

(2013)). Oral administration of Y-27632 was also able to improve coordination and balance in a rotarod performance test in the R6/2 model; the treatment also reduced the level of soluble huntingtin (Htt) protein (Li M et al., Neurobiol Dis. 36(3):413-20 (2009)). ROCKII interference (RI) with small hairpin RNA (ShRNA) also significantly improved movement disorder and attenuated dopaminergic (DA) neuron loss induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in a mouse model of Parkinson's disease. In addition, ROCK2 ShRNA inhibited the activation of M1 microglia in the substantia nigra (SN), exhibiting reduced activity of the TLR2/NF- κ B signaling pathway and decreased expression levels of iNOS and inflammatory factors, including interleukin (IL)-1 β and IL-6. (Zhang Q et al., Mol Med Rep. 14(6):4947-4956 (2016)). In another study Fasudil was also shown to have protective effects on the DN in the MPTP model. (Zhao Y et al., J Neurol Sci 353(1-2):28-37 (2015)). Further experiments with RNAi knockdown demonstrated that reduced expression of both ROCK1 and ROCK2 suppressed endogenous A β 40 production in neurons and A β 40 levels were reduced in brains of ROCK1 heterozygous knock-out mice compared to wild-type littermate controls suggesting ROCK may also be a valid target for the treatment of Alzheimer's disease (Henderson B et al., J Neurochem, 138(4):525-31 (2016)).

[0011] Several studies also demonstrate that ROCK inhibition will have utility in cancer therapy. Y-27632 and Fasudil have been shown to down regulate surviving expression in the pancreatic cell line PANC-1 and sensitised the cells to gemcitabine induced cell death. (Takeda H., Anticancer Res 36(12):6311-6318 (2016)). Oral administration of Fasudil has also been shown to reduce the tumour size in mouse transgenic model of human gastric cancer (Hinsenkamp I et al., Neoplasia 18(8):500-11 (2016)). Fasudil has also been shown to suppress proliferation and migration and induce apoptosis in urothelial cancer cells (Abe H et al., BMC Cancer 7;14:412 (2014)).

[0012] Furthermore, it is an aim of certain embodiments of this invention to provide new treatments, for example treatments for diabetes, inflammation, Alzheimer's, hypertension, fibrosis, cancer, pathologies of the central nervous system and other conditions associated with ROCK1 and/or ROCK2. In particular, it is an aim of certain embodiments of this invention to provide compounds which have comparable activity to existing ROCK therapies.

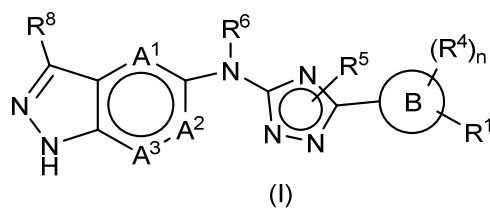
[0013] It is an aim of certain embodiments of this invention to provide compounds which exhibit reduced cytotoxicity or increased solubility relative to prior art compounds and existing therapies.

[0014] Another aim of certain embodiments of this invention is to provide compounds having a convenient pharmacokinetic profile and a suitable duration of action following dosing. A further aim of certain embodiments of this invention is to provide compounds in which the metabolised fragment or fragments of the drug after absorption are GRAS (Generally Regarded As Safe).

[0015] Certain embodiments of the present invention satisfy some or all of the above aims.

BRIEF SUMMARY OF THE DISCLOSURE

[0016] In ~~embodiments~~one aspect, the present ~~invention~~disclosure provides a compound of formula (I) and pharmaceutically acceptable salts thereof:



wherein

A¹, A² or A³ are each independently selected from CH, CR⁷ or N;

B represents a 5 to 10 membered carbocyclic ring system or a 5 to 10 membered heterocyclic ring system;

R¹ is L-R², wherein

L is a bond or -L¹-L²-,

wherein L¹ is selected from: a bond, -(CR^AR^B)₁₋₃-, -O(CR^AR^B)₁₋₃-, -(CR^AR^B)₀₋₃O-, and -NR^C(CR^AR^B)₁₋₃-, and

L² is selected from: a bond, -(CR^AR^B)₁₋₃-, -O-, -NR^D-, -C(O)NR^D-, -NR^DC(O)-, -C(O)O-, -OC(O)-, -C(O)-, -S(O)₂NR^D-, -NR^DS(O)₂-, -S(O)₂-, -S(O)(NR^D)-, -NR^DC(O)NR^E-, -OC(O)NR^D-, and -C(O)NR^DS(O)₂-, and

R² is selected from: H, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkyl substituted with -OR^F, C₁₋₆ alkyl substituted with -NR^FR^G, C₁₋₄ haloalkyl substituted with -OR^F, C₃₋₈ cycloalkyl substituted with OH, C₁₋₄ alkyl substituted with 3 to 8 membered heterocycloalkyl, C₁₋₄ alkyl substituted with 6 membered heteroaryl, -(CR^HR^I)₁₋₃OR^F, -(CR^HR^I)₁₋₃NR^FR^G, -(CR^NR^O)₁₋₃C(O)OR^F, -(CR^NR^O)₁₋₃C(O)NR^FR^G, C₃₋₁₀ carbocyclic ring system, and 3 to 10 membered heterocyclic ring system, wherein the carbocyclic ring or heterocyclic ring system is unsubstituted or substituted with: =O, -NR^FR^G, -C(O)R^F, halo, -CN, C₁₋₄ alkyl, C₁₋₄ haloalkyl, or C₁₋₄ alkyl substituted with -OR^F;

R⁴ is independently selected at each occurrence from: halo, C₁₋₄ alkyl, C₁₋₆ haloalkyl, -CN, -OR^J, =O, C₁₋₄ alkyl substituted with -OR^J, -NR^JR^K, C₁₋₄ alkyl substituted with -NR^JR^K, C₃₋₈ cycloalkyl, C₁₋₄ alkyl substituted with C₃₋₈ cycloalkyl, 3 to 8 membered heterocycloalkyl and C₁₋₄ alkyl substituted with 3 to 8 membered heterocycloalkyl;

R⁵ is selected from: H, C₁₋₄ alkyl, C₁₋₄ alkyl substituted with -OR^L, C₁₋₄ alkyl substituted with -NR^LR^L, C₃₋₈ cycloalkyl, substituted or unsubstituted phenyl, 3 to 8 membered heterocycloalkyl, C₁₋₄ alkyl substituted with C₃₋₈ cycloalkyl, C₁₋₄ alkyl substituted with 3 to 8 membered heterocycloalkyl and substituted or unsubstituted 5 or 6 membered heteroaryl, wherein the phenyl or heteroaryl group may be substituted by 1 or 2 R⁹;

R⁶ is selected from: H and C₁₋₄ alkyl;

R⁷ is selected from: H, halo, -OR^M, C₁₋₄ alkyl, C₁₋₆ haloalkyl, C₁₋₄ alkenyl, -CN, and C₃₋₈ cycloalkyl;

R⁸ is selected from: H, halo, C₁₋₄ alkyl, C₁₋₆ haloalkyl, -CN, and C₃₋₈ cycloalkyl;

R⁹ is selected from halo or C₁₋₄ alkyl;

n is 0, 1, or 2;

R^A and R^B are selected from H, C₁₋₄ alkyl, or C₁₋₄ haloalkyl or R^A and R^B together with the atom to which they are attached form a 3 to 6 membered cycloalkyl ring or a 3 to 6 membered heterocycloalkyl ring;

R^C, R^D, R^E, R^F and R^G are each independently selected from H, C₁₋₄ alkyl and C₁₋₄ haloalkyl;

R^H and R^I are each H except one pair of R^H and R^I on the same carbon atom, together with that carbon atom, form a 3 to 6 membered cycloalkyl ring or a 3 to 6 membered heterocycloalkyl ring; and

R^J, R^K, R^L, R^M, R^N and R^O are each independently at each occurrence selected from H or C₁₋₄ alkyl.

[0016a] In another aspect, the present disclosure refers to use of a compound as disclosed herein in the manufacture of a medicament for the treatment of a condition which is modulated by ROCK1 and/or ROCK2, wherein the condition that is modulated by ROCK1 and/or ROCK2 is a condition selected from: fibrotic diseases, auto-immune, inflammatory-fibrotic conditions, inflammatory conditions, central nervous system disorders, or cancer; and/or wherein the condition treatable by the inhibition of ROCK1 and/or ROCK2 is selected from: Sarcoidosis, sclerosis, primary biliary sclerosis, sclerosing cholangitis, dermatitis, atopic dermatitis, Still's disease, chronic obstructive pulmonary disease, Guillain-Barre disease, Graves' disease, Addison's disease, Raynaud's phenomenon, or autoimmune hepatitis. Arthritis, rheumatoid arthritis, psoriatic arthritis, osteoarthritis, degenerative arthritis, polymyalgia rheumatic, ankylosing spondylitis, reactive arthritis, gout, pseudogout, inflammatory joint disease, systemic lupus erythematosus, polymyositis, and fibromyalgia. Additional types of arthritis include achilles tendinitis, achondroplasia, acromegalic arthropathy, adhesive capsulitis, adult onset Still's disease, anserine bursitis, avascular necrosis, Behcet's syndrome, bicipital tendinitis, Blount's disease, brucellar spondylitis, bursitis, calcaneal bursitis, calcium pyrophosphate dihydrate deposition disease (CPPD), crystal deposition disease, Caplan's syndrome, carpal tunnel syndrome, chondrocalcinosis, chondromalacia patellae, chronic synovitis, chronic recurrent multifocal osteomyelitis, Churg-Strauss syndrome, Cogan's syndrome, corticosteroid-induced osteoporosis, costosternal syndrome, CREST syndrome, cryoglobulinemia, degenerative joint disease, dermatomyositis, diabetic finger sclerosis, diffuse idiopathic skeletal hyperostosis (DISH), discitis, discoid lupus erythematosus, drug-induced lupus, Duchenne's muscular dystrophy, Dupuytren's contracture, Ehlers-Danlos syndrome, enteropathic arthritis, epicondylitis, erosive inflammatory osteoarthritis, exercise-induced compartment syndrome, Fabry's disease, familial Mediterranean fever, Farber's lipogranulomatosis, Felty's syndrome, Fifth's disease, flat feet, foreign body synovitis, Freiberg's disease, fungal arthritis, Gaucher's disease, giant cell arteritis, gonococcal arthritis, Goodpasture's syndrome, granulomatous arteritis, hemarthrosis, hemochromatosis, Henoch-Schonlein purpura, Hepatitis B surface antigen disease, hip dysplasia, Hurler syndrome, hypermobility syndrome, hypersensitivity vasculitis, hypertrophic osteoarthropathy, immune complex disease, impingement syndrome, Jaccoud's arthropathy, juvenile ankylosing spondylitis, juvenile dermatomyositis, juvenile rheumatoid arthritis, Kawasaki disease, Kienbock's disease, Legg-Calve-

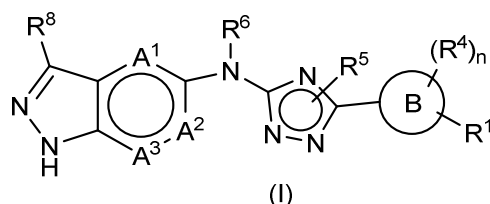
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[0016b] In another aspect, the present disclosure refers to use of a compound as disclosed herein in the manufacture of a medicament for the treatment of: fibrotic diseases, auto-immune, inflammatory-fibrotic conditions, inflammatory conditions, central nervous system disorders, or cancer.

[0016c] In another aspect, the present disclosure refers to use of a compound as disclosed herein in the manufacture of a medicament for the treatment of a condition selected from: Idiopathic Pulmonary Fibrosis (IPF); systemic sclerosis (SSC); interstitial lung disease (ILD); type 1 and type 2 diabetes; diabetic nephropathy; Nonalcoholic Steatohepatitis (NASH); Nonalcoholic fatty liver disease (NAFLD);

hypertension, atherosclerosis, restenosis, stroke, heart failure, coronary vasospasm, cerebral vasospasm, peripheral circulatory disorder, peripheral artery occlusive disease, ischemia/reperfusion injury, pulmonary hypertension and angina, erectile dysfunction, fibroid lung, fibroid liver and fibroid kidney, glaucoma, ocular hypertension, retinopathy, rheumatoid arthritis, psoriasis, psoriatic arthritis, Sjogren's syndrome, asthma, adult respiratory distress syndrome, chronic obstructive pulmonary disease (COPD), SLE, cGVHD, inflammatory bowel disease, stenosis of the bowel, disorders involving neuronal degeneration or physical injury to neural tissue, Huntington's disease, Parkinson's Disease, Alzheimer's, Amyotrophic lateral sclerosis (ALS), multiple sclerosis, liver cancer, bladder cancer, hepatoma, squamous carcinoma of the lung, non-small cell lung cancer, adenocarcinoma of the lung, small-cell lung cancer, various types of head and neck cancer, breast cancer, colon cancer, colorectal cancer, cancer of the peritoneum, hepatocellular cancer, gastrointestinal cancer, esophageal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, squamous cell cancer, pituitary cancer, astrocytoma, soft tissue sarcoma, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, kidney cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, brain cancer, endometrial cancer, testis cancer, cholangiocarcinoma, gallbladder carcinoma, gastric cancer and melanoma.

[0017] In ~~embodiment~~ examples, the present ~~invention~~ disclosure provides a compound of formula (I) and pharmaceutically acceptable salts thereof:



wherein

A¹, A² or A³ are each independently selected from CH, CR⁷ or N;

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R¹ is L-R², wherein

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R² is selected from: H, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkyl substituted with -OR^F, C₁₋₆ alkyl substituted with -NR^FR^G, C₃₋₈ cycloalkyl substituted with OH, C₁₋₄ alkyl substituted with 3 to 8 membered heterocycloalkyl, C₁₋₄ alkyl substituted with 6 membered heteroaryl, -(CR^HR^I)₁₋₃OR^F,

$-(\text{CR}^{\text{H}}\text{R}^{\text{I}})_{1-3}\text{NR}^{\text{F}}\text{R}^{\text{G}}$, C_{3-10} carbocyclic ring system, and 3 to 10 membered heterocyclic ring system, wherein the carbocyclic ring or heterocyclic ring system is unsubstituted or substituted with: $=\text{O}$, $-\text{NR}^{\text{F}}\text{R}^{\text{G}}$, halo, C_{1-4} alkyl, or C_{1-4} alkyl substituted with $-\text{OR}^{\text{F}}$;

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R^H and R^I are each H except one pair of R^H and R^I on the same carbon atom, together with that carbon atom, form a 3 to 6 membered cycloalkyl ring or a 3 to 6 membered heterocycloalkyl ring; and

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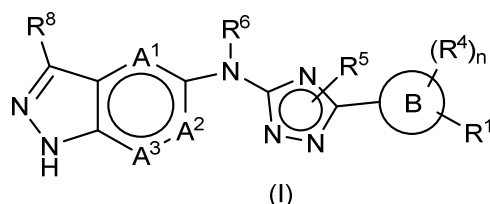
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R² is selected from: H, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkyl substituted with -OR^F, C₁₋₆ alkyl substituted with -NR^FR^G, C₃₋₈ cycloalkyl substituted with OH, C₁₋₄ alkyl substituted with 3 to 8 membered heterocycloalkyl, C₁₋₄ alkyl substituted with 6 membered heteroaryl, -(CR^HR^I)₁₋₃OR^F,

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R⁴ is selected from: halo, C₁₋₄ alkyl, C₁₋₆ haloalkyl, -CN, -OR^J, =O, C₁₋₄ alkyl substituted with -OR^J, -NR^JR^K, C₁₋₄ alkyl substituted with -NR^JR^K, C₃₋₈ cycloalkyl, C₁₋₄ alkyl substituted with C₃₋₈ cycloalkyl, 3 to 8 membered heterocycloalkyl and C₁₋₄ alkyl substituted with 3 to 8 membered heterocycloalkyl;

R⁵ is selected from: H, C₁₋₄ alkyl, C₁₋₄ alkyl substituted with -OR^L, C₃₋₈ cycloalkyl, substituted or unsubstituted phenyl, 3 to 8 membered heterocycloalkyl, C₁₋₄ alkyl substituted with C₃₋₈ cycloalkyl, C₁₋₄ alkyl substituted with 3 to 8 membered heterocycloalkyl and substituted or unsubstituted 5 or 6 membered heteroaryl, wherein the phenyl or heteroaryl group may be substituted by 1 or 2 R⁹;

R⁶ is selected from: H and C₁₋₄ alkyl;

R⁷ is selected from: H, halo, -OR^M, C₁₋₄ alkyl, C₁₋₆ haloalkyl, -CN, and C₃₋₈ cycloalkyl;

R⁸ is selected from: H, halo, C₁₋₄ alkyl, C₁₋₆ haloalkyl, -CN, and C₃₋₈ cycloalkyl;

R⁹ is selected from halo or C₁₋₄ alkyl;

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R^C, R^D, R^E, R^F and R^G are each independently selected from H and C₁₋₄ alkyl;

R^H and R^I are each H except one pair of R^H and R^I on the same carbon atom, together with that carbon atom, form a 3 to 6 membered cycloalkyl ring or a 3 to 6 membered heterocycloalkyl ring; and

R^J, R^K, R^L and R^M are each independently at each occurrence selected from H or C₁₋₄ alkyl.

[0018] In embodimentexamples, A¹, A² and A³ are each independently selected from: C-H, C-F, C-Cl, C-Me, C-Et, C-*i*-Pr, C-cyclopropyl, C-CN, C-CF₃ or N. Optionally, at least two of A¹, A² and A³ are C-H.

[0019] In embodimentexamples, A¹, A² and A³ are each independently selected from: C-H, C-F, C-Cl, C-Me, C-Et, C-*i*-Pr, C-cyclopropyl, C-ethenyl, C-propenyl, C-CN, C-CF₃ or N. Optionally, at least two of A¹, A² and A³ are C-H.

[0020] In embodimentexamples A¹ is C-H, C-Cl, C-F, C-ethenyl, C-propenyl, or C-Me. In embodimentexamples A² is C-H or C-F. In embodimentexamples A³ is C-H. In embodimentexamples A¹ is C-H, C-Cl, C-F, C-ethenyl, C-propenyl, or C-Me; A² is C-H or C-F; and A³ is C-H.

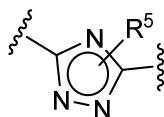
[0021] In embodimentexamples, A¹, A² and A³ are each C-H. In embodimentexamples A¹ is C-Cl, A² is C-H and A³ is C-H. In embodimentexamples A¹ is C-F, A² is C-H and A³ is C-H. In embodimentexamples A¹ is C-Me, A² is C-H and A³ is C-H. In embodimentexamples A¹ is C-H, A² is C-F and A³ is C-H. In embodimentexamples A¹ is C-ethenyl, A² is C-H and A³ is C-H. In embodimentexamples A¹ is C-propenyl, A² is C-H and A³ is C-H.

[0022] Accordingly, R⁷ may be H, Cl, F, CN, methyl, ethyl, iso-propyl, ethenyl, propenyl, trifluoromethyl or cyclopropyl. In embodimentexamples R⁷ is H, Cl, F, CN, methyl, ethyl or cyclopropyl.

[0023] R⁸ may be H, Cl, F, CN or Me. In embodimentexamples, R⁸ is H or methyl.

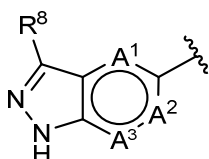
[0024] In embodiment examples R⁶ is selected from H or methyl. Preferably, R⁶ is H.

[0025] As the skilled person will be aware, and for the avoidance of doubt, the structure shown below:



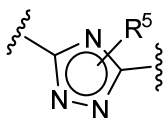
represents an aromatic 5 membered ring, where one of the nitrogen atoms within the ring is substituted by R⁵.

[0026] As the skilled person will be aware, and for the avoidance of doubt, the structure shown below:

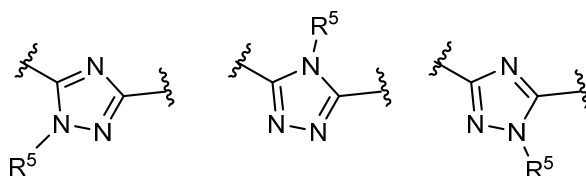


represents a bicyclic group with a 5-membered and a 6-membered ring, wherein the 6-membered ring is an aromatic ring.

[0027] In embodiment examples



represents:

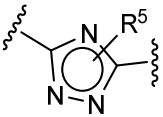


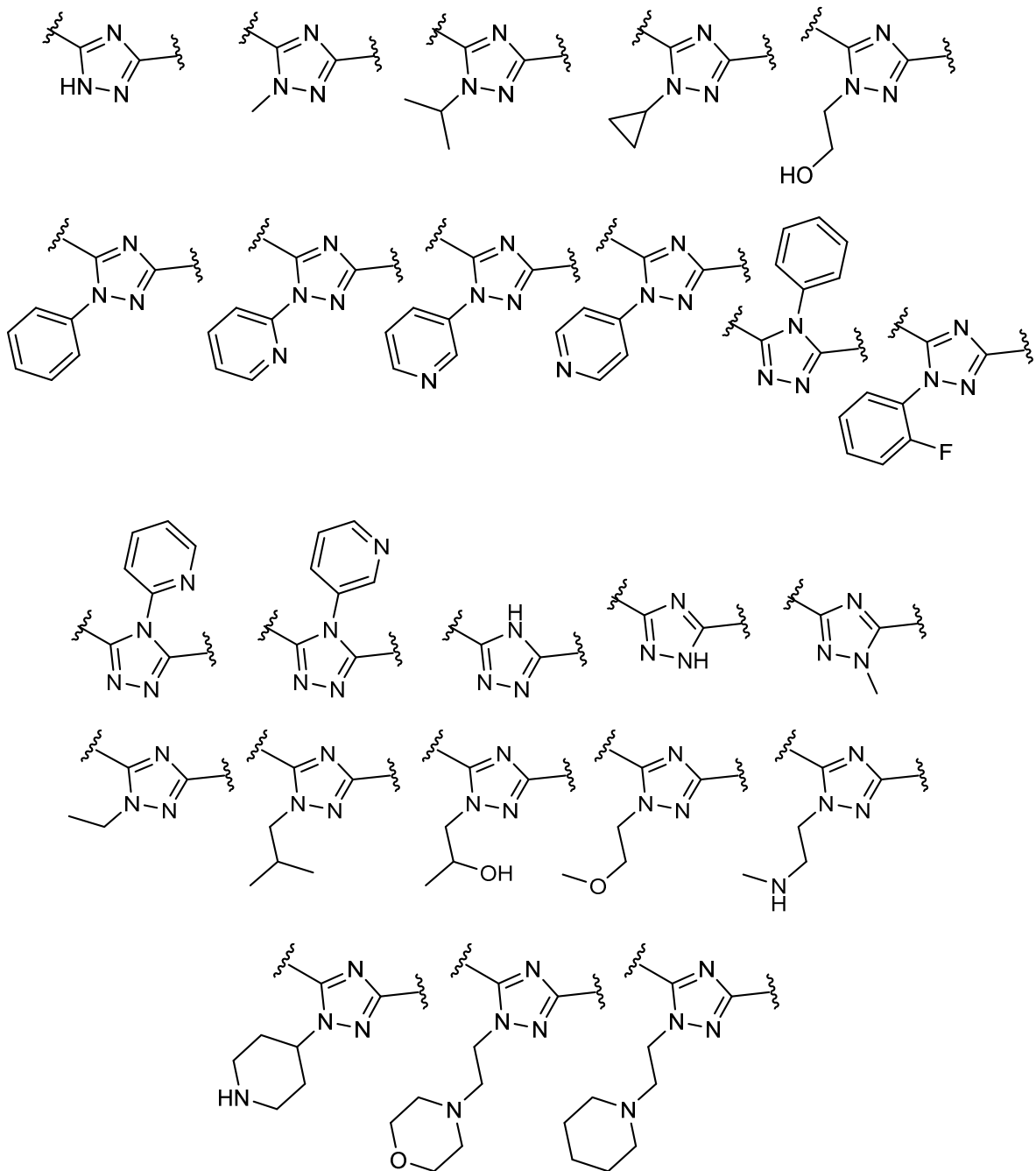
[0028] In embodiment examples R⁵ is selected from: H, C₁₋₄ alkyl, C₁₋₄ alkyl substituted with -OR^L, C₁₋₄ alkyl substituted with -NR^LR^L, C₃₋₈ cycloalkyl, substituted or unsubstituted phenyl, C₁₋₄ alkyl substituted with a 3 to 8 membered heterocycloalkyl, and substituted or unsubstituted 5 or 6 membered heteroaryl, wherein the phenyl or heteroaryl group may be substituted by 1 or 2 R⁹.

[0029] In embodiment examples R⁵ is selected from: H, C₁₋₄ alkyl, C₁₋₄ alkyl substituted with -OR^L, C₁₋₄ alkyl substituted with -NR^LR^L, C₃₋₈ cycloalkyl, substituted or unsubstituted phenyl, C₁₋₄ alkyl substituted with a 3 to 8 membered heterocycloalkyl, and substituted or unsubstituted 5 or 6 membered heteroaryl, wherein the phenyl or heteroaryl group may be substituted by 1 or 2 R⁹. Optionally, R⁵ is selected from: H or C₁₋₄ alkyl. Optionally, R^L is independently selected at each occurrence from: H or methyl.

[0030] In embodiment examples R⁵ is selected from: H, methyl, ethyl, isobutyl, isopropyl, isopropanol, cyclopropyl, -CH₂CH₂OH, -CH₂CH₂OCH₃, -CH₂CH₂NHCH₃, phenyl, fluorophenyl, pyridyl, piperidyl,

ethyl substituted with morpholine, and ethyl substituted with piperidine. Optionally, R⁵ may be selected from: H or methyl.

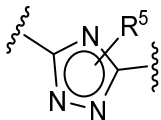
[0031] In ~~embodiment~~ examples  represents:



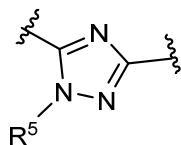
[0032] In ~~embodiment~~ examples R⁵ is selected from: H, C₁₋₄ alkyl, C₁₋₄ alkyl substituted with -OR^L, C₃₋₈ cycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted 5 or 6 membered heteroaryl, wherein the phenyl or heteroaryl group may be substituted by 1 or 2 R⁹.

[0033] In ~~embodiment~~examples R^5 is selected from: H, C_{1-4} alkyl, C_{1-4} alkyl substituted with $-OR^L$, C_{3-8} cycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted 5 or 6 membered heteroaryl, wherein the phenyl or heteroaryl group may be substituted by 1 or 2 R^9 . Optionally, R^5 is selected from: H or C_{1-4} alkyl.

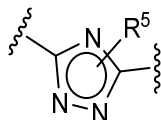
[0034] In ~~embodiment~~examples R^5 is selected from: H, methyl, isopropyl, cyclopropyl, $-CH_2CH_2OH$, phenyl, fluorophenyl, and pyridyl. Optionally, R^5 may be selected from: H or methyl.



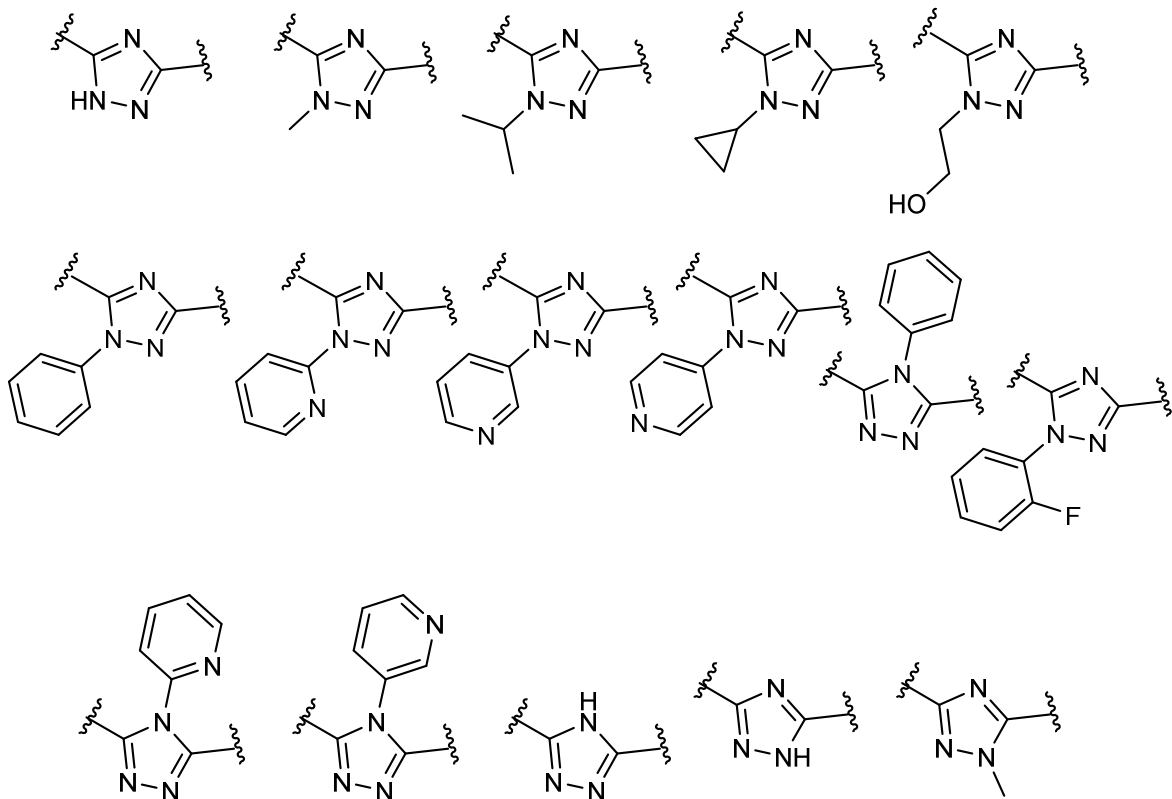
[0035] In preferred ~~embodiment~~examples represents:



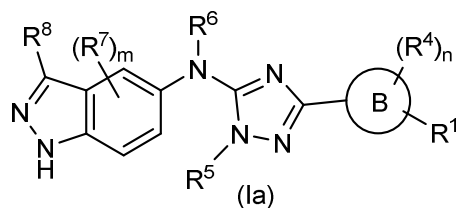
optionally wherein R^5 is methyl.



[0036] In ~~embodiment~~examples represents:



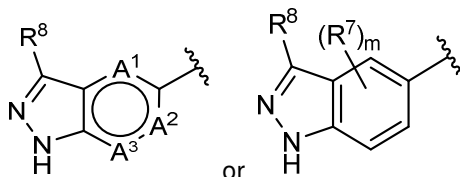
[0037] In ~~embodiment~~examples the compound of formula (I) is a compound according to formula (Ia):



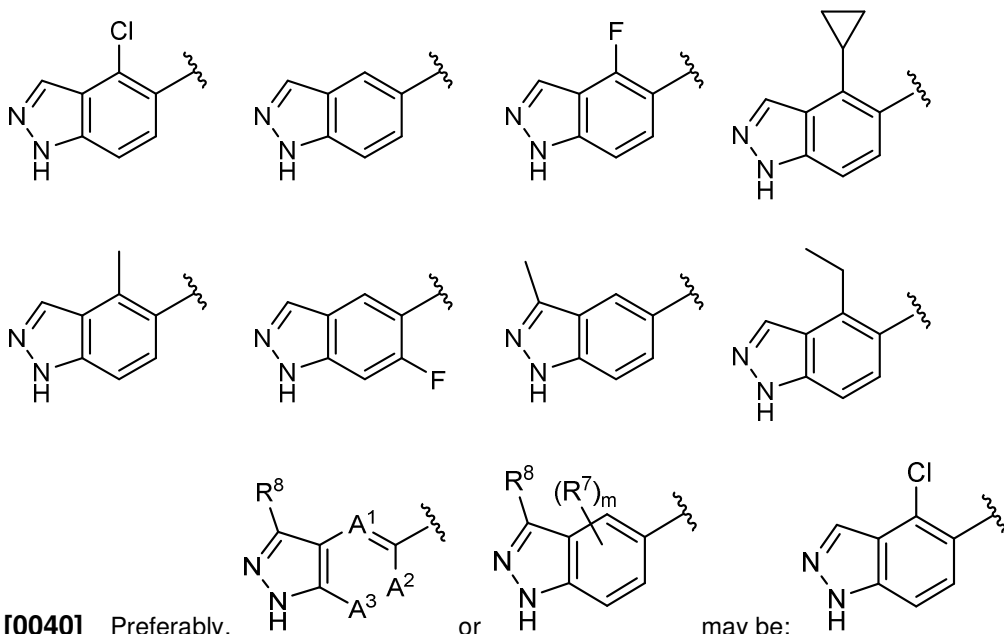
wherein m is 1 or 2.

[0038] Preferably, m is 1.

[0039] In embodiment examples



or may be:

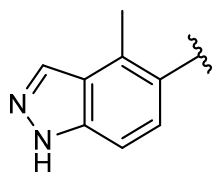


[0040] Preferably,

or

may be:

or



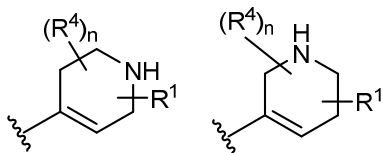
[0041] Any discussion of formula (I) in this application may relate equally to the compound of formula (Ia).

[0042] B may be selected from: a 5 or 6 membered carbocyclic ring which is aromatic or unsaturated, a 5 or 6 membered heterocyclic ring which is aromatic or unsaturated, a 9 or 10 membered carbocyclic bicyclic ring system, or a 9 or 10 membered heterocyclic bicyclic ring system, wherein the bicyclic ring system is either aromatic or one of the rings within the bicyclic ring system is aromatic or unsaturated and the other ring is saturated.

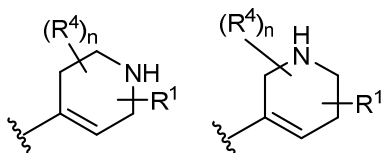
[0043] B may be selected from: a 5 or 6 membered carbocyclic ring which is aromatic or unsaturated. B may be selected from: a 5 or 6 membered heterocyclic ring which is aromatic or unsaturated. B may be selected from: a 9 or 10 membered carbocyclic bicyclic ring system wherein the bicyclic ring system is either aromatic or one of the rings within the bicyclic ring system is aromatic or unsaturated and the other ring is saturated. B may be selected from: a 9 or 10 membered heterocyclic bicyclic ring system, wherein the bicyclic ring system is either aromatic or one of the rings within the bicyclic ring system is aromatic or unsaturated and the other ring is saturated.

[0044] In a preferred ~~embodiment~~example B is selected from a 6 membered carbocyclic ring (optionally wherein the ring is aromatic or unsaturated) or a 10 membered heterocyclic fused bicyclic ring system (optionally wherein one of the rings is aromatic).

[0045] In ~~embodiment~~examples B is selected from: phenyl, pyrazole, pyridyl, piperidyl, azaindole, isoindoline, tetrahydroisoquinoline, tetrahydroisoquinolone, furan, indazole, benzpyrazole, pyrimidine, pyridone, tetrahydropyridine, dihydropyran, cyclopentene, cyclohexenyl, chromane, chromanone, benzodioxan, tetrahydronaphthalene, dihydrobenzoxazine, benzomorpholine, tetrahydroquinoline, naphthyridine, quinoline, isoquinoline, and dihydroisobenzofuran or B is

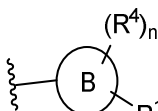


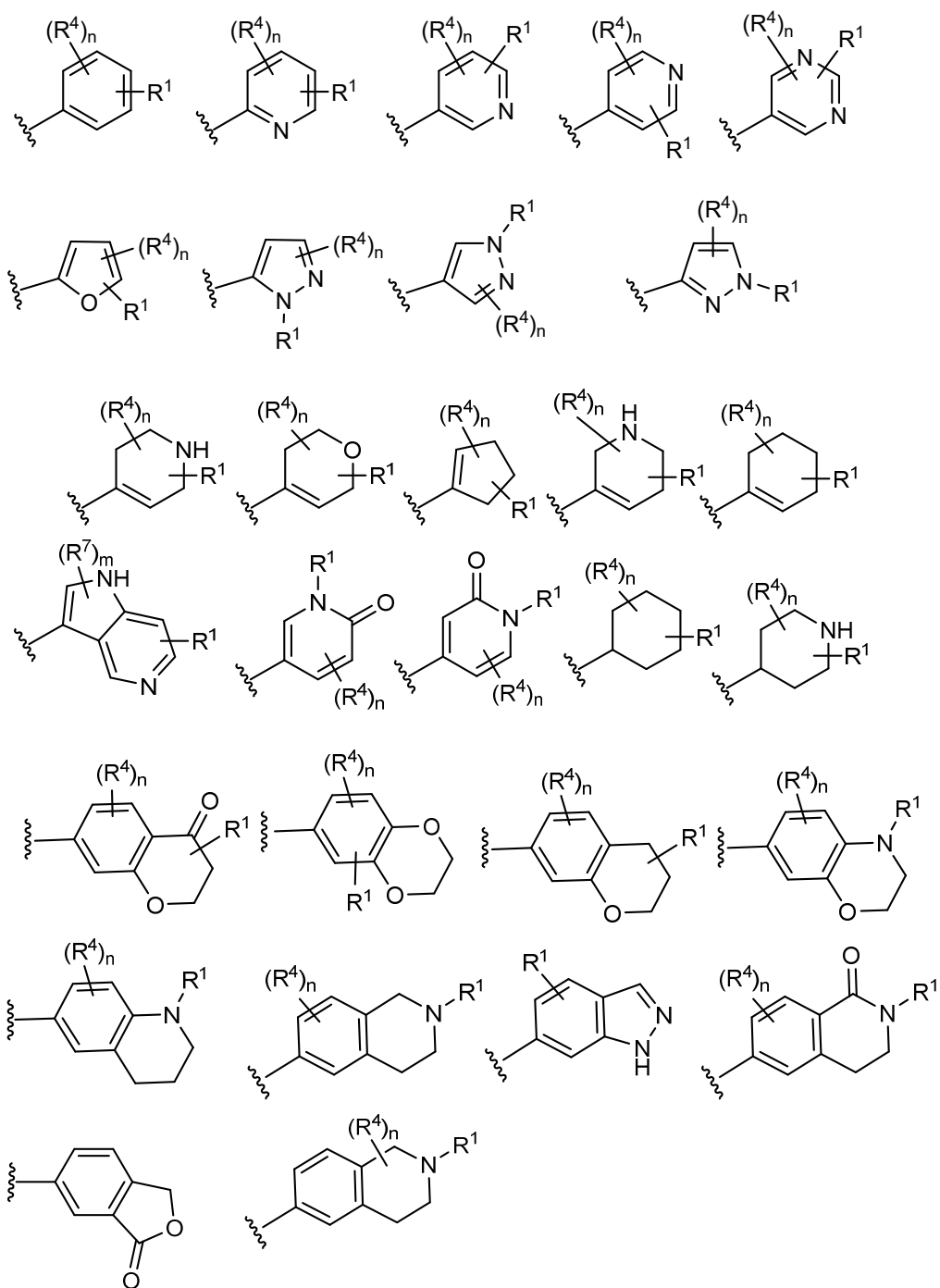
[0046] In ~~embodiment~~examples B is selected from: phenyl, pyrazole, pyridyl, azaindole, isoindoline, tetrahydroisoquinoline, tetrahydroquinolone, furan, indazole, benzpyrazole, pyrimidine, pyridone, tetrahydropyridine, dihydropyran, cyclopentene, cyclohexenyl, chromane, chromanone, benzodioxan, tetrahydronaphthalene, dihydrobenzoxazine, benzomorpholine and tetrahydroquinoline or B is



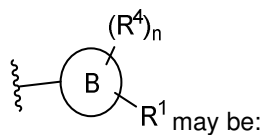
[0047] In ~~embodiment~~examples B is selected from: phenyl, pyridyl, tetrahydroisoquinoline, tetrahydroquinolone, and tetrahydroquinoline.

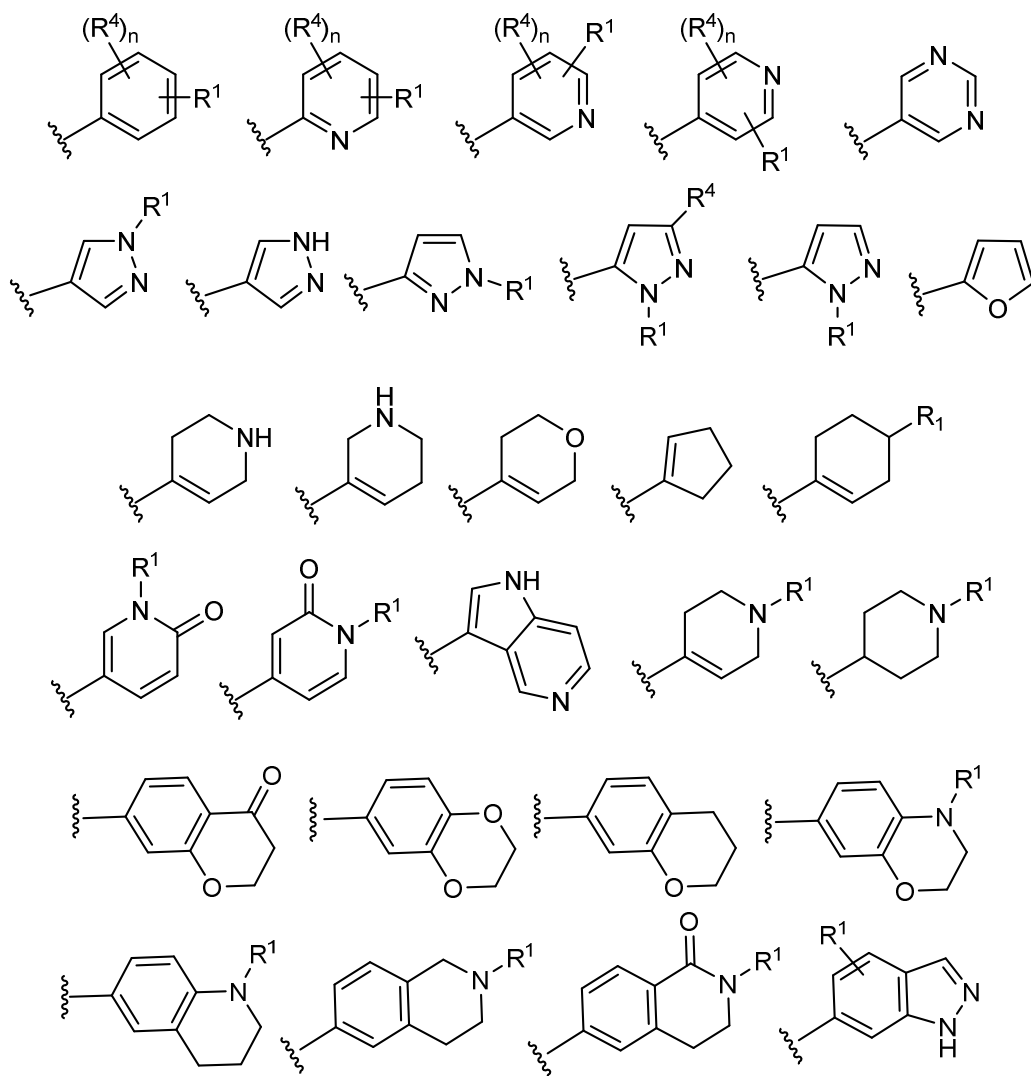
[0048] In ~~embodiment~~examples



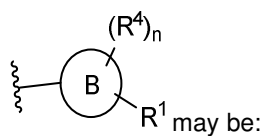


[0049] In embodiment examples

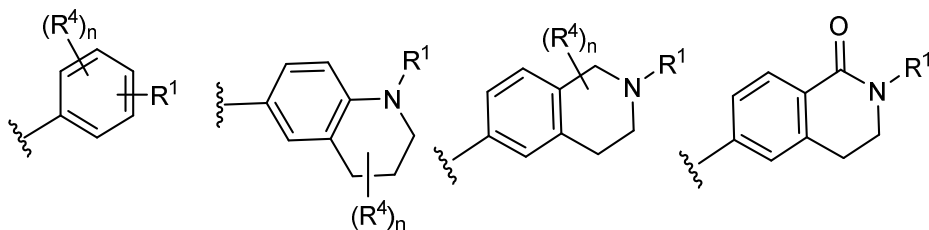




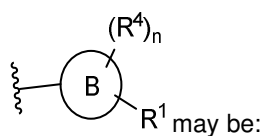
[0050] In ~~embodiment~~ examples



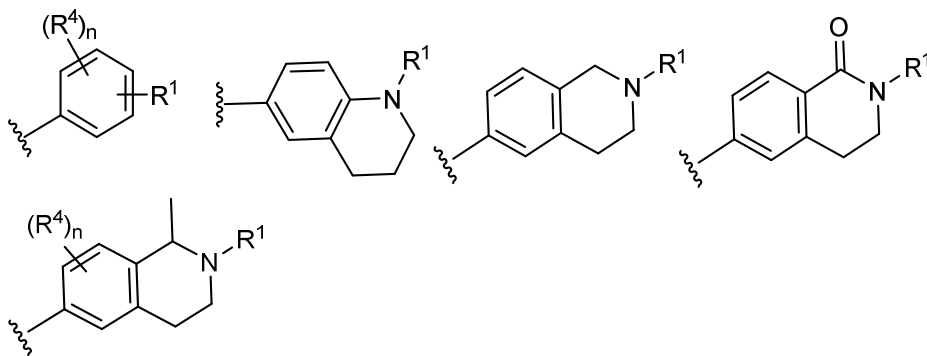
may be:



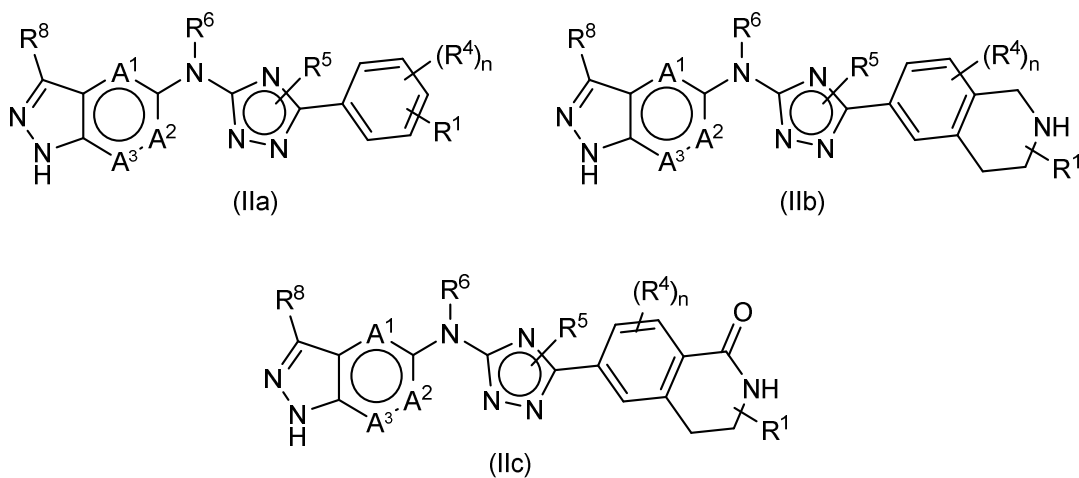
[0051] In ~~embodiment~~ examples



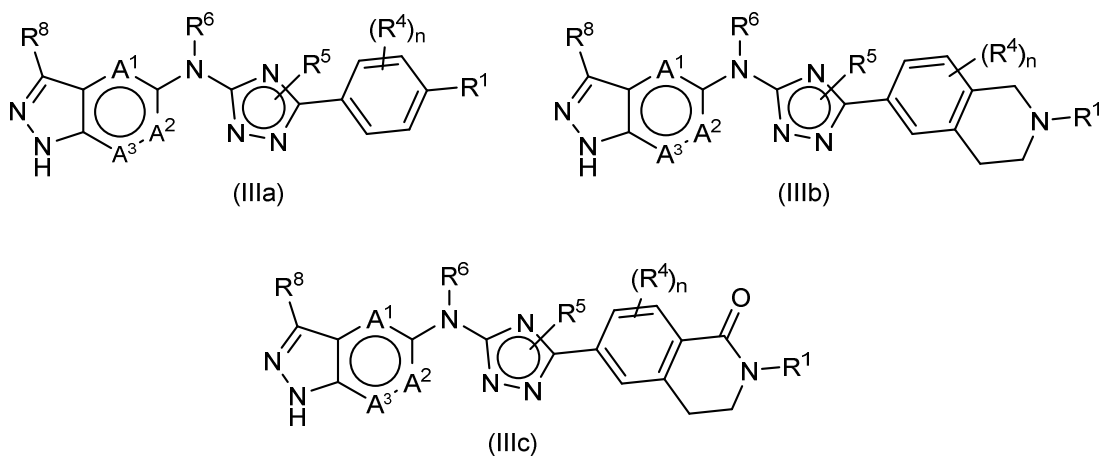
may be:



[0052] In ~~embodiment~~examples the compound of formula (I) is a compound according to formulae (IIa), (IIb), or (IIc):



[0053] In ~~embodiment~~examples the compound of formula (I) is a compound according to formulae (IIIa), (IIIb), or (IIIc):



[0054] L^1 may be selected from: a bond, $-(CR^A R^B)_{1-3}-$, and $-O(CR^A R^B)_{1-3}-$. Preferably, L^1 is a bond or $-O(CR^A R^B)_{1-3}-$.

[0055] L^2 may be selected from: a bond, $-NR^D$ -, $-C(O)NR^D$ -, $-NR^D C(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-NR^D C(O)NR^E$ -, and $-OC(O)NR^D$ -.

[0056] For the avoidance of doubt, when L^1 is a bond and L^2 is a bond then L in its entirety is a bond. This may be considered to result in L being absent.

[0057] In embodimentexamples L is selected from: bond, $-(CR^A R^B)_{0-3}O$ -, $-(CR^A R^B)_{0-3}NR^C$ -, $-(CR^A R^B)_{0-3}C(O)NR^C$ -, $-(CR^A R^B)_{0-3}NR^C C(O)$ -, $-(CR^A R^B)_{0-3}C(O)O$ -, $-(CR^A R^B)_{0-3}OC(O)$ -, $-C(O)$ -, $-(CR^A R^B)_{0-3}S(O)_2NR^C$ -, $-(CR^A R^B)_{0-3}NR^C S(O)_2$ -, $-S(O)_2$ -, $-NR^C C(O)NR^D$ -, $-(CR^A R^B)_{0-3}OC(O)NR^C$ -, $O(CR^A R^B)_{1-3}O$ -, $-O(CR^A R^B)_{1-3}NR^C$ -, $-O(CR^A R^B)_{0-3}C(O)NR^C$ -, $-O(CR^A R^B)_{1-3}S(O)_2NR^C$ -, $-O(CR^A R^B)_{1-3}C(O)NR^C S(O)_2$ -, and $-NR^D (CR^A R^B)_{1-3}C(O)NR^C$ -.

[0058] R^A and R^B may be independently selected from H, C_{1-4} alkyl, and C_{1-4} haloalkyl. Optionally, R^A and R^B may be independently selected from H, methyl, trifluoromethyl and difluoromethyl. Optionally, R^A and R^B may be H or methyl. Preferably, R^A and R^B are H.

[0059] R^C and R^D may be independently selected from H and methyl. Preferably, R^C and R^D are both H.

[0060] In embodimentexamples L is selected from: a bond, $-CH_2$ -, $-CH_2CH_2$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-OCH_2$ -, $-O(CH_2)_2$ -, $-OCH_2CH_2NH$ -, $-OCH_2C(O)NH$ -, $-OC(Me)HC(O)NH$ -, $-OC(Me)_2C(O)NH$ -, $-OCH_2C(O)O$ -, $-OCH_2S(O)_2NH$ -, $-OCH_2CH_2NHC(O)$ -, $-O(CH_2)_3NHC(O)$ -, $-OCH_2CH_2NHS(O)_2$ -, $-OCH_2CH_2NHC(O)NH$ -, $-CH_2NHC(O)$ -, $-CH_2NHS(O)_2$ -, $-CH_2NHC(O)NH$ -, $-CH_2C(O)$ -, $-(CH_2)_2C(O)$ -, $-CH_2C(O)NH$ -, $-(CH_2)_2C(O)NH$ -, $-CH_2C(O)O$ -, $-CH_2OC(O)NH$ -, $-C(O)$ -, $-C(O)CH_2NH$ -, $-C(O)NH$ -, $-C(O)NHCH_2$ -, $-NHCH_2C(O)$ -, $-NHCH_2C(O)NH$ -, $-N(Me)CH_2C(O)NH$ -, $-NHC(O)$ -, $-NHC(O)NH$ -, $-S(O)_2$ -, $-CH(CHF_2)NH$ - or $-CH(CF_3)NH$ -.

[0061] Optionally, L is selected from: a bond, $-O$ -, $-OCH_2$ -, $-OCH_2CH_2NH$ -, $-OCH_2C(O)NH$ -, $-OC(Me)HC(O)NH$ -, $-OC(Me)_2C(O)NH$ -, $-OCH_2CH_2NHC(O)$ -, $-O(CH_2)_3NHC(O)$ -, $-OCH_2CH_2NHC(O)NH$ -, $-CH_2NHC(O)$ -, $-CH_2NHC(O)NH$ -, $-CH_2C(O)NH$ -, $-(CH_2)_2C(O)NH$ -, $-CH_2OC(O)NH$ -, $-C(O)$ -, $-C(O)CH_2NH$ -, $-C(O)NH$ -, $-C(O)NHCH_2$ -, $-NHCH_2C(O)NH$ -, $-N(Me)CH_2C(O)NH$ -, $-NHC(O)$ -, $-NHC(O)NH$ -, $-CH(CHF_2)NH$ - or $-CH(CF_3)NH$ -.

[0062] Preferably, L is selected from: a bond, $-O$ -, $-OCH_2C(O)NH$ -, $-CH_2C(O)NH$ -, $-C(O)$ -, $-C(O)CH_2NH$ -, $-C(O)NH$ -, or $-C(O)NHCH_2$ -.

[0063] In embodimentexamples of formulae (IIa) or (IIIa) L^1 is preferably a bond, or $-O(CR^A R^B)_{1-3}$ -. In embodimentexamples of formulae (IIa) or (IIIa) L^2 is preferably $-C(O)NR^D$ -. In embodimentexamples of formulae (IIa) or (IIIa) L is preferably a bond, $-OCH_2C(O)NH$ -, or $-C(O)NH$ -.

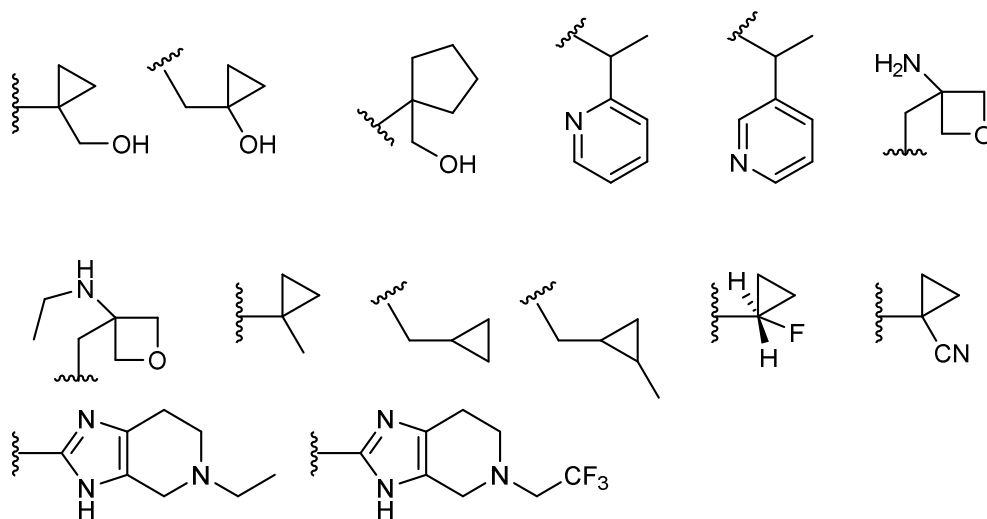
[0064] In embodimentexamples of formulae (IIb) or (IIIb) L^1 is preferably a bond. In embodimentexamples of formulae (IIb) or (IIIb) L^2 is preferably $-C(O)$ -. In embodimentexamples of formulae (IIb) or (IIIb) L is preferably a bond, or $-C(O)NH$ -.

[0065] In embodimentexamples of formulae (IIc) or (IIIc) L¹ is preferably a bond. In embodimentexamples of formulae (IIc) or (IIIc) L² is preferably a bond or -C(O)-. In embodimentexamples of formulae (IIc) or (IIIc) L is preferably a bond.

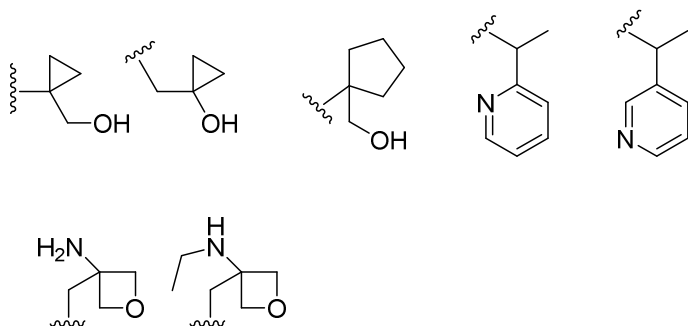
[0066] In embodimentexamples R² is selected from H, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkyl substituted with -OR^F, C₃₋₈ cycloalkyl (optionally C₃₋₅ cycloalkyl), C₄₋₆ cycloalkyl substituted with -OH, phenyl, 3 to 6 membered heterocyclic ring system, wherein the phenyl and heterocyclic ring system are unsubstituted or substituted with: halo, C₁₋₄ alkyl or -C(O)R^F.

[0067] In embodimentexamples R² is selected from H, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkyl substituted with -OR^F, C₃₋₈ cycloalkyl (optionally C₃₋₅ cycloalkyl), C₄₋₆ cycloalkyl substituted with -OH, 3 to 6 membered heterocyclic ring system, wherein the heterocyclic ring system is unsubstituted or substituted with: C₁₋₄ alkyl or -C(O)R^F.

[0068] In embodimentexamples R² is selected from: H, CN, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *tert*-butyl, *sec*-butyl, *tert*-pentyl, allyl, propargyl, difluoroethyl, difluoropropyl, trifluoroethyl, trifluoropropyl, trifluoroisopropyl, isopropanol, *n*-butanol, *sec*-butanol, propanol, *tert*-butanol, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopropanol, cyclobutanol, cyclopentanol, cyclohexanol, cycloheptanol, aziridinyl, *N*-acetylaziridinyl, *N*-alkylaziridinyl, azetidiny, *N*-acetylazetidiny, *N*-alkylazetidiny, 2-methylpropan-2-amine, phenyl, chlorophenyl, pyrrolidinyl, difluoropyrrolidinyl, trifluoroethylpyrrolidinyl, *N*-methylpyrrolidinyl, tetrahydrofuranyl, sulfolanyl, dihydropyran, tetrahydropyranyl, tetrahydropyranoimidazolyl, morpholinyl, imidazolyl, ethyltetrahydroimidazopyridine, methylimidazolyl, piperazinyl, *N*-methylpiperazinyl, trifluoromethylpiperazinyl, oxadiazolyl, dimethyldihydrooxazolyl, pyrazolyl, *N*-methylpyrazolyl, ethylpyrazolyl, 4-pyridone, 2-pyridone, pyridyl, methyl substituted with tetrahydrofuran, ethyl substituted with pyridine, ethyl substituted with -NMe₂, ethyl substituted with OMe, ethyl substituted with OH; or selected from:



N-methylpyrrolidinyl, sulfolanyl, tetrahydropyranyl, morpholinyl, pyridyl, methyl substituted with tetrahydrofuran, ethyl substituted with pyridine, ethyl substituted with -NMe₂, ethyl substituted with OMe, ethyl substituted with OH; or selected from:



[0072] In embodimentexamples R² is selected from: H, methyl, ethyl, isopropyl, tert-butyl, sec-butyl, trifluoroethyl, trifluoroisopropyl, isopropanol, *sec*-butanol, propanol, *tert*-butanol, cyclopropyl, cyclopentyl, cyclobutanol, cyclohexanol, azetidiny, *N*-acetylazetidiny, tetrahydrofuranyl, pyrrolidinyl, *N*-methylpyrrolidinyl, tetrahydropyranyl, morpholinyl, and pyridyl.

[0073] In embodimentexamples R² is not selected from H when B is a 6-membered monocyclic ring, e.g. phenyl, pyridyl, pyrimidinyl. In embodimentexamples R² is not selected from H when B is a phenyl ring. Accordingly, the skilled person will appreciate that this results in the situation where B cannot be an unsubstituted 6-membered ring or phenyl ring, as appropriate.

[0074] In embodimentexamples R⁴ is selected from: halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, -CN, C₁₋₄ alkyl substituted with -OR^J, C₁₋₄ alkyl substituted with -NR^JR^K, and 3 to 8 membered heterocycloalkyl.

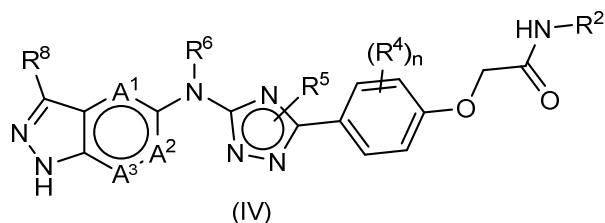
[0075] R^J and R^K are each independently at each occurrence selected from H or methyl.

[0076] In embodimentexamples R⁴ is F, Cl, methyl, CF₃, Et, *i*Pr, CN, OH, OMe, *Oi*-Pr, =O, CH₂OH, CH₂OMe, NH₂, NMe₂, CH₂NH₂, CH₂NMe₂, or morpholinyl.

[0077] In embodimentexamples n is 0. In an alternative embodimentexample n is 1.

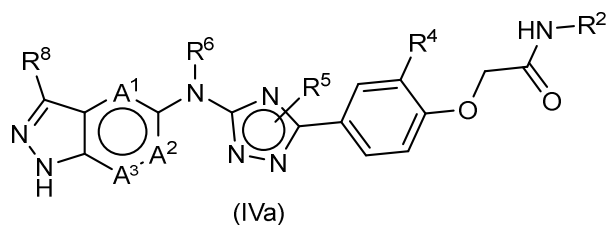
[0078] In embodimentexamples n is 1 or 2. In an alternative embodimentexample n is 2.

[0079] In embodimentexamples the compound of formula (I) is a compound according to formula (IV):

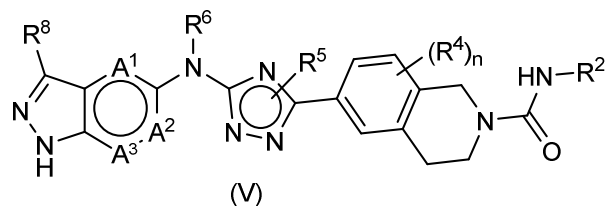


[0080] In embodimentexamples n is preferably 1. In embodimentexamples R⁴ is preferably -OMe. In embodimentexamples of formula (IV) n is preferably 1 and R⁴ is preferably -OMe.

[0081] In embodimentexamples the compound of formula (I) is a compound according to formula (IVa):

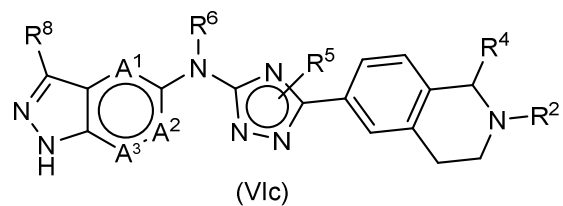
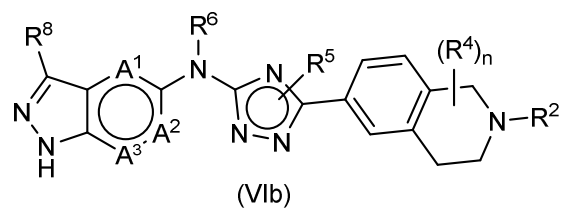
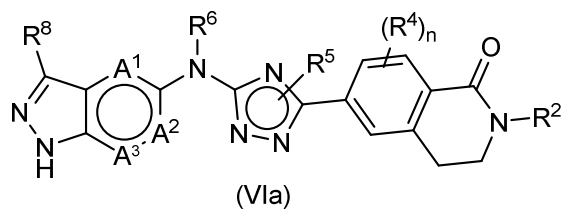


[0082] In ~~embodiment~~examples the compound of formula (I) is a compound according to formula (V):



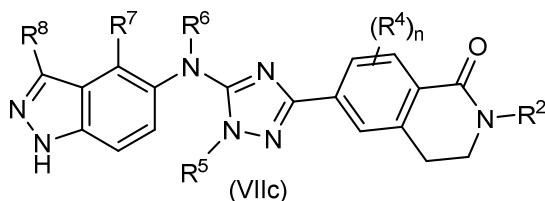
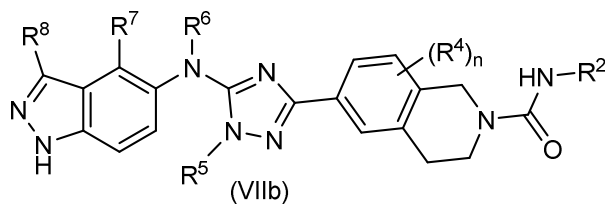
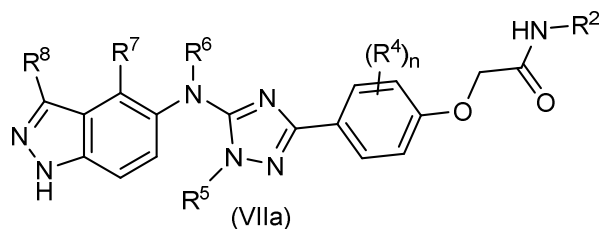
[0083] In ~~embodiment~~examples of formula (V) n is preferably 0.

[0084] In ~~embodiment~~examples the compound of formula (I) is a compound according to formulae (VIa), (VIb) or (VIc):



[0085] In ~~embodiment~~examples of formulae (VIa) or (VIb) n is preferably 0. In ~~embodiment~~examples of formulae (VIa) or (VIb) n may be 1 or 2.

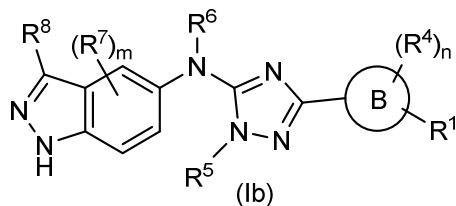
[0086] In ~~embodiment~~examples the compound of formula (I) is a compound according to formulae (VIIa), (VIIb) or (VIIc):



[0087] In ~~embodiment~~examples of formulae (VIIa), (VIIb) or (VIIc) R⁸ may be H. In ~~embodiment~~examples of formulae (VIIa), (VIIb) or (VIIc) R⁷ may be H, Cl, ethyl, or cyclopropyl. In ~~embodiment~~examples of formulae (VIIa), (VIIb) or (VIIc) R⁵ may be H or Me. In ~~embodiment~~examples of formulae (VIIa), (VIIb) or (VIIc) R⁴ may be OMe and n is 0 or 1. Any of the ~~embodiment~~examples of this paragraph may be combined in any way to provide an ~~embodiment~~example of the invention~~disclosure~~.

[0088] In ~~embodiment~~examples of formulae (VIIa), (VIIb) or (VIIc) R⁸ is H; R⁷ is H, Cl, ethyl, or cyclopropyl; R⁵ is H or Me; R⁴ is OMe; and n is 0 or 1.

[0089] In ~~embodiment~~examples, the present ~~invention~~disclosure provides the compound of formula (Ib) and pharmaceutically acceptable salts thereof:



wherein

B represents a 5 to 10 membered carbocyclic ring system or a 5 to 10 membered heterocyclic ring system, wherein the ring systems are either monocyclic or fused bicyclic systems;

R¹ is L-R^{2A}, R^{2B} or absent;

L is -L¹-L²-, wherein L¹ is selected from: a bond, -(CR^AR^B)₁₋₃-, -O(CR^AR^B)₁₋₃-, -(CR^AR^B)₀₋₃O-, and -NR^C(CR^AR^B)₁₋₃-, and

L² is selected from: -O-, -NR^D-, -C(O)NR^D-, -NR^DC(O)-, -C(O)O-, -OC(O)-, -C(O)-, -S(O)₂NR^D-, -NR^DS(O)₂-, -S(O)₂-, -NR^DC(O)NR^E-, -OC(O)NR^D-, and -C(O)NR^DS(O)₂-;

R^{2A} is selected from: H, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkyl substituted with -OR^D, C₁₋₆ alkyl substituted with -NR^FR^G, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl substituted with OH, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, 6 membered heteroaryl, C₁₋₄ alkyl substituted with 3 to 8 membered heterocycloalkyl, C₁₋₄ alkyl substituted with 6 membered heteroaryl, - (CR^HR^I)₁₋₃OR^F, -(CR^HR^I)₁₋₃NR^FR^G;

R^{2B} is a phenyl, C₁₋₄ alkyl substituted with phenyl, 5 to 10 membered heterocyclic ring system, C₁₋₄ alkyl substituted with a 5 to 10 membered heterocyclic ring system, -O-C₁₋₄ alkyl substituted with a 5 to 10 membered heterocyclic ring system, wherein the heterocyclic ring system is unsubstituted or substituted with: halo, C₁₋₄ alkyl or =O;

R⁴ is selected from: halo, C₁₋₄ alkyl, C₁₋₆ haloalkyl, -CN, -OR^J, =O, C₁₋₄ alkyl substituted with -OR^J, -NR^JR^K, C₁₋₄ alkyl substituted with -NR^JR^K, C₃₋₈ cycloalkyl, and 3 to 8 membered heterocycloalkyl;

R⁵ is selected from: H, C₁₋₄ alkyl, C₃₋₈ cycloalkyl, substituted or unsubstituted phenyl and substituted or unsubstituted 5 or 6 membered heteroaryl, wherein the phenyl or heteroaryl group may be substituted by 1 or 2 R⁹;

R⁶ is selected from: H and C₁₋₄ alkyl;

R⁷ is selected from: H, halo, C₁₋₄ alkyl, C₁₋₆ haloalkyl, -CN, and C₃₋₈ cycloalkyl;

R⁸ is selected from: H, halo, C₁₋₄ alkyl, C₁₋₆ haloalkyl, -CN, and C₃₋₈ cycloalkyl;

R⁹ is selected from halo or C₁₋₄ alkyl;

n is 0, 1, or 2

m is 0, 1, or 2

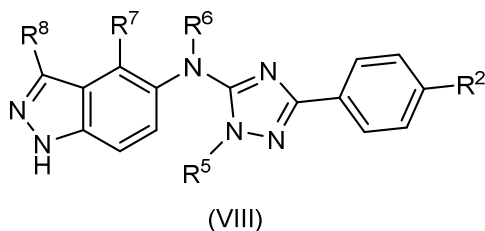
R^A and R^B are selected from H, C₁₋₄ alkyl, or C₁₋₄ haloalkyl or R^A and R^B together with the atom to which they are attached form a 3 to 6 membered cycloalkyl ring or a 3 to 6 membered heterocycloalkyl ring;

R^C, R^D, R^E, R^F and R^G are each independently selected from H and C₁₋₄ alkyl;

R^H and R^I are each H except one pair of R^H and R^I on the same carbon atom, together with that carbon atom, form a 3 to 6 membered cycloalkyl ring or a 3 to 6 membered heterocycloalkyl ring; and

R^J and R^K are selected from H or C₁₋₄ alkyl.

[0090] In ~~embodiment~~examples the compound of formula (I) is a compound according to formula (VIII):



[0091] In embodimentexamples of formula (VIII) R⁸ may be H. In embodimentexamples of formula (VIII) R⁷ may be C₃₋₈ cycloalkyl. In embodimentexamples of formula (VIII) R⁶ may be H. In embodimentexamples of formula (VIII) R⁵ may be C₁₋₄ alkyl. In embodimentexamples of formula (VIII) R² may be a substituted or unsubstituted 3 to 10 membered heterocyclic ring. Any of the embodimentexamples of this paragraph may be combined in any way to provide an embodimentexample of the inventiondisclosure.

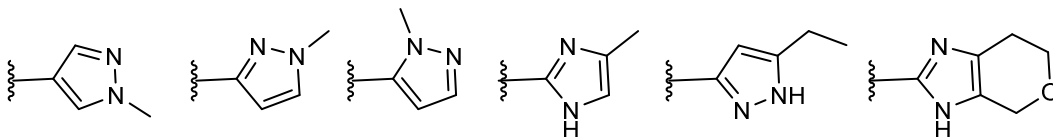
[0092] In embodimentexamples of formula (VIII) R⁸ is H; R⁷ is cyclopropyl; R⁶ is H; R⁵ is methyl; and R² is a substituted or unsubstituted 3 to 10 membered heterocyclic ring comprising two or three nitrogen atoms.

[0093] In embodimentexamples of formula (VIII) R² is a substituted or unsubstituted 5 membered ring comprising two nitrogen atoms. In embodimentexamples of formula (VIII) R² is a substituted or unsubstituted 9 membered ring comprising two nitrogen atoms. In embodimentexamples of formula (VIII) R² is a substituted or unsubstituted 9 membered ring comprising three nitrogen atoms.

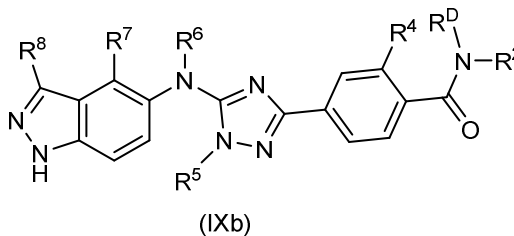
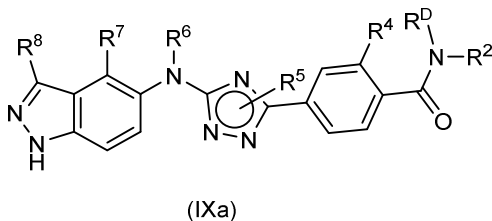
[0094] In embodimentexamples of formula (VIII) R² is a substituted or unsubstituted 9 membered heterocyclic ring comprising a 5 membered heterocyclic ring containing 1 or 2 nitrogen atoms fused to a 6 membered heterocyclic ring comprising 1 or 2 nitrogen atoms. In embodimentexamples of formula (VIII) R² is unsubstituted or substituted with: hydrogen, methyl, ethyl, *n*-propyl, *i*-propyl, halo, trifluoromethyl or trifluoroethyl.

[0095] In embodimentexamples of formula (VIII) R² is selected from: methylpyrazole, ethylpyrazole, methylimidazole, and tetrahydropyranoimidazole.

[0096] In embodimentexamples of formula (VIII), R² may be:



[0097] In embodimentexamples, the compound of formula (I) is a compound according to formulae (IXa) or (IXb):



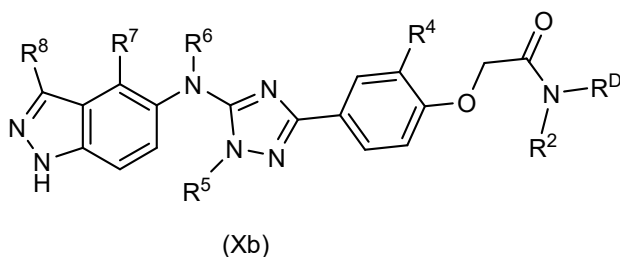
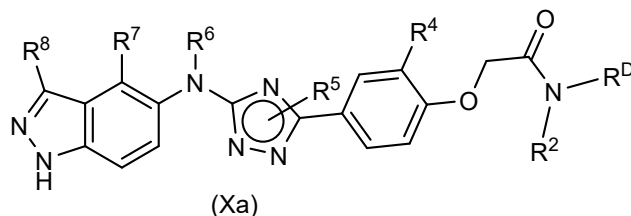
[0098] In embodimentexamples of formulae (IXa) or (IXb) R⁸ may be H. In certain embodimentexamples R⁷ may be H, halo, C₁₋₄ alkyl or C₃₋₈ cycloalkyl. In certain embodimentexamples R⁶ may be H. In certain embodimentexamples R⁵ may be C₁₋₄ alkyl. In certain embodimentexamples R⁴ may be H or -OR^j, wherein R^j is selected from H or C₁₋₄ alkyl. In certain embodimentexamples R^D may be H. In embodimentexamples R² may be C₁₋₆ alkyl, C₁₋₆ haloalkyl or C₃₋₈ cycloalkyl.

[0099] In embodimentexamples of formulae (IXa) or (IXb) R⁸ is H; R⁷ is C₁₋₄ alkyl or C₃₋₈ cycloalkyl; R⁶ is H; R⁵ is methyl, R⁴ is H or -OMe, R^D is H and R² is C₁₋₆ alkyl, C₁₋₆ haloalkyl or C₃₋₈ cycloalkyl.

[00100] In embodimentexamples of formulae (IXa) or (IXb) R⁷ is selected from methyl, ethyl, isopropyl, *tert*-butyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

[00101] In embodimentexamples of formulae (IXa) or (IXb) R² is selected from: methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *tert*-butyl, sec-butyl, tert-pentyl, difluoroethyl, difluoropropyl, trifluoroethyl, trifluoropropyl, trifluoroisopropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

[00102] In embodimentexamples, the compound of formula (I) is a compound according to formula (Xa) or (Xb):



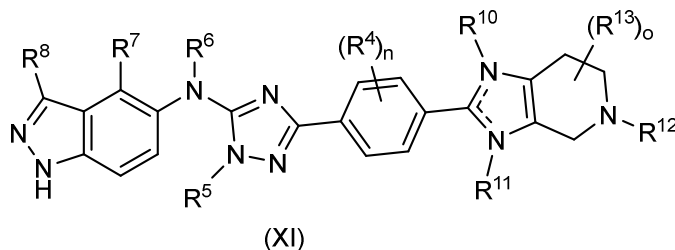
[00103] In embodimentexamples of formulae (Xa) or (Xb) R⁸ may be H. In certain embodimentexamples R⁷ may be C₁₋₄ alkyl or C₃₋₈ cycloalkyl. In certain embodimentexamples R⁶ may be H. In certain embodimentexamples R⁵ may be C₁₋₄ alkyl. In certain embodimentexamples R⁴ may be H or -OR^j, wherein R^j is selected from H or C₁₋₄ alkyl. In certain embodimentexamples R^D may be H. In embodimentexamples R² may be C₁₋₆ alkyl, C₁₋₆ haloalkyl or C₃₋₈ cycloalkyl.

[00104] In embodimentexamples of formulae (Xa) or (Xb) R⁸ is H; R⁷ is C₁₋₄ alkyl or C₃₋₈ cycloalkyl; R⁶ is H; R⁵ is methyl, R⁴ is H or -OMe, R^D is H and R² is C₁₋₆ alkyl, C₁₋₆ haloalkyl or C₃₋₈ cycloalkyl.

[00105] In embodimentexamples of formulae (Xa) or (Xb) R⁷ is selected from methyl, ethyl, isopropyl, *tert*-butyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

[00106] In ~~embodiment~~examples of formulae (Xa) or (Xb) R² is selected from: methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *tert*-butyl, sec-butyl, tert-pentyl, difluoroethyl, difluoropropyl, trifluoroethyl, trifluoropropyl, trifluoroisopropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

[00107] In ~~embodiment~~examples the compound of formula (I) is a compound according to formula (XI):



wherein:

R¹⁰ is absent, H, C₁₋₄ alkyl or C₁₋₄ haloalkyl;

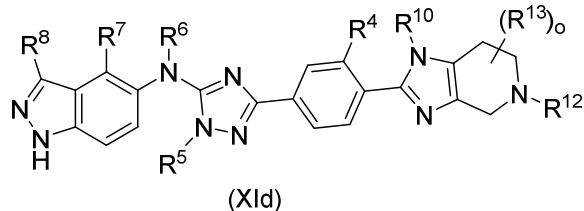
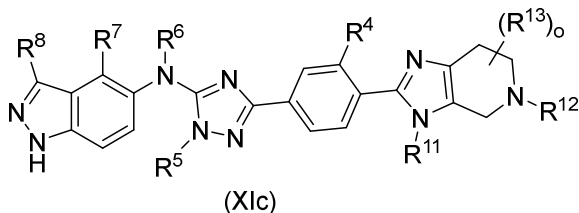
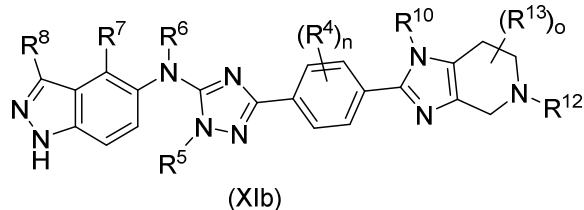
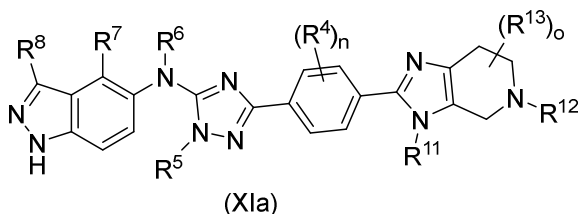
R¹¹ is absent, H, C₁₋₄ alkyl or C₁₋₄ haloalkyl;

R¹² is H, C₁₋₄ alkyl or C₁₋₄ haloalkyl;

R¹³ is independently selected at each occurrence from H, =O, -NR^FR^G, halo, -CN, C₁₋₄ alkyl, C₁₋₄ haloalkyl, or C₁₋₄ alkyl substituted with -OR^F; and

o is 1, 2 or 3.

[00108] In ~~embodiment~~examples the compound of formula (I) is a compound according to formulae (Xla), (Xlb), (Xlc) or (Xld):



[00109] In ~~embodiment~~examples of formulae (XI), (Xla), (Xlb), (Xlc) or (Xld) R⁸ may be H. In certain ~~embodiment~~examples R⁷ may be H, halo, C₁₋₄ alkyl or C₃₋₈ cycloalkyl. In certain ~~embodiment~~examples R⁶ may be H. In certain ~~embodiment~~examples R⁵ may be C₁₋₄ alkyl. In certain ~~embodiment~~examples R⁴ may be H or -OR^J, wherein R^J is selected from H or C₁₋₄ alkyl. In certain ~~embodiment~~examples R¹⁰ may be absent, H, C₁₋₄ alkyl, C₁₋₄ alkyl substituted with -OR^L, C₁₋₄ alkyl substituted with -NR^LR^L, C₃₋₈ cycloalkyl, 3 to 8 membered heterocycloalkyl, C₁₋₄ alkyl substituted with C₃₋₈ cycloalkyl, or C₁₋₄ alkyl substituted with 3 to 8

membered heterocycloalkyl. In certain embodimentexamples R¹¹ may be absent, H, C₁₋₄ alkyl, C₁₋₄ alkyl substituted with -OR^L, C₁₋₄ alkyl substituted with -NR^LR^L, C₃₋₈ cycloalkyl, 3 to 8 membered heterocycloalkyl, C₁₋₄ alkyl substituted with C₃₋₈ cycloalkyl, or C₁₋₄ alkyl substituted with 3 to 8 membered heterocycloalkyl. In certain embodimentexamples, R¹² may be H, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkyl substituted with -OR^L, C₁₋₄ alkyl substituted with -NR^LR^L, C₃₋₈ cycloalkyl, 3 to 8 membered heterocycloalkyl, C₁₋₄ alkyl substituted with C₃₋₈ cycloalkyl, or C₁₋₄ alkyl substituted with 3 to 8 membered heterocycloalkyl. In certain embodimentexamples, R¹³ is independently selected at each occurrence from H, =O, -NR^FR^G, halo, -CN, C₁₋₄ alkyl, C₁₋₄ haloalkyl, or C₁₋₄ alkyl substituted with -OR^F.

[00110] In embodimentexamples of formulae (XI), (XIa), (XIb), (XIc) or (XId) R¹⁰ is absent, H, C₁₋₄ alkyl, C₁₋₄ alkyl substituted with -OR^L, C₁₋₄ alkyl substituted with -NR^LR^L, C₃₋₈ cycloalkyl, 3 to 8 membered heterocycloalkyl, C₁₋₄ alkyl substituted with C₃₋₈ cycloalkyl, or C₁₋₄ alkyl substituted with 3 to 8 membered heterocycloalkyl. Optionally, R¹⁰ is absent, H or C₁₋₄ alkyl.

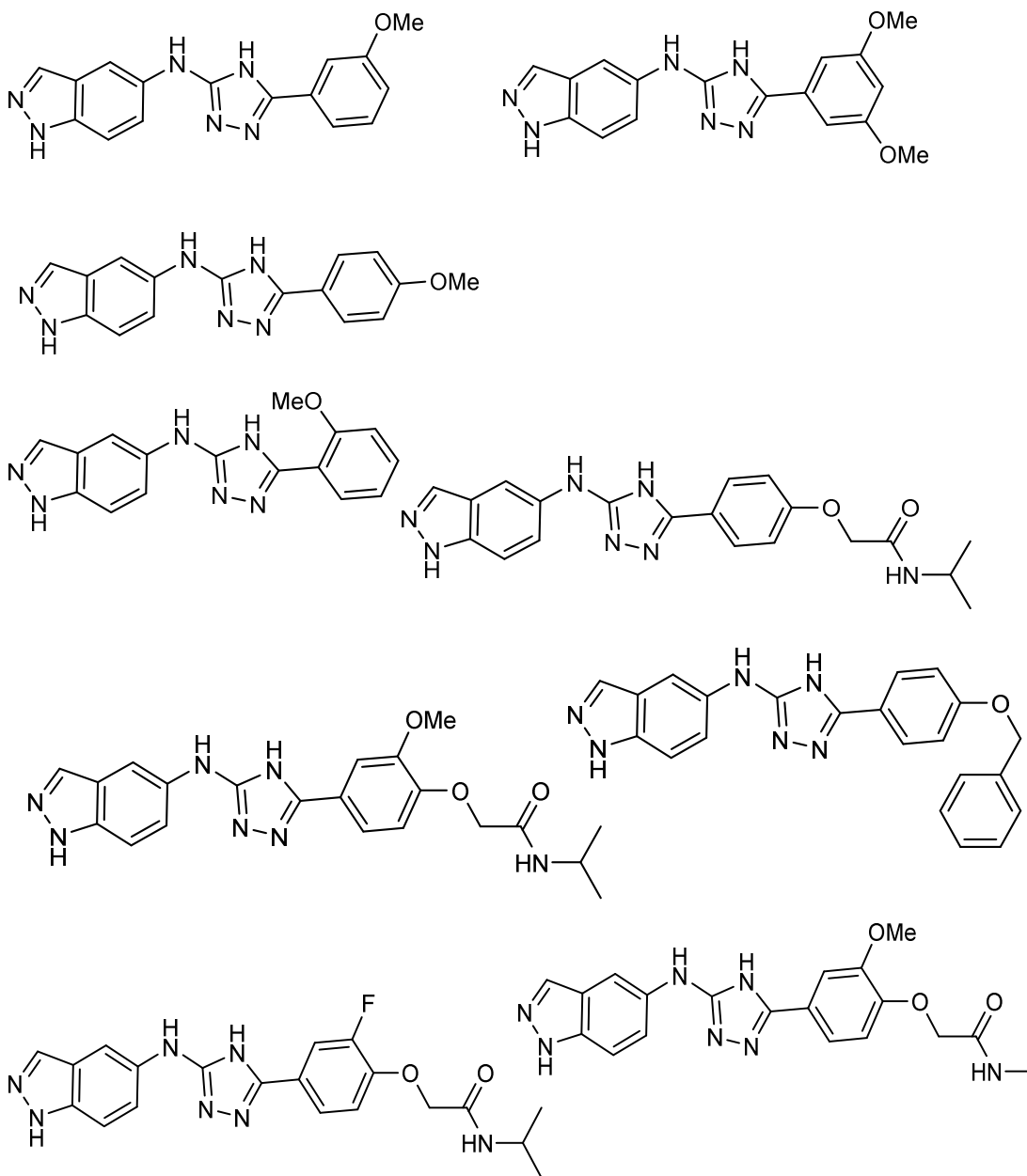
[00111] In embodimentexamples of formulae (XI), (XIa), (XIb), (XIc) or (XId) R¹¹ is absent, H, C₁₋₄ alkyl, C₁₋₄ alkyl substituted with -OR^L, C₁₋₄ alkyl substituted with -NR^LR^L, C₃₋₈ cycloalkyl, 3 to 8 membered heterocycloalkyl, C₁₋₄ alkyl substituted with C₃₋₈ cycloalkyl, or C₁₋₄ alkyl substituted with 3 to 8 membered heterocycloalkyl. Optionally, R¹¹ is absent, H or C₁₋₄ alkyl.

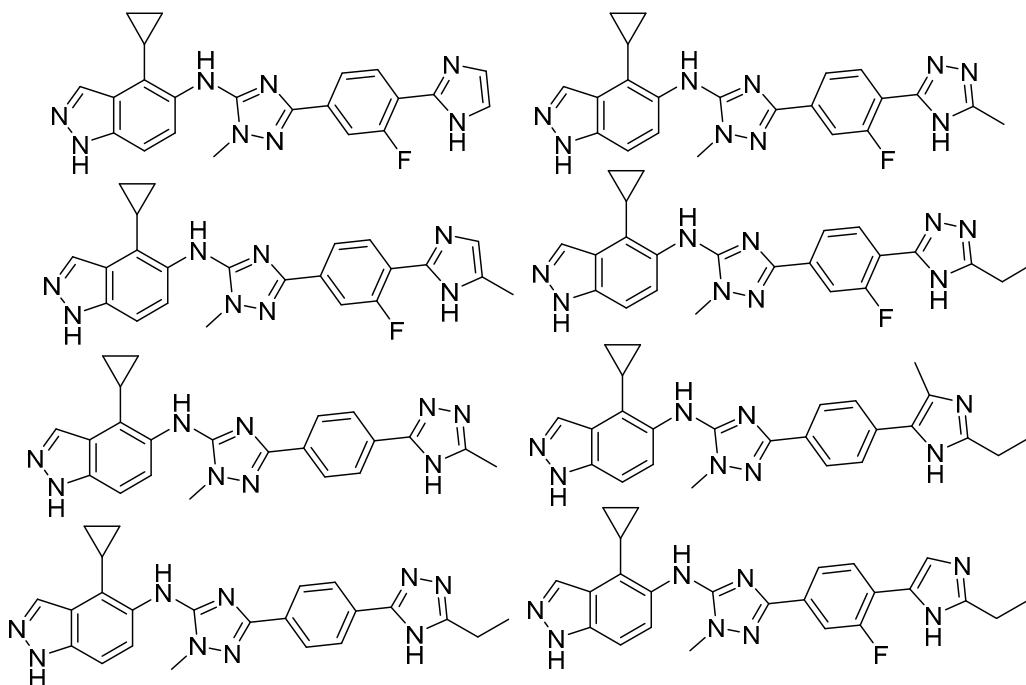
[00112] In embodimentexamples of formulae (XI), (XIa), (XIb), (XIc) or (XId) R¹² is H, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkyl substituted with -OR^L, C₁₋₄ alkyl substituted with -NR^LR^L, C₃₋₈ cycloalkyl, 3 to 8 membered heterocycloalkyl, C₁₋₄ alkyl substituted with C₃₋₈ cycloalkyl, or C₁₋₄ alkyl substituted with 3 to 8 membered heterocycloalkyl. Optionally R¹² is H, C₁₋₄ alkyl or C₁₋₄ haloalkyl.

[00113] In embodimentexamples of formulae (XI), (XIa), (XIb), (XIc) or (XId) R¹⁰ and R¹¹ are independently selected from: hydrogen, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *tert*-butyl, cyclopropyl, -CH₂CH₂OH, -CH₂CH₂OCH₃, -CH₂CH₂NHCH₃, piperidyl, ethyl substituted with morpholine, and ethyl substituted with piperidine. Optionally, R¹⁰ and R¹¹ are independently selected from: hydrogen, methyl, ethyl, *n*-propyl, *i*-propyl or *tert*-butyl.

[00114] In embodimentexamples of formulae (XI), (XIa), (XIb), (XIc) or (XId) R¹² is selected from: hydrogen, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *tert*-butyl, trifluoromethyl, trifluoroethyl, cyclopropyl, -CH₂CH₂OH, -CH₂CH₂OCH₃, -CH₂CH₂NHCH₃, piperidyl, ethyl substituted with morpholine, and ethyl substituted with piperidine. Optionally, R¹² is selected from hydrogen, methyl, ethyl, *n*-propyl, *i*-propyl, *tert*-butyl, trifluoromethyl or trifluoroethyl.

[00115] The present invention disclosure provides compounds of formula (I) selected from:





[00117] In an embodimentexample there is provided compounds of the present inventiondisclosure having a ROCK2 binding affinity within category +++ or ++++ as defined elsewhere herein. In an embodimentexample there is provided compounds of the present inventiondisclosure having a ROCK2 binding affinity IC₅₀ value of < 3 μ M. In an embodimentexample there is provided compounds of the present inventiondisclosure having a ROCK2 binding affinity IC₅₀ value of < 0.3 μ M. Optionally, the binding activity is determined using the assay for ROCK2 inhibition defined in the examples.

[00118] In an aspectexample of the inventiondisclosure there is provided the compounds of the present inventiondisclosure for use as a medicament.

[00119] In accordance with another aspectexample, the present inventiondisclosure provides a pharmaceutical formulation comprising a compound of the present inventiondisclosure and a pharmaceutically acceptable excipient.

[00120] In an embodimentexample, the pharmaceutical composition may be a combination product comprising an additional pharmaceutically active agent. The additional pharmaceutically active agent may be, for example anti-inflammatory agents, anti-fibrotic agents, chemotherapeutics, anti-cancer agents, immunosuppressants, anti-tumour vaccines, cytokine therapy, or tyrosine kinase inhibitors.

[00121] In accordance with another aspectexample, there is provided a compound of the present inventiondisclosure for use in the treatment of a condition which is modulated by ROCK1 and/or ROCK2. Usually conditions that are modulated by ROCKs (please note that ROCKs refer to either or both of ROCK1 and ROCK2) are conditions that would be treated by the inhibition of ROCKs using a compound of the present inventiondisclosure. A compound of any formula disclosed herein may be for use in the treatment of a condition treatable by the inhibition of ROCKs.

arthritis/Reiter's syndrome, reflex sympathetic dystrophy syndrome, relapsing polychondritis, retrocalcaneal bursitis, rheumatic fever, rheumatoid vasculitis, rotator cuff tendinitis, sacroiliitis, salmonella osteomyelitis, sarcoidosis, saturnine gout, Scheuermann's osteochondritis, scleroderma, septic arthritis, seronegative arthritis, shigella arthritis, shoulder-hand syndrome, sickle cell arthropathy, Sjogren's syndrome, slipped capital femoral epiphysis, spinal stenosis, spondylolysis, staphylococcus arthritis, Stickler syndrome, subacute cutaneous lupus, Sweet's syndrome, Sydenham's chorea, syphilitic arthritis, systemic lupus erythematosus (SLE), Takayasu's arteritis, tarsal tunnel syndrome, tennis elbow, Tietze's syndrome, transient osteoporosis, traumatic arthritis, trochanteric bursitis, tuberculosis arthritis, arthritis of Ulcerative colitis, undifferentiated connective tissue syndrome (UCTS), urticarial vasculitis, viral arthritis, Wegener's granulomatosis, Whipple's disease, Wilson's disease, yersinia arthritis and conditions involving vascularization and/or inflammation, include atherosclerosis, rheumatoid arthritis (RA), hemangiomas, angiofibromas, and psoriasis. Other non-limiting examples of angiogenic disease are retinopathy of prematurity (retrolental fibroplastic), corneal graft rejection, corneal neovascularization related to complications of refractive surgery, corneal neovascularization related to contact lens complications, corneal neovascularization related to pterygium and recurrent pterygium, corneal ulcer disease, and non-specific ocular surface disease, insulin-dependent diabetes mellitus, multiple sclerosis, myasthenia gravis, Chroff's disease, autoimmune nephritis, primary biliary cirrhosis, acute pancreatitis, allograft rejection, allergic inflammation, contact dermatitis and delayed hypersensitivity reactions, inflammatory bowel disease, septic shock, osteoporosis, osteoarthritis, cognition defects induced by neuronal inflammation, Osier-Weber syndrome, restinosis, and fungal, parasitic and viral infections, including cytomegalo viral infections.

[00124] Any of the conditions disclosed above as being treatable by ROCK1 and/or ROCK2 inhibition may be treated by a compound of the inventiondisclosure, or may be treated in a method comprising administering a compound of the inventiondisclosure, or may be treated by a medicament manufactured through the use of a compound of the present inventiondisclosure.

[00125] In an aspectexample of the inventiondisclosure, a compound of the inventiondisclosure may be for use in the treatment of: fibrotic diseases, auto-immune, inflammatory-fibrotic conditions, inflammatory conditions, central nervous system disorders, or cancer.

[00126] In embodimentexamples, a compound of the inventiondisclosure may be for use in the treatment of and condition selected from: Idiopathic Pulmonary Fibrosis (IPF); systemic sclerosis (SSC); interstitial lung disease (ILD); type 1 and type 2 diabetes; diabetic nephropathy; Nonalcoholic Steatohepatitis (NASH); Nonalcoholic fatty liver disease (NAFLD); hypertension, atherosclerosis, restenosis, stroke, heart failure, coronary vasospasm, cerebral vasospasm, peripheral circulatory disorder, peripheral artery occlusive disease, ischemia/reperfusion injury, pulmonary hypertension and angina, erectile dysfunction, fibroid lung, fibroid liver and fibroid kidney, glaucoma, ocular hypertension, retinopathy, rheumatoid arthritis, psoriasis, psoriatic arthritis, Sjogren's syndrome, asthma, adult respiratory distress syndrome, chronic obstructive pulmonary disease (COPD), SLE, cGVHD, inflammatory bowel disease, stenosis of the bowel, disorders involving neuronal degeneration or physical injury to neural

tissue, Huntington's disease, Parkinson's Disease, Alzheimer's, Amyotrophic lateral sclerosis (ALS), multiple sclerosis, liver cancer, bladder cancer, hepatoma, squamous carcinoma of the lung, non-small cell lung cancer, adenocarcinoma of the lung, small-cell lung cancer, various types of head and neck cancer, breast cancer, colon cancer, colorectal cancer, cancer of the peritoneum, hepatocellular cancer, gastrointestinal cancer, esophageal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, squamous cell cancer, pituitary cancer, astrocytoma, soft tissue sarcoma, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, kidney cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, brain cancer, endometrial cancer, testis cancer, cholangiocarcinoma, gallbladder carcinoma, gastric cancer and melanoma.

[00127] In an ~~aspect~~example of the ~~invention~~disclosure there is provided a method of treating a condition which is modulated by ROCK1 and/or ROCK2 wherein the method comprises administering a therapeutic amount of a compound of the ~~invention~~disclosure, to a patient in need thereof.

[00128] The method of treatment may be a method of treating a condition treatable by the inhibition of ROCK1 and/or ROCK2.

[00129] The ~~invention~~disclosure also provides a method of treating a condition selected from: fibrotic diseases, auto-immune, inflammatory-fibrotic conditions, inflammatory conditions, central nervous system disorders, or cancer, wherein the method comprises administering a therapeutic amount of a compound of any formula disclosed herein, to a patient in need thereof.

[00130] In ~~embodiment~~examples, the method may be for use in the treatment of a condition selected from: Idiopathic Pulmonary Fibrosis (IPF); systemic sclerosis (SSC); interstitial lung disease (ILD); type 1 and type 2 diabetes; diabetic nephropathy; Nonalcoholic Steatohepatitis (NASH); Nonalcoholic fatty liver disease (NAFLD); hypertension, atherosclerosis, restenosis, stroke, heart failure, coronary vasospasm, cerebral vasospasm, peripheral circulatory disorder, peripheral artery occlusive disease, ischemia/reperfusion injury, pulmonary hypertension and angina, erectile dysfunction, fibroid lung, fibroid liver and fibroid kidney, glaucoma, ocular hypertension, retinopathy, rheumatoid arthritis, psoriasis, psoriatic arthritis, Sjogren's syndrome, asthma, adult respiratory distress syndrome, chronic obstructive pulmonary disease (COPD), SLE, cGVHD, inflammatory bowel disease, stenosis of the bowel, disorders involving neuronal degeneration or physical injury to neural tissue, Huntington's disease, Parkinson's Disease, Alzheimer's, Amyotrophic lateral sclerosis (ALS), multiple sclerosis, liver cancer, bladder cancer, hepatoma, squamous carcinoma of the lung, non-small cell lung cancer, adenocarcinoma of the lung, small-cell lung cancer, various types of head and neck cancer, breast cancer, colon cancer, colorectal cancer, cancer of the peritoneum, hepatocellular cancer, gastrointestinal cancer, esophageal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, squamous cell cancer, pituitary cancer, astrocytoma, soft tissue sarcoma, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, kidney cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, brain cancer, endometrial cancer, testis cancer, cholangiocarcinoma, gallbladder carcinoma, gastric cancer and melanoma, wherein the method comprises administering a therapeutic amount of a compound of any formula disclosed herein, to a patient in need thereof.

[00131] In certain ~~embodiment~~examples, compounds of the ~~invention~~disclosure are for use in the treatment of or are used in a method of treatment of: Idiopathic Pulmonary Fibrosis (IPF); systemic sclerosis (SSC); interstitial lung disease (ILD); type 1 and type 2 diabetes; diabetic nephropathy; Nonalcoholic Steatohepatitis (NASH); Nonalcoholic fatty liver disease (NAFLD); hypertension, atherosclerosis, restenosis, stroke, heart failure, coronary vasospasm, cerebral vasospasm, peripheral circulatory disorder, peripheral artery occlusive disease, ischemia/reperfusion injury, pulmonary hypertension and angina, and erectile dysfunction, fibroid lung, fibroid liver and fibroid kidney.

[00132] In certain ~~embodiment~~examples compounds of the ~~invention~~disclosure are for use in the treatment of or are used in a method of treatment of: glaucoma, ocular hypertension, retinopathy, rheumatoid arthritis, psoriasis, psoriatic arthritis, Sjogren's syndrome, asthma, adult respiratory distress syndrome, chronic obstructive pulmonary disease (COPD), SLE and cGVHD, inflammatory bowel disease and stenosis of the bowel.

[00133] In certain ~~embodiment~~examples, compounds of the ~~invention~~disclosure are for use in the treatment of or are used in a method of treatment of central nervous system disorders. Such disorders may involve neuronal degeneration or physical injury to neural tissue, including without limitation, Huntington's disease, Parkinson's Disease, Alzheimer's, Amyotrophic lateral sclerosis (ALS), or multiple sclerosis.

[00134] In certain ~~embodiment~~examples compounds of the ~~invention~~disclosure are for use in the treatment of or are used in a method of treatment of cancer. Examples include but are not limited to: liver cancer, bladder cancer, hepatoma, squamous carcinoma of the lung, non-small cell lung cancer, adenocarcinoma of the lung, small-cell lung cancer, , various types of head and neck cancer, breast cancer, colon cancer, colorectal cancer, cancer of the peritoneum, hepatocellular cancer, gastrointestinal cancer, esophageal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, squamous cell cancer, pituitary cancer, astrocytoma, soft tissue sarcoma, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, kidney cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, brain cancer, endometrial cancer, testis cancer, cholangiocarcinoma, gallbladder carcinoma, gastric cancer and melanoma.

[00135] In another ~~aspect~~example of the ~~invention~~disclosure there is provided a pharmaceutical composition, wherein the composition comprises a compound of the ~~invention~~disclosure and pharmaceutically acceptable excipients.

[00136] In an ~~embodiment~~example the pharmaceutical composition may be a combination product comprising an additional pharmaceutically active agent. The additional pharmaceutically active agent may be one disclosed elsewhere herein.

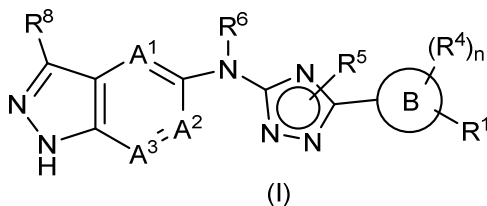
[00137] In an ~~aspect~~example of the present ~~invention~~disclosure there is provided the use of a compound of the ~~invention~~disclosure in the manufacture of a medicament for use in the treatment of any condition disclosed herein.

[00138] In an ~~embodiment~~example the compounds of the present ~~invention~~disclosure are at least five times more potent inhibitors of ROCK2 compared to ROCK1. Accordingly, the compounds of the ~~invention~~disclosure may be at least five times more selective towards ROCK2 than ROCK1.

DETAILED DESCRIPTION

CLAIMS

1. A compound of formula (I) and pharmaceutically acceptable salts thereof:



5 wherein

A¹, A² or A³ are each independently selected from CH, CR⁷ or N;

B represents a 5 to 10 membered carbocyclic ring system or a 5 to 10 membered heterocyclic ring system;

R¹ is L-R², wherein

10 L is a bond or -L¹-L²-,

wherein L¹ is selected from: a bond, -(CR^AR^B)₁₋₃-, -O(CR^AR^B)₁₋₃-, -(CR^AR^B)₀₋₃O-, and -NR^C(CR^AR^B)₁₋₃-; and

15 L² is selected from: a bond, -(CR^AR^B)₁₋₃-, -O-, -NR^D-, -C(O)NR^D-, -NR^DC(O)-, -C(O)O-, -OC(O)-, -C(O)-, -S(O)₂NR^D-, -NR^DS(O)₂-, -S(O)₂-, -S(O)(NR^D)-, -NR^DC(O)NR^E-, -OC(O)NR^D-, and -C(O)NR^DS(O)₂-; and

20 R² is selected from: H, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkyl substituted with -OR^F, C₁₋₆ alkyl substituted with -NR^FR^G, C₁₋₄ haloalkyl substituted with -OR^F, C₃₋₈ cycloalkyl substituted with OH, C₁₋₄ alkyl substituted with 3 to 8 membered heterocycloalkyl, C₁₋₄ alkyl substituted with 6 membered heteroaryl, -(CR^HR^I)₁₋₃OR^F, -(CR^HR^I)₁₋₃NR^FR^G, -(CR^NR^O)₁₋₃C(O)OR^F, -(CR^NR^O)₁₋₃C(O)NR^FR^G, C₃₋₁₀ carbocyclic ring system, and 3 to 10 membered heterocyclic ring system, wherein the carbocyclic ring or heterocyclic ring system is unsubstituted or substituted with: =O, -NR^FR^G, -C(O)R^F, halo, -CN, C₁₋₄ alkyl, C₁₋₄ haloalkyl or C₁₋₄ alkyl substituted with -OR^F;

25 R⁴ is independently selected at each occurrence from: halo, C₁₋₄ alkyl, C₁₋₆ haloalkyl, -CN, -OR^J, =O, C₁₋₄ alkyl substituted with -OR^J, -NR^JR^K, C₁₋₄ alkyl substituted with -NR^JR^K, C₃₋₈ cycloalkyl, C₁₋₄ alkyl substituted with C₃₋₈ cycloalkyl, 3 to 8 membered heterocycloalkyl and C₁₋₄ alkyl substituted with 3 to 8 membered heterocycloalkyl;

30 R⁵ is selected from: H, C₁₋₄ alkyl, C₁₋₄ alkyl substituted with -OR^L, C₁₋₄ alkyl substituted with -NR^LR^L, C₃₋₈ cycloalkyl, substituted or unsubstituted phenyl, 3 to 8 membered heterocycloalkyl, C₁₋₄ alkyl substituted with C₃₋₈ cycloalkyl, C₁₋₄ alkyl substituted with 3 to 8 membered heterocycloalkyl and substituted or unsubstituted 5 or 6 membered heteroaryl, wherein the phenyl or heteroaryl group may be substituted by 1 or 2 R⁹;

R⁶ is selected from: H and C₁₋₄ alkyl;

R⁷ is selected from: H, halo, -OR^M, C₁₋₄ alkyl, C₁₋₆ haloalkyl, C₁₋₄ alkenyl, -CN, and C₃₋₈ cycloalkyl;

R⁸ is selected from: H, halo, C₁₋₄ alkyl, C₁₋₆ haloalkyl, -CN, and C₃₋₈ cycloalkyl;

R⁹ is selected from halo or C₁₋₄ alkyl;

n is 0, 1, or 2;

- 5 R^A and R^B are selected from H, C₁₋₄ alkyl, or C₁₋₄ haloalkyl or R^A and R^B together with the atom to which they are attached form a 3 to 6 membered cycloalkyl ring or a 3 to 6 membered heterocycloalkyl ring;

R^C, R^D, R^E, R^F and R^G are each independently selected from H, C₁₋₄ alkyl and C₁₋₄ haloalkyl;

- 10 R^H and R^I are each H except one pair of R^H and R^I on the same carbon atom, together with that carbon atom, form a 3 to 6 membered cycloalkyl ring or a 3 to 6 membered heterocycloalkyl ring; and

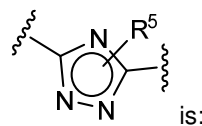
R^J, R^K, R^L, R^M, R^N and R^O are each independently at each occurrence selected from H or C₁₋₄ alkyl.

2. The compound of claim 1, wherein A¹, A² and A³ are each independently selected from: C-H, C-F, C-Cl, C-Me, C-Et, C-*i*-Pr, C-cyclopropyl, C-ethenyl, C-propenyl, C-CN, C-CF₃ or N-; and/or

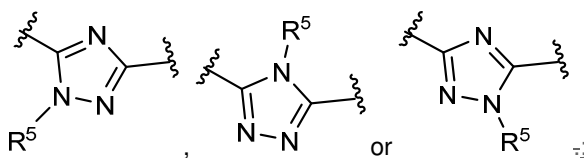
- 15 ~~3. The compound of claim 1 or claim 2, wherein R⁸ is H, Cl, F, CN or Me-; and/or~~

- ~~4. The compound of any preceding claim, wherein R⁶ is selected from H or methyl.~~

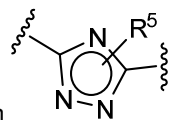
- ~~5.3. The compound of any preceding claim, wherein~~



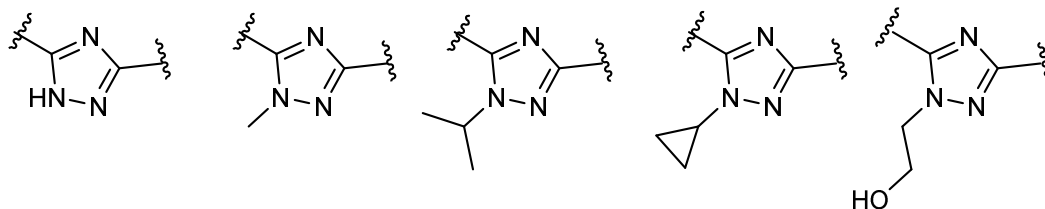
is:

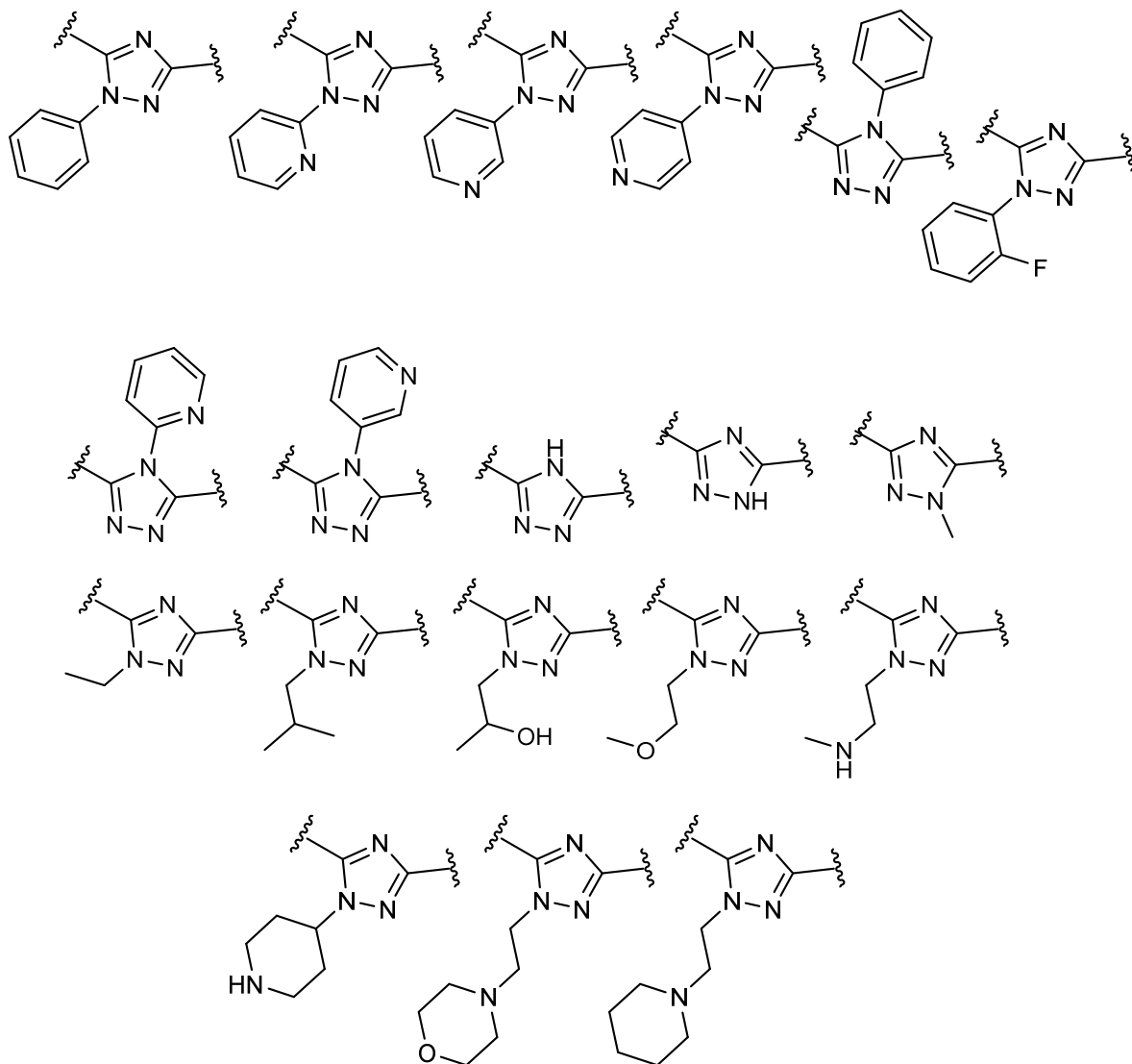


- ~~6. The compound of any preceding claim, or wherein~~



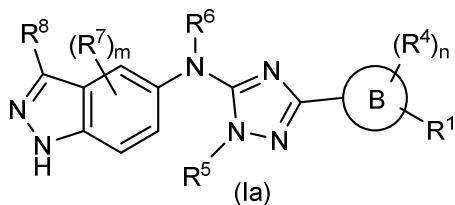
is selected from:





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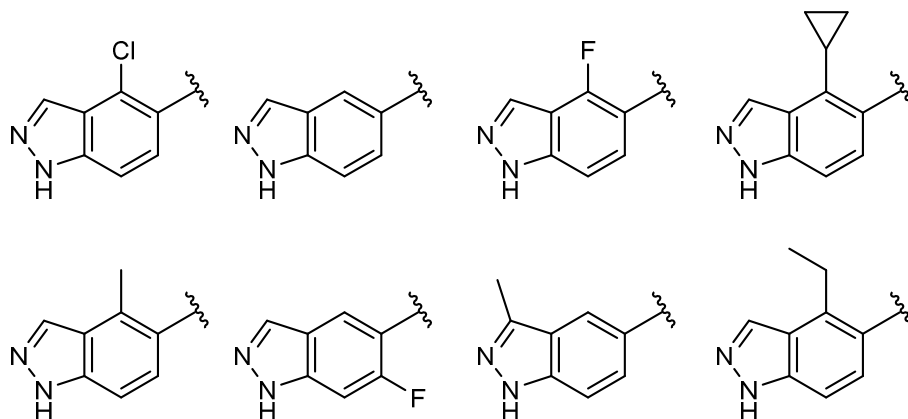
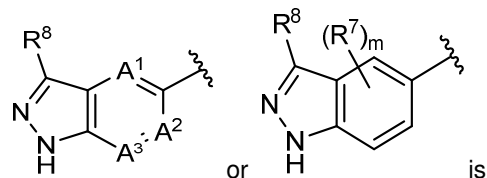
7.4. The compound of any one of claims 1 to 4 preceding claim, wherein the compound is a compound of formula (Ia):



wherein m is 1 or 2.

- 10 8.5. The compound of any preceding claim, wherein R⁵ is selected from: H, C₁₋₄ alkyl, C₁₋₄ alkyl substituted with -OR^L, C₁₋₄ alkyl substituted with -NR^LR^L, C₃₋₈ cycloalkyl, substituted or unsubstituted phenyl, C₁₋₄ alkyl substituted with a 3 to 8 membered heterocycloalkyl, and substituted or unsubstituted 5 or 6 membered heteroaryl, wherein the phenyl or heteroaryl group may be substituted by 1 or 2 R⁹.

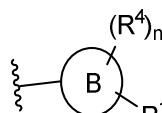
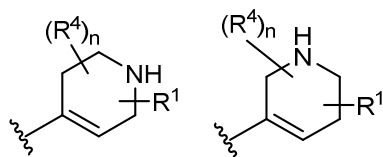
9-6. The compound of any preceding claim, wherein selected from:



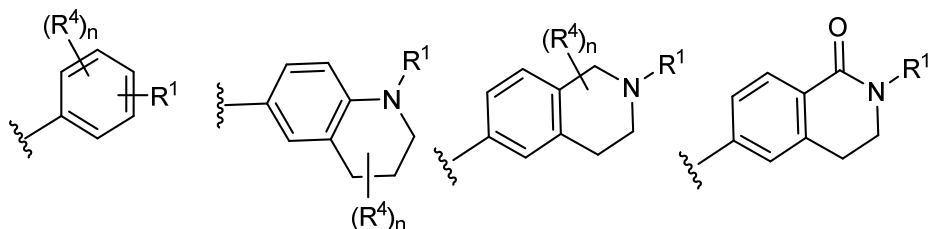
10-7. The compound according to any preceding claim, wherein B is selected from: a 5 or 6 membered carbocyclic ring which is aromatic or unsaturated, a 5 or 6 membered heterocyclic ring which is aromatic or unsaturated, a 9 or 10 membered carbocyclic bicyclic ring system, or a 9 or 10 membered heterocyclic bicyclic ring system, wherein the bicyclic ring system is either aromatic or one of the rings within the bicyclic ring system is aromatic or unsaturated and the other ring is saturated.

10 11-8. The compound according to ~~any preceding claim~~ 7, wherein B is selected from: a 6 membered carbocyclic ring, and a 10 membered heterocyclic fused bicyclic ring system.

12-9. The compound ~~of any preceding~~ according to claim 7 or claim 8, wherein B is selected from: phenyl, pyrazole, pyridyl, piperidyl, azaindole, isoindoline, tetrahydroisoquinoline, tetrahydroisoquinoline, furan, indazole, benzpyrazole, pyrimidine, pyridone, tetrahydropyridine, 15 dihydropyran, cyclopentene, cyclohexenyl, chromane, chromanone, benzodioxan, tetrahydronaphthalene, dihydrobenzoxazine, benzomorpholine, tetrahydroquinoline, naphthyridine, quinoline, isoquinoline, and dihydroisobenzofuran or B is:



13-10. The compound of any preceding claim, wherein B is selected from:

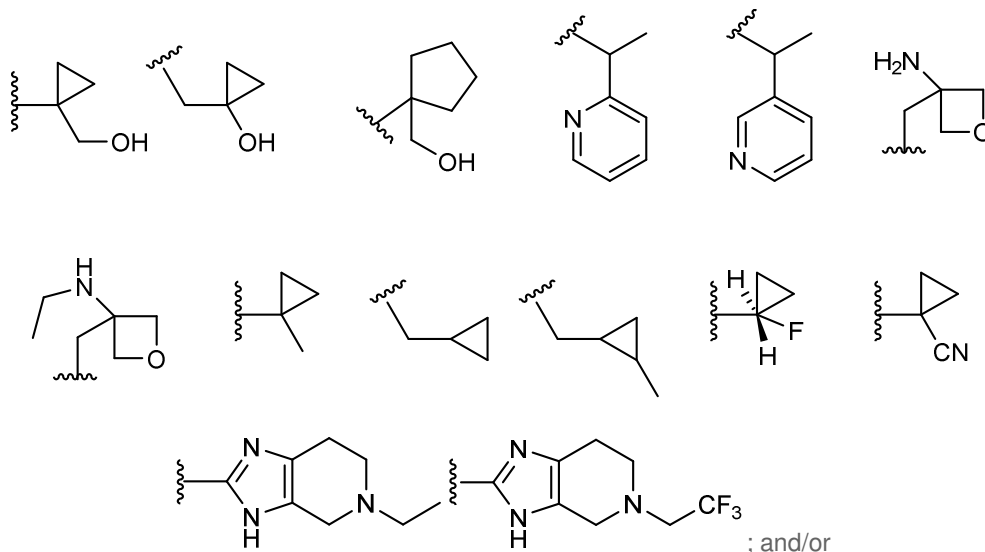


14.11. The compound of any preceding claim, wherein L¹ is selected from: a bond, -(CR^AR^B)₁₋₃-, and -O(CR^AR^B)₁₋₃-; and/or

5 ~~15. The compound of any preceding claim, wherein L² may be selected from: a bond, -NR^D-, -C(O)NR^D-, -NR^DC(O)-, -C(O)O-, -C(O)-, -NR^DC(O)NR^E-, and -OC(O)NR^D-.~~

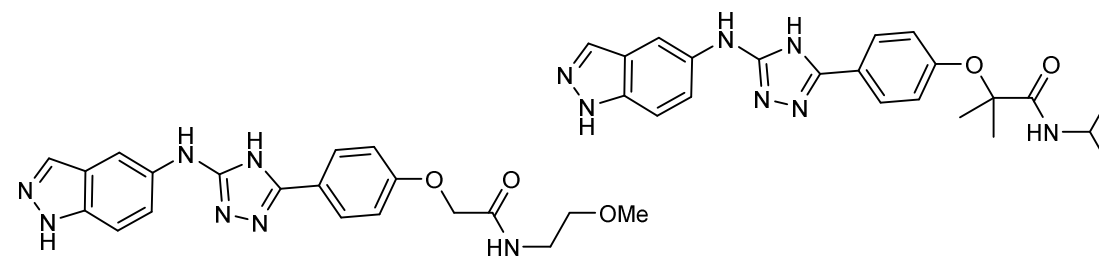
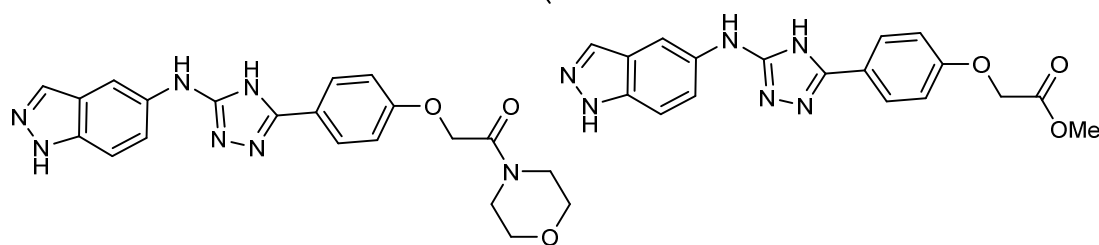
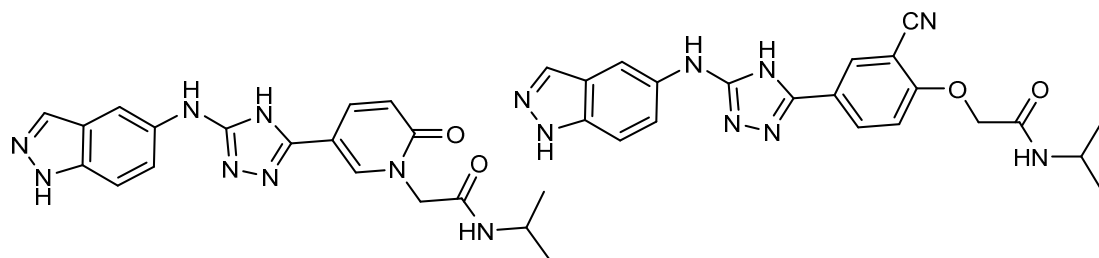
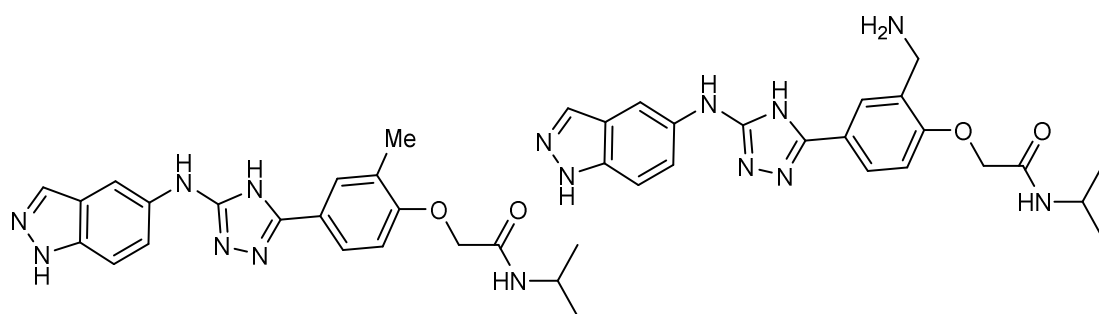
~~16.12. The compound of any preceding claim, wherein R^A and R^B are independently selected from H, C₁₋₄ alkyl and C₁₋₄ haloalkyl and/or R^C and R^D is independently selected from H and methyl-; and/or~~

10 ~~17. The compound of any preceding claim, wherein R² is selected from: H, CN, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *tert*-butyl, sec-butyl, *tert*-pentyl, allyl, propargyl, difluoroethyl, difluoropropyl, trifluoroethyl, trifluoropropyl, trifluoroisopropyl, isopropanol, *n*-butanol, sec-butanol, propanol, *tert*-butanol, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopropanol, cyclobutanol, cyclopentanol, cyclohexanol, cycloheptanol, aziridinyl, *N*-acetylaziridinyl, *N*-alkylaziridinyl, azetidiny, *N*-acetylazetidiny, *N*-alkylazetidiny, 2-methylpropan-2-amine, phenyl,~~
 15 chlorophenyl, pyrrolidinyl, difluoropyrrolidinyl, trifluoroethylpyrrolidinyl, *N*-methylpyrrolidinyl, tetrahydrofuranyl, sulfolanyl, dihydropyran, tetrahydropyranyl, tetrahydropyranoimidazolyl, morpholinyl, imidazolyl, ethyltetrahydroimidazopyridine, methylimidazolyl, piperazinyl, *N*-methylpiperazinyl, trifluoromethylpiperazinyl, oxadiazolyl, dimethyldihydrooxazolyl, pyrazolyl, *N*-methylpyrazolyl, ethylpyrazolyl, 4-pyridone, 2-pyridone, pyridyl, methyl substituted with
 20 tetrahydrofuran, ethyl substituted with pyridine, ethyl substituted with -NMe₂, ethyl substituted with OMe, ethyl substituted with OH; or selected from:

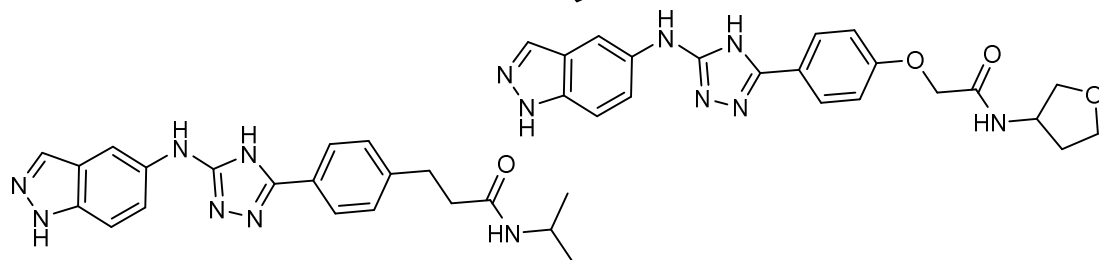
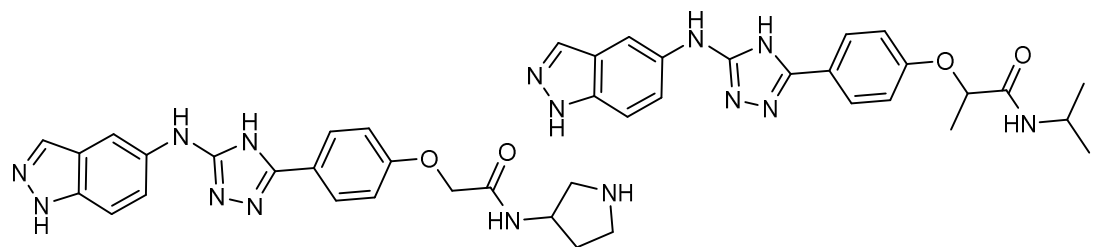


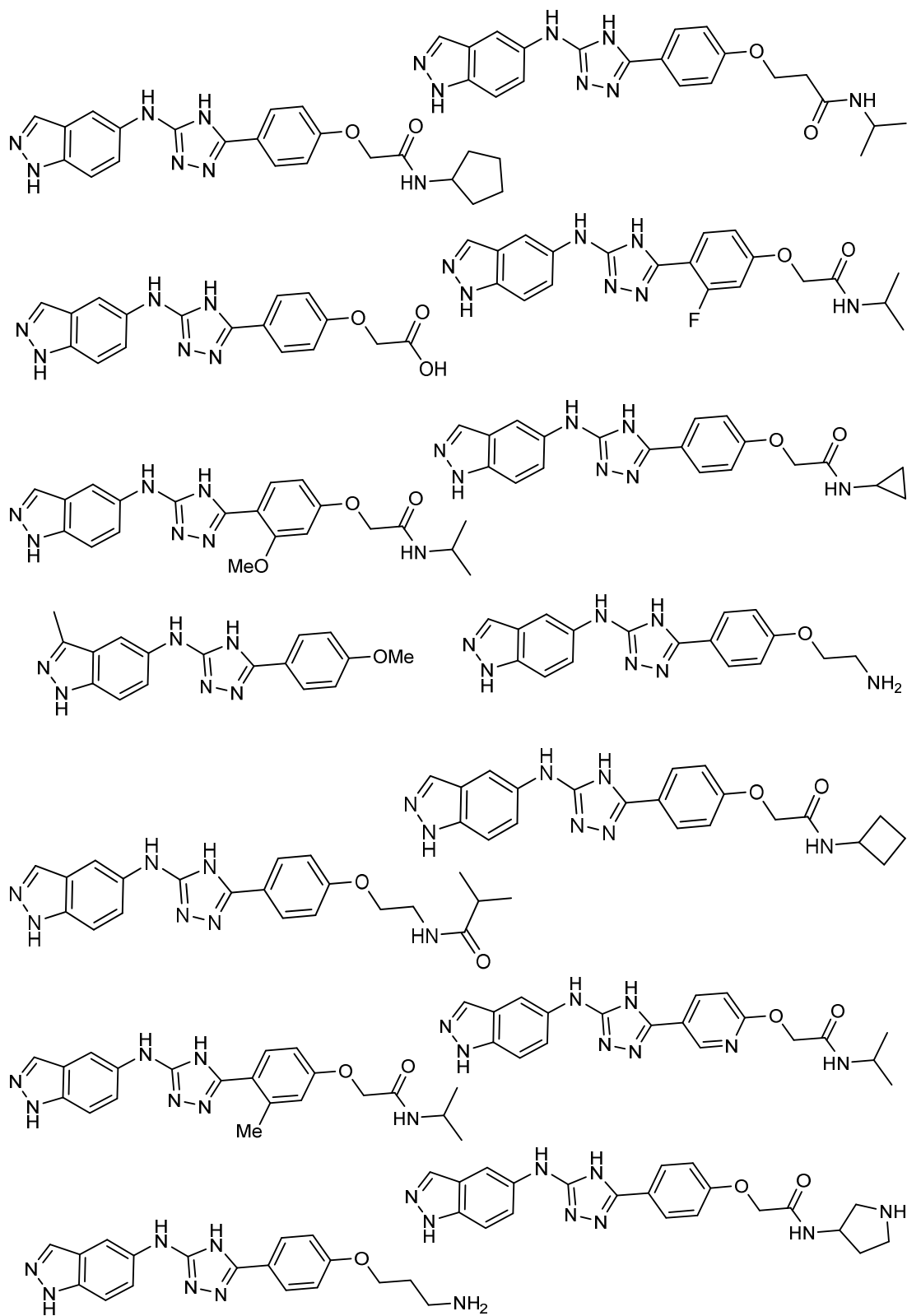
~~19.13.~~ The compound of claim 1, wherein the compound is selected from:

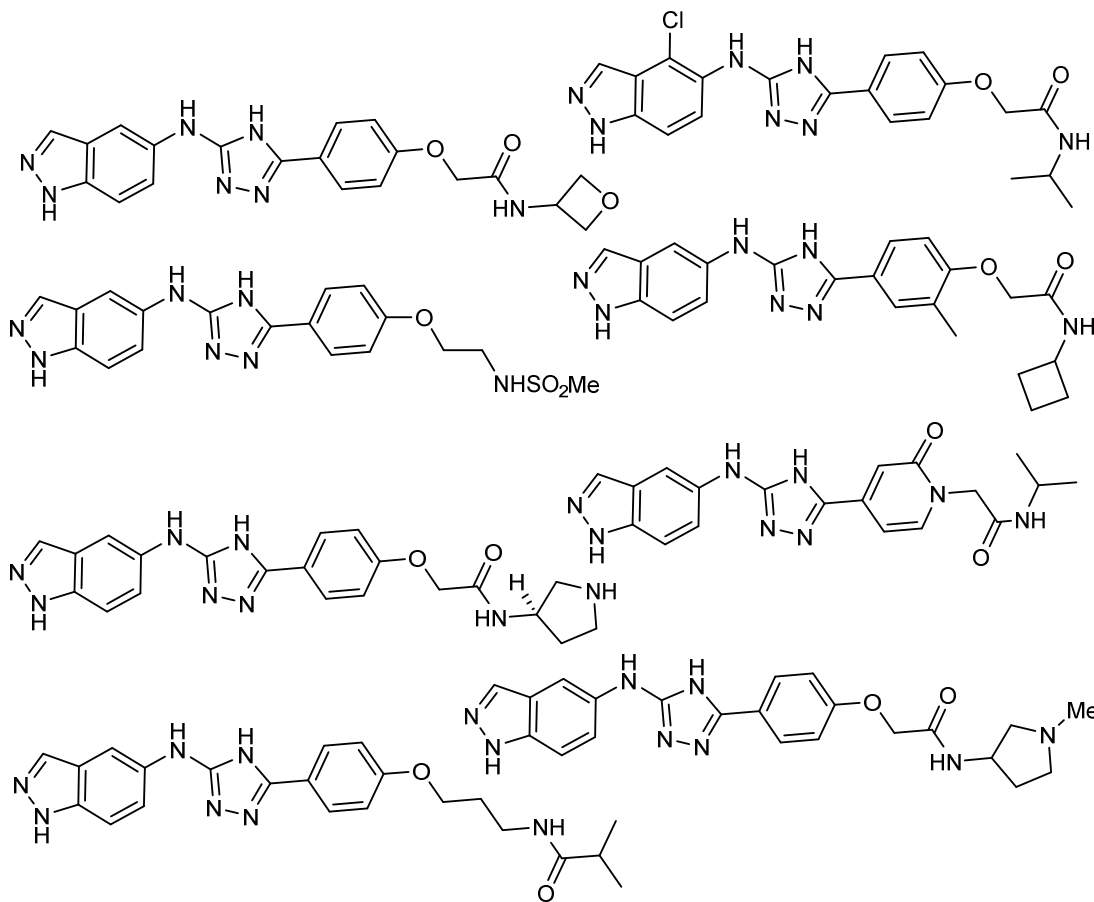
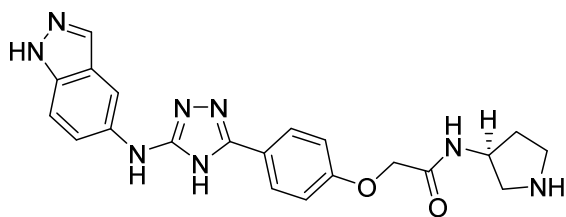
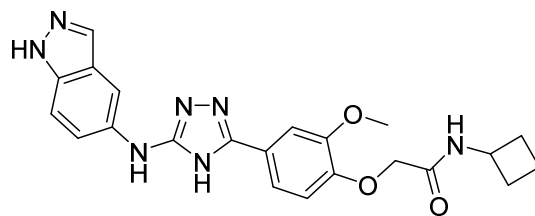
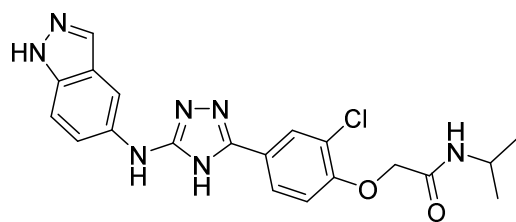


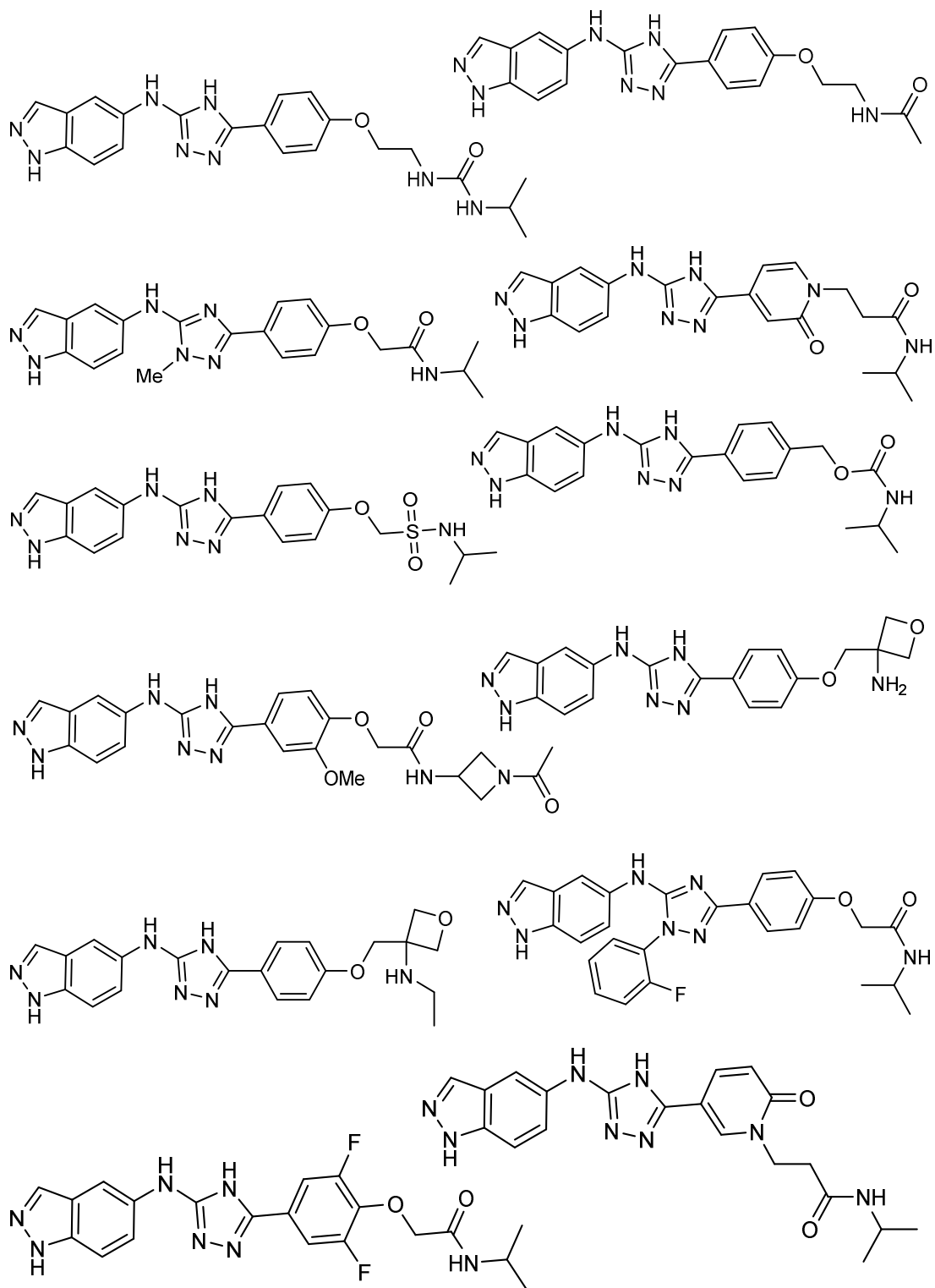


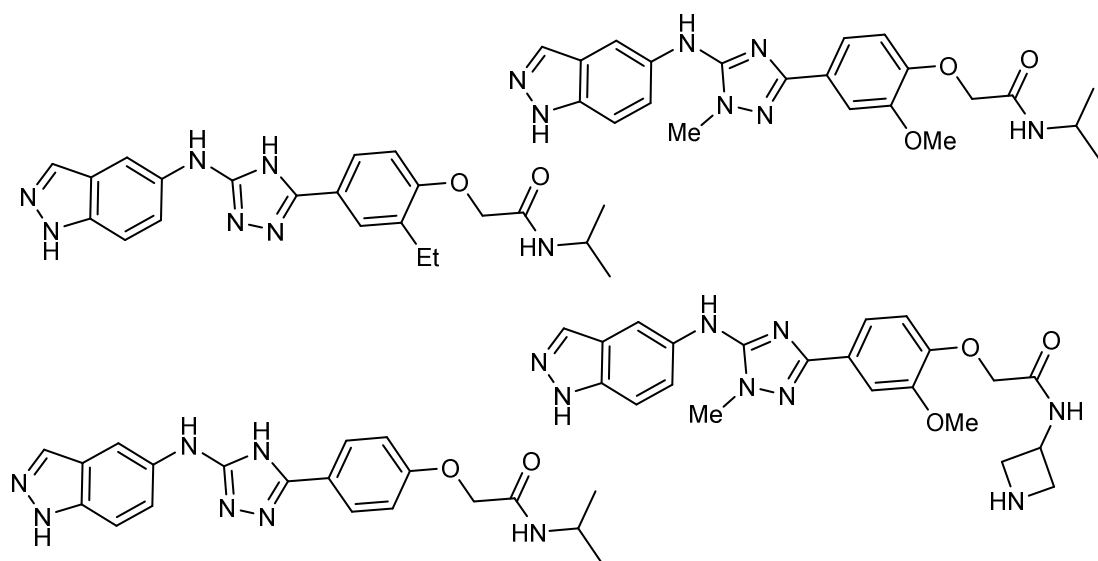
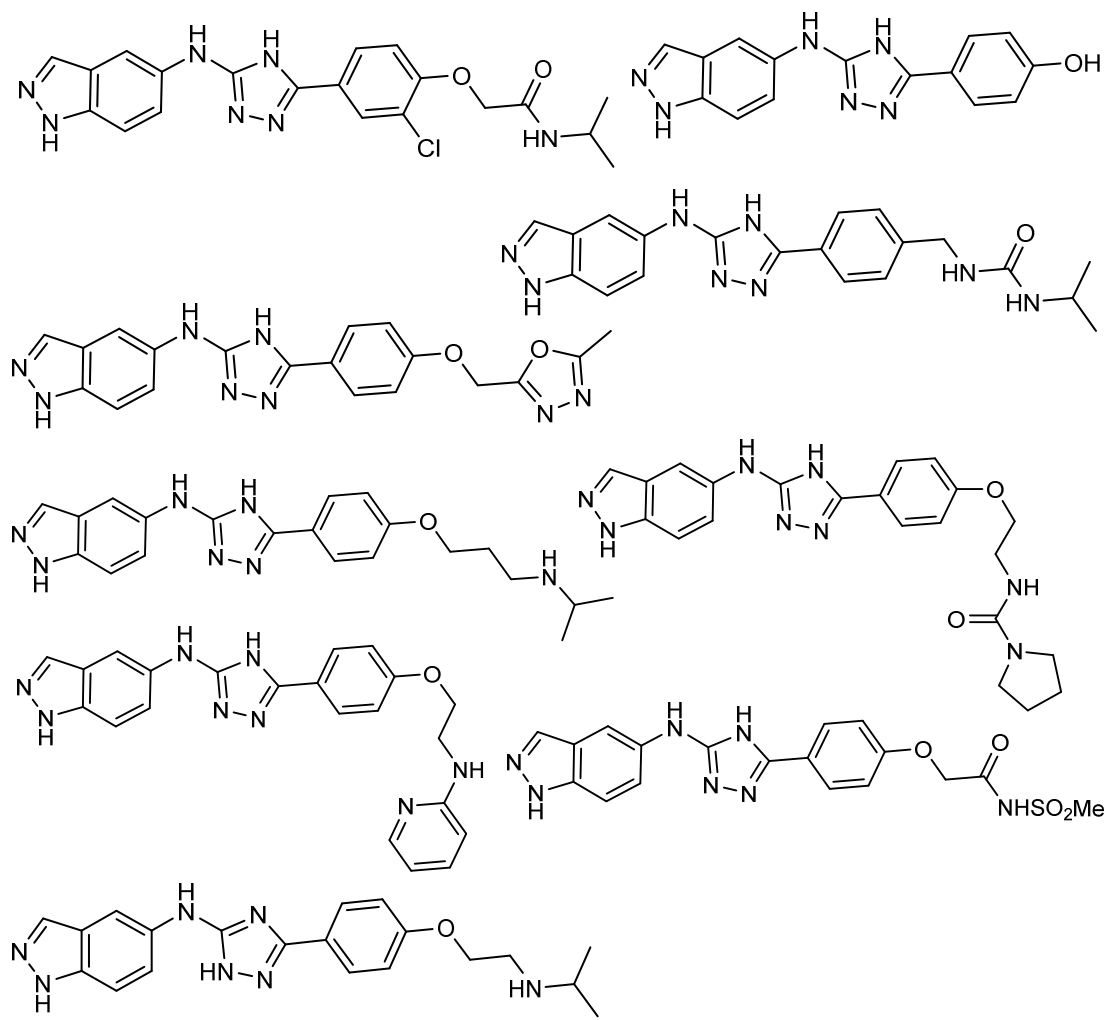
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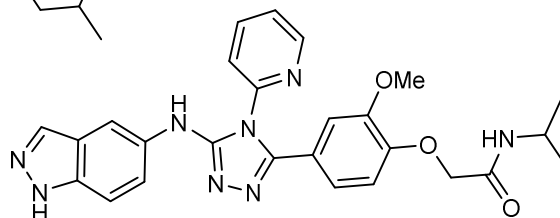
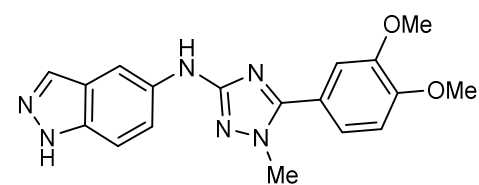
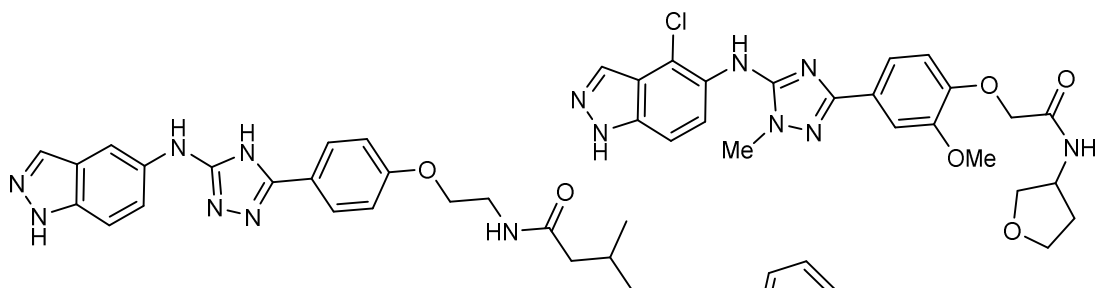
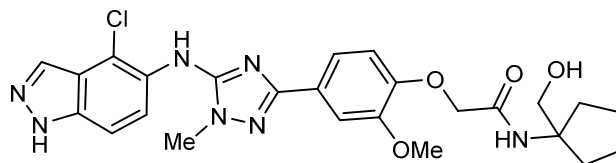
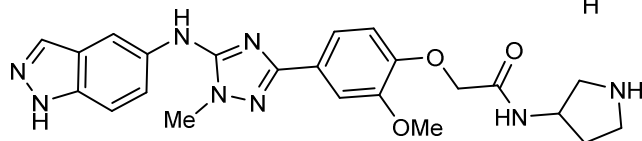
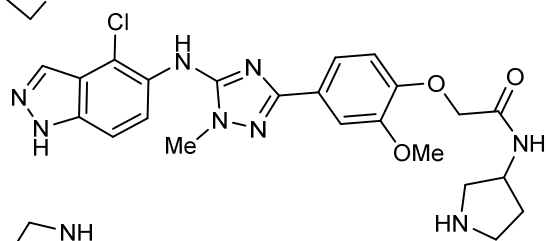
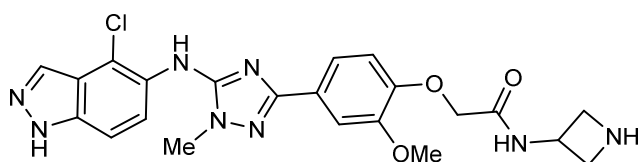
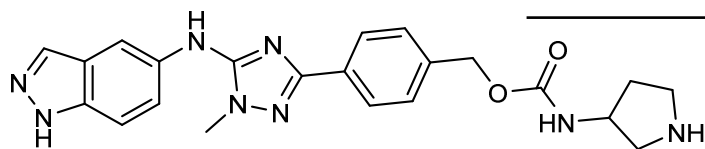
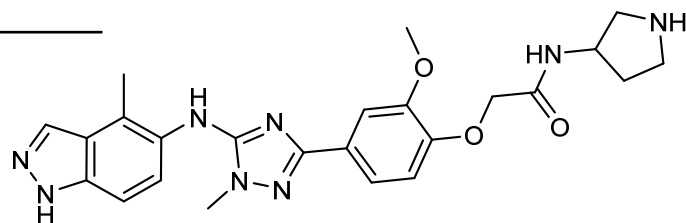
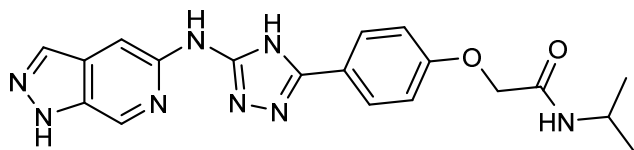


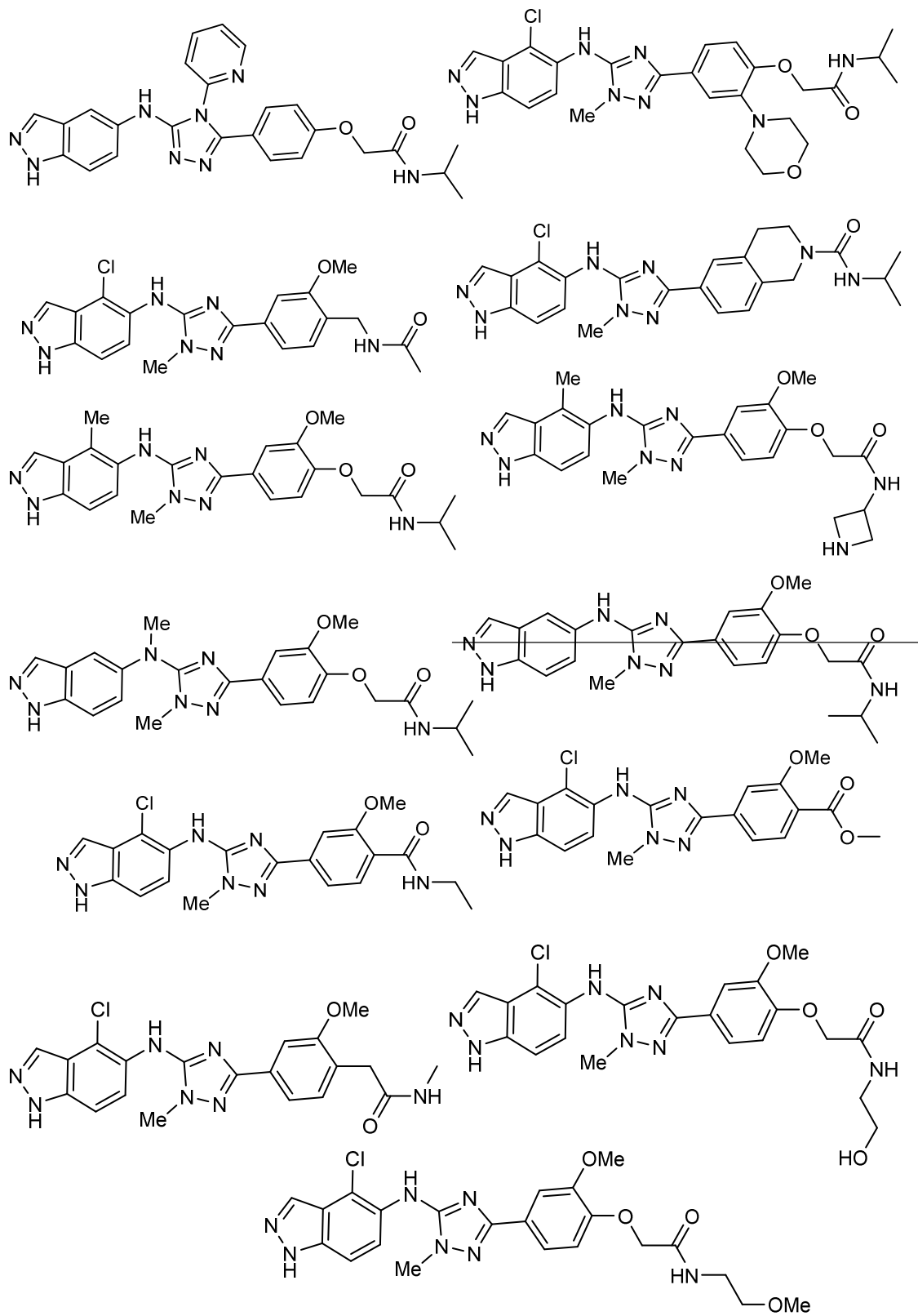


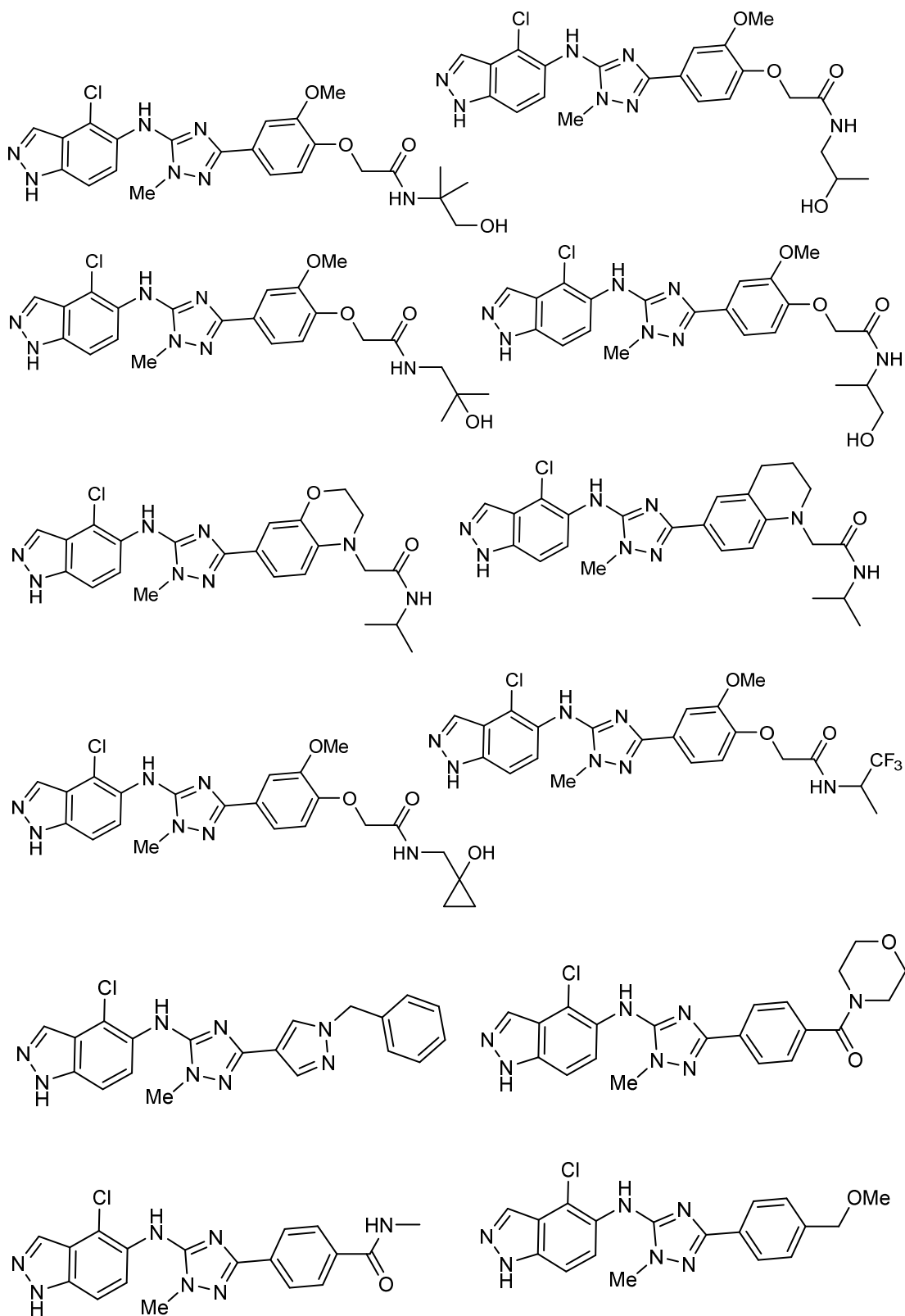


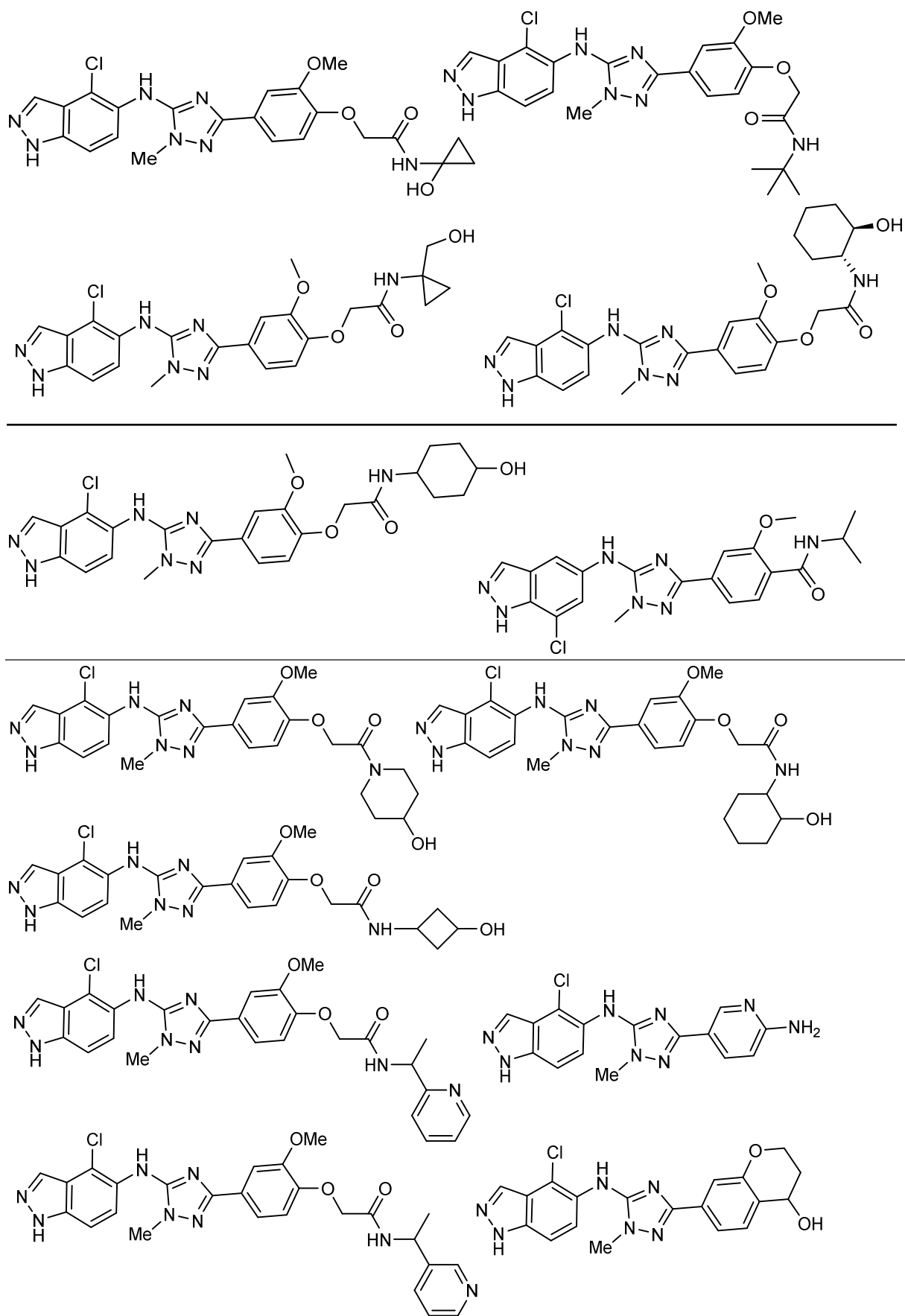


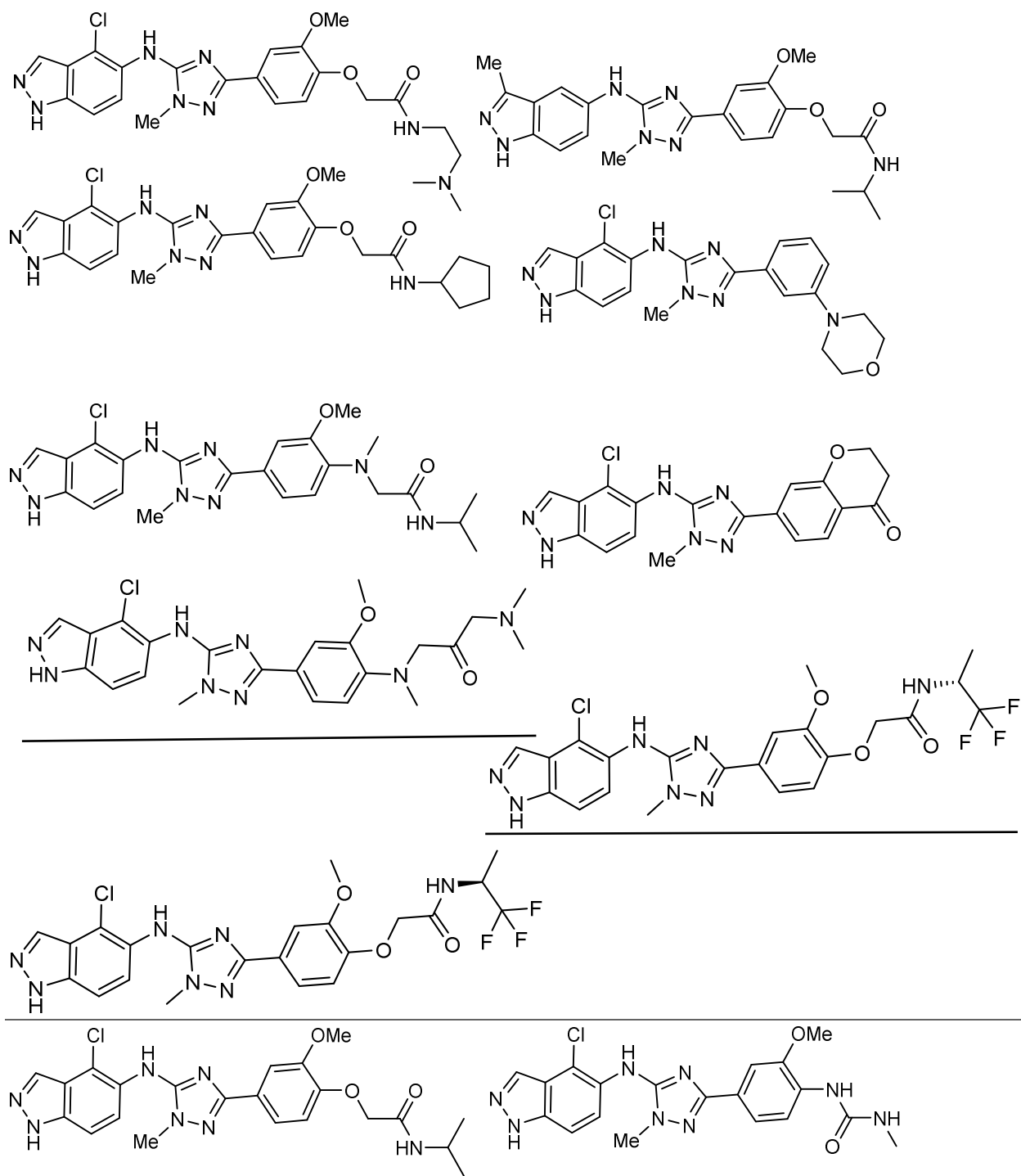


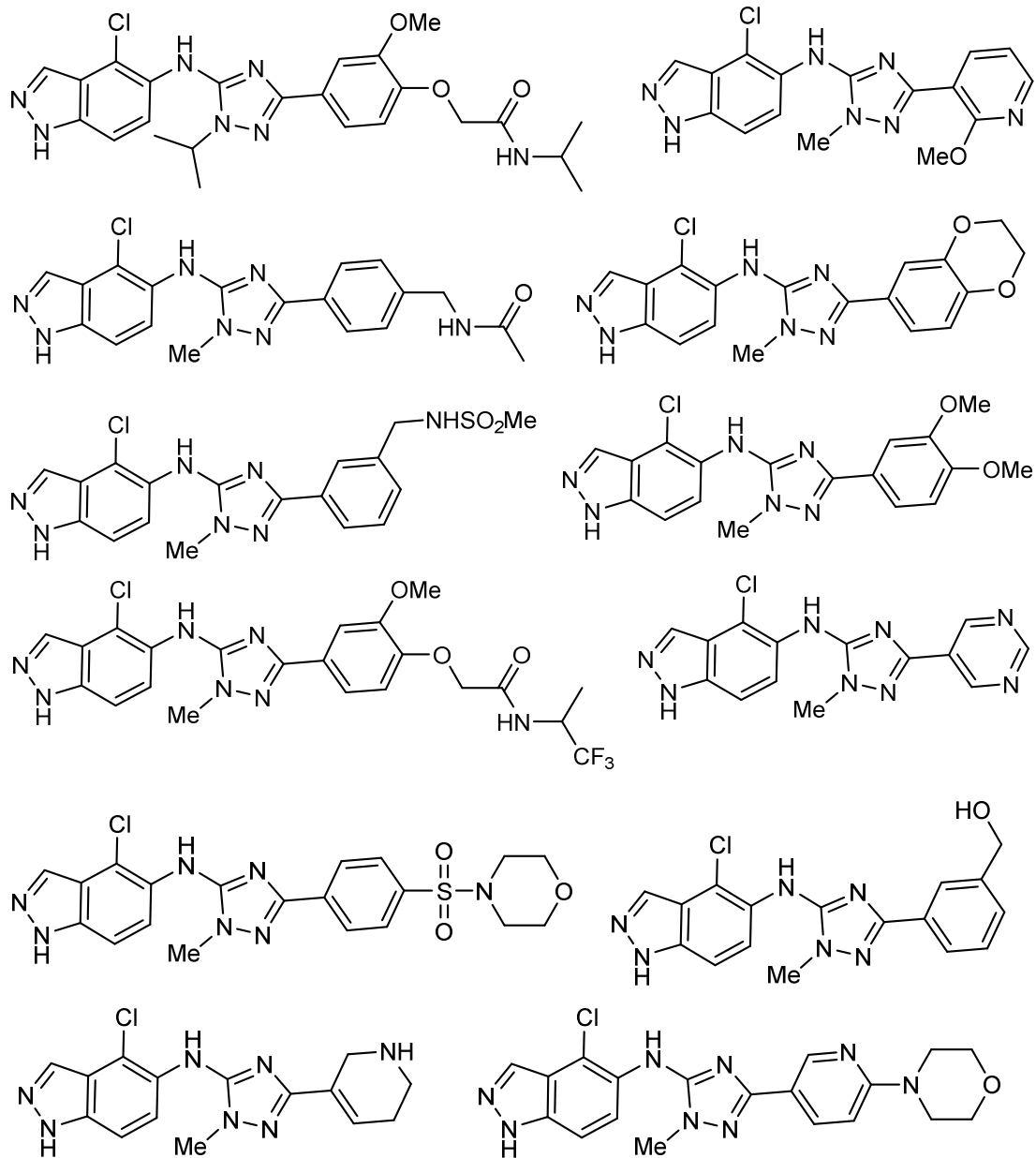


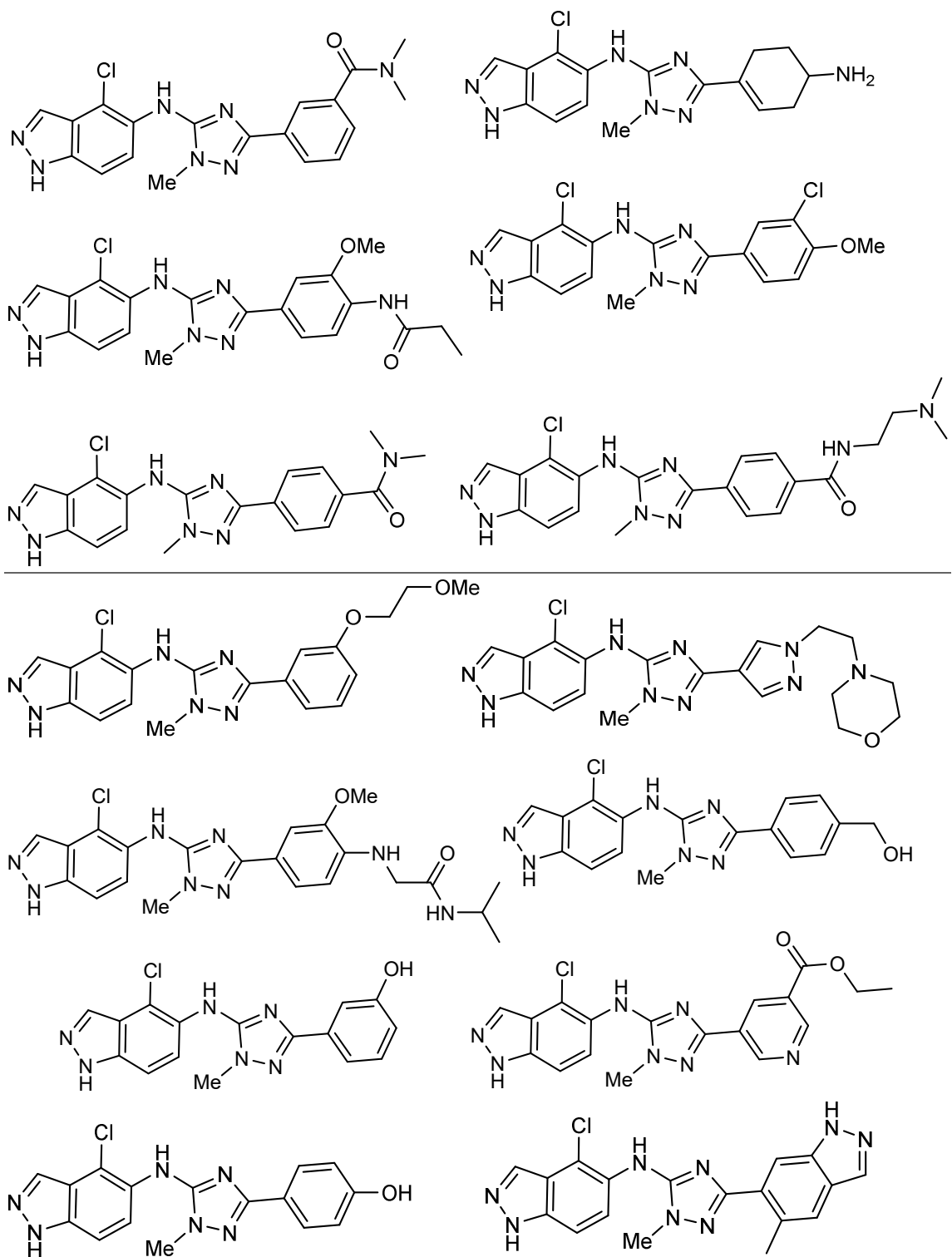


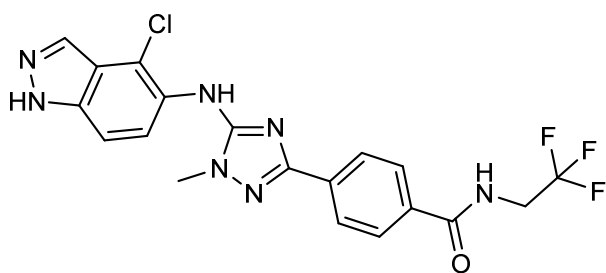
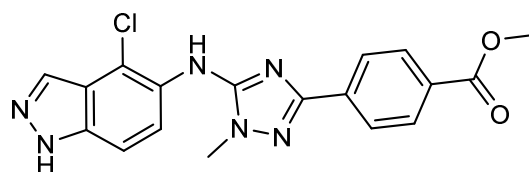
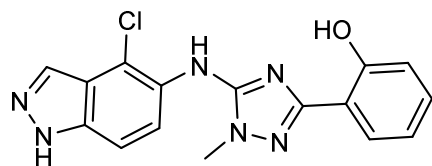
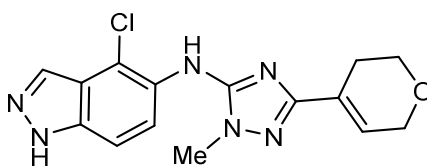
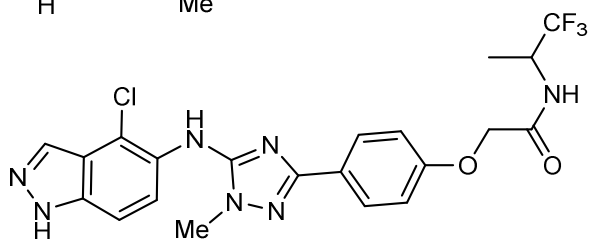
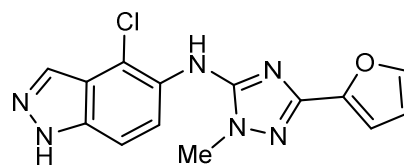
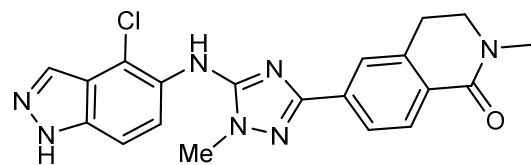
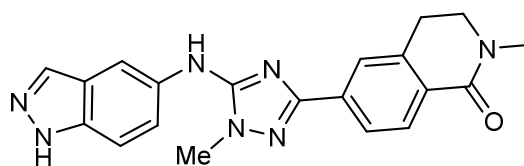
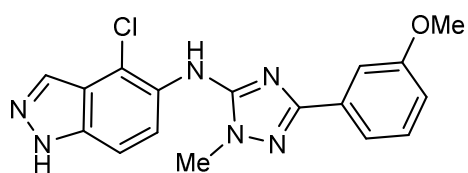
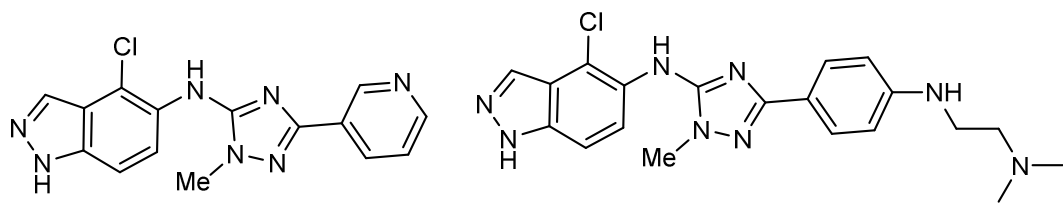


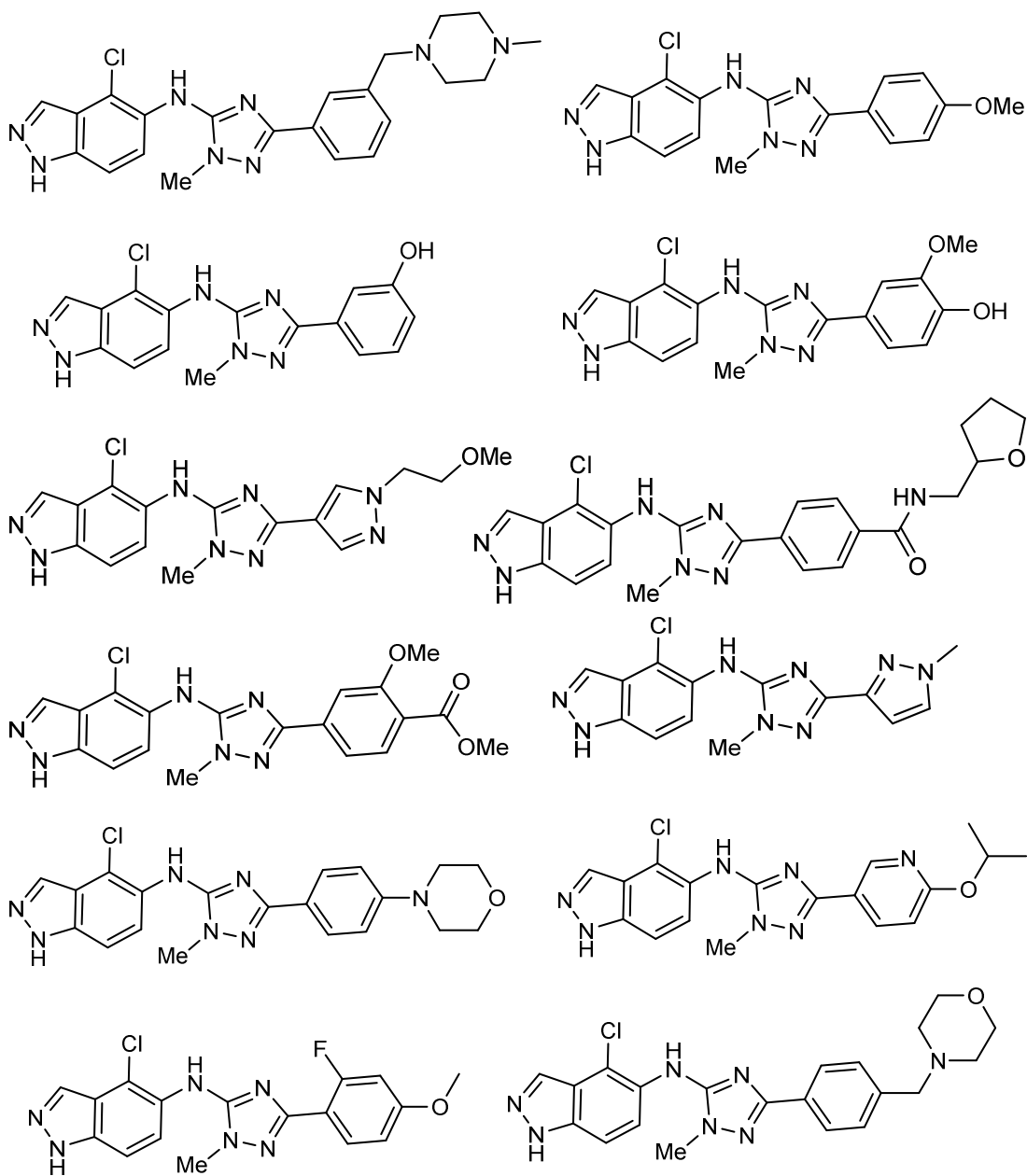


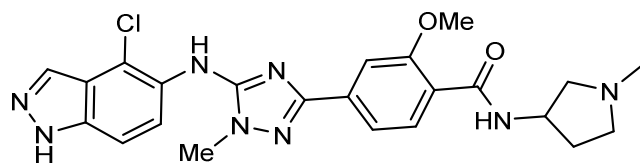
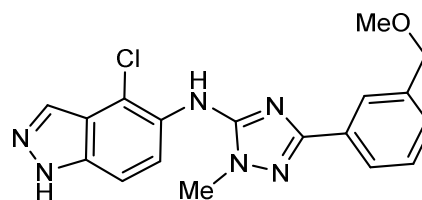
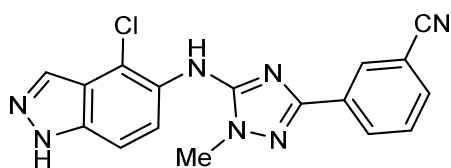
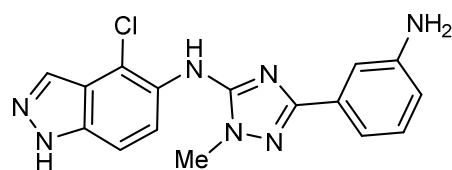
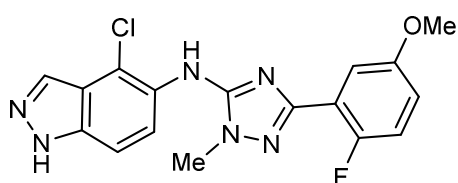
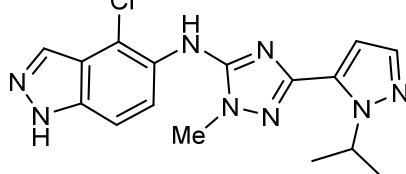
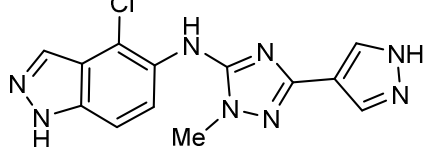
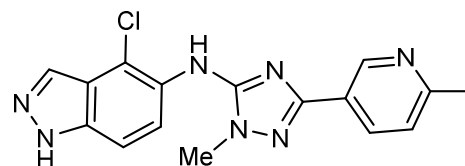
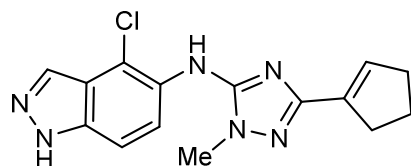
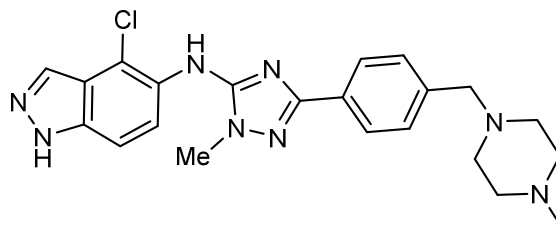
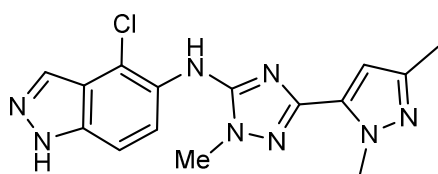




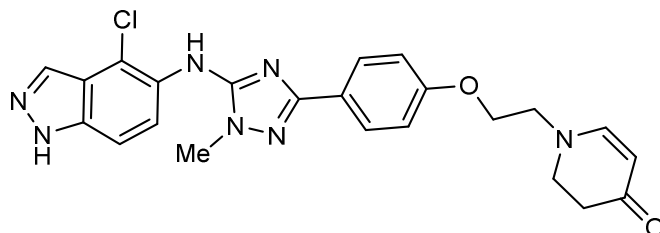
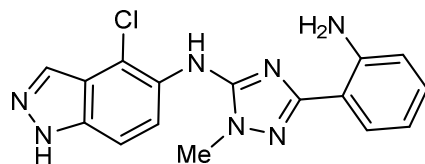
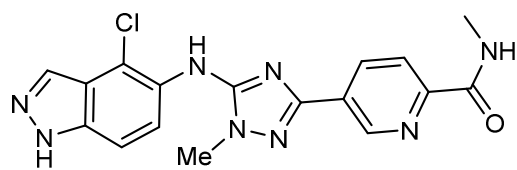
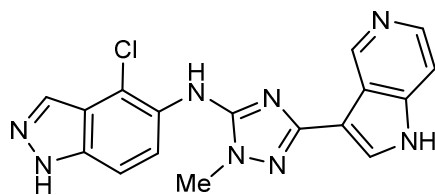


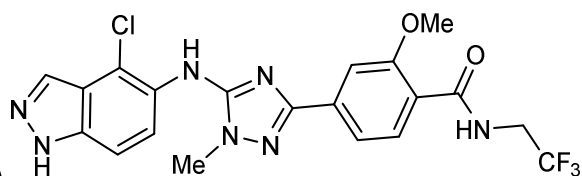
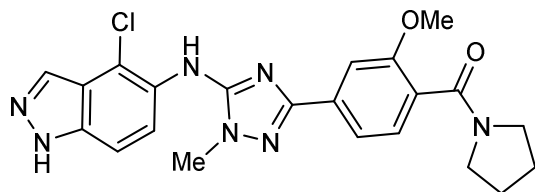
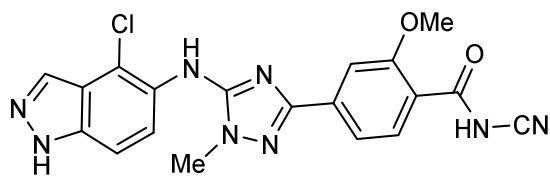
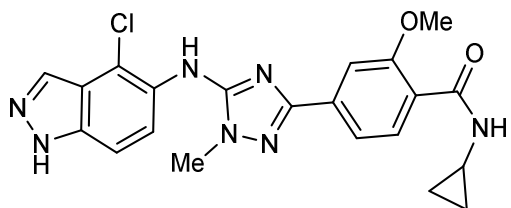
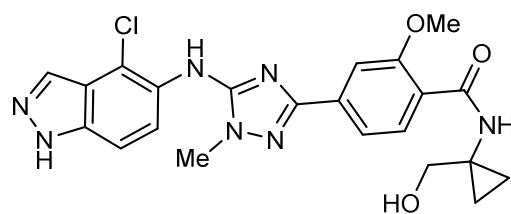
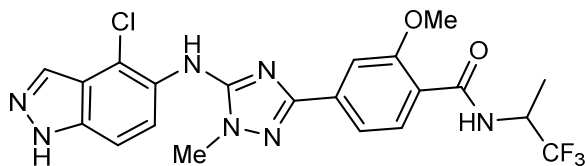
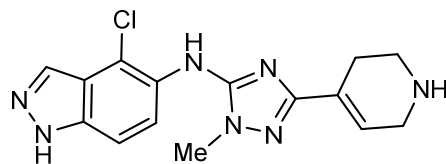
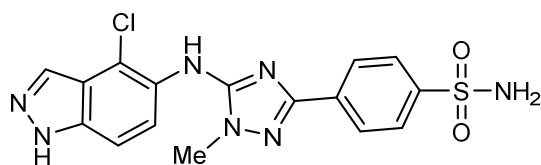
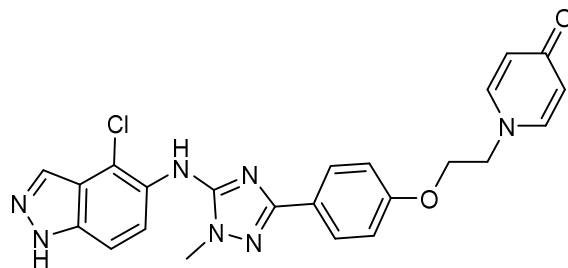
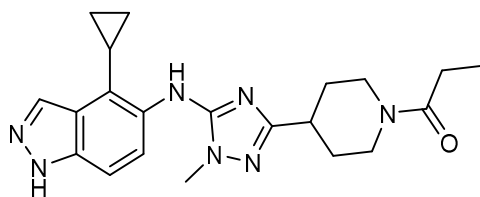




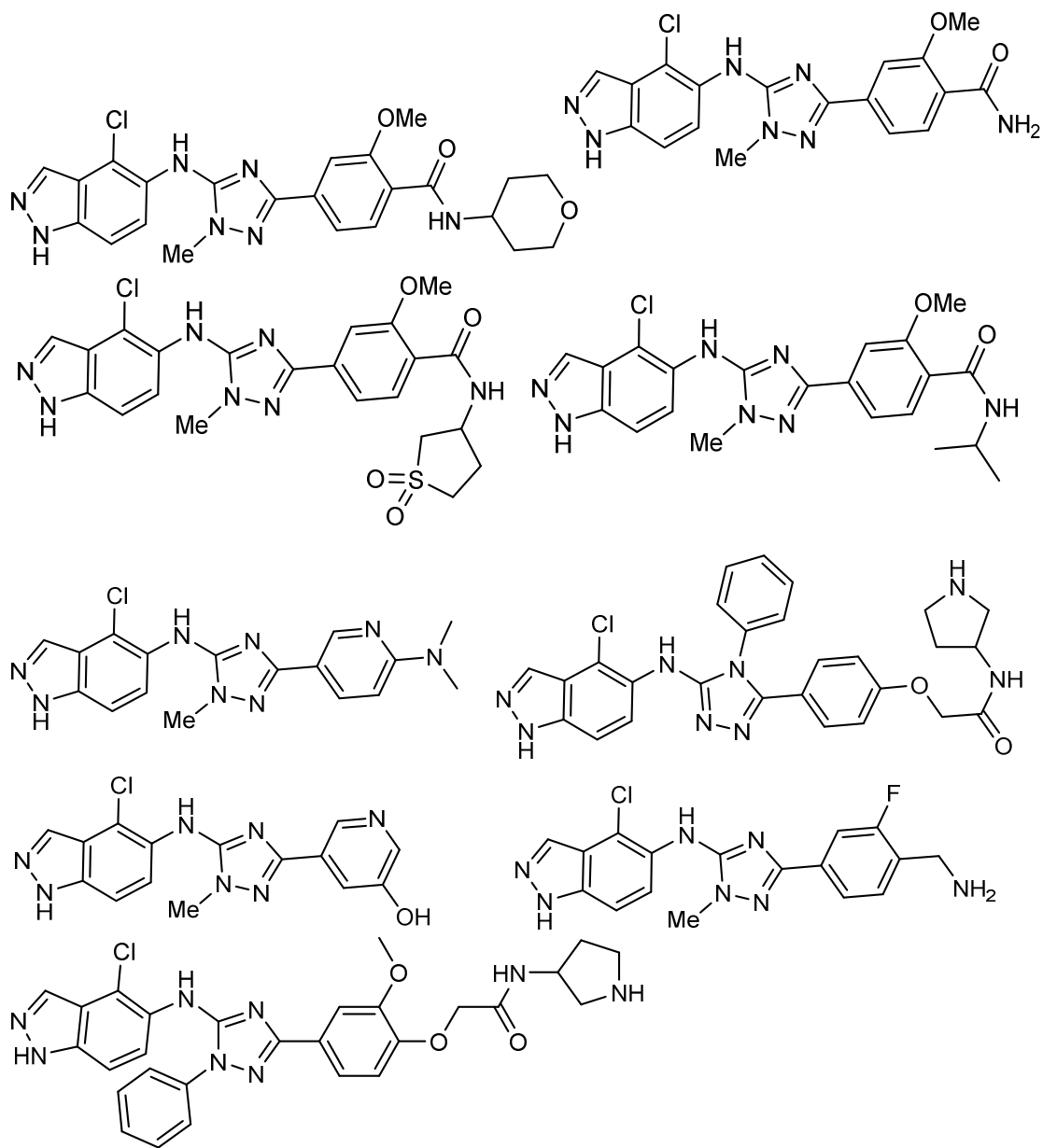


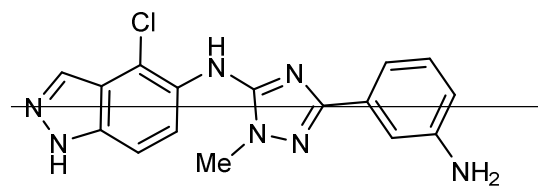
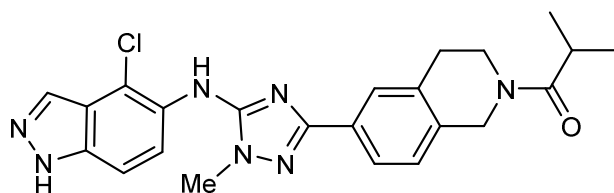
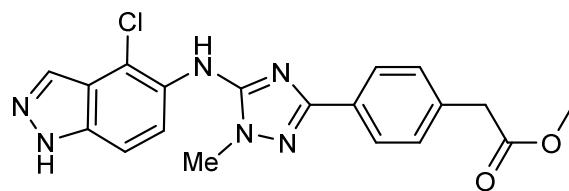
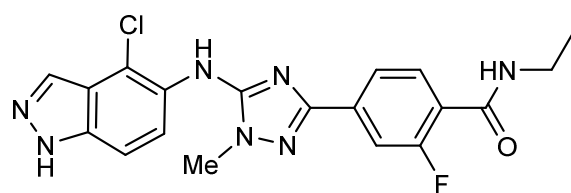
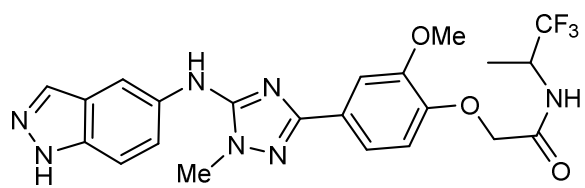
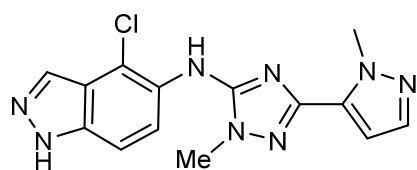
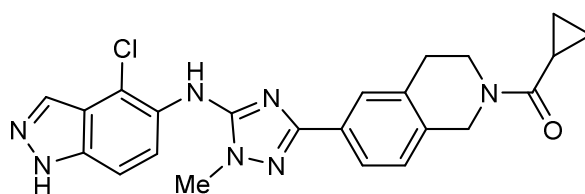
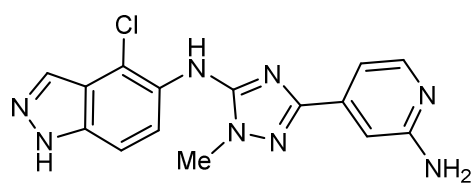
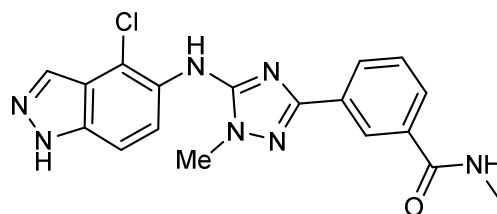
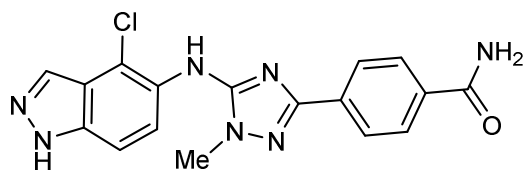
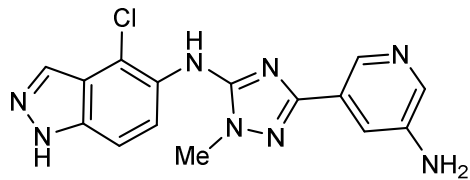
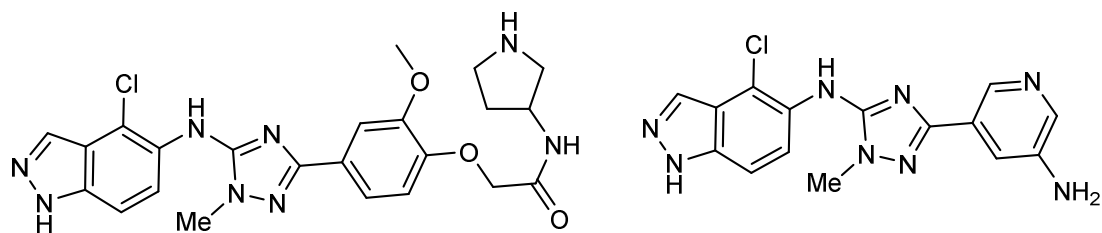
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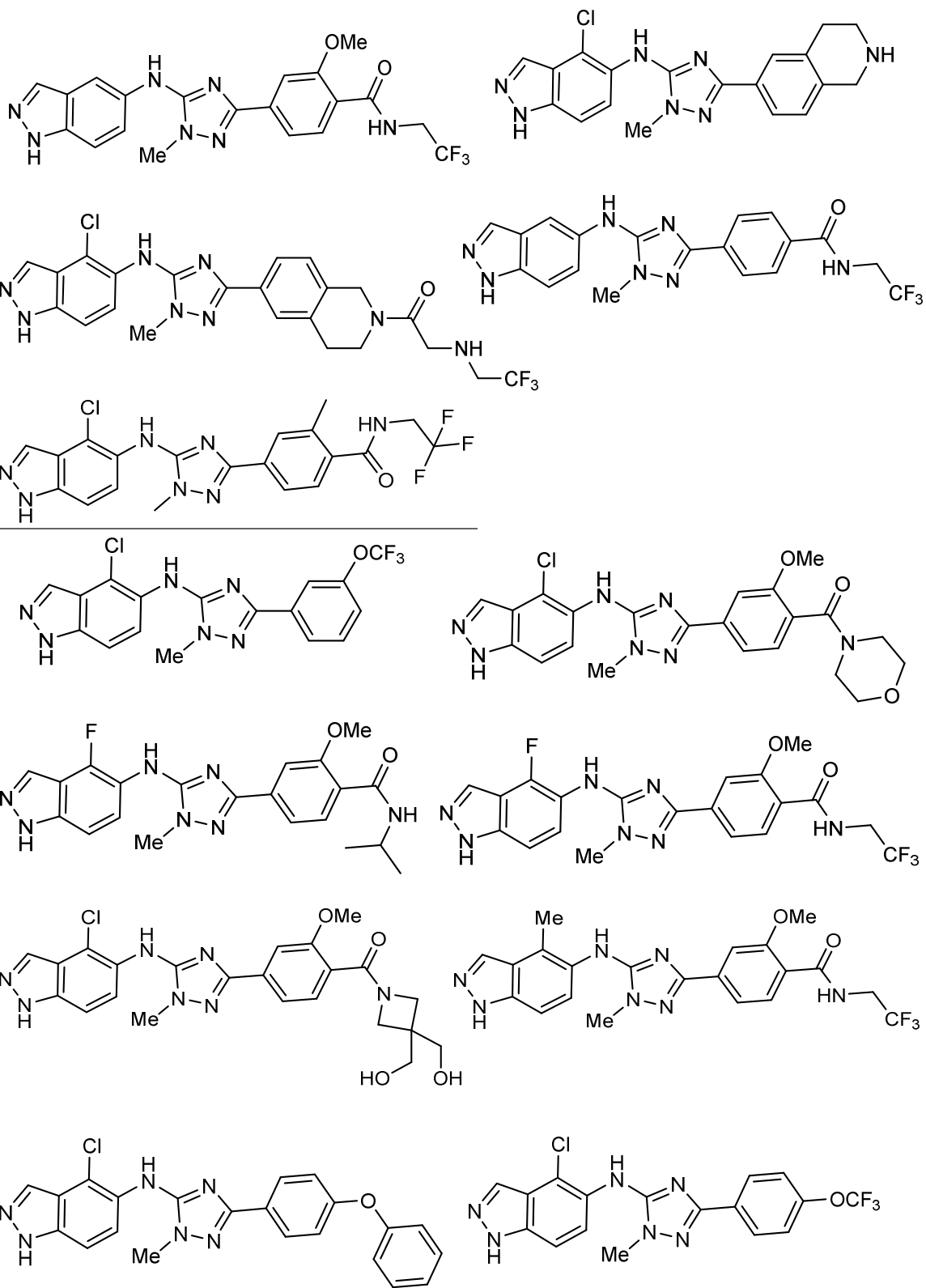




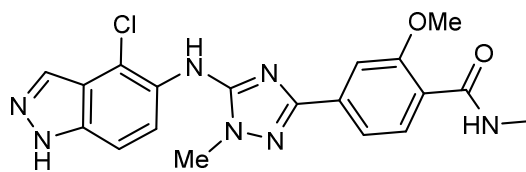
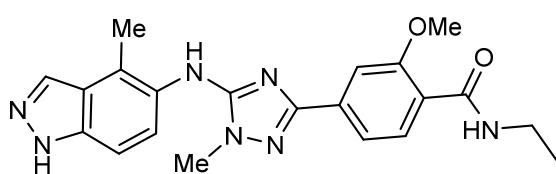
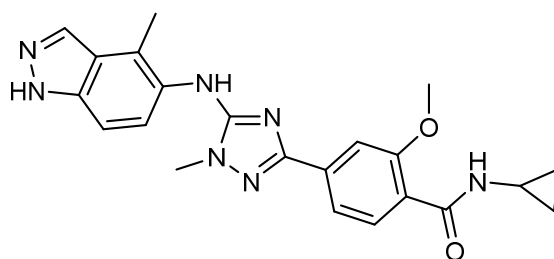
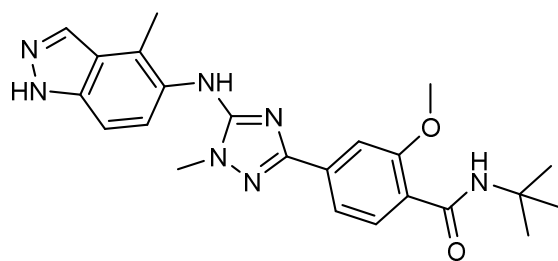
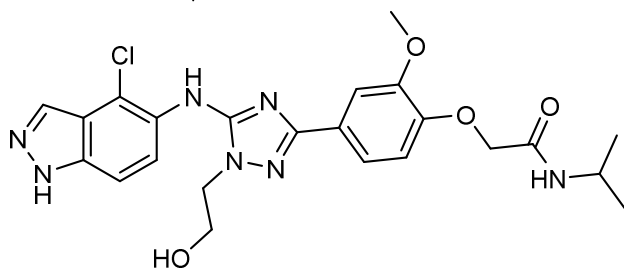
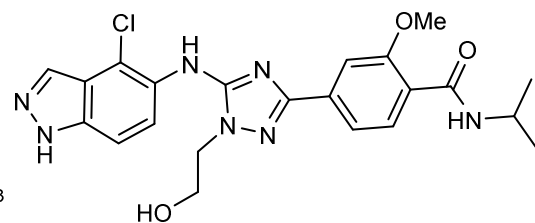
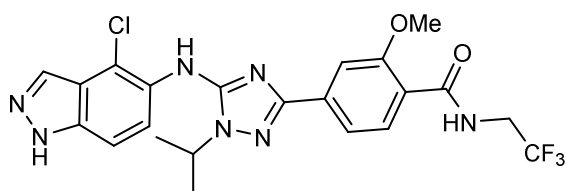
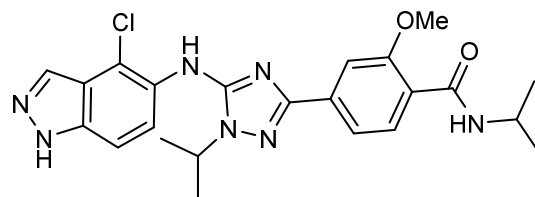
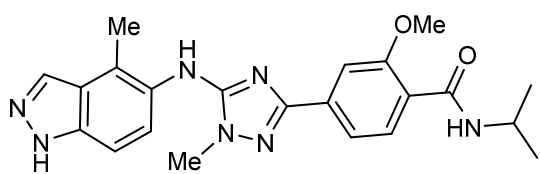
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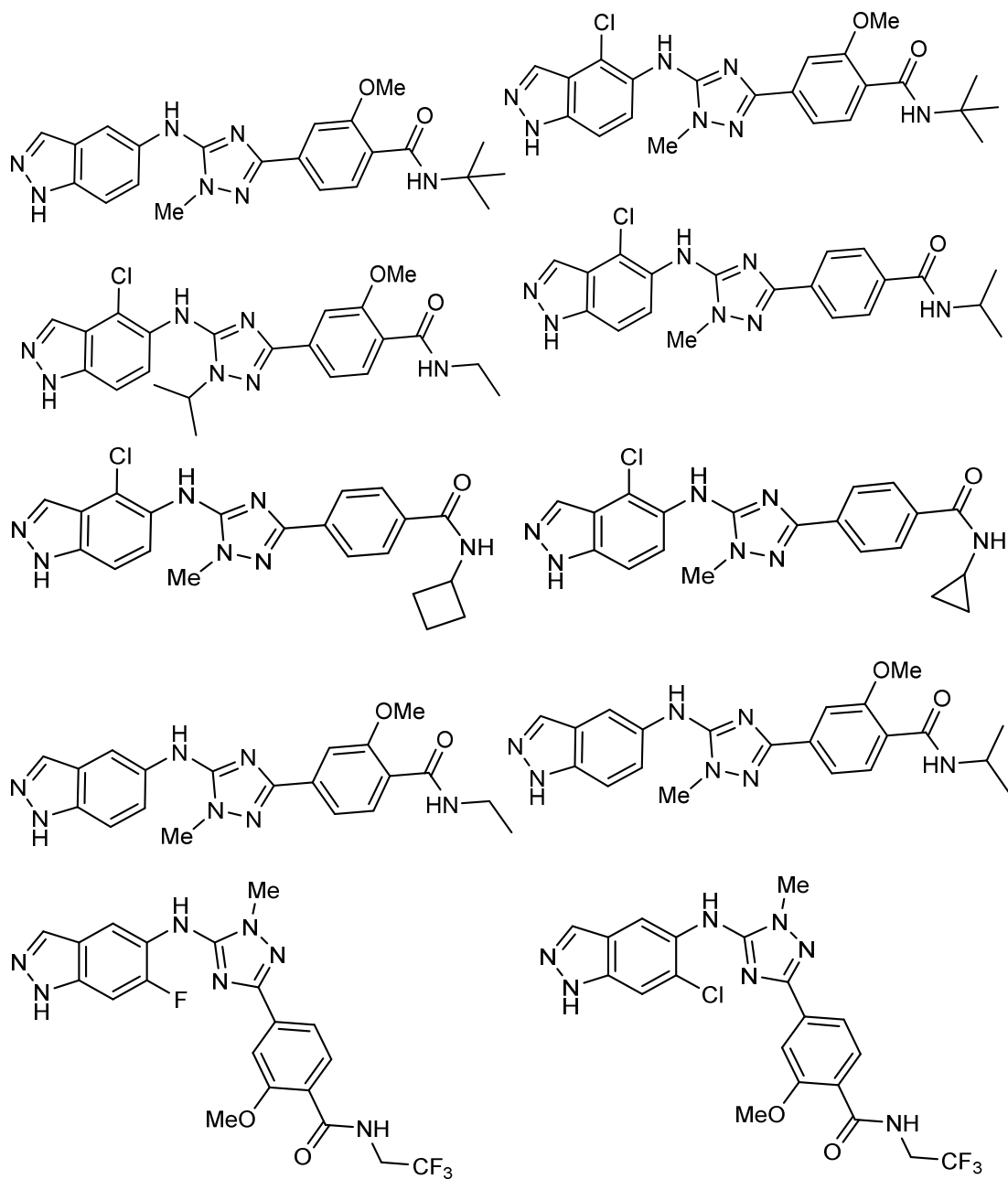


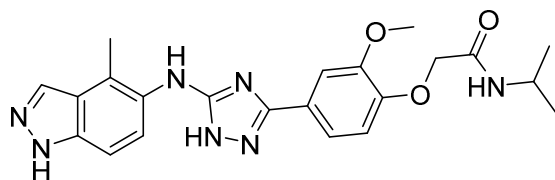
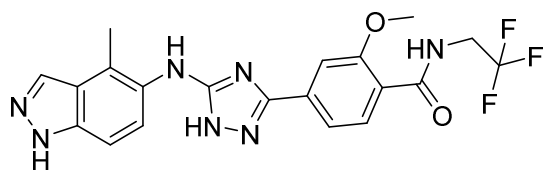
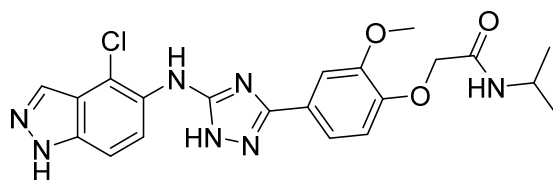
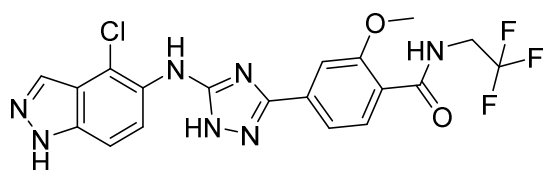
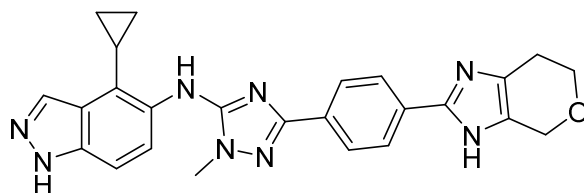
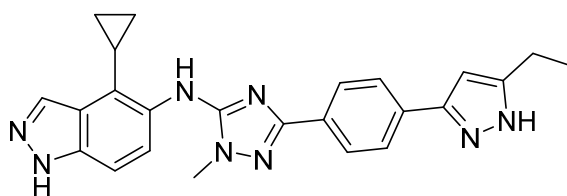
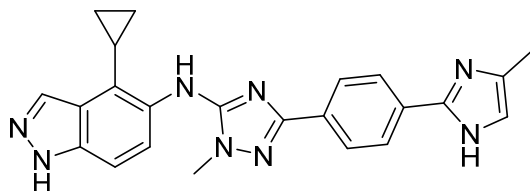
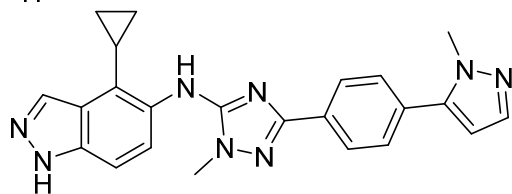
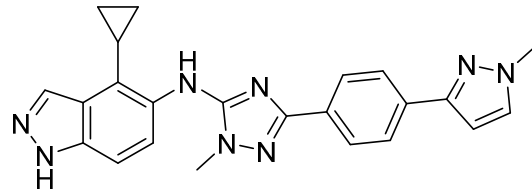
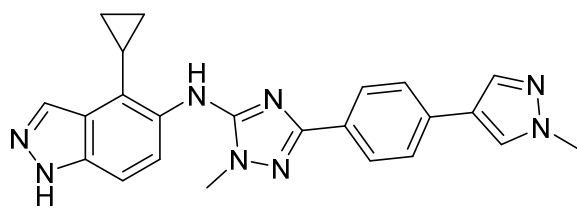


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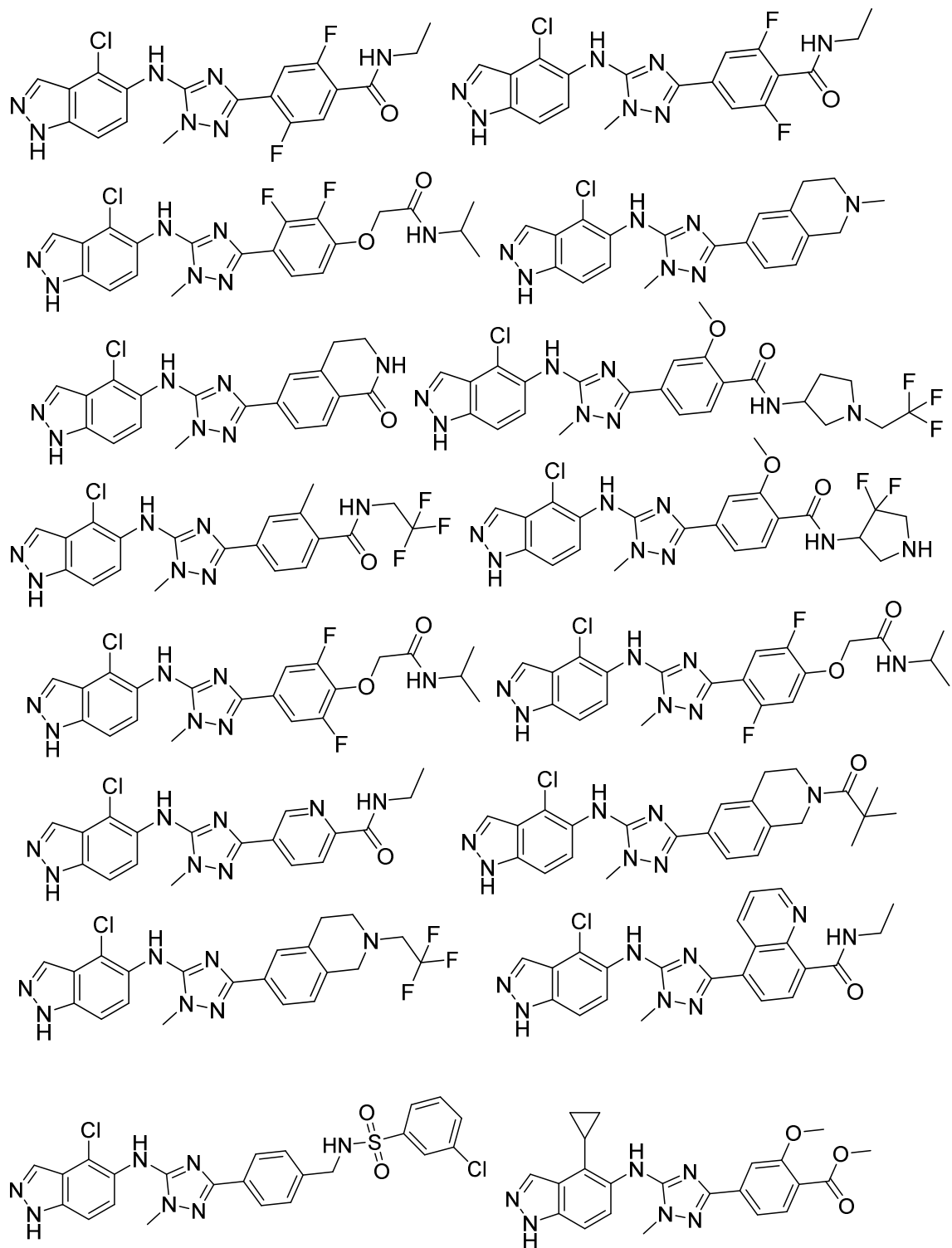


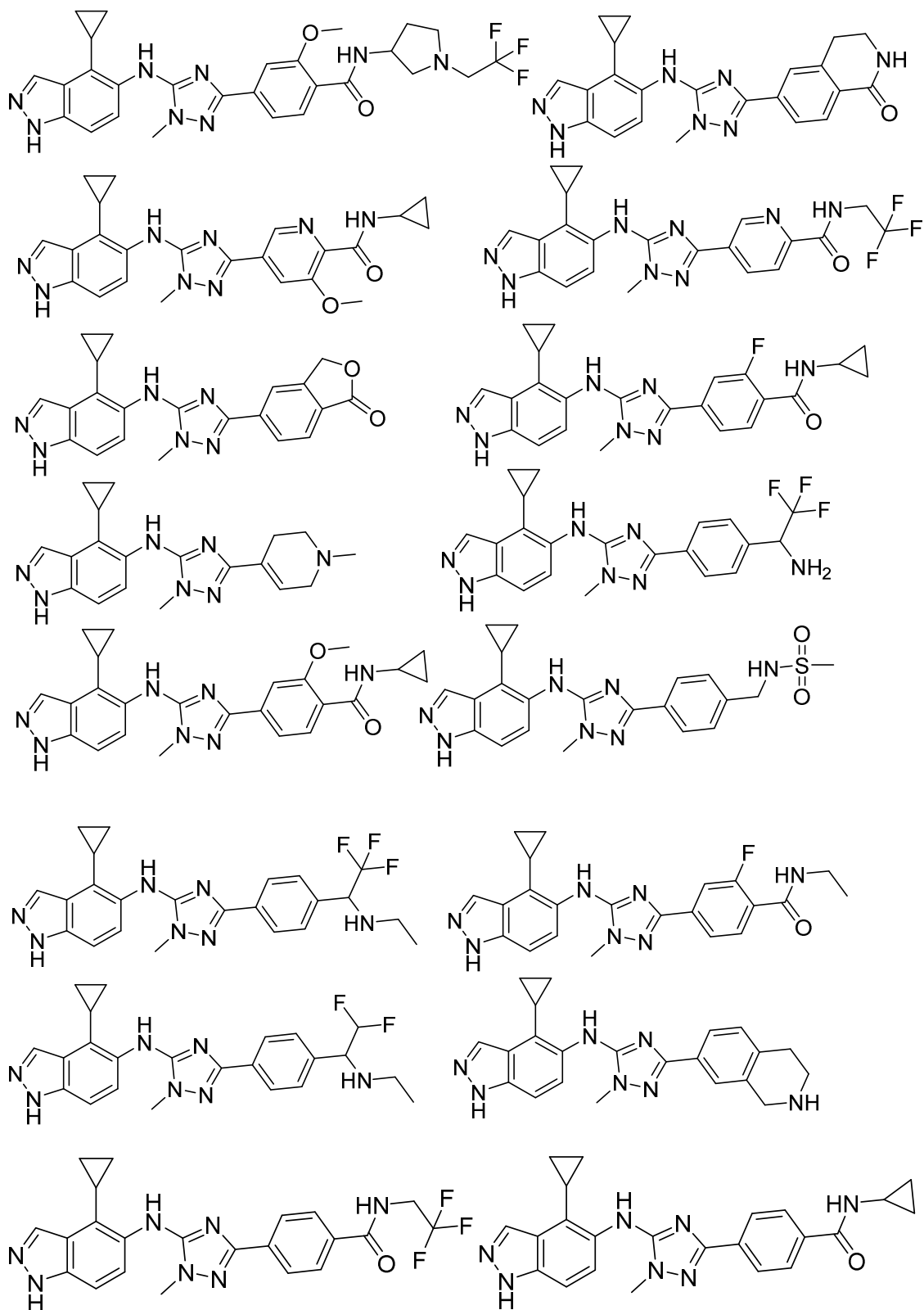
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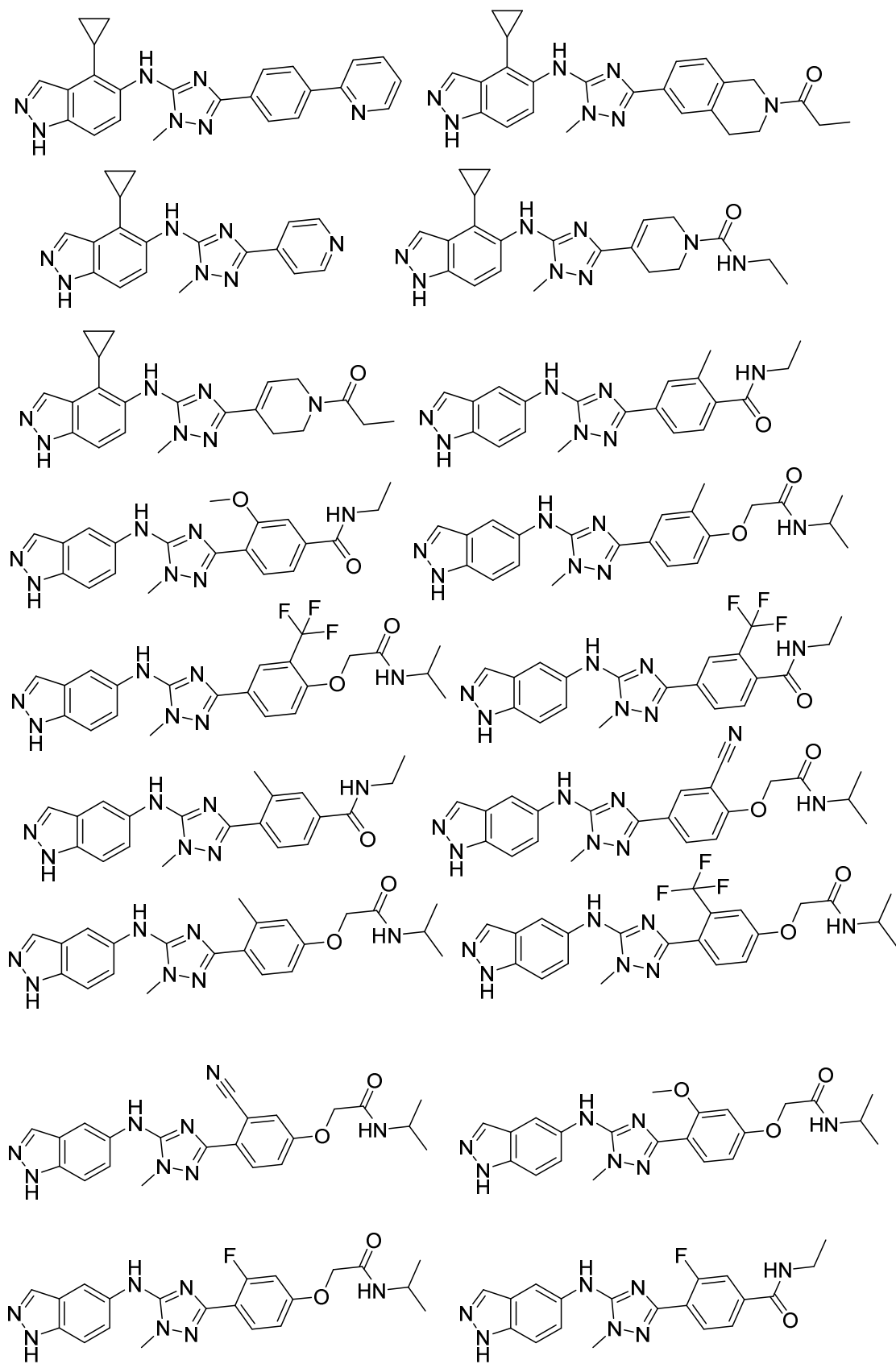




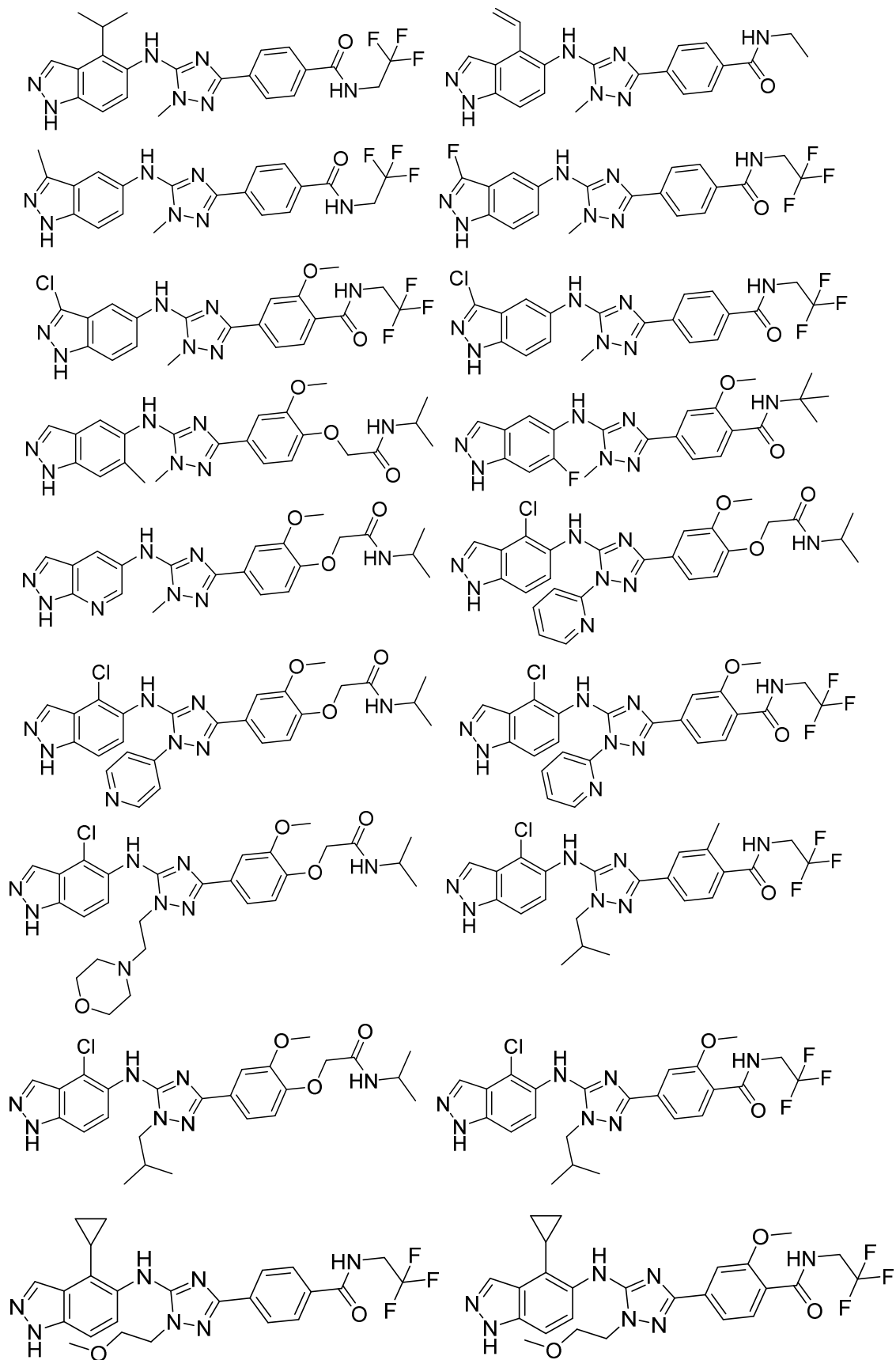


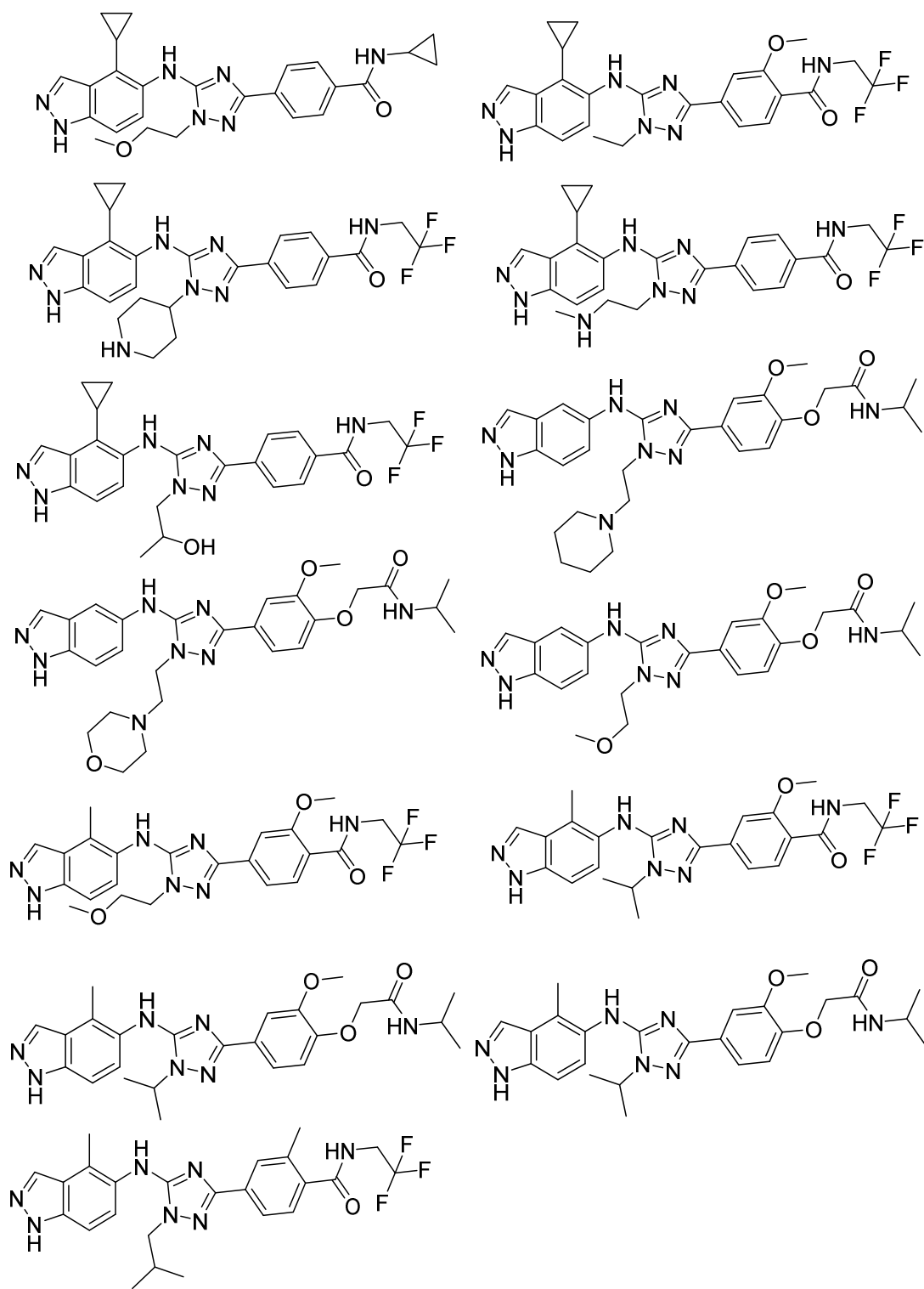




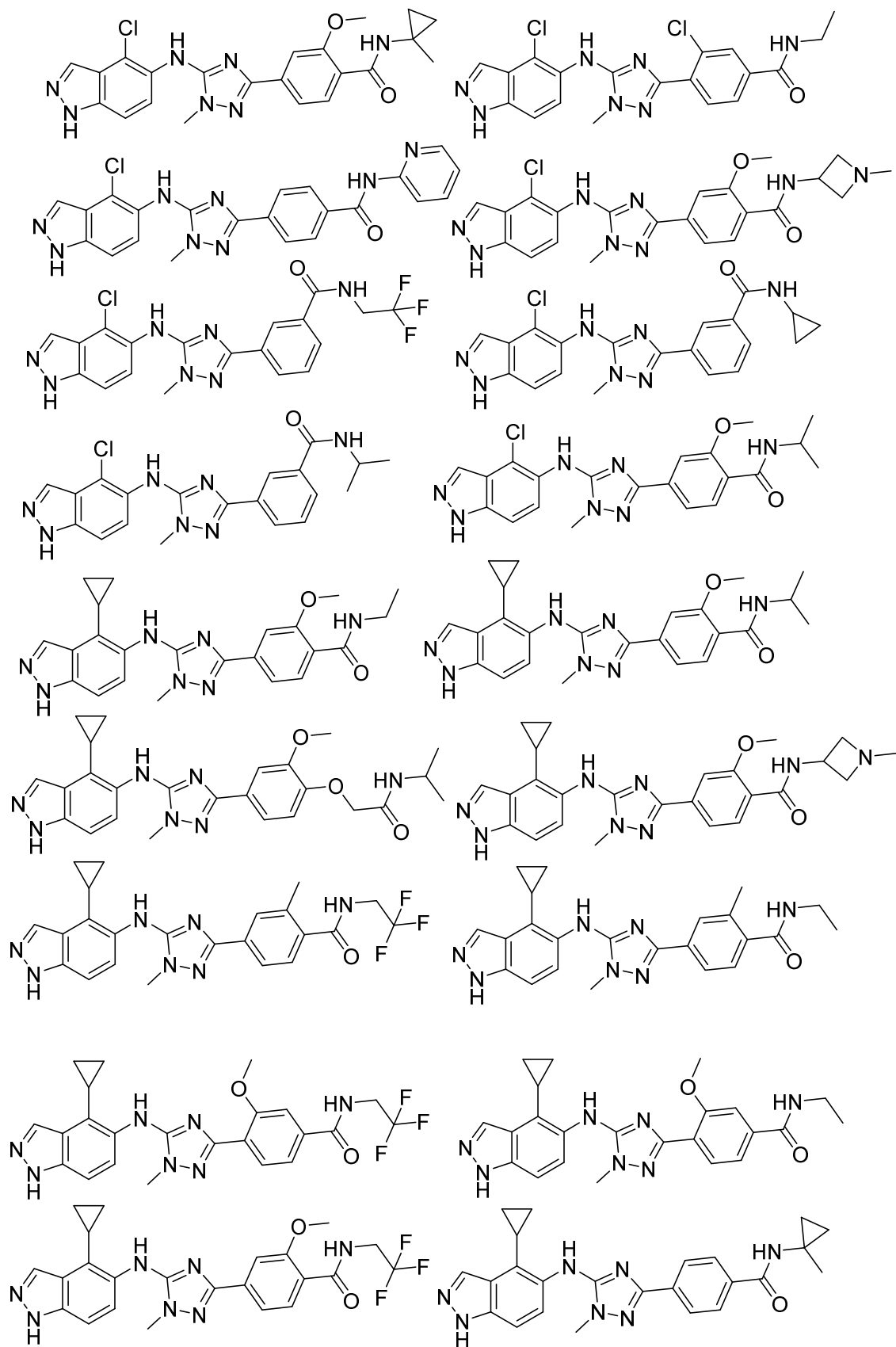




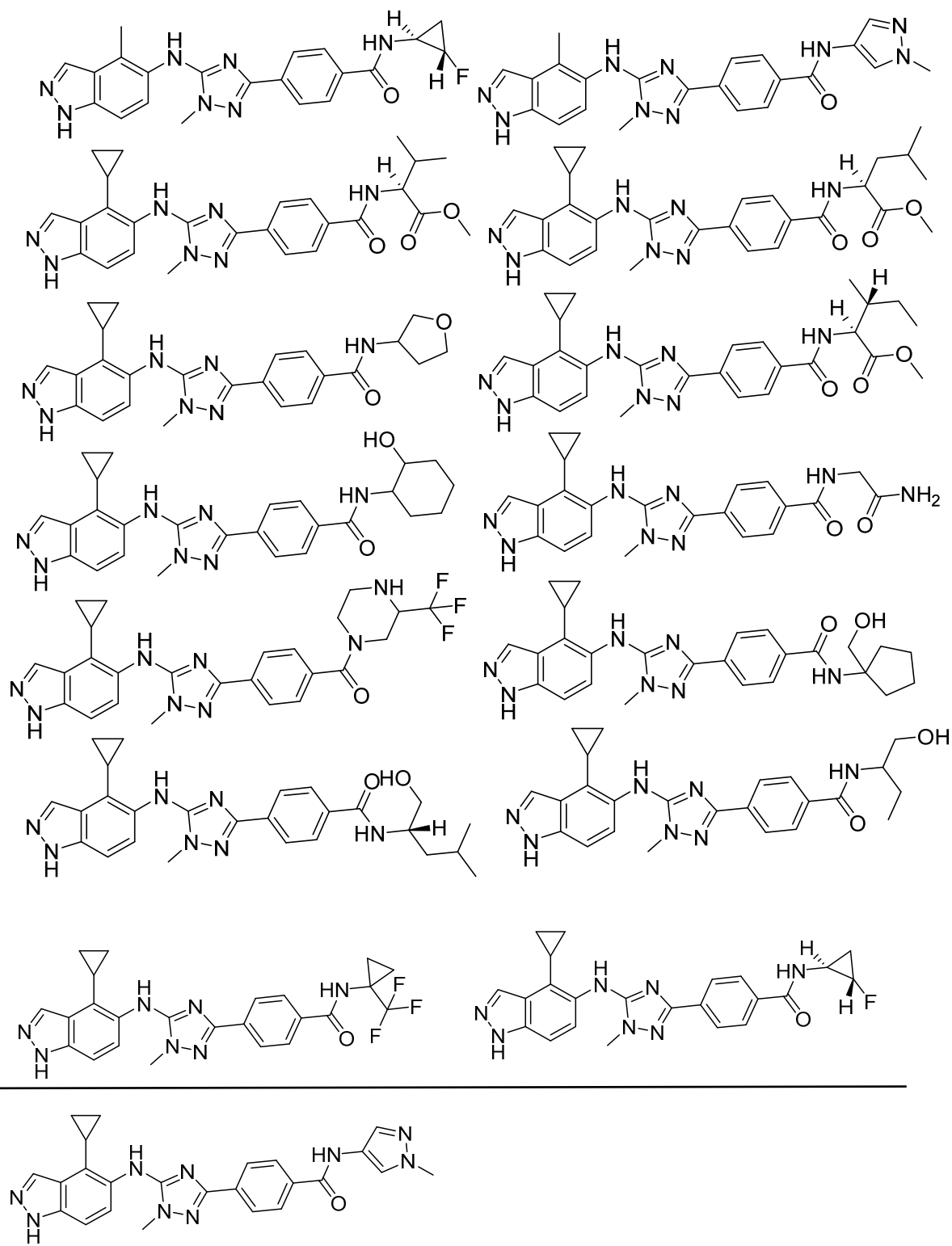


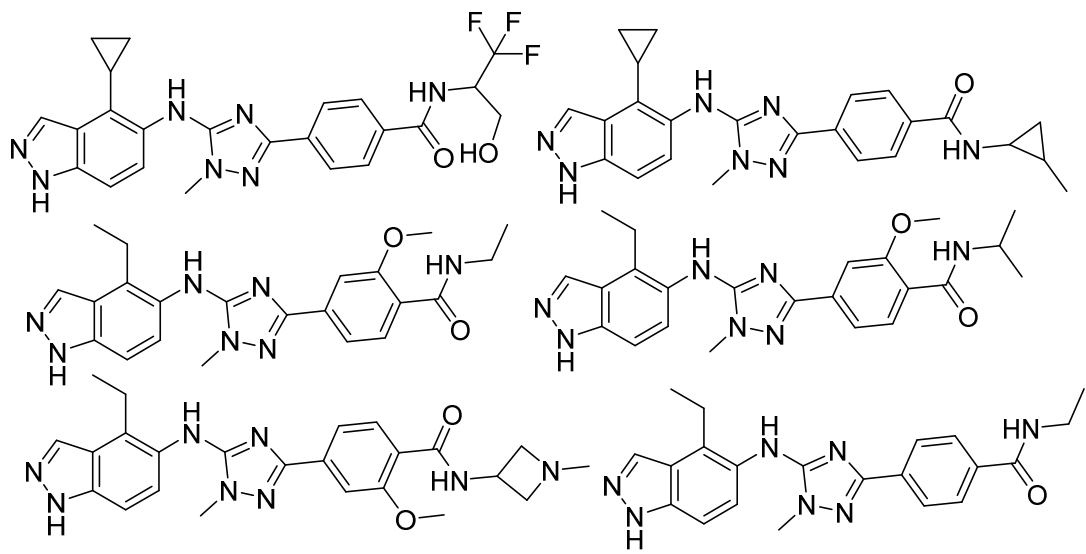




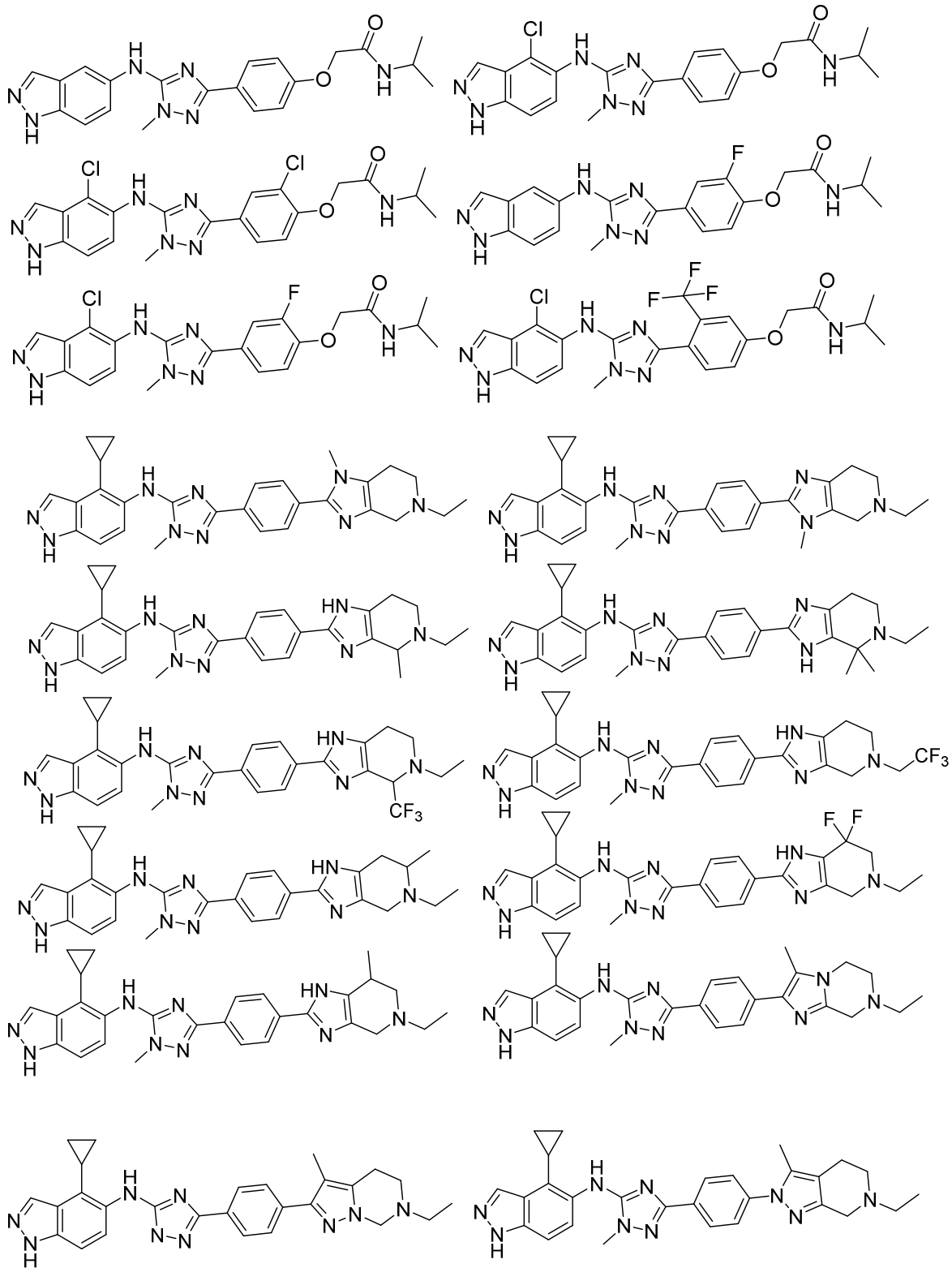


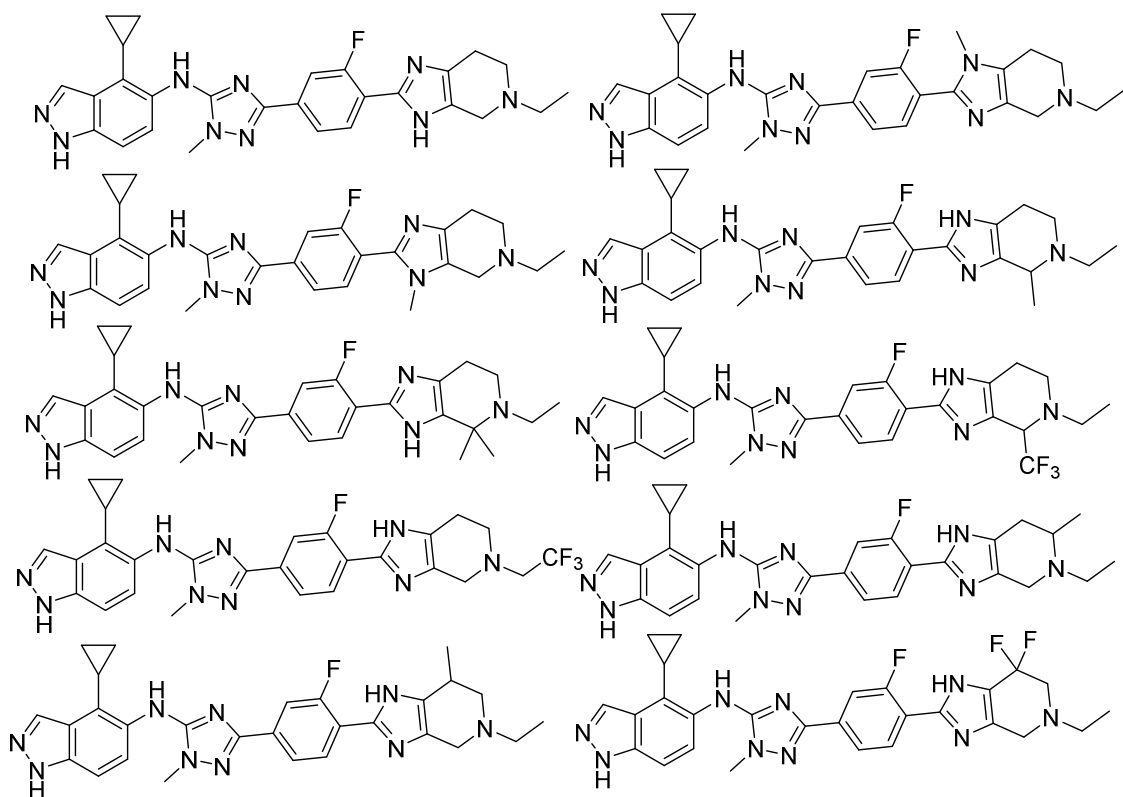
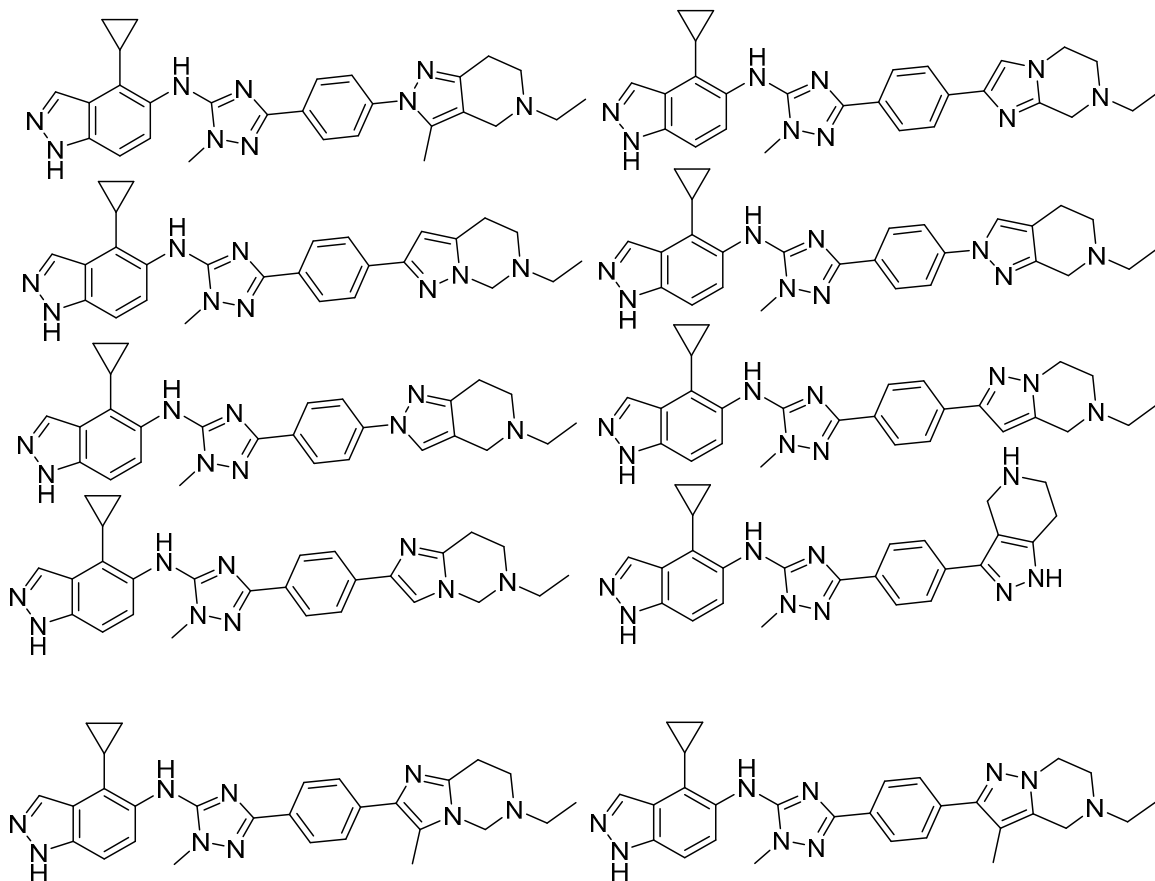


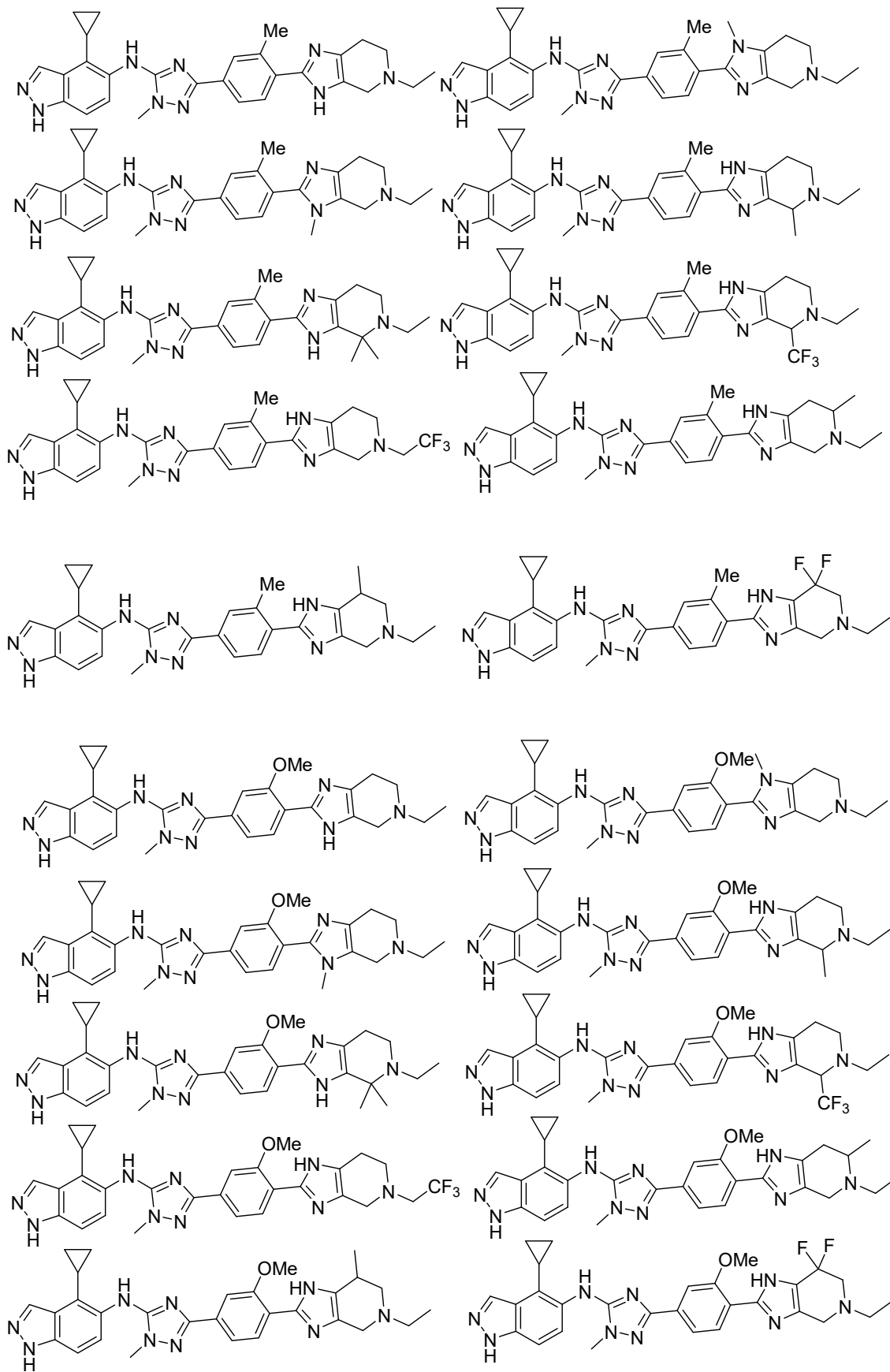


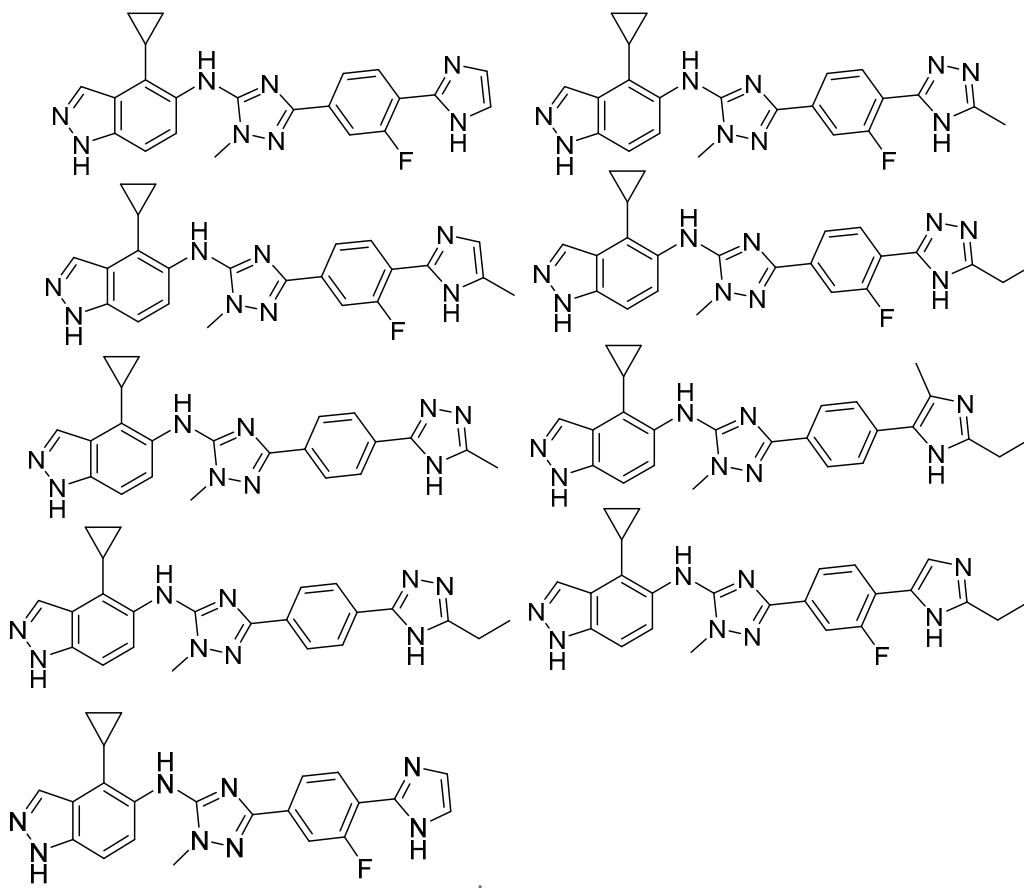












20-14. A compound of any preceding claim for use as a medicament.

5 21-15. A pharmaceutical ~~formulation composition~~ comprising a compound of any one of claims 1 to 1913 and a pharmaceutically acceptable excipient.

22-16. The pharmaceutical composition of claim 21-15, comprising an additional pharmaceutically active agent.

10 23-17. Use of Aa compound of any one of claims 1 to 1913 ~~in the manufacture of a medicament~~ for use in the treatment of a condition which is modulated by ROCK1 and/or ROCK2₁.

24. — The compound for use of claim 23, wherein the condition that is modulated by ROCK1 and/or ROCK2 is a condition selected from: fibrotic diseases, auto-immune, inflammatory-fibrotic conditions, inflammatory conditions, central nervous system disorders, or cancer₁; and/or

15 25. — The compound for use of claims 23 to 24, wherein the condition treatable by the inhibition of ROCK1 and/or ROCK2 is selected from: Sarcoidosis, sclerosis, primary biliary sclerosis, sclerosing cholangitis, dermatitis, atopic dermatitis, Still's disease, chronic obstructive pulmonary disease, Guillain-Barre disease, Graves' disease, Addison's disease, Raynaud's phenomenon, or autoimmune hepatitis. Arthritis, rheumatoid arthritis, psoriatic arthritis, osteoarthritis, degenerative arthritis, polymyalgia rheumatic, ankylosing spondylitis, reactive arthritis, gout, pseudogout,
20 inflammatory joint disease, systemic lupus erythematosus, polymyositis, and fibromyalgia.

Additional types of arthritis include achilles tendinitis, achondroplasia, acromegalic arthropathy, adhesive capsulitis, adult onset Still's disease, anserine bursitis, avascular necrosis, Behcet's syndrome, bicipital tendinitis, Blount's disease, brucellar spondylitis, bursitis, calcaneal bursitis, calcium pyrophosphate dihydrate deposition disease (CPPD), crystal deposition disease, Caplan's syndrome, carpal tunnel syndrome, chondrocalcinosis, chondromalacia patellae, chronic synovitis, chronic recurrent multifocal osteomyelitis, Churg-Strauss syndrome, Cogan's syndrome, corticosteroid-induced osteoporosis, costosternal syndrome, CREST syndrome, cryoglobulinemia, degenerative joint disease, dermatomyositis, diabetic finger sclerosis, diffuse idiopathic skeletal hyperostosis (DISH), discitis, discoid lupus erythematosus, drug-induced lupus, Duchenne's muscular dystrophy, Dupuytren's contracture, Ehlers-Danlos syndrome, enteropathic arthritis, epicondylitis, erosive inflammatory osteoarthritis, exercise-induced compartment syndrome, Fabry's disease, familial Mediterranean fever, Farber's lipogranulomatosis, Felty's syndrome, Fifth's disease, flat feet, foreign body synovitis, Freiberg's disease, fungal arthritis, Gaucher's disease, giant cell arteritis, gonococcal arthritis, Goodpasture's syndrome, granulomatous arteritis, hemarthrosis, hemochromatosis, Henoch-Schonlein purpura, Hepatitis B surface antigen disease, hip dysplasia, Hurler syndrome, hypermobility syndrome, hypersensitivity vasculitis, hypertrophic osteoarthropathy, immune complex disease, impingement syndrome, Jaccoud's arthropathy, juvenile ankylosing spondylitis, juvenile dermatomyositis, juvenile rheumatoid arthritis, Kawasaki disease, Kienbock's disease, Legg-Calve-Perthes disease, Lesch-Nyhan syndrome, linear scleroderma, lipoid dermatoarthritis, Lofgren's syndrome, Lyme disease, malignant synovioma, Marfan's syndrome, medial plica syndrome, metastatic carcinomatous arthritis, mixed connective tissue disease (MCTD), mixed cryoglobulinemia, mucopolysaccharidosis, multicentric reticulohistiocytosis, multiple epiphyseal dysplasia, mycoplasmal arthritis, myofascial pain syndrome, neonatal lupus, neuropathic arthropathy, nodular panniculitis, ochronosis, olecranon bursitis, Osgood-Schlatter's disease, osteoarthritis, osteochondromatosis, osteogenesis imperfecta, osteomalacia, osteomyelitis, osteonecrosis, osteoporosis, overlap syndrome, pachydermoperiostosis Paget's disease of bone, palindromic rheumatism, patellofemoral pain syndrome, Pellegrini-Stieda syndrome, pigmented villonodular synovitis, piriformis syndrome, plantar fasciitis, polyarteritis nodos, Polymyalgia rheumatic, polymyositis, popliteal cysts, posterior tibial tendinitis, Pott's disease, prepatellar bursitis, prosthetic joint infection, pseudoxanthoma elasticum, psoriatic arthritis, Raynaud's phenomenon, reactive arthritis/Reiter's syndrome, reflex sympathetic dystrophy syndrome, relapsing polychondritis, retrocalcaneal bursitis, rheumatic fever, rheumatoid vasculitis, rotator cuff tendinitis, sacroiliitis, salmonella osteomyelitis, sarcoidosis, saturnine gout, Scheuermann's osteochondritis, scleroderma, septic arthritis, seronegative arthritis, shigella arthritis, shoulder-hand syndrome, sickle cell arthropathy, Sjogren's syndrome, slipped capital femoral epiphysis, spinal stenosis, spondylolysis, staphylococcus arthritis, Stickler syndrome, subacute cutaneous lupus, Sweet's syndrome, Sydenham's chorea, syphilitic arthritis, systemic lupus erythematosus (SLE), Takayasu's arteritis, tarsal tunnel syndrome, tennis elbow, Tietze's syndrome, transient osteoporosis, traumatic arthritis, trochanteric bursitis, tuberculosis arthritis, arthritis of Ulcerative colitis, undifferentiated connective tissue syndrome (UCTS), urticarial vasculitis, viral arthritis, Wegener's granulomatosis, Whipple's disease, Wilson's disease, yersinia

arthritis and conditions involving vascularization and/or inflammation, include atherosclerosis, rheumatoid arthritis (RA), hemangiomas, angiofibromas, and psoriasis. Other non-limiting examples of angiogenic disease are retinopathy of prematurity (retrolental fibroplastic), corneal graft rejection, corneal neovascularization related to complications of refractive surgery, corneal neovascularization related to contact lens complications, corneal neovascularization related to pterygium and recurrent pterygium, corneal ulcer disease, and non-specific ocular surface disease, insulin-dependent diabetes mellitus, multiple sclerosis, myasthenia gravis, Chorv's disease, autoimmune nephritis, primary biliary cirrhosis, acute pancreatitis, allograft rejection, allergic inflammation, contact dermatitis and delayed hypersensitivity reactions, inflammatory bowel disease, septic shock, osteoporosis, osteoarthritis, cognition defects induced by neuronal inflammation, Osier- Weber syndrome, restinosis, and fungal, parasitic and viral infections, including cytomegalo viral infections.

~~26-18. Use of Aa~~ compound of any one of claims 1 to 13 in the manufacture of a medicament for use in the treatment of: fibrotic diseases, auto-immune, inflammatory-fibrotic conditions, inflammatory conditions, central nervous system disorders, or cancer.

~~27-19. Use of a~~The compound of any one of claims 1 to 13 in the manufacture of a medicament ~~for claim 26 for use in~~ the treatment of a condition selected from: Idiopathic Pulmonary Fibrosis (IPF); systemic sclerosis (SSC); interstitial lung disease (ILD); type 1 and type 2 diabetes; diabetic nephropathy; Nonalcoholic Steatohepatitis (NASH); Nonalcoholic fatty liver disease (NAFLD); hypertension, atherosclerosis, restenosis, stroke, heart failure, coronary vasospasm, cerebral vasospasm, peripheral circulatory disorder, peripheral artery occlusive disease, ischemia/reperfusion injury, pulmonary hypertension and angina, erectile dysfunction, fibroid lung, fibroid liver and fibroid kidney. glaucoma, ocular hypertension, retinopathy, rheumatoid arthritis, psoriasis, psoriatic arthritis, Sjogren's syndrome, asthma, adult respiratory distress syndrome, chronic obstructive pulmonary disease (COPD), SLE, cGVHD, inflammatory bowel disease, stenosis of the bowel, disorders involving neuronal degeneration or physical injury to neural tissue, Huntington's disease, Parkinson's Disease, Alzheimer's, Amyotrophic lateral sclerosis (ALS), multiple sclerosis, liver cancer, bladder cancer, hepatoma, squamous carcinoma of the lung, non-small cell lung cancer, adenocarcinoma of the lung, small-cell lung cancer, various types of head and neck cancer, breast cancer, colon cancer, colorectal cancer, cancer of the peritoneum, hepatocellular cancer, gastrointestinal cancer, esophageal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, squamous cell cancer, pituitary cancer, astrocytoma, soft tissue sarcoma, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, kidney cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, brain cancer, endometrial cancer, testis cancer, cholangiocarcinoma, gallbladder carcinoma, gastric cancer and melanoma.

~~28. A method of treating a condition which is modulated by ROCK1 and/or ROCK2, wherein the method comprises administering a therapeutic amount of a compound of any one of claims 1 to 19, to a patient in need thereof.~~

29. — The method of claim 28 is a method of treating a condition treatable by the inhibition of ROCK1 and/or ROCK2.

5 30. — A method of treating a condition, wherein the condition is selected from: fibrotic diseases, auto-immune, inflammatory-fibrotic conditions, inflammatory conditions, central nervous system disorders, or cancer, wherein the method comprises administering a therapeutic amount of a compound of any one of claims 1 to 19, to a patient in need thereof.

10 31. — The method of claims 28 to 30 for use in the treatment of a condition selected from: Idiopathic Pulmonary Fibrosis (IPF); systemic sclerosis (SSC); interstitial lung disease (ILD); type 1 and type 2 diabetes; diabetic nephropathy; Nonalcoholic Steatohepatitis (NASH); Nonalcoholic fatty liver disease (NAFLD); hypertension, atherosclerosis, restenosis, stroke, heart failure, coronary vasospasm, cerebral vasospasm, peripheral circulatory disorder, peripheral artery occlusive disease, ischemia/reperfusion injury, pulmonary hypertension and angina, erectile dysfunction, fibroid lung, fibroid liver and fibroid kidney, glaucoma, ocular hypertension, retinopathy, rheumatoid arthritis, psoriasis, psoriatic arthritis, Sjogren's syndrome, asthma, adult respiratory distress syndrome, chronic obstructive pulmonary disease (COPD), SLE, cGVHD, inflammatory bowel disease, stenosis of the bowel, disorders involving neuronal degeneration or physical injury to neural tissue, Huntington's disease, Parkinson's Disease, Alzheimer's, Amyotrophic lateral sclerosis (ALS), multiple sclerosis, liver cancer, bladder cancer, hepatoma, squamous carcinoma of the lung, non-small cell lung cancer, adenocarcinoma of the lung, small cell lung cancer, various types of head and neck cancer, breast cancer, colon cancer, colorectal cancer, cancer of the peritoneum, hepatocellular cancer, gastrointestinal cancer, esophageal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, squamous cell cancer, pituitary cancer, astrocytoma, soft tissue sarcoma, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, kidney cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, brain cancer, endometrial cancer, testis cancer, cholangiocarcinoma, gallbladder carcinoma, gastric cancer and melanoma.

32. — A pharmaceutical composition, wherein the composition comprises a compound of any one of claims 1 to 19 and pharmaceutically acceptable excipients.

30 33. — The pharmaceutical composition of claim 32 may be a combination product comprising an additional pharmaceutically active agent.

34. A compound of any one of claims 1 to 19 for use in the manufacture of a medicament for use in the treatment a condition is selected from: fibrotic diseases, auto-immune, inflammatory-fibrotic conditions, inflammatory conditions, central nervous system disorders, or cancer.