

S, and O, wherein the 4 to 6 membered monocyclic heterocyclic group is optionally substituted with 1 to 3 substituents independently selected from the group consisting of C₁₋₆ alkyl, C₁₋₃ alkoxy, -S-C₁₋₃ alkyl and -C₁₋₃ alkyl-C₁₋₃ alkoxy;

R² is selected from the group consisting of H, Cl, OMe, Me and F;

5 R³ is selected from the group consisting of H and F;

R⁴ is selected from the group consisting of H and F; and

R⁵ is selected from the group consisting of H, Me and F.

The disclosure also provides some crystalline forms of certain compounds, Form 1, Form 2, Form 2b, Form 3, and Form 4.

10 The invention also provides a pharmaceutical composition comprising a compound of the disclosure, or a pharmaceutically acceptable salt thereof, or a crystalline form of the disclosure, and a pharmaceutically-acceptable carrier.

The invention also provides a method of treating gastrointestinal inflammatory disease, in particular, ulcerative colitis, in a mammal, the method comprising
15 administering to the mammal a compound of the disclosure, or a pharmaceutically acceptable salt thereof, or a crystalline form of the disclosure, or a pharmaceutical composition of the disclosure.

In one aspect, there is provided the use of a compound as described herein, or a pharmaceutically acceptable salt thereof, or a crystalline form described herein for the
20 manufacture of a medicament for the treatment of a gastrointestinal inflammatory disease in a mammal.

The invention also provides a method of treating inflammatory diseases or disorders of the skin in a mammal, the method comprising applying a compound of the disclosure, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition
25 of the disclosure to the skin of the mammal.

In another aspect, there is provided the use of a compound as described herein or a pharmaceutically acceptable salt thereof, or a crystalline form described herein for the manufacture of a medicament for the treatment of an inflammatory skin disease in a mammal.

30 The invention also provides a method of treating cutaneous T-cell lymphoma in a mammal, the method comprising applying a pharmaceutical composition comprising a compound of the disclosure, or a pharmaceutically acceptable salt thereof, to the skin of the mammal.

In yet another aspect, there is provided the use of a compound as described herein, or a pharmaceutically acceptable salt thereof, or a crystalline form described herein, for
5 the manufacture of a medicament for the treatment of cutaneous T-cell lymphoma. In another aspect, the invention also provides a process described herein, which is useful for preparing the compounds of the disclosure.

The invention also provides a compound of the disclosure or a pharmaceutically acceptable salt thereof, as described herein for use in medical therapy, as well as the use
10 of a compound of the disclosure, or a pharmaceutically acceptable salt thereof, or a crystalline form thereof, in the manufacture of a formulation or medicament for treating a gastrointestinal inflammatory disease, or an inflammatory disease of the skin in a mammal.

may be incorporated into a compounds of the disclosure and a compound of formula (I), (II), (B), (C), compound 1, compound 3, compound 4, include, but are not limited to, ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{35}S , and ^{18}F . Of particular interest are compounds of the disclosure and compounds of formula (I), (II), (B), (C), compound 1, compound 3, and compound 4, enriched in tritium or carbon-14, which compounds can be used, for example, in tissue distribution studies. Also of particular interest are compounds of the disclosure and compounds of formula (I), (II), (B), (C), compound 1, compound 3, compound 4 enriched in deuterium especially at a site of metabolism, which compounds are expected to have greater metabolic stability. Additionally, of particular interest are compounds of the disclosure and compounds of formula (I), (II), (B), (C), compound 1, compound 3, compound 4, enriched in a positron emitting isotope, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , which compounds can be used, for example, in Positron Emission Tomography (PET) studies.

Definitions

When describing this invention including its various aspects and embodiments, the following terms have the following meanings, unless otherwise indicated.

The term "alkyl" means a monovalent saturated hydrocarbon group which may be linear or branched or combinations thereof. Unless otherwise defined, such alkyl groups typically contain from 1 to 10 carbon atoms. Representative alkyl groups include, by way of example, methyl (Me), ethyl (Et), n-propyl (n-Pr) or (nPr), isopropyl (i-Pr) or (iPr), n-butyl (n-Bu) or (nBu), sec-butyl, isobutyl, tert-butyl (t-Bu) or (tBu), n-pentyl, n-hexyl, 2,2-dimethylpropyl, 2-methylbutyl, 3-methylbutyl, 2-ethylbutyl, 2,2-dimethylpentyl, 2-propylpentyl, and the like.

The term "haloalkyl" refers to an alkyl group, as defined above, that is substituted by one or more halogen, e.g., trifluoromethyl, difluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo 2-fluoropropyl, 1,2-dibromoethyl, and the like.

When a specific number of carbon atoms are intended for a particular term, the number of carbon atoms is shown preceding the term. For example, the term " C_{1-3} alkyl" means an alkyl group having from 1 to 3 carbon atoms wherein the carbon atoms are in any chemically-acceptable configuration, including linear or branched configurations.

The term "alkoxy" means the monovalent group $-\text{O-alkyl}$, where alkyl is defined as above. Representative alkoxy groups include, by way of example, methoxy, ethoxy, propoxy, butoxy, and the like.

The term "pharmaceutically acceptable salt" means a salt that is acceptable for administration to a patient or a mammal, such as a human (e.g., salts having acceptable mammalian safety for a given dosage regime). Representative pharmaceutically acceptable salts include salts of acetic, ascorbic, benzenesulfonic, benzoic, 5 camphorsulfonic, citric, ethanesulfonic, edisylic, fumaric, gentisic, gluconic, glucuronic, glutamic, hippuric, hydrobromic, hydrochloric, isethionic, lactic, lactobionic, maleic, malic, mandelic, methanesulfonic, mucic, naphthalenesulfonic, naphthalene-1,5-disulfonic, naphthalene-2,6-disulfonic, nicotinic, nitric, orotic, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic and xinafoic acid, and the like.

10 The term "salt thereof" means a compound formed when the hydrogen of an acid is replaced by a cation, such as a metal cation or an organic cation and the like. For example, the cation can be a protonated form of a compound of formula (I), i.e. a form where one or more amino groups have been protonated by an acid. Typically, the salt is a pharmaceutically acceptable salt, although this is not required for salts of intermediate 15 compounds that are not intended for administration to a patient.

The term "amino-protecting group" means a protecting group suitable for preventing undesired reactions at an amino nitrogen. Representative amino-protecting groups include, but are not limited to, formyl; acyl groups, for example alkanoyl groups, such as acetyl and tri-fluoroacetyl; alkoxycarbonyl groups, such as *tert*-butoxycarbonyl 20 (Boc); arylmethoxycarbonyl groups, such as benzyloxycarbonyl (Cbz) and 9-fluorenylmethoxycarbonyl (Fmoc); arylmethyl groups, such as benzyl (Bn), trityl (Tr), and 1,1-di-(4'-methoxyphenyl)methyl; silyl groups, such as trimethylsilyl (TMS), triisopropylsilyl (TIPS), *tert*-butyldimethylsilyl (TBS or TBDMS), [2-(trimethylsilyl)-ethoxy]methyl (SEM); and the like. Numerous protecting groups, and their introduction 25 and removal, are described in T. W. Greene and P. G. M. Wuts, *Protecting Groups in Organic Synthesis*, Third Edition, Wiley, New York.

General Synthetic Procedures

Compounds of this disclosure, and intermediates thereof, can be prepared according to the following general methods and procedures using commercially-available 30 or routinely-prepared starting materials and reagents. The substituents and variables (e.g., A, X¹, X², R¹, R², R³, R^a, R^b etc.) used in the following schemes have the same meanings as those defined elsewhere herein unless otherwise indicated. Additionally, compounds having an acidic or basic atom or functional group may be used or may be produced as a salt unless otherwise indicated (in some cases, the use of a salt in a particular reaction will

ABX-464, PF-06700841, prednisolone, GLPG-0974, valganciclovir, ciclosporin, VB-201, tulinercept, MDGN-002, PTG-100, dexamethasone, GED-0507-34-Levo, bertilimumab, brazikumab, KHK-4083, rosiglitazone, mocravimod, sotrastaurin, KAG-308, PUR-0110, E-6007, balsalazide, basiliximab, LP-02, ASP-3291, Trichuris suis ova,
5 K(D)PT, midismase, DNVX-078, vatelizumab, alequel, low molecular weight heparin, metenkefalin, tridecactide, HMPL-004, SB-012, olsalazine, propionyl-L-carnitine, Clostridium butyricum and acemannan.

In another aspect, therefore, the invention provides a therapeutic combination for use in the treatment of gastrointestinal inflammatory disorders, the combination
10 comprising a compound of the disclosure, or a pharmaceutically acceptable salt thereof, and one or more other therapeutic agents useful for treating gastrointestinal inflammatory disorders, such as the ones illustrated above. For example, the invention provides a combination comprising a compound of the disclosure, or a pharmaceutically acceptable salt thereof, and one or more agents selected from aminosalicylates, steroids, systemic
15 immunosuppressants, anti-TNF α antibodies, anti-VLA-4 antibodies, anti-integrin $\alpha_4\beta_7$ antibodies, anti-bacterial agents, and anti-diarrheal medicines. Secondary agent(s), when included, are present in a therapeutically effective amount, i.e. in any amount that produces a therapeutically beneficial effect when co-administered with a compound of the disclosure or a pharmaceutically acceptable salt thereof.

20 Also provided, therefore, is a pharmaceutical composition comprising a compound of the disclosure, or a pharmaceutically acceptable salt thereof, or a crystalline form thereof, and one or more other therapeutic agents useful for treating gastrointestinal inflammatory disorders.

Further, in a method aspect, the invention provides a method of treating
25 gastrointestinal inflammatory disorders, the method comprising administering to the mammal a compound of the disclosure, or a pharmaceutically acceptable salt thereof, or a crystalline form thereof, and one or more other therapeutic agents useful for treating gastrointestinal inflammatory disorders.

When used in combination therapy, the agents may be formulated in a single
30 pharmaceutical composition, as disclosed above, or the agents may be provided in separate compositions that are administered simultaneously or at separate times, by the same or by different routes of administration. When administered separately, the agents are administered sufficiently close in time so as to provide a desired therapeutic effect. Such compositions can be packaged separately or may be packaged together as a kit. The

In one aspect, therefore, the invention provides a method of treating an inflammatory skin disease in a mammal (e.g., a human), the method comprising applying a pharmaceutical composition comprising a compound of the disclosure, or a pharmaceutically acceptable salt thereof, or a crystalline form thereof, and a
5 pharmaceutical carrier to the skin of the mammal. In one aspect, the inflammatory skin disease is atopic dermatitis.

Compounds of the disclosure, or a pharmaceutically acceptable salt thereof, or a crystalline form thereof, may also be used in combination with one or more compound useful to treat inflammatory skin diseases. In some embodiments, the one or more
10 compound is a steroid, Histamine H1 receptor antagonist, calcineurin inhibitor, IL-13 antagonist, PDE 4 inhibitor, G-protein coupled receptor-44 antagonist, IL-4 antagonist, 5-HT 1a receptor antagonist, 5-HT 2b receptor antagonist, Alpha 2 adrenoceptor agonist, cannabinoid CB1 receptor antagonist, CCR3 chemokine antagonist, collagenase inhibitor, cytosolic phospholipase A2 inhibitor, eotaxin ligand inhibitor, GATA 3 transcription
15 factor inhibitor, Histamine H4 receptor antagonist, IL-10 antagonist, IL-12 antagonist, IL-17 antagonist, IL-2 antagonist, IL-23 antagonist, IL-4 receptor modulator, IL-5 antagonist, immunoglobulin E antagonist, immunoglobulin E modulator, interferon gamma receptor antagonist, Interleukin 33 ligand inhibitor, Interleukin-31 receptor antagonist, Leukotriene antagonist, Liver X receptor agonist, Liver X receptor beta
20 agonist, nuclear factor kappa B inhibitor, OX-40 receptor antagonist, PGD2 antagonist, phospholipase A2 inhibitor, SH2 domain inositol phosphatase 1 stimulator, thymic stromal lymphoprotein ligand inhibitor, TLR modulator, TNF alpha ligand modulator, or vanilloid VR1 antagonist. In some embodiments, the one or more compound is a gram positive antibiotic, such as mupirocin or fusidic acid. In some embodiments, the one or
25 more compound is tranilast, tacrolimus, epinastine, SB-011, AM-1030, ZPL-521, MM-36, FB-825, PG-102, viomed, GBR-830, AVX-001, AMG-0101, E-6005, DMT-210, AX-1602, bertilimumab, rosiptor acetate, Q-301, ANB-020, VTP-38543, ZPL-389, lebrikizumab, tezepelumab, fexofenadine, pimecrolimus, bepotastine, crisaborole, tralokinumab, fexipiprant, doxycycline, desloratadine, ALX-101, nemolizumab,
30 asivatrep, ciclosporin, mepolizumab, dupilumab, secukinumab, timapiprant, or ustekinumab.

In one aspect, therefore, the invention provides a method of treating an inflammatory skin disease in a mammal, the method comprising applying a compound of the disclosure, or a pharmaceutically acceptable salt thereof, or a crystalline form thereof,

mammal a compound of the disclosure or a pharmaceutically-acceptable salt thereof, or a crystalline form thereof.

In one aspect, the respiratory disease is asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), pneumonitis, interstitial lung diseases (including
5 idiopathic pulmonary fibrosis), acute lung injury, acute respiratory distress syndrome, bronchitis, emphysema, bronchiolitis obliterans, bronchiolitis obliterans organizing pneumonia (also termed COS), primary Graft Dysfunction (PGD), organizing pneumonia (OP), acute rejection (AR), lymphocytic bronchiolitis (LB), chronic Lung Allograft Dysfunction (CLAD), restrictive CLAD (rCLAD or RAS), neutrophilic allograft
10 dysfunction, allergic rhinitis or sarcoidosis. In another aspect, the respiratory disease is asthma or chronic obstructive pulmonary disease.

In a further aspect, the respiratory disease is a lung infection, a helminthic infection, pulmonary arterial hypertension, sarcoidosis, lymphangioleiomyomatosis, bronchiectasis, or an infiltrative pulmonary disease. In yet another aspect, the respiratory
15 disease is drug-induced pneumonitis, fungal induced pneumonitis, allergic bronchopulmonary aspergillosis, hypersensitivity pneumonitis, eosinophilic granulomatosis with polyangiitis, idiopathic acute eosinophilic pneumonia, idiopathic chronic eosinophilic pneumonia, hypereosinophilic syndrome, Löffler syndrome, bronchiolitis obliterans organizing pneumonia, or immune-checkpoint-inhibitor induced
20 pneumonitis.

The disclosure further provides a method of treating a respiratory disease, the method comprising administering to the mammal a pharmaceutical composition comprising a compound of the disclosure or a pharmaceutically-acceptable salt thereof, or a crystalline form thereof, and a pharmaceutically-acceptable carrier.

25 Compounds of the disclosure, or a pharmaceutically acceptable salt thereof, or a crystalline form thereof, may also be used in combination with one or more compound useful to respiratory diseases.

Ocular Diseases

Many ocular diseases have been shown to be associated with elevations of
30 proinflammatory cytokines that rely on the JAK-STAT pathway.

The compounds of the disclosure, or a pharmaceutically acceptable salt thereof, or a crystalline form thereof, therefore, may be useful for the treatment of a number of ocular diseases that include, but are not limited to, uveitis, diabetic retinopathy, diabetic

days. An additional 0.5eq of tert-butyl 3-(hydroxymethyl)azetidine-1-carboxylate and cesium carbonate were added and the reaction was heated at 70°C overnight to provide full conversion. The reaction mixture was cooled to RT and then slowly poured into stirred ice-cold water (700ml). The resulting slurry was stirred for 20 minutes and then
5 filtered and dried to yield 32g of product. The product was crystallized from methanol-water by adding water slowly as antisolvent until cloudiness. A white slurry developed over time. The solid was filtered and dried to yield 28g of material over 98% pure.

Step 2B

Alternatively, potassium t-butoxide was added to a solution of tert-butyl 3-
10 (hydroxymethyl)azetidine-1-carboxylate in DMAc at 0°C. After 60 minutes, 6-Bromo-4-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole was added at 0°C and the reaction mixture was warmed up to room temperature giving clean complete conversion in less than 6 hours.

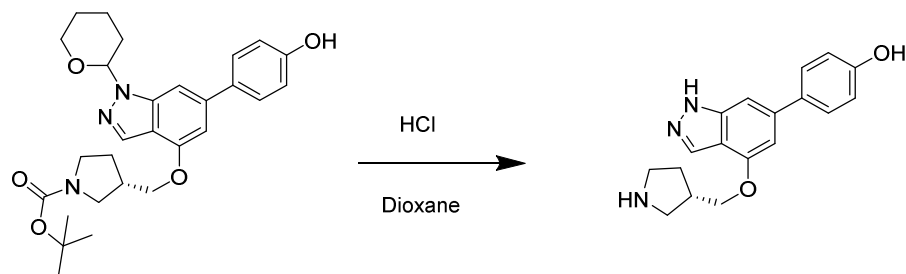
Step 3

15 In a 250 mL Schlenk flask was added tert-butyl 3-(((6-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)oxy)methyl)azetidine-1-carboxylate (10.0g, 21.44 mmol) and 80ml of dioxane. (4-Hydroxyphenyl)boronic acid (4.44 g, 32.2 mmol) was added. Potassium phosphate tribasic anhydrous (13.65 g, 64.3 mmol) was added with 20ml of water and the reaction mixture was purged with nitrogen. PdCl₂(dppf)-CH₂Cl₂ adduct
20 (0.876 g, 1.072 mmol) was added and the flask with a condenser was re-filled with nitrogen three times. The reaction mixture was heated at 110°C for 2h and 30 minutes to show complete conversion by HPLC. The reaction mixture was cooled to RT followed by removal of most of the dioxane. 150ml of saturated ammonium chloride was added followed by 150ml of ethyl acetate. The pH was adjusted to neutral with 1M aq HCl. The
25 phases were separated and the organic layer was dried with sodium sulfate followed by solvent removal. The crude product was dissolved in 150ml of DCM and loaded on 300g SiG column, eluted with 20-50 % ethyl acetate in hexanes. The pure fractions were combined and the solvent was evaporated. 100ml of MeTHF was added, followed by addition of crystalline seeds. A slurry developed over time. 100ml of DIPE was added
30 and the slurry was stirred overnight. Filtration and drying yielded 7.9g of pure material (>99%).

Step 4

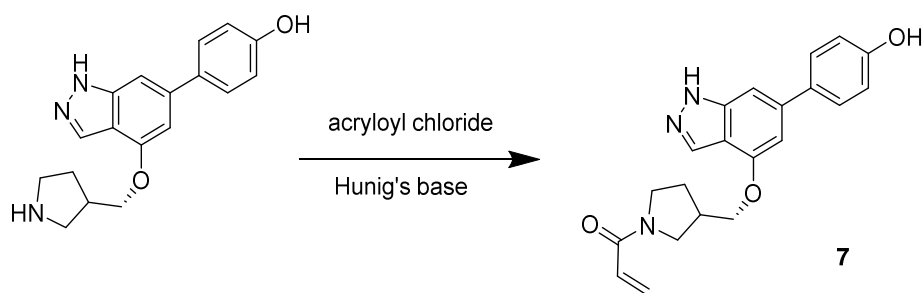
In a 50 mL round-bottomed flask was added tert-butyl 3-(((6-(4-hydroxyphenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)oxy)methyl)azetidine-1-carboxylate (85g,

Preparation 25: (S)-4-(4-(pyrrolidin-3-ylmethoxy)-1H-indazol-6-yl)phenol



4.0N HCl in dioxane (8.10 ml, 32.4 mmol) was added to a solution of tert-butyl
 5 (3S)-3-(((6-(4-hydroxyphenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)oxy)methyl)pyrrolidine-1-carboxylate (0.800 g, 1.62 mmol) in dioxane (6 ml), and the reaction mixture was stirred at 60 °C for 30 minutes. The reaction mixture was concentrated *in vacuo* to yield (S)-4-(4-(pyrrolidin-3-ylmethoxy)-1H-indazol-6-yl)phenol as an HCl salt (0.501 g, 1.62 mmol, 100 % yield). (*m/z*): [M+H]⁺ calcd for C₁₈H₁₉N₃O₂
 10 310.16 found 310.3.

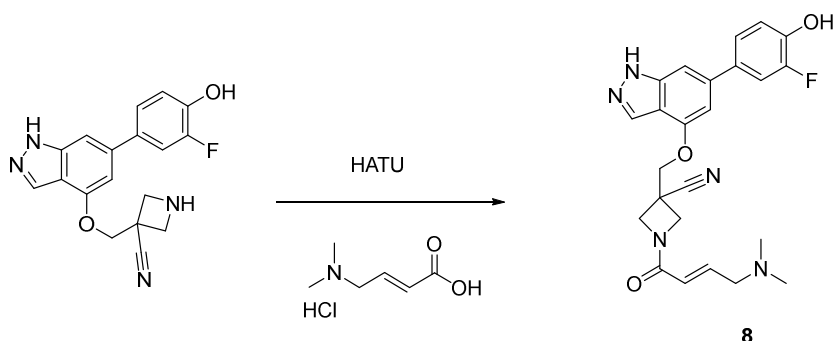
Example 7: (S)-1-(3-(((6-(3-chloro-4-hydroxyphenyl)-1H-indazol-4-yl)oxy)methyl)pyrrolidin-1-yl)prop-2-en-1-one



15 N,N-Diisopropylethylamine (2.83 ml, 16.2 mmol) was added to a solution of (S)-4-(4-(pyrrolidin-3-ylmethoxy)-1H-indazol-6-yl)phenol HCl salt (0.560 g, 1.62 mmol) in DMF (5 ml) at 0 °C, followed by acryloyl chloride (0.171 ml, 2.11 mmol). The reaction mixture was stirred at rt for 15 minutes then concentrated to a volume of about 2 mL. The
 20 crude liquid was purified via preparatory scale C18 column chromatography using a gradient of 30-90% acetonitrile in water with 0.05% trifluoroacetic acid to yield (S)-1-(3-(((6-(4-hydroxyphenyl)-1H-indazol-4-yl)oxy)methyl)pyrrolidin-1-yl)prop-2-en-1-one as a TFA salt (226 mg, 0.473 mmol, 29.2 % yield). (*m/z*): [M+H]⁺ calcd for C₂₁H₂₁N₃O₃ 364.17 found 364.2. ¹H NMR (400 MHz, DMSO-d₆) δ 13.00 (s, 1H), 10.31 (s, 1H),

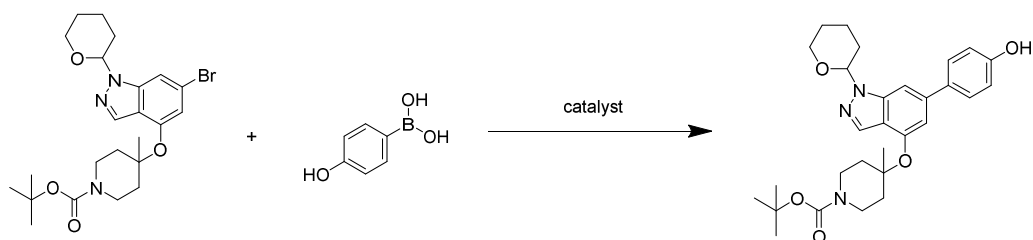
Tert-butyl 3-cyano-3-(((6-(3-fluoro-4-hydroxyphenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)oxy)methyl)azetidine-1-carboxylate (267 mg, 0.511 mmol) was dissolved in dichloromethane (1 ml) and TFA (1 ml) was slowly added. The clear solution was stirred at rt for 5 hours upon which LCMS indicated good conversion to the
 5 desired product. The reaction was concentrated down to provide 3-(((6-(3-fluoro-4-hydroxyphenyl)-1H-indazol-4-yl)oxy)methyl)azetidine-3-carbonitrile as a TFA salt (100% yield). (*m/z*): [M+H]⁺ calcd for C₁₈H₁₅FN₄O₂ 339.13 found 339.2.

**Example 8: (E)-1-(4-(dimethylamino)but-2-enoyl)-3-(((6-(3-fluoro-4-
 10 hydroxyphenyl)-1Hindazol-4-yl)oxy)methyl)azetidine-3-carbonitrile**



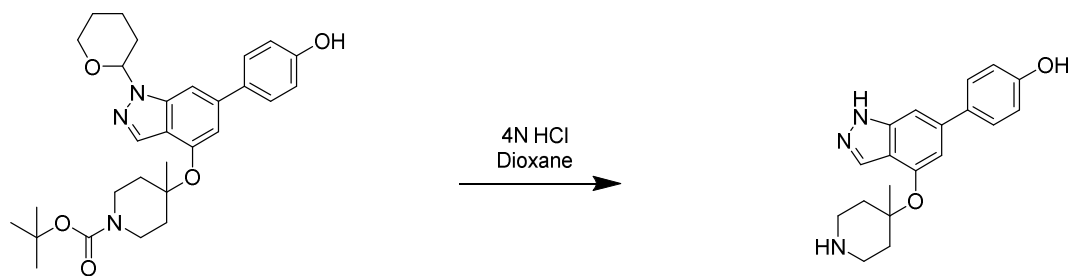
HATU (2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (121 mg, 0.318 mmol) was added to a solution of (E)-4-(dimethylamino)but-2-enoic acid hydrochloride (41.1 mg, 0.318 mmol) in DMF (2 mL).

The reaction mixture was stirred at rt for 5 minutes then 3-(((6-(3-fluoro-4-
 15 hydroxyphenyl)-1H-indazol-4-yl)oxy)methyl)azetidine-3-carbonitrile TFA salt (160 mg, 0.354 mmol) was added, followed by DIPEA (0.618 ml, 3.54 mmol). The reaction mixture was stirred at rt for 15 minutes and then concentrated *in vacuo* to yield a yellow liquid. The crude liquid was purified via preparatory scale Zorbax Bonus-RP (2.1x30mm,
 20 1.8 micron) column chromatography using 15-75% acetonitrile in water with 0.05% trifluoroacetic acid to yield (E)-1-(4-(dimethylamino)but-2-enoyl)-3-(((6-(3-fluoro-4-hydroxyphenyl)-1Hindazol-4-yl)oxy)methyl)azetidine-3-carbonitrile (56.2 mg, 0.121 mmol, 34 % yield). (*m/z*): [M+H]⁺ calcd for C₂₄H₂₄FN₅O₃ 450.19 found 450.0. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.94 (s, 1H), 9.77 (s, 1H), 7.85 (s, 1H), 7.47 (dd, *J* = 12.8, 2.2 Hz, 1H), 7.31 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.22 (s, 1H), 6.99 – 6.90 (m, 1H), 6.78 (s, 1H), 6.59 – 6.48 (m, 1H), 6.31 (d, *J* = 15.4 Hz, 1H), 4.67 – 4.60 (m, 3H), 4.40 (d, *J* = 9.1 Hz, 1H), 4.27 (d, *J* = 10.5 Hz, 1H), 4.12 (d, *J* = 10.4 Hz, 1H), 3.78 (d, *J* = 6.8 Hz, 2H), 2.66 (s, 6H).



A 1:1 mixture of Palladium acetate (9.1 mg, 0.040 mmol) and 1,1'-Bis(di-
 butylphosphino)ferrocene 98% (19.2 mg, 0.040 mmol) was added to a solution of 4-
 5 hydroxybenzeneboronic acid (42 mg, 0.30 mmol), tert-butyl 4-((6-bromo-1-(tetrahydro-
 2H-pyran-2-yl)-1H-indazol-4-yl)oxy)-4-methylpiperidine-1-carboxylate (100 mg, 0.202
 mmol), and Potassium phosphate, tribasic, 97%, anhydrous (129 mg, 0.607 mmol) in 1,4-
 Dioxane (2 ml) and Water (0.5 ml). The reaction mixture was degassed with nitrogen for
 10 minutes and then stirred at 110 °C for 2 hours. The reaction mixture was concentrated
in vacuo. A saturated aqueous solution of ammonium chloride (5 mL) was added and the
 mixture was extracted with ethyl acetate (2 x 5 mL). The ethyl acetate extracts were
 combined, dried over sodium sulfate and concentrated *in vacuo* to yield a brown liquid.
 The crude liquid was purified via combiflash column chromatography (12g) using 40%
 ethyl acetate in hexanes to yield tert-butyl 4-((6-(4-hydroxyphenyl)-1-(tetrahydro-2H-
 15 pyran-2-yl)-1H-indazol-4-yl)oxy)-4-methylpiperidine-1-carboxylate (96 mg, 0.189 mmol,
 94 % yield). (*m/z*): [M+H]⁺ calcd for C₂₉H₃₇N₃O₅ 508.28 found 508.3.

Preparation 31: 4-(4-((4-methylpiperidin-4-yl)oxy)-1H-indazol-6-yl)phenol

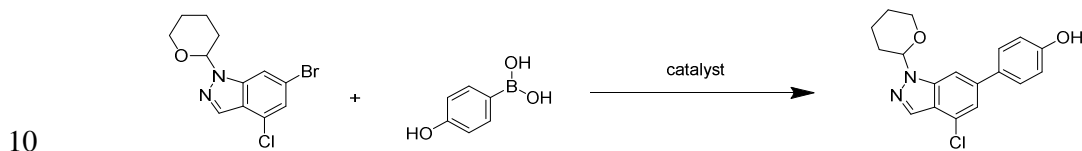


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Tert-butyl 4-((6-(4-hydroxyphenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-
 yl)oxy)-4-methylpiperidine-1-carboxylate (96 mg, 0.189 mmol) was dissolved in 1,4-
 dioxane (1 ml) and 4N HCl in 1,4-dioxane (1.18 ml, 4.73 mmol) was slowly added. The
 25 clear solution was stirred at rt for 5 hours upon which LCMS indicated good conversion
 to the desired product. The reaction was concentrated down to provide 4-(4-((4-

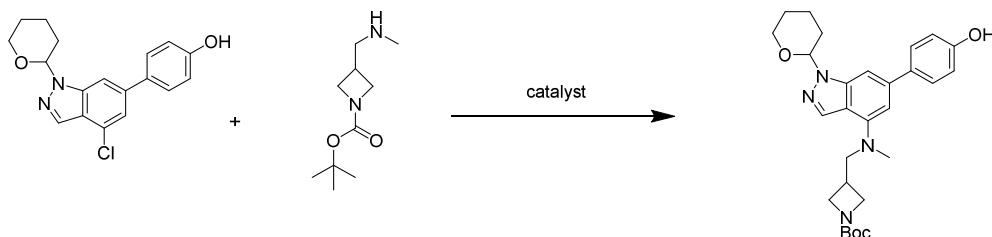
the mixture was extracted with ethyl acetate (3 x 100 mL). Ethyl acetate extracts were combined, washed with water (1 x 100 mL), brine (1 x 100 mL), dried over sodium sulfate and concentrated to yield a yellow solid. The crude solid was purified via trituration in n-pentane to yield 6-bromo-4-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (13.0 g, 41.2 mmol, 95 % yield). (m/z): [M+H]⁺ calculated for C₁₂H₁₂BrClN₂O 314.99 found 314.93.

Preparation 37: 4-(4-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)phenol



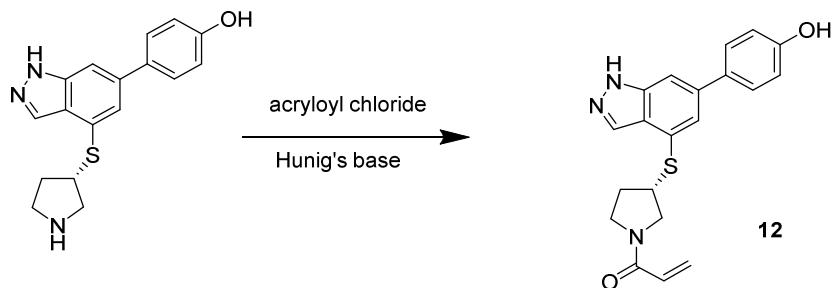
A solution of sodium carbonate (8.77 g, 82.8 mmol), 4-hydroxyphenylboronic acid (6.85g, 49.7 mmol) and 6-bromo-4-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (13.0 g, 41.4 mmol) in dioxane (200 mL) and water (50 mL) was degassed with nitrogen for 15 minutes. PdCl₂(dppf).DCM (3.37 g, 4.14 mmol) was added and the reaction mixture was degassed further for 5 minutes and then stirred at 125 °C for 2 hours. The reaction mixture was cooled to rt, ethyl acetate was added and the reaction mixture was filtered through a bed of Celite. Water was added (100 mL) and the mixture was extracted with ethyl acetate. The ethyl acetate extracts were combined, dried over sodium sulfate and concentrated *in vacuo* to yield a clear brown liquid. The crude liquid was purified via flash column chromatography using a 0-30% EtOAc in hexanes gradient to yield 4-(4-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)phenol (7.5 g, 22.9 mmol, 55 % yield). (m/z): [M+H]⁺ calculated for C₁₈H₁₇ClN₂O₂ 329.11 found 329.08.

25 **Preparation 38: tert-butyl 3-(((6-(4-hydroxyphenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)(methyl)amino)methyl)azetidine-1-carboxylate**



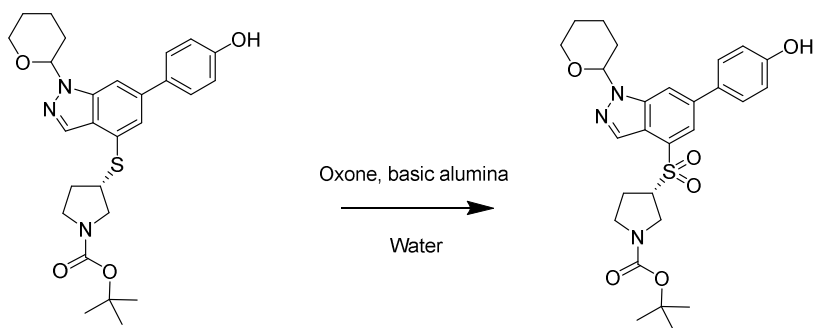
gradient of 20-80% acetonitrile in water with 0.05% trifluoroacetic acid to yield (S)-4-(4-(pyrrolidin-3-ylthio)-1H-indazol-6-yl)phenol as an TFA salt (175 mg, 0.411 mmol, 51 % yield). (*m/z*): [M+H]⁺ calcd for C₁₇H₁₇N₃OS 312.12 found 312.22.

5 Example 12: (S)-1-(3-(((6-(4-hydroxyphenyl)-1H-indazol-4-yl)thio)pyrrolidin-1-yl)prop-2-en-1-one



N,N-Diisopropylethylamine (0.079 ml, 0.450 mmol) was added to a solution of (S)-4-(4-(pyrrolidin-3-ylthio)-1H-indazol-6-yl)phenol TFA salt (38.5 mg, 0.091 mmol) in DMF (0.2 ml) at 0 °C, followed by acryloyl chloride (8.0 μL, 0.099 mmol). The reaction mixture was stirred at rt for 15 minutes and the crude liquid was purified via preparatory scale C18 column chromatography using a gradient of acetonitrile in water with 0.05% trifluoroacetic acid to yield (S)-1-(3-(((6-(4-hydroxyphenyl)-1H-indazol-4-yl)thio)pyrrolidin-1-yl)prop-2-en-1-one as a TFA salt (17.1 mg, 0.046 mmol, 51 % yield). (*m/z*): [M+H]⁺ calcd for C₂₀H₁₉N₃O₂S 366.13 found 366.1.

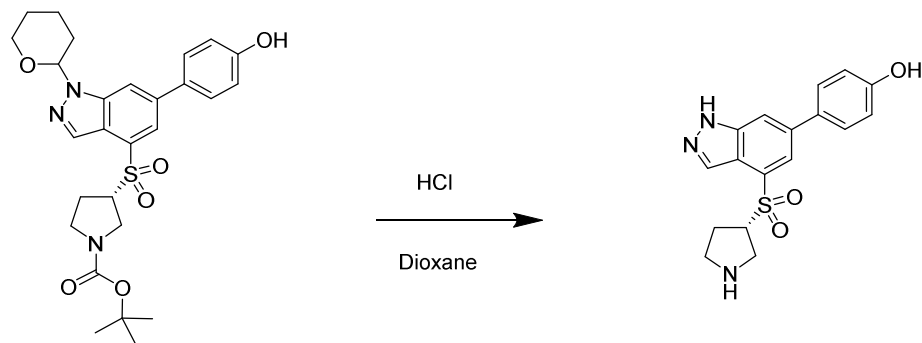
Preparation 42: tert-butyl (3S)-3-(((6-(4-hydroxyphenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)sulfonyl)pyrrolidine-1-carboxylate



Basic alumina (200 mg) and Oxone (744 mg, 2.42 mmol) were added to a solution of tert-butyl (3S)-3-(((6-(4-hydroxyphenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)thio)pyrrolidine-1-carboxylate (400 mg, 0.80 mmol) in chloroform (50 mL) and water

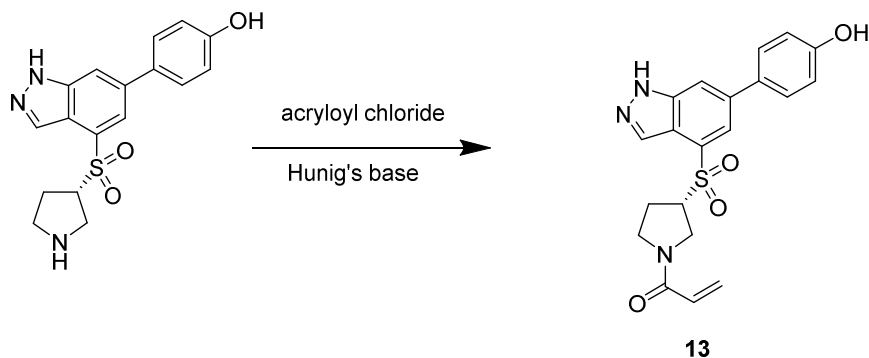
(1 mL) and the reaction mixture was stirred at 65 °C for 12 h. The reaction mixture was filtered through a bed of Celite, and the filtered material was washed with chloroform. The filtrates were combined, water was added and the mixture was extracted with chloroform (3 x 100 mL). The chloroform extracts were combined, washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The crude liquid was purified via flash column chromatography using a 30% EtOAc in hexanes to yield tert-butyl (3S)-3-((6-(4-hydroxyphenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)sulfonyl)pyrrolidine-1-carboxylate (200 mg, 0.379 mmol, 47 % yield). (*m/z*): [M+H]⁺ calculated for C₂₇H₃₃ClN₃O₆ 528.22 found 528.48.

Preparation 43: (S)-4-(4-(pyrrolidin-3-ylsulfonyl)-1H-indazol-6-yl)phenol



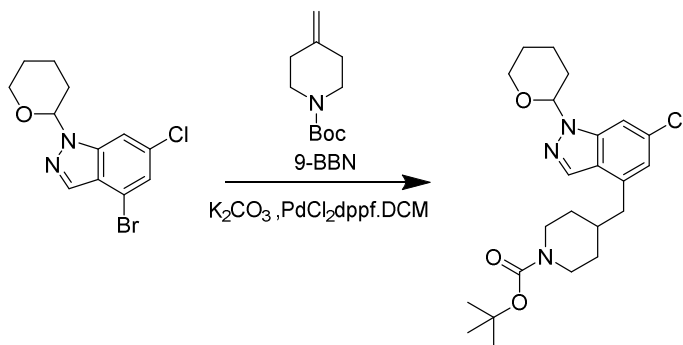
4.0N HCl in dioxane (10.0 mL, 40.0 mmol) was added to a solution of (3S)-3-((6-(4-hydroxyphenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)sulfonyl)pyrrolidine-1-carboxylate (200 mg, 0.379 mmol) in methanol (2 mL), and the reaction mixture was stirred at rt for 8 h. The reaction mixture was concentrated *in vacuo* and the resulting residue was triturated with diethyl ether to yield (S)-4-(4-(pyrrolidin-3-ylsulfonyl)-1H-indazol-6-yl)phenol as an HCl salt (140 mg, 0.369 mmol, 97 % yield). (*m/z*): [M+H]⁺ calcd for C₁₇H₁₇N₃O₃S 344.11 found 344.04.

Example 13: (S)-1-(3-(((6-(4-hydroxyphenyl)-1H-indazol-4-yl)sulfonyl)pyrrolidin-1-yl)prop-2-en-1-one



N,N-Diisopropylethylamine (0.079 ml, 0.450 mmol) was added to a solution of (S)-4-(4-
 5 (pyrrolidin-3-ylsulfonyl)-1H-indazol-6-yl)phenol HCl salt (31.0 mg, 0.082 mmol) in
 DMF (0.2 ml) at 0 °C, followed by acryloyl chloride (8.0 µL, 0.099 mmol). The reaction
 mixture was stirred at rt for 10 minutes and the crude liquid was purified via preparatory
 scale C18 column chromatography using a gradient of acetonitrile in water with 0.05%
 trifluoroacetic acid to yield (S)-1-(3-(((6-(4-hydroxyphenyl)-1H-indazol-4-
 10 yl)sulfonyl)pyrrolidin-1-yl)prop-2-en-1-one as a TFA salt (3.1 mg, 0.0061 mmol, 7 %
 yield). (*m/z*): [M+H]⁺ calcd for C₂₀H₁₉N₃O₄S 398.12 found 398.0.

Preparation 44: tert-butyl 4-(((6-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)methyl)piperidine-1-carboxylate

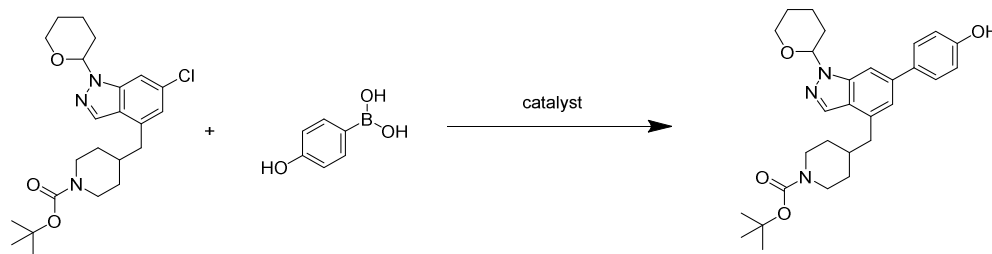


15

A 0.5 M solution of 9-BBN in THF (7.92 mL, 3.96 mmol) was added to tert-butyl 4-
 methylenepiperidine-1-carboxylate (468 mg, 2.37 mmol) and the reaction mixture was
 stirred at 80 °C for 2 h. The reaction mixture was cooled to rt and then cannulated into a
 preformed solution of 4-bromo-6-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (500
 20 mg, 1.58 mmol), potassium carbonate (548 mg, 3.96 mmol) and Pd(dppf)Cl₂.DCM (129
 mg, 0.15 mmol) in DMF (10.0 ml) & H₂O (2.0 ml). The reaction mixture was stirred at
 80 °C for 16 h. The reaction mixture was filtered through a bed of Celite, and the filtered

material was washed with ethyl acetate. The filtrates were combined, water (100 mL) was added and the mixture was extracted with ethyl acetate (2 x 150 mL). The ethyl acetate extracts were combined, washed with brine, dried over sodium sulfate and concentrated in vacuo. The crude liquid was purified via flash column chromatography using a 30% EtOAc in hexanes to yield tert-butyl 4-((6-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)methyl)piperidine-1-carboxylate (460 mg, 1.06 mmol, 67 % yield). (m/z): [M+H]⁺ calculated for C₂₃H₃₂ClN₃O₃ 434.22 found 434.47.

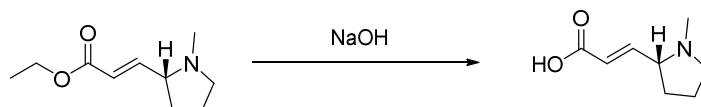
Preparation 45: tert-butyl 4-((6-(4-hydroxyphenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)methyl)piperidine-1-carboxylate



4-Hydroxyphenylboronic acid (195 mg, 1.41 mmol) was added to a suspension of tert-butyl 4-((6-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)methyl)piperidine-1-carboxylate (410 mg, 0.94 mmol) in dioxane (10.0 mL) and water (2.0 mL), followed by potassium phosphate (401 mg, 1.88 mmol) and the reaction mixture was degassed with nitrogen for 15 minutes. 2'-(Dimethylamino)-2-biphenyl-palladium(II) chloride dinorbornylphosphine complex (52 mg, 0.07 mmol) was added and the reaction mixture was heated under microwave irradiation at 100 °C for 1 hour. The reaction mixture was cooled to rt and then filtered through a bed of Celite. Water (100 mL) was added to the filtrate, which was then extracted with ethyl acetate (3 x 100 mL). The ethyl acetate extracts were combined, washed with water, brine, dried over sodium sulfate and concentrated *in vacuo*. The crude liquid was purified via flash column chromatography using 50% EtOAc in hexanes to yield tert-butyl 4-((6-(4-hydroxyphenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)methyl)piperidine-1-carboxylate (300 mg, 0.610 mmol, 65%). (m/z): [M+H]⁺ calculated for C₂₉H₃₇N₃O₄ 492.29 found 492.46.

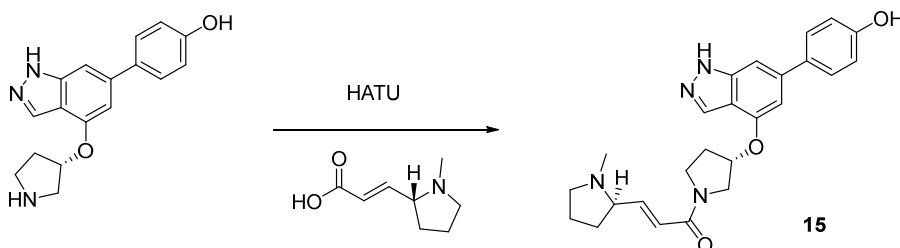
combined, washed with brine, dried over sodium sulfate and concentrated *in vacuo* to yield ethyl (R,E)-3-(1-methylpyrrolidin-2-yl)acrylate (0.900 g, 4.915 mmol, 78 % yield). (*m/z*): [M+H]⁺ calcd for C₁₀H₁₇NO₂ 184.14 found 184.0.

5 Preparation 49: (R,E)-3-(1-methylpyrrolidin-2-yl)acrylic acid

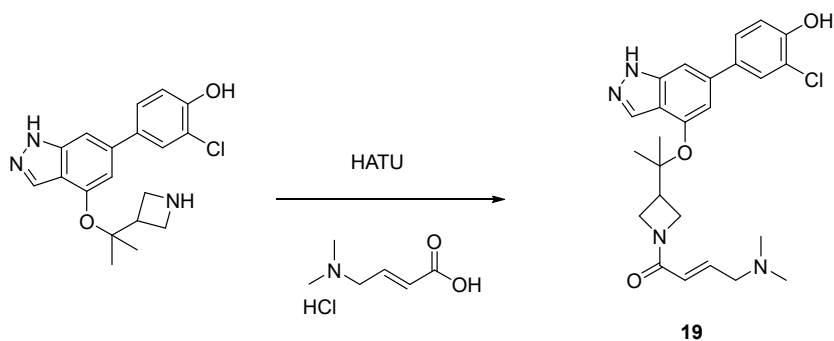


Sodium hydroxide (294 mg, 7.36 mmol) was added to a solution of ethyl (R,E)-3-(1-methylpyrrolidin-2-yl)acrylate (0.900 g, 4.915 mmol, 78 % yield) in 2:1 THF/water (15 mL) and the reaction mixture was stirred at rt for 4 h. The reaction mixture was concentrated *in vacuo* to yield (R,E)-3-(1-methylpyrrolidin-2-yl)acrylic acid (668 mg, 4.30 mmol, 88% yield). (*m/z*): [M+H]⁺ calcd for C₈H₁₃NO₂ 156.10 found 156.26.

15 Example 15: (E)-1-((S)-3-((6-(4-hydroxyphenyl)-1H-indazol-4-yl)oxy)pyrrolidin-1-yl)-3-((R)-1-methylpyrrolidin-2-yl)prop-2-en-1-one

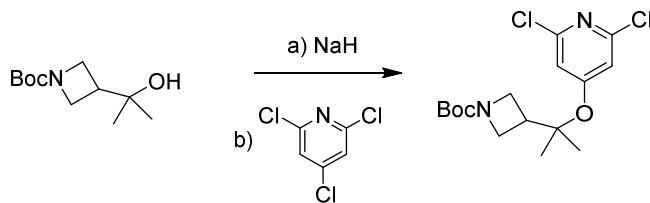


A solution of HATU (0.031 g, 0.083 mmol) in DMF (0.1 mL) was added to (R,E)-3-(1-methylpyrrolidin-2-yl)acrylic acid (14.0 mg, 0.090 mmol), followed by a solution of (S)-4-(4-(pyrrolidin-3-yloxy)-1H-indazol-6-yl)phenol hydrochloride (0.025 g, 0.075 mmol) and DIPEA (0.065 mL, 0.375 mmol), the reaction mixture was stirred at rt for 15 minutes and the crude liquid was purified via preparatory scale C18 column chromatography using a gradient of acetonitrile in water with 0.05% trifluoroacetic acid to yield ((E)-1-((S)-3-((6-(4-hydroxyphenyl)-1H-indazol-4-yl)oxy)pyrrolidin-1-yl)-3-((R)-1-methylpyrrolidin-2-yl)prop-2-en-1-one as a TFA salt (7.8 mg, 0.014 mmol, 19 % yield). (*m/z*): [M+H]⁺ calcd for C₂₅H₂₈N₄O₃ 433.23 found 433.1.



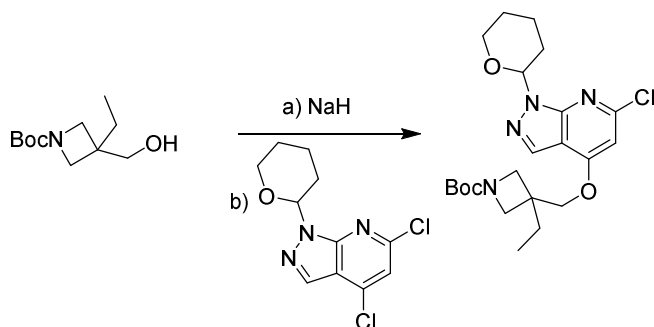
HATU (2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium
 5 hexafluorophosphate, 2.92 g, 7.07 mmol) was added to a solution of (E)-4-
 (dimethylamino)but-2-enoic acid hydrochloride (1.07 g, 6.48 mmol) in DMF (10 mL).
 The reaction mixture was stirred at rt for 10 minutes then 4-((2-azetidin-3-yl)propan-2-
 yl)oxy)-1-*H*-indazole-6-yl)-2-fluorophenol TFA salt (2.01 g, 5.89 mmol) was added,
 followed by DIPEA (3.08 mL, 17.7 mmol). The reaction mixture was stirred at rt for 15
 10 minutes and then concentrated *in vacuo* to yield a yellow liquid. The crude liquid was
 purified via preparatory scale C18 column chromatography using a gradient of 20-80%
 acetonitrile in water with 0.05% trifluoroacetic acid to yield (E)-4-(dimethylamino)-1-(3-
 (2-(((6-(3-fluoro-4-hydroxyphenyl)-1*H*-indazol-4-yl)oxy)propan-2-yl)cyclobutyl)but-2-en-
 1-one as a TFA salt (1.65 g, 3.65 mmol, 61.9 % yield). (*m/z*): [M+H]⁺ calcd for
 15 C₂₅H₃₀FN₄O₃ 453.23 found 453.3.

Preparation 54: tert-butyl 3-(2-((2,6-dichloropyridin-4-yl)oxy)propan-2-yl)azetidine-1-carboxylate



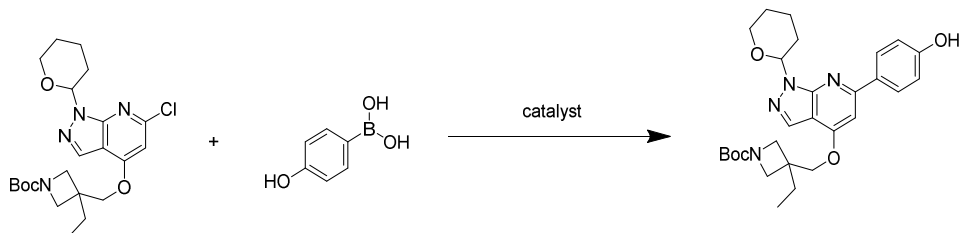
A solution of tert-butyl 3-(2-hydroxypropan-2-yl)azetidine-1-carboxylate (6.5 g,
 30.21 mmol) in DMSO (10 mL) was added dropwise to a solution of 60% by weight
 sodium hydride in mineral oil (1.65 g, 41.20 mmol) in DMSO (15 mL) and the reaction
 mixture was stirred at rt for 10 minutes. A solution of 2,4,6-trichloropyridine (5.0 g ,
 27.62 mmol) in DMSO (25 mL) was added dropwise to the resulting suspension, and the
 25 reaction mixture was stirred at 60 °C for 16 h. The reaction mixture was quenched using

Preparation 61: tert-butyl 3-(((6-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-yl)oxy)methyl)-3-ethylazetidine-1-carboxylate



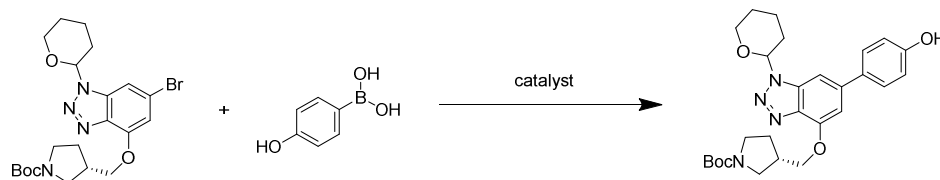
5 60% By weight sodium hydride in mineral oil (353 mg, 8.82 mmol) was added to a solution of tert-butyl 3-ethyl-3-(hydroxymethyl)azetidine-1-carboxylate (1.1 g, 4.85 mmol) in DMF (10 mL) at 0 °C and the reaction mixture was stirred at rt for 40 minutes. A solution of 4,6-dichloro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine (1.20 g, 4.41 mmol) in DMF (5 mL) was added at 0 °C and the reaction mixture was
10 stirred at rt for 1 hour. The reaction was quenched with addition of water and the mixture was extracted with ethyl acetate. The ethyl acetate extracts were combined, washed with water and a saturated aqueous solution of sodium chloride and then dried over sodium sulfate to yield the crude residue. The crude residue was purified via flash column chromatography using 5% ethyl acetate in hexanes to yield tert-butyl 3-(((6-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-yl)oxy)methyl)-3-ethylazetidine-1-carboxylate (900 mg, 4.39 mmol, 45.2 % yield). (m/z): [M+H]⁺ calcd for C₂₂H₃₂ClN₄O₄ 451.21 found 451.13.

Preparation 62: tert-butyl 3-ethyl-3-(((6-(4-hydroxyphenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-yl)oxy)methyl)azetidine-1-carboxylate



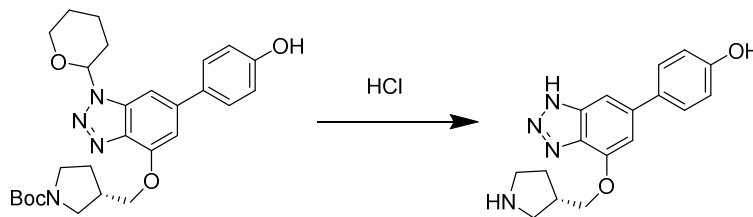
20 A solution of phenylboronic acid (413 mg, 2.99 mmol) and sodium carbonate (421 mg, 3.98 mmol) in water (2 mL) was added to solution of tert-butyl 3-(((6-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-yl)oxy)methyl)-3-ethylazetidine-1-carboxylate (900 mg, 4.39 mmol) in DMF (10 mL) at 0 °C and the reaction mixture was stirred at rt for 40 minutes. The reaction was quenched with addition of water and the mixture was extracted with ethyl acetate. The ethyl acetate extracts were combined, washed with water and a saturated aqueous solution of sodium chloride and then dried over sodium sulfate to yield the crude residue. The crude residue was purified via flash column chromatography using 5% ethyl acetate in hexanes to yield tert-butyl 3-ethyl-3-(((6-(4-hydroxyphenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-yl)oxy)methyl)azetidine-1-carboxylate (900 mg, 4.39 mmol, 45.2 % yield). (m/z): [M+H]⁺ calcd for C₂₈H₃₆N₄O₅ 504.26 found 504.13.

Preparation 67: tert-butyl (3S)-3-(((6-(4-hydroxyphenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-benzo[d][1,2,3]triazol-4-yl)oxy)methyl)pyrrolidine-1-carboxylate



Phenolboronic acid (192 mg, 1.40 mmol) was added to solution of tert-butyl (3S)-3-(((6-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-benzo[d][1,2,3]triazol-4-yl)oxy)methyl)pyrrolidine-1-carboxylate (450 mg, 0.93 mmol) in dioxane (10 mL) and water (2 mL), followed by potassium phosphate (394 mg, 1.86 mmol) and the reaction was degassed with argon for 15 minutes. 2'-(Dimethylamino)-2-biphenyl-palladium(II) chloride dinorbornylphosphine complex (52 mg, 0.093 mmol) was added and the reaction mixture was stirred at 110 °C for 40 minutes under microwave irradiation. The reaction mixture was filtered through Celite. Water was added and the mixture was extracted with ethyl acetate (3 x). The ethyl acetate extracts were combined, washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate and concentrated *in vacuo* to yield the crude residue. The crude residue was purified via flash column chromatography using 30% ethyl acetate in hexanes to yield tert-butyl (3S)-3-(((6-(4-hydroxyphenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-benzo[d][1,2,3]triazol-4-yl)oxy)methyl)pyrrolidine-1-carboxylate (300 mg, 0.607 mmol, 65.0 % yield). (m/z): [M+H]⁺ calcd for C₂₇H₃₅N₄O₅ 495.26 found 495.06.

Preparation 68: (S)-4-(4-(pyrrolidin-3-ylmethoxy)-1H-benzo[d][1,2,3]triazol-6-yl)phenol



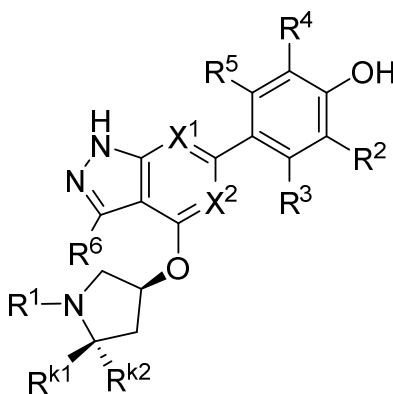
4M hydrochloric acid in dioxane (10.0 mL, 40 mmol) was added to a solution of tert-butyl ((3S)-3-(((6-(4-hydroxyphenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-benzo[d][1,2,3]triazol-4-yl)oxy)methyl)pyrrolidine-1-carboxylate (230 mg, 0.465 mmol) in methanol (2 mL) and the reaction mixture was stirred at rt for 5 hours. The reaction was concentrated *in*

4.0N HCl in dioxane (3.75 ml, 15.0 mmol) was added to a solution of the crude tert-butyl (3S)-3-(((6-(3-chloro-4-hydroxyphenyl)-3-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)oxy)pyrrolidine-1-carboxylate in methanol (0.5 mL), and the reaction mixture was stirred at 60 °C for 30 minutes. The reaction mixture was concentrated *in vacuo* to yield the crude intermediate (S)-2-chloro-4-(3-methyl-4-(pyrrolidin-3-yloxy)-1H-indazol-6-yl)phenol.

N,N-Diisopropylethylamine (4.59 ml, 26.3 mmol) was added to a solution of the crude intermediate (S)-2-chloro-4-(3-methyl-4-(pyrrolidin-3-yloxy)-1H-indazol-6-yl)phenol in methylene chloride (3.75 ml), followed by acryloyl chloride (60.9 µL, 0.750 mmol). The reaction mixture was stirred at rt for 30 minutes then concentrated *in vacuo* to yield the crude residue. The crude residue was purified via preparatory scale C18 column chromatography using a gradient of 0-40% acetonitrile in water with 0.05% trifluoroacetic acid to yield (S)-1-(3-(((6-(3-chloro-4-hydroxyphenyl)-3-methyl-1H-indazol-4-yl)oxy)pyrrolidin-1-yl)prop-2-en-1-one as a TFA salt (7.6 mg, 0.015 mmol, 0.98 % yield). (*m/z*): [M+H]⁺ calcd for C₂₁H₂₁ClN₃O₃ 398.13 found 398.3.

The compounds of Tables 1-18 were prepared using similar synthetic methods.

Table 1



Ex No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	X ¹	X ²	R ^{k1}	R ^{k2}	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
1-1		H	H	H	H	H	CH	CH	H	H	C ₂₃ H ₂₆ N ₄ O ₃	407.20	407
1-2		H	H	H	H	H	CH	CH	H	H	C ₂₀ H ₁₉ N ₃ O ₃	350.13	350
1-3		Cl	H	H	H	H	CH	CH	H	H	C ₂₃ H ₂₅ ClN ₄ O ₃	441.15	441.1

In Vitro Assay Results

All of the compounds of Examples 1 to 18 and Tables 1 to 18 were tested in one or more of the assays described above.

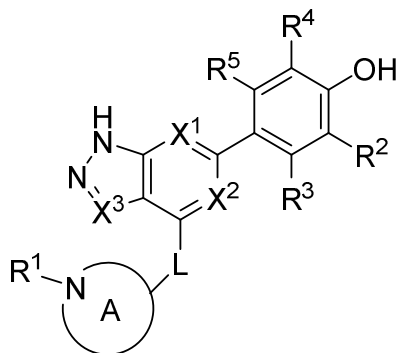
In Table 19 below, for the JAK1, JAK 2, JAK3, and TYK2 enzyme assays, A represents a pK_i value ≥ 10 ($K_i \leq 0.1$ nM), B represents a pK_i value between 9 and 10 (K_i between 1 nM and 0.1 nM), C represents a pK_i value between 8 and 9 (K_i between 10 nM and 1 nM), D represents a pK_i value between 7 and 8 (K_i between 100 nM and 10 nM), and E represents a pK_i value of 7 or below (K_i of 100 nM or above). For the Tall-1 Potency assay, A represents a pIC_{50} value ≥ 7.5 ($IC_{50} \leq 32$ nM), B represents a pIC_{50} value between 6.7 (included) and 7.5 (IC_{50} between 200 nM and 32 nM), and C represents a pIC_{50} value between 6 and 6.7 (IC_{50} between 1 μ M and 200 nM). For the JAK3 (pK_i)-JAK1 (pK_i) values, A represents a value of 3 or above, B represents a value of 2.3 to 3 and C represents a value of 1.8 to 2.3. For the Caco assay, A represents a value below 5×10^{-6} cm/sec, B represents a value between 5×10^{-6} and 10×10^{-6} cm/sec, C represents a value between 10×10^{-6} and 22×10^{-6} cm/sec.

Table 19

Example Number	JAK 1 (pK_i)	JAK 2 (pK_i)	JAK 3 (pK_i)	Tyk 2 (pK_i)	Tall-1 (pIC_{50})	JAK3 (pK_i)-JAK1 (pK_i)	Caco K_p 10^{-6} cm/sec
1	E	D	A	E	B	A	A
2	E	E	A	E	A	A	A
3	E	E	B	E	B	A	A
4	E	E	A	E	B	A	A
5	E	D	A	E	B	A	A
6	E	D	A	E	A	A	A
7	E	D	B	E	B	A	B
8	E	D	A	E	A	A	A
9	E		B		B	A	A
10	E	E	A	E	B	A	A
11	E	E	B	E	B	A	A
12	E	E	B	E	B	B	A
13	E	E	A	E	B	A	A

WHAT IS CLAIMED IS:

1. A compound of formula (I):

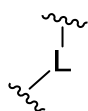


(I)

- 5 or a pharmaceutically acceptable salt thereof, wherein

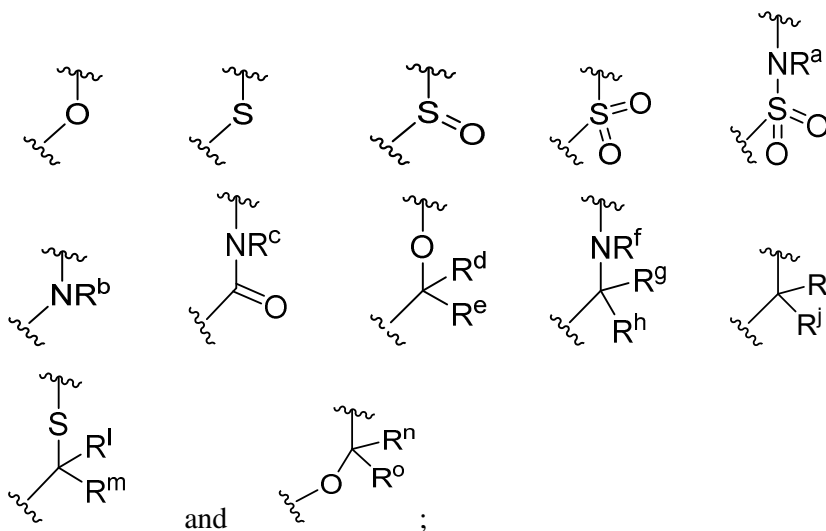
X¹ and X² are each independently selected from N and CH;

X³ is selected from the group consisting of N, CH, C-CH₃, C-CF₃, C-CHF₂, C-CH₂-O-CH₃, C-SMe, C-NMe₂, C-NH-CH₃, C-Cl, C-CN, and C-OMe;



is selected from the group consisting of

10



R^a, R^b, R^c, and R^f are each independently selected from the group consisting of H and C₁₋₃ alkyl;

- 15 R^d, R^e, R^g, R^h, Rⁱ, R^j, R^l, R^m, Rⁿ and R^o are each independently selected from the group consisting of H and C₁₋₃ alkyl wherein the C₁₋₃ alkyl group may be optionally substituted with 1 to 3 halogens;

optionally R^d and R^e may be joined to form a cyclopropyl ring;

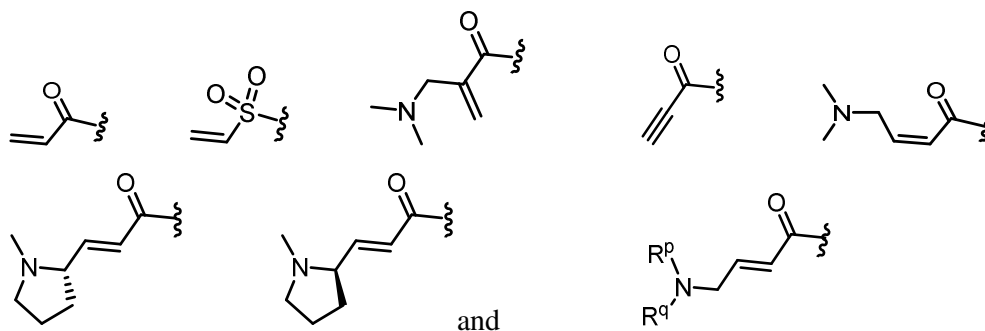
A is selected from the group consisting of

(a) a 4 to 10 membered monocyclic heterocyclic group containing one nitrogen atom and optionally containing one additional heteroatom selected from N, S, S(O)₂ and O, and

5 (b) a 6 to 10 membered multicyclic heterocyclic group containing one nitrogen atom and optionally containing one additional heteroatom selected from N, S, and O, wherein L is linked to a carbon atom in A and A is optionally substituted with 1 to 3 R^k groups;

each R^k is independently selected from the group consisting of F, CN, C₁₋₃ alkoxy, 10 cyclopropyl, and C₁₋₃ alkyl, wherein the C₁₋₃ alkyl group may be optionally substituted with OH, OMe or 1 to 3 halogens;

R¹ is selected from the group consisting of



15 wherein R^p and R^q are each independently selected from the group consisting of H, C₃₋₅ cycloalkyl and C₁₋₆ alkyl, wherein the C₁₋₆ alkyl group may be optionally substituted with 1 to 3 substituents independently selected from the group consisting of C₁₋₃ alkoxy and -S-C₁₋₃ alkyl,

or R^p and R^q form a 4 to 6 membered monocyclic heterocyclic group containing 20 one nitrogen atom and optionally containing one additional heteroatom selected from N, S, and O, wherein the 4 to 6 membered monocyclic heterocyclic group is optionally substituted with 1 to 3 substituents independently selected from the group consisting of C₁₋₆ alkyl, C₁₋₃ alkoxy, -S-C₁₋₃ alkyl and -C₁₋₃ alkyl-C₁₋₃ alkoxy;

R² is selected from the group consisting of H, Cl, OMe, Me and F;

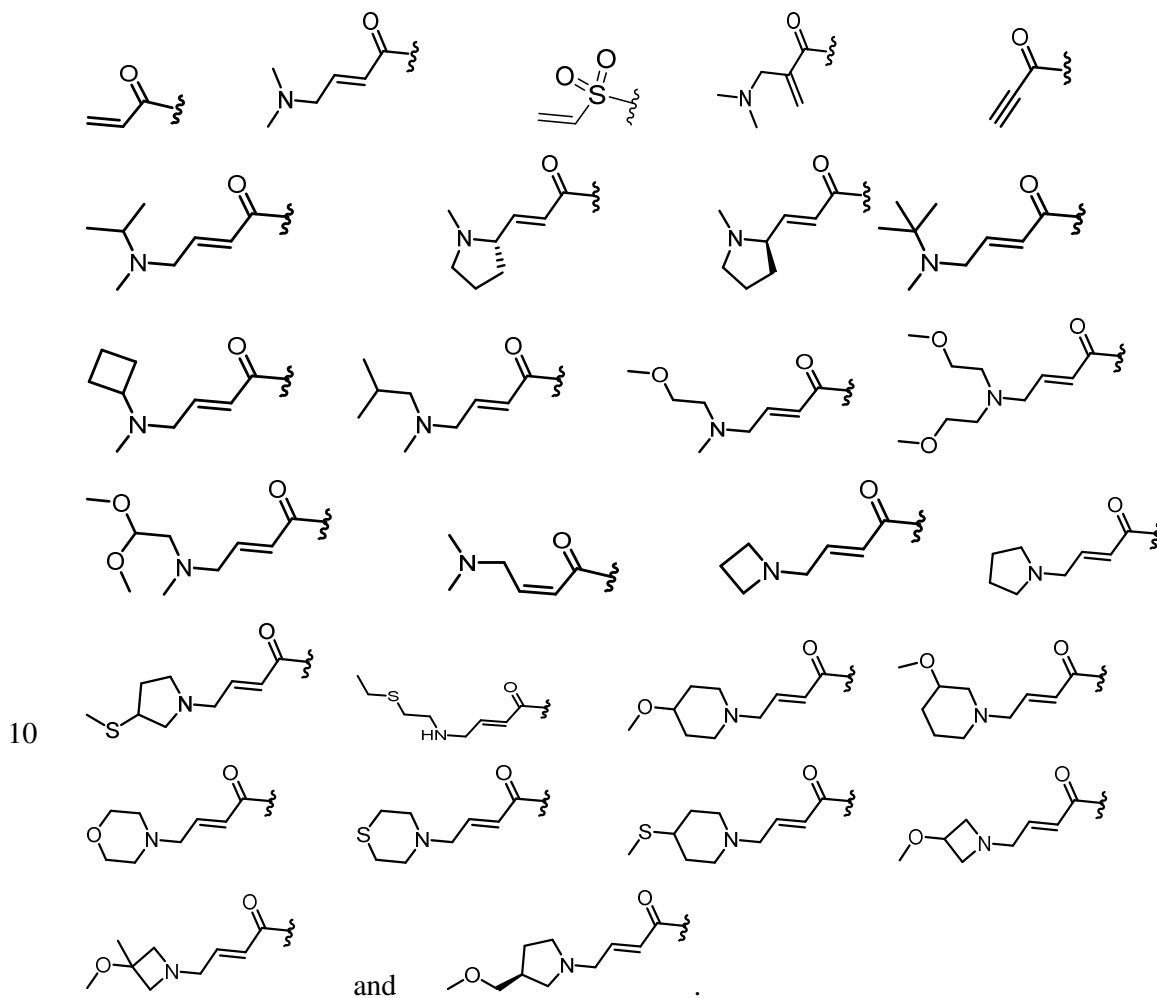
25 R³ is selected from the group consisting of H and F;

R⁴ is selected from the group consisting of H and F; and

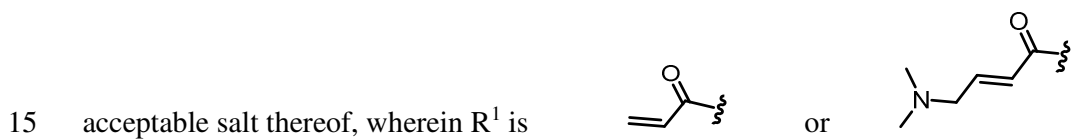
R⁵ is selected from the group consisting of H, Me and F.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein X^3 is CH.

3. The compound of any one of claims 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from the group consisting of



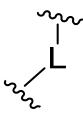
4. The compound of any one of claims 1 or 2, or a pharmaceutically

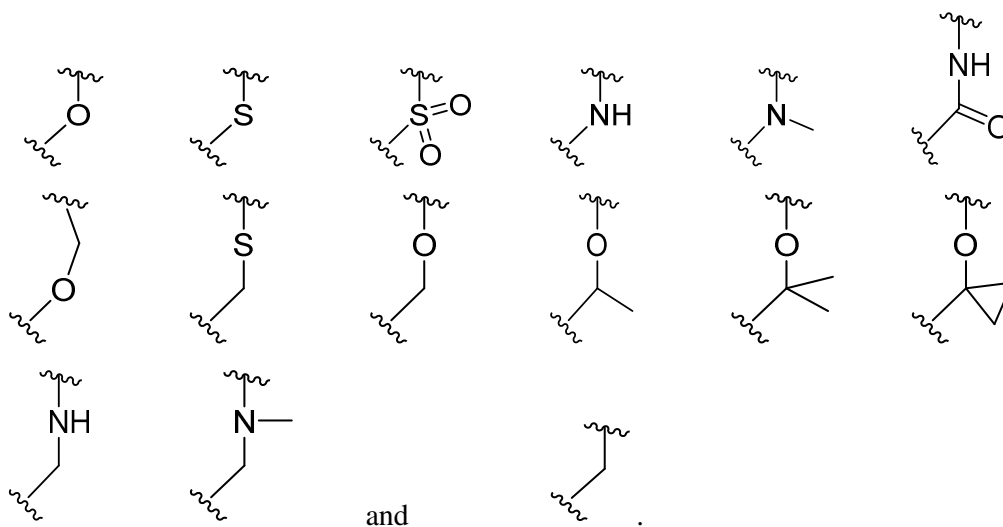


5. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein A is selected from the group consisting of

azetidine, pyrrolidine, piperidine, morpholine, 2-azaspiro[3.3]heptane, thiomorpholine, and nortropene.

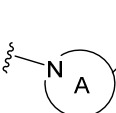
6. The compound of any one of claims 1 to 5, or a pharmaceutically

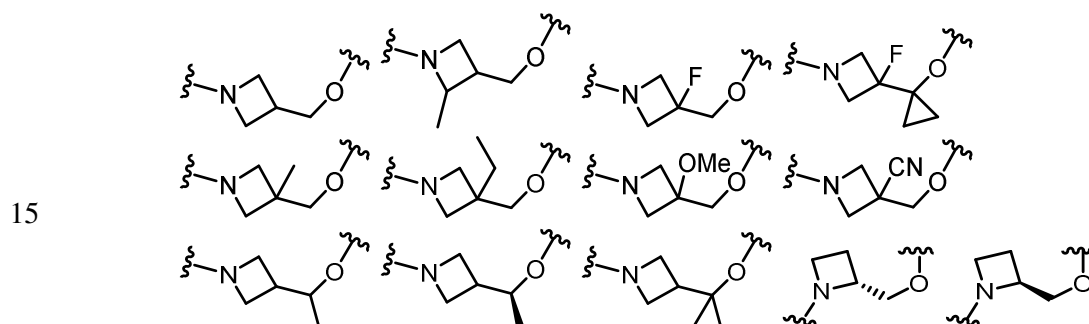
5 acceptable salt thereof, wherein  is selected from the group consisting of

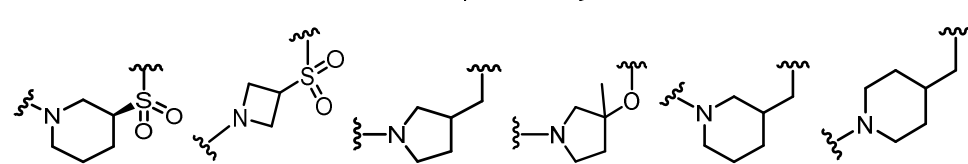
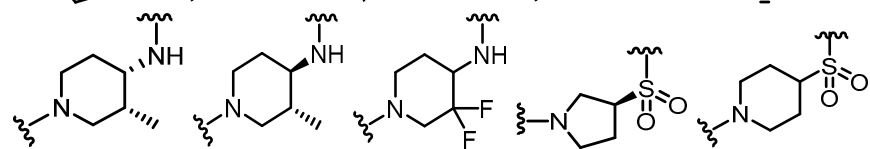
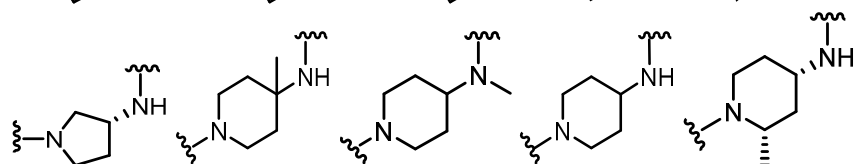
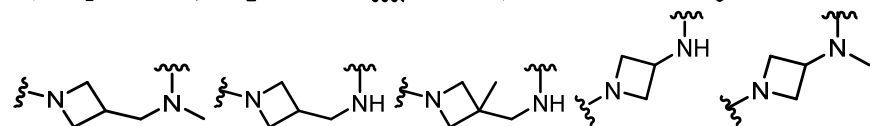
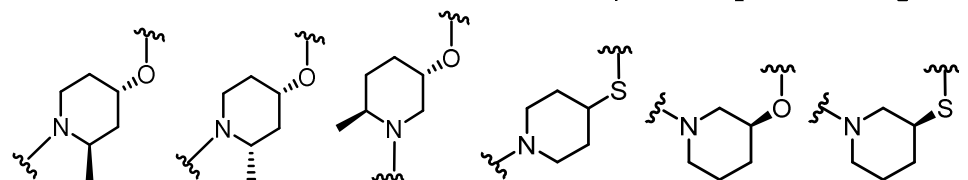
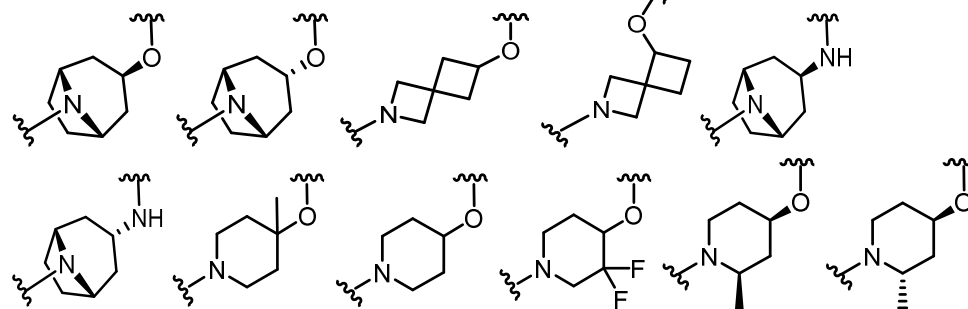
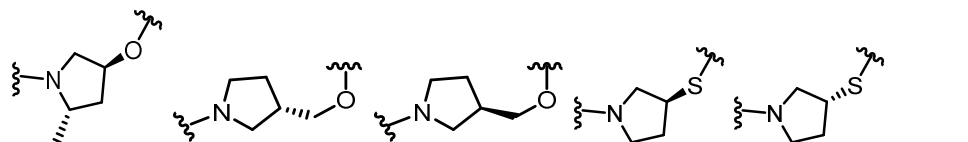
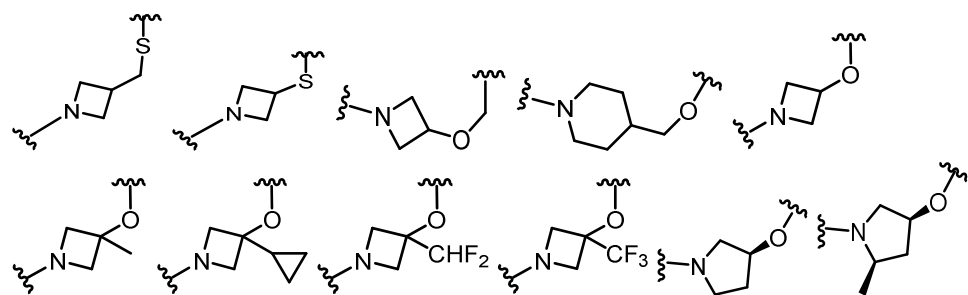


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7. The compound of any one of claims 1 to 4, or a pharmaceutically

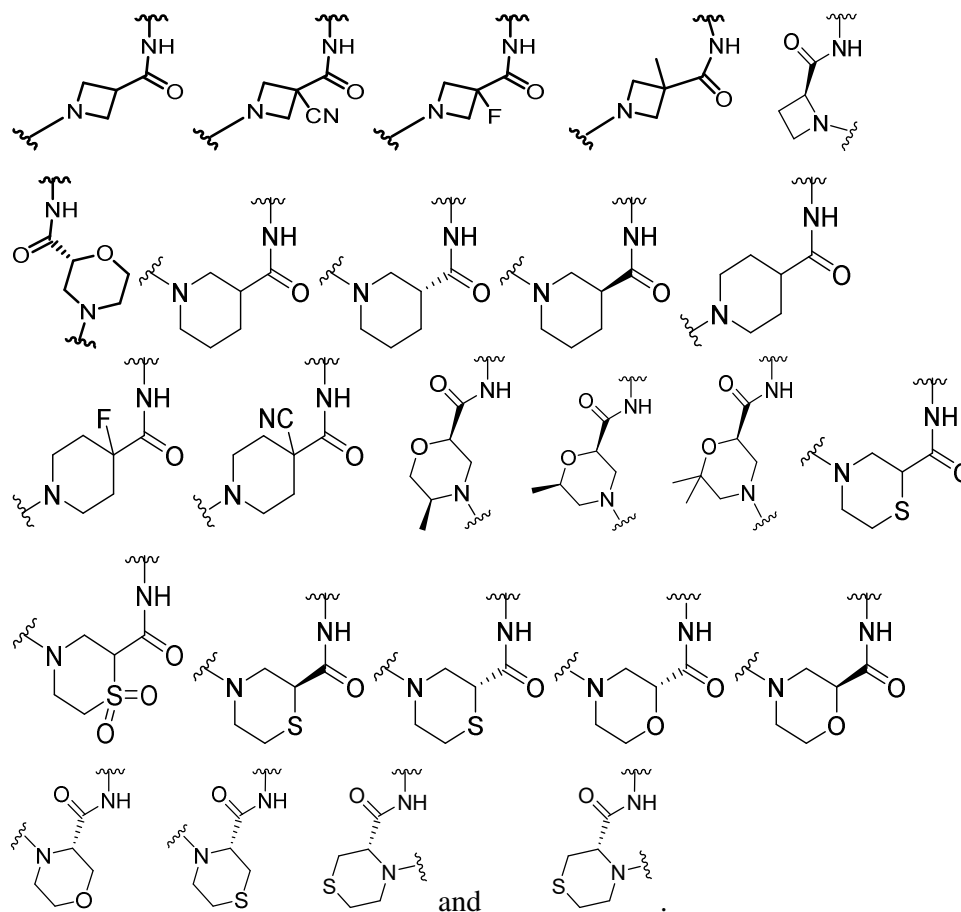
acceptable salt thereof, wherein  is selected from the group consisting of:





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8. The compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein X^1 and X^2 are both CH.

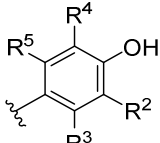
10 9. The compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein X^1 is N and X^2 is CH.

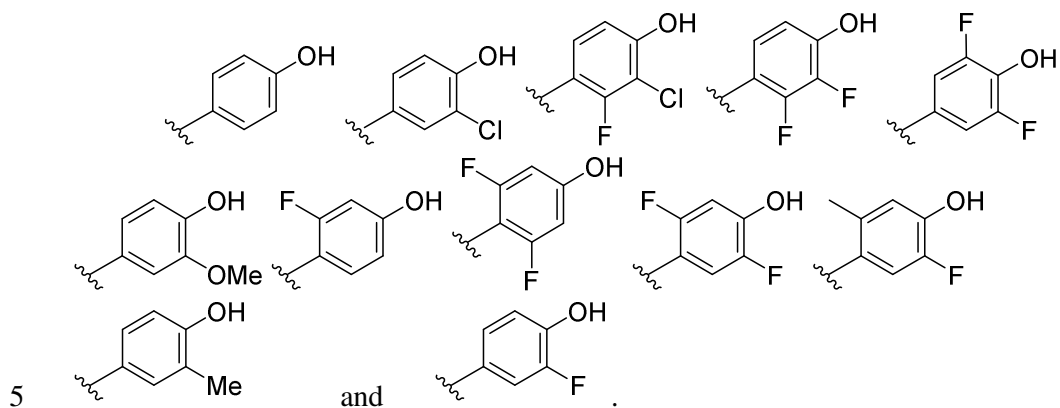
10. The compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein X^1 and X^2 are both N.

15

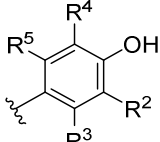
11. The compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein X^1 is CH and X^2 is N.

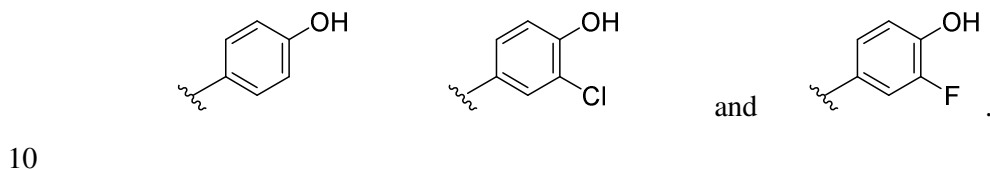
12. The compound of any one of claims 1 to 11, or a pharmaceutically

acceptable salt thereof, wherein  is selected from the group consisting of:

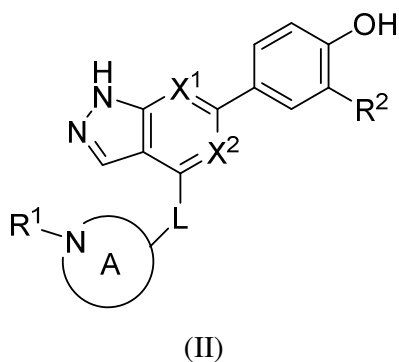


13. The compound of any one of claims 1 to 11, or a pharmaceutically

acceptable salt thereof, wherein  is selected from the group consisting of:

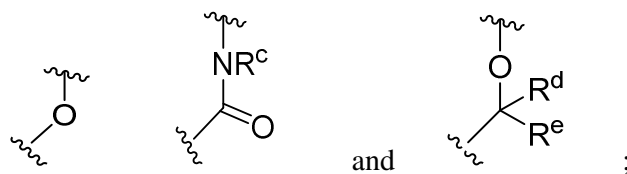
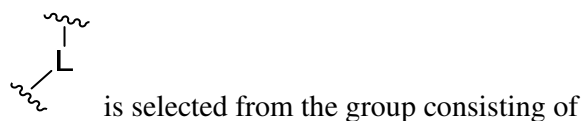


14. The compound of claim 1 having the formula (II):



or a pharmaceutically acceptable salt thereof, wherein

15 X^1 and X^2 are both CH, or X^1 and X^2 are both N, or X^1 is N and X^2 is CH;

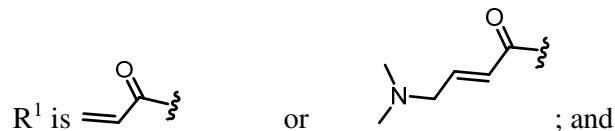


R^c , R^d , and R^e are each independently selected from the group consisting of H and methyl;

- 5 A is selected from the group consisting of azetidine, pyrrolidine, piperidine, and morpholine;

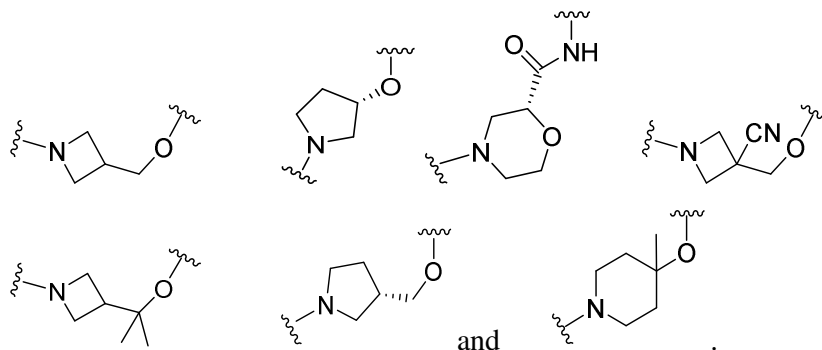
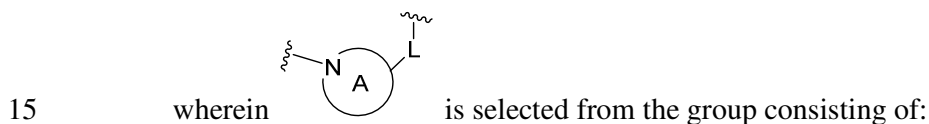
wherein L is linked to a carbon atom in A and A is optionally substituted with 1 to 2 R^k groups;

- 10 each R^k is independently selected from the group consisting of F, CN, methyl, ethyl and C_{1-2} haloalkyl;

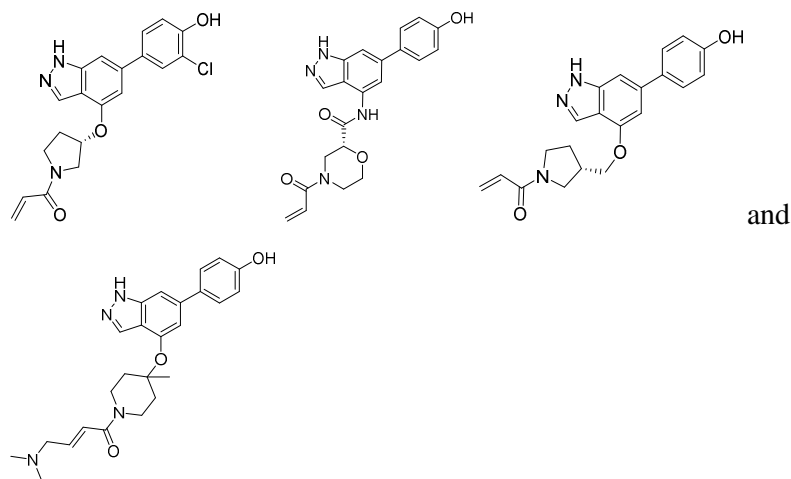


R^2 is selected from the group consisting of H, Cl, and F.

15. The compound of claim 14, or a pharmaceutically acceptable salt thereof,

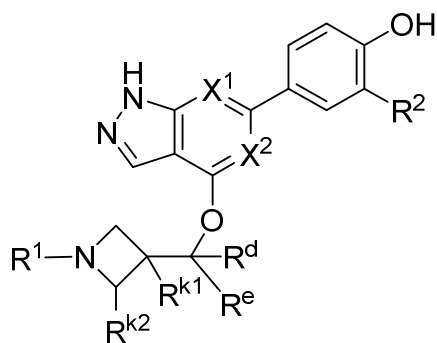


16. The compound of claim 14, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of



5

17. A compound of formula (B):



(B)

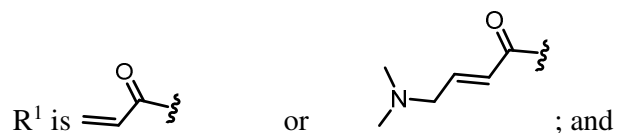
10 or a pharmaceutically acceptable salt thereof, wherein

X^1 and X^2 are each independently selected from N and CH;

R^d and R^e are each independently selected from the group consisting of H and C_{1-3} alkyl; optionally R^d and R^e may be joined to form a cyclopropyl ring;

R^{k1} is selected from the group consisting of H, F, CN, OMe, and C_{1-3} alkyl;

15 R^{k2} is selected from the group consisting of H and methyl;



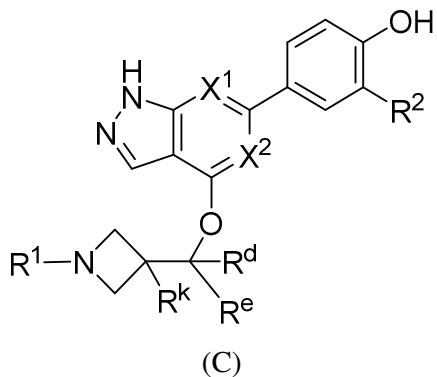
R^2 is selected from the group consisting of H, Cl, and F.

18. The compound of claim 17, or a pharmaceutically acceptable salt thereof,
wherein

R^d and R^e are each independently selected from the group consisting of H and
methyl; optionally R^d and R^e may be joined to form a cyclopropyl ring; and

5 R^{k1} is selected from the group consisting of H, F, CN, OMe, methyl and ethyl.

19. A compound of formula (C):

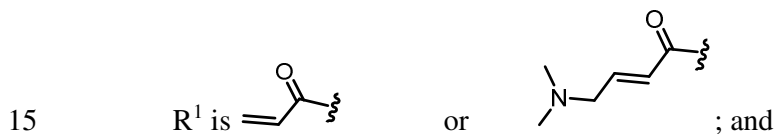


10 or a pharmaceutically acceptable salt thereof, wherein

X^1 and X^2 are both CH, or X^1 and X^2 are both N, or X^1 is N and X^2 is CH;

R^d and R^e are each independently selected from the group consisting of H and
methyl;

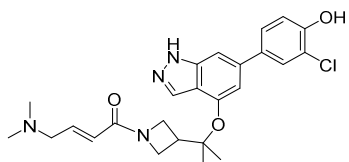
R^k is selected from the group consisting of H, CN, methyl and ethyl;



R^2 is selected from the group consisting of H, Cl, and F.

or a pharmaceutically acceptable salt thereof.

24. A crystalline form of the compound of formula:



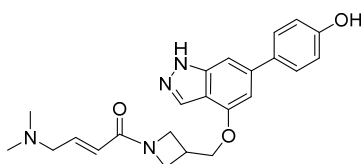
5 wherein the crystalline form is characterized by a powder X-ray diffraction pattern comprising diffraction peaks at 2θ values of 5.65 ± 0.20 , 14.22 ± 0.20 , 15.16 ± 0.20 , and 19.31 ± 0.20 .

25. The crystalline form of claim 24 wherein the powder X-ray diffraction
10 pattern is further characterized by having additional diffraction peaks at 2θ values of 7.12 ± 0.20 , 10.02 ± 0.20 , 11.16 ± 0.20 , 17.06 ± 0.20 , and 24.43 ± 0.20 .

26. The crystalline form of claim 25 wherein the powder X-ray diffraction
15 pattern is further characterized by having two or more additional diffraction peaks at 2θ values selected from 13.10 ± 0.20 , 14.82 ± 0.20 , 16.55 ± 0.20 , 20.08 ± 0.20 , 21.08 ± 0.20 , 21.65 ± 0.20 , 22.51 ± 0.20 , 22.98 ± 0.20 , 25.02 ± 0.20 , 25.72 ± 0.20 , 26.80 ± 0.20 , 27.06 ± 0.20 , 28.31 ± 0.20 , 30.08 ± 0.20 , 30.31 ± 0.20 and 32.08 ± 0.20 .

27. The crystalline form of claim 24 wherein the crystalline form is
20 characterized by a differential scanning calorimetry trace recorded at a heating rate of 10°C per minute which shows a maximum in endothermic heat flow with a peak at $162.9\pm3^\circ\text{C}$.

28. A crystalline form of the compound of formula:



25 wherein the crystalline form is characterized by a powder X-ray diffraction pattern comprising diffraction peaks at 2θ values of 9.67 ± 0.20 , 11.61 ± 0.20 , 17.61 ± 0.20 , 18.88 ± 0.20 , and 23.33 ± 0.20 .

29. The crystalline form of claim 28 wherein the powder X-ray diffraction pattern is further characterized by having additional diffraction peaks at 2θ values of 4.82 ± 0.20 , 15.69 ± 0.20 , and 16.19 ± 0.20 .

30. The crystalline form of claim 29 wherein the powder X-ray diffraction pattern is further characterized by having two or more additional diffraction peaks at 2θ values selected from 11.92 ± 0.20 , 12.98 ± 0.20 , 13.23 ± 0.20 , 16.45 ± 0.20 , 16.67 ± 0.20 , 19.39 ± 0.20 , 19.96 ± 0.20 , 20.14 ± 0.20 , 22.14 ± 0.20 , 23.84 ± 0.20 , 24.06 ± 0.20 , 24.29 ± 0.20 , 25.31 ± 0.20 , 25.63 ± 0.20 , 27.06 ± 0.20 , 27.31 ± 0.20 , 30.10 ± 0.20 , and 30.53 ± 0.20 .

31. The crystalline form of claim 28 wherein the crystalline form is characterized by a differential scanning calorimetry trace recorded at a heating rate of $10\text{ }^{\circ}\text{C}$ per minute which shows a maximum in endothermic heat flow with a peak at $201.3\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$.

32. The crystalline form of claim 28 wherein the crystalline form is characterized by a differential scanning calorimetry trace recorded at a heating rate of $10\text{ }^{\circ}\text{C}$ per minute which shows a maximum in endothermic heat flow at a temperature between $198\text{ }^{\circ}\text{C}$ and $204\text{ }^{\circ}\text{C}$.

33. A pharmaceutical composition comprising a compound of any one of claims 1 to 23, or a pharmaceutically acceptable salt thereof, or a crystalline form of any one of claims 24 to 32, and a pharmaceutically-acceptable carrier.

34. The pharmaceutical composition of claim 33 further comprising one or more other therapeutic agents useful for treating a gastrointestinal inflammatory disease.

35. Use of a compound of any one of claims 1 to 23, or a pharmaceutically acceptable salt thereof, or a crystalline form of anyone of claims 24 to 32, for the manufacture of a medicament for the treatment of a gastrointestinal inflammatory disease in a mammal.

36. The use of claim 35 wherein the gastrointestinal inflammatory disease is selected from the group consisting of immune checkpoint inhibitor induced colitis, CTLA-4 inhibitor-induced colitis, graft versus host disease-related colitis, celiac disease, collagenous colitis, lymphocytic colitis, Behcet's disease, ileitis, eosinophilic esophagitis, and infectious colitis.

37. The use of claim 35 wherein the gastrointestinal inflammatory disease is ulcerative colitis.

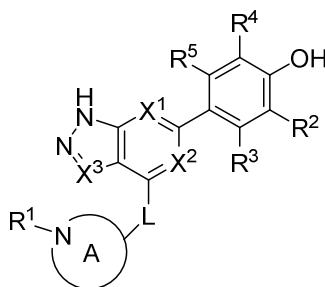
38. The use of claim 35 wherein the gastrointestinal inflammatory disease is Crohn's disease.

39. The use of claim 35, wherein one or more other therapeutic agents useful for treating a gastrointestinal inflammatory disease are to be administered with the medicament.

40. Use of a compound of any one of claims 1 to 23, or a pharmaceutically acceptable salt thereof, or a crystalline form of anyone of claims 24 to 32, for the manufacture of a medicament for the treatment of an inflammatory skin disease in a mammal.

41. Use of a compound of any one of claims 1 to 23, or a pharmaceutically acceptable salt thereof, or a crystalline form of anyone of claims 24 to 32, for the manufacture of a medicament for the treatment of cutaneous T-cell lymphoma.

42. A process for preparing a compound of formula (I) or a pharmaceutically acceptable salt thereof,

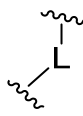


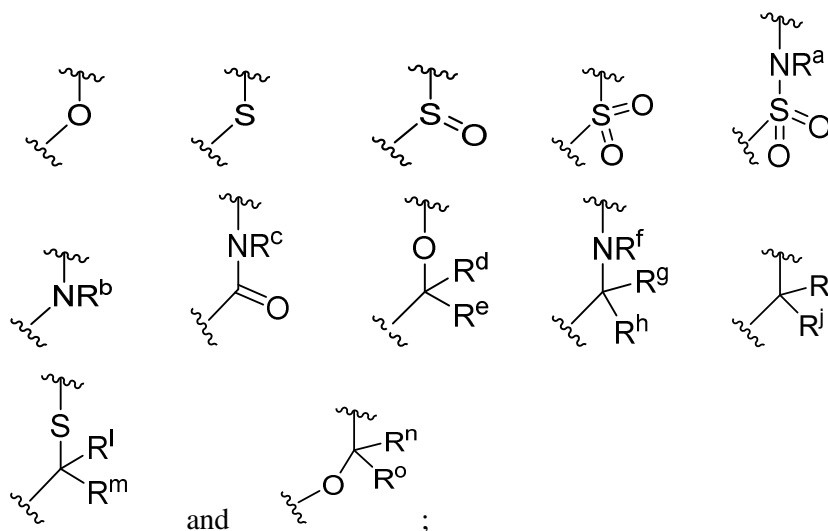
(I)

wherein

X^1 and X^2 are each independently selected from N and CH;

X^3 is selected from the group consisting of N, CH, C-CH₃, C-CF₃, C-CHF₂, C-CH₂-O-CH₃, C-SMe, C-NMe₂, C-NH-CH₃, C-Cl, C-CN, and C-OMe;

5  is selected from the group consisting of



10 R^a , R^b , R^c , and R^f are each independently selected from the group consisting of H and C₁₋₃ alkyl;

R^d , R^e , R^g , R^h , R^i , R^j , R^l , R^m , R^n and R^o are each independently selected from the group consisting of H and C₁₋₃ alkyl wherein the C₁₋₃ alkyl group may be optionally substituted with 1 to 3 halogens;

optionally R^d and R^e may be joined to form a cyclopropyl ring;

15 A is selected from the group consisting of

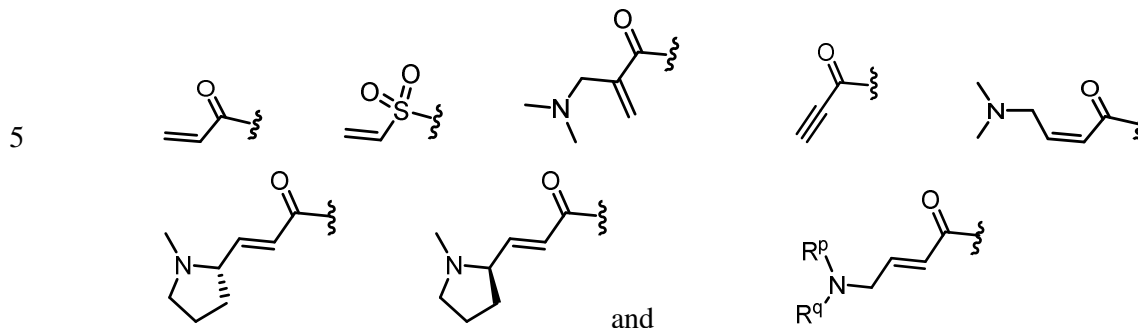
(a) a 4 to 10 membered monocyclic heterocyclic group containing one nitrogen atom and optionally containing one additional heteroatom selected from N, S, S(O)₂ and O, and

20 (b) a 6 to 10 membered multicyclic heterocyclic group containing one nitrogen atom and optionally containing one additional heteroatom selected from N, S and O,

wherein L is linked to a carbon atom in A and A is optionally substituted with 1 to 3 R^k groups;

each R^k is independently selected from the group consisting of F, CN, C_{1-3} alkoxy, cyclopropyl, and C_{1-3} alkyl, wherein the C_{1-3} alkyl group may be optionally substituted with OH, OMe or 1 to 3 halogens;

R^1 is selected from the group consisting of



wherein R^p and R^q are each independently selected from the group consisting of H, C_{3-5} cycloalkyl and C_{1-6} alkyl, wherein the C_{1-6} alkyl group may be optionally substituted with 1 to 3 substituents independently selected from the group consisting of C_{1-3} alkoxy and -S- C_{1-3} alkyl,

or R^p and R^q form a 4 to 6 membered monocyclic heterocyclic group containing one nitrogen atom and optionally containing one additional heteroatom selected from N, S, and O, wherein the 4 to 6 membered monocyclic heterocyclic group is optionally substituted with 1 to 3 substituents independently selected from the group consisting of

C_{1-6} alkyl, C_{1-3} alkoxy, -S- C_{1-3} alkyl and - C_{1-3} alkyl- C_{1-3} alkoxy;

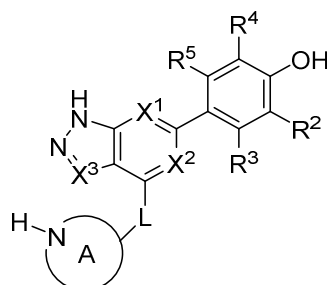
R^2 is selected from the group consisting of H, Cl, OMe, Me and F;

R^3 is selected from the group consisting of H and F;

R^4 is selected from the group consisting of H and F; and

R^5 is selected from the group consisting of H, Me and F.

the method comprising reacting a compound of formula (III):



(III)

with

(i) $Cl-R^1$, or

(ii) HO-R¹

and optionally forming a pharmaceutically-acceptable salt
to provide a compound of formula (I), or a pharmaceutically acceptable salt thereof.