-(6-((R)-3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-7-yl)piperidin-1-yl)-2-methoxypropan-1-one Analytical Data: 615.3; 1.545 min (Method E)
500	 (S)-1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-7-yl)piperidin-1-yl)-2-methoxypropan-1-one

	Analytical Data: 633.3; 1.564 min (Method E)
501	 1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-7-yl)piperidin-1-yl)-2-methoxy-2-methylpropan-1-one Analytical Data: 647.3; 1.908 min (Method)
502	 (R)-1-(4-(2-(6-(3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-7-yl)piperidin-1-yl)-2-methoxyethan-1-one Analytical Data: 601.3; 1.513 min (Method E)

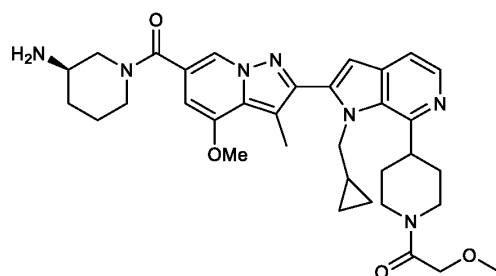
503	 1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-7-yl)piperidin-1-yl)-2-methoxyethan-1-one Analytical Data: 619.3; 1.529 min (Method E)
504	 (R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-(3-hydroxy-3-(trifluoromethyl)cyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 695.3; 1.712 min (Method E)
505	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-(3-hydroxy-3-(trifluoromethyl)cyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (mixture of diastereomers)

	Analytical Data: 713.3; 1.726 min (Method E)
506	 (R)-1-(4-(2-(6-(3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-7-yl)piperidin-1-yl)ethan-1-one Analytical Data: 571.3; 1.508 min (Method E)
507	 1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-7-yl)piperidin-1-yl)ethan-1-one Analytical Data: 589.2; 1.573 min (Method E)

508	 ((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-(tetrahydro-2H-pyran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (mixture of diastereomers) Analytical Data: 641.4; 1.732 min (Method E)
509	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-(tetrahydro-2H-pyran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (mixture of diastereomers) Analytical Data: 659.3; 1.711 min (Method E)

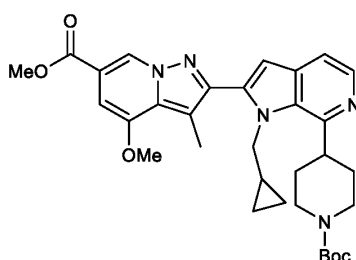
Example 510

(R)-1-(4-(2-(6-(3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)piperidin-1-yl)-2-methoxyethan-1-one



Intermediate 510A

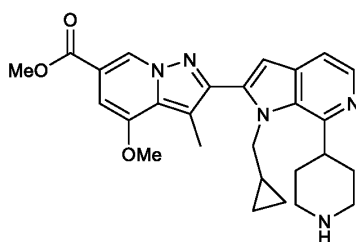
5 methyl 2-(7-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate



1-Amino-3-methoxy-5-(methoxycarbonyl)pyridin-1-ium 2,4 dinitro phenolate salt (2.120 g, 5.79 mmol) and copper(I) iodide (0.110 g, 0.579 mmol) were added to a stirred solution of Intermediate 44 (0.85 g, 1.929 mmol) in DMF (3 ml). The reaction mixture was stirred at 80°C for 30 hours, allowed to cool to a room temperature, diluted with water (20 ml), quenched with saturated NaHCO₃ solution (10 ml), and extracted with ethyl acetate (3×20 ml). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuum to obtain a crude product, which was purified using a silica gel column, eluting with 0-70% ethyl acetate in hexane to afford methyl 2-(7-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate (520 mg, 47%). LC-MS m/z: 574.3 [M+H]⁺.

Intermediate 510B

20 Methyl 2-(1-(cyclopropylmethyl)-7-(piperidin-4-yl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate



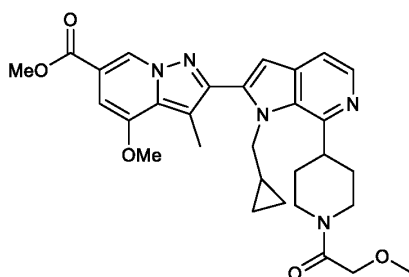
TFA (0.698 ml, 9.06 mmol) was added to a stirred solution of Intermediate 510A (520 mg, 0.906 mmol) in dichloromethane (10 ml). The reaction mixture was stirred at a room temperature for 16 hours, the salts thus obtained were treated with NaHCO₃

5 solution, and extracted with ethyl acetate (2×25 ml). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuum to afford methyl 2-(1-(cyclopropylmethyl)-7-(1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate (410 mg, 96%). LC-MS m/z: 474.2 [M+H]⁺.

10

Intermediate 510C

Methyl 2-(1-(cyclopropylmethyl)-7-(1-(2-methoxyacetyl)piperidin-4-yl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate

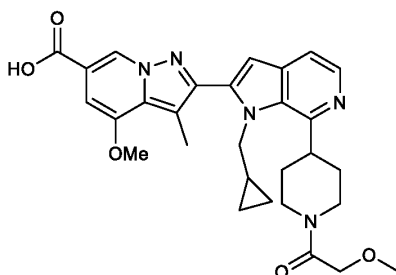


15 HATU (181 mg, 0.475 mmol) and 2-methoxyacetic acid (42.8 mg, 0.475 mmol) followed by DIPEA (0.138 ml, 0.792 mmol) were added to a stirred solution of Intermediate 510B (150 mg, 0.317 mmol) in DMF (2.0 ml). The reaction mixture was stirred for 2 hours, diluted with water (5 ml), quenched with saturated NaHCO₃ solution (10 ml), and extracted with ethyl acetate (3×25 ml). The combined organic layers were

20 washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuum to afford methyl 2-(1-(cyclopropylmethyl)-7-(1-(2-methoxyacetyl)piperidin-4-yl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate (130 mg, 75%) LC-MS m/z: 546.3 [M+H]⁺.

Intermediate 510D

2-(1-(Cyclopropylmethyl)-7-(1-(2-methoxyacetyl)piperidin-4-yl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylic acid



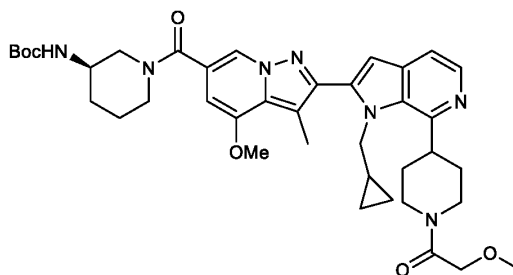
5

LiOH (30.7 mg, 1.283 mmol) was added to a stirred solution of Intermediate 510C (140 mg, 0.257 mmol) in THF (5 ml), MeOH (1 ml), water (2 ml). The reaction mixture stirred for 4 hours, diluted with water (5 ml) and 1N HCl (2 ml), and extracted with ethyl acetate (2×25ml). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuum to afford 2-(1-(cyclopropylmethyl)-7-(1-(2-methoxyacetyl)piperidin-4-yl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylic acid (90 mg, 66%). LC-MS m/z: 532.2 [M+H]⁺.

15

Intermediate 510E

(R)-1-(4-(2-(6-(3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)piperidin-1-yl)-2-methoxyethan-1-one



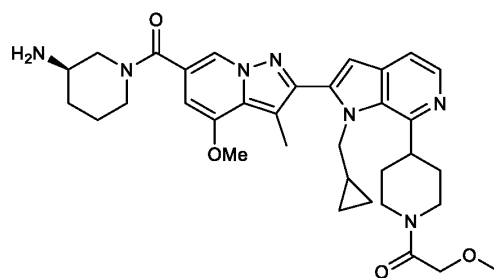
20

tert-Butyl (R)-piperidin-3-ylcarbamate (25.4 mg, 0.127 mmol), HATU (48.3 mg, 0.127 mmol) followed by DIPEA (0.037 ml, 0.212 mmol) were added to a stirred solution of Intermediate 510D (45 mg, 0.085 mmol) in DMF (1.0 ml). The reaction mixture was stirred 16 hours, diluted with water (5 ml), and extracted with ethyl acetate (2×10ml). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuum to afford tert-butyl (R)-(1-(2-(1-(cyclopropylmethyl)-7-(1-(2-methoxyacetyl)piperidin-4-yl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)piperidin-3-yl)carbamate (40 mg, 66%). LC-MS m/z: 714.3 [M+H]⁺.

10

Example 510

(R)-1-(4-(2-(6-(3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)piperidin-1-yl)-2-methoxyethan-1-one



15

TFA (0.043 ml, 0.560 mmol) was added to a stirred solution of Intermediate 510E (40 mg, 0.056 mmol) in dichloromethane (5 ml) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for 3 hours, concentrated in vacuum to obtain a crude compound, which was purified using preparative LC/MS with the following conditions: Column: Waters X Bridge C18, 150×19 mm, 5 μm particles; mobile phase A: 5:95 acetonitrile: water with 0.1% trifluoroacetic acid; mobile phase B: 95:5 acetonitrile: water with 0.1% trifluoroacetic acid; gradient: a 0-minute hold at 20% B, 20-40% B over 20 minutes, then a 5-minute hold at 100% B; flow rate: 20 ml/min; column temperature: 25°C. Fraction collection was triggered by signals. Fractions containing the desired product were combined and dried via centrifugal evaporation. The purified material was then diluted with a 1:1 mixture of ethylene dichloride and methanol (EDM), treated with Si-Pyridine, and shaken for a minimum of 2 hours, filtered and dried using centrifugal

25

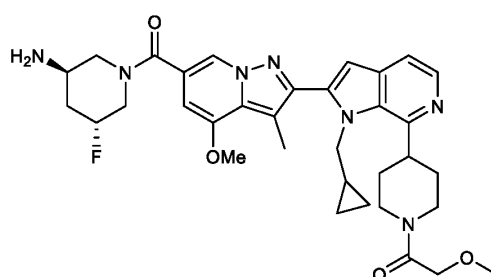
evaporation to afford (R)-1-(4-(2-(6-(3-aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)piperidin-1-yl)-2-methoxyethan-1-one. LC-MS m/z: 614.3 [M+H]⁺. Retention time: 1.188 min (Method E).

5

Example 511

1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)piperidin-1-yl)-2-methoxyethan-1-one

10



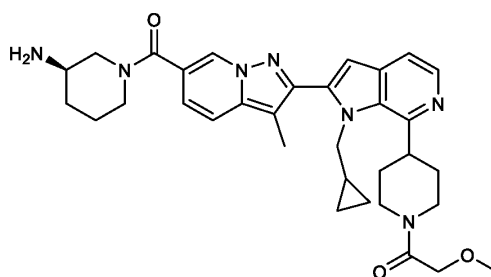
Compound of Example 511 was prepared following a procedure similar to the preparation of a compound of Example 510, by acid amine coupling of Intermediate 510B with appropriate carboxylic acid followed by ester hydrolysis and coupling with appropriate amine. LC-MS m/z [M+H]⁺: 632.3. HPLC retention time: 1.309 min (Method E)

15

Example 512

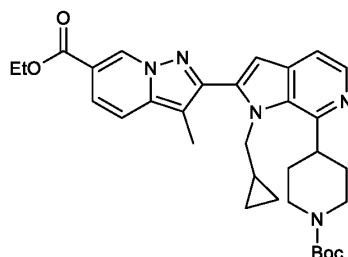
(R)-1-(4-(2-(6-(3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)piperidin-1-yl)-2-methoxyethan-1-one

20



Intermediate 512A

Ethyl 2-(7-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate



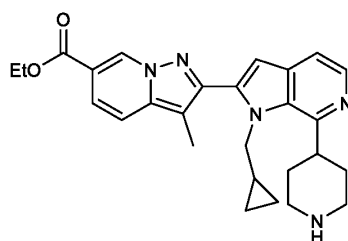
5

Intermediate 512A (480 mg, 45%) was prepared by following a similar procedure depicted for Intermediate 386A using the intermediates 44 and 8. LC-MS m/z: 558.3 [M+H]⁺; ¹H NMR (300 MHz, DMSO-d₆) δ ppm: 9.21 (s, 1H), 8.18-8.12 (m, 1H), 7.87 (d, J=9.4 Hz, 1H), 7.64 (d, J=9.4 Hz, 1H), 7.48 (d, J=5.3 Hz, 1H), 6.89 (s, 1H), 4.62-4.52 (m, 2H), 4.46-4.29 (m, 2H), 4.21-4.01 (m, 2H), 3.11-2.81 (m, 2H), 2.38 (s, 3H), 1.93-1.79 (m, 4H), 1.59-1.50 (m, 1H), 1.44 (s, 9H), 1.39-1.34 (m, 3H), 1.09-0.95 (m, 1H), 0.32-0.21 (m, 2H), -0.11--0.18 (m, 2H).

10

Intermediate 512B

Ethyl 2-(1-(cyclopropylmethyl)-7-(piperidin-4-yl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate



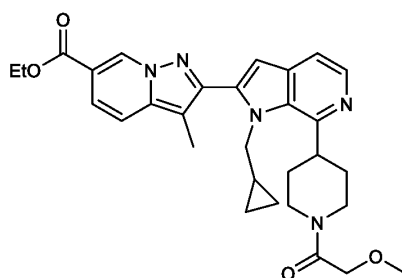
15

Intermediate 512B (320 mg, 81%) was prepared in similar fashion to Intermediate 510B. LC-MS m/z: 458.3 [M+H]⁺.

20

Intermediate 512C

ethyl 2-(1-(cyclopropylmethyl)-7-(1-(2-methoxyacetyl)piperidin-4-yl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate

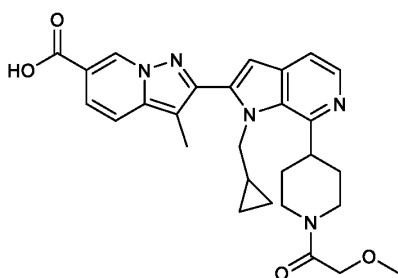


Intermediate 512C (130 mg, 0, 75%) was prepared in similar fashion to intermediate 510C. LC-MS m/z: 530.3 [M+H]⁺.

5

Intermediate 512D

2-(1-(cyclopropylmethyl)-7-(1-(2-methoxyacetyl)piperidin-4-yl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylic acid

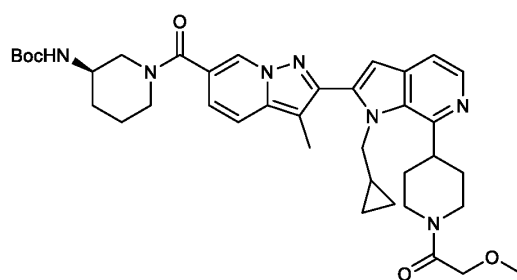


10

Intermediate 512D (90 mg, 68%) was prepared in similar fashion to intermediate 510D. LC-MS m/z: 502.2 [M+H]⁺

Intermediate 512E

15 tert-butyl (R)-(1-(2-(1-(cyclopropylmethyl)-7-(1-(2-methoxyacetyl)piperidin-4-yl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)piperidin-3-yl)carbamate

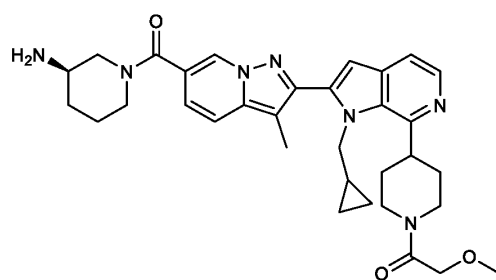


Intermediate 512E (40 mg, 65%). was prepared in similar fashion to intermediate 510E.
LC-MS m/z: 684.3 $[M+H]^+$

5

Example 512

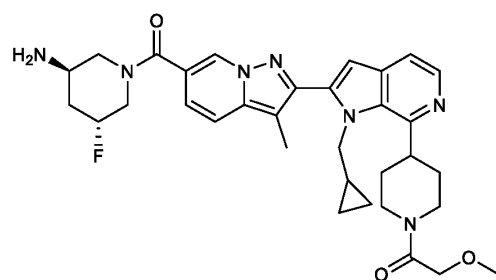
(R)-1-(4-(2-(6-(3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)piperidin-1-yl)-2-methoxyethan-1-one



10

Prepared in similar fashion to Example 510. LC-MS m/z: 584.3 $[M+H]^+$ 1.128 min (Method E)

Example 513



15

1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)piperidin-1-yl)-2-methoxyethan-1-one

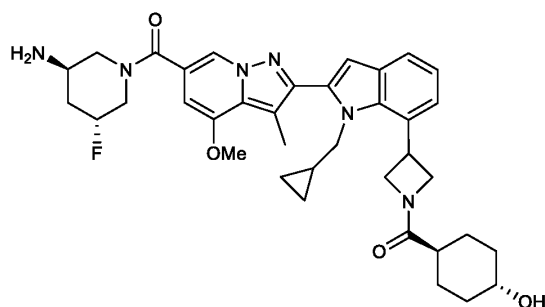
- 5 Compounds of Example 513 in Table 52 was prepared following a procedure similar to the preparation of a compound of Example 512, by acid amine coupling of Intermediate 512B with appropriate carboxylic acid followed by ester hydrolysis and coupling with appropriate amines

Analytical Data: LC-MS m/z [M+H]⁺; HPLC retention time (HPLC method

- 10 Analytical Data: 602.3, 1.188 min (Method E)

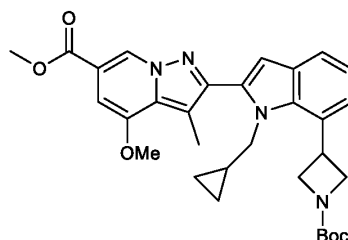
Example 514

- ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1R,4R)-4-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone
- 15



Intermediate 514A

- Methyl 2-(7-(1-(tert-butoxycarbonyl)azetidin-3-yl)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate
- 20

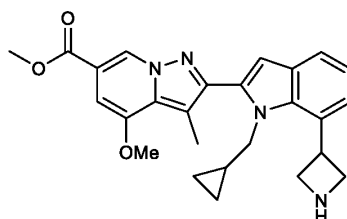


Intermediate 1 (3.20 g, 8.75 mmol) was added to a stirred solution of Intermediate 49 (1.2 g, 2.92 mmol) and CuI (0.167 g, 0.875 mmol) in DMF (10 ml). The reaction mixture was stirred at 80°C for 30 hours, diluted with water (20 ml), and extracted with ethyl acetate (3×30 ml). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuum. The crude compound thus obtained was purified using a silica gel column, eluting with 0-20% ethyl acetate in hexane to afford methyl 2-(7-(1-(tert-butoxycarbonyl)azetidin-3-yl)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate (1.3 g, 82%). LC-MS m/z: 545.4 [M+H]⁺.

10

Intermediate 514B

Methyl 2-(7-(azetidin-3-yl)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate

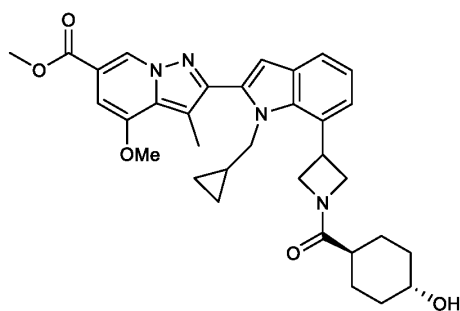


15 TFA (1.839 ml, 23.87 mmol) was added to a stirred solution of Intermediate 514A (1.3 g, 2.387 mmol) in dichloromethane (20 ml). The reaction mixture was stirred at a room temperature for 16 hours, diluted with water (10 ml), and saturated sodium bicarbonate solution (10 ml), and extracted with ethyl acetate (3×20 ml). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuum to afford methyl 2-(7-(azetidin-3-yl)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate (1 g, 94%). LC-MS m/z: 445.4 [M+H]⁺.

20

Intermediate 514C

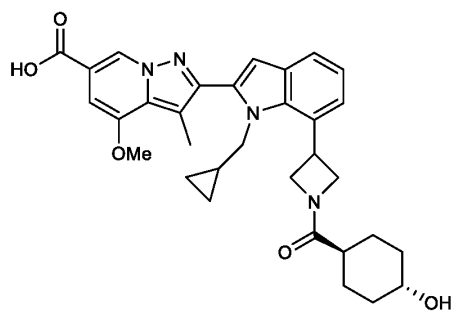
25 Methyl 2-(1-(cyclopropylmethyl)-7-(1-((1R, 4R)-4-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate



(1R,4R)-4-Hydroxycyclohexane-1-carboxylic acid (63.2 mg, 0.439 mmol) was added to a stirred solution of Intermediate 514B (150 mg, 0.337 mmol) in DMF (3 ml), followed by HATU (192 mg, 0.506 mmol) and DIPEA (0.118 ml, 0.675 mmol). The reaction mixture was stirred at a room temperature for 16 hours, diluted with water (20 ml), and extracted with ethyl acetate (3×30 ml). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuum. The crude product was purified using a silica gel column, eluting with 0-5% methanol in dichloromethane to afford methyl 2-(1-(cyclopropylmethyl)-7-(1-((1R,4R)-4-hydroxycyclohexane-1-carboxyl)azetidin-3-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate (110 mg, 57%). LC-MS m/z: 571.4 [M+H]⁺.

Intermediate 514D

2-(1-(cyclopropylmethyl)-7-(1-((1R,4R)-4-hydroxycyclohexane-1-carboxyl)azetidin-3-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylic acid



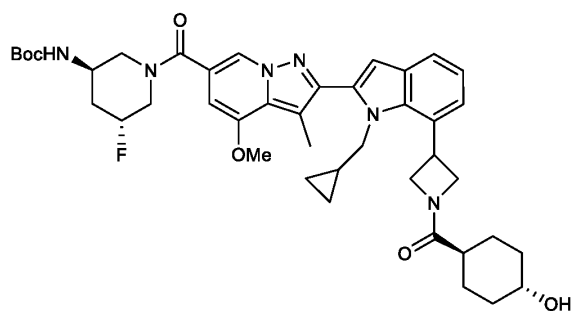
LiOH (25.2 mg, 1.051 mmol) was added to a stirred solution of Intermediate 514C (120 mg, 0.210 mmol) in THF (3 ml), water (0.5 ml), and MeOH (1 ml). The reaction mixture was stirred at a room temperature for 16 hours, diluted with water (5 ml) and 1N HCl (5 ml), and extracted with ethyl acetate (3×30 ml). The combined organic layers

were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuum to get 2-(1-(cyclopropylmethyl)-7-(1-((1R, 4R)-4-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylic acid (90 mg, 77%). LC-MS m/z: 557.4 [M+H]⁺.

5

Intermediate 514E

tert-Butyl ((3R,5R)-1-(2-(1-(cyclopropylmethyl)-7-(1-((1R,4R)-4-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



10

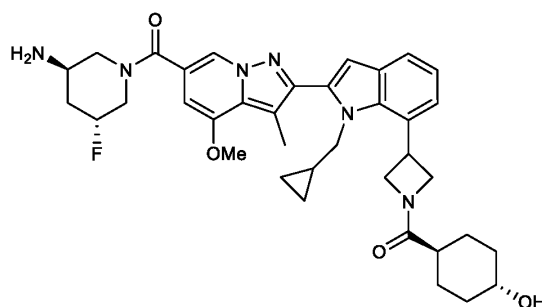
tert-Butyl ((3R,5R)-5-fluoropiperidin-3-yl)carbamate (21.17 mg, 0.097 mmol), HATU (46.1 mg, 0.121 mmol) followed by DIPEA (0.042 ml, 0.243 mmol) were added to a stirred solution of Intermediate 514D (45 mg, 0.081 mmol) in DMF (0.5 ml). The reaction mixture was stirred at a room temperature for 16 hours, diluted with water (5 ml) and 1 N HCl (5 ml), and extracted with ethyl acetate (3×30 ml). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuum to afford tert-butyl ((3R,5R)-1-(2-(1-(cyclopropylmethyl)-7-(1-((1R,4R)-4-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate (40 mg, 65%). LC-MS m/z: 757.6 [M+H]⁺.

20

Example 514

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1R,4R)-4-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone

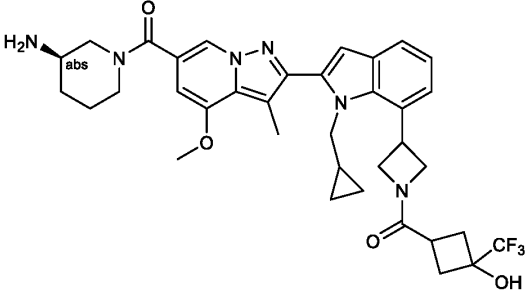
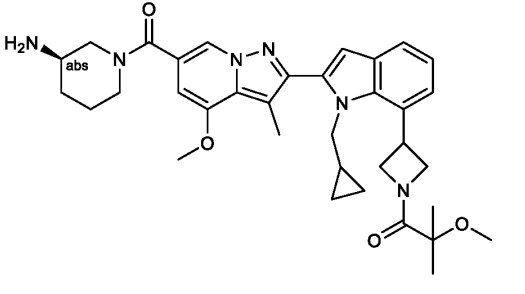
25

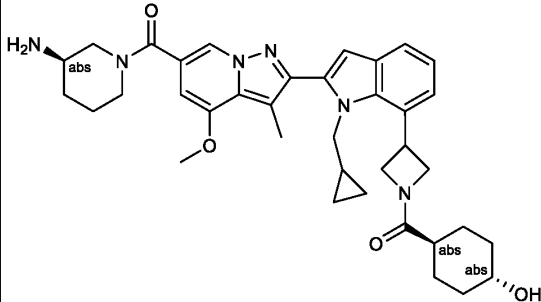
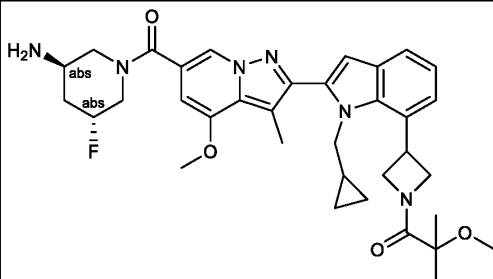
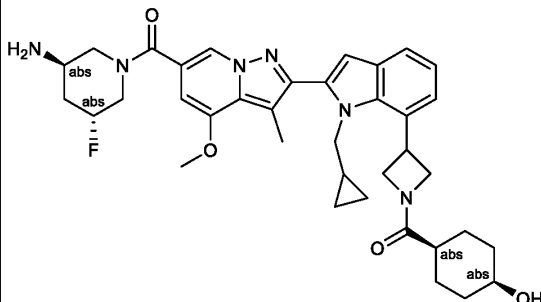


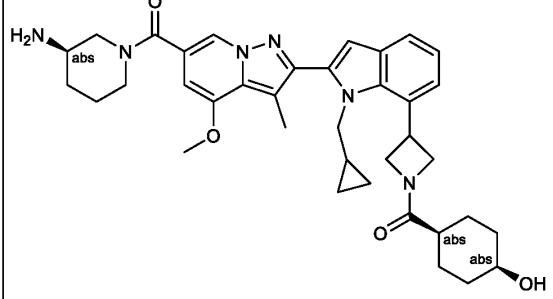
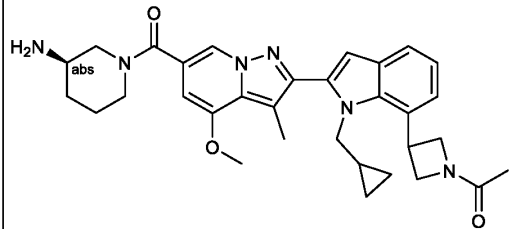
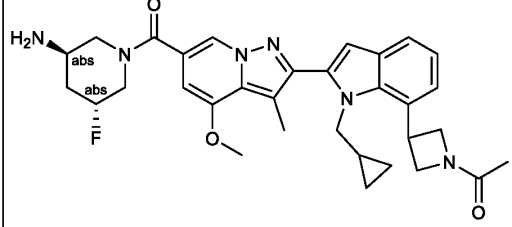
TFA (0.041 ml, 0.528 mmol) was added to a stirred solution of Intermediate 514E (40 mg, 0.053 mmol) in CH₂Cl₂ (3.0 ml). The reaction mixture was stirred at a room temperature for 6 hours, concentrated, and the crude material was purified using
 5 preparative LC/MS with the following conditions: Column: Waters X Bridge C18, 19×150 mm, 5 μm particles; mobile phase A: 10 mM ammonium acetate; mobile phase B: acetonitrile; gradient: 12-48% B over 25 minutes, then a 5-minute hold at 100% B; flow rate: 15 ml/min. Fractions containing the desired product were combined and dried using centrifugal evaporation. The purified material was then diluted with a 1:1 mixture
 10 of DCM and methanol, treated with Si-Pyridine, and shaken for a minimum of 2 hours. The resulting mixture was filtered and dried using centrifugal evaporation to afford ((3R,5R)-3-amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1r,4r)-4-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (11.2 mg, 32%). LC-MS m/z: 657.4
 15 [M+H]⁺. LCMS retention time: 1.537 min (method E). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.36 (s, 1H), 7.58-7.49 (m, 1H), 7.37 (d, J=7.3 Hz, 1H), 7.16 (t, J=7.6 Hz, 1H), 6.76 (s, 1H), 6.54 (d, J=0.8 Hz, 1H), 5.02-4.88 (m, 1H), 4.74-4.68 (m, 1H), 4.68-4.59 (m, 1H), 4.54 (br, d, J=3.0 Hz, 1H), 4.41-4.31 (m, 5H), 4.01 (br, dd, J=6.1, 9.4 Hz, 2H), 3.97 (s, 3H), 3.10-3.03 (m, 2H), 2.48 (s, 3H), 2.20 (tt, J=3.4, 11.6 Hz, 2H), 1.89-1.80 (m, 3H),
 20 1.76-1.49 (m, 3H), 1.43-1.30 (m, 2H), 1.23-1.11 (m, 3H), 0.83-0.72 (m, 1H), 0.16 (d, J=8.3 Hz, 2H), -0.16--0.34 (m, 2H)

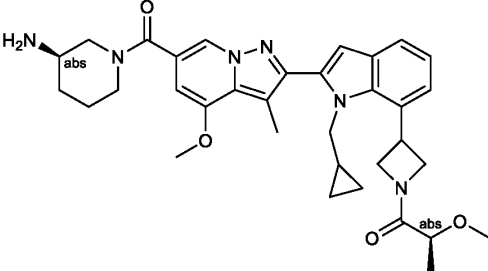
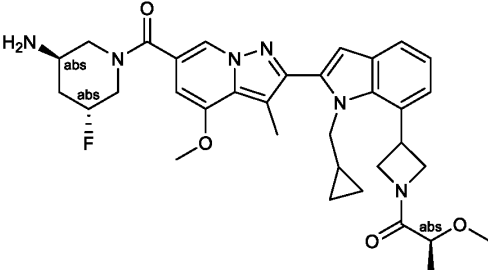
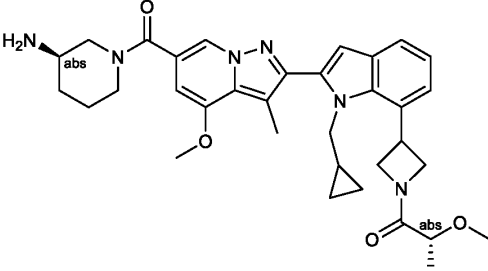
Compounds of Examples 515 to 529 in Table 51 were prepared following a procedure similar to the preparation of a compound of Example 514, by acid amine
 25 coupling of Intermediate 514B with appropriate carboxylic acid followed by ester hydrolysis and coupling with appropriate amines

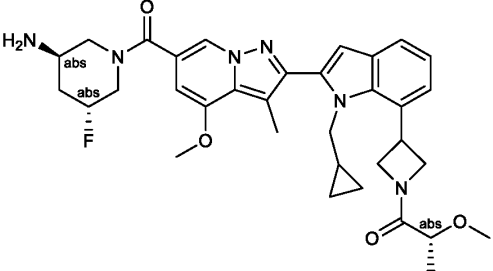
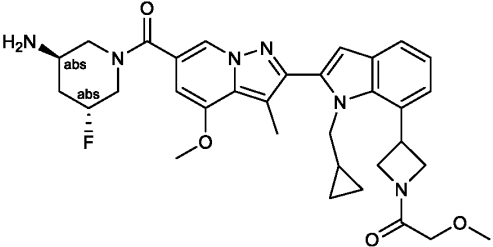
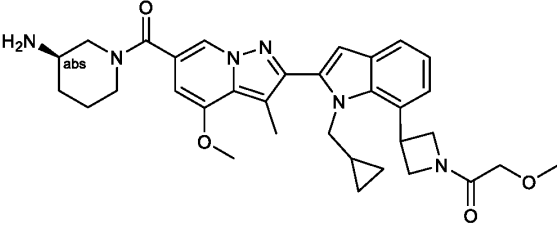
Table 51

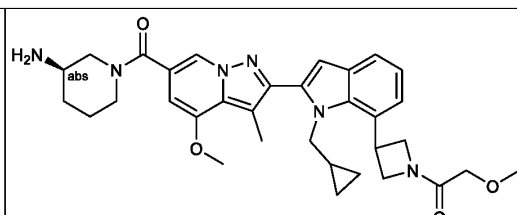
Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
515	 (R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxy-3-(trifluoromethyl)cyclobutane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (mixture of diastereomers) Analytical Data: 679.3, 1.754 min (Method E)
516	 (R)-1-(3-(2-(6-(3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)-2-methoxy-2-methylpropan-1-one Analytical Data: 613.3, 1.733 min (Method E)

517	 ((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1r,4r)-4-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 639.4, 1.489 min (Method E)
518	 1-(3-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)-2-methoxy-2-methylpropan-1-one Analytical Data: 631.3, 1.788 min (Method E)
519	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1s,4s)-4-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 657.4, 1.630 min (Method E)

520	 <chem>NC1CCN(C1)C(=O)c2cc3c(ncn3c2C)c4cc5c(cnc45)C6=CC=CC=C6N7CC8C=CC(=C8)C(=O)N9C[C@H](O)CC[C@H]9C7C6</chem> ((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1s,4s)-4-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 639.4, 1.581 min (Method E)
521	 <chem>CC(=O)N1CC[C@H]1c2cc3c(ncn3c2)C4=CC=CC=C4N5CC6=CC=CC=C6C(=O)N7CCN(C7)C(=O)c8cc9c(ncn89)C(C)c1cc(OC)cc(C1)c9</chem> (R)-1-(3-(2-(6-(3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)ethan-1-one Analytical Data: 555.3, 1.506 min (Method E)
522	 <chem>CC(=O)N1CC[C@H]1c2cc3c(ncn3c2)C4=CC=CC=C4N5CC6=CC=CC=C6C(=O)N7CCN(C7)C(=O)c8cc9c(ncn89)C(C)c1cc(OC)cc(C1)c9</chem> 1-(3-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)ethan-1-one Analytical Data: 573.3, 1.593 min (Method E)

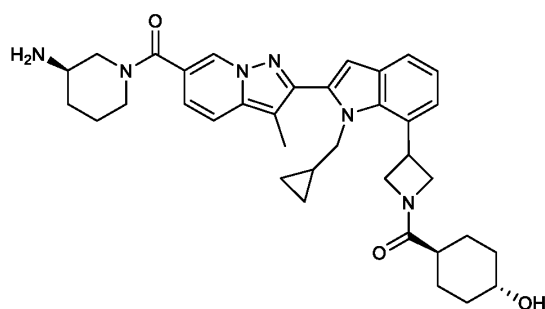
523	 (S)-1-(3-(2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)-2-methoxypropan-1-one Analytical Data: 599.3, 1.605 min (Method E)
524	 (S)-1-(3-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)-2-methoxypropan-1-one Analytical Data: 617.3, 1.638 min (Method E)
525	 (R)-1-(3-(2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)-2-methoxypropan-1-one Analytical Data: 599.3, 1.613 min (Method E)

526	 (R)-1-(3-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)-2-methoxypropan-1-one Analytical Data: 617.3, 1.533 min (Method F)
527	 1-(3-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)-2-methoxyethan-1-one Analytical Data: 603.2, 1.597 min (Method E)
528	 (R)-1-(3-(2-(6-(3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)-2-methoxyethan-1-one Analytical Data: 585.3, 1.607 min (Method E)

529	 (R)-1-(3-(2-(6-(3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)-2-methoxyethan-1-one Analytical Data: 585.3, 1.540 min (Method E)
-----	---

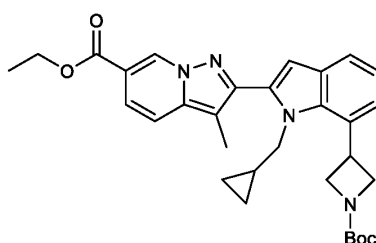
Example 530

((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1r,4r)-4-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone



Intermediate 530A

Ethyl 2-(7-(1-(tert-butoxycarbonyl)azetidin-3-yl)-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate

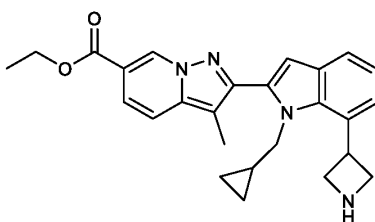


Intermediate 8 (3.83 g, 10.94 mmol) and copper(I) iodide (0.208 g, 1.08 mmol) were added to a stirred solution of Intermediate 49 (1.5 g, 3.65 mmol) in (10 ml). The reaction mixture was stirred at 80°C for 30 hours, diluted with water (15 ml), and extracted with ethyl acetate (3×30 ml). The combined organic layers were washed with

brine, dried over sodium sulphate, filtered, and concentrated in vacuum. The crude product was purified using a silica gel column, eluting 20% ethyl acetate in hexane to afford (110 mg, 57%) ethyl 2-(7-(1-(tert-butoxycarbonyl)azetidin-3-yl)-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate. LC-MS m/z: 529.3 [M+H]⁺.

Intermediate 530B

Ethyl 2-(7-(azetidin-3-yl)-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate



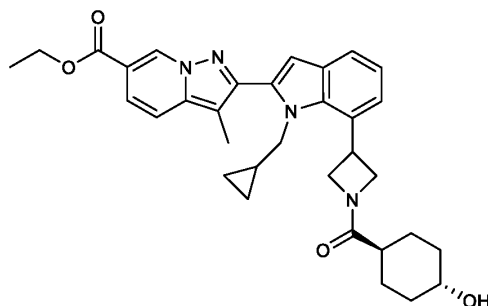
10

TFA (1.749 ml, 22.70 mmol) was added to a stirred solution of Intermediate 530A (1.2 g, 2.270 mmol) in dichloromethane (5 ml). The reaction mixture was stirred at a room temperature for 16 hours, concentrated, diluted with water (10 ml), washed with saturated NaHCO₃ solution (10 ml), and extracted with dichloromethane (3×20 ml). The combined organic layers were washed with brine, dried over sodium sulphate, filtered, and concentrated in vacuum to afford ethyl 2-(7-(azetidin-3-yl)-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate (crude 1.0 g). LC-MS m/z: 429.4 [M+H]⁺.

20

Intermediate 530C

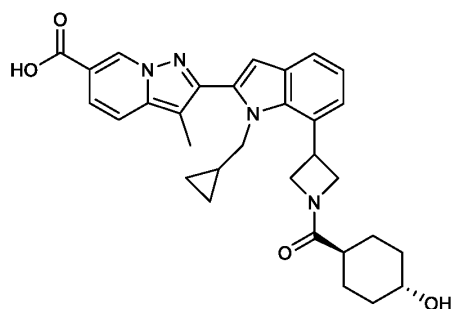
Ethyl 2-(1-(cyclopropylmethyl)-7-(1-((1R,4R)-4-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate



(1R,4R)-4-Hydroxycyclohexane-1-carboxylic acid (87 mg, 0.607 mmol), HATU (266 mg, 0.700 mmol) followed by DIPEA (0.245 ml, 1.400 mmol) were added to a stirred solution of Intermediate 530B (200 mg, 0.467 mmol) in DMF (5 ml). The reaction mixture was stirred at a room temperature for 1 hour, diluted with water (5 ml), and
5 extracted with ethyl acetate (3×10 ml). The combined organic layers were washed with brine, dried over sodium sulphate, filtered, and concentrated in vacuum. The crude product thus obtained was purified using a silica gel column, eluting 2% methanol in dichloromethane to afford (130 mg, 50%) ethyl 2-(1-(cyclopropylmethyl)-7-(1-((1R,4R)-4-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-
10 a]pyridine-6-carboxylate. LC-MS m/z: 555.4 [M+H]⁺.

Intermediate 530D

2-(1-(cyclopropylmethyl)-7-(1-((1R,4R)-4-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylic acid



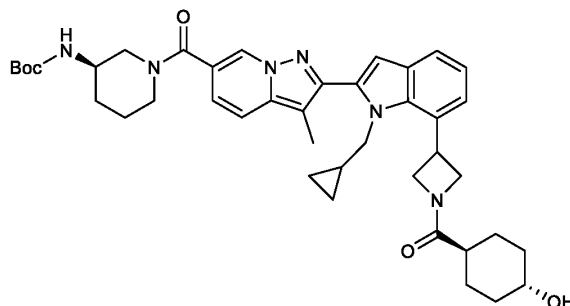
15

LiOH (17.27 mg, 0.721 mmol) was added to a stirred solution of Intermediate 530C (80 mg, 0.144 mmol) in THF (3 ml), methanol (1 ml), and water (0.5 ml). The reaction mixture was stirred at a room temperature for 16 hours, diluted with water (5 ml) and 1 N HCl (5 ml), and extracted with ethyl acetate (3×10 ml). The combined organic
20 layers were washed with brine, dried over sodium sulphate, filtered, and concentrated in vacuum to afford (crude 80 mg) 2-(1-(cyclopropylmethyl)-7-(1-((1R,4R)-4-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylic acid. LC-MS m/z: 527.3 [M+H]⁺.

25

Intermediate 530E

tert-Butyl ((R)-1-(2-(1-(cyclopropylmethyl)-7-(1-((1R,4R)-4-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)piperidin-3-yl)carbamate

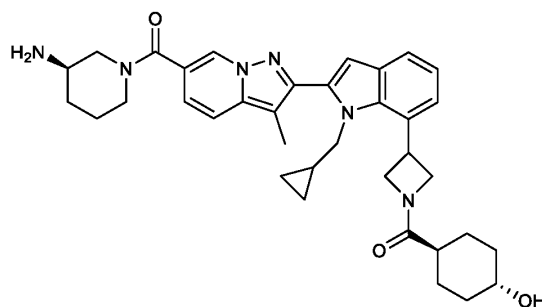


- 5 tert-Butyl (R)-piperidin-3-ylcarbamate (18.25 mg, 0.091 mmol), HATU (57.8 mg, 0.152 mmol), DIPEA (0.040 ml, 0.228 mmol) was added to a stirred solution of Intermediate 530D (40 mg, 0.076 mmol) in DMF (1 ml). The reaction mixture was stirred at a room temperature for 3 hours, diluted with water (5 ml) and 1N HCl (5 ml), and extracted with ethyl acetate (3×10 ml). The combined organic layers were washed with
- 10 brine, dried over sodium sulphate, filtered, and concentrated in vacuum to afford tert-butyl ((R)-1-(2-(1-(cyclopropylmethyl)-7-(1-((1R,4R)-4-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)piperidin-3-yl)carbamate (40 mg, 74%). LC-MS m/z: 709.6 [M+H]⁺.

15

Example 530

((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1R,4R)-4-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone



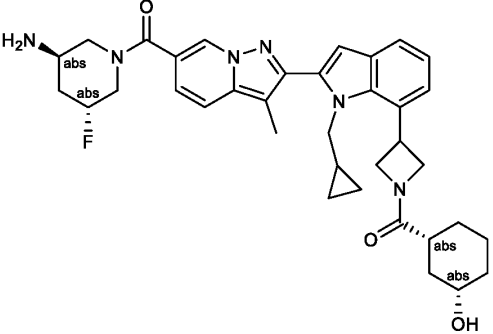
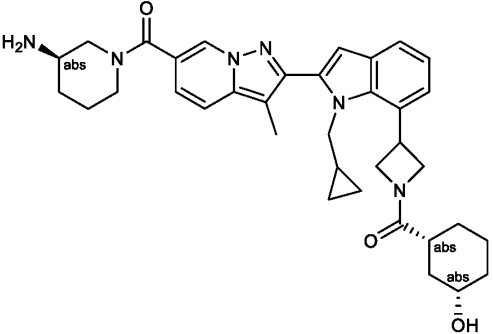
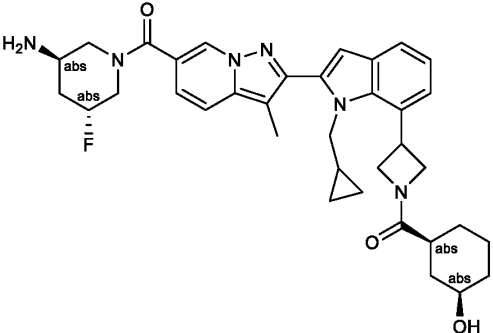
- 20 TFA (0.043 ml, 0.564 mmol) was added to a stirred solution of Intermediate 530E (40 mg, 0.056 mmol) in DCM (3 ml). The reaction mixture was stirred for 16 hours,

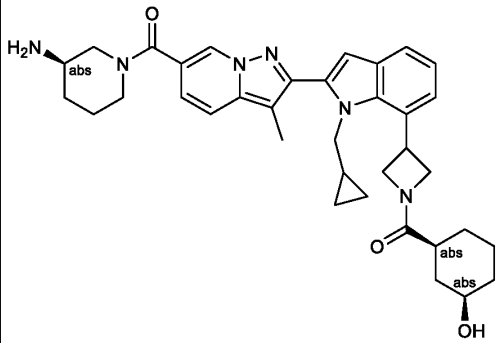
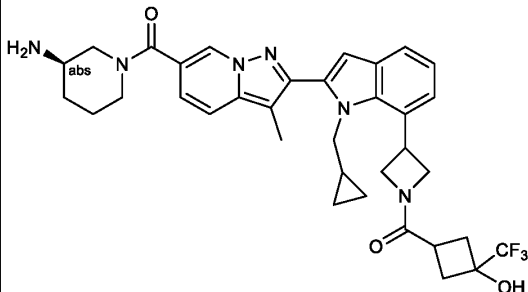
concentrated in vacuum to obtain a crude compound, which was purified using a preparative LC/MS with the following conditions: Column: Waters XBridge C18, 150×19 mm, 5 µm particles; mobile phase A: 5:95 acetonitrile: water with 0.1% trifluoroacetic acid; mobile phase B: 95:5 acetonitrile: water with 0.1% trifluoroacetic acid; gradient: a
 5 0-minute hold at 15% B, 15-30% B over 20 minutes, then a 5-minute hold at 100% B; flow rate: 20 ml/min; column temperature: 25°C. Fraction collection was triggered by signals. Fractions containing the desired product were combined and dried using centrifugal evaporation. The purified material was then diluted with a 1:1 mixture of ethylene dichloride and methanol (EDM), treated with Si-Pyridine, and shaken for a
 10 minimum of 2 hours. The resulting mixture was filtered and dried using centrifugal evaporation to afford ((R)-3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1R,4R)-4-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (6.9 mg, 11%). LC-MS m/z: 609.3 [M+H]⁺. LCMS retention time: 1.411 min (method E). ¹H NMR (400 MHz, DMSO-*d*₆) δ
 15 ppm: 8.86 (s, 1H), 7.99 (br, s, 2H), 7.81 (dd, J=0.7, 9.0 Hz, 1H), 7.57 (d, J=7.8 Hz, 1H), 7.38 (d, J=7.6 Hz, 1H), 7.28 (dd, J=1.5, 9.0 Hz, 1H), 7.17 (t, J=7.6 Hz, 1H), 7.16-6.98 (m, 1H), 6.83 (s, 1H), 4.75-4.61 (m, 2H), 4.58-4.52 (m, 1H), 4.47-4.31 (m, 4H), 4.02 (br, s, 2H), 3.82-3.74 (m, 1H), 3.29-3.19 (m, 3H), 2.39 (s, 3H), 2.24-2.16 (m, 1H), 2.06-1.95 (m, 1H), 1.90-1.55 (m, 7H), 1.43-1.29 (m, 2H), 1.23-1.06 (m, 2H), 0.84-0.74 (m, 1H), 0.17
 20 (br, d, J=8.1 Hz, 2H), 0.16-0.32 (m, 2H).

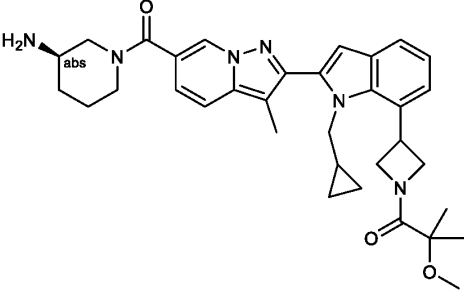
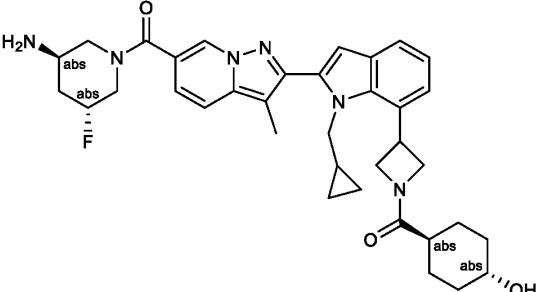
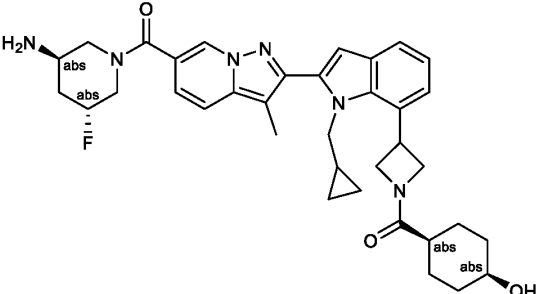
Compounds of Examples 531 to 565 in Table 52 were prepared following a procedure similar to the preparation of a compound of Example 530, by acid amine coupling of Intermediate 530B with appropriate carboxylic acid followed by ester
 25 hydrolysis and coupling with appropriate amines

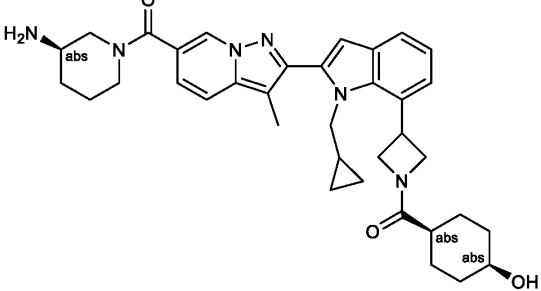
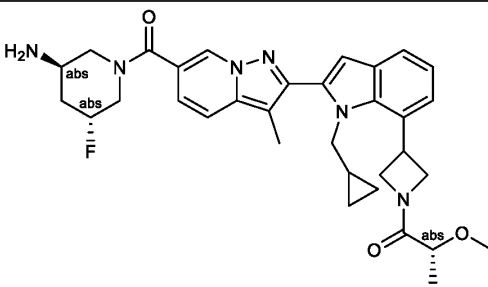
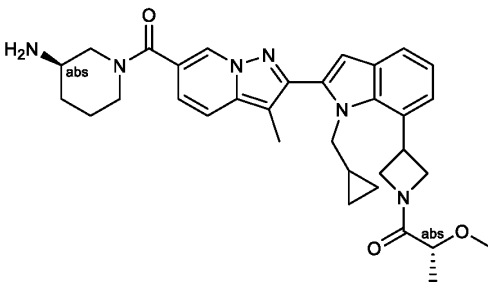
Table 52

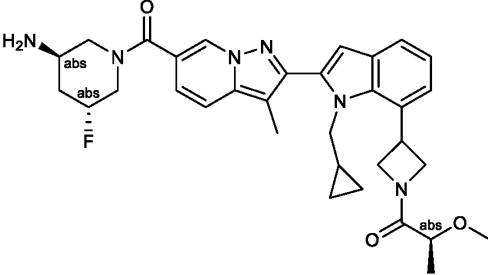
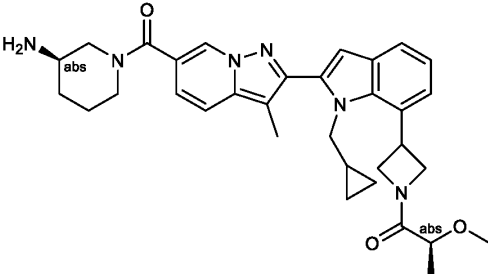
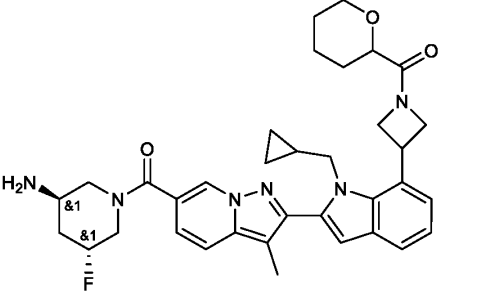
Example	Structure
	Name
	Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)

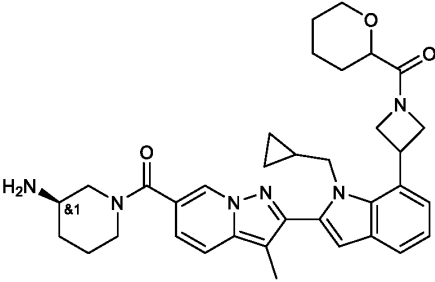
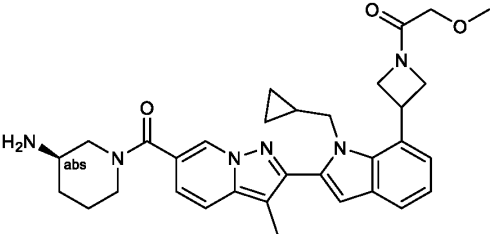
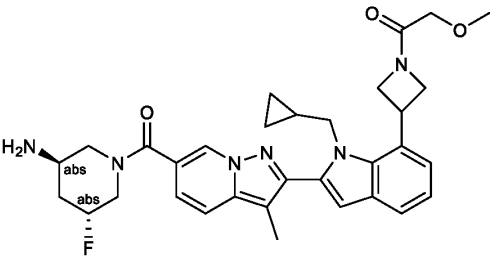
531	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1R,3S)-3-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 627.3, 1.510min (Method E)
532	 ((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1R,3S)-3-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 609.3, 1.446 min (Method E)
533	

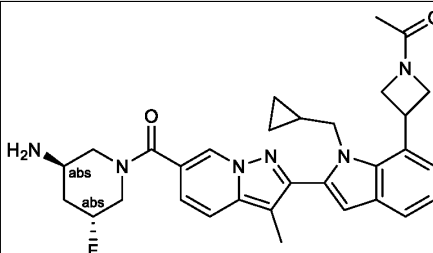
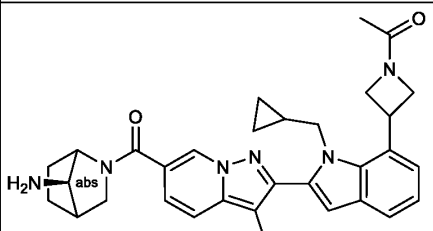
	((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1S,3R)-3-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 627.3, 1.499 min (Method E)
534	 ((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1S,3R)-3-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 609.3, 1.446 min (Method E)
535	 (R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxy-3-(trifluoromethyl)cyclobutane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (mixture of diastereomers) Analytical Data: 649.3, 1.656 min (Method E)

536	 (R)-1-(3-(2-(6-(3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)-2-methoxy-2-methylpropan-1-one Analytical Data: 583.3, 1.616 min (Method E)
537	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1r,4r)-4-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 627.3, 1.458 min (Method E)
538	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1s,4s)-4-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 627.3, 1.498 min (Method E)

539	 <chem>NC1CCN(C1)C(=O)c2ccc3nn(c2c3C)c4ccc5c6ccccc5n4C7CC7CN(C7)C(=O)C8CCC(O)C8</chem> ((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1s,4s)-4-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 609.3, 1.440 min (Method E)
540	 <chem>NC1CC(F)N(C1)C(=O)c2ccc3nn(c2c3C)c4ccc5c6ccccc5n4C7CC7CN(C7)C(=O)C8CCC(OC)C8=O</chem> (R)-1-(3-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)-2-methoxypropan-1-one Analytical Data: 587.2, 1.488 min (Method E)
541	 <chem>NC1CCN(C1)C(=O)c2ccc3nn(c2c3C)c4ccc5c6ccccc5n4C7CC7CN(C7)C(=O)C8CCC(OC)C8=O</chem> (R)-1-(3-(2-(6-((R)-3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)-2-methoxypropan-1-one Analytical Data: 569.3, 1.443 min (Method E)

542	 (S)-1-(3-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)-2-methoxypropan-1-one Analytical Data: 587.3, 1.486 min (Method E)
543	 (S)-1-(3-(2-(6-((R)-3-aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)-2-methoxypropan-1-one Analytical Data: 569.3, 1.441 min (Method E)
544	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(tetrahydro-2H-pyran-2-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (mixture of diastereomers) Analytical Data: 613.3, 1.653 min (Method E)

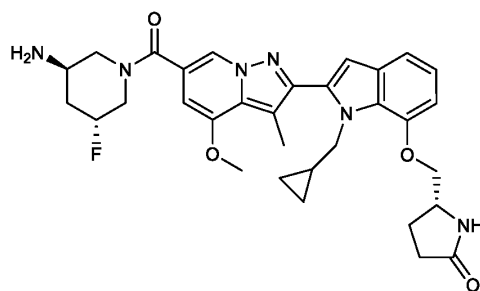
545	 ((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(tetrahydro-2H-pyran-2-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (mixture of diastereomers) Analytical Data: 595.3, 1.732 min (Method E)
546	 (R)-1-(3-(2-(6-(3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)-2-methoxyethan-1-one Analytical Data: 555.4, 6.864 min (Method D)
547	 1-(3-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)-2-methoxyethan-1-one Analytical Data: 573.2, 6.996 min (Method C)

548	 1-(3-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)ethan-1-one Analytical Data: 544.2, 7.161 min (Method D)
549	 1-(3-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)ethan-1-one Analytical Data: 537.4 ,6.854 min (Method D)

Example 550

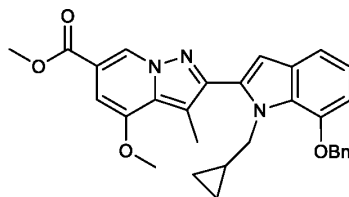
(R)-5-(((2-(6-((3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one

5



Intermediate 550A

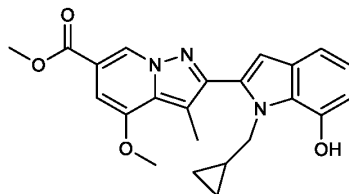
Methyl 2-(7-(benzyloxy)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate



Intermediate 50 (1.9g, 5.24 mmol) was added to a stirred solution of Intermediate 1 (2.28 g, 5.24 mmol) and copper(I) iodide (0.263 g, 1.380 mmol) in DMF (10 ml). The reaction mixture was heated to 80°C for 48 hours, quenched with water (100 ml) and extracted with ethyl acetate (2×100 ml). The combined organic layer was dried over sodium sulphate, filtered, and concentrated under reduced vacuum to obtain a crude product, which was purified using a silica gel column (10-20% of ethyl acetate in hexane) to afford methyl 2-(7-(benzyloxy)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate (500 mg, 37%). LC-MS m/z: 496.2 [M+H]⁺

Intermediate 550B

Methyl 2-(1-(cyclopropylmethyl)-7-hydroxy-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate

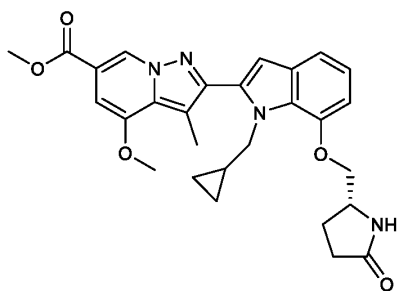


A solution of Intermediate 550A (500 mg, 1.009 mmol) in ethyl acetate (3 ml) was degassed with nitrogen for 5 min, followed by the addition of Pd/C (107 mg, 0.101 mmol). The reaction mixture was stirred under H₂ atmosphere for 4 hours, filtered through a celite bed, and washed with methanol. The combined filtrate was concentrated under reduced pressure to afford crude methyl 2-(1-(cyclopropylmethyl)-7-hydroxy-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate (350 mg, 86%) LC-MS m/z: 406.3 [M+H]⁺. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm: 9.77 (s, 1H), 8.85 (s, 1H), 7.05 (d, *J*=7.6 Hz, 1H), 6.90-6.81 (m, 2H), 6.67 (s, 1H), 6.60 (d, *J*=7.2 Hz, 1H), 4.56

(br, d, $J=6.4$ Hz, 2H), 4.09-3.94 (m, 3H), 3.90 (s, 3H), 3.32-3.17 (m, 3H), 1.02 (br, s, 1H), 0.26-0.12 (m, 2H), 0.05-0.01 (m, 2H)

Intermediate 550C

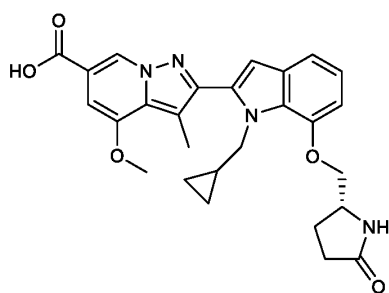
- 5 Indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate AR NO- A2C37-163



- Cesium carbonate (241 mg, 0.740 mmol), tetrabutylammonium iodide (27.3 mg, 0.074 mmol) and (R)-2-(1-(cyclopropylmethyl)-7-((5-oxopyrrolidin-2-yl)methoxy)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate (66.4 mg, 0.247 mmol) were added to a stirred solution of Intermediate 550B (100 mg, 0.247 mmol) in DMF (1 ml). The reaction mixture was heated to 60°C for 16 hours, quenched with water (100 ml), and extracted with ethyl acetate (2×100 ml). The combined organic layers were dried over sodium sulphate, filtered, and concentrated under reduced pressure to afford methyl (R)-2-(1-(cyclopropylmethyl)-7-((5-oxopyrrolidin-2-yl)methoxy)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate (105 mg, 85%). LC-MS m/z : 503.4 $[M+H]^+$.

Intermediate 550D

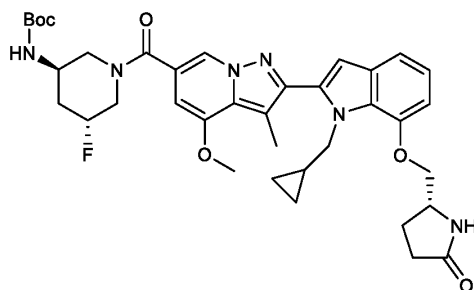
- (R)-2-(1-(Cyclopropylmethyl)-7-((5-oxopyrrolidin-2-yl)methoxy)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylic acid



LiOH (4.76 mg, 0.199 mmol) was added to a stirred solution of Intermediate 550C (100 mg, 0.199 mmol) in THF (1 ml), methanol (1.0 ml) and water (1 ml). The reaction mixture was stirred for 16 hours, concentrated under reduced pressure, then acidified with 1 N HCl, and the solids thus obtained were filtered through a Buchner funnel and dried under reduced pressure to afford (R)-2-(1-(cyclopropylmethyl)-7-((5-oxopyrrolidin-2-yl)methoxy)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylic acid (90 mg, 93%). LC-MS m/z: 489.3 [M+H]⁺

Intermediate 550E

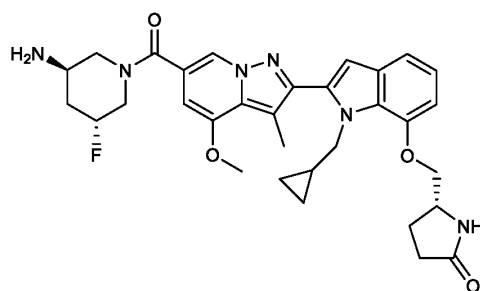
tert-butyl ((3R,5R)-1-(2-(1-(cyclopropylmethyl)-7-((R)-5-oxopyrrolidin-2-yl)methoxy)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



tert-Butyl ((3R,5R)-5-fluoropiperidin-3-yl)carbamate (22.34 mg, 0.102 mmol), DIPEA (0.054 ml, 0.307 mmol), HATU (58.4 mg, 0.154 mmol) were added to a stirred solution of Intermediate 550D (50 mg, 0.102 mmol) in DMF (1 ml). The reaction mixture was stirred 3 hours, quenched with water (50 ml), and extracted with ethyl acetate (2×50 ml). The combined organic layers were dried over sodium sulphate, filtered, and concentrated under reduced pressure to afford tert-butyl ((3R,5R)-1-(2-(1-(cyclopropylmethyl)-7-((R)-5-oxopyrrolidin-2-yl)methoxy)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate (50 mg, 71%). LC-MS m/z: 689.3 [M+H]⁺.

Example 550

(R)-5-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one



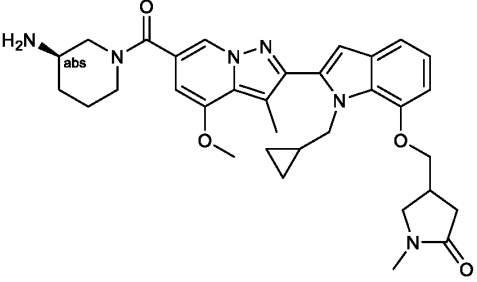
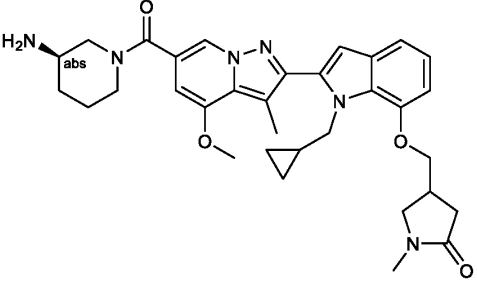
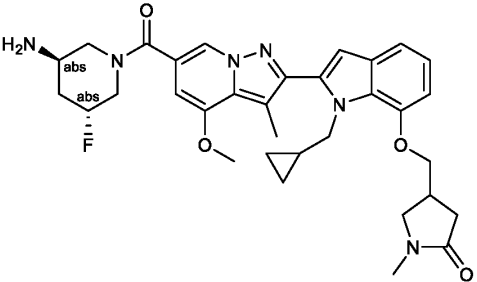
TFA (0.087 mmol) was added to a stirred solution of tert-butyl ((3R,5R)-1-(2-(1-(cyclopropylmethyl)-7-(((R)-5-oxopyrrolidin-2-yl)methoxy)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate (60 mg, 0.087 mmol) in DCM (1 ml) at 0°C. The reaction mixture was allowed to warm to a room temperature and stirred for 3 hours, concentrated in vacuo to afford a crude compound, which was purified using preparative HPLC to afford (R)-5-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (11.2 mg, 19%).

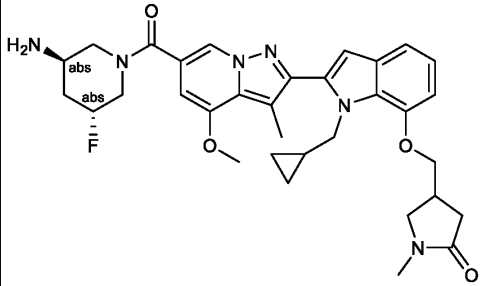
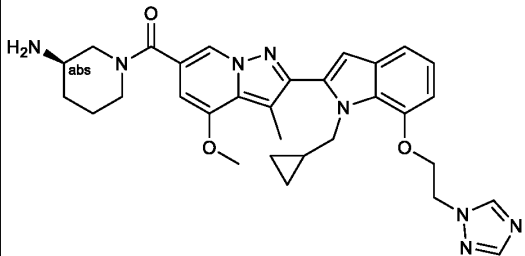
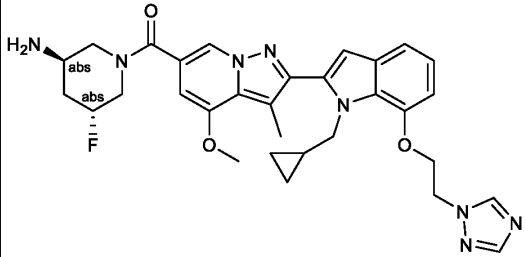
LC-MS m/z: 589.2 [M+H]⁺. LCMS retention time: 1.498 min (method E). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.36 (s, 1H), 7.87 (s, 1H), 7.21 (d, *J*=8.0 Hz, 1H), 6.99 (t, *J*=8.0 Hz, 1H), 6.76 (d, *J*=8.0 Hz, 1H), 6.67 (s, 1H), 6.54 (s, 1H), 5.05-4.86 (m, 1H), 4.52 (br, dd, *J*=3.1, 7.0 Hz, 2H), 4.15-4.00 (m, 4H), 3.98 (s, 3H), 3.09-3.01 (m, 3H), 2.47 (s, 3H), 2.31-2.14 (m, 4H), 2.07-1.99 (m, 1H), 1.68-1.49 (m, 1H), 1.07-0.98 (m, 1H), 0.22-0.13 (m, 2H), -0.05 (q, *J*=4.8 Hz, 2H).

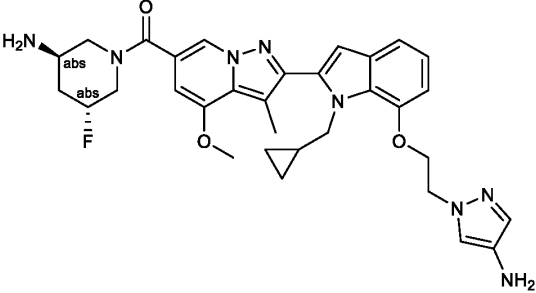
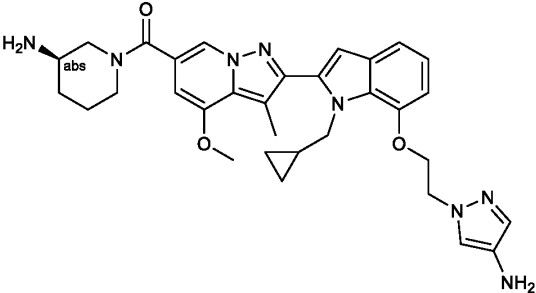
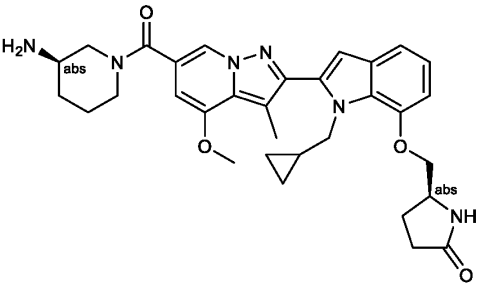
Compounds of Examples 551 to 565 in Table 53 were prepared following a procedure similar to the preparation of a compound of Example 550 in Table 55, by displacement reaction of Intermediate 550B with appropriate tosylate followed by ester hydrolysis and coupling with appropriate amines

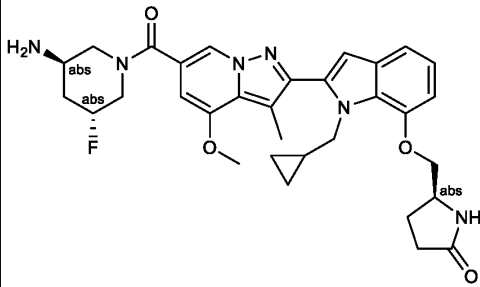
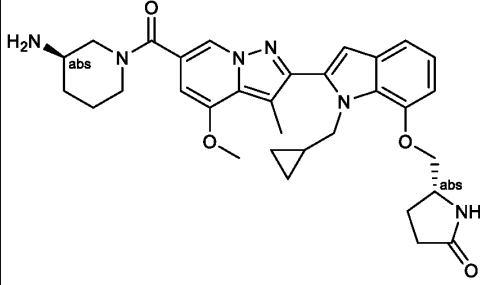
Table 53

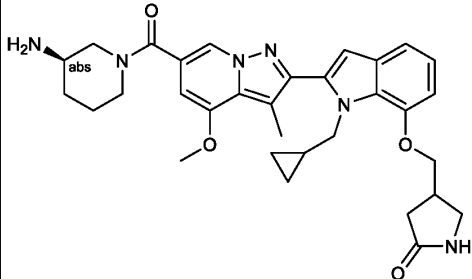
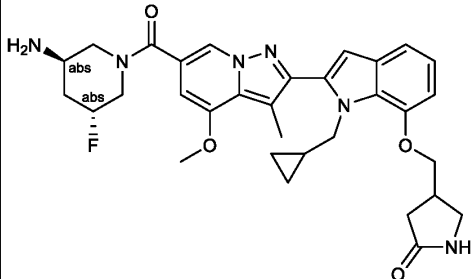
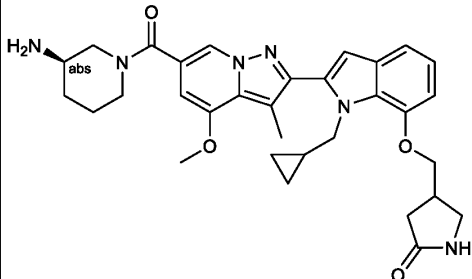
Example	Structure
	Name
	Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)

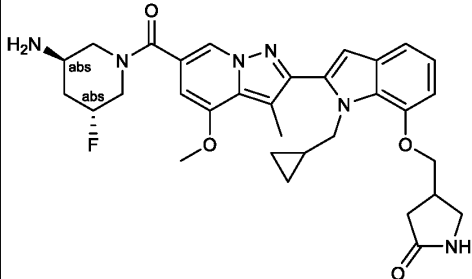
551	 4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)-1-methylpyrrolidin-2-one (isomer 1) Analytical Data: 585.3, 1.624 min (Method E)
552	 4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)-1-methylpyrrolidin-2-one (isomer 1) Analytical Data: 585.3, 1.629 min (Method E)
553	 4-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)-1-methylpyrrolidin-2-one (isomer 1) Analytical Data: 603.3, 1.645 min (Method E)

554	 4-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)-1-methylpyrrolidin-2-one (isomer 2) Analytical Data: 603.3, 1.640 min (Method E)
555	 (R)-(2-(7-(2-(1H-1,2,4-Triazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)(3-aminopiperidin-1-yl)methanone Analytical Data: 569.2, 1.482 min (Method E)
556	 (2-(7-(2-(1H-1,2,4-Triazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)((3R,5R)-3-amino-5-fluoropiperidin-1-yl)methanone Analytical Data: 587.3, 1.629 min (Method E)

557	 (2-(7-(2-(4-Amino-1H-pyrazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)((3R,5R)-3-amino-5-fluoropiperidin-1-yl)methanone Analytical Data: 601.2, 1.558 min (Method E)
558	 (R)-(2-(7-(2-(4-Amino-1H-pyrazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)(3-aminopiperidin-1-yl)methanone Analytical Data: 583.2, 1.264 min (Method E)
559	 (S)-5-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one

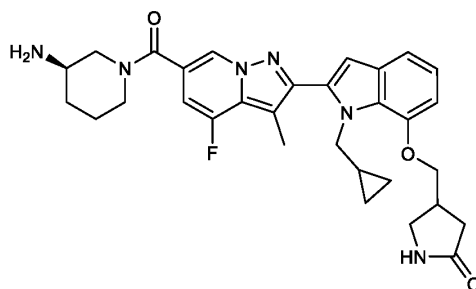
	Analytical Data: 571.3, 1.470 min (Method E)
560	 (S)-5-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one Analytical Data: 589.2, 1.489 min (Method E)
561	 (R)-5-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one Analytical Data: 571.2, 1.465 min (Method E)

562	 4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (isomer 1) Analytical Data: 571.2, 1.471 min (Method E)
563	 4-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (isomer 1) Analytical Data: 589.3, 1.492 min (Method E)
564	 4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (isomer 2) Analytical Data: 571.2, 1.476 min (Method E)

565	 4-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (isomer 2) Analytical Data: 589.3, 1.484 min (Method E)
-----	--

Example 566

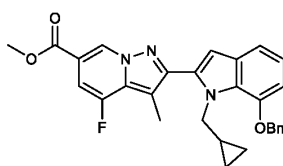
4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (isomer 1)



5

Intermediate 566A

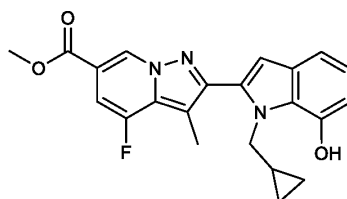
methyl 2-(7-(benzyloxy)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate



10 Intermediate 566A (0.7 g, 26%) was prepared following a procedure similar to the preparation of Intermediate 530A. as a gummy liquid. LC-MS m/z: 484.3 [M+H]⁺

Intermediate 566B

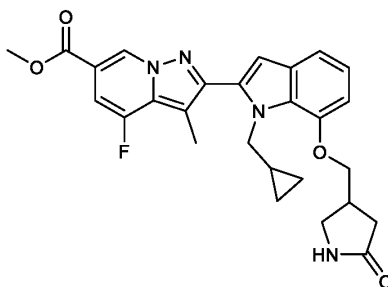
Methyl 2-(1-(cyclopropylmethyl)-7-hydroxy-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate



Intermediate 566B (0.31 g, 85%) was prepared following a procedure similar to the preparation of Intermediate 530B. LC-MS m/z: 394.3 [M+H]⁺; ¹H NMR (400 MHz, DMSO-d₆) δ ppm: 9.13 (d, *J*=1.0 Hz, 1H), 7.38 (d, *J*=11.5 Hz, 1H), 7.07 (d, *J*=8.0 Hz, 1H), 6.87 (t, *J*=7.8 Hz, 1H), 6.75 (s, 1H), 6.62 (d, *J*=7.5 Hz, 1H), 4.61 (d, *J*=6.5 Hz, 2H), 3.91 (s, 3H), 2.49-2.47 (m, 3H), 1.05-1.02 (m, 1H), 0.28-0.14 (m, 2H), 0.10-0.03 (m, 2H).

Intermediate 566C

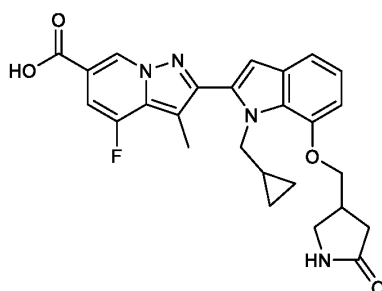
Methyl 2-(1-(cyclopropylmethyl)-7-((5-oxopyrrolidin-3-yl)methoxy)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate



Cesium carbonate (0.124 g, 0.381 mmol) and (5-oxopyrrolidin-3-yl)methyl 4-methylbenzenesulfonate (0.068 g, 0.254 mmol) were added to a stirred solution of Intermediate 566B (0.1 g, 0.254 mmol) in DMF (3 ml). The reaction mixture was stirred at 60°C for 2 hours, diluted with water, and the solids obtained were filtered and dried under reduced pressure to afford crude methyl 2-(1-(cyclopropylmethyl)-7-((5-oxopyrrolidin-3-yl)methoxy)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate (0.12 g, 96%) as a brown solid. LC-MS m/z: 491.3 [M+H]⁺.

Intermediate 566D

2-(1-(Cyclopropylmethyl)-7-((5-oxopyrrolidin-3-yl)methoxy)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carboxylic acid

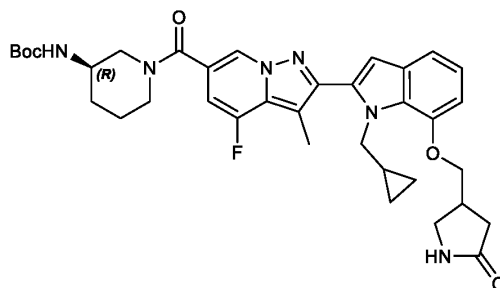


LiOH (0.029 g, 1.223 mmol) was added to a stirred solution of Intermediate 566C (0.12 g, 0.245 mmol) in ethanol (1ml), THF (1 ml), and water (1 ml). The reaction mixture was stirred for 2 hours, concentrated, and the residue obtained was neutralized using 1.5 N HCl solution. The solids thus obtained were filtered and dried under high vacuum to afford 2-(1-(cyclopropylmethyl)-7-((5-oxopyrrolidin-3-yl)methoxy)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carboxylic acid (0.11 g, 94%) as a white solid. LC-MS m/z: 477.3 [M+H]⁺

10

Intermediate 566E

tert-Butyl ((3R)-1-(2-(1-(cyclopropylmethyl)-7-((5-oxopyrrolidin-3-yl)methoxy)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)piperidin-3-yl)carbamate



15

Intermediate 566E (0.07 g, 84%) was prepared following a procedure similar to the preparation of Intermediate 530E. LC-MS m/z: 659.5 [M+H]⁺

Example 566

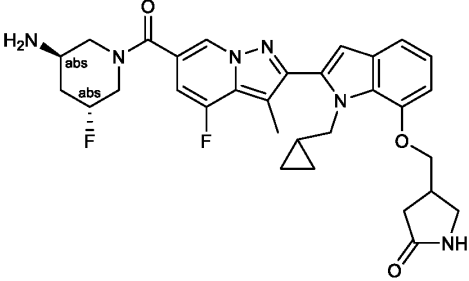
4-(((2-(6-((R)-3-aminopiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one. (isomer 1) LC-MS m/z: 559.2 [M+H]⁺; LCMS retention time: 1.52 min (method E); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.78 (s, 1H), 8.13 (br.s, 1H), 7.62 (s, 1H), 7.26-7.12

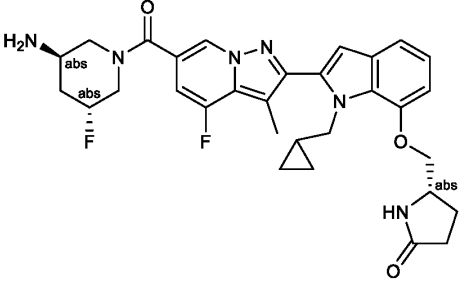
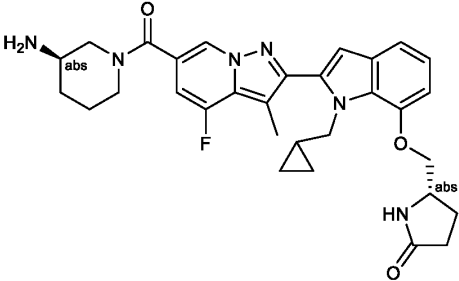
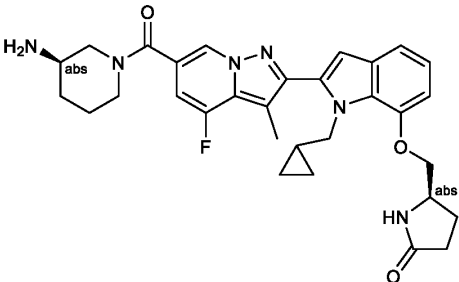
(m, 3H), 7.00 (t, $J=8.0$ Hz, 1H), 6.79 (d, $J=8.0$ Hz, 1H), 6.75 (s, 1H), 4.52 (d, $J=6.8$ Hz, 2H), 4.17 (d, $J=6.3$ Hz, 2H), 4.10-4.00 (m, 1H), 3.54-3.49 (m, 1H), 3.25-3.10 (m, 3H), 3.03-2.94 (m, 1H), 2.53-2.50 (m, 1H), 2.46 (s, 3H), 2.44-2.38 (m, 2H), 2.19 (dd, $J=7.3$, 16.8 Hz, 1H), 2.06-1.97 (m, 2H), 1.84-1.72 (m, 1H), 1.69-1.51 (m, 1H), 1.07-0.95 (m, 1H), 0.27-0.13 (m, 2H), 0.00--0.07 (m, 2H).

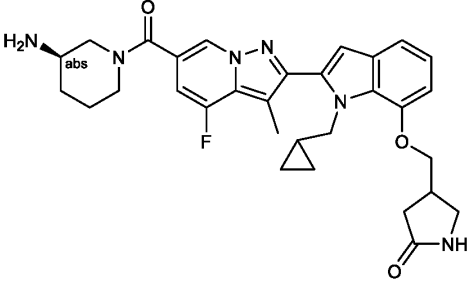
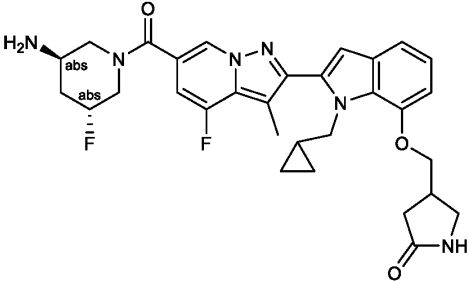
Compounds of Examples 567 to 572 in Table 54 were prepared following a procedure similar to the preparation of a compound of Example 566, by displacement reaction of Intermediate 566B with appropriate tosylate followed by ester hydrolysis and coupling with appropriate amines.

15

Table 54

Example	Structure Name Analytical Data: LC-MS m/z $[M+H]^+$; HPLC retention time (HPLC method)
567	 4-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (isomer 1) Analytical Data: 577.3; 1.493 min(Method E)

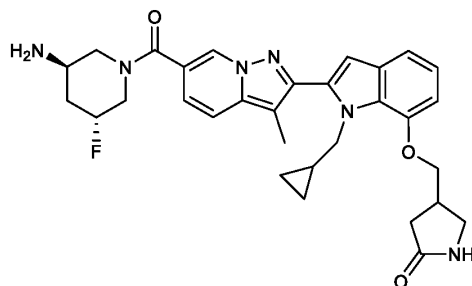
568	 (S)-5-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one Analytical Data: 577.2; 1.650 min (Method E)
569	 (S)-5-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one Analytical Data: 559.2; 1.588 min (Method E)
570	 (R)-5-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one Analytical Data: 559.2, 1.588 min (Method E)

571	 4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (isomer 2) Analytical Data: 559.2, 1.52 min (Method E)
572	 4-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (isomer 2) Analytical Data: 577.2, 1.58 min (Method E)

Example 573

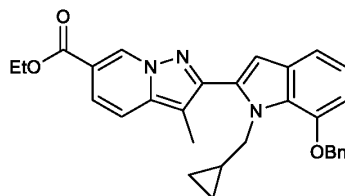
4-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (isomer 1)

5



Intermediate 573A

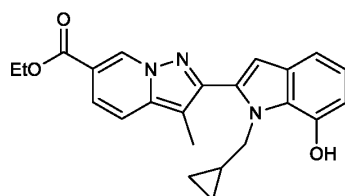
Ethyl 2-(7-(benzyloxy)-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate



5 Intermediate 573A (850 mg, 32%) was prepared following a procedure similar to the preparation of Intermediate 550A. LC-MS m/z: 480.2 [M+H]⁺

Intermediate 573B

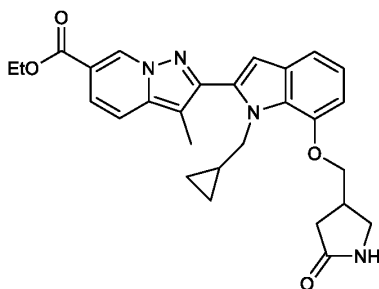
10 Ethyl 2-(1-(cyclopropylmethyl)-7-hydroxy-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate



Intermediate 573B (450 mg, 65%) was prepared following a procedure similar to the preparation of Intermediate 550B. LC-MS m/z: 390.4 [M+H]⁺

Intermediate 573C

15 Ethyl 2-(1-(cyclopropylmethyl)-7-((5-oxopyrrolidin-3-yl)methoxy)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate

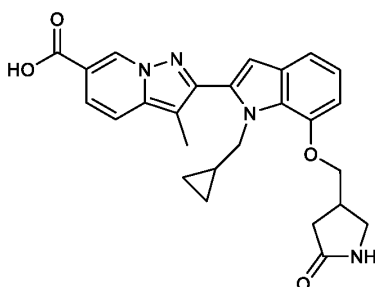


20 Cesium carbonate (251 mg, 0.770 mmol) and tetrabutylammonium iodide (28.5 mg, 0.077 mmol) and (5-oxopyrrolidin-3-yl)methyl 4-methylbenzenesulfonate (69.2 mg,

0.257 mmol) were added to a stirred solution of 573B (100 mg, 0.257 mmol) in DMF (1 ml). The reaction mixture was heated for at 60°C 16 hours, quenched with water (100 ml), and extracted with ethyl acetate (2×100ml). The combined the organic layers were dried over sodium sulphate, filtered, and concentrated under reduced pressure to afford
 5 crude ethyl 2-(1-(cyclopropylmethyl)-7-((5-oxopyrrolidin-3-yl)methoxy)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate (110 mg, 88%). LC-MS m/z: 487.3 [M+H]⁺

Intermediate 573D

10 2-(1-(Cyclopropylmethyl)-7-((5-oxopyrrolidin-3-yl)methoxy)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylic acid

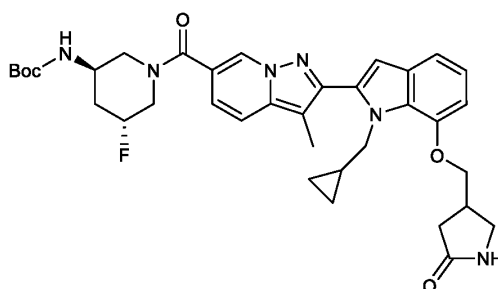


LiOH (5.91 mg, 0.247 mmol) was added to a stirred solution of Intermediate 573D (120 mg, 0.247 mmol) in THF (1 ml), methanol (1 ml), and water (1 ml). The
 15 reaction mixture was stirred for 16 hours, concentrated under reduced pressure to afford the crude salts, which were acidified with 1 N HCl. The solids obtained were filtered through a Buchner funnel and dried in vacuo to afford 2-(1-(cyclopropylmethyl)-7-((5-oxopyrrolidin-3-yl)methoxy)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylic acid (100 mg, 88%). LC-MS m/z: 459.2 [M+H]⁺

20

Intermediate 573E

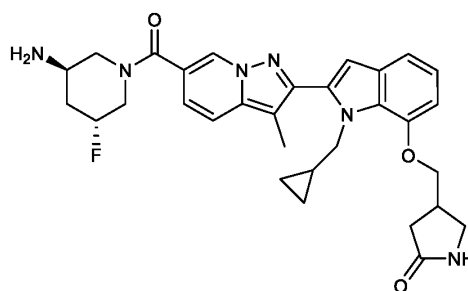
tert-Butyl ((3R,5R)-1-(2-(1-(cyclopropylmethyl)-7-((5-oxopyrrolidin-3-yl)methoxy)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



tert-Butyl ((3R,5R)-5-fluoropiperidin-3-yl)carbamate (23.80 mg, 0.109 mmol), DIPEA (0.057 ml, 0.327 mmol) and HATU (62.2 mg, 0.164 mmol) were added to a stirred solution of Intermediate 573D (50 mg, 0.109 mmol) in DMF (1 ml). The reaction mixture was stirred for 3 hours, diluted with water (50 ml), and extracted with ethyl acetate (2×50 ml). The combined organic layers were dried over sodium sulphate, filtered, and concentrated under reduced pressure to afford crude tert-butyl ((3R,5R)-1-(2-(1-(cyclopropylmethyl)-7-((5-oxopyrrolidin-3-yl)methoxy)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate (60 mg, 84%). LC-MS m/z: 659.3 [M+H]⁺.

Example 573

4-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (isomer 1)



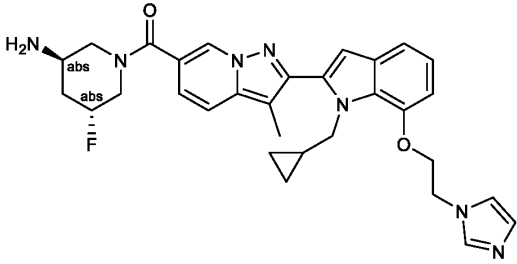
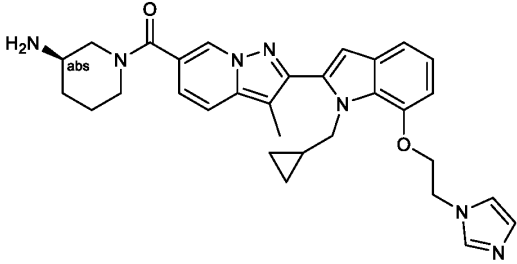
4-(((2-(6-((3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (isomer 1) (21.7 mg, 42%). LC-MS m/z: 559.2 [M+H]⁺. LCMS retention time: 1.384 min (method E). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.75 (s, 1H), 7.79 (d, *J*=9.0 Hz, 1H), 7.62 (s, 1H), 7.23- 7.17 (m, 2H), 6.99 (t, *J*=8.0 Hz, 1H), 6.77 (d, *J*=8.0 Hz, 1H), 6.73 (s, 1H), 5.03-4.98 (m, 1H), 4.60 (d, *J*=8.0 Hz, 2H), 4.16 (d, *J*=4.0 Hz, 2H), 3.50 (br, d,

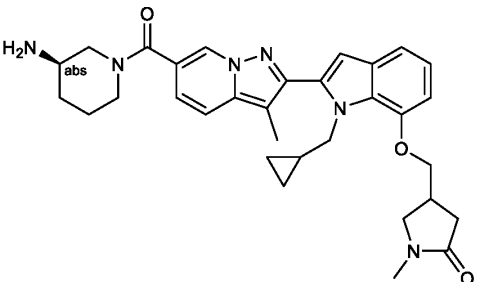
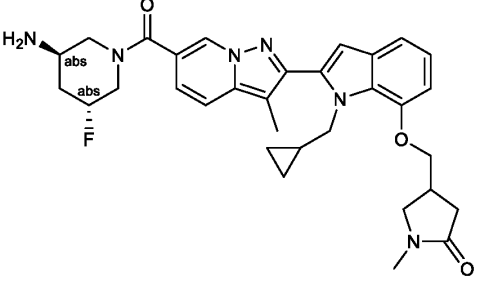
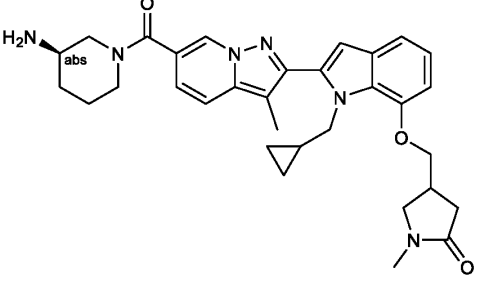
$J=6.4$ Hz, 1H), 3.23-2.94 (m, 5H), 2.44-2.39 (m, 1H), 2.37(s, 3H), 2.23-2.11 (m, 2H), 1.60-1.42 (m, 1H), 1.07-0.97 (m, 1H), 0.22-0.14 (m, 2H), 0.00--0.06 (m, 2H).

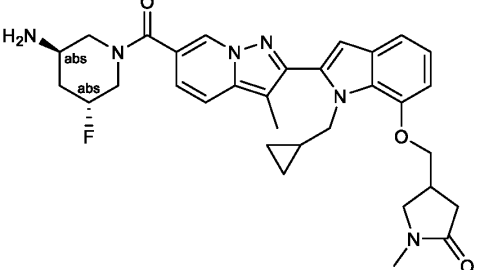
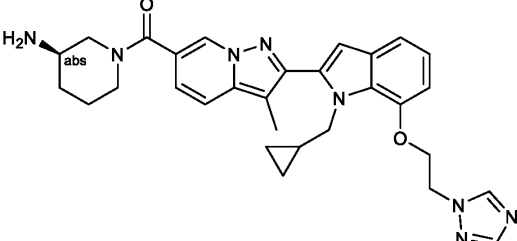
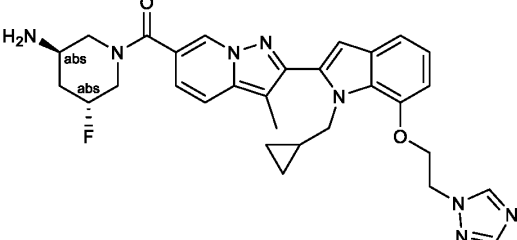
- Compounds of Examples 574 to 590 in Table 55 were obtained following a procedure similar to the preparation of a compound of Example 573, by displacement reaction of Intermediate 573B with appropriate tosylate followed by ester hydrolysis and coupling with appropriate amines.

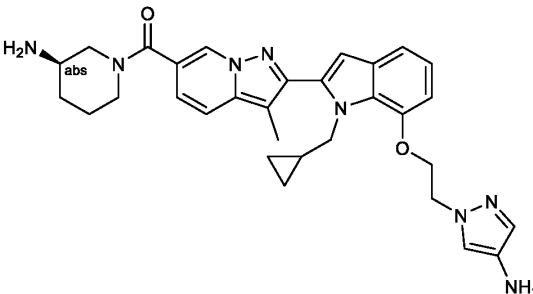
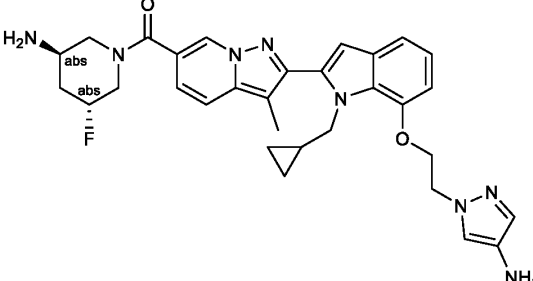
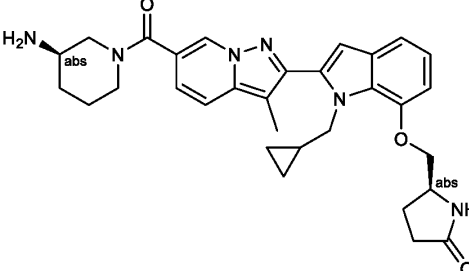
10

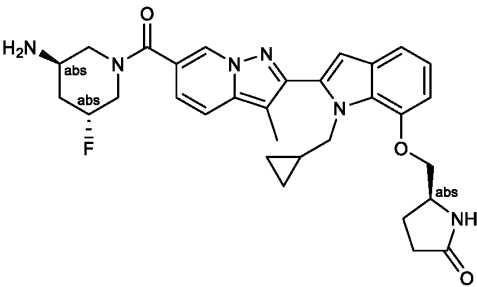
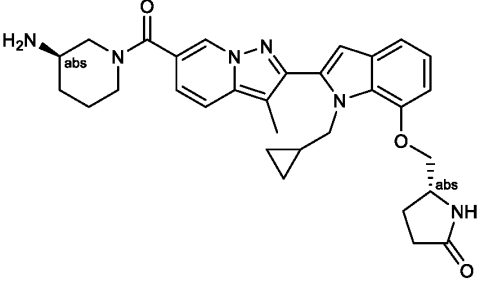
Table 55

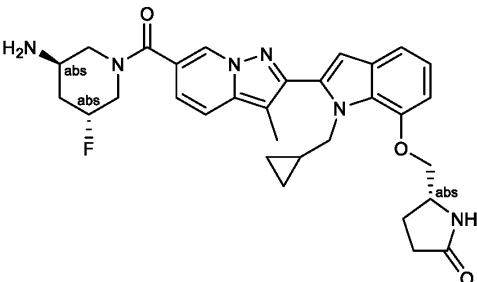
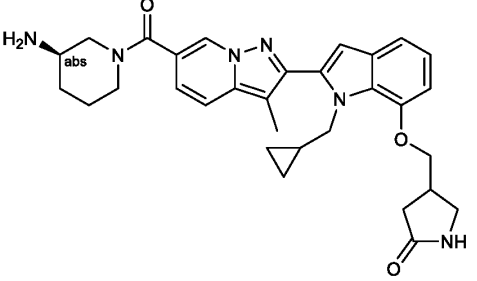
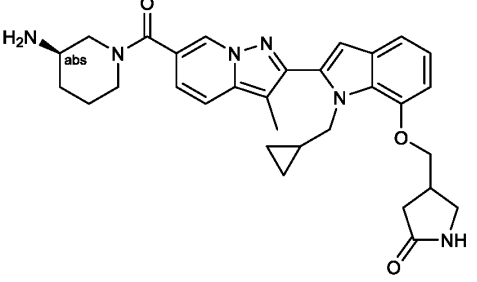
Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
574	 (2-(7-(2-(1H-Imidazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)((3R,5R)-3-amino-5-fluoropiperidin-1-yl)methanone Analytical Data: 556.3, 1.272 min (Method E)
575	 (R)-(2-(7-(2-(1H-Imidazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)(3-aminopiperidin-1-yl)methanone Analytical Data: 538.3, 1.278 min (Method E)

576	 4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)-1-methylpyrrolidin-2-one (isomer 1) Analytical Data: 555.3, 1.531 min (Method E)
577	 4-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)-1-methylpyrrolidin-2-one (isomer 1) Analytical Data: 573.2, 1.544 min (Method E)
578	 4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)-1-methylpyrrolidin-2-one (isomer 2) Analytical Data: 555.3, 1.524 min (Method E)

579	 4-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)-1-methylpyrrolidin-2-one (isomer 2) Analytical Data: 573.2, 1.546 min (Method E)
580	 (R)-(2-(7-(2-(1H-1,2,4-Triazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)(3-aminopiperidin-1-yl)methanone Analytical Data: 539.3, 1.384 min (Method E)
581	 (2-(7-(2-(1H-1,2,4-Triazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)((3R,5R)-3-amino-5-fluoropiperidin-1-yl)methanone Analytical Data: 557.2, 1.516 min (Method E)

582	 (R)-2-(7-(2-(4-Amino-1H-pyrazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl(3-aminopiperidin-1-yl)methanone Analytical Data: 553.3, 1.410 min (Method E)
583	 (2-(7-(2-(4-Amino-1H-pyrazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)((3R,5R)-3-amino-5-fluoropiperidin-1-yl)methanone Analytical Data: 571.3, 1.473 min (Method E)
584	 (S)-5-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one

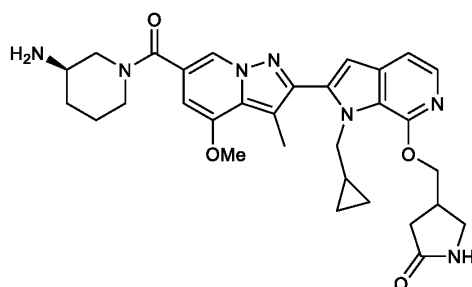
	Analytical Data: 541.3, 1.402 min (Method E)
585	 (S)-5-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one Analytical Data: 559.3, 1.386 min (Method E)
586	 (R)-5-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one Analytical Data: 541.3, 1.373 min (Method E)

587	 (R)-5-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one Analytical Data: 559.2 , 1.388 min (Method E)
588	 4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (isomer 1) Analytical Data: 541.2 , 1.375 min (Method E)
589	 4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (isomer 2) Analytical Data: 541.3, 1.372 min (Method E)

590	 4-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one (isomer 2) Analytical Data: 559.2, 1.382 min. Method E)
-----	---

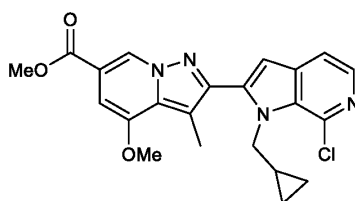
Example 591

4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one (isomer 1)



Intermediate 591A

Methyl 2-(7-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate



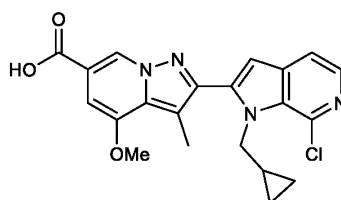
10

1-Amino-3-methoxy-5-(methoxycarbonyl)pyridin-1-ium (2.261 g, 12.34 mmol) was added to a stirred solution of (E)-7-chloro-1-(cyclopropylmethyl)-2-(2-nitroprop-1-en-1-yl)-1H-pyrrolo[2,3-c]pyridine (1.2 g, 4.11 mmol) in DMF (10 ml). The reaction

mixture was stirred at 80°C for 30 hours, diluted with water (20 ml), and extracted with ethyl acetate (3×30 ml). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuum. The crude product thus obtained was purified using a silica gel column, eluting with 0-20% ethyl acetate in n-hexane to afford (820 mg, 47%) of methyl 2-(7-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate as brown solid. LC-MS m/z: 425.2 [M+H]⁺.

Intermediate 591B

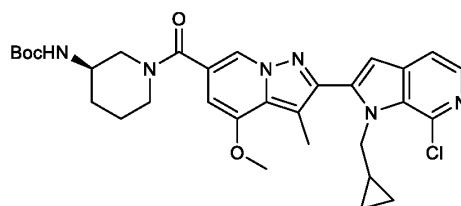
2-(7-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylic acid



Intermediate 591B (0.62 g, 92%) was prepared following a similar procedure depicted for example 550A. LC-MS m/z: 411.1 [M+H]⁺; ¹H NMR (400 MHz, DMSO-d₆) δ ppm: 8.82 (s, 1H), 8.02 (d, *J*=5.5 Hz, 1H), 7.68 (d, *J*=5.5 Hz, 1H), 6.99 (s, 1H), 6.91 (s, 1H), 4.69 (d, *J*=7.0 Hz, 2H), 4.02 (s, 3H), 2.47 (s, 3H), 1.06-1.03 (m, 1H), 0.29-0.22 (m, 2H), -0.02--0.05 (m, 2H).

Intermediate 591C

tert-butyl (R)-(1-(2-(7-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)piperidin-3-yl)carbamate



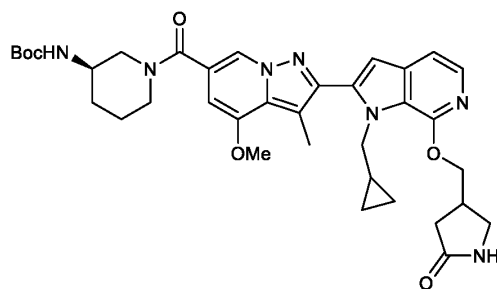
tert-Butyl (R)-piperidin-3-ylcarbamate (175 mg, 0.876 mmol), HATU (416 mg, 1.095 mmol), DIPEA (0.383 ml, 2.191 mmol) was added to a stirred solution of 2-(7-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-

methylpyrazolo[1,5-a]pyridine-6-carboxylic acid (300 mg, 0.730 mmol) in DMF (5 ml). The reaction mixture was stirred at a room temperature for 6 hours, diluted with water (10 ml), and extracted with ethyl acetate (20 ml). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuum. The crude product thus obtained was purified using comb flash chromatography (12 g, Redisep[®] SiO₂ column, eluting with 0-10% methanol in dichloromethane to afford tert-butyl (R)-(1-(2-(7-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)piperidin-3-yl)carbamate (380 mg, 88%) as brown solid. LC-MS m/z: 593.5 [M+H]⁺

10

Intermediate 591D

tert-Butyl ((3R)-1-(2-(1-(cyclopropylmethyl)-7-((5-oxopyrrolidin-3-yl)methoxy)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)piperidin-3-yl)carbamate



15

Racemic 4-(hydroxymethyl)pyrrolidin-2-one (88 mg, 0.674 mmol), Cs₂CO₃ (412 mg, 1.264 mmol), S-BINAP (52.5 mg, 0.084 mmol) and Pd₂(dba)₃ (38.6 mg, 0.042 mmol) were added to a stirred solution of tert-butyl (R)-(1-(2-(7-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)piperidin-3-yl)carbamate (250 mg, 0.421 mmol) in Toluene (3 ml). The reaction mixture was stirred at 95°C for 16 hours, diluted with water (10 ml), and extracted with ethyl acetate (2×20 ml). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuum. The crude product thus obtained was purified using a silica gel column, eluting with 0-8% Methanol in dichloromethane) to afford racemic compound, which was separated using a chiral SFC. Isomer 01: tert-butyl ((3R)-1-(2-(1-(cyclopropylmethyl)-7-((5-oxopyrrolidin-3-yl)methoxy)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-

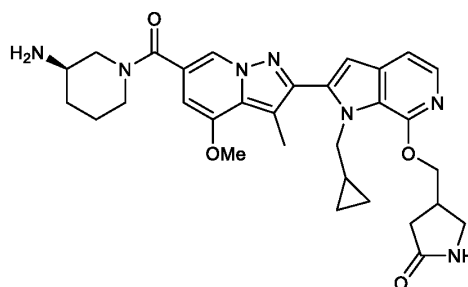
25

6-carbonyl)piperidin-3-yl)carbamate (30 mg, 10%); isomer 02: tert-butyl ((3R)-1-(2-(1-(cyclopropylmethyl)-7-((5-oxopyrrolidin-3-yl)methoxy)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)piperidin-3-yl)carbamate (30mg, 10%). LC-MS m/z: 672.4 [M+H]⁺ (Method H).

5

Example 591

4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one (isomer 1)



10

TFA (0.034 ml, 0.447 mmol) was added to a stirred solution of tert-butyl ((3R)-1-(2-(1-(cyclopropylmethyl)-7-((5-oxopyrrolidin-3-yl)methoxy)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)piperidin-3-yl)carbamate (30 mg, 0.045 mmol) in dichloromethane (5 ml). The reaction mixture was stirred at a room temperature for 16 hours, concentrated, and the crude product thus obtained was purified using a preparative LC/MS with the following conditions: Column: Waters XBridge C18, 19×150 mm, 5 μm particles, mobile phase A: 10 mM ammonium acetate; mobile phase B: acetonitrile; gradient: 12-48% B over 25 minutes, then a 5-minute hold at 100% B; flow rate: 15 ml/min. Fractions containing the desired product were combined and dried using centrifugal evaporation. The purified material was then diluted with a 1:1 mixture of DCM and methanol, treated with Si-Pyridine, and shaken for a minimum of 2 hours. The resulting mixture was filtered and dried using centrifugal evaporation to afford 4-(((2-(6-((R)-3-aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one (isomer 1) (18.8 mg, 74%). LC-MS m/z: 572.2 [M+H]⁺. Retention time: 1.309 min (Method E). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.40 (s, 1H), 7.69 (d, *J*=5.4 Hz, 1H), 7.60 (s, 1H), 7.23 (d, *J*=5.4 Hz, 1H), 6.75 (s, 1H), 6.59 (s,

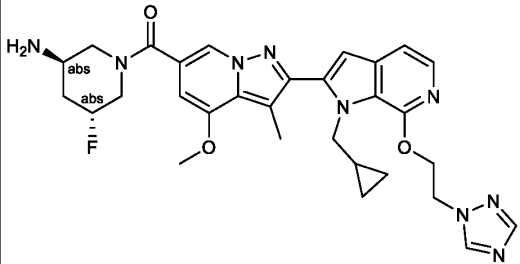
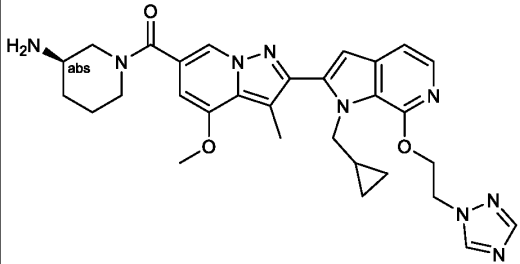
25

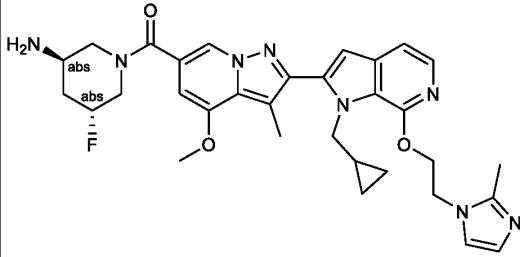
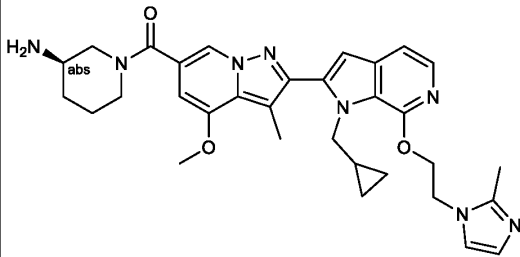
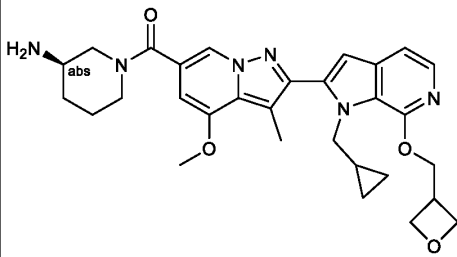
1H), 4.53-4.45 (m, 4H), 3.98 (s, 3H), 3.49-3.47 (m, 1H), 3.22-3.19 (m, 2H), 3.06-2.95 (m, 3H), 2.80-2.73 (m, 1H), 2.46 (s, 3H), 2.41-2.35 (m, 1H), 2.21-2.13 (m, 1H), 1.72-1.70 (m, 1H), 1.50-1.48 (m, 1H), 1.33-1.26 (m, 1H), 1.09-1.01 (m, 1H), 0.28-0.20 (m, 2H), 0.06-0.01 (m, 2H).

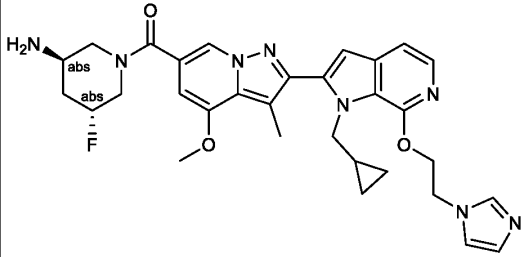
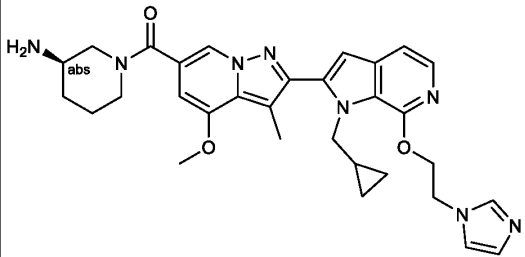
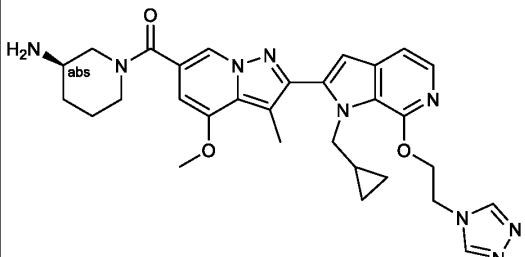
5

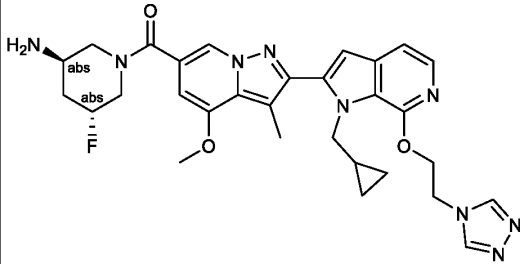
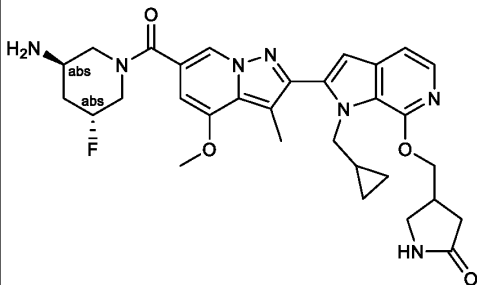
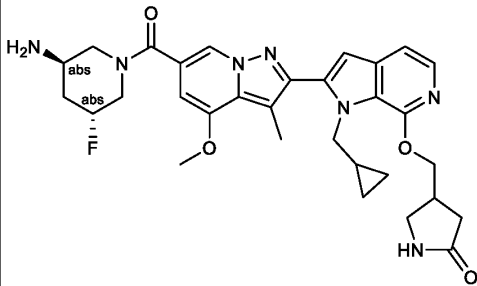
Compounds of Examples 592 to 608 in Table 56 were prepared following a procedure similar to the preparation of a compound of Example 591, by Buchwald etherification reaction of Intermediate 591C with appropriate alcohols

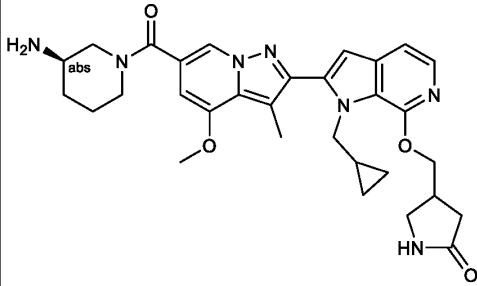
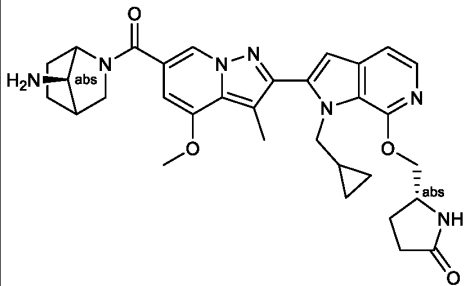
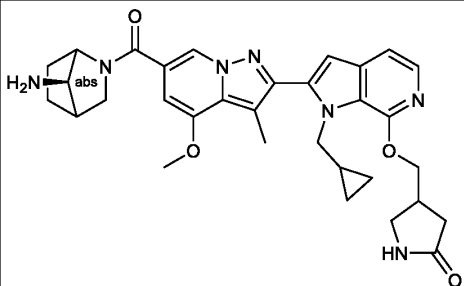
Table 56

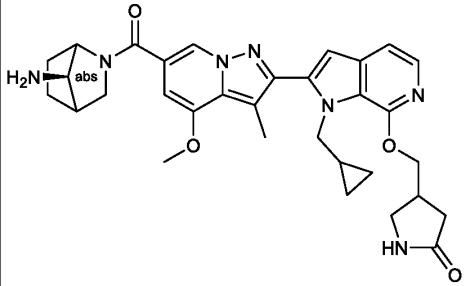
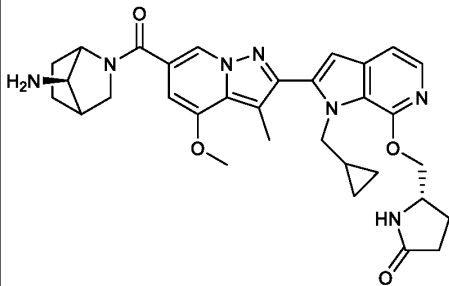
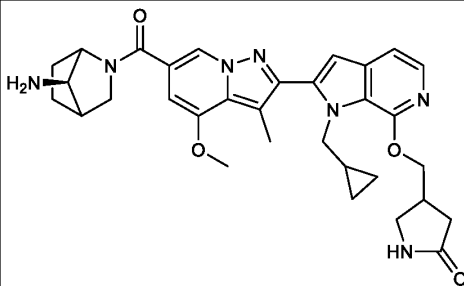
Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
592	 (2-(7-(2-(1H-1,2,4-Triazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)((3R,5R)-3-amino-5-fluoropiperidin-1-yl)methanone Analytical Data: 588.3, 1.476 min (Method E)
593	 (R)-(2-(7-(2-(1H-1,2,4-Triazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)(3-aminopiperidin-1-yl)methanone Analytical Data: 570.2, 1.405 min (Method E)

594	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(2-(2-methyl-1H-imidazol-1-yl)ethoxy)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 601.3, 1.513 min (Method E)
595	 (R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(2-(2-methyl-1H-imidazol-1-yl)ethoxy)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 571.3, 1.398 min (Method E)
596	 (R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(oxetan-3-ylmethoxy)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 545.3, 0.982 min (Method E)

597	 (2-(7-(2-(1H-Imidazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)((3R,5R)-3-amino-5-fluoropiperidin-1-yl)methanone Analytical Data: 587.3, 1.530min (Method E)
598	 (R)-(2-(7-(2-(1H-Imidazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)(3-aminopiperidin-1-yl)methanone Analytical Data: 569.3, 1.467 min (Method E)
599	 (R)-(2-(7-(2-(4H-1,2,4-Triazol-4-yl)ethoxy)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)(3-aminopiperidin-1-yl)methanone Analytical Data: 570.3, 1.313 min (Method E)

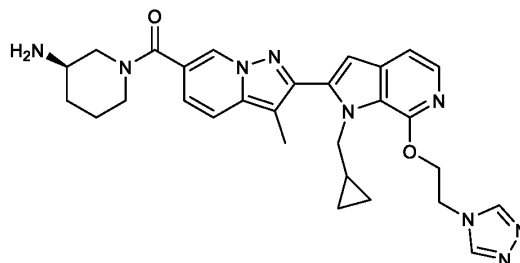
600	 (2-(7-(2-(4H-1,2,4-Triazol-4-yl)ethoxy)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)((3R,5R)-3-amino-5-fluoropiperidin-1-yl)methanone Analytical Data: 588.2, 1.369 min (Method E)
601	 4-(((2-(6-(((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one (isomer 1) Analytical Data: 590.3, 1.434 min (Method E)
602	 4-(((2-(6-(((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one (isomer 2) Analytical Data: 590.2, 1.436 min (Method E)

603	 4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one (isomer 2) Analytical Data: 572.2, 1.312 min (Method E)
604	 (5R)-5-(((2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one Analytical Data: 584.3, 1.438 min (Method E)
605	 4-(((2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one (isomer 1) Analytical Data: 584.3, 8.372 min (Method C)

606	 4-(((2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one (isomer 2) Analytical Data: 584.3, 8.335 min (Method C)
607	 (5R)-5-(((2-(6-((7S)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one Analytical Data: 584.4, 1.505 min (Method E)
608	 4-(((2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one (mixture of diastereomers) Analytical Data: 584.3, 1.456 min (Method E)

Example 609

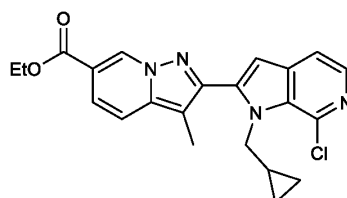
(R)-(2-(7-(2-(4H-1,2,4-Triazol-4-yl)ethoxy)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)(3-aminopiperidin-1-yl)methanone



5

Intermediate 609A

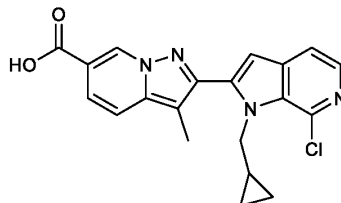
Ethyl 2-(7-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate



1-Amino-3-(ethoxycarbonyl)pyridin-1-ium (2.063 g, 12.34 mmol) was added to a stirred solution of (E)-7-chloro-1-(cyclopropylmethyl)-2-(2-nitroprop-1-en-1-yl)-1H-pyrrolo[2,3-c]pyridine (1.2 g, 4.11 mmol) in DMF (3 ml). The reaction mixture was stirred at 80°C for 30 hours, diluted with water (20 ml), and extracted with ethyl acetate (3×20 ml). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuum. A crude product thus obtained was purified using a silica gel column, eluting with 0-20% ethyl acetate in hexane to afford ethyl 2-(7-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate (1.0 g, 60%) as brown solid. LC-MS m/z: 409.3 [M+H]⁺; ¹H NMR (300 MHz, DMSO-d₆) δ ppm: 9.24 (s, 1H), 8.30 (td, J=2.1, 7.9 Hz, 1H), 8.07-7.97 (m, 1H), 7.88 (d, J=9.3 Hz, 1H), 7.71-7.55 (m, 3H), 7.05 (s, 1H), 4.78 (d, J=6.8 Hz, 2H), 4.42-4.31 (m, 2H), 2.38 (s, 3H), 1.40-1.30 (m, 3H), 1.08-1.03 (m, 1H), 0.40-0.19 (m, 2H), -0.01--0.04 (m, 2H).

Intermediate 609B

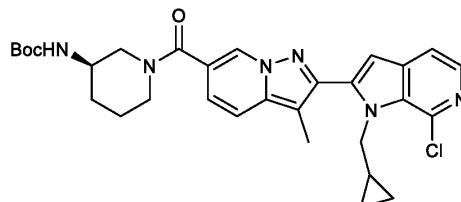
2-(7-Chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylic acid



5 2-(7-Chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carboxylic acid (0.55 g, 82%) was prepared using procedure similar to the preparation of Intermediate 510D as a brown solid as a brown solid. LC-MS m/z : 381.3 $[M+H]^+$; 1H NMR (300 MHz, DMSO- d_6) δ ppm: 9.16 (s, 1H), 8.02 (d, $J=5.3$ Hz, 1H), 7.85 (d, $J=9.4$ Hz, 1H), 7.69 (d, $J=5.3$ Hz, 1H), 7.64 (dd, $J=1.5$, 9.4 Hz, 1H), 7.04 (s, 1H), 4.77 (d, $J=6.8$ Hz, 2H), 2.38 (s, 3H), 1.23 (s, 1H), 1.18-0.96 (m, 1H), 0.25 (br, d, $J=7.9$ Hz, 2H), -0.01--0.06 (m, 2H).

Intermediate 609C

15 tert-Butyl (R)-(1-(2-(7-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)piperidin-3-yl)carbamate

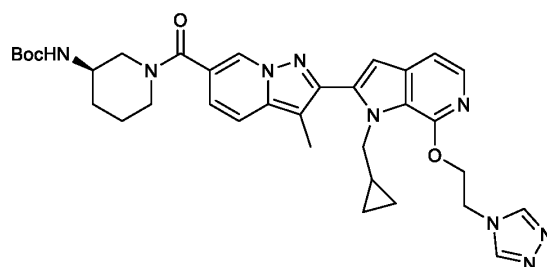


Intermediate 609C was prepared following a procedure similar to the preparation of Intermediate 386E (200 mg, 90%). LC-MS m/z : 563.3 $[M+H]^+$.

20

Intermediate 609D

tert-Butyl (R)-(1-(2-(7-(2-(4H-1,2,4-triazol-4-yl)ethoxy)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)piperidin-3-yl)carbamate

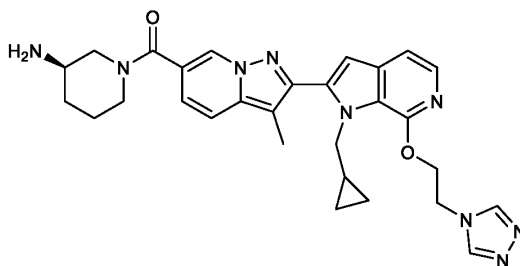


2-(4H-1,2,4-Triazol-4-yl)ethan-1-ol (30.1 mg, 0.266 mmol), Cs₂CO₃ (174 mg, 0.533 mmol), S-BINAP (22.12 mg, 0.036 mmol) and Pd₂(dba)₃ (16.26 mg, 0.018 mmol) were added to a stirred solution of tert-butyl (R)-(1-(2-(7-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)piperidin-3-yl)carbamate (100 mg, 0.178 mmol) in 1,4-dioxane (3 ml). The reaction mixture was degassed with argon for 5 and then stirred at 85°C for 16 hours, diluted with water (20 ml), and extracted with ethyl acetate (20 ml). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuum. A crude product thus obtained was purified using a silica gel column eluting with 0-8% MeOH in dichloromethane to afford (40 mg, 35%) tert-butyl (R)-(1-(2-(7-(2-(4H-1,2,4-triazol-4-yl)ethoxy)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)piperidin-3-yl)carbamate. LCMS m/z: 640.6 [M+H]⁺

15

Example 609

(R)-(2-(7-(2-(4H-1,2,4-Triazol-4-yl)ethoxy)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-yl)(3-aminopiperidin-1-yl)methanone



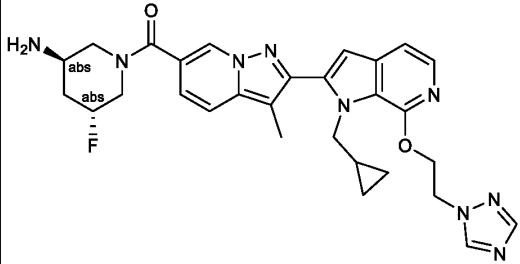
HCl in dioxane (4.0 M) (0.019 ml, 0.625 mmol) was added to a stirred solution of tert-butyl (R)-(1-(2-(7-(2-(4H-1,2,4-triazol-4-yl)ethoxy)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)piperidin-3-yl)carbamate (40 mg, 0.063 mmol) in 1,4-dioxane (1 ml). The reaction mixture was stirred at a room temperature for 1 hour, concentrated, and the crude product thus

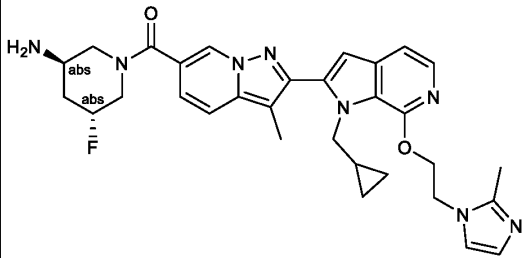
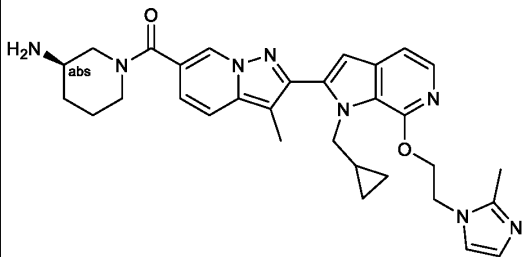
obtained was purified using a preparative LC/MS with the following conditions: Column: Waters XBridge C18, 19×150 mm, 5 μm particles; mobile phase A: 10 mM ammonium acetate; mobile phase B: acetonitrile; gradient: 10-30% B over 20 minutes, then a 5-minute hold at 100% B; flow rate: 20 ml/min. Fractions containing the desired product were combined and dried using centrifugal evaporation. The purified material was then diluted with a 1:1 mixture of ethylene dichloride and methanol (EDM), treated with Si-Pyridine, and shaken for a minimum of 2 hours. The resulting mixture was filtered and dried using centrifugal evaporation to afford (R)-(2-(7-(2-(4H-1,2,4-triazol-4-yl)ethoxy)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)(3-aminopiperidin-1-yl)methanone (8.9 mg, 26%). LC-MS m/z : 540.2 [M+H]⁺, LCMS retention time 1.195 min. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.84 (s, 1H), 8.64 (s, 2H), 7.82 (s, 1H), 7.70 (d, *J*=5.4 Hz, 1H), 7.27-7.24 (m, 2H), 6.79 (s, 1H), 4.85 (br, d, *J*=6.1 Hz, 2H), 4.57 (dd, *J*=3.9, 6.1 Hz, 2H), 4.43-4.41 (m, 2H), 3.29-3.03 (m, 3H), 2.89-2.84 (m, 1H), 2.53-2.53 (m, 1H), 2.36 (s, 3H), 1.92-1.89 (m, 2H), 1.24-1.00 (m, 2H), 0.82-0.80 (m, 1H), 0.17-0.14 (m, 2H), -0.10--0.13 (m, 2H)

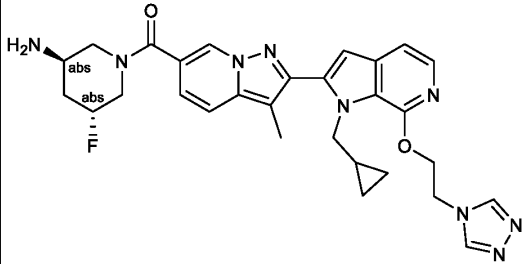
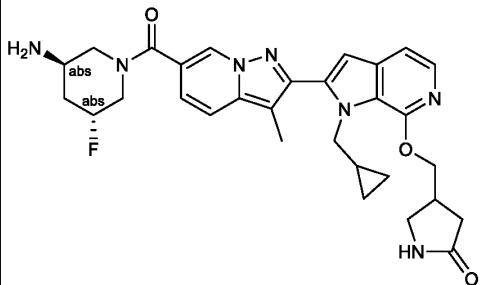
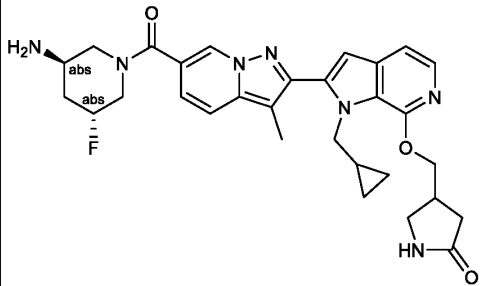
Compounds of Examples 610 to 619 in Table 57 were obtained following a procedure similar to the preparation of a compound of Example 610, by Buchwald etherification reaction of Intermediate 609C with appropriate alcohols

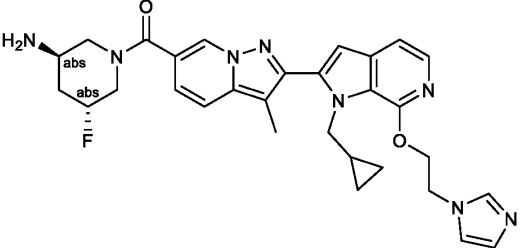
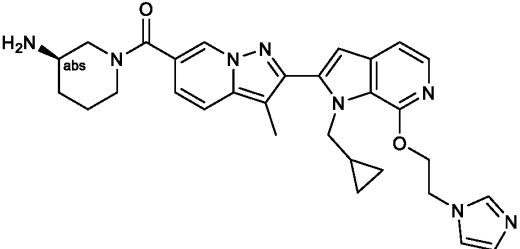
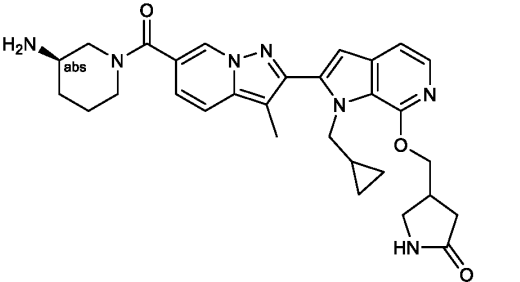
20

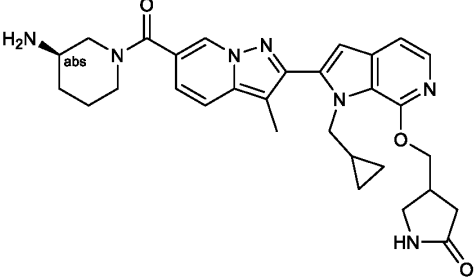
Table 57

Example	Structure Name Analytical Data: LC-MS m/z [M+H] ⁺ ; HPLC retention time (HPLC method)
610	 (2-(7-(2-(1H-1,2,4-Triazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)((3R,5R)-3-amino-5-fluoropiperidin-1-yl)methanone

	Analytical Data: 558.3, 1.357 min (Method E)
611	 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(2-(2-methyl-1H-imidazol-1-yl)ethoxy)-1H-pyrrolo[2,3-c]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 571.3, 1.398 min (Method E)
612	 (R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(2-(2-methyl-1H-imidazol-1-yl)ethoxy)-1H-pyrrolo[2,3-c]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone Analytical Data: 553.3, 1.337 min (Method E)

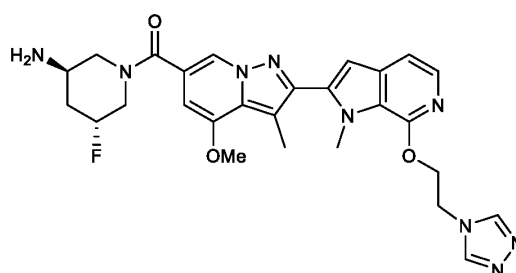
613	 (2-(7-(2-(4H-1,2,4-Triazol-4-yl)ethoxy)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)((3R,5R)-3-amino-5-fluoropiperidin-1-yl)methanone Analytical Data: 558.2, 1.262 min (Method E)
614	 4-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one (isomer 1) Analytical Data: 560.3, 1.340 min (Method E)
615	 4-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one (isomer 2) Analytical Data: 560.2, 1.329 min (Method E)

616	 (2-(7-(2-(1H-Imidazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)((3R,5R)-3-amino-5-fluoropiperidin-1-yl)methanone Analytical Data: 557.2, 1.414 min (Method E)
617	 (R)-(2-(7-(2-(1H-Imidazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)(3-aminopiperidin-1-yl)methanone Analytical Data: 539.2, 1.349 min (Method E)
618	 4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one (isomer 1) Analytical Data: 542.2, 1.256 min (Method E)

619	 4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one (isomer 2) Analytical Data: 542.2, 1.255 min (Method E)
-----	---

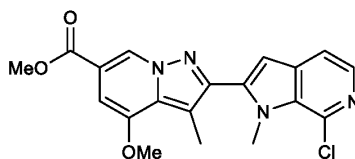
Example 620

(2-(7-(2-(4H-1,2,4-Triazol-4-yl)ethoxy)-1-methyl-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)((3R,5R)-3-amino-5-fluoropiperidin-1-yl)methanone



Intermediate 620A

Methyl 2-(7-chloro-1-methyl-2-(2-nitroprop-1-en-1-yl)-1H-pyrrolo[2,3-c]pyridine-6-carboxylate



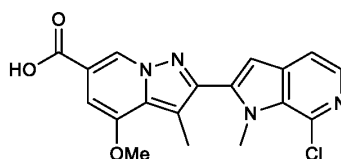
Intermediate 1 (4.37 g, 23.84 mmol) and copper(I) iodide (0.454 g, 2.384 mmol) were added to a solution of 7-chloro-1-methyl-2-(2-nitroprop-1-en-1-yl)-1H-pyrrolo[2,3-c]pyridine (2 g, 7.95 mmol) in DMF (10 ml). The reaction mixture was stirred for 16 hours, diluted with ethyl acetate (100 ml), washed with water (3×50 ml), dried over

Na₂SO₄, and concentrated to afford a crude compound, which was purified using a silica gel column using 0-30% ethyl acetate in Hexane to afford methyl 2-(7-chloro-1-methyl-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate (1.4 g, 46%) as brown solid. LC-MS m/z: 385.3 [M+H]⁺.

5

Intermediate 620B

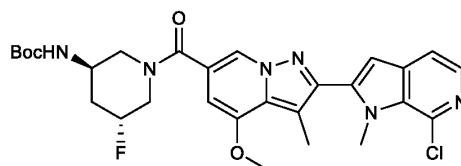
2-(7-Chloro-1-methyl-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylic acid



10 Intermediate 620B was prepared following a procedure similar to the preparation of Intermediate 519B (600 mg, 45%) as Off white solid. LC-MS m/z: 371.3 [M+H]⁺.

Intermediate 620C

15 tert-Butyl ((3R,5R)-1-(2-(7-chloro-1-methyl-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate

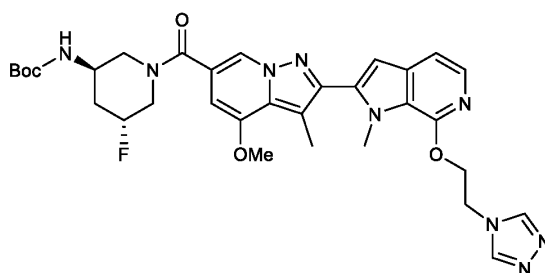


Intermediate 620C was prepared following a procedure similar to the preparation of Intermediate 519C (600 mg, 78%) as a brown solid. LC-MS m/z: 571.3 [M+H]⁺.

20

Intermediate 620D

tert-Butyl ((3R,5R)-1-(2-(7-(2-(4H-1,2,4-triazol-4-yl)ethoxy)-1-methyl-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate

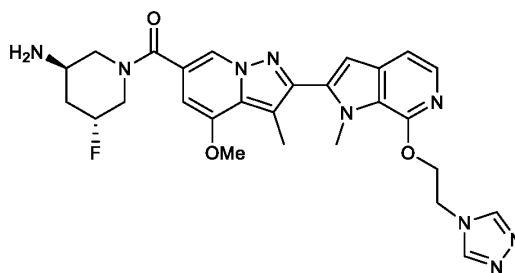


Intermediate 620D was prepared following a procedure similar to the preparation of Intermediate 519D (50 mg, 63%) as a brown solid. LC-MS m/z : 648.3 $[M+H]^+$.

5

Example 620

(2-(7-(2-(4H-1,2,4-Triazol-4-yl)ethoxy)-1-methyl-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)((3R,5R)-3-amino-5-fluoropiperidin-1-yl)methanone

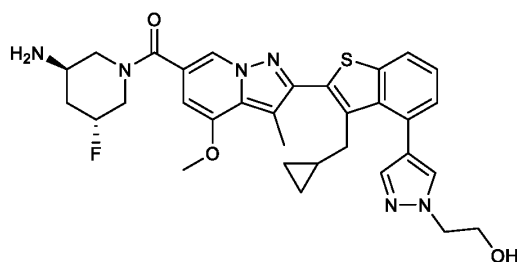


10 TFA (0.1 ml) was added to a solution of Intermediate 620D (20 mg, 0.031 mmol) in dichloromethane (5 ml), and the reaction mixture was stirred for 1 hour. The reaction mixture was concentrated to obtain a crude compound, which was purified using a preparative LC/MS with the following conditions: Column: Waters XBridge C18, 19×150 mm, 5 μ m particles; mobile phase A: 10 mM ammonium acetate; mobile phase B: 15 acetonitrile; gradient: 9-32% B over 25 minutes, then a 5-minute hold at 100% B; flow rate w: 20 ml/min. Fractions containing the desired product were combined and dried via centrifugal evaporation. The purified material was then diluted with a 1:1 mixture of ethylene dichloride and methanol (EDM), treated with Si-Pyridine, and shaken for a minimum of 2 hours. The resulting mixture was filtered and dried using centrifugal 20 evaporation to afford (2-(7-(2-(4H-1,2,4-triazol-4-yl)ethoxy)-1-methyl-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)((3R,5R)-3-amino-5-

fluoropiperidin-1-yl)methanone (3.2 mg, %). LC-MS m/z: 548.3 [M+H]⁺; LCMS retention time: 1.180 min [method E]

Example 621

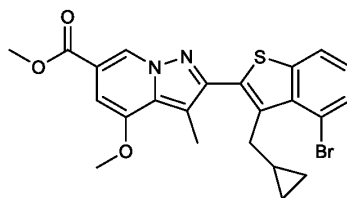
5 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl) (2-(3-(cyclopropylmethyl)-4-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)benzo[b]thiophen-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone



10

Intermediate 621A

Methyl 2-(4-bromo-3-(cyclopropylmethyl)benzo[b]thiophen-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate



15

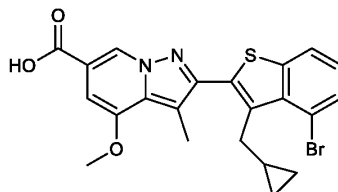
CuI (0.541 g, 2.84 mmol) was added to a stirred solution of Intermediate 62 (1 g, 2.84 mmol) and Intermediate 1 (1.040 g, 5.68 mmol) in DMF (5 ml). The reaction mixture was stirred for 3 hours at 80°C, the volatiles were evaporated to dryness under reduced pressure, water (100 ml) was added, and extracted with ethyl acetate (2×100 ml). The combined organic extracts were washed with water (100 ml) and brine solution (100 ml), dried over sodium sulphate, filtered, and volatiles were evaporated to dryness under reduced pressure. Residue thus obtained was purified using a silica gel column using a 50% ethyl acetate in hexane to afford methyl 2-(4-bromo-3-

20

(cyclopropylmethyl)benzo[b]thiophen-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylate (500 mg, 36%). LC-MS m/z: 485.3 [M+H]⁺.

Intermediate 621B

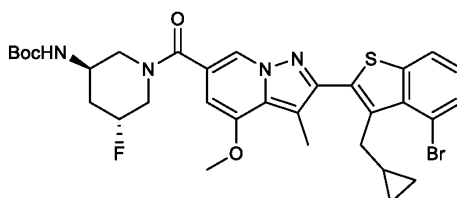
- 5 2-(4-Bromo-3-(cyclopropylmethyl)benzo[b]thiophen-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylic acid



- 10 Lithium hydroxide (74.0 mg, 3.09 mmol) in water (1 ml) was added to a stirred solution of Intermediate 621A (500 mg, 1.030 mmol) in THF (10 ml). The reaction mixture was stirred at a room temperature for 16 hours, the volatiles were evaporated to dryness under reduced pressure. A residue thus obtained was dissolved in water (15 ml), cooled to 0°C and the pH was adjusted to pH 5 using 1.5 N HCl solution. The solids thus
- 15 obtained were collected by vacuum filtration, and dried under vacuum at ambient temperature to afford 2-(4-bromo-3-(cyclopropylmethyl)benzo[b]thiophen-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carboxylic acid (400 mg, 82%). LC-MS m/z: 472.9 [M+H]⁺.

- 20 Intermediate 621C

tert-Butyl ((3R,5R)-1-(2-(4-bromo-3-(cyclopropylmethyl)benzo[b]thiophen-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



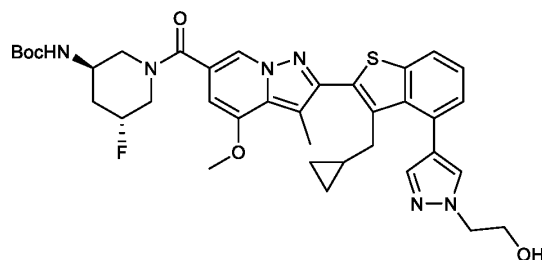
HATU (605 mg, 1.591 mmol) and DIPEA (0.556 ml, 3.18 mmol) were added to a stirred solution of Intermediate 621B (400 mg, 0.849 mmol), tert-butyl ((3R,5R)-5-fluoropiperidin-3-yl)carbamate (185 mg, 0.849 mmol) in DMF (2 ml). The reaction mixture was stirred at a room temperature for 16 hours, the volatiles were evaporated to dryness under reduced pressure, water (50 ml) was added, and extracted with ethyl acetate (2×50 ml). The combined organic extracts were washed with water (100 ml) and brine solution (100 ml), dried over sodium sulphate, filtered, and volatiles were evaporated to dryness under reduced pressure. A residue thus obtained was purified using a silica gel column (gradient of ethyl acetate in hexane), and the product was isolated at 40% ethyl acetate in hexane. Required fractions were collected and volatiles were evaporated to dryness under reduced pressure to afford tert-butyl ((3R,5R)-1-(2-(4-bromo-3-(cyclopropylmethyl)benzo[b]thiophen-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate (400 mg, 70%). LC-MS m/z: 673.1 [M+H]⁺.

15

Intermediate 621D

tert-Butyl ((3R,5R)-1-(2-(3-(cyclopropylmethyl)-4-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)benzo[b]thiophen-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate

20



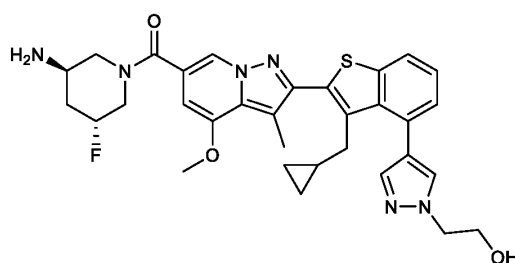
K₂CO₃ (30.9 mg, 0.223 mmol) and PdCl₂(dppf) (10.89 mg, 0.015 mmol) were added to a stirred solution Intermediate 621C (50 mg, 0.074 mmol) and 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)ethan-1-ol (17.73 mg, 0.074 mmol) in 1,4-dioxane (2 ml) under argon atmosphere. The reaction mixture was heated at 80°C for 2 hours, the volatiles were evaporated to dryness under reduced pressure, water (10 ml) was added, and extracted with ethyl acetate (2×10 ml). The combined organic extracts

25

were washed with water (10 ml) and brine solution (10 ml), organic layer was dried over sodium sulphate, filtered, and volatiles were evaporated to dryness under reduced pressure to afford tert-butyl ((3R,5R)-1-(2-(3-(cyclopropylmethyl)-4-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)benzo[b]thiophen-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate (40 mg, 76%). LC-MS m/z: 703.3 [M+H]⁺.

Example 621

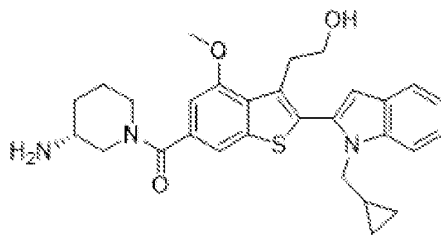
((3R,5R)-3-Amino-5-fluoropiperidin-1-yl) (2-(3-(cyclopropylmethyl)-4-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)benzo[b]thiophen-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone



TFA (0.044 ml, 0.569 mmol) was added to a stirred solution of Intermediate 621D (40 mg, 0.057 mmol) in DCM (2 ml). The reaction mixture was stirred for 1 hour at a room temperature, the volatiles were evaporated to dryness under reduced pressure, and the crude compound thus obtained was purified using reverse phase HPLC to afford ((3R,5R)-3-amino-5-fluoropiperidin-1-yl) (2-(3-(cyclopropylmethyl)-4-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)benzo[b]thiophen-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone (7.1 mg, 20%), LC-MS m/z: 603.3 [M+H]⁺. LCMS retention time: 1.558 min (method E).

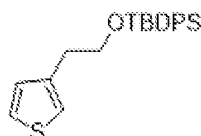
Example 622

(R)-(3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-3-(2-hydroxyethyl)-4-methoxybenzo[b]thiophen-6-yl)methanone



Intermediate 622A

tert-butyl diphenyl (2-(thiophen-3-yl)ethoxy) silane



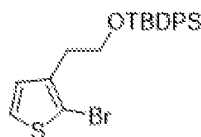
5

To a stirred solution of 2-(thiophen-3-yl)ethanol (10 g, 78.1 mmol) in DCM (500 mL) was added imidazole (15.9 g, 234.3 mmol) at 0 °C under nitrogen atmosphere. Then to this was added TBDPSCl (23.5 g, 85.9 mmol) at 0 °C. The reaction was stirred at room temperature for 2 h. The reaction was monitored by TLC and LCMS. The resulting solution was diluted with water (300 mL), then extracted with DCM (2 x 300 mL). The combined organic extracts were dried over anhydrous sodium sulphate concentrated under vacuum. The crude product was purified by silica gel column chromatography (petroleum ether : ethyl acetate = 20:1) to afford the title compound (27 g, 94.7%) as colorless oil. LCMS (ESI, m/z): 367 [M+H]⁺.

15

Intermediate 622B

(2-(2-bromothiophen-3-yl)ethoxy)(tert-butyl)diphenylsilane



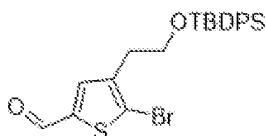
To a stirred solution of Intermediate 622A (5 g, 13.6 mmol) in MeCN (100 mL) was added NBS (3.6 g, 20.4 mmol) at 0 °C under nitrogen atmosphere. The reaction was stirred at room temperature for 12 h. The reaction was monitored by TLC and LCMS. The resulting solution was diluted with water (100 mL), then extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were dried over anhydrous sodium sulphate

concentrated under vacuum. The crude product was purified by silica gel column chromatography (petroleum ether : ethyl acetate = 20:1) to afford the title compound (5.5 g, 90.7%) as a yellow solid. LCMS (ESI, m/z): 445 $[M+H]^+$.

5

Intermediate 622C

5-bromo-4-(2-(tert-butyl diphenylsilyloxy)ethyl)thiophene-2-carbaldehyde

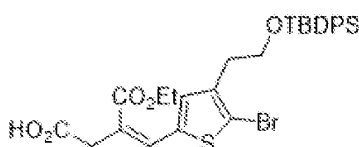


To a stirred solution of Intermediate 622B (5.5 g, 12.3 mmol) in THF (50 mL) was added $n\text{BuLi}$ (1 M in hexane) (18.5 g, 18.4 mmol) at -78°C under nitrogen atmosphere. The reaction was stirred at -78°C for 0.5 h. Then to this was added Et_2NH (1.8 g, 24.6 mmol) and DMF (1.1 g, 14.8 mmol) -78°C under nitrogen atmosphere. The reaction was stirred at 0°C for 2 h under nitrogen atmosphere. The reaction was monitored by TLC and LCMS. The resulting solution was diluted NH_4Cl (100 mL, aq.), then extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were dried over anhydrous sodium sulphate concentrated under vacuum. The crude product was purified by silica gel column chromatography (petroleum ether : ethyl acetate = 10:1) to afford the title compound (4.9 g, 84%) as yellow oil. LCMS (ESI, m/z): 472 $[M+H]^+$.

20

Intermediate 622D

(Z)-4-(5-bromo-4-(2-((tert-butyl diphenylsilyl)oxy)ethyl)thiophen-2-yl)-3-(ethoxycarbonyl)but-3-enoic acid

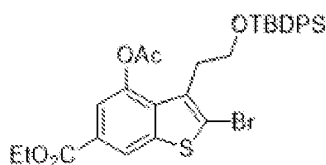


To a stirred solution of Intermediate 622C (4.9 g, 10.4 mmol) in tert-butanol (200 mL) was added diethyl butanedioate (7.2 g, 41.6 mmol) and $t\text{-BuOK}$ (1 M in THF) (21 mL, 20.8 mmol). The resulting mixture was stirred at 50°C for 1 h under nitrogen atmosphere. LCMS showed the reaction was complete, and the mixture was diluted with water (100 mL), then adjusted to pH 6~7 with HCl (2 M). The resulting mixture was

extracted with ethyl acetate (2 x 200 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by silica gel column chromatography (petroleum ether : ethyl acetate =5:1) to obtain the title compound (4 g, 64.5%) as yellow oil. LCMS (ESI, m/z): 601 [M+H]⁺.

Intermediate 622E

ethyl 4-acetoxy-2-bromo-3-(2-((tert-butyldiphenylsilyl)oxy)ethyl)benzo[b]thiophene-6-carboxylate



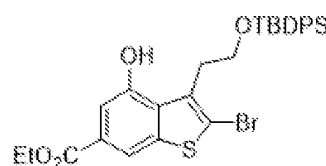
10

To a stirred solution of Intermediate 622D (4 g, 6.6 mmol) in Ac₂O (50 mL) was added NaOAc (2.4 g, 29.7 mmol). The resulting mixture was stirred at 70 °C for 1 h under nitrogen atmosphere. LCMS showed the reaction was complete, and the solids were filtered out. The resulting mixture was concentrated. The residue was purified by silica gel column chromatography (petroleum ether : ethyl acetate =5:1) to obtain the title compound (2.5 g, 60.9%) as yellow oil. LCMS (ESI, m/z): 625 [M+H]⁺.

15

Intermediate 622F

ethyl 2-bromo-3-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-4-hydroxybenzo[b]thiophene-6-carboxylate



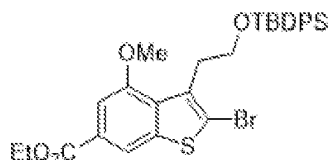
20

To a stirred solution of Intermediate 622E (2.5 g, 4 mmol) in Ethanol (50 mL) was added K₂CO₃ (1.1 g, 8 mmol). The resulting mixture was stirred at 70 °C for 1 h under nitrogen atmosphere. LCMS showed the reaction was complete, and the solids were filtered out. The resulting mixture was concentrated. The residue was purified by silica gel column chromatography (petroleum ether : ethyl acetate =2:1) to obtain the title compound (2 g, 85.8%) as a white solid. LCMS (ESI, m/z): 583 [M+H]⁺.

25

Intermediate 622G

ethyl 2-bromo-3-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-4-methoxybenzo[b]thiophene-6-carboxylate



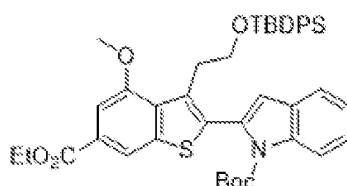
5

To a stirred solution of Intermediate 622F ATN-81-252615-6 (2 g, 3.4 mmol) in DMF (30 mL) was added K_2CO_3 (1.4 g, 10.2 mmol) and MeI (719 mg, 5.1 mmol). The resulting mixture was stirred at room temperature for 30 min. LCMS showed the reaction was complete, and the solids were filtered out. The resulting mixture was concentrated.

10 The residue was purified by silica gel column chromatography (petroleum ether : ethyl acetate = 5:1) to obtain the title compound (2 g, 97.6%) as a white solid. LCMS (ESI, m/z): 597 $[M+H]^+$.

Intermediate 622H

15 tert-butyl 2-(3-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-6-(ethoxycarbonyl)-4-methoxybenzo[b]thiophen-2-yl)-1H-indole-1-carboxylate



To a stirred solution of Intermediate 622G (150 mg, 0.25 mmol) in 1,4-dioxane (8 mL) and water (1.5 mL), was added 1-(tert-butoxycarbonyl)-1H-indol-2-ylboronic (130 mg, 0.5 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (43 mg, 0.05 mmol) and K_3PO_4 (212 mg, 1 mmol) at room temperature under nitrogen atmosphere. The reaction was stirred at 90 °C for 2 h. The reaction was monitored by TLC and LCMS. The reaction mixture was cooled to room temperature. The resulting solution was diluted with 50 mL of water, then extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, concentrated under vacuum. The crude product was purified by Prep-TLC (petroleum ether/ethyl acetate =

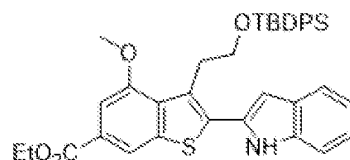
20

25

3:2) to afford the title compound (150 mg, 81.5%) as a yellow solid. LCMS (ESI, m/z): 734 [M+H]⁺.

Intermediate 622I

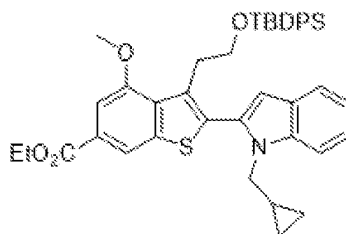
5 ethyl 3-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-2-(1H-indol-2-yl)-4-methoxybenzo[b]thiophene-6-carboxylate



To a stirred solution of Intermediate 622H (150 g, 0.20 mmol) in DCM (10 mL) was added silica gel (1.5 g). The mixture was concentrated under vacuum. The residue was stirred at 90 °C for 2 h under vacuum. The reaction was monitored by LCMS. The mixture was filtered through a Celite pad and washed with DCM / MeOH = 15:1 (80 mL). The combined organic extract was concentrated under vacuum to afford the title compound (110 mg, 85.2%) as yellow solid. LCMS (ESI, m/z): 634 [M+H]⁺.

15 Intermediate 622J

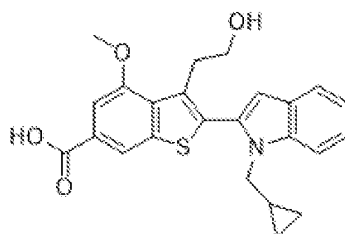
ethyl 3-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxybenzo[b]thiophene-6-carboxylate



To a stirred solution of Intermediate 622I (110 mg, 0.17 mmol) in DMF (3 mL) was added bromomethylcyclopropane (47 mg, 0.35 mmol) and Cs₂CO₃ (115 mg, 0.35 mmol). The reaction was stirred at 50 °C for 1 h. The reaction was monitored by LCMS. The mixture was quenched with water (15 mL), extracted with ethyl acetate (2 x 30 mL). The organic layer was washed with brine (2 x 50 mL) and concentrated under vacuum. The crude product was purified by column chromatography (petroleum ether/ethyl acetate=3/1) to afford the title compound (100 mg, 83.8%) as a yellow solid. LCMS (ESI, m/z): 688 [M+H]⁺.

Intermediate 622K

2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-3-(2-hydroxyethyl)-4-methoxybenzo[b]thiophene-6-carboxylic acid



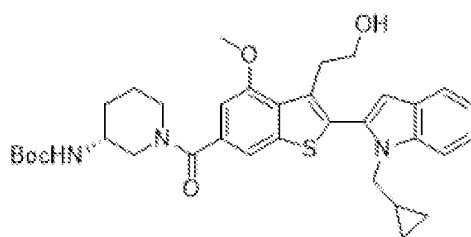
5

To a solution of Intermediate 622J (100 mg, 0.15 mmol) in MeOH (4 mL) and water (1 mL) were added NaOH (35 mg, 0.9 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 50 °C for 16 h. The reaction was monitored by TLC and LCMS. The pH value of the solution was adjusted to 2~3 with HCl(1M). The residue was purified by flash column chromatography on C18 silica (Mobile Phase A: water (0.5% TFA), Mobile Phase B: ACN; Flow rate: 40 mL/min; Gradient: 45% B to 50% B in 2.5 min; 254/210 nm) to afford the title compound (50 mg, 81.9%) as yellow oil. LCMS (ESI, m/z): 422 [M+H]⁺.

15

Intermediate 622L

tert-butyl (R)-(1-(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-3-(2-hydroxyethyl)-4-methoxybenzo[b]thiophene-6-carbonyl)piperidin-3-yl)carbamate



20

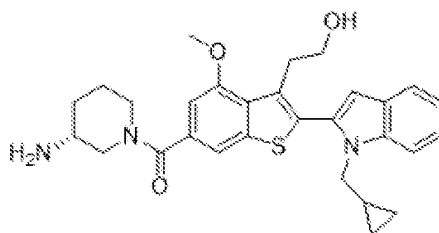
To a stirred solution of Intermediate 622K (50 mg, 0.12 mmol) in DMF (3mL) was added tert-butyl (R)-piperidin-3-ylcarbamate (35 mg, 0.18 mmol), HATU (67.65mg, 0.18 mmol) and DIEA (0.06mL, 0.36 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 1 h. The mixture was quenched with NH₄Cl (sat. aq) (10 mL) at 0 °C, and extracted with ethyl acetate (2 x 30 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under

vacuum. The obtained orange sticky oil was purified by column chromatography (DCM/MeOH = 20/1) to afford the title compound (65 mg, 90%) as a yellow oil. LCMS (ESI, m/z): 604 [M+H]⁺.

5

Example 622

(R)-(3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-3-(2-hydroxyethyl)-4-methoxybenzo[b]thiophen-6-yl)methanone

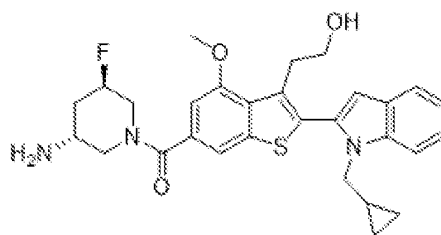


To a stirred solution of Intermediate 622L (65 mg, 0.11 mmol) in DCM (2.5 mL)
 10 was added TFA (0.7 mL) at room temperature. The resulting mixture was stirred at room temperature for 1 h. The reaction was monitored by TLC and LCMS. The mixture was concentrated under vacuum. The obtained orange sticky oil was purified using preparative RP-HPLC to afford the title compound (11.3 mg, 44%) as a pink solid. LCMS m/z: 504.3 [M+H]⁺. LCMS retention time: 1.583 min. (Method J). ¹H NMR (400 MHz, DMSO-*d*₆) δ
 15 8.12 – 7.84 (m, 3H), 7.68 – 7.54 (m, 3H), 7.24 (t, *J* = 7.6 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.00 (s, 1H), 6.71 (s, 1H), 4.05 (d, *J* = 6.8 Hz, 2H), 3.98 (s, 3H), 3.76 – 3.44 (m, 4H), 3.60 (t, *J* = 7.6 Hz, 3H), 3.22 – 3.15 (m, 1H), 3.05 (t, *J* = 7.5 Hz, 2H), 2.08 – 2.00 (m, 1H), 1.81 – 1.71 (m, 1H), 1.64 – 1.53 (m, 2H), 1.06 – 0.98 (m, 1H), 0.42 – 0.30 (m, 2H), 0.21 – 0.11 (m, 2H).

20

Example 623

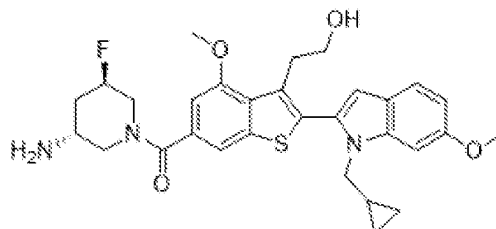
((3R,5R)-3-amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-3-(2-hydroxyethyl)-4-methoxybenzo[b]thiophen-6-yl)methanone



Example 623 was prepared by a similar method to Example 622 from common Intermediate 622J. The compound was purified using preparative RP-HPLC to afford the title compound (22.3 mg, 46 %) as a white solid. LCMS m/z: 522.25 [M+H]⁺. LCMS retention time: 2.648 min. (Method J). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.38 – 8.12 (m, 3H), 7.66 – 7.59 (m, 3H), 7.23 (t, *J* = 7.1 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 6.96 (s, 1H), 6.71 (s, 1H), 5.13 – 4.69 (m, 2H), 4.62 (t, *J* = 5.6 Hz, 1H), 4.04 (d, *J* = 6.8 Hz, 2H), 3.97 (s, 3H), 3.63 – 3.54 (m, 2H), 3.44 – 3.36 (m, 2H), 3.24 – 3.92 (m, 2H), 3.04 (t, *J* = 7.4 Hz, 2H), 2.44 – 2.31 (m, 1H), 2.03 – 1.77 (m, 1H), 1.09 – 0.95 (m, 1H), 0.43 – 0.29 (m, 2H), 0.22 – 0.11 (m, 2H).

Example 624

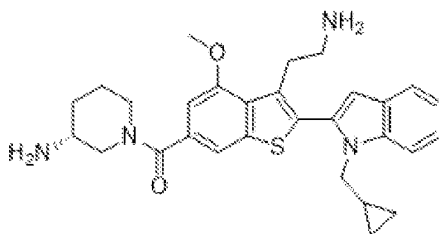
((3R,5R)-3-amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-methoxy-1H-indol-2-yl)-3-(2-hydroxyethyl)-4-methoxybenzo[b]thiophen-6-yl)methanone



Example 624 was prepared by a similar method to Example 622 from common Intermediate 622G. The compound was purified using preparative RP-HPLC to afford the title compound (10.2 mg, 29.8%) as a white solid. LCMS m/z: 552.25 [M+H]⁺. LCMS retention time: 2.501 min. (Method J). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.40 – 8.10 (m, 3H), 7.62 (s, 1H), 7.48 (d, *J* = 8.6 Hz, 1H), 7.14 (s, 1H), 6.95 (s, 1H), 6.77 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.63 (s, 1H), 5.14 – 4.56 (m, 3H), 4.02 (d, *J* = 6.8 Hz, 2H), 3.98 (s, 3H), 3.84 (s, 3H), 3.59 (t, *J* = 8.0 Hz, 2H), 3.49 – 3.35 (m, 2H), 3.05 (t, *J* = 7.5 Hz, 2H), 2.45 – 2.34 (m, 1H), 2.08 – 1.81 (m, 1H), 1.08 – 0.96 (m, 1H), 0.41 – 0.31 (m, 2H), 0.22 – 0.12 (m, 2H).

Example 625

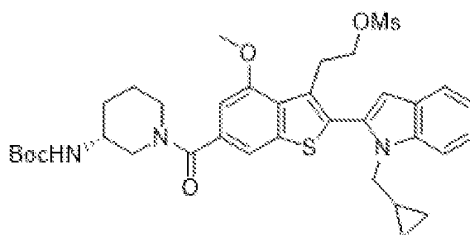
(R)-(3-(2-aminoethyl)-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxybenzo[b]thiophen-6-yl)(3-aminopiperidin-1-yl)methanone



5

Intermediate 625A

(R)-2-(6-(3-((tert-butoxycarbonyl)amino)piperidine-1-carbonyl)-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxybenzo[b]thiophen-3-yl)ethyl methanesulfonate



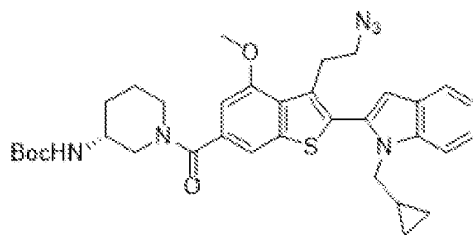
10

To a stirred solution of Intermediate 622L (80 mg, 0.13 mmol) in DCM (2 mL) was added TEA (54 mg, 0.53 mmol) and MsCl (31 mg, 0.27 mmol) at 0 °C. The resulting reaction solution was stirred at this temperature for 1 h. The reaction was monitored by TLC and LCMS. It was then quenched with saturated aqueous NaHCO₃ (15 mL), extracted with DCM (2 x 30 mL). The organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by column chromatography (MeOH/DCM = 1/50) to afford the title compound (78 mg, 86%) as a colorless oil. LCMS (ESI, m/z): 682 [M+H]⁺.

20

Intermediate 625B

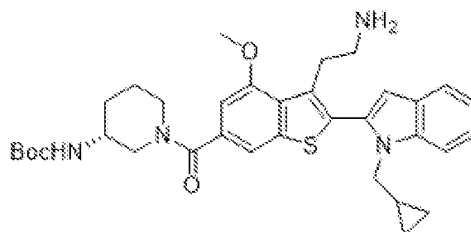
tert-butyl (R)-(1-(3-(2-azidoethyl)-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxybenzo[b]thiophene-6-carbonyl)piperidin-3-yl)carbamate



To a stirred solution of Intermediate 625A (78 mg, 0.11 mmol) in DMF (1.5 mL) was added NaN_3 (18 mg, 0.29 mmol) at room temperature. The resulting reaction mixture was heated to 70 °C for 5 h. The reaction was monitored by TLC and LCMS. The mixture was cooled to room temperature. It was extracted with ethyl acetate (2 x 30 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, concentrated under vacuum. The residue was purified by Prep-TLC (petroleum ether/ethyl acetate = 2:1) to afford title compound (62 mg, 86%) as a colorless oil. LCMS (ESI, m/z): 629 $[\text{M}+\text{H}]^+$.

Intermediate 625C

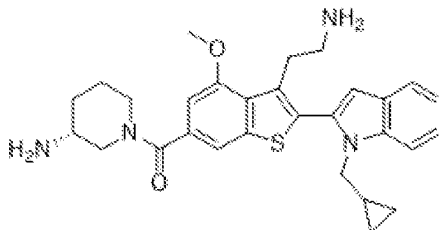
tert-butyl (R)-1-(3-(2-aminoethyl)-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxybenzo[b]thiophene-6-carbonyl)piperidin-3-yl)carbamate



To a stirred solution of Intermediate 625B (52 mg, 0.08 mmol) in methanol (5 mL) was added Pd/C (10 mg) under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 2 h under an atmosphere of hydrogen. The reaction was monitored by TLC and LCMS. The solution was filtered through a celite pad and the pad was washed with methanol (50 mL). The filtrate was evaporated to dryness to give crude product which was purified by Prep-TLC (DCM / MeOH = 5:1) to afford the title compound (30 mg, 60%) as a colorless oil. LCMS (ESI, m/z): 603 $[\text{M}+\text{H}]^+$.

Example 625

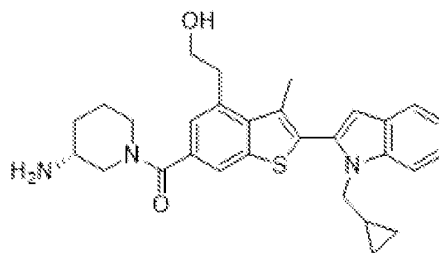
(R)-(3-(2-aminoethyl)-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxybenzo[b]thiophen-6-yl)(3-aminopiperidin-1-yl)methanone



- 5 To a stirred solution of Intermediate 625C (30 mg, 0.05 mmol) in DCM (2 mL) was added TFA (0.6 mL) at 0 °C. The resulting mixture was stirred at room temperature for 1 h. The reaction was monitored by TLC and LCMS. The reaction solution was concentrated under vacuum. The obtained orange sticky oil was purified by preparative RP-HPLC to afford the title compound (20.5 mg, 82%) as a light yellow solid. LCMS
- 10 m/z: 503.3 [M+H]⁺. LCMS retention time: 1.379 min. (Method J). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.08 – 7.90 (m, 3H), 7.87 – 7.77 (m, 3H), 7.71 – 7.62 (m, 3H), 7.26 (t, *J* = 8.0 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.03 (s, 1H), 6.77 (s, 1H), 4.16 – 3.96 (m, 3H), 4.02 (s, 3H), 3.32 – 3.22 (m, 2H), 3.20 – 3.12 (m, 4H), 3.08 – 2.96 (m, 3H), 2.07 – 2.00 (m, 1H), 1.79 – 1.72 (m, 1H), 1.66 – 1.55 (m, 2H), 1.04 – 0.96 (m, 1H), 0.42 – 0.33 (m, 2H),
- 15 0.20 – 0.14 (m, 2H).

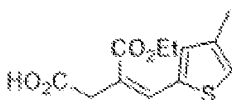
Example 626

(R)-(3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-4-(2-hydroxyethyl)-3-methylbenzo[b]thiophen-6-yl)methanone



Intermediate 626A

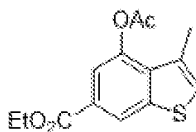
(Z)-3-ethoxycarbonyl-4-(4-methyl-2-thienyl)but-3-enoic acid



To a stirred solution of 4-methylthiophene-2-carbaldehyde (5 g, 39.63 mmol) in tert-butanol (20 mL) were added t-BuOK (1 M in THF) (47 mL, 47.55 mmol) and diethyl butanedioate (13.8 g, 79.25 mmol) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 50 °C for 2 h. LCMS showed the reaction was complete, and the mixture was diluted with water (100 mL), then adjusted to pH 6~7 with HCl (2 M). The resulting mixture was extracted with ethyl acetate (2 x 200 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum. The crude product was purified by silica column chromatography (Petroleum ether / ethyl acetate = 10:1) to afford the title compound (8 g, 79%) as a yellow solid. LCMS (ESI, m/z): 255 [M+H]⁺.

Intermediate 626B

Ethyl 4-acetoxy-3-methyl-benzothiophene-6-carboxylate



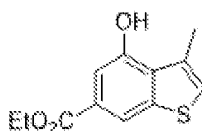
15

To a stirred solution of Intermediate 626A (8 g, 31.46 mmol) in Acetic anhydride (50 mL) were added NaOAc (11.6g, 141.57 mmol) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 70 °C for 2 h. The reaction was monitored by TLC and LCMS. LCMS showed the reaction was complete, and the solids were filtered out. The resulting mixture was concentrated. The crude product was purified by silica column chromatography (petroleum ether / ethyl acetate = 10:1) to afford the title compound (6 g, 68%) as a yellow solid. LCMS (ESI, m/z): 279 [M+H]⁺.

20

Intermediate 626C

Ethyl 4-hydroxy-3-methylbenzo[b]thiophene-6-carboxylate

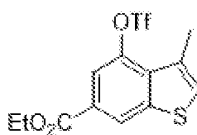


25

To a stirred solution of Intermediate 626B (6 g, 21.56 mmol) in Ethanol (50 mL) were added K_2CO_3 (5.9 g, 43.12 mmol) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 70 °C for 2 h. LCMS showed the reaction was complete, and the solids were filtered out. The resulting mixture was concentrated. The crude product was purified by silica column chromatography (Petroleum ether/ ethyl acetate = 2:1) to afford the title compound (4 g, 78%) as a yellow solid. LCMS (ESI, m/z): 237 $[M+H]^+$.

Intermediate 626D

10 Ethyl 3-methyl-4-(trifluoromethylsulfonyloxy)benzo[*b*]thiophene-6-carboxylate



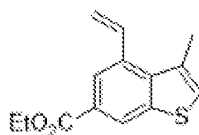
To a stirred solution of Intermediate 626C (4 g, 16.93 mmol) in DCM (50 mL) were added Et_3N (7.1 mL, 50.79 mmol) and Tf_2O (4.27 mL, 25.39 mmol) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 2 h.

15 The reaction was monitored by TLC and LCMS. The reaction was quenched by adding water (100 mL) and extracted with DCM (3 x 100 mL). The combined organic extracts were washed with brine (2 x 100 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum. The crude product was purified by silica column chromatography (Petroleum ether / ethyl acetate = 4:1) to afford the title compound (3.9 g, 62%) as a yellow solid. LCMS (ESI, m/z): 369 $[M+H]^+$.

20

Intermediate 626E

Ethyl 3-methyl-4-vinylbenzo[*b*]thiophene-6-carboxylate

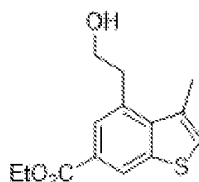


25 To a stirred solution of Intermediate 626D (3.9 g, 10.59 mmol) in 1,4-Dioxane (80 mL) and Water (16 mL) were added 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (3.3 g, 21.18 mmol), $Pd(PPh_3)_4$ (0.86 g, 0.74 mmol) and K_3PO_4 (8.98 g, 42.35 mmol) in portions at room temperature under nitrogen atmosphere. The resulting mixture was

stirred at 80 °C for 4 h under nitrogen atmosphere. The reaction was monitored by TLC and LCMS. The reaction was quenched by adding water (100 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with brine (2 x 200 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum. The crude product was purified by silica column chromatography (Petroleum ether/ ethyl acetate = 4:1) to afford the title compound (2.38 g , 91%) as a yellow oil. LCMS (ESI, m/z): 247 [M+H]⁺.

Intermediate 626F

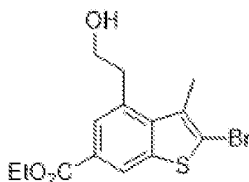
10 Ethyl 4-(2-hydroxyethyl)-3-methylbenzo[*b*]thiophene-6-carboxylate



To a stirred solution of Intermediate 626E (500 mg, 2.03 mmol) in THF (10 mL) were added BH₃ (1 M in THF) (4 mL) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 2 h. The reaction was monitored by TLC and LCMS. The reaction was quenched by adding water (30 mL) at 0 °C and extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum. The crude product was purified by silica column chromatography (Petroleum ether/ ethyl acetate = 2:1) to afford the title compound (300 mg, 55%) as a yellow solid. LCMS (ESI, m/z): 265 [M+H]⁺.

Intermediate 626G

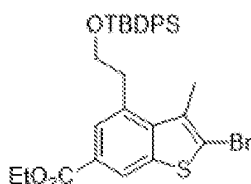
Ethyl 2-bromo-4-(2-hydroxyethyl)-3-methylbenzo[*b*]thiophene-6-carboxylate



To a stirred solution of Intermediate 626F (300 mg, 1.13 mmol) in chloroform (10 mL) was added Br₂ (190 mg, 1.19 mmol) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 0.5 h. The reaction was monitored by TLC and LCMS. The reaction was quenched by adding water (20 mL) and extracted with DCM (3 x 30 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum. The crude product was purified by silica column chromatography (petroleum ether/ ethyl acetate = 2:1) to afford the title compound (260 mg, 66%) as a yellow oil. LCMS (ESI, m/z): 343 [M+H]⁺.

Intermediate 626H

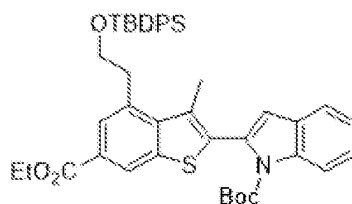
Ethyl 2-bromo-4-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-3-methylbenzo[*b*]thiophene-6-carboxylate



To a stirred solution of Intermediate 626G (260 mg, 0.76 mmol) in DCM (5 mL) were added imidazole (206 mg, 3.03 mmol) and TBDPSCI (0.24 mL, 0.91 mmol) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 2 h. The reaction was monitored by TLC and LCMS. The reaction was quenched by adding water (30 mL) and extracted with DCM (3 x 30 mL). The combined organic extracts were dried over anhydrous sodium sulphate and concentrated under vacuum. The crude product was purified by silica column chromatography (Petroleum ether/ethyl acetate = 10:1) to afford the title compound (400 mg, 90%) as a yellow solid. LCMS (ESI, m/z): 581 [M+H]⁺.

Intermediate 626I

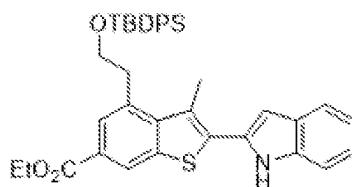
tert-Butyl 2-(4-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-6-(ethoxycarbonyl)-3-methylbenzo[*b*]thiophen-2-yl)-1H-indole-1-carboxylate



To a stirred solution of Intermediate 626H (400 mg, 0.69 mmol) in 1,4-dioxane (5 mL) and water (1 mL) were added Pd(PPh₃)₄ (60 mg, 0.05 mmol), K₃PO₄ (440 mg, 2.06 mmol) and (1-tert-butoxycarbonylindol-2-yl)boronic acid (197 mg, 0.76 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 80 °C for 4 h under nitrogen atmosphere. The reaction was monitored by TLC and LCMS. The reaction was quenched by adding water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried over anhydrous sodium sulphate and concentrated under vacuum. The crude product was purified by silica column chromatography (petroleum ether/ethyl acetate = 4:1) to afford the title compound (490 mg, 99%) as a yellow oil. LCMS (ESI, m/z): 718 [M+H]⁺.

Intermediate 626J

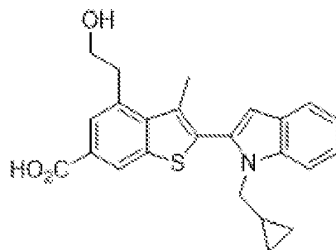
Ethyl 4-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-2-(1*H*-indol-2-yl)-3-methylbenzo[*b*]thiophene-6-carboxylate



Intermediate 626I (490 mg, 0.68 mmol) and silica gel (5 g) was dissolved in moderate DCM. Prior to the sealed stirring, the reagent should evaporate the solvent, and react under vacuum condition at 90 °C in oil bath. After 30 min stirring, the LCMS and TLC revealed that the reaction was complete. The crude product was finally purified by column chromatography using ethyl acetate as the eluent to afford the title compound (420 mg, 97%) as yellow solid. LCMS (ESI, m/z): 618 [M+H]⁺.

Intermediate 626K

2-(1-(Cyclopropylmethyl)-1*H*-indol-2-yl)-4-(2-hydroxyethyl)-3-methylbenzo[*b*]thiophene-6-carboxylic acid

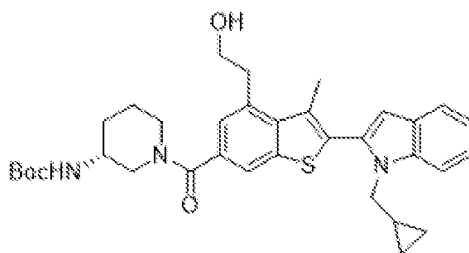


- 5 To a stirred solution of Intermediate 626J (460 mg, 0.74 mmol) in DMF (10 mL) were added NaH (53 mg, 2.23 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 0.5 h. Then to this was added bromomethylcyclopropane (150 mg, 1.12 mmol) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 2 h. The reaction was monitored by TLC and LCMS. The reaction was
- 10 quenched by adding water (5 mL). The mixture was purified directly by flash column chromatography on C18 silica (Mobile Phase A: water (0.5% TFA), Mobile Phase B: acetonitrile; Flow rate: 100 mL/min; Gradient: 30% B to 40% B in 2 min; UV: 254/210 nm) to obtain the title compound (130 mg, 43%) as a yellow oil. LCMS (ESI, *m/z*): 406 [M+H]⁺.

15

Intermediate 626L

tert-Butyl (*R*)-(1-(2-(1-(cyclopropylmethyl)-1*H*-indol-2-yl)-4-(2-hydroxyethyl)-3-methylbenzo[*b*]thiophene-6-carbonyl)piperidin-3-yl)carbamate

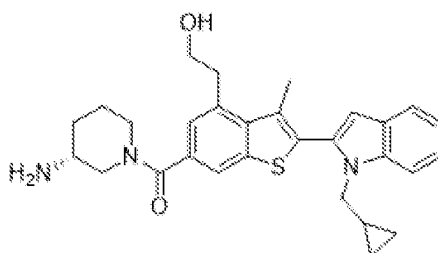


- 20 To a stirred solution of Intermediate 626K (60 mg, 0.15 mmol) in DMF (1.5 mL) were added *tert*-butyl (*R*)-piperidin-3-ylcarbamate (44 mg, 0.22 mmol), HATU (84 mg, 0.22 mmol) and DIEA (0.04 mL, 0.44 mmol) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 2 h. The

reaction was monitored by LCMS. The reaction was then quenched by adding water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with brine (2 x 40 mL), dried over anhydrous sodium sulphate and concentrated under vacuum. The crude product was purified by silica column chromatography (DCM / methanol = 20:1) to afford the title compound (75 mg, 86%) as a yellow solid. LCMS (ESI, m/z): 588 [M+H]⁺.

Example 626

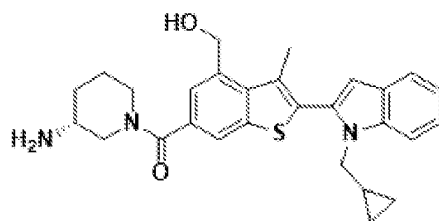
(*R*)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1*H*-indol-2-yl)-4-(2-hydroxyethyl)-3-methylbenzo[*b*]thiophen-6-yl)methanone



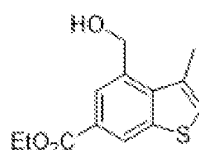
To a stirred solution of Intermediate 626L (70 mg, 0.12 mmol) in DCM (3 mL) was added TFA (1 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 0.5 h. The reaction solution was concentrated in vacuo and product was purified using preparative RP-HPLC to afford the title compound (29.6 mg, 50%) as a white solid. LCMS m/z: 488.25 [M+H]⁺. LCMS retention time: 1.736 min. (Method J). ¹H NMR (400 MHz, DMSO-*d*₆ + D₂O) δ 7.91 (s, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.59 (d, *J* = 8.2 Hz, 1H), 7.29 (s, 1H), 7.24 (t, *J* = 7.2 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 6.63 (s, 1H), 4.34 – 4.16 (m, 1H), 4.00 (t, *J* = 6.7 Hz, 3H), 3.71 (t, *J* = 7.0 Hz, 2H), 3.57 – 3.40 (m, 1H), 3.32 (t, *J* = 7.0 Hz, 2H), 3.28 – 3.11 (m, 3H), 2.49 (s, 3H), 2.09 – 1.97 (m, 1H), 1.81 – 1.47 (m, 3H), 1.01 – 0.89 (m, 1H), 0.36 – 0.27 (m, 2H), 0.11 – 0.01 (m, 2H).

Example 627

(*R*)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1*H*-indol-2-yl)-4-(hydroxymethyl)-3-methylbenzo[*b*]thiophen-6-yl)methanone



Intermediate 627A

Ethyl 4-(hydroxymethyl)-3-methylbenzo[*b*]thiophene-6-carboxylate

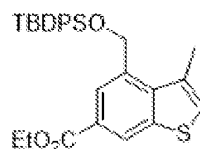
5

To a stirred solution of Intermediate 626D (500 mg, 1.36 mmol) in 1,4-Dioxane (10 mL) and water (2 mL) were added potassium;acetoxymethyl(trifluoro)boranuide (488 mg, 2.71 mmol), Pd₂(dba)₃ (124 mg, 0.14 mmol), Ruphos (126 mg, 0.27 mmol) and Na₂CO₃ (431 mg, 4.07 mmol) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 100°C for 12 h under nitrogen atmosphere. The reaction was monitored by LCMS. The reaction was then quenched by adding water (20 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were washed with brine (2 x 30 mL), dried over anhydrous sodium sulphate and concentrated under vacuum. The crude product was purified by silica column chromatography (petroleum ether/ethyl acetate = 2:1) to afford the title compound (260 mg, 76%) as a yellow solid.

LCMS (ESI, m/z): 251 [M+H]⁺.

15

Intermediate 627B

Ethyl 4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-methylbenzo[*b*]thiophene-6-carboxylate

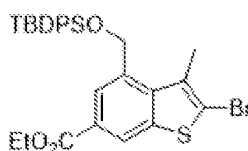
20

To a stirred solution of Intermediate 627A (260 mg, 1.04 mmol) in DCM (5 mL) were added imidazole (282 mg, 4.15 mmol) and TBDPSCl (0.32 mL, 1.25 mmol) in portions at room temperature under nitrogen atmosphere. The resulting mixture was

stirred at room temperature for 2 h. The reaction was monitored by TLC and LCMS. The reaction was quenched by adding water (30 mL) and extracted with DCM (3 x 30 mL). The combined organic extracts were dried over anhydrous sodium sulphate and concentrated under vacuum. The crude product was purified by silica column chromatography (petroleum ether/ ethyl acetate = 4:1) to afford the title compound (400 mg, 78%) as a yellow solid. LCMS (ESI, m/z): 489 [M+H]⁺.

Intermediate 627C

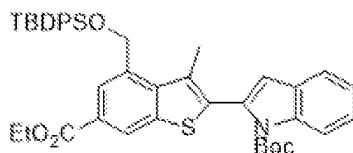
Ethyl 2-bromo-4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-methylbenzo[*b*]thiophene-6-carboxylate



To a stirred solution of Intermediate 627B (400 mg, 0.82 mmol) in chloroform (5 mL) were added Br₂ (0.11 mL, 0.9 mmol) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 2 h. The reaction was monitored by TLC and LCMS. The reaction was quenched by adding water (30 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were dried over anhydrous sodium sulphate and concentrated under vacuum. The crude product was purified by silica column chromatography (petroleum ether/ ethyl acetate = 4:1) to afford the title compound (360 mg, 77%) as a yellow solid. LCMS (ESI, m/z): 567 [M+H]⁺.

Intermediate 627D

tert-Butyl 2-(4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-6-(ethoxycarbonyl)-3-methylbenzo[*b*]thiophen-2-yl)-1*H*-indole-1-carboxylate

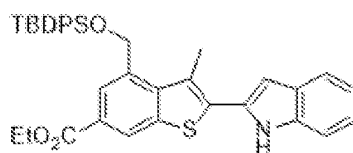


To a stirred solution of Intermediate 627C (360 mg, 0.63 mmol) in 1,4-dioxane (10 mL) and water (2 mL) were added (1-*tert*-butoxycarbonylindol-2-yl)boronic acid (331 mg, 1.27 mmol), K₃PO₄ (403 mg, 1.9 mmol) and Pd(PPh₃)₄ (53 mg, 0.06 mmol) in

portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 80°C for 4 h under nitrogen atmosphere. The reaction was monitored by TLC and LCMS. The reaction was quenched by adding water (30 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were dried over anhydrous sodium sulphate and concentrated under vacuum. The crude product was purified by silica column chromatography (petroleum ether/ ethyl acetate = 4:1) to afford the title compound (400 mg , 89%) as a yellow solid. LCMS (ESI, m/z): 704 [M+H]⁺.

Intermediate 627E

10 Ethyl 4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-(1*H*-indol-2-yl)-3-methylbenzo[*b*]thiophene-6-carboxylate

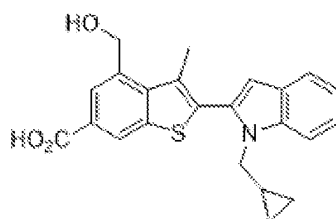


Intermediate 627D (400 mg, 0.57 mmol) and silica gel (4 g) was dissolved in moderate DCM. Prior to the sealed stirring, the reagent should evaporate the solvent, and react under vacuum condition at 90 °C in oil bath. After 30 min stirring, the LCMS and TLC revealed that the reaction was complete. The crude product was finally purified by column chromatography using ethyl acetate as the eluent to afford the title compound (250 mg, 72.8%) as yellow solid. LCMS (ESI, m/z): 604 [M+H]⁺.

20

Intermediate 627F

2-(1-(Cyclopropylmethyl)-1*H*-indol-2-yl)-4-(hydroxymethyl)-3-methylbenzo[*b*]thiophene-6-carboxylic acid



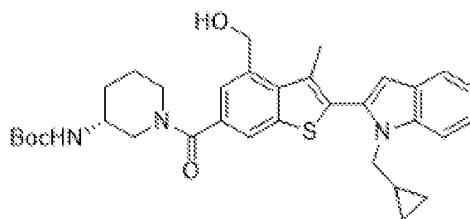
To a stirred solution of Intermediate 627E (100 mg, 0.17 mmol) in DMF (3 mL) was added NaH (13 mg, 0.33 mmol) in portions at 0 °C and was warmed to room

25

temperature under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 0.5 h. Then was added bromomethylcyclopropane (44 mg, 0.33 mmol) in portions at 0 °C and was warmed to room temperature under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 2 h. LCMS showed no starting material. Then the mixture was added methanol (1 mL) and NaOH (6 mg, 0.17 mmol) by turns. The resulting mixture was stirred at room temperature for 30 min. TLC showed the reaction was complete, and the mixture was concentrated to clean up methanol and then adjusted to pH 5~6 with hydrochloric acid and extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous sodium sulphate and concentrated under vacuum. The crude product was purified by silica column chromatography (DCM/ methanol = 10:1) to afford the title compound (41 mg, 63.2%) as yellow oil. LCMS (ESI, m/z): 392 [M+H]⁺.

Intermediate 627G

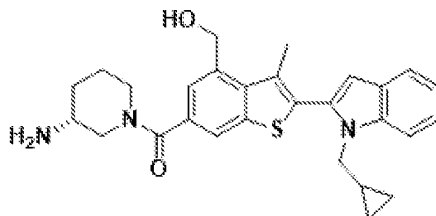
tert-Butyl (*R*)-(1-(2-(1-(cyclopropylmethyl)-1*H*-indol-2-yl)-4-(hydroxymethyl)-3-methylbenzo[*b*]thiophene-6-carbonyl)piperidin-3-yl)carbamate



To a stirred solution of Intermediate 627F (41 mg, 0.10 mmol) in DMF (3 mL) were added HATU (59 mg, 0.16 mmol) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 0.5 h. Then to this was added DIEA (40 mg, 0.31 mmol) and *tert*-butyl (*R*)-piperidin-3-ylcarbamate (31 mg, 0.16 mmol) in portions at 0 °C. The resulting mixture was stirred at room temperature for 1 h. The reaction was monitored by LCMS. The reaction was then quenched by adding water (20 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were washed with brine (2 x 30 mL), dried over anhydrous sodium sulphate and concentrated under vacuum. The crude product was purified by silica column chromatography (DCM/ methanol = 30:1) to afford the title compound (39 mg, 64.9%) as light-yellow oil. LCMS (ESI, m/z): 574 [M+H]⁺.

Example 627

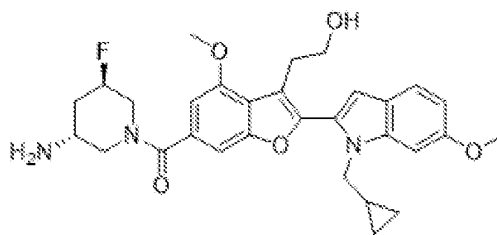
(*R*)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1*H*-indol-2-yl)-4-(hydroxymethyl)-3-methylbenzo[*b*]thiophen-6-yl)methanone



5 To a stirred solution of Intermediate 627G (39 mg, 0.07 mmol) in DCM (2 mL) was added TFA (0.5 mL) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 0.5 h. The reaction was monitored by LCMS and the mixture was concentrated in vacuo. Then added a little amount water, methanol and sodium methoxide stirring for 20 min. TLC and LCMS showed the reaction
10 was complete, and the product was purified using preparative RP-HPLC to afford the title compound (12.4 mg, 38.4%) as white solid. LCMS *m/z*: 474.30 [M+H]⁺. LCMS retention time: 1.737 min. (Method J). ¹H NMR (400 MHz, CD₃OD-*d*₄): δ 7.97 (d, *J* = 1.3 Hz, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.57 – 7.49 (m, 2H), 7.28 – 7.21 (m, 1H), 7.10 (t, *J* = 7.3 Hz, 1H), 6.61 (s, 1H), 5.16 (s, 2H), 4.05 (d, *J* = 6.7 Hz, 2H), 3.50 – 3.35 (m, 2H), 2.60
15 (s, 3H), 2.25 – 2.16 (m, 1H), 1.88 – 1.68 (m, 3H), 1.11 – 1.01 (m, 1H), 0.41 – 0.32 (m, 2H), 0.11 – 0.04 (m, 2H).

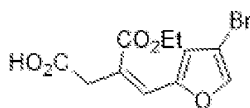
Example 628

20 ((3*R*,5*R*)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-methoxy-1*H*-indol-2-yl)-3-(2-hydroxyethyl)-4-methoxybenzofuran-6-yl)methanone



Intermediate 628A

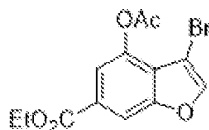
(*Z*)-4-(4-Bromofuran-2-yl)-3-(ethoxycarbonyl)but-3-enoic acid



To a solution of 4-bromofuran-2-carbaldehyde (5 g, 28.7 mmol) in *tert*-butanol (200 mL) was added diethyl butanedioate (20 g, 114.8 mmol) and *t*-BuOK (1 M in THF) (57 mL, 57.4 mmol). The resulting mixture was stirred at 50°C for 1h under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was diluted with water (150 mL), then adjusted to pH 6~7 with HCl (2 M). The resulting mixture was extracted with ethyl acetate (2 × 200 mL). The combined organic extracts were washed with brine (2×300 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by silica gel column chromatography (petroleum ether/ ethyl acetate = 5:1) to afford the title compound (5.2 g, 60%) as yellow oil. LCMS (ESI, *m/z*): 303 [M+H]⁺.

Intermediate 628B

Ethyl 4-acetoxy-3-bromobenzofuran-6-carboxylate



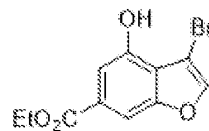
15

To a solution of Intermediate 628A (5.2 g, 17.1 mmol) in Ac₂O (60 mL) was added NaOAc (6.3 g, 77.4 mmol). The resulting mixture was stirred at 70°C for 1h under nitrogen atmosphere. The reaction was monitored by LCMS. The solids were filtered out. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography (petroleum ether/ ethyl acetate =5:1) to afford the title compound (3.4 g, 61%) as yellow oil. LCMS (ESI, *m/z*): 327 [M+H]⁺.

20

Intermediate 628C

Ethyl 3-bromo-4-hydroxybenzofuran-6-carboxylate

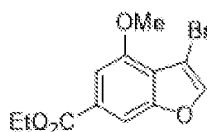


25

To a solution of Intermediate 628B (3.4 g, 10.4 mmol) in ethanol (50 mL) was added K_2CO_3 (2.9 g, 20.8 mmol). The resulting mixture was stirred at 70°C for 1h under nitrogen atmosphere. The reaction was monitored by LCMS. The solids were filtered out. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography (petroleum ether/ ethyl acetate =2:1) to afford the title compound (2 g, 67%) as a yellow solid. LC/MS m/z: 285 $[M+H]^+$.

Intermediate 628D

Ethyl 3-bromo-4-methoxybenzofuran-6-carboxylate



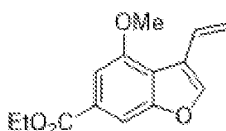
10

To a solution of Intermediate 628C (2 g, 7 mmol) in DMF (25 mL) was added K_2CO_3 (2.9 g, 21 mmol) and MeI (1.5 g, 10.5 mmol). The resulting mixture was stirred at room temperature for 1h. The reaction was monitored by LCMS. The solids were filtered out. The resulting mixture was concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ ethyl acetate = 5:1) to afford the title compound (1.8 g, 86%) as a white solid. LC/MS m/z: 299 $[M+H]^+$.

15

Intermediate 628E

Ethyl 4-methoxy-3-vinylbenzofuran-6-carboxylate



20

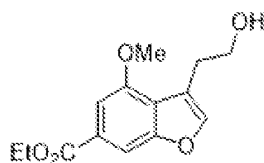
To a solution of Intermediate 628D (1.8 g, 6 mmol) in 1,4-Dioxane (30 mL) and Water (6 mL) were added 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (1.8 g, 12 mmol), $Pd(PPh_3)_4$ (693 mg, 0.6 mmol) and K_3PO_4 (5.9 g, 24 mmol) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 80°C for 4h under nitrogen atmosphere. The reaction was monitored by TLC and LCMS. The reaction was quenched by adding water (50 mL) and extracted with ethyl acetate (3×50 mL). The combined organic extracts were washed with brine (2×100 mL), dried over anhydrous sodium sulphate and concentrated under vacuum. The crude product was purified by

25

silica column chromatography (petroleum ether/ ethyl acetate = 5:1) to afford the title compound (1.2 g, 81%) as a yellow solid. LC/MS m/z: 247 [M+H]⁺.

Intermediate 628F

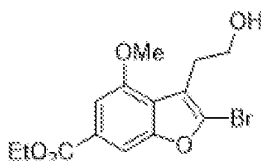
5 Ethyl 3-(2-hydroxyethyl)-4-methoxybenzofuran-6-carboxylate



To a solution of Intermediate 628E (1.2 g, 4.8 mmol) in THF (30 mL) was added BH₃ (1 M in THF) (5.7 mL, 5.7 mmol) in portions at 0°C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 2 h. Then to this was added H₂O₂ (30%) (3 mL) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 1 h. The reaction was monitored by TLC and LCMS. The reaction was quenched by adding Na₂SO₃ (aq.) (40 mL) at 0°C and extracted with ethyl acetate (2×50 mL). The combined organic extracts were washed with NaOH (1 M) (50 mL), dried over anhydrous sodium sulphate and concentrated under vacuum. The crude product was purified by silica column chromatography (petroleum ether/ethyl acetate = 2:1) to afford the title compound (700 mg, 55%) as a yellow solid. LC/MS m/z: 265 [M+H]⁺.

Intermediate 628G

20 Ethyl 2-bromo-3-(2-hydroxyethyl)-4-methoxybenzofuran-6-carboxylate



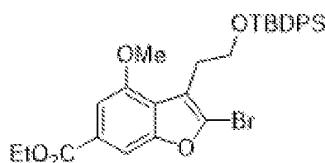
To a solution of Intermediate 628F (700 mg, 2.6 mmol) in Chloroform (10 mL) was added Br₂ (437 mg, 2.7 mmol) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 0.5h. The reaction was monitored by TLC and LCMS. The reaction was quenched by adding water (30 mL) and extracted with DCM (3×30 mL). The combined organic extracts were washed with brine (2×50

mL), dried over anhydrous sodium sulphate and concentrated under vacuum. The crude product was purified by silica column chromatography (petroleum ether/ ethyl acetate = 2:1) to afford the title compound (600 mg, 67%) as a yellow oil. LC/MS m/z: 343 [M+H]⁺.

5

Intermediate 628H

Ethyl 2-bromo-3-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-4-methoxybenzofuran-6-carboxylate



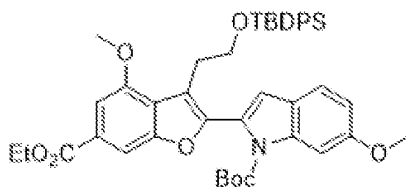
10 To a solution of Intermediate 628G (600 mg, 1.7 mmol) in DCM (10 mL) were added imidazole (578 mg, 8.5 mmol) and TBDPSCI (560 mg, 2 mmol) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 2h. The reaction was monitored by TLC and LCMS. The reaction was quenched by adding water (30 mL) and extracted with DCM (3×30 mL). The combined organic extracts were

15 dried over anhydrous sodium sulphate and concentrated under vacuum. The crude product was purified by silica column chromatography (petroleum ether/ethyl acetate = 10:1) to afford the title compound (950 mg, 96%) as a yellow solid. LC/MS m/z: 581 [M+H]⁺.

20

Intermediate 628I

tert-Butyl 2-(3-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-6-(ethoxycarbonyl)-4-methoxybenzofuran-2-yl)-6-methoxy-1*H*-indole-1-carboxylate



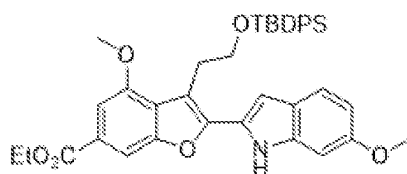
To a solution of Intermediate 628H (150 mg, 0.26 mmol) in THF (2 ml) and water

25 (1 ml) were added (1-*tert*-butoxycarbonyl-6-methoxy-indol-2-yl)boronic acid (90 mg,

0.31 mmol), Pd(PPh₃)₄ (29 mg, 0.03 mmol) and Na₂CO₃ (54 mg, 0.52 mmol) under a nitrogen atmosphere. The resulting mixture was stirred at 80°C for 6 h. The reaction was monitored by LCMS. The reaction was extracted with ethyl acetate (3×1 ml). The combined organic extracts were washed with water (3 ml) and brine (3 ml), dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by column chromatography (petroleum ether/ ethyl acetate = 10:1) to afford the title compound (165 mg, 85%) as white solid. LC/MS m/z: 748 [M+H]⁺.

Intermediate 628J

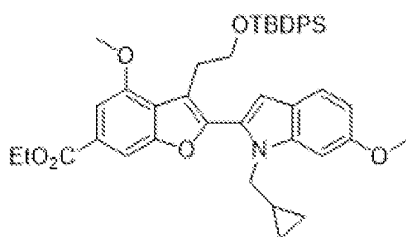
10 Ethyl 3-(2-(((tert-butyldiphenylsilyl)oxy)ethyl)-4-methoxy-2-(6-methoxy-1*H*-indol-2-yl)benzofuran-6-carboxylate



To a solution of Intermediate 628I (180 mg, 0.24 mmol) in DCM was added silica gel (2 g) and stirred evenly. Then DCM was removed under vacuum. The resulting solid mixture was stirred at 90°C for 1h. The reaction was monitored by LCMS. The crude product was purified by column chromatography (petroleum ether/ ethyl acetate = 1:2) to afford the title compound (150 mg, 96%) as a white solid. LC/MS m/z: 648 [M+H]⁺.

Intermediate 628K

20 Ethyl 3-(2-(((tert-butyldiphenylsilyl)oxy)ethyl)-2-(1-(cyclopropylmethyl)-6-methoxy-1*H*-indol-2-yl)-4-methoxybenzofuran-6-carboxylate



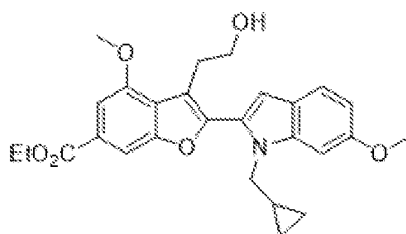
To a solution of Intermediate 628J (70 mg, 0.11 mmol) in DMF (2 ml) was added NaH (8 mg, 0.22 mmol) in portions at 0 °C. The resulting mixture was stirred at room

temperature for 0.5 h. To the above mixture was added bromomethylcyclopropane (21 mg, 0.16 mmol) drop wise at 0 °C. The resulting mixture was stirred for 2 h at room temperature. The reaction was monitored by LCMS. The reaction was quenched by adding water (10 ml), extracted with ethyl acetate (3×10 ml). The combined organic
5 extracts were washed with water (30 ml) and brine (30 ml), dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by column chromatography (petroleum ether/ethyl acetate = 1:1) to afford the title compound (75 mg, 97%) as a yellow solid. LC/MS m/z: 702 [M+H]⁺.

10

Intermediate 628L

Ethyl 2-(1-(cyclopropylmethyl)-6-methoxy-1*H*-indol-2-yl)-3-(2-hydroxyethyl)-4-methoxybenzofuran-6-carboxylate

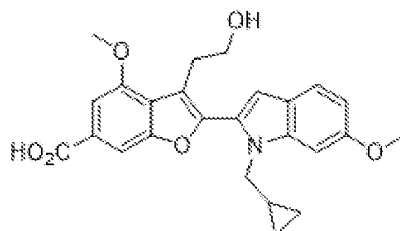


To a solution of Intermediate 628K (75 mg, 0.11 mmol) in THF (2 ml) was added 1
15 M TBAF in THF (1 ml). The resulting mixture was stirred at room temperature for overnight. The reaction was monitored by LCMS. the mixture was concentrated under vacuum. The crude product was purified by column chromatography (petroleum ether/ethyl acetate = 5:1) to afford the title compound (45 mg, 88%) as a white solid. LC/MS m/z: 464 [M+H]⁺

20

Intermediate 628M

2-(1-(Cyclopropylmethyl)-6-methoxy-1*H*-indol-2-yl)-3-(2-hydroxyethyl)-4-methoxybenzofuran-6-carboxylic acid

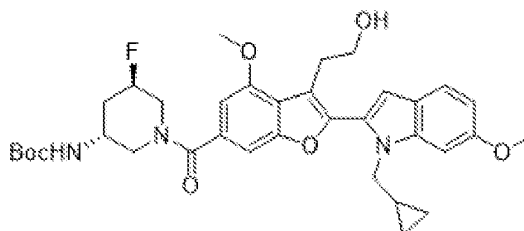


To a solution of Intermediate 628L (93 mg, 0.20 mmol) in methanol (2 ml) was added a solution of NaOH (80 mg, 2.01 mmol) in water (1 ml). The resulting mixture was stirred at 50°C for 1h. The reaction was monitored by LCMS. The reaction was quenched by adding water (5 ml), adjusted to pH 6~7 with 1M HCl (0.7 ml), extracted with ethyl acetate (3×5 ml). The combined organic extracts were washed with brine (15 ml), dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by column chromatography (petroleum ether/ ethyl acetate = 1:3) to afford the title compound (78 mg, 90%) as a yellow solid. LC/MS m/z: 436 [M+H]⁺

10

Intermediate 628N

tert-Butyl ((3*R*,5*R*)-1-(2-(1-(cyclopropylmethyl)-6-methoxy-1*H*-indol-2-yl)-3-(2-hydroxyethyl)-4-methoxybenzofuran-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate

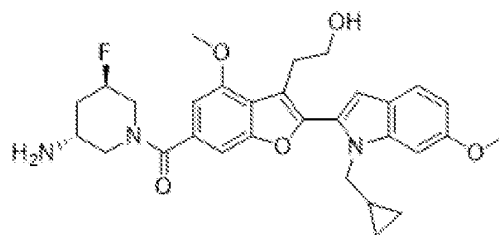


To a solution of Intermediate 628M (45 mg, 0.10 mmol) in DMF (2 ml) was added HATU (58 mg, 0.16 mmol). The resulting mixture was stirred at room temperature for 0.5 h. Then to this above mixture was added DIEA (0.05 ml, 0.31 mmol) and *tert*-butyl ((3*R*,5*R*)-5-fluoropiperidin-3-yl)carbamate (27 mg, 0.12 mmol) at 0°C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 1 h. The reaction was monitored by LCMS. The reaction was quenched by adding water (5 ml), extracted with ethyl acetate (10 ml). The combined organic extracts were washed with water (10 ml) and brine (10 ml), dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by column chromatography (petroleum ether/ ethyl acetate = 1:2) to afford the title compound (45 mg, 71%) as yellow oil. LC/MS m/z: 636 [M+H]⁺

25

Example 628

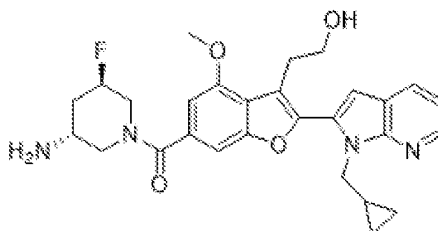
((3*R*,5*R*)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-methoxy-1*H*-indol-2-yl)-3-(2-hydroxyethyl)-4-methoxybenzofuran-6-yl)methanone



To a solution of Intermediate 628N (45 mg, 0.07 mmol) in DCM (2 ml) was added TFA (1 ml). The resulting mixture was stirred at room temperature for 0.5 h. The reaction was monitored by LCMS. The solvent was evaporated under vacuum. The crude product
 5 was purified by preparative to afford the title compound (13.5 mg, 36%). LC-MS m/z : 536.2 $[M+H]^+$. LC-MS retention time: 2.528 min. (Method K). 1H NMR (300 MHz, DMSO- d_6) δ ppm 8.23 (s, 3H), 7.28 (s, 1H), 7.22 (d, $J = 8.0$ Hz, 1H), 7.03 (t, $J = 7.9$ Hz, 1H), 6.91 (s, 1H), 6.86 (s, 1H), 6.80 (d, $J = 8.0$ Hz, 1H), 5.08 - 4.86 (m, 1H), 4.82 - 4.65 (m, 2H), 4.34 (d, $J = 7.0$ Hz, 2H), 3.96 (s, 3H), 3.94 (s, 3H), 3.73 (t, $J = 12.0$ Hz, 2H),
 10 3.49 - 3.27 (m, 4H), 2.95 (t, $J = 12.0$ Hz, 2H), 2.45 - 2.31 (m, 1H), 2.00 - 1.80 (m, 1H), 1.08 - 0.98 (m, 1H), 0.33 - 0.21 (m, 2H), 0.12 - 0.04 (m, 2H).

Example 629

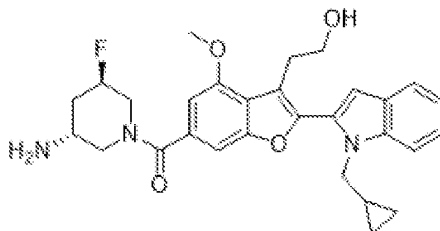
((3R,5R)-3-amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-
 15 b]pyridin-2-yl)-3-(2-hydroxyethyl)-4-methoxybenzofuran-6-yl)methanone



Example 629 was prepared by a similar method to Example 628 from common Intermediate 628H. The compound was purified by preparative RP-HPLC to afford the title compound (31.2 mg, 51%). LC-MS m/z : 507.3 $[M+H]^+$. LC-MS retention time:
 20 2.217 min. (Method K). 1H NMR (400MHz, DMSO- d_6) δ ppm 8.35 - 8.34 (m, 1H), 8.15 - 8.12 (m, 1H), 7.27 - 7.21 (m, 2H), 7.05 (s, 1H), 6.82 (s, 1H), 5.18 - 4.64 (m, 2H), 4.30 (d, $J = 6.8$ Hz, 2H), 3.93 (s, 4H), 3.75 - 3.72 (m, 2H), 3.42 - 3.34 (m, 2H), 3.03 - 3.00 (m, 3H), 2.49 - 2.37 (m, 1H), 1.94 - 1.77 (m, 1H), 1.09 - 1.05 (m, 1H), 0.33 - 0.29 (m, 2H), 0.20 - 0.16 (m, 2H).

Example 630

((3R,5R)-3-amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-3-(2-hydroxyethyl)-4-methoxybenzofuran-6-yl)methanone



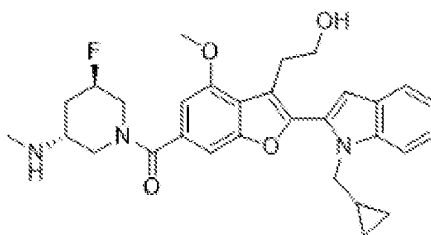
5

Example 630 was prepared by a similar method to Example 628 from common Intermediate 628H. The compound was purified by preparative RP-HPLC to afford the title compound (7.7 mg, 22%) as a white solid. LC-MS m/z: 506.2 [M+H]⁺. LC-MS retention time: 2.119 min. (Method K). ¹H NMR (400MHz, DMSO-*d*₆) δ ppm 7.63 (d, J = 7.6 Hz, 2H), 7.27 – 7.22 (m, 2H), 7.13 – 7.11 (m, 1H), 7.09 – 6.97 (m, 1H), 6.82 (s, 1H), 4.78 – 4.72 (m, 2H), 4.63 – 4.37 (m, 1H), 4.20 (d, J = 6.8 Hz, 2H), 3.95 (s, 4H), 3.77 – 3.72 (m, 2H), 3.01 – 2.67 (m, 5H), 2.14 – 1.95 (m, 3H), 1.64 – 1.37 (m, 1H), 1.12 – 1.07 (m, 1H), 0.37 – 0.33 (m, 2H), 0.20 – 0.16 (m, 2H).

15

Example 631

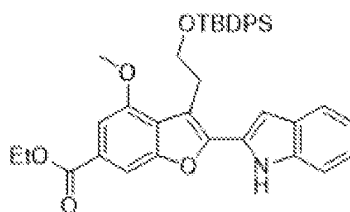
(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-3-(2-hydroxyethyl)-4-methoxybenzofuran-6-yl)((3R,5R)-3-fluoro-5-(methylamino)piperidin-1-yl)methanone



20

Intermediate 631A

ethyl 3-(2-(((tert-butyl)diphenylsilyl)oxy)ethyl)-2-(1H-indol-2-yl)-4-methoxybenzofuran-6-carboxylate

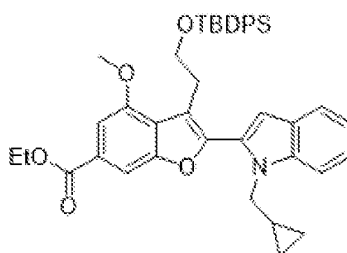


To a solution of Intermediate 628H (142 mg, 0.48 mmol) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (175 mg, 0.72 mmol) in THF (7 ml) and water (1.5 ml) was added Na_2CO_3 (126 mg, 1.19 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (20 mg, 0.03 mmol). The mixture was stirred at 80°C for 18h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting solution was concentrated under vacuum. The crude product was purified by column chromatography (petroleum ether/ ethyl acetate = 5:1) to afford the title compound (210 mg, 71%) as a yellow oil. LC/MS m/z: 618 $[\text{M}+\text{H}]^+$.

10

Intermediate 631B

ethyl 3-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxybenzofuran-6-carboxylate

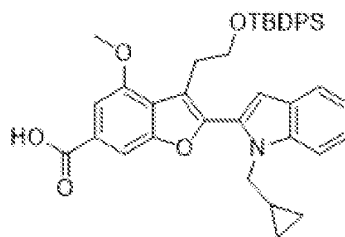


To a solution of Intermediate 631A (210 mg, 0.34 mmol) in DMF (3 ml), was added Cs_2CO_3 (223 mg, 0.68 mmol) and (bromomethyl)cyclopropane (69 mg, 0.51 mmol). The mixture was stirred at 50°C for 1h. The reaction was monitored by LCMS. The mixture was purified by flash column chromatography on C18 silica to afford the title compound (220 mg, 96%) as a yellow oil. LC/MS m/z: 672 $[\text{M}+\text{H}]^+$.

20

Intermediate 631C

3-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxybenzofuran-6-carboxylic acid

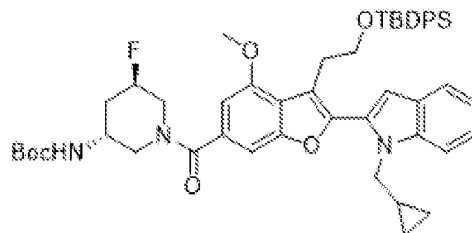


To a solution of Intermediate 631B (220 mg, 0.33 mmol) in THF (3 ml) and methanol (0.20 ml) was added NaOH (39 mg, 1.64 mmol). The mixture was stirred at room temperature for 1h. The reaction was monitored by LCMS. The resulting solution
 5 was adjusted to pH 6-7 with 1 M HCl. The mixture was extracted with DCM/ MeOH (10:1) (3×10 ml). The combined organic extracts were washed with brine (30 ml), dried over anhydrous sodium sulfate and concentrated under vacuum to afford the title compound (200 mg, 94%) as a yellow oil. LC/MS m/z: 644 [M+H]⁺.

10

Intermediate 631D

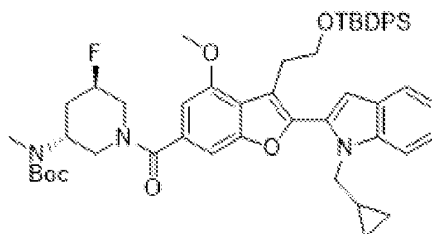
tert-butyl ((3R,5R)-1-(3-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxybenzofuran-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate



To a solution of Intermediate 631C (200 mg, 0.31 mmol) and DIEA (0.16 ml, 0.93
 15 mmol) in DMF (5 ml) was added HATU (177 mg, 0.47 mmol) at room temperature. The mixture was stirred at room temperature for 10 minute. Then the above resulting mixture was added into a solution of tert-butyl ((3R,5R)-5-fluoropiperidin-3-yl)carbamate (67.8 mg, 0.31 mmol) in DMF (1 ml) with drop wise at room temperature. The resulting mixture was stirred at room temperature for 1h. The reaction was monitored by LCMS.
 20 The reaction was then quenched by adding water (20 ml) and extracted with ethyl acetate (20 ml). The combined organic extracts were washed with water (2×20 ml) and brine (2×20 ml), dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by column chromatography (ethyl acetate) to afford the title compound (180 mg, 69%) as a yellow solid. LC/MS m/z: 844 [M+H]⁺.

Intermediate 631E

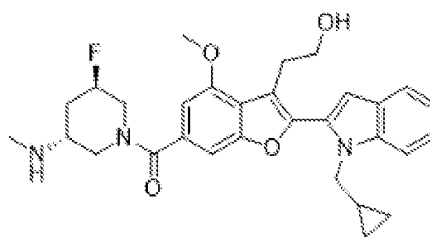
tert-butyl ((3R,5R)-1-(3-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-2-(1-(cyclopropylmethyl)-
1H-indol-2-yl)-4-methoxybenzofuran-6-carbonyl)-5-fluoropiperidin-3-
yl)(methyl)carbamate



To a solution of Intermediate 631D (110 mg, 0.13 mmol) in DMF (3 ml) was added NaH (10 mg, 0.39 mmol) in portions at 0°C. The resulting mixture was stirred at room temperature for 0.5h. To the above mixture was added MeI (0.01ml, 0.20 mmol) drop wise at 0°C. The resulting mixture was stirred at room temperature for 1h under nitrogen atmosphere. The reaction was monitored by LCMS. The reaction was quenched by adding water (10 ml), extracted with ethyl acetate (10 ml). The combined organic extracts were washed with water (2×10 ml) and brine (2×10 ml), dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by column chromatography (ethyl acetate) to afford the title compound (100 mg, 90%) as a yellow solid. LC/MS m/z: 858 [M+H]⁺.

Example 631

(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-3-(2-hydroxyethyl)-4-methoxybenzofuran-6-yl)((3R,5R)-3-fluoro-5-(methylamino)piperidin-1-yl)methanone



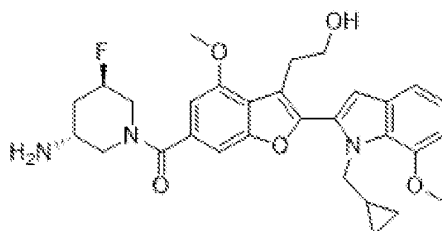
To a solution of Intermediate 631E (100 mg, 0.13 mmol) in THF (2 ml) was added HF-Py (13 mg, 0.13 mmol) at 0°C. The resulting solution was stirred at room temperature

for 1h. The reaction was monitored by LCMS. The resulting solution was concentrated under vacuum. The crude product thus obtained was purified using RP-HPLC to afford the title compound (33.9 mg, 50%) as a white solid. LC-MS m/z: 520 [M+H]⁺. LC-MS retention time: 1.640 min. (Method K). ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm 7.64 (s, 1H), 7.53 (d, *J* = 8 Hz, 1H), 7.29 – 7.25 (m, 2H), 7.14 – 7.1 (m, 1H), 6.92 (s, 2H), 5.07 – 4.88 (m, 2H), 4.24 (d, *J* = 6.8 Hz, 3H), 4.04 (s, 3H), 3.94 – 3.9 (m, 2H), 3.63 – 3.50 (m, 2H), 3.18 – 3.15 (m, 2H), 3.15 – 3.01 (m, 1H), 2.88 – 2.83 (m, 3H), 2.65 (s, 1H), 2.00 – 1.16 (m, 1H), 1.17 – 1.14 (m, 1H), 0.42 – 0.38 (m, 2H), 0.19 – 0.16 (m, 2H).

10

Example 632

((3R,5R)-3-amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-methoxy-1H-indol-2-yl)-3-(2-hydroxyethyl)-4-methoxybenzofuran-6-yl)methanone

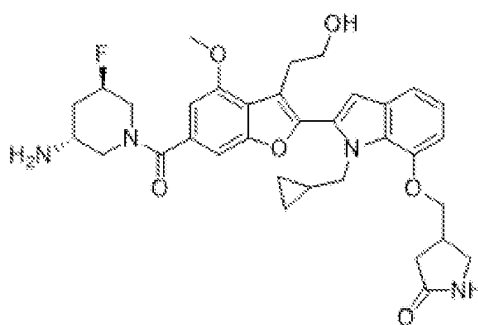


Example 632 was prepared by a similar procedure to Example 628 from common Intermediate 628H. The compound was purified by RP-HPLC to afford the title compound (18.9 mg, 50%). LC-MS m/z: 536.2 [M+H]⁺. LC-MS retention time: 1.622 min. (Method K). ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 8.23 (s, 3H), 7.28 (s, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.03 (t, *J* = 7.9 Hz, 1H), 6.91 (s, 1H), 6.86 (s, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 5.08 - 4.86 (m, 1H), 4.82 - 4.65 (m, 2H), 4.34 (d, *J* = 7.0 Hz, 2H), 3.96 (s, 3H), 3.94 (s, 3H), 3.73 (t, *J* = 12.0 Hz, 2H), 3.49 - 3.27 (m, 4H), 2.95 (t, *J* = 12.0 Hz, 2H), 2.45 - 2.31 (m, 1H), 2.00 - 1.80 (m, 1H), 1.08 - 0.98 (m, 1H), 0.33 - 0.21 (m, 2H), 0.12 - 0.04 (m, 2H).

25

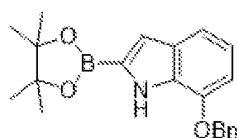
Example 633

4-(((2-(6-((3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl)-3-(2-hydroxyethyl)-4-methoxybenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one



Intermediate 633A

7-(benzyloxy)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole



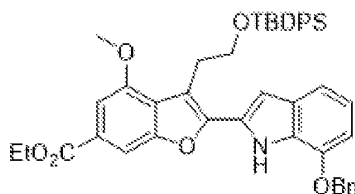
5

To a solution of 7-(benzyloxy)-1H-indole (500 mg, 2.24 mmol) in hexane (20 ml), was added 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (28 mg, 0.22 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (514 mg, 2.02 mmol), 4,4-Di-tert-butyl-2,2-dipyridyl (29 mg, 0.11 mmol) and Bis(1,5-cyclooctadiene)di-μ-methoxydiiridium(I) (73 mg, 0.11 mmol) under nitrogen atmosphere. The mixture was stirred at room temperature for overnight. The reaction was monitored by LCMS. The resulting solution was concentrated under vacuum. The crude product was purified by column chromatography (petroleum ether/ ethyl acetate = 10:1) to afford the title compound (400 mg, 51%) as a yellow solid. LC/MS m/z: 350 [M+H]⁺.

15

Intermediate 633B

ethyl 2-(7-(benzyloxy)-1H-indol-2-yl)-3-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-4-methoxybenzofuran-6-carboxylate

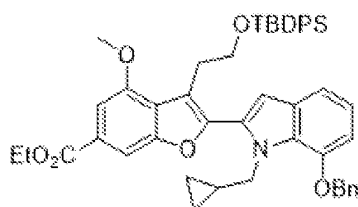


To a solution of Intermediate 633A (400 mg, 1.14 mmol) in THF (10 ml) and H₂O (2 ml), was added Intermediate 628H (793 mg, 1.37 mmol), Pd(PPh₃)₄ (127 mg, 0.11 mmol) and Na₂CO₃ (242 mg, 2.28 mmol) under nitrogen atmosphere. The resulting solution was stirred at 80°C for overnight. The reaction was monitored by LCMS. The reaction was then quenched by adding water (30 ml) and extracted with ethyl acetate (30 ml), washed with brine (10 ml), dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by column chromatography (petroleum ether/ ethyl acetate = 5:1) to afford the title compound (650 mg, 98%) as a yellow solid. LC/MS m/z: 724 [M+H]⁺.

10

Intermediate 633C

ethyl 2-(7-(benzyloxy)-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-(2-((tert-butyl)diphenylsilyl)oxy)ethyl)-4-methoxybenzofuran-6-carboxylate



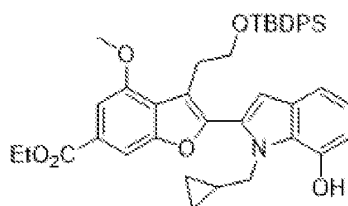
To a solution of Intermediate 633B (650 mg, 0.89 mmol) in DMF (8 ml), was added (bromomethyl)cyclopropane (180 mg, 1.33 mmol) and Cs₂CO₃ (870 mg, 2.67 mmol). The resulting solution was stirred at 50°C for 1h. The reaction was monitored by LCMS. The reaction was then quenched by adding water (30 ml) and extracted with ethyl acetate (30 ml), washed with water (2×30 ml) and brine (2×30 ml), dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by column chromatography (petroleum ether/ ethyl acetate = 10:1) to afford the title compound (623 mg, 90%) as a light yellow solid. LC/MS m/z: 778 [M+H]⁺.

20

Intermediate 633D

ethyl 3-(2-((tert-butyl)diphenylsilyl)oxyethyl)-2-(1-(cyclopropylmethyl)-7-hydroxy-1H-indol-2-yl)-4-methoxybenzofuran-6-carboxylate

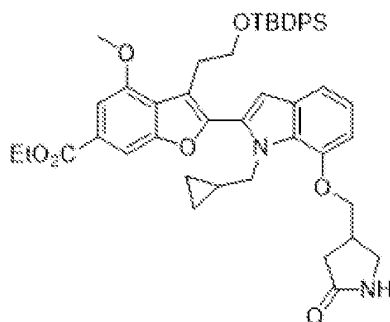
25



To a solution of Intermediate 633C (623 mg, 0.80 mmol) in methanol (10 ml), was added Pd/C (125 mg) under nitrogen atmosphere. The mixture was stirred at room temperature for overnight under hydrogen atmosphere. Solids were filtered out and the solvent was evaporated under vacuum. The crude product was purified by column chromatography (petroleum ether/ ethyl acetate = 5:1) to afford the title compound (396 mg, 72%) as a yellow solid. LC/MS m/z: 688 [M+H]⁺.

Intermediate 633E

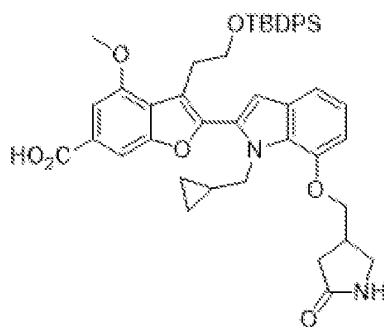
ethyl 3-(2-((tert-butyl(diphenyl)silyl)oxy)ethyl)-2-(1-(cyclopropylmethyl)-7-((5-oxopyrrolidin-3-yl)methoxy)-1H-indol-2-yl)-4-methoxybenzofuran-6-carboxylate



To a solution of Intermediate 633D (180 mg, 0.26 mmol) in acetone (3 ml), was added 4-(bromomethyl)pyrrolidin-2-one (93 mg, 0.52 mmol) and Cs₂CO₃ (256 mg, 0.78 mmol) under nitrogen atmosphere. The mixture was stirred at 60°C for overnight. The reaction was monitored by LCMS. The reaction mixture was concentrated under vacuum. The crude product was purified by column chromatography (DCM/ MeOH = 10:1) to afford (130 mg, 64%) as a yellow solid. LC/MS m/z: 785 [M+H]⁺.

Intermediate 633F

3-(2-((tert-butyl(diphenyl)silyl)oxy)ethyl)-2-(1-(cyclopropylmethyl)-7-((5-oxopyrrolidin-3-yl)methoxy)-1H-indol-2-yl)-4-methoxybenzofuran-6-carboxylic acid

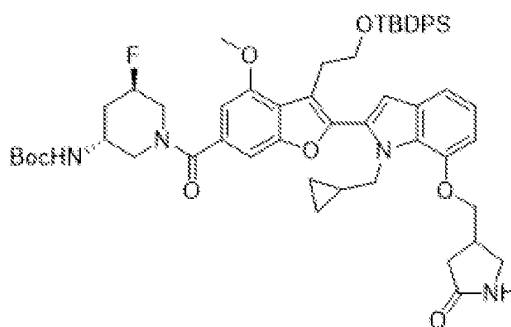


To a solution of Intermediate 633E (125 mg, 0.16 mmol) in THF (1.2 ml) and water (0.4 ml) was added LiOH (11 mg, 0.48 mmol). The resulting mixture was stirred at 50°C for overnight. The reaction was monitored by LCMS. The resulting solution was adjusted to pH 5-6 with HCl (1 M). The mixture was extracted with DCM/ MeOH (10:1) (3×10 ml). The combined organic extracts were washed with brine (30 ml), dried over anhydrous sodium sulfate and concentrated under vacuum to afford the title compound (110 mg, 91%) as a yellow oil. LC/MS m/z: 757 [M+H]⁺.

10

Intermediate 633G

tert-butyl ((3R,5R)-1-(3-(2-(((tert-butylidiphenylsilyl)oxy)ethyl)-2-(1-(cyclopropylmethyl)-7-((5-oxopyrrolidin-3-yl)methoxy)-1H-indol-2-yl)-4-methoxybenzofuran-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate

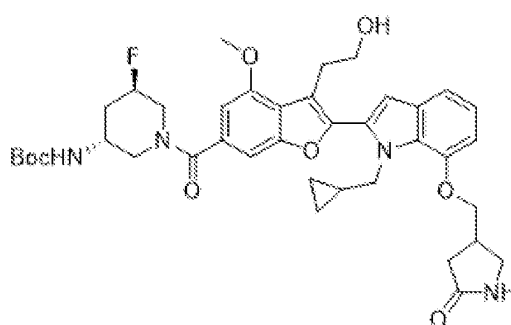


To a solution of Intermediate 633F (110 mg, 0.14 mmol) in DMF (2 ml) was added HATU (94 mg, 0.25 mmol). The resulting mixture was stirred at room temperature for 30 minute. To the above mixture was added DIEA (0.1 ml, 0.57 mmol) and tert-butyl ((3R,5R)-5-fluoropiperidin-3-yl)carbamate (47 mg, 0.21 mmol). The mixture was stirred at room temperature for 1h. The reaction was monitored by LCMS. The reaction was then

quenched by adding water (10 ml) and extracted with ethyl acetate (2×10 ml). The combined organic extracts were washed with water (2×20 ml) and brine (2×20 ml), dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by column chromatography (DCM/ MeOH =15:1) to afford the title compound
 5 (127 mg, 95%) as a yellow solid. LC/MS m/z: 957 [M+H]⁺.

Intermediate 633H

tert-butyl ((3R,5R)-1-(2-(1-(cyclopropylmethyl)-7-((5-oxopyrrolidin-3-yl)methoxy)-1H-indol-2-yl)-3-(2-hydroxyethyl)-4-methoxybenzofuran-6-carbonyl)-5-fluoropiperidin-3-yl)carbamate
 10

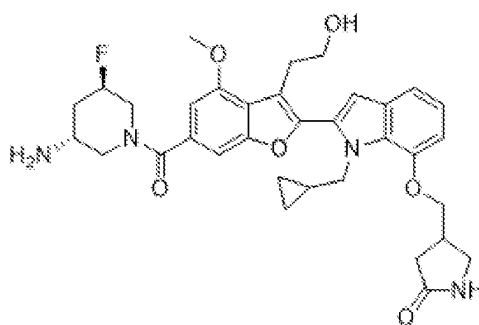


To a solution of Intermediate 633G (127 mg, 0.13 mmol) in THF (1 ml), was added TBAF (1 M in THF) (2 ml). The resulting solution was stirred at room temperature for overnight. The reaction was monitored by LCMS. The reaction was then quenched by
 15 adding water (10 ml) and extracted with ethyl acetate (10 ml), washed with water (5×10 ml) and brine (5×10 ml), dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by column chromatography (DCM/ MeOH = 10:1) to afford the title compound (76 mg, 81%) as a yellow solid. LC/MS m/z: 719 [M+H]⁺.

20

Example 633

4-(((2-(6-((3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl)-3-(2-hydroxyethyl)-4-methoxybenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one
 25 one

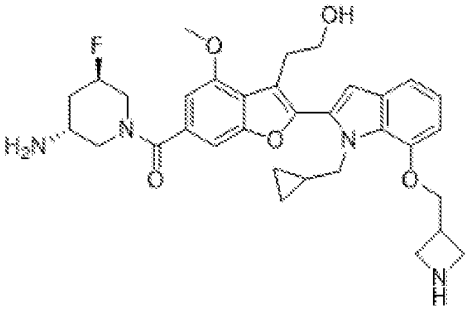
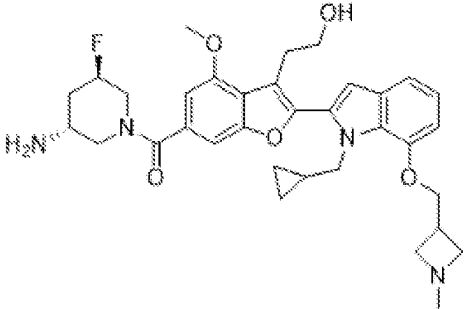


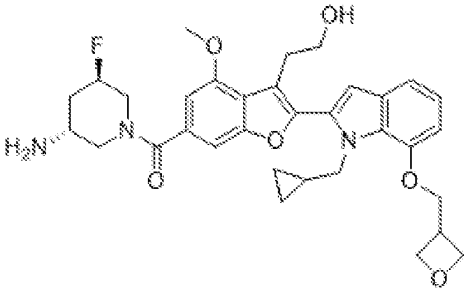
To a solution of Intermediate 633H (70 mg, 0.1 mmol) in DCM (2 ml), was added TFA (0.7 ml). The resulting solution was stirred for 0.5 h at room temperature. The reaction was monitored by LCMS. The solvent was evaporated under vacuum. The mixture product was diluted with MeOH and basified to PH 8 with saturated sodium bicarbonate solution. The resulting solution was stirred at room temperature for 0.5h. The reaction was monitored by LCMS. The reaction was then quenched by adding water (10 ml) and extracted with DCM/ MeOH (10:1) (3×10 ml). The combined organic extracts were washed with brine (20 ml), dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by RP-HPLC to afford the title compound (39.9 mg, 64%) as a white solid. LC-MS m/z: 619.4 [M+H]⁺. LC-MS retention time: 1.480 min. (Method K). ¹H NMR (300 MHz, DMSO-*d*₆+D₂O) δ 7.25 (t, *J* = 8.4 Hz, 2H), 7.02 (t, *J* = 7.8 Hz, 1H), 6.91 (s, 1H), 6.82 (t, *J* = 7.8 Hz, 2H), 5.19 – 4.63 (m, 2H), 4.33 (d, *J* = 6.0 Hz, 2H), 4.16 (d, *J* = 6.3 Hz, 2H), 3.96 (s, 3H), 3.73 (t, *J* = 6.9 Hz, 2H), 3.54 – 3.37 (m, 4H), 3.25 – 3.19 (m, 1H), 2.98 – 2.94 (m, 4H), 2.52 – 2.37 (m, 2H), 2.23 – 2.13 (m, 1H), 1.99 – 1.71 (m, 1H), 1.10 – 0.97 (m, 1H), 0.32 – 0.23 (m, 2H). 0.07 – -0.02 (m, 2H).

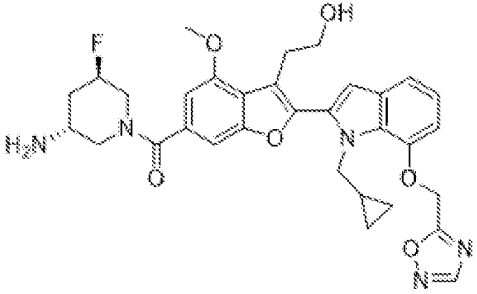
Compounds of Examples 634 to 639 in Table 58 were obtained following a procedure similar to the preparation of a compound of Example 633 by alkylation of Intermediate 633D with appropriate alkyl halides.

Table 58

Example	Structure	Name Analytical Data: LC-MS m/z [M+H] ⁺ ; LC-MS retention time (LC-MS method); ¹ H NMR (MHz, solvent)
634		((3R,5R)-3-amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(2-hydroxyethoxy)-1H-indol-2-yl)-3-(2-hydroxyethyl)-4-methoxybenzofuran-6-yl)methanone Analytical Data: 566.1, 1.477 min. (Method K); (400MHz, DMSO- <i>d</i> ₆) δ ppm 8.34 (s, 3H), 7.28 (s, 1H), 7.21 (d, <i>J</i> = 7.6 Hz, 1H), 6.99 (t, <i>J</i> = 7.8 Hz, 1H), 6.90 (s, 1H), 6.86 (s, 1H), 6.78 (d, <i>J</i> = 7.6 Hz, 1H), 5.04 – 4.77 (m, 4H), 4.42 (d, <i>J</i> = 6.8 Hz, 2H), 4.18 – 4.15 (m, 2H), 3.97 (s, 3H), 3.83 – 3.72 (m, 4H), 3.44 – 3.36 (m, 3H), 3.05 – 2.90 (m, 3H), 2.46 – 2.39 (m, 1H), 2.01 – 1.83 (m, 1H), 1.09 – 1.05 (m, 1H), 0.27 – 0.15 (m, 4H).
635		(2-(7-(2-(1H-1,2,4-triazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-(2-hydroxyethyl)-4-methoxybenzofuran-6-yl)((3R,5R)-3-amino-5-fluoropiperidin-1-yl)methanone Analytical Data: 617.3; 1.426 min. (Method K); (400 MHz, DMSO- <i>d</i> ₆): δ ppm 8.75 (s, 1H), 8.51 – 8.21 (m, 3H), 8.09 (s, 1H), 7.27 (s, 1H), 7.22 (d, <i>J</i> = 7.8 Hz, 1H), 7.01 (t, <i>J</i> = 7.8 Hz, 1H), 6.89 (s, 1H), 6.87 – 6.81 (m, 2H), 5.16

		– 4.85 (m, 1H), 4.78 – 4.71 (m, 2H), 4.64 – 4.51 (m, 4H), 4.14 (d, $J = 6.6$ Hz, 2H), 4.05 – 3.98 (m, 1H), 3.95 (s, 3H), 3.72 (t, $J = 7.0$ Hz, 2H), 3.48 – 3.30 (m, 2H), 3.07 – 2.87 (m, 3H), 2.46 – 2.31 (m, 1H), 2.04 – 1.80 (m, 1H), 0.84 – 0.73 (m, 1H), 0.21 – 0.11 (m, 2H), –0.05 – 0.14 (m, 2H).
636		((3R,5R)-3-amino-5-fluoropiperidin-1-yl)(2-(7-(azetidin-3-ylmethoxy)-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-(2-hydroxyethyl)-4-methoxybenzofuran-6-yl)methanone Analytical Data: 519.2; 1.325 min. (Method K); (400 MHz, DMSO-d_6): δ ppm 9.20 (s, 2H), 8.43 – 8.12 (m, 3H), 7.27 – 7.22 (m, 2H), 7.03 (t, $J = 7.8$ Hz, 1H), 6.92 (s, 1H), 6.88 – 6.78 (m, 2H), 5.20 – 4.51 (m, 4H), 4.44 – 4.24 (m, 4H), 4.16 – 4.04 (m, 2H), 3.97 (s, 3H), 3.95 – 3.87 (m, 3H), 3.75 (t, $J = 7.0$ Hz, 2H), 3.41 – 3.28 (m, 2H), 3.00 – 2.92 (m, 3H), 2.44 – 2.36 (m, 1H), 2.04 – 1.84 (m, 1H), 1.09 – 1.01 (m, 1H), 0.32 – 0.23 (m, 2H), 0.08 – 0.01 (m, 2H).
637		((3R,5R)-3-amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-((1-methylazetidin-3-yl)methoxy)-1H-indol-2-yl)-3-(2-hydroxyethyl)-4-methoxybenzofuran-6-yl)methanone Analytical Data: 605.3; 1.337 min. (Method K); (400 MHz, DMSO-d_6): δ

		ppm 10.7 – 10.9 (m, 1H), 8.62 – 8.15 (m, 3H), 7.29 – 7.22 (m, 2H), 7.05 (t, J = 7.8 Hz, 1H), 6.91 (s, 1H), 6.88 – 6.75 (m, 2H), 5.31 – 4.58 (m, 3H), 4.45 (d, J = 7.4 Hz, 1H), 4.37 – 4.21 (m, 4H), 4.17 – 3.99 (m, 4H), 3.96 (s, 3H), 3.72 – 3.67 (m, 3H), 3.34 – 3.22 (m, 3H), 3.01 – 2.89 (m, 2H), 2.87 – 2.79 (m, 3H), 2.43 – 2.31 (m, 1H), 2.03 – 1.81 (m, 1H), 1.12 – 1.00 (m, 1H), 0.34 – 0.22 (m, 2H), 0.07 – 0.01 (m, 2H).
638		((3R,5R)-3-amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(oxetan-3-ylmethoxy)-1H-indol-2-yl)-3-(2-hydroxyethyl)-4-methoxybenzofuran-6-yl)methanone Analytical Data: 592.1; 1.538 min. (Method K); (400MHz, DMSO-d_6) δ ppm 8.61 – 8.32 (m, 3H), 7.28 – 7.23 (m, 1H), 7.04 – 7.01 (m, 1H), 6.91 (d, J = 2 Hz, 1H), 6.86 – 6.82 (m, 3H), 4.81 – 4.77 (m, 2H), 4.58 – 4.55 (m, 1H), 4.39 – 4.36 (m, 3H), 4.27 – 4.18 (m, 2H), 3.97 (s, 3H), 3.93 – 3.87 (m, 2H), 3.74 – 3.67 (m, 2H), 3.40 – 3.33 (m, 3H), 2.98 – 2.95 (m, 3H), 2.42 – 2.37 (m, 2H), 1.97 – 1.87 (m, 1H), 1.09 – 1.05 (m, 1H), 0.29 – 0.25 (m, 2H), 0.05 – 0.04 (m, 2H).

639		(2-(7-((1,2,4-oxadiazol-5-yl)methoxy)-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-(2-hydroxyethyl)-4-methoxybenzofuran-6-yl)((3R,5R)-3-amino-5-fluoropiperidin-1-yl)methanone Analytical Data: 602.3; 1.074 min. (Method K); (400MHz, DMSO-<i>d</i>₆) δ ppm 8.37 – 8.02 (m, 2H), 7.29 – 7.25 (m, 2H), 7.02 – 7.01 (m, 1H), 6.99 – 6.87 (m, 2H), 6.67 (d, J = 7.6 Hz, 1H), 4.92 – 4.72 (m, 4H), 4.45 (d, J = 6.8 Hz, 2H), 3.97 (s, 4H), 3.75 – 3.72 (m, 3H), 3.68 – 3.51 (m, 3H), 3.05 – 2.95 (m, 3H), 2.38 – 2.33 (m, 1H), 1.97 – 1.83 (m, 1H), 1.24 – 1.08 (m, 1H), 0.25 – 0.23 (m, 2H), 0.15 – 0.13 (m, 2H)
-----	---	---

6. *Biological Assays*

- 5 Compounds of the present invention were assayed as inhibitors of PAD4 using the assay protocols described below.

RFMS human PAD4 Functional Assay 1:

- 10 Compounds were solubilized in 100% DMSO to achieve a 10 mM compound concentration. Compound stock solutions were stored at RT. A series of dilutions were prepared in DMSO and mixed 8 times with 20 μ L mixing volume. Final top concentration of compound in the assay is 50 μ M. Final assay conditions were as follows:

Reaction volume: 26 μ l

Assay buffer: 25 mM hepes, pH 7.5, 5 mM NaCl, 1 mM DTT, 0.2 mg/ml BSA, 0.01% CHAPS, 50 μ M Calcium, and 5 μ M TPEN

Final concentrations: 5 nM hPAD4 enzyme, 250 μ M BAEE, and 0.5% DMSO

Total incubation time: 30 mins compound and enzyme preincubation at 37 °C, 90 min
5 enzyme/substrate reaction, 30 min reaction with phenyl glyoxal at 37 °C

Stop solution: 40 μ l 5% TCA in ACN

0.13 μ L of compound solution was added to 13 μ L of 10 nM PAD4 in assay
buffer. After 30 min 13 μ l of 500 μ M of BAEE was added in 25 mM hepes, pH 7.5, 5
mM NaCl, 1 mM DTT, 0.2 mg/ml BSA, 0.01% CHAPS, 50 μ M Calcium, 5 μ M TPEN
10 was added and the reaction incubated for 90 min at 37 °C. The enzymatic reaction was
quenched by addition of 15 μ l of 6.1N TCA, 100% Final Concentration is 20%, 35 μ l of
8.5 mM phenyl glyoxal (final concentration 4 mM) is then added and the reaction is
incubated for 30 min at 37°C.

After 30 minutes the plates are spun down to remove all precipitate. The enzyme
15 reaction was quenched with an equal volume of methanol containing internal standard
(modified citrulline). Samples were loaded onto the Rapid Fire RF300 system (Agilent)
wherein they were first sipped for 1000 ms and then directly loaded to a C18 separations
cartridge using a mixture of acetonitrile containing 0.01% formic acid for 3000 ms
desalting. The flow rate of the mobile phase was 1.5 ml/min. Once the samples were
20 eluted from the cartridge, a mobile phase of acetonitrile containing 0.01% formic acid
was used to move the samples into the mass spectrometer for 4000 ms at a flow rate of
1.25 ml/min/ Sciex API5500 triple quadrupole mass spectrometer (Applied Biosystems)
equipped with ESI was used to analyze the peptidyl citrulline and internal standard ions.

MRM transition of product and internal standard were monitored at m/z 424.5 to
25 350.4 and m/z 293 to 247 respectively. The dwell time for each transition was set at 200
ms, and the ESI voltage was used at 5500 with a source temperature of 400°C. Extracted
ion peaks for each transition were integrated using the Rapid Fire Integrator software.
Peak area of analyte was normalized with internal standard.).

For a given compound example, Table 59 below shows the human PAD4
30 (hPAD4) IC₅₀ in the rapid-fire mass spectrum (RFMS) assay.

Table 59. PAD4 Activity

Example	hPAD4 RFMS IC ₅₀ (μM)
1	0.280
2	0.380
3	0.060
4	0.068
5	0.027
6	0.032
7	0.412
8	0.037
9	0.120
10	0.159
11	1.373
12	2.324
13	0.163
14	0.906
15	0.526
16	0.407
17	0.075
18	0.570
19	0.168
20	0.116
21	0.091
22	2.155
23	0.108
24	0.031
25	0.017
26	0.449
27	0.022
28	NA
29	1.020
30	0.084
31	0.065
32	0.414
33	0.534
34	0.042
35	0.139
36	0.782
37	3.614
38	0.158
39	0.087
40	0.025
41	0.085
42	0.009
43	0.150

44	1.485
45	0.101
46	0.041
47	1.482
48	0.326
49	0.036
50	0.074
51	0.109
52	0.882
53	0.446
54	0.358
55	0.543
56	0.468
57	0.781
58	0.083
59	0.291
60	0.083
61	NA
62	0.028
63	0.227
64	0.055
65	0.025
66	0.059
67	0.023
68	0.026
69	0.019
70	0.015
71	0.022
72	0.067
73	0.605
74	0.425
75	0.166
76	0.096
77	0.077
78	0.143
79	0.212
80	1.609
81	0.384
82	0.368
83	0.384
84	0.610
85	0.327
86	0.219
87	2.316
88	1.678
89	0.048
90	0.012

91	0.602
92	0.672
93	0.220
94	0.934
95	0.133
96	0.588
97	0.030
98	0.014
99	0.307
100	0.036
101	0.011
102	0.012
103	0.034
104	0.025
105	0.107
106	0.208
107	0.240
108	0.907
109	0.292
110	1.037
111	15.000
112	0.572
113	0.283
114	3.975
115	3.371
116	22.841
117	15.000
118	0.157
119	0.084
120	0.250
121	1.499
122	0.068
123	0.896
123	0.286
125	0.413
126	0.122
127	0.098
128	4.344
129	0.376
130	0.038
131	0.146
132	0.476
133	0.129
134	0.212
135	0.233
136	0.705
137	0.071

138	0.252
139	0.198
140	0.346
141	0.179
142	0.642
143	0.588
144	0.164
145	0.285
146	1.210
147	0.954
148	0.442
149	0.111
150	0.187
151	0.325
152	0.192
153	0.628
154	1.013
155	1.070
156	0.173
157	0.095
158	1.252
159	1.213
160	0.048
161	0.487
162	2.288
163	5.588
164	0.625
165	0.198
166	0.056
167	0.045
168	0.047
169	0.181
170	0.135
171	0.076
172	8.773
173	0.090
174	0.204
175	0.83
176	0.229
177	0.069
178	0.153
179	0.035
180	0.220
181	0.269
182	0.923
183	0.088
184	0.050

185	0.025
186	0.056
187	1.550
188	0.081
189	0.030
190	0.058
191	0.020
192	0.093
193	0.334
194	1.800
195	0.363
196	0.384
197	0.317
198	3.263
199	3.363
201	1.967
202	1.063
203	0.012
204	0.039
205	0.06
206	0.07
207	0.15
208	0.14
209	1.08
210	0.49
211	1.05
212	1.69
213	0.68
214	0.15
215	0.61
216	0.27
217	0.26
218	0.55
219	0.46
220	4.34
221	0.51
222	1.01
223	0.13
224	1.07
225	0.08
226	0.05
227	0.95
228	0.93
229	0.13
230	0.32
231	0.46
232	0.90

233	0.62
234	1.14
235	0.25
236	0.95
237	0.25
238	0.42
239	0.07
240	0.18
241	0.02
242	0.09
243	4.12
244	0.07
245	0.07
246	0.13
247	0.12
248	0.06
249	0.08
250	0.09
251	0.18
252	0.79
253	0.29
254	0.32
255	0.25
256	0.33
257	0.06
258	0.22
259	0.02
260	0.22
261	0.42
262	0.12
263	0.09
264	0.01
265	0.11
266	0.28
267	0.05
268	0.04
269	0.54
270	2.11
271	2.07
272	3.81
273	2.42
274	0.27
275	0.12
276	2.77
277	0.22
278	0.39
279	0.20

280	1.09
281	0.14
282	0.17
283	0.33
284	1.86
285	1.27
286	0.54
287	1.28
288	0.08
289	3.58
290	2.72
291	5.89
292	2.35
293	0.08
294	0.20
295	0.02
296	0.85
297	0.19
298	0.21
299	0.02
300	0.10
301	0.03
302	0.12
303	0.24
304	0.01
305	0.04
306	0.03
307	0.07
308	0.05
309	0.40
310	0.40
311	0.21
312	0.06
313	0.10
314	0.04
315	0.34
316	0.25
317	0.51
318	0.31
319	0.05
320	0.15
321	15.00
322	0.50
323	0.14
324	0.11
325	1.54
326	0.20

327	0.07
328	0.12
329	0.05
330	0.15
331	0.06
332	0.02
333	0.02
334	0.12
335	0.06
336	0.15
337	0.02
338	0.05
339	0.03
340	0.08
341	0.04
342	0.93
343	0.05
344	0.47
345	0.79
346	0.06
347	0.29
348	0.14
349	0.10
350	0.03
351	0.10
352	0.81
353	0.61
354	0.15
355	0.02
356	2.78
357	0.05
358	0.42
359	0.24
360	0.45
361	0.30
362	0.43
363	2.28
364	1.09
365	0.72
366	0.87
367	1.00
368	2.80
369	0.02
370	0.13
371	1.07
372	0.19
373	0.20

374	2.84
375	1.36
376	0.12
377	0.09
378	0.45
379	0.16
380	0.14
381	0.02
382	0.15
383	0.04
384	0.20
385	0.27
386	0.08
387	0.23
388	0.07
389	0.03
390	0.005
391	0.01
392	0.003
393	0.25
394	0.01
395	0.14
396	0.11
397	0.04
398	0.04
399	0.05
400	0.66
401	0.02
402	0.06
403	0.46
404	0.03
405	0.02
406	0.09
407	0.03
408	0.04
409	0.04
410	0.09
411	0.11
412	0.01
413	0.03
414	0.26
415	0.46
416	0.56
417	5.06
418	1.71
419	8.25
420	0.29

421	0.08
422	0.40
423	0.15
424	0.08
425	0.05
426	0.05
427	0.02
428	0.03
429	0.04
430	0.08
431	0.13
432	0.20
433	0.14
434	0.25
435	0.38
436	0.30
437	0.11
438	0.03
439	0.03
440	0.06
441	0.06
442	0.03
443	0.13
444	0.01
445	0.16
446	0.13
447	0.17
448	0.07
449	0.05
450	0.05
451	0.01
452	0.03
453	0.01
454	0.55
455	0.27
456	0.03
457	0.03
458	0.08
459	0.14
460	0.07
461	0.08
462	0.03
463	0.10
464	0.18
465	0.13
466	0.19
467	0.02

468	0.10
469	0.18
470	0.01
471	0.09
472	0.06
473	0.003
474	0.07
475	0.02
476	0.03
477	0.02
478	0.13
479	0.39
480	0.14
481	0.12
482	0.06
483	0.15
484	0.15
485	0.15
486	0.07
487	0.20
488	0.25
489	0.07
490	0.15
491	1.31
492	0.13
493	0.11
494	0.02
495	0.33
496	0.02
497	0.04
498	0.07
499	0.15
500	0.24
501	0.13
502	0.07
503	0.06
504	0.11
505	0.06
506	0.07
507	0.17
508	0.04
509	0.35
511	0.01
514	0.06
515	0.06
516	1.04
517	0.06

518	0.26
519	0.04
520	0.22
521	6.05
522	15.00
523	0.40
524	0.28
525	0.09
526	0.26
527	0.05
528	15.00
529	1.53
530	0.03
531	0.58
532	1.01
533	0.52
534	0.44
535	0.07
536	2.52
537	0.07
538	0.04
539	0.13
540	1.10
541	2.53
542	0.58
543	0.63
544	1.07
545	0.26
546	0.56
547	0.49
548	0.17
549	0.01
550	0.05
551	0.16
552	0.10
553	0.09
554	0.06
555	0.03
556	0.02
557	0.01
558	0.10
559	0.08
560	0.16
561	0.64
562	0.14
563	0.07
564	0.04

565	0.02
566	0.01
567	0.02
568	0.06
569	0.02
570	0.18
571	0.03
572	0.08
573	0.11
574	0.02
575	0.06
576	0.19
577	0.15
578	0.19
579	0.24
580	0.06
581	0.03
582	0.30
583	1.61
584	0.05
585	0.07
586	0.15
587	1.12
588	0.23
589	0.06
590	0.03
591	0.03
592	0.03
593	0.11
594	0.39
595	1.28
596	7.39
597	0.01
598	0.02
599	0.02
600	0.03
601	0.03
602	0.03
603	0.10
604	0.03
605	0.07
606	0.05
607	0.05
608	0.01
609	0.04
610	0.43
611	1.56

612	2.96
613	0.25
614	0.06
615	0.07
616	0.02
617	0.01
618	0.05
619	0.04
620	0.45
621	0.14

RFMS human PAD4 Functional Assay 2:

Compound preparation:

Stock compounds were dissolved and stored in 100% DMSO. Compound solutions were
 5 prepared via serial dilution at 3-fold intervals in DMSO with top compound concentration at 20 μ M in each assay. 0.25 μ l of compound solution was transferred from the compound plate to the assay plate by using an acoustic dispenser.

Final assay conditions:

Total reaction volume: 25 μ l

10 Assay buffer: 100 HEPES pH 7.4, 200 mM NaCl, 2 mM CaCl_2 , 5 mM DTT

35 nM recombinant human PAD4

500 μ M TSTGGRQGSHH peptide

1.2% DMSO

Stop solution: 10% formic acid

15 Reaction mixtures were incubated at room temperature for 30 minutes. 10 μ l each of the reaction mixtures was then mixed with 40 μ l of 10% formic acid in a microtiter plate. The plate was frozen at -80°C before shipping out on dry ice for RapidFire mass spectroscopy analysis.

Thawed samples were loaded onto the Rapid Fire 300 system (Agilent) wherein they
 20 were first sipped for 250 ms and then loaded onto an Agilent "C" (C18) cartridge using a mobile phase of water containing 0.09% formic acid/0.01% trifluoroacetic acid for 3000 ms desalting flowing at a rate of 1.5 ml/min. Once the samples were loaded and washed, a mobile phase of acetonitrile containing 0.09% formic acid/0.01% trifluoroacetic acid was used to elute the samples directly onto a Sciex API4000 triple quadrupole mass
 25 spectrometer for 3000 ms at a flow rate of 1.25ml/min.

MRM transitions for substrate and product were monitored in positive ESI mode at $m/z=562.3/969.7$ and $m/z=562.8/541.3$ respectively. The dwell time for each transition was set at 100 ms, and the ESI voltage was used at 5500 with a source temperature of 650°C. Extracted ion peaks for each transition were integrated using the Rapid Fire

5 Integrator software.

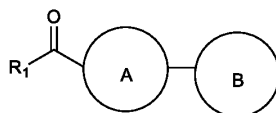
For a given compound example, the Table 60 below shows the human PAD4 (hPAD4) IC_{50} in the rapid-fire mass spectrum (RFMS) assay.

Table 60. PAD4 Activity

Example	hPAD4 RFMS IC_{50} μM
622	1.20
623	0.395
624	0.383
625	2.04
626	0.849
627	0.879
628	0.322
629	0.785
630	0.288
631	7.58
632	0.327
633	0.179
634	0.209
635	0.216
636	0.277
637	0.621
638	0.295
639	0.243

CLAIMS

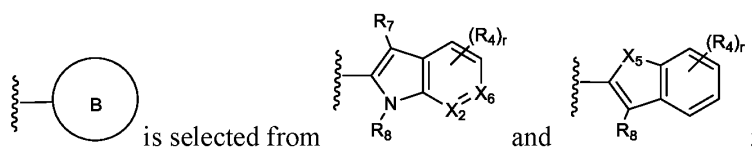
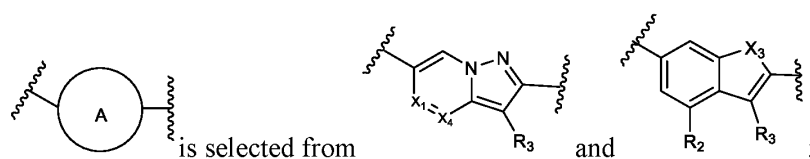
1. A compound of Formula (Ia):



5

(Ia)

or a pharmaceutically acceptable salt thereof, wherein:



- 10 X_1 is independently selected from CR_2 , and N;
 X_2 is independently selected from CR_4 , and N;
 X_3 is independently selected from O, and S;
 X_4 is independently selected from CR_2 , and N; provided X_1 and X_4 are not both N;
 X_5 is independently selected from O and S;
15 X_6 is independently selected from CR_4 , and N; provided 1) X_2 and X_6 are not both N; 2)
when X_2 and X_6 are both CR_4 , one of R_4 is H;
 R_1 is independently selected from $-NH-C_{1-5}$ alkyl optionally substituted with one or more
substituents selected from F, Cl, and NH_2 , 4-10 membered heterocyclyl, and $-NH-$
4-10 membered heterocyclyl, wherein said heterocyclyl is optionally substituted
20 with one or more substituents selected from F, Cl, CN, C_{1-3} alkyl, $=N-OR_b$, -
 $(CH_2)_rOR_b$, $-(CH_2)_rNR_aR_a$, $-NR_aC(=NH)C_{1-3}$ alkyl, $-NR_aC(=O)OR_b$, carbocyclyl,
and heterocyclyl;
 R_2 is independently selected from H, F, Cl, C_{1-4} alkyl optionally substituted with one or
more substituents selected from F, Cl, and OH, and $-OC_{1-4}$ alkyl;
25 R_3 is independently selected from H, F, Cl, CN, $-C(=O)OR_b$, and C_{1-3} alkyl optionally
substituted with one or more substituents selected from F, Cl, OH, NH_2 , and N_3 ;

- R_4 is independently selected from H, F, Cl, Br, $-C(=O)R_b$, C_{1-6} alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C_{3-6} cycloalkyl, $-NH-$ C_{1-6} alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C_{3-6} cycloalkyl, $-(CH_2)_r$ -aryl substituted with one or more R_5 , $-O-C_{1-6}$ alkyl substituted with one or more R_5 , $-(CH_2)_r-C_{3-12}$ cycloalkyl substituted with one or more R_5 , and $-(CH_2)_r-4-10$ membered heterocyclyl comprising carbon atoms and 1-5 heteroatoms selected from N, NR_6 , O, and S and substituted with one or more R_5 ;
- R_5 is independently selected from H, F, Cl, Br, CN, $=O$, C_{1-4} alkyl optionally substituted with one or more R_e , C_{2-4} alkenyl optionally substituted with one or more R_e , C_{2-4} alkynyl optionally substituted with one or more R_e , $-(CR_dR_d)_rOR_b$, $-(CR_dR_d)_rS(O)_pR_c$, $-(CR_dR_d)_rS(O)_pNR_aR_a$, $-(CR_dR_d)_rNR_aS(O)_pR_c$, $-(CR_dR_d)_rNR_aR_a$, $-(CR_dR_d)_rNR_aC(=O)R_b$, $-(CR_dR_d)_rNR_aC(=O)OR_b$, $-(CR_dR_d)_rNR_aC(=O)NR_aR_a$, $-(CR_dR_d)_rC(=O)R_b$, $-(CR_dR_d)_rC(=O)OR_b$, $-(CR_dR_d)_rC(=O)NR_aR_a$, $-(CR_dR_d)_rOC(=O)R_b$, $-(CR_dR_d)_rOC(=O)OR_b$, $-(CR_dR_d)_rO(CH_2)_rC(=O)NR_aR_a$, C_{3-6} cycloalkyl optionally substituted with one or more R_e , aryl optionally substituted with one or more R_e , and heterocyclyl optionally substituted with one or more R_e ;
- R_6 is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , $-S(O)_pR_c$, $-S(O)_pNR_aR_a$, $-C(=O)R_b$, $-C(=O)OR_b$, $-C(=O)NR_aR_a$, C_{3-6} cycloalkyl optionally substituted with one or more R_e , aryl optionally substituted with one or more R_e , and heterocyclyl optionally substituted with one or more R_e ;
- R_7 is independently selected from H, F, and Cl;
- R_8 is independently selected from H, and C_{1-6} alkyl optionally substituted with one or more substituents selected from F, Cl, and C_{3-6} cycloalkyl;
- R_a is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , C_{2-6} alkenyl optionally substituted with one or more R_e , C_{2-6} alkynyl optionally substituted with one or more R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_e ; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring optionally substituted with one or more R_e ;
- R_b is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , C_{2-6} alkenyl optionally substituted with one or more R_e , C_{2-6} alkynyl optionally

substituted with one or more R_e , $-(CH_2)_r$ -C₃₋₁₀ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_e ;

R_e is independently selected from C₁₋₆ alkyl optionally substituted with one or more R_e ,
 5 C₂₋₆ alkenyl optionally substituted with one or more R_e , C₂₋₆ alkynyl optionally substituted with one or more R_e , $-(CH_2)_r$ -C₃₋₁₀ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_e ;

R_d is independently selected from H, and C₁₋₆ alkyl optionally substituted with one or
 10 more R_e ;

R_e is independently selected from F, Cl, Br, CN, NH₂, $-NH$ -C₁₋₄ alkyl, $-N$ (C₁₋₄ alkyl)₂,
 $=O$, OH, $-OC$ ₁₋₆ alkyl, $-CO_2H$, C₁₋₆ alkyl optionally substituted with one or more R_f ,
 C₂₋₆ alkenyl, C₂₋₆ alkynyl, $-(CH_2)_r$ -C₃₋₆ cycloalkyl optionally substituted with one
 or more R_f , $-(CH_2)_r$ -aryl optionally substituted with one or more R_f , and $-(CH_2)_r$ -
 15 heterocyclyl optionally substituted with one or more R_f ;

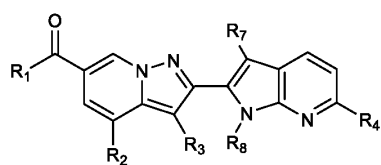
R_f is independently selected from F, Cl, Br, CN, OH, OC ₁₋₅ alkyl, C₁₋₅ alkyl optionally
 substituted with OH, C₂₋₅ alkenyl, C₂₋₅ alkynyl, C₃₋₆ cycloalkyl, and phenyl;

p , at each occurrence, is independently selected from zero, 1, and 2; and

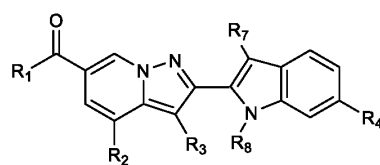
r , at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

20

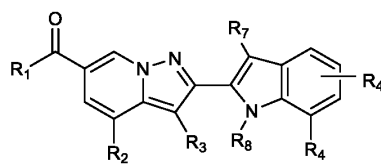
2. The compound according to claim 1, having Formulae (IIa)-(XIII):



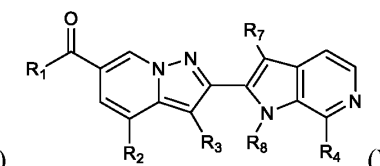
(IIa),



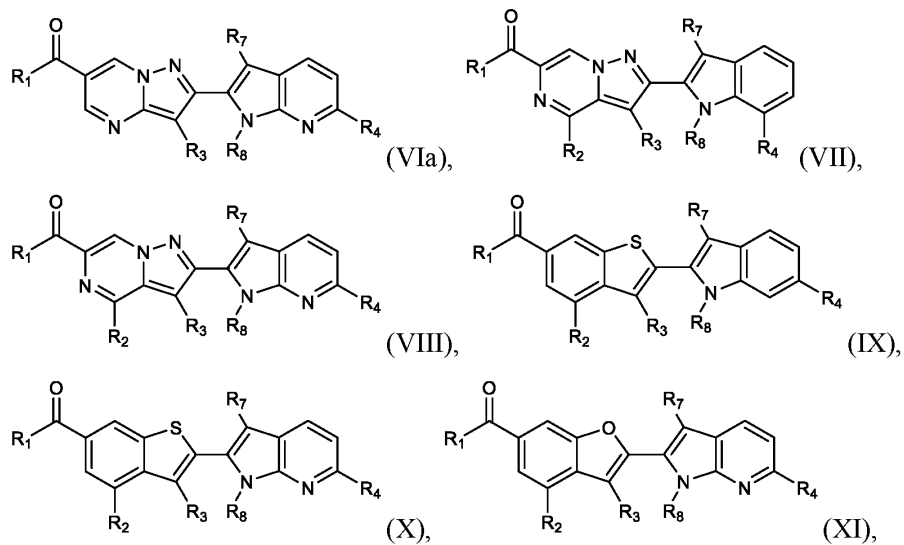
(IIIa),



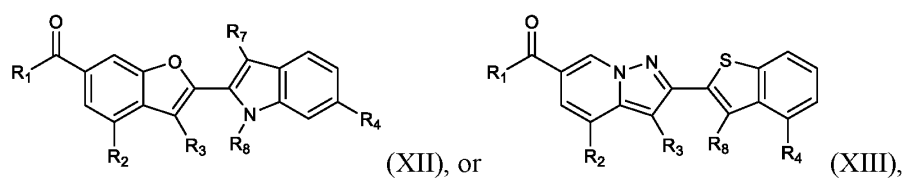
(IVa),



(Va),



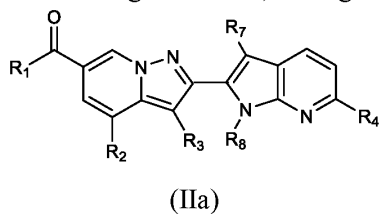
5



or a pharmaceutically acceptable salt thereof.

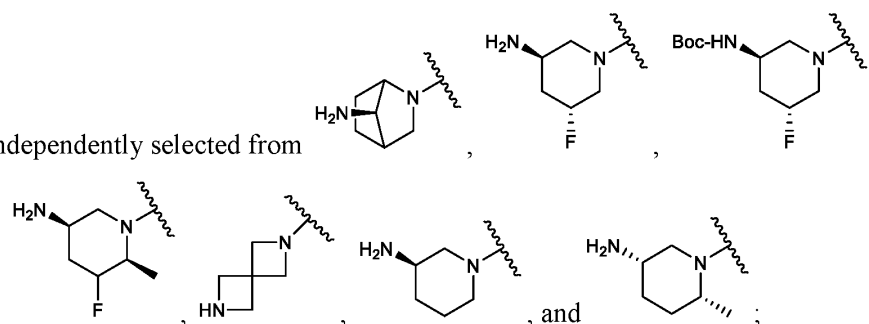
3. The compound according to claim 2, having Formula (IIa):

10



or a pharmaceutically acceptable salt thereof, wherein:

R₁ is independently selected from



- R_2 is independently selected from H, F, Cl, C_{1-3} alkyl optionally substituted with one or more substituents selected from F, Cl, and OH, and OC_{1-3} alkyl;
- R_3 is independently selected from H, F, Cl, and C_{1-3} alkyl optionally substituted with one or more substituents selected from F, Cl, and OH;
- 5 R_4 is independently selected from H, F, Cl, $-C(=O)R_b$, C_{1-6} alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C_{3-6} cycloalkyl, $-NH-C_{1-6}$ alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C_{3-6} cycloalkyl, $-(CH_2)_r$ -aryl substituted with one or more R_5 , $-O-C_{1-6}$ alkyl substituted with one or more R_5 , $-(CH_2)_r-C_{3-12}$ cycloalkyl substituted with one or more R_5 , and $-(CH_2)_r$ -4–10 membered heterocyclyl comprising carbon atoms and 1–5 heteroatoms selected from N, NR_6 , O, and S and substituted with one or more R_5 ;
- 10 R_5 is independently selected from H, F, Cl, $=O$, C_{1-4} alkyl optionally substituted with one or more R_e , $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rC(=O)NR_aR_a$, $-(CH_2)_rOC(=O)R_b$, $-(CH_2)_rOC(=O)OR_b$, $-(CH_2)_rO(CH_2)_rC(=O)NR_aR_a$, C_{3-6} cycloalkyl optionally substituted with one or more R_e , aryl optionally substituted with one or more R_e , and heterocyclyl optionally substituted with one or more R_e ;
- 15 R_6 is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , $C(=O)R_b$, $-C(=O)NR_aR_a$, C_{3-6} cycloalkyl optionally substituted with one or more R_e , aryl optionally substituted with one or more R_e , and heterocyclyl optionally substituted with one or more R_e ;
- 20 R_7 is independently selected from H, F, and Cl;
- R_8 is independently selected from H, and C_{1-6} alkyl optionally substituted with one or more substituents selected from F, Cl, and C_{3-6} cycloalkyl;
- R_a is independently selected from H, and C_{1-6} alkyl optionally substituted with one or more R_e ; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring optionally substituted with one or more R_e ;
- 25
- 30

R_b is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ heterocyclyl optionally substituted with one or more R_e ;

R_c is independently selected from C_{1-6} alkyl optionally substituted with one or more R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ heterocyclyl optionally substituted with one or more R_e ;

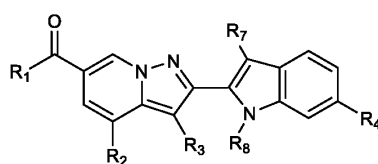
R_e is independently selected from F, Cl, Br, NH_2 , $-NH-C_{1-4}$ alkyl, $-N(C_{1-4} \text{ alkyl})_2$, $=O$, OH, $-OC_{1-6}$ alkyl, C_{1-6} alkyl optionally substituted with one or more R_f , $-(CH_2)_r-C_{3-6}$ cycloalkyl optionally substituted with one or more R_f , $-(CH_2)_r$ -aryl optionally substituted with one or more R_f , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_f ;

R_f is independently selected from F, Cl, OH, OC_{1-5} alkyl, C_{1-5} alkyl optionally substituted with OH, C_{3-6} cycloalkyl, and phenyl;

p , at each occurrence, is independently selected from zero, 1, and 2; and

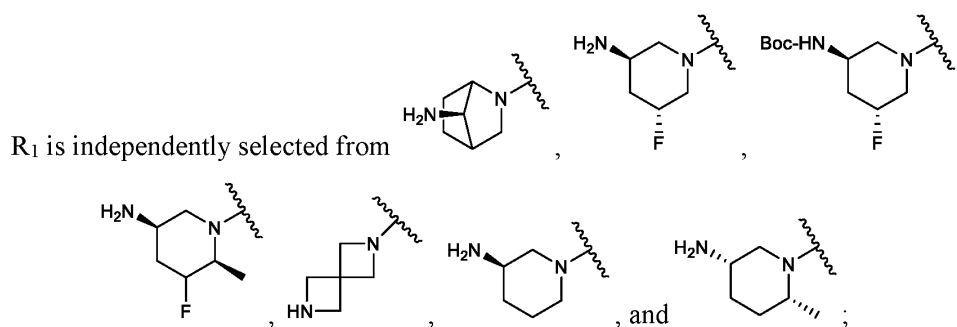
r , at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

4. The compound according to claim 1, having Formula (IIIa):



(IIIa)

or a pharmaceutically acceptable salt thereof, wherein:



R_2 is independently selected from H, F, Cl, C_{1-3} alkyl optionally substituted with one or more substituents selected from F, Cl, and OH, and OC_{1-3} alkyl;

- R_3 is independently selected from H, F, Cl, and C_{1-3} alkyl optionally substituted with one or more substituents selected from F, Cl, and OH;
- R_4 is independently selected from H, F, Cl, $-C(=O)R_b$, C_{1-6} alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C_{3-6} cycloalkyl, $-NH-$
- 5 C_{1-6} alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C_{3-6} cycloalkyl, $-(CH_2)_r$ -aryl substituted with one or more R_5 , $-O-C_{1-6}$ alkyl substituted with one or more R_5 , $-(CH_2)_r-C_{3-12}$ cycloalkyl substituted with one or more R_5 , and $-(CH_2)_r-4-10$ membered heterocyclyl comprising carbon atoms and 1-5 heteroatoms selected from N, NR_6 , O, and S and substituted with one or
- 10 more R_5 ;
- R_5 is independently selected from H, F, Cl, $=O$, C_{1-4} alkyl optionally substituted with one or more R_e , $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rC(=O)NR_aR_a$, $-(CH_2)_rOC(=O)R_b$, $-(CH_2)_rOC(=O)OR_b$, $-(CH_2)_rO(CH_2)_rC(=O)NR_aR_a$, C_{3-6} cycloalkyl optionally substituted with one or more R_e , aryl optionally substituted with one or more R_e , and heterocyclyl optionally substituted with one or more R_e ;
- 15 R_6 is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , $-C(=O)R_b$, $-C(=O)OR_b$, $-C(=O)NR_aR_a$, C_{3-6} cycloalkyl optionally substituted with one or more R_e , aryl optionally substituted with one or more R_e , and heterocyclyl optionally substituted with one or more R_e ;
- 20 R_7 is independently selected from H, F, and Cl;
- R_8 is independently selected from H, and C_{1-6} alkyl optionally substituted with one or
- 25 more substituents selected from F, Cl, and C_{3-6} cycloalkyl;
- R_a is independently selected from H, and C_{1-6} alkyl optionally substituted with one or more R_e ; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring optionally substituted with one or more R_e ;
- R_b is independently selected from H, C_{1-6} alkyl optionally substituted with one or more
- 30 R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ heterocyclyl optionally substituted with one or more R_e ;

R_c is independently selected from C_{1-6} alkyl optionally substituted with one or more R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_e ;

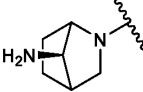
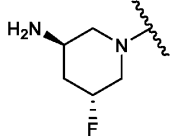
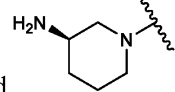
R_e is independently selected from F, Cl, Br, CN, NH_2 , $-NH-C_{1-4}$ alkyl, $-N(C_{1-4}$ alkyl) $_2$,
 5 $=O$, OH, $-OC_{1-6}$ alkyl, C_{1-6} alkyl optionally substituted with one or more R_f , $-(CH_2)_r-C_{3-6}$ cycloalkyl optionally substituted with one or more R_f , $-(CH_2)_r$ -aryl optionally substituted with one or more R_f , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_f ;

R_f is independently selected from F, Cl, OH, OC_{1-5} alkyl, C_{1-5} alkyl optionally substituted
 10 with OH, C_{3-6} cycloalkyl, and phenyl;

p , at each occurrence, is independently selected from zero, 1, and 2; and

r , at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

5. The compound according to claim 3 or 4, or a pharmaceutically acceptable
 15 salt thereof, wherein:

R_1 is independently selected from , , and ;

R_2 is independently selected from H, F, Cl, CH_3 , and OCH_3 ;

R_3 is independently selected from H, F, Cl, CH_3 , and CH_2OH ;

R_4 is independently selected from H, F, Cl, C_{1-5} alkyl optionally substituted with one or
 20 more substituents selected from F, Cl, OH, and C_{3-6} cycloalkyl, $-(CH_2)_r$ -aryl substituted with one or more R_5 , $-O-C_{1-6}$ alkyl substituted with one or more R_5 , $-(CH_2)_r-C_{3-12}$ cycloalkyl substituted with one or more R_5 , and $-(CH_2)_r$ -4-10 membered heterocyclyl comprising carbon atoms and 1-5 heteroatoms selected from N, NR_6 , O, and S and substituted with one or more R_5 ;

25 R_5 is independently selected from H, F, Cl, $=O$, C_{1-4} alkyl optionally substituted with one or more R_e , $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_2R_c$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_2R_c$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rC(=O)NR_aR_a$, $-(CH_2)_rOC(=O)R_b$, $-(CH_2)_rOC(=O)OR_b$, $-(CH_2)_rO(CH_2)_rC(=O)NR_aR_a$, C_{3-6} cycloalkyl optionally substituted with one or more
 30

R_e , aryl optionally substituted with one or more R_e , and heterocyclyl optionally substituted with one or more R_e ;

R_6 is independently selected from H and C_{1-65} alkyl optionally substituted with one or more R_e ;

5 R_7 is H;

R_8 is C_{1-3} alkyl substituted with one C_{3-6} cycloalkyl;

R_a is independently selected from H, and C_{1-4} alkyl;

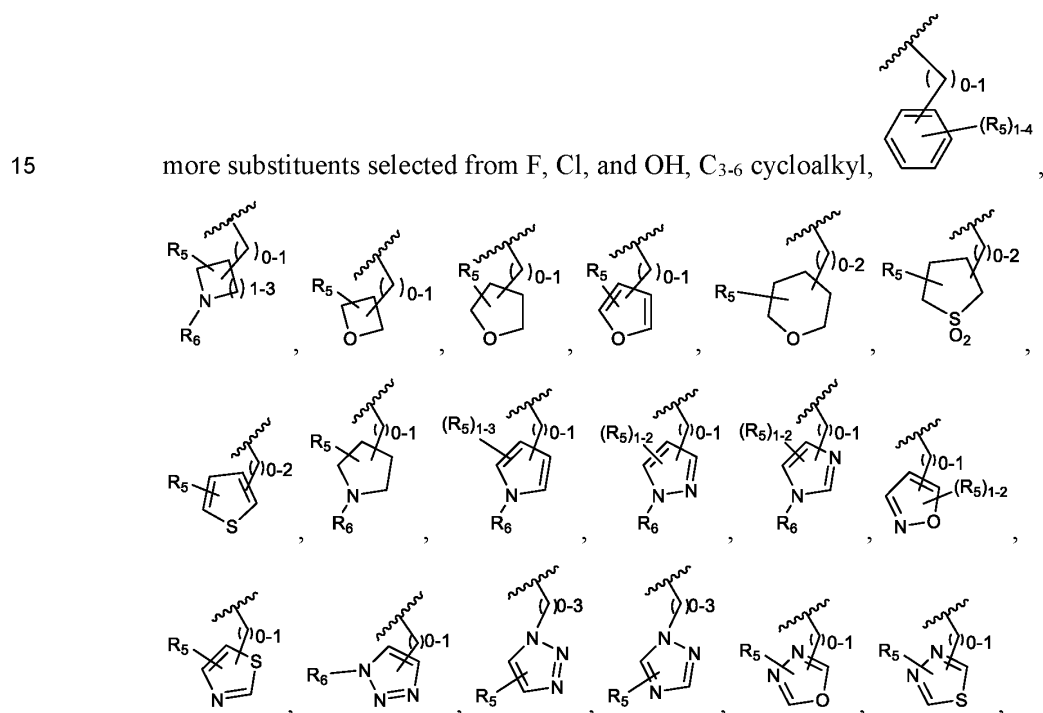
R_b is independently selected from H, C_{1-4} alkyl;

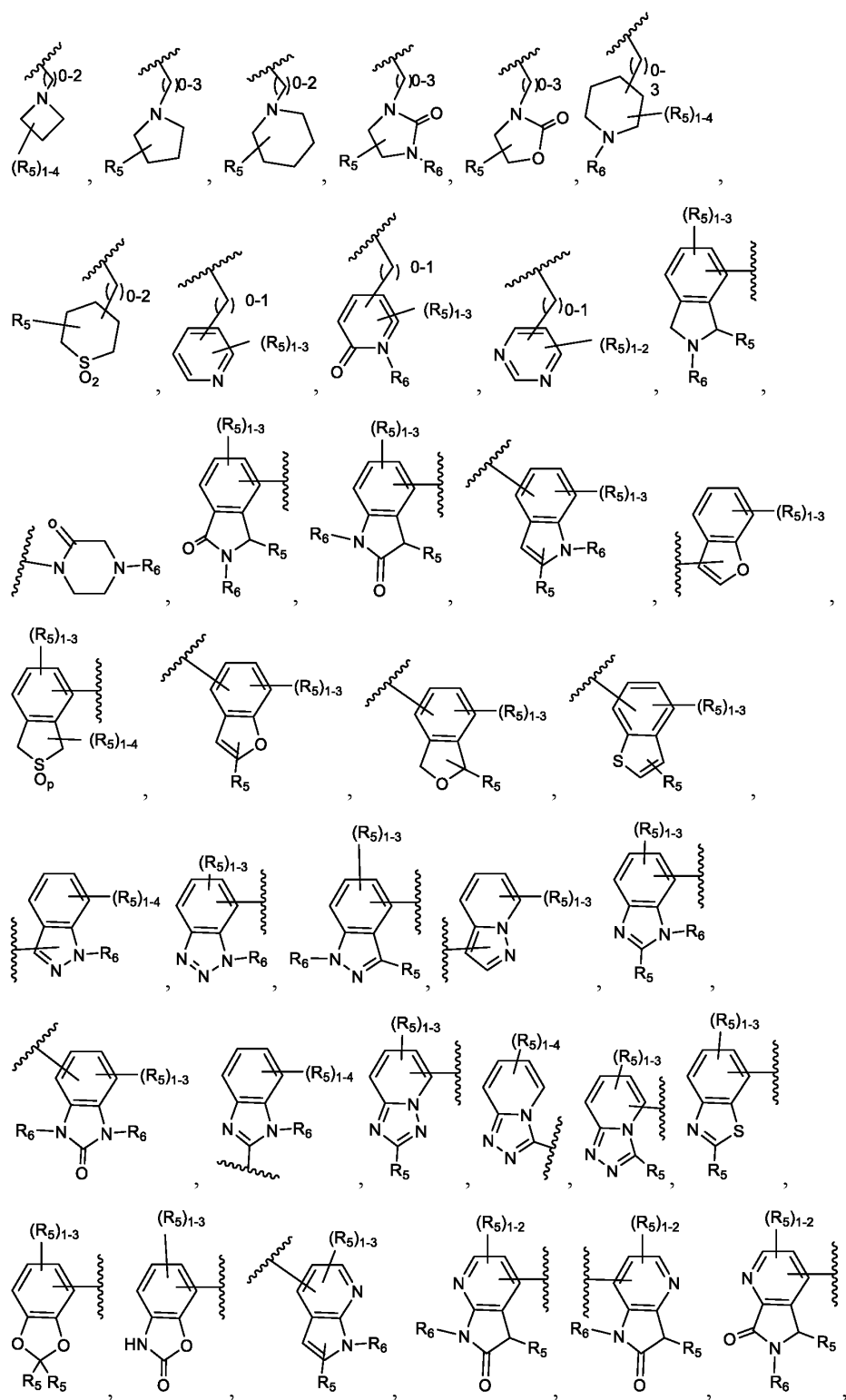
R_c is C_{1-4} alkyl; and

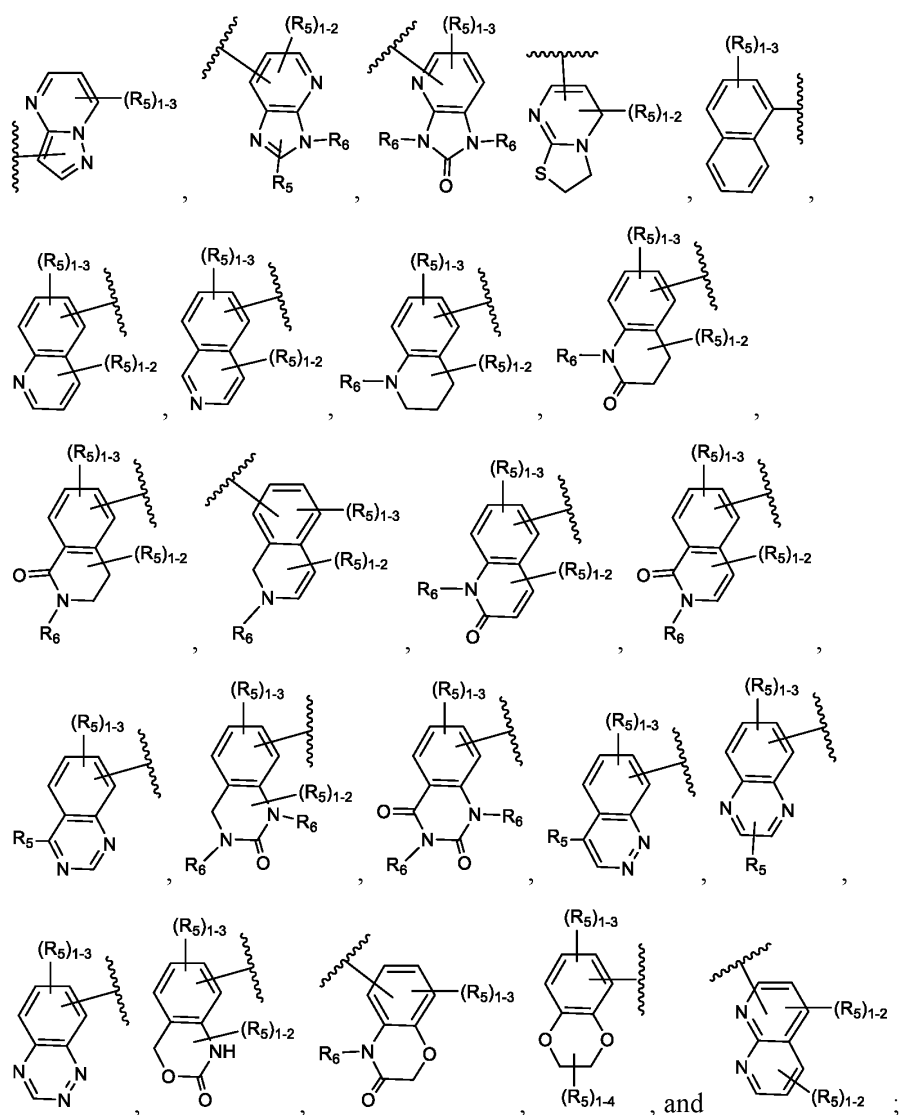
10 r , at each occurrence, is independently selected from zero, 1, and 2.

6. The compound according to claim 5, or a pharmaceutically acceptable salt thereof, wherein:

R_4 is independently selected from H, F, Cl, C_{1-5} alkyl optionally substituted with one or





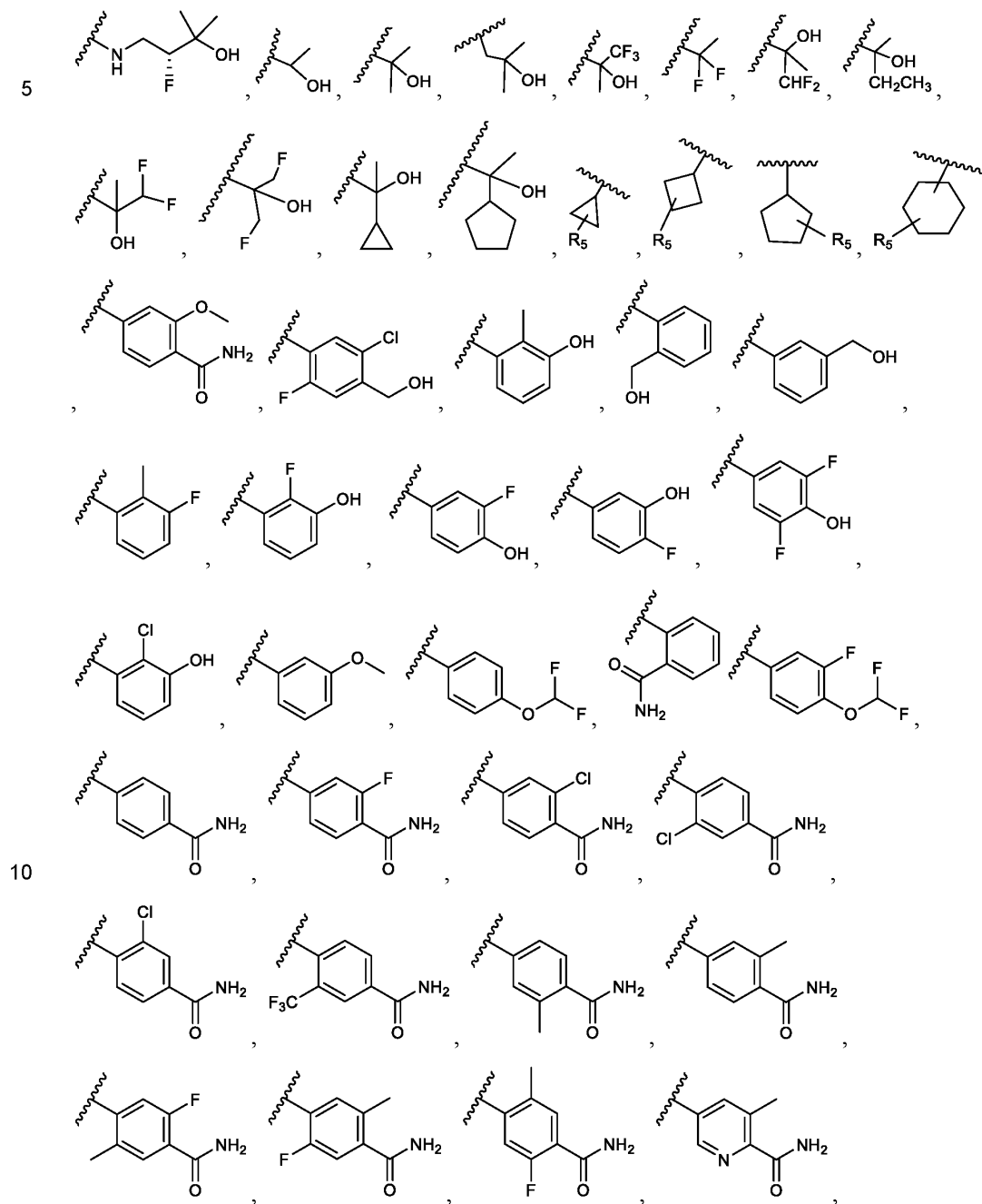


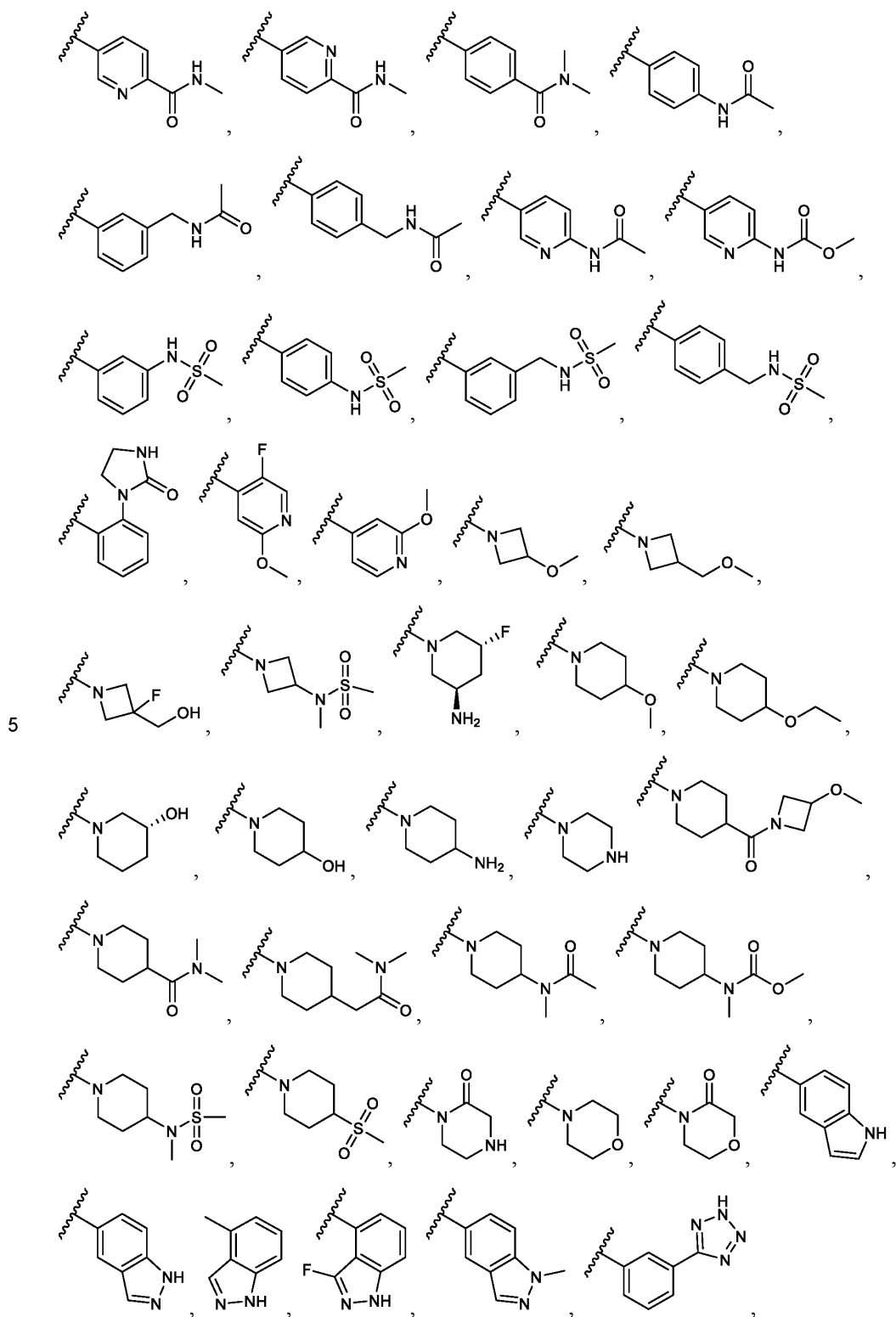
R_5 is independently selected from H, F, Cl, =O, C_{1-4} alkyl optionally substituted with one or more R_e , $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rC(=O)NR_aR_a$, $-(CH_2)_rOC(=O)R_b$, $-(CH_2)_rOC(=O)OR_b$, $-(CH_2)_rO(CH_2)_rC(=O)NR_aR_a$, C_{3-6} cycloalkyl optionally substituted with one or more R_e , aryl optionally substituted with one or more R_e , and heterocyclyl optionally substituted with one or more R_e ; and

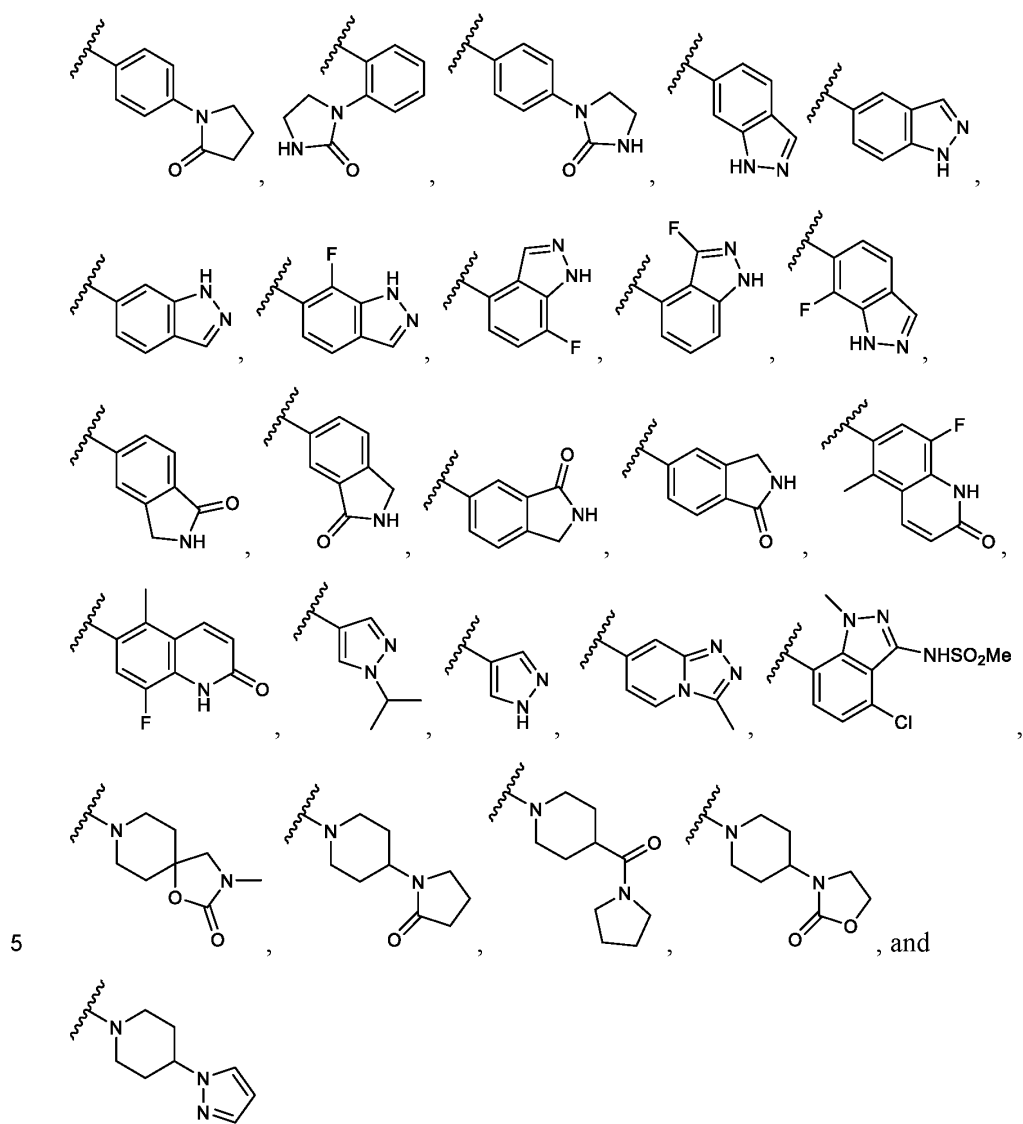
R_6 is independently selected from H and C_{1-5} alkyl.

7. The compound according to claim 6, or a pharmaceutically acceptable salt thereof, wherein:

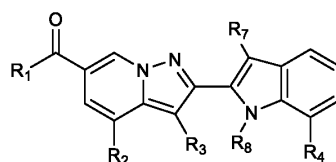
R_4 is independently selected from





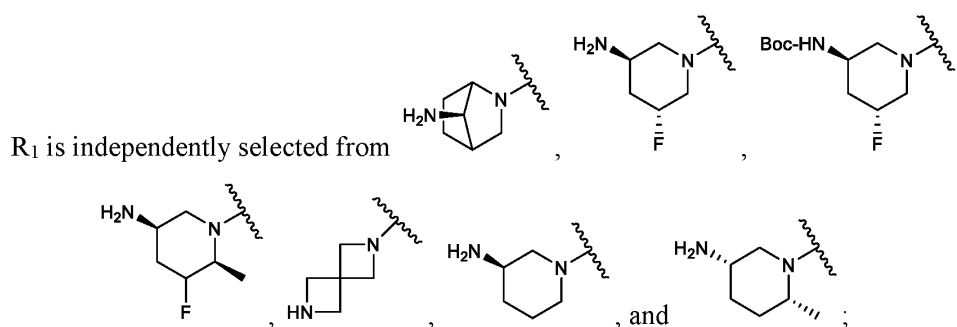


8. The compound according to claim 1, having Formula (IVa):



(IVa)

or a pharmaceutically acceptable salt thereof, wherein:



R₂ is independently selected from H, F, Cl, C₁₋₃ alkyl optionally substituted with one or more substituents selected from F, Cl, and OH, and OC₁₋₃ alkyl;

5 R₃ is independently selected from H, F, Cl, and C₁₋₃ alkyl optionally substituted with one or more substituents selected from F, Cl, and OH;

R₄ is independently selected from H, F, Cl, -C(=O)R_b, C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C₃₋₆ cycloalkyl, -NH-C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C₃₋₆ cycloalkyl, -(CH₂)_r-aryl substituted with one or more R₅, -O-C₁₋₆ alkyl substituted with one or more R₅, -(CH₂)_r-C₃₋₁₂ cycloalkyl substituted with one or more R₅, and -(CH₂)_r-4-10 membered heterocyclyl comprising carbon atoms and 1-5 heteroatoms selected from N, NR₆, O, and S and substituted with one or more R₅;

15 R₅ is independently selected from H, F, Cl, =O, C₁₋₄ alkyl optionally substituted with one or more R_e, -(CH₂)_rOR_b, -(CH₂)_rS(O)_pR_c, -(CH₂)_rS(O)_pNR_aR_a, -(CH₂)_rNR_aS(O)_pR_c, -(CH₂)_rNR_aR_a, -(CH₂)_rNR_aC(=O)R_b, -(CH₂)_rNR_aC(=O)OR_b, -(CH₂)_rNR_aC(=O)NR_aR_a, -(CH₂)_rC(=O)R_b, -(CH₂)_rC(=O)OR_b, -(CH₂)_rC(=O)NR_aR_a, -(CH₂)_rOC(=O)R_b, -(CH₂)_rOC(=O)OR_b, -(CH₂)_rO(CH₂)_rC(=O)NR_aR_a, C₃₋₆ cycloalkyl optionally substituted with one or more R_e, aryl optionally substituted with one or more R_e, and heterocyclyl optionally substituted with one or more R_e;

20 R₆ is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more R_e, -S(O)_pR_c, -S(O)_pNR_aR_a, -C(=O)R_b, -C(=O)OR_b, -C(=O)NR_aR_a, C₃₋₆ cycloalkyl optionally substituted with one or more R_e, aryl optionally substituted with one or more R_e, and heterocyclyl optionally substituted with one or more R_e;

R₇ is independently selected from H, F, and Cl;

R_8 is independently selected from H, and C_{1-6} alkyl optionally substituted with one or more substituents selected from F, Cl, and C_{3-6} cycloalkyl;

R_a is independently selected from H, C_{1-6} alkyl optionally substituted with one or more

R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and –
 5 $(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_e ; or R_a and R_a
 together with the nitrogen atom to which they are both attached form a heterocyclic
 ring optionally substituted with one or more R_e ;

R_b is independently selected from H, C_{1-6} alkyl optionally substituted with one or more
 R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and –

10 $(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_e ;

R_c is independently selected from C_{1-6} alkyl optionally substituted with one or more R_e , –
 $(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ -
 heterocyclyl optionally substituted with one or more R_e ;

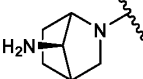
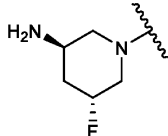
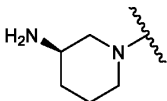
R_e is independently selected from F, Cl, Br, NH_2 , $-NH-C_{1-4}$ alkyl, $-N(C_{1-4}$ alkyl) $_2$, =O,
 15 OH, $-OC_{1-6}$ alkyl, C_{1-6} alkyl optionally substituted with one or more R_f , $-(CH_2)_r-C_{3-6}$
 cycloalkyl optionally substituted with one or more R_f , $-(CH_2)_r$ -aryl optionally
 substituted with one or more R_f , and $-(CH_2)_r$ -heterocyclyl optionally substituted
 with one or more R_f ;

R_f is independently selected from F, Cl, OH, OC_{1-5} alkyl, C_{1-5} alkyl optionally substituted
 20 with OH, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-6} cycloalkyl, and phenyl;

p , at each occurrence, is independently selected from zero, 1, and 2; and

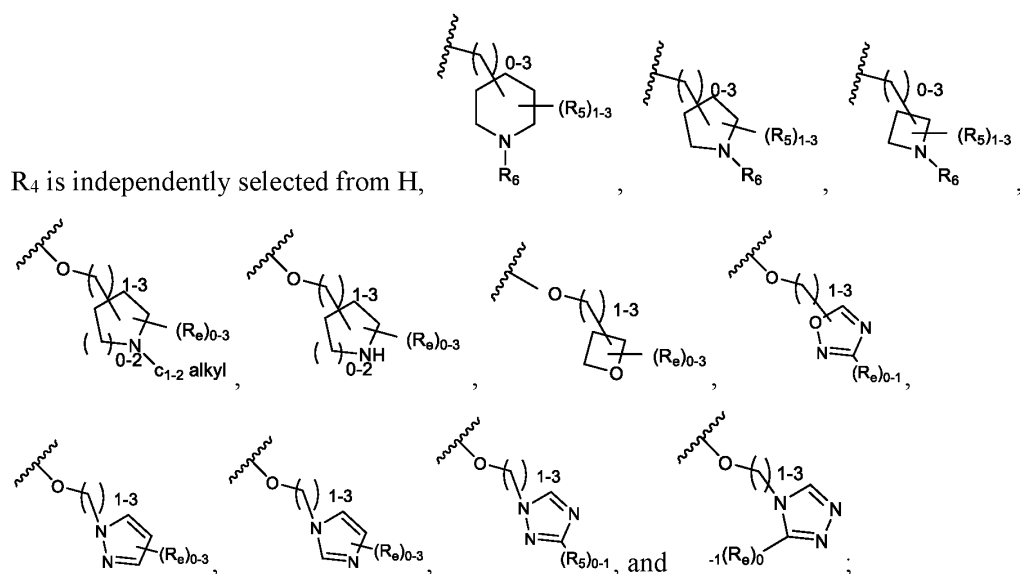
r , at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

9. The compound according to claim 8, or a pharmaceutically acceptable salt
 25 thereof, wherein:

R_1 is independently selected from , , and ;

R_2 is independently selected from H, F, Cl, and OCH_3 ;

R_3 is independently selected from F, Cl, and CH_3 ;



R₅ is independently selected from H, =O, C₁₋₄ alkyl, OH, and NH₂;

- 5 R₆ is independently selected from H, C₁₋₅ alkyl optionally substituted with one or more R_e, and -C(=O)R_b;

R_7 is H;

R₈ is C₁₋₂ alkyl optionally substituted with cyclopropyl;

R_b is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more

- 10 R_e , $-(CH_2)_r$ -C₃₋₁₀ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ heterocyclyl optionally substituted with one or more R_e ;

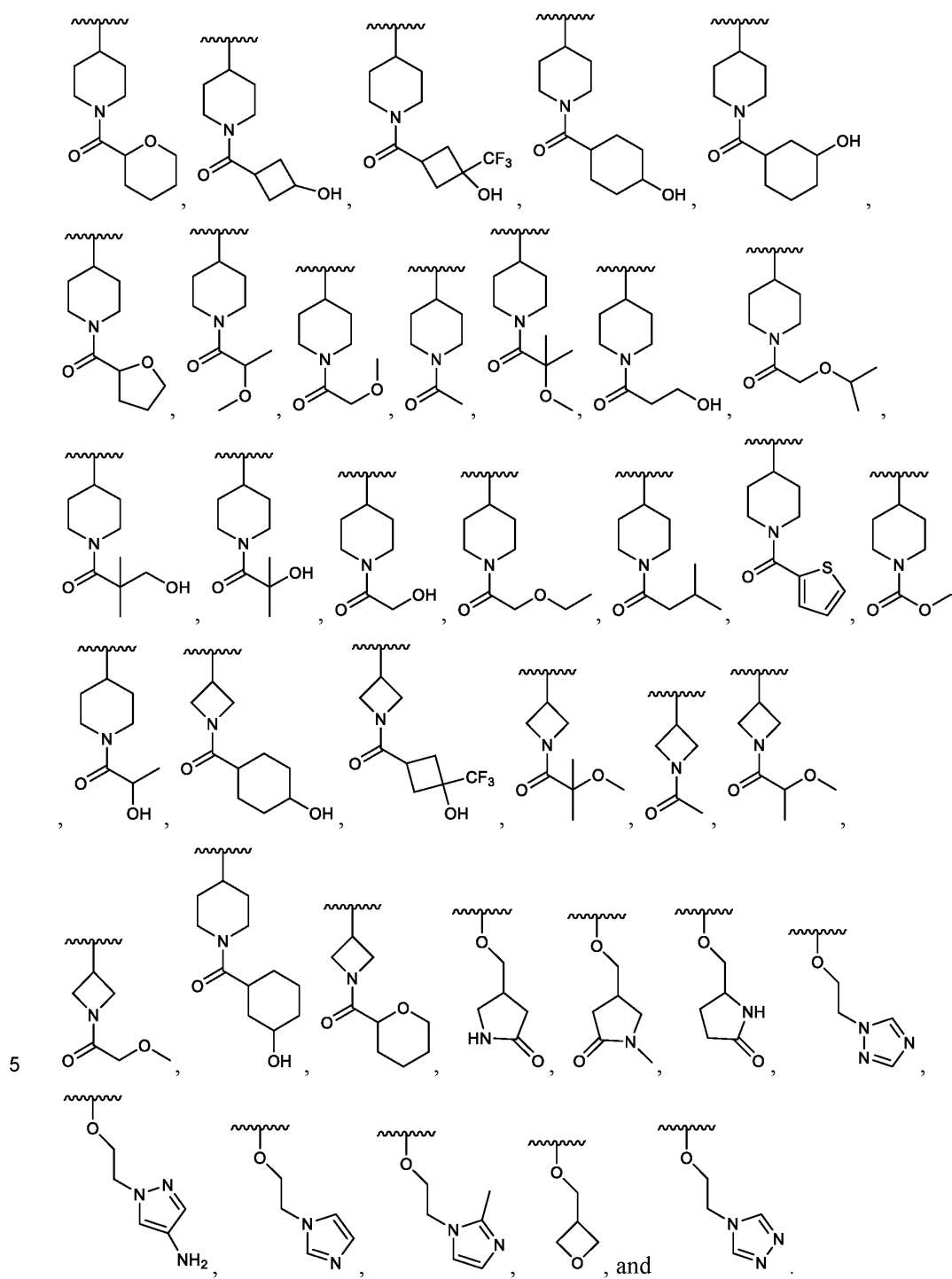
R_e is independently selected from NH₂ and C₁₋₅ alkyl optionally substituted with one or more R_f, and

R_f is independently selected from F, Cl, OH, and OC₁₋₅ alkyl.

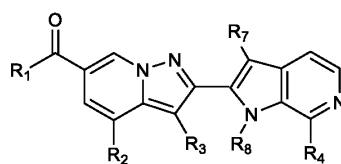
- 15

10. The compound according to claim 9, or a pharmaceutically acceptable salt thereof, wherein:

R_4 is independently selected from

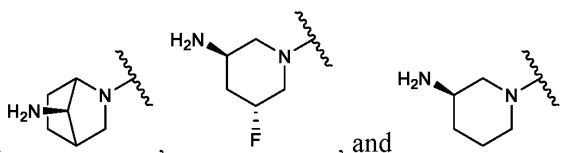


11. The compound according to claim 1, having Formula (Va):



(Va)

or a pharmaceutically acceptable salt thereof, wherein:



R₁ is independently selected from

5 R₂ is independently selected from H, F, Cl, CH₃, and OCH₃;

R₃ is independently selected from H, F, Cl, CN, CH₃, and CH₂OH;

R₄ is independently selected from H, F, Cl, -C(=O)R_b, C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C₃₋₆ cycloalkyl, -NH-C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C₃₋₆ cycloalkyl, -(CH₂)_r-aryl substituted with one or more R₅, -O-C₁₋₆ alkyl substituted with one or more R₅, -(CH₂)_r-C₃₋₁₂ cycloalkyl substituted with one or more R₅, and -(CH₂)_r-4-10 membered heterocyclyl comprising carbon atoms and 1-5 heteroatoms selected from N, NR₆, O, and S and substituted with one or more R₅;

15 R₅ is independently selected from H, F, Cl, =O, C₁₋₄ alkyl optionally substituted with one or more R_e, -(CH₂)_rOR_b, -(CH₂)_rS(O)_pR_c, -(CH₂)_rS(O)_pNR_aR_a, -(CH₂)_rNR_aS(O)_pR_c, -(CH₂)_rNR_aR_a, -(CH₂)_rNR_aC(=O)R_b, -(CH₂)_rNR_aC(=O)OR_b, -(CH₂)_rNR_aC(=O)NR_aR_a, -(CH₂)_rC(=O)R_b, -(CH₂)_rC(=O)OR_b, -(CH₂)_rC(=O)NR_aR_a, -(CH₂)_rOC(=O)R_b, -(CH₂)_rOC(=O)OR_b, -(CH₂)_rO(CH₂)_rC(=O)NR_aR_a, C₃₋₆ cycloalkyl optionally substituted with one or more R_e, aryl optionally substituted with one or more R_e, and heterocyclyl optionally substituted with one or more R_e;

20 R₆ is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more R_e, -C(=O)R_b, -C(=O)OR_b, -C(=O)NR_aR_a, C₃₋₆ cycloalkyl optionally substituted with one or more R_e, aryl optionally substituted with one or more R_e, and heterocyclyl optionally substituted with one or more R_e;

25 R₇ is independently selected from H, F, and Cl;

R_8 is independently selected from H, and C_{1-6} alkyl optionally substituted with one or more substituents selected from F, Cl, and C_{3-6} cycloalkyl;

R_a is independently selected from H, C_{1-6} alkyl optionally substituted with one or more

R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and –
 5 $(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_e ; or R_a and R_a
 together with the nitrogen atom to which they are both attached form a heterocyclic
 ring optionally substituted with one or more R_e ;

R_b is independently selected from H, C_{1-6} alkyl optionally substituted with one or more
 R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and –

10 $(CH_2)_r$ heterocyclyl optionally substituted with one or more R_e ;

R_c is independently selected from C_{1-6} alkyl optionally substituted with one or more R_e , –
 $(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ -
 heterocyclyl optionally substituted with one or more R_e ;

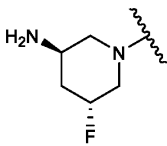
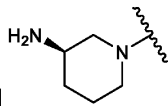
R_e is independently selected from F, Cl, Br, NH_2 , $-NH-C_{1-4}$ alkyl, $-N(C_{1-4}$ alkyl) $_2$, $=O$,
 15 OH, $-OC_{1-6}$ alkyl, $-CO_2H$, C_{1-6} alkyl optionally substituted with one or more R_f , –
 $(CH_2)_r-C_{3-6}$ cycloalkyl optionally substituted with one or more R_f , $-(CH_2)_r$ -aryl
 optionally substituted with one or more R_f , and $-(CH_2)_r$ -heterocyclyl optionally
 substituted with one or more R_f ;

R_f is independently selected from F, Cl, Br, CN, OH, C_{1-5} alkyl optionally substituted
 20 with OH, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-6} cycloalkyl, and phenyl;

p , at each occurrence, is independently selected from zero, 1, and 2; and

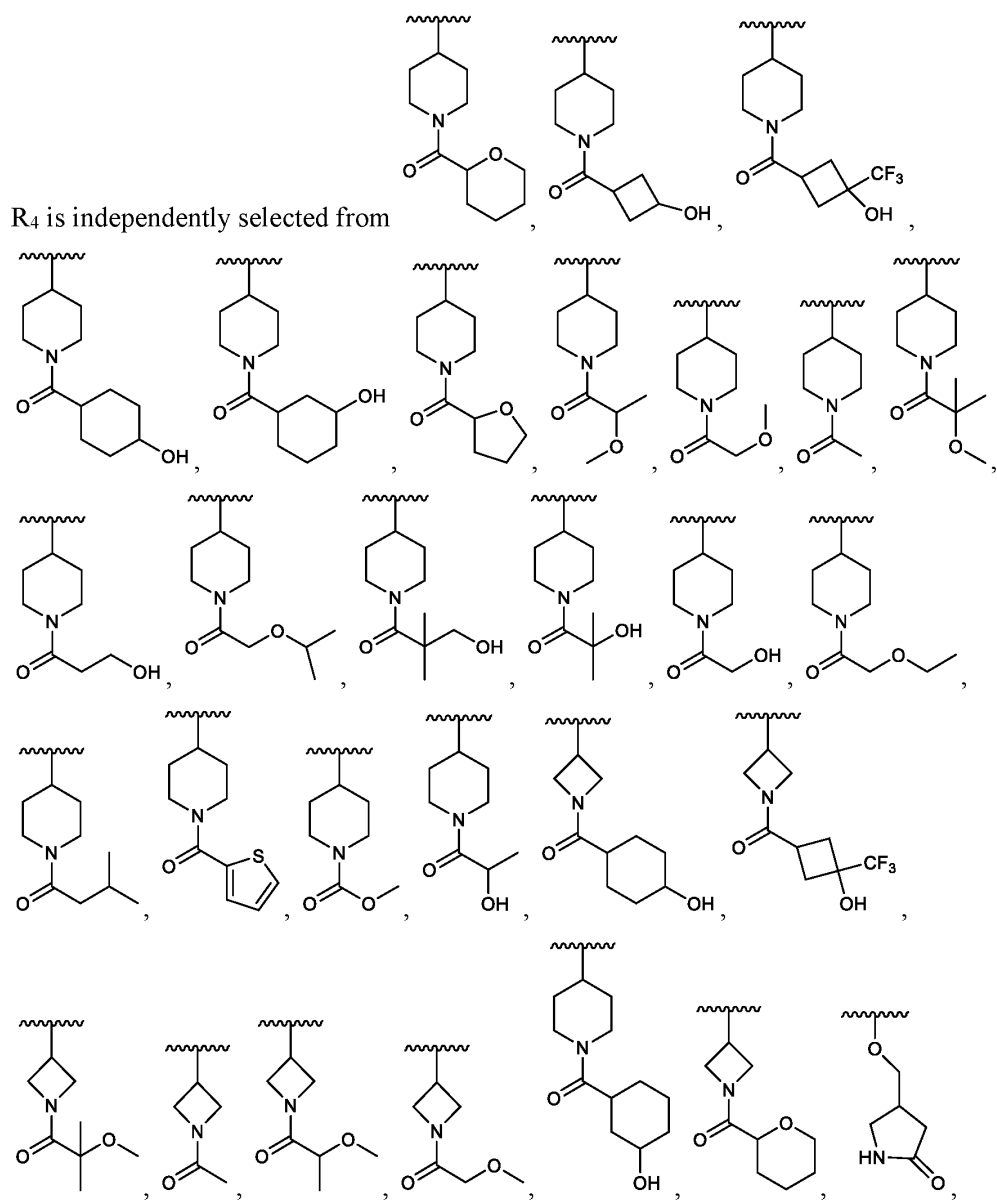
r , at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

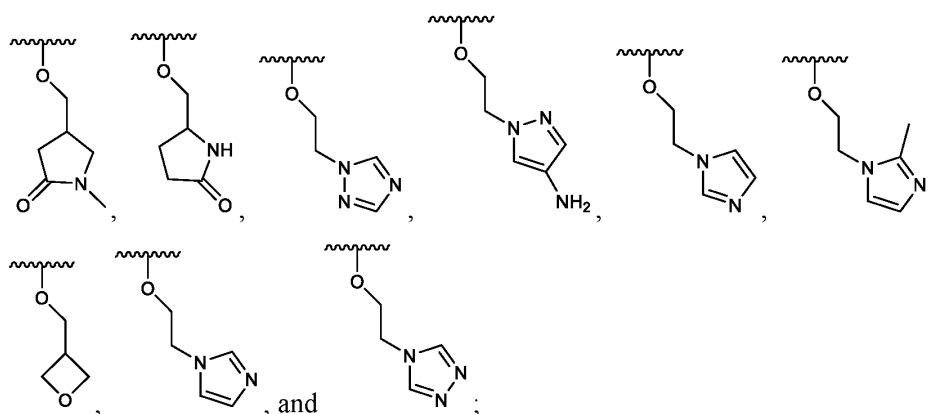
12. The compound according to claim 11, or a pharmaceutically acceptable
 25 salt thereof, wherein;

R_1 is independently selected from , and  ;

R_2 is CH_3 ;

R_3 is CH_3 ;



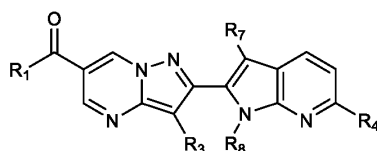


R₇ is H; and

R₈ is C₁₋₂ alkyl optionally substituted with cyclopropyl.

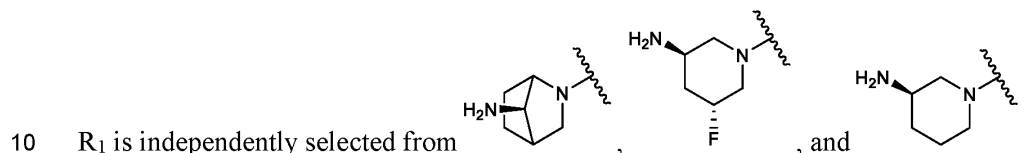
5

13. The compound according to claim 1, having Formula (VIa):



(VIa)

or a pharmaceutically acceptable salt thereof, wherein:



10 R₁ is independently selected from

R₃ is independently selected from H, F, and CH₃;

R₄ is independently selected from H, F, Cl, -C(=O)R_b, C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C₃₋₆ cycloalkyl, -NH-

15 C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C₃₋₆ cycloalkyl, -(CH₂)_r-aryl substituted with one or more R₅, -O-C₁₋₆ alkyl substituted with one or more R₅, -(CH₂)_r-C₃₋₁₂ cycloalkyl substituted with one or more R₅, and -(CH₂)_r-4-10 membered heterocyclyl comprising carbon atoms and 1-5 heteroatoms selected from N, NR₆, O, and S and substituted with one or more R₅;

20 R₅ is independently selected from H, F, Cl, Br, CN, =O, C₁₋₄ alkyl optionally substituted with one or more R_e, C₂₋₄ alkenyl optionally substituted with one or more R_e, C₂₋₄

alkynyl optionally substituted with one or more R_e , $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rC(=O)NR_aR_a$, $-(CH_2)_rOC(=O)R_b$, $-(CH_2)_rOC(=O)OR_b$, $-(CH_2)_rO(CH_2)_rC(=O)NR_aR_a$, C_{3-6} cycloalkyl optionally substituted with one or more R_e , aryl optionally substituted with one or more R_e , and heterocyclyl optionally substituted with one or more R_e ;

R_6 is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , $-C(=O)R_b$, $-C(=O)OR_b$, $-C(=O)NR_aR_a$, C_{3-6} cycloalkyl optionally substituted with one or more R_e , aryl optionally substituted with one or more R_e , and heterocyclyl optionally substituted with one or more R_e ;

R_7 is independently selected from H, F, and Cl;

R_8 is independently selected from H, and C_{1-6} alkyl optionally substituted with one or more substituents selected from F, Cl, and C_{3-6} cycloalkyl;

R_a is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , C_{2-6} alkenyl optionally substituted with one or more R_e , C_{2-6} alkynyl optionally substituted with one or more R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_e ; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring optionally substituted with one or more R_e ;

R_b is independently selected from H, C_{1-6} alkyl optionally substituted with one or more R_e , C_{2-6} alkenyl optionally substituted with one or more R_e , C_{2-6} alkynyl optionally substituted with one or more R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ heterocyclyl optionally substituted with one or more R_e ;

R_c is independently selected from C_{1-6} alkyl optionally substituted with one or more R_e , C_{2-6} alkenyl optionally substituted with one or more R_e , C_{2-6} alkynyl optionally substituted with one or more R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_e ;

R_e is independently selected from F, Cl, Br, CN, NH_2 , $-NH-C_{1-4}$ alkyl, $-N(C_{1-4}$ alkyl) $_2$, $=O$, OH, $-OC_{1-6}$ alkyl, $-CO_2H$, C_{1-6} alkyl optionally substituted with one or more R_f ,

C₂₋₆ alkenyl, C₂₋₆ alkynyl, -(CH₂)_r-C₃₋₆ cycloalkyl optionally substituted with one or more R_f, -(CH₂)_r-aryl optionally substituted with one or more R_f, and -(CH₂)_r-heterocyclyl optionally substituted with one or more R_f;

R_f is independently selected from F, Cl, Br, CN, OH, C₁₋₅ alkyl optionally substituted

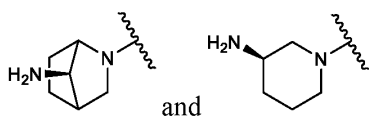
5 with OH, C₂₋₅ alkenyl, C₂₋₅ alkynyl, C₃₋₆ cycloalkyl, and phenyl;

p, at each occurrence, is independently selected from zero, 1, and 2; and

r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

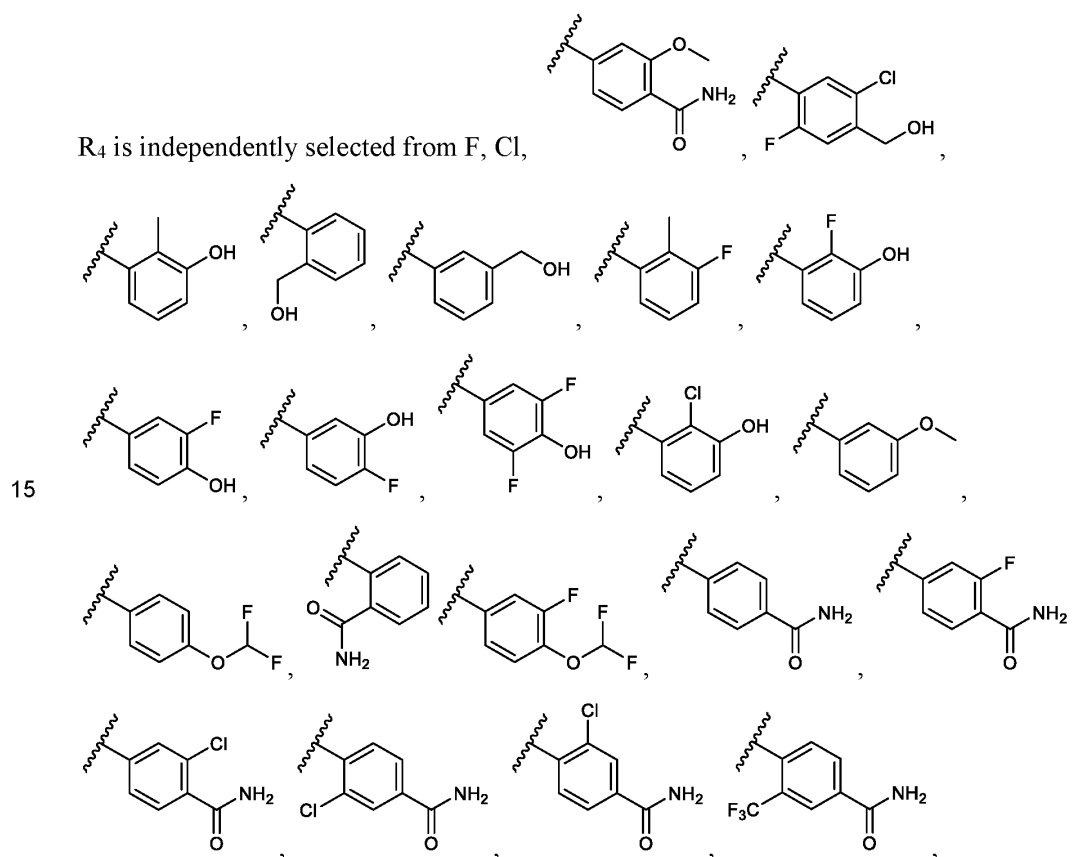
14. The compound according to claim 13, or a pharmaceutically acceptable salt thereof, wherein;

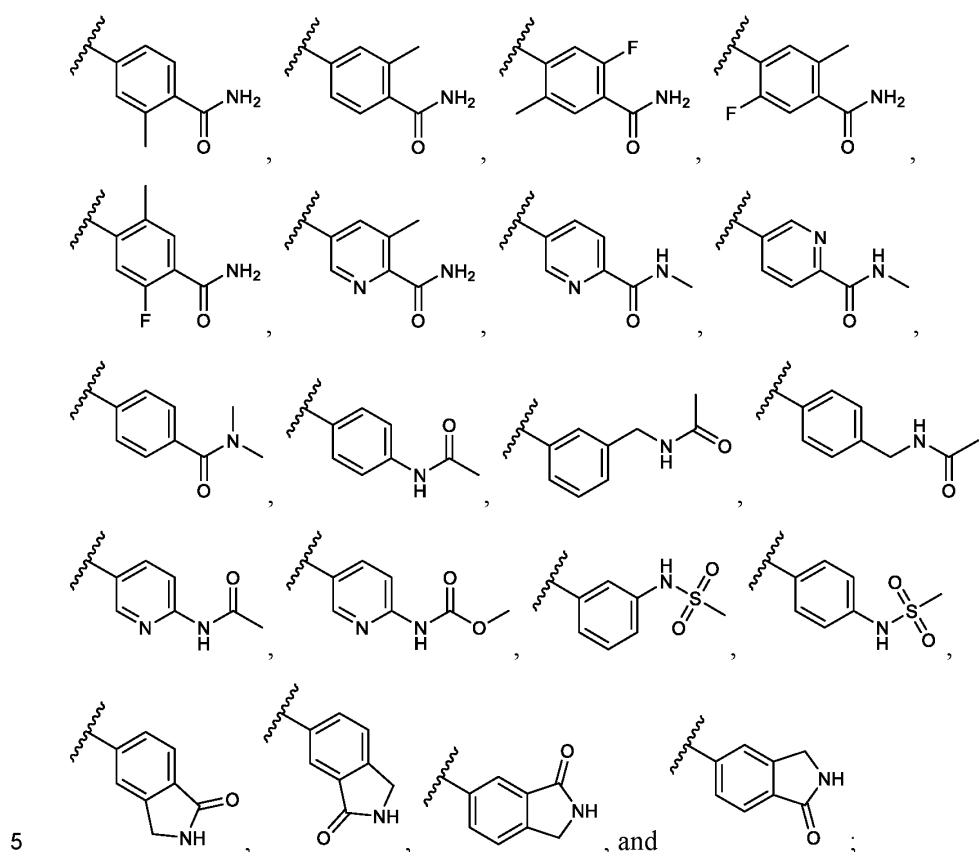
R₁ is independently selected from



R₃ is CH₃;

R₄ is independently selected from F, Cl,

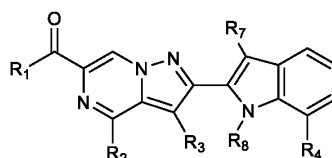




R₇ is H; and

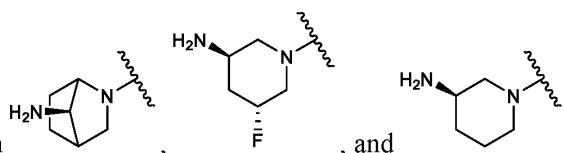
R₈ is C₁₋₂ alkyl optionally substituted with cyclopropyl.

15. The compound according to claim 1, having Formula (VII):



(VII)

or a pharmaceutically acceptable salt thereof, wherein:



R_1 is independently selected from

R₂ is independently selected from H, F, Cl, CH₃, and OCH₃;

15 R_3 is independently selected from H, F, and CH_3 ;

- R₄ is independently selected from H, F, Cl, Br, -C(=O)R_b, C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C₃₋₆ cycloalkyl, -NH-C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C₃₋₆ cycloalkyl, -(CH₂)_r-aryl substituted with one or more R₅, -O-C₁₋₆ alkyl substituted with one or more R₅, -(CH₂)_r-C₃₋₁₂ cycloalkyl substituted with one or more R₅, and -(CH₂)_r-4-10 membered heterocyclyl comprising carbon atoms and 1-5 heteroatoms selected from N, NR₆, O, and S and substituted with one or more R₅;
- R₅ is independently selected from H, F, Cl, Br, CN, =O, C₁₋₄ alkyl optionally substituted with one or more R_e, C₂₋₄ alkenyl optionally substituted with one or more R_e, C₂₋₄ alkynyl optionally substituted with one or more R_e, -(CH₂)_rOR_b, -(CH₂)_rS(O)_pR_c, -(CH₂)_rS(O)_pNR_aR_a, -(CH₂)_rNR_aS(O)_pR_c, -(CH₂)_rNR_aR_a, -(CH₂)_rNR_aC(=O)R_b, -(CH₂)_rNR_aC(=O)OR_b, -(CH₂)_rNR_aC(=O)NR_aR_a, -(CH₂)_rC(=O)R_b, -(CH₂)_rC(=O)OR_b, -(CH₂)_rC(=O)NR_aR_a, -(CH₂)_rOC(=O)R_b, -(CH₂)_rOC(=O)OR_b, -(CH₂)_rO(CH₂)_rC(=O)NR_aR_a, C₃₋₆ cycloalkyl optionally substituted with one or more R_e, aryl optionally substituted with one or more R_e, and heterocyclyl optionally substituted with one or more R_e;
- R₆ is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more R_e, -S(O)_pR_c, -S(O)_pNR_aR_a, -C(=O)R_b, -C(=O)OR_b, -C(=O)NR_aR_a, C₃₋₆ cycloalkyl optionally substituted with one or more R_e, aryl optionally substituted with one or more R_e, and heterocyclyl optionally substituted with one or more R_e;
- R₇ is independently selected from H, F, and Cl;
- R₈ is independently selected from H, and C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, and C₃₋₆ cycloalkyl;
- R_a is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more R_e, C₂₋₆ alkenyl optionally substituted with one or more R_e, C₂₋₆ alkynyl optionally substituted with one or more R_e, -(CH₂)_r-C₃₋₁₀ carbocyclyl optionally substituted with one or more R_e, and -(CH₂)_r-heterocyclyl optionally substituted with one or more R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring optionally substituted with one or more R_e;
- R_b is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more R_e, C₂₋₆ alkenyl optionally substituted with one or more R_e, C₂₋₆ alkynyl optionally

substituted with one or more R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ heterocyclyl optionally substituted with one or more R_e ;

R_e is independently selected from C_{1-6} alkyl optionally substituted with one or more R_e , C_{2-6} alkenyl optionally substituted with one or more R_e , C_{2-6} alkynyl optionally substituted with one or more R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_e ;

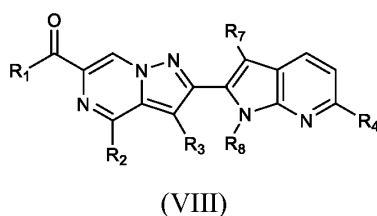
R_e is independently selected from F, Cl, Br, CN, NH_2 , $-NH-C_{1-4}$ alkyl, $-N(C_{1-4}$ alkyl) $_2$, $=O$, OH, $-OC_{1-6}$ alkyl, $-CO_2H$, C_{1-6} alkyl optionally substituted with one or more R_f , C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_r-C_{3-6}$ cycloalkyl optionally substituted with one or more R_f , $-(CH_2)_r$ -aryl optionally substituted with one or more R_f , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_f ;

R_f is independently selected from F, Cl, Br, CN, OH, C_{1-5} alkyl optionally substituted with OH, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-6} cycloalkyl, and phenyl;

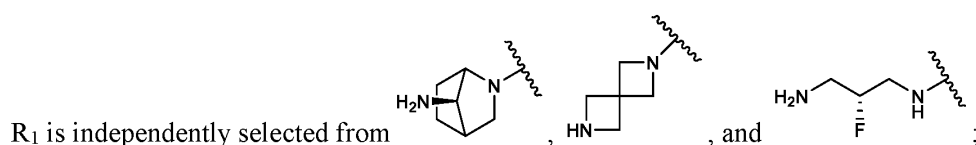
p , at each occurrence, is independently selected from zero, 1, and 2; and

r , at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

16. The compound according to claim 1, having Formula (VIII):



or a pharmaceutically acceptable salt thereof, wherein:



R_2 is independently selected from H, F, and OCH_3 ;

R_3 is independently selected from H, F, and CH_3 ;

R_4 is independently selected from H, F, Cl, Br, $-C(=O)R_b$, C_{1-6} alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C_{3-6} cycloalkyl, $-NH-C_{1-6}$ alkyl optionally substituted with one or more substituents selected from F, Cl,

OH, and C₃₋₆ cycloalkyl, $-(CH_2)_r$ -aryl substituted with one or more R₅, -O-C₁₋₆ alkyl substituted with one or more R₅, $-(CH_2)_r$ -C₃₋₁₂ cycloalkyl substituted with one or more R₅, and $-(CH_2)_r$ -4-10 membered heterocyclyl comprising carbon atoms and 1-5 heteroatoms selected from N, NR₆, O, and S and substituted with one or more R₅;

R₅ is independently selected from H, F, Cl, Br, CN, =O, C₁₋₄ alkyl optionally substituted with one or more R_e, C₂₋₄ alkenyl optionally substituted with one or more R_e, C₂₋₄ alkynyl optionally substituted with one or more R_e, $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rC(=O)NR_aR_a$, $-(CH_2)_rOC(=O)R_b$, $-(CH_2)_rOC(=O)OR_b$, $-(CH_2)_rO(CH_2)_rC(=O)NR_aR_a$, C₃₋₆ cycloalkyl optionally substituted with one or more R_e, aryl optionally substituted with one or more R_e, and heterocyclyl optionally substituted with one or more R_e;

R₆ is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more R_e, -C(=O)R_b, -C(=O)OR_b, -C(=O)NR_aR_a, C₃₋₆ cycloalkyl optionally substituted with one or more R_e, aryl optionally substituted with one or more R_e, and heterocyclyl optionally substituted with one or more R_e;

R₇ is independently selected from H, F, and Cl;

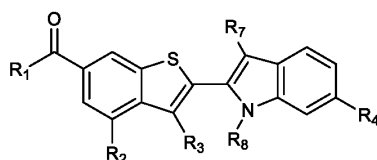
R₈ is independently selected from H, and C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, and C₃₋₆ cycloalkyl;

R_a is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more R_e, C₂₋₆ alkenyl optionally substituted with one or more R_e, C₂₋₆ alkynyl optionally substituted with one or more R_e, $-(CH_2)_r$ -C₃₋₁₀ carbocyclyl optionally substituted with one or more R_e, and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring optionally substituted with one or more R_e;

R_b is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more R_e, C₂₋₆ alkenyl optionally substituted with one or more R_e, C₂₋₆ alkynyl optionally substituted with one or more R_e, $-(CH_2)_r$ -C₃₋₁₀ carbocyclyl optionally substituted with one or more R_e, and $-(CH_2)_r$ heterocyclyl optionally substituted with one or more R_e;

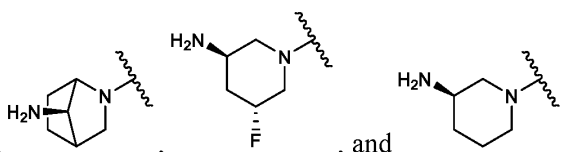
- R_c is independently selected from C_{1-6} alkyl optionally substituted with one or more R_e , C_{2-6} alkenyl optionally substituted with one or more R_e , C_{2-6} alkynyl optionally substituted with one or more R_e , $-(CH_2)_r-C_{3-10}$ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_e ;
- R_d is independently selected from H, and C_{1-6} alkyl optionally substituted with one or more R_e ;
- R_e is independently selected from F, Cl, Br, CN, NH_2 , $-NH-C_{1-4}$ alkyl, $-N(C_{1-4}$ alkyl) $_2$, $=O$, OH, $-OC_{1-6}$ alkyl, $-CO_2H$, C_{1-6} alkyl optionally substituted with one or more R_f , C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_r-C_{3-6}$ cycloalkyl optionally substituted with one or more R_f , $-(CH_2)_r$ -aryl optionally substituted with one or more R_f , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_f ;
- R_f is independently selected from F, Cl, Br, CN, OH, C_{1-5} alkyl optionally substituted with OH, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-6} cycloalkyl, and phenyl;
- p , at each occurrence, is independently selected from zero, 1, and 2; and
- r , at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

17. The compound according to claim 1, having Formula (IX):



(IX)

or a pharmaceutically acceptable salt thereof, wherein:



- R_1 is independently selected from , , and ;
- R_2 is independently selected from H, F, CH_3 , CH_2OH , CH_2CH_2OH , and OCH_3 ;
- R_3 is independently selected from H, F, Cl, CH_3 , CH_2OH , CH_2CH_2OH , CH_2NH_3 , $CH_2CH_2NH_2$, and $CH_2CH_2N_3$;
- R_4 is independently selected from H, F, Cl, Br, $-C(=O)R_b$, C_{1-6} alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C_{3-6} cycloalkyl, $-NH-$

C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C₃₋₆ cycloalkyl, $-(CH_2)_r$ -aryl substituted with one or more R₅, -O-C₁₋₆ alkyl substituted with one or more R₅, $-(CH_2)_r$ -C₃₋₁₂ cycloalkyl substituted with one or more R₅, and $-(CH_2)_r$ -4-10 membered heterocyclyl comprising carbon atoms and 1-5 heteroatoms selected from N, NR₆, O, and S and substituted with one or more R₅;

R₅ is independently selected from H, F, Cl, Br, CN, =O, C₁₋₄ alkyl optionally substituted with one or more R_e, C₂₋₄ alkenyl optionally substituted with one or more R_e, C₂₋₄ alkynyl optionally substituted with one or more R_e, $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rC(=O)NR_aR_a$, $-(CH_2)_rOC(=O)R_b$, $-(CH_2)_rOC(=O)OR_b$, $-(CH_2)_rO(CH_2)_rC(=O)NR_aR_a$, C₃₋₆ cycloalkyl optionally substituted with one or more R_e, aryl optionally substituted with one or more R_e, and heterocyclyl optionally substituted with one or more R_e;

R₆ is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more R_e, -S(O)_pR_c, -S(O)_pNR_aR_a, -C(=O)R_b, -C(=O)OR_b, -C(=O)NR_aR_a, C₃₋₆ cycloalkyl optionally substituted with one or more R_e, aryl optionally substituted with one or more R_e, and heterocyclyl optionally substituted with one or more R_e;

R₇ is independently selected from H, F, and Cl;

R₈ is independently selected from H, and C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, and C₃₋₆ cycloalkyl;

R_a is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more R_e, C₂₋₆ alkenyl optionally substituted with one or more R_e, C₂₋₆ alkynyl optionally substituted with one or more R_e, $-(CH_2)_r$ -C₃₋₁₀ carbocyclyl optionally substituted with one or more R_e, and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring optionally substituted with one or more R_e;

R_b is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more R_e, C₂₋₆ alkenyl optionally substituted with one or more R_e, C₂₋₆ alkynyl optionally substituted with one or more R_e, $-(CH_2)_r$ -C₃₋₁₀ carbocyclyl optionally substituted

with one or more R_e , and $-(CH_2)_r$ heterocyclyl optionally substituted with one or more R_e ;

R_e is independently selected from C_{1-6} alkyl optionally substituted with one or more R_e , C_{2-6} alkenyl optionally substituted with one or more R_e , C_{2-6} alkynyl optionally substituted with one or more R_e , $-(CH_2)_r$ - C_{3-10} carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_e ;

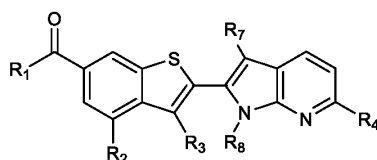
R_e is independently selected from F, Cl, Br, CN, NH_2 , $-NH-C_{1-4}$ alkyl, $-N(C_{1-4}$ alkyl) $_2$, $=O$, OH, $-OC_{1-6}$ alkyl, $-CO_2H$, C_{1-6} alkyl optionally substituted with one or more R_f , C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_r$ - C_{3-6} cycloalkyl optionally substituted with one or more R_f , $-(CH_2)_r$ -aryl optionally substituted with one or more R_f , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_f ;

R_f is independently selected from F, Cl, Br, CN, OH, C_{1-5} alkyl optionally substituted with OH, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-6} cycloalkyl, and phenyl;

p, at each occurrence, is independently selected from zero, 1, and 2; and

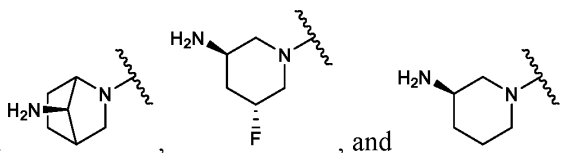
r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

18. The compound according to claim 1, having Formula (X):



(X)

or a pharmaceutically acceptable salt thereof, wherein:



R_1 is independently selected from , , and ;

R_2 is independently selected from H, FCH_3 , CH_2OH , CH_2CH_2OH , and OCH_3 ;

R_3 is independently selected from H, F, CH_3 , CH_2OH , CH_2CH_2OH , CH_2NH_3 ,

$CH_2CH_2NH_2$, and $CH_2CH_2N_3$;

R_4 is independently selected from H, F, Cl, Br, $-C(=O)R_b$, C_{1-6} alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C_{3-6} cycloalkyl, $-NH-$

C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C₃₋₆ cycloalkyl, $-(CH_2)_r$ -aryl substituted with one or more R₅, -O-C₁₋₆ alkyl substituted with one or more R₅, $-(CH_2)_r$ -C₃₋₁₂ cycloalkyl substituted with one or more R₅, and $-(CH_2)_r$ -4-10 membered heterocyclyl comprising carbon atoms and 1-5 heteroatoms selected from N, NR₆, O, and S and substituted with one or more R₅;

R₅ is independently selected from H, F, Cl, Br, CN, =O, C₁₋₄ alkyl optionally substituted with one or more R_e, C₂₋₄ alkenyl optionally substituted with one or more R_e, C₂₋₄ alkynyl optionally substituted with one or more R_e, $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rC(=O)NR_aR_a$, $-(CH_2)_rOC(=O)R_b$, $-(CH_2)_rOC(=O)OR_b$, $-(CH_2)_rO(CH_2)_rC(=O)NR_aR_a$, C₃₋₆ cycloalkyl optionally substituted with one or more R_e, aryl optionally substituted with one or more R_e, and heterocyclyl optionally substituted with one or more R_e;

R₆ is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more R_e, -S(O)_pR_c, -S(O)_pNR_aR_a, -C(=O)R_b, -C(=O)OR_b, -C(=O)NR_aR_a, C₃₋₆ cycloalkyl optionally substituted with one or more R_e, aryl optionally substituted with one or more R_e, and heterocyclyl optionally substituted with one or more R_e;

R₇ is independently selected from H, F, and Cl;

R₈ is independently selected from H, and C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, and C₃₋₆ cycloalkyl;

R_a is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more R_e, C₂₋₆ alkenyl optionally substituted with one or more R_e, C₂₋₆ alkynyl optionally substituted with one or more R_e, $-(CH_2)_r$ -C₃₋₁₀ carbocyclyl optionally substituted with one or more R_e, and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring optionally substituted with one or more R_e;

R_b is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more R_e, C₂₋₆ alkenyl optionally substituted with one or more R_e, C₂₋₆ alkynyl optionally substituted with one or more R_e, $-(CH_2)_r$ -C₃₋₁₀ carbocyclyl optionally substituted

with one or more R_e , and $-(CH_2)_r$ heterocyclyl optionally substituted with one or more R_e ;

R_e is independently selected from C_{1-6} alkyl optionally substituted with one or more R_e , C_{2-6} alkenyl optionally substituted with one or more R_e , C_{2-6} alkynyl optionally substituted with one or more R_e , $-(CH_2)_r$ - C_{3-10} carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_e ;

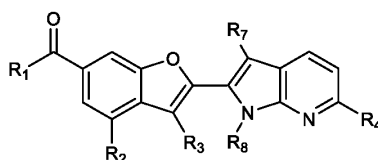
R_e is independently selected from F, Cl, Br, CN, NH_2 , $-NH-C_{1-4}$ alkyl, $-N(C_{1-4}$ alkyl) $_2$, $=O$, OH, $-OC_{1-6}$ alkyl, $-CO_2H$, C_{1-6} alkyl optionally substituted with one or more R_f , C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_r$ - C_{3-6} cycloalkyl optionally substituted with one or more R_f , $-(CH_2)_r$ -aryl optionally substituted with one or more R_f , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_f ;

R_f is independently selected from F, Cl, Br, CN, OH, C_{1-5} alkyl optionally substituted with OH, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-6} cycloalkyl, and phenyl;

p, at each occurrence, is independently selected from zero, 1, and 2; and

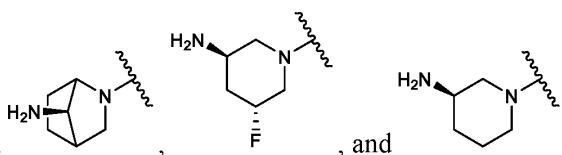
r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

19. The compound according to claim 1, having Formula (XI):



(XI)

or a pharmaceutically acceptable salt thereof, wherein:



R_1 is independently selected from , , and ;

R_2 is independently selected from H, F, CH_3 , CH_2OH , CH_2CH_2OH , and OCH_3 ;

R_3 is independently selected from H, F, CH_3 , CH_2OH , CH_2CH_2OH , CH_2NH_3 ,

$CH_2CH_2NH_2$, and $CH_2CH_2N_3$;

R_4 is independently selected from H, F, Cl, Br, $-C(=O)R_b$, C_{1-6} alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C_{3-6} cycloalkyl, $-NH-$

C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C₃₋₆ cycloalkyl, $-(CH_2)_r$ -aryl substituted with one or more R₅, -O-C₁₋₆ alkyl substituted with one or more R₅, $-(CH_2)_r$ -C₃₋₁₂ cycloalkyl substituted with one or more R₅, and $-(CH_2)_r$ -4-10 membered heterocyclyl comprising carbon atoms and 1-5 heteroatoms selected from N, NR₆, O, and S and substituted with one or more R₅;

R₅ is independently selected from H, F, Cl, Br, CN, =O, C₁₋₄ alkyl optionally substituted with one or more R_e, C₂₋₄ alkenyl optionally substituted with one or more R_e, C₂₋₄ alkynyl optionally substituted with one or more R_e, $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rC(=O)NR_aR_a$, $-(CH_2)_rOC(=O)R_b$, $-(CH_2)_rOC(=O)OR_b$, $-(CH_2)_rO(CH_2)_rC(=O)NR_aR_a$, C₃₋₆ cycloalkyl optionally substituted with one or more R_e, aryl optionally substituted with one or more R_e, and heterocyclyl optionally substituted with one or more R_e;

R₆ is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more R_e, -S(O)_pR_c, -S(O)_pNR_aR_a, -C(=O)R_b, -C(=O)OR_b, -C(=O)NR_aR_a, C₃₋₆ cycloalkyl optionally substituted with one or more R_e, aryl optionally substituted with one or more R_e, and heterocyclyl optionally substituted with one or more R_e;

R₇ is independently selected from H, F, and Cl;

R₈ is independently selected from H, and C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, and C₃₋₆ cycloalkyl;

R_a is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more R_e, C₂₋₆ alkenyl optionally substituted with one or more R_e, C₂₋₆ alkynyl optionally substituted with one or more R_e, $-(CH_2)_r$ -C₃₋₁₀ carbocyclyl optionally substituted with one or more R_e, and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring optionally substituted with one or more R_e;

R_b is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more R_e, C₂₋₆ alkenyl optionally substituted with one or more R_e, C₂₋₆ alkynyl optionally substituted with one or more R_e, $-(CH_2)_r$ -C₃₋₁₀ carbocyclyl optionally substituted

with one or more R_e , and $-(CH_2)_r$ heterocyclyl optionally substituted with one or more R_e ;

R_c is independently selected from C_{1-6} alkyl optionally substituted with one or more R_e , C_{2-6} alkenyl optionally substituted with one or more R_e , C_{2-6} alkynyl optionally substituted with one or more R_e , $-(CH_2)_r$ - C_{3-10} carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_e ;

R_d is independently selected from H, and C_{1-6} alkyl optionally substituted with one or more R_e ;

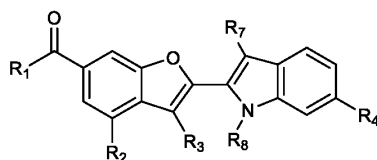
R_e is independently selected from F, Cl, Br, CN, NH_2 , $-NH-C_{1-4}$ alkyl, $-N(C_{1-4}$ alkyl) $_2$, $=O$, OH, $-OC_{1-6}$ alkyl, $-CO_2H$, C_{1-6} alkyl optionally substituted with one or more R_f , C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_r$ - C_{3-6} cycloalkyl optionally substituted with one or more R_f , $-(CH_2)_r$ -aryl optionally substituted with one or more R_f , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_f ;

R_f is independently selected from F, Cl, Br, CN, OH, C_{1-5} alkyl optionally substituted with OH, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-6} cycloalkyl, and phenyl;

p , at each occurrence, is independently selected from zero, 1, and 2; and

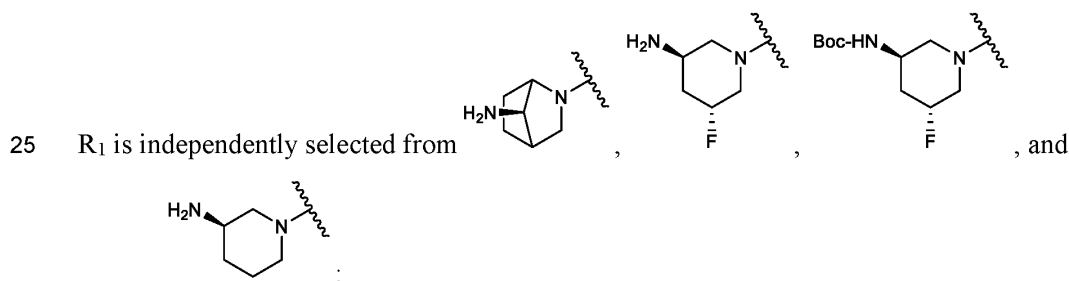
r , at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

20. The compound according to claim 1, having Formula (XII):



(XII)

or a pharmaceutically acceptable salt thereof, wherein:



R₂ is independently selected from H, F, CH₃, CH₂OH, CH₂CH₂OH and OCH₃;

R₃ is independently selected from H, F, and CH₃, CH₂OH, CH₂CH₂OH, CH₂NH₃,
CH₂CH₂NH₂, and CH₂CH₂N₃;

R₄ is independently selected from H, F, Cl, Br, -C(=O)R_b, C₁₋₆ alkyl optionally substituted
5 with one or more substituents selected from F, Cl, OH, and C₃₋₆ cycloalkyl, -NH-
C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl,
OH, and C₃₋₆ cycloalkyl, -(CH₂)_r-aryl substituted with one or more R₅, -O-C₁₋₆
alkyl substituted with one or more R₅, -(CH₂)_r-C₃₋₁₂ cycloalkyl substituted with one
or more R₅, and -(CH₂)_r-4-10 membered heterocyclyl comprising carbon atoms
10 and 1-5 heteroatoms selected from N, NR₆, O, and S and substituted with one or
more R₅;

R₅ is independently selected from H, F, Cl, Br, CN, =O, C₁₋₄ alkyl optionally substituted
with one or more R_e, C₂₋₄ alkenyl optionally substituted with one or more R_e, C₂₋₄
alkynyl optionally substituted with one or more R_e, -(CH₂)_rOR_b, -(CH₂)_rS(O)_pR_c, -
15 (CH₂)_rS(O)_pNR_aR_a, -(CH₂)_rNR_aS(O)_pR_c, -(CH₂)_rNR_aR_a, -(CH₂)_rNR_aC(=O)R_b, -
(CH₂)_rNR_aC(=O)OR_b, -(CH₂)_rNR_aC(=O)NR_aR_a, -(CH₂)_rC(=O)R_b, -
(CH₂)_rC(=O)OR_b, -(CH₂)_rC(=O)NR_aR_a, -(CH₂)_rOC(=O)R_b, -(CH₂)_rOC(=O)OR_b, -
(CH₂)_rO(CH₂)_rC(=O)NR_aR_a, C₃₋₆ cycloalkyl optionally substituted with one or more
R_e, aryl optionally substituted with one or more R_e, and heterocyclyl optionally
20 substituted with one or more R_e;

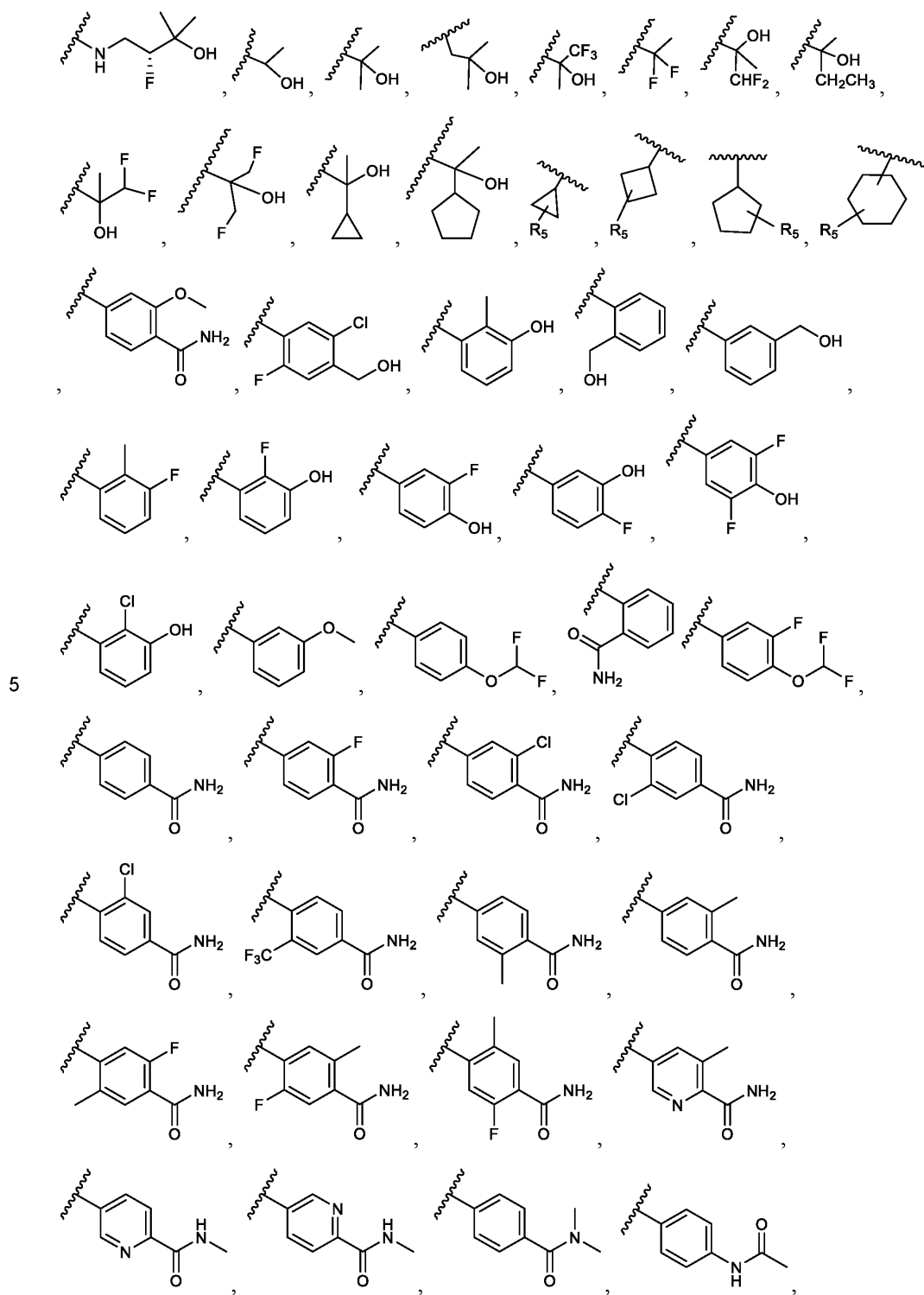
R₆ is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more
R_e, -S(O)_pR_c, -S(O)_pNR_aR_a, -C(=O)R_b, -C(=O)OR_b, -C(=O)NR_aR_a, C₃₋₆ cycloalkyl
optionally substituted with one or more R_e, aryl optionally substituted with one or
more R_e, and heterocyclyl optionally substituted with one or more R_e;

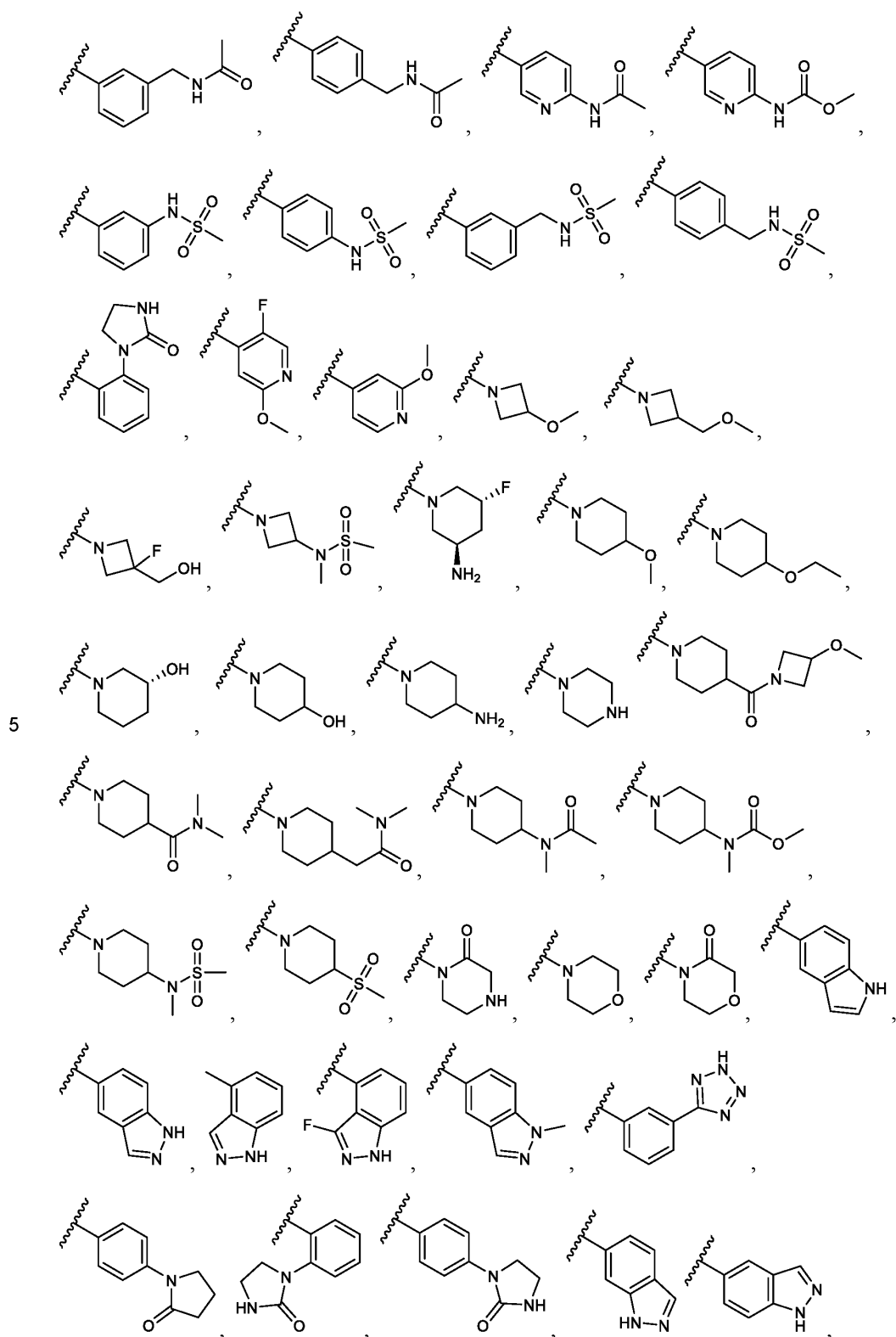
25 R₇ is independently selected from H, F, and Cl;

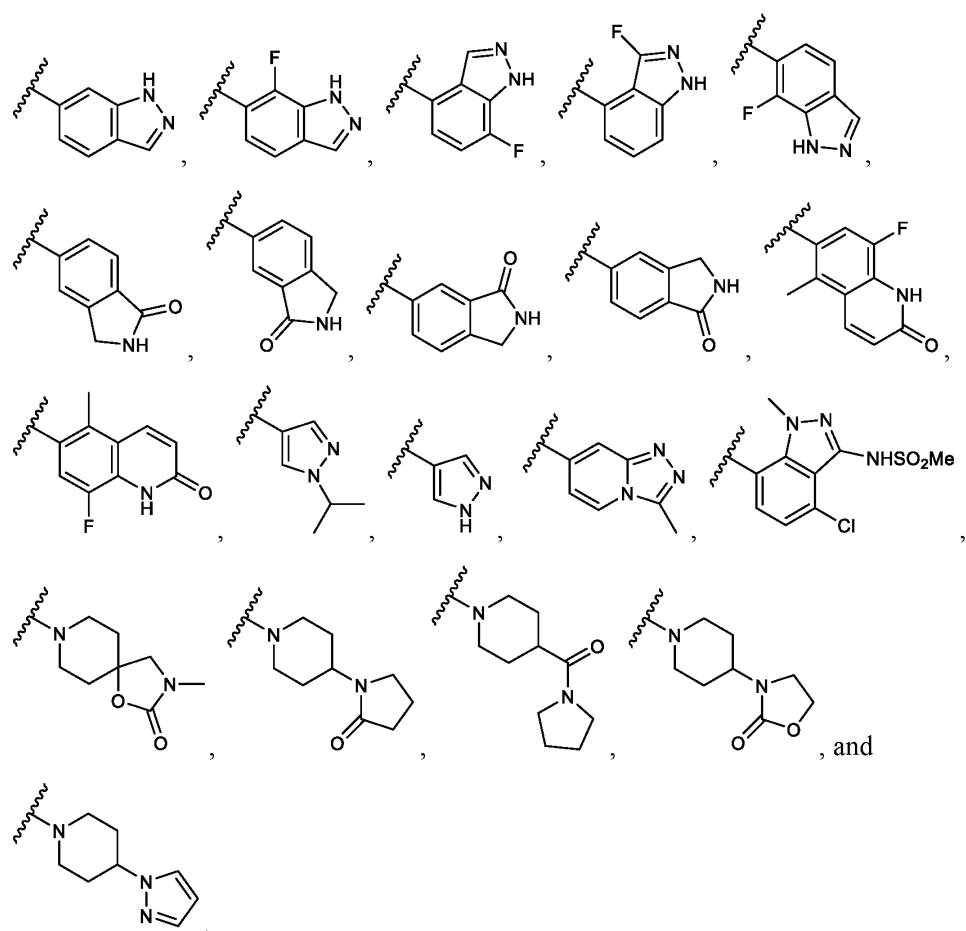
R₈ is independently selected from H, and C₁₋₆ alkyl optionally substituted with one or
more substituents selected from F, Cl, and C₃₋₆ cycloalkyl;

R_a is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more
R_e, C₂₋₆ alkenyl optionally substituted with one or more R_e, C₂₋₆ alkynyl optionally
30 substituted with one or more R_e, -(CH₂)_r-C₃₋₁₀ carbocyclyl optionally substituted
with one or more R_e, and -(CH₂)_r-heterocyclyl optionally substituted with one or

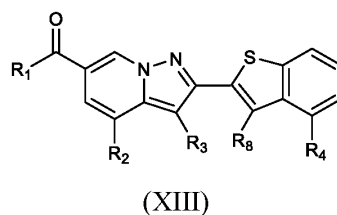
- more R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring optionally substituted with one or more R_e;
- R_b is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more R_e, C₂₋₆ alkenyl optionally substituted with one or more R_e, C₂₋₆ alkynyl optionally substituted with one or more R_e, $-(CH_2)_r$ -C₃₋₁₀ carbocyclyl optionally substituted with one or more R_e, and $-(CH_2)_r$ heterocyclyl optionally substituted with one or more R_e;
- R_c is independently selected from C₁₋₆ alkyl optionally substituted with one or more R_e, C₂₋₆ alkenyl optionally substituted with one or more R_e, C₂₋₆ alkynyl optionally substituted with one or more R_e, $-(CH_2)_r$ -C₃₋₁₀ carbocyclyl optionally substituted with one or more R_e, and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_e;
- R_d is independently selected from H, and C₁₋₆ alkyl optionally substituted with one or more R_e;
- R_e is independently selected from F, Cl, Br, CN, NH₂, -NH-C₁₋₄ alkyl, -N(C₁₋₄ alkyl)₂, =O, OH, -OC₁₋₆ alkyl, -CO₂H, C₁₋₆ alkyl optionally substituted with one or more R_f, C₂₋₆ alkenyl, C₂₋₆ alkynyl, $-(CH_2)_r$ -C₃₋₆ cycloalkyl optionally substituted with one or more R_f, $-(CH_2)_r$ -aryl optionally substituted with one or more R_f, and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_f;
- R_f is independently selected from F, Cl, Br, CN, OH, C₁₋₅ alkyl optionally substituted with OH, C₂₋₅ alkenyl, C₂₋₅ alkynyl, C₃₋₆ cycloalkyl, and phenyl;
- p, at each occurrence, is independently selected from zero, 1, and 2; and
- r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4.
21. The compound according to any one of claims 16-19, or a pharmaceutically acceptable salt thereof, wherein;
- R₄ is independently selected from H, F, Cl, Br,



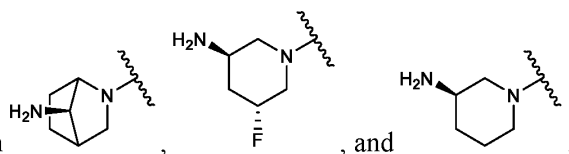




22. The compound according to claim 1, having Formula (XIII):



10 or a pharmaceutically acceptable salt thereof, wherein:



R₂ is independently selected from H, F, CH₃, and OCH₃;

R₃ is independently selected from H, F, and CH₃;

- R₄ is independently selected from H, F, Cl, Br, -C(=O)R_b, C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C₃₋₆ cycloalkyl, -NH-C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, OH, and C₃₋₆ cycloalkyl, -(CH₂)_r-aryl substituted with one or more R₅, -O-C₁₋₆ alkyl substituted with one or more R₅, -(CH₂)_r-C₃₋₁₂ cycloalkyl substituted with one or more R₅, and -(CH₂)_r-4-10 membered heterocyclyl comprising carbon atoms and 1-5 heteroatoms selected from N, NR₆, O, and S and substituted with one or more R₅;
- R₅ is independently selected from H, F, Cl, Br, CN, =O, C₁₋₄ alkyl optionally substituted with one or more R_e, C₂₋₄ alkenyl optionally substituted with one or more R_e, C₂₋₄ alkynyl optionally substituted with one or more R_e, -(CH₂)_rOR_b, -(CH₂)_rS(O)_pR_c, -(CH₂)_rS(O)_pNR_aR_a, -(CH₂)_rNR_aS(O)_pR_c, -(CH₂)_rNR_aR_a, -(CH₂)_rNR_aC(=O)R_b, -(CH₂)_rNR_aC(=O)OR_b, -(CH₂)_rNR_aC(=O)NR_aR_a, -(CH₂)_rC(=O)R_b, -(CH₂)_rC(=O)OR_b, -(CH₂)_rC(=O)NR_aR_a, -(CH₂)_rOC(=O)R_b, -(CH₂)_rOC(=O)OR_b, -(CH₂)_rO(CH₂)_rC(=O)NR_aR_a, C₃₋₆ cycloalkyl optionally substituted with one or more R_e, aryl optionally substituted with one or more R_e, and heterocyclyl optionally substituted with one or more R_e;
- R₆ is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more R_e, -S(O)_pR_c, -S(O)_pNR_aR_a, -C(=O)R_b, -C(=O)OR_b, -C(=O)NR_aR_a, C₃₋₆ cycloalkyl optionally substituted with one or more R_e, aryl optionally substituted with one or more R_e, and heterocyclyl optionally substituted with one or more R_e;
- R₇ is independently selected from H, F, and Cl;
- R₈ is independently selected from H, and C₁₋₆ alkyl optionally substituted with one or more substituents selected from F, Cl, and C₃₋₆ cycloalkyl;
- R_a is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more R_e, C₂₋₆ alkenyl optionally substituted with one or more R_e, C₂₋₆ alkynyl optionally substituted with one or more R_e, -(CH₂)_r-C₃₋₁₀ carbocyclyl optionally substituted with one or more R_e, and -(CH₂)_r-heterocyclyl optionally substituted with one or more R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring optionally substituted with one or more R_e;
- R_b is independently selected from H, C₁₋₆ alkyl optionally substituted with one or more R_e, C₂₋₆ alkenyl optionally substituted with one or more R_e, C₂₋₆ alkynyl optionally

substituted with one or more R_e , $-(CH_2)_r$ -C₃₋₁₀ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ heterocyclyl optionally substituted with one or more R_e ;

R_e is independently selected from C₁₋₆ alkyl optionally substituted with one or more R_e ,
 5 C₂₋₆ alkenyl optionally substituted with one or more R_e , C₂₋₆ alkynyl optionally substituted with one or more R_e , $-(CH_2)_r$ -C₃₋₁₀ carbocyclyl optionally substituted with one or more R_e , and $-(CH_2)_r$ -heterocyclyl optionally substituted with one or more R_e ;

R_d is independently selected from H, and C₁₋₆ alkyl optionally substituted with one or
 10 more R_e ;

R_e is independently selected from F, Cl, Br, CN, NH₂, $-NH$ -C₁₋₄ alkyl, $-N$ (C₁₋₄ alkyl)₂,
 $=O$, OH, $-OC$ ₁₋₆ alkyl, $-CO_2H$, C₁₋₆ alkyl optionally substituted with one or more R_f ,
 C₂₋₆ alkenyl, C₂₋₆ alkynyl, $-(CH_2)_r$ -C₃₋₆ cycloalkyl optionally substituted with one
 or more R_f , $-(CH_2)_r$ -aryl optionally substituted with one or more R_f , and $-(CH_2)_r$ -
 15 heterocyclyl optionally substituted with one or more R_f ;

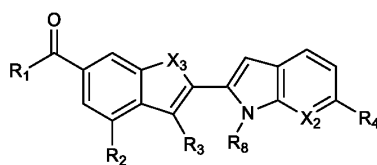
R_f is independently selected from F, Cl, Br, CN, OH, C₁₋₅ alkyl optionally substituted
 with OH, C₂₋₅ alkenyl, C₂₋₅ alkynyl, C₃₋₆ cycloalkyl, and phenyl;

p , at each occurrence, is independently selected from zero, 1, and 2; and

r , at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

20

23. The compound according to claim 1, having Formula (XIV):



(XIV)

or a pharmaceutically acceptable salt thereof, wherein:

25 X_2 is independently selected from CR₄ and N;

X_3 is independently selected from O and S;

R_1 is independently selected from , and ;

R₂ is independently selected from CH₂OH, CH₂CH₂OH and OCH₃;

R₃ is independently selected from CH₂OH, CH₂CH₂OH, CH₂NH₂, CH₂CH₂NH₂, and CH₂CH₂N₃;

R₄ is independently selected from H and -O-C₁₋₄ alkyl substituted with one or more R₅;

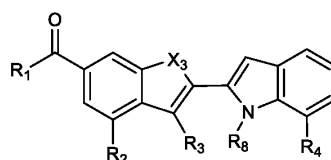
5 provided R₄ is not both -O-C₁₋₄ alkyl substituted with one or more R₅;

R₅ is independently selected from OH and heterocyclyl optionally substituted with one or more R_e;

R₈ is independently selected from H, and C₁₋₆ alkyl optionally substituted with C₃₋₆ cycloalkyl; and

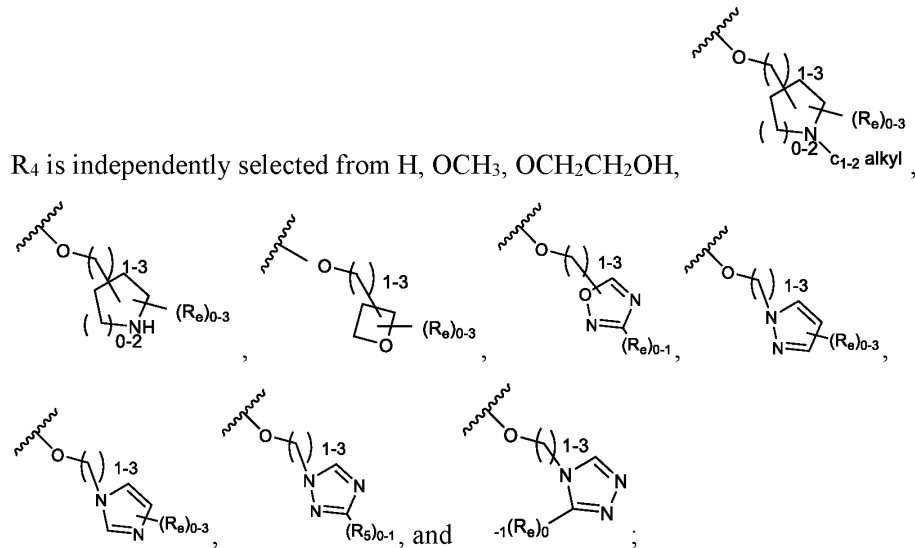
10 R_e is independently selected from NH₂ and C₁₋₃ alkyl.

24. The compound according to claim 23, having Formula (XV):

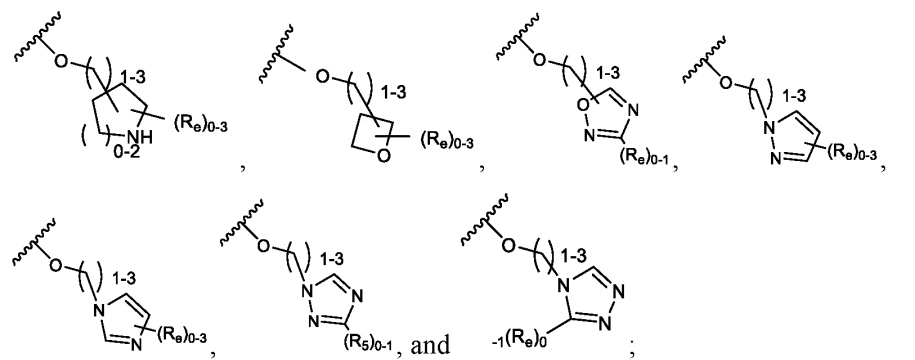


(XV)

15 or a pharmaceutically acceptable salt thereof, wherein:



R₄ is independently selected from H, OCH₃, OCH₂CH₂OH,



R₈ is C₁₋₃ alkyl substituted with C₃₋₆ cycloalkyl; and

20 R_e is independently selected from NH₂ and C₁₋₂ alkyl.

25. The compound according to claim 1, selected from:

5-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]-heptane-2-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one;

5 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-cyclopropyl-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

5-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one;

10 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-methyl-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

3((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

5-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one;

6-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one;

25 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-fluoro-3-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)-1H-indol-2-yl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

6-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one;

5 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-fluoro-4-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-fluoro-3-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

10 4-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorobenzamide;

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

15 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-cyclopropyl-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

20 6-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one;

5-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one;

25 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-hydroxypropan-2-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

30 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-(2-hydroxypropan-2-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-hydroxypropan-2-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(1,1,1-trifluoro-2-hydroxypropan-2-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

5 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-hydroxypropan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(1,1,1-trifluoro-2-hydroxypropan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

10 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(1-hydroxyethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-(4-aminopiperidin-1-yl)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylbenzo[b]thiophen-6-yl)methanone;

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-(4-aminopiperidin-1-yl)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylbenzofuran-6-yl)methanone;

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylbenzofuran-6-yl)methanonecyclopropylmethyl)-1H-indol-6-yl)isoindolin-1-one;

20 5-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)isoindolin-1-one;

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone;

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-methyl-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone;

30 4-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylbenzofuran-2-yl)-1-(cyclopropylmethyl)-1H-indol-6-yl)-2-fluorobenzamide;

((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-methoxypyridin-4-yl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone;

- ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(4-methoxypiperidin-1-yl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone;
- ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-(4-aminopiperidin-1-yl)-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone;
- 5 ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-hydroxypropan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-4-methoxy-3-methylbenzofuran-6-yl)methanone;
- ((7R)-7-Amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-(2-hydroxypropan-2-yl)-1H-indol-2-yl)-3-methylbenzofuran-6-yl)methanone;
- 10 N-[5-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)pyridin-2-yl]acetamide;
- (3R,5R)-1-{2-[1-(Cyclopropylmethyl)-6-(4-methanesulfonylpiperidin-1-yl)-1H-indol-2-yl]-4-methoxy-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-5-fluoropiperidin-3-
- 15 amine;
- 3-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-methylphenol;
- 5-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-fluoro-3-
- 20 methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-N-methylpyridine-2-carboxamide;
- 4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)morpholin-3-one;
- 25 (7R)-2-{2-[1-(Cyclopropylmethyl)-6-(4-methanesulfonylpiperidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine;
- (7R)-2-{2-[1-(Cyclopropylmethyl)-6-{3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl}-1H-indol-2-yl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-
- 30 azabicyclo[2.2.1]heptan-7-amine;

(7R)-2-{2-[1-(Cyclopropylmethyl)-6-(1H-indazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine;

3-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-methylphenol;

1-[4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)phenyl]pyrrolidin-2-one;

4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluoro-5-methylbenzamide;

(7R)-2-{2-[1-(Cyclopropylmethyl)-6-(7-fluoro-1H-indazol-6-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine;

Methyl N-[5-(2-{6-[(7R)-7-amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)pyridin-2-yl]carbamate;

4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)morpholin-3-one;

1-[4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]pyrrolidin-2-one;

(7R)-2-{2-[1-(Cyclopropylmethyl)-6-(1H-indazol-6-yl)-1H-indol-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine;

(7R)-2-{2-[1-(Cyclopropylmethyl)-6-(1H-indazol-5-yl)-1H-indol-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine;

N-[7-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-4-chloro-1-methyl-1H-indazol-3-yl]methanesulfonamide;

- 1-[2-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)phenyl]imidazolidin-2-one;
- 4-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)-2-chlorobenzamide;
- (7R)-2-{2-[1-(Cyclopropylmethyl)-6-(1H-pyrazol-4-yl)-1H-indol-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine;
- (7R)-2-{2-[1-(Cyclopropylmethyl)-6-(morpholin-4-yl)-1H-indol-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine;
- (3R,5R)-1-{2-[1-(Cyclopropylmethyl)-6-[4-(pyrrolidine-1-carbonyl)piperidin-1-yl]-1H-indol-2-yl]-3-methylpyrazolo[1,5-a]pyridine-6-carbonyl}-5-fluoropiperidin-3-amine;
- 3-[1-(2-{6-[(3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-indol-6-yl)piperidin-4-yl]-1,3-oxazolidin-2-one;
- 2-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-1,1-difluoropropan-2-ol;
- 2-(2-{6-[(7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-1,1,1-trifluoropropan-2-ol;
- ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(tetrahydro-2H-pyran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;
- ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxycyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;
- ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1r,4r)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

(R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxycyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

5 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(tetrahydrofuran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(tetrahydrofuran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

10 (R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxy-3-(trifluoromethyl)cyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxy-3-(trifluoromethyl)cyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

15 (R)-1-(4-(2-(6-(3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxyethan-1-one;

(S)-1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxypropan-1-one;

1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxyethan-1-one;

25 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1s,4s)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1r,4r)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-
((1r,4r)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-4-methoxy-3-
methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

1-(4-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-
5 methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-
yl)ethan-1-one;

(R)-1-(4-(2-(6-(3-Aminopiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-
a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)ethan-1-one;

(R)-1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-fluoro-3-
10 methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-
2-methoxypropan-1-one;

(R)-1-(4-(2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-fluoro-3-
methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-
2-methoxypropan-1-one;

15 1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-fluoro-3-
methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-
yl)ethan-1-one;

1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-fluoro-3-
methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-
20 2-methoxyethan-1-one;

1-(4-(2-(6-((3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl)-3-
methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-
2-hydroxyethan-1-one;

(R)-1-(4-(2-(6-(3-aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-
25 yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-hydroxyethan-1-one;

1-(4-(2-(6-((3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl)-3-
methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-
2-ethoxyethan-1-one;

((3R,5R)-3-amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-
30 ((1s,4s)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-
methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

((3R,5R)-3-amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1R,3S)-3-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

5 ((R)-3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1S,4S)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

((3R,5R)-3-amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1R,4R)-4-hydroxycyclohexane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

10 1-(4-(2-(6-((3R,5R)-3-amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)ethan-1-one;

15 1-(4-(2-(6-((7R)-7-amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-methoxyethan-1-one;

((R)-(3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxy-3-(trifluoromethyl)cyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

20 ((R)-3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(tetrahydro-2H-pyran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

((R)-3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-(tetrahydrofuran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

25 (4-(2-(6-((7R)-7-amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)(3-hydroxycyclobutyl)methanone;

Methyl 4-(2-(6-((7R)-7-amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidine-1-carboxylate;

30 (2R)-1-(4-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)-2-hydroxypropan-1-one;

(4-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)(thiophen-2-yl)methanone;

1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)ethan-1-one;

1-(4-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)ethan-1-one;

10 1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-7-yl)piperidin-1-yl)-3-methylbutan-1-one;

((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-(3-hydroxycyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

15 (R)-1-(4-(2-(6-((R)-3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-5-fluoro-1H-indol-7-yl)piperidin-1-yl)-2-methoxypropan-1-one;

((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-5-fluoro-7-(1-(tetrahydro-2H-pyran-2-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

1-(4-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)piperidin-1-yl)-2-methoxyethan-1-one;

25 ((3R,5R)-3-Amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1s,4s)-4-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

1-(3-(2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)-2-methoxyethan-1-one;

30

((R)-3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-(1-((1r,4r)-4-hydroxycyclohexane-1-carbonyl)azetidin-3-yl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)methanone;

1-(3-(2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)azetidin-1-yl)ethan-1-one;

4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one;

(R)-(2-(7-(2-(1H-1,2,4-Triazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)(3-aminopiperidin-1-yl)methanone;

(2-(7-(2-(1H-1,2,4-Triazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)((3R,5R)-3-amino-5-fluoropiperidin-1-yl)methanone;

(2-(7-(2-(4-Amino-1H-pyrazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-indol-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)((3R,5R)-3-amino-5-fluoropiperidin-1-yl)methanone;

4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one;

4-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one;

4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one;

4-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one;

(S)-5-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one;

4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-fluoro-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one;

- (2-(7-(2-(1H-Imidazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)((3R,5R)-3-amino-5-fluoropiperidin-1-yl)methanone;
- (2-(7-(2-(1H-1,2,4-Triazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)((3R,5R)-3-amino-5-fluoropiperidin-1-yl)methanone;
- 5 (S)-5-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one;
- 4-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)oxy)methyl)pyrrolidin-2-one;
- 10 4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one;
- (2-(7-(2-(1H-1,2,4-Triazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)((3R,5R)-3-amino-5-fluoropiperidin-1-yl)methanone;
- 15 (2-(7-(2-(1H-Imidazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)((3R,5R)-3-amino-5-fluoropiperidin-1-yl)methanone;
- (R)-(2-(7-(2-(1H-Imidazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)(3-aminopiperidin-1-yl)methanone;
- 20 (R)-(2-(7-(2-(4H-1,2,4-Triazol-4-yl)ethoxy)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)(3-aminopiperidin-1-yl)methanone;
- (R)-(2-(7-(2-(4H-1,2,4-Triazol-4-yl)ethoxy)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)((3R,5R)-3-amino-5-fluoropiperidin-1-yl)methanone;
- 25 (2-(7-(2-(4H-1,2,4-Triazol-4-yl)ethoxy)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-6-yl)((3R,5R)-3-amino-5-fluoropiperidin-1-yl)methanone;
- 4-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one;
- 30

4-(((2-(6-((3R,5R)-3-Amino-5-fluoropiperidine-1-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one;

(5R)-5-(((2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one;

4-(((2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one;

(5R)-5-(((2-(6-((7S)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one;

4-(((2-(6-((7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-4-methoxy-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one;

(R)-(2-(7-(2-(4H-1,2,4-Triazol-4-yl)ethoxy)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)(3-aminopiperidin-1-yl)methanone;

(2-(7-(2-(1H-Imidazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)((3R,5R)-3-amino-5-fluoropiperidin-1-yl)methanone;

(R)-(2-(7-(2-(1H-Imidazol-1-yl)ethoxy)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-3-methylpyrazolo[1,5-a]pyridin-6-yl)(3-aminopiperidin-1-yl)methanone;

4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one;

4-(((2-(6-((R)-3-Aminopiperidine-1-carbonyl)-3-methylpyrazolo[1,5-a]pyridin-2-yl)-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-c]pyridin-7-yl)oxy)methyl)pyrrolidin-2-one;

or a pharmaceutically acceptable salt thereof.

26. A pharmaceutical composition comprising a compound according to any one of the claims 1-25, or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a

pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers.

27. A method for treating a disease or a disorder associated with PAD4
5 enzyme activity, comprising administering to a subject in need of such treatment a therapeutically effective amount of at least one compound according to any one of the claims 1-25, or a stereoisomer, an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof.

10 28. A method for treating a disease or a disorder associated with PAD4 enzyme activity, comprising administering to a subject in need of such treatment a therapeutically effective amount of a composition according to claim 26.

29. Use of a compound according to any one of claims 1-25, or a stereoisomer,
15 an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease or a disorder associated with PAD4 enzyme activity.

30. A compound according to any one of claims 1-25, or a stereoisomer, an
20 enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof, for use in therapy.

31. The method according to any one of claims 27-28 or the use according to
claim 29, wherein the disease or the disorder associated with PAD4 enzyme activity is
25 selected from rheumatoid arthritis, Alzheimer's disease, multiple sclerosis, lupus, Parkinson's disease, and cancer.